Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part 36.[1] Stereochemistry of 7-Methyl-6,7,8,9,10,11,11a,11b,-12,13-decahydro-7a*H*-quino[1,2-*c*]quinazolines and 7-Methyl-6,7,7a,8,9-,10,10a,10b,11,12-decahydrocyclopenta[4,5]pyrimido[1,6-*a*]quinolines

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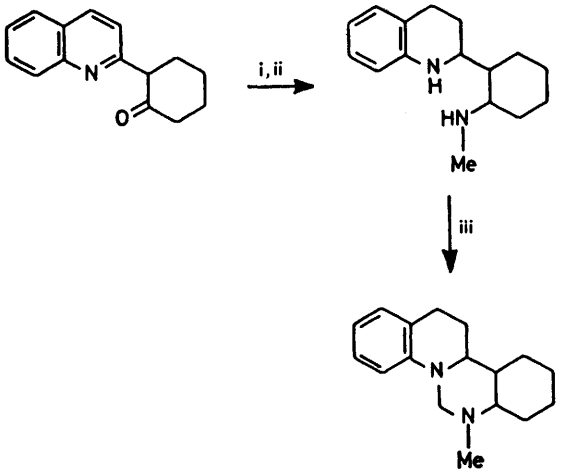
Three diastereoisomeric 7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]quinazolines and two 7-methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]pyrimido[1,6-*a*]quinolines have been synthesised and their configurations assigned by a combination of ^{1}H n.m.r. and i.r. spectroscopy and the application of conformational analysis. For the quino[1,2-*c*]quinazolines the *r*-7a,*c*-11a,*c*-11b-compound adopts (in solution) the *trans*-BC conformation with an equatorial *N*-methyl group. The *r*-7a,*c*-11a,*t*-11b-compound exists in solution as an equilibrium mixture of two conformations, both of which possess the *trans*-BC ring junction with that conformation with the axial *N*-methyl group predominating over the equatorial *N*-methyl conformation. The predominant conformation for the *r*-7a,*t*-11a,*t*-11b compound is that with the *cis*-BC ring junction and an equatorial *N*-methyl group. Similar conformational preferences are shown by the *r*-7a,*c*-10a,*c*-10b- and *r*-7a,*t*-10a,*t*-10b-cyclopenta-[4,5]pyrimido[1,6-*a*]quinolines.

As part of a study [2] of the stereochemistry of azasteroidal systems the 7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]quinazolines (1) and 7-methyl-



(1)

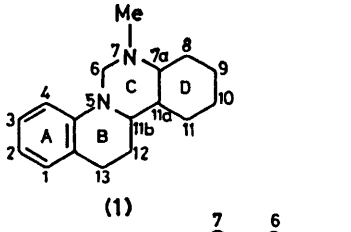
SCHEME Reagents: i, $MeNH_2$; ii, H_2–PtO_2; iii, aqueous 40% CH_2O

6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]-pyrimido[1,6-*a*]quinolines (2) were synthesised. For completeness the tricyclic compound 2-methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (3) was also prepared.

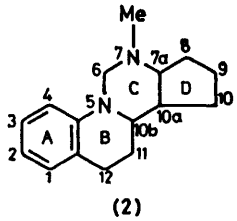
Syntheses.—The diastereoisomeric 7-methyl-6,7,8,9,-10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]quinazolines (1) were prepared by the route shown in the Scheme. The base obtained on passing dry methylamine gas into an ethanolic solution of the 2-(2-quinolyl)cyclohexanone [3] was hydrogenated under pressure in acetic acid solution over Adams platinum oxide catalyst. The isomeric *N*-methyl-2-(1,2,3,4-tetrahydro-2-quinolyl)cyclohexylamines produced were ring closed with aqueous formaldehyde. The isomeric 7-methyl-6,7,8,9,10,11,11a,11b,-12,13-decahydro-7a*H*-quino[1,2-*c*]quinazolines obtained were separated by column chromatography over Grade III Wöelm neutral alumina. Only three of the four possible isomers were obtained. These were further purified by sublimation and recrystallisation.

Synthesis of the isomeric 7-methyl-6,7,7a,8,9,10,10a,-10b,11,12-decahydrocyclopenta[4,5]pyrimido[1,6-*a*]-quinolines (2) was achieved by the same synthetic path used for the benzo analogues (1) (Scheme 1) but starting with 2-(2-quinolyl)cyclopentanone.[2] Only two of the four possible diastereoisomers of (2) were obtained and these were isolated by column chromatography over alumina and further purified by sublimation and recrystallisation.

Reaction between 2-vinylquinoline [4] and methylamine hydrochloride gave *N*-methyl-2-(2-quinolyl)ethylamine which was hydrogenated under pressure in acetic acid solution in the presence of Adams platinum oxide catalyst. The resultant *N*-methyl-2-(1,2,3,4-tetrahydro-2-quinolyl)ethylamine was ring closed with



(1)



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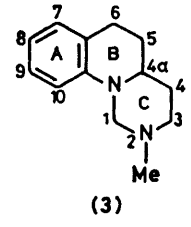
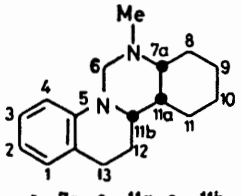


(3)

aqueous formaldehyde to yield 2-methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (3).

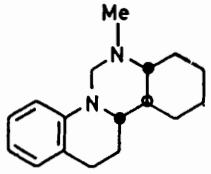
A priori *Discussion of Conformational Equilibria.*—The conformational analysis of (1) and (2) is complicated by the presence of two conformationally mobile nitrogen

atoms. In order to simplify the problem, Dreiding models of the possible all chair conformations of each of the four isomers (4)—(7) were examined for serious non-bonded interactions.



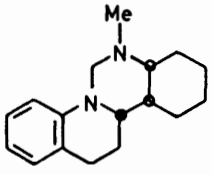
r—7a, *c*—11a, *c*—11b

(4)



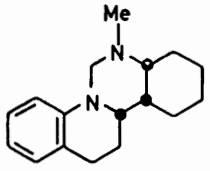
r—7a, *t*—11a, *c*—11b

(5)



r—7a, *c*—11a, *t*—11b

(6)



r—7a, *t*—11a, *t*—11b

(7)

A ready differentiation between the conformers (Figure 1) * of the *r*-7a,*c*-11a,*c*-11b compound (4) was possible, since severe steric interactions present in five of the conformations (4b—f) precluded any significant contribution from these to the equilibrium mixture. This leaves only (4a) as the predominant conformation for (4).

Of the four conformations possible (Figure 2) for the *r*-7a,*t*-11a,*c*-11b compound (5), conformer (5e) could be instantly disregarded because of the severe 1,3-*syn*-axial interaction. The more serious non-bonded interactions (as indicated by Dreiding models) present in the other conformations are shown in Table 1. It must be stressed that these non-bonded interactions are those observed in the relatively rigid Dreiding models. The

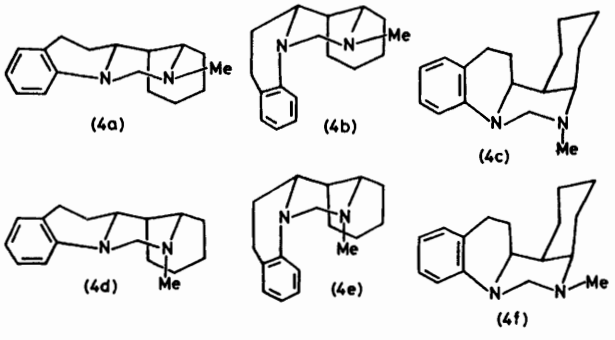


FIGURE 1 Possible conformations of *r*-7a,*c*-11a,*c*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]-quinazoline (4)

easy deformability [5] of the C–N–C angles and the relatively mobile B ring would probably result in a reduction in the magnitude of the interactions though not necessarily to the same degree in each conformation. Thus comparisons of the non-bonded interactions in the various conformations can only be qualitative.

* The compounds described in this reaction exist as racemates, and the structures are drawn for ease of representation and do not necessarily represent the same enantiomer in each case.

TABLE 1

Non-bonded interactions in conformations of *r*-7a,*t*-11a,-*c*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]quinazoline (5)

trans-BC-Conformations	*cis*-BC-*N*-Inside conformations [a]
(5a)	(5b)
Unfavourable anomeric effect	4-H, 6eq-H
4-H, 6eq-H	Ph,H [c]
2 × 'gb' [b]	Ph,N [c]
	3 × 'gb' [b]
(5d)	(5e)
4-H, 6eq-H	4-H, 6eq-H
1 × 'gp' [d]	Ph,H [c]
3 × 'gb' [d]	Ph,Me [c]
	4 × 'gb' [b]

[a] In Dreiding models of the *cis*-BC-*N*-inside conformations there are *syn*-axial interactions (H,H distance *ca.* 1.9 Å) between the 13-methylene and the 11a-protons, which are included as 'gb' interactions since they may be reduced by rotation about the C(12)–C(13) bond only at the expense of introducing torsional interactions between the 12- and 13-methylene groups. [b] An approximate *gauche*-butane interaction. Differing bond lengths will result in the value being different from that (0.85 kcal mol^{-1}) in cyclohexane derivatives. [c] Near *syn*-axial Ph,C–H interaction, Ph,N interaction, or Ph,Me interaction. [d] A *gauche*-propylamine interaction. Strictly this is not the interaction in *gauche*-propylamine but it is current practice to refer to the interaction between a nitrogen lone pair and a *syn*-axial CH_2 or CH_3 group in a saturated six-membered ring as such.

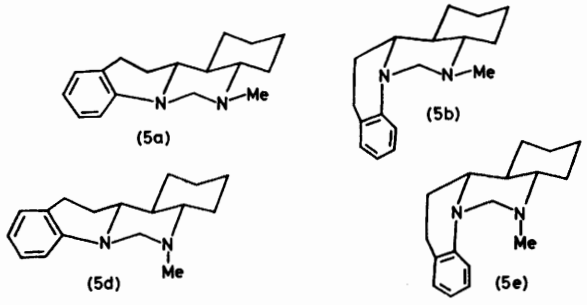


FIGURE 2 Possible conformations of *r*-7a,*t*-11a,*c*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]-quinazoline (5)

The *trans*-BC conformation (5a) contains the least number of non-bonded interactions and would thus be expected to predominate. The corresponding axial *N*-methyl conformation (5d), however, may not be ignored since the (5a) ⇌ (5d) equilibrium depends on a balance between the unfavourable generalised anomeric effect [6] present in (5a) and a *gauche*-butane together with a *gauche*-propylamine type interaction in (5d). The difference between a *gauche*-butane interaction and a *gauche*-propylamine interaction has been calculated [7] to be 0.70 kcal mol^{-1}, giving the latter interaction a value of 0.15 kcal mol^{-1} assuming the usual value of 0.85 kcal mol^{-1} for the *gauche*-butane interaction.[8] Thus ΔG° at ambient temperatures for the (5a) ⇌ (5d) equilibrium may well be of the order of 0.85 kcal mol^{-1} corresponding to *ca.* 20% of (5d). The *cis*-BC-*N*-inside conformation (5b) is of higher energy than (5d) since a *syn*-axial

Ph,C–H interaction is incurred, which in a cyclohexane system [8] would increase the energy of the system by *ca.* 1.5 kcal mol^{-1}. In the related 2-methylperhydropyrido[1,2-*c*]pyrimidine equilibrium (8) ⇌ (9) both ^{1}H n.m.r. spectral and dipole moment data show *ca.* 75% of (8) and 25% of (9) to be present at room temperature.[9] Thus one might expect isomer (5) to exist predominantly (*ca.* 80%) as conformation (5a) with perhaps 20% of (5d) in equilibrium.

A similar treatment can be applied to the possible conformations (Figure 3) of the *r*-7a,*c*-11a,*t*-11b compound (6). The more serious non-bonded interactions present in the conformations are shown in Table 2. Conformations (6c and e) can be ruled out immediately due to the presence of severe steric interactions and (6b) possessing a *syn*-axial Ph,C–H interaction cannot be expected to contribute significantly to the equilibrium. Conformers (6a and d) differ only by the difference between the unfavourable generalised anomeric effect present in (6a) and the *gauche*-propylamine interaction in (6d), and so the (6a) ⇌ (6d) equilibrium should be weighted more towards the axial *N*-methyl conformation relative to the corresponding (5a) ⇌ (5d) equilibrium. Although conformer (6f) suffers from fewer *gauche*-butane type interactions than conformers (6a and d), the generalised anomeric effect in (6f) must be of greater magnitude than that in (6a), since the bridgehead nitrogen atom lone pair is more localised. In addition the extra stability of conformers (6a and d) arising from the delocalisation of the bridgehead nitrogen atom lone pair into the aromatic π-electron system is lost in conformer (6f). Also present in this conformer is an interaction between the phenyl ring and 6ax-H. Thus it seems unlikely that (6f) will contribute to any significant degree to the equilibrium mixture and accordingly the *r*-7a,*c*-11a,*t*-11b compound (6) might be expected to exist as a *ca.* 50 : 50 mixture of conformations (6a and d).

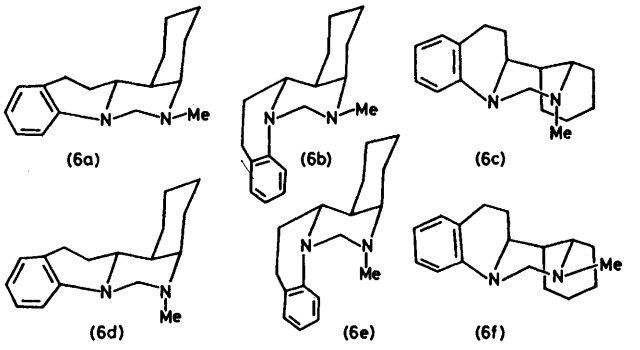


FIGURE 3 Possible conformations of *r*-7a,*c*-11a,*t*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]-quinazoline (6)

TABLE 2

Non-bonded interactions in conformations of *r*-7a,*c*-11a,-*t*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]quinazoline (6)

trans-BC-Conformations	*cis*-BC-*N*-Inside conformations [a]	*cis*-BC-*N*-Outside conformations
(6a)	(6b)	(6c)
Unfavourable anomeric effect	4-H, 6eq-H	Ph, 6ax-H [b]
4-H, 6eq-H	Ph,N	2 × Me,CH$_2$
5 × gb	Ph,N	1 × gp
	6 × gb	2 × gb
(6d)	(6e)	(6f)
4-H, 6eq-H	4-H, 6eq-H	Unfavourable anomeric effect
1 × gp	Ph,H	Ph, 6ax-H [b]
5 × gb	Ph,Me	3 × gp
	5 × gb	3 × gb

[a] In Dreiding models of the *cis*-BC-*N*-inside conformations there are *syn*-axial interactions (H,H distance *ca.* 1.9 Å) between the 13-methylene and the 11a-protons which are included as gb interactions since they may be reduced by rotation about the C(12)–C(13) bond only at the expense of introducing torsional interactions between the 12- and 13-methylene groups. [b] Interaction between phenyl ring and 6ax-H.

Only two conformations (Figure 4) need be considered for the *r*-7a,*t*-11a,*t*-11b compound (7) as the *trans*-BC conformations possess boat c rings. The parallel lone pair geometry in (7a) can only be relieved at the expense of introducing extra *gauche*-butane and *gauche*-propylamine interactions in (7b). Thus the overall energy difference between the two conformations is expected to be the same as that between (5a and d) with a similar expected position of equilibrium of *ca.* 80% (7a).

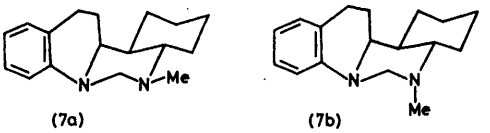


FIGURE 4 Possible conformations of *r*-7a,*t*-11a,*t*-11b-7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino[1,2-*c*]-quinazoline (7)

A similar treatment of the isomers of 7-methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]-pyrimido[1,6-*a*]quinoline (2), gives the same results since the non-bonded interactions present in the conformations do not differ markedly from those in the six-membered analogues.

Similar arguments (Table 3) applied to the conformational equilibrium (Figure 5) in 2-methyl-2,3,4,4a,5,6-

TABLE 3

Non-bonded interactions in the conformations of 2-methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (10)

trans-BC-Conformations	*cis*-BC-*N*-Inside conformations	*cis*-BC-*N*-Outside conformations
(10a)	(10b)	(10c)
Unfavourable anomeric effect	10-H, 1eq-H	Ph, 6ax-H
10-H, 1eq-H	Ph,H	1 × gp
	Ph,N	3 × gb
	1 × gb	
(10d)	(10e)	(10f)
10-H, 1eq-H	10-H, 1eq-H	Unfavourable anomeric effect
1 × gp	Ph,H	Ph, 6ax-H
1 × gb	Ph,Me	2 × gb
	2 × gb	

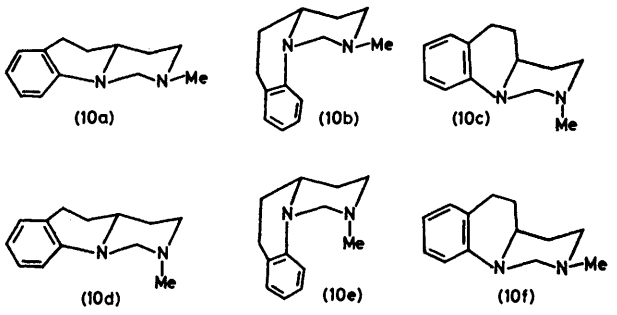


FIGURE 5 Possible conformations of 2-methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (3)

hexahydro-1*H*-pyrimido[1,6-*a*]quinoline (3) suggest an equilibrium containing *ca.* 80% (10a) and 20% (10d).

*Assignment of Stereochemistry to the 7-Methyl-6,7,8,9,10,11,1a,11b,12,13-decahydro-7a*h*-quino*[1,2-c]*-quinazolines.*—The presence or absence of bands (Bohlmann bands [10]) in the 2 800—2 600 cm^{-1} of the i.r. spectra of the quino[1,2-*c*]quinazolines (4)—(7) is an indication of the orientation of the NMe group. Strong Bohlmann bands will be observed if the NMe group is equatorial when one of the methyl group C–H bonds will be anticoplanar with the nitrogen lone pair. Very little contribution to Bohlmann absorption from C–H bonds adjacent to the 5-nitrogen atom is expected since this nitrogen carries an aromatic ring.[2]

Isomers (4) and (7) showed strong absorption in the 2 800—2 600 cm^{-1} region of the i.r. (Figure 6) suggesting a predominance of conformations with an equatorial NMe group, whereas the relatively weaker absorption observed for isomer (6) suggested (in the absence of any other data) a predominance of a conformation with an axial NMe group.

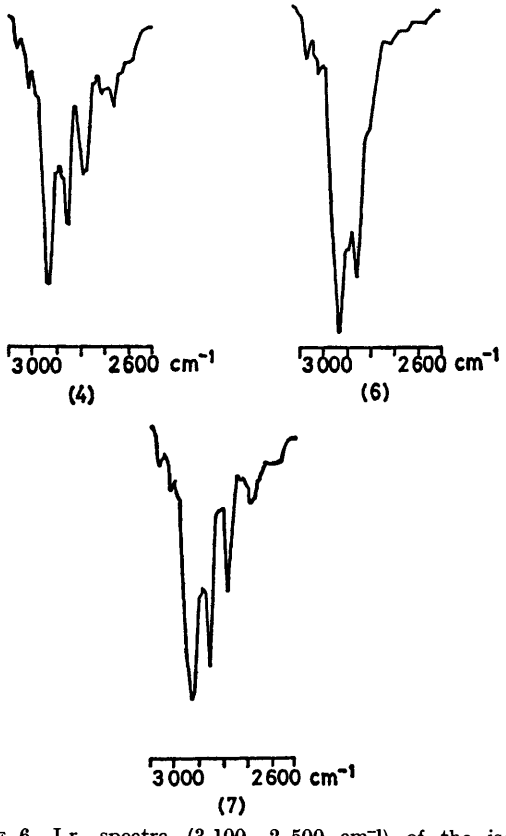


FIGURE 6 I.r. spectra (3 100—2 500 cm^{-1}) of the isomeric 7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino-[1,2-*c*]quinazolines

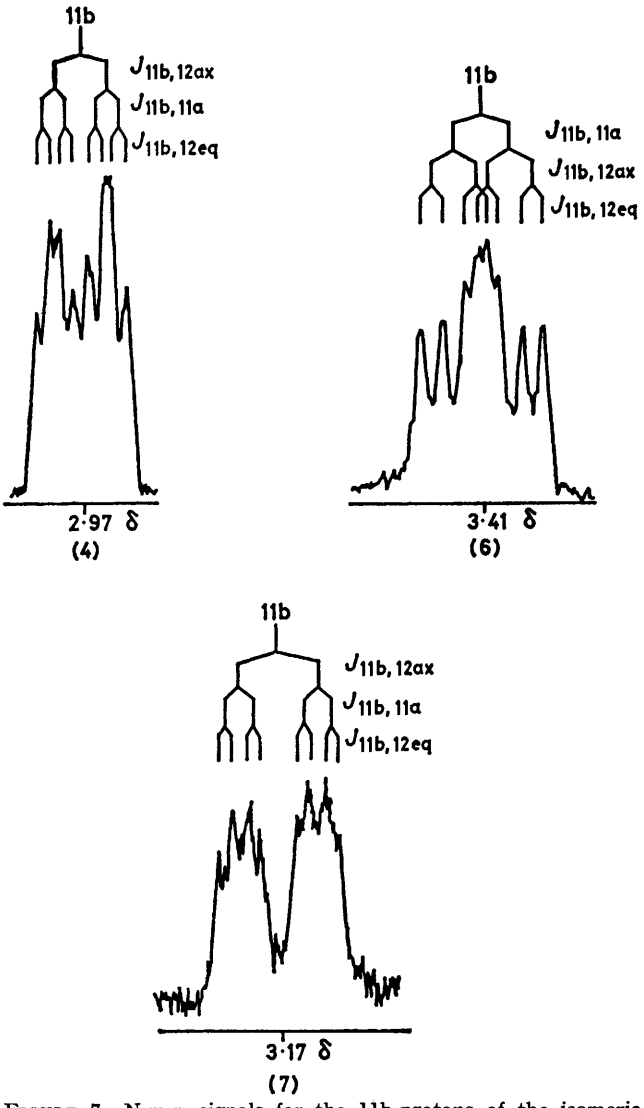


FIGURE 7 N.m.r. signals for the 11b-protons of the isomeric 7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino-[1,2-*c*]quinazolines

The u.v. spectra of the isomers (Table 4) showed for (4), $\lambda_{max.}$ 255 and 294 nm (ε 10 450 and 1 970), and for (6), $\lambda_{max.}$ 257 and 299.5 nm (ε 11 350 and 2 110), suggest-

TABLE 4

U.v. absorption spectra of compounds (1)—(3)

Compound	λ_{max}/nm	ε
(4)	255.0, 294.0	10 450, 1 970
(6)	257.0, 299.5	11 350, 2 110
(7)	248.0, 280.0	6 670, 1 160
(15)	256.5, 296.5	11 550, 2 010
(16)	254.0, 297.0	12 320, 2 090
(3)	254.0, 297.0	11 360, 2 070

ing conformations in which the bridgehead nitrogen lone pair is delocalised over the aromatic ring, as is possible in a *trans*-BC or *cis*-BC-*N*-inside conformation. The relative lower wavelength absorption and smaller extinction coefficients found in the spectrum of (7), $\lambda_{max.}$ 248 and 280 nm (ε 6 670 and 1 160), is indicative of a *cis*-BC-*N*-outside conformation in which the bridgehead nitrogen lone pair lies in the plane of the aromatic ring.

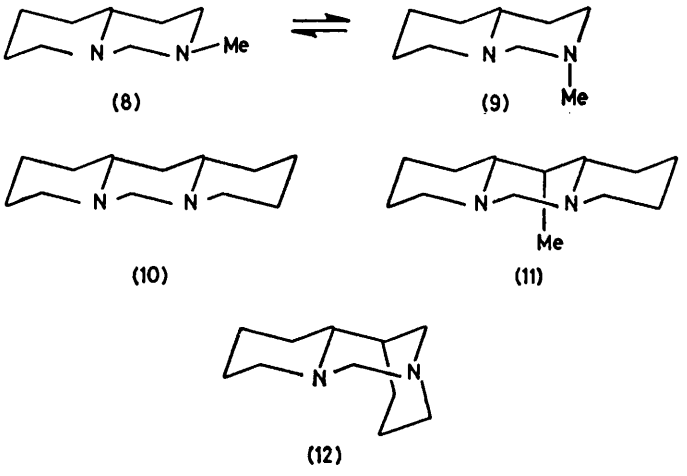
The n.m.r. spectra of the three isomers of (1) are summarised in Table 5, and the splitting patterns of the 11b-protons are depicted in Figure 7.

(i) 7-*Methyl*-6,7,8,9,10,11,c-11a,c-11b,12,13-*decahydro*-r-7aH-*quino*[1,2-c]*quinazoline*. The first isomer eluted from the chromatography column was assigned the *r*-7a,*c*-11a,*c*-11b configuration (4).

The main indication of the stereochemistry of this isomer was the high field chemical shift (δ 3.13) of the 6ax-proton, indicative of shielding by an axial ring methylene at C-11a, as exemplified by compound (11) in which the presence of the 12-axial methyl group results in a shielding of the 6ax-proton by 0.28 p.p.m. relative to the unsubstituted perhydrodipyrido-[1,2-*c* : 2′,1′-*f*]pyrimidine [11] (10). Only two conformations out of those possible for all four isomers (ignoring those already disregarded in the *a priori* discussion of conformational equilibria) possess this structural feature. These are (4a) and (6f), but in the latter conformation this shielding is counter-balanced by the deshielding effect of the axial 11b-methylene.[12] The large expected chemical shift difference between the 6-methylene protons for (4a) due to shielding of the 6ax-proton by the *trans*- and *axial*-lone pairs of both nitrogen atoms, the equatorial NMe group [13] and the axial 11a-methylene group was in fact observed (1.51 p.p.m.). The splitting pattern (Figure 7) for the 11b-proton is also consonant with structure (4a).

The presence of Bohlmann bands in the i.r. spectra of isomer (4) (Figure 6) indicates the predominance of a conformation such as (4a) with an equatorial NMe group. The u.v. spectrum (Table 4) provides support for this since in (4a) the lone pair on the bridgehead nitrogen atom is able to overlap with the π-electron system of the aryl ring.

A value of *ca.* −10.6 Hz would be predicted for $J_{6ax,6eq}$ in (4a) since in ArN–CH_2–X systems in which there is delocalisation of the nitrogen lone pair over the aryl ring, J_{gem} becomes *ca.* 2.1 Hz more negative than the value (*ca.* −8.5 Hz) for the 3-methylene in hexahydropyrimidines [14] [*e.g.* in (8)] containing parallel nitrogen lone pairs. The more positive value of −9.7 Hz observed for isomer (4) appears to be a peculiarity of systems containing the type of CD ring fusion present in (4a) and has been encountered in oxazino analogues.[2,15]



(ii) 7-*Methyl*-6,7,8,9,10,11,c-11a,t-11b,12,13-*decahydro*-r-7a*H*-*quino*[1,2-c]*quinazoline*. The second isomer eluted from the chromatography column was assigned the *r*-7a,*c*-11a,*t*-11b configuration (6).

TABLE 5

^{1}H N.m.r. spectra [a] of the quinoquinazoline isomers (4),(6), and (7)

	δ				*J*/Hz			
Isomer	6ax	6eq	11b	Me	6ax,6eq	11b,11a	11b,12ax	11b,12eq
(4)	3.13	4.64	2.97	2.26	−9.7	5.0 [b]	10.0	2.5 [b]
(6)	4.06	4.44	3.41	2.58	−12.1	11.0	8.4	4.0
(7)	3.57	3.99	3.17	2.37	−10.2	4.9 [c]	12.5	1.7 [c]

[a] The chemical shifts and coupling constant of the 6-protons were measured from 60 MHz spectra; the rest of the data was obtained from 220 MHz spectra. All spectra were run in $CDCl_3$ solution. [b,c] Tentative assignment, values may require reversal.

The stereochemistry represented by (7) was readily ruled out on the basis of the u.v. absorption spectrum (Table 4) leaving (5) and (6) for consideration. In the above discussion on the equilibria depicted in Figures 2 and 3 isomer (5) was predicted to exist as an equilibrium mixture of *ca.* 80% (5a) and 20% (5d) and isomer (6) as *ca.* 50% (6a) and 50% (6d).

Allowing for the overlap of the bridgehead nitrogen atom lone pair with the aromatic system in some conformations as evidenced by the u.v. spectrum (Table 4) of the second isomer, $J_{6ax,6eq}$ for conformer (5d) and (6d) is expected to be *ca.* −2.1 Hz more negative than J_{gem} (−11.2 Hz) for the corresponding 6-methylene protons in compound (12) [16] possessing one lone pair axial and one equatorial. If −13.3 Hz represents a conformation with one lone pair axial and one equatorial, and −10.6 Hz represents a conformation with parallel lone pairs, then the observed value of −12.1 Hz for $J_{6ax,6eq}$ in the second isomer represents an equilibrium containing *ca.* 56% (6d) or (5d) in equilibrium with 44% of conformation (6a) or (5a). This position of equilibrium is in keeping with that expected for (6) based on an examination of the conformations shown in Figure 3. Hence the second isomer may be assigned the *r*-7a,*c*-11a,*t*-11b configuration (6) existing in solution at room temperature as an equilibrium containing 56%

conformer (6d) and 44% conformer (6a). The proposed (6a) ⇌ (6d) equilibrium was supported by the low field chemical shift of the NMe group (δ 2.58) relative to that (δ 2.26) in isomer (4) existing predominantly in a conformation with the NMe group equatorial. In addition such an equilibrium would be characterised by small differences in chemical shift between the 6-methylene protons as is observed. An equilibrium containing *ca.* 80% of (5a) would be characterised by a chemical shift difference of *ca.* 1.0 p.p.m. The vicinal coupling constants (Figure 6) of the 11b-proton (11.0, 8.4, and 4.0 Hz) were in accord with both conformer (6d and a).

The presence of only weak Bohlmann bands and their altered appearance [relative to those of isomers (4) and (7)] in the i.r. spectrum of isomer (6) (Figure 6) is consistent with *ca.* 44% of conformer (6a) since in this conformation there are only two axial C–H bonds (6ax-H and one of the NMe C–H bonds) anticoplanar with the 7-nitrogen lone pair [*cf.* three such C–H bonds in (4a): 6ax-H, 8ax-H, and one of the NMe C–H bonds].

(iii) 7-*Methyl*-6,7,8,9,10,11,t-11a,t-11b,12,13-*deca-hydro*-r-7aH-*quino*[1,2-c]*quinazoline*. The third isomer eluted from the chromatography column was assigned the *r*-7a,*t*-11a,*t*-11b configuration (7).

The u.v. spectrum (Table 6) was in accord with either conformation (7a or b) (Figure 4), in which the bridgehead nitrogen lone pair is tipped into the plane of the aromatic ring such that delocalisation cannot occur.

In the *a priori* discussion of the conformational equilibrium it was predicted that the (7a) ⇌ (7b) equilibrium should contain *ca.* 80% of (7a). This expectation is borne out by the presence of strong Bohlmann bands in the i.r. spectrum (Figure 6) of this isomer, which indicates a predominance of a conformation in which the NMe group is equatorial.

The small chemical shift difference (Δ_{ae}) between the 6-methylene protons (0.42 p.p.m.) is consistent with a predominance of conformer (7a) in which the 6ax-proton is deshielded by the axial 11b-methylene [12] but shielded by the equatorial NMe group. Conformer (7b) would be characterised by a very small Δ_{ae} since the 6ax-proton is deshielded by the axial NMe group as well as by the axial 11b-methylene, and the 6eq-proton is shielded by the axial NMe group (*cf.* 0.4 p.p.m. shielding of an equatorial proton by a vicinal axial methyl group in cyclohexane systems).[12]

No values of J_{gem} have been recorded for NCH_2N protons in compounds existing in *cis*-BC-*N*-outside conformations such as (7a and b) in which the bridgehead nitrogen atom lone pair does not overlap with the π-orbitals of the aromatic ring. However there must be some effect on J_{gem} from the aromatic substituent as exemplified by the oxazino analogue (13). The J_{gem} for the 6-protons (−8.7 Hz) observed [2] for (13) is 0.7 Hz more negative than that (−8.0 Hz) in perhydropyrido-[1,2-*c*][1,3]oxazine (14).[17] Thus in the *cis*-BC-*N*-outside conformations (7a and b) J_{gem} may be predicted to be −9.2 and −11.9 Hz, respectively, these values being −0.7 Hz more negative than those (−8.5 and −11.2 Hz) in the corresponding conformations (8) and (12). Hence the observed J_{gem} (−10.2 Hz) for the 6-protons of isomer (7) represents a 63% predominance of conformer (7a).

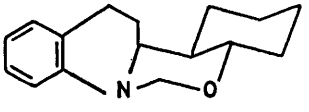
Assignment of Configuration and Preferred Conformations to the 7-Methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]pyrimido[1,6-a]quinolines.—The first isomer eluted from the chromatography column was assigned the *r*-7a,*c*-10a,*c*-10b configuration after comparison of the spectral data with that of the six-membered D ring analogues. All the spectral data was consistent with the existence of this isomer in the *trans*-BC conformation (15). Strong Bohlmann bands in the i.r. spectrum were indicative of an equatorial NMe group. The u.v. spectrum (Table 4) was in accord with a conformation (such as the *trans*-BC conformation) in which overlap of the bridgehead nitrogen lone pair with the aryl ring orbitals is possible.

TABLE 6

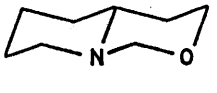
^{1}H N.m.r. spectra [a] of the isomers of 7-methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]-pyrimido[1,6-*a*]quinoline

	δ				*J*/Hz			
Isomer	6ax	6eq	10b	Me	6ax,6eq	10b,10a	10b,11ax	10b,11eq
(15)	3.17	4.48	3.29	2.27	−10.3	4.0	10.0	4.0
(16)	3.16	4.70	2.91	2.31	−11.1	10.0	8.0	4 8

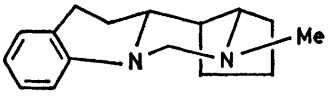
[a] The chemical shifts and coupling constants of the 6-protons were measured from 60 MHz spectra. The rest of the data was obtained from 220 MHz spectra. All spectra were run on solutions in $CDCl_3$.



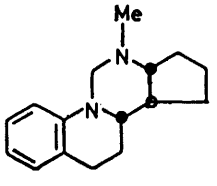
(13)



(14)



(15)



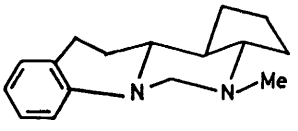
(16)

The n.m.r. data (Table 6) differed slightly from that of the analogue (4a). The 6eq-proton was shielded by 0.16 p.p.m. and the 10b-proton by 0.32 p.p.m. relative to the corresponding protons in (4a). The value of $J_{6ax,6eq}$ was −10.3 Hz, a larger value than that observed [J_{gem} in (4a)] and closer to that predicted (*ca.* −10.1 Hz)

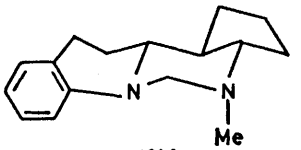
for such a system. These variations most probably are attributable to the effects of deformation of the C ring by *cis*-fusion to a five-membered ring.

The second isomer eluted from the chromatography column was assigned the *r*-7a,*t*-10a,*c*-10b configuration (16) after comparison of its n.m.r. spectrum (Table 6) with that of the three isomers of the six-membered D ring analogues failed to reveal any similarities even after allowing for possible C ring deformation by the fused five-membered ring. This suggested that this isomer corresponded to the six-membered ring analogue (5) which was not in fact obtained. Consideration of conformations analogous to those in Figure 2 suggested the existence of (16) as a (16a) ⇌ (16b) equilibrium containing *ca.* 80% of (16a), and the presence of strong Bohlmann bands in the i.r. spectrum of (16) showed the predominance of an equatorial NMe conformation.

The very large chemical shift difference observed between the 6-protons (1.54 p.p.m.) is consistent with a predominance of the parallel lone pair geometry found in (16a). The $J_{6ax,6eq}$ predicted for conformer (16a) is *ca.* −10.6 Hz [*ca.* −8.5 Hz for parallel lone pair geometry + (−2.1 Hz) for effect of aromatic system],



(16a)



(16b)

while that for conformer (16b) is −13.3 Hz. The actual observed value of −11.1 Hz for (16) represents an equilibrium containing *ca.* 81% of conformer (16a) with 19% of (16b).

Assignment of Preferred Conformation to 2-Methyl-2,3,4,4a,5,6-hexahydro-1H-pyrimido[1,6-a]quinoline.— There are six possible conformations of the tricyclic compound (3) interconvertible by ring inversion and nitrogen inversion (Figure 5). One of these (10e) may be neglected due to the presence of severe non-bonded interactions, and (10b) would be of considerably higher energy than the remaining conformations and thus would not contribute significantly to an equilibrium.

Strong Bohlmann bands in the i.r. spectrum indicated the predominance of a conformation in which the NMe group was equatorial [(10a or f)]. However, the u.v. spectrum (Table 4) was consistent with a predominance of either a *trans*-BC conformation and/or a *cis*-BC-*N*-inside conformation only. This result pointed to a predominance of conformer (10a) and was confirmed by the n.m.r. spectrum (Tables 7 and 8).

The large chemical shift difference (1.39 p.p.m.) between the 1-protons in the n.m.r. spectrum of (3) was indicative of a parallel lone pair geometry as present in (10a). Although this geometry is also present in conformer (10f), the 1ax-proton would be deshielded by the 4a-methylene group [12] giving rise to a small Δ_{ae}. The value of $J_{1ax,1eq}$ (−11.1 Hz) was in accord with a (10a) ⇌ (10d) equilibrium containing *ca.* 81% of conformer (10a).

TABLE 7

^{1}H N.m.r. spectrum [a] (coupling constants) of 2-methyl-2,3,4,4a,5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline

			J/Hz		
1ax,1eq	3ax,3eq	5ax,5eq	3ax,4ax	3ax,4eq	5ax,6ax
−11.1	−12.0	−13.0	12.0	3.0	5.0
5ax,6eq	5ax,4a	5eq,6ax	5eq,6eq	5eq,4a	1eq,3eq
5.0	5.0	3.0	3.0	3.0	1.6

[a] $J_{1ax,1eq}$ measured from 60 MHz spectrum, all other couplings measured from 220 MHz spectrum; both spectra were run in $CDCl_3$.

TABLE 8

^{1}H N.m.r. spectrum (chemical shifts) of 2-methyl-2,3,4,4a,-5,6-hexahydro-1*H*-pyrimido[1,6-*a*]quinoline

1ax	1eq	3ax	5ax	5eq	Me
3.24	4.63	2.28	2.05	1.54	2.33

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were recorded with a Perkin-Elmer 457 grating instrument for 0.2M solutions in deuteriochloroform in 0.2 mm matched cells. The n.m.r. spectra were determined with Varian T60 and HR-220 spectrometers for solutions in deuteriochloroform (Me_4Si as internal reference). U.v. spectra were recorded with a Unicam SP 800A instrument for solutions in ethanol.

N-Methyl-2-(2-quinolyl)cyclohex-1-enylamine.— Dry methylamine gas was bubbled into an ice-cooled solution of 2-(2-quinolyl)cyclohexanone [3] (7.5 g) in absolute ethanol (80 ml) until saturation was reached. The solution was allowed to slowly attain room temperature, then left to stand overnight to ensure complete reaction. The solution was evaporated to half bulk by passing nitrogen gas through the solution. The crystalline product which separated out on cooling of the solution was filtered off and recrystallised from light petroleum (b.p. 40—60°) to give *N-methyl-2-(2-quinolyl)cyclohex-1-enylamine* as pale yellow prismatic needles (6.5 g, 86%), m.p. 83—85° (Found: C, 80.9; H, 7.7; N, 11.7. $C_{16}H_{18}N_2$ requires C, 80.6; H, 7.6; N, 11.8%).

7-Methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7aH-quino[1,2-c]quinazolines.— *N*-Methyl-2-(2-quinolyl)cyclohex-1-enylamine (10 g) in glacial acetic acid (150 ml) was hydrogenated at *ca.* 60 lb in^{-2} on a Parr hydrogenator at room temperature in the presence of Adams platinum oxide catalyst (1 g). When the calculated volume of hydrogen (2.8 l) had been absorbed (25 min), the catalyst was filtered off and the acetic acid removed under reduced pressure. The viscous residue obtained was basified with 30% sodium hydroxide solution and ether extracted several times. The combined ether extracts were dried (Na_2SO_4) and evaporated to dryness leaving the mixture of isomeric *N*-methyl-2-(1,2,3,4-tetrahydro-2-quinolyl)cyclohexylamines as a light brown viscous residue (9.5 g).

The crude mixture of isomers (5 g) was shaken with 40% aqueous formaldehyde (5 ml) for 0.5 h, then warmed on a water-bath for 1 h, and finally left overnight at room temperature. The mixture was basified with 30% aqueous sodium hydroxide and extracted with chloroform several times. The combined chloroform extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* leaving a brown

viscous liquid (4.8 g). An n.m.r. spectrum of the residue showed the presence of more than one product. In an attempt to separate these products, the residue was chromatographed over Grade III Wöelm neutral alumina (200 g). The eluant was light petroleum (b.p. 40—60°) with increasing amounts of ether and 200 ml fractions were collected. The results of this separation are shown in Table 9. Three stereoisomers were obtained as crystalline solids after purification by vacuum sublimation and recrystallisation from light petroleum (b.p. 30—40°). M.p.s and analytical results are given in Table 9.

TABLE 9

Experimental results relating to the isomers of 7-methyl-6,7,8,9,10,11,11a,11b,12,13-decahydro-7a*H*-quino-[1,2-*c*]quinazolines

Fraction no.[a]	Isomer	Weight (g)	M.p. (°C)	C (%)[b]	H (%)[b]	N (%)[b]
10—16	(4)	0.21	59—61	79.6	9.5	10.7
20—27	(6)	1.26	56—57	79.3	9.7	10.8
31—33	(7)	0.59	63—64	79.2	9.2	10.6

[a] 200 ml fractions were collected and labelled in numerical order. [b] $C_{17}H_{24}N_2$ requires C, 79.6; H, 9.4; N, 10.9%.

N-Methyl-2-(2-quinolyl)cyclopent-1-enylamine.— Dry methylamine gas was bubbled into an ice-cooled solution of 2-(2-quinolyl)cyclopentanone (9.0 g) in absolute ethanol (100 ml) until saturation was reached. The solution was allowed to attain room temperature gradually then left overnight to ensure complete reaction. After evaporation of the solution to small bulk by bubbling in nitrogen and cooling, crystals separated out and were filtered off. Recrystallisation from light petroleum (b.p. 40—60°) yielded *N-methyl-2-(2-quinolyl)cyclopent-1-enylamine* as yellow prismatic needles (6.4 g, 67%), m.p. 45—46° (Found: C, 80.0; H, 7.3; N, 12.5. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5%).

7-Methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta-[4,5]pyrimido[1,6-a]quinolines.— *N*-Methyl-2-(2-quinolyl)-cyclopent-1-enylamine (10.0 g) in glacial acetic acid (100 ml) was hydrogenated at *ca.* 60 lb in^{-2} on a Parr hydrogenator at room temperature in the presence of Adams platinum oxide catalyst (1 g). After the calculated volume of hydrogen (3.2 l) had been absorbed (35 min), the catalyst was filtered off, and the acetic acid removed under reduced pressure. The residue was basified with 30% sodium hydroxide solution and ether extracted several times. The combined ethereal extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* leaving the isomeric *N*-methyl-2-(1,2,3,4-tetrahydro-2-quinolyl)cyclopentylamines as a dark brown viscous residue (7.0 g).

The crude mixture (5.0 g) was shaken with 40% aqueous formaldehyde (5 ml) for 0.5 h and left to stand overnight at room temperature. The mixture was then basified with 30% aqueous sodium hydroxide and extracted with chloroform several times. The combined chloroform extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to leave a dark brown viscous liquid (4.8 g). An n.m.r. spectrum of the residue indicated more than one product so the residue was chromatographed over Grade III Wöelm neutral alumina (200 g). The eluant was light petroleum (b.p. 30—40°) with increasing amounts of ether and 200 ml fractions were collected. The results of the separation are shown in Table 10. Recrystallisation of the separated isomers from light petroleum (b.p. 30—40°) yielded crystalline solids with m.p.s and analysis results as given in Table 10.

TABLE 10

Experimental results relating to the isomers of 7-methyl-6,7,7a,8,9,10,10a,10b,11,12-decahydrocyclopenta[4,5]-pyrimido[1,6-*a*]quinoline

Fraction no.[a]	Isomer	Weight (g)	M.p. (°C)	C (%)[b]	H (%)[b]	N (%)[b]
17—18	(15)	1.51	41—42	79.5	9.3	11.4
26—37	(16)	0.29	47—48	79.6	9.1	11.3

[a] 200 ml fractions were collected and labelled in numerical order. [b] $C_{16}H_{22}N_2$ requires C, 79.3; H, 9.2; N, 11.6%.

2-Methyl-2,3,4,4a,5,6-hexahydro-1H-pyrimido[1,6-a]-quinoline.—A solution of 2-vinylquinoline [4] (18.6 g) and methylamine hydrochloride (8.3 g) in absolute methanol (60 ml) was boiled under reflux overnight. The methanol was then removed *in vacuo* and the residue basified with 30% aqueous sodium hydroxide and extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated leaving the *N*-methyl-2-(2-quinolyl)ethylamine as a viscous residue (19.0 g) which was dissolved in glacial acetic acid (100 ml) and hydrogenated at 62 lb in^{-2} on a Parr hydrogenator at room temperature in the presence of Adams platinum oxide catalyst (1 g). The hydrogenation proceeded overnight when the theoretical amount of hydrogen (4.6 l) was absorbed. The catalyst was filtered off and the acetic acid removed under reduced pressure leaving the *N*-methyl-2-(1,2,3,4-tetrahydro-2-quinolyl)ethylamines as a viscous residue (15.3 g). The whole of this was shaken with 40% aqueous formaldehyde (16 ml) for 0.5 h. An exothermic reaction ensued on first shaking the mixture. The mixture was basified with 30% aqueous sodium hydroxide and ether extracted several times. The dried (Na_2SO_4) ethereal extracts were concentrated and distilled twice to yield the product as a mobile liquid (13.5 g, 83%), b.p. 129—131° at 0.52 mmHg. On cold storage the product solidified and was recrystallised from light petroleum ether (b.p. 30—40°) as *flowers*, m.p. 46—47° (Found: C, 77.3; H, 9.1; N, 13.8. $C_{13}H_{18}N_2$ requires C, 77.2; H, 9.0; N, 13.9%).

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