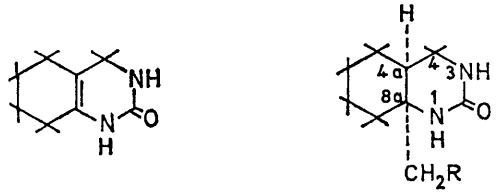
Quinazolines. Part XVI.[1] A Stereospecific *cis*-Addition of the Elements of Nitromethane across a Tetrasubstituted Ethylenic Double Bond

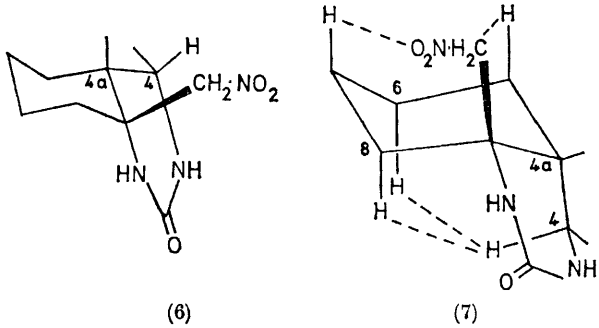
By **W. L. F. Armarego**, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia

The fusion of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one with nitroacetic acid at *ca.* 60° gave a high yield of 8a-nitromethyl-*cis*-octahydroquinazolin-2(1*H*)-one. The stereochemistry of this product was deduced by ^{1}H n.m.r. spectroscopy and by conversion, *via* the aminomethyl and bromomethyl derivatives, into 8a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one. An authentic sample of the latter was prepared from methyl *cis*-2-chlorocarbonyl-*trans*-2-methylcyclohexanecarboxylate. A Schmidt reaction gave the *cis*-2-amino-derivative, which was converted *via* the 1-carbohydrazide into *cis*-2-aminomethyl-1-methylcyclohexylamine, which was cyclised with phosgene. A Hofmann reaction with methyl *cis*-2-carbamoyl-*trans*-2-methylcyclohexanecarboxylate, however, gave *cis*-2-amino-1-methylcyclohexanecarboxylic acid, which was converted into 4a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one.

In connection with current work on the synthesis of simple analogues of Tetrodotoxin, I wished to prepare decahydroquinazolines with a carbon side-chain at C-8a. I had previously succeeded in adding the elements of nitromethane across the αβ-double bond of enamines and enamides by fusing them with nitroacetic acid.[2] Consequently, I fused 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (1) with nitroacetic acid at the decarboxylation temperature (*ca.* 60°) and obtained a quantitative conversion (as judged by ^{1}H n.m.r. spectroscopy) into the nitromethane adduct (2), which I had failed to prepare directly from nitromethane. The adduct was stable in boiling butan-1-ol and in dilute aqueous solutions of acid or base at room temperature, and did not eliminate nitromethane at its m.p. In its ^{1}H n.m.r. spectrum (see Table) the two C-4 protons formed the AB part of an ABX pattern (coupling with H-4a) with small vicinal coupling constants. Also the protons at positions 5—8 gave rise to a band with a narrow envelope ($W_{\frac{1}{2}}$ 20 Hz). Comparison with the spectra of several *cis*- and *trans*-2-substituted decahydroquinazolines suggested that the adduct (2) had *cis*-stereochemistry at the bridgehead carbon atoms and that it existed, in dimethyl sulphoxide solution, almost entirely in the conformation (6), rather than (7) in which there should be a large antiperiplanar coupling constant between the 4*ax*- and 4a-protons. The subsequent discussion describes a chemical verification of the *cis*-stereochemistry of the adduct (2).



(1) (2) R = NO_2 (3) R = NH_2 (4) R = Br (5) R = H



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The hexahydroquinazolinone (1) was obtained by condensation of 2-hydroxymethylenecyclohexanone with urea to give 2-ureidomethylenecyclohexanone, which was cyclised with alkali to 5,6,7,8-tetrahydroquinazolin-2(1*H*)-one and then reduced with aqueous sodium

[1] Part XV, W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1971, 238.
[2] W. L. F. Armarego, *J. Chem. Soc.* (*C*), 1969, 986.

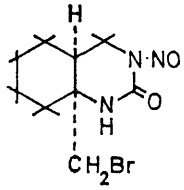
borohydride. Catalytic reduction of the adduct (2) in ethanol with palladium–charcoal failed, and platinum oxide was readily poisoned unless hydrochloric acid was added. The aminomethyl derivative (3) was best prepared by reduction of the adduct (2) over Raney nickel with hydrogen at 4 atm. A reaction of the amine with nitrosyl bromide gave 8a-bromomethyl-3-nitroso-*cis*-octahydroquinazolin-2(1*H*)-one (8), identified by comparison of its ^{1}H n.m.r. spectrum with that of the bromomethyl compound (4), which showed that the two H-4 protons were deshielded by the NO group, and by its mass spectrum (see Experimental section). It liberated brown fumes on treatment with 30% hydrogen bromide in acetic acid to give the bromomethyl compound (4). Reduction of the latter over Raney nickel gave a high yield of 8a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one (5). All the assigned structures are consistent with i.r. spectra, and all the decahydroquinazolines must have the same stereochemistry, since no reactions involving the bridgehead carbon atoms were carried out; their ^{1}H n.m.r. spectra had many features in common (see Table).

^{1}H N.m.r. spectra of *cis*-octahydroquinazolin-2(1*H*)-ones (τ values; 100 MHz; 34°) [a]

cis-Octahydroquinazolin-2-(1*H*)-one	H-4 [b] *eq*	H-4 [b] *ax*	8a-CH_2R	H-4a, 5, 6, 7, and 8 ($W_{\frac{1}{2}}$)	NH	Other H	Solvent
8a-Nitromethyl- (2)	6·57(q) (J_{vic} 4; J_{gem} −12)	7·21br(d) [c] ($W_{\frac{1}{2}}$ 6; J_{gem} −12)	5·35(d), 5·49(d) (J_{gem} −12) (R = NO_2)	8·1—9·0 (20)	3·62br [d]		$(CD_3)_2SO$
8a-Aminoethyl- (3) hydrochloride [e]	6·05(q) (J_{vic} 4·5; J_{gem} −13)	6·52(q) (J_{vic} 2; J_{gem} −13)	6·31(d), 6·49(d) (J_{gem} −13·5) (R = NH_3^+)	7·5—8·4 (46)			D_2O
8a-Bromomethyl-3-nitroso- (8)	6·23(q) (J_{vic} 2·5; J_{gem} −14·5) 6·13(q) (J_{vic} 2·5; J_{gem} −14·5)	6·53(q) (J_{vic} 5; J_{gem} −14·5) 6·43(q) [f]	6·56(s) (R = Br)	7·5—8·8 (55)	2·99br [d]		$CDCl_3$
			6·30(s) (R = Br)	7·5—8·8 (28)			CD_3OD [g]
8a-Bromomethyl- (4)	6·69(q) (J_{vic} 4; J_{gem} −12·5) *ca.* 6·7 [f]	7·24(q) (J_{vic} 2; J_{gem} −12·5) 7·06(q) (J_{vic} 2; J_{gem} −12·5)	6·45(d), 6·63(d) (J_{gem} −10) (R = Br)	8·0—9·0 (24)	3·79br [d]		$(CD_3)_2SO$
			6·45(d), 6·65(d) (J_{gem} −10) (R = Br)	8·0—8·8 (18)			CD_3OD [g]
8a-Methyl- (5)	6·42(q) (J_{vic} 3; J_{gem} −11·5)	7·05(q) (J_{vic} 3·5 [h]; J_{gem} −11·5)		8·1—8·8 (12)	4·48br, [d] 5·07br [d]	8·74(s) (8a-Me)	$CDCl_3$
4a-Methyl- (21)	6·96(q) (J_{vic} 3 [i]; J_{gem} −11·5)	7·12(q) (J_{vic} 2 [i]; J_{gem} −11·5)		8·1—8·9 (30)	4·31br, [d] 5·53br [d]	8·96(s) (4a-Me) *ca.* 6·94br (s, H-8a)	$CDCl_3$
4a-Methyl-*cis*-decahydroquinazoline	7·44(s)			8·0—8·8 (20)	8·26(s) [d]	9·13(s, 4a-Me), 7·40br (s, H-8a), 6·02(d) and 6·38(d) (J_{gem} −12·5, H-2)	$CDCl_3$

[a] Tetramethylsilane as internal standard; J and $W_{\frac{1}{2}}$ in Hz, J_{gem} assumed negative. [b] The upfield proton was taken as axial and the downfield proton as equatorial (*cf.* refs. 1, 6, and 7); J_{vic} caused by coupling with H-4a. [c] This doublet sharpens to $W_{\frac{1}{2}}$ 4 Hz on adding D_2O. [d] Exchanges with D_2O. [e] External tetramethylsilane standard. [f] Coupling masked by CH_2R and methanol signals. [g] At 60 MHz and 33°. [h] This J alters to *ca.* 1 Hz on adding D_2O. [i] This doublet becomes a sharp singlet on adding D_2O.

The starting material for the synthesis of authentic 8a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one (5) was 1-methyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride (9), which was obtained from a Diels–Alder reaction between butadiene and citraconic anhydride.[3] Methanolysis of the anhydride to give *cis*-6-methoxycarbonyl-1-methylcyclohex-3-enecarboxylic acid, followed by catalytic reduction, gave the known[4] half-ester (10). This was converted into the acid chloride (11), but on treatment with sodium azide in aqueous acetone this was hydrolysed back to the acid (10). However, treatment of the acid chloride with freshly prepared lithium azide in dry acetone (I thank Professor R. Huisgen for suggesting this reagent) followed by distillation, gave the isocyanato-ester (12), with retention of stereochemistry (*cf.* ref. 5), in high yield. The isocyanate was hydrolysed with dilute hydrochloric acid and the product was esterified to methyl *cis*-2-amino-*trans*-2-methylcyclohexanecarboxylate (13). The amino-ester was converted into the hydrazide, which was reduced to *cis*-2-aminomethyl-1-methylcyclohexylamine with lithium aluminium hydride; the product was cyclised to 8a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one (5), identical with the product obtained from the nitromethane adduct (2). No



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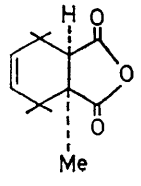

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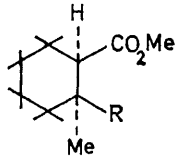
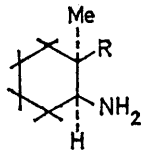


(10) R = CO_2H
(11) R = COCl
(12) R = NCO
(13) R = NH_2
(14) R = $CO{\cdot}NH_2$

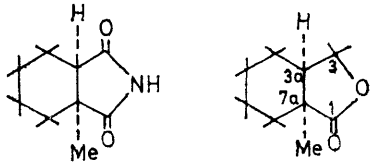


(15) R = CO_2H
(16) R = CO_2Me
(17) R = $CO{\cdot}NH{\cdot}NH_2$
(18) R = $CH_2{\cdot}NH_2$

inversion or epimerisation occurred at C-1 or C-2 in any of the foregoing reactions; there was no spectroscopic evidence for it and several similar reactions with both *cis*- and *trans*-isomers of 1,2-disubstituted cyclohexanes [1,6,7] showed no evidence of isomerisation.

[3] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1952, 289 (*Chem. Abs.*, 1955, **49**, 5363).
[4] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk. S.S.S.R., Ser. khim.*, 1954, 63 (*Chem. Abs.*, 1955, **49**, 2454).
[5] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' 2nd edn., Cornell University Press, 1969, p. 750.
[6] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1969, 1635.
[7] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc.* (*C*), 1970, 1597.

In an earlier attempt to prepare the authentic methyl compound (5) the *cis*-amido-ester (14) was prepared from the acid chloride (11) in benzene saturated with ammonia. A Hofmann reaction with alkaline hypobromite gave, unexpectedly, what was later shown to be *cis*-2-amino-1-methylcyclohexanecarboxylic acid (15). The mode of formation of this amino-acid became clear when it was found that brief treatment of the amido-ester (14) with alkali (1 equiv.) gave 1-methyl-*cis*-hexahydrophthalimide (19). It was at first thought that the structure assigned the half-ester (10) was incorrect, but it was confirmed by reduction with sodium and ethanol in liquid ammonia to give 7a-methyl-*cis*-perhydroisobenzofuran-1-one (20). In the ^{1}H n.m.r. spectrum the coupling between the two C-3 protons and the C-3a proton formed an ABX pattern. It has been shown that sodium and ethanol in liquid ammonia selectively reduce carboxylic esters to alcohols in the presence of a free carboxy-group.[8] Esterification of the amino-acid (15) under the usual conditions,[6,7] as used for the isomer (13), gave poor yields; the methyl ester (16) was obtained in 55% yield by more severe treatment. This difficulty may be ascribed to steric hindrance, since a tertiary carboxy-group is involved. Conversion of the ester (16) into the hydrazide (17) was always accompanied by some, as yet unexplained, hydrolysis to the acid (15), even when anhydrous hydrazine was used. Reduction of the hydrazide with lithium aluminium hydride gave the corresponding aminomethyl derivative (18), which was cyclised with phosgene in toluene to 4a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one (21). The structure of this isomer was deduced from the ^{1}H n.m.r. spectrum in which the signal for the two C-4 protons appeared as the AB portion of an ABX pattern; in this case X was the proton on N-3. This compound is the first decahydroquinazoline for which coupling between the C-4 and N-3 protons has been clearly observed (*cf.* refs. 1, 6, and 7). The vicinal couplings are small and are removed by addition of deuterium oxide leaving an AB quartet. The 8a-proton signal was partly masked by that of the two C-4 protons but was accounted for by integration. The aminomethyl compound (18) was also condensed with 37% aqueous formaldehyde to give 4a-methyl-*cis*-decahydroquinazoline (22). In this case the two C-4 protons gave rise to a singlet masking the 8a-proton signal (see Table).



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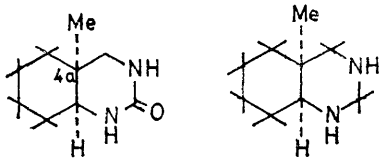

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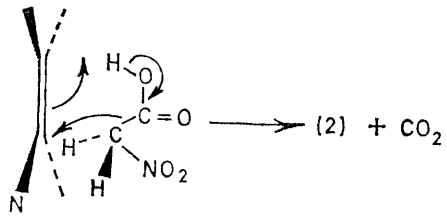
With regard to the mechanism of the *cis*-addition, I had suggested that the reaction of nitroacetic acid with aldehydes and enamines could proceed by a concerted mechanism.[2] Such a mechanism [*i.e.* as in (23)] may explain the stereospecific addition observed. In an alternative mechanism, protonation of the enamide (1) would give the carbonium ion (24) [mesomeric with (25)], which can be in equilibrium with the *cis*-adducts (6) and (7) and the *trans*-adduct (26). The *cis*-adduct (6) should be thermodynamically the most stable because it has only one 1,3-axial interaction, between the 8a-CH_2·NO_2 group and a hydrogen atom. The *trans*-adduct (26) has three such interactions and the *cis*-conformer (7) has two such interactions, in addition to two 1,4-axial interactions between H-4, H-6, and H-8. We are planning experiments to elucidate the mechanisms of the reactions of nitroacetic acid.



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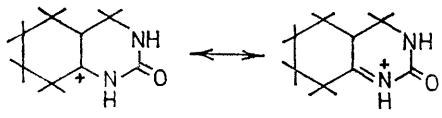

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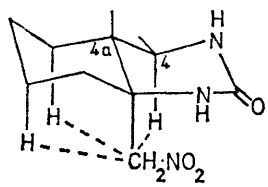

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EXPERIMENTAL

Microanalyses were performed by Dr J. E. Fildes and her staff; the instruments used are given in ref. 6. All extracts were dried over anhydrous sodium sulphate, and evaporations were performed at $<30°$ and 18 mmHg. I.r. spectra of solids were measured for potassium bromide discs and of liquids for films. The C–H stretching frequencies at *ca.* 2900 cm^{-1} present in the spectra of most compounds have not been included, and the assignments of bands are tentative. All ^{1}H n.m.r. spectra were at 60 MHz (33°) with tetramethylsilane as internal standard; *J* values are in Hz.

2-Ureidomethylenecyclohexanone.— 2-Hydroxymethylenecyclohexanone [9] (37·8 g, 1 mol. equiv.; freshly distilled) at 20° and a solution of urea (19·8 g, 1·1 mol. equiv.) in acetic acid (25 ml) at 70° were added together to acetic acid (15 ml)

[8] L. A. Paquette and N. A. Nelson, *J. Org. Chem.*, 1962, **27**, 2272.

[9] C. Ainsworth, *Org. Synth.*, 1959, **39**, 27.

at *ca.* 30°, and the mixture was set aside at 20° overnight. The pale orange solid was filtered off, washed with a little water, and dried at 100°. The *ureido-ketone* (52—64%), recrystallised from ethanol or butan-1-ol, formed pale yellow needles, m.p. 238° (effervescence) (Found: C, 57·3; H, 7·4; N, 16·7. $C_9H_{12}N_2O_2$ requires C, 57·1; H, 7·2; N, 16·7%), $\nu_{max.}$ 3370, 3280, and 3185 (NH str.), 1717 (C=O), 1663 (amide C=O), 1630 (C=C), and 1547 and 1513 (NH bend) cm^{-1}; τ [$(CD_3)_2SO$] 2·18 (d, =C*H*·N, *J* 13·8), 1·38 (d, =CH·N*H*, *J* 13·8), and 3·60 (NH_2); τ [$(CD_3)_2SO$–D_2O] 2·18 (s). Lower yields were obtained when the solvent was ethanol or butan-1-ol.

Similarly 2-*thioureidomethylenecyclohexanone* (66%), m.p. 206° (decomp.), was obtained (Found: C, 52·4; H, 6·8; N, 15·2. $C_8H_{12}N_2OS$ requires C, 52·2; H, 6·5; N, 15·2%), $\nu_{max.}$ 3355, 3280, and 3180 (NH str.), 1675 (C=O), 1630 (C=C), 1565br (NH bend), and 1225 (C=S) cm^{-1}.

5,6,7,8-*Tetrahydroquinazolin*-2(1H)-*one Hydrochloride*.—The foregoing ureido-ketone (5 g) in aqueous N-sodium hydroxide (100 ml) was boiled for 3—4 min; the mixture was filtered, acidified to pH 2 with concentrated hydrochloric acid, and evaporated to dryness. The residue was dried at 100° for 2 h and extracted with boiling ethanol (4 × 50 ml); the solution was filtered and evaporated to dryness and the product was dried again at 100° for 2 h. The residue was dissolved in the minimum volume of cold dry methanol, and ethyl acetate was added until crystallisation was complete. The drying was necessary for satisfactory crystallisation of the *hydrochloride* (4·1 g, 92%), m.p. 216—218° (decomp.) (Found: C, 51·5; H, 5·7; Cl, 18·7; N, 15·0. $C_8H_{10}N_2O$,HCl requires C, 51·5; H, 5·9; Cl, 19·0; N, 15·0%), $\nu_{max.}$ 3400br (NH), 1754 (amide C=O), 1714 (C=NH^+), 1623 (C=C), and 1575 (NH bend) cm^{-1}; τ [$(CD_3)_2SO$] 1·40 (s, H-4).

3,4,5,6,7,8-*Hexahydroquinazolin*-2(1H)-*one* (1).—The pH of a solution of the foregoing hydrochloride (10 g) in water (250 ml) was adjusted to 6·5—7·0 with N-sodium hydroxide, and sodium borohydride (7·6 g) was added slowly with stirring. After 2 h the insoluble *hexahydroquinazolinone* (9·0 g, 89%) was collected, dried at 100°, and recrystallised from methanol to give pale yellow prisms which decomposed slowly above 260° (Found: C, 63·3; H, 8·0; N, 18·7. $C_8H_{12}N_2O$ requires C, 63·1; H, 7·95; N, 18·4%), $\lambda_{max.}$ (MeOH) 247 nm (ε 2280); $\nu_{max.}$ 3250 and 3100 (NH), 1678br (C=C, C=O), and 1520 (NH bend) cm^{-1}; τ [$(CD_3)_2SO$ at 80°] 6·40br (H-4).

Similarly 3,4,5,6,7,8-*hexahydroquinazoline*-2(1H)-*thione*, m.p. 209—211°, was prepared from the thioureido-ketone in 56% yield (Found: C, 56·8; H, 7·0; N, 16·6; S, 19·0. $C_8H_{12}N_2S$ requires C, 57·1; H, 7·2; N, 16·6; S, 19·05%), $\nu_{max.}$ 3200br (NH str.), 1597 (C=C), 1525br (NH bend), and 1218 (C=S) cm^{-1}; τ [$(CD_3)SO$] 6·34 (s, H-4).

8a-*Nitromethyl*-cis-*octahydroquinazolin*-2(1H)-*one* (2).—3,4,5,6,7,8-Hexahydroquinazolin-2(1*H*)-one (1·82 g, 1 mol. equiv.) and nitroacetic acid (1·26 g, 2 mol. equiv.) were stirred and heated slowly until effervescence began. The temperature was maintained at 40—60° and stirring was continued until effervescence ceased. Excess of nitromethane was removed *in vacuo*, and the residue was fused again with nitroacetic acid (1·26 g) and evacuated. The ^1H n.m.r. spectrum (see Table) indicated complete reaction. The *nitromethylquinazolinone* (2·2 g, 86%) had m.p. 215—216° (from butan-1-ol) (Found: C, 50·4; H, 7·3; N, 19·6. $C_9H_{15}N_3O_3$ requires C, 50·7; H, 7·1; N, 19·7%), $\nu_{max.}$ 3240 and 3100 (NH str.), 1690 (C=O), and 1550 and 1385 (NO_2) cm^{-1}; *m/e* 213 (1%, M^+), 169 (50, $M^+ - H_2N{\cdot}CO$), and 153 [100, $M^+ - CH_2NO_2$, (24)].

8a-*Aminomethyl*-cis-*octahydroquinazolin*-2(1H)-*one Hydrochloride*.—The nitromethane adduct (2) (426 mg) in warm ethanol (75 ml) containing concentrated hydrochloric acid (0·5 ml) and platinum oxide (426 mg) was shaken with hydrogen at 20° and 720 mmHg. When reduction ceased (1—5 h), the catalyst was filtered off, washed with methanol (in which the hydrochloride was more soluble) and the solution was evaporated. The hydrochloride (354 mg, 81%) had m.p. 307—308° (decomp.) (from methanol–ether) (Found: C, 49·1; H, 8·6; Cl, 15·9; N, 18·8. $C_9H_{18}ClN_3O$ requires C, 42·9; H, 8·3; Cl, 16·1; N, 19·1%), $\nu_{max.}$ 3230 (NH), 3000br (NH_3^+), 1660 (C=O), and 1620 (NH) cm^{-1}. On occasions the reduction required much larger quantities of platinum oxide and longer hydrogenation times. A more satisfactory method was to reduce the nitro-compound (2·2 g crude) in ethanol (250 ml) containing Raney nickel [10] (5 g wet with ethanol) by shaking with hydrogen at 4·6 atm for 5 h. Filtration and evaporation gave a solid residue (1·53 g) which was suitable for the subsequent stage.

8a-*Bromomethyl*-cis-*octahydroquinazolin*-2(1H)-*one* (4).—The foregoing crude free base (1·5 g, 0·62 mol. equiv.) in 47% aqueous hydrobromic acid (0·97 ml) and water (5 ml) was added to a solution of potassium bromide (3·34 g, 2·1 mol. equiv.) in 2·5N-sulphuric acid (16·6 ml, 3·1 mol. equiv.) at 0°. While this temperature was maintained, sodium nitrite (0·87 g, 0·95 mol. equiv.) was added with stirring during 30 min, and stirring was continued for 30 min at 0°, then for 1 h at 20°.

The 8a-*bromomethyl*-3-*nitroso*-cis-*octahydroquinazolin*-2(1H)-*one* (0·81 g, 40%), m.p. 146—147° (efferv.), that crystallised out was collected and dried *in vacuo* for 24 h. Recrystallisation from benzene–light petroleum (b.p. 40—60°) or chloroform–carbon tetrachloride did not alter its m.p. or i.r. spectrum [$\nu_{max.}$ 3220 (NH), 1708 (C=O), 1550 (NH), and 1390 (NO) cm^{-1}], but it was not possible to obtain a satisfactory elemental analysis, possibly because of ready loss of nitric oxide. The ^1H n.m.r. spectrum was consistent with its structure (see Table); *m/e* 275 and 277 (2%, 1 : 1, M^+), 245 and 247 (4%, 1 : 1, M^+ —NO), 202 and 204 (10%, 1 : 1, M^+ — NO — HCNO), 182 (90, M^+ — CH_2Br), and 153 [100, M^+ — CHBr — NO (24)]. Some starting material (0·46 g) was recovered from the filtrate by adjusting the pH to 7—8 with N-sodium hydroxide, evaporating to dryness, extracting the residue with chloroform, and evaporating again. The same nitroso-compound was formed when the hydrochloride in water was added to potassium bromide in sulphuric acid as before.

The nitroso-compound (0·5 g) in 30% hydrogen bromide in acetic acid (1 ml) was evacuated at 20° and 18 mmHg for 3 h; brown fumes of nitrogen dioxide and most of the solvent were removed. Chloroform was added and the mixture was evaporated and then kept at 0·2 mmHg for 30 min. The gum, in chloroform (2 ml), was placed on an alumina (B.D.H.) column (5 × 0·75 in; prepared in benzene) and washed thoroughly with benzene (150 ml). Elution with ethanol gave 8a-*bromomethyl*-cis-*octahydroquinazolin*-2(1H)-*one* (396 mg, 89%), as needles, m.p. 213° (from benzene) (Found: C, 44·0; H, 6·3; N, 11·1. $C_9H_{15}BrN_2O$ requires C, 43·7; H, 6·1; N, 11·3%), $\nu_{max.}$ 3240 and 3100 (NH str.), 1785 (C=O), and 1523 (NH bend) cm^{-1}; *m/e* 244 and 246 (2%, 1 : 1, $M^+ - 2$), 203 and 204 (4%, 1 : 1, M^+ — HNCO), and 153 [100%, M^+ — CH_2Br (24)].

[10] D. J. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

cis-2-*Methoxycarbonyl*-1-*methylcyclohexanecarboxylic Acid*.—Citraconic anhydride (7 g) and 2,5-dihydrothiophen dioxide (10 g) in *o*-xylene (4 ml) were heated at 130—140° for 2 hr; the mixture was evaporated and the residue was treated with more sulphone (10 g) in *o*-xylene (4 ml). The process was repeated twice more, and the product was distilled to give 1-methyl-*cis*-1,2,3,6-tetrahydrophthalic anhydride (5·5 g, 54%), b.p. 84° at 0·5 mmHg; $\nu_{max.}$ 1842 and 1775 (anhydride) cm^{-1} (lit.,[3] b.p. 113—115° at 4 mmHg; prepared by the following method). This anhydride was best prepared (83%) from butadiene and citraconic anhydride as described in ref. 3 on four times the scale. It was converted into *cis*-6-methoxycarbonyl-1-methylcyclohex-3-enecarboxylic acid (40%) [$\nu_{max.}$ 2950br (OH), 1722 and 1203 (ester), 1695 (acid C=O), and 1645 (C=C) cm^{-1}] as in ref. 4 but on an 84 g scale. The mother liquors were hydrolysed to give 1-methyl-*cis*-1,2,3,6-tetrahydrophthalic acid (85%) by refluxing in 20% aqueous potassium hydroxide for 3 h and acidifying. The acid was then converted into the original anhydride (82%) by refluxing in thionyl chloride (4 vols.) for 1·5 h and distilling, and recycled. The unsaturated half ester (38·5 g) in dry benzene (400 ml) and platinum oxide (0·2 g) was shaken with hydrogen at 20° and 712 mmHg until 1·4 mol. equiv. of hydrogen had been absorbed. Absorption continued, if allowed, owing to reduction of the solvent. Filtration, followed by evaporation gave crude saturated half-ester (95%), m.p. 67—69° [$\nu_{max.}$ 2950br (OH), 1730 and 1203 (ester), and 1698 (acid C=O) cm^{-1}; τ ($CDCl_3$) 8·66 (s, CMe), 7·39 (t, H-2, *J* 6), 6·30 (s, OMe), and −0·45br (OH)] (lit.,[4] m.p. 69—70°), which was used directly in the subsequent stages.

7a-*Methyl*-cis-*perhydroisobenzofuran*-1-*one* (20).—To the foregoing half-ester (8 g) in dry ethanol (40 ml) and liquid ammonia (400 ml) sodium (8 g, 8·7 atom equiv.) was added slowly with stirring, and the ammonia was allowed to evaporate. Water (60 ml) was added to the residue, which was then acidified to pH 1 with concentrated hydrochloric acid. The solution was saturated with sodium chloride and extracted with chloroform; the extract was evaporated and the residue was distilled to give the *isobenzofuranone* (5 g, 81%), b.p. 80° at 5 mmHg, m.p. 39—40° (Found: C, 70·5; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%); $\nu_{max.}$ 1768 and 1206 (lactone) cm^{-1}; τ ($CDCl_3$) 8·76 (s, CMe) and 5·8 (octet, H-3, J_{vic} 6·5 and 5, J_{gem} 9).

Methyl-cis-2-*Isocyanato*-trans-2-*methylcyclohexanecarboxylate* (12).—*cis*-2-methoxycarbonyl-1-methylcyclohexane carboxylic acid (8 g) and oxalyl chloride (8 ml) were stirred at 20° for 1 h, then for 0·5 h at 40° and distilled to give the acid chloride (11), b.p. 90—93° at 1 mmHg (8·42 g, 97%), $\nu_{max.}$ 1785 (acid chloride C=O), and 1723 and 1202 (ester) cm^{-1} (lit.,[4] b.p. 110·5—111° at 3·5 mmHg). The acid chloride in dry acetone (40 ml) was added at 0° to a solution of freshly prepared lithium azide (2·54 g, 1·3 mol. equiv.) in dry acetone (140 ml); the mixture was refluxed for 0·5 h and concentrated to a small volume. Dry toluene (120 ml) was added, the acetone was distilled off, and the solution was refluxed for 1 h. Insoluble lithium chloride was removed, the filtrate was evaporated, and the residue was distilled to give the *isocyanato-ester* (6·4 g, 84%), b.p. 84° at 1·5 mmHg (Found: C, 60·9; H, 7·4; N, 6·9. $C_{10}H_{15}NO_3$ requires C, 60·9; H, 7·7; N, 7·1%); $\nu_{max.}$ 2280 (NCO), and 1737 and 1205 (ester) cm^{-1}; τ ($CDCl_3$) 8·60 (s, CMe), 7·76 (t, H-1, *J* 7), and 6·36 (s, OMe).

Methyl cis-2-*Amino*-trans-2-*methylcyclohexanecarboxylate* (13).—The foregoing isocyanato-ester (2·9 g) was refluxed with 2N-hydrochloric acid (20 ml) for 1·5 h; the solution was cooled and extracted with chloroform, and the aqueous solution was evaporated to dryness. The residue in dry methanol (100 ml) was saturated with dry hydrogen chloride at 0°, refluxed for 3 h, and evaporated. The residue was dissolved in water (20 ml), basified with saturated sodium carbonate followed by ammonia (*d* 0·88; 20 ml), and extracted with ether (10 × 50 ml). The extract gave the *amino-ester* (1·71 g, 68%), b.p. 60° at 1 mmHg (Found: C, 63·3; H, 9·7; N, 8·4. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%); $\nu_{max.}$ 3477 and 3425 (NH), and 1732 and 1205 (ester) cm^{-1}; τ ($CDCl_3$) 8·03 (s, CMe), 7·60 (t, H-1, *J* 7), and 6·25 (s, OMe).

cis-2-*Amino*-trans-2-*methylcyclohexanecarbohydrazide*.—The foregoing amino-ester (4·95 g) and hydrazine hydrate (10 ml) were refluxed for 2 h; the mixture was then distilled to give the *amino-hydrazide* (3·7 g, 73%) as a thick oil, b.p. 140° at 1 mmHg, which solidified (m.p. 111—112°) and was crystallised with difficulty from benzene–light petroleum (b.p. 40—60°) (Found: C, 56·3; H, 10·3; N, 24·3. $C_8H_{17}N_3O$ requires C, 56·1; H, 10·0; N, 24·5%); $\nu_{max.}$ 3240 and 3120 (NH), and 1620 and 1555 (amide) cm^{-1}; τ ($CDCl_3$) 8·84 (s, CMe) and 7·1br (NH).

cis-2-*Aminomethyl*-1-*methylcyclohexylamine*.—The hydrazide (3·8 g) in dry benzene (150 ml) was added to lithium aluminium hydride (4·0 g) in dry tetrahydrofuran (150 ml) and the mixture was refluxed for 24 h. Further hydride (2 g) in tetrahydrofuran (50 ml) was added, and refluxing was continued for 72 h. The mixture was decomposed as before;[2,6] the cis-*diamine* (2·6 g, 84%), b.p. 61—62° at 1 mmHg, readily absorbed carbon dioxide from the atmosphere (Found: C, 64·6; H, 11·5; N, 18·0. $C_8H_{18}N_2$,0·25CO_2 requires C, 64·7; H, 11·8; N, 18·3%); $\nu_{max.}$ 3350 and 3280 (NH str.), and 1600br (NH bend) cm^{-1}; τ ($CDCl_3$) 8·86 (s, CMe), 8·76 (NH), 7·17 (octet, $CH_2{\cdot}NH_2$, J_{vic} 2 and 8, J_{gem} 12). The *dipicrate*, m.p. 233° (decomp.), separated slowly from saturated aqueous picric acid and was recrystallised from water (Found: C, 39·7; H, 3·9; N, 18·4. $C_{20}H_{24}N_8O_{14}$ requires C, 40·0; H, 4·0; N, 18·7%).

8a-*Methyl*-cis-*octahydroquinazolin*-2(1H)-*one* (5).—(*a*) To the foregoing diamine (275 mg, 1 mol. equiv.) in water (2 ml) at 0° aqueous 2N-sodium hydroxide (3·88 ml, 4 mol. equiv.) and 12% phosgene in toluene (3·2 g, 2 mol. equiv.) were added dropwise simultaneously, with stirring, and the mixture was stirred in an open vessel for 3 days at 20°. The solid that separated was collected and sublimed at 150° and 1 mmHg to give authentic 8a-*methyl*-cis-*octahydroquinazolin*-2(1H)-*one* (254 mg, 78%), m.p. 226° [from benzene or chloroform–light petroleum (b.p. 40—60°)] (Found: C, 64·2; H, 9·8; N, 16·7. $C_9H_{16}N_2O$ requires C, 64·25; H, 9·6; N, 16·65%); $\nu_{max.}$ 3240 and 3090 (NH str.), 1685 (C=O), 1535 (NH bend), 1460sh, 1450, 1433, 1365, 1345, 1325, 1304, 1275, 1193, 1125, 788, 775, and 675 cm^{-1}; *m/e* 168 (40%, M^+), 153 [100, $M^+ - CH_3$ (24)], 125 (70, $M^+ - CH_3{\cdot}CO$), and 111 (40, $M^+ - CH_3{\cdot}NCO$).

(*b*) The *cis*-bromomethyl compound (4) (108 mg) in ethanol (100 ml) containing Raney nickel [10] (4·0 g) was shaken with hydrogen at 80—85° and 4·8 atm for 6 h. The product after sublimation at 170° and 1 mmHg and recrystallisation from benzene gave the 8a-*methyl*-cis-*quinazolinone* (>90%). Hydrogenation at 20° was very slow.

Methyl cis-2-*Carbamoyl*-trans-2-*methylcyclohexanecarboxylate* (14).—The chlorocarbonyl compound (11) [prepared from the half-ester (12 g) but not distilled] in dry

benzene (60 ml) was added to a solution of benzene saturated with dry ammonia (600 ml; prepared by bubbling ammonia at 5° for 35 min); the temperature rose from 5 to 17°. After 5 min. at 20°, ammonium chloride was filtered off and the filtrate was evaporated to give the *amido-ester* (5·7 g, 95%), m.p. 97—98° [from light petroleum (b.p. 60—80°)] (Found: C, 60·35; H, 8·3; N, 7·1. $C_{10}H_{17}NO_3$ requires C, 60·3; H, 8·6; N, 7·0%); $\nu_{max.}$ 3420 and 3325 (NH), 1720 and 1206 (ester), and 1657 and 1623 (amide) cm^{-1}; τ ($CDCl_3$) 8·77 (s, CMe), 7·30 (t, H-1, *J* 6), 6·30 (s, OMe), and 3·80br (NH). When methanolic ammonia at −70° was used the amide was difficult to purify.

1-*Methyl*-cis-*hexahydrophthalimide* (19).—The foregoing amido-ester (0·4 g, 1 mol. equiv.) was refluxed with 1·1N-sodium hydroxide (2 ml, 1·1 mol. equiv.) for 3 min, kept at 20° for 4 h, and then acidified with 2N-hydrochloric acid. The solid was collected, dried, and recrystallised from light petroleum (b.p. 60—80°) to give the *phthalimide* (150 mg, 40%), m.p. 97° (Found: C, 64·6; H, 7·7; N, 8·55. $C_9H_{13}NO_2$ requires C, 64·65; H, 7·8; N, 8·4%); $\nu_{max.}$ 3190 (NH), and 1770 and 1705 (imide C=O) cm^{-1}; τ ($CDCl_3$) 8·66 (s, CMe), 7·38 (t, H-2, *J* 6), and 1·1br (NH).

cis-2-*Amino*-1-*methylcyclohexanecarboxylic Acid* (15).—The amido-ester (14) (12 g, 1 mol. equiv.) was boiled with 4·5N-sodium hydroxide (13 ml); the mixture was cooled and added to a solution of sodium hypobromite [from bromine (2·5 ml, 1·5 mol. equiv.) and 8·5N-sodium hydroxide (18 ml), mixed below 10°] at 0°, followed by 4·5N-sodium hydroxide (13 ml). The mixture was heated at 75° for 20 min. The solution was acidified to pH 3 at 10° with concentrated hydrochloric acid and the solid that separated was removed. The filtrate was stirred at 20° for 30 min and evaporated to dryness, and the residue was dried *in vacuo* (KOH) overnight. The solid was extracted with boiling ethanol; the extract was filtered from insoluble salt, and evaporated to dryness. The residue in water was placed on a Dowex 50w column (350 ml), which was washed with water and eluted with 3N-ammonium hydroxide (1 l); the eluate was evaporated and the residue was dried (KOH). The crude *amino-acid* (6·5 g, 70%) had the expected i.r. spectrum and was suitable for the next stage, but it crystallised with difficulty from ethanol–ether (1 : 2) in rosettes which decomposed slowly above 265° (Found: C, 61·3; H, 9·4; N, 9·0. $C_8H_{15}NO_2$ requires C, 61·1; H, 9·6; N, 8·9%); $\nu_{max.}$ 2930br (NH), 1628 (CO_2^-), and 1558 (NH_3^+) cm^{-1}; τ (D_2O; HOD at τ 5·30 as standard) 8·81 (s, CMe) and 6·95br (H-2).

Methyl cis-2-*Amino*-1-*methylcyclohexanecarboxylate* (16).—The foregoing *amino-acid* (6·5 g) in dry methanol (40 ml) was treated cautiously at 0° with concentrated sulphuric acid (20 ml) and heated at 100° for 15 h. The solution was evaporated, basified with saturated aqueous sodium carbonate, and extracted with ether. The extract gave the *amino-ester* (50—55%), b.p. 83° at 0·4 mmHg (Found: C, 63·4; H, 9·9; N, 8·5. $C_9H_{17}NO_2$ requires C, 63·1; H, 10·0; N, 8·2%); $\nu_{max.}$ 3395 and 3320 (NH), and 1725 and 1208 (ester) cm^{-1}; τ ($CDCl_3$) 8·74 (s, CMe), 8·40 (NH), 7·43br (H-2), and 6·30 (s, OMe). The yields were considerably lower when boiling saturated methanolic hydrogen chloride was used (1 h, 18%; 4 h, 21%; see foregoing isomer and refs. 2 and 6). The aqueous solution was adjusted to pH 3 with hydrochloric acid, evaporated, extracted, and purified through a Dowex 50w column as in the previous preparation, and the recovered amino-acid (*ca.* 2 g) was recycled. The *hydrochloride*, prepared in 6·5% methanolic hydrogen chloride–ether, had m.p. 197—198° (Found: C, 52·25; H, 8·7; Cl, 17·5; N, 6·6. $C_9H_{18}ClNO_2$ requires C, 52·0; H, 8·7; Cl, 17·1; N, 6·7%); $\nu_{max.}$ 3000br (NH), and 1737 and 1232 (ester) cm^{-1}.

cis-2-*Amino*-1-*methylcyclohexanecarbohydrazide* (17).—The amino-ester (16) (5 g) was refluxed with freshly distilled anhydrous hydrazine [11] (13 g) for 2 h; the mixture was evaporated and the residue was dried *in vacuo* (H_2SO_4) for 48 h. The waxy solid was boiled with benzene (400 ml) and the mixture was filtered. The insoluble solid (870 mg) was identical with the amino-acid (15). The filtrate was evaporated and the residue was recrystallised from benzene–light petroleum (b.p. 60—80°) or sublimed at 70° and 4 mmHg to give the *hydrazide* (3·75 g, 73%), m.p. 65—67°, as waxy needles (Found: C, 56·2; H, 9·9; N, 24·7. $C_8H_{17}N_3O$ requires C, 56·1; H, 10·0; N, 24·5%); $\nu_{max.}$ 3300 and 3210 (NH str.), 1680 (C=O), and 1595 and 1543 (NH bend) cm^{-1}; τ ($CDCl_3$) 8·83 (s, CMe) and 7·15br (H-2). Similar results were obtained with hydrazine hydrate.

cis-2-*Aminomethyl*-trans-2-*methylcyclohexylamine* (18).—Reduction of the hydrazide (17) with lithium aluminium hydride as for the 2-amino-2-methylhydrazide gave the *diamine* (95%), b.p. 61° at 0·6 mmHg [Found: (dry box sampling) C, 67·6; H, 12·4; $C_8H_{18}N_2$ requires C, 67·55; H, 12·75%]; $\nu_{max.}$ 3350 and 3300 (NH str.) and 1600 (NH bend) cm^{-1}; τ ($CDCl_3$) 9·03 (s, CMe), 8·55 (s, NH), 7·32 (d, CH_2·NH_2, 4 Hz separation), and 7·35br (H-1). It slowly gave a *dipicrate*, m.p. 209—210° (decomp.) (from water) (Found: C, 39·8; H, 4·0; N, 18·9. $C_{20}H_{24}N_8O_{14}$ requires C, 40·0; H, 4·0; N, 18·7%).

4a-*Methyl*-cis-*octahydroquinazolin*-2(1H)-*one* (21).—The diamine (18) was treated with 12% phosgene in toluene as for the isomer (5) and gave the 4a-*methyl compound* (72%), m.p. 214—215°, which was recrystallised from ethyl acetate or chloroform–light petroleum (b.p. 60—80°) and sublimed at 230° and 0·5 mmHg. It absorbs moisture slowly (Found: C, 64·3; H, 9·6; N, 16·4. $C_9H_{16}N_2O$ requires C, 64·25; H, 9·6; N, 16·65%); $\nu_{max.}$ 3260 and 3105 (NH str.), 1683 (C=O), 1537 (NH bend), 1467, 1445, 1428, 1387, 1365, 1352, 1302, 1284, 1258, 1196, 1150, 1140, 1090, 764, 738, and 645 cm^{-1}; *m/e* 168 (100%, M^+), 153 [10, $M^+ - CH_3$ (24?)], 139 (50, $M^+ - HCO$), 124 (40, $M^+ - NHCO$), 111 (50, $M^+ - CH_3$·NCO or $M^+ - N_2HCO$), 110 (50, $M^+ - CH_3$·NHCO or $M^+ - N_2H_2CO$), 96 (50, $C_7H_{11}^+$), and 81 (70, $C_6H_9^+$).

4a-*Methyl*-cis-*decahydroquinazoline* (22).—The diamine (18) (356 mg, 1 mol. equiv.) was treated with 37% aqueous formaldehyde (0·31 ml, 1·5 mol. equiv.) at 0° and kept at 20° overnight. Saturated aqueous picric acid (200 ml) was added, followed by solid picric acid, until the pasty picrate crystallised. This was collected, washed with water, and recrystallised from methanol to give the *quinazoline dipicrate* (*ca.* 100%), m.p. 178—179° (Found: C, 41·0; H, 4·0; N, 18·2. $C_{21}H_{24}N_8O_{14}$ requires C, 41·2; H, 4·0; N, 18·3%). Decomposition of the picrate with N-sodium hydroxide and extraction with chloroform gave 4a-*methyl*-cis-*decahydroquinazoline* (220 mg, 71%), b.p. 108° at 6 mmHg (Found: C, 69·9; H, 11·7; N, 18·1. $C_9H_{18}N_2$ requires C, 70·1; H, 11·8; N, 18·2%).

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