U.D.C. 547.832.1/.5 : 582.675.4

27. Masao Tomita and Yasuo Watanabe : Studies on the Alkaloids of Menispermaceous Plants. CXXXII.[1] Alkaloids of *Stephania japonica* Miers (Suppl. 1). Hydrogenation of Epistephanine.

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

Epistephanine (I : R=CH_3) is one of the biscoclaurine-type alkaloids first isolated from *Stephania japonica* Miers by H. Kondo and Sanada,[2] and its structural work was later made by H. kondo and Tanaka,[3] who indicated that it has a unique structure with one of its two nitrogen atoms linked by a double bond to the adjacent carbon atom. The same workers also obtained, on reduction of this base with zinc and sulfuric acid, two dihydro derivatives, viz. hydroepistephanine-A (hydrochloride, m.p. 259~260°(decomp.), $[\alpha]_D^3$: +299.3° (H_2O)), and hydroepistephanine-B (hydrochloride, m.p. 258~259°(decomp.), $[\alpha]_D^{19}$: +92.0° (H_2O)), and stated that they must be diastereoisomers, which had been formed by undergoing hydrogenation in a different direction. On Hofmann degradation these dihydro derivatives afford the des-N-base identical with that derivable from trilobamine (daphnoline), one of the oxyacanthine-type alkaloids. On this basis they suggested that epistephanine belongs to the oxyacanthine series and that N-methylhydroepistephanine-A would be identical with O-methyloxyacanthine. However, further work still remained to confirm this assumption.

Shortly thereafter, Tomita *et al.*,[4] from a comparative study of the ultraviolet absorption spectra of a number of 3,4-dihydroisoquinoline derivatives, confirmed the proposed structure (I : R = CH_3) of epistephanine. Subsequently, Tomita and Fujita[5] revealed that on reductive cleavage with sodium-liquid ammonia, epistephanine was bisected into 1-(4′-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and *l*-1-(4′-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline. From this experimental result, it has become evident that, as shown in formula (I : R=CH_3), epistephanine is of the oxyacanthine type with one asymmetric center (−), and its secondary nitrogen is located at the left hand portion of the molecule.

Another alkaloid of *Stephania japonica* Miers is hypoepistephanine (I : R=H), which was first isolated by H. Kondo and Sanada.[2] It was later studied by H. Kondo and T. Nozoye,[6] who reported that on methylation with diazomethane it yielded epistephanine (I : R=CH_3).

Our particular interest has been directed to whether or not the dihydro derivatives of epistephanine might undergo selective hydrogenation, as reported by H. Kondo and Tanaka,[3] and some comments on this matter are made in this paper.

The literature[3] states that in the reduction of epistephanine with zinc and sulfuric acid, the deposited white zinc complex salt affords hydroepistephanine-A after liberation with alkali, and on the other hand, its filtrate, on alkalization, hydroepistephanine-B. In our present experiments, however, hydroepistephanine-B could in no way be detected, and various attempts ended only in yielding hydroepistephanine-

* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 渡辺恭男).

1) Part CXXXI. T. Nakano : This Bulletin, **4**, 69(1956).
2) H. Kondo, T. Sanada : J. Pharm. Soc. Japan, **47**, 177, 930(1927); *Ibid.*, **48**, 1141(1928).
3) H. Kondo, K. Tanaka : *Ibid.*, **63**, 267, 273(1943); K. Tanaka : *Ibid.*, **64**, 28(1944).
4) M. Tomita, S. Uyeo, K. Doi, T. Miwa : *Ibid.* **69**, 22(1949)(C. A. **44**, 4476(1950)).
5) M. Tomita, E. Fujita : This Bulletin, **2**, 378(1954).
6) H. Kondo, T. Nozoye : J. Pharm. Soc. Japan, **63**, 333(1943).

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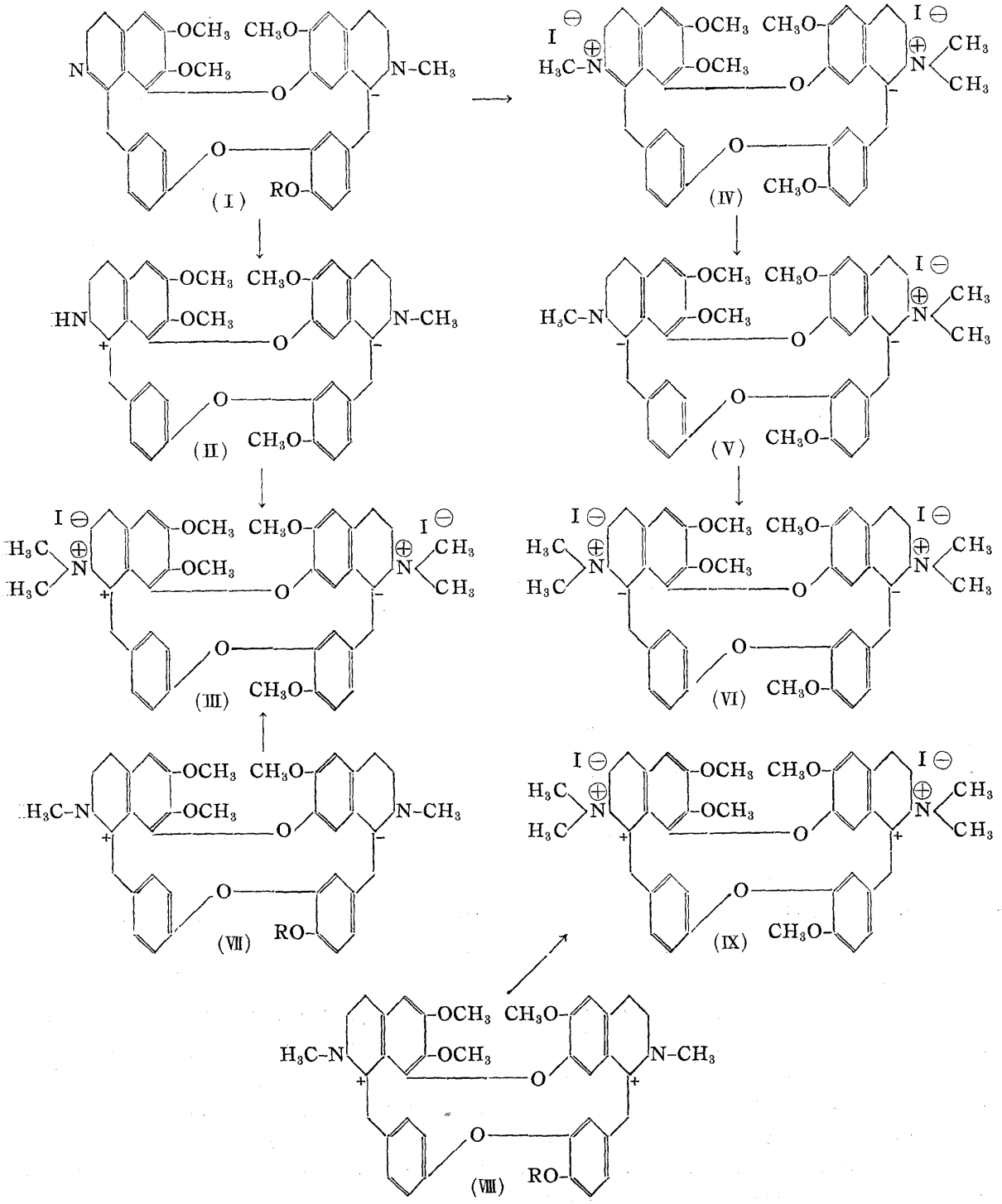

A (II). Hydroepistephanine-A (II) so obtained gave N-methylhydroepistephanine-A dimethiodide (III),** m.p. 260~262°(decomp.), $[\alpha]_D^{30}$: +42.55° (50% EtOH) after refluxing with methanolic alkali and methyl iodide. Meanwhile, methylation of oxyacanthine (VII : R=H) with methanolic alkali and methyl iodide afforded O-methyloxyacanthine dimethiodide[7] (III), m.p. 260~262°(decomp.), $[\alpha]_{12}^{D}$: +45.11° (50% EtOH). N-Methylhy-

** The literature[3] records that N-methylhydroepistephanine-A dimethiodide has m.p. 244~248° (decomp.), without description of the value of its specific rotation; N-methylhydroepistephanine-B dimethiodide does not crystallize.

7) E. Späth, A. Kolbe : Ber., 58, 2284(1925). O-Methyloxyacanthine dimethiodide, m.p. 255~260°(decomp.).

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Infrared Spectra of N-Methylhydroepistephanine Dimethiodide (Hydrate) in Nujol

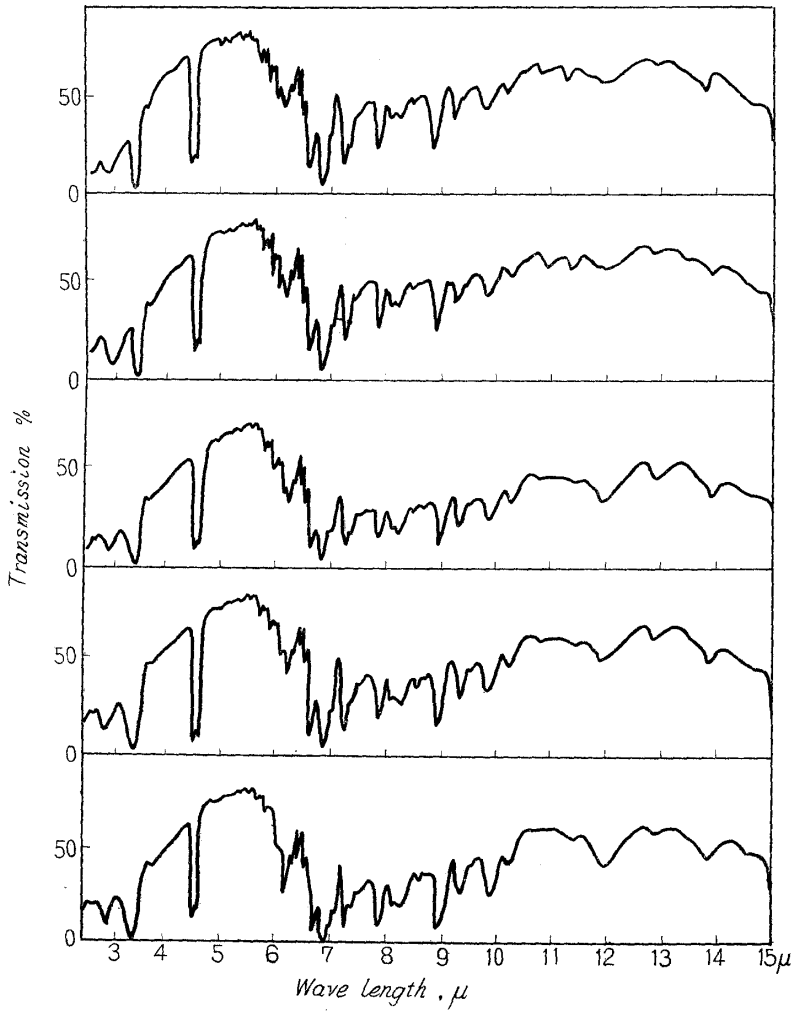

Fig. 1. O-Methyloxyacanthine Dimethiodide (III)

Fig. 2. N-Methylhydroepistephanine-A Dimethiodide (III)

Fig. 3. O-Methylrepandine Dimethiodide (IX)

Fig. 4. N-Methylhydroepistephanine-B Dimethiodide (VI) by Reduction with $NaBH_4$

Fig. 5. N-Methylhydroepistephanine-B Dimethiodide (VI) by Reduction with Zinc and dil. H_2SO_4

droepistephanine-A dimethiodide (III) and O-methyloxyacanthine dimethiodide thus obtained gave identical infrared spectra (Fig. 1 and 2), thereby confirming them to be identical.

It was well established by the previous work by Fujita[8] on the fission of O-methyloxyacanthine with sodium in liquid ammonia that it has a structure (VII : R=CH_3) with the asymmetric centers (+, −). It follows, therefore, that epistephanine (I : R=CH_3) underwent selective hydrogenation with zinc and sulfuric acid, causing the same optical configuration as that of oxyacanthine. This result gave a positive support to the suggestion by H. Kondo and Tanaka that O-methyloxyacanthine and N-methylhydroepistephanine-A would be identical.

Recently, Whaley and Robinson[9] reported that N-methyl-3,4-dihydroisoquinolinium iodides could be converted by sodium borohydride into the corresponding N-methyl-1,2,3,4-tetrahydroisoquinolines in a good yield. Similar phenomenon was also obtained by Witkop[10] when the methiodides of a number of Schiff bases were treated with sodium borohydride. However, in either of these cases, no mention was made of the optical rotations of the products formed.

8) E. Fujita : J. Pharm. Soc. Japan, **72**, 213, 217(1952).
9) W. M. Whaley, C. N. Robinson : J. Am. Chem. Soc., **75**, 2008(1953).
10) B. Witkop, J. B. Patrick : *Ibid.*, **75**, 2572, 4474(1953).

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The application of the above method to epistephanine dimethiodide (IV) offered an interesting fact. When (IV) prepared according to the literature[2] was reduced in methanolic solution with sodium borohydride, the methiodide portion at the right hand in formula (IV) was not affected by this reaction at all, yielding N-methylhydroepistephanine monomethiodide (V). Methylation of (V) with methyl iodide gave N-methylhydroepistephanine-B dimethiodide** (VI), m.p. 254~258°(decomp.), $[\alpha]_D^{20}$: +95.56°(50% EtOH). It is seen that the infrared spectrum (Fig. 4) of (VI) is different from that of O-methyloxyacanthine dimethiodide (III : Fig. 1), but identical with that of O-methylrepandine dimethiodide (IX), m.p. 262~264°(decomp.), $[\alpha]_D^{26}$: −92.66° (50% EtOH), derived from repandine (IX : R=H) following the method given in the literature[11] (Figs. 3 and 4).

Since the earlier work by Fujita and Saijoh[12] elucidated that O-methylrepandine has the structure (VIII : $R=CH_3$) and its asymmetric centers are (+, +), it follows that the right hand centers of asymmetry in epistephanine (I : $R=CH_3$) and O-methylrepandine (VIII : $R=CH_3$) are the reverse to each other. Furthermore, the fact that the value of the specific rotation of N-methylhydroepistephanine-B dimethiodide (VI) ($[\alpha]_D^{20}$: +95.56°) has the opposite sign to that of O-methylrepandine dimethiodide (IX) ($[\alpha]_D^{26}$: −96.22°) indicates clearly that (VI) is an antipode of (IX).

Further investigation was made as to what results would be brought about if another reagent was used in place of sodium borohydride in the reduction of epistephanine dimethiodide (IV). Reduction of (IV) with zinc and sulfuric acid yielded N-methylhydroepistephanine monomethiodide (V) as in the case of the borohydride which, on methylation with methyl iodide, gave N-methylhydroepistephanine-B dimethiodide (VI), m.p. 260~262°(decomp.), $[\alpha]_D^{15}$: +98.6°(50% EtOH). It was also confirmed that the infrared spectrum of (VI) is identical with that of O-methylrepandine dimethiodide (IX) (Figs. 3 and 5), and the value of its specific rotation showed the opposite sign to that of (IX).

The foregoing results are thus summarized as follows : The direct reduction of epistephanine (I : $R=CH_3$) with zinc and sulfuric acid gives rise to the dihydro derivative (II), whose dimethiodide (III) has the asymmetric centers (+, −), identical with those of O-methyloxyacanthine dimethiodide (III) (+, −). On the other hand, when epistephanine dimethiodide (IV) is submitted to the reduction with either sodium borohydride or zinc-sulfuric acid, it affords N-methylhydroepistephanine monomethiodide (V), from which the dimethiodide (VI), with the asymmetric centers (−, −), is obtained. In either of these cases, racemization does not take place during this reaction, and such an example of asymmetric induction as that while the same hydrogenating reagents are used, the selective reduction occurring in a different direction in each case, is a very interesting one. In addition, it is of significance to mention here that among the oxyacanthine series, an alkaloid whose asymmetric centers are (−, −) is not yet known in nature.

We are indebted to Dr. Y. Inubushi of this Institute for his good advices, to Messrs. Y. Matsui and M. Narisada of the Research Laboratory, Shionogi & Co., Ltd., for the measurement of the infrared spectra, and to Dr. M. Satomi and Mr. K. Takeda of Itsuu Laboratory, Tokyo, for their generous gift of a sample of hypoepistephanine. This work was supported partly by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which we are also grateful.

11) I. R. C. Bick, A. R. Todd : J. Chem. Soc., **1948**, 2170.
12) E. Fujita, T. Saijoh : J. Pharm. Soc. Japan, **72**, 1232(1952).

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Experimental[13]

Epistephanine (I : R=CH_3)—The ether solution (50 cc.) of CH_2N_2, prepared from nitrosomethylurea (5.0 g.), was added to the MeOH solution (150 cc.) of hypoepistephanine (I : R=H, 2.5 g.), and the mixture was allowed to stand for 2 days at room temperature. A small volume of AcOH was added dropwise to this solution to decompose the excess CH_2N_2 and the solvent was distilled off. The residue was dissolved in 5% HCl, alkalized with aq. NaOH under cooling, and extracted with ether. The ether extract was shaken with 2.5% aq. NaOH to remove the unreacted material and dried over anhyd. K_2CO_3. After removal of the solvent, the residue was crystallized from dehyd. MeOH, whereby epistephanine was obtained as colorless prisms, m.p. 202°; yield, 1.8 g.

Hydroepistephanine-A (II)—Epistephanine (0.18 g.) was dissolved in a mixture of 20% H_2SO_4 (3 cc.) and EtOH (3 cc.), Zn dust (0.36 g.) was then added, and the mixture was refluxed on a water bath, whereupon the orange yellow solution was decolorized immediately. 20% H_2SO_4(0.6 cc.) and Zn dust (0.06 g.) were added every 1 hr. After 5 hrs., the reaction mixture was filtered while hot from residual Zn dust, and the filtrate was kept standing overnight. Colorless plates (Zn-complex salt, 0.11 g.) deposited, which were filtered with suction. They were treated with $CHCl_3$, alkalized with 5% aq. NaOH, and shaken in a separating funnel. The $CHCl_3$ layer was dried over anhyd. K_2CO_3 and the solvent was distilled off. The residue was dissolved in a minimum amount of EtOH, and after addition of conc. HCl (2 drops) the solution was set aside for some time. Colorless needles appeared and were recrystallized from EtOH-ether. Hydroepistephanine-A hydrochloride, m.p. 258~262°(decomp.). $[\alpha]_D^{31}$: +298.24°(in H_2O, l=0.5 dm., c=0.288).

On the other hand, the acidic mother liquor separated from the above Zn complex salt was freed from EtOH under diminished pressure, alkalized with 2.5% aq. NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. K_2CO_3 and the solvent was removed. The residue was dissolved in a minimum amount of EtOH and after addition of conc. HCl (2 drops) the solution was allowed to stand, by which the hydrochloride crystallized as colorless needles. Recrystallization was effected from EtOH-ether. Hydroepistephanine-A hydrochloride, m.p. 261~264°(decomp.). Yield, 0.04 g. $[\alpha]_D^{29}$: +297.52°(in H_2O, l=0.5 dm., c=0.242). During this reacton, product corresponding to hydroepistephanine-B as described in the literature[3] was not obtained.

N-Methylhydroepistephanine-A Dimethiodide (III)—Methanolic MeONa (0.46 g. of Na in 15 cc. of 80% hydrated MeOH) and MeI (0.5 g.) were added to the MeOH solution (5 cc.) of the free base (0.032 g.), regenerated from the above hydrochloride, and the solution was refluxed for 3 hrs. during which period the solution was kept alkaline. After similar amount of Na and MeI were added, the solution was refluxed for further 3 hrs. Water (5 cc.) was then added and the remaining MeOH was expelled *in vacuo*. The MeOH-free solution was filtered while hot and upon standing, deposited crystals. They were treated with charcoal in boiling water, yielding slightly yellow microscopic needles (0.016 g.). The analytical sample was dried at 130° for 6 hrs. *in vacuo* over P_2O_5 before analysis. N-Methylhydroepistephanine-A dimethoiodide (III), decompn. 260~262° (without melting). $[\alpha]_D^{30}$: +42.55°(in 50% aq. EtOH, l=0.5 dm., c=0.282). *Anal.* Calcd. for $C_{40}H_{48}O_6N_2I_2 \cdot 6H_2O$: C, 47.34; H, 5.96. Found : C, 47.40; H, 5.93.

O-Methyloxyacanthine Dimethiodide (III)—Oxyacanthine (VII : R=H, 0.3 g.) was dissolved in methanolic MeONa (0.23 g. of Na in 20 cc. of 80% hydrated MeOH) and added with MeI (1.41 g.). After gentle digestion for 6 hrs., the solution was treated with water (5 cc.), concentrated *in vacuo* to remove MeOH and excess MeI, and filtered with charcoal while hot. O-Methyloxyacanthine dimethiodide (III) was obtained as microscopic yellow needles (0.15 g.), which decomposed at 260~262° without melting, after drying at 120° *in vacuo* for 6 hrs. over P_2O_5. $[\alpha]_D^{24}$: +45.11°(in 50% aq. EtOH, l=0.5 dm., c=1.041). *Anal.* Calcd. for $C_{40}H_{48}O_6N_2I_2 \cdot 6H_2O$: C, 47.34; H, 5.96. Found : C, 47.88; H, 6.14.

Epistephanine Dimethiodide (IV)—The methiodide was prepared according to the literature.[3] Epistephanine (0.6 g.) was refluxed in EtOH (40 cc.) with MeI (1.0 g.) for 1 hr. After concentration of the solution to a small volume, a small portion of ether was added dropwise, whereby yellow precipitation formed. This was recrystallized from a large amount of hot water. Epistephanine dimethiodide showed m.p. 242~245° after being dried at 100° for 6 hrs. over P_2O_5 *in vacuo*. Yield, 0.65 g.

N-Methylhydroepistephanine Monomethiodide (V) by Reduction of Epistephanine Dimethiodide (IV) with $NaBH_4$—To a solution of epistephanine dimethiodide (IV, 0.35 g.) in MeOH (10 cc.) was added $NaBH_4$ in small portions. The reaction took place immediately with vigorous bubbling.

13) All melting points are uncorrected. The authors are indebted to Dr. K. Hozumi, Mr. K. Imaeda, and Miss F. Tanase of the Microanalytical Laboratory of this Institute for the microanalyses.

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The whole amount of $NaBH_4$(0.1035 g.) was added during the course of 30 mins., and then the reaction mixture was allowed to stand for 1 hr. with occasional shaking at room temperature. After evaporation of the solvent at 32~35° *in vacuo*, the remaining solid was treated with $CHCl_3$ and 2.5% aq. NaOH. The $CHCl_3$ layer was dried over K_2CO_3 and distilled. After addition of MeOH and ether, the solution was allowed to stand, whereupon orange red prisms deposited. They were readily soluble in $CHCl_3$ and MeOH, soluble in hot EtOH and dioxane, and insoluble in other organic solvents. After recrystallization from MeOH-ether or MeOH-H_2O, and dried at 110° *in vacuo* for 11 hrs., they gave a positive Beilstein reaction. N-Methylhydroepistephanine monomethiodide (V) thus obtained had m.p. 221°(decomp., becoming yellow at 185°), $[\alpha]_D^{22}$: +91.69° (in $CHCl_3$, l=0.5 dm., c=0.349). *Anal.* Calcd. for $C_{39}H_{45}O_6N_2I \cdot 3\frac{1}{2} H_2O$: C, 56.57; H, 6.33; N, 3.38. Found: C, 56.33; H, 6.16; N, 3.25. The picrate of this compound formed yellow prisms, m.p. 172~175°.

N-Methylhydroepistephanine-B Dimethiodide (VI)—N-Methylhydroepistephanine monomethiodide (V, 0.25 g.) was refluxed in MeOH (5 cc.) with MeI (0.25 g.) for 3 hrs. After removal of the solvent and excess MeI, water (1 cc.) was added to the residue, and the solution was filtered while hot. The filtrate deposited crystals after standing. Recrystallization from hot water yielded slightly yellow needles (0.23 g.). The sample was dried *in vacuo* at 130° for 6 hrs., and then kept standing for 24 hrs. in the air before analysis. N-Methylhydroepistephanine-B dimethiodide (VI) decomposed at 254~258° without melting. $[\alpha]_D^{28}$: +95.56°(in 50% aq. EtOH, l=0.5 dm., c=0.293). *Anal.* Calcd. for $C_{40}H_{48}O_6N_2I_2 \cdot 6H_2O$: C, 47.34; H, 5.96. Found: C, 47.73; H, 6.01.

N-Methylhydroepistephanine-B Dimethiodide (VI) by the Reduction of Epistephanine Dimethiodide (IV) with Zn and dil. H_2SO_4—A solution of epistephanine dimethiodide (IV, 0.28 g.) in 20% H_2SO_4(2.5 cc.) and EtOH (2.5 cc.) was refluxed with Zn dust (0.28 g.) and after 30 mins. the yellow solution was decolorized. After 5 hrs., the remaining Zn dust was removed by filtration from this hot solution and the EtOH was evaporated under reduced pressure. The residual solution was made alkaline with 2.5% aq. NaOH and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and evaporated. The residue was treated with EtOH-ether, giving orange red prisms, m.p. 220~221°(decomp.), which gave a typical Beilstein reaction. They were refluxed with MeI (0.5 g.) in MeOH (10 cc.) for 3 hrs. After standing, crystals appeared, which were dried *in vacuo* at 130° for 8 hrs. over P_2O_5, and then kept standing for 24 hrs. in the air. N-Methylhydroepistephanine-B dimethiodide (VI) occurs in slightly yellow needles, decomposing at 260~262° without melting. $[\alpha]_D^{15}$: +98.6°(in 50% aq. EtOH, l=0.5 dm., c=0.365). *Anal.* Calcd. for $C_{40}H_{48}O_6N_2I_2 \cdot 6H_2O$: C, 47.34; H, 5.96. Found: C, 47.78; H, 5.90.

O-Methylrepandine Dimethiodide (IX)—According to the procedure described in literature,[11] repandine (VIII: R=H, m.p. 249~253°, 0.085 g.) was refluxed in methanolic MeONa (0.23 g. of Na in 10 cc. of 80% hydrated MeOH) with MeI (1.41 g.) for 3.5 hrs. Water (3 cc.) was then added, the solution was concentrated *in vacuo* to remove MeOH, and filtered while hot. The filtrate on cooling deposited colorless crystals (yield, 0.23 g.) which were collected, dried at 130° *in vacuo* for 8 hrs. over P_2O_5, and then kept standing for 24 hrs. in the air before analysis. O-Methylrepandine dimethiodide (IX) formed slightly yellow needles, which decomposed at 262~264° without melting. $[\alpha]_D^{26}$: −92.66°(in 50% aq. EtOH, l=0.5 dm., c=0.518). *Anal.* Calcd. for $C_{40}H_{48}O_6N_2I_2 \cdot 6H_2O$: C, 47.34; H, 5.96. Found: C, 47.20; H, 6.03.

Summary

Epistephanine (I: R= CH_3), an alkaloid of *Stephania japonica* Miers and its dimethiodide (IV), on hydrogenation, did not yield racemic compounds but optically active ones in either case.

Epistephanine (I: R=CH_3), on hydrogenation with zinc and sulfuric acid, afforded only hydroepistephanine-A (II) as the dihydro derivative. Treatment of (II) with methyl iodide gave N-methylhydroepistephanine-A dimethiodide (III), which was shown by direct comparison of their specific rotations and infrared spectra to be identical with O-methyloxyacanthine dimethiodide (III) (asymmetric centers, +, −).

Epistephanine dimethiodide (IV), when reduced with either sodium borohydride or zinc-sulfuric acid, afforded N-methylhydroepistephanine monomethiodide, from which N-methylhydroepistephanine-B dimethiodide (VI) was derived. It was found that (VI) is identical with O-methylrepandine dimethiodide (IX) (asymmetric centers, +, +) by infrared spectral determinations, and that since the values of their specific rotations have the opposite sign to each other, (VI) is an antipode of (IX) and hence its asymmetric centers are (−, −).

(Received February 21, 1956)

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