REVIEWS

Syntheses of Cyclic Ureas by α-Ureidoalkylation

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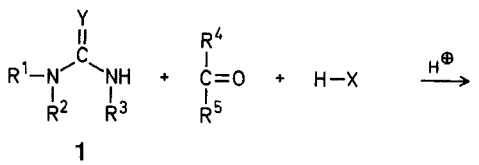
The cyclocondensation of ureas, thioureas, guanidines, or sulfamides with an aldehyde or ketone and a suitable nucleophilic compound in accordance with the principle of "α-ureidoalkylation" or "vinylogous ureidoalkylation" leads to the formation of saturated or unsaturated mono- and polycyclic heterocycles. The rings may be separated or may be linked in the 1,2- or 1,3-position. Spiro compounds can also be formed. The 5-, 6-, 7-, and 8-membered rings accessible in this way can contain further hetero atoms such as, for example, O, S, N, or P. Synthesis possibilities, properties, substitution reactions, and rearrangement reactions of these heterocycles are described.

Durch Cyclokondensation von Harnstoffen, Thioharnstoffen, Guanidinen oder Sulfamiden mit einem Aldehyd oder Keton und einer geeigneten nucleophilen Verbindung werden nach dem Prinzip der „α-Ureidoalkylierung" oder der „vinylogen Ureidoalkylierung" gesättigte und ungesättigte mono- und polycyclische Heterocyclen erhalten. Die Ringe können getrennt vorliegen, in 1,2- oder 1,3-Stellung verknüpft sein. Auch Spiroverbindungen können entstehen. Die auf diese Weise zugänglichen fünf-, sechs-, sieben- und achtgliedrigen Heterocyclen können weitere Heteroatome, wie beispielsweise O, S, N oder P enthalten. Synthesemöglichkeiten, Eigenschaften, Substitutions- und Umlagerungsreaktionen dieser Heterocyclen werden beschrieben.

1. Definition and Mechanisms of Cyclocondensations According to the Principle of α-Ureidoalkylation and Vinylogous Ureidoalkylation

By α-ureidoalkylation[1,2,3] is meant the linking of a nucleophilic substance through the carbonyl carbon atom of an aldehyde or ketone to the nitrogen atom of an acyclic or cyclic urea, thiourea, guanidine, or sulfamide (**1**):



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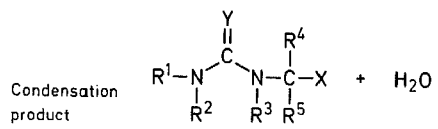
Ureido component | Carbonyl component | Nucleophilic component



Condensation product

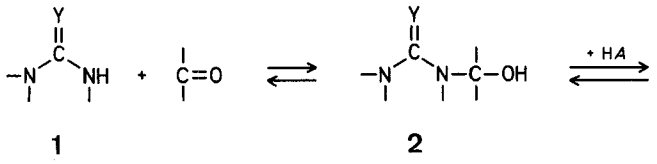
These condensations are related to α-aminoalkylation[4] and α-amidoalkylation[5,6]. The primary step of almost all α-ureidoalkylations consists of the addition of the NH group to the carbonyl group of an aldehyde or ketone, giving rise to an α-alkylol compound (**2**). This N-(1-hydroxyalkyl)-urea derivative is converted, in a generally acid-catalyzed reaction, into an α-ureidoalkylcarbenium ion (**3a**) which is mesomeric with the α-ureidoalkylimonium ion (**3b**)[7,8]. These α-ureidoalkyl-[carbenium-imonium] ions can enter into an electrophilic substitution reaction with a nucleophilic compound to give the condensation product **4**.

[1] H. Petersen, *Festschrift „Carl Wurster"*, BASF, Ludwigshafen, 1960, p. 339.

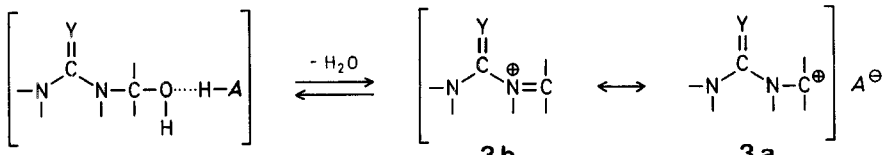
[2] H. Petersen, *Textil-Rundschau* **16**, 646 (1961): *Melliand Textil-Ber.* **43**, 380 (1962).

[3] H. Petersen, *Angew. Chem.* **76**, 909 (1964).

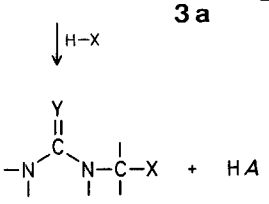
[4] H. Hellmann, G. Opitz, *Angew. Chem.* **68**, 265 (1956). H. Hellmann, G. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, 1960.



1 2



3b 3a



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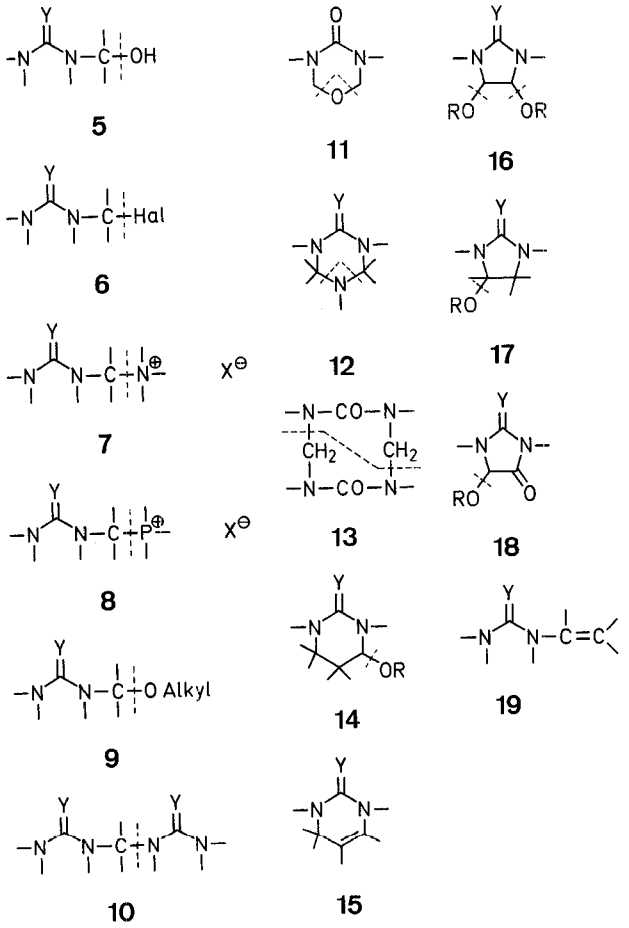
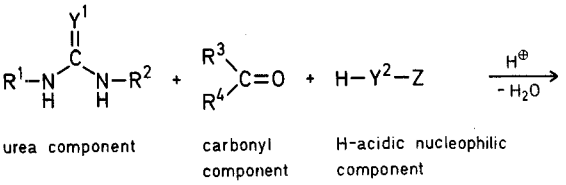
α-Haloalkylureas (**6**), α-ureidoalkylamonium salts (**7**), α-ureidoalkylphosphonium salts (**8**), α-alkoxyalkylureas (**9**), and α-alkylidene-bis-ureas (**10**) react in the same way as N-(1-hydroxyalkyl)-ureas (**5**). In many cases there may also be used heterocycles of the type of 4-oxotetrahydro-1,3,5-oxadiazines (**11**) and 2-oxo(thiono)-1,3,5-hexahydro-1,3,5-triazines (**12**), cyclic ureas of the type of dimethylenediureides (**13**), 2-oxo(thiono)-4-hydroxy(alkoxy)-hexahydropyrimidines (**14**) and 2-oxo(thiono)-tetrahydropyrimidines (**15**), 4,5-dihydroxy- and 4,5-dialkoxy-2-oxo(thiono)-imidazolidines (**16**), 4-hydroxy(alkoxy)-2-oxo(thiono)-imidazolidines (**17**), 4-hydroxy(alkoxy)-2-oxo(thiono)-hydantoins (**18**), and N-vinyl derivatives (**19**) and the like of ureas and thioureas, as well as corresponding guanidine and sulfamide derivatives.

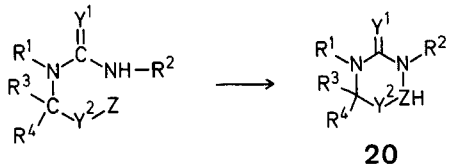


5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

If a nucleophilic compound such as an H-acidic compound H-Y^2-Z having a group Z which is linked with, or can react with, the second amino group of the urea is involved in an α-ureidoalkylation, a cyclization takes place (**20**)[3,9].



urea component carbonyl component H-acidic nucleophilic component



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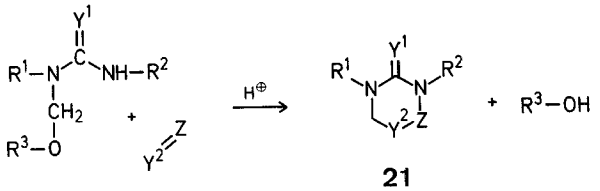
As the nucleophilic reagent for such cyclization reactions, compounds having an olefinic double bond or other polarized or polarizable double bond can also be employed. Such compounds include olefins with aromatic or aliphatic residues, vinyl ethers, enamines, vinylureas, ketones, and formaldehyde. Six-membered cyclic ureas (**21**) are formed.



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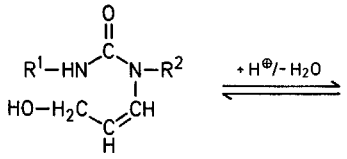
The mesomeric system of an α-ureidoalkyl-[carbenium-imonium] ion can be extended by insertion of a vinylene group (**23a, b**). The α,β-unsaturated γ-alkylol compounds (**22**) of ureas and the like are therefore to be regarded as vinylogous ureidoalkylating agents. When the second amino group of the urea molecule carries a substitutable hydrogen atom,

[5] H. Hellmann, *Angew. Chem.* **69**, 463 (1957).
[6] H. E. Zaugg, *Synthesis* **1970**, 49.
M. Tramontini, *Synthesis* **1973**, in press.

the γ-carbon atom can react with the second amino group of the urea to effect cyclization to **24**[39]:



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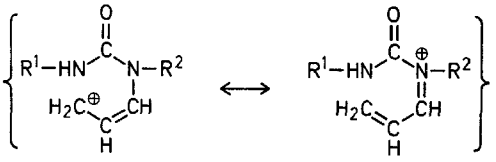
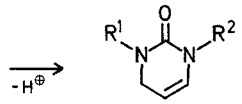
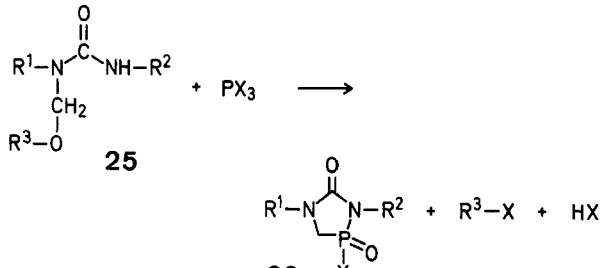


23 a **23 b**



24

Trivalent phosphorus compounds with marked nucleophilic character are also capable of reacting. Thus, N-alkoxymethyl compounds (**25**) of N,N'-dialkylureas and phosphorus trihalides react with elimination of alkyl halide and hydrogen halide to give 1,3-dialkyl-4-halo-2,4-dioxo-1,3,4-diazaphospholanes (**26**)[10]:



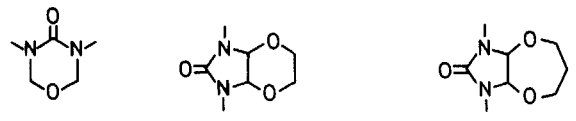
25 **26**

2. Cyclocondensations by α-Ureidoalkylation of H-Acidic Compounds

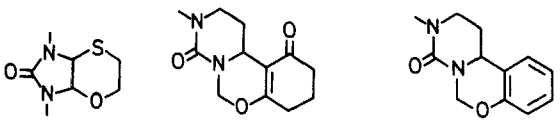
Saturated and unsaturated cyclic ureas, thioureas, guanidines, and sulfamides with 5, 6, 7, and 8 ring members, bicyclic and polycyclic heterocycles the rings of which are separate or are linked in the 1,2- or 1,3-position, and spiro compounds can be prepared according to the principle of α-ureidoalkylation. In the following sections, cyclocondensations by α-ureidoalkylation of OH-, SH-, NH-, and CH-acidic compounds, as well as of nucleophilic olefins and phosphorus compounds, are described separately.

2.1. Cyclocondensations by α-Ureidoalkylation of OH-Acidic Compounds

Suitable OH-acidic compounds are N-(α-hydroxyalkyl) compounds and compounds with alcoholic or phenolic hydroxy groups. Thus, N-(α-hydroxyalkyl)-ureas may be converted into 4-oxotetrahydro-1,3,5-oxadiazines (**27**); similarly compounds with alcoholic hydroxy groups are converted into the bicyclic heterocycles **28**, **29**, and **30**, and the tricyclic compounds **31**. The cyclocondensation of N-(α-hydroxyalkyl)-ureas with phenols leads to heterocycles of the type **32**.



27 **28** **29**

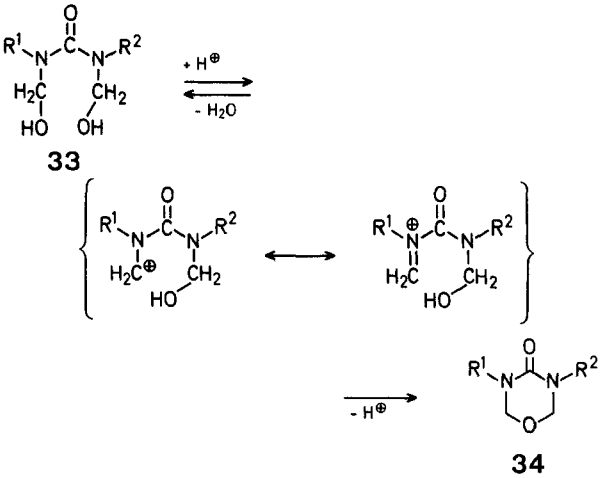


30 **31** **32**

2.1.1. Cyclocondensations with N-(1-Hydroxyalkyl) Groups and Transformations of the Condensation Products

2.1.1.1. Preparation of 4-Oxotetrahydro-1,3,5-oxadiazines

The condensation of symmetrically disubstituted ureas in a 1:2 molar ratio with formaldehyde in the presence of acids leads to cyclic ureas of the type of 4-oxotetrahydro-1,3,5-oxadiazine (**34**). These compounds were first described by Kadowaki[11] and called urones. Their preparation depends on a ureidomethylation of a hydroxymethyl group linked to the second N-atom of the urea.

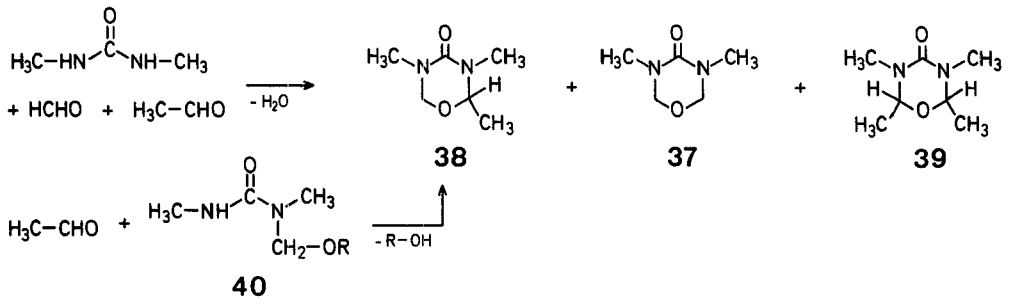


33 **34**

[7] H. Petersen, *Textilveredlung* **5**, 437 (1970); *Textile Research Journal* **41**, 239 (1971).

[8] H. Petersen, *Chemiker-Ztg.* **95**, 692 (1971).

[9] H. Petersen, *XXXVII Congrès Internationaux de Chemie Industrielle*, Madrid, 1967, Vol. 2, p. 933–940.

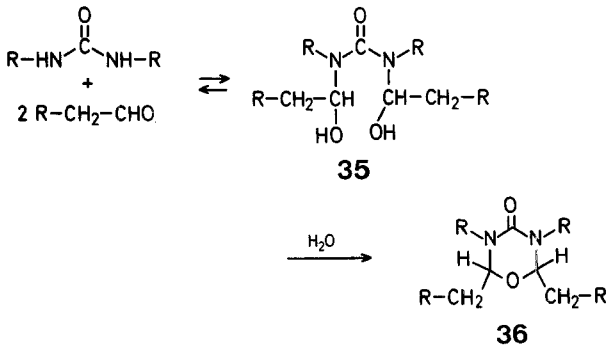


3,3-Dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (34; R^1, $R^2 = CH_3$)[9]:

Method A: N,N'-Dimethylurea (88 g, 1 mol) is added with stirring to 30% formaldehyde solution (200 g, 2 mol) and the mixture is treated with concentrated hydrochloric acid (1.5 ml) (the temperature rises to ~40°). After heating at 90–95° for 1 hr, the mixture is cooled, neutralized with sodium hydroxide, and evaporated at 60° under water-aspirator vacuum. After filtration from sodium chloride, the crude product (125 g, 96%) is purified by high-vacuum distillation; b.p. 75–76°/0.5 torr.

Method B: N,N'-Dimethylurea (440 g) is dissolved in 30% formaldehyde solution (1000 g), treated with Dowex® 50 cation-exchange resin (50 g), stirred at 95° for 30 min, filtered from cation-exchange resin, and evaporated at 50°/15 torr; yield of crude product: 649 g (99.8%). High-vacuum distillation gives pure 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine; yield: 630 g.

While the procedure described by Kadowaki is only applicable to the preparation of simple urones using formaldehyde, more recently it has been possible to prepare urones (**36**) by cyclocondensation of ureas with higher aldehydes[3,9]. The bis-[1-hydroxyalkyl]-ureas (**35**) occuring as intermediates generally have CH-acidic groups in addition to the OH-acidic alkylol groups. Ring-closure can therefore lead not only to the urone via the hydroxy group, but also via the CH-acidic group to the 2-oxo-tetrahydro- and 4-hydroxy-2-oxohexahydropyrimidines described below.

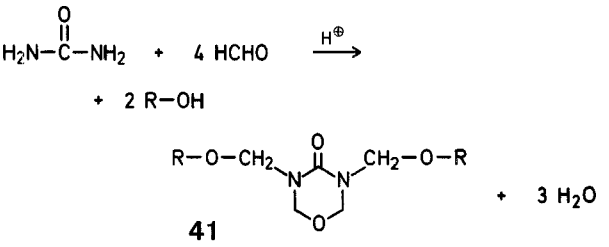


4-Oxotetrahydro-1,3,5-oxadiazines can also be prepared from ureas and two different aldehydes by this method. For instance, the joint condensation of N,N'-dimethylurea with formaldehyde and acetaldehyde affords as the main component 4-oxo-2,3,5-trimethyltetrahydro-1,3,5-oxadiazine (**38**) and as by-products 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (**37**) and 4-oxo-2,3,5,6-tetramethyltetrahydro-1,3,5-oxadiazine (**39**). If in this case one starts directly from the monomethylol or monomethoxymethyl derivative (**40**) of symmetrical dimethylurea and acetaldehyde, 4-oxo-2,3,5-trimethyltetrahydro-1,3,5-oxadiazine (**38**) is obtained in 68% yield[3,9].

4-Oxo-2,3,5-trimethyltetrahydro-1,3,5-oxadiazine (38)[3,9]:

A solution of N,N'-dimethyl-N-methoxymethylurea (**40**; 132 g, 1 mol) in water (200 ml) is stirred with acetaldehyde (44 g, 1 mol) and Dowex® 50 cation-exchange resin (50 g), at 30–35° for 3 hr, filtered from the cation-exchange resin, and evaporated in water-aspirator vacuum. The residue is fractionally distilled at 80–85°/0.6 torr; yield: 68%.

According to Kadowaki[11] and Oshima[12], 3,5-dialkoxymethyl-4-oxotetrahydro-1,3,5-oxadiazines (**41**) may be obtained directly by condensation of urea with formaldehyde and alcohols.



3,5-Dimethoxymethyl-4-oxotetrahydro-1,3,5-oxadiazine (41, R = CH_3)[12]:

Urea (300 g, 5 mol) is mixed with aqueous 37% formaldehyde solution (2433 g, 30 mol) and 40% sodium hydroxide solution (50 ml). After heating at 60° for 2 hr, the mixture is adjusted to pH 5–6 with formic acid and evaporated in water-aspirator vacuum. The syrupy residue is treated with methanol (3500 g) and hydrochloric acid (100 ml), stirred at 20–30° for 1 hr, and neutralized with concentrated sodium hydroxide solution. Water and excess methanol are removed by distillation in vacuo, and the residue is filtered. The filtrate is distilled in vacuo; yield: 764 g (80%); b.p. 116–118°/0.5–1.5 torr.

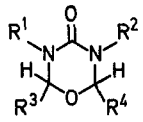
In an analogous manner, other saturated and unsaturated 3,5-dialkoxymethyl derivatives of 4-oxotetrahydro-1,3,5-oxadiazine, as well as 5-alkoxymethyl derivatives of 3-alkyl-4-oxo-tetrahydro-1,3,5-oxadiazines may be prepared.

2.1.1.2. Reactions of 4-Oxotetrahydro-1,3,5-oxadiazines

4-Oxotetrahydro-1,3,5-oxadiazines can react as α-ureidoalkylating agents with H-acidic compounds, the reactions being accompanied by ring cleavage. The N-alkoxymethyl-4-oxotetrahydro-1,3,5-oxadiazines display the typical ureidomethylation reactions, and ring cleavage can also occur in some cases here.

[10] H. Petersen, *Liebigs Ann. Chem.* **726**, 89 (1969).

Table 1. 4-Oxotetrahydro-1,3,5-oxadiazines

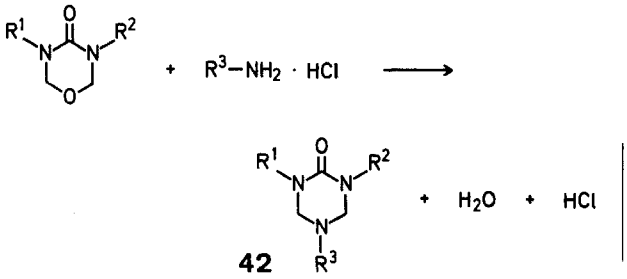


R^1	R^2	R^3	R^4	b.p./torr	m.p.	References
$-CH_3$	$-CH_3$	H	H	75–76°/0.5	38.5°	11
$-CH_3$	$-CH_2-O-CH_3$	H	H	89–90°/0.2		11
$-C_2H_5$	$-CH_2-O-CH_3$	H	H	91–93°/1		11
$-CH_2-O-CH_3$	$-CH_2-O-CH_3$	H	H	82–83°/0.1		11, 12
$-CH_2-O-CH_2-CH=CH_2$	$-CH_2-O-CH_2-CH=CH_2$	H	H	155–157°/3		12
$-CH_2-O-c-C_6H_{11}$	$-CH_2-O-c-C_6H_{11}$	H	H	160°/0.2	53°	12
$-CH_2-O-CH_2-C_6H_5$	$-CH_2-O-CH_2-C_6H_5$	H	H	180°/0.25		12
$-CH_2-O-n-C_8H_{17}$	$-CH_2-O-n-C_8H_{17}$	H	H	173–175°/0.1		12
$-CH_3$	$-CH_2-S-C_2H_5$	H	H	122–125°/1		11
$-C_2H_5$	$-CH_2-S-C_2H_5$	H	H		15.5°	11
$-CH_2-S-C_2H_5$	$-CH_2-S-C_2H_5$	H	H		59°	11
$-CH_3$	$-CH_3$	$-CH_3$	H	80–85°/0.6		3, 9
$-CH_3$	$-CH_3$	$-CH_3$	$-CH_3$	90–92°/0.5		3, 9
$-CH_2Cl$	$-CH_2Cl$	H	H		160° (dec)	16
$-CH_2-P(=O)(OCH_3)(OCH_3)$	$-CH_2-P(=O)(OCH_3)(OCH_3)$	H	H		110°	16
$-CH_2-\overset{\oplus}{P}(C_6H_5)_3\ Br^{\ominus}$	$-CH_2-\overset{\oplus}{P}(C_6H_5)_3\ Br^{\ominus}$	H	H		221–222°	15

The action of aqueous mineral acids on 3,5-dialkyl-4-oxotetrahydro-1,3,5-oxadiazines effects partial hydrolysis and recyclization to 2-oxo-1,3,5-trimethylhexahydro-1,3,5-triazines of the type **42**[3,9,13].

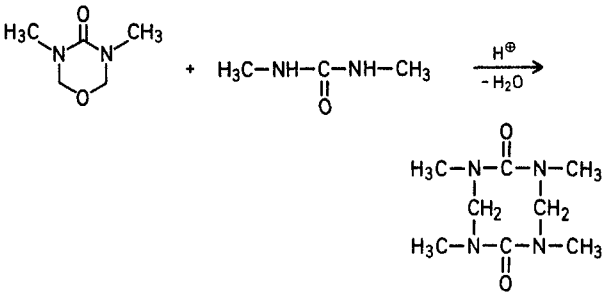
2-Oxo-1,3,5-trimethylhexahydro-1,3,5-triazine Hydrochloride (**42**, $R^1=R^2=R^3=CH_3$)[13]:
A solution of 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (50 g) in ethanol (50 ml) is treated with concentrated hydrochloric acid (30 ml) and heated at 60–65° for 5 min with stirring. After evaporation of the solvent, the syrupy residue is dissolved in ethanol (30 ml) and allowed to stand at room temperature. The product crystallizes out; yield: 25 g (72%); m.p. 170–173.

By reaction with the hydrochlorides or other salts of primary amines, the ring O-atom of 4-oxotetrahydro-1,3,5-oxadiazines can be exchanged for nitrogen by the mechanism of a transureidoalkylation, yielding 5-alkyl-2-oxohexahydro-1,3,5-triazines (**42**).



2-Oxo-1,3,5-trimethylhexahydro-1,3,5-triazine Hydrochloride (**42**, $R^1=R^2=R^3=CH_3$)[13]:
A solution of 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (13 g) in ethanol (20 ml) is heated with methylamine hydrochloride (6.75 g) at 50–55° for 10 min. The product crystallizes on cooling; yield: 10 g (56%); m.p. 170–173°

With N,N'-disubstituted ureas in the presence of catalytic amounts of acid, 3,5-dialkyl-4-oxotetrahydro-1,3,5-oxadiazines react with ring-enlargement to give the eight-membered tetraalkyl-dimethylenediureides[14] (e.g. **43**).



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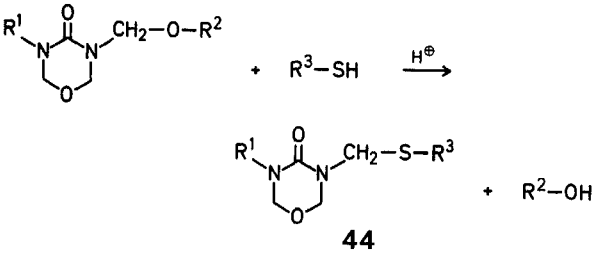
The 3-alkoxymethyl-5-alkyl- and 3,5-dialkoxymethyl-derivatives of 4-oxotetrahydro-1,3,5-triazines condense with alkylmercaptans in the presence of acids, without ring scission, to give 3-alkylmercaptomethyl 5-alkyl- or 3,5-dialkylmercaptomethyl-4-oxotetrahydro-1,3,5-oxadiazines (**44**)[11]:



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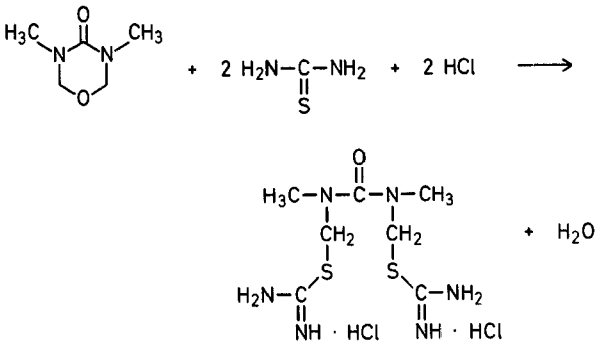
A few derivatives are listed in Table 1.

5-Ethyl-3-ethylthiomethyl-4-oxotetrahydro-1,3,5-oxadiazine[11] **(44**, $R^1=R^3=C_2H_5$**):**

A solution of 5-ethyl-3-methoxymethyl-4-oxotetrahydro-1,3,5-oxadiazine (6.6 g) in ethylmercaptan (12.4 g) is treated with conc. hydrochloric acid (3 drops), heated at 40–50° for 10 min, and neutralized with aqueous barium hydroxide. The product is extracted with ether, the ether evaporated from the extract, and the residue distilled in vacuo; yield: 7.7 g; b.p. 110–113°/1 torr. The product crystallizes on cooling; m.p. 15.5°.

3,5-Dialkyl-4-oxotetrahydro-1,3,5-oxadiazines may be converted into di-thiouronium salts (e.g. **45**) by reaction with thioureas[15].

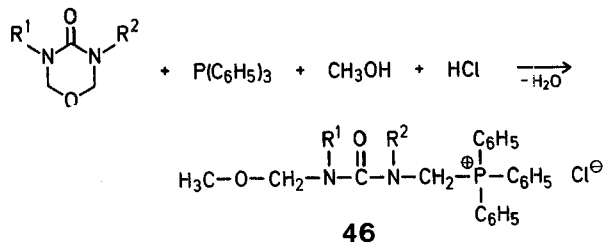


45

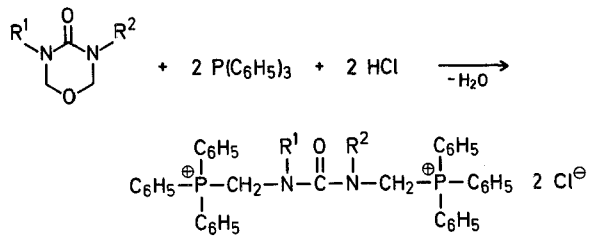
N,N′-Bis-[guanylthiomethyl]-N,N′-dimethylurea Dihydrochloride (N,N′-Dimethylurea-N,N′-bis-[methylthiouronium hydrochloride], 45)[15]**:**

Hydrogen chloride is passed for 3 hr at 0° into a solution of 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (52 g, 0.4 mol) and thiourea (60.8 g, 0.8 mol) in methanol (500 ml). Upon the addition of ether, the bis-thiouronium salt precipitates from the mixture; yield: 57 g (52%); m.p. 131° (from methanol).

The reaction of 4-oxotetrahydro-1,3,5-oxadiazines with the salts of tertiary phosphines proceeds with ring-opening, both the mono- and the corresponding diphosphonium salts (**46**, **47**) being obtained, depending on the molar ratio used[16].

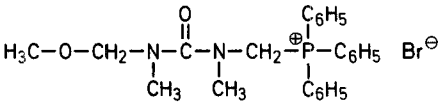


46



47

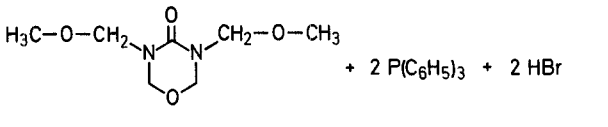
N′-Methoxymethyl-N,N′-dimethylureidomethyl-triphenylphosphonium Bromide (48)[15]**:**



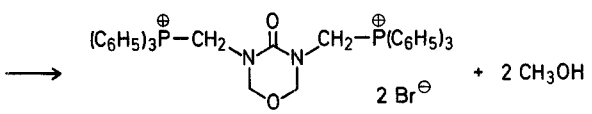
48

A solution of triphenylphosphine (26.3 g) in methanol (400 ml) is treated at 40° with 48% hydrogen bromide solution (30 g). A solution of 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (13 g) in methanol (50 ml) is then added with stirring. The mixture is stirred for 10 hr at 35–40°, the solvent is then removed in vacuo in a rotary evaporator, and the residue is treated with a small amount of ethyl acetate. After standing for 24 hr, the product (25.5 g) crystallizes out and is recrystallized from methanol/ethyl acetate; yield: 52%; m.p. 210° (dec).

The reaction of 1,3-bis-[alkoxymethyl]-4-oxotetrahydro-1,3,5-oxadiazines with tertiary phosphines in a molar ratio of 1:2 in the presence of hydrobromic acid gives rise to 3,5-bis-[triphenylphosphoniomethyl]-4-oxotetrahydro-1,3,5-oxadiazine bromides[15] (e.g. **49**).



41 R = CH_3

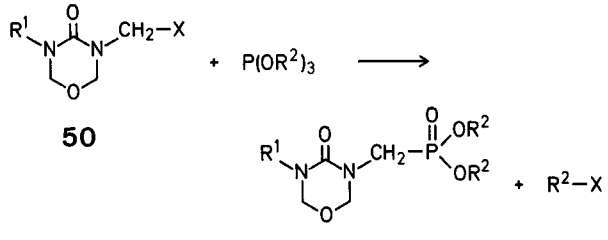


49

3,5-Bis-[trimethylphosphoniomethyl]-4-oxotetrahydro-1,3,5-oxadiazine Dibromide (49)[15]**:**

3,5-Bis-[methoxymethyl]-4-oxotetrahydro-1,3,5-oxadiazine (19 g) is added with stirring to a mixture of triphenylphosphine (52.4 g), methanol (30 g), and 48% hydrobromic acid (30 g). The mixture is heated at 50° for 3 hr and then cooled to ~0°, whereupon the product crystallizes; yield: 63 g (77%); m.p. 221–223° (dec; from methanol).

3-Alkoxymethyl-4-oxotetrahydro-1,3,5-oxadiazines react with thionyl halides to give 3-halomethyl-4-oxotetrahydro-1,3,5-oxadiazines (**50**)[16], which by further reaction with trialkyl phosphites may be converted into dialkyl 4-oxotetrahydro-1,3,5-oxadiazin-3-ylmethanephosphonates[16] (**51**).



50 **51**

3,5-Bis-[chloromethyl]-4-oxotetrahydro-1,3,5-oxadiazine (50, $R^1=CH_2Cl$, X = Cl**)**[16]**:**

A solution of thionyl chloride (238 g) in toluene (200 ml) is added dropwise with stirring at 60–70° to a solution of 3,5-bis-

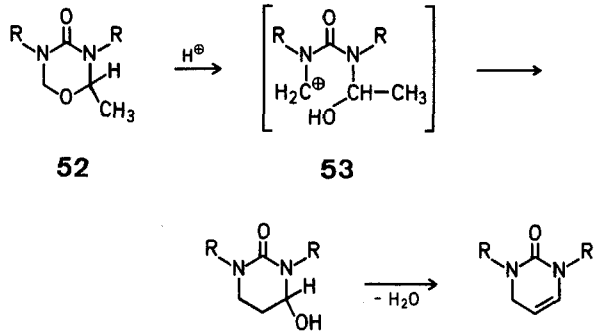
[11] H. Kadowaki, *Bull. Chem. Soc. Japan* **11**, 248 (1936).
[12] T. Oshima, *German Patent (DBP.)* 1 123 334 (1960), Sumitomo Chemical Co., *C.A.* **57**, 3460 (1962).
[13] W. Lengsfeld, BASF, Ludwigshafen, unpublished.
[14] H. Petersen, BASF, Ludwigshafen, unpublished.

[methoxymethyl]-4-oxotetrahydro-1,3,5-oxadiazine (190 g) in toluene (100 ml). The reaction mixture is held at 70 – 75° for 30 min and subsequently evaporated in water-aspirator vacuum; yield: 160 g (80%). The product can be purified by recrystallization from acetone; m. p. 160° (dec).

Tetramethyl 4-Oxotetrahydro-1,3,5-oxadiazine-3,5-dimethanephosphonate (3,5-Bis-[dimethylphosphonomethyl]-4-oxotetrahydro-1,3,5-oxadiazine, 51, $R^1 = -CH_2P(O)(OCH_3)_2$, $R^2 = CH_3$)[16]:

To a solution of 3,5-bis-[chloromethyl]-4-oxotetrahydro-1,3,5-oxadiazine (657 g) in toluene (1500 ml), trimethyl phosphite (820 g) is slowly added, dropwise and with stirring at 50°. The mixture is subsequently heated at 80° for 2 hr. On cooling to 0°, the product crystallizes. It is isolated by filtration; yield: 1110 g (97%); m. p. 110° (from acetone).

4-Oxotetrahydro-1,3,5-oxadiazines (e.g. **52**) obtained by cyclocondensation of ureas with CH-acidic aldehydes readily rearrange on heating in the presence of an acid to give 4-hydroxy-2-oxohexahydropyrimidines (**54**), which by elimination of water are converted into 2-oxotetrahydropyrimidines (**55**)[3,9]. This reaction sequence involves cleavage of the C—O bond, resulting in mesomerically stabilized α-ureidoalkyl-(carbenium-imonium) ions (**53**) which react with the CH-acidic group with formation of a C—C bond to give the 4-hydroxy-2-oxohexahydropyrimidine (**54**).



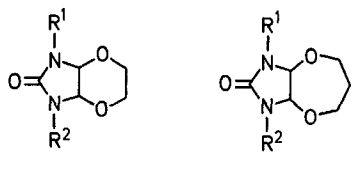
52 53 54 55

1,3-Dimethyl-2-oxotetrahydropyrimidine (**55**, $R = CH_3$)[3,9]:

A solution of 4-oxo-2,3,5-trimethyltetrahydro-1,3,5-oxadiazine (**52**; $R = CH_3$; 20 g) in methanol (50 ml) is treated with conc. hydrochloric acid (3 ml) and heated at reflux for 30 min. After neutralization and evaporation of the methanol under reduced pressure, the product may be recovered by fractional distillation in high vacuum; yield: 14 g (80%); b.p. 86–88°/0.5 torr.

2.1.2. Cyclocondensations with Alcoholic Hydroxy Groups

4,5-Dihydroxy-2-oxoimidazolidines react with *vic*-diols to give 8-oxo-2,5-dioxa-7,9-diazabicyclo[4.3.0]-nonanes (**56**) and with 1,3-diols to give 9-oxo-2,6-dioxa-8,10-diazabicyclo[5.3.0]decanes (**57**)[17].

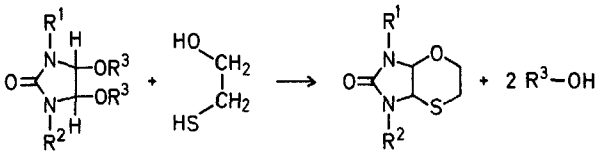


56 57

7,9-Dimethyl-8-oxo-2,5-dioxa-7,9-diazabicyclo[4.3.0]nonane (**56**, $R^1 = R^2 = CH_3$)[17]:

In a three-necked flask with stirrer and water separator is placed a solution of 1,3-dimethyl-2-oxoimidazolidine (146 g, 1 mol) and ethylene glycol (62 g, 1 mol) in benzene (150 ml). To this solution is added conc. sulfuric acid (0.5 ml) and the mixture is stirred at 90° for 4 hr under a weak vacuum; ~30 ml of water collect in the water separator and the benzene largely evaporates during the course of the reaction. The product crystallizes from the mixture at room temperature and is recrystallized from cyclohexane; yield: 91.3 g (53%); m.p. 65–66°.

Condensation of 4,5-dihydroxy-2-oxo- or 4,5-dialkoxy-2-oxoimidazolidines (**58**) with mercaptoethanol leads to α-ureidoalkylation of the OH- and SH-acidic groups, resulting in the formation of 8-oxo-2-oxa-5-thia-7,9-diazabicyclo[4.3.0]nonanes[7,10] (**59**).



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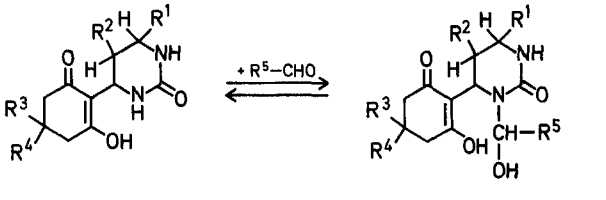
The reaction of 4-(2-hydroxy-6-oxocyclohexen-1-yl)-2-oxohexahydropyrimidines (**60**) with aldehydes in the presence of acids leads, via 3-(1-hydroxyalkyl)-4-(2-hydroxy-6-oxocyclohexen-1-yl)-2-oxohexahydropyrimidines (**61**), by an α-ureidoalkylation mechanism to the formation of 8,14-dioxo-3-oxa-1,13-diazatricyclo[8.4.0.0^{4,9}]tetradec-4^9-enes(4,11-dioxo-1,2,3,8,9,10,11,11b-octahydro-4*H*,6*H*-pyrimido-[1,6-*c*][1,3]benzoxazines, **62**)[18].



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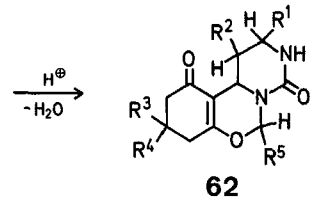

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Table 2. 8,14-Dioxo-3-oxa-1,13-diazatricyclo[8.4.0.0^{4,9}]tetradec-4^9-enes (**62**) from 4-(2-Hydroxy-6-oxocyclohexen-1-yl)-2-oxohexahydropyrimidines (**60**) and Aldehydes

R^1	R^2	R^3	R^4	R^5	Yield (%)	m.p.
C_2H_5	CH_3	CH_3	CH_3	C_2H_5	75	161°
C_2H_5	CH_3	CH_3	CH_3	n-C_3H_7	79	159°
n-C_3H_7	C_2H_5	CH_3	CH_3	CH_3	69	138°
n-C_3H_7	C_2H_5	CH_3	CH_3	n-C_3H_7	68	139°
n-C_3H_7	C_2H_5	CH_3	CH_3	C_6H_5	3	199°

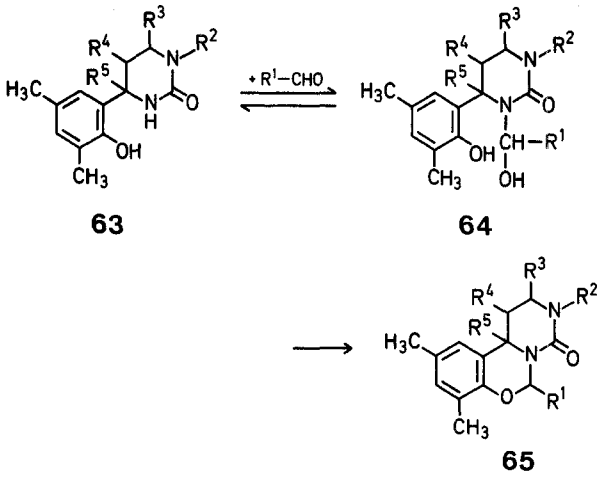
[15] H. Petersen, W. Reuther, BASF, Ludwigshafen, unpublished

[16] H. Petersen, W. Reuther, *Liebigs Ann. Chem.* **766**, 58 (1972).

2,12-Diethyl-6,6,11-trimethyl-8,14-dioxo-3-oxa-1,13-diazatricyclo[8.4.0.0^{4,9}]tetradec-4^9-ene
(62, $R^1=R^5=C_2H_5$, $R^2=R^3=R^4=CH_3$)[18]:
A mixture of 6-ethyl-4-(4,4-dimethyl-2-hydroxy-6-oxocyclohexen-1-yl)-5-methyl-2-oxohexahydropyrimidine (**60**, $R^1=C_2H_5$, $R^2=R^3=R^4=CH_3$; 2 g), propanal (15 ml), and 6*N* hydrochloric acid (8 drops) is refluxed for 2 hr. The mixture is then neutralized with solid sodium-hydrogen carbonate, filtered from the salts, and concentrated in vacuo at 70°. The product crystallizes upon triturating the residue with cyclohexane; yield: 74%; m.p. 161° (from benzene/cyclohexane (1:3).

2.1.3. Cyclocondensations with Phenolic Hydroxy Groups

In acidic medium, 4-(2-hydroxyphenyl)-2-oxohexahydropyrimidines (**63**) react with aldehydes to give, via the N-(1-hydroxyalkyl) compounds **64**, 4-oxo-1,2,3,11 b-tetrahydro-4*H*,6*H*-pyrimido[1,6-*c*][1,3]-benzoxazines[18–22] (e.g. **65**).



4-Oxo-2,6,8,10-tetramethyl-1,2,3,11 b-tetrahydro-4*H*,6*H*-pyrimido[1,6-*c*][1,3]benzoxazine (65, $R^1=R^3=CH_3$, $R^2=R^4=R^5=H$)[19]:
A mixture of 4-(3,5-dimethyl-2-hydroxyphenyl)-6-methyl-2-oxohexahydropyrimidine (**63**, $R^1=R^3=CH_3$, $R^2=R^4=R^5=H$; 0.5 g) acetaldehyde (20 ml), and 18% hydrochloric acid (3 drops) is refluxed for 2 hr (30–40°). The resultant mixture is treated with water (50 ml) and neutralized with sodium-hydrogen carbonate. The excess acetaldehyde is removed by passing air through the reaction mixture. The residual crystallizate is purified by recrystallization from ethanol; yield: 80%; m.p. 197°.

2.2. Cyclocondensations by α-Ureidoalkylation of SH-Acidic Compounds

So far only a few examples are known of cyclocondensations with SH-acidic compounds according to the principle of an α-ureidoalkylation. These include the preparation of bicyclic heterocycles of the type of 8-oxo-2-oxa-5-thia-7,9-diazabicyclo[4.3.0]nonanes (**66**), 3-imino-7-oxo-2-thia-4,6,8-triazabicyclo[3.3.0]-octanes (**67**), and 3,7-diimino-2,6-dithia-4,8-diazabicyclo[3.3.0]octanes (**68**).

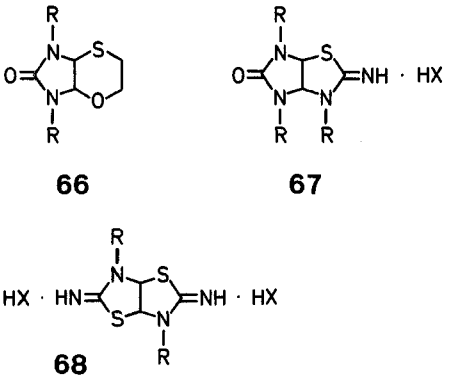
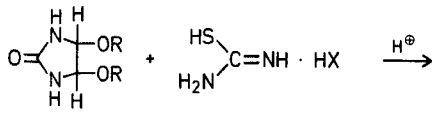


Table 3. 4-Oxo-1,2,3,11 b-tetrahydro-4*H*,6*H*-pyrimido[1,6-*c*][1,3]benzoxazines (**65**) from 4-(2-Hydroxyphenyl)-2-oxohexahydropyrimidines (**63**) and Aldehydes

R^1	R^2	R^3	R^4	R^5	Yield (%)	m.p.	References
CH_3	H	CH_3	H	H	80	197°	19
CH_3	H	C_2H_5	CH_3	H		184°	21
CH_3	H	n-C_3H_7	C_2H_5	H		162°	21
CH_3	H	H	H	H		194°	22
CH_3	CH_3	CH_3	H	H		148.5°	22
CH_3	—CO—CH_3	CH_3	H	H		127°	18
C_2H_5	H	CH_3	H	H	86	197°	18
C_2H_5	—CO—CH_3	CH_3	H	H		119°	18
n-C_3H_7	H	CH_3	H	H	82	190°	18
n-C_3H_7	—CO—CH_3	CH_3	H	H		95°	18
n-C_4H_9	H	CH_3	H	H	90	181°	18
i-C_4H_9	H	CH_3	H	H	90	186°	18
n-C_5H_{11}	H	CH_3	H	H	87	157°	18
i-C_5H_{11}	H	CH_3	H	H	87	171°	18
n-C_6H_{13}	H	CH_3	H	H	89	155°	18
C_6H_5—CH_2—	H	CH_3	H	H	61	207°	18
C_6H_5	H	CH_3	H	H	43	242°	18
C_6H_5	—CO—CH_3	CH_3	H	H		197°	18
	H	CH_3	H	H	10	187	18
	—CO—CH_3	CH_3	H	H		127	18
n-C_3H_7	H	n-C_3H_7	H	H	78	144	18
C_6H_5	H	n-C_3H_7	C_2H_5	H	47	208	18
n-C_3H_7	H	CH_3	H	CH_3	8	191	18
n-C_3H_7	H	CH_3	H	CH_3	8	142	18

The heterocycles of the type **66** have already been described in Section 2.1.2.[7,10]. Condensation of 4,5-dihydroxy-2-oxo- or 4,5-dialkoxy-2-oxoimidazolidines (**69**) with thiourea at temperatures below 50° in the presence of an equivalent amount of acid gives rise to compounds **67**[23].



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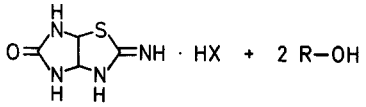


67

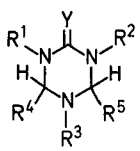
3-Imino-7-oxo-2-thia-4,6,8-triazabicyclo[3.3.0]octane Perchlorate (67):

70% Perchloric acid (143 g) is added dropwise with stirring and cooling at 5–10° to a solution of 4,5-dihydroxy-2-oxo-imidazolidine (118 g) and thiourea (76 g) in water (150 ml). The product crystallizes after stirring for ~1 hr at 5–10°; yield: 239 g. The product can be purified by recrystallization from water; m.p. 260° (dec).

2,5-Diimino-3,6-dithia-1,4-diazabicyclo[3.3.0]octane salts (**68**) may be prepared by reaction of glyoxal with thiourea in a 1:2 molar ratio in the presence of at least 2 equivalents of mineral acid at room temperature[23].

2.3. Cyclocondensations by α-Ureidoalkylation of Primary Amines

Ureas, thioureas, guanidines, and sulfamide undergo condensation with aldehydes and primary amines to give mono- and polycyclic hexahydro-1,3,5-triazines (**70**–**74**).



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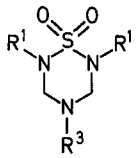

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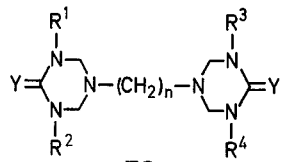

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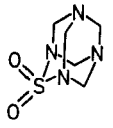

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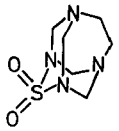

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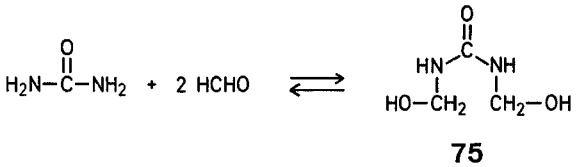
The condensation of urea or thiourea or their mono- or symmetrically disubstituted derivatives with 2 mol of formaldehyde and 1 mol of a primary amine leads to cyclic ureas of the type of 5-alkyl-2-oxo(thiono)-hexahydro-1,3,5-triazines (**77**)[24].



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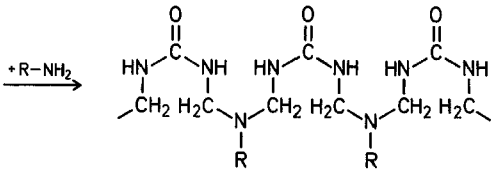

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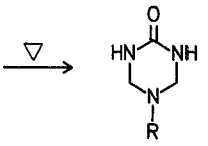

77

The direct reaction of ureas with formaldehyde and primary amines leads to the formation of primary methylolamines and Schiff bases. The Schiff base and the methylolurea or the free formaldehyde and urea present in the solution react to give a polycondensation product (**76**) which at higher temperatures is converted into the 5-alkyl-2-oxohexahydro-1,3,5-triazine (**77**) by the mechanism of an intramolecular transureidomethylation with cyclization[3,9].

5-Isobutyl-2-oxohexahydro-1,3,5-triazine (**70**, $R^1=R^2=R^4=R^5=H$, $R^3=i\text{-}C_4H_9$)[25]:

Isobutylamine (146 g; 2 mol) is added with stirring to a refluxing solution of urea (120 g, 2 mol) in 30% formaldehyde solution (400 g, 4 mol). The mixture is heated at 80° for 14 hr. After cooling and standing at 0° for 1 day, the precipitated condensation product is isolated by filtration; yield: 187 g. Further product (68 g) is obtained by evaporation of the filtrate in vacuo and recrystallization of the resultant residue. Total yield: 255 g (82%). The product is purified by recrystallization from ethanol; m.p. 193°.

The N-unsubstituted or N-substituted 2-oxo- or 2-thiono-5-alkylhexahydro-1,3,5-triazines may be prepared in a completely analogous manner.

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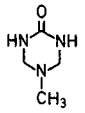
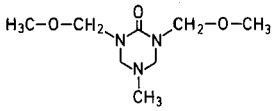
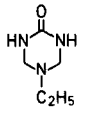
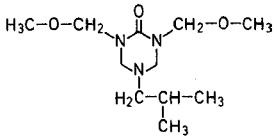
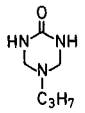
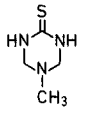
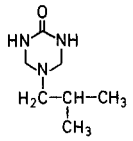
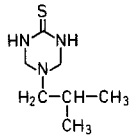
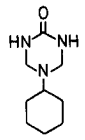
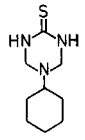
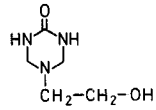
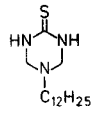
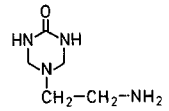
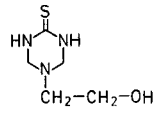
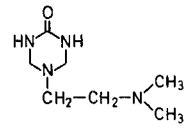
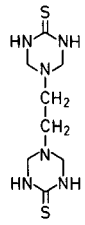
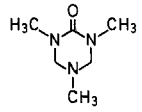
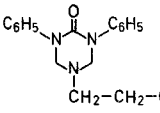
[26] A. Striegler, H. Wild, W. Hesse, *German Patent (DBP.)* 1089766 (1960), VEB Leuna-Werke; *C.A.* **56**, 3496 (1962).
[27] W. J. Burke, *J. Amer. Chem. Soc.* **69**, 2136 (1967).
[28] W. J. Burke, *U.S. Patent* 2304624 (1942), DuPont; *C.A.* **37**, 2852 (1943).
[29] W. J. Burke, *U.S. Patent* 2321989 (1942). DuPont; *C.A.* **37**, 6908 (1943).
[30] A. M. Paquin, *Angew. Chem.* **60**, 316 (1948).
[31] H. Schiff, *Liebigs Ann. Chem.* **189**, 159 (1877).
[32] H. Biltz, *Ber. dtsch. chem. Ges.* **40**, 4806 (1907).

Table 4. 2-Oxo- and 2-Thiono-5-alkylhexahydro-1,3,5-triazines from Formaldehyde, Primary Amines, and Ureas, Thioureas, or Guanidines

Products	Yield (%)	m.p.	References	Products	Yield (%)	m.p.	References
	97 62 55 68	201–202° 210° 210° 199°	26 27 28 24		64	(b.p. 120–122°/ 2–3 torr)	29
	99	190–192°	25			(b.p. 140–145°/ 5 torr)	29
	99 62	182° 182°	26 24		69 63	180° 169°	27 24
	34 51 82	200° 194° 193°	27 24 25		72 68	139° 142°	27 24
	96 64	205° 205°	26 24		85 72	172° 176°	27 24
	57 50	158° 158°	27 28		95	153°	27
	68	176–177°	24		50	162°	27
	36	114°	27		75	209–210° (dec)	24
	80	(b.p. 91–92°/ 0.3 torr	25				
	72	178°	27				

Instead of the mixture of urea, formaldehyde, and amine, it is also possible to start from the N,N′-dihydroxymethyl- or N,N′-dialkoxymethylureas and the primary amine[28].

Under mild reaction conditions it is also possible to employ higher aldehydes such as acetaldehyde or butanal instead of formaldehyde. In a few cases ammonia may also be used, it being advantageous to subject the crystalline aldehyde-ammonia compounds to the reaction with urea, thiourea, or their derivatives[24].

4,6-Dimethyl-2-oxohexahydro-1,3,5-triazine (70, $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = CH_3$)[24]:

Urea (60 g) is melted together with freshly prepared wet acetaldehyde-ammonia (149 g, 82%) and water (30 g) at 55–60°, then the temperature is raised to 75° within 30 min. The condensation proceeds with vigorous evolution of ammonia, the clear liquid becoming turbid after a few minutes and the reaction product beginning to crystallize. After cooling to 0°, the semisolid crystal mass is collected by filtration and recrystallized from ethanol with the addition of acetone (20%); yield: 71%; m.p. 190° (dec).

[33] D. F. Kutepov, A. A. Potashnik, D. N. Khokhlov, *Zh. Obshch. Khim.* **28**, 663 (1958).

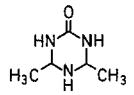
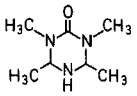
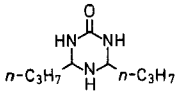
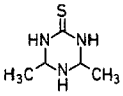
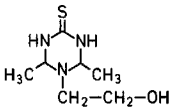
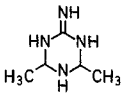
[34] D. F. Kutepov, A. A. Potashnik, D. N. Khokhlov, V. A. Tuzhilkina, *Zh. Obshch. Khim.* **29**, 840 (1959).

[35] L. K. Korobitsyna, Y. K. Yurev, O. I. Nefedova, *Zh. Obshch. Khim.* **24**, 188 (1954).

[36] J. Nematollahi, R. Ketcham, *J. Org. Chem.* **28**, 2378 (1963).

[37] F. B. Slézak, H. Bluestone, *U.S. Patent* 3187004 (1965). Diamond Alkali Co.; *C.A.* **63**, 13273 (1965).

Table 5. 2-Oxo(thiono, imino)-hexahydro-1,3,5-triazines from Aldehydes (except Formaldehydes), Primary Amines, and Urea, Thiourea, or Guanidine[24]

Product	Yield (%)	m.p.
	71	190° (dec)
	55	
	74	
	87	180° (dec)
	13	168°
	54	156–157° (dec)

The N,N′-bis[hydroxymethyl]- and N,N′-bis-[methoxymethyl]-5-alkyl-2-oxohexahydro-1,3,5-triazines have achieved technical importance in textile finishing for the crease-resistant finishing of cellulosic fabrics. The bis-hydroxymethyl compounds are prepared either by reaction of the 5-alkyl-2-oxohexahydro-1,3,5-triazines with formaldehyde or directly by reaction of urea with formaldehyde and a primary amine in a 1:4:1 molar ratio. The N,N′-bis-hydroxymethyl compounds are readily converted into the N,N′-dimethoxymethyl compounds by reaction with methanol in the presence of catalytic amounts of acid.

1,3-Dimethoxymethyl-5-methyl-2-oxohexahydro-1,3,5-triazine (70, $R^1=R^2=CH_2OCH_3$, $R^3=CH_3$, $R^4=R^5=H$)[29]:
Urea (120 g) is dissolved in 30% formaldehyde solution (850 g) and the resultant solution is treated with 35% methylamine solution (178 g). After heating at 60° for 4 hr, the solution is evaporated under reduced pressure. The product obtained is stirred with methanol (1000 ml) and conc. hydrochloric acid (10 ml) at 50° for 3 hr and neutralized with sodium hydroxide solution. Excess methanol is distilled off and the residue is fractionally distilled in high vacuum; yield: 230 g (64%); b.p. 120–122°/2–3 torr.

Analogous cyclocondensations may be carried out by reaction of sulfamide with formaldehyde and ammonia or primary amines[30]:

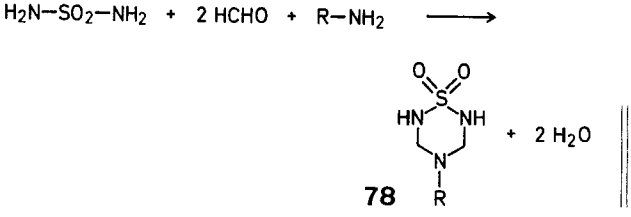
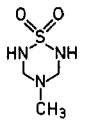
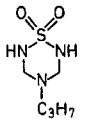
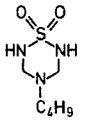
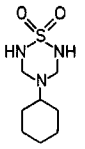
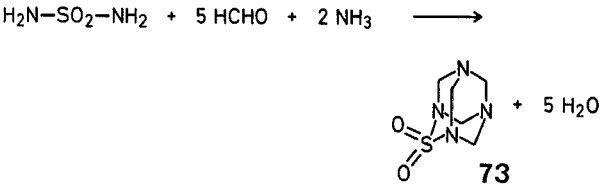


Table 6. 4-Alkyltetrahydro-1,2,4,6-thiatriazine 1,1-Dioxides (78) from Sulfamide, Formaldehyde, and Primary Amines

Product	Yield (%)	m.p.
	66	185–186° (dec)
	78	134°
	86	120°
	84	155°

4-Methyltetrahydro-1,2,4,6-thiatriazine 1,1-Dioxide (78, $R=CH_3$)[30]:
Sulfamide (96 g) and aqueous 25% methylamine solution (124 g) are dissolved in water (80 ml) and stirred with 30% formaldehyde solution (200 g) at 5–10°. The reaction product precipitates initially as a colorless mass which solidifies to a crystalline product on standing at room temperature; yield: 66%; m.p. 185–186° (dec. from methanol).

While condensation of urea with formaldehyde and ammonia gives hexamethylenetetramine as the main product, the reaction of sulfamide with formaldehyde and ammonia leads to "pentamethylenetetramine sulfone" (73)[30].



On boiling in aqueous solution, particularly after acidification with mineral acids, pentamethylenetetramine sulfone eliminates formaldehyde and ammonia. Nitration yields (as with hexamethylenetetramine) the explosive "Hexogen".

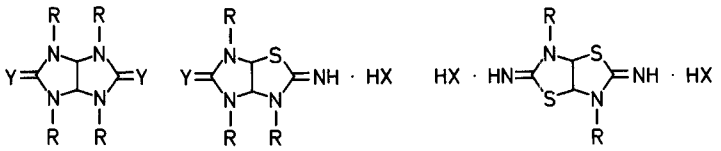
Pentamethylenetetramine Sulfone (73)[30]:
Sulfamide (96 g) is dissolved in aqueous 25% ammonia solution (136 g) and 40% formaldehyde solution (150 g) is added, the temperature being held at 50–55° by cooling. Further 40% formaldehyde (225 g) is thereafter rapidly poured in with stirring. The reaction product which crystallizes out is recrystallized from ethanol; yield: 88%; m.p. 224–225° (dec).

Ethylenediamine reacts with sulfamide and formaldehyde in almost quantitative yield to give homopentamethylenetetramine sulfone (74)[30].

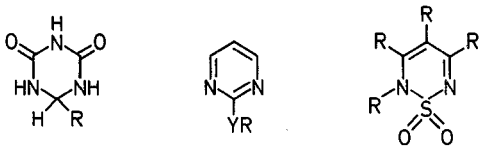
Homopentamethylenetetramine Sulfone (74)[30]:
Sulfamide (96 g) is dissolved in 30% formaldehyde (400 g). A 76% solution of ethylenediamine (79 g), diluted with the same amount of water, is slowly added with stirring. The rapidly rising temperature is held at 65–70° by cooling. After cooling to 0°, the crystallized reaction product is isolated and recrystallized from water; yield: 93%; m.p. 195–196° (dec).

2.4. Cyclocondensations by α-Ureidoalkylation of Ureas, Thioureas, Guanidines, and Sulfamides

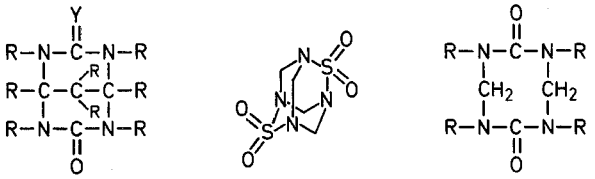
α-Ureidoalkylation of NH or NH_2 groups of a urea, thiourea, guanidine, or sulfamide provides a route to five-, six-, and eight-membered heterocyclic compounds.



79 80 68

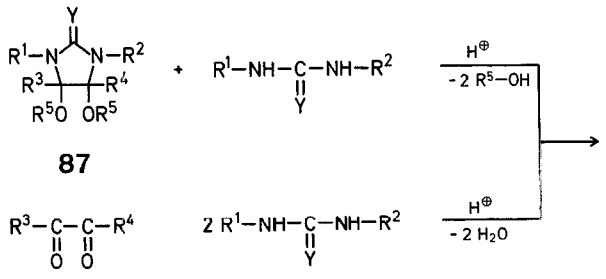


81 82 83



84 85 86

The five-membered heterocycles include the bicyclic ureas and thioureas of the type of 3,7-dioxo-, 3,7-dithiono- and 3-oxo-7-thiono-2,4,6,8-tetraazabicyclo-[3.3.0]octanes (**79**) as well as the 3-imino-7-oxo-2-thia-4,6,8-triazabicyclo[3.3.0]octanes (**80**) and 3,7-diimino-2,6-dithia-4,8-diazabicyclo[3.3.0]octanes (**68**) mentioned in Section 2.2. The syntheses of 2,4-dioxohexahydro-1,3,5-triazines (**81**), 2-oxy-, 2-mercapto-, and 2-aminopyrimidines (**82**), 1,2,6-thiadiazine, 1,1-dioxides (**83**), 3,7-dioxo-2,4,6,8-tetraazabicyclo-[3.3.1]nonanes (**84**), and of tetramethylene-disulfotetramine (**85**) are examples for 6-membered heterocycles. The dimethylenediureides (**86**) are representative of eight-membered cyclic ureas.



2.4.1. Cyclization to Five-membered Cyclic Ureas and Transformation of the Cyclization Products

4,5-Dihydroxy- or 4,5-dialkoxy-2-oxo(thiono)-imidazolidines react, with double α-ureidoalkylation, with urea or thiourea or their mono- or symmetrically disubstituted derivatives to give bicyclic ureas of the type **88**.

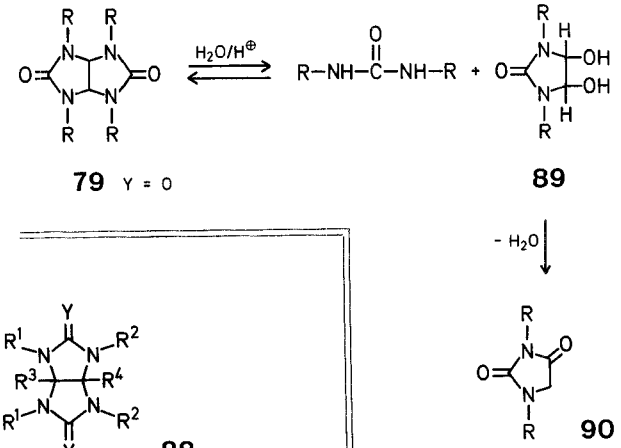
Bicyclic heterocycles of the type **88** may in many cases also be prepared directly by condensation of glyoxal, α-oxoaldehydes, or *vic*-diketones with urea, thiourea, guanidine, or suitable derivatives in the presence of an acid[31,32]. These cyclocondensations may also be carried out with *o*-quinones and phenanthrenequinones[32] in yields of ~90%, as well as with cycloaliphatic 1,2-diketones[33,34].

3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane (88, $R^1-R^4=H$, Y = O):

Method A; from 4,5-Dihydroxy-2-oxoimidazolidine and Urea: A solution of 4,5-dihydroxy-2-oxoimidazolidine (**87**, $R^1-R^5=H$, Y = O; 118 g, 1 mol) and urea (60 g) in water (500 ml) is treated with conc. hydrochloric acid (20 ml) and heated at ~80° with stirring for 1 hr. The poorly soluble reaction product is isolated by filtration, washed with water, and dried; yield: 130 g (91%); m.p. 360°.

Method B; from Urea and Glyoxal[31]: A mixture of urea (66 g) and 29% glyoxal solution (100 g) is heated with conc. hydrochloric acid (2 ml) at 70–80° for 1 hr. After only a short time, the product precipitates as a crystalline mass; yield: 42 g (54%); m.p. 360°.

In the presence of strong mineral acids at elevated temperatures, 3,7-dioxo-2,4,6,8-tetraazabicyclo-[3.3.0]octanes (**79**) may be converted into hydantoins. The formation of hydantoins probably proceeds via a postulated hydrolysis of **79** to 4,5-dihydroxy-2-oxoimidazolidines (**89**), which readily undergo dehydration to hydantoins (**90**)[39].



79 Y = O 89 88 90

[38] W. E. Parham, J. Heberling, *J. Amer. Chem. Soc.* **77**, 1175 (1955).

Table 7. 3,7-Dioxo-, 3,7-Dithiono-, and 3,7-Diimino-2,4,6,8-tetraazabicyclo[3.3.0]octanes

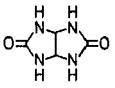
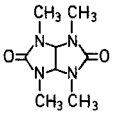
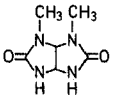
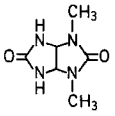
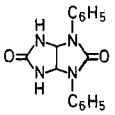
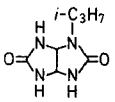
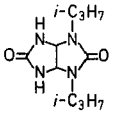
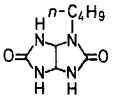
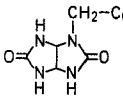
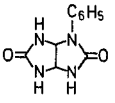
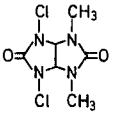
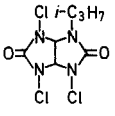
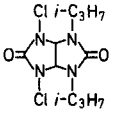
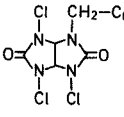
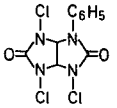
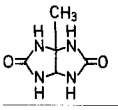
Product	Yield (%)	m.p.	References
	78	>360° (dec)	31, 32, 36
	61	225–227°	36, 44
		298–300°	36
	27	254–256° 268–270°	37 36
	22	375–380°	36
	37	248–249°	37
	71	315°	37
	55	267–268°	37
	65	283–284°	37
	82	300°	37
		114–116°	37
		125–126°	37
		148–149°	37
		160–161°	37
		140–141°	37
	29	258–259°	37

Table 7, continued

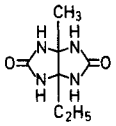
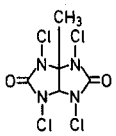
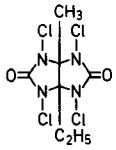
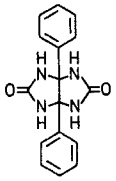
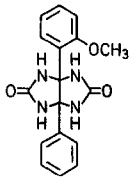
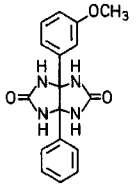
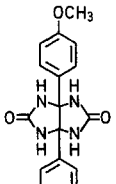
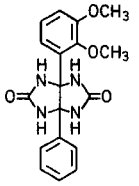
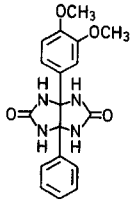
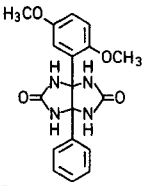
Product	Yield (%)	m.p.	References
	50	320–321°	37
		147–148°	37
		205–208°	37
		330°	38
	12	330–333°	39
	48	334–337°	39
	35	351°	39
	7	337–339°	39
	11	342–344°	39
	26	351–353°	39

Table 7, continued

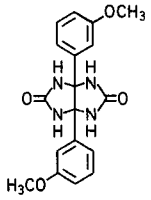
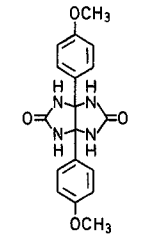
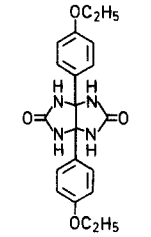
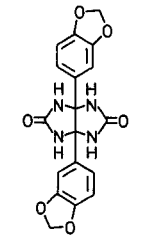
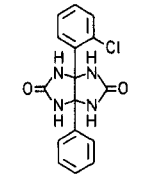
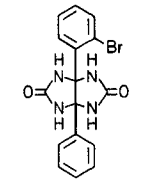
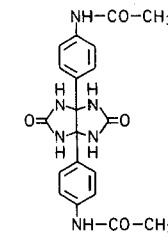
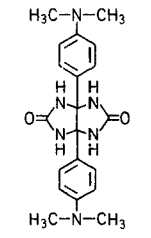
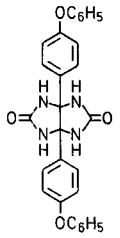
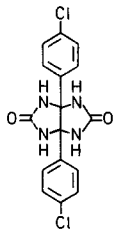
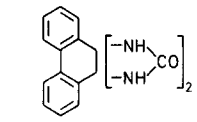
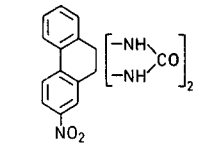
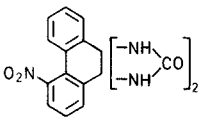
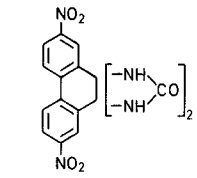
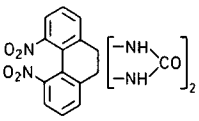
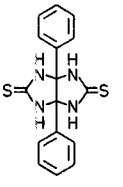
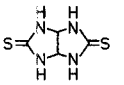
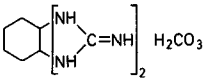
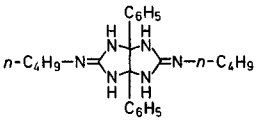
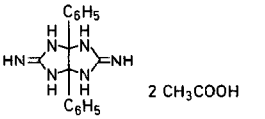
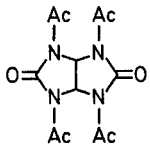
Product	Yield (%)	m.p.	References
	46	345–348°	39
	42	329–331°	39
		147–149°	40
	19	360°	39
	8	318–320°	39
	6	317–320°	39
		237–239°	40
		199–201°	40

Table 7, continued

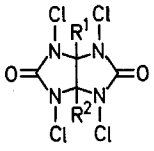
Product	Yield (%)	m.p.	References
		215–217°	40
		285–287°	40
	85	336–339°	33
	70	303–306°	33
	88	310–315° (dec)	33
	70	342–345° (dec)	33
	86	305–308° (dec)	33
		> 300° (dec)	41, 42
		> 300°	43
	61	189–190° (dec)	34
	44	235–236°	45
		247°	45

1,3-Dimethylhydantoin (90, R = CH_3)[46]:
In a stirring flask, a mixture of 3,7-dioxo-2,4,6,8-tetraaza-bicyclo[3.3.0]octane (**79**, R = CH_3; 99 g), water (200 ml), and hydrochloric acid (50 ml) is heated at 90–100° for 3 hr with stirring. After neutralization and filtration, the reaction mixture is evaporated under reduced pressure and again filtered. The filtrate is distilled in vacuum; yield: 30 g (47%); b.p. 67–68°/0.1 torr.

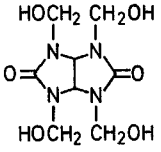
The NH groups of 3,7-dioxo- and 3,7-dithiono-2,4,6,8-tetraazabicyclo[3.3.0]octanes may be acylated (e.g., to give **91**), and they react with halogen as well as with aldehydes (e.g., to give **92** and **93**, respectively).



91



92



93

The tetrachloro compounds **92** are used as chlorine carriers for mild chlorination reactions and as bleaching agents for textiles[47,48,49].

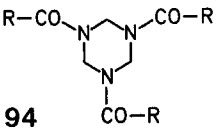
3,7-Dioxo-1-methyl-2,4,6,8-tetrachloro-2,4,6,8-tetraazabicyclo-[3.3.0]octane (92, $R^1 = CH_3$, $R^2 = H$)[37]:
Chlorine (32 g, 0.44 mol) is introduced in the course of 75 min at room temperature into a strongly stirred suspension of 3,7-dioxo-1-methyl-2,4,6,8-tetraazabicyclo[3.3.0]octane (15.6 g, 0.1 mol) in water (2000 ml); yield: 26.2 g (87%). The product is recrystallized from carbon tetrachloride; m.p. 147–148°.

The N-hydroxymethyl derivatives of 3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octanes (**93**) are used in the finishing of textiles as crease-resistant finishing agents and, in the form of their saturated or unsaturated N-alkoxymethyl derivatives, in the paint industry as crosslinking agents.

3,7-Dioxo-2,4,6,8-tetrakis-[hydroxymethyl]-2,4,6,8-tetraazabicyclo[3.3.0]octane (93)[50]:
A mixture of 3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane (**79**, R = H; 142 g) and 40% formaldehyde solution (400 g) is adjusted to pH 9–10 with 20% aqueous sodium hydroxide and heated at 50° with stirring for 2 hr, a ~50% solution of **93** being formed after a short time.

2.4.2. Cyclizations to Six-membered Cyclic Ureas

Carboxamides can be condensed with formaldehyde in strongly acidic, anhydrous solution to give 1,3,5-triacylhexahydro-1,3,5-triazines (**94**)[51]. Sulfonamides likewise react with formaldehyde to give 1,3,5-trisulfonylhexahydro-1,3,5-triazines[52–55] (**95**). Similarly, 1,3,5-trialkoxycarbonylhexahydro-1,3,5-triazines[56] (**96**) and 1,3-dialkoxycarbonylimidazolidines[57] (**97**) can result from reaction of urethanes with formaldehyde.



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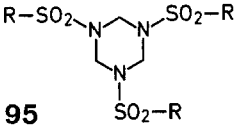

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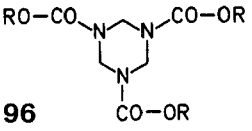

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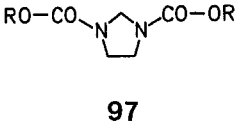
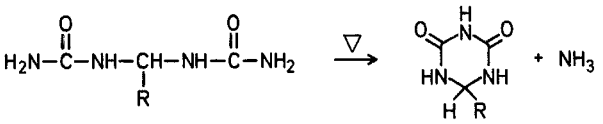


97

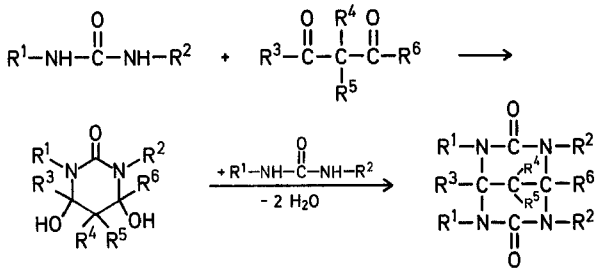
In an analogous manner, biuret reacts with aldehydes in mineral acid solution to give 2,4-dioxohexahydro-1,3,5-triazines (**81**). Since the ring closure proceeds only in low yields, the thermal condensation of α-alkylidene-bis-ureas (**98**) is a more suitable way of preparing 2,4-dioxohexahydro-1,3,5-triazines[58].



98 **81**

2,4-Dioxo-6-isopropylhexahydro-1,3,5-triazine (81, R = i-C_3H_7)[58]:
Isobutylidenediurea (**98**, R = i-C_3H_7; 87 g, 0.5 mol) in Lutrol (100 ml) is stirred at 190–195° while passing a weak stream of nitrogen through the solution, until no more ammonia is evolved. After cooling to room temperature, water is added and the product isolated by filtration; yield 23 g; m.p. >300°.

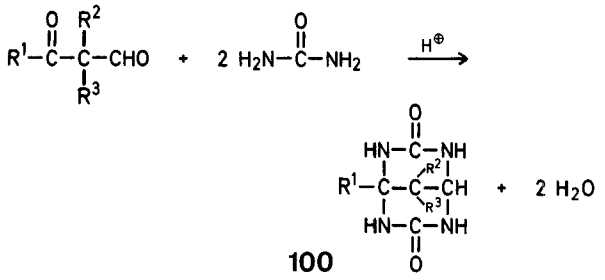
The condensation of 1,3-dialdehydes, β-diketones, or β-oxoaldehydes with ureas proceeds via the intermediate stage of 4,6-dihydroxy-2-oxohexahydropyrimidines (**99**), which have not yet been isolated, to 3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.1]nonanes (**84**):



99 **84** Y = O

The course of the synthesis is smooth only with 1,3-dialdehydes, β-diketones, and β-oxoaldehydes in which the groups R^4 and R^5 are other than hydrogen. 3,7-Dioxo-1,9,9-trialkyl-2,4,6,8-tetraazabicyclo-[3.3.1]nonanes (**100**) may be prepared in good yields from 2,2-dialkyl-3-oxoaldehydes by reaction with urea in the presence of acids[59] (Method A).

[39] W. Dietz, R. Mayer, *J. Prakt. Chem.* [4] **37**, 78 (1968).
[40] W. R. Dunnavant, Floyd L. James, *J. Amer. Chem. Soc.* **78**, 2740 (1956).
[41] R. Anschütz, H. Geldermann, *Liebigs Ann. Chem.* **261**, 129 (1891).
[42] R. Anschütz, K. Schwickerath, *Liebigs Ann. Chem.* **284**, 9 (1895).
[43] H. Pauly, H. Sauter, *Ber. dtsch. chem. Ges.* **63**, 2063 (1930).
[44] A. P. N. Franchimont, E. A. Klobbic, *Rec. Trav. Chim.* **7**, 248 (1888).
[45] M. Lempert-Sréter, V. Solt, L. Lempert, *Chem. Ber.* **96**, 168 (1963).
[46] H. Petersen, *Textile Research Journal* **40**, 335 (1970).
[47] H. Biltz, H. Behrens, *Ber. dtsch. chem. Ges.* **43**, 1984 (1910).
[48] H. Adkins, *U.S. Patent* 2638434 (1953), US Secretary of the Navy; *C.A.* **47**, 8328 (1953).
J. W. Williams, *U.S. Patent* 2649389 (1954); *C.A.* **48**, 8267 (1954).



100

addition of the carbonyl groups to the NH_2 groups, leading to the formation of 2-oxo(thiono-, imino)-4,6-dihydroxyhexahydropyrimidines (**101**). In the presence of acids, the mesomerically stabilized α-ureidoalkyl-(carbenium-imonium) ions **102** are obtained as intermediates; at elevated temperatures, compounds **102** are rearranged by a β-elimination mechanism to give 2-hydroxy-, 2-mercapto-, or 2-amino-pyrimidines (**103**).

Table 8. 3,7-Dioxo-2,4,6,8-tetraazabicyclo[3.3.1]nonanes (**84**)

R^1	R^2	R^3	R^4	R^5	R^6	Method	Yield (%)	m.p.	References
H	H	CH_3	CH_3	CH_3	H	A	93	> 300°	59
CH_3	H	CH_3	CH_3	CH_3	H		84	> 300°	59
H	H	CH_3	n-C_3H_7	CH_3	H		77	> 300°	60
H	H	H	CH_3	CH_3	H			> 300°	60
H	H	Cl-C$_6$H$_4$-O-CH_2-	CH_3	CH_3	H			> 300°	60
H	H	n-C_5H_{11}	CH_3	CH_3	H			292°	60
H	H	C$_6$H$_5$-	CH_3	CH_3	H			105°	60
H	H	O_2N-C$_6$H$_4$-	CH_3	CH_3	H			> 300°	60
H	H	H	n-C_4H_9	C_2H_5	H			> 300°	59
O_2N-C$_6$H$_4$-	and H	H	CH_3	CH_3	H			308° (dec)	59
H	H	H	$-CH_2-COOC_2H_5$	CH_3	H			340–350° (dec)	59
H	H	H	C$_6$H$_5$-	CH_3	H			303–308°	59
H	H	CH_3	H	H	CH_3			290° (dec)	61
H	H	CH_3	CH_3	H	CH_3			310° (dec)	61
H	H	CH_3	CH_3	CH_3	CH_3			> 360°	61

Compounds **100** may also be prepared from semiacetal chlorides ("α-chloroethers"), carbonyl chloride, dimethylformamide, and urea[59] (Method B).

3,7-Dioxo-1,9,9-trimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane (**100**, $R^1=R^2=R^3=CH_3$)[59,60]:

Method A: 2,2-Dimethyl-3-oxobutanal (114 g) is heated to 120°. Urea (132 g) is gradually added with stirring, the temperature being allowed to rise to 140°. After cooling, the reaction product is dissolved in conc. hydrochloric acid and reprecipitated by the addition of water; yield: 185 g (93%); m.p. >300° (from formic acid).

Method B: Carbonyl chloride (105 g) is conducted with stirring at 55° into a mixture of dimethylformamide (73 g) and 1-chloro-1-methoxy-2-methylpropane (123 g). The mixture is briefly heated at 110° and urea (120 g) is added, hydrogen chloride being evolved. After completion of the addition, water (1000 ml) is added and the resultant precipitate isolated; yield: 150 g (76%); m.p. >300°.

The condensation of urea or thiourea with β-dicarbonyl compounds having active methylene hydrogens between the two carbonyl groups gives bicyclic ureas of the type of 3,7-dioxo- or 3,7-dithiono-2,4,6,8-tetraazabicyclo[3.3.1]nonane (**105**) only under special conditions and only in low yields. 2-Hydroxy- or 2-mercapto-pyrimidines (**103**) are generally obtained under these conditions. The synthesis of 2-hydroxy-, 2-mercapto-, and 2-aminopyrimidines by condensation of β-dicarbonyl compounds with ureas, thioureas, or guanidines, respectively, proceeds via an

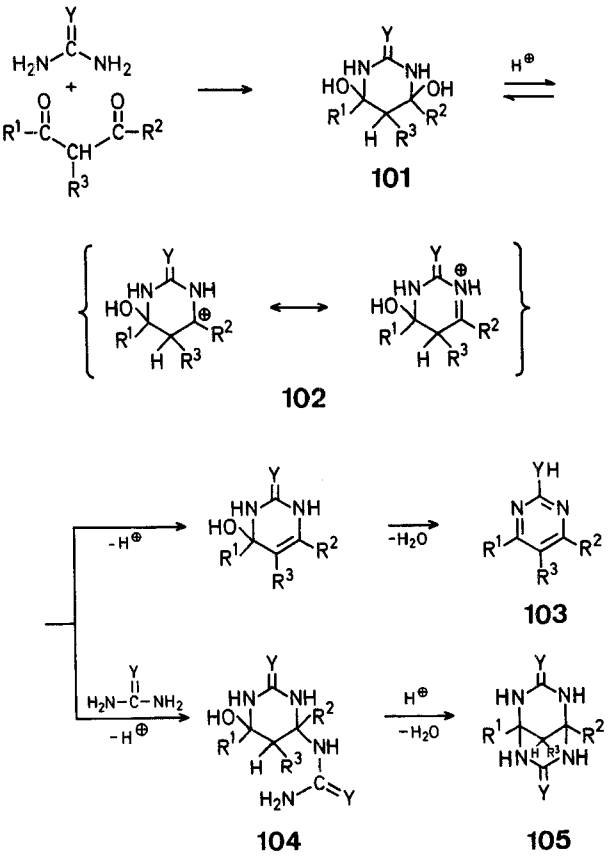


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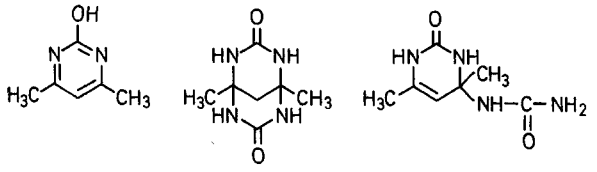
Table 9. 2-Hydroxy- and 2-Mercaptopyrimidines (**103**)

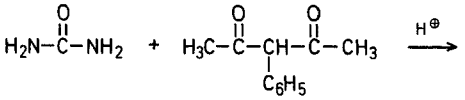
Y	R^1	R^2	R^3	Yield (%)	m.p.	References
O	CH_3	CH_3	H	88		62
O	CH_3	C_6H_5	H	69	229–231°	62
O	CH_3	$-CH_2-C_6H_5$	H	52	59–61°	62
O	H	CH_3	H	86	hydrochloride: 200° (dec); free base: 150°	64
O	CH_3	CH_3	C_6H_5	89	hydrochloride: 245°	62
S	CH_3	CH_3	H		210°	63, 65
S	CH_3	C_6H_5	H		199–200°	66
S	H	CH_3	H	95	hydrochloride: 230°; free base: 200°	64
S	CH_3	CH_3	C_6H_5	24	hydrochloride: 241–242.5°	62
NH	C_6H_5	CH_3	H		173°	65
NH	$C_6H_5-CH_2-$	CH_3	H		108°	65

Thus, for example, the reaction of urea with acetylacetone yields 4,6-dimethyl-2-hydroxypyrimidine (**106**) as the main product and 1,5-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.1]nonane (**107**) and 4,6-dimethyl-2-oxo-4-ureido-1,2,3,4-tetrahydropyrimidine (**108**) as by-products.



106 **107** **108**

In an analogous way, condensation of 2,4-dioxo-3-phenylpentane (**109**) with urea yields 4,6-dimethyl-2-hydroxy-5-phenylpyrimidine (**110**), not the bicyclic urea[62].



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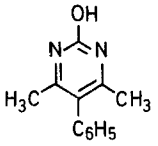
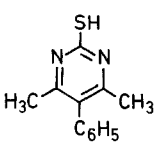


110

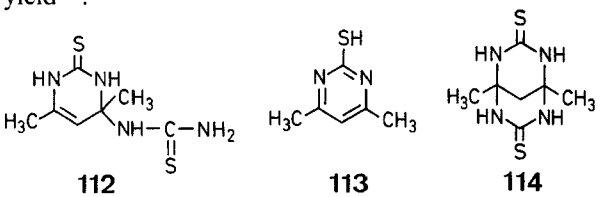
Condensation of **109** with thiourea affords 4,6-dimethyl-2-mercapto-5-phenylpyrimidine[62] (**111**).



111

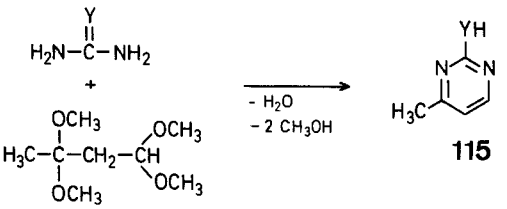
4,6-Dimethyl-2-hydroxy-5-phenylpyrimidine (110)[62]: A solution of 2,4-dioxo-3-phenylpentane (1.77 g, 0.01 mol), urea (0.96 g, 0.016 mol), and conc. hydrochloric acid (1 ml) in ethanol (80 ml) is heated at reflux temperature for 10 hr. After cooling, ether is added, and the reaction product precipitates in crystalline form as the hydrochloride; yield: 89%; m.p. 245° (dec).

In aqueous solution thiourea reacts with acetylacetone to give 4,6-dimethyl-2-thiono-4-thioureidotetrahydropyrimidine (**112**), while in alcoholic solution in the presence of acids the reaction gives 4,6-dimethyl-2-mercaptopyrimidine (**113**). When a mixture of acetylacetone and thiourea is subjected to the action of sunlight for a month at room temperature, 1,5-dimethyl-3,7-dithiono-2,4,6,8-tetraazabicyclo[3.3.1]nonane (**114**) is formed in low yield[63].



112 **113** **114**

Acetoacetaldehyde bis-[dimethyl acetal] reacts with urea or thiourea in the presence of acids to give 2-hydroxy- or 2-mercapto-4-methylpyrimidine (**115**), respectively[64].

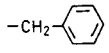


115

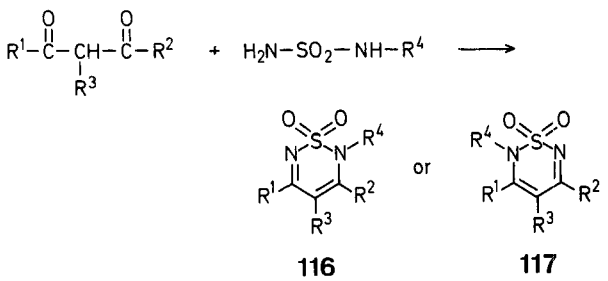
2-Hydroxy-4-methylpyrimidine Hydrochloride (115, Y = O)[64]: Urea (30 g) is dissolved in ethanol (350 ml) and the solution is treated with acetoacetaldehyde bis-[dimethyl acetal] (89 g). Conc. hydrochloric acid (100 ml) is then slowly added. After a short time, yellow to reddish-yellow crystals precipitate which after 1 day are isolated by filtration and washed with methanol; yield: 63 g (86%). The substance darkens above 200° without melting. In order to prepare the free pyrimidine, the aqueous solution of the hydrochloride is neutralized with potassium hydroxide and evaporated to dryness in vacuo. The residue is heated with benzene. Crystallization occurs on cooling; m.p. 150°.

[49] H. Steinbrink, I. Amende, *German Patent (DBP.)* 1020024 (1957), Chemische Werke Hüls; *C.A.* **54**, 2361 (1960).

Table 10. 1,2,6-Thiadiazine 1,1-Dioxides[67] (**116** and/or **117**) from Sulfamides and β-Diketones

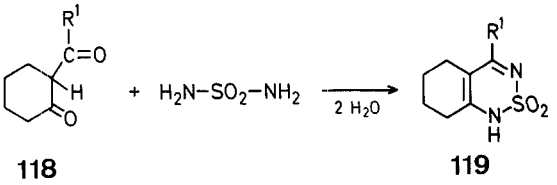
R^1	R^2	R^3	R^4	Yield (%)	m.p.
		H	H	95	278–279°
		H	H	88	288–290°
	$-CH_3$	H	H	68	67–69°
$-CH_3$	$-COOC_2H_5$	H	H	69	101.5–103°
$-CH_3$	$-CO-NH_2$	H	H	61	243° (dec)
$-CH_3$	$-CO-NH-CH_3$	H	H	70	245° (dec)
	$-COOC_2H_5$	H	H	92	188–190°
	$-CO-NH_2$	H	H	27	265° (dec)
	$-CO-NH-CH_3$	H	H	93	265° (dec)
	$-COOH$	H	H	67	203° (dec)
	$-COOC_2H_5$	H	H	85	176–177°
	$-CO-NH-NH_2$	H	H	43	233° (dec)
	$-COOC_2H_5$	H	H	81	170.5–172.5°
	$-CO-NH_2$	H	H	26	225° (dec)
	$-CO-NH-CH_3$	H	H	55	268° (dec)
	$-CH_3$	H	H	55	291° (dec)
	$-CH_3$	H	H	77	276° (partial dec)
$-CH_3$	$-CH_3$		H	73	195–195.5°
		H	n-C_4H_9	39	99–100°

Sulfamides react smoothly with β-diketones to give 1,2,6-thiadiazine 1,1-dioxides, for which the tautomeric forms **116** and **117** are assumed[67].



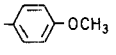
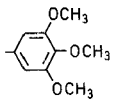
116 **117**

The reaction can also be extended to 2-acylcyclohexanones (**118**), which undergo condensation with sulfamides to give 5,6,7,8-tetrahydro-1*H*-2,1,3-benzothiazine 2,2-dioxides[67] (**119**).



118 **119**

Table 11. 5,6,7,8-Tetrahydro-1*H*-2,1,3-benzothiazine 2,2-Dioxides (**119**) from 2-Acylcyclohexanones (**118**) and Sulfamides

R^1	Yield (%)	m.p.
CH_3	86	180–181°
n-C_4H_9	84	141–142°
	83	149–151°
	100	214–216°

[50] J. Lintner, H. Scheuermann, *German Patent (DBP.)* 859019 (1941), BASF; *Chem. Zentralblatt* **1953**, 4779.

[51] R. Wegler, H. Herlinger, *Polyadditions- bzw. Polykondensationsprodukte von Carbonyl- und Thiocarbonyl-Verbindungen*, in: Houben-Weyl, *Methoden der Organischen Chemie*, 4th Edit., edited by Eu. Müller, Vol. XIV/2, Georg Thieme Verlag, Stuttgart, 1963, p. 372.

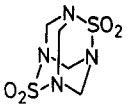
3,5-Diphenyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (**116**, $R^1 = R^2 = C_6H_5$, $R^3 = R^4 = H$)[67]:

A mixture of sulfamide (48 g), 1,3-dioxo-1,3-diphenylpropane (112.1 g), and absolute ethanol (400 ml) is saturated with dry hydrogen chloride for ~15 min and heated at 60° for 3 hr. After cooling and filtration, the filtrate is evaporated under reduced pressure. The residue is combined with the filter cake,

extracted repeatedly with ether, and then repeatedly with water. The filter residue obtained is recrystallized from ethanol; yield: 95%; m.p. 278–279°.

4-Methyl-5,6,7,8-tetrahydro-1*H*-2,1,3-benzothiadiazine 2,2-Dioxide (119, $R^1 = CH_3$)[67]:
Hydrogen chloride is introduced into a stirred mixture of 2-acetylcyclohexanone (86 g), sulfamide (58.8 g), and absolute ethanol (480 ml) until a temperature of 60° is reached. The resultant mixture is subsequently heated at reflux temperature for 30 min, then evaporated in vacuo. The residue is recrystallized from ethanol; yield: 86%; m.p. 180–181°.

Similar to urea, sulfamide is capable of condensing with formaldehyde. Thus, the reaction of sulfamide with formaldehyde in concentrated hydrochloric acid or 60% sulfuric acid yields the cyclic compound **120**, which has a structure similar to that of hexamethylenetetramine[68].



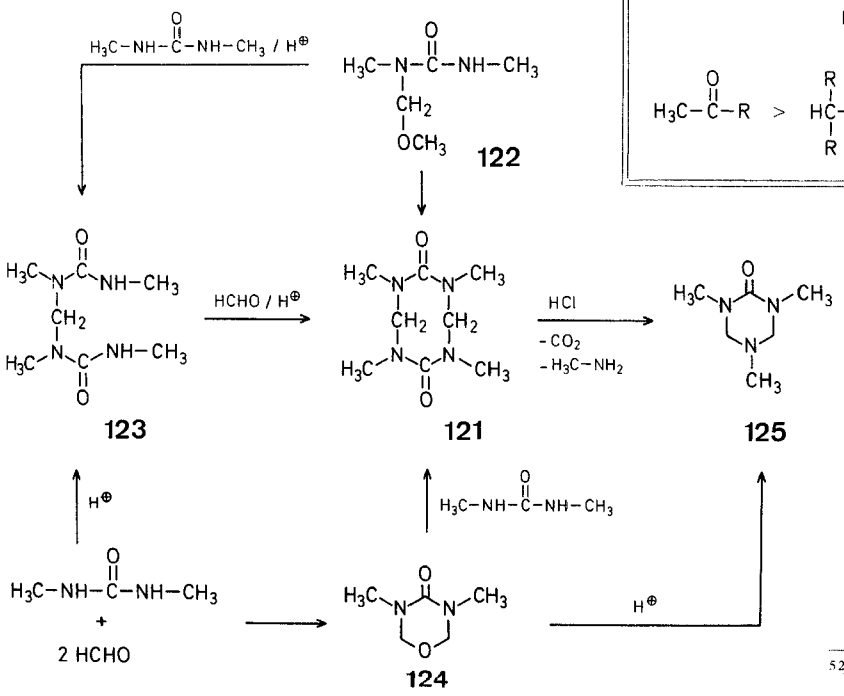
120

Tetramethylene-disulfotetramine (**120**) has extraordinarily *high toxicity* and is five times more active than strychnine as a poison attacking the central nervous system[69].

Tetramethylene-disulfotetramine (120)[68]:
Sulfamide (2 mol) is dissolved in concentrated hydrochloric acid or 60% sulfuric acid and stirred with aqueous formaldehyde (4 mol). After a short time, compound **120** precipitates as fine crystals in almost quantitative yield; m.p. 255–260° (from acetone).

2.4.3. Cyclizations to Eight-membered Cyclic Ureas

By condensation of N,N'-dimethylurea with formaldehyde, Kadowaki[11] obtained tetramethyl-dimethylenediureide (**121**) in a yield of 13%. Compound **121** is obtained in 50–60% yield from N,N'-dimethyl-N-methoxymethyurea (**122**) in the presence of small amounts of acid at room temperature[70].



Kinetic studies of the dimerizing cyclocondensation of **122** in relation to the concentration, the amount of acid, and the temperature led to the finding that the yields are particularly favorable at low acid concentrations and low temperatures[70].

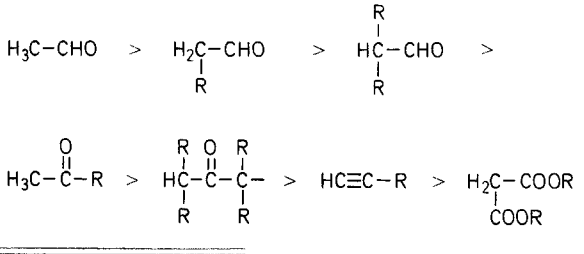
When the temperature and the acid concentration are raised, 2-oxo-1,3,5-trimethylhexahydro-1,3,5-triazine (**125**) is obtained from the methoxymethyl derivative **122** due to partial hydrolysis.

2,6-Dioxo-1,3,5,7-tetramethyloctahydro-1,3,5,7-tetraazocine (Tetramethyl-dimethylenediureide, 121)[70]:
N,N'-Dimethyl-N-methoxymethylurea (**122**; 66 g, 0.5 mol) is dissolved in dioxan (100 ml) and stirred at room temperature with a 0.1 *N* solution of hydrogen chloride in dioxan (1 ml). Precipitation of the product begins after a few minutes; yield: 30 g (60%).

Compound **121** is also formed by reaction of methylene-bis-[N,N'-dimethylurea] (**123**) with formaldehyde in the presence of catalytic amounts of acid or, in low yields, by condensation of 3,5-dimethyl-4-oxotetrahydro-1,3,5-oxadiazine (**124**) with N,N'-dimethylurea. Treatment of **121** with hydrochloric acid results in a hydrolytic degradation with ring contraction to give 2-oxo-1,3,5-trimethylhexahydro-1,3,5-triazine (**125**)[70].

2.5. Cyclocondensations by α-Ureidoalkylation of CH-Acidic Compounds

The synthetic possibilities of cyclizing α-ureidoalkylation of CH-acidic compounds are particularly many-sided. This relates to CH-acidic aldehydes and ketones, alkynes, and carboxylic acid esters. The behavior of aliphatic CH-acidic compounds on cyclizing α-ureidoalkylation is indicated by the order of reactivity set out below.



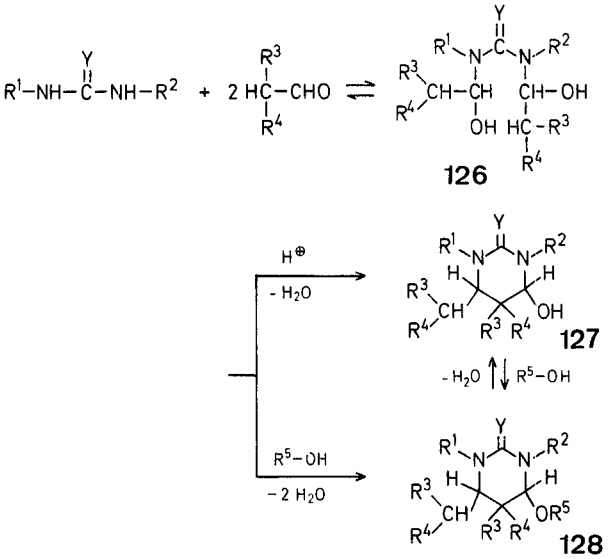
[52] E. Hug, *Bull. Soc. Chim. France* **1934**, 990.

2.5.1. Cyclocondensations with CH-Acidic Aldehydes

The aldehydes occupy a special position among the CH-acidic compounds, since they are capable of reacting not only as nucleophilic but also at the same time as carbonyl components in these cyclocondensations.

2.5.1.1. 4-Hydroxy(Alkoxy)-2-oxo(thiono)-hexahydropyrimidines

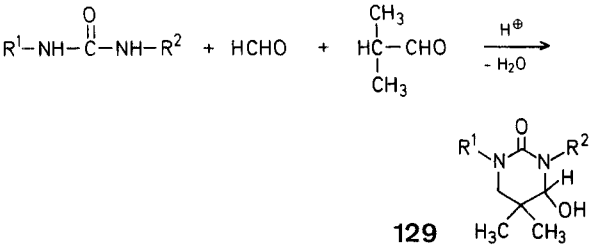
In reactions with urea or compounds containing NH groups under mild conditions, i.e. in weakly acidic medium, aliphatic and aromatic aldehydes generally behave only as carbonyl components and give linear condensation products similar in structure to the condensation products of urea with formaldehyde. In more strongly acidic medium and at elevated temperature, however, an α-ureidoalkylation also occurs at the CH-acidic group of the aldehyde. In the presence of an acid, condensation of urea, thiourea, or guanidine, or their mono- or symmetrically disubstituted derivatives, with aldehydes having at least one H-atom in the α-position to the carbonyl group affords 2-oxo-, 2-thiono-, or 2-imino-4-hydroxyhexahydropyrimidines (**127**), respectively[1,3,9,71,72].



The reaction proceeds via the intermediacy of symmetrical N,N′-bis-[1-hydroxyalkyl] compounds (**126**) as well as poly-α-alkylideneureas and the like, all of which contain the functions necessary for a cyclocondensation in accordance with the principle of α-ureidoalkylation, namely the NH-component, one mol of the aldehyde as the carbonyl component, and a second mol of the aldehyde as the CH-acidic nucleophilic component. In the cyclocondensation, the CH-acidic group of one α-alkylol moiety is linked via the C-atom of the second α-alkylol moiety with the N-atom of the urea, thiourea, or guanidine residue to give the 4-hydroxy-hexahydropyrimidine derivatives **127**.

5,5-Dimethyl-4-hydroxy-6-isopropyl-2-oxohexahydropyrimidine (127, $R^1=R^2=H$, $R^3=R^4=CH_3$)[71]:
A solution of urea (300 g, 5 mol) in water (1 l) is treated with conc. hydrochloric acid (100 g), then isobutyraldehyde (720 g, 10 mol) is added with stirring (use a reflux condenser). Immediately after addition of the aldehyde, a white precipitate of polyisobutyleneurea is deposited and the temperature rises to 55–60°. On heating to 85°, the precipitate dissolves again and after a short time at 85°, a crystalline precipitate is deposited. After heating at 85° for 2 hr, the mixture is cooled and the precipitate isolated by filtration, washed with water, and dried; yield: 760 g (82%). On neutralization of the filtrate with sodium hydroxide, a further 140 g (15%) are precipitated; total yield: 900 g (97%). The product may be recrystallized from water; m.p. 185–190° (dec).

4-Alkoxy-2-oxo(thiono)-hexahydropyrimidines (**128**) are formed if this condensation is carried out in the presence of alcohols[1,3,9,72,73]. These cyclocondensations may be applied to the reactions of ureas and thioureas with two different aldehydes, provided that at least one of these displays a CH-acidic character. Thus, for example, cyclocondensation of one mol of a urea with one mol of formaldehyde and one mol of isobutyraldehyde in the presence of an acid gives rise to 5,5-dimethyl-4-hydroxy-2-oxohexahydropyrimidine (**129**)[1,3,9,71].



4-Methoxy-2-oxo-1,3,5,5-tetramethylhexahydropyrimidine[73]:
Hydrogen chloride (30 g) is introduced within 10–15 min at 30° into a mixture of N,N′-dimethylurea (88 g), paraformaldehyde (30 g), isobutyraldehyde (72 g), and methanol (500 g) with constant stirring and cooling of the reaction vessel in an ice bath. The paraformaldehyde dissolves after a short time. After stirring at 50–55° for 1 hr, the reaction solution is neutralized with sodium hydroxide at room temperature, then sodium chloride is filtered off, and the filtrate is freed from methanol and water of reaction under reduced pressure; yield of crude product: 140 g (75%); the product can be purified by distillation in high vacuum; b.p. 113–115°/1 torr.

Table 12 lists not only the 4-hydroxy(alkoxy)-2-oxo-(thiono)-hexahydropyrimidines obtainable by α-ureidoalkylation of CH-acidic aldehydes and ketones, but also the derivatives accessible by vinylogous ureidoalkylation.

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[58] R. A. Wiesboeck, *U.S. Patent* 3470175 (1969), U.S. Agrichemicals Inc.; *C.A.* **72**, 43750 (1970).
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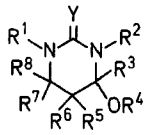
[60] H. Spänig, W. Schönleben, BASF, Ludwigshafen, unpublished

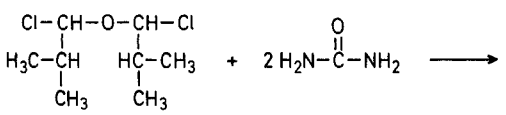
Table 12. 4-Hydroxy(Alkoxy)-2-oxo(thiono)-hexahydropyrimidines



Y	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	m.p.	References
O	H	H	H	H	CH_3	CH_3	H	H	252–254°	3, 9
O	H	H	H	H	CH_3	CH_3	*i*-C_3H_7	H	220–222°	71
O	H	CH_3	H	H	H	H	CH_3	H	176°	72
O	H	C_2H_5	H	H	H	H	CH_3	H	150°	72
O	H	—CH_2—C_6H_5	H	H	H	H	CH_3	H	174°	72
O	H	—CH_2—C_6H_{11}-*c*	H	H	H	H	CH_3	H	159°	72
O	H	H	H	CH_3	H	H	CH_3	H	167°	74
O	CH_3	CH_3	H	H	CH_3	CH_3	H	H	93°	71
O	CH_3	CH_3	H	CH_3	H	H	H	H	(b.p. 85–88°/0.4 torr)	74
O	CH_3	CH_3	H	CH_3	CH_3	CH_3	H	H	(b.p. 113–115°/1 torr)	73
O	CH_3	CH_3	H	CH_3	H	H	CH_3	H	(b.p. 99–102°/0.4 torr)	
O	H	H	H	*i*-C_3H_7	H	H	CH_3	H	141°	72
O	H	CH_3	H	C_2H_5	H	H	CH_3	H	143°	72
O	H	CH_3	H	*i*-C_3H_7	H	H	CH_3	H	134°	72
O	H	C_2H_5	H	C_2H_5	H	H	CH_3	H	120°	72
O	H	C_2H_5	H	*i*-C_3H_7	H	H	CH_3	H	111°	72
O	H	—CH_2—C_6H_5	H	C_2H_5	H	H	CH_3	H	176°	72
O	H	—CH_2—C_6H_{11}-*c*	H	*n*-C_3H_7	H	H	CH_3	H	125°	72
O	H	—CH_2—C_6H_5	H	*i*-C_3H_7	H	H	CH_3	H	162°	72
O	H	—CH_2—C_6H_5	H	*n*-C_4H_9	H	H	CH_3	H	92°	72
O	H	—CH_2—C_6H_5	H	*i*-C_4H_9	H	H	CH_3	H	97°	72
O	H	—CH_2—C_6H_5	H	—CH_2—C_6H_5	H	H	CH_3	H	106°	72
S	H	H	CH_3	H	H	H	H	H	151–152°	75
S	H	H	CH_3	H	H	H	CH_3	CH_3	246–248°	75
S	H	H	CH_3	H	H	H	C_6H_5	H	191–194°	75
S	H	H	C_6H_5	H	H	H	C_6H_5	H	178–180°	75
S	H	H	H	H	CH_3	CH_3	*i*-C_3H_7	H	162°	71

The 4-hydroxy-2-oxo(thiono)-hexahydropyrimidines are semicyclic acetal amides the hydroxy groups of which can, similarly to the case with an N-hydroxymethyl compound, readily be substituted by nucleophilic agents.

Condensation of urea with α,α′-dichlorodiisobutyl ether (**130**) affords 4-chloro-2,8-diisopropyl-6-oxo-3,3,9,9-tetramethylhexahydro-4*H*-pyrimido[4,3-*b*]-1,3-oxazine (**131**, R = Cl), which in the presence of water is readily hydrolyzed to the 4-hydroxy derivative (**131**, R = OH)[82].



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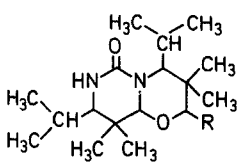

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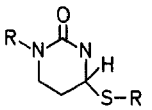
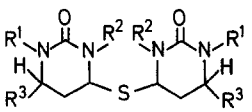
The acetalization of 4-hydroxy-2-oxo-hexahydropyrimidines with alcohols proceeds readily at room temperature in the presence of catalytic amounts of acid or cation-exchange resin. Compounds of the type of 4-hydroxy- and 4-alkoxy-5,5-dialkyl-2-oxohexahydropyrimidine are used in the form of their N,N′-bis-hydroxymethyl derivatives for the finishing of cellulosic fabrics[83].

2.5.1.2. 4-Alkylthio(Arylthio)-2-oxohexahydropyrimidines

Mercaptans and thiophenols react with 4-hydroxy-(alkoxy)-2-oxohexahydropyrimidines to give 4-alkylthio(arylthio)-2-oxohexahydropyrimidines (**132**)[72,77,78]. The action of hydrogen sulfide on 4-hydroxy-2-oxohexahydropyrimidines leads to bis-[2-oxohexahydro-4-pyrimidyl] sulfides[72] (**133**).



132



133

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[66] A. von Merkatz, *Ber. dtsch. chem. Ges.* **52**, 869 (1919).
[67] J. B. Wright, *J. Org. Chem.* **29**, 1905 (1964); *U.S. Patent* 3203954 (1965), Upjohn Co; *C.A.* **63**, 14888 (1965).

Table 13. Substitution Reactions of 4-Hydroxy-2-oxo(thiono)-hexahydropyrimidines in the 4-Position

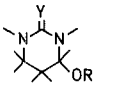
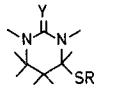
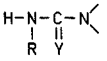
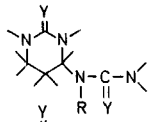
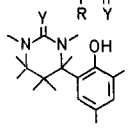
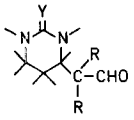
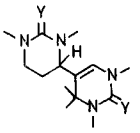
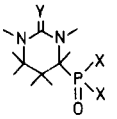
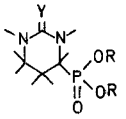
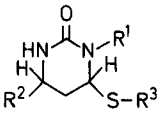
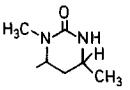
Nucleophilic Compound	Product	Section	References
H–OR		2.5.1.1.	3, 9, 72, 73, 74, 76
H–SR		2.5.1.2.	72, 77, 78
		2.5.1.3.	3, 9, 19, 20, 21, 76, 79
		2.5.1.4.	72
		2.5.1.4.	9, 80
		2.5.1.4.	72
PX_3 X = Cl, Br		2.5.1.5.	9
		2.5.1.5.	9, 81

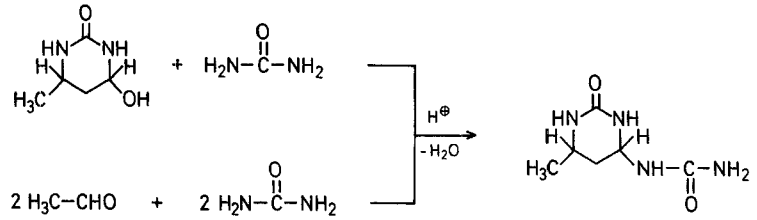
Table 14. 4-Alkylthio(Arylthio)-2-oxohexahydropyrimidines (**133**) from 4-Hydroxy-, 4-Alkoxy-, or 4-Ureido-2-oxohexahydropyrimidines and Alkyl- or Arylmercaptans[72]



R^1	R^2	R^3	Yield (%)	m.p.
H	CH_3	n-C_4H_9	78	123°
H	CH_3		94	189°
H	CH_3		37	214°
CH_3	CH_3		90	148°
	CH_3		96	151°
C_2H_5	CH_3		78	133°
H	C_2H_5		48	184°
CH_3	CH_3		30	231°

2.5.1.3. 2-Oxo(thiono)-4-ureidohexahydropyrimidines

4-Hydroxy-2-oxo- and 4-hydroxy-2-thionohexahydropyrimidines unsubstituted or only monosubstituted in the 5-position react with ureas to give the corresponding 2-oxo- or 2-thiono-4-ureidohexahydropyrimidines, respectively.



134

Preparation of 4-Alkylthio- and 4-Arylthio-2-oxohexahydropyrimidines (132); General Procedure[72]:

4-Hydroxy-2-oxo-, 4-alkoxy-2-oxo-, or 2-oxo-4-ureidopyrimidine (0.1 mol) is heated at boiling with alkyl- or arylmercaptan (1.5 mol), conc. hydrochloric acid (4 ml), and 50% ethanol (30 ml) for 15 min, then excess mercaptan is removed with dilute sodium hydroxide solution and the residual crystallizate or oil is dried, triturated with acetone, and recrystallized from ethanol.

Bis-[3,6-dimethyl-2-oxohexahydro-4-pyrimidyl] Sulfide (133, $R^1 = H$, $R^2 = R^3 = CH_3$)[72]:

A solution of 3,6-dimethyl-4-ethoxy-2-oxohexahydropyrimidine (10 g) in benzene (150 ml) is treated with a solution of oxalic acid (1 spatula tip) in acetone (10 ml), then hydrogen sulfide is passed into the solution while the benzene is simultaneously slowly distilled off via a column until the residual volume is 20 ml. The residue crystallizes upon treatment with acetone; yield: 30%; m.p. 231° (from ethanol).

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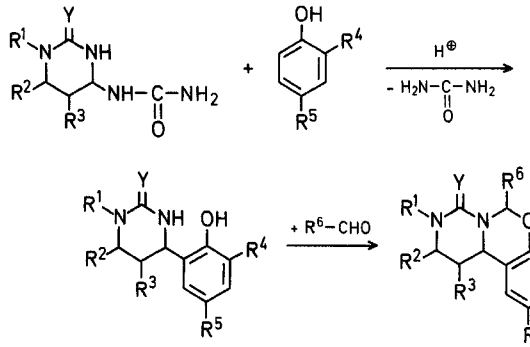
Under the influence of acids, 2-oxo-4-ureidohexahydropyrimidines react with phenols to form 4-(hydroxyphenyl)-2-oxo(thiono)-hexahydropyrimidines[19] (**135**).

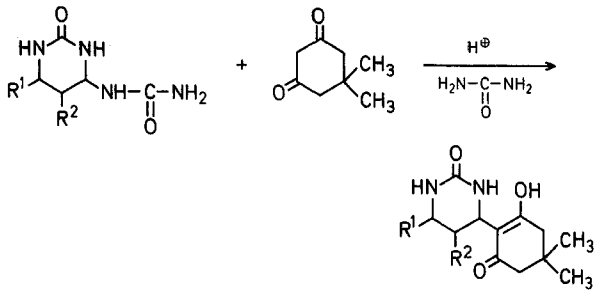


135 **136**

The condensation of **135** with aldehydes in acidic medium leads to 4-oxo-1,2,6,10-tetramethyl-1,2,3,11b-tetrahydro-4*H*,6*H*-pyrimido[1,6-*c*][1,3]-benzoxazines[19] (**136**; see Section 2.1.3.).

4-(2-Hydroxy-3,5-dimethylphenyl)-6-methyl-2-oxohexahydropyrimidine (**135**, $R^1=R^3=H$, $R^2=R^4=R^5=CH_3$)[19]:
6-Methyl-2-oxo-4-ureidohexahydropyrimidine (1 g) is heated at 50° with 2,4-xylenol (10 ml) and ethanolic hydrogen chloride (6 ml) for 4 hr, the mixture steam-distilled, and the product recrystallized from ethanol; yield: 92%; m.p. 256°.

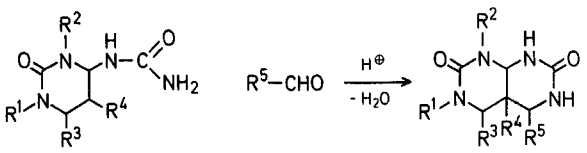
2-Oxo-4-ureidohexahydropyrimidines can be converted by reaction with dimedone in acidic medium into 4-(2-hydroxy-4,4-dimethyl-6-oxocyclohexen-1-yl)-2-oxohexahydropyrimidines[21] (**137**).



137

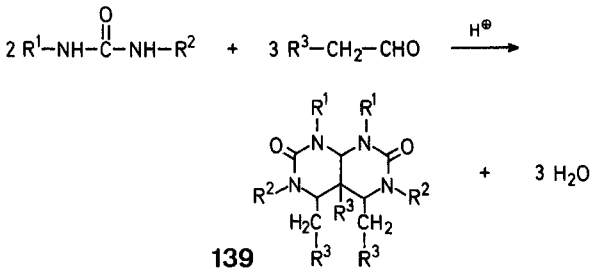
4-(4,4-Dimethyl-2-hydroxy-6-oxocyclohexen-1-yl)-6-ethyl-5-methylhexahydropyrimidine (**137**, $R^1=C_2H_5$, $R^2=CH_3$)[21]:
6-Ethyl-5-methyl-2-oxo-4-ureidohexahydropyrimidine (2.5 g) is heated on a water bath with dimedone (5 g) in 50% ethanol (48 ml) for 3 hr and the solvent is evaporated in vacuo. The residue is taken up in acetone, dissolved in dioxan/methanol (7:3), and brought to crystallization by the addition of the same amount of cyclohexane; yield: 1.5 g; m.p. 206°.

2-Oxo-4-ureidohexahydropyrimidines carrying at least one substitutable hydrogen atom in the 5-position react with aldehydes in the presence of catalytic amounts of acid according to the principle of α-ureidoalkylation to give 2,7-dioxodecahydropyrimido[4,5-α]pyrimidines[19,20,21] (**138**).



138

2,7-Dioxodecahydropyrimido[4,5-*d*]pyrimidines (**139**) are also obtained in relatively good yields by direct reaction of urea or its monosubstituted or symmetrically disubstituted derivatives with aldehydes of the general formula $R^3—CH_2—CHO$ in the presence of acids[19,20,21].

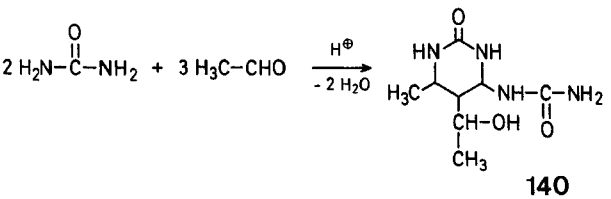


139

4,5-Dimethyl-2,7-dioxodecahydropyrimido[4,5-*d*]pyrimidine (**138**, $R^1=R^2=R^4=H$, $R^3=R^5=CH_3$)[19]:
Urea (10 g) is moistened with conc. hydrochloric acid (1 ml). The mixture is treated under a reflux condenser with acetaldehyde (25 ml), held at 38° with occasional stirring for 8 hr, well triturated with ethanol (30 ml), and allowed to stand for 12–15 hr; yield: 50%; m.p. 277° (from ethanol).

2,7-Dioxo-1,3,4,5,6,8-hexamethyldecahydropyrimido[4,5-*d*]-pyrimidine (**139**, $R^1=R^2=CH_3$, $R^3=H$)[9]:
N,N'-Dimethylurea (176 g, 2 mol) is dissolved in water (500 ml) with conc. hydrochloric acid (25 ml). Acetaldehyde (132 g, 3 mol) is introduced dropwise into the solution through a dropping funnel with stirring (use a reflux condenser). The reaction solution is heated at 60° for 2 hr. After neutralization and evaporation of the methanol, the reaction product is subjected to fractional distillation. 2,7-Dioxo-1,3,4,5,6,8-hexamethyldecahydropyrimido-[4,5-*d*]pyrimidine is obtained (in addition to 2-oxo-1,3,4-trimethyltetrahydropyrimidine and N,N'-dimethylurea) as a high-boiling fraction; boiling range: 220–225°/0.5 torr. The product may be recrystallized from methanol.

From the reaction of urea with acetaldehyde in the presence of acids, 5-(1-hydroxyethyl)-6-methyl-2-oxo-4-ureidohexahydropyrimidine (**140**) is obtained as a by-product[3].



140

[78] H. Petersen, *Textilveredlung* **4**, 254 (1969).
[79] H. Petersen, H. Brandeis, R. Fikentscher, *German Patent (DBP.)* 1223843 (1962), BASF; *C.A.* **66**, 28797 (1967).
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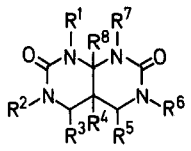
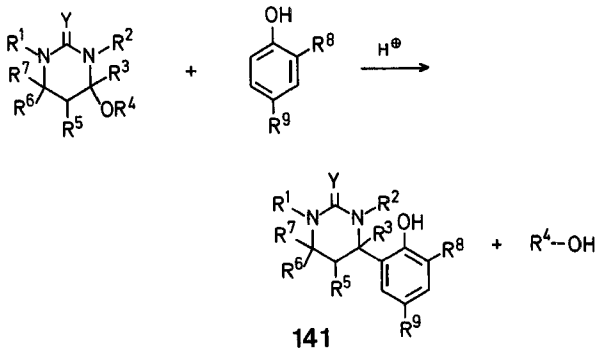
Table 16. 2,7-Dioxodecahydropyrimido[4,5-*d*]pyrimidines



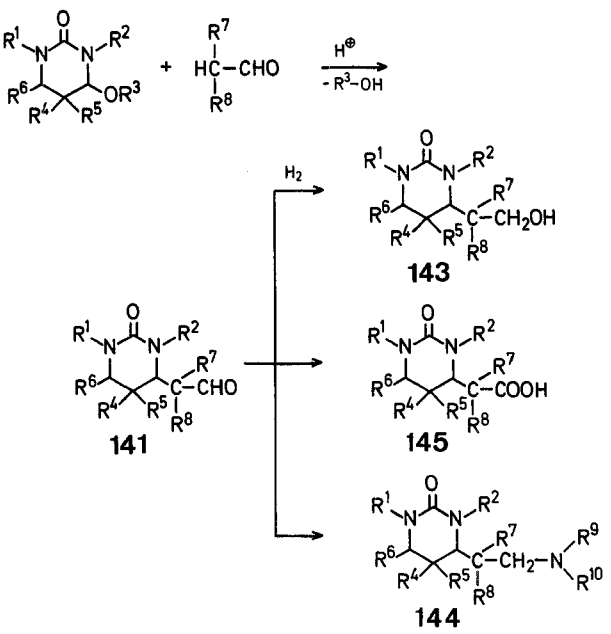
R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	m.p.	References
H	H	CH_3	H	CH_3	H	H	H	277°	19
CH_3	CH_3	CH_3	H	CH_3	CH_3	CH_3	H	(b.p. 220–225°/ 0.5 torr)	9
CH_3	H	CH_3	H	C_6H_5	CH_3	H	H	302°	20
CH_3	—CO—CH_3	CH_3	H	C_6H_5	CH_3	—CO—CH_3	H	172°	20
CH_3	H	CH_3	H	CH_3	CH_3	H	H	283°	20
CH_3	H	CH_3	H	n-C_3H_7	CH_3	H	H	282°	20
CH_3	—CO—CH_3	CH_3	H	n-C_3H_7	CH_3	—CO—CH_3	H	137°	20
CH_3	H	C_2H_5	CH_3	C_2H_5	CH_3	H	H	298°	21
CH_3	—CO—CH_3	C_2H_5	CH_3	C_2H_5	CH_3	—CO—CH_3	H	200°	21
H	H	H	H	H	H	H	CH_3	275°	87
H	CH_3	H	H	H	CH_3	H	CH_3	191°	87
H	H	H	H	—CH_2—CH_2OH	H	H	H	310°	86

2.5.1.4. Reactions of 4-Hydroxy(Alkoxy)-2-oxo(thiono)-hexahydropyrimidines with CH-Acidic Compounds

In the presence of acids, 4-hydroxy(alkoxy)-2-oxo-(thiono)-hexahydropyrimidines condense with a few classes of compounds such as phenols, CH-acidic aldehydes and ketones, and 2-oxo(thiono)-hexahydropyrimidines. The reaction with phenols leads to 4-(hydroxyphenyl)-2-oxo(thiono)-hexahydropyrimidines (**141**).



The reaction of 4-hydroxy(alkoxy)-hexahydropyrimidines with CH-acidic aldehydes results in C—C coupling to give α-(2-oxohexahydropyrimidin-4-yl)-aldehydes (**142**)[9,94,95]. Reduction of **142** leads to 4-(2-hydroxyalkyl)-2-oxohexahydropyrimidines (**143**), aminative hydrogenation gives 4-(2-aminoalkyl)-2-oxohexahydropyrimidines (**144**), and oxidation produces α-(2-oxohexahydropyrimidin-4-yl)-carboxylic acids (**145**)[9,94].



Hydrolysis gives rise to polyfunctional aminoalcohols, aminocarboxylic acids, and polyamines[9,94].

2-Methyl-2-(2-oxo-1,3,5,5-tetramethylhexahydropyrimidin-4-yl)-propanal (142, $R^1=R^2=R^4=R^5=R^7=R^8=CH_3$, $R^6=H$)[94,95]: 4-Hydroxy-2-oxo-1,3,5,5-tetramethylhexahydropyrimidine (334 g) is dissolved in water (1000 ml) in a flask fitted with a stirrer and an efficient reflux condenser and treated with isobutyraldehyde (160 g) and conc. hydrochloric acid (50 ml). The reaction mixture is heated under reflux for 8 hr and then neutralized with sodium hydroxide solution. It is then shaken with chloroform and the chloroform phase concentrated under reduced pressure. The residue is fractionally distilled and the fraction boiling at 150 to 168°/0.5–1 torr collected; yield: 260 g (57%).

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[89] G. Zigeuner, E. Fuchs, W. Galatik, *Monatsh. Chem.* **97**, 43 (1966).

Table 17. 4-(Hydroxyphenyl)-2-oxo(thiono)-hexahydropyrimidines (**141**) by α-Ureidoalkylation of Phenols

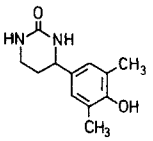
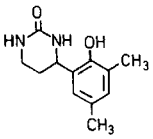
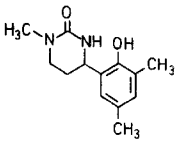
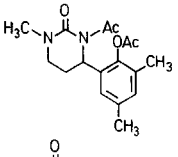
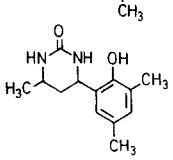
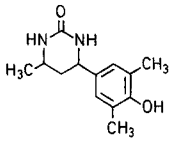
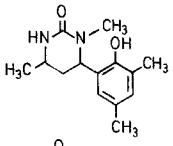
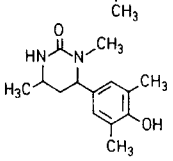
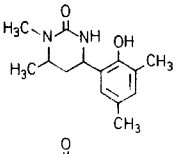
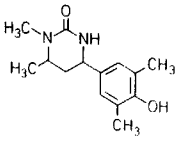
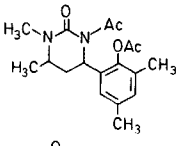
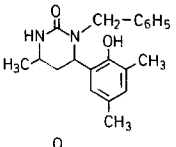
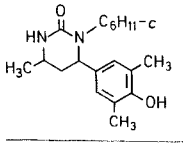
Product	m.p.	References
	230°	22
	267°	22
	229°	22
	138	22
	256°	19
	233°	19
	180°	20
	210°	20
	197°	22
	176–177°	22
	111°	22
	196°	72
	338°	72

Table 17. continued

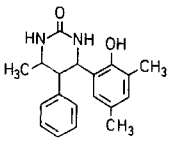
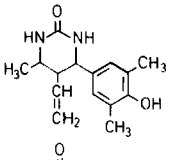
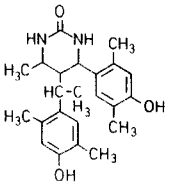
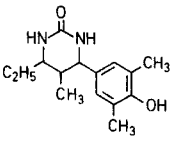
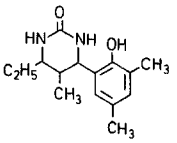
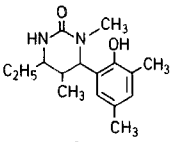
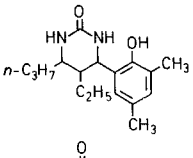
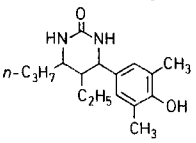
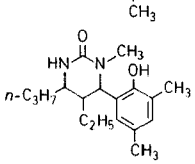
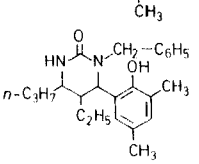
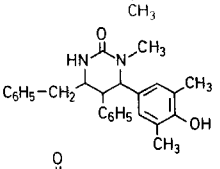
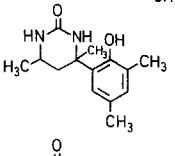
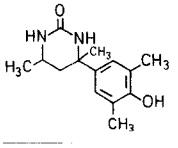
Product	m.p.	References
	285°	72
	290°	19
	282°	19
	191°	21
	240°	21
	170°	21
	216°	21
	227°	21
	208°	21
	204°	72
	175°	72
	236°	18, 91
	243°	91

Table 17. continued

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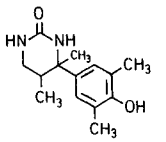
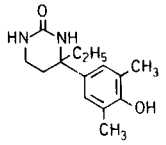
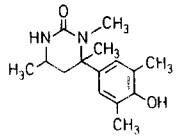
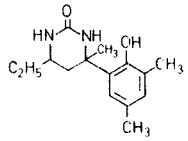
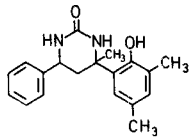
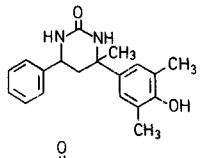
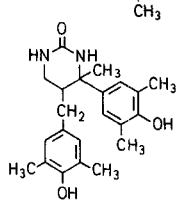
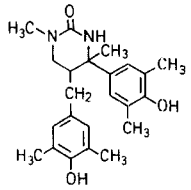
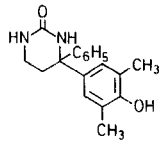
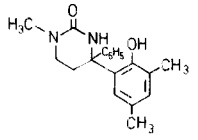
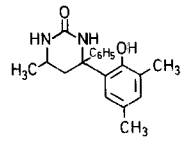
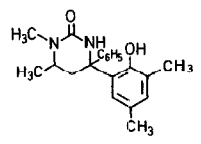
	287°	93
	231°	93
	228°	91
	233°	91
	257°	91
	222°	91
	315°	87
	268°	87
	247°	92
	252°	18
	245°	92
	231°	92

Table 17. continued

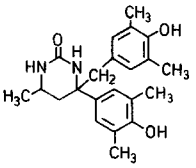
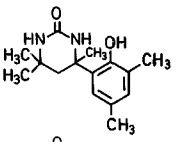
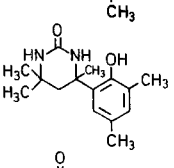
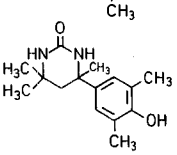
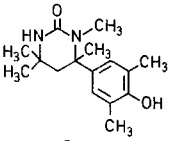
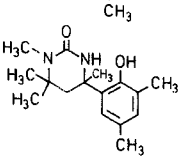
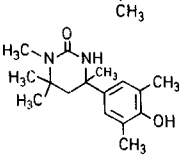
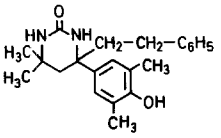
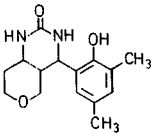
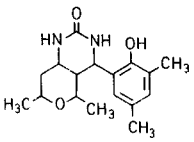
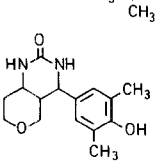
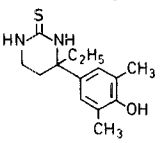
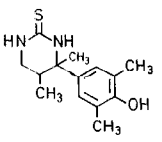
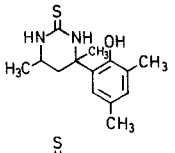
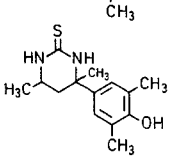
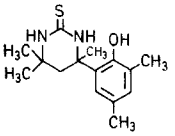
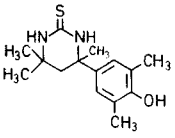
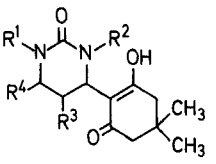
Product	m.p.	References
	290°	90
	233°	89
	230°	88
	205°	88
	210°	88
	237°	89
	223°	89
	208[2]	89
	231°	86
	275° (dec)	86
	250° (dec)	86
	214°	93
	270°	93

Table 17. continued

Product	m.p.	References
	260°	18
	234°	91
	228°	88
	260°	88

Ketones react similarly with active methylene groups. For example, condensation of dimedone with 4-hydroxy(alkoxy)-2-oxohexahydropyrimidines produces[72] compounds **146** (cf. Section 2.1.2.).

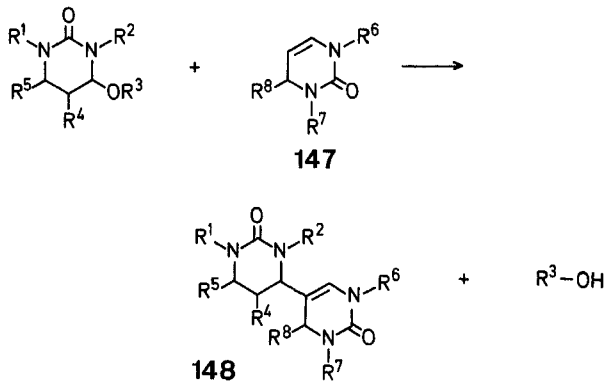


146

Table 18. 4-(4,4-Dimethyl-2-hydroxy-6-oxocyclohexen-1-yl)-2-oxohexahydropyrimidines (**146**)

R^1	R^2	R^3	R^4	m.p.	References
H	H	CH_3	C_2H_5	206°	21
H	H	C_2H_5	n-C_3H_7	191°	21
H	CH_3	C_2H_5	n-C_3H_7	165°	21

2-Oxotetrahydropyrimidines (**147**) are able to react as CH-acidic compounds with 4-hydroxy(alkoxy)-2-oxohexahydropyrimidines to give 2-oxo-4-(2-oxotetrahydropyrimidin-4-yl)-hexahydropyrimidines[72] (**148**).



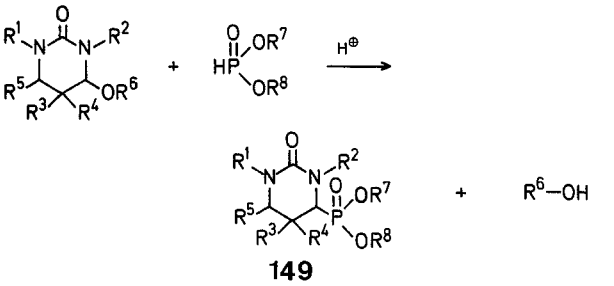
147 **148**

6-Methyl-2-oxo-4-(6-methyl-2-oxotetrahydropyrimidin-4-yl)-hexahydropyrimidine(148, $R^1=R^2=R^4=R^6=R^7=H$, $R^5=R^8=CH_3$)[72]:

4-Hydroxy-6-methyl-2-oxohexahydropyrimidine (2 g) is dissolved in water (20 ml) containing conc. hydrochloric acid (10 drops). The mixture is allowed to stand at 50° for 24 hr. The resultant crystalline product is isolated by filtration and recrystallized from water; yield: 0.1 g; m.p. 330–335° (dec).

2.5.1.5. Reactions of 4-Hydroxy(Alkoxy)-2-oxohexahydropyrimidines with Nucleophilic Phosphorus Compounds

Condensation of 4-hydroxy(alkoxy)-2-oxohexahydropyrimidines with PH-acidic compounds such as dialkyl phosphonates produces a very stable C—P bond, e.g. yielding dialkyl 2-oxohexahydropyrimidine-4-phosphonates (**149**)[9,94,96].



149

Diethyl 2-Oxo-1,3,5,5-tetramethylhexahydropyrimidine-4-phosphonate (**149**, $R^1-R^4=CH_3$, $R^5=H$, $R^7=R^8=C_2H_5$)[96]:

4-Hydroxy-2-oxo-1,3,5,5-tetramethylhexahydropyrimidine (86 g) and diethyl phosphonate (100 g) are heated with stirring at 90–100° for 2 hr. After 10 min, a clear solution is formed. The water produced and excess diethyl phosphonate are then removed under reduced pressure. The product is distilled under high vacuum; yield: 120 g (82.5%); b.p. 89–92°/2 torr.

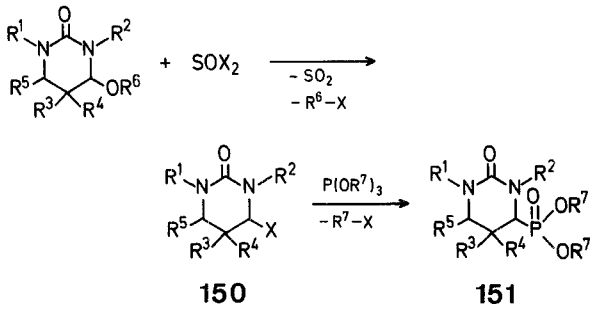
Table 19. 2-Oxo-4-(2-oxotetrahydropyrimidin-4-yl)-hexahydropyrimidines (**148**)

R^1	R^2	R^4	R^5	R^6	R^7	R^8	m.p.	References
H	H	H	CH_3	H	H	CH_3	330–335°	72
—CO—CH_3	—CO—CH_3	H	CH_3	—CO—CH_3	—CO—CH_3	CH_3	129°	72
CH_3	H	H	CH_3	H	CH_3	CH_3	235°	22
CH_3	—CO—CH_3	H	CH_3	H	CH_3	CH_3	197°	22
—CO—CH_3	CH_3	H	CH_3	CH_3	—CO—CH_3	CH_3	185°	72

[90] G. Zigeuner, H. Hamberger, H. Blaschke, H. Sterk, *Monatsh. Chem.* **97**, 1408 (1966).

[91] G. Zigeuner, W. Nischk, B. Juraszovits, *Monatsh. Chem.* **97**, 1611 (1966).

Compounds **149** are obtained in better yields by reaction of 4-halo-2-oxohexahydropyrimidines (**150**) with trialkyl phosphites[97]. Compounds **150** are prepared from 4-hydroxy(alkoxy)-2-oxohexahydropyrimidines and thionyl chloride[97].

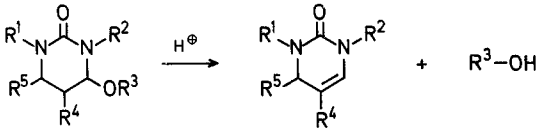


150 **151**

Dimethyl 5,5-Dimethyl-2-oxohexahydropyrimidine-4-phosphonate (**151**, $R^1=R^2=R^5=H$, $R^3=R^4=R^7=CH_3$)[97]:
Thionyl chloride (218 ml) is added to a stirred solution of 5,5-dimethyl-4-methoxy-2-oxohexahydropyrimidine (474 g) in dioxan (1200 ml) at 50° within 10–15 min with cooling. The reaction mixture is heated at 50° for 30 min and then concentrated under reduced pressure. Trimethyl phosphite (353 ml) is added to the concentrated solution. The mixture is warmed for 2 hr, allowed to cool, and the crystalline residue isolated by filtration; yield: 450 g (64%); m.p. 201–203° (from methanol).

2.5.1.6. 2-Oxo(thiono)-1,2,3,6-tetrahydropyrimidines

4-Hydroxy(alkoxy)-2-oxohexahydropyrimidines can be converted to 2-oxo-1,2,3,6-tetrahydropyrimidines (**152**) in the presence of acids by elimination of water or alcohol[72].



152

3-Benzyl-6-methyl-2-oxo-1,2,3,6-tetrahydropyrimidine (**152**, $R^1=R^4=H$, $R^2=-CH_2-C_6H_5$, $R^5=CH_3$)[72]:
3-Benzyl-4-hydroxy-6-methyl-2-oxohexahydropyrimidine (5 g) is heated for 2 hr with acetic anhydride (10 ml) and pyridine (3 ml). The mixture is concentrated in vacuum and the residue treated with cyclohexane and a little ether; yield: 55%; m.p. 106° (from cyclohexane).

In many cases, 2-oxo-tetrahydropyrimidines (**152**) can be prepared in good yield by the reaction of ureas with α,β-unsaturated aldehydes or α,β-unsaturated ketones via a vinylogous ureidoalkylation[3,9,19,21,72]. The 2-oxo(thiono)-tetrahydropyrimidines obtainable by α-ureidoalkylation of aldehydes and ketones and by vinylogous ureidoalkylation as well as the derivatives from further reactions are summarized in Tables 20 and 21.

[92] G. Zigeuner, M. Bayer, F. Paltauf, E. Fuchs, *Monatsh. Chem.* **98**, 22 (1967).
[93] G. Zigeuner, A. Frank, H. Dujmovits, W. Adam, *Monatsh. Chem.* **101**, 1415 (1970).
[94] H. Petersen, *Textilveredlung* **4**, 258 (1969).

Table 20. 2-Oxo-1,2,3,6-tetrahydropyrimidines (and Products Derived therefrom)

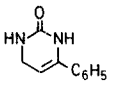
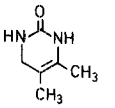
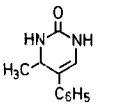
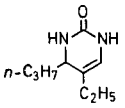
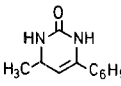
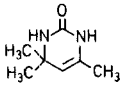
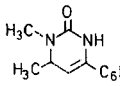
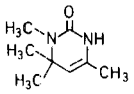
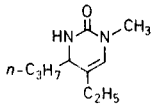
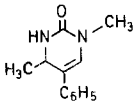
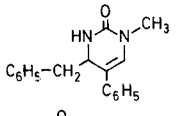
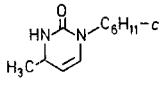
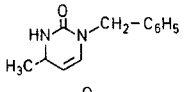
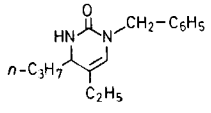
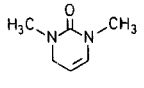
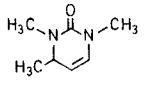
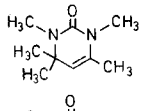
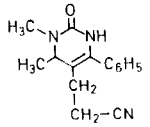
Compound	m.p.	References
	195°	92
	241°	93
	204°	72
	105°	72
	170°	92
	139°	3, 9, 89, 104
	141°	92
	121–122°	89
	58°	72
	118°	72
	130°	72
	160°	72
	106°	72
	195°	72
	(b.p. 86–90°/ 0.5 torr)	3
	(b.p. 95–102°/ 0.5 torr)	3
	(b.p. 84–86°/ 0.5 torr)	3, 9, 105
	210°	92

Table 20. continued

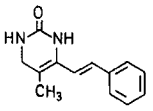
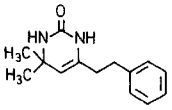
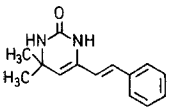
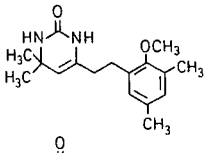
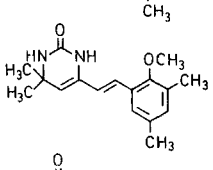
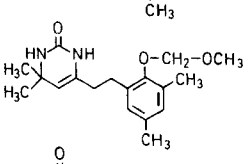
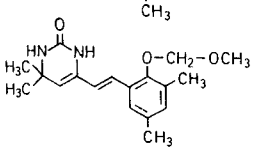
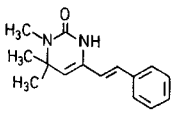
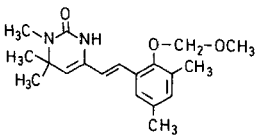
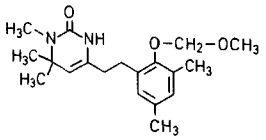
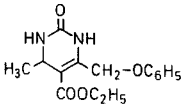
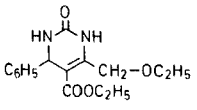
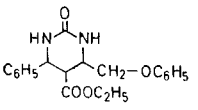
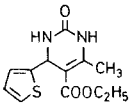
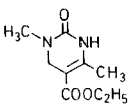
Compound	m.p.	References
	222°	93
	155°	89
	254°	89
	207°	100
	215°	100
	158°	100
	188°	100
	230°	89
	172°	100
	99°	100
	137°	90
	127°	90
	169°	90
	111°	103
	183°	90

Table 20. continued

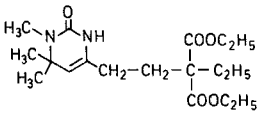
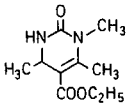
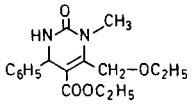
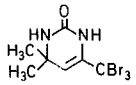
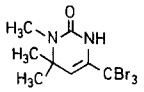
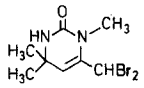
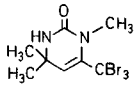
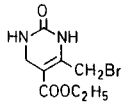
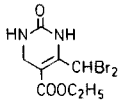
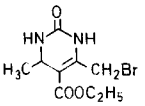
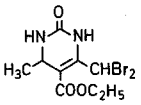
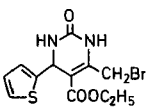
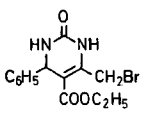
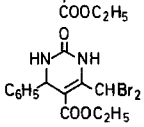
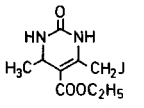
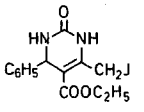
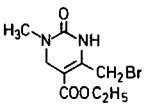
Compound	m.p.	References
	147°	102
	111°	90
	141°	90
	181°	90
	180°	90
	197°	90
	180°	90
	175°	90
	130°	90
	148°	90
	161°	90
	175°	103
	150°	90
	181°	90
	148°	90
	157°	90
	140°	90

Table 20. continued

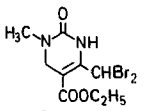
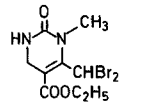
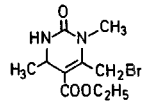
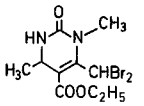
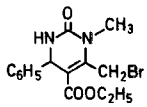
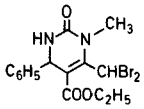
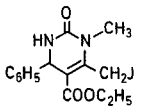
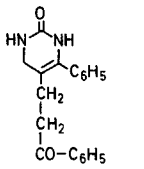
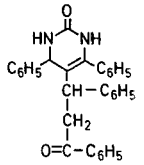
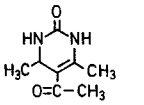
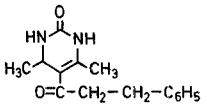
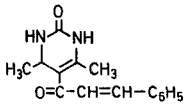
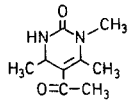
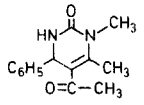
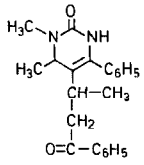
Compound	m.p.	References
	150°	90
	115°	90
	147°	90
	136°	90
	170°	90
	171°	90
	153°	90
	190°	92
	252°	92
	190°	91
	170°	91
	223°	91
	126°	91
	148°	91
	207°	92

Table 20. continued

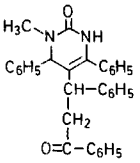
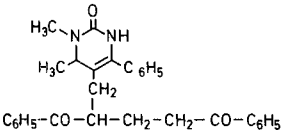
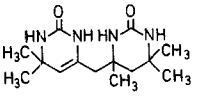
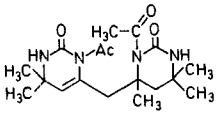
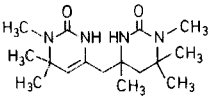
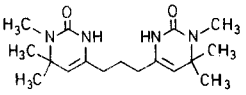
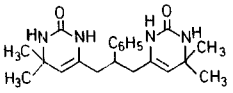
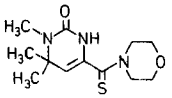
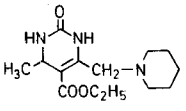
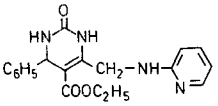
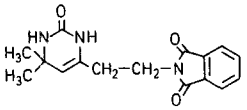
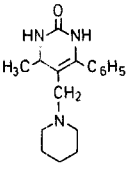
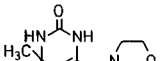
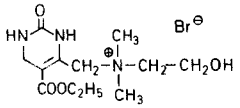
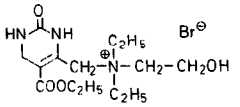
Compound	m.p.	References
	230°	92
	284°	92
	292°	89, 93
	202°	89
	201°	89
	320°	102
	329–330°	89
	156°	101
	88°	90
	195°	103
	219–220°	102
	205°	92
	287°	101
	170°	90
	160°	90

Table 20. continued

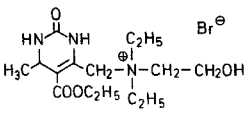
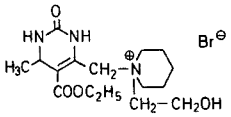
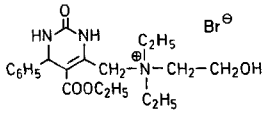
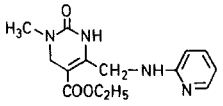
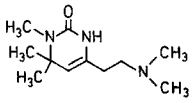
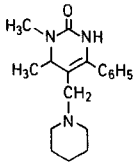
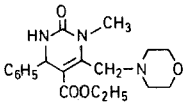
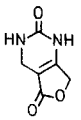
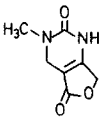
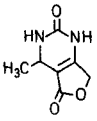
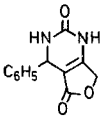
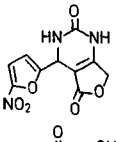
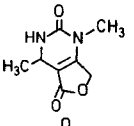
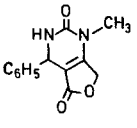
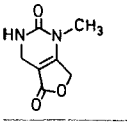
Compound	m.p.	References
	207°	90
	176°	90
	182°	90
	158°	103
	120°	98
	158–159°	98
	168°	90
	290°	90
	258°	90
	265°	90
	272°	90
	270°	90
	216°	90
	218°	90
	238°	90

Table 20. continued

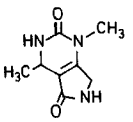
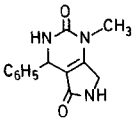
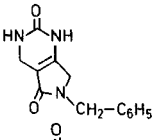
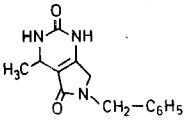
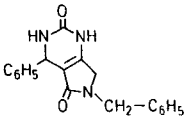
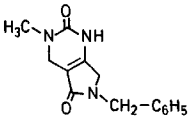
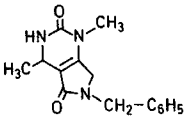
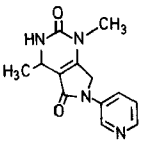
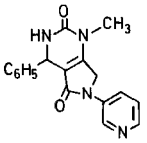
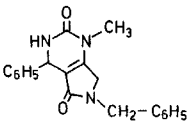
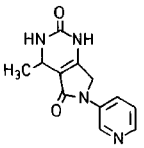
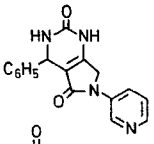
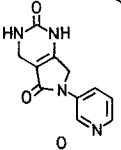
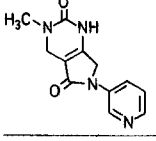
Compound	m.p.	References
	228°	103
	244°	103
	235°	103
	255°	103
	248°	103
	208°	103
	159°	103
	213°	103
	248°	103
	172°	103
	360°	103
	288°	103
	270°	103
	278°	103

Table 20. continued

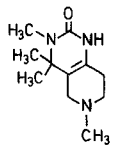
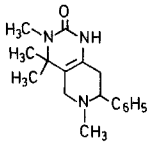
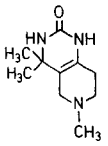
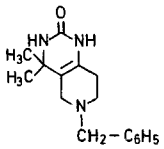
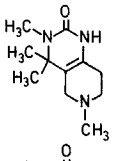
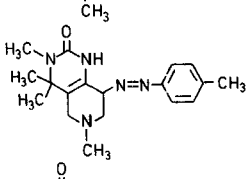
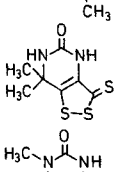
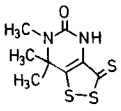
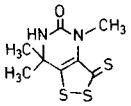
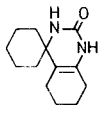
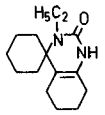
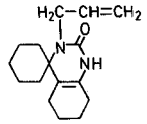
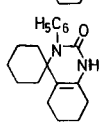
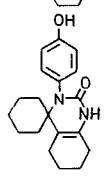
Compound	m.p.	References
	hydrochloride: 158°; free base: 164°	98
	hydrochloride: 218°	98
	237–238°	102
	185–187°	102
	160–164°	102
	175–177°	102
	176°	101
	140°	101
	222°	101
	188–190°	9, 99, 106, 107, 108
	164–166°	107, 108
	154–155°	107, 108
	233°	107, 108
	268–269°	107, 108

Table 20. continued

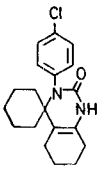
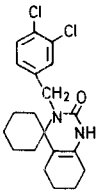
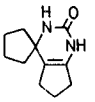
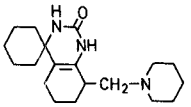
Compound	m.p.	References
	241–243°	107, 108
	243–244°	107, 108
	237–238°	106
	220–224°	99

Table 21. 2-Thiono-1,2,3,6-tetrahydropyrimidines

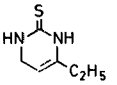
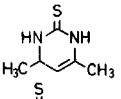
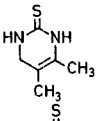
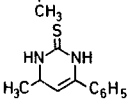
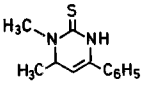
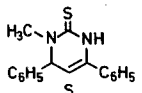
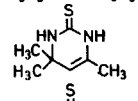
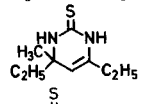
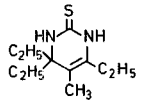
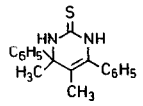
Compound	m.p.	References
	143°	93
	220°	93
	206°	93
	197°	92
	123°	92
	179°	92
	260–265° 281–282° 242°	109 110 112
	245°	110
	187–189°	109
	172°	109

Table 21. continued

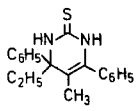
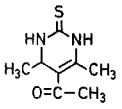
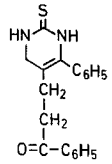
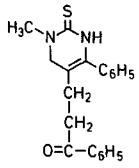
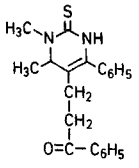
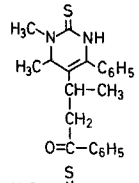
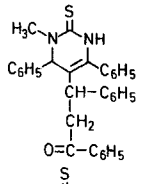
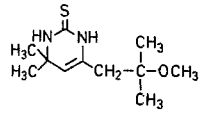
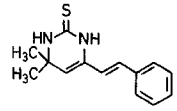
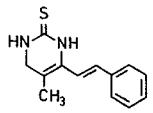
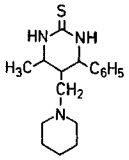
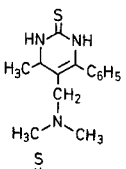
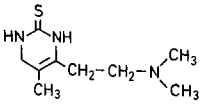
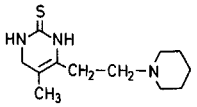
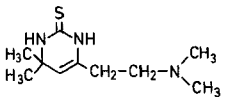
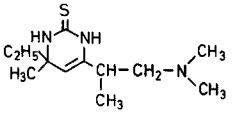
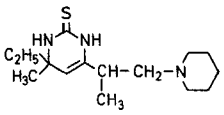
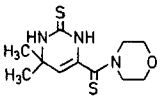
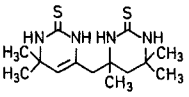
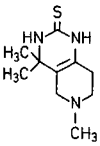
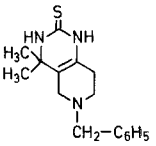
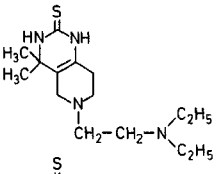
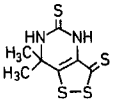
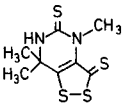
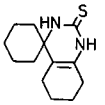
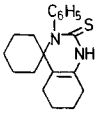
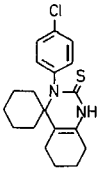
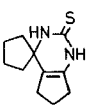
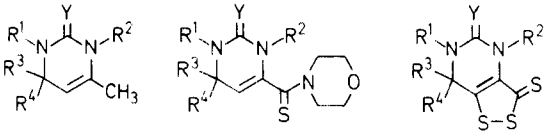
Compound	m.p.	References
	229–235°	109
	194°	91
	186°	92
	169°	92
	171°	92
	181°	92
	206°	92
	224°	88
	218°	93
	170°	93
	178°	92
	183°	92
	230°	93

Table 21. continued

Compound	m.p.	References
	155°	93
	135°	93
	115°	93
	119°	93
	244°	101
	227–228°	93
	238°	93
	246°	93
	182°	93
	289°	101
	217°	101
	274–276° 232–235° 277–278° 263°	107, 108 109 110 111
	195° (dec)	107, 108
	211° (dec)	107, 108
	263–264° 250–252°	110 109

6-Methyl-2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines (**153**) undergo the Willgerodt-Kindler reaction with sulfur and morpholin, whereby 2-oxo(thiono)-1,2,3,6-tetrahydropyrimidine-6-thiocarboxylic acid morpholides (**154**) are formed. Treatment of **153** with sulfur and dimethylformamide or tetramethylurea leads to 5-oxo-3-thiono- or 3,5-dithiono-4,5,6,7-tetrahydro-3*H*-1,2-dithiolo[4,3-*d*]pyrimidines (**155**).



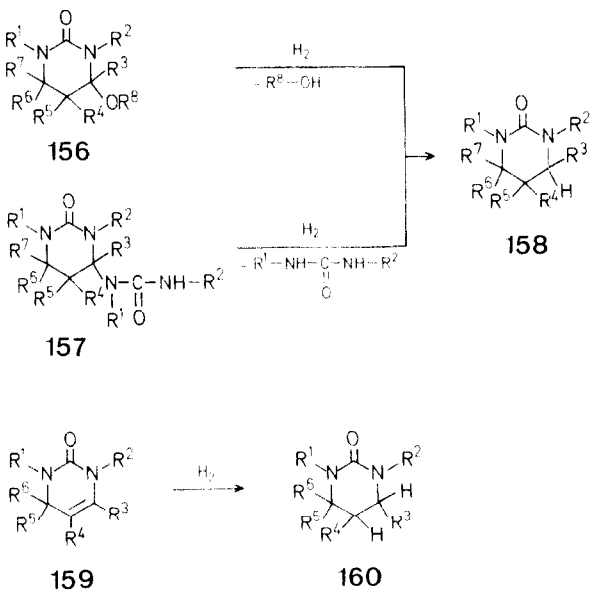
153 154 155

6,6-Dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-thiocarboxylic Acid Morpholide (**154**, $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$)[101]:
2-Oxo-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine (14 g), sulfur (4.6 g), and morpholine (25 g) are mixed, heated at 120° for 3–4 hr, and then heated to boiling. The mixture is poured into ethanol (25 mol) and water (75 ml) and the product allowed to crystallize overnight; yield: 18 g; m.p. 287° (from dimethylformamide).

7,7-Dimethyl-5-oxo-3-thiono-4,5,6,7-tetrahydro-3*H*-1,2-dithiolo-[4,3-*d*]pyrimidine (**155**, $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$)[101]:
2-Oxo-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine (14 g), sulfur (12.8 g), and tetramethylurea (15 g) are heated at 150° for 10–15 min; a vigorous reaction takes place. Ethanol (5 ml) is added to the warm mixture which is well mixed and then allowed to stand until crystallization is finished. The mixture is washed with a little carbon disulfide to remove excess sulfur and then recrystallized from ethanol; yield: 12 g; m.p. 176°.

2.5.1.7. Hydrogenation of 4-Hydroxy(alkoxy, ureido)-2-oxohexahydropyrimidines and 2-Oxo-tetrahydropyrimidines to 2-Oxohexahydropyrimidines

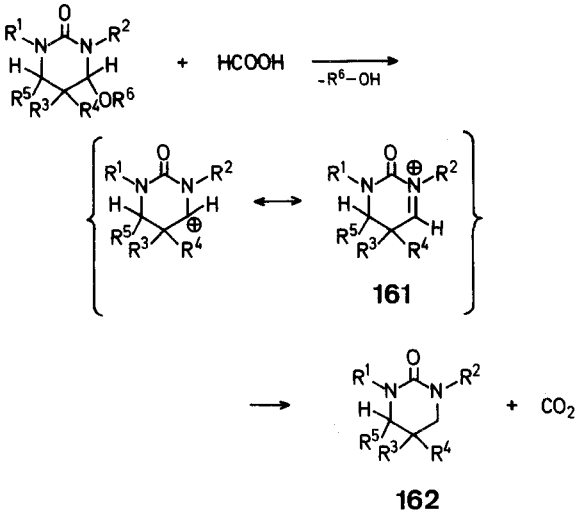
Catalytic hydrogenation converts 4-hydroxy-(alkoxy)-2-oxohexahydropyrimidines (**156**) as well as 2-oxo-4-ureidohexahydropyrimidines (**157**) and 2-oxo-1,2,3,6-tetrahydropyrimidines (**159**) to 2-oxohexahydropyrimidines (**158** and **160**)[3,9,22,72,89,91,99,100,113].



156 157 158 159 160

5,5-Dimethyl-6-isopropyl-2-oxohexahydropyrimidine[113]:
5,5-Dimethyl-4-hydroxy-6-isopropyl-2-oxohexahydropyrimidine (186 g), Raney-nickel (50 g), and methanol (1000 ml) are put into a stainless-steel autoclave. The autoclave is then charged to 200 atm with hydrogen and heated at 100°. The hydrogenation is completed after 1 hr. The Raney-nickel is filtered off and the filtrate evaporated to dryness. The product is recrystallized from methanol; yield: 163 g (96%).

4-Hydroxy(Alkoxy)-2-oxohexahydropyrimidines can also be reduced by formic acid at 80–100°[114]. The reaction probably proceeds via the corresponding α-ureidoalkyl-[carbenium-imonium] formate (**161**). After cleavage of carbon dioxide the hydride ion remaining from this formate can be α-ureidoalkylated.



161 162

2-Oxo-1,3,5,5-tetramethylhexahydropyrimidine[114]:
4-Hydroxy-2-oxo-1,3,5,5-tetramethylhexahydropyrimidine (172 g) is stirred with 100% formic acid (250 g). The resultant clear solution is heated with stirring at 80° for 3 hr and the carbon dioxide formed is lead off. The water formed and excess formic acid are removed under reduced pressure. The crude product is purified by fractional distillation; yield: 145 g (93%); b.p. 80–82°/0.2 torr.

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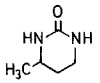
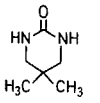
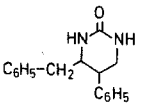
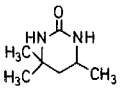
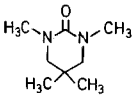
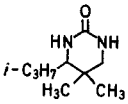
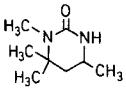
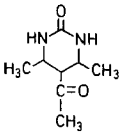
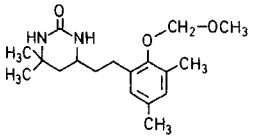
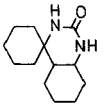
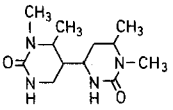
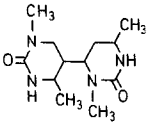
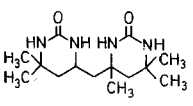
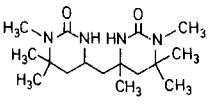
[106] A. F. McKay, C. Podesva, E. J. Tarlton, J. M. Billy, *Can. J. Chem.* **42**, 10 (1964).

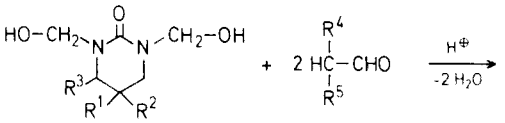
Some of the 2-oxo-hexahydropyrimidines obtainable by hydrogenation are listed in Table 22.

Table 22. 2-Oxohexahydropyrimidines

Compound	m.p.	References
	208–209°	113, 114
	219°	113, 114
	181°	22
	202°	22
	(b.p. 80–82°/ 0.2 torr)	113, 114
	155°	113, 114
	136°	89
	216°	91
	129°	100
	190°	99
	244°	22
	260°	72
	255°	89
	237°	89

[107] C. Podesva, E. J. Tarlton, A. F. McKay, *Can. J. Chem.* **40**, 1403 (1962).

Some 2-oxohexahydropyrimidines, in the form of their N,N′-bis-hydroxymethyl derivatives (**163**), have been used for crease-proofing cellulose-containing textiles[115]. Compounds **163** condense with CH-acidic aldehydes in the presence of acids to give 2-oxo-hexahydropyrimidine-1,3-bis-propanals (**164**)[9,94,116]. These condensations, however, are only successful with α,α-dialkylaldehydes.



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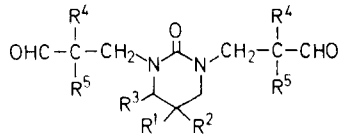
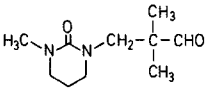
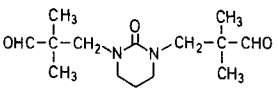
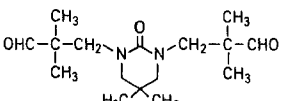
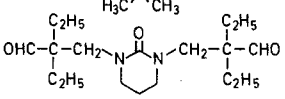


164

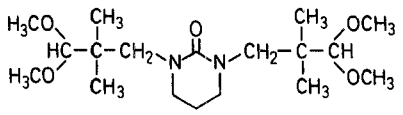
2-Oxohexahydropyrimidine-1,3-bis-[2,2-dimethylpropanal] (164, $R^1=R^2=R^3=H$, $R^4=R^5=CH_3$)[9,94,116]:

A mixture of 2-oxohexahydropyrimidine (600 g), 30% formaldehyde solution (1200 g), and isobutyraldehyde (900 g) is treated with 50% sulfuric acid (150 g) and then heated under reflux for 3 hr. The reflux temperature increases during the first 30 min from 60° to 95°. The reaction solution is then neutralized with sodium hydroxide solution and the product extracted with chloroform. The chloroform is evaporated off to leave the crude product which can be purified by distillation under high vacuum; yield: 1580 g (98%); b.p. 190–192°/0.5 torr.

Table 23. 2-Oxohexahydropyrimidine-1-propanals and 2-Oxohexahydropyrimidine-1,3-bis-propanals (**164**)[9,94,116]

Compound	Yield (%)	b.p./torr
	94	148–152°/2
	98	190–193°/0.5
	98	166–170°/0.5
	95	240–243°/0.5

Dialdehydes **164** are readily acetalated by alcohols in the presence of anhydrous acids. Thus, 1,3-bis-[3,3-dimethoxyneopentyl]-2-oxohexahydropyrimidine (**165**) or the cyclic acetal **166** (from the reaction of the aldehyde with 1,3-dihydroxy-2,2-dimethylpropane) can be obtained in practically quantitative yields[9,94]. The acetalation of compounds **164** with tetrakis-[hydroxymethyl]-methane (pentaerythritol) leads to linear polycycloureido-polyacetals (**167**)[9,94].



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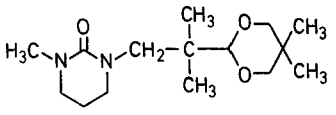

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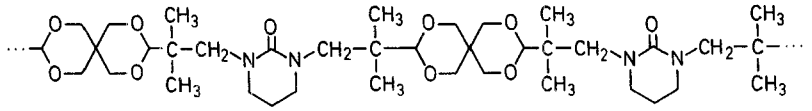
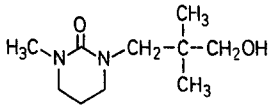


167

Catalytic hydrogenation of 2-oxohexahydropyrimidine-1-propanals and-1,3-bis-propanals (**164**) gives 1-(3-hydroxypropyl)- (**168**) and 1,3-bis-[3-hydroxypropyl]-2-oxohexahydropyrimidines (**169**)[9,94], respectively.



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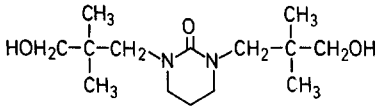
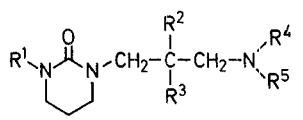


169

1,3-Bis-[2,2-dimethyl-3-hydroxypropyl]-2-oxohexahydropyrimidine (169)[9,94]:
A solution of 2-oxohexahydropyrimidine-1,3-bis-[2,2-dimethylpropanal] (268 g) in methanol (1000 ml) is hydrogenated in the presence of Raney nickel (25 g) in an autoclave with stirring. The initial pressure is 180 atm and the auctoclave is heated at 90°. A strong absorption of hydrogen occurs during heating and the hydrogen consumed is continuously replaced. The absorption of hydrogen is complete after ~2–3 hr. The mixture is allowed to cool and then filtered. The filtrate is evaporated under reduced pressure; yield 97%; m.p. 83–74°.

The reaction of compounds **163** with dicarboxylic acids or their esters leads as expected to polycycloureidoalkylene-polycarboxylic acid esters, which, however, show low thermal stability. Hydrolysis of these products provides a relatively simple route to univalent and multivalent amino-alcohols with primary and secondary amino groups which, in general, are not accessible or are obtainable only in low yields via the Mannich condensation.

1-(3-Aminopropyl)- and 1,3-bis-[3-aminopropyl]-2-oxohexahydropyrimidines (**170**) can be obtained in good yield by aminative hydrogenation of 2-oxohexahydropyrimidine-1-propanals[9,94,117]. The aldehyde group of 2-oxohexahydropyrimidine-1-propanals may be oxidized by oxygen or air in the presence of copper- or silver salts or by hydrogen peroxide, dichromate, or permanganate to give 3-(2-oxohexahydropyrimidin-1-yl)-propanoic acids[118] (**171**).



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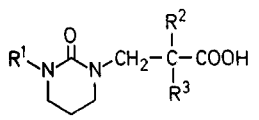
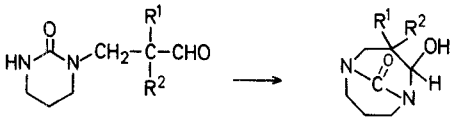


171

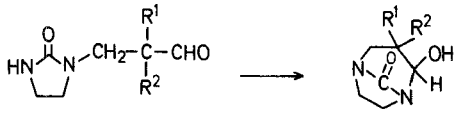
1,3-Bis-[3-amino-2,2-dimethylpropyl]-2-oxohexahydropyrimidine [170, $R^1 = H_2N—CH_2—C(CH_3)_2—CH_2—$, $R^2 = R^3 = CH_3$, $R^4 = R^5 = H$][117]:
2-Oxohexahydropyrimidine-1,3-bis-[2,2-dimethylpropanal] (804 g), methanol (1500 ml), and Raney-Nickel (100 g) in a stirring autoclave are purged with nitrogen and then treated with liquid ammonia (500 ml). Hydrogen is then passed into the mixture and the hydrogenation carried out at 150 atm at 80–90° for 4 hr. The mixture is allowed to cool, filtered, and distilled; yield: 770 g (95%); b.p. 152–156°/0.2 torr.

2-Oxohexahydropyrimidine-1,3-bis-[2,2-dimethylpropanoic acid] [171, $R^1 = HOOC—C(CH_3)_2—CH_2—$, $R^2 = R^3 = CH_3$][118]:
A stirred solution of sodium hydroxide (21 g) in water (800 ml) is warmed to 55°; copper(I) oxide (30 g) and a solution of silver nitrate (6 g) in water (50 ml) are added. Oxygen is passed through this mixture and 3-oxohexahydropyrimidine-1,3-bis-[2,2-dimethylpropanal] (161 g) and sodium hydroxide (42 g) in water (150 ml) are added. The temperature of the reaction mixture rises and is held at 63–65° by cooling. Finally, the mixture is maintained at this temperature with continuous passage of oxygen or air for 3 hr. The mixture is then filtered to remove the catalyst, the filtrate allowed to cool, and acidified to pH 3.5 with 20% hydrochloric acid. The filtrate is allowed to stand for several hours and then the product is isolated by filtration; yield: 160 g. Further 8 g are obtained by concentration of the mother liquor; total yield: 93.5%. The product is purified by recrystallization from ethyl acetate; m.p. 163–165°.

Condensation of 2-oxohexahydropyrimidine-1,3-bis-[propanoic acids] with alkylidenediamines, e.g. hexamethylenediamine, gives transparent, fibrous polycycloureidoalkylene-polyamides[9,94]. N-Monomethylol-or N-monalkoxymethylderivatives of 2-oxohexahydropyrimidines or 2-oxoimidazolidines condense in acid solution with α,α-dialkylaldehydes to give bicyclic ureas of the type 3,3-dialkyl-4-hydroxy(alkoxy)-9-oxo-1,5-diazabicyclo[3.3.1]nonane (**173**) or 2,2-dialkyl-3-hydroxy(alkoxy)-8-oxo-1,4-diazabicyclo[3.2.1]octane (**175**) via the intermediates **172** and **174**, respectively[9].



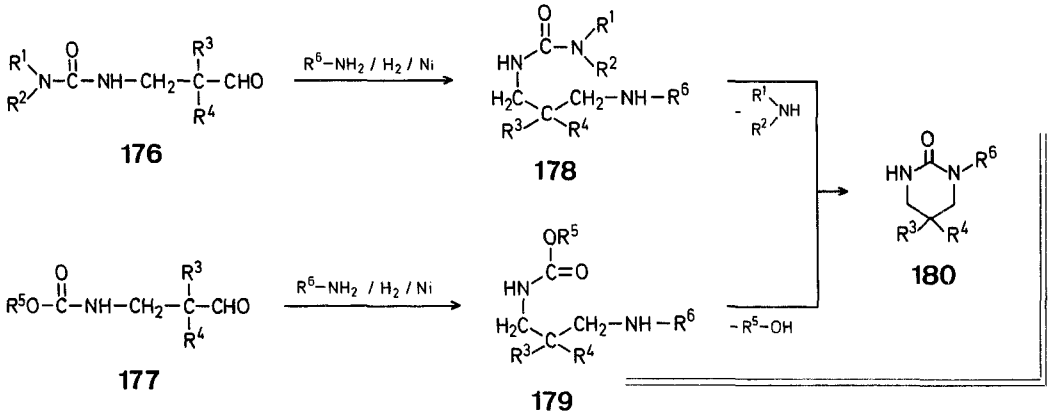
172 173



174 175

[108] C. Podesva, A. F. McKay, *U.S. Patent* 2948752 (1960), Monsanto Canada Ltd.; *C.A.* **55**, 16451 (1961).
[109] H. Hartmann, R. Mayer, *J. Prakt. Chem.* [4] **30**, 87 (1965).
[110] G. Jaenicke, *Z. Chem.* **6**, 109 (1966).

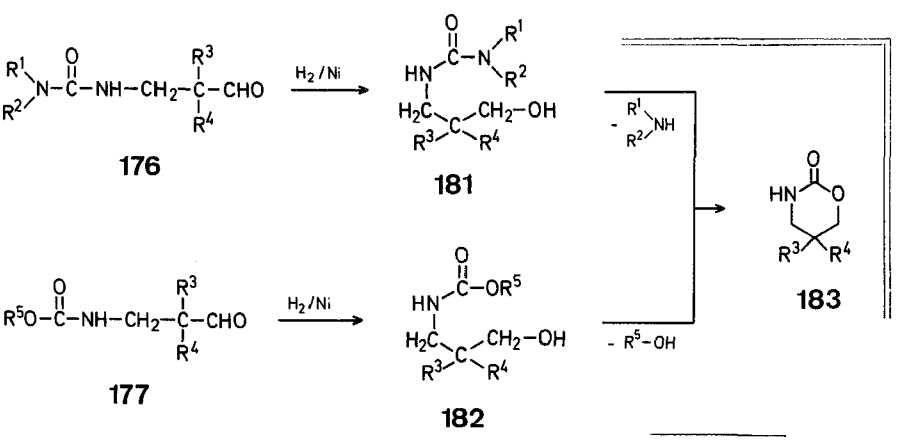
2-Oxohexahydropyrimidines of the type **180** are obtained by aminative hydrogenation of neopentanal derivatives and their homologues from unsymmetrical disubstituted ureas (**176**) or carbamates (**177**) with ammonia or primary amines via the intermediate corresponding neopentylamine derivative (**178** or **179**) under cleavage of dialkylamine or alcohol[9,119]. It may be assumed that these cyclization reactions proceed via an isocyanate intermediate.



5,5-Dimethyl-2-oxohexahydropyrimidine (**180**, $R^3=R^4=CH_3$, $R^6=H$)[119]:

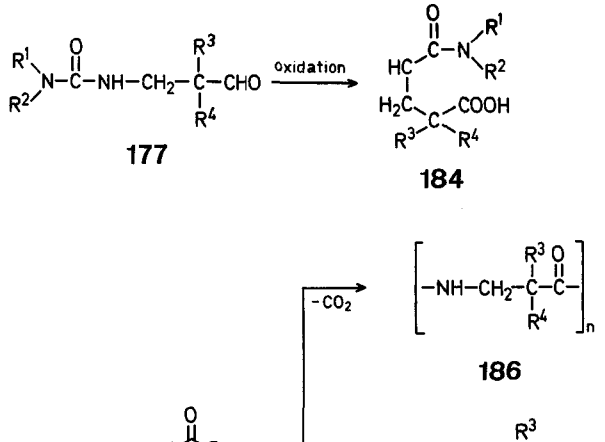
N',N'-Dimethylureidoneopentanal (344 g), methanol (800 ml), and Raney-nickel (50 g) are put into an autoclave and purged with nitrogen. Liquid ammonia (300 ml) and hydrogen to a pressure of 150 atm are then added. The reaction mixture is stirred and heated at 120° and the hydrogen consumed in the reaction continuously replaced. When the hydrogen absorption is finished, the reaction mixture is allowed to cool and then concentrated. The methanol, water, excess ammonia, and the dimethylamine formed by the cyclization are thus removed. The residue is recrystallized from water; yield: 232 g (91 %); m.p. 219.

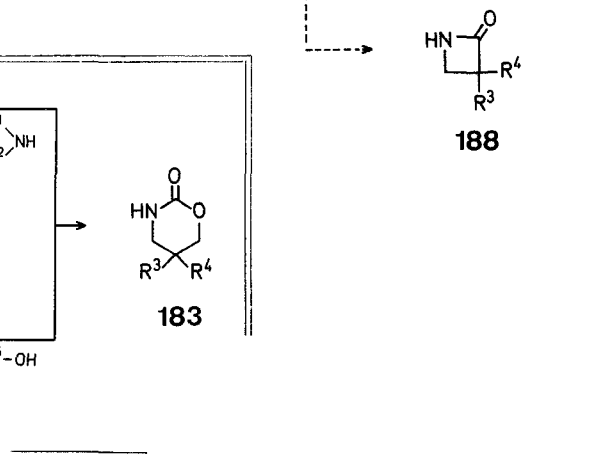
Neopentanals and their homologues derived from unsymmetrical dialkylureas (**176**) and carbamates (**177**) can be converted into the corresponding N-neopentyl alcohols (**181** or **182**) by catalytic hydrogenation. These compounds, on warming to 120–140°, cyclize with cleavage of dialkylamine or alcohol to give hydrogenated 2-oxotetrahydro-1,3-oxazines (**183**)[9,120].



5,5-Dimethyl-2-oxotetrahydro-1,3-oxazine (**183**, $R^3=R^4=CH_3$)[120]:

N',N'-Dimethylureidoneopentanal (172 g), methanol (300 ml), and Raney-nickel (40 g) were put into an autoclave. The apparatus was flushed with nitrogen and then charged with hydrogen to a pressure of 150 atm. The mixture was then stirred and warmed at 150°; the hydrogen consumed during the reaction was replaced continually. When the absorption of hydrogen had finished, the reaction mixture was cooled, filtered and concentrated. Methanol and the dimethylamine released by the cyclization were thus removed and the product remained as residue; yield: 110 g (85 %); m.p. 112–113°; b.p. 149–151°/0.1 torr.



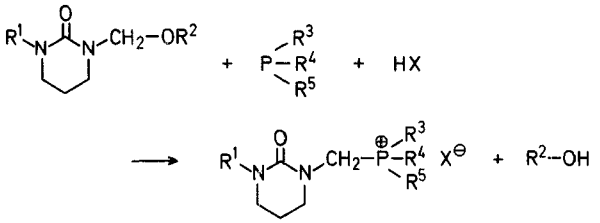


[111] A. K. Bhattacharya, *Indian J. Chem.* **5**, 62 (1967).
[112] R. Zimmermann, *Angew. Chem.* **75**, 1025 (1963).
[113] H. Petersen, *German Patent (DOS.)* 1545613 (1965), *Brit. Patent* 1173432 (1966), BASF.
[114] H. Petersen, *German Patent (DOS.)* 1545614 (1965), BASF.

Oxidation of N',N'-dialkylureidoneopentanals (**176**) and their homologs leads to N',N'-dialkylureidopivalic acids (**184**) or their homologs, respectively, which are cyclized at 100° with elimination of dialkylamine to give 5,5-dialkyl-2,4-dioxotetrahydro-1,3-oxazines (**185**)[9,94]. Compounds **185** are thermally unstable and are converted into polyamides (**186**) with elimination of carbon monoxide[9,94] at temperatures above 120°.

As well as polyamides, small quantities of 3,3-dialkyl-2-oxoazetidines (**188**) are formed by thermal cracking. These β-lactams are valuable intermediates for the preparation of polyamides. Hydrolytic cleavage gives β-aminocarboxylic acids (**187**)[9,94].

The N-hydroxymethyl and N-alkoxymethyl derivatives of 2-oxohexahydropyrimidines can be converted into 1-trialkyl(aryl)phosphoniomethyl- and 1,3-bis-[trialkyl(aryl)phosphoniomethyl]-2-oxohexahydropyrimidine salts (**189**) by treatment with trialkyl- or triarylphosphines in the presence of at least one equivalent of acid[121].

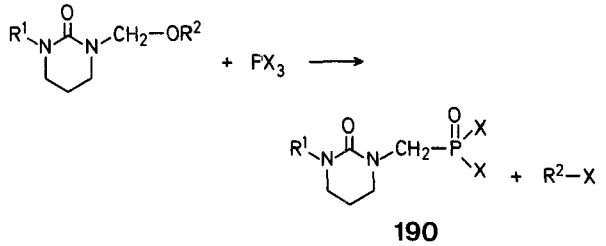


189

1,3-Bis-[triphenylphosphoniomethyl]-2-oxohexahydropyrimidine Bromide [**189**, $R^1=(C_6H_5)_3\overset{\oplus}{P}-CH_2-$, $R^3=R^4=R^5=C_6H_5$, $X=Br$][16,121]:

1,3-Bis-[methoxymethyl]-2-oxohexahydropyrimidine (37.6 g) in methanol (80 ml) is added to a solution of triphenylphosphine (104.8 g) in methanol (800 ml) and 48% hydrobromic acid (100 g) with stirring. The reaction mixture is heated at 64–65° for 3 hr and then cooled to 0°, whereby the product crystallizes out; yield: 149 g (92%); m.p. 148°.

N-Hydroxymethyl- and N-alkoxymethyl-2-oxohexahydropyrimidines react with phosphorus(III) halides to give 1,3-bis-[dichlorophosphonylmethyl]-2-oxohexahydropyrimidines[122] (**190**).



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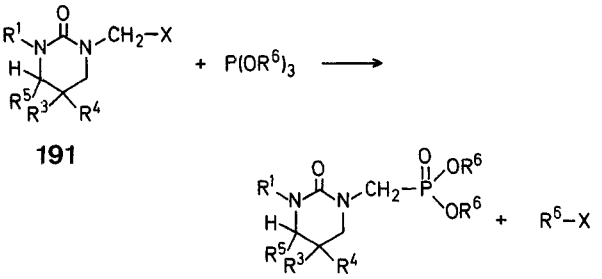
1,3-Bis-[dichlorophosphonylmethyl]-2-oxohexahydropyrimidine (**190**, $R^1=-CH_2-POCl_2$, $X=Cl$)[16,122]:

1,3-Bis-[methoxymethyl]-2-oxohexahydropyrimidine (94 g) is dissolved in ether (200 ml). Phosphorus(III) chloride (138 g) is added in portions with stirring, the temperature being held at 20° by cooling. The mixture is stirred for 1 hr, the lower phase separated, and the ether distilled off from the lower phase. The syrupy residue is mixed with trichloroethane (50 ml) and allowed to stand at 0° for several days. The crystalline product is isolated by filtration and dried with strict exclusion of moisture; yield: 102 g (56%); m.p. 150–160° (dec).

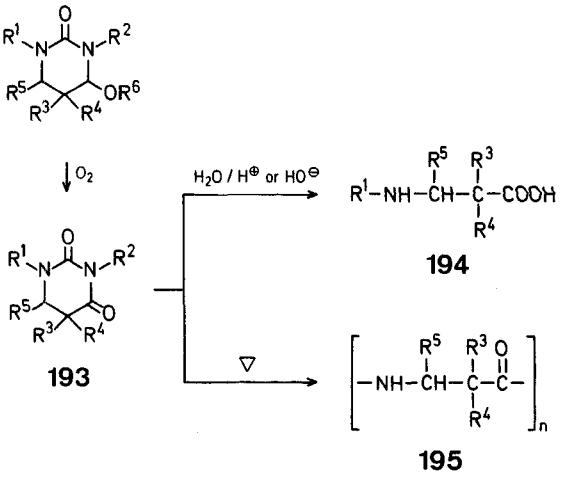
N-(O,O)-Dialkylphosphonomethyl)-2-oxohexahydropyrimidines (**192**) can be prepared either by reaction of **190** with alcohols or by condensation of N-halomethyl-2-oxohexahydropyrimidines (**191**) with trialkyl phosphites[16].



191 **192**

2.5.1.8. Oxidation of 4-Hydroxy(Alkoxy)-2-oxohexahydropyrimidines to 2,4-Dioxohexahydropyrimidines

4-Hydroxy(alkoxy)-2-oxohexahydropyrimidines can be oxidized with hydrogen peroxide or oxygen to give 2,4-dioxohexahydropyrimidines (**193**), which react with water in the presence of acids or alkali metal alkoxides to give β-aminoacids (**194**) or, on heating with exclusion of water, give polyamides (**195**)[9,94,123].



193 **194** **195**

Thus, a technically simple route for the preparation of aminopivalic acid has become possible. Firstly, 5,5-dimethyl-4-hydroxy-2-oxohexahydropyrimidine is prepared from the cheap starting materials urea, formaldehyde, and isobutyraldehyde. This cyclic urea is then oxidized to 5,5-dimethyl-2,4-dioxohexahydropyrimidine, which is finally subjected to a hydrolytic cleavage.

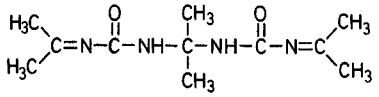
5,5-Dimethyl-2,4-dioxohexahydropyrimidine (**193**, $R^1=R^2=R^5=H$, $R^3=R^4=CH_3$)[123]:

5,5-Dimethyl-4-hydroxy-2-oxohexahydropyrimidine (44 g) is dissolved in hot water (500 ml). 30% Hydrogen peroxide solution (120 g) is added in portions to the warm (60–70°) solution within 90 min. The reaction mixture is heated at 80–90° for 12 hr and then allowed to cool. The product is then isolated by filtration. Concentration of the mother liquor under reduced pressure gives a further 10.5 g of product; total yield: 102.5 g (72%); m.p. 248–250° (from water or acetonitrile.)

2.5.2. Cyclocondensations with CH-Acidic Ketones

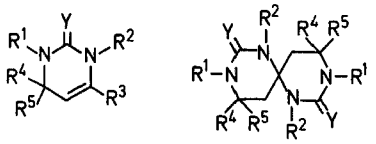
Ketones with labile hydrogen atoms in the α-positions to the carbonyl group can, as with CH-acidic aldehydes, simultaneously react as a carbonyl compound and as a nucleophilic reaction partner with ureas to give mono-, di-, and polycyclic heterocycles according to the α-ureidoalkylation principle. As most ketones have more than one labile hydrogen atom it is often difficult to predict which position on the ketone will undergo the α-ureidoalkylation.

One of the earliest reactions of a ketone with urea was that by Weinschenk[124] who allowed urea to react with acetone in the presence of hydrogen chloride. This reaction produced a crystalline compound for which elemental analysis indicated a constitution of two molecules of urea to three molecules of acetone. The structure suggested by Weinschenk (**196**) consisted of three separate acetone groups joined by urea bridges.



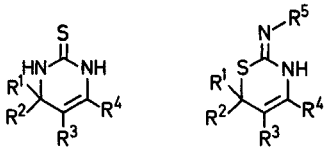
196

Recent investigations have shown that the condensation of urea or thiourea with dialkyl ketones produces heterocycles of the type 2-oxo(thiono)-hexahydropyrimidine-⟨4-spiro-4⟩-2-oxo(thiono)-hexahydropyrimidine (**198**) which will be discussed in more detail later[3,9,88,94,105,125]. These condensations proceed via the intermediate 4-alkyl-2-oxo(thiono)-1,2,3,4-tetrahydropyrimidines (**197**)[9,105].



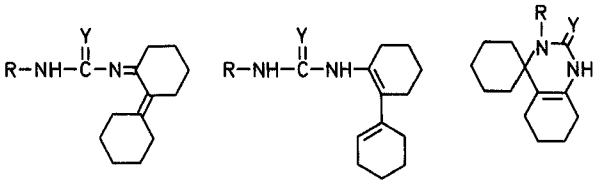
197 **198**

Heterocycles of the type **197** can be prepared in good yield by the reaction of urea or thiourea with α,β-unsaturated ketones according to the principle of a vinylogous ureidoalkylation[104,105,109,110,112]. Thiourea reacts with ketones to give 2-thiono-1,2,3,6-tetrahydropyrimidines (**199**) as well as 2-imino-2,3-dihydro-6*H*-1,3-thiazines[110] (**200**).



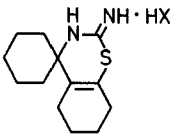
199 **200**

Contrary to the reports of Podesva[107,108], the condensations of cyclohexanone with urea, thiourea, or suitable derivatives in the presence of acids do not give 1-(2-cyclohexylidenecyclohexylidene)-ureas or thioureas (**201**) or 1-(2-cyclohexenecyclohexenyl)-ureas or thioureas (**202**)[107] but cyclohexane-⟨spiro-4⟩-2-oxo(thiono-1,2,3,4,5,6,7,8-octahydroquinazolines (**203**)[9,99,105,109,110].



201 **202** **203**

The reaction of thiourea with cyclohexanone in the presence of hydrogen chloride leads to the formation of cyclohexane-⟨spiro-4⟩-2-iminooctahydrobenzo-1,3-thiazine hydrochlorides[111] (**204**).



204

Other cycloalkanones react analogously.

2-Oxo-1,3,4,6,6-pentamethyltetrahydropyrimidine (**197**, $R^1-R^5 = CH_3$, Y = O)[105]:
Hydrogen chloride (27 g) is conducted at 30° into a suspension of N,N'-dimethylurea (176 g) in mesityl oxide (2-methyl-4-oxo-2-pentene, 270 g). The mixture is warmed at 40° for 1 hr. The resultant brown solution is allowed to cool to room temperature, poured into water (400 ml), and neutralized with aqueous sodium hydroxide. The upper layer is separated and distilled under vacuum. The main fraction distils at b.p. 84–86°/0.7 torr.

Cyclohexane-⟨spiro-4⟩-2-thiono-1,2,3,4,5,6,7,8-octahydroquinazoline (**203**, R = H, Y = S)[107,108,110]:
A mixture of thiourea (72 g), cyclohexanone (98 g), and conc. hydrochloric acid (100 g) is stirred at reflux temperature for 45 min and then allowed to stand at room temperature for 1 day. The crystalline product is isolated by filtration, washed with ethanol, and recrystallized from chloroform; yield: 67%; m.p. 274–276°.

Some of the 2-oxo- and 2-thionotetrahydropyrimidines obtainable in this way are listed in Tables 20 and 21. Some of the 2-imino-2,3-dihydro-6*H*-1,3-thiazine hydrochlorides (**200**) obtainable by condensation of ketones with thioureas in dry ethanol in the presence of hydrochloric acid are listed in Table 24.

2-Phenylamino-4,6,6-trimethyl-2,3-dihydro-6*H*-1,3-thiazine Hydrochloride (**200**, $R^3 = H$, $R^1 = R^2 = R^4 = CH_3$, $R^5 = C_6H_5$)[126]:
Dry hydrogen chloride is passed through a solution of phenylthiourea (5 g) in acetone (100 ml) for 15 min. The solution is then filtered, concentrated under reduced pressure, and the residue poured into stirred, dry toluene. The product crystallizes out and may be recrystallized from dilute hydrochloric acid: m.p. 105°.

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[115] W. Rümens, G. Burkhardt, H. Petersen, W. Rüttiger, *Textilveredlung* **5**, 334 (1970); **6**, 16 (1971).

[116] H. Petersen, *German Patent (DOS.)* 1670133 (1966), Brit. *Patent* 1191869 (1967), BASF; *C.A.* **73**, 35391 (1970).
A. Zeidler, A. Fischer, G. Bürger, *U.S. Patent* 3551429 (1970) ≡ *South African Patent* 68/02008, BASF; *C.A.* **70**, 96818 (1969).

[117] H. Petersen, *German Patent (DOS.)* 1670259 (1967), *Brit. Patent* 1225407 (1968), BASF.

Table 24. 2-Imino-2,3-dihydro-6*H*-1,3-thiazines

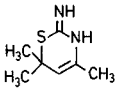
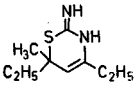
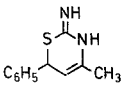
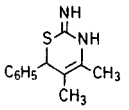
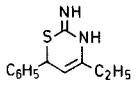
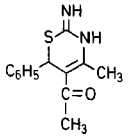
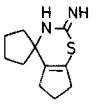
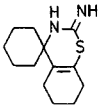
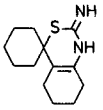
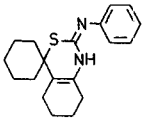
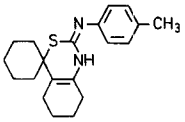
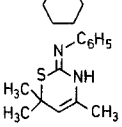
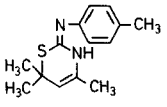
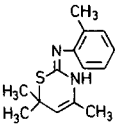
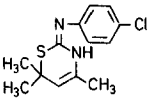
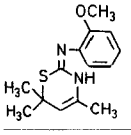
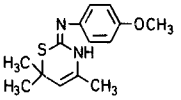
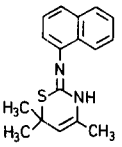
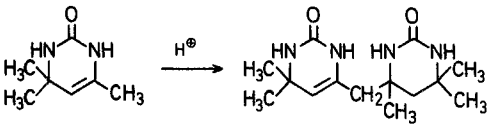
Compound	m.p. of Hydrochloride	m.p. of Free Base	References
	208–209° 199–200°	76–77.5°	110, 1126 112
	201–202°	49–51°	110
	124°		112
	235–236°		112
	228°		112
	150°	228°	112
	200–202°	97–99°	110
	246–248°	197–199°	110
	243°	194° (dec)	111
	208°	196°	111
	186°	194°	111
	105°	152°	126
	135°	149°	126
	115°	131°	126
	110°	168°	126
	90°	127°	126

Table 24. continued

Compound	m.p. of Hydrochloride	m.p. of Free Base	References
	119°	150°	126
	127°	187°	126

Some 4-alkyl-2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines show a tendency to dimerize in the presence of acids. The CH-acidic alkyl group in position 4 forms a bond to the C=C double bond of a second 4-alkyl-2-oxo(thiono)-tetrahydropyrimidine to produce a 2-oxo(thiono)-1,2,3,6-tetrahydropyrimidin-4-yl-[2-oxo(thiono)-hexahydropyrimidin-4-yl]-methane[89] (e.g. **205**).

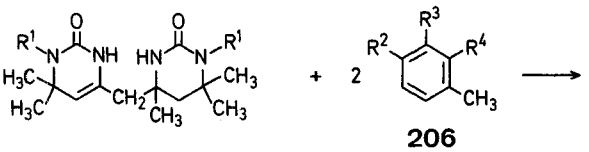


205

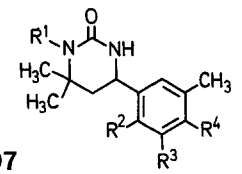
Table 20 contains some of these dimerisation products.

6,6-Dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl-[2-oxo-4,6,6-trimethylhexahydropyrimidin-4-yl]-methane (205)[89]: 2-Oxo-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine (0.5 g), conc. hydrochloric acid (3 drops), and 70% ethanol (5 ml) are mixed and allowed to stand at 50° for 40 hr. The product crystallizes out; yield: 0.49 g; m.p. 292° (from 50% ethanol).

Compounds of the type **205** revert partially to the monomeric form in aqueous-alcoholic hydrochloric acid. Phenols (**206**) react with compounds **205** to give 4-hydroxyphenyl-2-oxohexahydropyrimidines (**206**) in quantitative yields[89] (see Table 17).

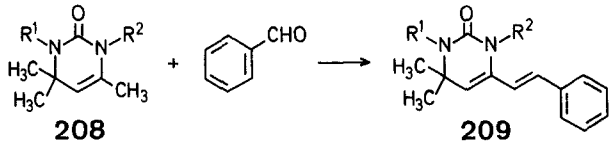


206



207

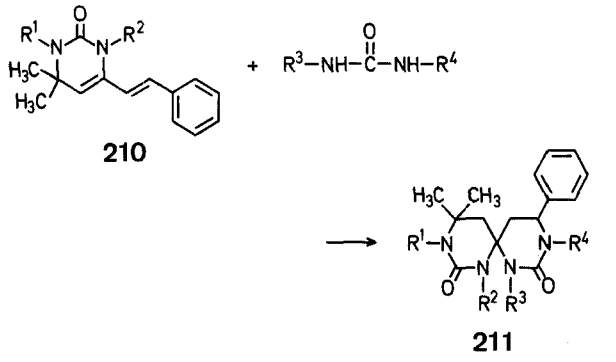
In the presence of alkali, 2-oxo-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidines (**208**) condense with benzaldehyde to form 6,6-dimethyl-2-oxo-4-styryl-1,2,3,6-tetrahydropyrimidines[89] (**209**).



208 209

6,6-Dimethyl-2-oxo-4-styryl-1,2,3,6-tetrahydropyrimidine (209, $R^1=R^2=H$)[89]:
20% aqueous potassium hydroxide (5 ml) is added to a mixture of 2-oxo-4,6,6-trimethyl-tetrahydropyrimidine (1 g), benzaldehyde (2 g), and 70% ethanol (5 ml). The mixture is allowed to stand at room temperature for several hours and the reaction product crystallizes out; yield: 1.8 g; m.p. 254° (from chlorobenzene).

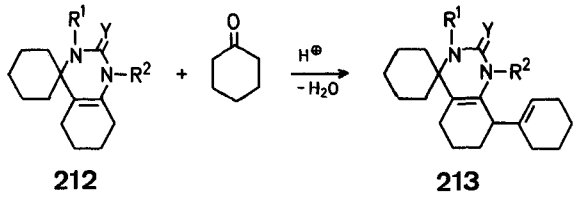
Urea adds to compounds **210** in acid media to produce 6,6-dimethyl-2-oxohexahydropyrimidine-⟨4-spiro-4⟩-2-oxo-6-phenylhexahydropyrimidines[89] (**211**).



210 211

6,6-Dimethyl-2-oxohexahydropyrimidine-⟨4-spiro-4⟩-2-oxo-6-phenylhexahydropyrimidine (211, $R^1-R^4=H$)[89]:
6,6-Dimethyl-2-oxo-4-styryl-1,2,3,6-tetrahydropyrimidine (0.8 g), urea (0.5 g), ethanol (5 ml), and conc. hydrochloric acid (5 drops) are mixed and allowed to stand at 50° for 15 hr. The resultant crystalline product is isolated by filtration; m.p. 268° (from 70% ethanol).

The spirocyclic urea derivatives **212** as well as the 4-methyl-2-oxo-1,2,3,6-tetrahydropyrimidines **208** contain CH-acidic groups and can therefore react with suitable aldehydes or ketones. Thus, for example compounds **212** condense with cyclohexanone to give the cyclohexenyl derivatives **213**[9,105].

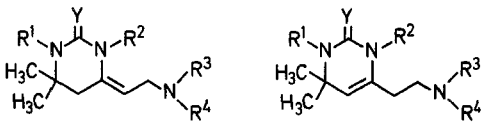


212 213

Polycyclic heterocycles of the type **213** can also be obtained by acid condensation of cyclohexanone with urea, thiourea, or suitable derivatives[9,105].

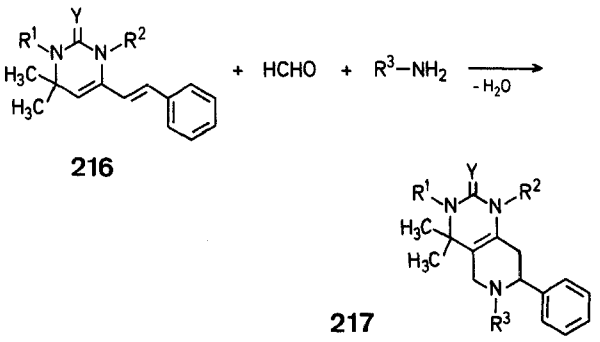
Cyclohexane-⟨spiro-4⟩-8-(cyclohexen-1-yl)-2-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (213, $R^1=R^2=H$, $Y=O$)[9,105]:
Hydrogen chloride (100 g) is passed into a mixture of cyclohexanone (441 g, 4.5 mol) and urea (90 g, 1.5 mol) in a flask fitted with a reflux condenser and a stirrer. The temperature is maintained at 70–74° using external cooling. After the addition of the gas, the mixture is heated at 70–75° for 3 hr, during which time the color of the solution changes from yellow to light brown. The mixture is then allowed to stand for 24 hr whereby two phases form. The mixture is neutralized with conc. sodium hydroxide solution. The reaction product precipitates out and crystallizes after a short time; yield: 390 g.

4-Alkyl-2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines react with formaldehyde and primary or secondary amines to give Mannich bases in the form of 4-(2-dialkylaminoethylidene)-2-oxo(thiono)-hexahydropyrimidines (**214**) or 4-(2-dialkylaminoethyl)-2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines (**215**)[98].



214 215

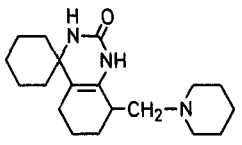
α-Aminoalkylation of the 2-oxo(thiono)-4-styryl-1,2,3,6-tetrahydropyrimidines **216** results in the formation of 6-alkyl-7-aryl-2-oxo(thiono)-1,2,3,4,5,6,7,8-octahydropyrido[4,3-*d*]pyrimidines[98] (**217**).



216 217

2-Oxo-7-phenyl-3,4,4,6-tetramethyl-1,2,3,4,5,6,7,8-octahydropyrido[4,3-*d*]pyrimidine (217, $R^1=R^3=CH_3$, $R^2=H$, $Y=O$)[89]:
A mixture of 2-oxo-4-styryl-1,6,6-trimethyl-tetrahydropyrimidine (2 g), methylamine hydrochloride (0.6 g), paraformaldehyde (0.27 g), and ethanol (30 ml) is heated under reflux for 3 hr. The reaction mixture is then concentrated under vacuum and the residue recrystallized from isopropanol; m.p. of hydrochloride: 218°.

Compounds **212** can likewise be aminomethylated to give Mannich products of the type **218**.



218

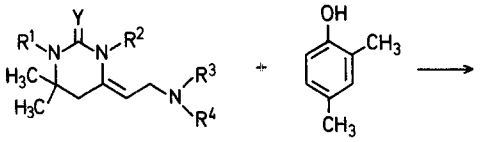
Cyclohexane-⟨spiro-4⟩-2-oxo-8-piperidinomethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (218)[99]:
Cyclohexane-⟨spiro-4⟩-2-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (1 g) is heated on a water bath with paraformaldehyde (0.15 g), piperidine hydrochloride (0.55 g), and ethanol (20 ml) for 3 hr. The product is recrystallized from acetone/water; m.p. of hydrochloride: 198°; m.p. of free base: 220–224° (from ethanol).

[118] H. Petersen, K. Renner, *German Patent (DOS.)* 1670263 (1967), *Brit. Patent* 1228408 (1968), BASF.

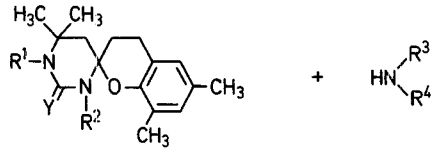
[119] H. Petersen, *German Patent (DOS.)* 1670241 (1967), *U.S. Patent* 3551425 (1970), *Brit. Patent* 1226623 (1971), BASF.

Some examples of the aminomethylation of CH-acidic 2-oxotetrahydropyrimidines are listed in Table 20.

4-(2-Dialkylaminoethylidene-2-oxo(thiono)-hexahydropyrimidines (**214**) condense with CH-acidic compounds under C-alkylation. With 2,4-dimethylphenol (**219**), 2-oxo(thiono)-hexahydropyrimidine-⟨4-spiro-2⟩-6,8-dimethylchromans (**220**) are obtained[98].



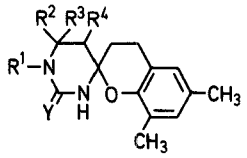
214 **219**



220

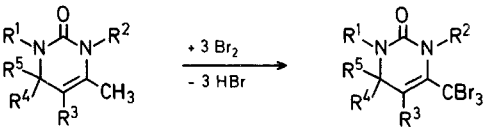
2-Oxo-1,6,6-trimethylhexahydropyrimidine-⟨4-spiro-2-⟩-6,8-dimethylchroman (220, $R^1 = CH_3$, $R^2 = H$, $Y = O$)[98]:
A mixture of 4-(2-dimethylaminoethylidene)-2-oxo-1,6,6-trimethylhexahydropyrimidine (0.4 g) and 2,4-dimethylphenol is heated at 140° for 4 hr. Excess 2,4-dimethylphenol is removed by steam distillation and the product is recrystallized from ethanol; m.p. 221°.

Table 25. 2-Oxo(thiono)-hexahydropyrimidine-⟨4-spiro-2⟩-chromans



R^1	R^2	R^3	R^4	Y	m.p.	References
CH_3	CH_3	CH_3	H	O	221°	98
H	CH_3	CH_3	H	O	212°	100
H	CH_3	CH_3	H	S	247°	93
H	H	H	CH_3	S	225°	93

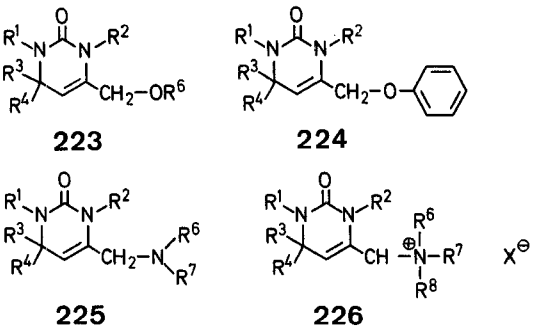
Bromination of 4-methyl-2-oxotetrahydropyrimidines (**221**) proceeds via substitution at the methyl group in position 4 to form the tribromomethyltetrahydropyrimidines[90] (**222**). Some brominated and iodinated 4-methyl-2-oxotetrahydropyrimidines are listed in Table 20.



221 **222**

6,6-Dimethyl-2-oxo-4-tribromomethyl-1,2,3,6-tetrahydropyrimidine[90]:
2-Oxo-4,6,6-trimethyl-1,2,3,6-tetrahydropyrimidine (0.01 mol) is dissolved or suspended in chloroform (20 ml). A solution of bromine (0.03 mol) in chloroform is added dropwise with stirring at 4°. The mixture is allowed to stand for 12 hr and then concentrated to a thick syrupy consistency. After being mixed with ethanol, the product crystallizes.

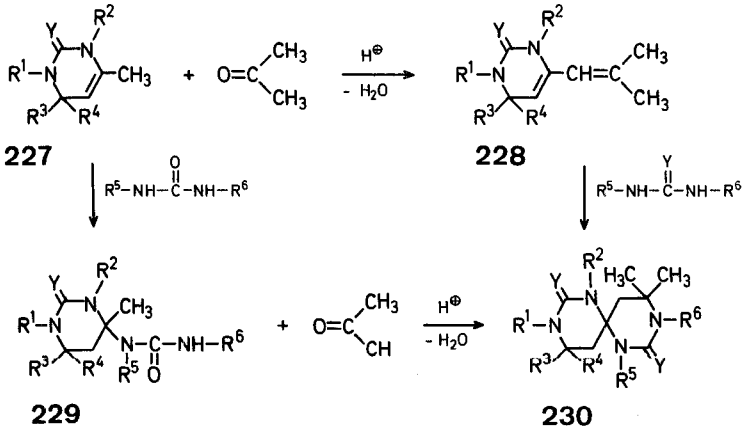
4-Bromomethyl-2-oxotetrahydropyrimidines react with alkali metal alkoxides to give 4-alkoxymethyl-2-oxotetrahydropyrimidines (**223**), with phenoxides to give 2-oxo-4-phenoxymethyltetrahydropyrimidines (**224**), with secondary amines to give 4-aminomethyl-2-oxotetrahydropyrimidines (**225**), and with tertiary amines to give the quarternary compounds **226**[90].



223 **224**

225 **226**

4-Methyl-2-oxo(thiono)-tetrahydropyrimidines (**227**) can undergo condensation with acetone in the presence of acids to form 4-isobutylidene-2-oxo-(thiono)-tetrahydropyrimidines (**228**) which, on reaction with ureas or thioureas, give 2-oxo(thiono)-tetrahydropyrimidine-⟨4-spiro-4⟩-2-oxo(thiono)-tetrahydropyrimidines (**230**). Addition of ureas or thioureas to **227** results in the formation of 4-methyl-2-oxo(thiono)-4-ureido(thioureido)-hexahydropyrimidines (**229**) which also give **230** on acidic condensation with acetone[105].



227 **228**

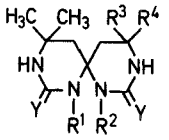
229 **230**

Spiro compound **230** ($R^1=R^2=R^5=R^6=H$, $R^3=R^4=CH_3$, $Y=O$) is also accessible by the direct condensation of urea with acetone in the presence of hydrogen chloride[124]. The addition product from 2 mol of urea and 1 mol of phorone is identical to that obtained from acetone and urea and can thus be used as evidence for the constitution[3,9,88,105].

6,6-Dimethyl-2-oxohexahydropyrimidine-⟨4-spiro-4⟩-6,6-dimethyl-2-oxohexahydropyrimidine (**230**, $R^1=R^2=R^5=R^6=H$, $R^3=R^4=CH_3$, $Y=O$)[124]:

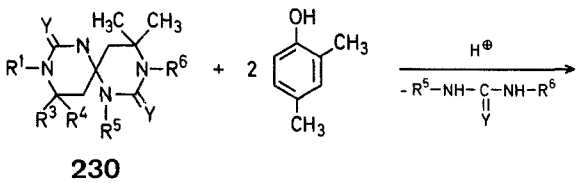
Urea (300 g) is suspended in acetone (1.5 l). With stirring and cooling, a strong current of hydrogen chloride is passed through the solution, the temperature being kept below 30°. The urea is rapidly dissolved. The reaction mixture is then warmed at 55–60° for 6 hr. The product begins to precipitate out after 30 min. The mixture is allowed to stand for 24 hr, the product isolated by filtration, and washed with acid-free water; yield: 237 g. Recrystallization from water gives the hydrate; m.p. 266°.

Table 26. 2-Oxo(thiono)-hexahydropyrimidine-⟨4-spiro-4⟩-2-oxo(thiono)-hexahydropyrimidines

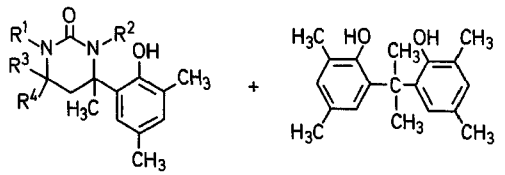


R^1	R^2	R^3	R^4	Y	m.p.	References
H	H	CH_3	CH_3	O	252°	3, 9, 88, 94, 105
CH_3	CH_3	CH_3	CH_3	O	301°	88
H	H	CH_3	CH_3	S	241°	88
CH_3	CH_3	CH_3	CH_3	S	252°	88
H	H	H	C_6H_5	O	268°	89

Compounds **230** are cleaved by treatment with 2,4- or 2,6-dimethylphenol in acid media to form 4-hydroxyphenyl-2-oxo(thiono)-hexahydropyrimidines (**231**) and 2,2-bis-[hydroxyphenyl]-propanes (**232**)[88].

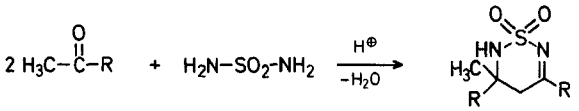


230



231 **232**

Sulfamide reacts with monoketones in the presence of hydrochloric acid to yield 5,6-dihydro-4*H*-1,2,6-thiadiazine 1,1-dioxides (**233**)[127].



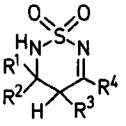
233

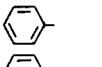
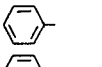
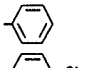
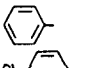
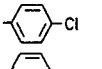
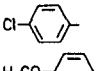
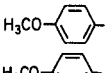
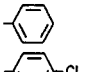
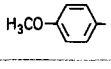
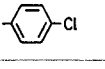
Compounds **233** can also be prepared from the reaction of sulfamide with α,β-unsaturated ketones according to the principle of a vinylogous ureidoalkylation[128].

3,5,5-Trimethyl-5,6-dihydro-4*H*-1,2,6-thiadiazine 1,1-Dioxide (**233**, $R=CH_3$)[127]:

Hydrogen chloride is passed through a mixture of sulfamide (5 g, 0.052 mol) and acetone (30 ml, 0.41 mol) for 5 min. The mixture is then heated at 70° for 6 hr. Excess acetone is distilled off in vacuum and the residue extracted with chloroform. The insoluble sulfamide is isolated by filtration and the filtrate concentrated. The residue is recrystallized from acetone/petroleum ether (80–110°); yield: 66%; m.p. 142°.

Table 27. 5,6-Dihydro-4*H*-1,2,6-thiadiazine 1,1-Dioxides



R^1	R^2	R^3	R^4	m.p.	References
CH_3	CH_3	H	CH_3	142°	127, 128
CH_3	C_2H_5	H	C_2H_5	130°	127
CH_3	C_2H_5	CH_3	CH_3	158°	127
C_2H_5	C_2H_5	CH_3	C_2H_5	117°	127
CH_3	n-C_3H_7	H	n-C_3H_7	78°	127
H		H		164–165°	128
CH_3		H		137°	127
H		H		201°	128
H		H		212–213°	128
H		H		199–200°	128
H		H		210°	128

[120] H. Petersen, *German Patent (DOS.)* 1670245 (1967), BASF.

[121] H. Petersen, W. Reuther, *Austrian Patent* 289838 (1969), *German Patent (DOS.)* 1768276 (1968), BASF; *C.A.* **76**, 153923 (1972).

[122] H. Petersen, *German Patent (DOS.)* 1817337 (1968), BASF; *C.A.* **73**, 88019 (1970).

[123] F. Merger, H. Petersen, *German Patent (DOS.)* 1670232 (1967), *Brit. Patent* 1216760 (1970), BASF.

[124] A. Weinschenk, *Ber. dtsch. chem. Ges.* **34**, 2185 (1901).

[125] H. Hatt, A. Triffet, *Chem. Commun.* **1965**, 439.

[126] S. N. Pandeya, G. V. Nair, *Indian J. Chem.* **3**, 165 (1965).

[127] A. Ouchi, T. Moeller, *J. Org. Chem.* **29**, 1865 (1964).

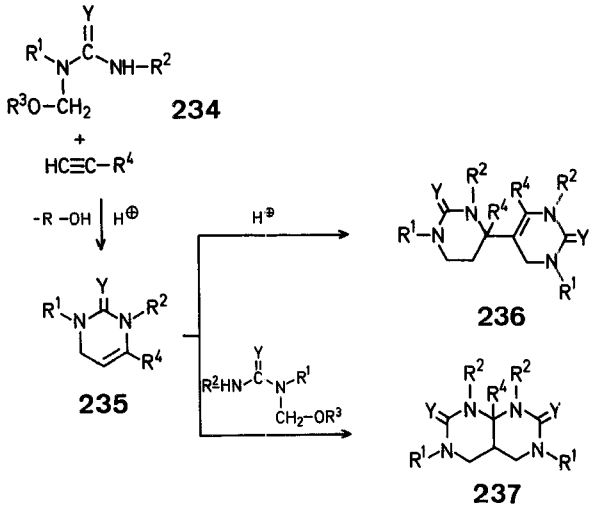
[128] R. Zimmermann, H. Hotze, *Angew. Chem.* **75**, 1025 (1963).

[129] R. Merten, G. Müller, *Angew. Chem.* **74**, 866 (1962).

[130] R. Merten, *German Patent (DBP.)* 1238921 (1960), Farbenfabriken Bayer; *C.A.* **68**, 69034 (1968).

2.5.3. Cyclocondensations with CH-Acidic Alkynes

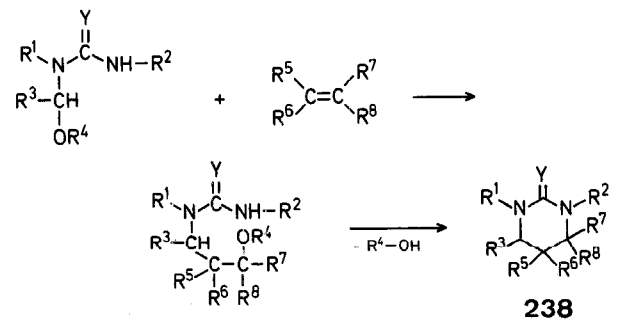
The cyclocondensations with CH acidic alkynes are clearest with acidic reactions of N-hydroxymethyl- or N-alkoxymethylureas (**234**), whereby 2-oxo(thiono)-tetrahydropyrimidines (**235**) are formed. These compounds dimerize readily in the presence of acids to give 2-oxo(thiono)-4-[2-oxo(thiono)-tetrahydropyrimidin-5-yl]-hexahydropyrimidines (**236**)[14].



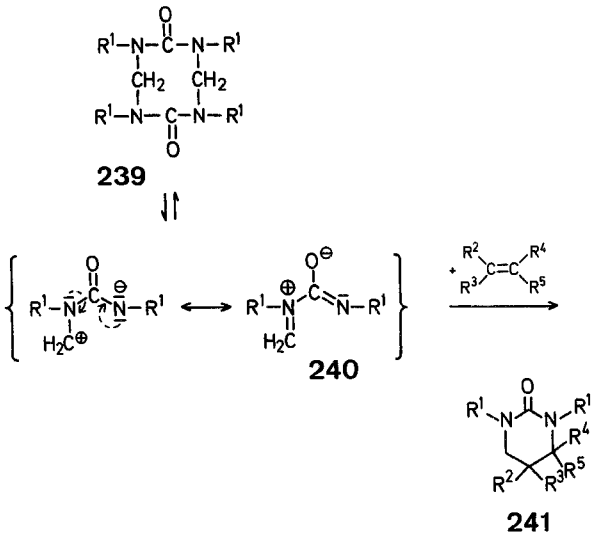
If the ureidomethylating agent is used in excess, bicyclic ureas or thioureas of the type 2,7-dioxo-(thiono)-decahydropyrimido[4,5-*d*]pyrimidine (**237**) are obtained as well as 2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines (**236**)[14].

3. Cyclocondensations with Olefins and Other Unsaturated Compounds

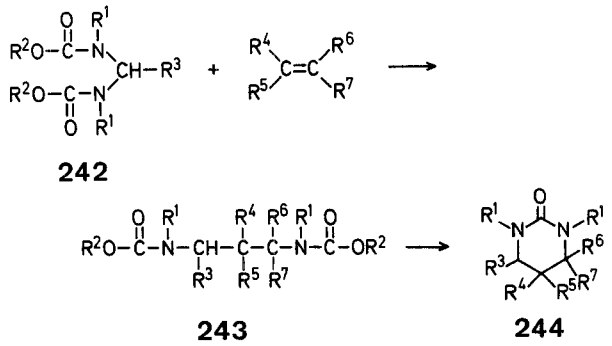
α-Ureidoalkylation of olefins can only be carried out with strongly polarized olefins. Suitable olefins are, for example, styrene, isobutylene, and isoprene. Mono-(1-hydroxyalkyl)-, mono-(1-alkoxyalkyl)-, and monohaloalkyl derivatives of ureas and thioureas can be used as α-ureidoalkylation agents. Also, alkylidene-bis-ureas and -thioureas can be employed. Mono-(1-alkoxyalkyl)-ureas and mono-(1-haloalkyl)-ureas are in many cases preferable because of their better solubilities. Firstly, an addition of the mesomery-stabilized 1-ureidoalkyl-[carbenium-imonium] ion to the olefinic double bond occurs and finally cyclization to the 2-oxo-(thiono)-hexahydropyrimidine (**238**) follows[3,8].



The preparations of 4-alkyl- and 4-aryl-2-oxohexahydropyrimidines (**241**) by the reactions of tetraalkyl-dimethylene-diureides (**239**) with olefins is noteworthy in this respect. Here, an addition of the ureidoalkylating agent on the double bond occurs with ring cleavage of the tretaalkyl-dimethylene-diureide. This is a 1,4-dipolar cycloaddition. Cleavage of the eight-membered ring of the tetraalkyl-dimethylene-diureide (**239**) produces a 1,4 dipole (**240**), the positive center of which forms a mesomerically stabilized ureidomethyl-[carbenium-imonium] ion and the negative center is an amide anion which is also stabilized by mesomery with the neighbouring carbonyl double bond.

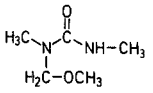
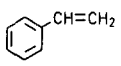
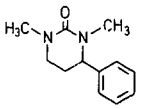
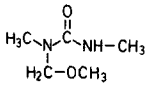
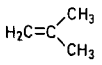
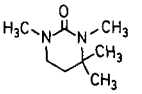
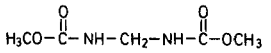
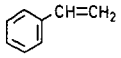
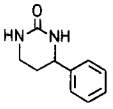
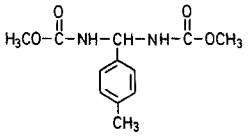
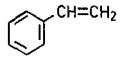
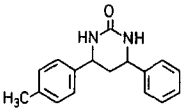
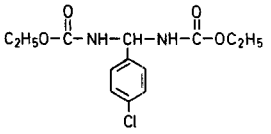
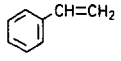
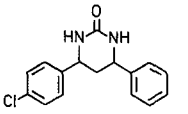
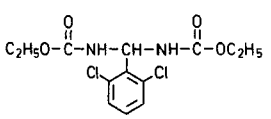
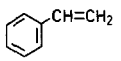
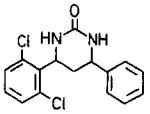
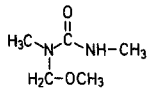
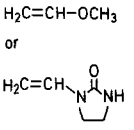
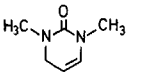


1,3-Bis-[alkoxycarbonylamino]-propanes (**243**) can be prepared from 1,1-bis-[alkoxycarbonylamino]-alkanes (**242**) and olefins in the presence of water-free Lewis acids, especially boron trifluoride, via a similar mechanism. Compound **243** can be converted into 2-oxohexahydropyrimidines (**244**) by treatment with boiling ethanolic potassium hydroxide or with acids in an autoclave at up to 230° via an intramolecular aminolysis[9,129,130].

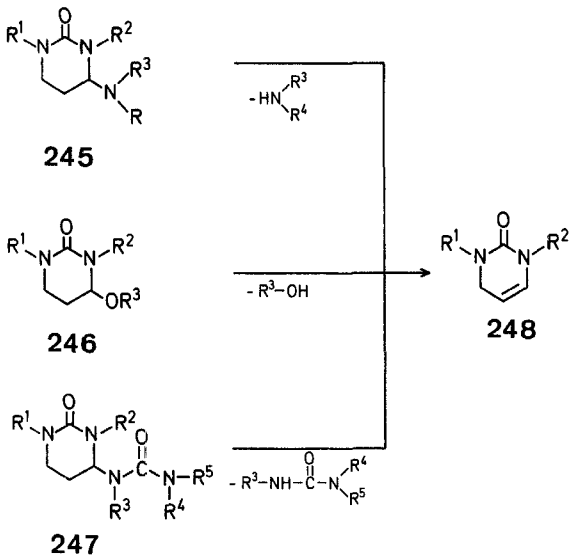


Enamines cyclize with monohydroxymethyl-ureas or monoalkoxymethyl-ureas to give 4-dialkylamino-2-oxohexahydropyrimidines (**245**), vinyl ethers to 4-alkoxy-2-oxohexahydropyrimidines (**246**), and vinylureas to 2-oxo-4-ureidohexahydropyrimidines (**247**)[9]. When a labile hydrogen atom is present in position

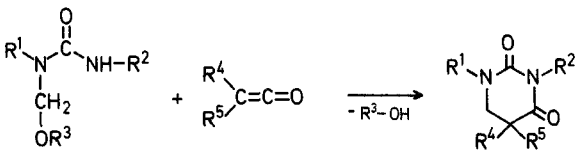
Table 28. 2-Oxohexahydropyrimidines and 2-Oxo-1,2,3,6-tetrahydropyrimidines by α-Ureidoalkylation of Olefins

Urea	Olefin	Product	m.p. or b.p.	References
			b.p. 121–123°/ 0.3 torr	9
			b.p. 80–83°/ 0.5 torr	9
			m.p. 237–238°	129, 130
			m.p. 234–235°	129, 130
			m.p. 249°	130
			m.p. 278–280°	130
			b.p. 86–90°/ 0.5 torr	9

5, these compounds can eliminate the dialkylamine, alcohol, or ureido group to form 2-oxo-1,2,3,6-tetrahydropyrimidines (**248**).



Ketenes react with hydroxymethylureas and alkoxymethylureas in the presence of acids to yield 2,4-dioxohexahydropyrimidines[9] (**249**).



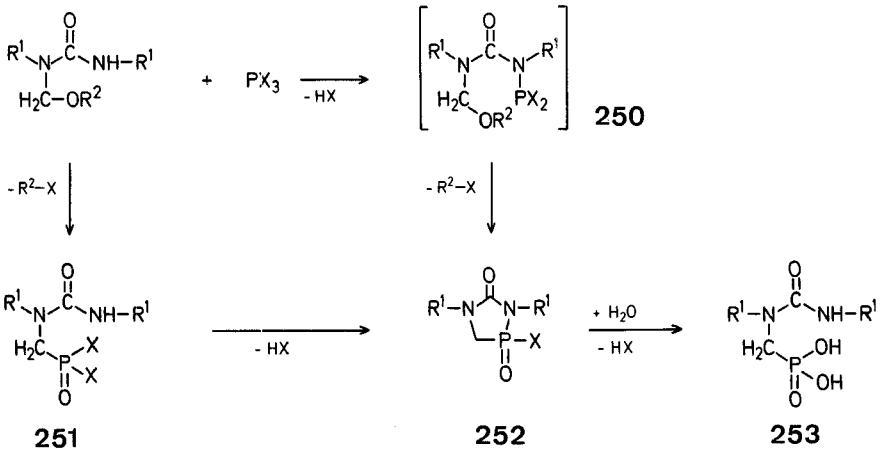
1,3-Dimethyl-2-oxo-4-phenylhexahydropyrimidine[3,9]:
Hydrogen chloride (20 g) is passed into a solution of N,N'-dimethyl-N-methoxymethylurea (66 g) and styrene (52 g) in 1,2-dichloromethane (500 ml). The reaction mixture is heated with stirring at 75–78° for 6 hr. The solution is then decomposed with water (300 ml), shaken, and the organic phase separated. The organic phase is dried with sodium sulfate, filtered, and concentrated; yield (of hydrochloride): 70 g. The crystalline hydrochloride is recrystallized from ethanol. Treatment with aqueous sodium hydroxide and extraction with 1,2-dichloroethane gives the free base; b.p. 121–123°/0.3 torr.

2-Oxo-4-phenylhexahydropyrimidine[129,130]:
Paraformaldehyde (100 g), methyl carbamate (450 g), conc. sulfuric acid (10 g), and benzene (1000 g) are heated under reflux (water separator) until the azeotropic water separation has ended. A further quantity of sulfuric acid (50 g) is added and styrene (312 g) added at 90° within 4 hr. The mixture is then heated at 90–100° for 15 hr, the acid catalyst washed out using dilute alkali, and the mixture concentrated at 160°/12 torr to give the corresponding diurethane; yield: 689 g. The addition product (200 g) is dissolved in ethanol (300 g), water (100 g) is added, and the

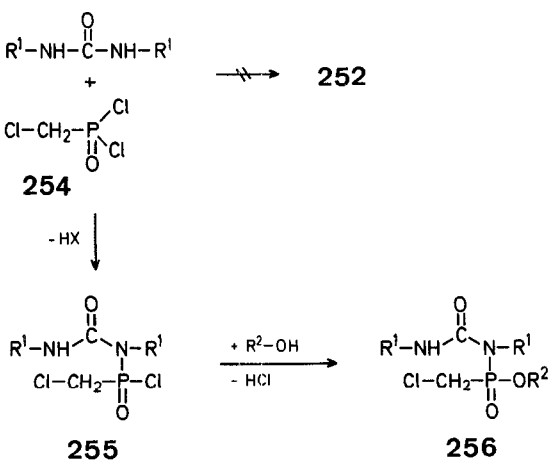
mixture charged into an autoclave together with carbon dioxide to a pressure of 60 atm. The solution is then heated at 230° for 4 hr. It is then allowed to cool and the product is isolated by filtration; yield: ~70 g. The product may be purified by recrystallization from ethanol; m.p. 237–238°.

4. Cyclocondensations with Nucleophilic Phosphorus Compounds

Because of the marked nucleophilic character of trivalent phosphorus compounds, 1,3-dialkyl-2,4-dioxo-4-halo-1,3,4-diazaphospholidines (**252**) are obtained from N-alkoxy-N,N'-dialkylureas and phosphorus(III) halides by cleavage of alkyl halides and hydrogen halide following a ureidomethylation mechanism[10,131].



In these reactions it could not be determined whether the phosphorus trihalide reacts first with the NH group of the N-monoalkoxymethylurea to form an N-alkoxymethylureido-N'-phosphoramidous dihalide (**250**) and then with the alkoxymethyl group by cyclization and cleavage of alkyl halide, or whether a ureidomethylphosphonic dihalide (**251**) is formed first and which then cyclizes with cleavage of hydrogen halide. However, compounds **252** could not be prepared by the reaction of chloromethanephosphonic dichloride (**254**) with urea. Only the ureidochloromethanephosphonoamidic chloride (**255**) which reacts, for example, with alcohols to give the corresponding alkyl phosphonoamidates[10] (**256**).



The P-N bonds in the 1,3-dialkyl-2,4-dioxo-4-halo-1,3,4-diazaphospholidines (**252**) are susceptible to hydrolysis in both acid and alkaline solutions. Compounds **252** are therefore readily hydrolyzed to ureidomethanephosphonic acids[10] (**253**).

4-Chloro-1,3-dimethyl-2,4-dioxo-1,3,4-diazaphospholidine (252, $R^1 = CH_3$; X = Cl)[10,133]:
N-Methoxymethyl-N,N'-dimethylurea (132 g, 1 mol) is added with stirring and cooling at 50–55° dropwise to phosphorus trichloride (206 g, 1.5 mol). The mixture is stirred at 50° for 1 hr; methyl chloride and hydrogen chloride are evolved. It is then concentrated in vacuum at 50°. The product then crystallizes out at room temperature and is recrystallized from acetone; yield: 156 g (86%); decomposition point: 75°.

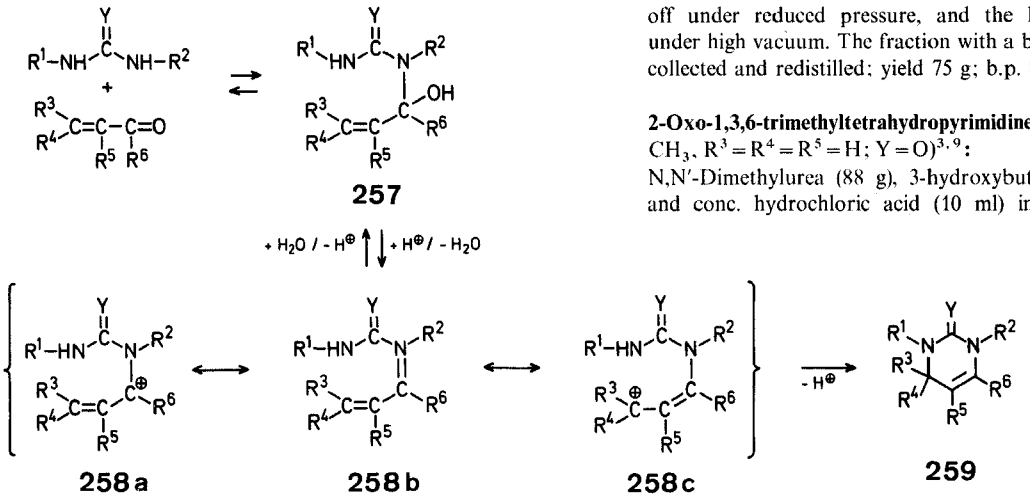
N,N'-Dimethylureidomethanephosphonic acid (253, $R^1 = CH_3$)[10]:
4-Chloro-1,3-dimethyl-2,4-dioxo-1,3,4-diazaphospholidine (100 g, 0.55 mol) is added with stirring to water (300 ml). The mixture is stirred for 1 hr, concentrated in vacuum at 50°, and the crystalline residue recrystallized from methanol; yield: 82 g (82%); m.p. 154°.

5. Cyclocondensations by Vinylogous Ureidoalkylation

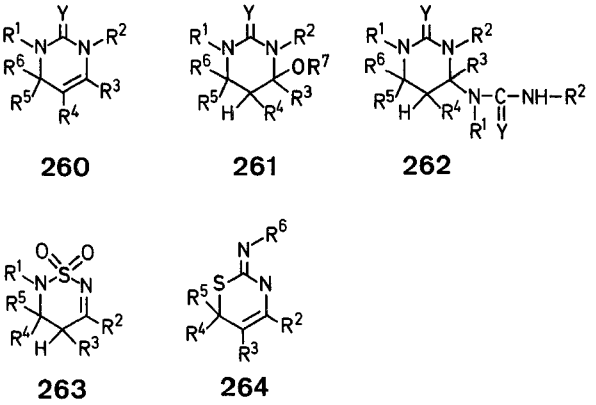
Vinylogous alkylating agents are obtained by addition of an NH- or NH_2-group, of urea, thiourea, guanidine, or a sulfamide to the carbonyl group of an α,β-unsaturated aldehyde or ketone[1,2,3,9,10].

The treatment of β,γ-unsaturated N-(1-hydroxyalkyl)-ureas (**257**) with acid catalysts results in the formation of ureidoalkylcarbenium ions (**258c**) which are stabilized by mesomerism. These ions can react with a second NH or NH_2-group of the urea, thiourea, guanidine, or sulfamide under cyclization to give 2-oxo(thiono,imino)-tetrahydropyrimidines (**259**) and similar products.

[131] H. Petersen, *German Patent (DOS.)* 1813648 (1968), BASF; *C.A.* **74**, 13271 (1971).
[132] G. D. Johnson, *J. Amer. Chem. Soc.* **75**, 2728 (1935).



Vinylogous ureidoalkylating agents can also be prepared from the reactions of ureas and similar compounds with aldols or β-hydroxy-ketones[1,2,3,9], whereby 2-oxo(thiono,imino)-tetrahydropyrimidines (**260**) are also formed. In the presence of water or alcohols, 4-hydroxy(alkoxy)-2-oxo(thiono,imino)-hexahydropyrimidines (**261**) are produced under mild reaction conditions. The use of an excess of the urea or thiourea component results in the formation of 2-oxo(thiono)-4-ureidohexahydropyrimidines (**262**). In the presence of hydrogen chloride, thioureas can react with α,β-unsaturated ketones following the vinylogy principle to give 2-imino-2,3-dihydro-6*H*-1,3-thiazines (**264**).



Some of the 2-oxo-1,2,3,6-tetrahydropyrimidines (**260**, Y = O) obtainable using the principle of vinylogous ureidoalkylation are listed in Table 20. Examples of the 2-thionotetrahydropyrimidines (**260**, Y = S) are included in Table 21, 4-hydroxy(alkoxy)-2-oxo(thiono)-hexahydropyrimidines (**261**); in Table 12, 2-oxo(thiono)-4-ureidohexahydropyrimidines (**262**) in Table 15, 5,6-dihydro-4*H*-1,2,6-thiadiazine 1,1-dioxides (**263**) in Table 27, and 2-imino-2,3-dihydro-6*H*-1,3-thiazines (**264**) in Table 24.

1,3-Dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (**260**, $R^1 = R^2 = CH_3$, $R^3 = R^4 = R^5 = R^6 = H$, Y = O)[3,9]:
N,N'-Dimethylurea (88 g) is added to a mixture of acrolein (56 g) and dioxan (100 ml) and treated with conc. hydrochloric acid (1 ml). The mixture is warmed at 40–45° for 2 hr, neutralized with sodium hydroxide solution, the dioxan evaporated off under reduced pressure, and the liquid residue distilled under high vacuum. The fraction with a boiling range 80–120° is collected and redistilled; yield 75 g; b.p. 86–90°/0.5 torr.

2-Oxo-1,3,6-trimethyltetrahydropyrimidine (**260**, $R^1 = R^2 = R^6 = CH_3$, $R^3 = R^4 = R^5 = H$; Y = O)[3,9]:
N,N'-Dimethylurea (88 g), 3-hydroxybutanal (acetaldol, 88 g), and conc. hydrochloric acid (10 ml) in dioxan (500 ml) are heated at 60° for 2 hr. The mixture is then neutralized with sodium hydroxide solution, the dioxan evaporated off under reduced pressure, and the reaction product separated by fractional distillation under high vacuum; yield: 82 g; b.p. 96–105°/0.5 torr.

2-Oxo-4,6,6-trimethyltetrahydropyrimidine
(**260**, $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = R^6 = CH_3$, Y = O)[104]:
Urea (240 g) and mesityl oxide (540 g) are placed in a flask fitted with a reflux condenser and a stirrer. Hydrogen chloride (56 g) is passed into the mixture, the temperature being maintained at ~40° by external cooling. The reaction mixture is then stirred for 15–20 min and allowed to stand overnight. It is then poured into water (800 ml), neutralized with sodium hydroxide solution, and allowed, to stand for 24 hr. The crystalline product is isolated by filtration, washed with water, dried, and recrystallized from ethanol/water (1:1); yield: 369 g; m.p. 139°.

Cyclohexane-⟨spiro-4⟩-2-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**203**, R = H, Y = O)[9,99,105,107,108]:
Hydrogen chloride (25 g) is passed into a mixture of urea (60 g, 1 mol) and 2-cyclohexylidenecyclohexanone (178 g, 1 mol) in ethanol (200 ml). The mixture is stirred at 90° for 2 hr, cooled, and the precipitated reaction product (90 g) isolated by filtration. Neutralization of the filtrate gives a further crop of product (75 g). The product can be recrystallized from methanol or ethanol; m.p. 188–190°.

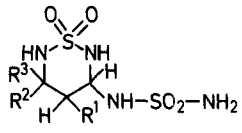
4-Hydroxy-2-thiono-4,6,6-trimethylhexahydropyrimidine (**261**, $R^1 = R^2 = R^4 = R^7 = H$, $R^3 = R^5 = R^6 = CH_3$, Y = S)[75]:
A mixture of mesityl oxide (30 g), thiourea (23 g), and sodium (1.5 g) in methanol (75 g) is heated with stirring on a water bath for 15 min. It is then heated to boiling and then allowed to cool. The precipitate is isolated by filtration, washed with water, and dried; yield: 42 g (78.8%); m.p. 246–248° (from isopropanol).

1,3-Dimethyl-4-methoxy-2-oxohexahydropyrimidine (**261**, $R^1 = R^2 = R^7 = CH_3$, $R^3 - R^6 = H$, Y = O)[74]:
N,N'-Dimethylurea (440 g) and methanol (1000 ml) are put into a flask fitted with a stirrer and a reflux condenser. Hydrochloric acid (50 ml) and then acrolein (280 g) are added. The mixture is stirred at 40–45° for 3 hr, neutralized with sodium hydroxide solution, filtered, and excess methanol evaporated off under reduced pressure. The crude product (720 g) is purified by distillation under high vacuum; b.p. 85–88°/0.4 torr.

6-Methyl-2-oxo-4-ureidohexahydropyrimidine (**262**, $R^1 - R^5 = H$, $R^6 = CH_3$, Y = O)[85]:
A mixture of urea (120 g), water (30 ml), ethanol (70 g), and conc. hydrochloric acid (6 g) is stirred until a clear solution forms. Crotonaldehyde (70 g) is then added and, on warming at 55–60°, the product begins to crystallize; m.p. 245° (from ethanol).

2-Phenylimino-4,6,6-trimethyl-2,3-dihydro-6*H*-1,3-thiazine (264, $R^1=R^3=H$, $R^2=R^4=R^5=CH_3$, $R^6=C_6H_5$)[126]:
Phenylthiourea (15.2 g) is suspended in a solution of mesityl oxide (9.8 g) in chloroform (100 ml). A strong stream of hydrogen chloride is passed through the mixture for 10 min. After 30 min, the mixture is filtered and the filtrate concentrated under reduced pressure. The half-crystalline residue is added to toluene and the product crystallized; yield: 21 g (90%); m.p. (of hydrochloride): 105° (from dilute hydrochloric acid).

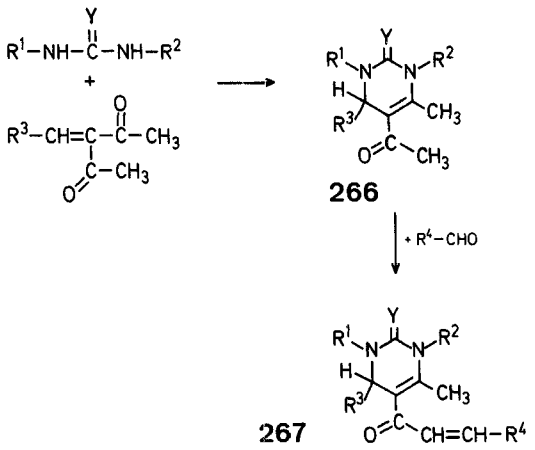
3-Sulfamidotetrahydro-1,2,6-thiadiazine 1,1-dioxides (**265**) are obtained from the condensation of an α,β-unsaturated aldehyde or aldol with an excess of sulfamide in the presence of acids[85].



265

5-Methyl-3-sulfamidotetrahydro-1,2,6-thiadiazine 1,1-Dioxide (265, $R^1=R^2=H$, $R^3=CH_3$)[85]:
Crotonaldehyde (70 g) is added to a mixture of sulfamide (192 g), ethanol (140 g), and conc. hydrochloric acid. The mixture is warmed at 55–60° and, after a short time, the reaction product begins to precipitate out; m.p. (from ethanol).

5-Acetyl-6-methyl-2-oxo-1,2,3,6-tetrapyrimidines (**266**) can be prepared by a vinylogous ureidoalkylation using the reaction of ureas with 3-acetyl-4-oxo-2-pentene or benzylidenacetone[91].



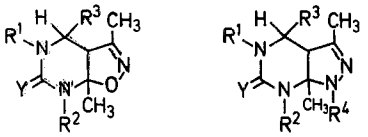
267

Benzaldehyde and 4-nitrobenzaldehyde do not react with the methyl group in position 4 of **266** but attack the acetyl group to give 5-cinnamoyl(4-nitrocinnamoyl)-2-oxo(thiono)-1,2,3,6-tetrahydropyrimidines[91] (**267**).

5-Acetyl-4,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (266, $R^1=R^2=H$, $R^3=CH_3$, $Y=O$)[91]:
A solution of urea (20 g) in 70% ethanol (30 ml) is stirred with 3-acetyl-4-oxo-2-pentene (20 g) and conc. hydrochloric acid (30 drops). The mixture is allowed to stand at 50° for 6 hr and the crystalline product isolated by filtration; yield: 18 g; m.p. 190° (from water).

5-Cinnamoyl-4,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (267, $R^1=R^2=H$, $R^3=CH_3$, $R^4=C_6H_5$, $Y=O$)[91]:
A solution of 5-acetyl-4,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (3 g) in ethanol (4 ml) is stirred with benzaldehyde (3 g) and 20% potassium hydroxide solution (1.5 ml), and the mixture allowed to stand at 50° for 12 hr. The product is recrystallized from chloroform; yield: 1.1 g; m.p. 223°.

Hydroxylamine reacts with compounds **266** (Y=O) to give 6-oxo-3a,4,5,6,7,7a-hexahydro-1,2-oxazolo-[5,4-*d*]pyrimidines (**268**, Y=O); analogously, phenylhydrazine reacts with **266** to give 6-oxo-1-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-pyrazolo[4,3-*d*]pyrimidines (**269**, $R^4=C_6H_5$, Y=O)[91].

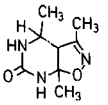
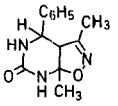
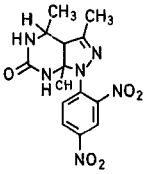
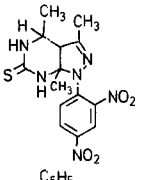
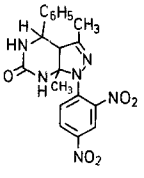
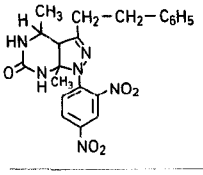


268 **269**

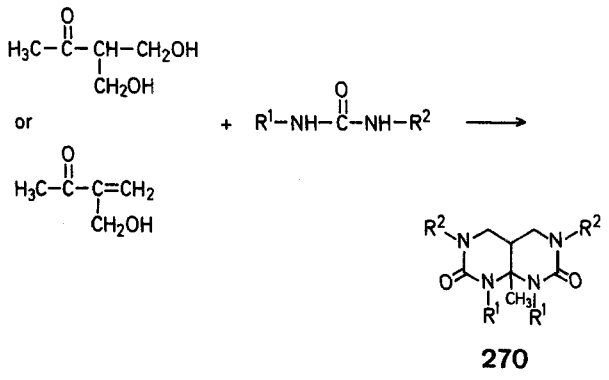
6-Oxo-3,4,7a-trimethyl-3a,4,5,6,7,7a-hexahydro-1,2-oxazolo-[5,4-*d*]pyrimidine (268, $R^1=R^2=H$, $R^3=CH_3$, Y=O)[91]:
5-Acetyl-4,6-dimethyl-2-oxo-1,2,3,6-tetrahydropyrimidine (1 g) and hydroxylamine hydrochloride (1.5 g) are heated under reflux in pyridine (5 ml) and absolute ethanol (10 ml) for 2 hr. The mixture is then evaporated to dryness in vacuum and the residue recrystallized from water; yield: 0.9 g; m.p. 229°.

1-(2,4-Dinitrophenyl)-6-oxo-3,4,7-trimethyl-3a,4,5,6,7,7a-hexahydro-1*H*-pyrazolo[3,4-*d*]pyrimidine [269, $R^1=R^2=H$; $R^3=CH_3$; $R^4=C_6H_3(NO_2)_2$][91]:
A mixture of 5-acetyl-4,6-dimethyl-2-oxotetrahydropyrimidine (1 g), ethanol (10 ml), and a phosphoric acid solution of 2,4-dinitrophenylhydrazine[132] (24 ml) is allowed to stand for 2 hr with frequent rubbing. The product is recrystallized from butanol; yield: 0.6 g; m.p. 237°.

Table 29. 6-Oxo-3a,4,5,6,7,7a-hexahydro-1,2-oxazolo[5,4-*d*]-pyrimidines[91] (**268**) and 6-Oxo-1-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-pyrazolo[3,4-*d*]pyrimidines[91] (**269**)

Compound	Yield (%)	m.p.
	83	229°
	86	206°
	29	237°
	55	201°
	62	172°
	95	216°

2,7-Dioxodecahydropyrimido[4,5-*d*]-pyrimidines (**270**) are formed according to the principle of vinylogy by the reactions of 1-hydroxy-2-hydroxymethylbutanone or 2-hydroxymethyl-3-oxo-1-butene with urea or derivatives of urea in the presence of acids[87].

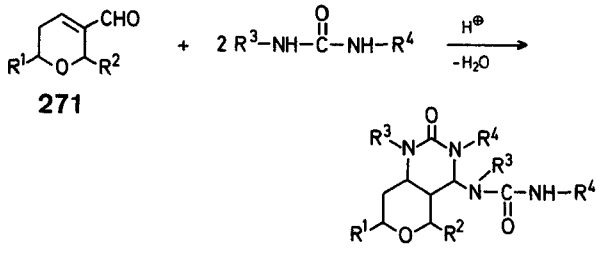


270

2,4-Dioxo-8a-methyldecahydropyrimido[4,5-*d*]pyrimidine (270, $R^1=R^2=H$)[87]:

A mixture of 1-hydroxy-2-hydroxymethylbutanone (5 g), urea (5.9 g), and conc. hydrochloric acid (10 drops) in 70% ethanol (5 ml) is allowed to stand at 50° for 24 hr. The precipitated crystals are isolated, washed with 70% ethanol, and recrystallized from water; yield: 3 g; m.p. 275°.

Following the vinylogy principle, ureas also react with 5,6-dihydro-2*H*-pyran-3-aldehydes (**271**) to give 2-oxo-4-ureidooctahydropyrano[4,3-*d*]pyrimidines[86] (**272**).



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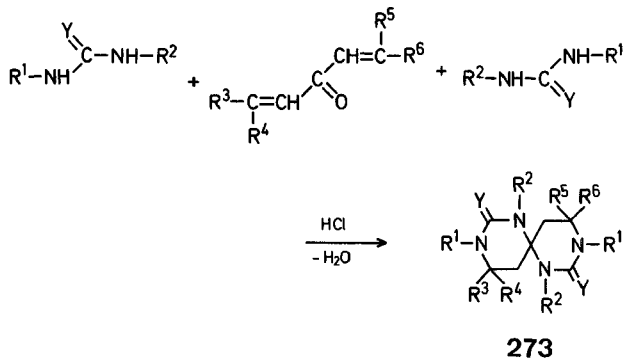
272

2-Oxo-4-ureidooctahydropyrano[4,3-*d*]pyrimidine (272, $R^1-R^4=H$)[86]:

5,6-Dihydro-2*H*-pyran-3-aldehyde (56 g), urea (120 g), ethanol (50 ml), water (20 ml), and conc. hydrochloric acid (4 ml) are mixed and allowed to stand at 50° for 12 hr. The product is washed with ethanol and recrystallized from ethanol/water (8:2); yield: 43 h; m.p. 258°.

Similar to the reaction of α,β-unsaturated aldehydes with urea, the reactions of double α,β-unsaturated



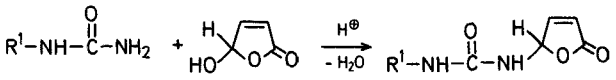
273

ketones with suitable ureas or thioureas in acidic media results in the formation of 2-oxo(thiono)-hexahydropyrimidine-⟨4-spiro-4⟩-2-oxo(thiono)-hexahydropyrimidines (**273**)[3,9,88,105,125].

2-Oxohexahydropyrimidine-⟨4-spiro-4⟩-2-oxohexahydropyrimidine (273, $R^1=R^2=H$, $R^3-R^6=CH_3$, $Y=O$)[3,9,105]:

Urea (30 g) is added to a solution of phorone (34.5 g) in methanol (50 ml). Hydrogen chloride is passed into the solution, the temperature being held at 35° by cooling, until a weight increase of 10 g has occurred. The mixture is then warmed at 60° for 1 hr. The reaction product precipitates out on cooling; yield: 55 g (92%). The product is recrystallized from water to give the hydrate; m.p. 252°. This can be dehydrated by heating at 140° in high vacuum.

During studies on the cyclization of ureas with α,β-unsaturated aldehydes, the reactions of ureas with 5-hydroxy-2-oxo-2,5-dihydrofuran (**274**) and maleic acid aldehyde (**276**) were also investigated[10]. Urea and monoalkylureas undergo condensation with **274** in the presence of catalytic amounts of acid to produce 2-oxo-5-ureido-2,5-dihydrofurans (**275**) with retention of the dihydrofuran ring.



274 **275**

In contrast, the reactions of **274** with N,N'-dialkylureas lead to 2-oxoimidazoline derivatives[10] (**281**).

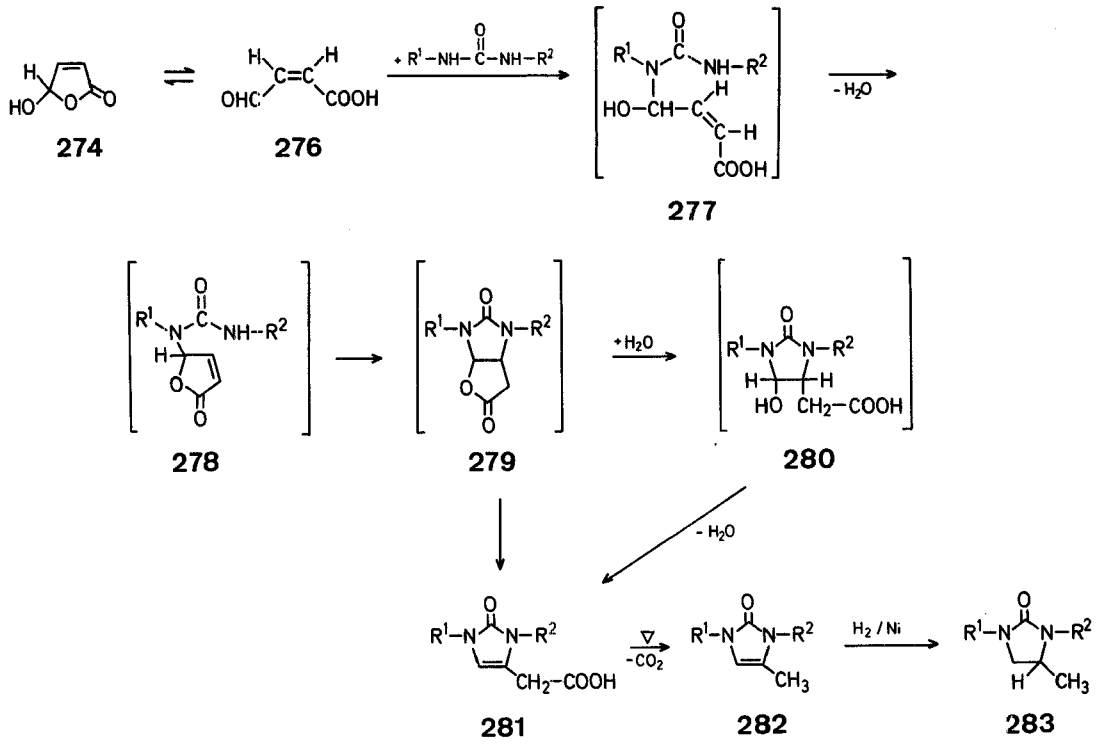
Here, compounds **274** can condense with an N,N'-dialkylurea in the presence of acid with cleavage of water to give **278** or, in its open-chain form, the aldehyde group can add to an NH group of the dialkylurea to give **277**. The following cyclization step does not, as with the α,β-unsaturated aldehydes, lead to hydrogenated or partly hydrogenated 2-oxopyrimidines but to cyclic ureas with five ring atoms. Cleavage of water from **280** or cleavage of the tetrahydrofuran ring from **279** results in the formation of a 3-carboxymethyl-1,3-dialkyl-2-oxoimidazoline (**281**) which, on warming at 100°, undergoes decarboxylation to give a 1,3-dialkyl-4-methyl-2-oxoimidazoline (**282**). Compounds **281** can also be prepared by the reaction of the dimethyl acetal of maleic acid aldehyde methyl ester with N,N'-dialkylureas in the presence of an acid.

4-Carboxymethyl-1,3-dimethyl-2-oxoimidazoline (281, $R^1=R^2=CH_3$)[10]:

A mixture of N,N'-dimethylurea (264 g) and 5-hydroxy-2-oxo-2,5-dihydrofuran (**274**; 300 g) in methanol (500 ml) is stirred with conc. hydrochloric acid (2 ml) at 60–65° for 2 hr. The mixture is then allowed to cool. The crystalline product is isolated by filtration and recrystallized from methanol; yield: 207 g. Concentration of the methanolic filtrate and recrystallization gives a further crop of product (80 g). Total yield: 287 g (56%); decomposition point: 144° (decarboxylation to 1,3,4-trimethyl-2-oxoimidazoline **282**, $R^1=R^2=CH_3$).

2-Oxo-1,3,4-trimethylimidazoline (282, $R^1=R^2=CH_3$)[10]:

4-Carboxymethyl-1,3-dimethyl-2-oxoimidazoline (67 g) is heated 150° for 1 hr. Decarboxylation takes place. Fractional distillation gives the pale yellow liquid product; yield: 42.1 g (85%); b.p. 75–78°/0.2 torr.



274 276 277

278 279 280

281 282 283

6. Closing Comments

Cyclic ureas, prepared according to the principle of a cyclizing α-ureidoalkylation from nucleophilic compounds, have achieved technical significance in several fields. Although some individual examples have been known for some years, the principles of synthesis have only been recognized and expanded in the last few years. Interesting heterocyclic compounds can be prepared from the technically readily available and cheap starting materials such as urea and its derivatives, formaldehyde, higher aldehydes, and ketones. Some of the products have complex structures and have attained prominence in the fields pharmaceutical synthesis, the processing of textiles, fertilizers, varnish additives, chemicals for leather processing, and for the preparation of versatile intermediates.

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