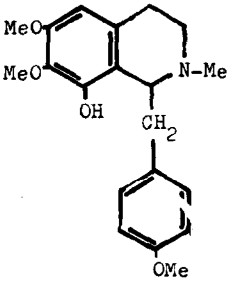
Tetrahedron Letters No.38, pp. 3345-3349, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF CORPAVERINE

Tetsuji Kametani, Kazumi Ohkubo and Isao Noguchi
Pharmaceutical Institute, School of Medicine,
Tohoku University
No. 85, Kitayobancho, Sendai, Japan
R. H. F. Manske
Dominion Rubber Co. Ltd., Research Laboratories,
Guelph, Ontario, Canada

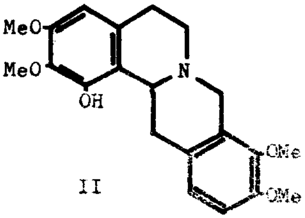
(Received 23 July 1965)

CORPAVERINE, $C_{20}H_{25}O_4N$, m.p. 138°, was isolated from Corydalis aurea Willd (1) by Manske in 1938. The structure of corpaverine was assigned as (I) by chemical methods (2). However, a total synthesis of corpaverine has not yet been elucidated.



I

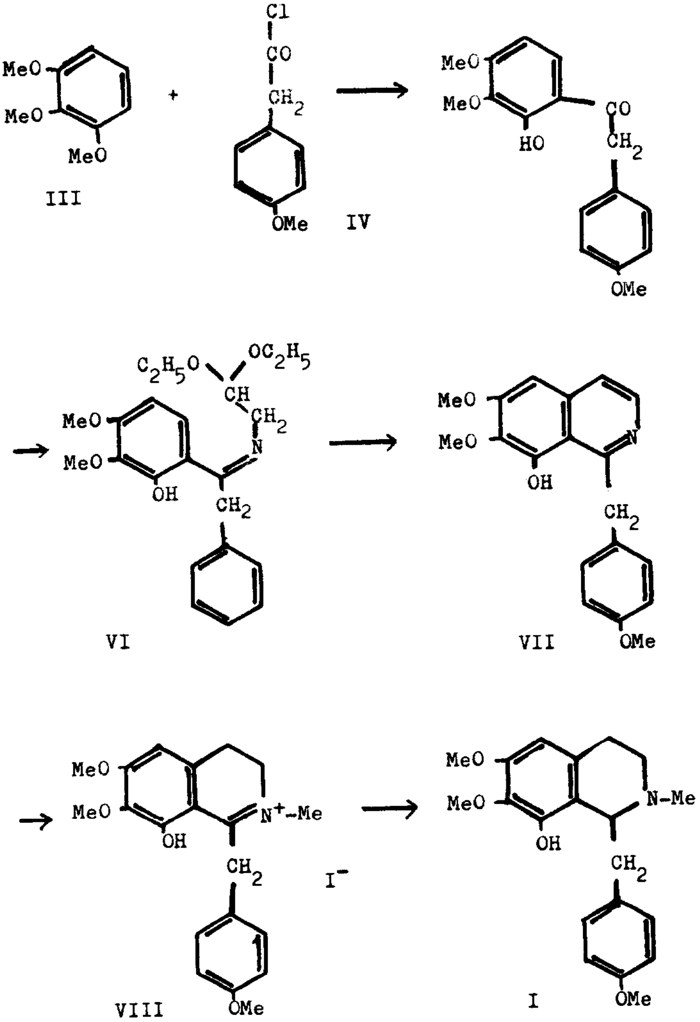
The purpose of the present investigation was to study the Pomeranz-Fritsch reaction of the ketone (V) in order to obtain the corresponding isoquinoline derivative (VII) as a possible intermediate for the synthesis of corpaverine; separation of natural corpaverine by recrystallization and thin-layer chromatography was also studied, leading eventually to reveal that natural corpaverine is a mixture of capaurine (II) and unknown compound, which is under examination.



II

Friedel-Crafts reaction (3,4) of pyrogallol trimethyl ether (III) with 4-methoxyphenacetyl chloride (IV) in the presence of aluminium chloride gave the demethylated ketone (V) as pale yellow needles, m.p. 121 - 122° (from methanol) [Found: C, 67.54; H, 6.00. $C_{17}H_8O_5$ requires C, 67.37; H, 6.03%], which was converted into the Schiff base (VI) by the condensation with aminoacetal. Pomeranz-Fritsch reaction of the above compound (VI) in the presence of polyphosphoric acid (5) gave the isoquinoline derivative (VII), which was characterized as its hydrochloride as colourless needles (from methanol-ether), m.p. 165 - 166.5° (decomp.) [Found: C, 59.58; H, 5.83; N, 3.79. $C_{19}H_{19}O_4N \cdot HCl \cdot H_2O$ requires C, 60.08; H, 5.84; N, 3.69%].

Reduction of the amorphous methiodide (VIII), which could


MeO
MeO
MeO
III
Cl
CO
CH_2
OMe
IV
MeO
MeO
HO
CO
CH_2
OMe
C_2H_5O
OC_2H_5
CH
CH_2
N
MeO
MeO
OH
CH_2
VI
MeO
MeO
N
OH
CH_2
VII
OMe
MeO
MeO
N^+–Me
OH
CH_2
I^-
VIII
OMe
MeO
MeO
N–Me
OH
CH_2
I
OMe

not be purified by recrystallization, with sodium borohydride in methanol afforded 1-(4-methoxybenzyl)-2-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline, which was recrystallized from benzene-ether-petroleum ether to give a pale yellow powder, m.p. 136 - 139°. Recrystallization of the hydrochloride from methanol-ether gave colourless needles, m.p. 134°.

The infrared and nuclear magnetic resonance spectra of the natural corpaverine were not identical with those of our synthetic sample (I) as above. Therefore, since the structure of corpaverine was found to be ambiguous, the thin-layer chromatography of natural product was examined to give two spots. Attempted separation of the hydrochloride of the natural corpaverine by recrystallization from methanol-ether-petroleum ether gave two components, namely, colourless cubes, m.p. 202 - 207°, and colourless prisms, m.p. 181 - 185°. Recrystallization from n-hexane of the free base of the latter compound gave one of the basic substance as colourless needles, m.p. 163 - 164°, whose infrared spectrum was superimposable on that of natural capaurine (6), m.p. 164°.

Recrystallization from n-hexane of the free base of the former compound afforded colourless cubes, m.p. 140 - 141.5°, whose infrared and nuclear magnetic resonance spectra were not superimposable on those of our synthetic sample. A mixture of the above two compounds showed m.p. 136 - 138°.

These facts reveal that natural corpaverine is a mixture of a larger amount of capaurine and an unknown compound. One of the products separated from the natural corpaverine, m.p. 140 - 141.5°, was not enough for elmentary analysis. Accordingly, the structure of the above unknown compound has not yet been elucidated, but the structure elucidation of the above compound by physical methods is now under examination.

We thank Mrs. F. Seto and Miss N. Nanjo for microanalyses, and Miss T. Oikawa for infrared spectra.

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. M. Weizmann and S. Patai, J. Amer. Chem. Soc., **68**, 150 (1946).
4. Y. Inubushi and K. Fujitani, Yakugaku Zasshi, **78**, 486 (1958).
5. T. Kametani, S. Shibuya and I. Noguchi, Yakugaku Zasshi, in the press.
6. R. H. F. Manske and H. L. Holmes, J. Amer. Chem. Soc., **67**, 95 (1945).