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23. **Masao Tomita and Yoshio Sasaki:** Studies on the Alkaloids of Menispermaceous Plants. CXVI.[1] Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia. (2)[2]. The Structure of Cepharanthine.

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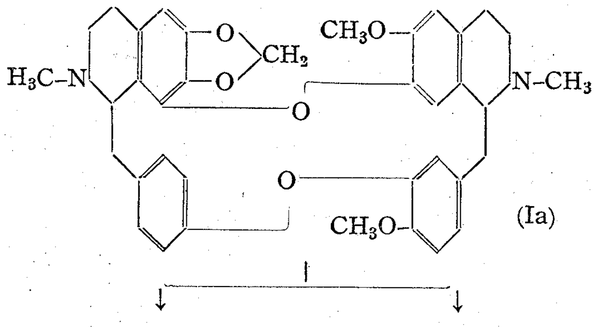
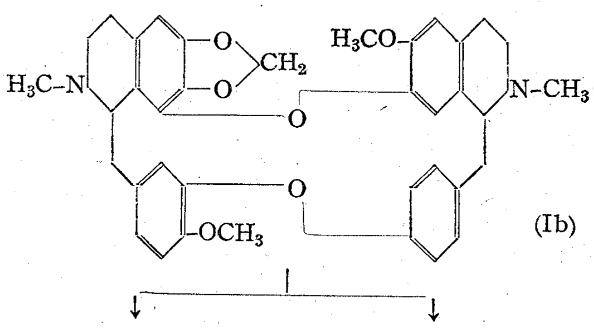
During the course of an investigation on the cleavage reaction of cepharanthine by metallic sodium in liquid ammonia, as reported in the preceding paper[2] of this series, Tomita and Sasaki found it difficult to isolate from a mixture of the phenolic bisected bases corresponding to (IIa) + (IIIa) or (IIb) + (IIIb), obtained by this reaction, each component in crystalline form, and so by methylation of this mixture with diazomethane, they identified it as the substance corresponding to *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IV) and *l*-1-(4′-methoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (V). Merely from the result that by the cleavage reaction of cepharanthine, the substances (IV) and (V) could be obtained, it would appear impossible to judge whether the structure of cepharanthine should be (Ia) or (Ib). The reason why formula (Ia) of the oxyacanthine type was surmised for cepharanthine, however, was due partly to the fact that from a mixture of the phenolic bases obtained by the scission of cepharanthine, the base of (IIIb) type, which, as Tomita had experienced, crystallizes most readily, could not be detected, and partly to the fact that as a result of determination of specific rotations of the bisected bases, cepharanthine was considered to have undergone completely the same mode of cleavage as the oxyacanthine type of bases.



(Ia)



(Ib)

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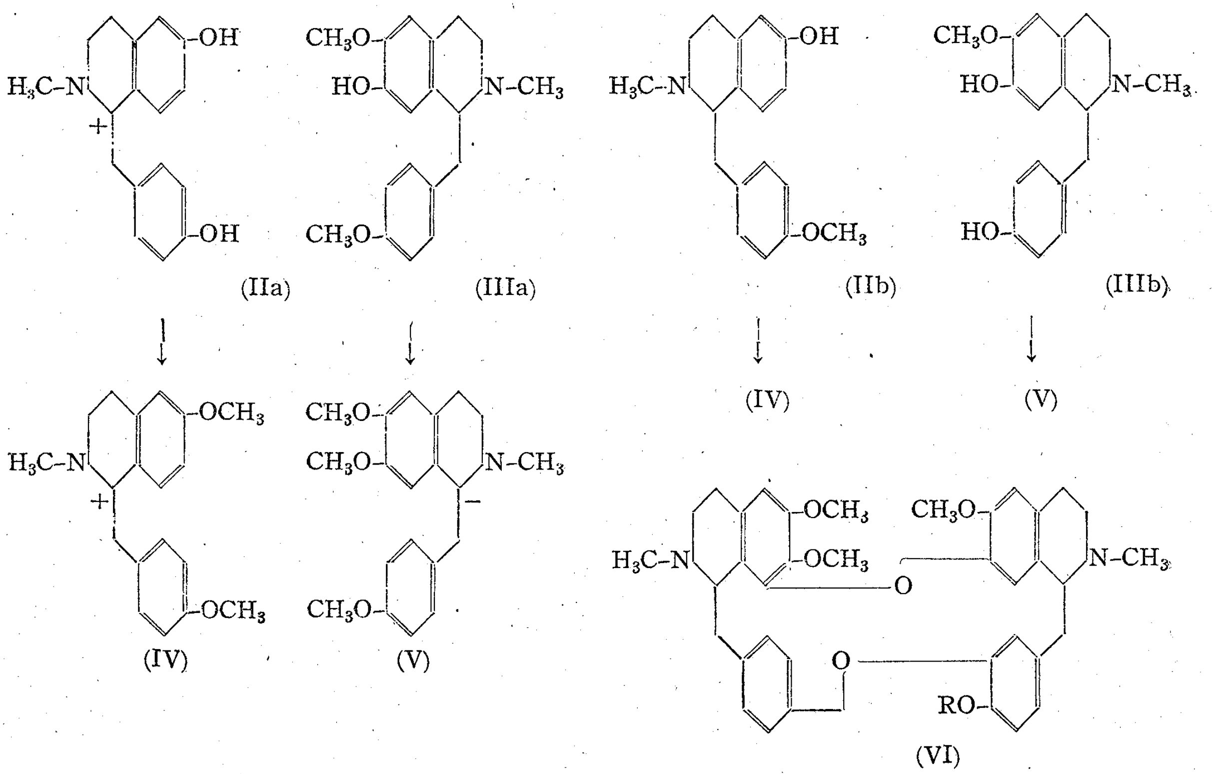
[1] Part CXV: Y. Inubushi: This Bulletin, 2, 11 (1954).

[2] M. Tomita, Y. Sasaki: This Bulletin, 1, 105 (1953).



(IIa) (IIIa) (IIb) (IIIb)

(IV) (V) (IV) (V)

(VI)

In the present series of experiments, the authors have been successful in isolating a crystalline phenolic base directly from a mixture of the phenolic bisected bases obtained by allowing cepharanthine to cleave by metallic sodium in liquid ammonia. As described in the experimental section, a mixture of the phenolic bases obtained by this cleavage was purified by chromatography and furnished a crystalline phenolic base having the m.p. of 205~207°(decomp.). This substance crystallizes from acetone in the form of colorless pillars and once it crystallizes, it has a tendency to become comparatively sparingly soluble in organic solvents. Its analytical values correspond to a composition of $C_{17}H_{19}O_2N$. It containes no methoxyl group as determined by the Vieböck's method; $[\alpha]_D^{10}$: + 341° (CH_3OH). On methylation with diazomethane, this substance afforded a product crystallizing in the form of colorless needles, m.p. 115~116°, the identity of which was confirmed by admixture with the substance²⁾ of m.p. 116~117°, corresponding to *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IV).

From the foregoing results, it is evident that the phenolic base, m.p. 205~207° (decomp.), containing no methoxyl group, referred to above, does not have the structure of (IIb) but of (IIa), and this strongly supports the assumption that, as noted in the previous paper²⁾, cepharanthine should not be represented by (Ib) but by (Ia), belonging to the oxyacanthine type (VI, R=H). On comparison of the structure of cepharanthine (Ia) with that of O-methyloxyacanthine (VI, R=CH_3), the difference in the structure between the two bases is due solely to the fact that in the case of cepharanthine, the two contiguous methoxyl groups in the benzene portion constituting the isoquinoline nucleus in oxyacanthine are replaced by a methylenedioxy group and that both seem to have the same stereochemical arrangements about the two asymmetric centers. Attempts to isolate from the two bases obtained by the cleavage reaction of cepharanthine the other bisected base having the structure of (IIIa), and to synthesize the bases corresponding to (IIa) and (IV) are now being made, the details of which will be published in the near future.

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Experimental[3]

Cleavage Reaction of Cepharanthine by Metallic Sodium in Liquid Ammonia—The cleavage reaction was conducted in liquid ammonia by dissolving 1.5 g. of cepharanthine-benzene adduct in the minimum amount of anhydrous xylene followed by the addition of 0.9 g. of metallic sodium, by a procedure similar to that described in the previous paper[2]. The reaction mixture was allowed to stand overnight to volatilize ammonia and the residue which remained was treated with water to dissolve the solidified mass. The alkaline aqueous solution was extracted with ether to remove a non-phenolic material and excess xylene. The aqueous phase was made acid with concentrated hydrochloric acid, and shaken up with ether to remove the ether-soluble portion. The acidified solution was made alkaline with sodium bicarbonate, and the liberated phenolic bisected bases were extracted by means of a large amount of ether. The ether extract was dried with anhydrous potassium carbonate and evaporated, leaving a yellowish glutinous products. A mixture of the phenolic bisected bases thus obtained was dissolved in the minimum amount of acetone, passed over a column of acetone-moistened alumina (1.3×20 cm.), and the chromatogram developed with the same solvent. The early part of the eluate fractions, on removal of the solvent, did not crystallize, whereas the latter part deposited prismatic crystals soon after removal of the solvent. Recrystallized from acetone, they crystallized in the form of colorless pillars, m.p. 205~207° (decomp.). This substance is soluble in caustic alkali and insoluble in alkali carbonates. It contains no methoxyl group as determined by the Vieböck's method. $[\alpha]_D^{10}$: +341° (4.116 mg. subst. in 5 cc. methanol, l=0.5 dm.). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.83 ; H, 7.06. Found : C, 75.82 ; H, 7.35.

20 mg. of the above substance, m.p. 205~207° (decomp.), was dissolved in 10 cc. of methanol, followed by the addition of 70 cc. of an ether solution of diazomethane, prepared from nitrosomethylurea, and the mixture was allowed to stand for 2 days. On removal of the ether and excess diazomethane, colorless needles appeared. They were recrystallized from ether and melted at 115~116°. A mixed m.p. with a sample of the crystals, m.p. 116~117°, which, as reported in the previous paper[2], are considered identical with *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IV), showed 115~116°, no depression being observed.

Summary

The cleavage reaction of cepharanthine was conducted in liquid ammonia by means of metallic sodium, and from a mixture of the phenolic bisected bases thus obtained there was isolated a crystalline base having the m.p. of 205~207° (decomp.). As a result of detailed examination, this substance was confirmed to correspond to *d*-1-(4′-hydroxybenzyl)-6-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IIa). Thus it has been positively proved that the structure of cepharanthine should be represented by (Ia).

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[3] Melting points are uncorrected. The authors are indebted to Messrs. Hozumi, Imaeda, and Kinoshita in the Microanalytical Laboratory of this Institute for the microanalyses reported herein.