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The Stereochemistry of Perhydroacridines and Perhydrophenanthridines[1)]

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The configurations of three stereoisomers, α, β and γ, of perhydroacridine and those, α, β and γ, of perhydrophenanthridine have been assigned as *trans,syn,trans, trans,anti,cis, trans,syn,cis, trans,anti,trans, trans,syn,cis* and *cis,syn,cis,* respectively, on the basis of both the process of their syntheses and the rate of formation of methiodides of the *N*-methyl derivatives. These configurations are consistent with the infrared-spectral behavior of their *N*-methyl derivatives in carbon tetrachloride solutions containing *n*-butanol as well as with the result of their exhaustive methylations. The relative steric requirement of the lone pair and the hydrogen on the N atom is also discussed.

One decade ago we reported[2)] on the preparation of three stereoisomers, α, β and γ (I, II and III), of perhydroacridine, whose configurations were assigned tentatively as *trans,trans, trans,cis,* and *cis,cis,* respectively. In a continuing study, these compounds were converted into the corresponding *N*-methyl derivatives (Ia, IIa and IIIa), mp 38—40°C, 36—38°C and 46—48°C, and it was attempted to prepare these derivatives from *N*-methyl-*trans*- and *cis*-1,2,3,4,4a,9,9a,10-octahydroacridines[3),4)] (IVa and Va). Contrary to the expectation, hydrogenation of IVa over platinum at room temperature produced Ia and IIIa in moderate yields, but no IIa, and that of Va gave IIIa as a major product along with a small amount of a new isomer (VIa), named *N*-methyl-δ-perhydroacridine. Since (1) both I and II have been obtained from *trans*-octahydroacridine (IV) by hydrogenation under the same conditions, and both II and III from the *cis* isomer (V),[2)] and (2) the *trans* isomer IV has been recovered unchanged on treatment under the conditions differing from the afore-mentioned only in replacement of hydrogen by nitrogen, the configuration of III must be revised to be *trans,cis* (Chart 1). Thus, both β- and γ-perhydroacridines II and III have one *trans* and one *cis* linkages, one of them being a *trans,anti,cis* modification, and the other a *trans,syn,cis.* On the other hand, α-perhydroacridine I involves at least one *trans* linkage[2)] and, therefore, should have a *trans,trans* structure.

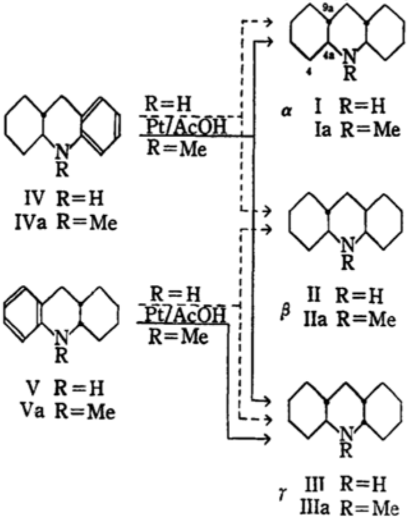

Chart 1

Only one perhydrophenanthridine (VII) has been reported: hydrogenation of 7,8,9,10-tetrahydrophenanthridine over Raney nickel at high temperature has afforded VII in a good yield, while that over platinum at room temperature a compound (VIII) assigned as a dodecahydro derivative.[5)] Since VII has also been obtained from *trans*-5,6,6a,7,8,9,10,10a-octahydrophenanthridine[3)] (IX) by hydrogenation over platinum at room

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[1)] Part XVII of "The Condensed Polynuclear Perhydro-compounds Containing Nitrogen": Refs. 21a and 15 are considered as Parts XV and XVI of this series.

[2)] T. Masamune and S. Wakamatsu, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.),* **77**, 1145 (1956).

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

[4)] D. A. Archer, H. Booth, P. C. Crisp and J. Parrick, *J. Chem. Soc.,* **1963**, 330; H. Booth, *Tetrahedron,* **19**, 91 (1963).

[5)] T. Masamune and Y. Kubota, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.),* **77**, 1467 (1956).

temperature,[5] reduction of the corresponding *cis* isomer[3] (X) was undertaken under the same conditions to obtain a new stereoisomer. However, the reaction led to formation of a good yield of compound VIII, which was also produced in a good yield by hydrogenation of *trans*-1,2,3,4,4a,5,6,10b-octahydrophenanthridine[6] (XI) in the presence of platinum in ethanol containing hydrochloric acid.[7] This fact, coupled with repeated analyses, led to the assignment of VIII as a perhydro compound, which was confirmed by the mass spectrum. The same treatment of a *cis* isomer[6] (XII) of XI gave a new perhydrophenanthridine (XIII), mp 37—38°C, and VIII, suggesting that the *cis* isomer XII would rearrange partially to the *trans* isomer XI under the acidic conditions used. These results (Chart 2) indicate that the stereoisomers VII, VIII and XIII, named α-, β- and γ-perhydrophenanthridines, have *trans,trans*, *trans,cis* and *cis,cis* configurations, respectively, in view of the well-known stereochemistry in hydrogenation of 1,2,3,4-tetrahydroisoquinoline.[8] The relative configurations of hydrogens at C-9a and C-8a in the perhydroacridines and those at C-10a and C-10b in the perhydrophenanthridines will be determined in the following.

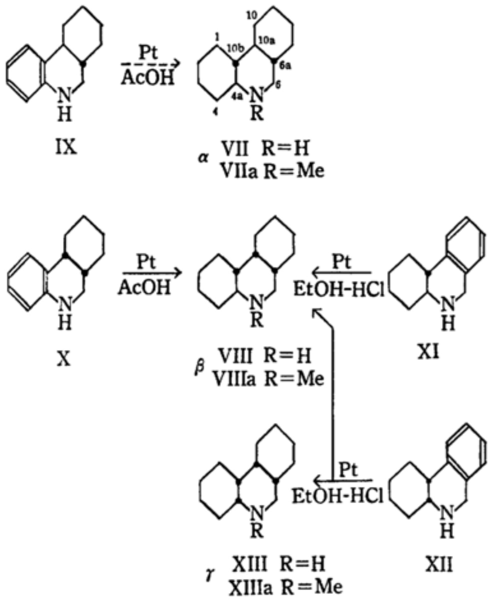

Chart 2

Formation of Methiodides of *N*-Methyl Derivatives. The rates of reaction with methyl iodide were determined for *N*-methyl derivatives of three perhydroacridines I, II and III, three perhydrophenanthridines VII, VIII and XIII, two octahydrophenanthridines XI and XII, *trans*- and *cis*-perhydroquinolines[9] (XIV and XV), piperidine (XVI), *cis*-perhydroindole[10] (XVII) and perhydrocarbazole[11] (XVIII), and the result is summarized in Table 1. In view of the fact that, in the absence of important steric hindrance, a stronger base reacts faster with a given alkyl halide,[12] the basicities of these *N*-methyl compounds were also measured. The transition state in the formation of these methiodides is supposed to have a steric arrangement similar to an ammonium cation formed by addition of a proton to each tertiary amine. Because of the small size of proton, a serious steric hindrance against the addition would hardly exist. To the contrary, it is expected that the presence of an axial methylene (β-axial methylene) group at the β-position to the N atom of a piperidine ring in these compounds would remarkably retard the rate of the quarternization, because either one of two methyl groups (N-$\underline{CH_3}$ and $\underline{CH_3}$I) on the N atom exists in an axial conformation.[13] In order to clarify these steric effects,

TABLE 1. THE REACTION RATE WITH METHYL IODIDE AND BASICITY OF *N*-METHYLPERHYDROACRIDINES AND RELATED COMPOUNDS

Compound (*N*-methyl derivative)	Rate constant[a] $k\times10^2$ (l/min·mol)	Basicity[b] pK_a
I	0.41	9.63
II	0.42×10^{-2}	9.67
III	0.44	9.65
VII	2.05	9.47
VIII	1.98	9.54
XIII	1.95	9.49
XI	0.52	8.54
XII	0.48	8.48
XIV	1.60	9.37
XV	1.67	9.41
XVI	1.30	9.11
XVII	3.09	9.73
XVIII	$<10^{-3}$	9.90

a) Measured at 20°C in 99.5% ethanol.
b) Measured at 20°C in 60% ethanol.

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[6] T. Masamune, M. Ohno, M. Koshi, S. Ohuchi and T. Iwadare, *J. Org. Chem.*, **29**, 1419 (1964).

[7] *Cf.* J. M. Devereux, K. R. Payne and E. R. A. Pealing, *J. Chem. Soc.*, **1957**, 2845.

[8] For example, B. Witkop, *J. Am. Chem. Soc.*, **70**, 2617 (1948); W. Hückel and F. Stepf, *Ann.*, **453**, 163 (1927).

[9] M. Ehrenstein and W. Bunge, *Ber.*, **67**, 1715 (1934).

[10] F. E. King, J. A. Baltrop and R. J. Walley, *J. Chem. Soc.*, **1945**, 277.

[11] T. Masamune, M. Ohno and M. Koshi, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **77**, 1017 (1956).

[12] For example, H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 445 (1949); H. C. Brown, *J. Chem. Soc.*, **1956**, 1248; R. T. Arnold, V. J. Webers and R. M. Dodson, *J. Am. Chem. Soc.*, **74**, 368 (1953); K. E. Weale, *J. Chem. Soc.*, **1954**, 2959.

[13] For the stereochemistry of piperidine quaternization, see A. T. Bottini and M. K. O'Rell, *Tetrahedron Letters*, **1967**, 423, and references cited there.

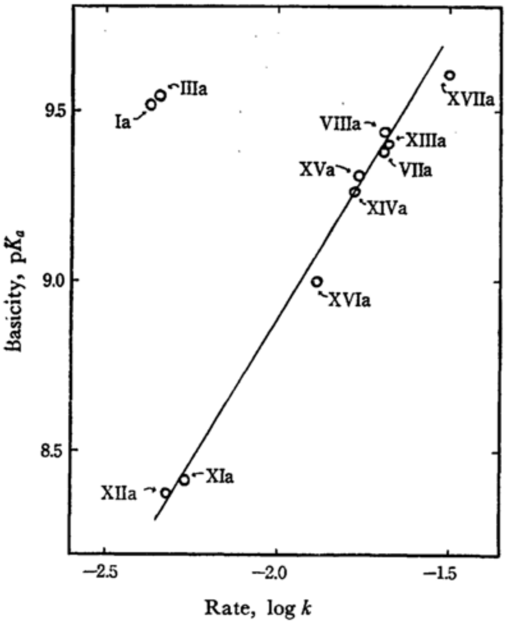

Fig. 1. The relation between the rate of N-methyl methiodides formation and the basicity of N-methylperhydroacridines and related compounds.

the logarithms of the rate constants were plotted against their pK_a values (Fig. 1).

trans-Perhydroquinoline (XIV), *trans*-octahydrophenanthridine (XI) and probably α-perhydrophenanthridine (VII) have only β-equatorial methylene substituents in the respective piperidine ring. Accordingly, the transition states in the reaction of their N-methyl derivatives would have approximately equal steric interactions, suggesting the presence of a linear relationship. In fact, it was true as shown in Fig. 1. Besides these bases, the corresponding *cis* isomers XVa, XIIa, VIIIa and also N-methyl-γ-perhydrophenanthridine (XIIIa) fell on this line, reflecting that these compounds involve the same steric requirement for the reaction as their stereoisomers. This linear relation indicates that these compounds contain no β-axial methylene substituents, as far as all the rings adopt chair conformations; namely, compounds VII, VIII and XIII have *trans,anti,trans*, *trans,syn,cis* and *cis,syn,cis* configurations, respectively.[*4] N-Methyl derivatives, XVIa and XVIIa, of piperidine and *cis*-perhydroindole deviated slightly from the line. In the former, the deviation would be attributed to the absence of an α-substituent, and in the latter it would be due to the fact that a methylene group in a five-membered ring offers less steric hindrance than that in a six-membered ring.[14] With N-methyl-α- and γ-perhydroacridines Ia and IIIa, considerable deviations were observed, which apparently resulted from the substitution of two α-methylene groups in the piperidine ring. On the other hand, N-methyl-β-perhydroacridine IIa and N-methylperhydrocarbazole XVIIIa revealed conspicuous decrease in the rate (the outside of Fig. 1). Whilst the rate of the latter is not interpretable well owing to its whole ambiguous steric arrangement, it is evident that the presence of a β-axial methylene group in the piperidine ring of IIa has brought about the remarkable retardation. This result, coupled with the synthetic process, establishes that the configurations of α-, β- and γ-perhydroacridines are *trans,syn,trans*, *trans,anti,cis* and *trans,syn,cis*, respectively.

Formation of Hydrogen Bonds with *n*-Butanol.[15] The method for determination of the configurations described in the preceding section is based on measurement of the reaction rates and rather troublesome. Furthermore, no consideration is given to the conformation in tertiary amine of compounds in which ring inversion is possible. As an attempt to approach to these problems by more practical experiments under mild conditions, we examined the infrared spectra near 3400 cm^{-1} of carbon tetrachloride solutions containing the afore-mentioned tertiary amines (0.1 to 0.2 M) and *n*-butanol. To avoid the confusion due to association of the butanol itself,[16] the concentration was fixed to be 0.05 M, where only absorptions at 3640 cm^{-1} (free OH) and near 3520 cm^{-1} (dimeric OH) were observed.

The ternary solution containing N-methyl-α-perhydroacridine Ia exhibited a definitely different spectrum from the corresponding containing the β-isomer IIa (Fig. 2); in the former a broad band centered at *ca.* 3240 cm^{-1} appeared in addition to a sharp band at 3640 cm^{-1} due to unassociated hydroxyl groups, while in the latter a new absorption with relatively weak intensity was instead centered at *ca.* 3420 cm^{-1} along with the sharp band. These broad absorptions near 3240 and 3420 cm^{-1} are undoubtedly attributed to the hydroxyl group (OH–N) bonded with the lone pairs of N atom. Kuhn,[17] Nakamoto[18] and others[19] showed, from measurement of the infrared spectra of a number of hydrogen-bonded compounds in the crystalline state, that an approximately

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[*4] If compound XIII had a *cis,anti,cis* configuration, the rate of quarternization would be reduced, no matter what conformation of the piperidine ring is taken, a chair or a twist-boat form.

14) R. T. Arnold and P. N. Craig, *J. Am. Chem. Soc.*, **72**, 2728 (1950), and references cited there.

15) T. Masamune, *Chem. Commun.*, **1968**, 244.

16) W. C. Coburn, Jr., and E. Grunwald, *J. Am. Chem. Soc.*, **80**, 1318 (1958).

17) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

18) K. Nakamoto, M. Margoshes and R. E. Rundle, *ibid.*, **77**, 6480 (1955).

19) R. M. Badger, *J. Chem. Phys.*, **8**, 288 (1940); R. C. Lord and R. E. Merrified, *ibid.*, **21**, 166 (1953).

linear relation exists between the length of hydrogen bond and the shift of frequency of the associated hydroxyl group from that of the unassociated. This correlation comes into existence if the hydrogen bond is of linear type and, especially, becomes important if the relevant tertiary amines have equal basicities such as the present compounds Ia and IIa. The observed difference in the frequency shifts between Ia and IIa (400 and 240 cm^{-1}, respectively) apparently arises from that in the hydrogen bond length between both the isomers, provided that the correlation holds for the compounds in the liquid (solution) state. Thus, this result indicates that there exists a steric hindrance in IIa, which obstructs proximity of the butanol molecule to the lone pair of N atom and which must result from the presence of a β-axial methylene group. This inference is consistent with the well-established fact that the *N*-methyl group is almost exclusively oriented equatorial in *N*-methylpiperidines.[20] The ternary solutions containing *N*-methyl derivatives of γ-perhydroacridine (III), α- and β-perhydrophenanthridines (VII and VIII), *trans*-perhydroquinoline (XIV) displayed practically the same spectra in the relevant region as the corresponding containing Ia, whereas *N*-methylperhydrocarbazole (XVIIIa) showed essentially the same absorption pattern concerning the spectrum of the solution in question as IIa. These spectral behaviors are in good accord with the result obtained in the preceding section.

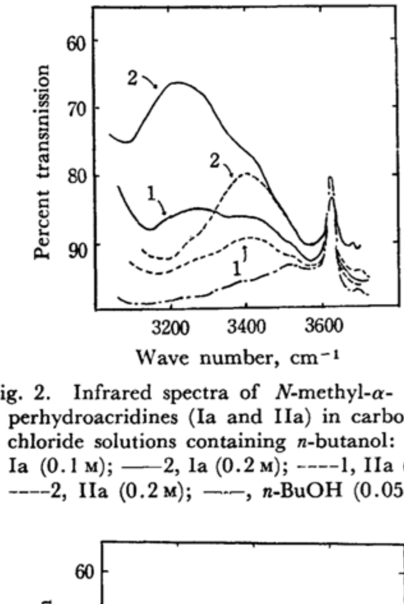

Fig. 2. Infrared spectra of *N*-methyl-α- and β-perhydroacridines (Ia and IIa) in carbon tetrachloride solutions containing *n*-butanol: —— 1, Ia (0.1 M); ——2, Ia (0.2 M); ----1, IIa (0.1 M); ----2, IIa (0.2 M); —·—, *n*-BuOH (0.05 M).

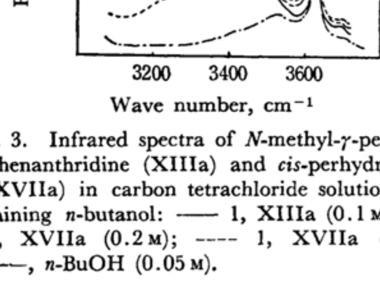

Fig. 3. Infrared spectra of *N*-methyl-γ-perhydrophenanthridine (XIIIa) and *cis*-perhydroindole (XVIIa) in carbon tetrachloride solutions containing *n*-butanol: —— 1, XIIIa (0.1 M); ---- 2, XVIIa (0.2 M); ---- 1, XVIIa (0.1 M); —·—, *n*-BuOH (0.05 M).

N-Methyl derivatives of γ-perhydrophenanthridine (XIII), *cis*-perhydroquinoline (XV) and also *cis*-perhydroindole (XVII) exhibited interesting absorption bands in the spectra of their ternary solutions (Fig. 3). In the former two compounds XIIIa and XVa, both the relevant bands centered near 3240 and 3420 cm^{-1} were observed. The intensities of the latter band increased and, conversely, those of the former decreased, when compared with the corresponding bands of the respective *trans* isomers (XIIIa and VIIIa, and XVa and XIVa). With compound XVIIa such a tendency was further intensified, and the spectrum became rather similar to that of compound IIa. These facts may be explicable well on the basis of the following: compounds XIIIa and XVa involve no *trans* linkage and, therefore, would exist as an equilibrium mixture of conformers formed through ring inversion, one having β-equatorial methylene group(s) and the other β-axial. For compound XVIIa, the similar discussion would be applied, if we consider that the pyrrolidine ring adopts a half-chair conformation or we regard XVIIa as a cyclohexane derivative substituted vicinally with methylene and amino groups. This inference is not contradictory to the previous conclusion but rather supports the configuration of compound XIII.

We next measured the spectrum of the solution containing *n*-butanol (0.05 M) and the secondary amine I or II (0.15 M), in each of which both the relevant, broad and sharp bands appeared near 3240 and 3640 cm^{-1} (Fig. 4). The broad bands are ascribed to the hydroxyl groups bonded to the N atoms, because compound I or II showed only weak absorptions ($\varepsilon < 5$) near 3300 cm^{-1} at the concentration of 0.02 to 1.25 M in carbon tetrachloride and, therefore, the intensities due to the free and *N*- or *O*-bonded imino groups would be negligibly small. In the spectrum of the solution containing I, the broad band appeared with stronger intensity than the sharp. The situation became the opposite in the case of II, where the intensity of the broad band was weaker than that in the case of I. This behavior is interpretable well

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20) For example, a) N. L. Allinger, J. G. D. Carpenter and F. M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965), and b) J. B. Lambert, R. G. Keske, R. E. Carhart and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967).

on the basis of that the lone pair takes largely an axial conformation in both the compounds and, when the alcohol is added, only compound II is partly inverted to a less stable conformer with the lone pair equatorial and forms the hydrogen bond of almost the same length as I. This provides additional qualitative evidence supporting arguments21) that the lone pair is smaller than the hydrogen atom.

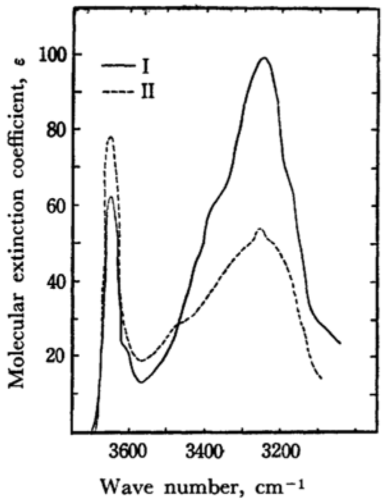
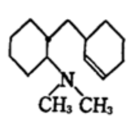
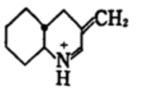


Fig. 4. Infrared spectra of α- and β- perhydroacridines (I and II) in carbon tetrachloride solutions containing *n*-butanol: I and II (0.15 M), *n*-BuOH (0.05 M), cell 0.5 mm.
The intensity ε denotes the difference of the molecular extinction coefficient between each ternary solution and the corresponding containing no *n*-butanol.

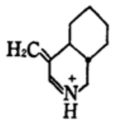
The Hofmann Degradation. The exhaustive methylation of the stereoisomers of perhydroacridine and perhydrophenanthridine was next investigated. The addition of methyl iodide into ether or acetone solutions of the *N*-methyl derivatives of the compounds readily yielded the corresponding *N*-methyl methiodides (Ib), mp 273—275°C, (IIb), mp 210—212°C, (IIIb), mp 262—264°C, (VIIb), mp 265—267°C, (VIIIb), mp 272—274°C, and (XIIIb), mp 315—316°C. Pyrolysis of the methohydroxides obtained by treatment of all the methiodides except IIb with silver oxide produced the respective original *N*-methyl compounds in 65—80% yields. On the other hand, the same treatment of IIb gave an oily product, from which a base (XVIII) $C_{15}H_{27}N$, bp 154—156°C/17 mmHg, was isolated in 65% yield in pure state through the picrate, mp 147—149°C. The compound XVIII showed absorption maxima at 1660 and 720 cm^{-1} in the infrared spectrum and gave the dihydro derivative by catalytic hydrogenation. It also afforded the glycol by oxidation with osmium tetroxide, which was readily converted into the diacetate. These facts showed the presence of a disubstituted and probably *cis* double bond. Treatment of XVIII with boiling acetic acid followed by addition of potassium iodide yielded a mixture consisting mainly of Ib, showing that no ring contraction was encountered during the pyrolysis. Hence, compound XVIII can be assigned as 3-(2′-dimethylaminocyclohexylmethyl)-cyclohexene.



XVIII



XIX



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The methohydroxide obtained from IIb underwent the normal Hofmann degradation to give XVIII, as expected from its steric arrangement. Furthermore, with the methohydroxides which are derived from Ib, IIIb, VIIb and VIIIb and have rigid conformations, a suitable geometrical disposition22) is not available for the normal E2 process leading to olefin, and it would not be unreasonable that only elimination of methanol took place in the degradation. On the other hand, the remaining methohydroxide derived from XIIIb may adopt at least two conformations, one having two axial β-methylene substituents in respect to the piperidine ring and the other two equatorial. The former is an unfavorable conformation owing to the severe 1,3-diaxial interaction between the axial *N*-methyl and the two methylene groups in question, although it satisfies the stereochemical arrangement required for E2 elimination. This is inferred from the observed rate in the formation of the methiodide and, in fact, the degradation has led mainly to the elimination of methanol, proving the preference of the latter conformation.

Experimental23)

α-, β- and γ-Perhydroacridines (I, II and III). These compounds were prepared according to the procedures described previously,2) and complementary data are described here.

Compound I; mass spectrum, m/e 193 (M$^+$), 192, 151, 150, 136, and *ca.* 117 (a metastable ion). The strongest peak at m/e 150 would be due to an ion formulated as XIX.24) The picrate had mp 192—194°C (lit.,2) 173—176°C) after preparation in ether or benzene and recrystallization from ether-ethanol. The hydroiodide melted over 360°C after addition of aqueous

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21) a) T. Masamune and M. Takasugi, *Chem. Commun.*, **1967**, 625 b) K. Brown, A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, *(B)*, **1967**, 487; H. Booth and A. H. Bostock, *Chem. Commun.*, **1967**, 177; Ref. 20a.

22) *Cf.* A. C. Cope, *Org. Reactions*, **11**, 317 (1960).

23) All the melting points are uncorrected.

24) *Cf.* The mass spectra of IV and V; m/e 187 (M$^+$), 186, 144, 130, and *ca.* 110 (a metastable ion).

hydrogen iodide into I in acetone and recrystallization from ethanol.

Found: N, 13.01%. Calcd for $C_{19}H_{26}O_7N_4$: N, 13.26%.

Found: N, 4.55%. Calcd for $C_{13}H_{24}NI$: N, 4.36%.

Compound II had mp 51—53°C (lit.,2) 48—51°C) after purification described in the following; the crude base before recrystallization was converted into the hydroiodide, mp >300°C, by addition of aqueous hydrogen iodide in acetone, which on regeneration followed by recrystallization from petroleum ether afforded II having mp 51—53°C. Compound II showed practically the same mass spectrum as I, and its benzoyl derivative had mp 87—89°C on recrystallization from petroleum ether.

Found: N, 4.88%. Calcd for $C_{20}H_{27}ON$: N, 4.71%.

Compound III showed essentially the same mass spectrum as I, and its picrate had mp 211—213°C on recrystallization from ethanol.

Found: N, 13.15%. Calcd for $C_{19}H_{26}O_7N_4$: N, 13.26%.

***N*-Methyl-α-, β-, γ- and δ-Perhydroacridines (Ia, IIa, IIIa and VIa) and Their Methiodides (Ib, IIb and IIIb).** *a) Methylation wtih Formic Acid and Formalin.* A mixture of I (2.8 g), formic acid (1.5 m*l*) and 33% formalin (2.8 m*l*) was gently refluxed for 6 hr, and into the cooled mixture was added water (50 m*l*) and ether (30 m*l*). After separation of the aqueous layer, the ether solution was shaken with 1 N aqueous acetic acid. The aqueous and acetic acid solutions were combined and made alkaline to yield oily substance, which was extracted with ether, dried and subjected to distillation under reduced pressure. A fraction (2.3 g) boiling at 155—161°C/15 mmHg was collected and refluxed in acetic anhydride (7 g) for 30 min. The whole solution was warmed with water (50 m*l*) on a water bath for 1 hr and then treated with ether. The aqueous solution gave oil on alkalization, which was purified by distillation. The *N*-methyl derivative (Ia, 2.0 g) thus obtained had bp 158—160°C/17 mmHg and mp 38—40°C on recrystallization from petroleum ether.

Found: C, 81.20; H, 12.25; N, 6.67%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76%.

The picrate and the hydroiodide had mp 169—170°C (from ethanol) and mp 220—222°C (from ethanol), respectively.

Found: C, 55.28; H, 6.74; N, 13.08%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47; N, 12.84%.

Found: C, 49.93; H, 7.80; N, 3.88%. Calcd for $C_{14}H_{26}NI$: C, 50.15; H, 7.82; N, 4.18%.

N-Methyl derivatives (IIa and IIIa) of II and III were prepared in the same way as Ia. These bases and their derivatives had the following melting points. IIa, mp 36—38°C (from petroleum ether): the picrate, mp 211—213°C (from ethanol); the hydroidodie was not obtained in crystalline state.

Found: C, 81.00; H, 12.18; N, 6.65%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76%.

Found: C, 54.98; H, 6.53%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47%.

IIIa, mp 46—48°C (from petroleum ether); the picrate, mp 164—166°C (from ethanol); the hydroiodide was not obtained in crystalline state.

Found; C, 80.78; H, 12.20; N, 6.88%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76%.

Found: C, 54.89; H, 6.81%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47%.

b) Hydrogenation of N-Methyl-trans-1,2,3,4,4a,9,9a,10-Octahydroacridine (IVa) over Platinum. Compound IVa3) (2.1 g) in acetic acid (20 m*l*) was hydrogenated over Adams' platinum (0.4 g as pltainum oxide) at room temperature for 1.5 hr, when 790 m*l* of hydrogen had been consumed (the calculated for complete hydrogenation, 770 m*l*). After removal of the catalyst and the solvent, the residue was shaken with ether and water, and the ether solution gave an oily mixture of bases on being dried and evaporated, which was dissolved in acetone. To the acetone solution was added aqueous hydrogen iodide (bp 125°C), when the hydroiodide precipitated and was collected by filtration. This compound (1.8 g) had mp 218—220°C on recrystallization from ethanol and was then reconverted to a free base (0.85 g), mp 36—38°C, which was identified as Ia. The filtrate free from this hydroiodide was concentrated under reduced pressure and then treated with 2 N sodium hydroxide solution and ether. The ether extract, after evaporation, was converted into the picrate in methanol, which had mp 153—155°C on recrystallization from ethanol and amounted to 1.5 g. This picrate was reconverted into IIIa (0.65 g), mp 46—48°C.

c) Hydrogenation of N-Methyl-cis-1,2,3,4,4a,9,9a,10-Octahydroacridine (Va) over Platinum. Compound Va (5.0 g) was hydrogenated over Adams' platinum (0.5 g) in the same manner as mentioned above, and 1850 m*l* of hydrogen was consumed (the calculated, 1770 m*l*) after 4 hr. An oily mixture of bases obtained by usual methods was dissolved in acetone and treated with aqueous hydrogen iodide, when a hydroiodide (0.4 g) separated out and was collected by filtration. It had mp 224—226°C on recrystallization from ethanol, which was depressed to 185—200°C on admixture with the hydroiodide of Ia, mp 220—222°C. Regeneration gave a free base, bp 157—160°C/20 mmHg. As the hydroiodide of IIa or IIIa was not obtained in crystalline state, this base would be a new isomer (VIa) named δ, but the compound was not further characterized because of the small amount.

Found: C, 80.80; H, 12.03%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15%.

Found: C, 49.88; H, 8.03%. Calcd for $C_{14}H_{26}NI$: C, 50.15; H, 7.82%.

The aqueous acetone solution obtained on filtration of the hydroiodide of VIa was evaporated, made alkaline and extracted with ether. The ether extract, after removal of the solvent, was converted into the picrate in methanol, from which the picrate (6.0 g), mp 154—156°C, of IIIa, was isolated. Regeneration followed by distillation afforded IIIa (2.6 g), mp 45—47°C.

d) Methiodides. To an acetone or ether solution of Ia (1.7 g) was added methyl iodide (8.0 g) dropwise under cooling, when the methiodide separated out and was collected by filtration. Recrystallization from ethanol gave Ib (1.9 g), mp 273—275°C. On concentration of the mother liquor, an additional amount (0.3 g) of the crude methiodide, mp 263—266°C, was obtained.

Found: C, 51.63; H, 7.99%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

Compound IIa (1.2 g) in acetone was refluxed with an excess of methyl iodide for 1 hr. Recrystallization of the resulting methiodide from 95% ethanol afforded IIb (1.2 g), mp 210—212°C.

Found: C, 51.33; H, 8.28%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

Compound IIIa (2.0 g) was converted into the corresponding methiodide (IIIb, 2.7 g) in the same manner as Ia, which had mp 262—264°C on recrystallization from ethanol.

Found: C, 51.64; H, 8.24%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

α-Perhydrophenanthridine (VII). Compound VII was prepared according to the method reported previously[5] and had mp 103—104°C; mass spectrum, *m/e* 193 (M^+), 192, 151, 150, 136, and *ca.* 117 (a metastable ion). The strongest peak would be due to an ion formulated as XX.[25] The picrate had mp 231—233°C (lit.,[5] 210—212°C) on recrystallization from ethanol.

Found: N, 13.21%. Calcd for $C_{19}H_{26}O_7N_4$: N, 13.26%.

β-Perhydrophenanthridine (VIII). a) Compound VIII was obtained in 25% yield by hydrogenation of 7,8,9,10-tetrahydrophenanthridine over Adams' platinum.[5]

b) *trans*-1,2,3,4,4a,5,6,10b-Octahydrophenanthridine[6] (XI, 1.0 g) in ethanol (30 m*l*) containing 2.4 N hydrochloric acid[12] (2.5 m*l*) was hydrogenated over Adams' platinum (0.2 g) at room temperature for 5 hr, when 460 m*l* of hydrogen had been adsorbed (the calculated, 450 m*l*). The reaction mixture, after being worked up as usual, gave a solid base (0.85 g) melting at 105—118°C. Recrystallization from petroleum ether afforded a pure sample (0.7 g) of VIII, mp 122—123°C (lit.,[5] 119—121°C).

Found: C, 80.80, 80.95, 81.00; H, 12.02, 12.27, 11.74; N, 7.25%. Calcd for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25%.

Compound VIII showed essentially the same mass spectrum as VII, and the picrate had mp 223—225°C on recrystallization from ethanol.

Found: C, 54.33; H, 6.54%. Calcd for $C_{19}H_{26}O_7N_4$: C, 54.02; H, 6.20%.

c)[26] *cis* - 5,6,6a,7,8,9, 10, 10a - Octahydrophenanthridine[5] (X, 500 mg) was hydrogenated over Adams' platinum (50 mg) at room temperature in acetic acid for 4 hr, when 200 m*l* of hydrogen had been consumed (the calculated, 180 m*l*). The reaction product, after being worked up as usual, crystallized, amounted to 522 mg, and melted at 115—120°C. Recrystallization from petroleum ether gave VIII (338 mg), mp 118—120°C.

γ-Perhydrophenanthridine (XIII). *cis*-1,2,3,4,4a,-5,6,10b-Octahydrophenanthridine[6] (XII, 1.35 g) was hydrogenated over Adams' platinum (0.50 g) at room temperature in ethanol (70 m*l*) containing 2.4 N hydrochloric acid (3.5 m*l*). The reaction ceased after 24 hr, when 500 m*l* of hydrogen had been consumed (the calculated, 530 m*l*). The product (1.30 g) obtained after usual treatment was semi-solid and recrystallized from petroleum ether to yield XIII (0.32 g), mp 122—123°C. The mother liquor on the recrystallization was evaporated to dryness, and the residue (0.75 g) was converted into the picrate in ether. Upon repeated recrystallizations of the picrate from methanol, three kinds of picrates having mp 194—196°C (0.96 g), mp 178—180°C (60 mg) and mp 180—181°C (20 mg) were isolated, but the last two were not further examined. Regeneration of the picrate of mp 196°C gave a free base (348 mg), mp 35—37°C. Recrystallization from petroleum ether afforded an analytical sample (100 mg) of XIII, mp 37—38°C, which showed practically the same mass spectrum as VII.

Found: C, 80.60; H, 12.17; N, 7.48%. Calcd for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25%.

Found: N, 12.98%. Calcd for $C_{19}H_{26}O_7N_4$: N, 13.26%.

***N*-Methyl-α-, β- and γ-perhydrophenanthridines (VIIa, VIIIa and XIIIa) and Their Methiodides (VIIb, VIIIb and XIIIb).** a) These *N*-methyl derivatives were prepared from the respective secondary amines (VII, VIII and XIII) by the same treatment (formic acid and formalin) as Ia, and had the following melting and/or boiling points. Compound VIIa had mp 26—28°C on recrystallization from petroleum ether and bp 155—157°C/20 mmHg, and the picrate mp 199—201°C after preparation in ether and recrystallization from 95% ethanol.

Found: C, 81.26; H, 11.99; N, 6.56%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76%.

Found: C, 54.88; H, 6.61%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47%.

Compound VIIIa and its picrate had mp 62—64°C (from petroleum ether) and mp 190—192°C (95% ethanol).

Found: C, 81.22, 80.00; H, 12.20, 11.91; N, 6.42%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 11.99; N, 6.56%.

Found: C, 55.19; H, 6.71%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47%.

Compound XIIIa, oil, boiled at 155—159°C/20 mmHg, and its picrate had mp 198—199°C after preparation in ether and recrystallization from methanol.

Found: C, 81.35; H, 11.89; N, 6.88%. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76%.

Found: C, 55.23; H, 6.56%. Calcd for $C_{20}H_{28}O_7N_4$: C, 55.03; H, 6.47%.

b) Methiodides. Methylation of these *N*-methyl derivatives (VIIa, VIIIa and XIIIa) with methyl iodide proceeded as smoothly as Ia to give the corresponding methiodides (VIIb, VIIIb and XIIIb) in good yields, which on recrystallization from ethanol had mp 265—267°C, 272—274°C and 315—316°C, respectively.

Found (VIIb): C, 51.33; H, 8.12%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

Found (VIIIb): C, 51.56; H, 8.05%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

Found (XIIIb): C, 51.36; H, 7.89%. Calcd for $C_{15}H_{28}NI$: C, 51.57; H, 8.08%.

Formation of Methiodides. The rate of the methiodide formation was measured in 20 m*l* of a 99.5% ethanol solution. In practice, 10 m*l* of the ethanol solution of a tertiary amine (0.03—0.05 M) and equal volume of the ethanol solution containing 1 m*l* of methyl iodide (*ca.* 1.5 M) was separately brought to constant temperature and then mixed in a brown flask closed with a tightly fitting stopper. After suitable intervals, 2 m*l* of the solution was drawn and 5 m*l* of 0.02 N hydrochloric acid was added. The excess of the acid was back-titrated with an aqueous barium hydroxide

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[25] *Cf.* The mass spectra of IX and X; *m/e*, 187 (M^+), 186, 144, 130, and *ca.* 90 (a metastable ion).

[26] Carried out with Mrs. Masayo Murata.

solution, using methyl-red as an indicator. It was found that 5.0 m*l* of the hydrochloric acid was equivalent to 2.96 m*l* of the barium hydroxide solution. The rate constant was then calculated using the usual expression for a second-order reaction in which methyl iodide was present substantially in a constant concentration. The result is summarized in Table 1.

Measurement of Basicity. This was carried out at 20°C in 60% aqueous ethanol according to the method of Thomson.27) The basicity is expressed by the pK_a value of a conjugate acid of each base and the result is summarized in Table 1.

Formation of Hydrogen Bonds with *n*-Butanol. Infrared absorption spectra were determined at 20°C using a Nihon Bunko double-beam spectrophotometer, Model DS 301, equipped with sodium chloride optics. The measurement was run at 0.1—0.2 M of tertiary or secondary amines in carbon tetrachloride containing 0.05 M of *n*-butanol. The sodium chloride cell of 0.5 mm of thickness was used and the absorption of the solvent was compensated by placing a cell of the same thickness filled with the solvent in the reference beam.

Carbon tetrachloride used as the solvent was first washed with conc. sulfuric acid, dil. sodium carbonate solution and water, successively, dried with anhydrous sodium sulfate, and distilled over phosphorus pentoxide. *n*-Butanol was used after being refluxed with calcium oxide for 20 hr and distilled under reduced pressure.

The Hofmann Degradation of Methiodides of *N*-Methyl-*α*- and *γ*-perhydroacridines (Ia and IIIa) and of *N*-Methyl-*α*-, *β*- and *γ*-perhydrophenanthridines (VIIa, VIIIa and XIIIa). A solution of Ia (1.2 g) in 50% aqueous ethanol (20 m*l*) was shaken with silver oxide prepared from silver nitrate (0.8 g) at room temperature for 3 hr. After filtration followed by evaporation of the filtrate, the syrupy residue was heated to 180°C (bath temperature) under reduced pressure. The pyrolysis of the methohydroxide took place violently at 140—150°C. The distillate was extracted with ether, and the ether solution gave a solid base (0.45 g) on removal of the solvent, which had mp 38—40°C on recrystallization from petroleum ether and was identified as Ia. The picrate melted at 170—172°C on recrystallization from ethanol.

The pyrolysis of IIIb, VIIb, VIIIb and XIIIb was carried out in the same manner as Ia. Compound IIIb (2.8 g) produced IIIa (1.1 g), mp 46—48°C; the picrate, mp 162—164°C. Compound VIIb (1.8 g) gave VIIa (0.7 g), bp 152—153°C/18 mmHg and mp *ca.* 25°C; the picrate, mp 198—200°C. Compound VIIIb (1.1 g) afforded VIIIa (0.4 g), mp 62—64°C; the picrate, mp 190—192°C. Compound XIIIb (100 mg) gave XIIIa (52 mg), oil, which was converted into the picrate, mp 198—199°C.

The Hofmann Degradation of *N*-Methyl-*β*-perhydroacridine Methiodide (IIb).28) Compound IIb (1.2 g) was converted into the syrupy methohydroxide by treatment with silver oxide prepared from silver nitrate (0.6 g), which decomposed at 120—130°C (bath temperature). The product was purified by distillation under reduced pressure followed by conversion into the picrate in ether-methanol, which had mp 147—149°C on recrystallization from ethanol. Regeneration of the picrate gave a free base, which was again distilled to yield an oily base (XVIII, 0.4 g) in pure state, bp 154—156°C/17 mmHg; IR, ν_{max}^{film} 1660 (w) and 720 (m) cm^{-1}.

Found: C, 81.25; H, 12.09; N, 6.25%. Calcd for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33%.

Found: C, 56.09; H, 6.68%. Calcd for $C_{21}H_{30}O_7N_4$: C, 55.99; H, 6.71%.

Compound XVIII (0.20 g) in acetic acid (10 m*l*) was hydrogenated over Adams' platinum (0.05 g) at room temperature for 3 hr. The reaction mixture was worked up as usual and gave the dihydro derivative (0.10 g), oil, which showed no absorption near 1660 and 720 cm^{-1} and gave the picrate, mp 147—149°C (from ethanol).

Found: C, 80.47; H, 13.23; N, 6.26%. Calcd for $C_{15}H_{29}N$: C, 80.64; H, 13.09; N, 6.27%.

Found: C, 55.51; H, 7.09; N, 12.19%. Calcd for $C_{21}H_{32}O_7N_4$: C, 55.74; H, 7.13; N, 12.38%.

Compound XVIII (100 mg) was oxidized with osmium tetroxide (173 mg) in dry benzene (5 m*l*) at room temperature. After 24 hr black osmate precipitated out, was centrifugalized and collected by filtration. The osmate (280 mg) was treated with sodium sulfite (1550 mg as $Na_2SO_3 \cdot 7H_2O$) for 5 hr in a refluxing mixture of water (10 m*l*) and ethanol (7 m*l*). After filtration of the resulting precipitate, the aqueous ethanol solution was evaporated under reduced pressure and shaken with ether repeatedly. The ether solution afforded an oily glycol (70 mg), which without further purification was acetylated with acetic anhydride (0.7 m*l*) and pyridine (0.15 m*l*) on a water bath for 2 hr. The mixture gave an oily acetate (60 mg) after being worked up as usual and distilled under reduced pressure, which showed no absorption near 3400 cm^{-1}.

Found: C, 67.28; H, 9.94; N, 3.88%. Calcd for $C_{19}H_{33}O_4N$: C, 67.22; H, 9.80; N, 4.13%.

Compound XVIII (0.30 g) was refluxed in acetic acid (10 m*l*) for 3 hr. The solution was then evaporated under reduced pressure, made alkaline with aqueous potassium hydroxide solution, and treated with ether to remove ether-soluble substance. To the aqueous solution was added potassium iodide, and the resulting solution was again evaporated to dryness and extracted with hot ethanol. Concentration of the ethanol solution gave a mixture of methiodides, from which *N*-methyl-*α*-perhydroacridine methiodide (Ib, 0.18 g), mp 272—275°C, was isolated on recrystallization from ethanol.

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27) G. Thomson, *J. Chem. Soc.*, **1946**, 1113.

28) Carried out with Shuichi Tonooka.