Quinazolines. Part XVIII.[1] A Second Stereospecific *cis*-Addition of the Elements of Nitromethane across a Tetrasubstituted Ethylenic Double Bond. A Concerted Mechanism for the Reaction of Nitroacetic Acid with Enamines

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The reaction of ethyl 3,4,5,6-tetrahydroanthranilate with nitroacetic acid gave, stereospecifically, ethyl *cis*-2-amino-*trans*-2-nitromethylcyclohexanecarboxylate (7) in 70% yield. The stereochemistry was deduced by the following sequence of reactions: (7) → ethyl *cis*-2-amino-*trans*-2-aminomethylcyclohexanecarboxylate (8) → 3a-amino-*trans*-perhydroisoindol-1-one (9) → 3a-(*N'*-phenylureido)-*trans*-perhydroisoindol-1-one (10) → 8a-aminomethyl-3-phenyl-*cis*-perhydroquinazoline-2,4-dione hydrochloride (18) → 8a-bromomethyl-3-phenyl-*cis*-perhydroquinazoline-2,4-dione (19) → 8a-methyl-3-phenyl-*cis*-perhydroquinazoline-2,4-dione (20), in which the configuration at the asymmetric centres was preserved. Compound (20) was prepared from authentic methyl *trans*-2-methyl-*cis*-2-(*N'*-phenylureido)cyclohexanecarboxylate (22) by cyclisation with methanolic sodium hydroxide. Although this cyclisation in a deuteriated medium proceeded with complete exchange of the 4a-proton in the dione (20), it was shown to occur with retention of configuration by reduction with sodium dihydrobis-(2-methoxyethoxy)aluminate to *cis*-2-anilinomethyl-1,*N*-dimethylcyclohexylamine (25) and then to 1,8a-dimethyl-3-phenyl-*cis*-perhydroquinazoline (26), whose ^{1}H n.m.r. spectrum was unambiguous.

The *trans* stereochemistry of the isoindolone (9) was confirmed by reduction to 3a-amino-*trans*-perhydroisoindole (14) whose ^{1}H n.m.r. spectrum was similar to that of 3a-methylanalogue (15) but different from that of 3a-methyl-*cis*-perhydroisoindole (16).

This second observation of a stereospecific *cis*-addition of the elements of nitromethane strongly supports a concerted mechanism for the reaction of nitroacetic acid with enamines. Further evidence is reported from experiments in [$^2H_3$]nitromethane which show that no deuterium was incorporated into the nitromethane adducts.

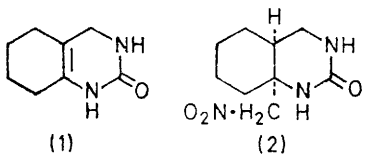
N.m.r. spectra of various compounds are discussed in connection with the generality of application of the principle that the protons in the alicyclic six-membered rings of reduced six–five, six–six and six–seven membered fused ring systems give a narrow band envelope for *cis* ring fusion and a wide band envelope for *trans* ring fusion.

PREVIOUSLY one of us has shown [2] that the fusion of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (1) with nitroacetic acid gives exclusively 8a-nitromethyl-*cis*-perhydroquinazolin-2-one (2). In an alternative approach to the synthesis of 8a-substituted quinazolines with a reactive side chain, we have fused ethyl 3,4,5,6-tetrahydroanthranilate (4) with nitroacetic acid and obtained ethyl *cis*-2-amino-*trans*-2-nitromethylcyclohexanecarboxylate (7) in good yield. The stereochemistry of this addition, which is described here, was studied in the hope that it would reveal some important aspects of the mechanism of the reaction of nitroacetic acid with enamines, and because the complete structure of the quinazolines derived from it was required for further work. It has been suggested [2] that the *cis* addition to give compound (2) resulted from either (i) a concerted addition–decarboxylation mechanism or (ii) protonation of the enamine (1), followed by equilibration of the intermediate carbonium ion (3) with the nitromethane anion to form the thermodynamically more stable *cis* product. Evidence in support of the concerted mechanism is now presented. The ester (7), unlike the adduct (2), readily lost the elements of nitromethane on attempted distillation or on mild treatment with acid or base. It gave a stable picrate, but could not be recovered from it without extensive loss of nitromethane. These properties suggested that a *trans* addition of nitromethane had taken place but the following study clearly shows that the addition was *cis*.

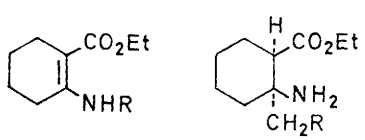
Attempts to prepare malonic ester or nitromethane adducts of the esters (4)—(6) in the usual ways were uniformly unsuccessful and indicated that the reaction with nitroacetic acid was not a typical Michael reaction. The nitro-compound (7) was reduced catalytically to the diamino-ester (8), which could not be isolated because it

[1] Part XVII, W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 2502.
[2] Part XVI, W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1971, 1812.

cyclised to 3a-aminoperhydroisoindol-1-one (9). If no inversion occurred at C-7a during the cyclisation, then the determination of the stereochemistry of this stable isoindol-1-one should show whether the nitromethane

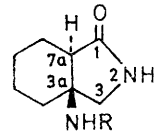


(1) (2) (3)

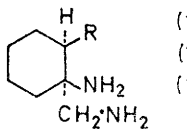


(4) R = H
(5) R = CHO
(6) R = Bz

(7) R = NO_2
(8) R = NH_2



(9) R = H
(10) R = CO·NHPh



(11) R = CO_2H
(12) R = CH_2·OH
(13) R = CH_2Cl

addition was *cis* or *trans*. The possibility of inversion was excluded because reduction of the nitromethyl ester (7) with lithium aluminium hydride gave 2-amino-2-aminomethyl-1-hydroxymethylcyclohexane (12), which was converted into the 1-chloromethyl derivative (13) by boiling thionyl chloride, and was cyclised, with sodium hydroxide, to 3a-aminoperhydroisoindole (14). This was identical with the product from the reduction of the isoindolone (9) with lithium aluminium hydride. Reduction of carbonyl groups with lithium aluminium hydride is known to proceed without epimerisation or inversion of the α-hydrogen atoms.[3] Moreover, ring cleavage of the isoindolone (9) to the diamino-acid (11) without exchange of the proton at C-7a occurred on boiling in 5N-deuterium chloride in deuterium oxide. The signal for this proton can be observed clearly in the n.m.r. spectra of compounds (9) and (11). The C-1 proton of the diamino-acid (11) also could not be exchanged by deuterium on heating in 4·8N-sodium deuteroxide at 100°. These conditions are more drastic than those used in the cyclisation of the diamino-ester (8). Hence the stereochemistry (unspecified at this stage) at the bridgehead carbon atoms of the isoindoline (14) and the isoindolone (9) is the same.

The ^{1}H n.m.r. spectra of several *cis*- and *trans*-perhydroquinazolines and 2-substituted derivatives have shown [4,5] that a narrow band envelope for the C-5, -6, -7, and -8 protons is associated with *cis*-structures whereas a broad band envelope is characteristic of *trans*-structures. If this generalisation holds for saturated six–five membered fused ring systems then the large $W_{\frac{1}{2}}$ value (74 Hz) observed for the C-4, -5, -6, and -7 protons of the isoindol-1-one (9) suggests a *trans*-fused compound. The corresponding $W_{\frac{1}{2}}$ value for the derived isoindoline (14) was also large (64 Hz) (see Table). To test this generalisation (which turns out to be correct; see also later) and for comparison, authentic 3a-methyl-*trans*- (15) and 3a-methyl-*cis*- (16) perhydroisoindoles were prepared. These were expected to be good models for the aminoisoindoline (14) because the effect of the methyl group on the protons in the cyclohexane ring was thought to be similar to that of an amino-group. In this case the $W_{\frac{1}{2}}$ values for the *trans*- and *cis*-compounds were 60 and 9 Hz, respectively. We concluded that the isoindoles (9) and (14) have *trans*-fused rings and that the original nitromethane adduct was ethyl *cis*-2-amino-*trans*-2-aminomethylcyclohexanecarboxylate (7) (*i.e.* from a *cis*-addition).

Although the foregoing spectroscopic evidence is acceptable, a correlation from synthesis was sought in order to strengthen the case for *cis*-addition. In attempts to convert 3a-aminoperhydroisoindol-1-one (9) into the 3a-guanidino-derivative, the former was fused with *S*-methylisothiouronium sulphate (we hoped then to open the isoindole ring and recyclise the system to yield an 8a-substituted 2-aminoquinazoline). No reaction took place at 20°, and at 160° elimination of ammonia (*trans*) occurred giving 2,3,4,5,6,7-hexahydroisoindol-1-one (17). This product was also obtained by a similar fusion with cyanamide, and was identified by its i.r. and ^{1}H n.m.r. spectra and elemental analysis. Phenyl isocyanate, on the other hand, reacted rapidly with the isoindol-1-one (9) in boiling benzene to give a high yield of 3a-(*N'*-phenylureido)perhydroisoindol-1-one (10). The isocyanate must have reacted with the 3a-amino-group and not with N-2 because the product showed three separate peaks for amide NH (exchangeable) in the ^{1}H n.m.r. spectrum (see Table). On heating compound (10) with 5N-hydrochloric acid, the ring amide bond was cleaved and cyclisation gave 8a-aminomethyl-3-phenylperhydroquinazoline-2,4-dione hydrochloride (18), identified by elemental analysis, i.r., ^{1}H n.m.r., and mass spectra, and the subsequent series of reactions. Nitrosyl bromide converted the hydrochloride (18) (or the corresponding hydrobromide) into the bromomethyl derivative (19), which had a typical imide i.r. spectrum and showed signals for the phenyl protons in the ^{1}H n.m.r. spectrum. It gave two molecular ions of equal intensity (*m/e* 336 and 338) in the mass spectrum and a base peak at $M^+ - CH_2Br$ by a fragmentation typical of the 8a-substituted *cis*-perhydroquinazolin-2-ones studied earlier.[2] Reduction of the bromomethyl derivative with Raney nickel and hydrogen gave 8a-methyl-3-phenyl-*cis*-perhydroquinazoline-2,4-dione (20) quantitatively. The product was identical with material prepared by independent synthesis (see later).

At this stage it was necessary to prove that inversion

[3] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 28.

[4] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 238.

[5] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1969, 1635.

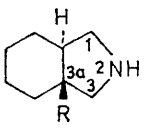
of the proton-bearing asymmetric centre did not take place during the foregoing transformations. The ureido-compound (10) was prepared under conditions unlikely to cause epimerisation (boiling benzene for 15 min). It was converted into the 8a-aminomethylquinazoline-dione (18) as before but in boiling 5N-deuterium chloride in deuterium oxide; the signal for the C-4a proton in the salt was clearly present in the ^{1}H n.m.r. spectrum and integrated for one proton. The bromination of the salt (18) was performed in 2·5N-deuteriosulphuric acid in deuterium oxide; again the 4a-proton was clearly visible in the ^{1}H n.m.r. spectrum of the product. Thus no epimerisation or inversion occurred at the asymmetric centre concerned. The possibility of inversion in the last step, *i.e.* the reduction to the methyl derivative (20), was excluded by the fact that the same methyl compound was obtained by reduction of the bromo-compound (19) with sodium dihydrobis-(2-methoxyethoxy)aluminate in benzene.

^{1}H N.m.r. spectra of isoindoles and quinazolines (δ in p.p.m.) [a]

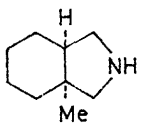
Isoindole	H-1	H-3	H-7a	CMe	Other H	NH	H-4, -5, -6, and -7 ($W_{\frac{1}{2}}$)	Field [b]	Solvent
3a-Amino-1-oxo-*trans*-perhydro- (9)		3·23(s) 3·60(s) 3·60(s)	2·32br (s) 2·69br (d, J 12) 2·70(q, J_{ax} 12, J_{eq} 4)				1·1—2·0 (18) 1·0—2·2 (50) 1·7—2·8 (74)	60 60 100	D_2O D_2O–DCl D_2O–DCl [d]
1-Oxo-3a-(*N'*-phenylureido)-*trans*-perhydro- (10)		3·12(d) 3·98(d) (J_{gem} −11)	2·68(m)		6·8—7·7 (m, aromatic)	3·12(s) [c] 6·20(s), [c] 8·56(s) [c]	1·1—2·4 (28)	60	$(CD_3)_2SO$
3a-Amino-*trans*-perhydro- (14)	2·68(q, J_{vic} 7·2 2·98(q, J_{vic} 9·3 (J_{gem} −10·1)	2·66(d), 2·80(d) (J_{gem} −12·0)				2·14(s) [c]	1·0—1·9 (64)	100	$CDCl_3$
3a-Methyl-*trans*-perhydro- (15)	2·97(q, J_{vic} 7·5) 2·56(q, J_{vic} 9·5) (J_{gem} −9·8)	2·50(d), 2·75(d) (J_{gem} 9·7)		0·90(s)		2·26(s) [c]	1·0—1·9 (60)	100	$CDCl_3$
3a-Methyl-*cis*-perhydro- (16)	2·85(q, J_{vic} 6·5) 3·08(q, J_{vic} 7·5) (J_{gem} −10·4)	2·57(d), 2·81(d) (J_{gem} −10·0)	[e]	1·03(s)			2·2—2·8 (9)	100	$CDCl_3$
trans-Perhydro-	3·08(q, J_{vic} 5·5, J_{gem} −9·0) [f]	2·48(t, J_{vic} 9·0, J_{gem} −9·0) [g]				2·67(s) [c]	1·6—2·0(t) (24) [h] 0·8—1·6(m) (25) [i]	100	$CDCl_3$
	3·14(q, J_{vic} 5·5, J_{gem} −9·0) [f]	2·52(t, J_{vic} 9·0, J_{gem} −9·0) [g]				2·78(s)	1·65—2·2(m) (18) [h] 0·9—1·65(m) (15) [i]	60	$CDCl_3$
cis-Perhydro- [j]	3·02(q, J_{vic} 7·1, J_{gem} −10·0) [f]	2·78(q, J_{vic} 5·2, J_{gem} −10·0) [g]	2·00br (H-7a and -3a)			2·04(s) [c]	1·1—1·8 (7)	60	$CDCl_3$
3,4,5,6,7-Hexahydro-1-oxo-2*H*- (17)		3·84(s)					1·73(10) and 2·37(13)	60	$CDCl_3$

3-Phenyl-*cis*-perhydro-quinazoline-2,4-dione	H-4a	8a-CH_2R	Aromatic H	NH	H-5, -6, -7, and -8 ($W_{\frac{1}{2}}$)		
8a-Aminomethyl- (HCl) (18)	3·33(q, J_{eq} 5·5, J_{ax} 10·0)	3·67(d), 3·91(d) (J_{gem} −14·0) (R = NH_3^+	7·66—7·80(q), 7·96—8·12(t)		1·8—2·6 (56)	100	D_2O–DCl
8a-Bromomethyl- (19)	2·88 (t, J_{vic} 7·0)	3·53(s) (R = Br)	7·18—7·70(m)	6·33(s) [c]	1·2—2·2 [k]	60	$CDCl_3$
8a-Methyl- (20)	2·55(t, J_{vic} 8·0)	1·36(d), (R = H)	1·15—1·65(m)	6·05(s) [c]	1·1—2·1 [k]	60	$CDCl_3$
1,8a-Dimethyl-3-phenyl-*cis*-perhydroquinazoline (26)	3·32(d, $W_{\frac{1}{2}}$ 6, H-4) 3·91(d) and 4·13(d) (J_{gem} −10, H-2)	1·12(s, 8a-Me) 2·28(s, 1-Me)	6·7—7·7 (m, Ph)		6·62—7·62 (includes H-4a)	60	$CDCl_3$

[a] J (±0·3 Hz) and $W_{\frac{1}{2}}$ values are in Hz. J_{gem} Values are assumed negative. Tetramethylsilane as internal standard. [b] 60 and 100 MHz fields are at 33·3 and 34·0°, respectively. [c] Exchanged by D_2O. [d] Tetramethylsilane as external standard. [e] This proton is in the H-4, -5, -6, and -7 envelope. [f] These are from the *quasi*-equatorial H-1 and H-3. [g] These are from the *quasi*-axial H-1 and H-3. [h] Equatorial H-4, -5, -6, and -7. [i] Axial H-4, -5, -6, and -7 and axial H-3a and -7a. [j] The pattern for H-1 and H-3 is identical with that for the corresponding protons in perhydroisobenzofuran (*cf.* ref. 8). [k] These form two band envelopes.



(14) R = NH_2
(15) R = Me



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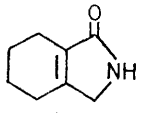

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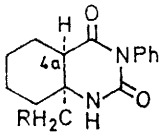
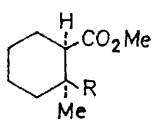
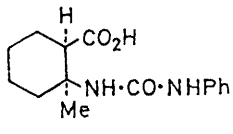


(18) R = NH_3^+ Cl^-
(19) R = Br
(20) R = H



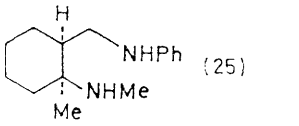
(21) R = NCO
(22) R = NH·CO·NHPh
(23) R = NH_2



(24)

The starting material for the synthesis of authentic 8a-methyl-3-phenyl-*cis*-perhydroquinazoline-2,4-dione (20) was methyl *cis*-2-isocyanato-*trans*-2-methylcyclohexanecarboxylate (21), of established stereochemistry.[2] This reacted with aniline to give methyl *trans*-2-methyl-*cis*-2-(*N'*-phenylureido)cyclohexanecarboxylate (22), identical with material prepared from methyl *cis*-2-amino-*trans*-2-methylcyclohexanecarboxylate (23) (also of established stereochemistry) [2] and phenyl isocyanate in benzene. When the ureido-ester was kept in methanol containing 2N-sodium hydroxide at 20° overnight the major product was the 8a-methylquinazolinedione (20), identical with that already obtained; a minor quantity of the ureido-acid (24) was also formed. However, when this cyclisation was carried out in a deuteriated medium (MeOD–2N-NaOD–D_2O) the 4a-proton of the quinazolinedione (20) formed was completely replaced by deuterium as shown by the ^{1}H n.m.r. spectrum. Further, when this deuteriated compound was treated with methanolic sodium hydroxide as before, the deuterium was completely replaced by hydrogen. Although these results show that the 4a-proton is readily replaced in the presence of sodium hydroxide, it does not follow that inversion at C-4a had occurred to give the *trans*-

fused quinazolinedione. Attempts to cyclise the ureido-ester (22) (*e.g.* in boiling tetralin, benzene containing pyridine, 2-picoline, or concentrated sulphuric acid) failed. Similarly it was not possible to cyclise the acid (24) to the quinazoline (20). Also the quinazolinedione was unchanged by concentrated deuteriosulphuric acid at 100° in 3 h. On the other hand, it was slowly cleaved by aqueous 2N-sodium hydroxide in methanol at 20°; when the ureido-ester (22) was thus treated the relative yields of the dione (20) and the ureido-acid (24) were 10 and 1·8 after 18 and 48 h, respectively. The dione was rapidly hydrolysed to the ureido-acid by boiling in aqueous 2N-sodium hydroxide for a short period. The ureido-acid (24) gave the ester (22) when treated with diazomethane in methanol.



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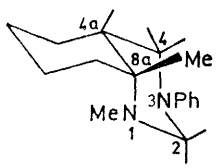

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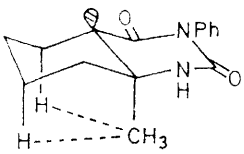

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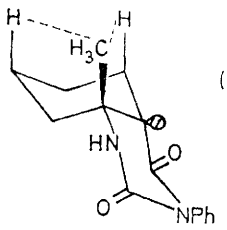

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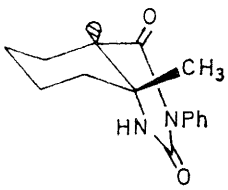
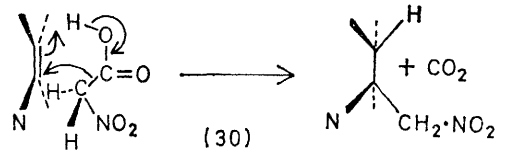
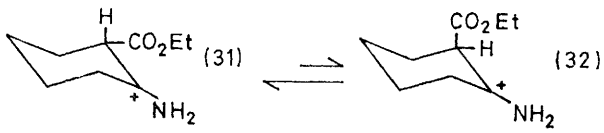


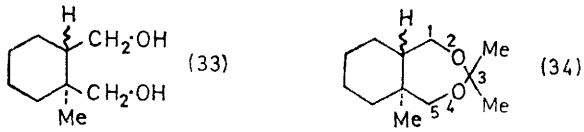
(29)

That inversion did not take place in the deuterium exchange reactions of the dione (20) was shown as follows. Reduction of the dione (20) with sodium dihydrobis-(2-methoxyethoxy)aluminate in boiling benzene was complete in 48 h and gave *cis*-2-anilinomethyl-1,*N*-dimethylcyclohexylamine (25) in high yield. The mode of cleavage of the intermediate perhydroquinazoline was confirmed by cyclisation with formaldehyde to 1,8a-dimethyl-3-phenyl-*cis*-perhydroquinazoline (26). We have reported [5] a similar reduction of a perhydroquinazoline with lithium aluminium hydride to give *N*(1)-methyl-2-methylaminocyclohexylamine and not the isomeric 2-(methylaminomethyl)cyclohexylamine. The *cis* stereochemistry of the perhydroquinazoline (26) was deduced from the ^{1}H n.m.r. spectrum, which was closely similar to that of *cis*- but different from that of *trans*-perhydroquinazoline. The signal for the two C-4 protons formed a narrow doublet, $W_{\frac{1}{2}}$ 6 Hz (*i.e.* no *trans*-diaxial coupling) and the protons at C-4a, -5, -6, -7 and 8 formed a band envelope with $W_{\frac{1}{2}}$ 26 Hz (*cf.* $W_{\frac{1}{2}}$ 15 and 54 Hz for *cis*- and *trans*-perhydroquinazolines, respectively).[5] When this quinazoline (26), in dimethyl sulphoxide, was heated to 180° the H-2 AB quartet did not collapse. The coalescence temperature of the H-2 quartet in *cis*-perhydroquinazoline under similar conditions was 160° ± 4°.[5] The presence of the 1- and 8a-methyl and the 3-phenyl groups must confer greater stability on the conformer (26) of the two possible *cis*-chair conformers, than in the case of the unsubstituted *cis*-perhydroquinazoline.

These results show that the stereochemistry of the dione (20) and the other quinazolines (18) and (19) is *cis*, that the stereochemistry of the isoindoles (9), (10), and (14) is *trans*, and that the original nitromethane addition is *cis*. It is clear that the deuterium exchange of the C-4a proton in the dione (20) occurred with retention of configuration, a result which has some theoretical justification. Of the three possible intermediate carbanions (27)—(29) in the reaction, the conformer (29) should be thermodynamically more stable because it has no 1,3-diaxial hydrogen–methyl interactions. It should undergo hydrogen exchange without epimerisation or inversion. The equilibrium between the equatorial and axial conformers of methylcyclohexane (undiluted, at −110°) is about 100 : 1 in favour of the equatorial conformer,[6] indicating that the 1,3-diaxial interactions between a methyl group and a hydrogen atom are significant.







The two reported additions of nitroacetic acid to enamine double bonds [to form the nitromethyl adducts (2) and (7)] are *cis* stereospecific, which strongly supports the concerted mechanism (30) postulated earlier.[2] In mechanism (ii) (see before) the carbonium ions (31) and (32) are formed by protonating the enamine (4) [*cf.* the cation (3)],[2] and by removing a nitromethyl anion from a *cis*- or a *trans*-adduct. There does not appear to be much steric advantage for a *cis*- over a *trans*-addition of the nitromethyl anion to these carbonium ions. Such a two-step mechanism, which would involve a free nitromethyl anion, was excluded by performing fusions of the enamines (1) and (4) with nitroacetic acid in the presence

[6] F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *J. Amer. Chem. Soc.*, 1971, **93**, 258.

of equivalent amounts of [$^2H_3$]nitromethane and comparing the ^1H n.m.r. spectra of the products with those from control experiments using nitromethane. No incorporation (within experimental error) of deuterium in the $CH_2{\cdot}NO_2$ group was observed in either case. Thus the proton and the nitromethyl group that add across the double bond originate from the same nitroacetic acid molecule.

Proton Magnetic Resonance.—Further to the examination of the effect of ring fusion in bicyclic reduced heterocycles on the band width at half height for the alicyclic protons, the spectra of *cis* and *trans*-perhydroisoindoles were measured. The hydrochloride of the latter was supplied by Professor H. Christol (Montpellier).[7] The signal for the protons at C-4, -5, -6, and -7 gave a small $W_{\frac{1}{2}}$ value for the *cis*-compound and a large value for the *trans*-isomer (see Table). In the spectrum of the *cis*-compound the AB pattern corresponding to protons at C-1 and C-3 was identical with that observed in *cis*-perhydroisobenzofuran.[8] It was anticipated that the oxygen analogues of the methyl derivatives (15) and (16), *i.e.* 3a-methyl-*cis*- and 3a-methyl-*trans*-perhydroisobenzofuran should behave similarly. However, attempts to convert *cis*- and *trans*-1,2-bis(hydroxymethyl)-1-methylcyclohexane (33) into the isobenzofurans by a method previously described [9] for the 1,2-bis(hydroxymethyl)cyclohexanes gave the *cis* and *trans* six–seven membered fused ring isopropylidene derivatives (34). In these examples also (see Experimental section) the cyclohexane protons in the *cis*-compound gave a narrower band envelope than in the *trans*-isomer. Caution must be exercised when assigning the stereochemistry of reduced bicyclic systems from band envelope widths. The ruling does not necessarily hold when the compounds have several substituents or have magnetically anisotropic groups because these may seriously influence the relative chemical shifts of axial and equatorial protons. Thus the $W_{\frac{1}{2}}$ values for the C-5, -6, -7, and -8 protons in the *cis*-dioxo-compounds (18) and (19), and related compounds,[2] are large. It is important also that the magnetic field used is the same, because the $W_{\frac{1}{2}}$ values at 100 MHz are generally larger than those at 60 MHz.

EXPERIMENTAL

Microanalyses were performed by Dr. J. E. Fildes and her staff. Instruments used are given in ref. 5. All extracts were dried over anhydrous sodium sulphate, and evaporations were performed at 30° and 18 mmHg. Potassium bromide discs (solids) and films (liquids) were used for i.r. spectra. The C–H stretching frequencies at *ca.* 2900 cm^{-1} in most compounds are not recorded, and the assignments of bands are tentative. The ^1H n.m.r. spectra were run at 60 MHz (33·3°) with tetramethylsilane as internal standard, unless stated otherwise; J and $W_{\frac{1}{2}}$ values are in Hz.

Ethyl 2-*Formamidocyclohex*-1-*enecarboxylate* (5).—Ethyl 2-aminocyclohex-1-enecarboxylate [10] (85 mg; redistilled, b.p. 120° at 6 mmHg) was kept in acetic formic anhydride [11] (1 ml) at 20° overnight. The mixture was then evaporated to give the *formamido-compound* [needles from ethanol–light petroleum (b.p. 40—60°)] (94 mg, 95%), m.p. 70·5—71° (Found: C, 61·1; H, 7·45; N, 6·9. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%); $\nu_{max.}$ 1694 (ester CO) and 1668 and 1613 (amide and C=C) cm^{-1}; δ ($CDCl_3$) 8·70br (d, CHO) and 11·2br (d, J 12, NH) p.p.m.

Ethyl 2-*Benzamidocyclohex*-1-*enecarboxylate* (6).—To the ester (4) (840 mg) in pyridine (5 ml) benzoyl chloride (0·7 g, 1 mol. equiv.) was added dropwise at 0°. The mixture was stirred at 20° for 5 h, then evaporated, and the *benzamide* was recrystallised from ethanol–ether, m.p. 99—100° (1·04 g, 76%) (Found: C, 70·55; H, 7·2; N, 5·1. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%); $\nu_{max.}$ 1685 (ester CO) and 1656 and 1625 (amide and C=C) cm^{-1}.

Ethyl cis-2-*Amino*-trans-2-*nitromethylcyclohexanecarboxylate* (7).—The enamino-ester (4) (2 g) was stirred with nitroacetic acid [12] (2·48 g, 2 mol. equiv.) at 20—25° under nitrogen. When effervescence ceased (*ca.* 1 h) the mixture was evaporated under vacuum to remove excess of nitromethane. The residue was stirred with more nitroacetic acid (2·48 g) and evaporated again after effervescence ceased. A solution of the residue in benzene (80 ml) was filtered (Celite) and evaporated. The ^1H n.m.r. spectrum of the residual oil (2·33 g) indicated that it contained 70% of the nitromethyl adduct; $\nu_{max.}$ 1720 and 1195 (ester) and 1570 and 1383 (NO_2) cm^{-1}; δ ($CDCl_3$) 4·58 ($CH_2{\cdot}NO_2$) p.p.m. With saturated aqueous picric acid it gave the *picrate*, m.p. 141—143° (decomp.) (66%) (from 50% aqueous ethanol) (Found: C, 42·0; H, 4·5; N, 14·9. $C_{16}H_{21}N_5O_{11}$ requires C, 41·8; H, 4·6; N, 15·25%); δ [$(CD_3)_2SO$] 4·98 (s, $CH_2{\cdot}NO_2$) p.p.m.

2-*Methylthio*-5,6,7,8-*tetrahydroquinazolin*-4(3H)-*one*.—The foregoing crude nitromethyl adduct (from 0·42 g of enamino-ester) and a solution of *S*-methylisothiouronium sulphate (0·7 g) and sodium hydroxide (0·2 g) in ethanol (5 ml) were stirred at 20° for 10 days. The solvent was evaporated off and the residue was treated with water. The crystalline solid was extracted with ether [which gave the enamino-ester (90%)] and the insoluble solid was recrystallised from methanol–ether to give the *methylthioquinazolinone*, m.p. 220·5—222° (10 mg) (Found: C, 52·6; H, 6·3; N, 13·9; S, 15·9. $C_9H_{12}N_2OS,0{\cdot}5H_2O$ requires C, 52·7; H, 6·3; N, 13·7; S, 15·6%).

3a-*Amino*-trans-*perhydroisoindol*-1-*one* (9).—The crude nitromethane adduct (7) (from 2 g. of enamino-ester) in ethanol (100 ml) containing platinum oxide (650 mg) was shaken with hydrogen at 4·4 atm for 4 h. The catalyst was removed and the filtrate evaporated. The residue was dissolved in 2N-hydrochloric acid (15 ml) and extracted with ether. The aqueous solution was placed on a Dowex 50 W × 4 (H^+) column (150 ml), which was washed with water until the washings were neutral and eluted with aqueous 2·5N-ammonia (300 ml). The solid obtained by evaporating the eluate was sublimed at 150° and 0·5 mmHg to give the trans-*isoindol*-1-*one* (35—50%), m.p. 166—167° (from benzene) (Found: C, 62·3; H, 9·3; N, 18·1. $C_8H_{14}N_2O$ requires C, 62·3; H, 9·15; N, 18·2%); $\nu_{max.}$ 3185 and 3110br (NH) and 1678 and 1599 (amide) cm^{-1}. Occasionally the

[7] H. Christol, A. Donche, and F. Plénat, *Bull. Soc. chim. France*, 1966, 1315.
[8] P. R. Stapp and J. C. Randall, *J. Org. Chem.*, 1970, **35**, 2948.
[9] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 1953, 389.
[10] K. J. Liska, *J. Pharm. Sci.*, 1964, **53**, 1427.
[11] W. Stevens and A. van Es, *Rec. Trav. chim.*, 1964, **83**, 863.
[12] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1969, 986.

residue from the ion-exchange chromatography contained much diamino-acid (11) from hydrolysis and could not be sublimed without decomposition. It was therefore esterified by boiling with saturated ethanolic hydrogen chloride (3 h); the mixture was evaporated and the chromatographic purification was repeated.

cis-2-*Amino*-trans-2-*aminomethylcyclohexanecarboxylic Acid* (11).—The foregoing isoindolone (308 mg) in 5N-hydrochloric acid (2 ml) was boiled for 1 h and evaporated. The residue was passed through a Dowex 50W × 4 (H^+) column and eluted with 2·5N-ammonia to give the *diamino-acid* (275 mg, 80%), m.p. 221—222° (decomp) (from methanol) (Found: C, 55·2; H, 9·6; N, 16·0. $C_8H_{16}N_2O_2$, $0{\cdot}1H_2O$ requires C, 55·2; H, 9·3; N, 16·1%); $\nu_{max.}$ 1620 (NH_3^+) and 1570 (CO_2^-) cm^{-1}; δ (10N-DCl–D_2O) 2·90 (m, $W_{\frac{1}{2}}$ 14, H-1) and 3·48 (s, $CH_2{\cdot}NH_3^+$) p.p.m.

3a-(*N'-Phenylureido*)-trans-*perhydroisoindol*-1-*one* (10).—To the aminoisoindol-1-one (9) (154 mg) dissolved in boiling benzene (20 ml) was added phenyl isocyanate (130 mg, 1·1 mol. equiv.) in benzene (3 ml) and the mixture was refluxed. After 5 min needles started to separate and crystallisation was complete after 15 min. The solid was filtered off, washed with benzene, and dried at 70° for 1 h to give pure *ureido-compound* (252 mg, 86%), m.p. 208—210° (Found: C, 67·7; H, 7·3; N, 14·6. $C_{15}H_{19}N_3O_2$, $0{\cdot}25$-C_6H_6 requires C, 67·7; H, 7·2; N, 14·4%), and after being dried at 100° for 4 h it had m.p. 229—230° (Found: C, 65·6; H, 7·0; N, 15·1. $C_{15}H_{19}N_3O_2$ requires C, 65·9; H, 7·0; N, 15·4%); $\nu_{max.}$ 3465 and 3380 (NH), 1705sh, 1670br (CO), 1604, 757, and 683 (Ph) cm^{-1}. More ureido-compound (16 mg, 5·5%) was obtained from the filtrate.

1-*Aminomethyl*-cis-2-*hydroxymethylcyclohexylamine* (12).—The crude nitromethane adduct (7) (2·3 g) in benzene (60 ml) was added slowly to a stirred suspension of lithium aluminium hydride (3 g) in ether (50 ml) at 0°, and the mixture was stirred at 20° overnight. Saturated aqueous potassium carbonate (30 ml) was added cautiously at 0° and the mixture was refluxed for 30 min, filtered, and evaporated. The residue dissolved in 2N-hydrochloric acid (15 ml) was extracted with ether; the aqueous layer was basified with 10N-sodium hydroxide, 14N-ammonia (3 ml) was added to avoid the formation of isonitriles, and the resulting solution was extracted with chloroform. The dried extract was evaporated and the residue was distilled at 128—130° and 2·5 mmHg to give the *diamino-alcohol* (842 mg, 58%) (Found: C, 60·9; H, 11·3. $C_8H_{18}N_2O$ requires C, 60·7; H, 11·5%); $\nu_{max.}$ 3300br (NH str.) and 1602br (NH bend) cm^{-1}; δ ($CDCl_3$) 2·75 (s, $CH_2{\cdot}NH_2$) and 3·65br (s, $W_{\frac{1}{2}}$ 7, $CH_2{\cdot}OH$) p.p.m. The *dipicrate* had m.p. 204—206° (decomp.) (from ethanol) (Found: C, 39·9; H, 4·2; N, 18·1. $C_{20}H_{24}N_8O_{15}$ requires C, 40·0; H, 3·9; N, 18·2%).

3a-*Amino*-trans-*perhydroisoindole* (14).—(*a*) 3a-Amino-*trans*-perhydroisoindol-1-one (0·5 g) in warm benzene (150 ml) was added to a stirred suspension of lithium aluminium hydride (2·5 g) in ether (125 ml); the mixture was refluxed with stirring for 48 h, then cooled and decomposed with saturated aqueous potassium carbonate (25 ml) as in the foregoing reduction. The residual oil was distilled to give 3a-*amino*-trans-*perhydroisoindole* (300 mg, 68%), b.p. 52° at 0·5 mmHg, m.p. *ca.* 34° (Found: C, 68·3; H, 11·4; N, 19·8. $C_9H_{16}N_2$ requires C, 68·5; H, 11·5; N, 20·0%); $\nu_{max.}$ 3280br (NH str.), 1605 and 1504 (NH bend), and 1455 cm^{-1}. The *dipicrate* had m.p. 265—266° (decomp) (from acetic acid) (Found: C, 39·9; H, 3·9; N, 18·9. $C_{20}H_{22}N_8O_{14}$ requires C, 40·1; H, 3·7; N, 18·7%); $\nu_{max.}$ 3425br, 1635, 1612, 1570, 1537, 1370, 1332, 1280, 1170, 1085, 915, 795, 747, and 715 cm^{-1}.

(*b*) A mixture of 1-aminomethyl-*cis*-2-hydroxymethylcyclohexaylamine (12) (300 mg) and thionyl chloride (10 ml) was refluxed for 1 h and then evaporated. The residue was basified with cold 2N-sodium hydroxide and 14N-ammonia (0·5 ml), and extracted with chloroform. The dried extract gave 3a-amino-*trans*-perhydroisoindole (100 mg, 38%), i.r. and ^1H n.m.r. spectra as in (*a*); its dipicrate had m.p. and mixed m.p. 265—266° (decomp) and i.r. spectrum as in (*a*).

3a-*Methyl*-cis-*perhydroisoindole* (16).—1-Methyl-*cis*-hexahydrophthalimide (1·1 g) (prepared from hydrolysis of methyl *cis*-2-carbamoyl-*trans*-2-methylcyclohexanecarboxylate with 1·1 mol. equiv. of aqueous sodium hydroxide; the product was distilled at 122° and 1 mmHg; *cf.* ref. 2) in benzene (40 ml) was added to a suspension of lithium aluminium hydride (2·2 g) in tetrahydrofuran (75 ml) and the mixture was boiled under reflux with stirring for 48 h. Decomposition as usual gave, after distillation, 3a-*methyl*-cis-*perhydroisoindole* (700 mg, 76%), b.p. 69° at 4·5 mmHg, m.p. *ca.* 35° (Found: C, 77·5; H, 12·3; N, 10·1. $C_9H_{17}N$ requires C, 77·6; H, 12·3; N, 10·1%); $\nu_{max.}$ 3300br (NH str), 1617 and 1541br (NH bend), and 1414 cm^{-1}. The *picrate* had m.p. 178° (from water) (Found: C, 48·8; H, 5·4; N, 15·0. $C_{15}H_{20}N_4O_7$ requires C, 48·9; H, 5·5; N, 15·2%).

3a-*Methyl*-trans-*perhydroisoindole* (15).—1-Methyl-*trans*-hexahydrophthalic anhydride [13] (from 4 g of acid and boiling acetyl chloride) was dissolved in ice-cold saturated methanolic ammonia (100 ml); the solution was stored at 20° overnight, and then evaporated. The residue was dissolved in water (30 ml) and the pH was adjusted to 1; the mixture of amido-acids (2·62 g), m.p. 140—145° crystallised slowly during 3 days. To the mixture of acids (3·7 g) in methanol was added excess of 2·8% diazomethane in ether [14] (80 ml); the solution was stored at 20° for 2 h and evaporated. The residual oil was dissolved in benzene and evaporated twice, but the residue did not crystallize and its ^1H n.m.r. spectrum indicated the presence of a mixture of esters in the ratio 1 : 3·5 [δ ($CDCl_3$) 3·76 and 3·70 p.p.m. (s, OMe)]. The methanol-free mixture of *trans*-amido-esters (3·5 g) in tetrahydrofuran (70 ml) was added to lithium aluminium hydride (7 g) in tetrahydrofuran (100 ml) and the mixture was refluxed with stirring for 48 h. Decomposition as before gave a mixture of *trans*-amino-alcohols (1 : 3·5) which on distillation gave a major fraction, b.p. 124—125° at 1·5 mmHg, which was cis-2-*hydroxymethyl*-1-*methylcyclohexylamine* (Found: C, 68·9; H, 12·2; N, 9·1. $C_9H_{19}NO$ requires C, 68·7; H, 12·2; N, 8·9%); $\nu_{max.}$ 3300br, 1600, 1475, 1415, 1380, 1076, and 1035 cm^{-1}; δ ($CDCl_3$–D_2O) 0·87 (s, CMe), 2·54 and 2·67 (q, $CH_2{\cdot}NH_2$, J_{gem} 13·5), and 3·30 and 3·59 (octet, $CH_2{\cdot}OH$, J_{vic} 4 and 9, J_{gem} 12·5); total yield of distillate (*i.e.* mixture of amino-alcohols) 2·7 g (98%).

Thionyl chloride (3 ml; freshly distilled from quinoline) was added dropwise to the amino-alcohol mixture (500 mg) in an ice–salt bath and the mixture was refluxed for 2 h. Excess of thionyl chloride was removed *in vacuo*, cold water

[13] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1952, 289 (*Chem. Abs.*, 1955, **47**, 5363).
[14] F. Arndt, *Org. Synth.*, 1943, Coll. Vol. II, p. 165.

(35 ml) was added to the residue, and the solution was washed with chloroform (washings discarded).

The pH of the aqueous solution was adjusted to 11 with 10N-sodium hydroxide and 14N-ammonia (5 ml) and the mixture was extracted with chloroform. The dried extract gave 3a-*methyl*-trans-*perhydroisoindole* (270 mg, 61%), b.p. 62° at 2 mmHg, which readily absorbs carbon dioxide from the atmosphere (Found: C, 73·9; H, 11·8; N, 9·3. $C_9H_{17}N,0{\cdot}25CO_2$ requires C, 73·9; H, 11·4; N, 9·3%); $\nu_{max.}$ 3400br (NH str.), 1549 (NH bend), 1470, 1445, 1423, and 1380 cm^{-1}. The *picrate* had m.p. 203—204° (from water) (Found: C, 48·9; H, 5·5; N, 14·9. $C_{15}H_{20}N_4O_7$ requires C, 48·9; H, 5·5; N, 15·2%).

cis- or *trans*-Perhydroisoindoles could not be prepared by the foregoing reaction ($SOCl_2$ and NaOH) with cis-2-*hydroxymethyl*-N-*methylcyclohexylamine*, b.p. 118° at 2 mmHg (Found: C, 66·8; H, 12·0; N, 9·9. $C_8H_{17}NO$ requires C, 67·1; H, 12·0; N, 9·8%); $\nu_{max.}$ 3325 (NH str.), 1600 (NH bend), 1453, 1040, and 1030 cm^{-1}; δ ($CDCl_3$) 2·85 (m, $CH_2{\cdot}NH_2$) and 3·65 (m, $CH_2{\cdot}OH$) p.p.m.; or trans-2-*hydroxymethyl*-N-*methylcyclohexylmethylamine*, b.p. 124° at 3·5 mmHg (Found: C, 66·7; H, 11·8; N, 9·5. $C_8H_{17}NO$ requires C, 67·1; H, 12·0; N, 9·8%); $\nu_{max.}$ 3340 and 3290 br (NH str.), 1600br (NH bend), 1450, 1038, and 1020 cm^{-1}; δ ($CDCl_3$) 2·75 (m, $CH_2{\cdot}NH_2$) and 3·50 (m, $CH_2{\cdot}OH$) p.p.m., prepared by reduction of methyl *cis*- or *trans*-2-carbamoylcyclohexanecarboxylate,[15] respectively, with lithium aluminium hydride. *cis*-Perhydroisoindole (b.p. 52° at 2 mmHg) was prepared by reduction of *cis*-hexahydrophthalimide [15] with lithium aluminium hydride (*cf.* ref. 16).

2,3,4,5,6,7-*Hexahydroisoindol*-1-*one* (17).—The perhydroisoindolone (9) (51 mg) was fused with *S*-methylisothiouronium sulphate (50 mg) at 160° for 8 h. The mixture was dissolved in ethanol and the solution was filtered and evaporated to give the *hexahydroisoindol*-1-*one* (23 mg, 50%), m.p. 113—114° after sublimation at 110° and 1 mmHg (Found: C, 70·1; H, 8·4; N, 10·1. $C_8H_{11}NO$ requires C, 70·0; H, 8·4; N, 10·2%); $\nu_{max.}$ 3200 (NH) and 1680 (amide CO) cm^{-1}.

8a-*Aminomethyl*-3-*phenyl*-cis-*perhydroquinazoline*-2,4-*dione Hydrochloride* (19).—The *N'*-phenylureidoisoindolone (10) (144 mg) in 5N-hydrochloric acid (1·1 ml) was heated at 100° for 1 h. The pure crystalline *hydrochloride* collected had m.p. 256—257° (decomp) (150 mg, 92%) [Found (sample dried at 100° for 1 h): C, 58·3; H, 6·6; Cl, 11·3; N, 13·2. $C_{15}H_{20}ClN_3O_2$ requires C, 58·15; H, 6·5; Cl, 11·45; N, 13·55%]; $\nu_{max.}$ 3360(NH), 3110 (NH_3^+), and 1723 and 1688 (imide CO) cm^{-1}. In 5N-deuteriohydrochloric acid the hydrochloride was less soluble and the yields were slightly higher. The N–D stretching frequencies of the *N*-deuteriated salt were at 2470, 2350, and 2190 cm^{-1}.

8a-*Bromomethyl*-3-*phenyl*-cis-*perhydroquinazoline*-2,4-*dione* (19).—The foregoing hydrochloride (115 mg, 0·35 mol. equiv.) was dissolved in a solution of potassium bromide (320 mg, 2·1 mol. equiv.) in 2·5N-sulphuric acid (1·5 ml) at −5°. Sodium nitrite (79 mg, 0·95 mol. equiv.) was added to the stirred solution at −5° to 0° during 30 min. The solution was diluted with water (3 ml) and stirred at 0° for 30 min., then at 20° for 1 h. The crystalline solid was filtered off and dried at 80° for 2 h to give the pure *bromoquinazolinedione* (90 mg, 80%), m.p. 155—157° (effervescence) (Found: 53·4; H, 5·0; Br, 23·8; N, 8·2. $C_{15}H_{17}BrN_2O_2$ requires C, 53·4; H, 5·1; Br, 23·7; N, 8·3%); $\nu_{max.}$ 3230(NH), 1717 and 1605 (imide CO), and 1433 cm^{-1}; *m/e* 339 and 337 (1 : 1, $M^+ + 1$, 7%), 338 and 336 (1 : 1, M^+, 30) and 243 ($M^+ - CH_2Br$, 100). The hydrobromide of the original amide reacted equally well. The reaction in 2·5N-deuteriosulphuric acid in deuterium oxide was carried out at 5—10° (under nitrogen) because the solution froze at 0°, but the yield was unaltered. The N–D absorption was at 2370 cm^{-1}.

Methyl trans-2-*Methyl*-cis-2-(N'-*phenylureido*)*cyclohexanecarboxylate* (22).—(*a*) Methyl *cis*-2-amino-*trans*-2-methylcyclohexanecarboxylate [2] (23) (684 mg) and phenyl isocyanate (500 mg, 1·05 mol. equiv.) in dry benzene (8 ml) were refluxed for 0·75 h and evaporated. The oily residue was dissolved in methanol and the solution was evaporated, leaving a crystalline solid which was washed with light petroleum (b.p. 40—60°) and kept in air for 48 h to give the *ureido-ester* (1·16 g, 96%), m.p. 62—63° (Found: C, 63·2; H, 7·7; N, 9·3. $C_{16}H_{22}N_2O_3,0{\cdot}75H_2O$ requires C, 63·2; H, 7·8; N, 9·2%); $\nu_{max.}$ 3370 (NH), 1720 and 1250 (ester), 1665 (amide CO), 1603, and 751 and 693 (Ph) cm^{-1}; δ ($CDCl_3$) 1·42 (s, CMe), 3·10 (d, *J* 11, H-1*ax*), 3·72 (s, OMe), 6·1br (s, NH), 7·05br (s, NH), 7·50br (s, NH), and 7·50br (d, Ph).

(*b*) Methyl *cis*-2-isocyanato-*trans*-2-methylcyclohexanecarboxylate [2] (21) (290 mg) and aniline (150 mg, 1·1 mol. equiv.; freshly distilled) were heated under nitrogen at 110°. The reaction was complete after 3 h as observed by loss of the NCO absorption at 2280 cm^{-1}. The glassy residue crystallised only after treatment with methanol as in (*a*) to yield the *N'*-phenylureido-ester (95%).

8a-*Methyl*-3-*phenyl*-cis-*perhydroquinazoline*-2,4-*dione* (20).—(*a*) The foregoing ureido-ester (0·5 g) in methanol (8·6 ml) and aqueous 2N-sodium hydroxide (1·7 ml) was kept at 20° for 18 h. The solution was evaporated, water (10 ml) was added to the residue, and the insoluble crystals were filtered off, dried, and recrystallised from benzene–light petroleum (b.p. 40—60°) to give the *quinazolinedione* (364 mg, 82%), m.p. 198—199° (Found: 70·0; H, 7·3; N, 11·0. $C_{15}H_{18}N_2O_2$ requires C, 69·75; H, 7·0; N, 10·9%); $\nu_{max.}$ 3250 (NH), 2950 and 2868 (CH str.), 1720 and 1680 (imide CO), 1600, 1547, 1505, 1497, 1417, 1315, 1285, 1267, 1230, 1202, 1187, 1165, 1140, 1115, 1073, 1029, 920, 765, and 695 cm^{-1}; *m/e* 258 (M^+, 100%), 243 (M^+ — Me, 45), 229(20), 216(80), 119(55), and 94(55). The aqueous filtrate was acidified to give *methyl* trans-2-*methyl*-cis-2-(N'-*phenylureido*)*cyclohexanecarboxylate* (35 mg, 7·7%), m.p. 158—159° [Found (sample dried at 100° for 3 h): C, 64·9; H, 7·4; N, 10·2. $C_{15}H_{20}N_2O_3$ requires C, 65·2; H, 7·3; N, 10·1%]; $\nu_{max.}$ 3435br, 1692 (CO_2H), 1646 (urea CO), 1602, 1552, 1505, 1245, 750, and 692 cm^{-1}. When the alcoholic alkaline solution in this reaction was kept at 20° for 48 h the yields of the quinazolinedione (54·5%) and ureido-acid (30·7%) had altered. This reaction in methan[^{2}H]ol and 2N-sodium deuteroxide in deuterium oxide, with final washing of solids with water, gave yields similar to those first obtained. The signal of the 4a-proton of the quinazolinedione (δ 2·55 p.p.m.) was absent in the ^{1}H n.m.r. spectrum, and the region between 1300 and 1100 cm^{-1} in the i.r. spectrum was different for this deuteriated quinazolinedione: $\nu_{max.}$ 3240 (NH), 2940 and 2860 (CH str.), 1720 and 1680 (imide CO), 1600, 1547, 1505, 1497, 1417, 1315, 1272, 1260, 1234m, 1206, 1186, 1156, 1140, 1073, 1045, 1003, 767, and 695 cm^{-1}.

(*b*) The 8a-bromomethylquinazolinedione (19) (90 mg) in

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ethanol (100 ml) containing Raney nickel [17] (5 g, wet) was shaken with hydrogen at 80—85° and 5 atm for 6 h. The catalyst was filtered off and the filtrate evaporated. The residue dissolved in hot benzene (4 ml) was diluted with light petroleum (b.p. 40—60°) and the 8a-methylquinazolinedione (70 mg, 98%) crystallised slowly.

(*c*) The 8a-bromomethylquinazolinedione (19) (70 mg) in benzene (15 ml) was stirred with a 7·5% solution of sodium dihydrobis-(2-methoxyethoxy)aluminate in benzene (5·6 ml) at 20° overnight. Cold saturated potassium carbonate solution was added (6 ml); the benzene layer was separated, washed with 2N-sodium hydroxide, dried, and evaporated. The residue was passed through an alumina (B.D.H.) column (6 × ¼ in; in benzene), which was washed with benzene (150 ml) and eluted with ethanol. The product was sublimed at 180—190° and 1 mmHg to give the 8a-methylquinazolinedione (10 mg, 18%), identical with that obtained before.

Hydrolysis of 8a-*Methyl*-3-*phenyl*-cis-*perhydroquinazoline*-2,4-*dione*.—The dioxo-compound (30 mg) was refluxed with aqueous 2N-sodium hydroxide (3 ml). The solid dissolved after 10 min and an oil started to separate; boiling was continued for a total of 45 min. The cooled solution was extracted with ether and the residue from the extract was identified as aniline. The aqueous solution, acidified to pH 1, gave *trans*-2-methyl-*cis*-2-(*N'*-phenylureido)cyclohexanecarboxylic acid (5 mg, 15%). When boiling was discontinued after 15 min. the yield of acid was 10 mg (30%); boiling with 0·5N-sodium hydroxide gave a 49% yield of the acid.

1,8a-*Dimethyl*-3-*phenyl*-cis-*perhydroquinazoline* (26).—The 8a-methylquinazolinedione (20) (420 mg) in benzene (30 ml) was added to a 25% solution of sodium dihydrobis-(2-methoxyethoxy)aluminate in benzene (16 ml) and the mixture was refluxed for 36 h. Decomposition of the solution as in the previous reduction gave an oil, which was placed on an alumina (B.D.H.) column (7 × ¾ in; in benzene); the column was washed with benzene (100 ml) and eluted with ethanol to give 2-cis-*anilinomethyl*-1,N-*dimethylcyclohexylamine* (25), b.p. 176° at 10 mmHg (246 mg) (Found: N, 12·3. $C_{15}H_{24}N_2$ requires N, 12·1%); $\nu_{max.}$ 3365 and 3290 (NH str.), 1600br, 1465, 1444, 1378, 1068, and 1025 cm^{-1}; δ ($CDCl_3$) 1·18 (s, CMe), 2·30 (s, NMe), 3·25 (m, CH_2·N), and 6·6—7·5 (m, aromatic H) p.p.m. The diamine (230 mg) was mixed with aqueous 37% formaldehyde (0·2 ml) and set aside at 20° overnight. Saturated aqueous picric acid was added, followed by solid picric acid until the oily picrate solidified. The *monopicrate* had m.p. 173—174° (decomp.) (from ethanol) (Found: C, 56·1; H, 5·7; N, 14·7. $C_{22}H_{27}N_5O_7$ requires C, 55·8; H, 5·75; N, 14·8%) and was decomposed with sodium hydroxide to give 1,8a-*dimethyl*-3-*phenyl*-cis-*perhydroquinazoline* (195 mg, 49%), b.p. 187—188° at 4·5 mmHg, as a thick oil which absorbed carbon dioxide from the atmosphere (Found: C, 76·6; H, 9·5; N, 10·7. $C_{16}H_{24}N_2$,0·25CO_2 requires C, 76·4; H, 9·5; N, 11·0%); $\nu_{max.}$ 2800 and 2700 (N–CH_3 str.), 1600, 1500, 1190, 750, and 690 cm^{-1}.

cis- *and* trans-1,2-*Bis*(*hydroxymethyl*)-1-*methylcyclohexane* (33).—To a stirred suspension of lithium aluminium hydride (4 g) in tetrahydrofuran (150 ml) was added a solution of *cis*-2-methoxycarbonyl-1-methylcyclohexanecarboxylic acid [2] (5 g) in benzene (50 ml) and the mixture was boiled under reflux overnight. More hydride (0·5 g) in benzene (25 ml) was added and boiling and stirring were continued for 48 h. The cooled solution was decomposed by dropwise addition of water (45 ml), shaken at 20° for 15 min, and filtered. The filtrate gave the cis-*diol*, b.p. 131° at 2 mmHg (3·36 g, 85%) (Found: C, 68·1; H, 11·3. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%); $\nu_{max.}$ 3240br (OH), 1453, 1095, 1040, 1015, and 980 cm^{-1}; δ ($CDCl_3$–D_2O) 1·05 (s, CMe) and 3·0—4·1 [two complex multiplets, (CH_2·OH)$_2$] p.p.m.

Similarly, dimethyl 1-methyl-*trans*-hexahydrophthalate [13] gave the trans-*diol*, b.p. 141·5—143° at 2·5 mmHg and 119—120° at 0·6 mmHg (37%) (Found: C, 68·4; H, 11·7. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%); $\nu_{max.}$ 3300br (OH) 1474, 1452, 1090, 1068, 1025, and 990 cm^{-1}; δ ($CDCl_3$) 0·86 (s, CMe), 3·1—3·9 [complex multiplet, (CH_2·OH)$_2$], and 4·75br (s, OH) p.p.m.

3,3,5a-*Trimethyl*-cis *and* -trans-*perhydro*-2,4-*benzodioxepin* (34).—The foregoing *cis*-diol (2 g) in dry acetone (30 ml) and sulphuric acid (*d* 1·84; 0·2 ml) was kept over anhydrous sodium sulphate (5 g) for 66 h. Sodium hydrogen carbonate was added to neutralise the acid, and the solution was filtered and evaporated. The residue was dissolved in saturated aqueous sodium hydrogen carbonate and extracted with ether. The extract gave the cis-*dioxepin* (1·33 g, 53%), b.p. 80° at 4 mmHg (Found: C, 72·9; H, 11·0. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%); $\nu_{max.}$ 3000, 2940, 2865 (CH str.), 1473, 1455, 1375, and 1224 (C–O–C str.) cm^{-1}; δ ($CDCl_3$; 100 MHz) 1·33 (s, *gem*-Me_2), 0·94 (s, 5a-Me), 1·2—1·8 (m, $W_{\frac{1}{2}}$ 36, [CH_2]$_4$), and 3·50br (d, 1- and 5-CH_2·O) p.p.m.; *m/e* 198 (M^+, 5%), 183 (95), 168 (25), 140 (30), 123 (15), 110 (100), 95 (60), and 81 (55).

The trans-*isomer*, b.p. 56° at 0·7 mmHg, was similarly prepared (Found: C, 72·5; H, 10·9. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%); $\nu_{max.}$ 3000, 2940, 2888 (CH), 1476, 1458, 1385, 1374, and 1225 (C–O–C) cm^{-1}; δ ($CDCl_3$; 100 MHz) 1·32 (s, *gem*-Me_2), 0·94 (5a-Me), 1·0—1·9 (m, $W_{\frac{1}{2}}$ 75, [CH_2]$_4$), 3·03 (d) and 3·47 (d) (J_{gem} 12·0, H-5), 3·18 (q, J_{vic} 2, J_{gem} 12·5, H-1 quasi-*ax*), and 3·60 (q, J_{vic} 9·8, J_{gem} 12·5, H-1 quasi-*eq*) p.p.m.; *m/e* 198 (M^+, 5%), 183 (7), 168 (2), 140 (10), 123 (18), 110 (100), 95 (50), and 81 (60).

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