62. Eiichi Fujita : Studies on the Alkaloids of Menispermaceous Plants.
(Masao Tomita) XC.¹⁾ On the Structure of Biscoclaurine Alkaloids. (8).

Cleavage of *O*-Methoxyacanthine by Metallic
Sodium in Liquid Ammonia. (2).

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In the previous paper,¹⁾ metallic sodium in liquid ammonia was reacted on *O*-methoxyacanthine (II), by which *d*-1-(4'-hydroxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (*d*-armepavine) (III) was obtained as one of the bisected phenolic base, as the result of which it was recognized that this cleavage was carried out by the schema as shown in formula (II). Accordingly, it was proved directly that the structure of oxyacanthine was represented by formula (I).

As a result of the continued effort to obtain the other bisected base (IV), an interesting new fact has been discovered. As reported in the previous paper, a mixture of the bisected phenolic bases, obtained by reacting metallic sodium in liquid ammonia on *O*-methoxyacanthine (II) by the usual method, was dissolved in alcohol and some saturated solution of oxalic acid in alcohol was added by which *d*-1-(4'-hydroxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (*d*-armepavine) (III) alone precipitated as the hardly-soluble oxalate, which was able to be isolated easily. Alcohol was distilled off the mother liquid from which the said substance had been filtered, and the residue was alkalinized by ammonia. The free phenolic base (IV) obtained was hard to crystallize, in spite of various treatments. Therefore, this base was methylated by diazomethane and purified by chromatography, by which colorless prismatic crystals, m. p. 60° (sint. at 56°), soluble in various organic solvents except in petroleum ether, were obtained. It was impossible to purify further by recrystallization, because of the

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1) E. Fujita : (Part. LXXXIX.) This Journal, 72, 213 (1952).

small quantity of the crystals. By admixture of this substance with *d*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (m. p. 62°)²⁾, which had been obtained previously by Tomita, et al. through the cleavage of tetrandrine with metallic sodium in liquid ammonia, it distinctly showed a depression of the melting point, by melting at 48~51°. But, by admixture of the same with the *l*-compound³⁾ which had been obtained by the same workers through the cleavage of isotetrandrine (*O*-methylberbamine) with metallic sodium in liquid ammonia, it showed no depression of the melting point melting at 62° (sint. at 58°). The specific rotation of this substance was $[\alpha]_D^{27} = -82.36^\circ$ (in chloroform), and the data were found to be quite identical with those of *l*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (V), $[\alpha]_D = -84.48^\circ$ (in chloroform)⁴⁾ or $[\alpha]_D^{26} = -83.26^\circ$ (in chloroform).³⁾ Consequently, it is certain that this non-phenolic base is none other than *l*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (V). Judging from the specific rotation of oxyacanthine ($[\alpha]_D^{25} = +258^\circ$), Bruchhausen's presumption⁵⁾ and the experimental results previously obtained by Tomita, Fujita, et al. about the berbamine series, the author supposed that the substance (IV) or (V) would naturally be the *d*-form but he has come to prove indirectly, through its methylated substance [V], that it was the *l*-form substance that has actually been obtained. Though the raw material, *O*-methoxyoxyacanthine, is an amorphous powder, the specific rotation measured showed $[\alpha]_D^{27} = +278.36^\circ$ (in chloroform), which is identical with the datum described in the literature ($[\alpha]_D^{28} = +289.1^\circ$ in chloroform).⁶⁾ This shows that the steric configuration of the two asymmetric centers in the oxyacanthine-molecule were clearly (+, +). Accordingly, fact that the bisected *l*-type base was obtained contrary to anticipation, must be attributed to the inversion of the steric configuration taking place during the reaction.

Recently, Bick and Todd⁷⁾ studied the structure of repandine, m. p. 255° (decomp.), $[\alpha]_D^{15} = -106^\circ$ (in chloroform), an alkaloid of *Daphnandra repandura*, and reported that it was a diastereoisomer of oxyacanthine, and identical with the base, m. p. 260°, $[\alpha]_D = -94.9^\circ$ (in chloroform) which Bruchhausen and Schultze⁸⁾ obtained, when they made 1/2 equivalent mol. of the hydrochloric acid react upon oxyacanthine. Against this, Bruchhausen⁹⁾ emphasized that oxyacanthine would isomerize comparatively easily to a structure corresponding to that of repandine by undergoing Walden's inversion in one of its asymmetric centers and, denying Bick and Todd's opinion of repandine itself existing in Berberidaceous plants, he observed that the original oxyacanthine would have caused Walden's inversion and the isomeric repandine would have been formed secondarily.

Thus, Walden's inversion has been considered until now to be characteristic to oxyacanthine and although Bruchhausen and Schultze carried out the same reaction upon other substances such as *O*-methoxyoxyacanthine and berbamine, they reported that in neither case such phenomenon ever occurred. Walden's inversion of oxyacanthine has occurred, up to the present, only when it was treated with hydrochloric acid corresponding to the 1/2 equivalent mole; and the configuration (+, +) of the asymmetric centers in the oxyacanthine molecule is considerably unstable and has a strong tendency to form a more stable configuration (+, -). Though Bruchhausen and Schultze reported

2) M. Tomita, E. Fujita, F. Murai: (Part. LXXXII.) This Journal, **71**, 1039 (1951).

3) M. Tomita, E. Fujita, F. Murai: This Journal, **71**, 226, 301 (1951); *ibid.*, **71**, 1035 (1951).

4) Kononova, Junusov, Orechov: Ber., **68**, 2158 (1935).

5) Bruchhausen, Oberembt, Feldhaus: Ann. **507**, 144 (1933).

6) H. Kondo, K. Yano: This Journal, **52**, 855 (1932).

7) I. R. C. Bick, A. R. Todd: J. Chem. Soc., **1948**, 2170.

8) F. v. Bruchhausen, H. Schultze: Arch. Pharmaz. **267**, 623 (1929).

9) F. v. Bruchhausen: Arch. Pharmaz. **283**, 44 (1950).

that no inversion occurred when *O*-methoxyacanthine was treated with 1/2 equivalent mole. of hydrochloric acid as described above, the author has a doubt about it. By the fact that the author obtained one *l*-type bisected base, contrary to his anticipation, by reacting metallic sodium on *O*-methoxyacanthine in liquid ammonia, he has been able to prove that *O*-methoxyacanthine undergoes inversion of steric configuration in the *O*-methoxyacanthine undergoes inversion of steric configuration in the alkaline medium as well. It has also been proved that the steric configuration of one of the two asymmetric centers in the oxyacanthine molecule is unstable. Moreover, from his recent experimental result, it has been clarified that one unstable asymmetric center which changes easily in the oxyacanthine molecule is the asymmetric carbon atom in the right tetrahydroisoquinoline in formula (I). Accordingly, the structure of repandine, a stereoisomer of oxyacanthine should be represented by formula (VI), and it can be concluded that the asymmetric center belonging to the left tetrahydroisoquinoline is the + configuration, and the one at the right is the - configuration.

This research was carried out under the kind and continuous guidance of Prof. Dr. Masao Tomita, to whom the author wishes to extend his sincere and heartfelt gratitude. The expenses for this research were furnished by the Scientific Research Funds provided by the Ministry of Education, for which he also expresses his profound gratitude.

Experimental

***l*-1-(4'-Methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (V)** —As described in the experimental part of the previous report¹⁾, *O*-methoxyacanthine was bisected by metallic sodium in liquid ammonia and from the crude phenolic base obtained *d*-armepavine was removed as its oxalate. After alcohol is distilled away from the mother liquid, the residue is alkalinized with ammonia and a free base is extracted with ether. When the solvent is distilled off, the residue is a viscous oil with light pink color. In spite of various treatments it failed to crystallize. It was then dissolved in a small quantity of methanol, and some ethereal solution of diazomethane added. After being left standing for two days to complete methylation, the solvent was distilled off; and the residue is purified by the usual method. By further purification of its benzene solution by chromatography through alumina, colorless prismatic crystals are obtained. These are easily soluble in various organic solvents except petroleum ether. By recrystallization of this substance from a mixture of ether and petroleum ether, the substance obtained shows m.p. 60° (sint. at 56°). By admixture with *d*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (m.p. 62°), the melting point drops to 48~51°. By its admixture with *l*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (m.p. 62°), they melted at 62° (sint. at 58°) with no depression of the melting point. $[\alpha]_D^{27} = -82.36^\circ$ (Subst. 0.0221 g. in chloroform 7 cc., $l = 1/2$ dm.).

The Specific Rotation of *O*-Methoxyacanthine : $-\alpha]_D^{27} = +278.36^\circ$ (Subst. 0.2209 g. in chloroform 25 cc., $l = 1/2$ dm.).

Summary

As a result of search for the other bisected base, which is obtained besides *d*-armepavine (III) when *O*-methoxyacanthine (II) was reacted with metallic sodium in liquid ammonia, the *l*-type bisected base was obtained, contrary to anticipation. It is considered to have been formed by the Walden inversion taking place during the reaction.

(Received October 2, 1951)