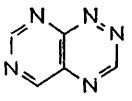
958. *Polyazanaphthalenes. Part I. Synthesis of Pyrimido-[5,4-e]-as-triazines.*

By J. B. Polya and G. F. Shanks.

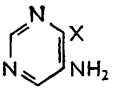
2,4-Dichloro-5-nitropyrimidines are converted into unsymmetrical 4-hydrazino-derivatives by careful treatment with acylhydrazines. Reduction of the nitro-group and cyclisation affords derivatives of dihydropyrimido-[5,4-*e*]-*as*-triazine (VI); one of these compounds was oxidized to the "aromatic" substance (VII; X = H, R′ = H, R″ = OH).

Compounds containing the pyrimido[5,4-*e*]-*as*-triazine (I) ring system have recently assumed practical importance. Robins, Cheng, and Daves [1] showed that toxoflavin (identical with the antibiotic xanthothricin) and fervenulin (a crystalline antibiotic from *Streptomyces fervens* n.sp.) are both derivatives of (I). The first syntheses in this field made use of 1,3-dimethyl-6-hydrazinouracil,[2] 6-chloro-5-formamido-3,4-dihydro-2-hydroxy-1-methylpyrimidin-4-one,[3] and derivatives of 5-amino-4-hydrazinopyrimidine (IIa, b, c).[4-6]

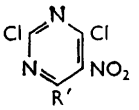
The method adopted in this work employed 2,4-dichloro-5-nitropyrimidines (III) which gave monosubstituted products (IV; X = Cl) on careful treatment with acylhydrazides. Formohydrazide could not be used as it hydrolysed too fast under the reaction conditions. Reduction of the nitro-group to give the amine (V), followed by cyclisation, afforded derivatives of dihydropyrimido[5,4-*e*]-*as*-triazine (VI). Oxidation to the "aromatic" structure (VII) is difficult but was achieved in one instance.



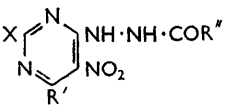
(I)



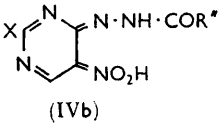
(IIa: X = NH·NH$_2$)
(IIb: X = NMe·NH$_2$)
[IIc: X = N(CH$_2$Ph)·NH$_2$]



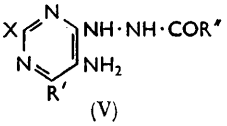
(III)



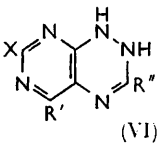
(IVa)



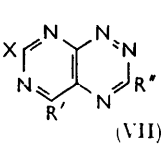
(IVb)



(V)



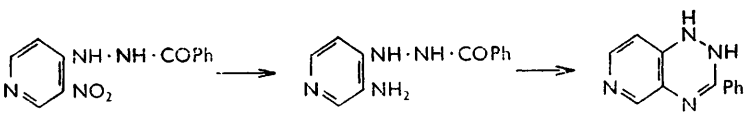
(VI)



(VII)

The 2-chloro-substituent of the hydrazide (IV) was replaced by reaction with sodium acetate buffer, amines, or alcoholic potassium hydrogen sulphide to give hydroxy-, amino-, and mercapto-derivatives, respectively. The difficulties of hydrogenolytic removal of chlorine from 2-chloro-5-nitropyrimidines have been noted [7,8] but very active palladised charcoal catalysts are appropriate for the purpose.

The general method can be extended to the synthesis of other azanaphthalenes, as exemplified by the synthesis of 1,2-dihydropyrido[3,4-*e*]-*as*-triazines, *e.g.*, (X).



(VIII) (IX) (X)

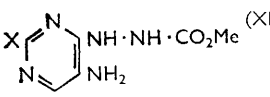
[1] Robins, Cheng, and Daves, *J. Amer. Chem. Soc.*, 1961, **83**, 5256.
[2] Pfleiderer and Schündehütte, *Annalen*, 1958, **615**, 42.
[3] Robins, Cheng, and Daves, *J. Amer. Chem. Soc.*, 1961, **83**, 3904.
[4] Taylor, Barton, and Paudler, *J. Org. Chem.*, 1961, **26**, 4961.
[5] Montgomery and Temple, *J. Amer. Chem. Soc.*, 1960, **82**, 4592.
[6] Montgomery and Temple, *J. Org. Chem.*, 1963, **28**, 923, 3038.
[7] Whittaker, *J.*, 1951, 1565.
[8] Roblin, Winnek, and English, *J. Amer. Chem. Soc.*, 1942, **64**, 567.

The tendency of acylhydrazines to form symmetrically substituted derivatives is known [9-11] and expected from the deactivation of amide nitrogen as a nucleophilic centre. The reaction between benzohydrazide and 2-chloro-4-methylpyrimidine [12] is closely analogous to conversions of (III) into (IV) and has been shown to afford the symmetrically substituted hydrazine. Cyclisation of the amines (V) to the azanaphthalenes (VI), distinct from aminopurines, confirms the structure of the 6-substituent.

The selective reactivity of 2,4-dichloro-5-nitro-pyrimidines has been extensively studied and reviewed; [13-16] the greater reactivity of the 4-chlorine atom in reactions with nucleophilic reagents is not in doubt. Conversion into the azanaphthalene (VI) confirms the structure of (IVa). Tautomeric *aci*-forms (IVb) are presumably responsible for the deep red colour of its alkali-metal salts. Analogous observations for 4-amino-5-nitropyrimidines [17] and *o*-nitrophenylguanidine [18] have been described.

Cyclodehydration by means of hydrochloric acid has been used for the synthesis of benzo-*as*-triazines.[19] Benziminazoles are also formed in this reaction. Although acyl-group migration can occur under the conditions employed,[20] the increased yield of benziminazoles with prolonged heating indicates opening of the dihydrotriazine ring and subsequent cyclisation, rather than the alternative transacylation before cyclisation.[21] Cyclisation of diaminopyrimidines with oxalic acid [22] or glycollic acid [23,24] may occur with purine formation; 5-amino-4-hydrazinopyrimidine is cyclised by formic acid to 9-formamidopurine.[5] On the other hand 9-formamido-6-methylpurine, on treatment with hydrochloric acid, is rearranged to the hydrochloride of 1,2-dihydro-5-methylpyrimido[5,4-*e*]-*as*-triazine [4] which resembles compound (VI). This supports the suggested structure of the latter except for the uncertain location of the two hydrogens.

The hydroxy-compounds (VI; X = OH) have been obtained by eliminating methanol from 5-amino-4-(2-methoxycarbonylhydrazino)pyrimidines (XI). The reaction occurred spontaneously with (XIb), required boiling with N-sodium hydroxide in case of (XIa), and failed with (XIc). The reaction appeared to occur with (XId) but no product could be



(XI) a: R′ = Me, X = H
b: R′ = Me, X = OH
c: R′ = Me, X = Cl
d: R′ = NH_2, X = H

isolated. This reaction resembles the more readily achieved synthesis of 6-hydroxypteridines,[25] and is closely analogous with the syntheses of hydroxynaphthotriazines by Diels.[26,27]

Although the aromatization of tetrahydro-1,2,4-triazine failed,[28] oxidation of dihydrobenzo-1,2,4-triazines to aromatic forms have been frequently described.[19,29,30] Similar

[9] Evans, *Rev. Pure Appl. Chem.* (*Australia*), 1962, **12**, 157.
[10] Gehlen, *Annalen*, 1949, **563**, 185; Gehlen and Eichlepp, *ibid.*, 1955, **594**, 14.
[11] Diels and Fritzsche, *Ber.*, 1911, **44**, 3025.
[12] Sirakawa, Bau, and Yoneda, *J. Pharm. Soc. Japan*, 1953, **73**, 598.
[13] Brown, in "The Chemistry of Heterocyclic Compounds," ed. Weissberger, Wiley, New York, 1962, p. 16.
[14] Brown, *J. Appl. Chem.*, 1952, **2**, 239.
[15] Boon and Jones, *J.*, 1951, 591.
[16] Gabriel and Sonn, *Ber.*, 1907, **40**, 4850.
[17] Rose, *J.*, 1954, 4116.
[18] Arndt, *Ber.*, 1913, **46**, 3522.
[19] Abramovitch and Schofield, *J.*, 1955, 2326.
[20] Theiler, in "Schwab's Handbuch der Katalyse," Springer-Verlag, Vienna, 1943, Vol. 7, p. 302.
[21] Horwitz, "Heterocyclic Compounds," ed. Elderfield, Wiley, New York, 1961, Vol. 7, p. 734.
[22] Traube *et al.*, *Annalen*, 1923, **432**, 266.
[23] Albert, *J.*, 1955, 2690.
[24] Hull, *J.*, 1958, 4069.
[25] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[26] Diels, *Ber.*, 1921, **54**, 213.
[27] Diels, *Annalen*, 1922, **429**, 1.
[28] Grundmann and Raetz, *Chem. Ber.*, 1958, **91**, 1766.
[29] Bischler, *Ber.*, 1889, **22**, 2801.
[30] Bischler and Brodsky, *Ber.*, 1889, **22**, 2809.

procedures failed in the case of 1,2-dihydro-5-methyl-3-phenylpyrimido[5,4-*e*]-*as*-triazine. Resistance to oxidation or hydrolytic fission in alkaline potassium ferricyanide are explanations of this failure. The analogous experience of Taylor and his co-workers with tetrahydropteridine [31] makes the former alternative more likely. 1,2-Dihydro-3-hydroxypyrimido[5,4-*e*]-*as*-triazine and its 5-methyl derivative were oxidised to the triazines with alkaline potassium permanganate. The yield were very low especially when compared with the yield obtained in the comparable oxidative preparation of 6-hydroxypteridine.[25]

Experimental

4-(2-*Acylhydrazino*)-2-*chloro*-5-*nitropyrimidines* (IV).—Results are summarised in Table 1. Representative preparative methods were as follows.

(*a*) *Reaction of* 2,4-*dichloro*-6-*methyl*-5-*nitropyrimidine with acetohydrazide.* (i) 2,4-Dichloro-6-methyl-5-nitropyrimidine [25] (4·16 g.) in ether (40 ml.) was treated with a solution of acetohydrazide [32] (1·48 g.) in ethanol (25 ml.). The temperature was kept below 10° throughout the addition, and the mixture was stirred for 3 hr. The solvent was removed by slow distillation under reduced pressure without heating. The residue was extracted with warm benzene (4 × 50 ml.) and the combined extracts were reduced to 40 ml. and treated with light petroleum (b. p. 80—100°; 250 ml.). The yellow solid which precipitated was filtered after 1 hr. and dried in air (0·56 g., 11%), m. p. 199—201°.

The filtrate was evaporated under reduced pressure. The residue (2·58 g.) was recrystallised from light petroleum (b. p. 60—80°) to give starting material, prisms (62%), m. p. 53°.

Table 1.

4-(2-Acylhydrazino)-2-chloro-5-nitropyrimidines (IV; X = Cl).

Compound				Found (%)					Required (%)			
R′	R″	Yield (%)	M. p.	C	H	N	Cl	Formula	C	H	N	Cl
H	Me	36	137° [a]	31·65	3·0	29·6	15·4	$C_6H_6ClN_5O_3$	31·1	2·6	30·25	15·3
H	Ph	71	169 [b]	45·45	3·05	23·9	12·1	$C_{11}H_8ClN_5O_3$	45·0	2·75	23·85	12·05
H	OMe	46	148 [a]	29·25	2·25	27·45	14·5	$C_6H_6ClN_5O_4$	29·1	2·45	28·3	14·3
Me	Me	49	201 [b]	34·5	3·25	26·85	14·5	$C_7H_8ClN_5O_3$	34·2	3·25	28·5	14·45
Me	Ph	74	162 [b]	47·25	3·3	23·0	11·6	$C_{12}H_{10}ClN_5O_3$	46·85	3·3	22·75	11·5
Me	OMe	56	143 [b]	32·2	3·05	27·0	13·1	$C_7H_8ClN_5O_4$	32·15	3·1	26·75	13·55
NH_2	OMe	64	222 [b]	27·9	2·9	3·6	13·4	$C_6H_7ClN_6O_4$	27·45	2·7	32·0	13·5

[a] From light petroleum (b. p. 80—100°). [b] From ethanol.

(ii) 2,4-Dichloro-6-methyl-5-nitropyrimidine (4·16 g.) was dissolved in dry ether (40 ml.) and the solution cooled in ice–salt to 5°. A solution of acetohydrazide (1·48 g.) in ethanol (25 ml.) was added dropwise with stirring, keeping the temperature below 10°. The clear solution was stirred for 0·5 hr., then treated dropwise with a solution of sodium hydrogen carbonate (1·68 g.) in water (25 ml.) over 2 hr. The rate of addition was adjusted so that the mixture was kept acid. The solution was yellow when acidic but turned red when basic. The solution was cooled in a refrigerator overnight, then filtered to give a yellow solid (2·68 g. after drying in air). Evaporation of the filtrate to half its volume under reduced pressure without heating gave a further 1·16 g. of product. The combined solid was dissolved in benzene and filtered. The filtrate was reduced to 40 ml. and diluted with light petroleum (b. p. 80—100°; 250 ml.). The precipitated solid was collected by filtration after 1 hr., and dried in air (2·26 g., 46%).

(iii) In an attempt to isolate the *aci*-nitro-tautomer (IVb) 4-(2-acetylhydrazino)-2-chloro-6-methyl-5-nitropyrimidine (0·49 g.) was dissolved in ethanol (50 ml.), treated dropwise, with stirring, with 0·906N-alcoholic potassium hydroxide (22·1 ml.) at room temperature, stirred for 1 hr., and filtered. The residue was recrystallised from ethanol to give red plates with a metallic lustre (0·39 g., 69%). The compound exploded at 200°. A solution of this solid (0·25 g.) in water (2 ml.) was treated with 10N-hydrochloric acid dropwise until the solution turned from red to yellow. Cooling gave yellow prisms, m. p. and mixed m. p. with starting material, 200—201°.

[31] Taylor, Carbon, Garland, Hoff, Howell, and Sherman, "Chemistry and Biology of Pteridines," Ciba Foundation Symposium, ed. Wolstenholme and Cameron, Ciba Foundation, London, 1954, p. 119.
[32] Curtius, Schöfer, and Schwan, *J. prakt. Chem.*, 1895 [2], **51**, 180.

(*b*) *Reaction of 2,4-dichloro-6-methyl-5-nitropyrimidine with benzohydrazide.* Benzohydrazide was prepared from ethylbenzoate and hydrazine.[33] 2,4-Dichloro-6-methyl-5-nitropyrimidine (4·16 g.) was dissolved in ethanol (50 ml.). The solution was cooled to 5°. Solid benzohydrazide (2·72 g.) was added in small portions during 0·5 hr. with stirring. The temperature was not allowed to rise above 10° during the addition. After stirring for a further 0·25 hr., a solution of sodium hydrogen carbonate (1·68 g.) in water (20 ml.) was added dropwise. The rate of addition was controlled so that the mixture was kept acidic and the temperature was maintained below 10°. A yellow solid started to precipitate when half the alkali had been added.

The mixture was cooled in a refrigerator overnight, then filtered. The solid was dissolved in benzene (300 ml.), filtered, and the filtrate evaporated to 100 ml. Yellow needles crystallised as the solution cooled. The product was filtered and kept over paraffin for 24 hr. (4·55 g., 74%), m. p. 162°.

(*c*) *Reaction of 2,4-dichloro-6-methyl-5-nitropyrimidine with hydrazinocarbonic acid methyl ester.* 2,4-Dichloro-6-methyl-5-nitropyrimidine (4·16 g.) was dissolved in ethanol (40 ml.) and the solution cooled below 5°. Solid hydrazinocarbonic acid methyl ester hydrochloride [11] (2·53 g.) was added in small portions with stirring during 10 min. The suspension was treated with a solution of sodium hydrogen carbonate (1·68 g.) in water (20 ml.) during 5 min., and the resulting clear yellow solution was stirred for a further 0·5 hr. at 5—10°. A solution of sodium hydrogen carbonate (1·68 g.) in water (20 ml.) was added dropwise. The addition was regulated so that the temperature was maintained below 10°, and the mixture did not become alkaline. (The mixture turned deep red when an excess of alkali was present.) Solid started to precipitate when *ca.* two-thirds of the alkali had been added. The mixture was cooled overnight in a refrigerator, then filtered. The residue (3·8 g.) was dissolved in benzene, filtered, the filtrate concentrated to 50 ml., and boiling light petroleum (250 ml.; b. p. 80—100°) added. Colourless plates formed as the mixture cooled. The mixture was set aside for 2 hr. at room temperature, filtered, and the crystals (2·93 g., 56%) were dried in a desiccator over paraffin.

Metatheses from 2-chloro-compounds.—Results are summarised in Table 2. Representative preparative methods were as follows.

TABLE 2.

2-Substituted 4-(2-acylhydrazino)-5-nitropyrimidines (IV).

Compound			Yield		Found (%)				Required (%)		
X	R′	R″	(%)	M. p.	C	H	N	Formula	C	H	N
HO	Me	OMe	60	210° [a]	33·35	4·15	27·25	$C_7H_9N_5O_5,\frac{1}{2}H_2O$	33·35	3·95	27·8
HO	NH_2	OMe	78	265 [a]	29·9	3·5	34·45	$C_6H_8N_6O_5$	29·5	3·3	34·4
HS	Me	Ph	89	234 (decomp.) [b]	47·1	3·75	21·9	$C_{12}H_{11}N_5O_3S$ [c]	47·2	3·65	22·95
NEt_2	Me	OMe	62	130—131 [d]	45·0	6·4	28·05	$C_{11}H_{18}N_6O_4$	44·3	6·1	28·15
PhNH	Me	OMe	91	212 [b]	48·95	4·5	26·55	$C_{13}H_{14}N_6O_4$	49·05	4·45	26·4
H_2N	Me	OMe	87	210 [e]	35·3	4·45	34·85	$C_7H_{10}N_6O_4$	34·7	4·15	34·7
PhNH	Me	Ph	93	275 [b]	61·1	5·0	21·5	$C_{18}H_{16}N_6O_3$	59·35	4·45	23·05

[a] From water. [b] From methanol. [c] Found S: 9·95; required S, 10·5%. [d] From ethanol. [e] From aqueous methanol.

(*a*) *Hydrolyses.* 2-Chloro-4-(2-methoxycarbonylhydrazino)-6-methyl-5-nitropyrimidine (1·046 g.) was dissolved in glacial acetic acid (20 ml.). A solution of fused sodium acetate (0·328 g.) in water (20 ml.) was added, and the resulting yellow solution boiled under reflux for 1 hr., evaporated to dryness under reduced pressure, and the residue washed with warm ethyl acetate (2 × 20 ml.) and water. The yellow solid (0·82 g.) was recrystallised from a small volume of water to give needles (0·58 g., 60%), m. p. 210° (decomp.).

(*b*) *Replacement by amines.* (i) 2-Chloro-4-(2-methoxycarbonylhydrazino)-6-methyl-5-nitropyrimidine (0·53 g.) was added to ammonium acetate (0·308 g.) dissolved in ethanol (40 ml.). The red solution was boiled under reflux for 1 hr.; the colour of the solution changed to yellow after 0·75 hr., and the solvent was removed by distillation under reduced pressure. The residue was washed with water, dried in air, and recrystallised from aqueous methanol to give needles (0·43 g., 87%), m. p. 210°.

(ii) 4-(2-Methoxycarbonylhydrazino)-2-chloro-6-methyl-5-nitropyrimidine (0·523 g.) was dissolved in warm benzene (30 ml.). Diethylamine (0·5 ml.) was added and the deep red solution

[33] Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1957, p. 300.

was stirred for 3 hr. at room temperature, set aside overnight, and evaporated to dryness on a steam-bath. The residue was washed with water and dried in air. Recrystallisation from ethanol gave plates (0·37 g., 62%), m. p. 130—131°.

(iii) Treatment of 4-(2-methoxycarbonylhydrazino)-2-chloro-6-methyl-5-nitropyrimidine with aniline proceeded in a similar manner to (ii), except that a red solution was not formed in the initial stage. After evaporation of the solvent, the solid was washed with dilute hydrochloric acid, dried in air, then recrystallised from methanol to give plates, m. p. 212°.

(*c*) *Replacement by mercapto-group.* 4-(2-Benzoylhydrazino)-2-chloro-6-methyl-5-nitropyrimidine (1·23 g.) was dissolved in methanol (50 ml.) containing 0·982N-methanolic potassium hydroxide (4·1 ml.). The red solution was saturated with hydrogen sulphide until the red colour was discharged. The solution was stoppered and shaken for 0·5 hr. A yellow solid started to precipitate after 2 min.; it was filtered, washed with water, and air dried. Recrystallisation from methanol gave 4-(2-*benzoylhydrazino*)-2-*mercapto*-6-*methyl*-5-*nitropyrimidine*, needles (1·07 g., 89%), m. p. 234°.

TABLE 3.

4-(2-Acylhydrazino)-5-aminopyrimidines (V).

Compound			Yield		Found (%)					Required (%)			
X	R′	R″	(%)	M. p.	C	H	N	Cl	Formula	C	H	N	Cl
Cl	Me	Me	57	195° [a]	38·93	4·68	31·78	16·5	$C_7H_{10}ClN_5O$	38·98	4·67	32·47	16·44
Cl	Me	Ph	82	210 [b]	48·80	4·85	22·52	12·5	$C_{12}H_{12}ClN_5O,H_2O$	48·73	4·77	23·68	11·99
Cl	Me	OMe	68	140 [a]	33·87	5·02	27·81	14·4	$C_7H_{10}ClN_5O_2,H_2O$	33·68	4·84	28·05	14·20
H	Me	Me	88 [c]	137 [d]	41·89	5·91	33·98	17·8	$C_7H_{11}N_5O,HCl$	41·69	6·00	34·73	17·58
H	Me	Ph	29	168 [a]	55·12	6·01	26·62	—	$C_{12}H_{13}N_5O,H_2O$	55·17	6·04	26·82	—
H	Me	OMe	57	206 [a]	42·01	5·57	35·50	—	$C_7H_{11}N_5O_2$	42·64	5·58	35·53	—
H	H	Ph	93 *	175 [a]	49·43	4·62	25·39	13·5	$C_{11}H_{11}N_5O,HCl$	49·72	4·55	26·36	13·35
H	H	OMe	91 *	188 [a]	32·22	4·98	30·59	16·9	$C_6H_9N_5O_2,HCl$	32·80	4·59	31·88	16·14
PhNH	Me	OMe	66	212—213 [b]	53·55	5·84	28·49	—	$C_{13}H_{16}N_6O_2$	54·15	5·59	29·15	—
H	NH_2	OMe	91 *	205 [d]	30·33	4·89	34·85	14·8	$C_6H_{10}N_6O_2,HCl$	30·71	4·72	35·81	15·11

[a] From water. [b] From aqueous ethanol. [c] Hydrochloride. [d] Precipitated.

Catalytic Reductions.—Results are summarised in Table 3. The following reactions are typical examples.

(i) 2-Chloro-4-(2-methoxycarbonylhydrazino)-6-methyl-5-nitropyrimidine (1·046 g.) in methanol (100 ml.) was hydrogenated at room temperature and 1·1 atm. in the presence of W5 Raney nickel catalyst [34] [269 ml. hydrogen taken up; 1·046 g. requires 275 ml. (3 mol.)]. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was recrystallised from water (charcoal) to give colourless prisms (0·54 g., 68%), m. p. .140°. A sample for analysis was dried over phosphorus pentoxide at 140°/0·3 mm.

(ii) 4-(2-Benzoylhydrazino)-2-chloro-6-methyl-5-nitropyrimidine (1·23 g.) in methanol (100 ml.) was hydrogenated at room temperature and 1·1 atm. in the presence of 5% palladium–charcoal (0·2 g.) [353 ml. hydrogen taken up during 2 hr.; 1·23 g. requires 358·6 ml. (4 mol.)]. The catalyst was filtered off and the solvent was removed by vacuum distillation. The brown oil was taken up in methanol (5 ml.) and diluted with dry ether (20 ml.). Trituration gave a brown powder which was collected by filtration (0·829 g., 74%). This hydrochloride was dissolved in water (3 ml.) and the solution was treated with solid sodium hydrogen carbonate (0·25 g.). The precipitate was collected by filtration and recrystallised from water to give 5-*amino*-4-(2-*benzoylhydrazino*)-6-*methylpyrimidine* as silky needles (0·28 g., 29%), m. p. 168°.

Cyclizations.—Results are shown in Table 4. Representative methods were as follows.

5-Amino-4-(2-benzoylhydrazino)-6-methylpyrimidine hydrochloride (0·65 g.) was dissolved in dry methanol (30 ml.). The solution was saturated with hydrogen chloride and heated under reflux for 1 hr. The initial orange solution turned deep red after 5 min. and a red solid started to precipitate. The solution was cooled and filtered. The solid was recrystallised from water to give orange-red needles (0·46 g., 74%) which slowly decomposed above 265°. The same product was obtained (61%) on heating the amine hydrochloride (0·2 g.) in 5N-hydrochloric acid (10 ml.) at 95° for 0·25 hr.

[34] Linstead, Elvidge, and Whalley, "Modern Techniques of Organic Chemistry," Butterworths, London, 1955, p. 91.

TABLE 4.

1,2-Dihydropyrimido[5,4-*e*]-*as*-triazines (VI).

Compound			Yield		Found (%)					Required (%)			
X	R′	R″	(%)	M. p.	C	H	N	Cl	Formula	C	H	N	Cl
H	H	Ph	69	250—251° [a]	51·82	4·22	27·86	14·0	$C_{11}H_9N_5,HCl,\frac{1}{2}H_2O$	51·47	4·32	27·28	13·81
H	Me	Ph	74	>265 [a]	51·50	5·12	25·29	12·9	$C_{12}H_{11}N_5,HCl,H_2O$	51·52	5·04	25·04	12·68
PhNH	Me	Ph	66	230 [b]	61·21	4·52	23·57	9·6	$C_{18}H_{16}N_6,HCl$	61·45	4·58	23·89	10·08
H	H	OH	42	>280 [a]	39·81	3·37	45·16	—	$C_5H_5N_5O$	39·73	3·33	46·34	—
H	Me	OH	53	>280 [a]	43·69	4·33	41·65	—	$C_6H_7N_5O$	43·63	4·27	42·41	—
HO	Me	OH	86	>280 [c]	39·83	3·92	37·98	—	$C_6H_7N_5O$	39·78	3·90	38·66	—
PhNH	Me	OH	60	>280 [a]	55·70	4·73	32·78	—	$C_{12}H_{12}N_6O$	56·24	4·72	32·80	—

[a] From water. [b] From 5% hydrochloric acid. [c] Precipitated.

A solution of 5-amino-4-(2-methoxycarbonylhydrazino)-6-methylpyrimidine (0·591 g.) in N-sodium hydroxide (3 ml.) was heated at the boiling point for 2 min. The red solution was cooled, diluted with an equal volume of water, then acidified with glacial acetic acid. Scratching of the vessel caused a brown solid to precipitate. Filtration and recrystallisation from water (charcoal) gave needles (0·26 g., 53%), m. p. >280°. An analytical sample was dried over phosphorus pentoxide at 140°/0·3 mm. for 24 hr. Similar results were obtained when the hydrochloride was treated with 2 moles of 2N-sodium hydroxide solution.

Oxidations.—(*a*) 1,2-Dihydro-3-hydroxypyrimido[5,4-*e*]-*as*-triazine (0·4 g.) in N-sodium hydroxide (4 ml.) was treated with 0·1N-potassium permanganate (17 ml.) at room temperature with shaking for 0·25 hr. The mixture was centrifuged then decanted. The manganese dioxide cake was washed with hot water (5 ml.) and filtered. The combined filtrate and supernatant liquors were acidified with glacial acetic acid and chilled overnight in a refrigerator. The yellow solid was collected by filtration and dried in air (0·053 g., 12%). Recrystallisation from water gave 3-*hydroxypyrimido*[5,4-e]-as-*triazine* (VII; R′ = X = H, R″ = OH) as needles. An analytical sample was dried over phosphorus pentoxide at 140°/0·3 mm. for 24 hr. (Found: C, 36·45; H, 3·0; N, 41·35. $C_5H_3N_5O,H_2O$ requires C, 35·95; H, 3·0; N, 41·9%).

(*b*) 1,2-Dihydro-3-hydroxy-5-methylpyrimido[5,4-*e*]-*as*-triazine (0·4 g.), on similar treatment, gave a yellow solid (0·032 g., 7%). Recrystallisation from water gave prisms in insufficient quantity for analysis.

The solution obtained by heating 5,6-diamino-4-(2-methoxycarbonylhydrazino)pyrimidine hydrochloride (0·71 g.) with 2N-sodium hydroxide (3 ml.) was treated with potassium permanganate. Acidification of the filtrate gave a brown gelatinous precipitate which could not be obtained in a crystalline form.

1,2-*Dihydro*-3-*phenylpyrido*[3,4-e]-as-*triazine* (X).—Chelidonic acid [35] was converted into 4-hydroxypyridine by the procedure of King and Ware.[36] Nitration by the method of Crowe [37] gave 4-hydroxy-3-nitropyridine, which was converted into 4-chloro-3-nitropyridine using a mixture of phosphorus pentachloride and phosphorus oxychloride. The product was distilled under reduced pressure and recrystallised from ether.[38] This product (2·11 g.) in methanol (20 ml.) was warmed on a steam-bath until solution occurred. Benzohydrazide (1·18 g.) was added with stirring, followed by the dropwise addition of a solution of sodium hydrogen carbonate (1·12 g.) in water (10 ml.) until the deep purple colour was just discharged. A yellow solid started to precipitate when a quarter of the alkali had been added. The mixture was cooled to room temperature and the yellow solid collected by filtration. Recrystallisation from aqueous ethanol gave 4-(2-*benzoylhydrazino*)-3-*nitropyridine* (VIII) as plates (2·41 g., 70%), m. p. 172—173° (Found: C, 52·2; H, 4·65; N, 20·3. $C_{12}H_{10}N_4O_3,H_2O$ requires: C, 52·15; H, 4·4; N, 20·3%).

A solution of the hydrazide (VIII) (1·29 g.) in methanol (100 ml.) was hydrogenated at 1·1 atm. and room temperature in the presence of freshly prepared W5 Raney nickel. The initial deep red solution was colourless when hydrogenation was complete [hydrogen uptake 341 ml. after 4 hr.; 1·29 g. requires 336 ml. (3 mol.)]. The catalyst was removed by filtration, and the

[35] Riegel and Zwilgmeyer, *Org. Synth.*, 1937, **17**, 40.
[36] King and Ware, *J.*, 1939, 873.
[37] Crowe, *J.*, 1925, 2028.
[38] Bishop, Cavell, and Chapman, *J.*, 1952, 437.

filtrate was evaporated to dryness under reduced pressure. The residue was recrystallised from aqueous ethanol to give the 3-*amino-compound* (IX), m. p. 138° (Found: C, 60·95; H, 5·0; N, 23·8. $C_{12}H_{12}N_4O,\frac{1}{2}H_2O$ requires C, 60·75; H, 5·5; N, 23·6%).

A solution of the 3-amino-compound (0·5 g.) in dry methanol (50 ml.) was saturated with hydrogen chloride. The orange solution was heated under reflux for 1 hr. The solution turned deep red after 5 min., and bumping started after 15 min. The mixture was evaporated to dryness under reduced pressure, and the residue was recrystallized from water to give deep red needles of 1,2-*dihydro*-3-*phenylpyrido*[3,4-e]-as-*triazine* (X) *hydrochloride* (0·37 g., 68%), m. p. 234—235° (Found: C, 52·75; H, 5·2; Cl, 13·2; N, 20·4. $C_{12}H_{10}N_4,HCl,1{\cdot}5H_2O$ requires C, 52·7; H, 5·15; Cl, 12·95; N, 20·5%).

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Department of Chemistry, University of Tasmania,
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