the berbamine type, it seems also possible to consider that the decomposition products were obtained in this reaction without inversion, and according to this thinking, the steric configuration so far considered for oxyacanthine (+, +), and repandine (+, −) were now considered as necessitating reversal, giving oxyacanthine (+, −) and repandine (+, +). However, experimental data hitherto obtained are not sufficient to conclude which of these two views would be correct.

(Received February 27, 1953)

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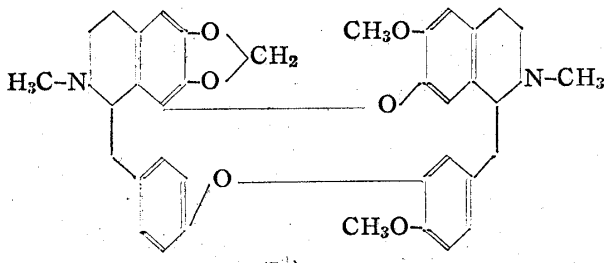
25. Masao Tomita and Yoshio Sasaki: Studies on the Alkaloids of Menispermaceous Plants. CVI. On the Structure of Biscoclaurine Alkaloids. (13). Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia.

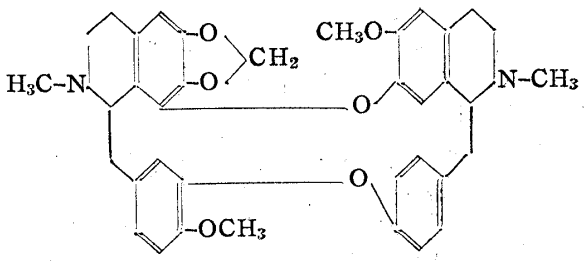
(Pharmaceutical Institute, Medical Faculty, University of Kyoto)*

In recent years, M. Tomita and his collaborators clarified that when metallic sodium was reacted on biscoclaurine-type alkaloids in liquid ammonia, the ethereal oxygen linkages forming diphenyl ethers in their molecules were bisected under exactly the same mechanism to yield two coclaurine-type molecules, and by the examination of their bisected bases, up to date, they were able to determine the structural difference between the alkaloids of the oxyacanthine-berbamine series,[1] and of cycleanine.[2] Also they demonstrated that the biscoclaurine-type alkaloids possessing the phenolic hydroxyl group showed a resistance to this mode of cleavage reaction. For example, in berbamine[3], possessing a phenolic hydroxyl group in the ortho-position of the ethereal oxygen forming diphenyl ether, the oxygen link in that position was not cleaved, and this was the same with the alkaloids possessing a diphenylene dioxide nucleus in their molecules, such as the alkaloids of the trilobine-isotrilobine series. For example, when the cleavage by metallic sodium in liquid ammonia was applied to diphenylene dioxide[4] itself, 2-hydroxydiphenyl ether was formed, and the cleavage reaction did not proceed any further.

Cepharanthine, one of the alkaloids of the biscoclaurine group, is a main base of *Stephania cepharantha* Hayata[5] (Japanese name "Tamasaki-tsuzurafuji") and *Stephania Sasakii* Hayata[6] (Japanese name "Kohtoh-tsuzurafuji"), and the structure of this alkaloid



(Ia)



(Ib)

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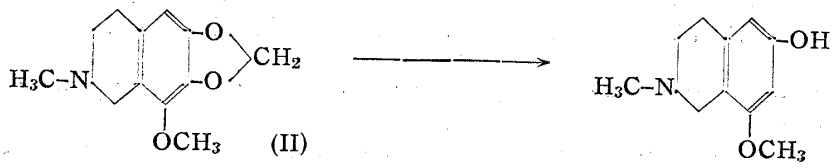
* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 佐々木喜男).

1) M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, **71**, 226, 301, 1035 (1951); E. Fujita, F. Murai: *Ibid.*, **71**, 1039 (1951); M. Tomita, Y. Inubushi, H. Niwa: *Ibid.*, **72**, 211 (1952); E. Fujita: *Ibid.*, **72**, 213, 217 (1952); E. Fujita, T. Saijoh: *Ibid.*, **72**, 1232 (1952); Y. Inubushi, H. Niwa: *Ibid.*, **72**, 762 (1952).
2) E. Fujita, F. Murai: *Ibid.*, **71**, 301, 1043 (1951).
3) M. Tomita, Y. Inubushi, H. Niwa: *Ibid.*, **72**, 220 (1952).
4) M. Tomita, Y. Inubushi, H. Niwa: *Ibid.*, **72**, 206 (1952).
5) H. Kondo, M. Tomita, M. Satomi, T. Ikeda: *Ibid.*, **58**, 920 (1938).
6) M. Tomita: *Ibid.*, **59**, 542 1939).

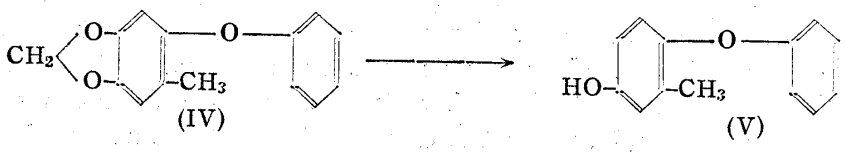
was studied by H. Kondo and I. Keimatsu[7], who, by various decomposing reactions, followed by partial syntheses, proposed formula (Ia) or (Ib) for its representation.

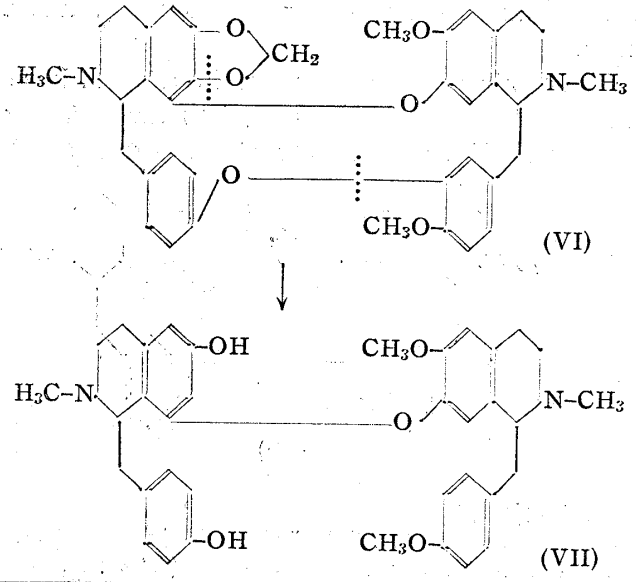
Since cepharanthine belongs to the alkaloids of the oxyacanthine-berbamine series, it seems possible to discern which of (Ia) or (Ib) better represents its structure by applying this cleavage reaction to it. However, this base is unique in that it is the only base among the biscoclaurine bases which has a methylenedioxy group.

Sowa[8] and his co-workers reported on the cleavage of miscellaneous diphenyl ether derivatives by metallic sodium in liquid ammonia, but no literature has yet appeared on the reaction of compounds possessing a methylenedioxy group. Recently, Clayson[9] carried out the same method of cleavage on cotarnine and many of its derivatives, and reported that in all cases the methylenedioxy group underwent scission. The following is one such example.



Accordingly, when cepharanthine (Ia) or (Ib) is subjected to this cleavage reaction, it may be assumed that the methylenedioxy group will first undergo scission, and the phenolic hydroxyl group resulting from this scission will hinder the bisection of the ethereal oxygen linkages forming diphenyl ethers in the molecules of cepharanthine, as in the case of berbamine.[3] Therefore, as one of the fundamental experiments, M. Tomita, Fujita, and Abe[10] carried out the same cleavage reaction on 3,4-methylenedioxy-6-methyldiphenyl ether (IV),





and found that, as expected, 4-hydroxy-6-methyldiphenyl ether (V) was formed, and the ethereal oxygen linkage forming diphenyl ether did not undergo cleavage, the reaction having stopped at (V).

On the basis of these experimental facts, attempt was made to apply this cleavage reaction to cepharanthine with the following idea. When metallic sodium is reacted on cepharanthine (VI) in liquid ammonia, the cleavage of the ethereal oxygen linkage of diphenyl ether binding the two benzyl groups will first occur, as shown in formula (VI). At the same time, the methylenedioxy group will be cleaved

7) H. Kondo, Y. Yamashita, I. Keimatsu: J. Pharm. Soc. Japan, 54, 620 (1934); H. Kondo, I. Keimatsu: *Ibid.*, 55, 121, 894 (1935); *ibid.*, 58, 907 (1938); Ber., 71, 2553 (1938).
8) P. A. Sartoretto, F. J. Sowa: J. Am. Chem. Soc., 59, 603 (1937); A. L. Kranzfelder, F. J. Sowa: *Ibid.*, 59, 1488 (1937); F. C. Weder, F. J. Sowa: *Ibid.*, 60, 94 (1938).
9) D. B. Clayson: J. Chem. Soc., 1949, 2016.
10) M. Tomita, E. Fujita, T. Abe: J. Pharm. Soc. Japan, 72, 384 (1952).

to yield a new phenolic hydroxyl group, and due to its hindrance, the ethereal oxygen linkage combining the two isoquinoline nuclei will not be cleaved and a phenolic base of (VII) type will be formed. The substance (VII) thereby obtained can be converted into ethyl ether by ethylation, and again submitted to the same cleavage reaction. In this case, the cleavage reaction will proceed satisfactorily until the compound is bisected into two benzylisoquinoline-type molecules. The examination of these bisected bases will determine the structure of cepharanthine. This idea is based on the same technique employed by M. Tomita, Inubushi, and Niwa[3] in the decomposition of berbamine.

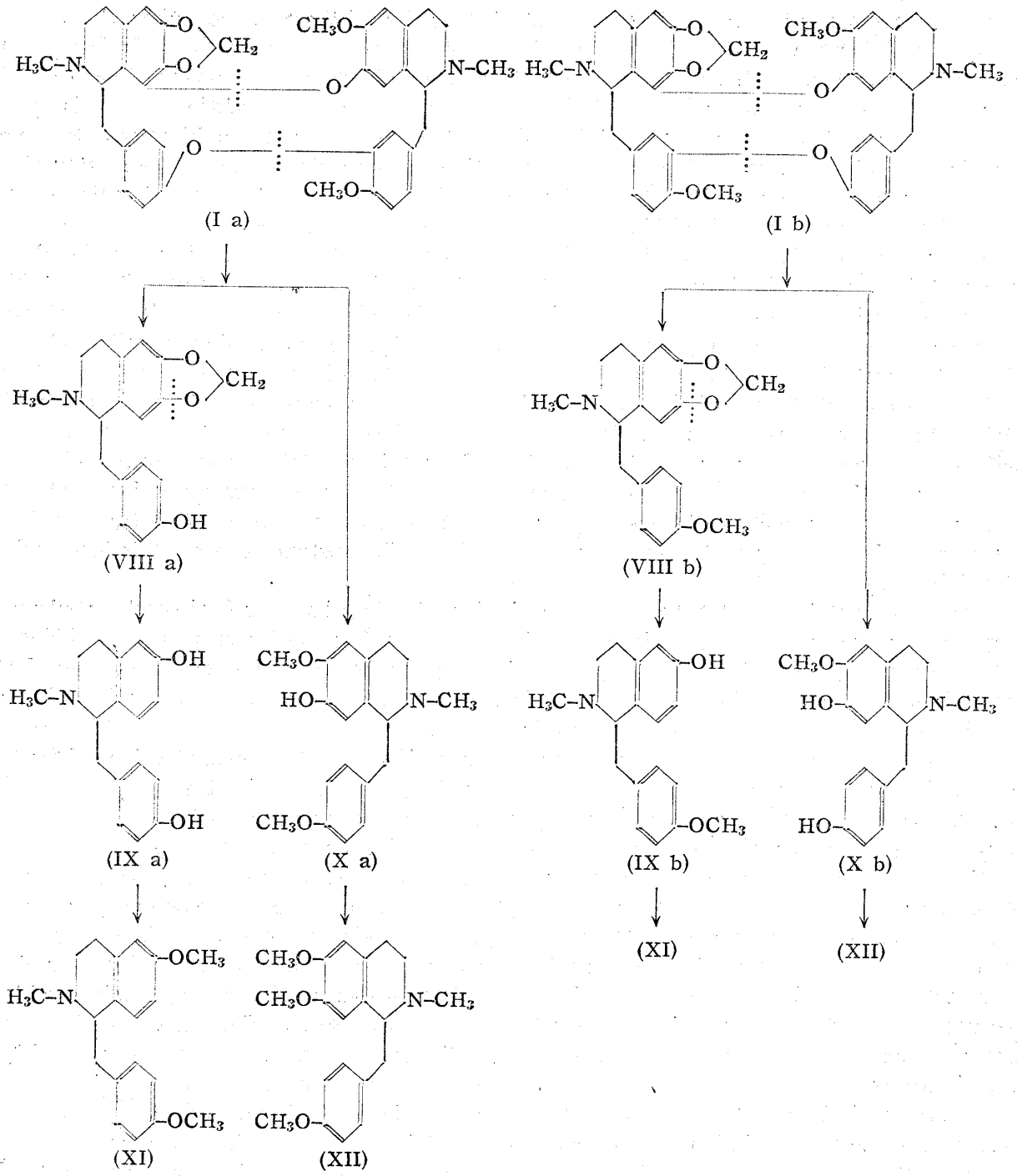
According to this idea Tomita and Fujita carried out the following reaction[11] on cepharanthine as a preliminary experiment. Cepharanthine, when reacted with metallic sodium in liquid ammonia by the usual method, yielded a phenolic base (the substance presumed to be identical with (VII)) which gave a negative methylenedioxy test[12] and was difficult to crystallize. Subsequently, this was ethylated by diazoethane but the ethyl ether obtained also resisted crystallization. For the sake of confirmation, amorphous though this substance was, its specific rotation was determined which proved to be $[\alpha]_D^{25}$: $-15°$ ($CHCl_3$) (cepharanthine $[\alpha]_D$: $+300°$ ($CHCl_3$)). When this substance, considered to be the ethyl ether of (VII), was subjected to the second-stage of the same cleavage reaction, contrary to their expectations, the reaction did not proceed at all and no amount of metallic sodium was spent, only the raw material being recovered. This substance could be distilled easily in a high vacuum.

Since no crystalline substance could be obtained in the above preliminary experiment adequate discussion cannot be given on this reaction. However, it may well be deduced that, contrary to the anticipation, cepharanthine must have been bisected into two coclaurine-type molecules by only one stage of this cleavage, as in the case of ordinary non-phenolic bases of the oxyacanthine-berbamine series.

Meanwhile, the present authors thought that, if fortunate, cepharanthine might be converted into either O-methyloxyacanthine or O-methylberbamine-type base by the methylation of the dihydroxy compound formed by the cleavage of only the methylenedioxy group in cepharanthine. As the means to this aim, as is often employed, a mild reaction in which anhydrous aluminum bromide is allowed to react in the benzene, chlorobenzene, or nitrobenzene solution, was selected. In the case of the compound possessing both the methylenedioxy and methoxyl groups, it is usually possible to cleave only the methylenedioxy group by this reaction with ease at room temperature or by warming slightly. When this reaction was applied to cepharanthine, however, only cepharanthine was recovered, when the reaction temperature was below 80°. When the reaction was performed at 80°, as described in the experimental part, a phenolic base showing a positive methylenedioxy test and which was assumed to have been formed by the elimination of the methyl radical from the methoxyl group was obtained. This substance regenerated to cepharanthine by methylation with diazomethane. When the reaction temperature was raised beyond 100°, all the reaction products became resinous. This fact shows that the bond of the methylenedioxy group in the cepharanthine molecules is extraordinarily stable, differing from the usual one.

Judging from the various experimental results obtained to date, it became necessary to reëxamine the reaction by modifying the view so far held regarding the cleavage of cepharanthine. If the phenolic base to be obtained by cleaving cepharanthine with metallic sodium in liquid ammonia is transformed by ethylation into an ethyl ether, then, the examination of the latter should make it possible to determine whether the structure of cepharanthine should be indicated by (Ia) or (Ib). However, the aim was to clarify whether the idea is right or not, the methyl ether was considered as the experiment.

11) Unpublished. 12) Color reaction by phloroglucinol-H_2SO_4.



If cepharanthine (Ia) or (Ib) is reacted with metallic sodium in liquid ammonia, it will be decomposed first into (VIIIa)+(Xa) or (VIIIb)+(Xb), two molecules of the coclaurine type in one step, and (VIIIa) or (VIIIb), by further undergoing the scission of the methylenedioxy group by the action of the excess metallic sodium, will yield the mixed phenolic bases of (IXa)+(Xa) or (IXb)+(Xb) in the end. If these two kinds of mixed phenolic bases are methylated by diazomethane, they will ultimately furnish the mixed bases of (XI)+(XII), according to whichever structure of (Ia) or (Ib) cepharanthine may have.

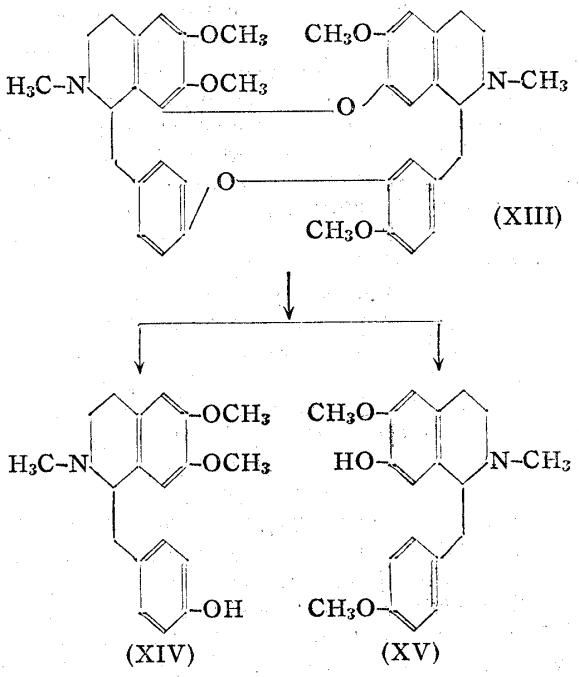
According to this idea, the reaction was applied to cepharanthine, and a reaction product was obtained as a mixture of phenolic bases, all showing a negative methylenedioxy test. These resisted crystallization, and were difficult to purify as phenolic bases. As far

as we have ever experienced[12], one of the phenolic bases (Xb) precipitates quantitatively as its oxalate on account of being very sparingly soluble in alcohol. However, no crystalline oxalate precipitated from the mixed phenolic bases obtained above. The mixed phenolic bases were, therefore, methylated with diazomethane and a mixture of methyl ethers thus obtained was purified thoroughly through the chromatographic method, and after taking much trouble, the mixture was separated into colorless needles, m.p. 116~117°, comparatively sparingly soluble in ether, and colorless clustered needles, m.p. 63~64° (sint. at 60°), readily soluble in ether. From the analytical results, the former represents the composition of $C_{19}H_{23}O_2N$ and contains two methoxyl groups, $[\alpha]_D^{16}$: +49.40° ($CHCl_3$). Considering from the constitution of cepharanthine and its decomposition process, it seems that this base should have the structure of (XI). On the other hand, the latter, m.p. 62~63°, shows $[\alpha]_D^8$: −80.49° ($CHCl_3$), the identity of which was confirmed by comparison with *l*-O,O,N-trimethylcoclaurine[13] (XII), m.p. 62°.

These experimental results have shown that the decomposing reaction of cepharanthine has yielded *l*-O,O,N-trimethylcoclaurine (XII) and a substance corresponding to *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XI) and this fact proves that the authors' idea regarding the reaction process of cepharanthine by metallic sodium in liquid ammonia had been correct.

The substance corresponding to (XI), obtained above, is now being studied, the particulars of which will be reported in the succeeding issues of this journal. It must be remembered, however, that no ample proof can be afforded only by this experiment as to whether cepharanthine has the structure (Ia), or (Ib). It is hoped that the mixed phenolic bases obtained by decomposition could be converted into ethyl ethers and examined further, report on which will be published later.

In this connection, it should be noted, however, that although cepharanthine has $[\alpha]_D$: +300° ($CHCl_3$), two kinds of bisected bases are *d*-type (XI) and *l*-type (XII). Previously, Fujita[14] carried out this cleavage reaction on O-methyloxyacanthine (XIII) ($[\alpha]_D$: +278° ($CHCl_3$)), the two asymmetric centers of which, according to the hypothesis by Bruchhausen, *et al.*[15], are surmized to be (+, +), and proved as the bisected bases *d*-type (XIV) and *l*-type (XV). Subsequently, Fujita and Saijoh[16] applied the same reaction to O-methylrepandine ($[\alpha]_D$: −80° ($CHCl_3$)), the two asymmetric centers of which are surmized to be (+, −) and which has the same structure as O-methyloxyacanthine and is its optical isomer, and gained *d*-type (XIV) and *d*-type (XV).



In favor of Bruchhausen's view[17] that oxyacanthine has a tendency to change into repandine by undergoing the Walden inversion by hydrochloric acid, they thought that the asymmetric center located at the right-hand tetrahydroisoquinoline nucleus

13) M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, 72, 1035 (1952).
14) E. Fujita: *Ibid*, 72, 213 (1952).
15) F. v. Bruchhausen, H. Oberembt, A. Feldhaus: Ann., 507, 144 (1933).
16) E. Fujita, T. Saijoh: J. Pharm. Soc. Japan, 72, 1232 (1952).
17) F. v. Bruchhausen: Arch. Pharm., 283, 44 (1950).

in both O-methyloxyacanthine and O-methylrepandine underwent the Walden inversion by this reaction.

The authors have found, in addition to the above two instances of the oxyacanthine-type bases, third instance, and this holds good also with cepharanthine. Similar examples have never hitherto been found in the case of berbamine-type bases, and such reaction must be characteristic of the oxyacanthine bases. From the point of such a view, it seems reasonable to presume indirectly that cepharanthine has the oxyacanthine-type structure represented by formula (Ia).

As Tomita and Fujita stated in detail in the previous paper[18], one of the asymmetric centers, supposed to be (+, +), in the molecule of cepharanthine, may have undergone inversion by this cleavage reaction and thereby yielded *d*-type (XI) and *l*-type (XII). Another way of thinking is that in cepharanthine as in oxyacanthine, the configuration of its two asymmetric centers is (+, −) from the beginning and that the absolute configuration of its asymmetry is not disturbed by inversion by this reaction.

As stated above, it has been presumed indirectly that cepharanthine would have the oxyacanthine-type structure, represented by formula (Ia), but final confirmation must be made later after more studies are made.

The authors wish to express their appreciation to Mr. M. Akasu of Kaken Chem. Drug. Co. Ltd., who kindly provided them with the expensive cepharanthine without charge. The authors also wish to acknowledge that a part of the expenses for this study was defrayed by the Scientific Research Fund provided by the Ministry of Education.

Experimental*

Cleavage of methylenedioxy group in cepharanthine by $AlBr_3$—0.5 g. (1 mole) of cepharanthine-benzene adduct was dissolved in 50 cc. of dry benzene. With stirring, a solution of 0.47 g. (2.5 mole) of $AlBr_3$ in 50 cc. of dry benzene was added slowly from the dropping funnel during the course of 15 minutes, at room temperature. After the completion of the addition, the mixture was heated to the boiling point of benzene and maintained at this temperature for 45 minutes. The mixture cooled on standing, was poured with stirring, into 50 cc. of 5% aqueous hydrobromide, and the yellow precipitate that separated was filtered with suction. The filtrate was separated into aqueous and benzene layers. When potassium iodide was added to the aqueous layer, further crop of the yellow precipitate was obtained. The combined precipitate was dissolved in a large amount of water, the solution was made alkaline with 10% aqueous sodium hydroxide, and extracted with ether to remove a non-phenolic portion. The orange red alkaline solution thus obtained was acidified with conc. hydrochloric acid. Then the solution was again rendered alkaline by the addition of sodium bicarbonate, and extracted with chloroform to collect the chloroform-soluble portion. The chloroform extract was dried with anhydrous sodium sulfate, and the solvent removed, yielding an amorphous yellowish brown powder. This substance gave a positive Gaebel's methylenedioxy reaction, and caused violet coloration by ferric chloride solution. The phenolic substance thus obtained was difficult to crystallize even by various treatments, and it was straightway dissolved in a mixture of methanol and ether, and methylated with diazomethane. The methyl ether obtained by treating the above solution in the usual manner was a yellowish brown amorphous powder, which was purified by chromatography using alumina as the adsorbent and benzene as the solvent. The product thereby obtained was dissolved in acetone, and after adding a small amount of benzene, allowed to stand, and crystallized to m.p. 103°. When this substance was mixed with cepharanthine-benzene adduct, no melting point depression was observed.

When the reaction temperature was below 80°, the reaction did not proceed, only ending in recovering cepharanthine. While the reaction temperature was raised beyond 100°, the bulk of the reaction product became resinous. When nitrobenzene or chlorobenzene was used as the solvent instead of benzene, the result was exactly the same.

Cleavage of cepharanthine by metallic sodium in liquid ammonia—A solution of 2.5 g. of cepharanthine-benzene adduct dissolved in the minimum amount of xylene was added dropwise into a vigorously-stirring 400 cc. of liquid ammonia placed in a 1-L. three-necked flask. Simultaneously, 1.2 g. of metallic sodium was added in small portions, until the blue color of the reaction liquor

18) M. Tomita, E. Fujita: This Bulletin, 1, 101 (1953).

* Melting points are uncorrected. Microanalyses were carried out by Mr. K. Hozumi, Mr. K. Imaeda, and Miss H. Iwata in the Microanalytical Laboratory of the Pharmaceutical Institute, University of Kyoto.

persisted for a considerably long time. The reaction temperature was between −35° to −40°. After standing overnight, liquid ammonia was allowed to volatilize, the residue was treated with water, and extracted with ether. The aqueous layer showed a strong alkalinity, in which the phenolic reaction product was dissolved as the sodium salt. The ether extract was washed with 1% aqueous sodium hydroxide, and the washing and the aqueous layer were combined. This alkaline solution was acidified with hydrochloric acid and extracted with ether to remove the ether-soluble substance. Then the acidified solution was again rendered alkaline with sodium bicarbonate, and the deposited phenolic bases were taken up in ether. The ether extract was dried over anhydrous potassium carbonate, and the solvent removed. The yield of the phenolic residue was 2.0 g. These phenolic bases were difficult to crystallize after various treatments. To the alcohol solution of this substance was added a saturated alcohol solution of oxalic acid, but no oxalate precipitated. The amorphous mixture of phenolic bases was dissolved in a mixture of methanol and ether, and methylated by adding the ether solution of diazomethane. After standing for 48 hrs., the excess diazomethane and the solvent were removed. The residue was dissolved in ether, and after shaking with 1% aqueous sodium hydroxide the solvent was distilled off, leaving a reddish brown glutinous substance. This substance was dissolved in benzene and repeatedly purified through the chromatographic method using alumina as the adsorbent, whereupon it was separated into a portion (B) readily adsorbed and a portion (A) the less readily adsorbed upon alumina. (A) yielded colorles needles comparatively sparingly soluble in ether. They were recrystallized from ether and melted at 116～117°. $[\alpha]_D^{18}$: +49.40° (25.03 mg. subst. in 3 cc. $CHCl_3$, l=0.5 dm.) *Anal.* Calcd. for $C_{19}H_{23}O_2N$: C, 76.76; H, 7.74; N, 4.71; OCH_3, 20.88. Found: C, 77.01; H, 7.81; N, 4.97; OCH_3, 20.91.

The mother liquor left after removing the crystals, m.p. 116～117°, as completely as possible and a portion (B) were again purified through chromatography, and gave colorless clustered needles, m.p. 60～63°, readily soluble in ether. They were recrystallized from a mixture of ether-petroleum ether and showed m.p. 63～64° (sint. at 60°). $[\alpha]_D^{8}$: −80.49° (9.841 mg. subst. in 3 cc. $CHCl_3$, l= 0.5 dm.). When this substance was fused with *d*-1-(4′-methoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline, m.p. 62° (sint. at 60°), obvious melting point depression occurred, melting at 42～51°, and when fused with the *l*-isomer, m.p. 62° (sint. at 60°), no melting point depression was observed, melting at 62～63°.

Summary

The authors carried out cleavage reaction on cepharanthine, an alkaloid of *Stephania cepharantha* Hayata and *Stephania Sasakii* Hayata, by means of metallic sodium in liquid ammonia. Consequently, they gained two kinds of bisected bases, viz., the substance presumed to be *d*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XI), and *l*-1-(4′-methoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XII). On considerations from various points, they proposed formula (Ia) for the representation of cepharanthine.

(Received February 27, 1953)