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THE SYNTHESIS AND STEREOCHEMISTRY OF ISOQUINUCLIDINE DERIVATIVES

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Schenker reported the ingenious synthesis of isoquinuclidine derivatives which involves the cycloaddition of acrylonitrile (II) with 1-methyl-3-cyano-1,6-dihydropyridine(I), affording III and IV.[1)] According to their report, hydrogenation of III with Pd/C in ethyl acetate yielded only one product(V), and the similar hydrogenation of IV gave VI with an oily product (picrate, m.p. 215-217°), to which they assigned the formula (VII'). Moreover, the orientation of this cycloaddition reaction has been established through the Hofmann degradation of III-methiodide and formation of the imide(VIII) from V and VI. The same workers also provided the chemical evidences about the conformations of cyano groups of these products.[1)]

In connection with the synthetic works of iboga alkaloids, the Schenker's procedure was followed and modified in this laboratory, and our results proved to be partly different from theirs. Hydrogenation of III with Pt in ethyl acetate under 30 lb./in.^{2} pressure of hydrogen (Parr apparatus) smoothly proceeded to yield V, m.p. 168-168.5°(lit.[1)] m.p. 164-165°), and the previously undescribed product, colorless prisms, m.p.

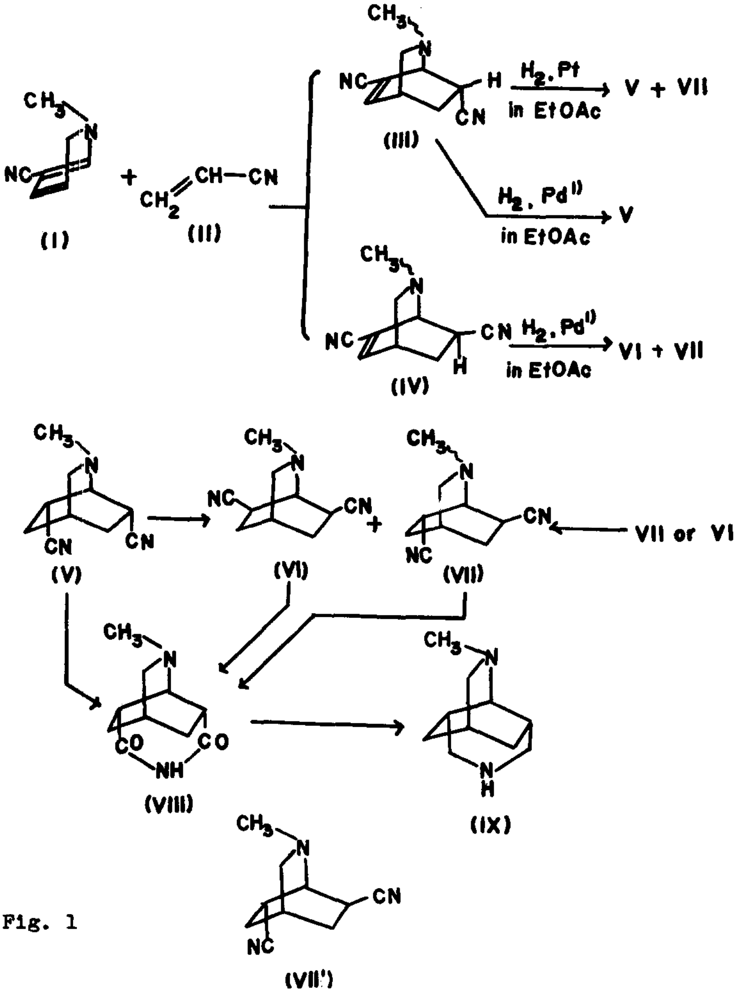
(I)
(II)
(III)
(IV)
H₂, Pt in EtOAc → V + VII
H₂, Pd1) in EtOAc → V
H₂, Pd1) in EtOAc → VI + VII
(V)
(VI)
(VII)
VII or VI
(VIII)
(IX)
(VII')

Fig. 1

117.6-119.4°(picrate, m.p. 184-186.8°) in the ratio of 3 : 2. When hydrogenated by the Schenker's procedure, IV gave VI, m.p. 89-91.8°(lit.[1]) m.p. 76°), as a main product along with a small amount of the compound same as above, m.p. 117.6-119.4°, but the product described as VII' by Schenker was not detected. The structure of the new compound (Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98%. Found: C, 68.51; H, 7.49; N, 24.22%. IR$\nu_{C\equiv N}$ 2250 cm.$^{-1}$) was established to be VII in the following. (1) The mass spectra of V, VI and VII gave the almost identical fragmentation patterns (m/e, 175, 121, 97, 82). (2) The compound(VII) was hydrolyzed to the imide(VIII), m.p. 206-208.5°, which was identified with the one from V and VI. (3) It is noteworthy to have found that a solution of the compound(V) in t-BuOH containing a catalytic amount of t-BuOK was heated at reflux for 30 hrs. to afford a mixture of VI and VII (1 : 4.1)[*1], which actually gave only

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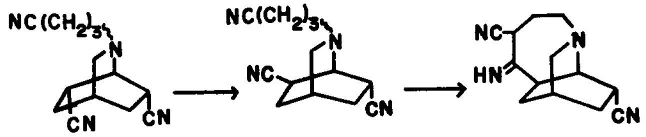
[*1] The composition of the product was proved by Rf values of two spots which were identified with those of authentic samples simultaneously developed on thin layer chromatography. And the ratio of components was deduced by comparison of the relative intensities of the N-Me signals in the n.m.r. spectrum of the mixture. Furthermore, this epimerization was successfully applied to the conversion of V-A into VII-A, the latter of which was more advantageous for the subsequent Ziegler reaction compared with the former. Thus, the finding of this reaction let us construct the fundamental skeleton of ibogaine much easier than before. (Unpublished data).



(V-A)

(VII-A)

TABLE 1

Chemical Shifts (τ values) of N-Methyl Protons in NMR Spectra of Isoquinuclidine Derivatives (at 60 Mc.).

Compounds	Free Bases in $CDCl_3$ *1	Perchlorates in 56% $HClO_4$ *2		
III	7.70	6.90	6.68 (1:0.41)*3	
IV	7.67	6.85		
V	7.65		6.72	
VI	7.21			6.48
VII	7.55		6.68	6.50 (1:0.45)*3
IX	7.53			

*1 Tetramethylsilane(TMS) was used as internal reference.
*2 TMS was used as external reference.
*3 The ratios in the parentheses indicate the relative intensities of two doublets.

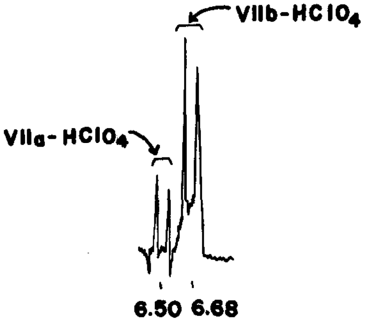


Fig. 2 The Methyl Signals of VII in 56% $HClO_4$.

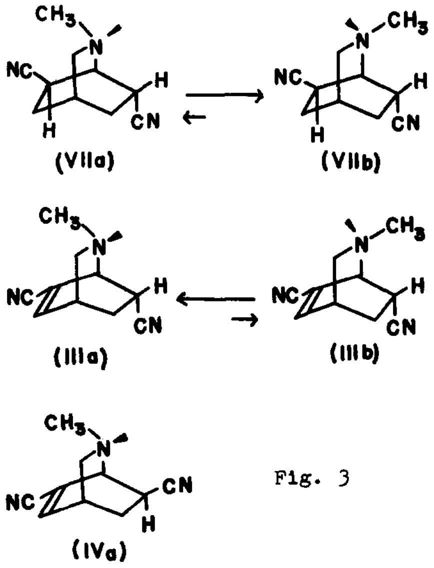


Fig. 3

VII as pure material after a single recrystallization in a good yield.[2] Also, the compound(either VI or VII) was treated in the similar way to afford VII as a readily isolable product. In any case of this epimerization, there has never been found the compound described as VII'.

Since the inversion of substituent on the trivalent nitrogen is a process of low activation energy,[3] the compound(VII) should be expected to exist as a rapidly interconverting mixture of the conformers(VIIa and VIIb), for which confirmation there were checked the chemical shifts of N-Me protons in their n.m.r. spectra in $CDCl_3$ and in an acidic solution(Table 1).

The methyl proton resonances of III and VII in 56% $HClO_4$ solution appear as two doublets (Fig. 2), in contrast to those of the other compounds(V and VI) being one doublet expectedly under the same condition. The methyl signals of VI both in $CDCl_3$(τ 7.21) and in 56% $HClO_4$ solution(τ 6.48) appear at the significantly lower field compared with those(τ 7.65[*2] and τ 6.72, respectively) of V, which should be primarily ascribed to the diamagnetic anisotropic effect of the C≡N triple bond toward

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[*2] Although A. D. Cross et al.(J. Amer. Chem. Soc. 85, 3223 (1963)) pointed out that the long range deshielding effect by the anisotropy of the higher polar C_5-C≡N single bond, plays a more significant role in the chemical shifts of C-19 methyl protons in the steroids, rather than the long range shielding effect due to the C≡N triple bond. But, when the methyl signal(τ 7.65 in $CDCl_3$) of V is compared with the one (τ 7.53 in $CDCl_3$) of IX with no cyano group, it may be concluded that such a long range effect could not be operative in the present system.

the methyl group of VI, being parallelly located at 1,3-position as to the cyano group at either side. The signals of VII centered at τ6.68 and of III at τ6.68 in $HClO_4$ solution are comparable to that of V at τ6.72, indicating that these are the methyl proton resonances of conformers(VIIa and IIIb, respectively) in the equilibrium. Similarly, the other signal of VII at τ6.50 appearing at the almost identical region with that of VI at τ6.48 is due to the conformer(VIIa), whose methyl proton resonances are apparently effected by the diamagnetic anisotropy of the closely oriented cyano group. Thus, the equilibrium between these conformers could be qualitatively demonstrated in Fig. 3, since the relative intensities should reflect their stabilities.4)

Furthermore, it is noteworthy that the compound(IV) indicates only one doublet at τ6.85 when measured in 56% $HClO_4$ solution, suggesting that this compound is not equilibrated, as the cyano group could be assumed to push the methyl substituent toward the unhindered double bond side, which is delineated as IVa in Fig. 3. These data have been substantially useful for the synthetic studies on iboga alkaloids, which will be published in the forthcoming paper.

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