methanol, 1.21 g. (93%) of the aldehyde (VIIIa) was obtained as slightly tan needles, m.p. 145–157° dec.

Slight variations in the above procedures affect the yield considerably; it is especially important that at least a tenfold excess of sodium nitrite is used in A as well as in B.

By the same method as above 69% of **4,6-di-*p*-tolyl-*s*-triazine-2-aldehyde** (VIIIb), from 2-methyl-4,6-di-*p*-tolyl-*s*-triazine (Ie), was obtained as small colorless needles from carbon tetrachloride, m.p. 195–197° dec. The vacuum-dried aldehyde had sharp infrared bands at 1735 and 2820 cm.$^{-1}$, $\lambda_{\max}^{\text{MeOH}}$ 283 mμ ($\epsilon_{\max}$ 47,500), and was easily soluble in acetone, benzene, chloroform, and carbon tetrachloride.

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.32; H, 5.21; N, 14.68.

2,4-Dinitrophenylhydrazine of VIIIb was obtained as small, orange, felted needles (from pyridine), m.p. 269–273° dec.

Anal. Calcd. for $C_{24}H_{19}N_7O_4$: C, 61.40; H, 4.08; N, 20.89. Found: C, 61.35; H, 4.18; N, 20.71.

The Synthesis and Exhaustive Methylation of 5,6,7,8,9,10,6a,10a-Octahydrophenanthridines and Related Compounds[1]

TADASHI MASAMUNE, MITSUO TAKASUGI, HIROSHI SUGINOME, AND MASAYO YOKOYAMA

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

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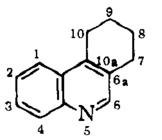
Several methods for preparation of *trans*- and *cis*-5,6,7,8,9,10,6a,10a-octahydrophenanthridines (II) and (V) are described. The confirmation of the configuration of these compounds by stereospecific synthesis and the conformation of the *cis* isomer are discussed. The exhaustive methylation of the stereoisomeric octahydrophenanthridines and octahydroacridines resulted in elimination of methanol.

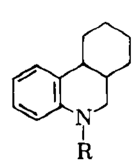
Several years ago we reported the synthesis of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine.[2] The configuration was presumed to be a *trans* modification but was not confirmed. We wish to report the stereospecific synthesis of stereoisomeric octahydrophenanthridines and the exhaustive methylation of these and related compounds.

It appeared that the most logical synthetic route to such bases would involve formation of stereoisomeric amino acids or related compounds which would be cyclized to the phenanthridine nucleus. At first, in view of the stereospecific condensation[3] of *trans*-2-phenylcyclohexanol to *cis*-octahydrophenanthrene, stereoisomers of 2-anilinomethylcyclohexanol were prepared and their condensations attempted. The reduction of 2-anilinocarboxycyclohexanone[4] with lithium aluminum hydride afforded a mixture from which two 2-anilinomethylcyclohexanols, m.p. 80–82° and 102–104°, were isolated by repeated recrystallizations. However, acid treatment of these cyclohexanols did not lead to the formation of octahydrophenanthridines; that is, these alcohols were recovered unaffected by treatment with 90% sulfuric acid at room temperature; but, at 100°, each of these alcohols was converted to a mixture containing 7,8,9,10-tetrahydrophenanthridine[5] (I) as a main product.

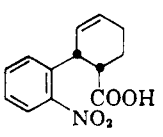
In 1951, Braude, *et al.*,[6] reported a synthesis of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine (II) of m.p. 72° which involved the Diels–Alder condensation of acrolein to *o*-nitrophenylbutadiene. Furthermore, they obtained two 2-(*o*-nitrophenyl)-1,2,5,6-tetrahydrobenzoic acids (III), m.p. 141° and 123°, by the addition reaction of the butadiene derivative with acrylic acid. The configurations of the acids were tentatively assigned as *trans* and *cis*, respectively, and those acids appeared to be appropriate intermediates for our purpose. The present re-examination of the reactions under various conditions showed that the acid of m.p. 141° was obtained at the reaction temperature of 50–80° and that of m.p. 123° at that of 150–160°. They gave the identical spectra in chloroform (not in Nujol), and the apparent discrepancy over the melting points of those acids was due to polymorphism. Catalytic hydrogenation of III in the presence of platinum smoothly gave hexahydrophenanthridone (IV), m.p. 207–208°, along with a small amount of an amino acid, $C_{13}H_{17}O_2N$, m.p. 144–145°. The lactam (IV) also was produced by esterification of III with diazomethane followed by hydrogenation. Reduction[7] of IV with lithium aluminum hydride resulted in formation of 5,6,7,8,9,10,6a,10a-octahydrophenanthridine (V), m.p. 41–42°. Although the mixture melting point of the bases (II and V) was not depressed, their infrared spectra were different in both Nujol and chloroform, thus proving that V was a new stereoisomer.



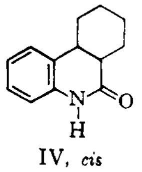
I



II, R = H; *trans*
V, R = H; *cis*
IX, R = CH_3; *cis*
XV, R = CH_3; *trans*



III



IV, *cis*
XIV, *trans*

If the new isomer (V) had the *cis* configuration, it was expected to be formed by catalytic hydrogenation[8]

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[1] Part XII of "The Condensed Polynuclear Perhydro-compounds Containing Nitrogen"; Part XI, T. Masamune and M. Koshi, *Bull. Chem. Soc. Japan*, **32**, 1005 (1959).

[2] T. Masamune, Y. Kubota, G. Homma, and M. Ohno, *J. Chem. Soc. Japan*, **77**, 1467 (1956).

[3] R. A. Barnes and A. D. Olin, *J. Am. Chem. Soc.*, **78**, 3830 (1956).

[4] B. K. Blount, W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 1975 (1929); H. K. Sen and U. Basu, *J. Indian Chem. Soc.*, **6**, 309 (1929).

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

[6] E. A. Braude and J. S. Fawcett, *ibid.*, 3113 (1951).

[7] *Cf.*, C. A. Grob and Hj. U. Schmid, *Helv. Chim. Acta*, **33**, 1955 (1950).

[8] For a recent and comprehensive review, see R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957).

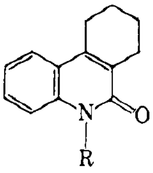
TABLE I

THE BASICITIES AND NEAR-ULTRAVIOLET SPECTRA OF *trans*- AND *cis*-OCTAHYDROPHENANTHRIDINES

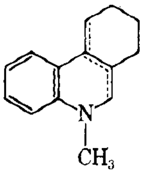
Compound	Absorption maxima, $\lambda_{max}^{solvent}$, mμ(ε) Isooctane	Ether	Ethanol	Hydrochloric acid (0.1 *N*)	Basicities,[a] pK_a
II	302 (2950)	305.5 (3120)	303.5 (2310)	267 (250) 260 (320)	4.58
V	302 (2860)	305.5 (3360)	303.5 (2580)	267 (290) 260 (350)	4.59

[a] Measured at 15° in 50% aqueous ethanol.

of a double bond at C_{6a}–C_{10a} of a suitable phenanthridine derivative. 7,8,9,10-Tetrahydrophenanthridone[4] (VI) was selected as a starting material, since neither II nor V was isolated by hydrogenation[2] of I. In contrast to 2-quinolinol, which was easily hydrogenated,[9] VI and its N-methyl derivative[10] (VII) were resistant to catalytic hydrogenation over platinum at room temperature. An attempted hydride reduction of VI resulted only in formation of I. On the other hand, VII underwent the hydride reduction to N-methylhexahydrophenanthridine (VIII), m.p. 40–43°, which was very unstable to air. The base (VIII) could be hydrogenated over platinum in an acidic solution to render N-methyloctahydrophenanthridine, which was proved to be identical with the N-methyl derivative (IX) of the new isomer (V). During this hydrogenation N-methylhexahydrophenanthridine (X), isomeric with VIII, was formed as a by-product. The base (X) also was obtained by acid treatment of VIII. It was characterized only as a salt, namely the hydrochloride, m.p. 94.5–95.5°. As a structure of this base, 5,6,7,8,9,6a-hexahydrophenanthridine (XI) might be considered, but in view of the stronger basicity of X compared with IX, the formula X would be more probable. This formation of the isomerized product (X) showed the possibility that the formation of IX from VIII might take place not by the direct hydrogenation but through the intermediate (X).



VI, R = H
VII, R = CH_2

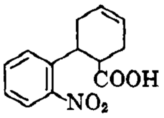


VIII, with $\Delta^{6a(10a)}$
X, with $\Delta^{6(6a)}$
XI, with $\Delta^{10(10a)}$

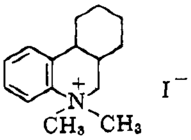
In 1956 Taylor, *et al.*,[11] prepared 2-(*o*-nitrophenyl)-1,2,3,6-tetrahydrobenzoic acid (XII) of m.p. 184° by condensation of *trans*-*o*-nitrocinnamic acid with butadiene. A similar reaction of the *cis* isomer[12] with butadiene in xylene at 160° has now afforded a small amount of a stereoisomeric adduct (XIII), m.p. 148–149.5°, the most part of the starting material having been recovered unchanged. Adducts XII and XIII were converted to the corresponding hexahydrophenanthridones of m.p. 220–221° (XIV) and 211–212°. The latter compound was identical with IV mentioned above. It is evident, on the basis of the well-established stereochemistry of Diels–Alder reaction, that phenanthridones XIV and IV possess, respectively, *trans* and *cis* configurations. Hydride reduction of these lactams gave rise to the *trans*-octahydrophenanthridine (II), m.p. 69–70°, and the *cis* isomer (V), m.p. 40–41°. The former, thus obtained, was found to be identical with the octahydro base previously obtained by Braude,[6] Kruber,[13] and Masamune, *et al.*[2]

The conformation of V was determined according to the method[14] previously mentioned. The basicities and near-ultraviolet spectra of II and V were measured, and the results are shown in Table I. Identical values for both compounds indicated that the formation of the hydrogen bond between the lone pair of nitrogen and hydroxyl group of ethanol (solvent for measurement of the spectra) took place in the same degree for II and V, meaning that the methylene group located at the β-position relative to the N-atom of the *trans* isomer (II) and that of the *cis* isomer (V) existed in the same conformation, equatorial with respect to tetrahydroquinoline ring.

In a previous report[15] it has been shown that *cis*-hexahydrocarbazole underwent the normal degradation to an olefin in the exhaustive methylation, whereas the corresponding *trans* base rendered N-methyl-*cis*-hexahydrocarbazole along with the olefin. In relation to this stereochemical rearrangement, the exhaustive methylation of II, V, and *trans*- and *cis*-octahydroacridines was investigated.



XII, *trans*
XIII, *cis*



XVI, *trans*
XVII, *cis*

The addition of methyl iodide to acetone solution of II and V or their N-methyl derivatives (XV and IX) easily yielded the corresponding methiodides XVI, m.p. 208–210°, and XVII, m.p. 208–209°. Pyrolysis of the methohydroxide obtained by treatment of XVI with silver oxide furnished an oily base, and examination of the infrared spectrum suggested it was a mixture of XV and IX. The vapor phase chromatographic analysis of the mixture showed that it consisted of only XV and IX, the ratio being 4 to 1. The similar treatment of XVII gave an analogous result, the ratio of XV and IX being 2 to 3.

The Hofmann degradation of the methohydroxide obtained from N-methyl-*trans*-octahydroacridine methiodide, m.p. 193–194°, readily proceeded at relatively

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[9] R. Huisgen, *Ann.*, **559**, 101 (1948); E. Späth and F. Galinovsky, *Ber.*, **69**, 2059 (1936).

[10] R. E. Bowman, A. Campbell, and E. M. Tanner, *J. Chem. Soc.*, 444 (1959).

[11] E. C. Taylor, Jr., and E. J. Strojny, *J. Am. Chem. Soc.*, **78**, 5104 (1956).

[12] R. Stoermer and P. Heymann, *Ber.*, **45**, 3099 (1912).

[13] O. Kruber, *ibid.*, **72**, 771 (1939).

[14] T. Masamune, *J. Am. Chem. Soc.*, **79**, 4418 (1957).

[15] T. Masamune, *Bull. Chem. Soc. Japan*, **30**, 491 (1957).

low temperature (below 100°) and the original tertiary amine, N-methyl-*trans*-octahydroacridine, was produced. The formation and pyrolysis of the methiodide, m.p. 182–184°, of the *cis* isomer were analogously carried out and N-methyl-*cis*-octahydroacridine was obtained.

With the two *trans*-methohydroxides described above a suitable geometrical disposition[16] is not available for the normal E2 process leading to olefin, and it would not be unreasonable, therefore, that elimination of methanol was encountered in the degradation. On the other hand, it is to be noted that the two *cis* compounds, with which the stereochemical arrangement required for E2 elimination is possible irrespective of unfavorable conformation, behaved similarly to the *trans* bases, and a detailed discussion will be reserved until further investigation.

Experimental

Ultraviolet absorption measurements were made using a Hitachi recording spectrophotometer, Type EPS-2, or a Beckman quartz spectrophotometer, Model DU; ethanol was usually used as a solvent. The absorption curves described in Table I were measured using the latter instrument, and the spectra were examined at 0.5-mμ intervals near maxima and at 3-mμ intervals in another region of 215 to 350 mμ.

Infrared absorption spectra were measured in Nujol, unless otherwise mentioned, using a Nihon Bunko spectrophotometer, Model DS-401G.

Basicity measurements were carried out at 15° in 50% aqueous ethanol according to the method of Thomson,[17] and the results were expressed as pK_a values for the conjugated acids. Solutions were prepared in "50% aqueous ethanol" by dissolving *a* g. of the bases in less than 10 ml. of ethanol, adding *b* ml. of 0.094 *N* hydrochloric acid, then adding (12.5 − *b*) ml. of distilled water, and making the volume up to 25 ml. with ethanol in a standard flask. (See Table II.)

TABLE II

OCTAHYDROPHENANTHRIDINE

trans				*cis*			
a, g.	pH	*b*, ml.	pK_a	*a*, g.	pH	*b*, ml.	pK_a
0.0255	4.20	1.00	4.55	0.0344	4.48	1.10	4.59
0.0305	4.42	1.00	4.60	0.0277	4.25	1.10	4.61
		Mean	4.58	0.0320	4.38	1.10	4.56
						Mean	4.59

2-Anilinomethylcyclohexanols.—A mixture of 2-carbethoxycyclohexanone[18] (28.6 g.), aniline (15.7 g.), and a small amount of pyridine (15 drops) was put into an oil bath of about 160° and heated at 200° until ethanol was completely distilled (15–20 min.). The reaction mixture became crystalline upon cooling and this crude product was recrystallized from aqueous ethanol. After removal of the first crop (2.3 g.) of m.p. 225–231° and the second (1.0 g.) of m.p. 101–197°, the mother liquor gave crystals (12.8 g.) of m.p. 99–101°. Recrystallization from benzene–petroleum ether (b.p. 30–60°) afforded 2-anilinocarboxycyclohexanone (11.4 g.), m.p. 103–104°.

To 2-anilinocarboxycyclohexanone (3.0 g.) suspended in dry ether (200 ml.) was added gradually lithium aluminum hydride (6.0 g.) in dry ether (150 ml.) under stirring, and the mixture was refluxed for 20 hr. After decomposition of the metal complex with water followed by removal of the insoluble material by filtration, the ether layer was extracted with three 35-ml. portions of 2 *N* hydrochloric acid. A crude base (2.43 g.) of m.p. 79–90° was obtained on alkalization of the acidic solution and was recrystallized repeatedly to yield two kinds of 2-anilinomethylcyclohexanols having m.p. 102–104° and 80–82°, respectively. The latter was isolated from the more soluble part and the yield was 1.39 g. The isomeric alcohol of m.p. 104° amounted to 0.57 g.

Anal. (of the alcohol of m.p. 104°). Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.08; H, 9.22.

Anal. (of the alcohol of m.p. 82°). Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.39; H, 9.38.

2-(*o*-Nitrophenyl)-1,2,5,6-tetrahydrobenzoic Acid[6] (III). A.—A mixture of *o*-nitrophenylbutadiene[6] (7.2 g.) and acrylic acid (7.2 g.) was heated at 70° for 25 hr. The cooled mixture gave crystals (6.0 g.), m.p. 133–135°, on standing. These were collected by filtration and were recrystallized from ethanol to yield analytically pure 2-(*o*-nitrophenyl)-1,2,5,6-tetrahydrobenzoic acid (III), m.p. 139–141°, λ_{max} 251 mμ (ε 4900).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.39; H, 5.58.

B.—A solution of *o*-nitrophenylbutadiene (2.0 g.) in acrylic acid (1.4 g.) was refluxed for 12 hr. at 150–160° (bath temperature). The dark brown product was dissolved in 10% aqueous sodium carbonate, and this solution was washed with three 150-ml. portions of ether and acidified to give a resinous product. The latter was crystallized from aqueous ethanol. Repeated recrystallizations from aqueous ethanol produced the acid (III, 0.2 g.) of m.p. 121–123°, λ_{max} 251 mμ (ε 4700).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.18; H, 5.36.

***cis*-7,8,9,10,6a,10a-Hexahydrophenanthridone (IV) from 2-(*o*-Nitrophenyl)-1,2,5,6-tetrahydrobenzoic Acid (III). A.**—The acid (III, 0.5 g.) in ethyl acetate (19 ml.) was subjected to hydrogenation in the presence of platinum oxide (0.1 g.) at room temperature and 4 moles of hydrogen were absorbed for about 3 hr. Removal of the catalyst and the solvent afforded crude lactam (0.4 g.). On recrystallization from methanol, *cis*-hexahydrophenanthridone (IV), m.p. 208–210°, λ_{max} 250 mμ (ε 13,000), was obtained.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.38; H, 7.59.

Evaporation of the mother liquor followed by crystallization of the residue from aqueous ethanol gave an amino acid, 1,2,3,4,5,6-hexahydro-2′-aminodiphenyl-2-carboxylic acid, m.p. 144–145°, λ_{max} 257 mμ (ε 12,000).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82. Found: C, 71.08; H, 7.75.

B.—The acid (III, 0.23 g.) was treated with an excess of diazomethane in ether and allowed to stand overnight. Removal of the ether and recrystallization of the residue from aqueous acetone gave the methyl ester (0.2 g.), m.p. 79–80°, λ_{max} 252 mμ (ε 4200).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.71; H, 6.02.

The ester (1.0 g.) in ethyl acetate (150 ml.) was hydrogenated over platinum oxide (0.1 g.) for 5.5 hr. and gave crude lactam (0.7 g.). Fractional recrystallizations from aqueous ethanol yielded *cis*-hexahydrophenanthridone (IV), m.p. 207–208°.

***cis*-5,6,7,8,9,10,6a,10a-Octahydrophenanthridine (V).**—To *cis*-hexahydrophenanthridone (IV, 0.2 g.) in tetrahydrofuran (10 ml.) was added lithium aluminum hydride (0.37 g.) in tetrahydrofuran (20 ml.), and the whole was refluxed for 8 hr. After decomposition of the metal complex with water (3 ml.) and removal of the solvent, the residue was dissolved in 6 *N* hydrochloric acid (2 ml.) and washed with ether. Alkalization of the aqueous layer and extraction with ether afforded an oily base (0.15 g.), which gradually solidified. Sublimation followed by recrystallization from aqueous ethanol or petroleum ether gave *cis*-octahydrophenanthridine (V), m.p. 41–42°, λ_{max} 251 mμ (ε 8300) and 303.5 (2600).

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.39; H, 9.04; N, 7.38.

The picrate had m.p. 173–174° on recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{20}N_4O_7$: C, 54.80; H, 4.84. Found: C, 54.48; H, 5.07.

7,8,9,10-Tetrahydrophenanthridone[4] (VI).—A mixture of freshly distilled 2-carbethoxycyclohexanone (30 g.) and aniline (16.2 g.) was heated at about 200° (bath temperature) until the distillation of ethanol ceased (about 15 min.). After cooling, it was dissolved in concentrated sulfuric acid (50 ml.) and warmed for 20 min. on a steam bath. This solution was poured into water and the crude lactam was precipitated. On recrystallization from ethanol, tetrahydrophenanthridone (10.4 g.), m.p. 266–267°, was obtained; lit.[4] m.p. 273°.

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(16) For a recent review, see A. C. Cope, *Org. Reactions*, **11**, 317 (1960).

(17) G. Thomson, *J. Chem. Soc.*, 1113 (1946).

(18) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 531.

Reduction of 7,8,9,10-Tetrahydrophenanthridone (VI) with Lithium Aluminum Hydride.—To tetrahydrophenanthridone (2.0 g.) in tetrahydrofuran (190 ml.) was added slowly lithium aluminum hydride (1.72 g.) in tetrahydrofuran (55 ml.), and the mixture was refluxed for 24 hr. under stirring. The product was worked up according to the usual procedure and the crude base (1.3 g.) of m.p. 50–57° was obtained. The base showed no band attributable to amino NH stretching frequency. On recrystallization it had m.p. 58–61° and proved to be 7,8,9,10-tetrahydrophenanthridine[5] (I) by the mixture melting point method and comparison of the infrared spectra.

N-Methyl-7,8,9,10-tetrahydrophenanthridone[10] (VII).—A mixture of tetrahydrophenanthridone (VI, 10 g.) and methyl iodide (40 g.) in dry acetone (400 ml.) was refluxed for 24 hr. with potassium carbonate (20 g.). After filtration of inorganic salts and removal of the solvent, the residue was recrystallized from petroleum ether, giving the N-methyl derivative (VII, 8.43 g.), m.p. 98–98.5°; $\lambda_{\max}$ 228 mμ (ϵ 38,000), 271 (7500), 281 (6800), and 324 (8400). The reference[10] gives m.p. 63–64°, and, when conducted according to the reference, the reaction resulted only in recovery of the starting material.

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.97; H, 7.16; N, 6.47.

N-Methyl-5,6,7,8,9,10-hexahydrophenanthridine (VIII).—Lithium aluminum hydride (4.0 g.) gradually was added to a solution of N-methyltetrahydrophenanthridone (VII, 5.0 g.) in dry ether (320 ml.), and the mixture was heated on a water bath for 10 hr. The mixture was worked up as usual, and an oily product thus obtained was submitted to distillation in a nitrogen stream under reduced pressure, and a fraction of b.p. 167–168° (3 mm.) was collected. It crystallized on cooling and was recrystallized from petroleum ether to yield N-methylhexahydrophenanthridine (VIII, 3.38 g.), m.p. 40–43°, $\lambda_{\max}$ 234 mμ (ϵ 26,000) and 324 (3400). The picrate melted at 158–159°.

Anal. Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71. Found: C, 56.34; H, 4.80.

Catalytic Hydrogenation of N-Methyl-5,6,7,8,9,10-hexahydrophenanthridine (VIII).—N-Methylhexahydrophenanthridine (VIII, 4.58 g.) in acetic acid (115 ml.) was treated with hydrogen in the presence of platinum oxide (0.92 g.) for 42 hr. and absorbed 585 ml. of hydrogen. After removal of the catalyst and evaporation of acetic acid, the residue was treated with 5% aqueous sodium hydrogen carbonate (60 ml.) and ether. The ether solution gave an oily substance, which was distilled under reduced pressure, yielding N-methyl-*cis*-octahydrophenanthridine (IX, 1.07 g.), b.p. 145–149° (2.5 mm.), $\lambda_{\max}$ 257 mμ (ϵ 12,000) and 304 (3500).

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.22; H, 9.81; N, 6.77.

The picrate was prepared in ether and was recrystallized from ethanol; it had m.p. 145–147°.

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.73; H, 5.42.

The aqueous sodium hydrogen carbonate solution obtained above was made strongly alkaline with 6 *N* aqueous sodium hydroxide (20 ml.) and extracted with ether. Into a part of the ether solution was passed dry hydrogen chloride. The hydrochloride of N-methyl-5,7,8,9,10,10a-hexahydrophenanthridine (X) separated as an oil at first, gradually solidified, and was recrystallized from aqueous acetone; it had m.p. 94.5–95.5°, $\lambda_{\max}$ 234 mμ (ϵ 47,000) and 315 (7600). The remaining part of the ether solution was converted into the picrate by addition of picric acid in ether. On recrystallization from ethanol, it had m.p. 171–172°.

Anal. (of the hydrochloride). Calcd. for $C_{14}H_{18}NCl$: C, 71.27; H, 7.64. Found: C, 71.29; H, 7.70.

Anal. (of the picrate). Calcd. for $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.71. Found: C, 55.98; H, 4.42.

Isomerization of VIII (0.1 g.) was almost completed by shaking it in acetic acid (5 ml.) for 1.5 hr. at room temperature. The mixture was worked up according to the procedure mentioned above and X was obtained quantitatively.

***cis-o*-Nitrocinnamic Acid.**[12]—*trans-o*-Nitrocinnamic acid (10.0 g.) was dissolved in pyridine (100 ml.) in a Pyrex flask and the solution was exposed to sunlight for 20 days. When 6 *N* hydrochloric acid (about 200 ml.) was added to the solution, the unchanged *trans* acid crystallized and was separated by filtration. The ether extract of the filtrate gave *cis*-cinnamic acid (3.4 g.), m.p. 141–143°, after removal of the ether and recrystallization from benzene; lit.[12] yield 22%.

***cis*-2-(*o*-Nitrophenyl)-1,2,3,6-tetrahydrobenzoic Acid (XIII).**—A mixture of *cis-o*-nitrocinnamic acid (4.0 g.) and butadiene (12 ml.) in xylene containing hydroquinone (0.04 g.) was heated at 160° for 20 hr. in a sealed tube. After removal of the unchanged *cis-o*-nitrocinnamic acid (3.0 g.) from the cooled mixture by filtration, the filtrate was evaporated to dryness, and the residue was extracted with 5% aqueous sodium bicarbonate. The aqueous solution was acidified and extracted with ether. Evaporation of the ether from this extract gave a mixture of acids (0.83 g.) which was dissolved in benzene. The benzene solution was concentrated until no more pure *cis-o*-nitrocinnamic acid was isolated, and subjected to filtration. After evaporation of the filtrate, the residue was recrystallized from benzene repeatedly to give *cis*-2-(*o*-nitrophenyl)-1,2,3,6-tetrahydrobenzoic acid (XIII, 0.19 g.), m.p. 148–149.5°, $\lambda_{\max}$ 254 mμ (ϵ 4200).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.41; H, 5.40.

***cis*-7,8,9,10,6a,10a-Hexahydrophenanthridone (IV) from *cis*-2-(*o*-Nitrophenyl)-1,2,3,6-tetrahydrobenzoic Acid (XIII).**—A solution of *cis*-2-(*o*-nitrophenyl)-1,2,3,6-tetrahydrobenzoic acid (XIII, 0.12 g.) in ethyl acetate (10 ml.) was hydrogenated over prereduced Adams' platinum (0.2 g.) at room temperature. During the hydrogenation a considerable amount of crystals separated, and 80 ml. of hydrogen was absorbed after 19 hr. The product was worked up as usual and *cis*-hexahydrophenanthridone (80 mg.), m.p. 211–212°, was obtained after recrystallization from methanol. This hexahydrophenanthridone was proved to be identical with the lactam (IV) obtained from III by the mixture melting point method and by comparison of the infrared spectra in Nujol.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.66; H, 7.44; N, 7.06.

***trans*-7,8,9,10,6a,10a-Hexahydrophenanthridone (XIV).**—A starting material, *trans*-2-(*o*-nitrophenyl)-1,2,3,6-tetrahydrobenzoic acid, was prepared according to the procedure by Taylor, *et al.*[11] Hydrogenation of the acid (0.31 g.) in ethyl acetate (30 ml.) was carried out using pre-reduced Adams' platinum (0.03 g.). After uptake of 90 ml. of hydrogen, platinum oxide (0.06 g. and 0.16 g.) was added to the solution. The total consumption after 10 hr. amounted to 115 ml. (3.9 moles). The product was worked up as usual and *trans*-hexahydrophenanthridone (XIV), m.p. 220–221°, $\lambda_{\max}$ 249 mμ (ϵ 13,000), was obtained almost quantitatively. The mixture melting point was depressed to 180–190° on admixture with the corresponding *cis* isomer (IV).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.32; H, 7.34; N, 7.16.

***trans*-5,6,7,8,9,10,6a,10a-Octahydrophenanthridine (II) from *trans*-7,8,9,10,6a,10a-Hexahydrophenanthridone (XIV).**—To lithium aluminum hydride (0.25 g.) in tetrahydrofuran (10 ml.) was added slowly *trans*-hexahydrophenanthridone (0.14 g.) dissolved in tetrahydrofuran (7 ml.), and the whole mixture was refluxed for 12 hr. under stirring. After addition of water (2 ml.) and removal of insoluble precipitates thus formed, the tetrahydrofuran solution was evaporated to give an oily substance. It was extracted with 6 *N* hydrochloric acid and the acidic solution, after being washed with ether, was treated with 6 *N* aqueous sodium hydroxide to separate crude *trans*-octahydrophenanthridine (0.07 g.), m.p. 62–68°. It was purified by distillation under reduced pressure (55–62° at 2 mm.), followed by recrystallization from petroleum ether to give m.p. 69–70°, $\lambda_{\max}$ 253 mμ (ϵ 7900) and 303.5 (2300). This *trans* base was found to be identical with octahydrophenanthridine (II) prepared by Braude, *et al.*,[6] and by Masamune, *et al.*,[2] by the mixture melting point method and by comparison of the infrared spectra of bases, picrates, and benzoyl derivatives.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.28; H, 9.08; N, 7.35.

The picrate and the benzoyl derivative[2] had m.p. 171–172° (from ethanol) and m.p. 132–134° (from aqueous ethanol), respectively. The acetyl derivative prepared by refluxing with acetic anhydride melted at 72–74° (from petroleum ether).

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.85; H, 8.59; N, 6.17.

N-Methyl-*cis*- and -*trans*-octahydrophenanthridines (IX and XV).—A mixture of *cis*-octahydrophenanthridine (V, 1.0 g.) and methyl iodide (2.0 g.) was warmed in ethanol (6 ml.) containing potassium hydroxide (0.9 g.) for 4.5 hr. After removal of the excess methyl iodide and the solvent, the whole mixture was shaken with ether and 30% aqueous potassium hydroxide. Crystalline substances insoluble in both the ethereal and aqueous alkaline solution were collected by filtration and recrystallized from ethanol. N-Methyl-*cis*-octahydrophenanthridine methiodide (XVII, 0.27 g.), m.p. 208–209°, was obtained.

Anal. Calcd. for $C_{15}H_{22}NI$: C, 52.51; H, 6.41. Found: C, 52.55; H, 6.65.

The ether layer gave an oil (0.73 g.) on removal of the ether, which was refluxed with acetic anhydride (2.2 ml.) for 1 hr. The reaction product was warmed with water on a steam bath for 30 min., and a mixture of aqueous acetic acid and an oil thus formed was treated with ether. The ether solution was washed with 1 *N* hydrochloric acid (10 ml.) and was dried. On evaporation of the ether, N-acetyl-*cis*-octahydrophenanthridine (0.44 g.) was obtained, which was not further purified. The aqueous acetic acid and hydrochloric acid solutions were combined, made basic and an oil which separated was extracted with ether. The ether solution gave N-methyl-*cis*-octahydrophenanthridine (IX, 0.29 g.), b.p. 146–148° (bath temperature, 2 mm.), $\lambda_{\max}$ 256 mμ (ϵ 14,000) and 304 (3900), which was found as a single compound by vapor phase chromatographic analysis.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.34; H, 9.76.

The base gave a picrate, m.p. 148–149°, after preparation in ether and recrystallization from ethanol. The hydroiodide was prepared by addition of hydroiodic acid in acetone and recrystallized from acetone to have m.p. 173–175°. Infrared spectra of the base and the derivatives showed that the base was identical with N-methyloctahydrophenanthridine (IX) prepared from VIII by hydrogenation.

Anal. (of the picrate). Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.84; H, 5.30.

Anal. (of the hydroiodide). Calcd. for $C_{14}H_{20}NI$: N, 4.25. Found: N, 4.20.

Similarly, *trans*-octahydrophenanthridine (II, 0.5 g.) was methylated and the methiodide (0.24 g.), m.p. 208–210° (from ethanol), N-acetyl derivative (0.23 g.), m.p. 68–71° (from petroleum ether), and N-methyl derivative (XV, 0.19 g.) oil, $\lambda_{\max}$ 257 mμ (ϵ 12,000) and 302 (3000), were obtained.

The picrate and hydroiodide of N-methyl derivative had m.p. 172–174° (from acetone) and m.p. 173–175° (from ethanol).

Anal. (of the N-methyl derivative). Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.51; H, 9.55.

Anal. (of the methiodide). Calcd. for $C_{15}H_{22}NI$: C, 52.51; H, 6.41. Found: C, 52.44; H, 6.57.

Anal. (of the picrate). Calcd. for $C_{20}H_{22}N_4O_7$: N, 13.02. Found: N, 13.29.

Anal. (of the hydroiodide). Calcd. for $C_{14}H_{20}NI$: N, 4.25. Found: N, 4.24.

The Exhaustive Methylation of N-Methyl-*cis*- and -*trans*-octahydrophenanthridines (IX and XV).—A warm solution of the N-methyl *cis*-methiodide (XVI, 0.65 g.) in a mixture of methanol (5 ml.) and water (2.5 ml.) was shaken for 1 hr. with silver oxide freshly prepared from silver nitrate (0.39 g.). After removal of the inorganic compounds and the solvent below 80° under reduced pressure, the residue was heated to 180°. The decomposition was almost completed at 145°. The product was treated with ether and 1 *N* aqueous sodium hydroxide and the ether solution gave an oil (0.28 g.). N-Methyl-*trans*-methiodide (XVI, 0.43 g.) was treated similarly and an oil (0.18 g.) was obtained.

The oily bases from XVII and XVI were examined by vapor phase chromatography using a Hitachi gas chromatographic analyzer KGL-II. They were analyzed at 200° using helium gas and polyethylene glycol (Shimazu 6000). The peaks designated were only N-methyl-*cis*- and -*trans*-octahydrophenanthridines in both cases. With the oil from XVII, the relative ratio of N-methyl-*cis*- and -*trans*-octahydro derivatives was 3 to 2 and with that from XVI, 1 to 4.

N-Methyl-*cis*- and -*trans*-octahydroacridines.—A mixture of *cis*-octahydroacridine[19] (4.5 g.) and methyl iodide (7.0 g.) was refluxed with potassium hydroxide (4.0 g.) in ethanol (30 ml.) for 8 hr. After filtration of inorganic compounds followed by removal of ethanol and methyl iodide, the residue was shaken with ether (50 ml.), water (50 ml.), and 6 *N* aqueous potassium hydroxide (10 ml.) for 30 min. An oily base obtained from the ether solution was then refluxed with acetic anhydride (10 ml.) for 30 min. The product was warmed with water (80 ml.) on a steam bath for 30 min. and a mixture of an oil formed, and the aqueous acetic acid solution was extracted with ether. After being washed with 1 *N* hydrochloric acid, dried, and evaporated, the ether solution gave N-acetyl-*cis*-octahydroacridine[19] (1.0 g.) which had m.p. 134–136° on recrystallization from ethanol. The aqueous acetic acid and hydrochloric acid solutions were combined, made basic and shaken with ether. An oily residue obtained from the ethereal solution was converted into the picrate, m.p. 173–174° (prepared in ethanol and recrystallized from the same solvent), or the hydroiodide, m.p. 172–174° (prepared in acetone and recrystallized from acetone–ethanol). An oily base regenerated from those salts with 6 *N* aqueous ammonia was subjected to distillation and N-methyl-*cis*-octahydroacridine (2.5 g.), b.p. 183–186° (22 mm.), $\lambda_{\max}$ 256 mμ (ϵ 15,000) and 305 (3700), was obtained.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.40; H, 9.40.

Anal. (of the picrate). Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.90; H, 5.40.

trans-Octahydroacridine (4.5 g.) was treated similarly to yield N-acetyl-*trans*-octahydroacridine[20] (1.0 g.), m.p. 84–86° (from petroleum ether), and N-methyl-*trans*-octahydroacridine (2.2 g.), m.p. 69–71° (from petroleum ether), $\lambda_{\max}$ 260 mμ (ϵ 14,000) and 301 (3900). The picrate and hydroiodide had m.p. 138–140° (from ethanol) and m.p. 198–200° (from ethanol), respectively.

Anal. Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.35; H, 9.53.

Anal. (of the picrate). Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 56.02; H, 5.37.

The Exhaustive Methylation of N-Methyl-*cis*- and -*trans*-octahydroacridines.—A solution of N-methyl-*cis*-octahydroacridine (4.5 g.) in methyl iodide (15 g.) was heated on a steam bath for 15 min. in a sealed tube, when a small amount of black resinous oil was formed in the upper part. The mixture became solid on cooling and was collected by filtration and washed with acetone. The crude methiodide thus obtained had m.p. 182–184° and was used for the subsequent exhaustive methylation. On recrystallization from ethanol it had m.p. 185–186°.

Anal. Calcd. for $C_{15}H_{22}NI$: C, 52.48; H, 6.46. Found: C, 52.86; H, 6.25.

Similarly a mixture of N-methyl-*trans*-octahydroacridine (2.5 g.) and methyl iodide (8.5 g.) gave crude *trans*-methiodide (3.9 g.), m.p. 191–193°. On recrystallization from acetone, it had m.p. 193–194°.

Anal. Calcd. for $C_{15}H_{22}NI$: C, 52.48; H, 6.46. Found: C, 52.09; H, 6.22.

A solution of N-methyl-*cis*-octahydroacridine methiodide (3.0 g.) in 50% aqueous ethanol (40 ml.) was treated for 4 hr. with silver oxide prepared from silver nitrate (2.0 g.). The product, obtained by filtration of silver iodide and an excess of silver oxide and subsequent removal of ethanol and water under reduced pressure, was heated to 150°. The pyrolysis was practically completed at 120°. The resulting oil was collected with ether and then subjected to distillation. A fraction, b.p. 183–186° (22 mm.), was collected and amounted to 1.2 g. It was converted into the picrate in ethanol, which had m.p. 173–174° on recrystallization from ethanol. It was proved to be identical with N-methyl-*cis*-octahydroacridine by comparison of the infrared spectrum of the base and by the mixture melting point method of the picrate.

Treatment of N-methyl-*trans*-octahydroacridine methiodide (3.0 g.) under the similar condition gave a base (1.4 g.) of m.p. 62–64°. On recrystallization from petroleum ether it had m.p. 69–71°. The picrate melted at 138–140° on recrystallization from ethanol. There was no depression of the melting point on admixture of the base or the picrate with the corresponding specimens.

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[19] W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 2583 (1928); W. H. Perkin, Jr., and W. G. Sedgwick, *ibid.*, 438 (1926).

[20] M. M. Cartwright and S. G. P. Plant, *ibid.*, 1898 (1931).