51. *Synthetical and Stereochemical Investigations of Reduced Cyclic Bases. Part III.* The Synthetic* cis- *and* trans-*Octahydroindoles and the Anomalous Exhaustive Methylation Products of the* trans-*Base.*

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Syntheses are described, from *cyclo*hexane derivatives of known stereochemical structure, of both *cis*- and *trans*-octahydroindole. The *cis*-configuration provisionally attributed (King, Barltrop, and Whalley, *J.*, 1945, 277) to the octahydro- and octahydro-*N*-methyl-indoles obtained by catalytic reduction of indole has thus been confirmed.

trans-Octahydrodimethylindolinium iodide is converted by Hofmann's procedure into an unsaturated amine $C_{10}H_{19}N$ and a dibasic ether $C_{20}H_{40}ON_2$. Reduction of the unsaturated base gives a product $C_{10}H_{21}N$ isomeric but not identical with either of the predictable alternatives, *viz.*, 2-dimethylaminoethyl*cyclo*hexane, $Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_{11}$, or *trans*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine, $Me_2N{\cdot}C_6H_{10}Et$.

The catalytic hydrogenation of indole (Willstätter and Jacquet, *Ber.*, 1918, **51**, 777; Adkins and Coonradt, *J. Amer. Chem. Soc.*, 1941, **63**, 1563) affords an octahydro-derivative in which, for reasons outlined in Part I (King, Barltrop, and Whalley, *J.*, 1945, 277), the constituent rings were assumed to have the *cis*-configuration. An octahydro-*N*-methylindole obtained by reduction of indole over Raney nickel in methanol (Part I) was likewise regarded as a member of the *cis*-series, but no data were available from which it was possible to determine the precise configuration of these reduction products or even to confirm their relationships.

The problem has therefore been investigated by synthesis, and, as in the case of the decahydroquinolines (King, Henshall, and Whitehead, *J.*, 1948, 1373), the two stereoisomeric octahydroindoles have now been obtained by ring-closure of the appropriate *cyclo*hexane derivatives of known configuration. The assumed *cis*-configuration of the octahydro- and the octahydro-*N*-methyl-indoles previously prepared has thereby been confirmed; a minor by-product sometimes found in the Raney nickel–methanol hydrogenation has been identified as the *trans*-*N*-methyl base.

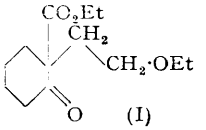
First, 2-ethoxyethyl bromide was condensed with ethyl sodio-2-keto*cyclo*hexanecarboxylate in alcohol, but whereas 3-ethoxypropyl bromide yielded 66% of the substituted keto-ester (Part II), only diethyl α-2-ethoxyethylpimelate, $EtO_2C{\cdot}[CH_2]_4{\cdot}CH(CO_2Et){\cdot}[CH_2]_2{\cdot}OEt$, was obtained under these conditions. When, however, this difficulty was overcome by employing toluene as solvent, ketonic hydrolysis of the resulting ester (I) was much reduced by partial ring-fission to the substituted pimelic acid. It was found better, therefore, to perform the synthesis with alcohol and afterwards to recyclise the resulting pimelic ester, the product, presumably (II; R = CO_2Et) (cf. Openshaw and Robinson, *J.*, 1937, 945), being hydrolysed to the ketone (II; R = H) without difficulty.

Reduction of the ketoxime with sodium in alcohol afforded an amine which in its production under alkaline conditions is presumed from Skita's generalised observation (see Part I) to be the *trans*-2-2′-ethoxyethyl*cyclo*hexylamine (III; R = OEt). In boiling hydrobromic acid the ethoxy-group was replaced by bromine, giving a homogeneous crystalline hydrobromide of *trans*-2-2′-bromoethyl*cyclo*hexylamine (III; R = Br) which after liberation from its salt with alkali underwent ring closure to the hitherto unknown *trans*-octahydroindole (IV), a liquid characterised by several crystalline derivatives.

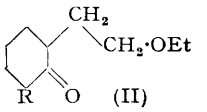
When heated in a sealed tube with ammonium formate (Leuckart reaction) the ethoxyethyl*cyclo*hexanone (II; R = H) was converted into an oily mixture of stereoisomers, principally the *cis*-2-2′-ethoxyethyl-*N*-formyl*cyclo*hexylamine. The formation of both isomers was also observed in the corresponding stage of the *cis*-decahydroquinoline synthesis (Part II).

* Part II, *J.*, 1948, 1373.

Part of the oily product was hydrolysed with dilute hydrochloric acid and the *cis*-2-2′-ethoxyethyl*cyclo*hexylamine purified by fractional crystallisation of the picrolonate. Both the regenerated amine and remaining formamide were then converted into the bromo-amine hydrobromide, in contrast to its *trans*-isomer, an uncrystallisable syrup, and hence into *cis*-octahydroindole. The melting points of the benzenesulphonamide and picrate of both specimens agreed with those recorded for the corresponding products from the octahydro-base prepared by the hydrogenation of indole (Willstätter; Adkins), and the picrolonate showed no depression of melting point with the specimen described in Part I.



(I)



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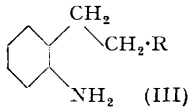

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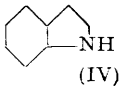
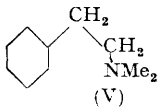


(IV)



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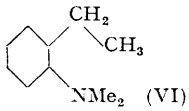

(VI)

Determinations of density and refractive index were made on both the *cis*- and the *trans*-amine, after purification through suitable salts. In agreement with the Auwers rule (see Part I) the constants of the *cis*-octahydroindole are slightly greater than those of the *trans*-isomer.

It has been shown (Part I) that the octahydro-*N*-methyl- and -*N*-ethyl-indole which are formed when indole is hydrogenated respectively in methanol and ethanol can be prepared more readily than the unalkylated base, and the exhaustive methylation data already published were ascertained from experiments on the resulting octahydro-*N*-methyl compound. When the *N*-methyl derivatives of both synthetic octahydroindoles were prepared by the formaldehyde–formic acid method, the methiodide and methopicrate of the *cis*-compound proved to be identical with those originating from the material formed by catalytic reduction in methanol.

An alternative synthesis of octahydroindole was investigated which was based on the existence of 2-2′-nitroethyl*cyclo*hexanone, prepared from 2-dimethylaminomethyl*cyclo*hexanone and nitromethane by Reichert and Posemann (*Arch. Pharm.*, 1937, **275**, 67). Neutral catalytic reduction of the nitro-ketone resulted, even before isolation of the product, in ring-closure to a hexahydroindole. This was resistant to further hydrogenation over catalysts but could be saturated by treatment with sodium in alcohol. Being an alkaline reduction, it might possibly have given a *trans*-product, but, with the fused dicyclic system pre-existent in the molecule, the greater stability of the *cis*-configuration is evidently the deciding factor in the reduction, since the octahydroindole obtained in this experiment proved to be the *cis*-isomeride.

In the earlier stages of this enquiry (Part I) exhaustive methylation was applied to the octahydro-*N*-methylindole obtained by reduction, in the belief that an *NN*-dimethyl-2-vinyl*cyclo*hexylamine would be obtained which would reveal the stereochemical configuration of the octahydro-compound by giving, when saturated, either the *cis*- or the *trans*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine (VI) synthesised at that time as reference compounds. This impression was based on the behaviour of the decahydroquinolines and of octahydro-2-methylindole in the exhaustive methylation process, but, in contrast, the octahydroindole yielded an unsaturated base which by its reduction to 2-dimethylaminoethyl*cyclo*hexane (V) proved that the link from the nitrogen to the *cyclo*hexane ring had been severed. This has been confirmed in the present work, during which the exhaustive methylation of the *trans*-compound has also been examined and found to give an unsaturated amine $C_{10}H_{19}N$ and a higher-boiling product $C_{20}H_{40}ON_2$. The latter was a saturated diacidic base, and with boiling hydrobromic acid was hydrolysed to a crystalline bromo-amine hydrobromide $C_{10}H_{20}NBr,HBr$, thus showing it to be an ether. The more volatile substance readily yielded a dihydro-base $C_{10}H_{21}N$, but from the properties of the picrate, picrolonate, and methiodide of the reduced product it was clearly not 2-dimethylaminoethyl*cyclo*-

hexane. On the other hand, it was also not identical with either *trans*- or even the *cis*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine (VI), whence it follows that the transformation has been attended by further molecular rearrangement. To provide products for direct comparison the synthesis of the two stereoisomeric 2-ethyl-*NN*-dimethyl*cyclo*hexylamines has also been repeated. The salt, m. p. 182°, previously described as the *trans*-amine methiodide (Part I) was shown to be the tertiary amine hydriodide, the authentic methiodide having m. p. 231° (decomp.).

The structure of the exhaustive methylation products of *trans*-octahydroindole will be discussed in a further communication.

Experimental

Ethyl 1-2′-*Ethoxyethyl*-2-*keto*cyclo*hexanecarboxylate* (I).—To the suspension of sodium salt formed in 2 hours from ethyl 2-keto*cyclo*hexanecarboxylate (52 g.) and powdered sodium (6·5 g.) in boiling xylene (250 c.c.), 2-ethoxyethyl bromide (43·5 g.) was added, and refluxing continued for 12—15 hours. When cooled, washed with dilute acid, dried and distilled, the xylene solution yielded a fraction, b. p. 147—167°/12 mm., from which was obtained the keto-ester (I) (33·6 g., 49%), b. p. 152—158°/10 mm. Its *semicarbazone*, rods from ethyl acetate–light petroleum, has m. p. 128° (Found : C, 56·3; H, 8·5; N, 14·2. $C_{14}H_{25}O_4N_3$ requires C, 56·3; H, 8·4; N, 14·0%).

Diethyl α-2-*Ethoxyethylpimelate*.—The mass of salt formed from ethyl 2-keto*cyclo*hexanecarboxylate (200 g.) and a solution of sodium (27 g.) in ethanol (360 c.c.) was refluxed for 4 hours with 2-ethoxyethyl bromide (216 g.) and then for another 2 hours after a further addition of sodium (4·7 g.) in alcohol (70 c.c.). Solvent was then distilled off and the residue treated with water, etc., to give the product (155—165 g.), b. p. *ca.* 175°/9 mm., refractionated to give the pure *pimelate* (Found : C, 62·5; H, 9·8. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·8%). Hydrolysis with boiling 30% barium hydroxide gave α-2-*ethoxyethylpimelic acid* b. p. 238—242°/7 mm. (Found : C, 56·5; H, 8·6. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·7%).

2-2′-*Ethoxyethyl*cyclo*hexanone* (II; R = H).—(*a*) Diethyl α-2-ethoxyethylpimelate (160 g.) was added to sodium (25 g.) dispersed in xylene (500 c.c.), and the condensation initiated with ethanol (1—2 c.c.). When the reaction moderated, the mixture was refluxed for 2 hours and then poured into dilute acid and ice. The oil isolated from the xylene layer was hydrolysed under reflux with barium hydroxide solution (385 g. in 1100 c.c.) for 6 hours. Acidification and extraction with ether gave the ketone (68 g.), b. p. 127—129°/15 mm., characterised by its *semicarbazone*, needles (from water), m. p. 126° (Found : C, 58·1; H, 9·1; N, 18·3. $C_{11}H_{21}O_2N_3$ requires C, 58·1; H, 9·3; N, 18·5%), and by the 2 : 4-*dinitrophenylhydrazone*, m. p. 75° (Found : C, 54·5; H, 6·5; N, 16·0. $C_{16}H_{22}O_5N_4$ requires C, 54·8; H, 6·3; N, 16·0%).

(*b*) The 2-keto*cyclo*hexanecarboxylate (I) (15·7 g.) was heated under reflux with barium hydroxide (36 g.) in water (100 c.c.) for 6 hours. The oil liberated on acidification was dissolved in ether and then washed with 10% aqueous sodium hydroxide, thus leaving the ketone (II; R = H) (2·2 g., 20%), b. p. 105—110°/10 mm., identified by its derivatives. The sodium hydroxide washings contained α-2-ethoxyethylpimelic acid (3·1 g., 20%), b. p. 238—242°/77 mm. (Found : C, 56·5; H, 8·6%).

2-2′-*Ethoxyethyl*cyclo*hexanone Oxime*.—The optimum yield of the *oxime*, obtained from hydroxylamine hydrochloride (15 g.), sodium acetate (30 g.), and the ketone (II; R = H) (34 g.) in 60% aqueous alcohol (220 c.c.), was 78% ; the derivative had b. p. 176—179°/29 mm. (Found : C, 64·9; H, 10·3; N, 7·2. $C_{10}H_{19}O_2N$ requires C, 64·8; H, 10·3; N, 7·6%).

trans-2-2′-*Ethoxyethyl*cyclo*hexylamine* (III; R = OEt).—Sodium (40 g.) was added in portions to a boiling solution of the ketoxime (29 g.) in ethanol (250 c.c.) ; afterwards, a slight excess of acid was introduced and the alcohol evaporated under reduced pressure. By-products were removed by ether and then the trans-*amine* (III; R = OEt) was liberated by concentrated potassium hydroxide as an oil (19·1 g., 71%), b. p. 116—118°/18 mm. It formed a *picrate*, m. p. 100°, from water (Found : C, 47·8; H, 6·1; N, 13·8. $C_{10}H_{21}ON,C_6H_3O_7N_3$ requires C, 48·0; H, 6·0; N, 14·0%), and a *picrolonate*, m. p. 180°, as needles from ethanol (Found : C, 55·3; H, 6·6; N, 16·1. $C_{10}H_{21}ON,C_{10}H_8O_5N_4$ requires C, 55·1; H, 6·7; N, 16·1%). The *benzoyl* derivative separated from light petroleum or ethanol as a crystalline mass, m. p. 120° (C, 74·5; H, 8·7; N, 4·9. $C_{17}H_{25}O_2N$ requires C, 74·1; H, 9·1; N, 5·1%).

trans-2-2′-*Bromoethyl*cyclo*hexylamine Hydrobromide*.—The *trans*-amine (III; R = OEt) (21 g.) was refluxed with 50% hydrobromic acid (800 c.c.) for 7 hours. After distillation of the acid under reduced pressure, the residue solidified, and crystallisation from ethyl acetate

or acetone gave the *hydrobromide* of the *trans*-bromo-amine (III; R = Br) as needles, m. p. 191° (Found: C, 33·2; H, 6·3; N, 5·0; Br, 56·1. $C_8H_{16}NBr,HBr$ requires C, 33·5; H, 5·9; N, 4·9 Br, 55·7%). A *picrate*, prepared by mixing aqueous solutions of the salt and of picric acid, crystallised from benzene–ethyl acetate in yellow needles, m. p. 118° (Found: C, 38·9; H, 4·4 N, 13·0; Br, 18·4. $C_8H_{16}NBr,C_6H_3O_7N_3$ requires C, 38·6; H, 4·4; N, 12·9; Br, 18·4%).

trans-*Octahydroindole* (IV).—The hydrobromide of the *trans*-bromide (III; R = Br) (32·5 g.) was dissolved in water (200 c.c.) and added during 2 hours to a cold stirred solution of sodium hydroxide (25 g.) in water (150 c.c.). After a further 1½ hours the product was extracted with ether, and distillation gave *trans*-octahydroindole (11·65 g., 82%) as a colourless oil, b. p. 72—73°/19 mm. It formed the following derivatives: *picrolonate*, yellow-orange prisms, m. p. 234°, from ethanol (Found: C, 55·3; H, 6·0; N, 18·0. $C_8H_{15}N,C_{10}H_8O_5N_4$ requires C, 55·6; H, 5·9; N, 18·0%); *picrate*, crystallising from benzene in yellow rhombohedra, m. p. 147° (Found: C, 47·2; H, 5·1; N, 15·5. $C_8H_{15}N,C_6H_3O_7N_3$ requires C, 47·5; H, 5·1; N, 15·8%); *benzenesulphonamide*, prisms, m. p. 62—63°, from light petroleum (Found: C, 63·3; H, 7·2; N, 5·4. $C_{14}H_{19}O_2NS$ requires C, 63·4; H, 7·2; N, 5·3%); 3 : 5-*dinitrobenzoate*, prepared in alcohol and separating from ethyl acetate as a microcrystalline mass, m. p. 178° (Found: C, 53·6; H, 5·6; N, 13·0. $C_{15}H_{19}O_6N_3$ requires C, 53·4; H, 5·6; N, 12·5%). A sample of *trans*-octahydroindole purified through the picrate had b. p. (Siwoloboff) 186·0°/767 mm., d_4^{24} 0·930, n_D^{24} 1·484, $[M]_R$ 38·45 (Calc., 38·34).

cis-2-2′-*Ethoxyethyl*cyclo*hexylamine*.—The ketone (II; R = H) (25 g.) was heated with ammonium formate (48 g.) in sealed tubes at 200° for 10 hours. After the addition of water, the formamide (23 g., 78%), b. p. 196—202°/17 mm., was isolated with ether, and a portion (5 g.) refluxed with 3% hydrochloric acid (25 c.c.) for 15 minutes. The clear solution was basified with potassium hydroxide and the extracted mixed amines (1·7 g.), b. p. 119°/17 mm., were treated with picrolonic acid (2·6 g.) in hot ethanol (66 c.c.). The picrolonate (0·7 g.), m. p. and mixed m. p. 180°, which separated on cooling was of the *trans*-amine (II; R = OEt). The addition of water then precipitated the *cis*-amine *picrolonate* crystallising from ethyl acetate as orange cubes (2·8 g.), m. p. 148° (Found: C, 54·8; H, 6·5; N, 16·3%).

cis-*Octahydroindole*.—(*a*) The picrolonate of the *cis*-amine (III; R = OEt), dissolved in ethanol (10 c.c.), was shaken with warm 40% aqueous potassium hydroxide (40 c.c.). The suspension was shaken with ether, and the extracted oil refluxed for 5 hours with 50% hydrobromic acid. When evaporated under reduced pressure the solution left a syrupy product; it was shaken for several hours with aqueous ammonia and ether. The amine (0·6 g.) extracted from the ether with acid and then precipitated by alkali gave a picrolonate as spherical clusters (from ethanol), m. p. 218°, undepressed by the picrolonate of octahydroindole obtained by catalytic reduction (Part I) (Found: C, 55·5; H, 6·0; N, 17·8%).

(*b*) The formamide (10 g.), b. p. 196—202°, from the Leuckart reaction similarly treated with boiling hydrobromic acid (400 c.c.) gave a syrupy hydrobromide. It was cyclised as above with aqueous ammonia and the resulting base (2·5 g., 40%), b. p. 73—76°/18 mm., identified by the picrolonate, m. p. 218°; the method using sodium hydroxide which gave 82% of the *trans*-amine was not devised until later. In addition to the picrolonate, *cis*-octahydroindole gave the following derivatives: picrate, yellow prisms, m. p. 137°, from benzene (Willstätter, Seitz, and von Braun, *Ber.*, 1925, **56**, 385, give m. p. 137°), mixed m. p. with the *trans*-picrate 111—120° (Found: C, 47·2; H, 4·9; N, 16·1. $C_8H_{15}N,C_6H_3O_7N_3$ requires C, 47·5; H, 5·1; N, 15·8%); *benzenesulphonamide*, colourless spiky needles, m. p. 70° and 59—62° mixed with the *trans*-isomer (Willstätter *et al.*, 70—71°; Adkins and Coonradt, *loc. cit.*, 69·5—70·5°) not previously analysed (Found: C, 63·2; H, 7·1; N, 4·9; S, 11·7. $C_{14}H_{19}O_2NS$ requires C, 63·5; H, 7·2; N, 5·3; S, 12·1%); 3 : 5-*dinitrobenzoate* (from ethyl acetate), m. p. 192°, and 160—186° mixed with the *trans*-isomer (Found: C, 53·0; H, 5·6; N, 12·4%). A sample of *cis*-octahydroindole purified through the 3 : 5-dinitrobenzoate had b. p. (Siwoloboff) 187·5°/767 mm., d_4^{18} 0·945, n_D^{19} 1·4899, $[M]_R$ 38·24 (Calc., 38·34) (Willstätter *et al.* give b. p. 185·5°/760 mm., d_4^{24} 0·9472, n_D^{20} 1·4892, and Adkins and Coonradt, n_D^{25} 1·4833.

trans-*Octahydro*-N-*methylindole*.—*trans*-Octahydroindole (5 g.) was refluxed for 4 hours with a mixture of 40% aqueous formaldehyde (5 g.) and 90% formic acid (6·5 g.). *trans*-Octahydro-*N*-methylindole (3·5 g.), b. p. 54—55°/8 mm., was isolated by basifying the solution and extracting it with ether. It afforded the following derivatives: *picrate*, crystallising from ethanol in yellow needles, m. p. 196° (Found: C, 48·6; H, 5·5; N, 15·1. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4; N, 15·2%); *picrolonate*, orange-yellow aggregates, m. p. 182° (Found: C, 56·3; H, 6·1; N, 17·6. $C_9H_{17}N,C_{10}H_8O_5N_4$ requires C, 56·6; H, 6·2; N, 17·4%); *methiodide*, crystallising from acetone in plates, m. p. 229° (Found: C, 42·7; H, 7·1; N, 4·7; I, 43·9. $C_{10}H_{20}NI$ requires

C, 42·75; H, 7·1; N, 5·0; I, 45·2%); *methopicrate*, which crystallised from ethanol in orange prisms, m. p. 171° (Found: C, 50·4; H, 5·7. $C_{16}H_{22}O_7H_4$ requires C, 50·3; H, 5·8%); *bis*-3 : 5-*dinitrobenzoate*, which crystallised from ethyl acetate in needles, m. p. 129° (Found: C, 49·0; H, 4·4; N, 12·6. $C_{23}H_{25}O_{12}N_5$ requires C, 49·0; H, 4·4; N, 12·5%).

cis-*Octahydro*-N-*methylindole*.—(*a*) Prepared similarly to the *trans*-isomer, the cis-N-*methyl* base had b. p. 57°/9 mm. and was characterised by the following derivatives: *picrate*, yellow needles, m. p. 204°, from ethanol (Found: C, 48·8; H, 5·5; N, 14·9%); *picrolonate*, microcrystalline yellow mass, m. p. 168°, from ethanol (Found: C, 56·9; H, 6·3; N, 17·1%); *methiodide* crystallising in needles, m. p. 208°, from acetone–ether (Found: C, 43·1; H, 6·8; N, 4·7; I, 43·7%); *methopicrate*, foliated prisms, m. p. 195°, from ethanol, not depressed by the methopicrate, m. p. 194°, of the octahydro-*N*-methylindole prepared by catalytic reduction (Part I) (Found: C, 50·2; H, 5·5; N, 14·9. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·8; N, 14·7%). The methiodide, m. p. 201° (Part I), is now known to have been contaminated with the less soluble *trans*-metho-salt, m. p. 229°. Up to 5% of *trans*-amine, calculated on methiodide, is sometimes present in the indole reduction product.

(*b*) *cis*-Amine was also derived from 2-2′-nitroethyl*cyclo*hexanone; the yield of nitro-ketone, reported by Reichert and Posemann (*loc. cit.*) to be 70% is, after distillation, 30%. The product, b. p. 126—129°/0·8 mm., gave the semicarbazone, m. p. 151—152°, described by these authors (Found: C, 47·0; H, 6·7. Calc. for $C_9H_{16}O_3N_4$: C, 47·5; H, 7·0%). The nitro-ketone was hydrogenated over Raney nickel at N.T.P. in 3—4 hours, and the product gave the *picrate* of a hexahydroindole, crystallising from ethanol in yellow prisms, m. p. 133° (Found: C, 47·4; H, 4·4; N, 15·7. $C_8H_{13}N,C_6H_3O_7N_3$ requires C, 47·7; H, 4·5; N, 15·9%). The base, b. p. 76°/11 mm., resinified on attempted reduction with amalgamated zinc and hydrochloric acid, and resisted hydrogenation over palladised charcoal. Without being isolated the product from the reduction of 7 g. of nitro-ketone was treated in alcohol (130 c.c.) with sodium (11 g.). After evaporation of solvent from the acidified solution *cis*-octahydroindole (1·2 g.; b. p. 72°/13 mm.) was isolated and identified by mixed m. p.s of the picrolonate, m. p. 218°, and 3 : 5-dinitrobenzoate, m. p. 192°.

trans-2-*Ethyl*-NN-*dimethyl*cyclo*hexylamine* (VI).—Repetition of the synthesis of this amine shows that it affords a *methiodide* which separates from acetone–ethyl acetate in plates, m. p. 231° (decomp.), not 182° as recorded in Part I (Found: C, 44·5; H, 7·9; N, 4·8; I, 43·1. $C_{11}H_{24}NI$ requires C, 44·4; H, 8·1; N, 4·7; I, 42·8%). The compound, m. p. 182°, is the trans-2-*ethyl*-NN-*dimethyl*cyclo*hexylamine hydriodide*, and the specimen incorrectly named in Part I had mixed m. p. 182° with a sample made from the tertiary base and hydriodic acid (Found: C, 42·4; H, 7·7; N, 4·8; I, 44·7. $C_{10}H_{21}N,HI$ requires C, 42·5; H, 7·8; N, 5·0; H, 45·0%). Also prepared were the *picrate*, yellow rhombohedra, m. p. 126°, from ethanol (Found: C, 50·3; H, 6·3; N, 14·5. $C_{10}H_{21}N,C_6H_3O_7N_3$ requires C, 50·0; H, 6·25; N, 14·8%), and the *picrolonate*, yellow square tablets, m. p. 170°, from ethanol (Found: C, 57·5; H, 6·7; N, 16·8. $C_{10}H_{21}N,C_{10}H_8O_5N_4$ requires C, 57·3; H, 7·0; N, 16·7).

cis-2-*Ethyl*-NN-*dimethyl*cyclo*hexylamine*.—The new sample of this amine gave a methiodide, m. p. 232° (decomp.) (recorded in Part I, 231°). The *picrate* crystallised from ethanol in yellow prisms, m. p. 159° (Found: C, 50·0; H, 6·7; N, 14·9%).

Exhaustive Methylation of trans-*Octahydroindole*.—A solution of the *trans*-methiodide, m. p. 229° (10 g.), in water (25 c.c.) was shaken in the dark with freshly prepared silver oxide (4·5 g.) for 3 hours. The filtered solution was then heated under reduced pressure, first at 50° and afterwards slowly to 100° at 10—12 mm. When distillation ceased, solid potassium hydroxide was added to the distillate which on ether-extraction yielded a base (0·9—2·3 g.), b. p. 65°/9 mm. It formed a *picrate* crystallising from ethanol in yellow flat prisms, m. p. 117—118° (Found: C, 50·4; H, 5·8; N, 14·5. $C_{10}H_{19}N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·8; N, 14·7%), a *picrolonate*, yellow prisms, m. p. 163°, from aqueous ethanol (Found: C, 57·5; H, 6·5; N, 16·7. $C_{10}H_{19}N,C_{10}H_8O_5N_4$ requires C, 57·6; H, 6·5; N, 16·8%), and a *methiodide*, precipitated from acetone by ether, m. p. 203° (Found: C, 44·7; H, 7·3; N, 4·8; I, 43·6. $C_{11}H_{22}NI$ requires C, 44·7; H, 7·5; N, 4·8; I, 43·05%).

When dissolved in ethanol (30 c.c.) and neutralised with concentrated hydrochloric acid, the methine base (1 g.) was reduced at N.T.P. over palladised charcoal within 20 min. Isolation in the normal manner gave the dihydro-base (0·8 g.), b. p. 66°/9 mm., which formed a *picrate*, crystallising from ethanol in yellow needles, m. p. 106° (Found: C, 49·6; H, 6·3; N, 14·1. $C_{10}H_{21}N,C_6H_3O_7N_3$ requires C, 50·0; H, 6·25; N, 14·6%), a *picrolonate*, fine yellow needles, m. p. 160°, from ethanol (Found: C, 57·6; H, 6·9; N, 16·5. $C_{10}H_{21}N,C_{10}H_8O_5N_4$ requires C, 57·3; H, 7·0; N, 16·7%), and a *methiodide*, prisms, m. p. 221°, from acetone–ethyl

acetate (Found : C, 44·7; H, 8·0; N, 3·9; I, 42·0. $C_{11}H_{24}NI$ requires C, 44·4; H, 8·1; N, 4·7; I, 42·8%).

When distilled, the residue from which the methine-base had originally been evaporated was obtained as a colourless oil (1—2·1 g.), b. p. 130°/10 mm., insoluble in water [Found : C, 74·1; H, 12·4; N, 8·8%; *M* (Rast), 310. $C_{20}H_{40}ON_2$ requires C, 74·0; H, 12·4; N, 8·6%; *M*, 324]. It formed a *dipicrate*, yellow prisms, m. p. 161°, from ethanol (Found : C, 49·4; H, 5·7; N, 14·3. $C_{20}H_{40}ON_2,2C_6H_3O_7N_3$ requires C, 49·1; H, 5·9; N, 14·3%), identical with a specimen prepared from the base before distillation. Other derivatives of the *diamino-ether* prepared were the *dipicrolonate*, yellow needles, m. p. 181°, from acetone (Found : C, 56·3; H, 6·6; N, 16·3. $C_{20}H_{40}ON_2,2C_{10}H_8O_5N_4$ requires C, 56·2; H, 6·8; N, 16·4%), and *distyphnate* (Found : N, 13·7. $C_{20}H_{40}ON_2,2C_6H_3O_8N_3$ requires N, 14·1%).

The diamino-ether (1·5 g.) was heated under reflux with 50% hydrobromic acid (10 c.c.) for ½ hour, and the solution then evaporated under reduced pressure. The solid residue of *bromoamine hydrobromide* crystallised from acetone in needles (2·1 g., 72%), m. p. 167° (Found : C, 38·1; H, 6·8; Br, 51·5. $C_{10}H_{20}NBr,HBr$ requires C, 38·1; H, 6·7; Br, 50·7%).

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