The Exhaustive Methylation of cis- and trans-Hexahydrocarbazoles[1]

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It has been established by King, Baltrop and Walley[2] that in the exhaustive methylation, *cis*-octahydroindole undergoes a fission of the N-C_8 bond to yield 1-(2-dimethylaminoethyl)-cyclohexene, while the corresponding *trans*-base produces no compound expected from the normal opening of the pyrrolidine ring. The methine $C_{10}H_{19}N$ (I) resulting from the *trans*-base was suggested to be II[3] and to be produced by a Wagner-Meerwein type rearrangement (a) of the carbonium ion (III) formed by ring-scission at C_8 (Fig. 1). However, the structure (II) was not verified experimentally. As it is desirable to investigate the behavior of similar compounds, the present author subjected *cis*- and *trans*-hexahydrocarbazoles to the exhaustive methylation. These bases may be regarded as analogs of octahydroindoles and are much more easily obtainable than *trans*-octahydroindole.

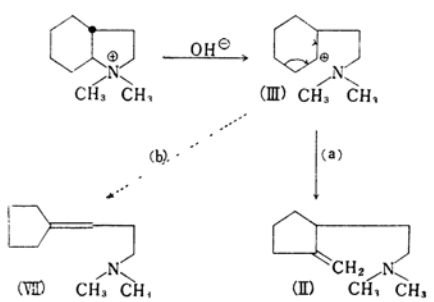
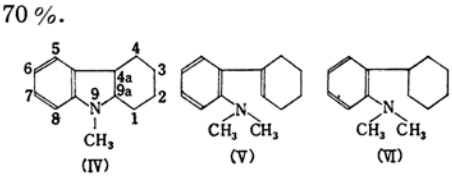


Fig. 1. The exhaustive methylation of *trans*-octahydro-N-methylindole methiodide.

Treatment of *cis*-hexahydrocarbazole and of its N-methyl-derivative (IV) with methyl iodide easily yielded the methiodide. Distillation of the compound obtained by treating an aqueous solution of the methiodide with silver oxide yielded an oily base, from which an unsaturated base $C_{14}H_{19}N$ (V) was isolated in a yield of 70%.



In order to determine its constitution the methine base (V) was subjected to

1) Part IX of "The Condensed Polynuclear Perhydro-Compounds Containing Nitrogen"; Part VIII, T. Masamune and M Koshi, This Bulletin, **30**, 307 (1957).

2) F. E. King, J. A. Baltrop and R. J. Walley, *J. Chem. Soc.*, **1945**, 277; B. Bailey, R. D. Haworth and J. McKenna, ibid., **1954**, 967.

3) F. E. King and H. Booth, ibid., **1954**, 3798.

Emde reduction. The resulting hydrocarbon gave δ-benzoylvaleric acid on oxidation and thus was found to be 1-phenylcyclohexene. Then, it follows that the product from the exhaustive methylation is 1-(*o*-dimethylaminophenyl)-cyclohexene (V). That the double bond in the cyclohexene ring is conjugated with the phenyl ring is concluded from the following fact. Comparison of the ultraviolet spectra of the methine base (V) and its dihydro-derivative (VI) with that of N-dimethyl-*o*-toluidine indicated that

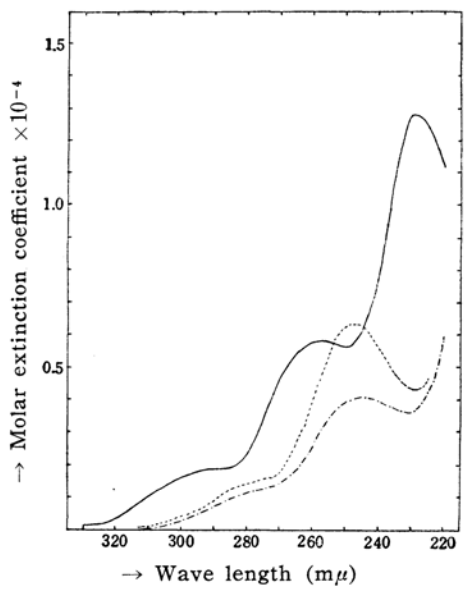


Fig. 2. Ultraviolet absorption spectra of *o*-toluidine derivatives.
Solvent: ethanol; conc. M×10⁻⁴
—— 1-(*o*-Dimethylaminophenyl)-cyclohexene (V)
- - - *o*-Dimethylaminophenylcyclohexane (VI)
-·-· N-dimethylamino-*o*-toluidine

there was no maximum in either of Doub's "secondary" bands[4] (Fig. 2). This may suggest that the bases are *o*-substituted N-dimethylanilines[5]. The absorption curves of base VI and N-dimethyl-*o*-toluidine had maxima at the almost identical wave length (247 mμ) of each "primary" band, whereas that of base V had a maximum at 259 mμ showing the existence of a double bond conjugated with the phenyl ring.

The formation of 1-(*o*-dimethylaminophenyl)-cyclohexene involves both fission of the N-C_{9a} bond and attack of the hydroxide ion on the most acidic β-hydrogen atom in a *trans*-position to the bond, and may be reasonable in the light of stereochemistry[6] and of Hofmann's rule[7].

Formation and decomposition of *trans*-hexahydro-N-methyl-carbazole methohydroxide were investigated analogously to the case of the *cis*-base. Then a mixture of two bases was produced, one being 1-(*o*-dimethylaminophenyl)-cyclohexene identical with the base resulting from the exhaustive methylation of the *cis*-base, and the other *cis*-hexahydro-N-methylcarbazole (IV). This result was borne out by the mixed melting point determination of their picrates with authentic specimens, by comparison of the ultraviolet spectra, and by dehydrogenation experiment. The yield of the former was 50% of the theoretical and that of the latter 25%.

With *trans*-hexahydro-N-methylcarbazole methohydroxide, the stereochemical effect required for the usual Hofmann degradation is not satisfied. Therefore, a rearranged base was expected to appear considering the behavior of *trans*-octahydro-N-methylindole in the exhaustive methylation. But no such base could be isolated and base V was obtained instead. This is probably attributable to the ease in the elimination of the acidic β-hydrogen at C_{4a} caused by the anilinium ion. Several examples of this type of elimination have already been reported[8]. On the other hand, the formation of base IV probably involves an elimination of methanol and a subsequent stereochemical rearrangement. Elimination of methanol is encountered in the exhaustive methylation of several alkaloids[9]. But no example is so far known of this type of elimination accompanied by a stereochemical rearrangment.

In the next place, the preparation of

4) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).
5) H. B. Klevens and J. R. Platt, ibid., **71**, 1714 (1949); W. R. Remington, ibid., **67**, 1838 (1945); H. E. Ungnade, ibid.. **76**. 5133 (1954).
6) For reviews see W. Klyne in "Progress in Stereochemistry" ed. W. Klyne, Vol. 1. Butterworth's Scientific Publications. London (1954), p. 64.
7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University press, Ithaca, N. Y., (1953), p. 427.
8) J. Weinstock, R. G. Pearson and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 3473 (1956); E. D. Hughes, C. K. Ingold and R. Pasternak, *J. Chem. Soc.*, **1953**, 3832; S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.*, **74**, 2913 (1952); S. I. Miller and R. M. Noyes,ibid., **74**, 629 (1952).
9) Cuscohygrine, lupanine, matrine, etc., do not undergo a ring fission in the exhaustive methylation, methanol being eliminated. See, for example, T. A. Henry, "The Plant Alkaloids", 4th Ed., Churchill Ltd., London (1949), p. 103, 129 and 147; J. Read and J. Walker., *J. Chem. Soc.*, **1934**, 308; N. L. McNiven and J. Read, ibid., **1952**, 153, 159.

γ-dimethylaminopropylcyclopentane was undertaken, because this compound may be produced by the Hofmann degradation of *trans*-octahydroindole, if the Wagner-Meerwein type rearrangement of III proceeds through another possible course as indicated in Fig. 1 (b), and if the methine base (VII) thus formed is hydrogenated.

A Grignard reagent from cyclopentylmethyl bromide was treated with β-chloroethyl-*p*-toluenesulfonate to yield γ-cyclopentylpropyl chloride. The latter in ethanol was heated with dimethylamine in a closed vessel. γ-Dimethylaminopropylcyclopentane thus obtained was converted into the picrate, m.p. 108–110°, and into the picrolonate, m.p. 156–158°.

King et al.[2] reported that a hydrogenation product $C_{10}H_{21}N$ from I gave a picrate of m.p. 106° and a picrolonate of m.p. 160°. The present author's substances may be identical with theirs, but a direct comparison has not yet been possible because *trans*-octahydroindole is not easily available.

Experimental

***cis*-Hexahydro-N-methylcarbazole Methiodide.**—(a) Ten grams of *cis*-hexahydrocarbazole[10] was heated with 8.5 g. of methyl iodide in 40 cc. of ethanol for 6 hours on a water-bath. After removal of ethanol and methyl iodide under a reduced pressure, the residual oil was shaken for half an hour with 100 cc. of ether, 50 cc. of water, and 20 cc. of 6 N potassium hydroxide solution, when crystals insoluble in both layers precipitated. After separation of the ethereal solution by decantation, the precipitate was isolated from the alkaline solution by filtration. Treatment with hot acetone for half an hour on a water-bath and subsequent filtration gave the methiodide, m.p. 196–198°. Yield 3.3 g.

Anal. Found: C, 51.01; H, 5.95. Calcd. for $C_{14}H_{20}NI$: C, 51.07; H, 6.16%.

The ethereal solution was shaken with 3.5 g. of benzoyl chloride and N sodium hydroxide solution for 5 hours, separated from the alkali solution, treated with N hydrochloric acid, and evaporated to yield 4.2 g. of crude *cis*-hexahydro-N-benzoylcarbazole. Recrystallized from ethanol, the substance showed m. p. 103–105°.

The hydrochloric acid solution was made alkaline and the basic oil was collected with ether. On evaporation, the ethereal solution yielded 3 g. of *cis*-hexahydro-N-methylcarbazole[11], which gave a picrate melting at 144–145°.

Anal. Found: C, 54.99; H, 4.71. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84.%.

(b) A mixture of 3 g. of *cis*-hexahydro-N-methylcarbazole and 3 g. of methyl iodide was allowed to stand over night at the room temperature in a closed vessel. A crystalline substance thus obtained was collected by filtration. Recrystallization from acetone gave the methiodide, m.p. 196–197°. Further quantity of the methiodide, m.p. 193–195°, was obtained on concentration of the mother liquor and addition of ether. The total yield was 3.3 g.

***trans*-Hexahydro-N-methylcarbazole Methiodide.**—(a) A mixture of 2.3 g. of *trans*-hexahydrocarbazole[10] and 4.4 g. of methyl iodide in 15 cc. of ethanol was refluxed for 8 hours on a water-bath. After removal of ethanol and methyl iodide under a diminished pressure, the product was treated with 50 cc. of ether, 40 cc. of water, and 10 cc. of 6 N potassium hydroxide solution. The precipitate and the ethereal solution were separated similarly as from the *cis*-base. Treatment of the precipitate with 20 cc. of hot acetone gave 1.8 g, of *trans*-hexahydro-N-methylcarbazole methiodide, m.p. 233–234°.

Anal. Found: C, 51.46; H, 6.20. Calcd. for $C_{14}H_{20}NI$: C, 51.07; H, 6.16%.

The ethereal solution was shaken with benzoyl chloride and aqueous alkali and, after 4 hours, treated with N hydrochloric acid. Crude *trans*-hexahydro-N-benzoyl-carbazole (0.8 g.) from the ethereal solution was recrystallized from ethanol and showed m.p. 130–132°. The hydrochloric acid solution gave a solid base on alkalification. Recrystallization of the base from ethanol gave 0.4 g. of *trans*-hexahydro-N-methylcabazole, m.p. 59–61°.

Anal. Found: C, 83.57; H, 9.08. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15%.

Treatment of the base with picric acid in ethanol and recrystallization of the product from the same solvent yielded a pure picrate, m.p. 122–124°.

Anal. Found: C, 55.13; H, 4.66. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84%.

(b) A mixture of 1 g. of *trans*-hexahydro-N-methylcarbazole and 1 g. of methyl iodide was heated on a water-bath for one hour and the methiodide, m.p. 231–233°, was obtained substantially in a quantitative yield by a method similar to that used in the case of the *cis*-base.

Exhaustive Methylation of *cis*-Hexahydro-N-methylcarbazole Methiodide.—A solution of 3.5 g. of *cis*-hexahydro-N-methylcarbazole methiodide in a warm mixture of 30 cc. of water and 5 cc. of ethanol was shaken for 5 hours in the dark with silver oxide, freshly prepared from 2 g. of silver nitrate. The mixture was filtered and the filtrate was evaporated under a reduced pressure at about 60°. After most of the water was removed, the temperature was gradually raised. The syrupy quaternary hydroxide decomposed violently at 140–150°. The distillate was taken with ether and subjected to redistillation, yielding 1.4 g. (70%) of 1-(*o*-dimethylaminophenyl)-cyclohexene, b.p. 144–145° (12 mm.). Its

10) J. Gurney, W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **1927**, 2676.

11) W. H. Perkin and S. G. P. Plant, ibid., **1924**, 1503.

12) K. V. Auwers and W. Treppmann, *Ber.*, **48**, 1207 (1915); L. F. Fieser and J. Szmuszkvicz, *J. Am. Chem. Soc.*, **70**, 3352 (1948).

picrate showed m.p. 165–167° on recrystallization from ethanol.

Anal. Found: C, 55.87; H, 4.98. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15%.

The methiodide of 1-(*o*-dimethylaminophenyl)-cyclohexene was prepared in the following manner. The base (5.5 g.) was refluxed with 17 g. of methyl iodide. In half an hour, a small amount (0.3 g.) of a crystalline substance was formed and collected by filtration. This salt had a formula $C_{14}H_{20}NI$, corresponding to a simple addition of methyl iodide to 1-(*o*-monomethylaminophenyl)-cyclohexene.

Anal. Found: C, 51.42, 51.00, 51.41; H, 5.88, 6.11, 6.14. Calcd. for $C_{14}H_{20}NI$: C, 51.07; H, 6.14%.

The solution separated from the salt was continuously refluxed for 60 hours, the precipitates thus formed being removed by filtration every 6 hours. The precipitates were combined and recrystallized from acetone. The purified methiodide decomposed at 195–196° (at 190–192° on slow heating), and amounted to 2.3 g.

Anal. Found: C, 52.45, 52.94: H, 6.24, 6.58. Calcd. for $C_{15}H_{22}NI$; C, 52.48; H, 6.47%.

The filtered solution gave 2 g. of unchanged 1-(*o*-dimethylaminophenyl)-cyclohexene on complete removal of methyl iodide.

1-(*o*-Dimethylaminophenyl)-cyclohexene (0.45g.) in 20 cc. of methanol was hydrogenated in the presence of 0.5g. of 10% palladium-charcoal at the room temperature under the atmospheric pressure for half an hour. After filtration, the solution was made slightly acidic with dil. hydrochloric acid and evaporated. The residue was treated with aqueous alkali and ether, and the ethereal solution gave 0.35 g. of oily dihydro-derivative. Its picrate showed m.p. 185–187° on recrystallization from ethanol.

Anal. Found: C, 55.20; H, 5.34. Calcd. for $C_{20}H_{24}O_4N_7$: C, 55.55; H, 5.59%.

Emde Reduction of 1-(*o*-Dimethylaminophenyl)-cyclohexene Methochloride. — 1-(*o*-Dimethylaminophenyl)-cyclohexene methiodide (2 g.) in 30 cc. of warm water was shaken for 45 minutes with silver chloride, freshly prepared from 10 g. of silver nitrate. The methochloride solution was filtered and heated on a water-bath with stirring, while 200 g. of sodium amalgam (5%) was added in portions during 6 hours. The resulting hydrocarbon was extracted with ether. From the ethereal solution 0.55 g. of the hydrocarbon[12], b.p. 134–136° (22mm.), was obtained.

Anal. Found: C, 91.04; H, 9.60. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92%. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06%.

The hydrocarbon (0.50 g.) was dissolved in a mixture of 35 cc. of acetone and 5 cc. of water, and 1 g. of potassium permanganate was added in portions at 40–50° during 2 hours. After addition of 10 cc. of water, the solution was filtered from manganese dioxide and concentrated on a water-bath. The residue was treated with ether to remove unchanged hydrocarbon and then acidified with conc. hydrochloric acid. The oil thus separated was collected with ether and solidified after removal of ether. Upon recrystallization from benzine, δ-benzoylvaleric acid, m.p. 72–74°, was obtained in a yield of 0.18 g. An authentic specimen[12] had m.p. 75–76°, and the mixed melting point was 73–75°.

Anal. Found: C, 69.50; H, 6.59. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84%.

Treatment of this acid with semicarbazide hydrochloride and sodium acetate in aqueous ethanol and subsequent recrystallization from methanol gave its semicarbazone, m.p. 184–186°, the melting point being undepressed on admixture with an authentic specimen, m.p. 185–186°.

Anal. Found: C, 59.46; H, 6.43. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51%.

Exhaustive Methylation of *trans*-Hexahydro-N-methylcarbazole Methiodide. The reaction was carried out as already described for the *cis*-isomer. The quaternary hydroxide which was obtained by treatment of 2.8 g. of *trans*-hexahydro-N-methylcarbazole methiodide with silver oxide, prepared from 1.8 g. of silver nitrate, decomposed vigorously at 160–170°, a slightly higher temperature than in the case of the *cis*-isomer, and yielded 1.25 g. of an oil, b.p. 145–149° (13 mm.). Treatment of 0.5 g. of the base with 0.6 g. of picric acid in ethanol and two recrystallizations from the same solvent yielded 0.5 g. of the pure picrate, m.p. 168–170°, of 1-(*o*-dimethylaminophenyl)-cyclohexene, the melting point being undepressed in admixture with the picrate of the base obtained by the Hofmann degradation of the *cis*-base. The base (0.1 g.), regenerated from the picrate, was dehydrogenated with 0.4 g. of palladium charcoal (10%) at 280–300° for 30 minutes. An oil isolated by ether-extration of the reaction product was separated into a neutral and a basic fraction with 2N hydrochloric acid, the former (0.03 g.), m.p. 68–70°, being identified as biphenyl by the mixed melting point with an authentic specimen.

The ethanolic mother liquors of the picrate were combined and evaporated. The substance, obtained when the residue was refluxed with a small amount of acetone and the mixture was cooled, was again recrystallized from ethanol containing a small amount of acetone, yielding 0.25 g. of the picrate, m.p. 141–143°, of *cis*-hexahydro-N-methylcarbazole. The melting point was undepressed in admixture with an authentic specimen. An oily base (0.01 g.), obtained by decomposition of the picrate, was dehydrogenated with 0.03 g. of 10% palladium-charcoal at 220° for one hour to give 0.005g. of N-methylcarbazole, m.p. 84–86°, which was identified by the mixed melting point and by comparizon of ultraviolet spectra.

δ-Dimethylaminopropylcyclopentane. — A Grignard reagent was prepared from 10 g. of cyclopentylmethyl bromide[13], 1.5g. of magnesium, and a small amount of iodine in 15 cc. of ether, in a three-necked flask fitted with a separating funnel, a mechanical stirrer, and a reflux condenser. After addition of 5 cc. of ether, 24 g. of β-chloroethyl-*p*-toluenesulfonate[14] in 25 cc. of

13) C. R. Noller and R. Adams, ibid., **48**, 1080 (1926).
14) S. S. Rossander and C. S. Marvel, ibid., **50**, 1497 (1928).

ether was added with stirring during one hour at such a rate that the ether refluxed gently. The reaction mixture was then refluxed gently for 8 hours to give a large amount of a white precipitate. Additional ether was added from time to time in order to keep the mixture fluid enough for efficient stirring. The reaction mixture was then decomposed with cracked ice and treated with ether and enough dil. hydrochloric acid to dissolve the basic magnesium salts. The ethereal solution was subjected to distillation and a fraction, b.p. 68–80° (20 mm.), was collected, consisting mainly of γ-chloropropylcyclopentane.

Two grams of this fraction and 15 cc. of 15% ethanolic dimethylamine were heated in a sealed tube at 160–180° for 8 hours. The reaction mixture was made acidic with dil. hydrochloric acid and then ethanol was removed by evaporation. The residue was treated with ether and water. After separation of the ethereal solution, the aqueous solution was made alkaline and the oil thus formed was removed to ether. The ethereal solution gave 0.6 g. of an oil, b.p. 80–84° (20 mm.), on fractional distillation. This oil gave the picrate, m.p. 108–110°, of γ-dimethylaminopropylcyclopentane on treatment with picric acid and recrystallization from ethanol.

Anal. Found: C, 49.85; H, 6.00. Calcd. for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29%.

The picrolonate was prepared by dissolving the oil in an ethanolic solution of picrolonic acid. It showed m.p. 156–158° on recrystallization from ethanol.

Anal. Found: C, 57.16; H, 6.70. Calcd. for $C_{20}H_{29}N_5O_5$: C, 57.26; H, 6.97%.

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