Tetrahedron Letters No.48, pp. 4317-4326, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF SENDAVERINE AND ITS TOTAL SYNTHESIS

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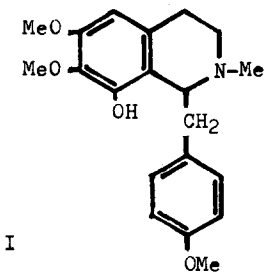
(Received 5 October 1965)

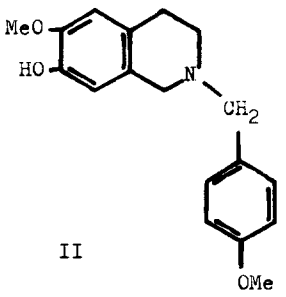
CORPAVERINE, $C_{20}H_{25}O_4N$, m.p. 138°, was isolated from Corydalis aurea Willd. by Manske in 1938 (1) and assigned as (I) by chemical methods (2). Kametani, et al (3) recently revealed that the corpaverine was a mixture of capaurine and an unknown compound, m.p. 140 - 141.5°, by separation of natural corpaverine by recrystallization and thin-layer chromatography. However, the structure of this compound has not yet been elucidated, and its total synthesis also not accomplished.



I

The purpose of the present investigation was to study the comparison of the above unknown compound with the alkaloid termed "F-28" by Manske (1), leading eventually to reveal that both compounds were completely the same. Therefore, since the name of

corpaverine seems to be ambiguous, we propose to term sendaverine for both compounds. Furthermore, re-examination of the experimental data by chemical methods previously reported by Manske (2) and structural elucidation by physical methods and its total synthesis were carried out, leading eventually to confirm formula (II) for the sendaverine, which is the first example of a new structural type of benzylisoquinoline alkaloid.



II

Recrystallization from n-hexane of the alkaloid F-28 donated by Dr. Manske gave colourless needles, m.p. 139 - 140°, whose infrared spectrum in chloroform was superimposable on that of the unknown compound separated from the so-called corpaverine. Alkaloid F-28 also showed no depression of melting point on admixture with the compound as above. Both specimens behaved similarly on thin layer chromatography. TLC (WAKOGEL B-5 activated at 110° for 1 hr.): R_F 0.76 (sendaverine), R_F 0.76

(alkaloid F-28) [chloroform-acetone-methanol (50: 40: 3) as solvent; the spots were detected by fume nitric acid]. Recrystallization of its hydrochloride from methanol-ether afforded colourless needles, m.p. 202 - 207° (Found: C, 64.37; H, 6.71. $C_{18}H_{21}O_3N$,HCl requires C, 64.37; H, 6.60%).

Manske (2) has already revealed that mild oxidation of corpaverine gave p-anisic acid which melted sharply at 184°. This fact reveals that one part of the corpaverine, namely, sendaverine, was oxidized to give p-anisic acid and it is therefore obvious that this alkaloid has a p-methoxybenzyl group. Furthermore, since analytical data of alkaloid F-28 (Found: C, 72.17; H, 7.03; N, 5.09; OMe, 20.64%) was previously given by Manske, its empirical formula must be $C_{18}H_{21}O_3N$ (Anal. Calcd., C, 72.21; H, 7.07; N, 4.68%) instead of $C_{17}H_{19}O_3N$, the analytical figures being about equally good for both.

IR spectrum of II showed a hydroxylic band at 3546 $cm.^{-1}$ and the characteristic absorption band which is similar to Bohlmann's absorption (4) was observed at 2762, 2801 and 2841 $cm.^{-1}$ in chloroform as is shown in Fig. 1. UV spectrum [$\lambda_{max.}$ 255 log ε 4.33) and 283.5 mμ (log ε 3.70 in ethanol)] showed 1,2, 3,4-tetrahydroisoquinoline type (5).

NMR spectrum (Fig. 2)*1 was observed as follows. The AA'BB'

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*1 Nuclear magnetic resonance spectrum was determined on a Varian A-60 spectrophotometer with deuterochloroform as solvent and tetramethylsilane as internal reference.

type at 2.76 τ (2H) and 3.19 τ (2H) ($J_{\alpha\beta}=J_{\alpha'\beta'}=8.5$ cps) was assigned to the aromatic protons as doublet signal, respectively. The doublet at 3.19 τ is presumably due to the proton adjacent to 4'-methoxyl group. Two singlet signals at 3.50 τ (1H) and 3.55 τ (1H) due to the aromatic ring proton were observed at 5- and 8-position. Two singlet signals at 6.22 τ (3H) and 6.25 τ (3H) were assigned to the protons at 6- and 4'-methoxyl groups. The methylene protons at 1-position and 2-benzyl radical were also observed at 6.45 τ (2H) and 6.55 τ (2H). Furthermore, the protons of the methylene radical at 3- and 4-position were observed at 7.20 - 7.38 τ (4H). These facts reveal that sendaverine has two methoxyl groups and lacks N-methyl radical.

The base ion peak in the mass spectrum*2 of the compound (II) (molecular ion at m/e 299) occurs at m/e 121 and is presumably due to the loss of isoquinoline unit by β-cleavage to form ion (a). The presence of metastable ion at m/e 49.3 ($121^2/299$ = 49.0) seems to substantiate such a process. The peak at m/e 178 is due to the loss of C_8H_9O unit (ion a) from the molecular ion to form ion (b), which is supported by the existence of a metastable ion at 106.0 ($178^2/299$ = 106.0). Elimination of $-CH_2N-$ unit from ion (b) furnishes the ion (c) (m/e 150), which decomposed

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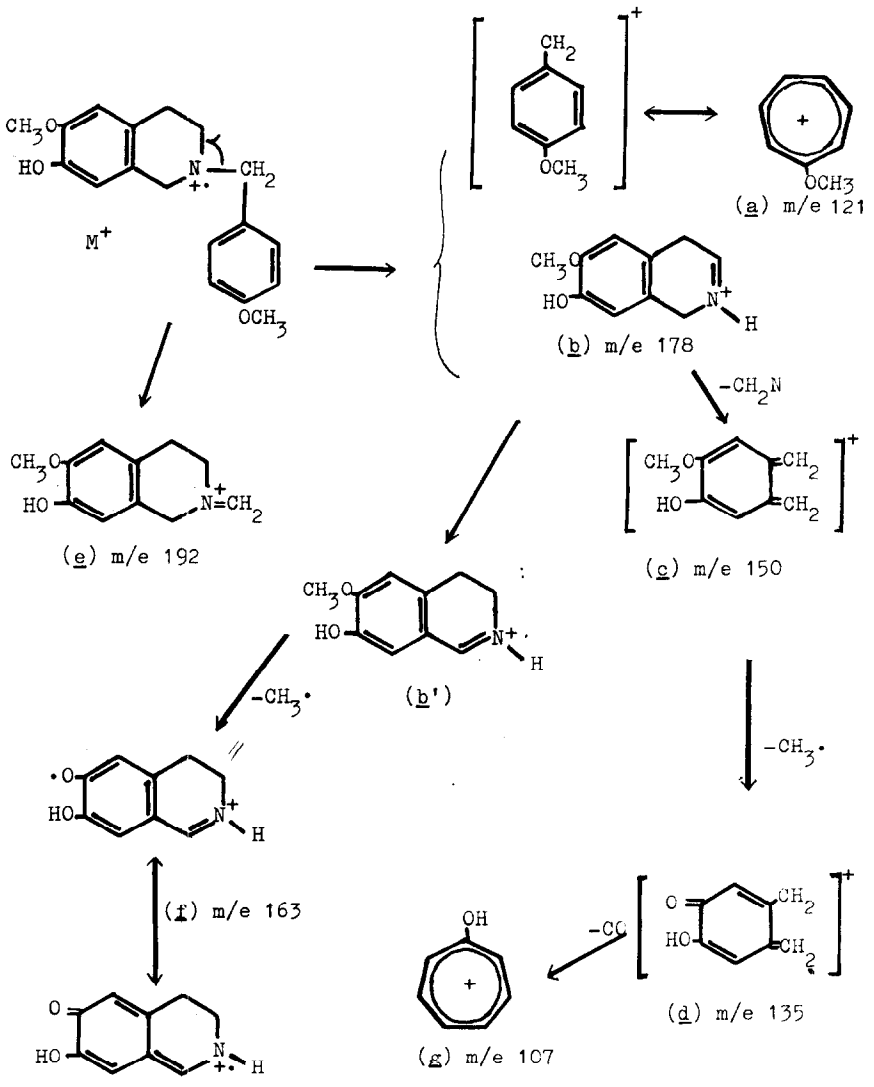
*2 The mass spectrum was measured with a Hitachi mass spectrometer equipped with a direct inlet system: Accel. voltage, 1800 V; Chamber voltage, 70 V; Total emission, 80 μA; Target current, 60 μA; Evaporation/source Temp., 150°C/200°C.

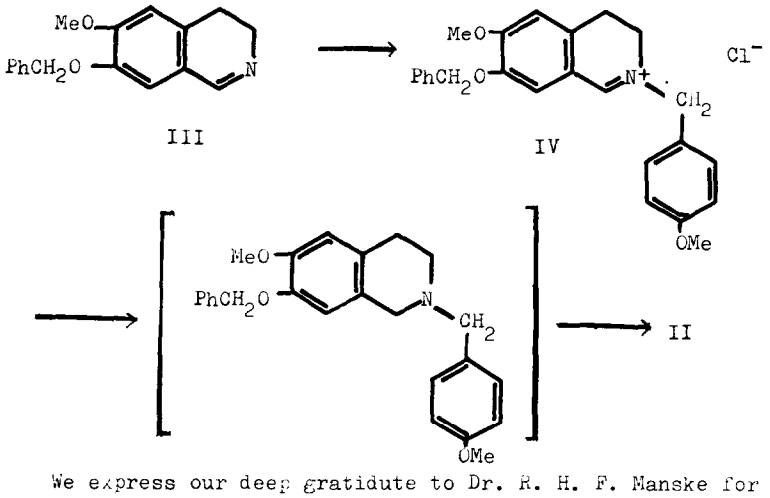
further through explusion of a methyl radical to ion (d) (m/e 135). The operation of this process is supported by the existence of a metastable ion at 121.5 ($135^2/150 = 121.5$). Furthermore, the ion (e) (m/e 192) is also formed from the molecular ion through β-cleavage. This fragmentation seems to support the existence of benzyl group at 2-position. Loss of CO radical from ion (d) gave the ion (g) (m/e 107). The only other ion of appreciable intensity is associated with the further explusion of a methyl radical from ion (b') to give the mesomeric ion radical (f) (m/e 163), but it is only of very low abundance. If the ion (b') would be mainly existed, the appearance of the ion (c) could not be explained and the ion corresponding to m/e 150 is not detectable in case of 1-(2-hydroxybenzyl)-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (6). This fact reveals that the possibility of the existence of ion (b') is scarce and this fragmentation is not analogous to the other 1-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives.

Condensation of 7-benzyloxy-3,4-dihydro-6-methoxyisoquinoline (III)(7) with 4-methoxybenzyl chloride in the presence of toluene gave 7-benzyloxy-3,4-dihydro-6-methoxy-2-(4-methoxybenzyl)isoquinolinium chloride (IV)*3, which was reduced with tin and ethanol-concentrated hydrochloric acid to afford 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-(4-methoxybenzyl)isoquinoline (II) as colourless needles, m. p. 134°. Recrystallization from n-hexane gave

*3 All reported compounds gave a correct elementary analysis.


M+
(a) m/e 121
(b) m/e 178
(c) m/e 150
(d) m/e 135
(e) m/e 192
(f) m/e 163
(g) m/e 107
(b') m/e 178
-CH2N
-CH3·
-CO

colourless needles, m.p. 139 - 140°, which showed no depression of melting point on admixture with natural product*4. The infrared spectrum was superimposable on that of natural sendaverine (II) in chloroform. The existence of this alkaloid in natural plants seems to be very interesting and important from the point of biogenesis. Furthermore, it is indeed surprising that such a simple 2-benzylisoquinoline alkaloid has for so long excaped detection.



We express our deep gratidute to Dr. R. H. F. Manske for the gift of corpaverine, capaurine, and alkaloid F-28.

*4 M. p. s. were determined on a Kofler hot stage apparatus and uncorrected.

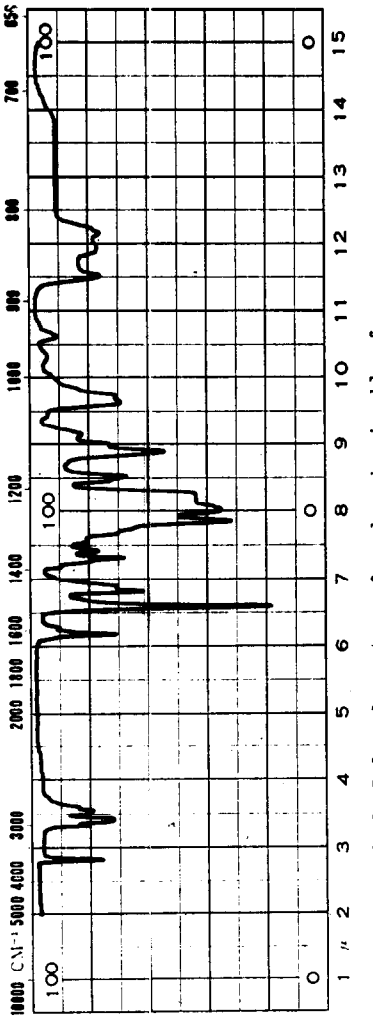


Fig. 1. Infrared spectrum of sendaverine in chloroform

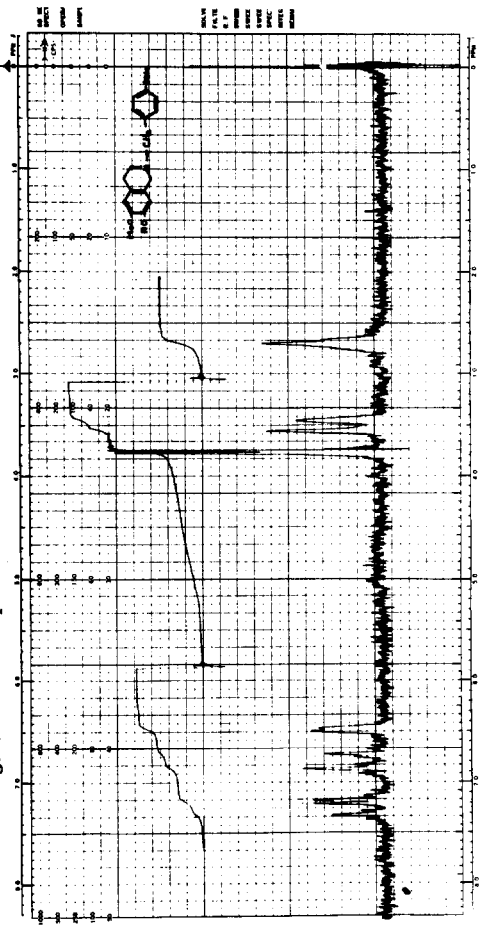


Fig. 2. 60 Mc NMR spectrum of sendaverine

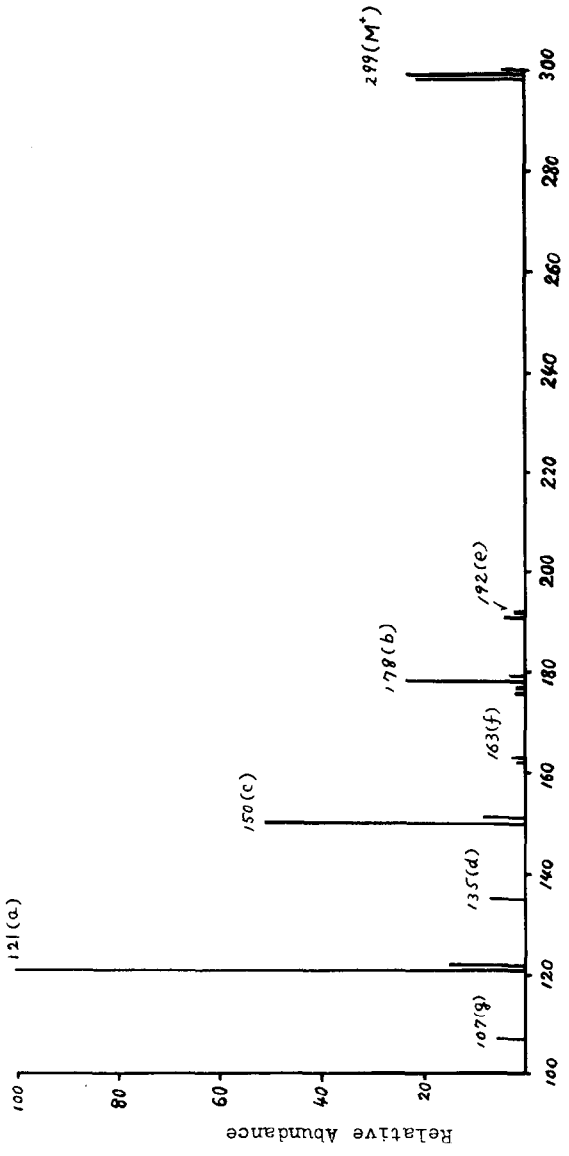


Fig. 3. Mass spectrum of sendaverine

REFERENCES

1. R. H. F. Manske, Can. J. Research, B16, 81 (1938).
2. R. H. F. Manske, J. Amer. Chem. Soc., 74, 2864 (1952).
3. T. Kametani, K. Ohkubo, I. Noguchi, and R. H. F. Manske, Tetrahedron Letters, No. 38, 3345 (1965).
4. F. Bohlmann, Ber., 91, 2157 (1958).
5. Y. Ban, O. Yonemitsu, and M. Terashima., Chem. Pharm. Bull., (Tokyo), 8, 194 (1960).
6. H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 1, Alkaloids, p. 174, Hoden-Day, Inc., 1964.
7. M. Tomita and H. Watanabe, J. Pharm. Soc. Japan (Yakugaku Zasshi), 58, 783 (1938).