Synthetic and Stereochemical Investigations of Reduced Cyclic Bases. Part IV. The Constitutions of the Exhaustive Methylation Products of* trans-*Octahydro*-N-*methylindole and of* cis- *and* trans-*Decahydro*-N-*methyl*isoquinoline.

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The probable constitutions of the exhaustive methylation products of *trans*-octahydro-*N*-methylindole have been elicited and the investigations extended to the *cis*- and *trans*-decahydro-*N*-methyl*iso*quinolines.

The mixed bases obtained by Raney nickel reduction of *iso*quinoline with methanol as solvent, or by methylation of the secondary amines similarly prepared in *cyclo*hexane, have been separated by crystallisation of the amine picrates or of their salts with 3 : 5-dinitrobenzoic acid.

Exhaustive methylation of the *cis*- and *trans*-amines by Hofmann's method gave respectively *cis*- and *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane. The methine bases were reduced to the corresponding ethyl*cyclo*hexanes and further degraded to 1-ethyl-2-methylene*cyclo*hexane.

IT has been established by Barltrop, King, and Walley (*J.*, 1945, 277) that the decomposition of *cis*-octahydro-*NN*-dimethylindolinium hydroxide involves fission of the $N–C_{(8)}$ bond since the resulting methine $C_{10}H_{19}N$ yields 2-dimethylaminoethyl*cyclo*hexane as its dihydro-derivative. On the other hand, degradation of the corresponding *trans*-methohydroxide (I) produces a new methine $C_{10}H_{19}N$ and a dibasic ether $C_{20}H_{40}ON_2$, the dihydro-derivative of the unsaturated amine differing from either compound theoretically obtainable from the normal opening of the pyrrolidine ring (see King, Bovey, Mason, and Whitehead, Part III *).

Further consideration of this anomalous reaction suggests that the methine base arises from a Wagner–Meerwein type rearrangement of the carbonium ion (II) formed by ring-scission at $C_{(8)}$, thus indicating (III) as its probable structure. Data provided by *C*-methyl analysis, which was negative for the methine base but gave a value corresponding to one terminal methyl group for the dihydro-compound, are in agreement with this conclusion.

The contrasting behaviour of the *cis*- and *trans*-octahydroindole methohydroxides may be due to conformational differences in the respective molecules. In one at least of the feasible structures of the *cis*-compound (A) the necessary requirement for the normal Hofmann reaction is satisfied, *viz.*, coplanarity of the four participating centres N–C–C–H, although, because this cannot apply to the relevant centres in the pyrrolidine ring, ring scission follows a different course from that observed in the decahydroquinolines. In the *trans*-base (B), however, the necessary coplanarity does not exist and methine formation is inhibited, but by a simple electronic transition a carbonium ion is obtained which permits of molecular rearrangement by ring contraction, for example, of the kind cited by Barton (*J.*, 1953, 1032).†

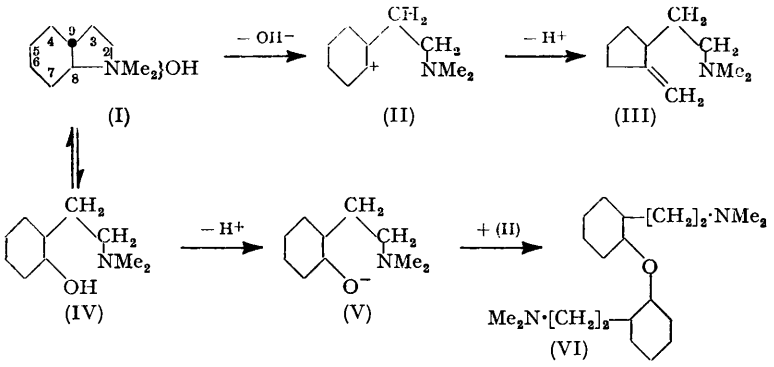
The formation of the ether $C_{20}H_{40}ON_2$ is similar to that of bimolecular products from quinolinium hydroxides (R. C. Elderfield, "Heterocyclic Compounds," J. Wiley and Sons, New York, 1952, Vol. IV, p. 232), and presumably arises from the intervention of the related alcohol (IV) by combination of the anion (V) with (II), whence its constitution is apparently (VI).

Experimental verification of these conclusions by a further study of the two amines (III) and (VI) is rendered difficult by the relative inaccessibility of *trans*-octahydroindole. The possibility that more available cyclic amines might be of use in this undertaking led to

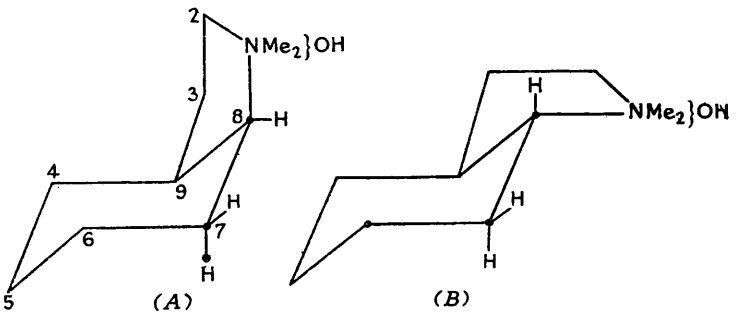
* Part III, *J.*, 1953, 250.

† This interpretation of our results was personally communicated to Dr. J. McKenna who subsequently included it in an article on the stereochemical course of Hofmann elimination in reduced cyclic amines (*Chem. and Ind.*, 1954, 406). F. E. K.

an investigation of the preparation and exhaustive methylation of *cis*- and *trans*-decahydro-*N*-methyl*iso*quinoline (VII and its geometrical isomer), which, were the methylene base (VIII) to be the primary product, would afford, *e.g.*, by oxidation to the related *cyclo*hexanone, a relatively easy route to the required products.



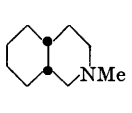
The complete hydrogenation of *iso*quinoline was described first by Skita (*Ber.*, 1924, **57**, 1977) who used colloidal platinum in acetic acid and obtained a decahydro*iso*quinoline which was probably largely the *cis*-isomer. Witkop (*J. Amer. Chem. Soc.*, 1948, **70**, 2617) found that with a platinum catalyst in acetic acid containing sulphuric acid the product consisted of approximately 70—80% of *cis*- and 20% of *trans*-decahydro*iso*quinoline which were separated by fractional crystallisation of the picrates. Hydrogenation in methyl*cyclo*hexane over Raney nickel (*idem*, *ibid.*, 1949, **71**, 2559) yielded a mixture containing some 80% of the *trans*-amine, the pure *trans*-base being isolated by removal of the *cis*-compound in a selective dehydrogenation process.



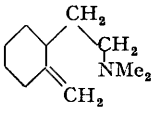
In the present investigation *iso*quinoline was hydrogenated in methanol solution over Raney nickel (W5) at 190°. At this temperature alkylation by the solvent takes place and a mixture of *cis*- and *trans*-decahydro-*N*-methyl*iso*quinoline was obtained. In contrast to Witkop's results with the secondary amines, it was not possible to secure a satisfactory separation of the mixed tertiary bases with picric acid; crystallisation, from acetone, gave less than 10% of the *trans*-amine picrate, indicating thereby a large preponderance of the *cis*-base. With 3 : 5-dinitrobenzoic acid, on the other hand, approximately 50—60% of the less-soluble *cis*-compound was obtained at the first crystallisation, the precise amount apparently depending on the batch of catalyst used. After separation of the *cis*-decahydro-*N*-methyl*iso*quinoline 3 : 5-dinitrobenzoate, the residue was worked up as the picrate, the first crystallisation yielding some 16% of the *trans*-amine salt.

Reduction in *cyclo*hexane solution at 195°, which was appreciably slower than in methanol, gave the mixed decahydro*iso*quinolines which before separation were methylated with formaldehyde–formic acid. Fractionation of the resulting tertiary amines as before,

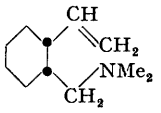
first as 3 : 5-dinitrobenzoates and then as picrates, gave nearly equal quantities of the two isomers, but owing to losses in crystallisation the yields of crude derivatives afford only an approximate estimate of the relative quantities of the amines formed in the reduction, although it is evident that the ratio of *cis* and *trans* is diminished when *cyclo*hexane replaces methanol as solvent. Measurements on the pure *cis*- and *trans*-decahydro-*N*-methyl*iso*quinolines afford further evidence for the hypothesis (see von Auwers and Ottens, *Ber.*, **1924, 67,** 437) that the density and refractive index of *cis*-isomerides exceed those of the corresponding *trans*-compounds.



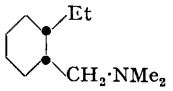
(VII)



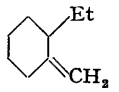
(VIII)



(IX)



(X)



(XI)

Distillation of the compound obtained by treating an aqueous solution of *cis*-decahydro-*N*-methyl*iso*quinoline methiodide with silver oxide yielded an unsaturated base which was presumed to be (VIII) or (IX). In order to decide its constitution the unsaturated amine was hydrogenated and the resulting dihydro-derivative likewise subjected to the Hofmann reaction. Oxidation of the hydrocarbon thus obtained gave 2-ethyl*cyclo*hexanone, thereby identifying it as 1-ethyl-2-methylene*cyclo*hexane (XI); it therefore follows that the primary exhaustive methylation product is *cis*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane (IX), its dihydro-derivative having the structure (X). Owing to decomposition by loss of methanol, distillation of the methohydroxide of (X) led to a 50% recovery of the parent amine. On the other hand, only traces of the *cis*-decahydro-*N*-methyl*iso*quinoline were regenerated during its conversion into (IX), which were easily eliminated in the crystallisation of derivatives of the methine base.

The decomposition of *trans*-decahydro-*N*-methyl*iso*quinoline methohydroxide was analogous to that of the *cis*-hydroxide in giving *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane. The identity of the methine was ascertained as in the case of the corresponding *cis*-amine, *i.e.*, by reduction and further application of the Hofmann reaction to the dihydro-base. This afforded the ethylmethylene*cyclo*hexane previously obtained from the *cis*-base (X) as was again shown by its oxidation to 2-ethyl*cyclo*hexanone.

Experimental

cis-*Decahydro*-N-*methyl*iso*quinoline*.—(*a*) *iso*Quinoline (20 g.), in methanol (50 c.c.), was hydrogenated over Raney nickel (W5) at 190° and an initial pressure of 130 atm. After 8 hr. a further quantity of catalyst was introduced and the reduction continued for an additional 8 hr. The filtered solution was acidified with 8% hydrochloric acid, then heated to remove methanol, and non-basic material was removed with ether. The aqueous solution was made alkaline and the basic oil collected in ether. The mixed amines (21·5 g.), b. p. 85·5—89·5°/15 mm., were treated with 3 : 5-dinitrobenzoic acid (30 g.) dissolved in the minimum of boiling ethyl acetate and, on cooling, cis-*decahydro*-N-*methyl*iso*quinoline* 3 : 5-*dinitrobenzoate* (25 g., 49%) crystallised in square prisms, m. p. 157—162°. Further recrystallisations from ethyl acetate gave the pure salt, m. p. 165—168° (Found: C, 55·9; H, 6·5; N, 11·4. $C_{17}H_{23}O_6N_3$ requires C, 55·9; H, 6·3; N, 11·5%). Decomposition of the salt with aqueous alkali and ether-extraction gave cis-*decahydro*-N-*methyl*iso*quinoline*, b. p. 95·5°/24 mm. The base had b. p. (Siwoloboff) 212°/765 mm., d_4^{23} 0·910, n_D^{23} 1·4819, $[M]_R$ 48·01 (calc. 48·18), and afforded the following derivatives: picrate, crystallising from ethanol in yellow needles, m. p. 210—211° (Witkop, *loc. cit.*, records m. p. 210°) (Found: C, 50·3; H, 5·8; N, 14·8. Calc. for $C_{16}H_{22}O_7N_4$: C, 50·2; H, 5·8; N, 14·7%); *picrolonate*, crystallising from ethanol in clusters of needles, m. p. 183·5—185° (Found: C, 57·3; H, 6·5; N, 16·5. $C_{20}H_{27}O_5N_5$ requires C, 57·5; H, 6·5; N, 16·8%); *methiodide*, needles, m. p. 319° (decomp.), from ethanol (Found: C, 44·8; H, 7·5; N, 4·6; I, 43·4. $C_{11}H_{22}NI$ requires C, 44·8; H, 7·5; N, 4·7; I, 43·0%); *methopicrate*, crystallising from ethanol in prisms, m. p. 149—150° (Found: C, 51·7; H, 6·2; N, 14·1. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%).

(*b*) A solution of *iso*quinoline (20 g.) in *cyclo*hexane (50 c.c.) was hydrogenated over Raney nickel at 195° and an initial pressure of 130 atm. for 20 hr., fresh catalyst being introduced after 10 hr. The mixed decahydro*iso*quinolines were extracted from the filtered solution with 8% hydrochloric acid and when liberated with alkali were isolated with ether and heated with 40% aqueous formaldehyde (20 c.c.) and 90% formic acid (35 c.c.) under reflux for 12 hours. The oily tertiary amines (21·5 g.) were isolated by extraction of the basified solution with ether and treated with 3 : 5-dinitrobenzoic acid (30 g.); the resulting salt was crystallised from ethyl acetate, giving *cis*-decahydro-*N*-methyl*iso*quinoline 3 : 5-dinitrobenzoate (10·9 g.) as square prisms, m. p. 156—160°. A further quantity (1·7 g.), m. p. 143—149°, was isolated from the mother-liquors, bringing the total yield of crude salt to 25%.

trans-*Decahydro*-N-*methyl*iso*quinoline*.—(*a*) *iso*Quinoline (20 g.), in methanol (50 c.c.), was hydrogenated over Raney nickel as in the preparation of *cis*-decahydro-*N*-methyl*iso*quinoline. The mother-liquors from the crystallisation of the *cis*-base 3 : 5-dinitrobenzoate were evaporated to dryness and the residue decomposed with dilute alkali. The liberated base (10·3 g.) was recovered by extraction into ether. Treatment of the base with picric acid (15·5 g.) and crystallisation of the picrate from acetone yielded *trans*-decahydro-*N*-methyl*iso*quinoline picrate (7·4 g.), m. p. 227—229°. A further quantity (1·3 g., total yield 16%), having m. p. 224—226°, was recovered from the mother-liquors. Further recrystallisations from acetone gave the pure *trans*-picrate, m. p. 237° (decomp.) (Witkop, *loc. cit.*, records 237°) (Found: C, 50·4; H, 5·7; N, 14·9%). Decomposition of the picrate with lithium hydroxide yielded trans-*decahydro*-N-*methyl*iso*quinoline*, b. p. 104°/40 mm. The base had b. p. (Siwoloboff) 209·5°/752 mm., d_4^{20} 0·893, n_D^{20} 1·4756, $[M]_R$ 48·4 (calc., 48·18), and afforded the following derivatives: picrolonate, crystallising from ethanol in square prisms, m. p. 221—222° [Witkop, *J. Amer. Chem. Soc.*, 1949, **71**, 2559, records m. p. 216—219° (sinters at 198°)] (Found: C, 57·7; H, 6·2; N, 17·0%); *methiodide*, needles, m. p. 283—284°, from ethanol (Found: C, 44·9; H, 7·5; N, 4·4; I, 43·3%); *methopicrate*, crystallising from water in yellow needles, m. p. 108—109° (Found: C, 51·2; H, 6·4; N, 14·2%); *mono*-3 : 5-*dinitrobenzoate*, which crystallised from ethyl acetate in needles, m. p. 146—148·5° (Found: C, 55·9; H, 6·0; N, 11·5%); *bis*-3 : 5-*dinitrobenzoate*, prepared as prisms, m. p. 115—117·5°, by mixing ethereal solutions of the two components (Found: C, 50·3; H, 4·7; N, 12·3. $C_{24}H_{27}O_{12}N_5$ requires C, 49·9; H, 4·7; N, 12·1%).

(*b*) *iso*Quinoline (20 g.), in *cyclo*hexane (50 c.c.), was hydrogenated over Raney nickel as in the preparation of *cis*-decahydro-*N*-methyl*iso*quinoline. The filtrates from the crystallisation of the *cis*-base 3 : 5-dinitrobenzoate were evaporated to dryness and the residue was decomposed with dilute alkali to give the free base (13·5 g.) which was recovered by ether-extraction. Treatment of the base with picric acid (20·2 g.) and crystallisation from acetone gave *trans*-decahydro-*N*-methyl*iso*quinoline picrate (11·4 g.), m. p. 231—233°. A further quantity (4·0 g., total yield 29%), m. p. 222—224°, was recovered from the mother-liquors.

Exhaustive Methylation of cis-*Decahydro*-N-*methyl*iso*quinoline*.—A solution of the *cis*-decahydro-*N*-methyl*iso*quinoline methiodide (21·7 g.) in water (300 c.c.) was shaken in the dark with silver oxide, freshly prepared from silver nitrate (24 g.) and sodium hydroxide (7 g.). When a sample of the filtered solution gave a negative iodide test (*ca.* 5 hr.), the mixture was filtered and the filtrate evaporated under reduced pressure at 45—50°. After most of the water had been removed, the temperature was raised to 120—130°; the syrupy quaternary hydroxide yielded a distillate of cis-1-NN-*dimethylaminomethyl*-2-*vinyl*cyclo*hexane* (IX) (9·9 g., 81%), b. p. 108—109° 46 mm. The base gave the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 111—113° (Found: C, 51·4; H, 5·8; N, 14·2. $C_{17}H_{24}O_7N_4$ requires C, 51·5; H, 6·1; N, 14·1%); *methiodide*, crystallising in plates, m. p. 253—254°, from acetone or acetone–ethyl acetate (Found: C, 46·5; H, 7·5; N, 4·2; I, 41·5. $C_{12}H_{24}NI$ requires C, 46·6; H, 7·8; N, 4·5; I, 41·0%); *methopicrate*, prisms, m. p. 139—140°, from ethanol (Found: C, 53·1; H, 6·2; N, 13·7. $C_{18}H_{26}O_7N_4$ requires C, 52·7; H, 6·4; N, 13·7%). When the methiodide (9·6 g.) of the crude base was dissolved in cold acetone (150 c.c.) a residue of *cis*-decahydro-*N*-methyl*iso*quinoline methiodide (0·12 g.), m. p. 306—307°, was obtained.

A sample of *cis*-1-NN-dimethylaminomethyl-2-vinyl*cyclo*hexane purified through the picrate had b. p. (Siwoloboff) 210°/763 mm., n_D^{20} 1·4679.

cis-1-NN-*Dimethylaminomethyl*-2-*ethyl*cyclo*hexane* (X).—The unsaturated base (IX) (10·3 g.) was hydrogenated in the form of its hydrochloride in methanol (100 c.c.) over palladised charcoal at room temperature and pressure. After filtration, the solution was evaporated and the residue treated with aqueous alkali and extracted with ether. cis-1-NN-*Dimethylaminomethyl*-2-*ethyl*-cyclo*hexane* (10 g., 96%) was thus isolated as an oil, b. p. 93·5°/24 mm., which yielded the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 105—107° (Found: C,

51·6; H, 6·8; N, 14·2. $C_{17}H_{26}O_7N_4$ requires C, 51·3; H, 6·6; N, 14·1%); *methiodide*, plates, m. p. 278—279°, from acetone (Found: C, 46·4; H, 8·0; N, 4·2; I, 41·2. $C_{12}H_{26}NI$ requires C, 46·3; H, 8·4; N, 4·5; I, 40·8%); *methopicrate*, crystallising from ethanol in prisms, m. p. 145—146° (Found: C, 52·7; H, 6·7; N, 13·4. $C_{18}H_{28}O_7N_4$ requires C, 52·4; H, 6·8; N, 13·6%). A sample of the base purified through the picrate had b. p. (Siwoloboff) 208°/759 mm., n_D^{19} 1·4595.

1-*Ethyl*-2-*methylene*cyclo*hexane* (XI).—A solution of the methiodide (6·15 g.) in water (150 c.c.) was shaken with silver oxide freshly prepared from silver nitrate (8 g.). The filtered solution was evaporated at 45—50° and the syrupy residue heated under reduced pressure at 120°. An oil (0·9 g.) isolated by ether-extraction of the distillate was resolved with dilute hydrochloric acid into a neutral and a basic fraction, the latter (0·4 g.) being identified as *cis*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (IX) by mixed m. p. of the picrate, m. p. 105—107°, and methiodide, m. p. 280°. The neutral fraction (0·45 g.) consisting of 1-ethyl-2-methylene-*cyclo*hexane, had b. p. (Siwoloboff) 152—153°/766 mm., n_{19}^{D} 1·4581. The olefin (0·35 g.) was dissolved in acetone (100 c.c.) and potassium permanganate (1 g.) was added at intervals during 2 days. Finally, after refluxing for 10 min. the solution was filtered from manganese dioxide and evaporated. The oily residue (0·2 g.) gave 2-ethyl*cyclo*hexanone 2 : 4-dinitrophenylhydrazone, crystallising from alcohol in red needles, m. p. 162·5—163·5° (Found: N, 18·1. Calc. for $C_{14}H_{18}O_4N_4$: N, 18·3%). An authentic specimen had m. p. 161·5—162° (cf. King, Barltrop, and Walley, *J.*, 1945, 279) and the mixed m. p. was 162—162·5°.

Exhaustive Methylation of trans-*Decahydro*-N-*methyl*iso*quinoline*.—This was carried out as already described for the *cis*-isomer. The *trans*-methiodide (6·5 g.) yielded *trans*-1-*NN*-dimethylaminomethyl-2-vinyl*cyclo*hexane (3·0 g., 81%). The base gave the following derivatives: *picrate*, crystallising from ethanol in prisms, m. p. 101—102° (85—97° when mixed with the *cis*-isomer) (Found: C, 51·4; H, 6·3; N, 14·4%); *methiodide*, plates, m. p. 212°, from acetone–ethyl acetate (Found: C, 46·2; H, 7·8; N, 4·2; I, 41·1%); *methopicrate*, crystallising in prisms, m. p. 113—115°, from ethanol (Found: C, 52·5; H, 6·5; N, 13·8%).

trans-1-NN-*Dimethylaminomethyl*-2-*ethyl*cyclo*hexane* (VI).—The unsaturated *trans*-base (5·45 g.) gave, on hydrogenation over palladium–charcoal, *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (4·8 g., 87%). The base yielded a *picrate*, crystallising from ethanol in plates, m. p. 111—112° (94—103° if mixed with the *cis*-isomer) (Found: C, 50·9; H, 6·5; N, 14·1%), a *methiodide*, needles (from ethanol), m. p. 261° (decomp.) (Found: C, 46·5; H, 8·1; N, 4·2; I, 41·0%), and *methopicrate*, plates (from ethanol), m. p. 116·5—118° (Found: C, 52·1; H, 6·5; N, 13·4%).

The decomposition of *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane methiodide (7·0 g.) was carried out as described for the *cis*-compound. From the distillate 1-ethyl-2-methylene-*cyclo*hexane (0·65 g.) was obtained and *trans*-1-*NN*-dimethylaminomethyl-2-ethyl*cyclo*hexane (0·27 g.) was recovered. Oxidation of the hydrocarbon gave 2-ethyl*cyclo*hexanone of which the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 162—163°.

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