The Synthesis and the Exhaustive Methylation of the *cis* and *trans* Isomers of 1,2,3,4,4a,5,6,10b-Octahydrophenanthridine and 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline[1]

TADASHI MASAMUNE, MASAJI OHNO, MASATO KOSHI, SHIGEHIRO OHUCHI, AND TSUKASA IWADARE

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

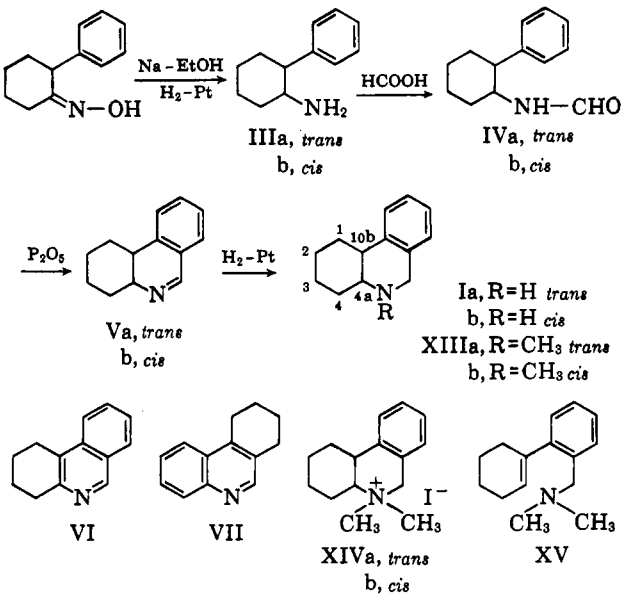
Received October 1, 1963

Preparation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines (Ia and Ib) and *trans*- and *cis*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (IIa and IIb) is described. The configuration of those compounds was established on the basis of the stereospecific synthesis. The exhaustive methylation of Ia and Ib resulted in formation of *o*-dimethylaminomethylphenylcyclohexene (XV), involving the splitting of hydrogen on carbon substituted with a phenyl group. The same reaction of IIa and IIb afforded an analogous result, producing 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (XVI).

In the course of an investigation of the exhaustive methylation of hydrogenated tricyclic bases,[2,3] it became desirable to prepare *trans*- and *cis*-1,2,3,4,4a,5,6,-10b-octahydrophenanthridines (Ia and Ib) and 1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]quinolines[4] (IIa and IIb). The present paper describes the synthesis and exhaustive methylation of those bases.

The synthesis of octahydrophenanthridines (Ia and Ib) employed the Bischler–Napieralski reaction,[5] and 2-phenylcyclohexanone, prepared by the method of Newman and Farbman,[6,7] was selected as a starting substance. Reduction of the oxime with sodium and ethanol gave 1-amino-2-phenylcyclohexane (IIIa), m.p. 60–61°, quantitatively. Treatment of IIIa with formic acid at 150–160° for several hours rendered the N-formyl derivative (IVa), m.p. 97–98°, in a yield of 75%. On the other hand, catalytic hydrogenation of the oxime in the presence of Adams' platinum in acetic acid resulted in the formation of a semisolid mixture of IIIa and the stereoisomer IIIb, the ratio being found to be 1 to 2 by gas chromatography. As it was difficult to isolate IIIb from the mixture at this stage, the mixture was subjected to formylation without further purification, and 1-formylamino-2-phenylcyclohexane (IVb), m.p. 112–113°, stereoisomeric with IVa, was isolated in low yield. A pure sample of IIIb was obtained by hydrolysis of IVb and showed m.p. about 20°. It is clear on the basis of the well-known stereochemistry of similar reductions[8,9] that IIIa has the *trans* configuration and IIIb, the *cis* configuration.

Treatment of the *trans*-formylamino derivative (IVa) with phosphorus pentoxide in refluxing tetralin led to formation of *trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (Va), m.p. 52–53°, in only 15% yield, and IIIa and 1,2,3,4-tetrahydrophenanthridine (VI), an oil, were isolated as by-products. The latter base VI was obtained in good yield by dehydrogenation of Va and could be well differentiated from 7,8,9,10-tetrahydrophenanthridine[10] (VII) by its characteristic ultraviolet spectrum (Fig. 1). Cyclodehydration of the *cis*-formylamino derivative (IVb) similarly produced *cis*-hexahydrophenanthridine (Vb), m.p. 52.5–54°, in almost the same yield as in the case of the *trans* isomer. The base Vb appeared to be more unstable than the corresponding *trans* isomer; prolonged treatment of the reaction mixture sometimes gave VI as a main product. Hydrogenation of the *trans*- and *cis*-hexahydro derivatives (Va and Vb) proceeded smoothly to yield *trans*-octahydrophenanthridine (Ia), m.p. 89.5–90.5°, and the corresponding *cis* isomer (Ib), an oil, respectively.



Recently, Nelson, *et al.*,[11] reported the elegant synthesis of N-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinoline (VIIIb), the configuration of which was tentatively assigned to be a *cis* modification. On the other hand, Bamberger and Müller[12] had obtained 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIa). The present investigation started with the re-examination of Bamberger's experiment; reduction of benzo[*f*]-quinoline (IX) with sodium and amyl alcohol gave IIa,

(1) Part XIII of "The Condensed Polynuclear Perhydro Compounds Containing Nitrogen"; part XII, ref. 3.

(2) T. Masamune, *Bull. Chem. Soc. Japan*, **30**, 49 (1957).

(3) T. Masamune, M. Takasugi, H. Suginome, and M. Yokoyama, *J. Org. Chem.*, **29**, 681 (1964).

(4) The synthesis and exhaustive methylation of IIa and IIb were reported as a communication: T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **32**, 1006 (1959).

(5) W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.

(6) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

(7) J. W. Cook, C. K. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).

(8) D. H. R. Barton, *ibid.*, 1027 (1953); F. E. King, T. Henshall, and R. L St. D. Whitehead, *ibid.*, 1373 (1948); F. E. King, J. A. Barltrop, and R. J. Willey, *ibid.*, 277 (1945).

(9) J. McKenna and A. Tulley, *ibid.*, 945 (1962); for a recent review of conformational analysis, see D. H. R. Barton and G. A. Morrison, "Progress in The Chemistry of Organic Natural Products," Vol. 19, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1961, p. 165.

(10) B. L. Hollingsworth and V. Petrow, *J. Chem. Soc.*, 1537 (1948).

(11) N. A. Nelson, J. E. Ladburg, and R. S. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(12) E. Bamberger and R. Müller, *Ber.*, **24**, 2648 (1891).

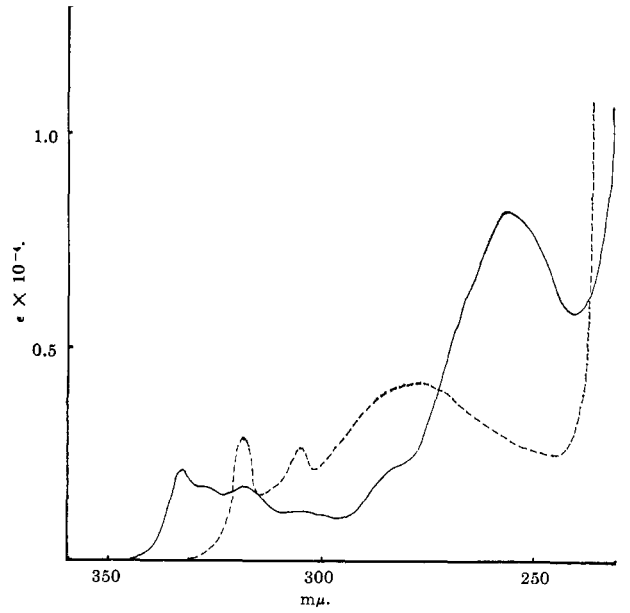


Fig. 1.—Ultraviolet absorption spectra of tetrahydrophenanthridines: solvent, ethanol; ———, 1,2,3,4-tetrahydrophenanthridine; and – – – –, 7,8,9,10-tetrahydrophenanthridine.

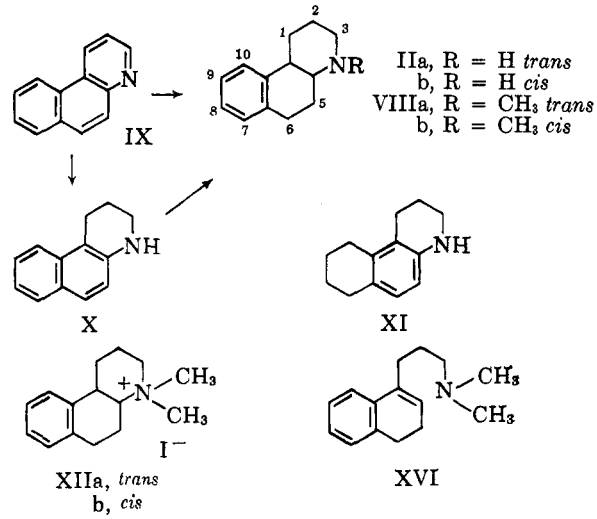
m.p. 88–90°, in 3% yield along with the 1,2,3,4-tetrahydro derivative[13] (X) and the 1,2,3,4,7,8,9,10-octahydro derivative[12] (XI). Methylation of IIa with methyl iodide gave the corresponding methiodide (XIIa), m.p. 238–240°, whereas the methiodide (XIIb) obtained from VIIIb has been reported to melt at 295°. The discrepancy of the melting points strongly suggested that XIIa and XIIb are stereoisomers. Catalytic hydrogenation of IX over Raney nickel at 150° has now afforded a new 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIb) as an oil. It was isolated in 5% yield as the carbonate from the ether solution of the oily reaction product. The main product was XI and no isomer (IIa) could be isolated. In an attempt to produce IIb in better yield the 1,2,3,4-tetrahydro derivative was hydrogenated in the presence of platinum in acetic acid, but the main product was XI, and IIb was obtained only in 3% yield along with IIa (4.5%). Formation of stereoisomers IIa and IIb would occur not only because the solvent was acidic but also because a long hydrogenation was required for the consumption of 2 moles of hydrogen.[14] Hydrogenation of the hydrochloride of X in ethanol[15] over platinum gave only IIb (4%) besides XI. Methylation of IIb gave rise to the methiodide (XIIb), m.p. 294–295°. While direct comparison was not attained, there is no doubt from comparison of the melting points that XIIb is the same compound as Nelson's methiodide.[11] It is apparent on the basis of the reduction conditions[9] and Nelson's assignment[11] that IIa is a *trans* isomer and IIb a *cis* isomer, although no rigid proof can be given for the configuration of IIa and IIb.

(13) Bamberger's tetrahydrobenzo[*f*]quinoline is a molecular compound of IX and X [(a) T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **30**, 307 (1957); (b) E. Bamberger and R. Müller, *Ber.*, **24**, 2641 (1891)].

(14) Hydrogenation of quinoline, 1,2,3,4,4a,9,9a,10-octahydroacridines and *trans*-5,6,6a,7,8,9,10,10a-octahydrophenanthridine over platinum in acetic acid gives the corresponding perhydro compounds with *trans*-fused rings. [W. Hückel and F. Stept, *Ann.*, **453**, 163 (1927); T. Masamune and S. Wakamatsu, *J. Chem. Soc. Japan*, **77**, 1145 (1956); T. Masamune and Y. Kubota, *ibid.*, **77**, 1467 (1956); also see G. R. Clemo, J. G. Cook, and R. Paper, *J. Chem. Soc.*, 1183 (1938)].

(15) *Cf.* N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

Methylation of Ia and Ib with formalin and formic acid gave the N-methyl-*trans* and -*cis* derivatives (XIIIa and XIIIb), respectively. Addition of methyl iodide to an acetone solution of XIIIa or XIIIb gave N-methyl-*trans*-octahydrophenanthridine methiodide (XIVa), m.p. 265–267°, or the corresponding *cis*-methiodide (XIVb), m.p. 242–244°. The Hofmann degradation of XIVa produced a single oily base (XV),



$C_{15}H_{21}N$, in 65% yield, which was found to be identical with the degradation product of XIVb. The ultraviolet spectrum of XV resembled closely that of *o*-methylphenylcyclohexene. Taking into consideration that XV was produced from each of the stereoisomers XIVa and XIVb, it might be reasonably concluded that XV is *o*-dimethylaminomethylphenylcyclohexene. In a similar way the exhaustive methylation of XIIa gave the same oily base (XVI), $C_{15}H_{21}N$, as that of XIIb. The base (XVI) showed a similar ultraviolet spectrum to 1,2-dihydronaphthalene[16] and XVI was, therefore, formulated as 1-(3-dimethylaminopropyl)-3,4-dihydronaphthalene (XVI). The structure for the degradation product of *cis*-methiodide (XIIb) has been confirmed to be XVI by Nelson, *et al.*[11]

From a study of molecular models it is clear that the *trans* compounds in both series must have a quasi-axial hydrogen at position 10b. In the *cis* series the 10b hydrogen may be either quasi-axial or quasi-equatorial. The two principle conformations of the *cis* compounds should be readily interchangeable, at least under conditions of the Hofmann elimination. In each *cis* series it is possible to arrive at a conformation in which the 10b hydrogen is ideally situated for an E2 elimination reaction. For each *trans* compound this is not true, and it was expected that elimination of methanol from the methohydroxide (substitution reaction) would take place.[3] In the present experiment the 10b hydrogen has been eliminated preferentially by the influence of the phenyl group.[17] It would appear that the *trans* compounds undergo a two-step elimination.[18a,b]

(16) E. Boyland and J. B. Solomon, *Biochem. J.*, **59**, 518 (1955).

(17) H. Wieland, W. Koschara, E. Dane, J. Renz, W. Schwarze, and W. Linde, *Ann.*, **540**, 103 (1939); C. Schöpf, E. Schmidt, and W. Braun, *Ber.*, **64**, 683 (1931); J. Weinstock, R. G. Pearson, and F. G. Bordwell, *J. Am. Chem. Soc.*, **78**, 3468 (1956); S. J. Cristol, J. Q. Welber, and M. C. Brindell, *ibid.*, **78**, 598 (1956).

(18) (a) A. C. Cope and E. R. Trumbull, "Organic Reactions," Vol. XI, A. C. Cope, Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 317; (b) we are indebted to a referee for these suggestions.

Experimental

Ultraviolet and infrared spectra were measured in ethanol and in Nujol, respectively, unless otherwise stated.

trans-**1-Amino-2-phenylcyclohexane (IIIa).**—The starting material, 2-phenylcyclohexanone, was prepared according to the method of Newman and Farbman[8] and was converted quantitatively into the oxime, m.p. 174–175°. To the oxime (52 g.) dissolved in warm absolute ethanol (500 ml.) was added sodium (63 g.) little by little, and the solution was further refluxed for 1 hr. After cooling, the mixture was acidified with concentrated hydrochloric acid, when sodium chloride precipitated. After separation of the salt and the solvent, the residue was treated with water and ether. The aqueous solution was made alkaline to yield a crude base which was extracted with ether. The base was then submitted to distillation and a fraction of b.p. 133–136° (12 mm.) was collected and solidified on cooling. On recrystallization from petroleum ether, *trans*-1-amino-2-phenylcyclohexane (39 g.), m.p. 60–61°, was obtained (lit.[19] m.p. 60°).

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.10; H, 9.88.

The hydrochloride was prepared by addition of dry hydrogen chloride to the ether solution of the base and melted at 249–251° on recrystallization from acetone (lit.[19] m.p. 253°). The picrate was prepared in ether and recrystallized from a mixture of ether and acetone to give m.p. 181–182°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: N, 13.70.

trans-**1-Formylamino-2-phenylcyclohexane (IVa).**—A mixture of *trans* base (IIIa, 17 g.) and formic acid (9.0 g.) was heated at 150–160° (bath temperature) for 4 hr. To the cooled mixture was added ether and water, and the ether solution was washed with 1 *N* hydrochloric acid. The aqueous and hydrochloric acid solutions were combined and made basic to give the crude starting base (IIIa, 2.0 g.). The ether solution yielded the solid N-formyl derivative on removal of ether. Recrystallization from a mixture of petroleum ether (b.p. 30–60°, 200 ml.) and a small volume of ethanol followed by quick washing with a small volume of ether yielded *trans*-1-formylamino-2-phenylcyclohexane (IVa, 13 g.), m.p. 88–90°. Upon concentration of the combined filtrates followed by distillation, a further quantity (1.0 g.) of IVa, b.p. 200–205° (16 mm.) and m.p. 87–90°, was obtained. The samples of m.p. 90° could be used for the subsequent cyclodehydration without further purification, but an analytical sample had m.p. 97–99° after recrystallization from petroleum ether or aqueous ethanol, ν_{max} 1655 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 77.02; H, 8.13.

cis-**1-Amino-2-phenylcyclohexane (IIIb) and the N-Formyl Derivative (IVb).**—2-Phenylcyclohexanone oxime (10.0 g.) was hydrogenated over Adams' platinum (0.6 g.) at room temperature in acetic acid (500 ml.), and 2750 ml. of hydrogen was consumed after 24 hr., the calculated value for 3 moles of hydrogen being 2600 ml. After removal of the catalyst and acetic acid, the reaction mixture was shaken with ether and water. The aqueous solution was made basic and treated with ether. An oily base obtained from the ether solution was a mixture of *trans*- and *cis*-1-amino-2-phenylcyclohexanes (IIIa and IIIb), and the ratio of IIIa to IIIb was found to be 1 to 2 by gas chromatographic examination.[20] The mixture was formylated without further purification; the mixture (10 g.) of IIIa and IIIb was heated with formic acid (4 ml.) at 140–160° for 8 hr. The reaction mixture was worked up similarly as in the case of IIIa and an oily formyl compound (10.0 g.) was obtained. When allowed to stand in a refrigerator overnight, it solidified partially and the solid was collected by filtration. An oily substance included in the solid was removed by treatment with warm petroleum ether (about 150 ml.) and the crude *cis*-N-formyl derivative (IVb, 2.7 g.), m.p. 100–106°, was obtained. Recrystallization from benzene gave pure *cis*-1-formylamino-2-phenylcyclohexane (IVb, 1.85 g.), m.p. 112–113°, ν_{max} 1650 cm.$^{-1}$. On admixture of IVb with IVa, the melting point was depressed to 67–74°. The sample of m.p. 106° mentioned above showed practically the same infrared spectrum as the pure compound.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.80; H, 8.15.

The *cis*-N-formyl compound (IVb, 0.5 g.) of m.p. 113° was hydrolyzed with 6 *N* hydrochloric acid (1 ml.) in refluxing ethanol (3 ml.) for 5 hr. The reaction mixture was worked up as usual and pure *cis*-1-amino-2-phenylcyclohexane (IIIb, 0.38 g.), m.p. *ca.* 20° and b.p. 140–142° (15 mm.), was obtained.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.01; H, 9.65.

The picrate melted at 182–184° after preparation in ether and recrystallization from acetone. The mixture melting point with the corresponding *trans* isomer was depressed to 160–169°.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: N, 13.59.

trans-**1,2,3,4,4a,10b-Hexahydrophenanthridine (Va).**—In a three-necked flask fitted with a reflux condenser and a stirrer, *trans*-1-formylamino-2-phenylcyclohexane (IVa, 23 g.) was dissolved in boiling tetralin (230 ml., distilled over phosphorus pentoxide). To the solution was added phosphorus pentoxide (35 g.) in small quantities for 35 min. under vigorous stirring, and the solution was continuously refluxed for 1 hr. After cooling, it was treated with ether (300 ml.) and 2 *N* hydrochloric acid (300 ml.). An oily substance which separated by alkalinization of the acidic solution was distilled to yield a fraction (6.6 g.) of b.p. 157–172° (22 mm.), which solidified on cooling. In order to prepare *trans*-octahydrophenanthridine (Ia), it is convenient to hydrogenate this crude base without further purification. Recrystallization from petroleum ether gave *trans*-hexahydrophenanthridine (Va, 3.5 g.), m.p. 52–53°, λ_{max} 254 mμ (ϵ 15,500) and ν_{max} 1620 and 1571 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{15}N$: C 84.28; H, 8.16. Found: C, 84.31; H, 8.03.

The picrate melted at 190–192° on recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38. Found: C, 55.31; H, 4.01.

The hydrochloride melted at 220–222° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{16}ClN$: C, 70.41; H, 7.28. Found: C, 70.20; H, 7.50.

The mother liquors obtained on recrystallization of the crude hexahydrophenanthridine were combined and evaporated to dryness. The residue was acetylated with refluxing acetic anhydride. The reaction mixture was worked up as usual and gave *trans*-1-acetylamino-2-phenylcyclohexane (2.2 g.), m.p. 128–130° on recrystallization from aqueous ethanol, which was identified by the mixture melting point method with an authentic specimen[19] of m.p. 128–130°.

Cyclodehydration of IVa under more drastic conditions gave 1,2,3,4-tetrahydrophenanthridine (VI). In such a case it was found convenient to purify the reaction product through the picrate; IVa (10 g.) was refluxed with phosphorus pentoxide (15 g.) for 8 hr. An oily base obtained from the reaction product was converted into the picrates in ethanol, when two kinds of crystals, needles and plates, appeared. The former (3.5 g.) had m.p. 190–192 ° and the latter (0.28 g.) had m.p. 192–193°. It was shown, by regeneration of those picrates into the corresponding free bases followed by comparison of their infrared spectra with those of authentic specimens, that the former was the picrate of Va and the latter of VI.

1,2,3,4-Tetrahydrophenanthridine (VI).—A solution of *trans*-hexahydrophenanthridine (Va, 0.5 g.) in tetralin (10 ml.) was refluxed with 30% palladized charcoal[21] (0.25 g.) for 4 hr. The reaction mixture was treated with ether and 6 *N* hydrochloric acid, and the acidic solution was made basic to yield an oily base which was extracted with ether. The oily base (0.4 g.) obtained on removal of ether was converted into the picrate, which had m.p. 192–193° on recrystallization from ethanol or by washing with ethanol. The picrate was regenerated into the free base, 1,2,3,4-tetrahydrophenanthridine (VI, 0.3 g.).

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.20; H, 7.15. Found: C, 85.01; H, 7.30.

The hydrochloride melted at 282–284° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{14}ClN$: C, 71.06; H, 6.42. Found: C, 70.78; H, 6.29.

trans-**1,2,3,4,4a,5,6,10b-Octahydrophenanthridine (Ia).**—*trans*-Hexahydrophenanthridine (Va, 0.5 g.) was hydrogenated over Adams' platinum (0.2 g.) at room temperature in acetic acid and took up 100 ml. of hydrogen (1 mole) after 30 min. Hydrogenation did not proceed beyond this stage. The reaction

(19) J. van Braun, H. Gruber, and G. Kirschbaum, *Ber.*, **55**, 3664 (1922).

(20) The gas chromatography was conducted at 200° using polyethylene glycol (Shimazu 6000).

(21) A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, **23**, 781 (1940).

product was worked up as usual and gave a solid base. Recrystallization from petroleum ether or aqueous methanol gave rise to *trans*-octahydrophenanthridine (Ia, 0.39 g.), m.p. 89.5–90.5°, λ_{max} 273 mμ (ε 370) and 266 mμ (ε 380), and ν_{max} 1502, 1485, and 1442 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.10.

The picrate melted at 178–179° on recrystallization from acetone–ether.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.55; H, 4.59.

The hydrochloride had m.p. 280–282° on recrystallization from a mixture of acetone and a small amount of ethanol.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 69.77; H, 8.29. Found: C, 69.78; H, 8.11.

The crude hexahydrophenanthridine (6.6 g.) of b.p. 157–172° (22 mm.) obtained in preparation of Va was hydrogenated over Adams' platinum (0.3 g.) under similar conditions and 600 ml. of hydrogen (0.7 mole) was consumed. Recrystallization of hydrogenated bases gave Ia (3.7 g.), m.p. 88–90°.

***cis*-1,2,3,4,4a,10b-Hexahydrophenanthridine (Vb).**—To *cis*-1-formylamino-2-phenylcyclohexane (IVb, 5.0 g.), m.p. 113°, dissolved in boiling tetralin (150 ml.) was added phosphorus pentoxide (10 g.) during 10 min. under stirring, and the whole solution was refluxed for 50 min. The product was worked up as above, and crude *cis* base (Vb, 1.5 g.), b.p. 148–152° (17 mm.), was obtained. It gradually crystallized and, on recrystallization from petroleum ether, *cis*-hexahydrophenanthridine (Vb, 0.7 g.), m.p. 52.5–54°, was obtained, λ_{max} 258 mμ (ε 10,500) and ν_{max} 1622 and 1571 cm.$^{-1}$. Concentration of the mother liquor gave a further quantity (0.45 g.) of Vb, m.p. 51.5–54°.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16. Found: C, 84.10; H, 8.35.

It was difficult to prepare the picrate in pure state. The hydrochloride melted at 210–212° on recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{16}ClN$: C, 70.41; H, 7.28. Found: C, 70.15; H, 7.41.

Prolonged treatment of IVb with phosphorus pentoxide in boiling tetralin rendered only VI as an isolated product; IVb (2.0 g.) gave an oily base (0.2 g.) by treatment with phosphorus pentoxide (3.0 g.) for 4 hr., and the oil was converted into picrate (0.15 g.) which melted at 190–192° on recrystallization from methanol and was identified as the picrate of VI. Since the picrate of Vb could not be obtained in crystalline form in methanol, the yield of Vb was not determined. However, the oily mixture was found to contain at least 50% of VI, judging from the intensity of its ultraviolet spectrum.

***cis*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridine (Ib).**—*cis*-Hexahydrophenanthridine (Vb, 2.0 g.) of m.p. 52.5–54° was hydrogenated in the presence of platinum oxide (0.5 g.) at room temperature in acetic acid (100 ml.) and took up 440 ml. of hydrogen, the calculated value for 1 mole of hydrogen being 425 ml. The usual treatment of the product yielded *cis*-octahydrophenanthridine (IIb, 1.95 g.), b.p. 141–5° (17 mm.), which was shown to be a single compound by gas chromatography,[20] λ_{max} 273 mμ (ε 400) and 266 mμ (ε 420) and ν_{max} 1490, 1465, and 1451 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.30.

The picrate melted at 165–166° after preparation in ether and recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.68; H, 4.99.

The hydrochloride melted at 225–227° on recrystallization from acetone–methanol.

Anal. Calcd. for $C_{13}H_{18}ClN$: C, 69.77; H, 8.29. Found: C, 69.60; H, 8.40.

Methylation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridines (Ia and Ib).—A mixture of *trans*-octahydrophenanthridine (Ia, 2.0 g.), formic acid (1.0 ml.), and 33% formalin (2 ml.) was gently refluxed for 6 hr. with a small free flame, and the cooled mixture then was treated with ether (30 ml.) and water (50 ml.). The ether solution was washed with 2 *N* aqueous acetic acid. The aqueous solution and the acidic washings were combined, made basic, and treated with ether. An oily base (1.6 g.) obtained from the ether solution was refluxed with acetic anhydride (5 ml.) for 30 min. The reaction mixture afforded an oily base after decomposition of the excess of acetic anhydride with hot water (30 ml.) followed by alkalinization of the aqueous layer. It was again extracted with ether and distilled under reduced pressure to yield N-methyl-*trans*-octahydrophenanthridine (XIIIa, 1.3 g.), b.p. 161–163° (15 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.30; H, 9.68.

The picrate melted at 167–168° on preparation in ether and recrystallization from a small amount of ethanol or acetone.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 56.02; H, 5.01.

Into an acetone solution of the N-methyl derivative (XIIIa, 0.5 g.) was added an excess of methyl iodide under cooling, and the precipitate thus formed was washed with acetone and ether. On recrystallization from acetone–ethanol, N-methyl-*trans*-octahydrophenanthridine methiodide (XIVa, 0.55 g.), m.p. 265–267°, was obtained.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.30; H, 6.58.

In a similar way, *cis*-octahydrophenanthridine was methylated to the N-methyl derivative (XIIIb), b.p. 165–170° (15 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.23; H, 9.85.

The picrate could not be obtained in a crystalline form. The methiodide (XIVb) had m.p. 242–244° on recrystallization from acetone–ethanol.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.30; H, 6.70.

The Exhaustive Methylation of N-Methyl-*trans*- and -*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine Methiodides (XIVa and XIVb).—A solution of *trans*-methiodide (XIVa, 0.50 g.) in a mixture of water (5 ml.) and methanol (5 ml.) was shaken for 1 hr. with silver oxide freshly prepared from silver nitrate (0.30 g.). After removal of silver oxide and silver iodide by filtration, the solution was evaporated to dryness. The resulting sirupy methohydroxide was heated to 170° (bath temperature) under reduced pressure and the decomposition was completed practically at 145°. The product extracted with ether was purified by distillation, and *o*-dimethylaminomethylphenylcyclohexene (XV, 0.20 g.), b.p. 140–160° (bath temperature, 15 mm.), was obtained.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.50; H, 9.80.

The picrate melted at 170–172° after preparation in ethanol and recrystallization from the same solvent.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.42; H, 5.52.

Similar treatment of N-methyl-*cis*-octahydrophenanthridine methiodide (XIVb, 0.18 g.) gave an oily base (0.06 g.). The base (XV), b.p. 140–160° (bath temperature, 15 mm.), and its picrate, m.p. 170–172° (from ethanol), showed the same infrared spectra as the corresponding specimens obtained from the *trans* isomer.

Catalytic Hydrogenation of Benzo[*f*]quinoline (IX) over Raney Nickel.—A starting substance, benzo[*f*]quinoline (IX), was prepared according to the method of Clem and Hamilton,[22] and had m.p. 92–93°, lit.[22] m.p. 93°; λ_{max} 346 mμ (ε 3000), 330 (2600), 316 (1400), 267 (15,000), and 234 (21,000).

Benzo[*f*]quinoline (IX, 20 g.) was hydrogenated over Raney nickel (2.0 g.) at 100° under high pressure (70 atm.) for 1 hr. and absorbed 2 moles of hydrogen. The cooled reaction mixture was extracted with ethanol and then distilled under reduced pressure after removal of ethanol. 1,2,3,4-Tetrahydrobenzo[*f*]-quinoline (X, 20 g.), b.p. 200–202° (14 mm.), was obtained, with λ_{max} 360 mμ (ε 2200), 300 (6600), 288 (7500), and 277 (5300). The infrared spectrum was identical with that of the authentic specimen.[13a]

When IX (20 g.) was similarly treated at 150°, about 4 moles of hydrogen were consumed after 1 hr. The ethanol solution of the product was acidified with acetic acid and then ethanol was distilled. The residue was diluted with water, and the aqueous solution was washed with ether and then made basic. The oily substance which separated was extracted with ether, and into the ether solution was passed carbon dioxide, when the carbonate precipitated. It was collected by filtration, washed with ether, and had m.p. 88–90°.

Anal. Calcd. for $C_{13}H_{17}N \cdot 0.5H_2CO_3$: C, 74.28; H, 8.31. Found: C, 74.08; H, 8.19.

(22) W. J. Clem and C. S. Hamilton, *J. Am. Chem. Soc.*, **62**, 2349 (1940); and H. Hepneo, *Monatsh.*, **27**, 1044 (1906).

Regeneration of the carbonate yielded *cis*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIb, 1.0 g.), b.p. 160–165° (5 mm.). As analysis of the free base was difficult because of rapid absorption of atmospheric carbon dioxide, IIb was converted into the hydrochloride, which melted at 258–259° on recrystallization from aqueous acetone.

Anal. Calcd. for $C_{13}H_{18}ClN \cdot H_2O$: H_2O, 8.78. Found: H_2O, 8.23. Calcd. for $C_{13}H_{18}ClN$: C, 64.65; H, 8.28. Found: C, 64.46; H, 8.09.

The benzoyl derivative was prepared by shaking the ether solution of IIb with benzoyl chloride and 1 *N* aqueous sodium hydroxide, and melted at 96–97° on recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.65; H, 7.10.

The picrate had m.p. 197–198.5° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.55; H, 4.85.

On the other hand, the ethereal filtrate and washings obtained on isolation of the carbonate of IIb were combined, washed with alkaline solution, and dried. On removal of the solvent and recrystallization of the residue from petroleum ether, 1,2,3,4,7,8,9,-10-octahydrobenzo[*f*]quinoline (XI, 15 g.), m.p. 64–66°, was obtained.

Reduction of Benzo[*f*]quinoline (IX) with Sodium and Amyl Alcohol.—The reduction was conducted in essentially the same way as described by Bamberger and Müller.[12] To small pieces of sodium (30 g.) was added rapidly benzo[*f*]quinoline (10 g.) dissolved in hot amyl alcohol (200 ml.) under stirring, when vigorous boiling took place and, after about 10 min., ceased. The solution was continuously refluxed until all the sodium disappeared. To the cooled reaction mixture was added water (500 ml.), and the aqueous layer was acidified with hydrochloric acid. After the amyl alcohol was distilled by steam distillation, the acidic solution was made basic and then treated with ether. Into the ether solution was passed carbon dioxide to give the precipitate of carbonate. The precipitate, after washing with ether, was reconverted into a solid free base, from which *trans*-1,2,3,4,-4a,5,6,10b-octahydrobenzo[*f*]quinoline (IIa, 0.3 g.), m.p. 88–90°, was obtained after recrystallization from petroleum ether (lit.[12] m.p. 91°).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.25; H, 9.12.

The hydrochloride melted at 251–253°, lit.[12] m.p. 252°, and the picrate melted at 189–190° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 55.06; H, 5.04.

The benzoyl derivative, prepared like the corresponding *cis* isomer, melted at 100–102° on recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.69; H, 7.16.

The ethereal filtrate and washings obtained on separation of the carbonate were combined, washed with alkali, and dried. On removal of the solvent, a semisolid mixture of base was obtained. The solid was collected by filtration and recrystallized from petroleum ether to give 1,2,3,4,7,8,9,10-octahydrobenzo[*f*]-quinoline (XI, 3.0 g.), m.p. 64–66°, lit.[12] m.p. 60.5°, λ_{max} 300 mμ (ε 2000) and 251 mμ (ε 8500).

Anal. Calcd. for $C_{13}H_{17}N$: C, 82.37; H, 9.15. Found: C, 82.62; H, 8.97.

The hydrochloride melted at 220–222°, lit.[12] m.p. 219°; the picrate melted at 150–152° (from ethanol).

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 55.03; H, 4.95.

The benzoyl derivative melted at 144–146° (from ethanol).

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.60; H, 7.25.

The oily filtrate (4.0 g.) obtained on isolation of XI was found to consist mainly of X on the basis of the ultraviolet and infrared spectra, but it was not further examined.

Catalytic Hydrogenation of Tetrahydrobenzo[*f*]quinoline (X) over Platinum. A.—Tetrahydrobenzo[*f*]quinoline (4.0 g.) was hydrogenated over platinum oxide (0.4 g.) at room temperature in acetic acid (30 ml.). During the hydrogenation, three 0.1-g. portions of the catalyst were added, and after 15 hr. 2 moles of hydrogen was absorbed. The reaction mixture was worked up as usual and gave a mixture of bases, which was dissolved in ether. Carbon dioxide was passed into the ether solution for 3 hr. and the precipitate thus formed was separated from the ether solution. The carbonate was again regenerated to a semisolid mixture (0.5 g.) of bases, which was allowed to stand in air for 7 to 10 days. A part of the mixture was again converted to the carbonate, which was collected after treatment with ether. The carbonate was reconverted into the *cis*-octahydro derivative (IIb, 0.12 g.), b.p. 160–165° (5 mm.). On the other hand, the ether solution afforded *trans* isomer (IIa, 0.18 g.), m.p. 88–90°, on removal of the solvent followed by recrystallization of the residue from petroleum ether. Identification was carried out by comparison of their infrared spectra with those of pure samples mentioned above. The ether solution free from the carbonates of IIa and IIb yielded a solid base, which was recrystallized from petroleum ether to give the 1,2,3,4,7,8,9,10-octahydro derivative (XI, 3.0 g.), m.p. 61–63°.

B.—The hydrochloride[13a] (7.0 g.) of X was hydrogenated in presence of Adams' platinum (0.5 g.) at room temperature in ethanol. During the hydrogenation more platinum oxide (0.1 g.) was added and 2 moles of hydrogen were consumed after 10 hr. The reaction product was worked up as mentioned above, and *cis*-octahydrobenzo[*f*]quinoline (IIb, 0.27 g.) and the 1,2,3,4,7,8,-9,10-octahydro derivative (XI, 5.0 g.) were obtained. No *trans* isomer (IIa) could be isolated.

Methylation of *trans*- and *cis*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines (IIa and IIb).—*trans*-Octahydrobenzo[*f*]-quinoline (3.5 g.) was gently refluxed with methyl iodide (3.0 g.) in methanol (20 ml.) for 2 hr. After removal of the excess of methyl iodide and methanol, the residue was shaken with ether and 6 *N* aqueous potassium hydroxide (20 ml.), when the crude methiodide (2.0 g.), insoluble in the two layers, separated and was collected by filtration. By passing carbon dioxide into the ether solution, the carbonate of IIa was obtained. The ether solution free from the carbonate gave a crude N-methyloctahydro derivative (1.5 g.), which was again used in formation of the methiodide without further purification; it was treated with methyl iodide under similar conditions and the crude methiodide (1.8 g.) was formed. Recrystallization of the combined methiodides from acetone afforded N-methyl-*trans*-octahydrobenzo[*f*]-quinoline methiodide (XIIa, 2.5 g.), m.p. 238–240°.

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.24; H, 6.44.

An analytical sample of N-methyl-*trans*-octahydrobenzo[*f*]-quinoline (VIIIa), b.p. 145–150° (4 mm.), was obtained by purification through the picrate.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.57; H, 9.51. Found: C, 83.45; H, 9.62.

The picrate melted at 210–212° after crystallization from ethanol.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.67; H, 4.98.

cis-Octahydrobenzo[*f*]quinoline (IIb, 3.5 g.) was methylated under the same conditions to give the *cis*-methiodide (XIIb, 3.0 g.), m.p. 294–295° (from acetone).

Anal. Calcd. for $C_{15}H_{22}IN$: C, 52.48; H, 6.46. Found: C, 52.26; H, 6.26.

The N-methyl derivative (VIIIb) had b.p. 145–151° (4 mm.).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.57; H, 9.51. Found: C, 83.39; H, 9.48.

The picrate melted at 165–167° (from ethanol).

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 56.09; H, 5.31.

The Exhaustive Methylation of N-Methyl-*trans*- and -*cis*-1,2,3,-4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Methiodides (XIIa and XIIb).—A solution of the *trans*-methiodide (XIIa, 2.5 g.) in 50% aqueous ethanol (50 ml.) was treated with silver oxide in the dark for 12 hr. After removal of the inorganic compounds by filtration, the reaction product was evaporated to dryness below 70° under reduced pressure. The sirupy residue was heated to 170° under reduced pressure (4 mm.) and decomposition took place at about 140°. The product was extracted with ether, and the ether solution was subjected to distillation after drying. 1-(3-Dimethylaminopropyl)-3,4-dihydronaphthalene (XVI, 0.5 g.), b.p. 150–155° (4 mm.), was obtained, λ_{max} 261 mμ (ε 8900). Ultraviolet spectrum[16] of 1,2-dihydronaphthalene showed λ_{max} 262 mμ (ε 10,230).

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.45; H, 9.78.

The base (XVI) was converted into the picrate, m.p. 87–88° (from acetone).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.98; H, 5.43.

The Hofmann degradation of the *cis*-methiodide (XIIb, 3.0 g.) was conducted in practically the same way, and the base (XVI, 0.8 g.) was obtained. The ultraviolet and infrared spectra of the product were completely identical with those of the base from the *trans* isomer.

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.66; H, 9.83. Found: C, 83.79; H, 9.68.

The picrate melted at 87–88° (from acetone).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.40; H, 5.26.

Acknowledgment.—The authors are greatly indebted to Professor T. Irie for his continuous encouragement during this work, and to Miss A. Maeda for microanalyses.

Degradation of α-Methyl-3,4-dihydroxyphenylalanine (α-MethylDOPA)

H. L. SLATES, D. TAUB, C. H. KUO, AND N. L. WENDLER

Merck Sharp and Dohme Research Laboratories, Merck and Company, Inc., Rahway, New Jersey

Received December 16, 1963

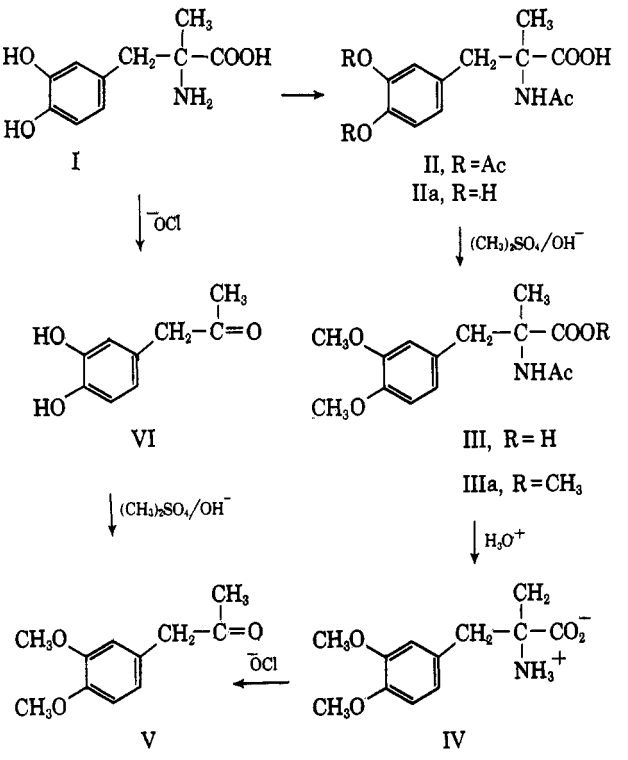
α-MethylDOPA has been degraded in high yield by several pathways to derivatives of 3,4-dihydroxyphenylacetone. These degradations comprise recycle routes for the utilization of D-(+)-α-methylDOPA in the synthesis of L-(−)-α-methylDOPA.

The importance of α-methylDOPA as an antihypertensive agent is well recognized.[1] The synthesis of this substance from 3,4-dimethoxyphenylacetone *via* the Strecker hydantoin sequence[2] requires an optical resolution whereby the biologically inactive D-(+) isomer is made available in equal amount with the active component, L-(−)-α-methylDOPA.[3]

It became of interest to examine possible modes for utilization of the biologically inactive D-(+) isomer for resynthesis of its optical antipode. In view of the character of substitution at the optically active α-position and the consequent inaccessibility of the latter to normal racemization procedures, attention was directed to degradation of the α-methylDOPA system to a precursor, namely, 3,4-dimethoxyphenylacetone. As a result of this investigation, two methods were developed for effecting this degradation in 85–90% conversion and a third method was found effective to the extent of 70–75%.

The great instability to alkali of the catechol system present in α-methylDOPA had long represented a formidable deterrent to procedural undertakings designed to inactivate this portion of the molecule, and, thereby, provide latitude for chemical manipulation of the amino acid segment. It subsequently was discovered that, by scrupulous exclusion of air and by working with solutions previously purged with nitrogen, α-methylDOPA could be handled in alkaline solution without decomposition. A further observation was made as well, namely, that the N-acetyl group of acetylated α-methylDOPA is exceedingly resistant to alkaline saponification and is stable, for example, to 10% sodium hydroxide solution at 150°. Pursuant to these observations, the O,O′,N-triacetate of α-methylDOPA (II),[3] obtained quantitatively from α-methylDOPA, was methylated with dimethyl sulfate and potassium hydroxide, in a typical Schotten–Baumann manner, to give 95% of the N-acetyl dimethyl ether (III), m.p. 187–188°, together with 5% of the corresponding methyl ester (IIIa), m.p. 126–127°. The total methylation product (III + IIIa) was hydrolyzed essentially quantitatively with hydrochloric acid to α-methylDOPA dimethyl ether (IV).[2] Thus, α-methylDOPA could be converted to its dimethyl ether in nearly quantitative over-all conversion. Methylation of α-methylDOPA unprotected by the N-acetyl group resulted in N-methylation products. The N-acetyl derivative of α-methylDOPA, on the other hand, was easily prepared by hydrolysis of the corresponding triacetate and it, in turn, gave results similar to its precursor in the methylation reaction. The transformation of α-methylDOPA dimethyl ether to 3,4-dimethoxyphenylacetone (V) was effected oxidatively with sodium hypochlorite[4] in 90% yield. Thus, the total

CHART I



(1) See, for example: L. Gillespie, Jr., *Ann. N. Y. Acad. Sci.*, **88**, 1011 (1960); H. Smirk, *Brit. Med. J.*, 146 (1963), and references therein.

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