Quinazolines. Part XX.[1] Synthesis and Stereochemistry of *N*-Methyl-*cis*-perhydroquinazolin-2-ones and *N*-Methyl-*cis*-perhydroquinazolines; a New Conformation for *cis*-perhydroquinazolines

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Catalytic hydrogenation of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (1) and its 1- and 3-methyl derivatives [(2) and (3)] gave exclusively the *cis*-perhydro-derivatives (9), (11), and (10), respectively. The structures of the last two compounds were confirmed by syntheses from *cis*-2-*p*-tolylsulphonylaminocyclohexanecarboxylic acid (22). 1-Benzyl- (12) and 1,3-dimethyl-*cis*-perhydroquinazolin-2-one (13) and 1-methyl- (36), 3-methyl- (37), and 1,3-dimethyl-*cis*-perhydroquinazoline (38) were also synthesised. ^{1}H N.m.r. spectra showed that in solution 3-methyl-*cis*-perhydroquinazolin-2-one (10) and 3-methyl-*cis*-perhydroquinazoline (37) exist predominantly in the conformation type (14), whereas the previously unobserved conformation type (19) was strongly favoured by 1-methyl- (11), 1-benzyl- (12), and 1,3-dimethyl-*cis*-perhydroquinazolin-2-one (13). The spectra also implied that 1-methyl- (36) and 1,3-dimethyl-*cis*-perhydroquinazoline (38) existed mainly in the conformation (40) [≡(19)].

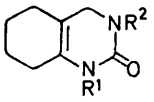
CATALYTIC hydrogenation of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (1) was found to be stereospecific, giving a quantitative yield of *cis*-perhydroquinazolin-2-one (9). We then examined the reduction of the *N*-methyl derivatives (2) and (3), and found that these reactions also proceeded with high *cis*-stereospecificity.

The preparation of 3,4,5,6,7,8-hexahydro-3-methylquinazolin-2(1*H*)-one (3) in 40% yield from 2-hydroxymethylcyclohexanone (5) and *N*-methylurea has been reported.[2] Although the 1-methyl derivative (2) could have conceivably been formed, the structure of the product was not rigorously established. In our hands, and under a variety of conditions, the yield of this product was never better than 11% and the unused *N*-methylurea was recovered. Spectroscopic data were

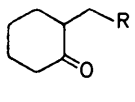
[1] W. L. F. Armarego and B. A. Milloy, *J.C.S. Perkin I*, 1973, 2814.

[2] G. Zigumer, V. Eisenreich, and W. Immel, *Monatsh.*, 1970, **101**, 1745.

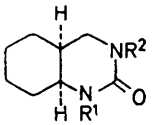
consistent with a hexahydroquinazolin-2-one structure but did not differentiate between *N*-methyl isomers. Catalytic hydrogenation of this compound gave a



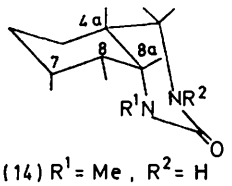
(1) $R^1 = R^2 = H$
(2) $R^1 = Me$, $R^2 = H$
(3) $R^1 = H$, $R^2 = Me$
(4) $R^1 = CH_2Ph$, $R^2 = H$



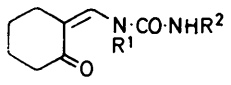
(5) R = OH
(6) R = Cl
(7) $R = O{\cdot}SO_2Me$
(8) R = OAc



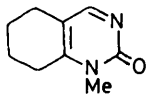
(9) $R^1 = R^2 = H$
(10) $R^1 = H$, $R^2 = Me$
(11) $R^1 = Me$, $R^2 = H$
(12) $R^1 = CH_2Ph$, $R^2 = H$
(13) $R^1 = R^2 = Me$



(14) $R^1 = Me$, $R^2 = H$



(15) $R^1 = H$, $R^2 = Me$
(16) $R^1 = Me$, $R^2 = H$



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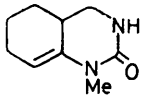

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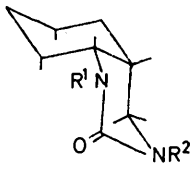
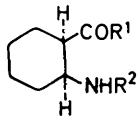
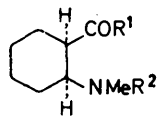


(19) $R^1 = Me$, $R^2 = H$
(20) $R^1 = CH_2Ph$, $R^2 = H$

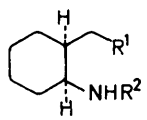
high yield of what was later shown to be 3-methyl-*cis*-perhydroquinazolin-2-one (10). The ^1H n.m.r. spectrum showed that it was a *cis*-perhydroquinazoline in the conformation (14) (the pattern of signals was similar to that observed before [3,4]) but again gave no information regarding the position of the methyl group. In an alternative synthesis, 2-hydroxymethylenecyclohexanone was condensed with *N*-methylurea to give the ureido-compound (15). The ^1H n.m.r. spectrum of the product revealed two methyl signals and two olefinic doublets (ratio 1 : 2) each showing coupling to N*H*; this suggested the presence of two conformers and ruled out contamination with the isomeric ureido-compound (16). Compound (15) was cyclised in high yield to 1-methyl-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (17). Reduction of compound (17) with sodium borohydride in water, ethanol, or 1,2-dimethoxyethane gave a mixture of the isomeric octahydroquinazolin-2-ones (2) and (18), which was sometimes contaminated with the perhydroquinazolin-2-one. Catalytic hydrogenation over platinum oxide in ethanol, on the other hand, gave the octahydroquinazolin-2-one (2) free from the isomer (18) but always contaminated with a little perhydro-compound. Catalytic reduction of these mixtures in acetic acid was complete and gave 1-methylperhydroquinazolin-2-one. The ^1H n.m.r. spectrum of this product was different from that of its isomer (10) in that one of the C-4 protons had two large coupling constants and that a broad band envelope was observed for protons at positions 5—8 (see Table). The position of the *N*-methyl group in this case also could not be deduced from the spectrum, which could be due to either a *cis*-perhydroquinazolin-2-one structure in the conformation (19) or a *trans*-perhydroquinazolin-2-one. Hydrogenation of 1-benzyl-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (4) gave the perhydro-compound (12), which had a similar ^1H n.m.r. spectrum.



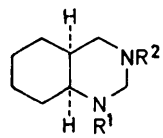
(21) $R^1 = OH$, $R^2 = H$
(22) $R^1 = OH$, $R^2 = Ts$
(23) $R^1 = NHMe$, $R^2 = Ts$
(24) $R^1 = NHMe$, $R^2 = H$
(25) $R^1 = OH$, $R^2 = CO_2{\cdot}CH_2Ph$
(26) $R^1 = NH$, $R^2 = CO_2{\cdot}CH_2Ph$
(27) $R^1 = NHMe$, $R^2 = CO_2{\cdot}CH_2Ph$



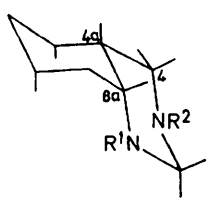
(28) $R^1 = OH$, $R^2 = Ts$
(29) $R^1 = NH_2$, $R^2 = Ts$
(30) $R^1 = NHMe$, $R^2 = Ts$
(31) $R^1 = NH_2$, $R^2 = H$
(32) $R^1 = NHMe$, $R^2 = H$



(33) $R^1 = NH_2$, $R^2 = Me$
(34) $R^1 = NHMe$, $R^2 = H$
(35) $R^1 = NHMe$, $R^2 = Me$



(36) $R^1 = Me$, $R^2 = H$
(37) $R^1 = H$, $R^2 = Me$
(38) $R^1 = R^2 = Me$



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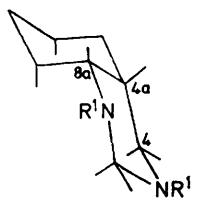

(40)

Unambiguous syntheses of 1- and 3-methyl-*cis*-perhydroquinazolin-2-one were undertaken in order to

[3] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1971, 1812.
[4] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 3222.

establish the structures of the foregoing methylquinazolin-2-ones. The reaction of hexahydroanthranilic esters with alcoholic ammonia or methylamine was sluggish and gave low yields of the required amides.[5,6] To improve the method we needed to protect the amino-group; thus *cis*-hexahydroanthranilic acid (21) was converted into its *N*-*p*-tolylsulphonyl derivative (22) which was the common intermediate. Treatment of this with oxalyl chloride followed by methylamine gave good overall yields of the methylamide (23). The *p*-tolylsulphonylamino-acid (22) was also methylated in alkaline medium to give *cis*-2-*N*-methyl-*p*-tolylsulphonylaminocyclohexanecarboxylic acid (28), which was converted into the acid chloride and thence into the amide (29) and the methylamide (30). All three sulphonamides [(23), (29), and (30)] were detosylated by sodium in liquid ammonia to give the respective *cis*-2-aminocyclohexanecarboxamides [(24), (31), and (32)]. Preliminary attempts at a synthesis from *cis*-2-benzyloxycarbonylaminocyclohexanecarboxylic acid (25) were abandoned because the intermediate steps proved less satisfactory. The acid (25) could not be converted into the acid chloride without considerable debenzylation, but was converted into the amide (26) and methylamide (27) by use of the mixed anhydride method followed by treatment with ammonia and methylamine, respectively. Also, reduction of *cis*-2-benzyloxycarbonylaminocyclohexane-*N*-methylcarboxamide (27) with lithium aluminium hydride resulted in loss of the benzyloxycarbonyl group and gave *cis*-1-methylamino-2-methylaminomethylcyclohexane (32), *i.e.* the benzyloxycarbonylamino-group was converted into a methylamino-group and benzyl alcohol.

Reduction of all three amides (24), (31), and (32) with lithium aluminium hydride gave the corresponding *cis*-aminomethylcyclohexylamines (33)—(35) in high yields. Examination of all products showed no evidence of epimerisation, *i.e.* all compounds retained the original *cis*-configuration of the hexahydroanthranilic acid (21). Cyclisation of the amines (33) and (35) with phosgene in the presence of alkali gave authentic 1-methyl (11) and 1,3-dimethyl-*cis*-perhydroquinazolin-2-one (13). *cis*-2-Methylaminomethylcyclohexylamine, on the other hand, gave mainly intractable material with phosgene, but with *NN'*-carbonyldi-imidazole it gave the desired 3-methyl-*cis*-perhydroquinazolin-2-one (10). The 1-methyl (11) and the 3-methyl compound (10) were identical with the products obtained from 2-hydroxymethylenecyclohexanone and 2-hydroxymethylcyclohexanone, respectively. The amines (33)—(35) also gave the corresponding 1-methyl- (36), 3-methyl- (37), and 1,3-dimethyl- (38) *cis*-perhydroquinazolines when condensed with formaldehyde.

Proton Magnetic Resonance.—The spectra of *cis*-perhydroquinazolines,[3,5,7] *cis*-perhydroquinazolin-2-ones,[3,5] a 2-thione,[5] and 2-amino-*cis*-3,4,4a,5,6,7,8,8a-octahydroquinazolines [5] in $CDCl_3$, $(CD_3)_2SO$, or D_2O at 33° reported previously showed that these compounds existed predominantly in the *cis*-conformation of type (14) [≡(39)]. The criteria used for assigning this conformation were the small values of $J_{4,4a}$ (J 3—5 Hz) and the narrow band envelope ($W_{\frac{1}{2}}$ 15—20 Hz) corresponding to the protons at positions 5—8. In contrast, the *trans*-perhydroquinazolines have one small (3—6 Hz) and one large $J_{4,4a}$ value (10—12 Hz) (in addition to the large J_{gem}) and a broad H-5—8 band envelope ($W_{\frac{1}{2}}$ 40—70 Hz).[4,7] There is little doubt that the *cis*-compounds contain a very small amount of the other extreme conformer type (40) because the quartet from the C-2 protons in *cis*-decahydroquinazoline collapsed to a singlet when the temperature was raised.[7]

The spectrum of 3-methyl-*cis*-perhydroquinazolin-2-one shows that it is in the conformation (14), like all the above-mentioned *cis*-hydroquinazolines. 1-Methyl-, 1-benzyl-, and 1,3-dimethyl-*cis*-perhydroquinazolin-2-one, on the other hand, are in the previously unobserved *cis*-hydroquinazoline conformation type (19).

The major conformer of *cis*-decahydroquinoline was also shown to be of type (39) [≡(14)],[8] but more recently it was found that some *N*-ethyl-*cis*-decahydroquinolines existed in the other conformation type (40) [≡(19)].[9] In the quinazoline series, unlike the quinoline series, these two conformers can be distinguished clearly by the pattern of the C-4 proton n.m.r. signals because these protons are deshielded by N-3. In the conformer type (19) the torsion angle between the axial C-4 proton and H-4a is close to 180°, resulting in a large coupling constant, and the angle between the equatorial C-4 proton and H-4a is *ca.* 60° which gives the small J value observed. In this conformer 1,4-diaxial interactions between the protons in the separate rings may be the cause for the broad H-5—8 band envelope. The spectrum of the 1-methyl compound (14) in $(CD_3)_2SO$ was the same as in $CDCl_3$, but when the former solution was heated the triplet from H-4 (axial) gradually disappeared and the spectrum at 135° was similar to that of the 3-methyl compound. Dreiding stereomodels show that the 1-methyl group of 1-methyl- and 1,3-dimethyl-*cis*-perhydroquinazolin-2-one is very close to H-7 (axial) and H-8 (equatorial) in the conformer type (14). The resulting repulsive interactions are probably responsible for the displacement of the equilibrium towards the conformer type (19), where these interactions are absent.

The spectrum of 3-methyl-*cis*-decahydroquinazoline (37), like that of the oxo-compound (10), showed two small $J_{4,4a}$ values in addition to the large J_{gem}, indicating that the conformer (39; R^1 = H, R^2 = Me) predominated. The spectra of 1-methyl- (36) and 1,3-dimethyl-*cis*-perhydroquinazoline (38) on the other

[5] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 238.
[6] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 2502.
[7] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1969, 1635.
[8] H. Booth and D. V. Griffiths, *J.C.S. Perkin II*, 1973, 842.
[9] H. Booth and D. V. Griffiths, *J.C.S. Chem. Comm.*, 1973, 666.

hand are quite different, as in the case of the corresponding *cis*-perhydroquinazolin-2-ones (11) and (13). In these examples, however, the difference in chemical shifts between the two C-4 protons is too small to show clearly the coupling with H-4a, but as in the 2-oxo-compounds the signal from H-8a in the 1-methyl (36) and 1,3-dimethyl compounds (38) is about 0·6 p.p.m. upfield from that of H-8a in the 3-methyl derivative (37). By analogy, the former compounds

α-proton, however, is smaller than that observed for H-8a: compare the chemical shift difference between the two C-2 protons of *cis*-decahydroquinazoline (Δδ 0·36 p.p.m.) with those of the *N*-methyl derivatives (36)—(38) (Δδ 0·72, 0·71, and 0·82, respectively) (see Table). This effect is not, however, solely caused by the *N*-methyl group; the orientation of the nitrogen lone electron pair may be another contributing factor. In the *cis*-decahydroquinazoline cations the difference

^{1}H N.m.r. spectra of hydroquinazolines (δ values; Me_4Si internal standard) [a]

Hydroquinazolin-2-(1*H*)-one	H-2	H-4	H-4a	H-8a	NH	NCH_3	Other H	H-5,6,7,8	Solvent
1-Methyl-5,6,7,8-tetra-		8·30 (s)				3·52 (s)		2·63br (s), 1·84br (s)	$CDCl_3$ [b]
1-Benzyl-5,6,7,8-tetra-		8·35 (s)					5·30 (s, CH_2Ar), 7·29 (s, Ph)	2·57br (s) 1·69br (s)	$CDCl_3$ [b]
1-Methyl-3,4,5,6,7,8-hexa-		3·76 (s)			5·43br(s)	3·06		1·50—2·4br (m)	$CDCl_3$ [b]
1-Benzyl-3,4,5,6,7,8-hexa-		3·83 (s)			5·60br (s)		4·86 (s, CH_2Ar), 7·29 (s, Ph)	1·4—2·2vbr (d)	$CDCl_3$ [b]
3-Methyl-3,4,5,6,7,8-hexa-		3·68 (s)			4·29br(s)	2·86 (s)		1·75br (m)	$CDCl_3$ [b]
1-Methyl-*cis*-per-		*ax* 3·42 (t, $J_{4,4}$ −11·0, $J_{4,4a}$ 11·0) *eq* 3·08 (q, $J_{4,4}$ −11·0, $J_{4,4a}$ 5·0)	2·28 (m)	*ca.* 3·1 (m)		2·92 (s)		1·1—2·0 (m)	$CDCl_3$ [d,e]
1-Benzyl-*cis*-per-		*ax* 3·48 (t, $J_{4,4}$ −11·3, $J_{4,4a}$ 11·3) *eq* 3·08 (q, $J_{4,4}$ −11·3, $J_{4,4a}$ 5·6)	*ca.* 2·2 (m) [c]	*ca.* 3·1 (m) [c]	5·70 (s)		5·14, 4·00 (2d, J_{gem} −16·0, CH_2Ar) 7·26 (s, Ph)	1·0—2·3 (m)	$CDCl_3$ [d–f]
3-Methyl-*cis*-per-		*eq* 3·36 (q, $J_{4,4}$ −11·8, $J_{4,4a}$ 4·3) *ax* 2·97 (q, $J_{4,4}$ −11·8 $J_{4,4a}$ 3·8)	*ca.* 1·9 (m) [c]	3·60 (m)		2·94 (s)		1·1—2·1 (m)	$CDCl_3$ [d–f]
1,3-Dimethyl-*cis*-per-		*ax* 3·48 (t, $J_{4,4}$ −11·2, $J_{4,4a}$ 11·2) *eq* 3·00 (q, $J_{4,4}$ −11·2), $J_{4,4a}$ 5·1)	2·25m	*ca.* 2·9 (m) [c]		2·85 (s)		1·2—1·9 (m)	$CDCl_3$ [d,e]
Unsubstituted *cis*-	*eq* 4·02 (d),[g] *ax* 3·66 (d) [g] (J_{gem} −12·5)	2·91 (t, *J* 1·7)		3·02 (m)	1·82 (s)			1·1—2·0 (m) [h]	$CDCl_3$ [d,i]
dication (as dipicrate)	4·40 (s)	3·55br (s)		3·20 (m)				1·2—2·2 (m) [h]	$(CD_3)_2SO$ [d,i]
1-Methyl-*cis*-	*eq* 3·71 (d),[g] *ax* 2·99 (d) [g] (J_{gem} −11·2)	2·81 (s), 2·78 (s)		2·20 (m)		2·12 (s)		1·2—2·0 (m) [h]	$CDCl_3$ [d,e]
dication	4·93 (s)	3·79 (s), 3·91 (s)	2·90br (s)	2·94br (s)		3·18 (s)		1·3—2·5 (m)	$CF_3{\cdot}CO_2H$ [b]
3-Methyl-*cis*-	*eq* 3·65 (d),[g] *ax* 2·94 (d) [g] (J_{gem} −10·8)	*eq* 2·65 (q, $J_{4,4}$ −11·0, $J_{4,4a}$ 1·0) *ax* 2·20 (q, $J_{4,4}$ −11·0, $J_{4,4a}$ 3·0)		2·83 (s)		2·08 (s)		1·2—1·9 (m) [h]	$CDCl_3$ [d,e]
dication	4·28 (s)	3·65 (s), 3·75 (s)	2·75br (s)	4·00br (s)		3·91 (s)		1·4—2·4 (m)	$CF_3{\cdot}CO_2H$ [b]
1,3-Dimethyl-*cis*-	*eq* 3·49 (d),[g] *ax* 2·60 (d) [g] (J_{gem} −9·2)	2·53 (s) 2·63 (s)		2·20 (m)		2·17 (s), 2·26 (s)		1·2—2·0 (m) [h]	$CDCl_3$ [d,e]
dication	4·75 (s), 4·91 (s) [j]	3·75 (s), 3·88 (s)	2·90br (s)	4·02br (s)		3·19 (s), 3·28 (s)		1·3—2·4 (m)	$CF_3{\cdot}CO_2H$ [b]

[a] *J* Values are in Hz and J_{gem} values are assumed negative. [b] 60 MHz at 33°. [c] Approximate because signal is partly obscured by the other signals. [d] 100 MHz at 44°. [e] Contains a drop of D_2O. [f] Values taken from ref. 1 for comparison; see Discussion section. [g] Signal due to equatorial proton is broader than that of axial proton because of W-type coupling with equatorial H-4. [h] Includes H-4a signal. [i] Values taken from ref. 7 for comparison. [j] The 'wings' of these signals are very weak but indicate a J_{gem} value of *ca.* −12 Hz.

are most probably in the *cis*-formation of type (40) [≡(19)] with the stabilising effect as described above for the 2-oxo-compounds.

The differences in chemical shift of H-8a in the two sets of compounds may be attributed partly to the C(8a)–H bond being equatorial (with respect to the carbocyclic ring) in one case [*i.e.* (39)] and axial in the other [*i.e.* (40)]; compare the H-8a signal of *cis*-decahydroquinazoline (39; $R^1 = R^2 = H$) at δ 3·02 with that of *trans*-decahydroquinazoline (rigid conformation with H-8a axial) at δ 2·20.[7] Another factor which may contribute to this difference is the presence or absence of a methyl group on N-1. The effect of the *N*-methyl group on the chemical shift of the

in chemical shift between the two C-2 protons is less than 0·16 p.p.m., in contrast with the *trans*-cations [6] (Δδ 0·44—0·58).

The J_{gem} values for the C-2 protons of *cis*-decahydroquinazolines are in the order: unsubstituted (−12·5 Hz) > 1-methyl (−11·5 Hz) > 3-methyl (−10·8 Hz) > 1,3-dimethyl (−9·2 Hz), comparable with that observed in *trans*-decahydroquinazolines: unsubstituted (−12·6 Hz) > 1-methyl (−11·3 Hz) ≃ 3-methyl (−11·3 Hz) > 1,3-dimethyl (−9·4 Hz).[6] This close resemblance could be fortuitous, the *cis*-3-methyl compound being in a different conformation from the other two, or it could be that the stereochemistry of the pyrimidine rings (*i.e.* orientation of the nitrogen

lone electron pair and *N*-methyl groups) in the corresponding *cis*- and *trans*-isomers is the same, and that the situation is unaffected by the stereochemical relationship with the fused carbocyclic ring.

EXPERIMENTAL

Elemental analyses were determined by the Australian National University Analytical Services Unit. The instruments used are described in ref. 7. All i.r. assignments (KBr discs for solids and films for liquids) are tentative, and C–H stretching vibrations near 3000 cm^{-1} are not included. All extracts were dried with Na_2SO_4 and evaporations were carried out below 30° and at *ca.* 18 mmHg. N.m.r. spectra were run at 60 MHz and 33° with Me_4Si as internal standard unless otherwise stated; *J* values are in Hz.

3,4,5,6,7,8-*Hexahydro*-3-*methylquinazolin*-2(1H)-*one* (3) (with B. A. Milloy).—2-Hydroxymethylcyclohexanone [10] (25 g; b.p. 93—95° at 6 mmHg) in xylene (50 ml) was added to a hot solution of *N*-methylurea (44 g) in xylene (300 ml) and the mixture was refluxed under a Dean–Stark trap until water elimination appeared complete. The solution was evaporated to a small volume and acetone was added. The solid was collected, washed with water, and recrystallised from acetone to give the quinazolin-2-one (3·9 g, 11%), m.p. 194° (lit.,[2] yield 40%, m.p. 194°). In attempts to discover a more active starting material, experiments with the derivatives (6) and (7) failed, but heating 2-acetoxymethylcyclohexanone (8) [10] (1·28 g; b.p. 91° at 0·7 mmHg; $\nu_{max.}$ 1712 and 1738 cm^{-1}) with *N*-methylurea (2 g) at 160° for 4 h, followed by addition of water, gave the quinazolinone (3) (10%) (Found: C, 64·6; H, 8·5; N, 16·5. Calc. for $C_9H_{14}N_2O$: C, 65·0; H, 8·5; N, 16·8%); $\nu_{max.}$ 1660 cm^{-1}.

2-N′-*Methylureidomethylenecyclohexanone* (15) (with B. A. Milloy).—2-Hydroxymethylenecyclohexanone [11] (8·4 g) was added to a hot solution of *N*-methylurea (5·42 g, 1·1 mol. equiv.) in acetic acid (20 ml). After 3 days at 25° the solid was collected and recrystallised from water to give the *ureido-ketone* (7·0 g, 59%), m.p. 196—196·5° (Found, after drying at 100° for 18 h: C, 59·3; H, 7·7; N, 15·5. $C_9H_{14}N_2O_2$ requires C, 59·3; H, 7·7; N, 15·4%); $\nu_{max.}$ 1720 (CO) and 1663 (urea CO) cm^{-1}; δ [$(CD_3)_2SO$] 8·50 (d, NH, *J* 12), 7·71 (d, C=CH, *J* 12, major isomer), 7·10 (d, C=CH, *J* 12, minor isomer), 7·45br (m, NH), 2·65 (d, NCH_3, *J* 5, major isomer), 2·60 (d, NCH_3, *J* 5, minor isomer), 2·0—2·5 (m, 3- and 6-H_2), and 1·4—1·9 (m 4- and 5-H_2).

Similarly 2-N′-*benzylureidomethylenecyclohexanone*, m.p. 206° (from dioxan), was obtained in 80% yield (Found: C, 69·9; H, 7·1; N, 10·9. $C_{15}H_{18}N_2O_2$ requires C, 69·7; H, 7·0; N, 10·85%), $\nu_{max.}$ 1722 and 1665 cm^{-1}.

5,6,7,8-*Tetrahydro*-1-*methylquinazolin*-2(1H)-one (17).—2-N′-Ureidomethylenecyclohexanone (1 g) was refluxed with aqueous N-sodium hydroxide (30 ml) for 4 min. The solution was cooled and extracted with chloroform (4 × 100 ml). Evaporation of the dried extract gave the quinazolin-2(1*H*)-one as a hygroscopic, low melting solid (0·82 g) which could not be recrystallised; $\nu_{max.}$ 1667 and 1560 (amide) cm^{-1}, δ ($CDCl_3$) 8·30 (s, H-4), 3·52 (s, NCH_3), 2·63 (m, 5- and 8-H_2), and 1·84 (m, 6- and 7-H_2). The *picrate* had m.p. 180° (decomp.) (from MeOH) (Found: C, 45·8; H, 3·8; N, 17·6. $C_{18}H_{15}N_5O_8$ requires C, 45·8; H, 3·8; N, 17·8%).

Similarly 1-*benzyl*-5,6,7,8-*tetrahydroquinazolin*-2(1H)-*one picrate*, m.p. 165° (from EtOH) (Found: C, 53·5; H, 4·1; N, 15·2. $C_{21}H_{21}N_5O_8$ requires C, 53·5; H, 4·5; N, 14·9%), was prepared from 2-N′-benzylureidomethylenecyclohexanone.

Hexahydro-1-*methylquinazolin*-2(1H)-*one* (2) (with B. A. Milloy).—2-N′-Methylureidomethylenecyclohexanone (2 g) was refluxed with N-sodium hydroxide (60 ml) for 4 min. The mixture was then cooled, sodium borohydride (1·6 g) was added, and the solution was stirred for 2 h. The pH was adjusted to 8 and the solution was extracted with chloroform. Evaporation of the extract gave hexahydro-1-methylquinazolin-2-one, b.p. 174° at 1·5 mmHg (1·3 g, 71%) (Found: C, 64·8; H, 8·8; N, 16·4. Calc. for $C_9H_{14}N_2O$: C, 65·0; H, 8·5; N, 16·8%); $\nu_{max.}$ 3200br (NH), and 1665 and 1510 (amide) cm^{-1}. The ^1H n.m.r. spectrum indicated that it was a *ca.* 2 : 1 mixture of 3,4,4a,5,6,7- (18) [δ ($CDCl_3$; 100 MHz) 3·04 (d, 4-H_2), 5·69 (d, H-8), and 2·87 (s, NCH_3)] and 3,4,5,6,7,8-hexahydro- (2) [δ ($CDCl_3$; 100 MHz) 3·76br (s, 4-H_2) and 2·89 (s, NCH_3)] derivatives; and the mixture prior to distillation also contained *ca.* 10% of 1-methylperhydroquinazolin-2-one. 1-Methyl-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (2), free from its isomer, was obtained by hydrogenating the tetrahydro-compound (preceding preparation) over 5% Pd–C in ethanol and stopping the reduction after absorption of 1 mol. equiv. of hydrogen. The product could not be obtained analytically pure; it was always contaminated with a little (<5%) perhydroquinazoline and/or starting material.

1-*Benzyl*-3,4,5,6,7,8-*hexahydroquinazolin*-2(1H)-*one*.—1-Benzyl-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (212 mg) in ethanol (25 ml) containing PtO_2 (50 mg) was hydrogenated at atmospheric pressure (uptake 1 mol. equiv.) to give the *hexahydroquinazolin*-2-*one* (169 mg, 81%), m.p. 158·5° (from MeOH) (Found: C, 74·2; H, 7·4; N, 11·5. $C_{15}H_{18}N_2$ requires C, 74·3; H, 7·5; N, 11·6%), $\nu_{max.}$ 3250, 3090 (NH), 1707 (CO), 1670 (C=C), and 1492 (NH bend) cm^{-1}.

cis-*Perhydroquinazolin*-2-*one* (9).—3,4,5,6,7,8-Tetrahydroquinazolin-2(1*H*)-one [3] (0·8 g) in acetic acid (50 ml) containing PtO_2 (100 mg) was shaken with hydrogen at 5 atm and 20° for 5 h. Filtration and evaporation gave compound (9) (780 mg, 97%), m.p. 233—235°, identical with authentic material.[5] No reduction occurred with 5% Pd–C in ethanol as catalyst. The *picrate* had m.p. 146—147° (from MeOH) (Found: C, 44·1; H, 4·5; N, 18·3. $C_{14}H_{17}N_5O_8$ requires C, 43·9; H, 4·5; N, 18·3%).

Similarly 1-benzyl-3,4,5,6,7,8-hexahydroquinazolin-2-one (12) was reduced. The product was purified by chromatography over alumina (B.D.H.) (gradient elution with 0—10% ethanol–benzene). The latter fractions were evaporated and the residue sublimed (160° at 0·5 mmHg) to give 1-*benzyl*-cis-*perhydroquinazolin*-2-*one* (56%) as a glassy solid (Found: N, 11·5. $C_{15}H_{20}N_2O_2$ requires 11·5%), $\nu_{max.}$ 1662 (CO), 1517 (C=C), and 1458 (NH bend) cm^{-1}. The *picrate*, m.p. 125—126° (from EtOH), separated (3 days) from aqueous picric acid (Found: C, 53·3; H, 5·1; N, 14·8. $C_{21}H_{23}N_5O_8$ requires C, 53·3; H, 4·9; N, 14·8%).

[10] C. Mannich and W. Brose, *Ber.*, 1923, **56**, 833.
[11] C. Ainsworth, *Org. Synth.*, 1959, **39**, 27.

cis-2-*Benzyloxycarbonylaminocyclohexanecarboxylic Acid* (25).—To a stirred solution of *cis*-2-aminocyclohexanecarboxylic acid [12] (4·29 g) in aqueous 2N-sodium hydroxide (15 ml) at 0° were added simultaneously 0·46M-benzyl chloroformate in toluene [13] (15 ml, 2·3 mol. equiv.) and aqueous 4N-sodium hydroxide (8 ml) during 15 min. The mixture was stirred for 2 h, then extracted with ether (discarded), and the aqueous layer was cooled (to 0°) and acidified to pH 2 with 11·3N-hydrochloric acid. The *carboxylic acid* (5·86 g, 74%) had m.p. 130—131° (from EtOH) and sublimed at 140—150° and 1 mmHg (Found: C, 65·0; H, 6·9; N, 5·0. $C_{15}H_{19}NO_4$ requires C, 65·0; H, 6·9; N, 5·05%); $\nu_{max.}$ 1711 (CO_2H) and 1672 (CO) cm^{-1}.

cis-2-*Benzyloxycarbonylaminocyclohexane*-N-*methylcarboxamide* (27).—To the acid (25) (1·4 g) and triethylamine (0·7 ml, 1 mol. equiv.) in ethanol-free chloroform (25 ml) at −5°, ethyl chloroformate (0·5 ml, 1 mol. equiv.) was added. After 2 h at −5°, 1·1M-methylamine in chloroform (5 ml, 5·5 mol. equiv.) was added (CO_2 evolved), and the mixture was set aside for 4 h. It was then washed with 2N-sodium hydroxide and 2N-hydrochloric acid, dried, and evaporated to give the N-*methylamide* (1·03 g, 71%), m.p. 137·5—138° (from EtOH–H_2O, 4 : 1) (Found: C, 65·7; H, 7·4; N, 9·5. $C_{16}H_{22}N_2O_3$ requires C, 66·1; H, 7·6; N, 9·6%), $\nu_{max.}$ 3300 (NH), and 1680 and 1650 (amide) cm^{-1}.

cis-2-p-*Tolylsulphonylaminocyclohexanecarboxylic Acid* (22).—*cis*-2-Aminocyclohexanecarboxylic acid (5·8 g) in 2N-sodium hydroxide (22 ml, 1·02 mol. equiv.) mixed with toluene-*p*-sulphonyl chloride (15·2 g, 1 mol. equiv.) in ether (40 ml) was shaken for 1 h. A further three additions of 2N-sodium hydroxide (20 ml) were made at 1 h intervals, and the mixture was then shaken for 6 h. The ether was separated and the aqueous layer was filtered and acidified to yield the *acid* (10·6 g, 90%), m.p. 172° (from 1 : 1 H_2O–MeOH) (Found: C, 56·1; H, 6·4; N, 4·5. $C_{14}H_{19}NO_4S$ requires C, 56·1; H, 6·4; N, 4·7%), $\nu_{max.}$ 1702 (CO) cm^{-1}.

cis-2-p-*Tolylsulphonylaminocyclohexane*-N-*methylcarboxamide* (23).—The acid (22) (14·8 g) in oxalyl chloride (60 ml) was stirred at 25° for 1 h, then at 40—45° for 15 min. The solution was evaporated and the residue was treated with aqueous 40% methylamine (100 ml) at 0°. After 15 min, the excess of methylamine was removed *in vacuo* and the precipitate was filtered off, dried, and recrystallised from benzene to give the *methylamide* (12 g, 78%), m.p. 151° (Found: C, 57·9; H, 7·2; N, 8·9. $C_{15}H_{22}N_2O_3S$ requires C, 58·0; H, 7·1; N, 9·0%), $\nu_{max.}$ 3400 and 3200 (NH), 1665 (CO), and 1320 and 1160 (SO_2NH) cm^{-1}.

Similarly cis-2-(N-*methyl*-p-*tolylsulphonylamino*)*cyclohexanecarboxamide* (29), m.p. 169° (from benzene) (sublimed at 170° and 0·15 mmHg), was obtained from the *N*-methyl acid (see below) and an excess of ammonia (*d* 0·880) in 84% yield (Found: C, 57·7; H, 7·0; N, 8·7. $C_{15}H_{22}N_2O_3S$ requires C, 58·0; H, 7·1; N, 9·0%); $\nu_{max.}$ 3400 (NH) 1660 and 1400 (amide), and 1330 and 1160 (SO_2NH) cm^{-1}.

cis-2-(N-*Methyl*-p-*tolylsulphonylamino*)*cyclohexane*-N-*methylcarboxamide* (30).—The acid (22) (7·4 g) in 2N-sodium hydroxide (75 ml) and methyl iodide (20 ml) was heated at 65—88° with vigorous stirring in a sealed bomb for 40 min. The mixture was cooled, acidified (pH 3) with 11N-hydrochloric acid, and extracted with chloroform. The extract gave *cis*-2-(*N*-methyl-*p*-tolylsulphonylamino)-cyclohexanecarboxylic acid (7·6 g) as a glassy solid which was treated with oxalyl chloride and then methylamine as above. The crude methylamide was dissolved in benzene; the solution was extracted with 10N-sodium hydroxide and the organic layer was dried and evaporated. Recrystallisation of the residue from benzene gave the N-*methylcarboxamide*, m.p. 133—134° (Found: C, 59·3; H, 7·6; N, 8·5. $C_{16}H_{20}N_2O_3S$ requires C, 59·2; H, 7·5; N, 8·6%), $\nu_{max.}$ 3360 (NH), and 1648 and 1556 (amide) cm^{-1}; δ ($CDCl_3$) 7·57 (q, aromatic H), 6·18br (s, NH), 3·85br (m, H-1), 2·73 (s, TsN·CH_3), 2·75 (d, *J* 5, CO·NH·CH_3), 2·43 (s, aromatic CH_3), and 1·80br (m, alicyclic H).

cis-2-*Methylaminocyclohexanecarboxamide* (31).—The amide (29) (1·2 g) was dissolved in liquid ammonia (25 ml) and sodium was added until the blue colour persisted for at least 10 min. After 20 min, ammonium chloride was added and the ammonia evaporated off. The residue was dissolved in 2N-sodium hydroxide (50 ml) and extracted with chloroform. The extract gave the *carboxamide* (590 mg, 92%), m.p. 95—96° [from 1 : 10 benzene–light petroleum (b.p. 40—60°)] (Found: C, 61·7; H, 10·3; N, 18·0. $C_8H_{16}N_2O$ requires C, 61·5; H, 10·3; N, 17·9%), $\nu_{max.}$ 3370 and 3220 (NH), 2810 (NCH_3), and 1670 (CO) cm^{-1}, δ ($CDCl_3$) 9·08br (s, NH), 6·05br (s, NH_2), and 2·42 (s, NCH_3).

cis-1-*Aminomethyl*-2-*methylaminocyclohexane* (33).—The amide (31) (1·7 g) in benzene (200 ml) was added to lithium aluminium hydride (5·1 g) in dry ether (70 ml). The mixture was refluxed with stirring overnight, cooled, decomposed with saturated aqueous potassium carbonate (20 ml), and refluxed for 30 min. The solution was filtered, and the filtrate evaporated to yield the *diamine* (1·43 g, 93%), b.p. 40—42° at 2·5 mmHg (Found: C, 67·6; H, 12·7; N, 19·9. $C_8H_{18}N_2$ requires C, 67·6; H, 12·8; N, 19·7%), $\nu_{max.}$ 3300 (NH), 2800 (NCH_3), and 1590 (NH bend) cm^{-1}, δ ($CDCl_3$) 2·38 (s, NCH_3). The *dipicrate* had m.p. 212·5—213° (from MeOH) (Found: C, 40·0; H, 4·4; N, 18·5. $C_{20}H_{24}N_8O_{14}$ requires C, 40·0; H, 4·0; N, 18·7%).

cis-1-*Amino*-2-*methylaminomethylcyclohexane* (34).—Detosylation of the amide (23) with sodium in liquid ammonia as above gave *cis*-1-aminocyclohexane-*N*-methylcarboxamide, $\nu_{max.}$ 3320 (NH), and 1650 and 1570 (amide) cm^{-1}, δ ($CDCl_3$) 2·77 (d, NCH_3, *J* 5). The crude amide (5 g) in benzene (300 ml) was reduced with lithium aluminium hydride (14·6 g) in ether (100 ml) as before and gave the cis-*diamine* (3·9 g, 86%), b.p. 58° at 0·7 mmHg (Found: C, 67·7; H, 12·8; N, 19·8. $C_8H_{18}N_2$ requires C, 67·6; H, 12·8; N, 19·7%), $\nu_{max.}$ 3320 (NH), 2800 (NCH_3), and 1590 (NH bend) cm^{-1}, δ ($CDCl_3$) 2·40 (s, NCH_3). The *dipicrate* had m.p. 206—210° (from MeOH) (Found: C, 40·1; H, 4·4; N, 18·3. $C_{20}H_{24}N_8H_{14}$ requires C, 40·0; H, 4·0; N, 18·7%).

cis-1-*Methylamino*-2-*methylaminomethylcyclohexane* (35).—Crude *cis*-2-methylaminocyclohexane-*N*-methylcarboxamide [prepared from the tosylamide (30) as above; $\nu_{max.}$ 1645 and 1565 (amide) cm^{-1}, δ ($CDCl_3$) 2·77 (d, *J* 4 CH·NH·CH_3) and 2·38 (s, NCH_3)] was reduced with lithium aluminium hydride as above and gave the cis-*diamine* (93%), b.p. 48° at 0·2 mmHg (Found: C, 69·1; H, 12·7; N, 17·6. $C_9H_{20}N_2$ requires C, 69·2; H, 12·9; N, 17·9%), $\nu_{max.}$ 3360 (NH), 2830 (NCH_3) and 1560 (NH bend) cm^{-1},

[12] H. Plieninger and K. Schneider, *Chem. Ber.*, 1959, **92**, 1594.
[13] H. Carter, R. Frank, and H. Johnston, *Org. Synth.*, 1955, Coll. Vol. 3, p. 167.

δ ($CDCl_3$) 2·43 (s, NCH_3) and 2·40 (s, NCH_3). (This diamine was also obtained by a similar reduction of *cis*-2-benzyloxycarbonylaminocyclohexane-*N*-methylcarboxamide.) The *dipicrate* had m.p. 220·5—221·5° (from MeOH) (Found: C, 41·3; H, 4·4; N, 18·2. $C_{21}H_{26}N_8O_{14}$ requires C, 41·0; H, 4·3; N, 18·2%).

1-*Methyl*-cis-*perhydroquinazolin*-2-*one* (11).—(*a*) (with B. A. Milloy). The mixture of 3,4,4a,5,6,7- and 3,4,5,6,7,8-hexahydro-1-methylquinazolin-2(1*H*)-one was reduced with PtO_2 in acetic acid as for the unsubstituted compound (1) and gave 1-*methyl*-cis-*perhydroquinazolin*-2-*one* (91%), b.p. 170° at 2 mmHg, as a hygroscopic oil (Found: C, 63·7; H, 9·7; N, 15·9. $C_9H_{16}N_2O,\frac{1}{3}H_2O$ requires C, 63·4; H, 9·6; N, 16·4%), which crystallised after 1 week. It was sublimed at 100° and 3 mmHg; m.p. 76° (Found: C, 64·5; H, 9·65; N, 16·6%; M^+, 168. $C_9H_{16}N_2O$ requires C, 64·3; H, 9·6; N, 16·65%; *M*, 168), $\nu_{max.}$ 3303, 3205, and 3060 (NH), 1660 and 1530 (amide), 1455, 1405, 1290, 1280, and 760 (all strong) cm^{-1}.

(*b*) To *cis*-1-aminomethyl-2-methylaminocyclohexane (71 mg) suspended in water (0·5 ml) at 0° were added simultaneously with stirring a solution of phosgene in toluene (0·65 ml, 12%; 2 mol. equiv.) and aqueous 2N-sodium hydroxide (0·7 ml, 4 mol. equiv.). The mixture was stoppered and stirred for 2 days, then extracted with chloroform. The extract was dried and evaporated to yield a thick oil (40 mg, 48%), identical with the product from (*a*).

3-*Methyl*-cis-*perhydroquinazolin*-2-*one* (10).—(*a*) (with B. A. Milloy). 3,4,5,6,7,8-Hexahydro-3-methylquinazolin-2(1*H*)-one was reduced catalytically as above and gave a thick oil, b.p. 150° at 1·5 mmHg (80%), which slowly solidified. T.l.c. showed a small amount of impurity which was not observed in the u.v. (*i.e.* no absorption), i.r. and ^1H n.m.r. spectra but could be removed by formation of the *picrate*, m.p. 125—126° (from MeOH and H_2O) (Found: C, 45·5; H, 4·9; N, 17·4. $C_{15}H_{19}N_5O_8$ requires C, 45·3; H, 4·8; N, 17·7%). Decomposition of this with 10N-sodium hydroxide gave pure 3-*methyl*-cis-*perhydroquinazolin*-2-*one*, m.p. 122° [from light petroleum (b.p. 80—100°) followed by sublimation at 110° and 1·5 mmHg] (Found: C, 64·2; H, 9·7; N, 16·6. $C_9H_{16}N_2O$ requires C, 64·1; H, 9·9; N, 16·6%), $\nu_{max.}$ 3320, 3240, and 3090 (NH), 1655 and 1527 (amide), 1410, 1318, 1294, 1090, and 763 (all strong) cm^{-1}.

(*b*) *cis*-1-Amino-2-methylaminomethylcyclohexane (71 mg) and *NN'*-carbonyldi-imidazole (90 mg, 1 mol. equiv.) in dry tetrahydrofuran (2·5 ml) were stirred at 20° for 12 h and then refluxed for 4 h. The solution was evaporated and the residue was dissolved in chloroform which was then washed with 2N-hydrochloric acid, dried, and evaporated to give compound (10) (17 mg, 20%), identical with that from (*a*). When phosgene was used, only a trace of perhydroquinazolinone was sublimed out of the intractable residue.

1,3-*Dimethyl*-cis-*perhydroquinazolin*-2-*one* (13).—The diamine (35) (156 mg) was treated with phosgene in toluene as above and gave *compound* (13) as a thick oil which was distilled onto a cold finger in 65% yield (Found: C, 65·7; H, 9·9; N, 15·6. $C_{10}H_{18}N_2O$ requires C, 65·9; H, 9·9; N, 15·4%), $\nu_{max.}$ 1640 (CO), 1516, 1452, 1402, 1275, 1238, and 1046 cm^{-1}. An attempted preparation of this compound from *diethyl* 2-*oxo*-cis-*perhydroquinazoline*-1,3-*dicarboxylate* [b.p. 120° at 0·5 mmHg (Found: C, 56·4; H, 7·7; N, 9·7. $C_{14}H_{22}N_2O_5$ requires C, 56·4; H, 7·4; N, 9·4%), $\nu_{max.}$ 1787 and 1740 (CONCO), and 1200 (COC) cm^{-1}, prepared by boiling *cis*-perhydroquinazolin-2-one in ethyl chloroformate] by reduction with lithium aluminium hydride gave *cis*-perhydroquinazolin-2-one.

1-*Methyl*-cis-*perhydroquinazoline Picrate*.—*cis*-1-Aminomethyl-2-methylaminocyclohexane (142 mg) was mixed with aqueous 37% formaldehyde (95 mg, 1·2 mol. equiv.) and kept at 20° for 2 days. Saturated aqueous picric acid was added and the *dipicrate* separated (608 mg, 99%), m.p. 171—173° (from MeOH) (Found: C, 41·4; H, 4·3; N, 18·2. $C_{21}H_{24}N_8O_{14}$ requires C, 41·2; H, 4·0; N, 18·3%). The dipicrate was decomposed with 10N-sodium hydroxide and gave the free base (122 mg, 86%), which was spectroscopically pure, $\nu_{max.}$ 3315 and 1540 cm^{-1}.

Similarly 3-*methyl*-cis-*perhydroquinazoline dipicrate*, m.p. 173—174° (Found: C, 41·3; H, 4·0; N, 18·3. $C_{21}H_{24}N_8O_{14}$ requires C, 41·2; H, 4·0; N, 18·3%), and 1,3-*dimethyl*-cis-*perhydroquinazoline dipicrate*, m.p. 186—187° (Found: C, 42·1; H, 4·6; N, 17·6. $C_{22}H_{26}N_8O_{14}$ requires C, 42·2; H, 4·2; N, 18·0%), were obtained in 90% yields. They gave the respective free bases, with 10N-sodium hydroxide, as oils in >80% yields, which were spectroscopically pure but the quantities (83 and 112 mg) were too small for adequate distillation.

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