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The Dimroth Rearrangement. XVII* The Rearrangement of Some 1,6-Dihydro-6-imino-1,2-polymethylenepyrimidines into 2,N^6-Polymethylene-bridged 6-Aminopyrimidines

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Abstract

The cyclic imino ether, 2-ethoxy-3,4,5,6,7,8-hexahydroazocine (4; $n = 6$), condenses with aminomethylenemalononitrile (3; R = CN) to give the bicyclic imine, 6,7,8,9,10,11-hexahydro-4-imino-4*H*-pyrimido[1,2-*a*]azocine-3-carbonitrile (5f), which undergoes Dimroth rearrangement in boiling butanol to yield a β-bridged isomer, 2,10,13-triazabicyclo[7,3,1]trideca-1(13),9,11-triene-12-carbonitrile (7a). Imino ethers (4) with fewer than six methylene groups give bicyclic imines which are incapable of rearrangement; those with more than six methylene groups give imines which cannot be isolated on account of their extremely facile rearrangement into β-bridged isomers. Ionization constants and the ultraviolet, infrared, proton magnetic resonance and mass spectra of the main products are discussed.

Introduction

Although 1,3(or β)-bridged homocyclic compounds have been studied quite widely,[1,2] the few examples of β-bridged six-membered nitrogenous heteroaromatic compounds appear to be confined mainly to the pyridine[3] and quinoline[4] series. It occurred to us that Dimroth rearrangement of 1,6-dihydro-6-imino-1,2-polymethylenepyrimidines (5; X = NH) could provide a unique route to 6-aminopyrimidines (7), β-bridged by a polymethylene chain between the amino group and the original 2-position. We naturally expected a lower limit to the number of methylene groups required; moreover, in order to enhance the rate of rearrangement,[5] we decided to use, for this initial study, substrates (5; X = NH) bearing an electron-withdrawing group (R = CN, $CONH_2$ or CO_2Et) adjacent to the imino group.

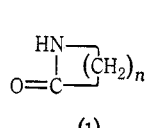
Syntheses

To synthesize the imines (5; X = NH), we adapted a rarely used route[6,7] to 4-amino- or 4-hydroxy-pyrimidines involving the condensation of an imino ether

* Part XVI, *J. Chem. Soc., Perkin Trans. 1*, 1974, 372.

[1] Smith, B. H., 'Bridged Aromatic Compounds' (Academic Press: New York 1964).
[2] Parham, W. E., and Rinehart, J. K., *J. Amer. Chem. Soc.*, 1967, **89**, 5668.
[3] Biemann, K., Büchi, G., and Walker, B. H., *J. Amer. Chem. Soc.*, 1957, **79**, 5558.
[4] Parham, W. E., Davenport, R. W., and Biasotti, J. B., *Tetrahedron Lett.*, 1969, 557; *J. Org. Chem.*, 1970, **35**, 3775.
[5] Brown, D. J., in 'Mechanisms of Molecular Migrations' (Ed. B. S. Thyagarajan) p. 209 (Interscience: New York 1968).
[6] Hromatka, O., Ger. Pat. 667,990 (1938) (*Fortschr. Teerfarbenfabrikation* (*Friedlaender*), 1942, **25**, 432).
[7] Ried, W., and Stock, P., *Justus Liebigs Ann. Chem.*, 1966, **700**, 87.

with aminomethylenemalononitrile (3; R = CN) or a related compound. The required cyclic imino ethers (4; n = 4–7) were prepared, either from appropriate commercially available lactams (1; n = 4–7) and ethyl chloroformate according to the general procedure[8] as used by Suydam *et al.*,[9] or from the cycloalkanone oximes (2; n = 4, 5, or 7) by Beckmann rearrangement using benzenesulphonyl chloride followed by treatment with sodium ethoxide.



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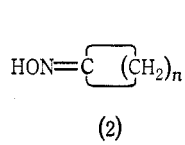

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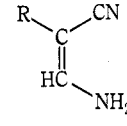

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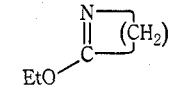

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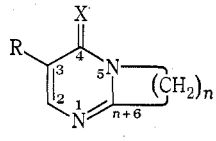
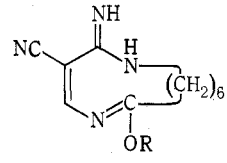


	R	X	n
(5a)	CN	NH	4
(5b)	CN	NH	5
(5c)	$CONH_2$	NH	5
(5d)	CO_2Et	NH	5
(5e)	$CONH_2$	O	5
(5f)	CN	NH	6
(5g)	CN	NH	7
(5h)	$CONH_2$	NH	7
(5i)	CO_2Et	NH	7



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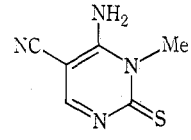

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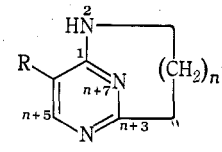
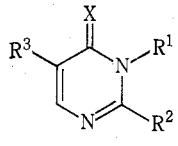
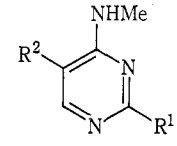


	R	n
(7a)	CN	6
(7b)	CN	7
(7c)	$CONH_2$	7
(7d)	CO_2Et	7
(7e)	CN	4
(7f)	CN	5
(7g)	$CONH_2$	5
(7h)	CO_2Et	5



	R^1	R^2	R^3	X
(8a)	Me	H	CN	NH
(8b)	Me	SMe	CN	NH
(8c)	H	H	CN	O
(8d)	Me	H	H	NH



	R^1	R^2
(10a)	H	CN
(10b)	Me	CN
(10c)	H	H

The ethoxytetrahydropyridine (4; n = 4) reacted with aminomethylenemalononitrile (3; R = CN) in boiling ethanol to give the tetrahydro-4-iminopyridopyrimidinecarbonitrile (5a) in good yield; similarly the ethoxytetrahydro-2*H*-azepine (4; n = 5) with the nitriles (3; R = CN, $CONH_2$, or CO_2Et) gave the cyano, carbamoyl and ethoxycarbonyl hexahydroiminopyrimidoazepines (5b–d) respectively. None of the above bicyclic imines underwent Dimroth rearrangement on prolonged boiling in butanol or in warm alkaline media; when heated under reflux at pH 10, the amide (5c) gave only the corresponding oxo compound (5e).

In contrast to its lower homologues, the ethoxyhexahydroazocine (4; n = 6) with aminomethylenemalononitrile gave two major products, the hexahydroimino-4*H*-

[8] Hechelhammer, W., Ger. Pat. 948,973 (1956) (*Chem. Zentralbl.*, 1957, **128**, 5704).
[9] Suydam, F. H., Greth, W. E., and Langerman, N. R., *J. Org. Chem.*, 1969, **34**, 292.

pyrimidoazocinecarbonitrile (5f) and its β-bridged isomer, triazabicyclotridecatriene-carbonitrile (7a). The proportion of the first product was favoured by a short reaction time, that of the second by a longer time. The isolated imine (5f) rearranged into the bridged compound (7a) in 60% yield on a preparative scale during prolonged boiling in butanol; a $t_{1/2}$ of *c.* 19 h was indicated by monitoring the respective fall and rise of the n.m.r. peaks for H 2 (at δ 7·82 in the substrate) and H 11 (at δ 8·71 in the rearranged material). A transitory species, possibly the intermediate (6; R = Bu), was also detected.

When the polymethylene chain was lengthened further by condensing the ethoxy-hexahydro-2*H*-azonine (4; $n = 7$) with the nitriles (3; R = CN, $CONH_2$, or CO_2Et), each reaction gave only the appropriate triazabicyclotetradecatriene (7b–d), unaccompanied by an imino-precursor (5g–i), no matter how gentle the conditions.

It was concluded that a lengthy seven-membered polymethylene chain in the imines (5g–i) presented no hindrance to the formation of the required β-bridge during rearrangement to the products (7b–d). On the other hand, a six-membered chain did present a significant, but not insurmountable, barrier resulting in a slow rearrangement (5f) → (7a); while a four- or five-membered chain was too short to serve as a bridge and hence precluded the rearrangements (5a–d) → (7e–h). Molecular models proved consistent with these experimental conclusions.

For comparison, efforts were made to prepare the monocyclic imine (8a): a Whitehead synthesis from malononitrile, *N*-methylthiourea and triethyl orthoformate gave the thione (9), confirmed in structure by an n.m.r. singlet methyl peak at δ 3·85. Both the thione (9) and the derived *S*-methyl compound (8b) underwent desulphurization by Raney nickel with concomitant rearrangement to the methylaminopyrimidine (10a), even under strictly neutral conditions. A further attempt to prepare the imine (8a) by condensation of ethyl *N*-methylformimidate and aminomethylenemalononitrile gave the same rearranged product (10a). This was identified by comparison with an authentic sample which was prepared[10] by chlorination and subsequent methylaminolysis of the 4-oxopyrimidine-5-carbonitrile (8c), itself made in 95% yield by an improved method involving treatment of aminomethylenecyanoacetamide (3; R = $CONH_2$) with triethyl orthoformate–acetic anhydride. The homologue (10b) was made similarly.

Ionization and Spectra

The imines (5a) and (5b) proved (Table 1) to be quite weak bases ($pK_a < 6·5$) by virtue of their powerfully electron-withdrawing 3-cyano group which, in a comparable situation, usually decreases the basic strength of pyrimidines by *c.* 3 units [e.g., compare 4-methylaminopyrimidine[11] (10c) pK_a 6·1 with its 5-cyano derivative (10a) of pK_a 3·3].

The corresponding amide (5c) and ester (5d) were slightly stronger bases on account of the progressively milder electron-withdrawal of their 3-substituent. Although comparable in strength to the analogous pyrimidine (10b), pK_a 3·9, the β-bridged rearranged compounds (7a–d) were only 2–2·5 units weaker than the above correspondingly substituted imines: this is rather less than the usual 3–4 unit decrease

[10] Bredereck, H., Simchen, G., and Traut, H., *Chem. Ber.*, 1967, **100**, 3664.
[11] Brown, D. J., and Short, L. N., *J. Chem. Soc.*, 1953, 331.

associated with rearrangement of a 4-imino-3-methyl- to a 4-methylamino-pyrimidine.[12]

Table 1. Ultraviolet spectra and ionization constants

Inflexions and shoulders in *italics*; data for peaks below 220 nm are inexact

Compound	pK_a' (anal. λ)	pH	λ_{max}
(5a)	6·48±0·03 (335)	10	243 (4·05), 336 (3·76)
		4	242 (3·99), 301 (3·91)
(5b)	6·13±0·02 (340)	10	215 (4·14), 242 (4·08), 341 (3·74)
		4	212 (4·12), 240 (3·92), 303 (3·81)
(5c)	8·20±0·04 (298)	11	243 (3·98), 335 (3·63)
		5	238 (3·94), 298 (3·75)
(5d)	8·45±0·05 (335)	11	245 (3·93), 340 (3·30)
		5	240 (3·84), 301 (3·83)
(5e)	1·57±0·06 (295)	4·6	227 (4·13), 273 (3·78)
		0·3	225 (4·01), 295 (3·92)
(7a)	4·39±0·04 (315)	8	255 (4·03), 313 (3·60)
		2	260 (4·11), *290* (3·60)
(7b)	4·18±0·05 (308)	9	252 (4·21), 308 (3·66)
		2	258 (4·27), *287* (3·64)
(7c)	5·74±0·06 (315)	10	253 (4·08), 309 (3·62)
		3	259 (4·11), *290* (3·58)
(7d)	6·12±0·03 (320)	9	252, 313
		4	257, *285*
(10a)	3·29±0·06 (315)	5·5	248 (4·14), 308 (3·52)
		1·8	255 (4·22), *290* (3·54)
(10b)	3·92±0·03 (313)	7	248 (4·13), 305 (3·64)
		2	254 (4·17), *286* (3·80)

The ultraviolet spectra (Table 1) of the imines (5a–d) differed considerably from those of the rearranged products (7a–d): on rearrangement, the long-wavelength band of the neutral imines underwent a considerable hypsochromic shift of *c.* 30 nm whereas the shorter band showed a smaller bathochromic shift of *c.* 10 nm; as cations, the shifts were in the same respective directions but that of the long band was 10–15 nm while that of the short band approached 20 nm. This behaviour differed somewhat from that observed[12] in analogous simple pyrimidines.

In the proton magnetic resonance spectra (Table 2), the methylene groups at each end of the polymethylene chain, whether in the cyclic imino ethers (4) or the bicyclic systems (5) and (7), were quite distinguishable (sometimes even as the theoretical triplet or quartet) from the remaining methylene groups, which remained unresolved. In the bicyclic systems, the most characteristic and useful peak was that representing H2 in the imines (5) or H(n+5) in the β-bridged compounds (7). Other signals were all consistent with the formulated structures.

The infrared spectra of the β-bridged amines (7a–d) were unusual in having only a single NH-stretching band [(7a): 3400; (7b): 3380; (7c): 3330; (7d): 3400 cm^{-1}] associated with the secondary amino group on account of the constraint imposed by the polymethylene bridge; in contrast, the simple unconstrained methylamino derivative (10a) had two such bands (3270, 3170 cm^{-1}) as did also those analogues described[12] recently (3300, 3200–3100 cm^{-1}).

[12] Brown, D. J., and Ienaga, K., *J. Chem. Soc., Perkin Trans. 1*, 1974, 372.

Although the mass spectra (Table 3) of the simple imine (8d) and 4-methylaminopyrimidine (10c) indicated rearrangement of the former prior to fragmentation, the bicyclic imines (5; X = NH) behaved quite differently. Thus the imines (5b) and

Table 2. Proton magnetic resonance spectra

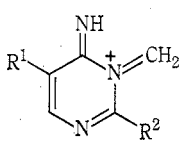
δ values ex $SiMe_4$, J in Hz

Compound	Solvent	δ values and assignments
(4; n = 6)	$CDCl_3$	1·25 (t, J 7, Me), 1·50 [s, br, 4,5,6,7-$(CH_2)_4$], 2·30 (s, br, 3-CH_2), 2·43 (t, J 6, 8-CH_2), 4·03 (q, J 7, CH_2 of Et)
(4; n = 7)	$CDCl_3$	1·25 (t, J 7, Me), 1·51 [s, br, 4,5,6,7,8-$(CH_2)_5$], 2·33 (s, br, 3-CH_2), 2·48 (t, J 6, 9-CH_2), 4·07 (q, J 7, CH_2 of Et)
(5a)	$(CD_3)_2SO$	1·80 [s, br, 7,8-$(CH_2)_2$], 2·80 (s, br, 9-CH_2), 3·77 (s, br, 6-CH_2), 7·12[A] (s, br, NH), 7·98 (s, H 2)
	$CDCl_3$[B]	1·92, 2·91, 4·00, 6·80, 7·92
(5b)	$(CD_3)_2SO$	1·72 [s, br, 7,8,9-$(CH_2)_3$], 2·98 (s, br, 10-CH_2), 4·40 (s, br, 6-CH_2), 7·10[A] (s, br, NH), 7·96 (s, H 2)
	$CDCl_3$[B]	1·80, 2·97, 4·46, 7·05, 7·73
(5c)	$(CD_3)_2SO$	1·60 [s, br, 7,8,9-$(CH_2)_3$], 2·81 (s, br, 10-CH_2), 4·22 (s, br, 6-CH_2), 7·18[A] (s, br, NH), 7·80 (s, H 2), 8·76[A] (s, br, NH_2)
(5d)	$(CD_3)_2SO$[C]	1·35 (t, J 8, Me), 1·82 [s, br, 7,8,9-$(CH_2)_3$], 3·30 (s, br, 10-CH_2), 4·40 (q, J 8, CH_2 of Et), 4·45 (s, br, 6-CH_2), 8·90 (s, H 2), 9·64[A] (s, br, NH)
	$CDCl_3$[B]	1·37, 1·85, 2·97, 4·34, 4·68, 8·17, 8·88
(5e)	$(CD_3)_2SO$	1·90 [s, br, 7,8,9-$(CH_2)_3$], 3·20 (s, br, 10-CH_2), 4·50 (s, br, 6-CH_2), 8·75 (s, H 2)
	$CDCl_3$[B]	1·87, 3·10, 4·41, 8·90
(5f)	$CDCl_3$	1·60 [s, br, 7,8,9,10-$(CH_2)_4$], 2·91 (t, J 6, 11-CH_2), 4·35 (t, J 5, 6-CH_2), 7·06[A] (s, br, NH), 7·82 (s, H 2)
(6; R = Et)	$CDCl_3$	1·26 (t, J 8, Me), 1·47 [s, br $(CH_2)_4$], 2·33 (s, br, CH_2), 3·59 (t, J 6, CH_2), 4·18 (q, J 8, CH_2 of Et), 5·88 (s, br, NH), 8·51 (s, br, NH), 8·75 (s, CH)
(7a)	$CDCl_3$	1·10 (s, br, CH_2), 1·75 [s, br, $(CH_2)_3$], 2·81 (t, J 6, 8-CH_2), 3·71 (q, J 6, 3-CH_2), 6·08[A] (s, br, NH), 8·39 (s, H 11)
(7b)	$CDCl_3$	1·60 [m, br, 4,5,6,7,8-$(CH_2)_5$], 2·90 (s, br, 9-CH_2), 3·59 (s, br, 3-CH_2), 6·08[A] (s, br, NH), 8·45 (s, H 12)
	$(CD_3)_2SO$[B]	1·50, 2·78, 3·44, —, 8·50
(7c)	$(CD_3)_2SO$	1·45 [m, br, 4,5,6,7,8-$(CH_2)_5$], 2·72 (t, J 6, 9-CH_2), 3·45 (q, J 6, 3-CH_2), 8·61 (s, H 12)
(7d)	$CDCl_3$	1·60 [m, br, 4,5,6,7,8-$(CH_2)_5$], 2·90 (s, br, 9-CH_2), 3·55 (s, br, 3-CH_2), 8·80 (s, H 12)
(8b)[C]	$(CD_3)_2SO$	2·56 (s, Me), 3·47 (s, Me), 8·03 (s, H 4)
(9)	$(CD_3)_2SO$	3·85 (s, Me), 8·22 (s, 6H)
(10a)	$(CD_3)_2SO$	2·92 (d, J 6, Me), 8·18 (s, br, NH), 8·64 (s, H 2 or H 4), 8·71 (H 4 or H 2)
	$CDCl_3$[B]	3·12, —, 8·50, 8·80
(10b)	$CDCl_3$	2·61 (s, 2-Me), 3·15 (d, J 6, NMe), 5·75 (s, br, NH), 8·51 (s, H 6)

[A] Disappeared on addition of D_2O. [B] Assignments etc. as above. [C] Hydriodide salt used.

(5c) each fragmented in two ways: the major path involved an initial 6,7-bond cleavage followed by degradation of the hydrocarbon side chain; the minor one, a 5,6-bond cleavage followed by degradation. In both cases, the pyrimidine ring remained intact in all major fragments. The β-bridged amines (7) fragmented by two

less simple pathways involving initial 2,3- or 3,4-bond cleavage respectively. Major fragments are formulated in Table 3; the complete patterns will be presented elsewhere.[13]



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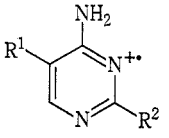

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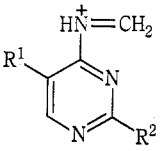

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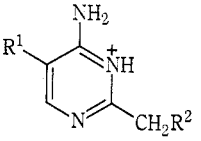

(14)

	R^1	R^2		R^1	R^2
(a)	CN	$CH_2CH{=}CH_2$	(h)	$CONH_2$	CH_3
(b)	CN	$CH_2\dot{C}H_2$	(i)	CN	$CH_2CH_2\dot{C}H_2$
(c)	CN	$CH{=}CH_2$	(j)	CN	$\dot{C}H_2$
(d)	CN	CH_3	(k)	CN	$CH_2CH_2CH_2\dot{C}H_2$
(e)	$CONH_2$	$CH_2CH{=}CH_2$	(l)	CN	$CH_2CH_2CH{=}CH_2$
(f)	$CONH_2$	$CH_2\dot{C}H_2$	(m)	$CONH_2$	$CH_2CH_2CH_2\dot{C}H_2$
(g)	$CONH_2$	$CH{=}CH_2$	(n)	$CONH_2$	$CH_2CH_2CH{=}CH_2$

Table 3. Major fragments in mass spectra

Compound	*m/e*, abundance (%) (in *italics*) and formulation
(5b)	188, *52* (5b); 173, *24* (11a); 160, *37* (11b); 159, *100* (11c); 134, *32*, (12d)
(5c)	206, *100* (5c); 191, *15* (11e); 178, *18* (11f); 177, *40* (11g); 152, *13* (12h)
(7a)	202, *100* (7a); 174, *48* (13i); 173, *47* (13a); 161, *30* (14c); 159, *32* (13c); 148, *36* (14j); 134, *20* (12d)
(7b)	216, *100* (7b); 188,[A] *50* (13k); 187, *40* (13l); 175, *21* (14a); 173,[B] *33* (13a); 162, *26* (14b); 147, *26* (13d); 134,[C] *48* (12d)
(7c)	234, *100* (7c); 206, *42* (13m); 205, *28* (13n); 193, *10* (14e); 191, *13* (13e); 180, *21* (14f); 152, *14* (12h)
(8d)[D]	109, *100*; 80, *20·5*; 53, *26·2* [20·5/26·2 = 0·782]
(10c)[D]	109, *100*; 80, *38·2*; 53, *49·1* [38·2/49·1 = 0·778]

[A] 188·1064 ($C_{10}H_{12}N_4$ requires 188·1062).
[B] 173·0829 ($C_9H_9N_4$ requires 173·0827).
[C] 134·0593 ($C_6H_6N_4$ requires 134·0592).
[D] For formulation see Brown, D. J., and Ienaga, K., *J. Chem. Soc., Perkin Trans. 1*, 1974, 372.

Experimental

Analyses were done by the A.N.U. Analytical Services Unit. The u.v. and i.r. spectra were recorded on Unicam SP1800 and SP200 instruments respectively, p.m.r. spectra on a Varian T60A instrument at 35° with Me_4Si as internal standard and mass spectra on an MS9 instrument. Ionization constants were determined spectrometrically[14] at 20° and at concentrations below 10^{-3}M in buffers[15] of 10^{-2}M ionic strength; no thermodynamic corrections were applied.

The lactams, cyclooctanone, and oximes of cyclopentanone and cyclohexanone were Fluka *purum* quality.

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[15] Perrin, D. D., *Aust. J. Chem.*, 1963, **16**, 572.

*6,7,8,9-Tetrahydro-4-imino-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (5a)*

(A) A mixture of 5-pentanelactam (1; $n = 4$) (9·9 g) and ethyl chloroformate (11·0 g) was stirred at 40–45° for 4 h and then allowed to stand at 25° for 16 h. After trituration with a little light petroleum, the residue was mixed with aqueous 25% potassium carbonate (30 ml). The oily layer was extracted into benzene and the aqueous phase was again extracted with benzene. Distillation of the extracts gave 2-ethoxy-3,4,5,6-tetrahydropyridine (4; $n = 4$) (65%), b.p. 88–90°/70 mm (cf. 86–88°/70 mm for material made[16] less conveniently using triethyloxonium tetrafluoroborate as ethylating agent).

(B) Benzenesulphonyl chloride (8·8 g) was added dropwise to a stirred solution of cyclopentanone oxime (2; $n = 4$) (5·4 g) in acetone (25 ml) at 0°. After stirring the solution for a further 1 h at 20–25°, ethanolic sodium ethoxide (30 ml; from sodium: 1·2 g) was added with gentle external cooling to mitigate the reaction. The mixture was heated under reflux for 1 h and then evaporated under reduced pressure. The residue was suspended in benzene (100 ml) to which was then slowly added potassium carbonate (6·9 g) dissolved in water (8 ml). After filtration, the layers were separated. The aqueous phase was extracted with benzene (2 × 50 ml). The extracts and original organic layer were combined, dehydrated (K_2CO_3) and distilled to give the ethoxytetrahydropyridine (4; $n = 4$) (45%), identical in b.p. and spectra with that from (A).

A solution of the foregoing ethoxytetrahydropyridine (2·7 g) and aminomethylenemalononitrile[17] (3; R = CN) (1·9 g) in ethanol (20 ml) was boiled under reflux for 3 h. The residue from evaporation under reduced pressure was dissolved in chloroform and then passed through an alumina column. Evaporation of the eluate gave the *tetrahydro-4-iminopyridopyrimidinecarbonitrile* (83%), m.p. 154° (from ethanol) (Found: C, 62·4; H, 5·8; N, 31·9. $C_9H_{10}N_4$ requires C, 62·1; H, 5·8; N, 32·2%).

*4,6,7,8,9,10-Hexahydro-4-iminopyrimido[1,2-*a*]azepine-3-carbonitrile (5b) and -3-carboxamide (5c) and Ethyl 4,6,7,8,9,10-Hexahydro-4-iminopyrimido[1,2-*a*]azepine-3-carboxylate (5d)*

(A) *O*-Ethylation of 6-hexanelactam (1; $n = 5$) with ethyl chloroformate,[8] as for pentanelactam above, gave 7-ethoxy-3,4,5,6-tetrahydro-2*H*-azepine (4; $n = 5$) (63%), b.p. 70°/15 mm (cf. 81–82°/26 mm for material obtained[18] in 52% yield by ethylation with diethyl sulphate).

(B) Rearrangement of cyclohexanone oxime (2; $n = 5$), as for cyclopentanone oxime above, also gave the azepine (4; $n = 5$) (43%), identified by b.p. and spectra.

This ethoxytetrahydro-2*H*-azepine (1·41 g), aminomethylenemalononitrile (0·95 g) and ethanol (10 ml) were heated under reflux for 15 h. Treatment as for the preceding pyridopyrimidine gave the *hexahydro-4-iminopyrimidoazepinecarbonitrile* (71%), m.p. 85° (from ethanol) (Found: C, 64·1; H, 6·3; N, 29·8. $C_{10}H_{12}N_4$ requires C, 63·8; H, 6·4; N, 29·8%). [Heating the starting materials under reflux in tetrahydrofuran (20 ml) containing a trace of *p*-toluenesulphonic acid for 48 h gave the same yield of product.]

The ethoxytetrahydro-2*H*-azepine (15 g), aminomethylenecyanoacetamide[19] (11·1 g) and butanol (500 ml) were heated under reflux for 48 h. Concentration gave a solid (12 g) and column chromatography of the mother liquors (alumina; chloroform–ethanol) produced a further 5·7 g. Recrystallization from ethanol gave the *hexahydro-4-iminopyrimidoazepinecarboxamide* (85%), m.p. 205° (Found: C, 58·5; H, 6·8; N, 27·1. $C_{10}H_{14}N_4O$ requires C, 58·2; H, 6·8; N, 27·2%).

The ethoxytetrahydro-2*H*-azepine (1·7 g), ethyl aminomethylenecyanoacetate[20] (1·4 g) and ethanol (10 ml) were heated on the steam bath for 16 h. Evaporation and treatment of the residue with hydriodic acid in ethanol followed by concentration gave the *ethyl hexahydro-4-iminopyrimidoazepinecarboxylate hydriodide* (88%), m.p. 180° (from ethanol) (Found: C, 39·7; H, 5·0; N, 11·4. $C_{12}H_{17}N_3O_2$,HI requires C, 39·7; H, 5·0; N, 11·6%).

*4,6,7,8,9,10-Hexahydro-4-oxopyrimido[1,2-*a*]azepine-3-carboxamide (5e)*

The above hexahydro-4-iminopyrimidoazepinecarboxamide (1·03 g) and aqueous buffer (pH 10; 50 ml) were heated under reflux for 2 h and then the cooled solution was extracted with chloroform.

[16] Oishi, T., Nagai, M., Onuma, T., Moriyama, H., Tsutae, K., Ochiai, M., and Ban, Y., *Chem. Pharm. Bull.* (Tokyo), 1969, **17**, 2306.
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[18] Benson, R. E., and Cairns, T. L., *Org. Synth.*, 1963, Coll. Vol. IV, 588.
[19] Wellcome Foundation, Brit. Pat. 1,200,445 (1970) (*Chem. Abstr.*, 1970, **73**, 109794).
[20] Kenner, G. W., Lythgoe, B., Todd, A. R., and Topham, A., *J. Chem. Soc.*, 1943, 388.

Evaporation of the extract gave the *oxopyrimidoazepine* (81%), m.p. 233–235° (from ethanol) (Found: C, 58·2; H, 6·0; N, 20·4. $C_{10}H_{13}N_3O_2$ requires C, 58·0; H, 6·3; N, 20·3%).

6,7,8,9,10,11-Hexahydro-4-imino-4H-pyrimido[1,2-a]azocine-3-carbonitrile (5f) and 2,10,13-Triazabicyclo[7,3,1]trideca-1(13),9,11-triene-12-carbonitrile (7a)

A mixture of ethyl chloroformate (54·2 g) and 7-heptanelactam (62·5 g) was stirred at 45° for 4 h. After washing with a little light petroleum, the residual mixture was diluted with chloroform (50 ml) and stirred at 0° while a 50% aqueous solution of potassium carbonate (35 g) was added dropwise. When evolution of carbon dioxide had ceased, the filtrate was dried over solid potassium carbonate and then fractionally distilled to give unchanged lactam (34 g), b.p. 158°/10 mm, and *2-ethoxy-3,4,5,6,7,8-hexahydroazocine* (4, $n = 6$) (28 g), boiling at 90–100°/22 mm (Found: C, 69·9; H, 10·9; N, 9·3. $C_9H_{17}NO$ requires C, 69·6; H, 11·0; N, 9·0%).

(A) The ethoxyhexahydroazocine (2·5 g), aminomethylenemalononitrile[17] (0·93 g) and butanol (10 ml) were boiled under reflux for 30 min. Evaporation followed by column chromatography (alumina; chloroform) gave the hexahydroiminopyrimidoazocinecarbonitrile (33%) which could not be obtained analytically pure: even elution gave material which then showed minor t.l.c. spots for the rearranged isomer and another compound. The u.v. and p.m.r. spectra for the best material obtained (see Tables 1 and 2) were consistent with the formulation.

The imine (0·1 g) was heated under reflux in butanol (2 ml) for 40 h. Evaporation and chromatography as above gave the rearranged *triazabicyclotridecatrienecarbonitrile* (61%), m.p. 103° (from ethanol) (Found: C, 65·5; H, 6·9; N, 27·6. $C_{11}H_{14}N_4$ requires C, 65·3; H, 7·0; N, 27·7%).

(B) Prolonged heating (48 h) of the initial reaction mixture used in (A), gave the rearranged product (identified by mixed m.p. and spectra) but only in 15% yield.

(C) Replacement of the butanol in (B) by tetrahydrofuran containing *p*-toluenesulphonic acid (0·2 g) gave the imine (9%), rearranged product (16%) and a third substance indicated as the intermediate (6; R = OEt) by its n.m.r. spectrum (Table 2).

2,11,14-Triazabicyclo[8,3,1]tetradeca-1(14),10,12-triene-13-carbonitrile (7b) and -13-carboxamide (7c) and Ethyl 2,11,14-Triazabicyclo[8,3,1]tetradeca-1(14),10,12-triene (7d)

(A) 8-Octanelactam (3·5 g) and ethyl chloroformate (5·4 g) were stirred together at 45° for 4 h and then left at 20–25° for 12 h. The excess of ester was removed under reduced pressure and the residue was treated as for the ethoxyhexahydroazocine above to give *9-ethoxy-3,4,5,6,7,8-hexahydro-2H-azonine* (4; n = 7) (1·6 g), b.p. 56°/0·3 mm (Found: C, 70·7; H, 11·0; N, 8·1. $C_{10}H_{19}NO$ requires C, 71·0; H, 11·3; N, 8·3%); lactam (1·7 g) was recovered.

(B) Cyclooctanone was converted into its oxime by the general procedure of Bousquet[21] and thence by rearrangement, as its lower homologues above, into the azonine (4; $n = 7$), identical with that in (A).

The ethoxyhexahydro-2*H*-azonine (2·1 g), aminomethylenemalononitrile[17] (0·93 g) and ethanol (10 ml) were heated under reflux for 18 h. Concentration and filtration gave a first crop and chromatography (alumina; chloroform) of the filtrate gave a second. The *triazabicyclotetradecatrienecarbonitrile* (91%) had m.p. 126° (from ethanol) (Found: C, 66·6; H, 7·7; N, 25·7. $C_{12}H_{16}N_4$ requires C, 66·6; H, 7·5; N, 25·9%). [The use of tetrahydrofuran (containing a little *p*-toluenesulphonic acid) in place of ethanol, gave the same product (61%).]

The same ethoxyhexahydro-2*H*-azonine (1·6 g), aminomethylenecyanoacetamide[19] (1·2 g) and butanol (30 ml) were heated under reflux for 15 h. T.l.c. indicated two products which were then separated on an alumina column (chloroform–ethanol). One proved to be the *triazabicyclotetradecatrienecarboxamide* (39%), m.p. 245° (from ethanol) (Found: C, 61·7; H, 7·8; N, 23·8. $C_{12}H_{18}N_4O$ requires C, 61·5; H, 7·7; N, 23·9%); the other, in almost equal amount, appeared to be an uncyclized intermediate which was converted slowly into the final product by further heating in butanol.

Similarly, the ethoxyhexahydro-2*H*-azonine (3·3 g) and ethyl aminomethylenecyanoacetate[20] (2·8 g) in butanol (50 ml) gave the *ethyl triazabicyclotetradecatrienecarboxylate* (32%), m.p. *c.* 94°, best characterized as the *picrate*, m.p. 184° (Found: C, 46·8; H, 5·1; N, 16·7. $C_{20}H_{24}N_6O_9,H_2O$ requires C, 47·1; H, 5·1; N, 16·5%).

[21] Bousquet, E. W., *Org. Synth.*, 1943, Coll. Vol. II, 314.

3,4-Dihydro-4-oxopyrimidine-5-carbonitrile (*8c*)

Aminomethylenecyanoacetamide[17] (3·0 g), triethyl orthoformate (30 ml) and acetic anhydride (30 ml) were boiled under reflux for 2 h. The residue from evaporation recrystallized from water to give the carbonitrile (8c) (95%), m.p. 247° (cf. Bredereck *et al.*:[22] 30%, m.p. 245°).

4-Amino-2,3-dihydro-3-methyl-2-thioxopyrimidine-5-carbonitrile (*9*)

Malononitrile (22 g), *N*-methylthiourea (30 g) and triethyl orthoformate (142 g) were stirred on the steam bath for 4 h. Evaporation gave an intermediate solid which was heated under reflux in ethanolic sodium ethoxide (from 7·7 g sodium and 500 ml ethanol) for 6 h. The residue from evaporation was dissolved in water and acidified with acetic acid to give the *carbonitrile* (9) (60%), m.p. 255° (from ethanol) (Found: C, 43·2; H, 3·9; N, 33·3. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; N, 33·7%).

4-Methylaminopyrimidine-5-carbonitrile (*10a*)

(A) The carbonitrile (9) (5·0 g), ammonium chloride (5·6 g), Raney nickel (10 g) and ethanol (400 ml) were stirred and heated under reflux for 15 h. The filtered solution was evaporated to dryness. The residue was extracted twice with boiling methanol. The cooled solution was diluted with acetone to precipitate ammonium chloride. The filtrate was evaporated to give the methylaminopyrimidinecarbonitrile (81%), m.p. 223° (from aqueous ethanol) (cf.[10] 222–223°).

(B) Crude 5-cyano-1,6-dihydro-6-imino-1-methyl-2-methylthiopyrimidine hydriodide (2·0 g; derived from the thione with methyl iodide), ammonium iodide (0·5 g) and Raney nickel (4·0 g) were treated as in (A) to give the same product (62%).

(C) Ethyl *N*-methylformimidate hydrochloride[23] (3·0 g) in tetrahydrofuran (10 ml) was treated with triethylamine (1 ml). The filtered solution together with aminomethylenemalononitrile[17] (0·93 g) and *p*-toluenesulphonic acid (0·1 g) was boiled under reflux for 24 h. Concentration gave the methylaminopyrimidinecarbonitrile (90% after recrystallization).

2-Methyl-4-methylaminopyrimidine-5-carbonitrile (*10b*)

Aminomethylenemalononitrile[17] (0·93 g), methyl *N*-methylacetimidate[23] (1·8 g), tetrahydrofuran (10 ml) and *p*-toluenesulphonic acid (30 mg) were heated under reflux for 72 h. Evaporation and column chromatography (alumina; chloroform) gave the methylmethylaminopyrimidinecarbonitrile (52%), m.p. 153–154° (lit.[24] 152°); ν_{max} (NH) 3180, 3400 cm^{-1}.

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[24] Nesbitt, P., and Sykes, P., *J. Chem. Soc.*, 1954, 3057.