465. *Synthetic and Stereochemical Investigations of Reduced Cyclic Bases. Part V.* The Exhaustive Methylation of Some Partially Reduced Cyclic Bases.*

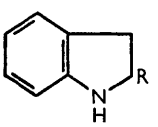
By H. Booth, F. E. King, and J. Parrick.

Decomposition of the *N*-methyl methohydroxides of 2 : 3-dihydro- and 2 : 3-dihydro-2-methyl-indole, of *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro- and *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-11-methyl-carbazole, and of *cis*-1 : 2 : 3 : 3a : 4 : 8b-hexahydro*cyclo*pent[*b*]indole, results in the expected unsaturated *ortho*-substituted *NN*-dimethylanilines. The hydrogenation of tetrahydro*cyclo*pent[*b*]indole to the required hexahydro-derivative occurred almost quantitatively with Raney nickel catalyst, but reduction of the 1 : 2 : 3 : 4-tetrahydrocarbazole under a variety of conditions gave only poor yields of hexahydrocarbazole.

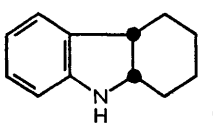
cis- and *trans*-1-Dimethylamino-2-*cyclo*hexyl*cyclo*hexane have been prepared by hydrogenation in acidic and alkaline media of the methine base from 1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, the structures of the products being confirmed by stereospecific syntheses from 2-*cyclo*hexyl*cyclo*hexanone.

Experiments on the synthesis and exhaustive methylation of several reduced cyclic bases described in Part I—IV have been extended to some incompletely saturated cyclic amines, more particularly those containing a 2 : 3-dihydroindole nucleus (I; R = H).

The dihydroindole system was considered by von Braun [1] to be one of the most resistant of the simpler cyclic amines to degradation by Hofmann exhaustive methylation, but no experimental results were presented in support of this conclusion. Fission of quaternary ammonium bases is a bimolecular elimination reaction,[2] and is therefore appreciably affected by substitution at the β-carbon atom, being impeded by the inductive effect of alkyl groups and assisted by the electromeric character of aromatic substituents at the β-



(I)



(II)

position. On theoretical grounds, therefore, the Hofmann degradation of 2 : 3-dihydroindoles should present no difficulties, and this has been confirmed by the formation of the expected *o*-dimethylaminostyrene from 1 : 1-dimethylindolinium hydroxide below 100° (experiments by K. G. Mason).

2 : 3-Dihydro-2-methylindole (I; R = Me) has twice been the subject of studies of this kind. In both cases [3,4] it is stated that distillation of the methohydroxide regenerates the dihydro-1 : 2-dimethylindole by expelling methanol, but the amine obtained was not identified by comparison with an authentic specimen. In the present investigation, a pure specimen of the *N*-methyl base (picrate, m. p. 128—130°) was prepared by distillation of 2 : 3-dihydro-1 : 2-dimethylindole methochloride. Hofmann fission of the amine methohydroxide proceeded smoothly at 70° and gave *NN*-dimethyl-*o*-propenylaniline (picrate, m. p. 168—170° compared with 158° recorded by von Braun *et al.*[4]), having ultraviolet absorption closely resembling that of *o*-dimethylaminostyrene. Hydrogenation of the unsaturated base over palladised charcoal gave *NN*-dimethyl-*o*-*n*-propylaniline giving a picrate of m. p. 176—178°, whereas for the picrate of the presumably

* Part IV, *J.*, 1954, 378.

[1] von Braun, *Ber.*, 1916, **49**, 2629; 1918, **51**, 96.

[2] Cf. Ingold, "Structure and Mechanism in Organic Chemistry," J. Bell and Sons, Ltd., London, 1953, p. 422.

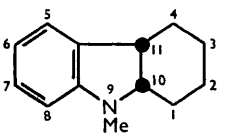
[3] Bamberger and Sternitzki, *Ber.*, 1893, **26**, 1291.

[4] von Braun, Heider, and Neumann, *Ber.*, 1916, **49**, 2613.

identical product obtained by Emde degradation of 2 : 3-dihydro-1 : 2-dimethylindole methochloride von Braun *et al.*[4] record m. p. 150°.

cis-Hexahydrocarbazole (II) is readily prepared by several methods,[5] and from the product obtained by reducing a large quantity of tetrahydrocarbazole with tin and hydrochloric acid Gurney, Perkin, and Plant [6] were able to isolate 1—2% of *trans*-hexahydrocarbazole. The configurations of the two isomers have not been rigidly proved but rest on the well-established generalisation that there is preferential formation of the less strained (*cis*) modification. Various methods for the preparation of hexahydrocarbazole have been re-examined in the hope of obtaining larger quantities of the *trans*-isomer for exhaustive methylation.

Hydrogenation of 1 : 2 : 3 : 4-tetrahydrocarbazole using catalysts of Raney nickel (60—120°) and copper chromite (160—170°) at 120 atm. initial pressure generally resulted in conversions into the hexahydro-derivative not exceeding 20%, thus broadly confirming the observations by Adkins and Coonradt.[7] The tetrahydro-*N*-methylcarbazole yielded 10% (with Raney nickel) and 15% (with copper chromite) of the corresponding hexahydrobase which however Adkins and Coonradt failed to obtain by hydrogenation of *N*-methylcarbazole. The more basic hexahydro-compound was isolated from the reaction mixture with dilute acid but even before recrystallisation it was apparent from m. p. determinations



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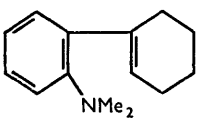

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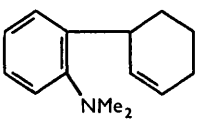

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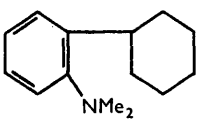

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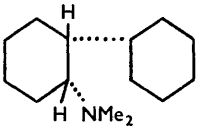

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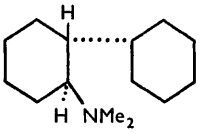


(VIII)

that the products were *cis*-base (II) with no significant content of the *trans*-isomeride. Reduction of tetrahydrocarbazole by nascent hydrogen, which in the case of tin and hydrochloric acid gave 1—2% of the *trans*-hexahydro-compound,[6] was therefore re-examined, and the possibility that the proportion of the two stereoisomers might be affected by pH led to the consideration of alkaline reducing agents. The reduction of carbazole to tetrahydrocarbazole by sodium and pentyl alcohol has been mentioned by a number of workers,[8,9] and it has been reported by Sanna [9] that prolonged reduction leads also to the formation of *cis*- and *trans*-hexahydrocarbazole. In our experiments, Sanna's method yielded only tetrahydrocarbazole; moreover, neither tetrahydrocarbazole nor tetrahydro-9-methylcarbazole gave any acid-soluble material after prolonged treatment with sodium and boiling pentyl alcohol. An attempted reduction of tetrahydro-9-methylcarbazole with lithium aluminium hydride was also unsuccessful (cf. Julian and Printy [10]). Further degradation studies were therefore restricted to the available *cis*-compounds.

Exhaustive methylation of *cis*-hexahydrocarbazole has been carried out by von Braun, Heider, and Neumann [4] who claimed that distillation of *cis*-hexahydro-9-methylcarbazole

[5] Graebe and Glaser, *Annalen*, 1872, **163**, 352; *Ber.*, 1872, **5**, 12; Schmidt and Sigwart, *Ber.*, 1912, **45**, 1779; Carrasco, *Gazzetta*, 1908, **38**, 303; Perkin and Plant, *J.*, 1924, 1503; Borsche, Bothe, and Witte, *Annalen*, 1908, **359**, 49; Clemo and Felton, *J.*, 1951, 700; Mears, Oakeshott, and Plant, *J.*, 1934. 272.

[6] Gurney, Perkin, and Plant, *J.*, 1927, 2676.

[7] Adkins and Coonradt, *J. Amer. Chem. Soc.*, 1941, **63**, 1563.

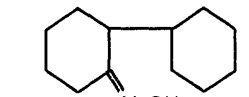
[8] Zanetti, *Ber.*, 1893, **26**, 2006; Schmidt and Schale, *Ber.*, 1907, **40**, 3225; Barclay, Campbell, and Gow, *J.*, 1946, 997.

[9] Sanna, *Gazzetta*, 1950, **80**, 572.

[10] Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206.

methohydroxide produced an oil consisting of the *N*-methyl base (III) contaminated with a small quantity of *o-cyclo*hex-1-enyl-*NN*-dimethylaniline (IV). In the present work, heating *cis*-hexahydro-9-methylcarbazole methohydroxide to *ca.* 90° caused decomposition exclusively to an unsaturated base, $C_{14}H_{19}N$, which was presumed to be (IV) or (V) and in the presence of palladised charcoal absorbed hydrogen to yield a dihydro-derivative (VI). The unsaturated base formed a methiodide only on prolonged refluxing with methyl iodide, thus exhibiting the usual low reactivity of *ortho*-substituted dimethylanilines.[11] The ultraviolet absorption spectrum of the unsaturated amine closely resembled that of *o*-vinyldimethylaniline which is entirely different from the spectra of dimethylanilines with large saturated *ortho*-alkyl groups.[12] There is thus little doubt that the constitution of the methine base is *o-cyclo*hex-1-enyl-*NN*-dimethylaniline (IV). This result has recently been confirmed by Masamune.[13]

The product (IV) failed to undergo dehydrogenation to 2-dimethylaminodiphenyl with either palladium–charcoal or chloranil. On the other hand, hydrogenation in acetic acid over a platinum catalyst gave 1-dimethylamino-2-*cyclo*hexyl*cyclo*hexane (VII). In view of the reduction conditions, the product is assumed to have the *cis*-configuration while the isomer prepared by hydrogenation at high temperature and pressure over Raney nickel is regarded as the *trans*-compound (VIII). The reduction products (VII) and (VIII) were independently synthesised from 2-*cyclo*hexyl*cyclo*hexanone oxime[14] (IX). Thus, hydrogenation of the oxime using Adams catalyst in acetic acid and methylation of the resulting primary amine gave a 1-dimethylamino-2-*cyclo*hexyl*cyclo*hexane, identical



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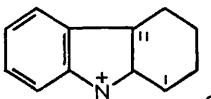
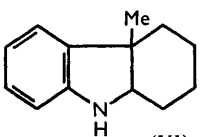


(X)

with the base (VII) which on the basis of the Auwers–Skita rule, confirmed in this case by the application of conformational analysis, is the *cis*-isomer. When the oxime was reduced with sodium and ethanol the methylated product was the *trans*-compound identical with (VIII).

Examination of a model of one of the feasible structures for *cis*-hexahydro-9-methylcarbazole methohydroxide (X) (cf. conformation of *cis*-octahydro-1-methylindole methohydroxide, Part IV) shows that the necessary conformational requirement for easy Hofmann fission is satisfied by elimination of either the axial 1-hydrogen atom or the hydrogen atom attached to $C_{(11)}$. Thus, in the exhaustive methylation, formation of base (IV) can occur either by elimination of a β-proton from $C_{(11)}$ or, alternatively, elimination from $C_{(1)}$ and subsequent shift of the double bond into conjugation. Elimination



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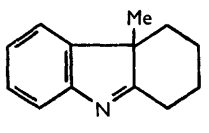

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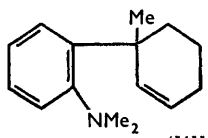


(XIII)

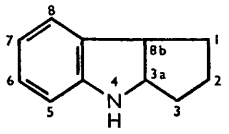
from $C_{(11)}$ is favoured on electronic grounds, since the hydrogen atom at $C_{(11)}$ is very acidic owing to the adjacent aromatic residue. Moreover, Weinstock and Bordwell[15] have shown that 3-phenyl*cyclo*hexene does not rearrange to 1-phenyl*cyclo*hexene under the conditions of a Hofmann elimination. It is therefore likely that the degradation proceeds by direct elimination of a proton from position **11**. However, it was of interest to discover whether, for any reason, elimination from $C_{(1)}$ was impossible. For this purpose, the

[11] Fahim and Fleifel, *J.*, 1951, 2761; Evans, Watson, and Williams, *J.*, 1939, 1348.
[12] Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838.
[13] Masamune, *Bull. Chem. Soc. Japan*, 1957, **30**, 491.
[14] Hückel and Doll, *Annalen*, 1936, **526**, 103.
[15] Weinstock and Bordwell, *J. Amer. Chem. Soc.*, 1955, **77**, 6706.

exhaustive methylation of *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-11-methylcarbazole (XI) was examined.

The base (XI) has been prepared by reducing tetrahydro-11-methylcarbazolenine (XII) with tin and hydrochloric acid.[16] This preparation was successfully repeated but the product was more conveniently prepared by reduction with sodium and ethanol; no indication of the presence of an isomer was obtained. Decomposition of *cis*-hexahydro-9 : 11-dimethylcarbazole methohydroxide at 115—120° gave a mixture consisting of an unsaturated base, presumably *NN*-dimethyl-*o*-(1-methyl*cyclo*hex-2-enyl)aniline (XIII), and 6—7% of hexahydro-9 : 11-dimethylcarbazole. The unsaturated base was even more inert to methyl iodide than was the methine (IV) derived from hexahydrocarbazole, being unchanged by methyl iodide for 6 hours at 100° in a sealed tube.

cis-1 : 2 : 3 : 3a : 4 : 8b-Hexahydro*cyclo*pent[*b*]indole (XIV) was first prepared by Plant and Rippon [17] by reduction of tetrahydro*cyclo*pent[*b*]indole (XV) electrolytically in acid solution. In the present investigation, the tetrahydro-compound was hydrogenated in dioxan over Raney nickel at 70—75° and 75 atmospheres' pressure,[18] theyield of base (XIV) being almost theoretical in remarkable contrast to the hydrogenation of tetrahydrocarbazole (see above). Reduction of tetrahydro*cyclo*pent[*b*]indole with tin and hydrochloric acid gave no hexahydro-compound, possibly owing to rapid oxidation of the unstable tetrahydro-compound [19] under these conditions. Ring scission of hexahydro-



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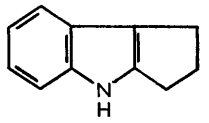

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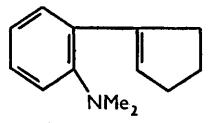

(XVI)

*cyclo*pent[*b*]indole occurred extremely readily, decomposition of the methohydroxide beginning at 35—45° and becoming vigorous at 80—100°. Formulation of the product as *NN*-dimethyl-*o*-*cyclo*pent-1-enylaniline (XVI) is based on ultraviolet absorption measurements which reveal the conjugated system as with the corresponding product from hexahydro-9-methylcarbazole methohydroxide, and on the profound change in the spectrum which follows reduction to *NN*-dimethyl-*o*-*cyclo*pentylaniline.

Experimental

2 : 3-*Dihydro*-1 : 1-*dimethylindolium Iodide*.—2 : 3-Dihydroindole [20] (7 g.) was converted by the usual procedure into 2 : 3-dihydro-1 : 1-dimethylindolium iodide (14 g., 87%). Crystallisation from ethanol gave colourless plates, m. p. 196—197° (decomp.) (von Braun and Neumann [21] give m. p. 195—196°). The *picrate* crystallised from aqueous methanol in yellow needles, m. p. 120—121° (Found: C, 51·0; H, 4·3; N, 14·7. $C_{16}H_{16}O_7N_4$ requires C, 51·1; H, 4·3; N, 14·9%).

Exhaustive Methylation of 2 : 3-*Dihydroindole* (with K. G. Mason).—The above methiodide (13·5 g.) was dissolved in water (125 c.c.) and shaken in the dark with silver oxide, freshly prepared from silver nitrate (13 g.) and sodium hydroxide (4·2 g.). When a sample of the filtered solution gave a negative test for iodide ions, the mixture was filtered and the filtrate evaporated under reduced pressure at 45—50°. When most of the water had been removed, the temperature was raised to 130°. The syrupy quaternary hydroxide decomposed at 80—110° yielding a distillate of *o*-dimethylaminostyrene (5·1 g., 71%), b. p. 101°/25 mm. (Seeley, Yates, and Noller [22] record b. p. 78—80°/3 mm.), n_D^{25} 1·5602 (Found: C, 81·5; H, 8·6; N, 9·3. Calc.

[16] Plancher, Cecchetti, and Ghigi, *Gazetta*, 1929, **59**, 334.
[17] Plant and Rippon, *J.*, 1928, 1906.
[18] Cf. Heseltine and Brooker, U.S.P. 2,636,035/1953.
[19] Cf. Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2196; Witkop, Patrick, and Rosenblum, *ibid.*, p. 2641.
[20] Barltrop, King, and Walley, *J.*, 1945, 277.
[21] von Braun and Neumann, *Ber.*, 1916, **49**, 1283.
[22] Seeley, Yates, and Noller, *J. Amer. Chem. Soc.*, 1951, **73**, 772.

for $C_{10}H_{13}N$: C, 81·6; H, 8·9; N, 9·5%), $\lambda_{max.}$ 202, 234, 257 (infl.), and 309 mμ (ε 15,340, 16,990, 8860, and 2380 respectively in EtOH). The base gave the *picrate* (from ethanol), prisms, m. p. 116—117° (Found: C, 50·9; H, 4·1; N, 14·9. $C_{16}H_{16}O_7N_4$ requires C, 51·1; H, 4·3; N, 14·9%), *picrolonate*, needles, m. p. 158° (decomp.) (from ethanol) (Found: C, 58·3; H, 5·2; N, 17·0. $C_{20}H_{21}O_5N_5$ requires C, 58·4; H, 5·1; N, 17·0%), and *methiodide*, plates (from methanol), m. p. 186—187° (decomp.) (Found: C, 45·5; H, 5·4. $C_{11}H_{16}NI$ requires C, 45·7; H, 5·6%).

o-*Ethyl*-NN-*dimethylaniline*.—*o*-Dimethylaminostyrene (3·85 g.) was hydrogenated in the form of its hydrochloride in methanol 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. *o*-Ethyl-*NN*-dimethylaniline (2·1 g., 54%) was thus obtained as an oil, b. p. 81·5—82°/14 mm. (von Braun and Neumann [21] record b. p. 87—88°/19 mm.), n_D^{21} 1·5177 (Found: C, 80·7; H, 10·0; N, 9·3. Calc. for $C_{10}H_{15}N$: C, 80·5; H, 10·1; N, 9·4%), $\lambda_{max.}$ 208 and 247 mμ (ε 14,210 and 4780 respectively in EtOH) (cf. *o*-methyl-*NN*-dimethylaniline [12]). It gave a picrate (from ethanol), long prisms, m. p. 149—150° (von Braun and Neumann,[21] m. p. 145°) (Found: C, 50·5; H, 4·9; N, 14·7. Calc. for $C_{16}H_{18}O_7N_4$: C, 50·8; H, 4·8; N, 14·8%), *picrolonate* (from ethanol), prisms, m. p. 165° (decomp.) (Found: C, 58·0; H, 5·5; N, 16·6. $C_{20}H_{23}O_5N_5$ requires C, 58·1; H, 5·6; N, 16·9%), and *hydriodide* (from acetone–ethyl acetate), plates, m. p. 154—155° (Found: C, 43·3; H, 5·7. $C_{10}H_{16}NI$ requires C, 43·3; H, 5·8%). The *methiodide*, m. p. 196—197°, was formed very slowly from the base and methyl iodide (von Braun and Neumann [21] record m. p. 162—164°) (Found: C, 45·1; H, 6·2. $C_{11}H_{18}NI$ requires C, 45·4; H, 6·2%).

2 : 3-*Dihydro*-1 : 1 : 2-*trimethylindolium Iodide*.—2 : 3-Dihydro-2-methylindole [23] (4·5 g.) was heated on a water-bath with methyl iodide (11 g.) and aqueous sodium hydroxide (1·4 g. in 15 c.c. of water). After 2 hr., the solution was cooled and extracted with chloroform. The dried ($MgSO_4$) extracts were concentrated and then poured into ether, the methiodide (8·5 g., 86%) being precipitated. Crystallisation from methanol–ethyl acetate gave colourless prisms, m. p. 208—210° (Bamberger and Sternitzki [3] record m. p. 211°; von Braun, Heider, and Neumann [4] record m. p. 202°; Adkins and Coonradt [7] record m. p. 208—210°) (Found: C, 45·9; H, 5·3. Calc. for $C_{11}H_{16}NI$: C, 45·7; H, 5·5%).

2 : 3-*Dihydro*-1 : 2-*dimethylindole*.—The above methiodide (8 g.) was dissolved in water and treated with silver chloride, freshly prepared from silver nitrate (12 g.). The mixture was kept overnight, then filtered and evaporated under reduced pressure at 40—50°. When most of the water had been removed, the syrupy residue was decomposed by heating it at 220°. Extraction of the distillate with ether yielded 2 : 3-*dihydro*-1 : 2-*dimethylindole* (2·9 g., 71%), b. p. 100—105° (bath-temp.)/25 mm., n_D^{18} 1·5505 (Found: C, 81·5; H, 8·7. $C_{10}H_{13}N$ requires C, 81·6; H, 8·8%). The *picrate* crystallised from ethanol in plates, m. p. 128—130° (Found: C, 50·8; H, 4·3. $C_{16}H_{16}O_7N_4$ requires C, 51·1; H, 4·3%). The *picrolonate* crystallised from ethanol in prisms, m. p. 167—168° (Found: C, 58·5; H, 5·2. $C_{20}H_{21}O_5N_5$ requires C, 58·4; H, 5·1%). The methiodide, prepared by refluxing an ethereal solution of the base with methyl iodide for 15 hr., had m. p. and mixed m. p. 208—210°.

Exhaustive Methylation of 2 : 3-*Dihydro*-2-*methylindole*.—This was carried out as described for 2 : 3-dihydroindole. The methohydroxide from 2 : 3-dihydro-1 : 1 : 2-trimethylindolinium iodide (6·5 g.) decomposed at 70°, yielding NN-*dimethyl*-o-*propenylaniline* (2·8 g., 77%), b. p. 95—98° (bath-temp.)/15 mm., n_D^{19} 1·5556 (Found: C, 81·8; H, 9·2. $C_{11}H_{15}N$ requires C, 82·1; H, 9·3%), $\lambda_{max.}$ 202, 233, and 303 mμ (ε 16,130, 15,880, and 2136 respectively in EtOH). The base gave a *picrate*, prisms, m. p. 168—170° (from ethanol) (von Braun *et al.*[4] record m. p. 158° for the picrate of the exhaustive methylation product) (Found: C, 52·5; H, 4·8. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6%), and a *picrolonate*, leaflets, m. p. 165—166° (from ethanol) (Found: C, 59·5; H, 5·7. $C_{21}H_{23}O_5N_5$ requires C, 59·3; H, 5·4%).

NN-*Dimethyl*-o-n-*propylaniline*.—*NN*-Dimethyl-*o*-propenylaniline (1·3 g.) was hydrogenated in ethanol (20 c.c.) over palladised charcoal at room temperature and pressure (1·15 mol. absorbed). After filtration, the solution was evaporated and distilled, giving NN-*dimethyl*-o-n-*propylaniline* (1·1 g.), b. p. 87—90° (bath-temp.)/15 mm., n_D^{16} 1·5137 (Found: C, 81·2; H, 10·5. $C_{11}H_{17}N$ requires C, 81·0; H, 10·4%), $\lambda_{max.}$ 208 and 248 mμ (ε 13,640 and 4690 respectively in EtOH). The *picrate* crystallised from ethanol in prisms, m. p. 176—178° (Found: C, 52·2; H, 5·1. $C_{17}H_{20}O_7N_4$ requires C, 51·2; H, 5·1%), and the *picrolonate* in rods, m. p. 136—138° (Found: C, 58·8; H, 5·5. $C_{21}H_{25}O_5N_5$ requires C, 59·1; H, 5·85%).

[23] Clarke and Pope, *J.*, 1904, **85**, 1331.

Catalytic Reduction of 1 : 2 : 3 : 4-*Tetrahydrocarbazole*.—The following indicates the standard procedure when using Raney nickel. Tetrahydrocarbazole (20 g.) in methanol (50 c.c.) was hydrogenated at an initial pressure of 120 atm.; and after removal of the catalyst and solvent, the product was treated with ether and dilute hydrochloric acid. Evaporation of the ethereal solution gave tetrahydrocarbazole, m. p. 118—119°, and when the acid extract was basified 1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, m. p. 98—99°, was precipitated. If the reaction time exceeded 10 hr. basification of the acidic extracts produced an uncrystallisable oil, which was not further investigated.

1 : 2 : 3 : 4-*Tetrahydro*-9-*methylcarbazole and its Catalytic Reduction*.—Tetrahydrocarbazole (45 g.) was methylated by the procedure used by Gilman and Spatz [24] for carbazole. The tertiary base (37 g., 76%) crystallised from methanol in plates, m. p. 49—50° (Perkin and Plant [25] record m. p. 50°).

The reduction procedure used was similar to that indicated for tetrahydrocarbazole. The products were *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-9-methylcarbazole, m. p. 50—51° (Gurney and Plant [26] record m. p. 50°), and unchanged tetrahydro-compound, m. p. 49—50°.

cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-9-*methylcarbazole* (cf. Stevens and Tucker [27]).—*cis*-Hexahydrocarbazole (1·7 g.) was dissolved in a mixture of acetone (10 c.c.) and 66% potassium hydroxide solution (10 c.c.). Dimethyl sulphate (5 g.) was added in 10 portions, with shaking, during 15 min. The mixture was then shaken for a further 30 min., then poured into water. Isolation by ether-extraction yielded *cis*-hexahydro-9-methylcarbazole (0·6 g.), b. p. 140—145° (bath-temp.)/12 mm. (Perkin and Plant [5] and von Braun and Schörnig [28] give b. p. 144°/15 mm.). The picrate formed leaflets, m. p. 145—146° [Perkin and Plant [5] give m. p. 143—144° (decomp.)] (Found: C, 54·8; H, 4·8; N, 13·5. Calc. for $C_{19}H_{20}O_7N_4$: C, 54·7; H, 4·6; N, 13·5%). The methiodide crystallised from ethanol in square prisms, m. p. and mixed m. p. with a sample prepared by the method of von Braun *et al.*,[4] 192—193° (von Braun *et al.* record m. p. 187°) (Found: C, 51·1; H, 6·1; N, 4·3. Calc. for $C_{14}H_{20}NI$: C, 51·2; H, 6·3; N, 4·3%). The *methopicrate* crystallised from ethanol in needles, m. p. 168—170° (Found: C, 56·1; H, 5·1. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1%).

Exhaustive Methylation of cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydrocarbazole*.—This was carried out as described for 2 : 3-dihydroindole. The methohydroxide from *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-9-methylcarbazole methiodide [4] (42 g., m. p. 192—193°) was decomposed at 85—90°, yielding o-cyclo*hex*-1-*enyl*-NN-*dimethylaniline* (20·1 g., 78%), b. p. 141—142°/14 mm., 275°/767 mm. (Siwoloboff), n_D^{21} 1·5605 (Found: C, 83·7; H, 9·1; N, 6·9. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5; N, 7·0%), $\lambda_{max.}$ 210, 226, and 260 mμ (ε 11,300, 14,400, and 5600 respectively in EtOH). The base afforded a *picrate* (from ethanol), leaflets, m. p. 164—166° (decomp.) (Found: C, 55·7; H, 5·4; N, 13·1. $C_{20}H_{22}O_7N_4$ requires C, 55·8; H, 5·1; N, 13·0%), *methiodide* (formed very slowly), needles (from acetone), m. p. 171—172° (Found: C, 52·8; H, 6·5. $C_{15}H_{22}NI$ requires C, 52·5; H, 6·4%), and *methopicrate*, plates (from ethanol), m. p. 168·5—169·5° (Found: C, 57·1; H, 5·4. $C_{21}H_{24}O_7N_4$ requires C, 56·8; H, 5·4%).

o-cyclo*Hexyl*-NN-*dimethylaniline*.—*o-cyclo*Hex-1-enyl-*NN*-dimethylaniline (4 g.) was hydrogenated in ethanol (45 c.c.) over 5% palladised charcoal (2 g.) during 12 hr. at room temperature. Working up in the usual way gave o-cyclo*hexyl*-NN-*dimethylaniline* (3·1 g., 75%), b. p. 145—148° (bath-temp.)/15 mm., n_D^{22} 1·5256 (Found: C, 82·9; H, 10·6. $C_{14}H_{21}N$ requires C, 82·8; H, 10·4%), $\lambda_{max.}$ 209 mμ (ε 9350). The *picrate* crystallised from ethanol in leaflets, m. p. 162—164° (Found: C, 55·6; H, 5·6; N, 13·1. $C_{20}H_{24}O_7N_4$ requires C, 55·6; H, 5·6; N, 13·0%). A mixed m. p. with *o-cyclo*hex-1-enyl-*NN*-dimethylaniline picrate was at 141—152°.

cis-1-*Dimethylamino*-2-cyclo*hexyl*cyclo*hexane*.—The above base (1 g.) was hydrogenated in glacial acetic acid (25 c.c.) over Adams catalyst (300 mg.) at 70° and normal pressure (3·3 mols. absorbed in 12 hr.). After filtration, the liquid was evaporated under reduced pressure to remove acetic acid and then basified. Extraction with ether yielded cis-1-*dimethylamino*-2-cyclo*hexyl*cyclo*hexane*, b. p. 145—148° (bath-temp.)/12 mm., n_D^{18} 1·4964 (Found: C, 80·5; H, 12·9. $C_{14}H_{27}N$ requires C, 80·3; H, 13·0%). The *picrate* crystallised from ethanol as

[24] Gilman and Spatz, *J. Org. Chem.*, 1952, **17**, 860.
[25] Perkin and Plant, *J.*, 1921, 1825.
[26] Gurney and Plant, *J.*, 1927, 1318.
[27] Stevens and Tucker, *J.*, 1923, 2140.
[28] von Braun and Schörnig, *Ber.*, 1925, **58**, 2156.

needles, m. p. and mixed m. p. (see below) 110—111° (Found: C, 55·1; H, 6·5. $C_{20}H_{30}O_7N_4$ requires C, 54·8; H, 6·8%).

trans-1-*Dimethylamino*-2-cyclo*hexyl*cyclo*hexane*.—*o-cyclo*Hex-1-enyl-*NN*-dimethylaniline (2 g.) was hydrogenated in methanol (30 c.c.) over Raney nickel at 200—220°/180 atm. for 20 hr. After filtration, the solution was evaporated and the residue dissolved in ether. The basic material was extracted into dilute hydrochloric acid and recovered by basification and extraction with ether. 1-*Dimethylamino*-2-cyclo*hexyl*cyclo*hexane* (0·9 g.) was thus obtained as an oil, b. p. 150—154° (bath-temp.)/15 mm., n_D^{18} 1·4902 (Found: C, 80·5; H, 12·8%). The *picrate* crystallised from ethanol in needles, m. p. and mixed m. p. (see below), 167—168° (Found: C, 54·7; H, 6·8%).

2-*Dimethylaminodiphenyl*.—2-Aminodiphenyl was prepared from 2-nitrodiphenyl [29] by 6 hours' heating in ethanol with tin and concentrated hydrochloric acid (cf. Scarborough and Waters,[30] who used stannous chloride). The distilled base (5 g.) was methylated with dimethyl sulphate according to the method of Popkin, Perretta, and Selig.[31] The methylated bases were isolated by ether-extraction. After evaporation of the ethereal extracts, the residue was heated with acetic anhydride (15 c.c.) under reflux for 1 hr. The solution was cooled, then boiled with water (25 c.c.) for a few minutes to decompose excess of anhydride. Acetylated material was extracted into ether, and the tertiary base was recovered from the aqueous solution by basification and ether-extraction. This gave 2-dimethylaminodiphenyl (1·5 g., 26% based on the 2-aminodiphenyl), b. p. 146—148°/12 mm., n_D^{14} 1·6070 (Found: C, 85·3; H, 7·7. Calc. for $C_{14}H_{15}N$: C, 85·3; H, 7·6%) (Popkin *et al.*[31] record b. p. 118—120°/2·5 mm., n_D^{20} 1·6052—1·6058 and 1·6046—1·6050). The *picrate* crystallised from ethanol in prisms, m. p. 190—191° (decomp.) (Found: C, 56·3; H, 4·4. $C_{20}H_{18}O_7N_4$ requires C, 56·3; H, 4·2%). The *methiodide* (formed slowly) crystallised from acetone–ethyl acetate in prisms, m. p. 178—179° [Hey and Jackson [32] record m. p. 228° (decomp.)] (Found: C, 53·4; H, 5·4. $C_{15}H_{18}NI$ requires C, 53·1; H, 5·3%).

2-cyclo*Hexyl*cyclo*hexanone Oxime*.—2-*cyclo*Hexyl*cyclo*hexanone [33,34] (25 g.) with hydroxylamine hydrochloride (20 g.) and sodium hydroxide (11·5 g.) in aqueous ethanol formed the oxime (24 g., 89%), m. p. 99—102° (Wallach [33] records m. p. 100°; Hückel and Doll [14] give m. p. 101—102° and m. p. 103—104° for the isomeric oximes).

trans-2-cyclo*Hexyl*cyclo*hexylamine*.—The above oxime (6 g.) was reduced in refluxing ethanol (100 c.c.) by sodium (10 g.) added during 1½ hr. After acidification with dilute hydrochloric acid, the solution was concentrated to 25 c.c. and kept overnight at 0°. The base hydrochloride was filtered off at the pump, dissolved in water, and basified with excess of aqueous ammonia. trans-2-cyclo*Hexyl*cyclo*hexylamine*, recovered by extraction with ether, had b. p. 145—148° (bath-temp.)/11 mm., n_D^{17} 1·4970 (Found: C, 79·4; H, 12·2; N, 7·9. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7; N, 7·8%). The benzoyl derivative crystallised from aqueous ethanol in needles, m. p. 157—158° (Hückel and Doll [14] record m. p. 157—158°). The *hydrochloride* crystallised from acetone–ether in hexagonal plates, m. p. 215—216° (Found: C, 66·2; H, 11·2. $C_{12}H_{24}NCl$ requires C, 66·2; H, 11·0%).

trans-1-*Dimethylamino*-2-cyclo*hexyl*cyclo*hexane*.—*trans*-2-*cyclo*Hexyl*cyclo*hexylamine (1 g.), 40% aqueous formaldehyde (1·5 c.c.), and 95% formic acid (1 g.) were heated on a water-bath for 5 hr. The tertiary base (0·7 g.) was isolated by ether-extraction of the basified solution and had b. p. 140—145° (bath-temp.)/10 mm., n_D^{18} 1·4893 (Found: C, 80·6; H, 12·5%). The picrate crystallised from ethanol in needles, m. p. 167—168°.

cis-2-cyclo*Hexyl*cyclo*hexylamine*.—2-*cyclo*Hexyl*cyclo*hexanone oxime (4 g.) was hydrogenated in glacial acetic acid (30 c.c.) over Adams catalyst (150 mg.) at room temperature and pressure. Absorption of hydrogen was slow and the catalyst was added in 3 portions of 50 mg. each at intervals of 24 hr. After filtration, the solution was heated to remove acetic acid, and the crude amine was isolated by ether-extraction of the basified solution. Dry hydrogen chloride was bubbled through the ethereal solution, cis-2-cyclo*hexyl*cyclo*hexylamine hydrochloride* (3·5 g., 78%) being precipitated. Crystallisation from acetone–ether gave needles, m. p.

[29] Bell, Kenyon, and Robinson, *J.*, 1926, 1239.
[30] Scarborough and Waters, *J.*, 1927, 89.
[31] Popkin, Perretta, and Selig, *J. Amer. Chem. Soc.*, 1944, **66**, 833.
[32] Hey and Jackson, *J.*, 1934, 645.
[33] Wallach, *Annalen*, 1911, **381**, 95.
[34] Rapson, *J.*, 1941, 15.

166—168° (Found: C, 65·9; H, 11·0%). The hydrochloride was converted in the usual way into the base, b. p. 138—141° (bath-temp.)/12 mm., n_D^{19} 1·4976 (not analysed owing to rapid carbonate formation). The *benzoyl derivative* crystallised from ethanol in plates, m. p. 136—137° (Found: C, 79·7; H, 9·3. $C_{19}H_{27}ON$ requires C, 80·0; H, 9·5%).

cis-1-*Dimethylamino*-2-cyclo*hexyl*cyclo*hexane*.—The above primary base (0·6 g.), methylated as was its *trans*-isomer, gave the tertiary *base*, b. p. 144—148° (bath-temp.)/10 mm., n_D^{20} 1·4960 (Found: C, 80·6; H, 12·8%). The picrate crystallised from ethanol in needles, m. p. 110—111°.

cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-11-*methylcarbazole*.—(i) (cf. Plancher, Cecchetti, and Ghigi [16]) 1 : 2 : 3 : 4-Tetrahydro-11-methylcarbazolenine [35] (65 g.), ethanol (120 c.c.), concentrated hydrochloric acid (260 c.c.), and granulated tin (130 g.) were heated under reflux on a water-bath for 5 hr. After filtration through glass wool, the hot mixture was allowed to cool; the base chlorostannate crystallised and was filtered off at the pump. After decomposition of the chlorostannate with 40% sodium hydroxide solution (600 c.c.) and repeated ether-extraction, the base was obtained as an oil (40 g.), b. p. 144—146°/14 mm. An attempt to purify it through the hydrochloride, m. p. 217—220° (Plancher *et al.*[16] record m. p. 220°), failed owing to the decomposition of the hydrochloride. The base (40 g.) was heated under reflux with acetic anhydride (100 c.c.) for 1 hr. The solution was basified and ether-extracted, yielding cis-9-*acetyl*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-11-*methylcarbazole*. Crystallisation from ethanol gave colourless prisms (39 g.), m. p. 87—88° (Found: C, 78·7; H, 8·6. $C_{15}H_{19}ON$ requires C, 78·6; H, 8·3%). The recrystallised acetyl compound was hydrolysed with boiling 10% sodium hydroxide solution (200 c.c.) for 2 hr. Extraction with ether then gave pure *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-11-methylcarbazole (27·5 g., 42%), b. p. 144—146°/14 mm., n_D^{17} 1·5700 (Found: C, 83·6; H, 9·3. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1%). The *benzoyl derivative* crystallised from aqueous ethanol or ethyl acetate in prisms, m. p. 96—97° (Found: C, 82·4; H, 7·4. $C_{20}H_{21}ON$ requires C, 82·5; H, 7·2%).

(ii) 1 : 2 : 3 : 4-Tetrahydro-11-methylcarbazolenine (8 g.), in ethanol (350 c.c.), was gently boiled under reflux while sodium (30 g.) was added during 1½ hr. The cooled solution was acidified with dilute hydrochloric acid and then heated under reduced pressure to remove ethanol. Basification with ammonia and ether-extraction gave 1 : 2 : 3 : 4 : 10 : 11-hexahydro-11-methylcarbazole (7·3 g., 90%), b. p. 140—143°/10 mm., n_D^{17} 1·5700. The acetyl derivative, prepared in 96% yield, had m. p. and mixed m. p. with the acetyl compound prepared as above, 86·5—88°.

cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-9 : 11-*dimethylcarbazole*.—Dimethyl sulphate (5 c.c.) was added dropwise to a stirred mixture of hexahydro-11-methylcarbazole (1 g.), acetone (10 c.c.), and 66% potassium hydroxide solution (10 c.c.). Then the mixture was stirred for 1 hr. and poured into water (10 c.c.). Extraction with ether yielded cis-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-9 : 11-*dimethylcarbazole* (0·4 g.), b. p. 145—149° (bath-temp.)/10 mm., n_D^{19} 1·5049 (Found: C, 83·3; H, 9·4. $C_{14}H_{19}N$ requires C, 83·6; H, 9·5%). The *methiodide*, prepared by refluxing the base and methyl iodide in ether for 20 hr., crystallised from acetone–ethyl acetate in prisms, m. p. 192—193° (Found: C, 52·4; H, 6·3. $C_{15}H_{22}NI$ requires C, 52·5; H, 6·4%). The *methopicrate* crystallised from ethanol in orange prisms, m. p. 155—156° (Found: C, 56·1; H, 4·9. $C_{21}H_{24}O_7N_4$ requires C, 56·1; H, 4·7%).

cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-9 : 9 : 11-*trimethylcarbazolium Iodide*.—This compound was most conveniently prepared from hexahydro-11-methylcarbazole (27·5 g.), acetone (50 c.c.), 40% potassium hydroxide solution (21 c.c.), and excess of methyl iodide heated under reflux for 12 hr. After evaporation to remove methyl iodide and acetone, the mixture was cooled and filtered. Recrystallisation of the solid from water or ethanol–ether gave the pure methiodide (30 g., 59%) as prisms, m. p. and mixed m. p. with a sample prepared from the tertiary base, 192—193°.

Exhaustive Methylation of cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-11-*methylcarbazole*.—This was carried out as described for 2 : 3-dihydroindole. The methohydroxide from the above methiodide (18 g.) decomposed at 115—120°. When the temperature was raised further, the product distilled as an oil (11·3 g.), b. p. 138—140°/14 mm. The oil (1·2 g.) was heated with excess of methyl iodide under reflux for 3 days. After evaporation, dry ether was added and the precipitated solid (0·13 g.) was removed. Crystallisation from ethanol–ether gave colourless prisms of 1 : 2 : 3 : 4 : 10 : 11-hexahydro-9 : 9 : 11-trimethylcarbazolium iodide, m. p. and

[35] Pausacker, *J.*, 1950, 621.

mixed m. p. 190—192°. Evaporation of the ethereal filtrate gave an oil (1 g.) which was converted into the picrate. Crystallisation from aqueous ethanol gave NN-*dimethyl*-o-(1-*methyl*cyclo*hex*-2-*enyl*)*aniline picrate* as yellow needles, m. p. 124—125° (Found: C, 56·7; H, 5·5; N, 12·2. $C_{21}H_{24}O_7N_4$ requires C, 56·8; H, 5·4; N, 12·6%). Decomposition of the picrate with 10% lithium hydroxide solution, followed by extraction with ether, gave the *base*, b. p. 139—140°/14 mm., n_D^{20} 1·5400 (Found: C, 83·4; H, 9·6. $C_{15}H_{21}N$ requires C, 83·7; H, 9·8%), $\lambda_{max.}$ 209 mμ (ε 11,430 in EtOH).

NN-*Dimethyl*-o-(1-*methyl*cyclo*hexyl*)*aniline*.—The above unsaturated base (1·2 g.) was completely hydrogenated in 6 hr. in ethanol (10 c.c.) over palladised charcoal at room temperature and pressure. Isolation in the usual way gave NN-*dimethyl*-o-(1-*methyl*cyclo*hexyl*)-*aniline*, b. p. 135—140° (bath-temp.)/12 mm., n_D^{18} 1·5331 (Found: C, 82·8; H, 10·5. $C_{15}H_{23}N$ requires C, 83·0; H, 10·6%), $\lambda_{max.}$ 210 mμ (ε 9485 in EtOH). The *picrate* crystallised from aqueous ethanol in prisms, m. p. 160—161° (Found: C, 56·8; H, 5·8. $C_{21}H_{26}O_7N_4$ requires C, 56·7; H, 5·8%).

cis - 1 : 2 : 3 : 3*a* : 4 : 8*b* - *Hexahydro*cyclo*pent*[b]*indole* (Heseltine and Brooker [18]) 1 : 2 : 3 : 4-Tetrahydro*cyclo*pent[*b*]indole [36] (21 g.) in dioxan (80 c.c.) was reduced for 24 hr. at 70—75° with hydrogen at an initial pressure of 75 atm. and in the presence of Raney nickel. The mixture was filtered and evaporated under reduced pressure to remove dioxan. The residue was dissolved in ether and extracted several times with dilute sulphuric acid. The crude base was recovered by ether-extraction of the basified extracts. *cis*-1 : 2 : 3 : 3a : 4 : 8b-Hexahydro*cyclo*pent[*b*]indole was thus isolated as an oil (20 g., 94%), b. p. 131—134°/13 mm. (Plant and Rippon [17] record b. p. 152°/16 mm; Heseltine and Brooker [18] give b. p. 98—100°/10 mm.). The picrate, acetyl derivative, and benzoyl derivative had m. p. 157—159°, 77—79°, and 86—87° respectively (Plant and Rippon [17] give m. p. 159°, 78°, and 86° respectively).

cis-1 : 2 : 3 : 3*a* : 4 : 8*b*-*Hexahydro*-4-*methyl*cyclo*pent*[b]*indole*.—Dimethyl sulphate (50 g.) was added dropwise during 1 hr. to a stirred mixture of the above base (20 g.), acetone (100 c.c.), and 10% sodium hydroxide solution (100 c.c.). The mixture was stirred for a further 30 min., evaporated to remove acetone, and then extracted several times with ether. Evaporation of the dried ethereal extracts yielded the crude tertiary base, which was heated under reflux with acetic anhydride (30 c.c.) for 30 min. The solution was evaporated under reduced pressure to remove excess of anhydride, treated with sodium hydrogen carbonate solution, and extracted with ether. The ethereal solution was shaken with dilute hydrochloric acid, and the tertiary base was recovered from the acid extract in the usual way. *cis*-1 : 2 : 3 : 3a : 4 : 8b-Hexahydro-4-methyl*cyclo*pent[*b*]indole was thus isolated as a colourless oil (6·2 g., 28%), b. p. 127—129°/10 mm., n_D^{17} 1·5668 (Found: C, 82·8; H, 8·8. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7%). The *picrate* crystallised from ethanol in yellow plates, m. p. 121—122° (Found: C, 54·0; H, 4·7. $C_{18}H_{18}O_7N_4$ requires C, 53·8; H, 4·5%) (Plant and Rippon [17] record b. p. 136—137°/15 mm., picrate, m. p. 116°).

The aqueous solution remaining after the first ether-extraction in the above procedure was treated with concentrated aqueous potassium iodide: the base methiodide was precipitated. Crystallisation from acetone gave *cis*-hexahydro-4 : 4-dimethyl*cyclo*pent[*b*]indolium iodide as prisms (23 g.), m. p. 187—189° (Found: C, 49·5; H, 5·7. Calc. for $C_{13}H_{18}NI$: C, 49·6; H, 5·8%) (Plant and Rippon [17] give m. p. 189°). The quaternary *picrate* crystallised from ethyl acetate–ethanol in elongated prisms, m. p. 133—134° (Found: C, 54·9; H, 4·9. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8%).

Exhaustive Methylation of cis-1 : 2 : 3 : 3*a* : 4 : 8*b*-*Hexahydro*cyclo*pent*[b]*indole*—This was carried out as described for 2 : 3-dihydroindole. Decomposition of the methohydroxide from 23 g. of methiodide commenced at 35—45° and was completed at 100—110°. Extraction with ether gave NN-*dimethyl*-o-cyclo*pent*-1-*enylaniline* (10·9 g., 80%), b. p. 125—126°/10 mm., n_D^{19} 1·5668 (Found: C, 83·4; H, 9·2. $C_{31}H_{17}N$ requires C, 83·4; H, 9·2%), $\lambda_{max.}$ 205, 231, and 301 mμ (ε 17,220, 16,210, and 1926 respectively in EtOH). The *picrate* crystallised from ethanol in plates, m. p. 152—153° (Found: C, 54·8; H, 4·9. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8%).

NN-*Dimethyl*-o-cyclo*pentylaniline*.—The exhaustive methylation product (3 g.) was hydrogenated in ethanol (50 c.c.) over 10% palladised charcoal (1 g.) at room temperature and

[36] Perkin and Plant, *J.*, 1923, **123**, 3242.

pressure, 1·1 mols. being absorbed in 1 hr. The solution was filtered, evaporated, and finally distilled, giving NN-*dimethyl*-o-cyclo*pentylaniline* (2·1 g., 69%), b. p. 123—124°/9 mm., n_D^{21} 1·5400 (Found: C, 82·2; H, 10·3. $C_{13}H_{19}N$ requires C, 82·5; H, 10·1%), $\lambda_{max.}$ 211 and 249 mμ (ε 13,790 and 4860 respectively in EtOH). The *picrate* crystallised from ethyl acetate–ethanol in elongated prisms, m. p. 133—134° (Found: C, 54·9; H, 4·9. $C_{19}H_{22}O_7N_4$ requires C, 54·5; H, 5·3%).

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