The Dimroth Rearrangement. Part XVIII.[1] Syntheses and Rearrangement of 4-Iminoquinazolines and Related Systems

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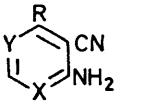
o-Aminobenzonitrile is converted by triethyl orthoformate–acetic anhydride into its *N*-ethoxymethylene derivative (2), which can undergo alkylaminolysis followed by spontaneous cyclization to 3-alkyl-3,4-dihydro-4-iminoquinazolines (3; X = CH); these rearrange in alkali to 4-alkylaminoquinazolines. The related 3,4-dihydro-4-imino-2,3-polymethylenequinazolines (8; X = NH) are also prepared from *o*-aminobenzonitrile, either by condensation with appropriate cyclic imino-ethers or by cyclodehydration with lactams; when the 2,3-polymethylene chain is longer than five CH_2 units, Dimroth rearrangement occurs in alkali to give the isomeric β-bridged 2,*N*(4)-polymethylene-4-aminoquinazolines (9; X = CH). Aza-analogues of the above systems are prepared by analogous routes. Rates of rearrangement are discussed.

We have reported recently some new synthetic routes to 1,6-dihydro-6-iminopyrimidines bearing a 1-alkyl substituent [2] or a 1,2-polymethylene bridge;[1] also the subsequent Dimroth rearrangement of such imines into 6-alkylaminopyrimidines or 2,*N*(6)-polymethylene-6-aminopyrimidines, respectively. This work is now extended to the 4-iminoquinazolines (3; X = CH) and (8; X = NH) and to the related systems (3; X = N) and (10); Dimroth rearrangement has been studied only briefly [3] in the 2-iminoquinazoline series and even less [4] in the 4-iminoquinazoline group by use of unsatisfactory compounds such as the imine (3a).

For the synthesis of simple 3-alkyl-3,4-dihydro-4-iminoquinazolines (3; X = CH), a method analogous to that [1] used for 6-iminopyrimidines proved effective: *o*-aminobenzonitrile (1; X = Y = CH, R = H) condensed with triethyl orthoformate in the presence of acetic anhydride to give ethoxymethyleneaminobenzonitrile (2), which underwent ready aminolysis by methyl-, isopropyl-, or t-butyl-amine followed by spontaneous cyclization to give the imines (3b—d); a similar reaction with triethyl orthoacetate gave the 2,3-dimethyl imine (3e) but when 2-amino-6-methylbenzonitrile (1; X = Y = CH, R = Me) was treated with triethyl orthoformate followed by methylamine, the isomer (4f) of the expected imine (3f) was the sole product. The same general synthesis was used to convert 2-aminopyridine-3-carbonitrile [5] (1; X = N, Y = CH, R = H) into the iminopyridopyrimidine (3g). The imine (3e) was also made by a new single-stage route involving condensation of *o*-aminobenzonitrile with methyl *N*-methylacetimidate [MeC(:NMe)·OMe] in boiling xylene containing phosphorus pentoxide.

The simple imines (3b—e and g) rearranged to their respective isomers (4b—e and g) by warming in M-alkali; in a single case (3e) some hydrolysis occurred also to give a little of the quinazolinone (5).

The tricyclic imines (8; X = NH, n = 5—7) were each made by two methods: (*a*) fusion of *o*-aminobenzonitrile with the cyclic imino-ethers (6; n = 5—7); and (*b*) cyclodehydration of the same nitrile with the lactams (7; n = 5—7) by use of phosphorus pentaoxide in xylene. The imine (8; X = NH, n = 9) was prepared only by method (*b*) with the lactam (7; n = 9); the imine (10; n = 5) was made by fusion of 4-aminopyrimidine-5-carbonitrile with the cyclic imino-ether (6; n = 5); but attempts to prepare the homologous imine (10; n = 7) from the same nitrile with the imino-ether (6; n = 7) gave only an isomer (9; X = N, n = 7).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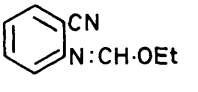
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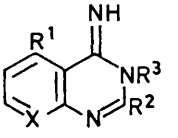
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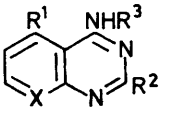
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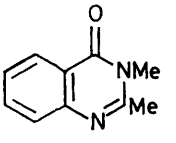
	X	R^1	R^2	R^3
a:	CH	H	SH	Ph
b:	CH	H	H	Me
c:	CH	H	H	Pr^i
d:	CH	H	H	Bu^t
e:	CH	H	Me	Me
f:	CH	Me	H	Me
g:	N	H	H	Me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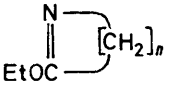
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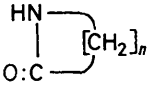
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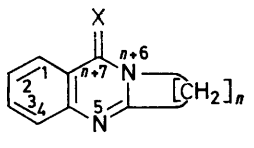
In aqueous alkali, the imine (8; X = NH, n = 5)

[1] Part XVII, D. J. Brown and K. Ienaga, *Austral. J. Chem.*, 1975, **28**, 119.
[2] D. J. Brown and K. Ienaga, *J.C.S. Perkin I*, 1974, 372.
[3] H. L. Wheeler, T. B. Johnson, and D. F. McFarland, *J. Amer. Chem. Soc.*, 1903, **25**, 787; R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 1960, 3540; D. J. Brown and B. T. England, *Austral. J. Chem.*, 1968, **21**, 2813.
[4] E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, 1962, **27**, 2622.
[5] H. U. Sieveking and W. Lüttke, *Angew. Chem.*, 1969, **81**, 432.

gave only the corresponding oxo-compound (8; X = O, $n = 5$) because the chain of five methylene groups was



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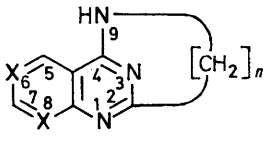

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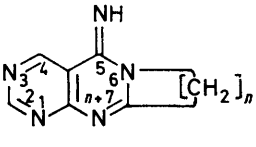

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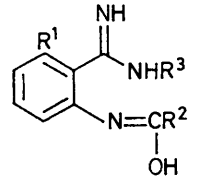

(11)

too short to permit the existence of a rearranged isomer (9; X = CH, $n = 5$) without considerable strain; the next higher homologous imine (8; X = NH, $n = 6$) gave a mixture of the oxo-analogue (8; X = O, $n = 6$) and the β-bridged isomer (9; X = CH, $n = 6$); and the homologues (8; X = NH, $n = 7$ or 9), with adequately long chains, gave only their respective rearranged isomers (9; X = CH, $n = 7$ or 9), in high yield. Apart from ammonia, no identifiable product was obtained from the imine (10; $n = 5$) in alkali.

The pK_a values and u.v. spectra (Experimental section) of the above imines and their derived isomers indicated that the rearrangements could be followed spectrometrically at pH 13. Thus at 70 °C, the spectra of most of the imines changed progressively to those of their respective isomers, maintaining good isosbestic points for >90% of each reaction. The changes in optical density proved to be first-order and rates are expressed as $t_{\frac{1}{2}}$ values in the Table.

Rearrangement of imines at pH 13

Imine	$t_{\frac{1}{2}}$ (70 °C)/min	Analyt. λ/nm
(3b)	4.8 [a]	315
(3c)	35	315
(3d)	37	315
(3e)	68	295
(3f)	*b*	
(3g)	<2	300
(8; X = NH, $n = 5$)	*c*	
(8; X = NH, $n = 6$)	*d*	
(8; X = NH, $n = 7$)	185	295
(8; X = NH, $n = 9$)	124	295
(10; $n = 5$)	*c*	
(10; $n = 7$)	*b*	

[a] 280 min at 20 °C. [b] Fast rearrangement during attempted preparation. [c] Hydrolysis only. [d] Rearrangement much slower than hydrolysis.

The imines (3c and d), each bearing a bulky branched *N*-alkyl group, rearranged much more slowly than the lower *N*-methylated homologue (3b). The reason(s) for this could have been (*a*) steric hindrance to hydration of the 2,3-bond prior to its fission to yield the intermediate (11) and/or (*b*) a steric interference between the bulky group (R^3) and the *ortho*-hydrogen atom (R^1) in the intermediate (11) during the 180° rotation of the amidine group necessary for recyclization to the rearranged product. Reason (*a*) was consistent with the 14-fold decrease in rearrangement rate observed between the imine (3b) and its 2-methyl derivative (3e); in contrast, 5-methylation of the imine (3b) to give the derivative (3f) actually increased the rearrangement rate, a fact apparently inconsistent with reason (*b*). However, models suggested that this increase could have resulted from instability engendered by steric interference between the imino- and the 5-methyl group in the imine (3f). The marked effect of electron withdrawal by a doubly bonded nitrogen on the rate of Dimroth rearrangement [6] was exemplified in the relative $t_{\frac{1}{2}}$ values for the imine (3b) and its 8-aza-analogue (3g).

As expected from the behaviour of simple analogues,[1] rearrangement of the pentamethyleneimine (8; X = NH, $n = 5$) proved impossible because the chain was too short to form a stable β-bridged amine (9; X = CH, $n = 5$); for the same reason, rearrangement of the imine (8; X = NH, $n = 6$) was very slow. However, the higher homologues (8; X = NH, $n = 7$ or 9) rearranged satisfactorily at 70 °C with $t_{\frac{1}{2}}$ values of 185 and 124 min, respectively. The latter figure approached that ($t_{\frac{1}{2}}$ 68 min) for the 2,3-dimethyl imine (3e), which might be considered akin to an imine (8; X = NH, $n = \infty$).

EXPERIMENTAL

Analyses were performed by the Australian National University Analytical Services Unit. The rearrangement rates were measured at pH 13 as described previously.[2] Ionization constants were measured spectrometrically [7] (analytical wavelength 285 nm) at 20 °C and 10^{-3}M concentration in buffers [8] of 10^{-2}M ionic strength; thermodynamic corrections were not applied. ^{1}H N.m.r. and u.v. spectral data are available as Supplementary Publication No. SUP 21481 (5 pp.).*

3,4-Dihydro-4-imino-3-methylquinazoline (3b).—*o*-Aminobenzonitrile (5.9 g), triethyl orthoformate (45 ml), and acetic anhydride (5 ml) were heated under reflux for 10 min. The residue from evaporation was triturated with light petroleum to give crude *o*-(ethoxymethyleneamino)benzonitrile (2) which was added to ethanolic methylamine (*ca* 30%; 50 ml) at room temperature. After 15 min, the solution was evaporated. Trituration of the residue with light petroleum gave the *imino-3-methylquinazoline* (97%), m.p. 178° (from ethanol) (Found: C, 67.75; H, 5.9; N, 26.2. $C_9H_9N_3$ requires C, 67.9; H, 5.7; N, 26.4%); pK_a 8.19 ± 0.03.

3,4-Dihydro-4-imino-3-isopropylquinazoline (3c).—The crude intermediate (2), prepared on the same scale as above, was stirred in ethanolic 30% isopropylamine (55 ml) at 25 °C for 15 h. Partial evaporation and filtration gave the *imino-3-isopropylquinazoline* (92%), m.p. 123—125° (from

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[6] D. J. Brown in ' Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1968, vol. 1, p. 209 *et seq.*

[7] A. Albert and E. P. Serjeant, Determination of Ionization Constants,' Chapman and Hall, London, 1971.

[8] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.

ethanol) (Found: C, 70.3; H, 7.0; N, 22.6. $C_{11}H_{13}N_3$ requires C, 70.6; H, 7.0; N, 22.4%); pK_a 8.06 ± 0.03.

3,4-*Dihydro*-4-*imino*-3-*t*-*butylquinazoline* (3d).—The intermediate (2) and ethanolic t-butylamine reacted as above for 3 weeks to give the *t*-*butyl*-4-*iminoquinazoline* (81%), m.p. 95—96° (from ethanol) (Found: C, 71.4; H, 7.6; N, 21.3. $C_{12}H_{15}N_3$ requires C, 71.6; H, 7.5; N, 20.9%).

3,4-*Dihydro*-4-*imino*-2,3-*dimethylquinazoline* (3e).—(*a*) *o*-Aminobenzonitrile (1.18 g), triethyl orthoacetate (7.5 ml), and acetic anhydride (2.5 ml) were heated under reflux for 20 min. The residue from evaporation was stirred with 30% ethanolic methylamine (45 ml) for 10 days at 25 °C to give the *iminodimethylquinazoline* (60%), m.p. 157—158° (from ethanol) (Found: C, 69.2; H, 6.4; N, 24.2. $C_{10}H_{11}N_3$ requires C, 69.3; H, 6.4; N, 24.3%); pK_a 8.35 ± 0.04.

(*b*) Phosphorus pentaoxide (10 g) was added to a stirred solution of *o*-aminobenzonitrile (1.2 g) and methyl *N*-methylacetimidate [9] (1.1 g) in anhydrous xylene. The suspension was then boiled under reflux for 15 min and allowed to cool. The solid were added to stirred ice–water (500 ml), which was then made alkaline with aqueous 50% potassium hydroxide and immediately extracted with chloroform. Evaporation of the extract and column chromatography (alumina; chloroform) gave a product (32%) identical with that from (*a*) (mixed m.p. and spectra).

3,4-*Dihydro*-4-*imino*-3-*methylpyrido*[2,3-d]*pyrimidine* (3g).—2-Aminopyridine-3-carbonitrile [5] (1; X = N, Y = CH, R = H) (0.30 g), triethyl orthoformate (4.5 ml), and acetic anhydride (1 ml) was heated under reflux for 90 min. The residue from evaporation was added to ethanolic 30% methylamine (3 ml). After 20 min, evaporation and trituration with light petroleum gave the *iminopyridopyrimidine* (41%), m.p. 243° (Found: C, 60.25; H, 4.9; N, 35.4. $C_8H_8N_4$ requires C, 60.0; H, 5.0; N, 35.0%).

4-*Alkylaminoquinazolines* (4; X = CH).—The imine (3 b) (0.50 g) and M-sodium hydroxide (50 ml) were warmed [60 °C for 1 h]. Evaporation of a chloroform extract gave the crude product, which was purified by passing through an alumina column in chloroform to give 4-methylaminoquinazoline (94%), m.p. 201° (from ethanol) (lit.,[10] 196°); pK_a 6.37 ± 0.06.

The imine (3c) rearranged similarly [80 °C for 12 h] to give 4-*isopropylaminoquinazoline* (4c) (91%), m.p. 175° (Found: C, 70.6; H, 7.0; N, 22.5. $C_{11}H_{13}N_3$ requires C, 70.6; H, 7.0; N, 22.4%); pK_a 6.39 ± 0.05.

The imine (3d) gave [100 °C for 24 h] 4-*t*-*butylaminoquinazoline* (4d) (93%), m.p. 95—96° (Found: C, 71.4; H, 7.6; N, 21.3. $C_{12}H_{15}N_3$ requires C, 71.6; H, 7.5; N, 20.9%).

The imine (3e) gave [80 °C for 6 h] 2-*methyl*-4-*methylaminoquinazoline* (4e) (82%), m.p. 134° (Found: C, 69.5; H, 6.2; N, 24.2. $C_{10}H_{11}N_3$ requires C, 69.3; H, 6.4; N, 24.3%); pK_a 7.43 ± 0.04; and 2,3-*dimethylquinazolin*-4-*one* (5) (5%), m.p. 111° (Found: C, 69.1; H, 5.9; N, 16.1. $C_{10}H_{10}N_2O$ requires C, 68.95; H, 5.8; N, 16.1%).

2-Amino-6-methylbenzonitrile [11] (1; X = Y = CH, R = Me) (6.6 g), triethyl orthoformate (50 ml), and acetic anhydride (5 ml) were heated under reflux for 15 min. The residue from evaporation was ground with a little light petroleum, filtered off, and then added to methylamine (20 g) in ethanol (40 ml). After 10 min the solution was evaporated. Trituration of the residue with light petroleum gave 5-*methyl*-4-*methylaminoquinazoline* (4f) (85%), m.p. 178° (from ethanol) (Found: C, 68.9; H, 6.4; N, 23.9. $C_{10}H_{11}N_3$ requires C, 69.3; H, 6.4; N, 24.3%)

4-*Methylaminopyrido*[2,3-d]*pyrimidine* (4g).—The imine (3 g) (80 mg) was warmed in M-sodium hydroxide (10 ml) at 60 °C for 30 min to give, as for the quinazoline (4b), the *methylaminopyridopyrimidine* (64%), m.p. 231° (Found: C, 60.1; H, 5.05; N, 34.8. $C_8H_8N_4$ requires C, 60.0; H, 5.0; N, 35.0%).

6,7,8,9,10,12-*Hexahydro*-12-*iminoazepino*[2,1-b]*quinazoline* (8; X = NH, *n* = 5).—(*a*) *o*-Aminobenzonitrile (1.18 g) and 7-ethoxy-3,4,5,6-tetrahydro-2*H*-azepine [1] (6; *n* = 5) (1.6 g) were fused together at 150 °C for 24 h. The cooled mixture was dissolved in the minimum quantity of ethanol and then a little hydriodic acid was added. Evaporation and trituration of the residue with ethyl acetate gave the *iminoazepinoquinazoline hydriodide* (86%), m.p. 281° (Found: C, 45.8; H, 4.8; N, 12.1. $C_{13}H_{16}IN_3$ requires C, 45.8; H, 4.7; N, 12.3%).

(*b*) Phosphorus pentaoxide (10 g) was added to a stirred mixture of *o*-aminobenzonitrile (1.18 g), hexane-6-lactam (7; *n* = 5), and anhydrous xylene (50 ml). The suspension was boiled under reflux for 15 min and then cooled. The solid was added with stirring to ice–water (500 ml) and then made alkaline with aqueous 50% potassium hydroxide. Extraction with chloroform and evaporation of the extract gave the *base* (71%), m.p. 124—125° (from ethanol) (Found: C, 72.9; H, 7.0; N, 14.4. $C_{13}H_{15}N_3$ requires C, 73.2; H, 7.1; N, 19.7%), identical with a specimen prepared from the hydriodide in (*a*).

6,7,8,9,10,11-*Hexahydro*-13-*imino*-13H-*azocino*[2,1-b]-*quinazoline* (8; X = NH, *n* = 6).—(*a*) *o*-Aminobenzonitrile (1.18 g) and 2-ethoxy-3,4,5,6,7,8-hexahydroazocine [1] (6; n = 6) (1.18 g) were heated at 190 °C for 36 h to give the *iminoazocinoquinazoline* (68%), m.p. 153° (from ethanol) (Found: C, 74.1; H, 7.3; N, 18.4. $C_{14}H_{17}N_3$ requires C, 74.0; H, 7.5; N, 18.5%).

(*b*) Cyclodehydration of *o*-aminobenzonitrile (1.16 g) and heptane-7-lactam (7; *n* = 6) (1.14 g) with phosphorus pentaoxide as above gave the same product (65%) as in (*a*).

6,7,8,9,10,11,12,14-*Octahydro*-14-*iminoazonino*[2,1-b]*quinazoline* (8; X = NH; *n* = 7).—(*a*) *o*-Aminobenzonitrile (1.18 g) and 9-ethoxy-3,4,5,6,7,8-hexahydro-2*H*-azonine [1] (6; n = 7) at 190 °C for 24 h gave the *iminoazoninoquinazoline* (70%), m.p. 146° (from ethanol) (Found: C, 74.4; H, 8.0; N, 17.7. $C_{15}H_{19}N_3$ requires C, 74.65; H, 7.9; N, 17.4%).

(*b*) Cyclodehydration of *o*-aminobenzonitrile (1.16 g) and octane-8-lactam (7; *n* = 7) (1.56 g) gave a product (74%) identical with that from (*a*).

6,7,8,9,10,11,12,13,14,16-*Decahydro*-16-*iminoazacycloundecino*[2,1-b]*quinazoline* (8; X = NH, *n* = 9).—Cyclodehydration of *o*-aminobenzonitrile (2.36 g) and decane-10-lactam (7; *n* = 9) (3.6 g) gave the *iminoazacycloundecinoquinazoline* (67%), m.p. 158° (from ethanol) (Found: C, 76.1; H, 8.65; N, 15.6. $C_{17}H_{23}N_3$ requires C, 75.8; H, 8.6; N, 15.6%).

Action of Alkali on the Imines (8; X = NH, *n* = 5—7 *or* 9).—The hexahydroiminoazepinoquinazoline (0.50 g) and M-potassium hydroxide (150 ml) were heated on a steam-bath for 18 h. The cooled solution was extracted with chloroform. The solute in the extract was purified by column chromatography (alumina; chloroform) to give a

[9] H. Bredereck, F. Effenberger, and E. Henseleit, *Chem. Ber.*, 1965, **98**, 2754.

[10] E. Hayashi, T. Higashino, and S. Tomisaki, *J. Pharm. Soc. Japan*, 1967, **87**, 578.

[11] S. Gabriel and A. Thieme, *Ber.*, 1919, **52***B*, 1079.

single major product, 7,8,9,10-tetrahydrodroazepino[2,1-*b*]quinazolin-12(6*H*)-one (8; X = O, *n* = 5), m.p. 97° (lit.,[12] 95°).

Similarly, the hexahydroiminoazocinoquinazoline gave starting material (19%) and two products, separated by chromatography (alumina; benzene–ethyl acetate). 6,7,8,9,10,11-*Hexahydroazocino*[2,1-b]*quinazolin*-13-*one* (8; X = O, *n* = 6) (43%), had m.p. 112° (Found: C, 73.6; H, 7.1; N, 12.3. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%). The second product was 4,2-*iminohexanoquinazoline* (9; X = CH, *n* = 6) (21%), m.p. 207° (Found: C, 73.8; H, 7.3; N, 18.5. $C_{14}H_{17}N_3$ requires C, 74.0; H, 7.5; N, 18.5%).

Similar treatment of the octahydroiminoazoninoquinazoline in 3 : 1 aqueous-ethanolic M-sodium hydroxide gave only 4,1-*iminoheptanoquinazoline* (9; X = CH, *n* = 7) (91%), m.p. 244° (from ethanol) (Found: C, 74.6; H, 7.7; N, 17.6. $C_{15}H_{19}N_3$ requires C, 74.65; H, 7.9; N, 17.4%).

In the same way, the decahydroiminoazacycloundecinoquinazoline gave 4,2-*iminononanoquinazoline* (9; X = CH; *n* = 9) (85%), m.p. 158° (from ethanol) (Found: C, 76.0, H, 8.7; N, 15.3. $C_{17}H_{23}N_3$ requires C, 75.8; H, 8.6; N, 15.6%).

5,7,8,9,10,11-*Hexahydro*-5-*iminopyrimido*[4′,5′:4,5]*pyrimido*[1,2-a]*azepine* (10; *n* = 5).—4-Aminopyrimidine-5-carbonitrile [13] (0.6 g) and 7-ethoxy-3,4,5,6-tetrahydro-2*H*-azepine [1] (6; *n* = 5) (0.8 g) were heated at 150 °C for 12 h. Trituration of the cooled mixture with light petroleum gave the *iminopyrimidopyrimidoazepine* (93%), m.p. *ca.* 130° (decomp.) (Found: C, 61.3; H, 6.3. $C_{11}H_{13}N_5$ requires C, 61.4; H, 6.1%).

4,2-*Iminoheptanopyrimido*[4,5-d]*pyrimidine* (9; X = N, *n* = 7).—4-Aminopyrimidine-5-carbonitrile [13] (10.7 g) and 9-ethoxy-3,4,5,6,7,8-hexahydro-2*H*-azonine [1] (6; *n* = 7) (0.93 g) were heated together at 100 °C for 12 h. Trituration of the residue in light petroleum gave the *iminoheptanopyrimidopyrimidine* (91%), m.p. 126° (decomp.) (Found: C, 63.8; H, 7.1. $C_{13}H_{17}N_5$ requires C, 64.2; H, 7.0%).

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