Zusammenfassung

Einige Methyl- und Methoxyl-Derivate des Pyrimidin-N-oxydes wurden neu hergestellt. Sie sind im Vakuum destillierbar, beständig gegen die Reduktion mit Schwefligersäure bei Zimmertemperatur und werden beim Behandeln mit Phosphortrichlorid in Chloroform-Lösung in das entsprechende Pyrimidin reduziert.

6-Methyl-4-methoxypyrimidin-N-oxyd gibt bei der Einwirkung von Tosylchlorid und darauffolgender Behandlung mit verd. Pottasche-Lösung 2-Oxy-6-methyl-4-methoxypyrimidin. 4-Methyl- bzw. 4-Methoxy-6-methylpyrimidin-N-oxyd geht beim Behandeln mit Benzoylchlorid bei Gegenwart von Alkalicyanid-Lösung in das entsprechende 2-Cyanopyrimidin über. 2,6-Dimethylpyrimidin-N-oxyd gibt bei analoger Reaktion 4-Cyano-2,6-dimethylpyrimidin.

(Eingegangen am 16. Februar 1955)

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34. Yoshio Sasaki, Hirotaka Ohnishi, and Nobukatsu Satoh : Studies on the Alkaloids of Menispermaceous Plants. CXXV.[1] Cleavage of Cepharanthine by Metallic Sodium in Liquid Ammonia. (4).[2]*

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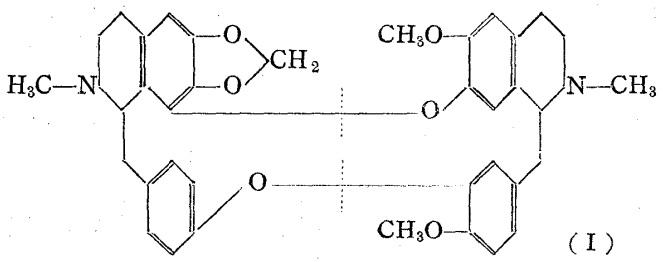
In a previous investigation on the fission of cepharanthine (I) with sodium in liquid ammonia, Tomita and Sasaki obtained two phenolic bases; one of them (A-base) was found by analysis to possess an empirical formula $C_{17}H_{19}O_2N$, m.p. 205~207°(decomp.), and to furnish by methylation with diazomethane the O,O-dimethyl ether, $C_{19}H_{23}O_2N$, m.p. 116~117°. On the basis of an information provided by Clayson,[3] who obtained (V) from hydrocotarnine (IV) by an analogous mode of reaction, as well as the hitherto obtained experimental evidences[4] with regard to the direction of cleavage of the ether linkages of the biscoclaurine bases, they[5] suggested A-base to be *d*-1-(4'-hydroxybenzyl)-6-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II). On the other hand, another phenolic bisected base (B-base) was isolated as the picrate, which they proved to be identical with *l*-1-(4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (III) picrate.[2] In this series, attempts to confirm the structure of A-base have been made, the details of which follow.



(I)

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* This work is a part of series entitled "Studies on the Alkaloids of Menispermaceous Plants" by M. Tomita.

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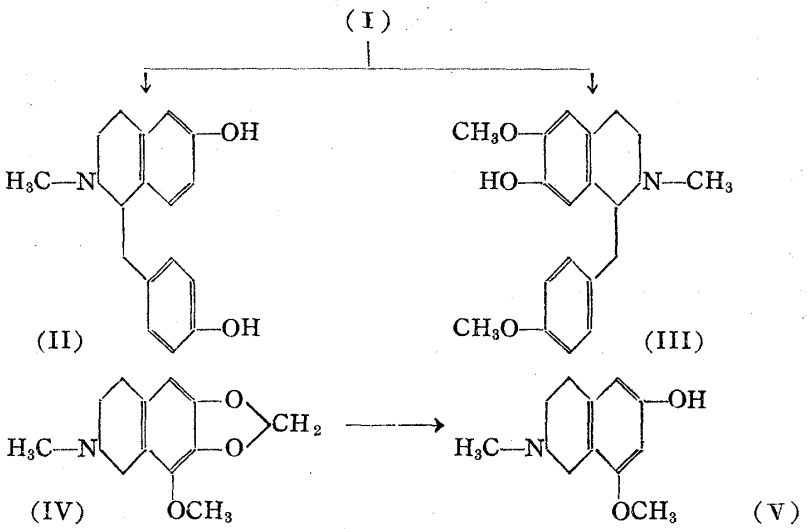
1) Part CXXIV : M. Tomita, T. Kikuchi : This Bulletin, **3**, 100 (1955).
2) Part (3) : M. Tomita, Y. Sasaki : This Bulletin, **2**, 375(1954).
3) D. B. Clayson : J. Chem. Soc., **1949**, 2016.
4) M. Tomita : Fortschr. Chem. org. Naturstoffe, **9**, 175(1952).
5) Part (2) : M. Tomita, Y Sasaki : This Bulletin, **2**, 89(1954).



When A-base was treated with dimethyl sulfate and alkali, and then degradated by the Hofmann procedure, it yielded only one methine, which was isolated as the picrate, m.p. 158°. The methiodide has no optical rotation. Similar results were also obtained by the Hofmann degradation of O,O-dimethyl ether methiodide of the A-base.

On the assumption that A-base must have structure (II), a plan was made to synthesize *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XII), corresponding to its O,O-dimethyl ether, convert it into the methyl-methine bases (XIII + XIV), and then to compare them with those obtained from the natural A-base. Regarding the syntheses of (XII) and its precursor *dl*-1-(4′-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XI), papers have been published by Preobrazhenskii, *et al.*[6] and by Chakravatri, *et al.*,[7] but no detailed information was available that the synthesis of (XII) was attempted according to a route in Fig. 1.

The condensation of *m*-methoxybenzaldehyde[8] (VI) with nitromethane gave *m*-methoxy-ω-nitrostyrene[9] (VII), which was derived by reduction with lithium aluminum hydride to *m*-methoxyphenethylamine (VIII). The acid amide[6,7] (IX) was obtained from (VIII) and *p*-methoxyphenethylacetic acid by the Schotten-Baumann method, the ring closure of which was then effected by the Bischler-Napieralsky reaction to form 1-(4′-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (X). Subsequently, the hydrochloride of (X) was reduced in 50% acetic acid with zinc dust, yielding *dl*-1-(4′-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline[7] (XI). The methylation of (XI) with formic acid and formaldehyde arrived at the objective *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline[6] (XII).

On being submitted to the Hofmann degradation, (XI) and (XII), unlike the natural A-base, afforded two kinds of methine bases in each case, one was a crystalline α-methine, m.p. 64°, and the other, an amorphous β-methine. The former gave a crystalline picrate of m.p. 175°, and the latter, of m.p. 146°, but neither of these picrates was found to be identical with O,O-dimethyl ether methyl-methine picrate, m.p. 158°, of the A-base by the mixed melting point determinations. Both α-methine and β-methine picrates, after being freed from the picric acid, were further degradated by

6) N. E. Preobrazhenskii, R. S. Livshits, G. I. Bazilevskaya, M. S. Bainova, O. E. Dobrovinskaya: J. Gen. Chem.(U.S.S.R.), **17**, 1671(1947); C. A., **42**, 2606(1948).
7) S. N. Chakravatri, N. A. Vaidyanathan, A. Venkatausbban: J. Indian Chem. Soc., **9**, 573(1932); C. A., **27**, 1887(1933).
8) Org. Syntheses, **29**, 63.
9) J. M. Gulland, C. J. Virden: J. Chem. Soc., **1929**, 1791.

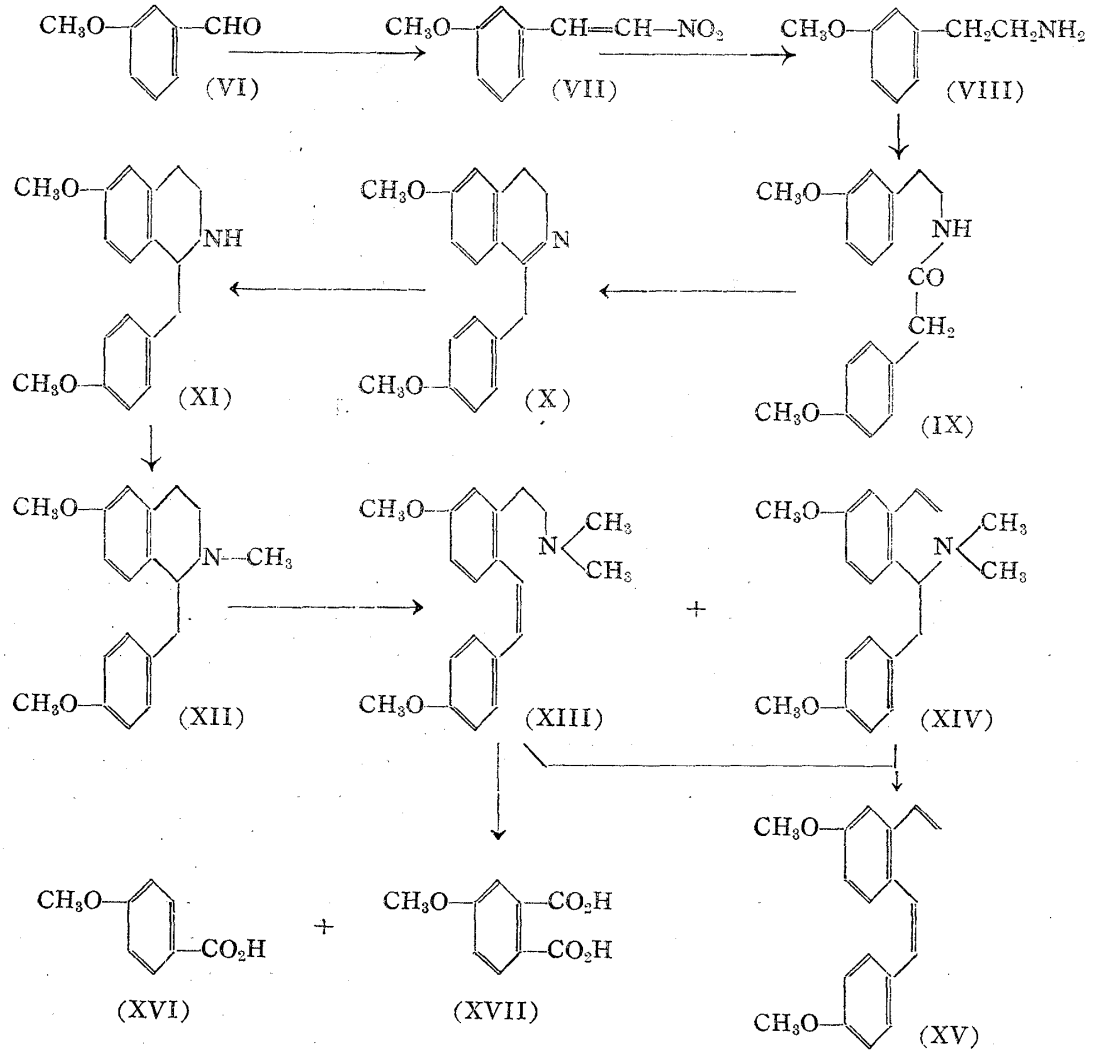


Fig. 1.

the Hofmann method, whereupon they furnished identical des-N-base (XV), from which it is clear that they are isomers (XIII and XIV), whose direction of the fission between the C-N linkages differ from each other.

Inasmuch as no confirmatory evidence has yet been offered in the literatures[6,7] concerning the ring-closing direction of the acid amide (IX) in the Bischler-Napieralsky reaction, the reinvestigation as to this point was desired. The oxidation of the α-methine (XIII) with potassium permanganate furnished anisic acid (XVI) and an amino acid. The latter, on subsequent oxidation with potassium permanganate, afforded 4-methoxyphthalic acid anhydride (XVII), which revealed that the ring closure in question had occurred in the *para*-position of the acid amide (IX). The foregoing results lead to a decisive conclusion that A-base is not *d*-1-(4'-hydroxybenzyl)-6-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (II). In other words, it follows that, contrary to the expectation so far held, A-base should be *d*-1-(4'-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XIX) whose phenolic hydroxyl group is situated at the 7-position of the isoquinoline nucleus.

In the earlier paper,[10] Tomita and Sasaki already suggested the mode of fission of cepharanthine by the sodium-liquid ammonia process as shown by Fig. 2. According to this assumption, the two ether linkages constituting the diphenyl ethers may first

10) Part (1). M. Tomita, Y. Sasaki: This Bulletin, **1**, 105(1953).

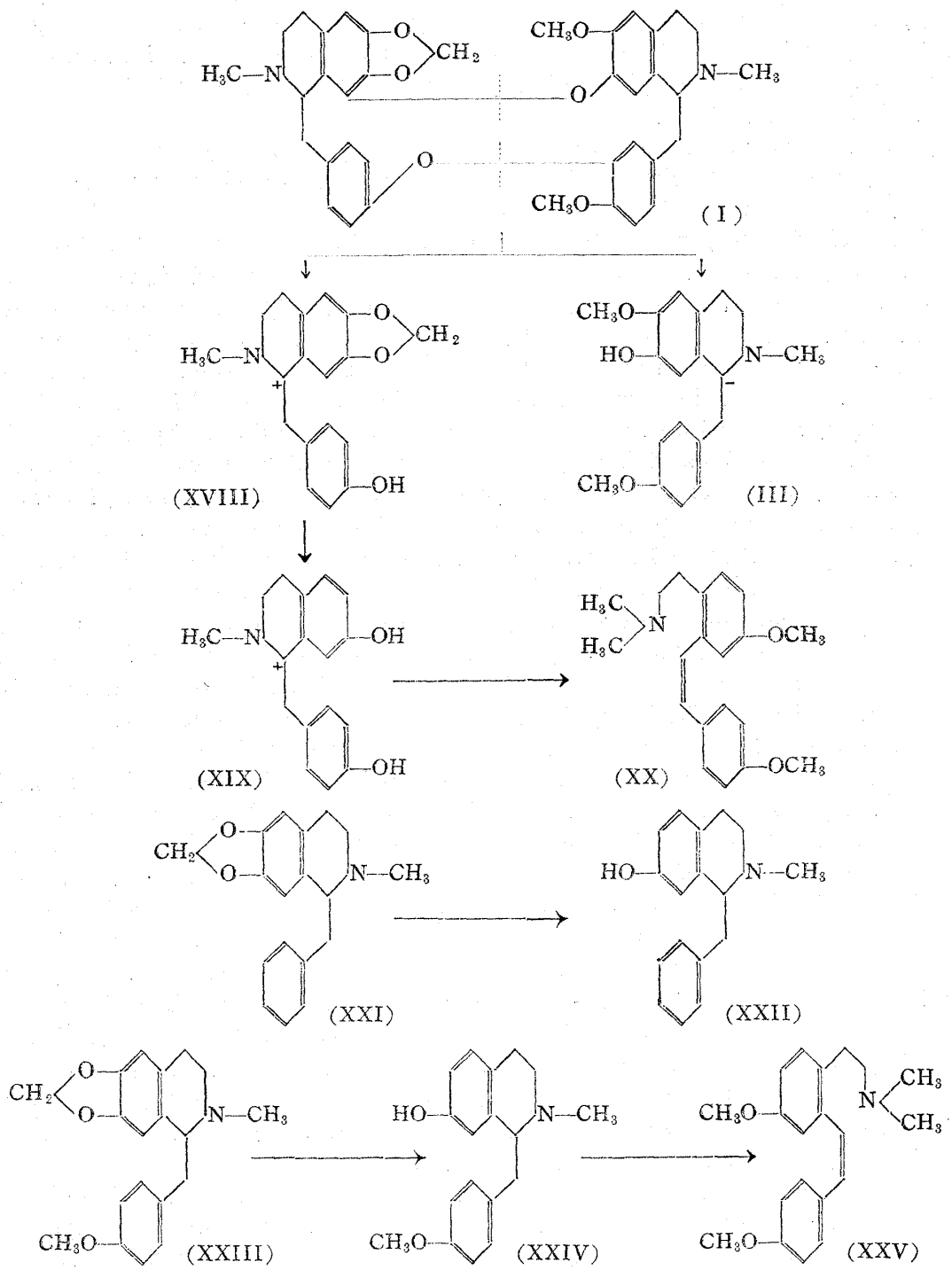


Fig. 2.

undergo cleavage, and then followed by the fission of the methylenedioxy group, whereby another phenolic hydroxyl may be formed.

Supposing that this mode of fission is correct, as a precursor of A-base, the presence of *d*-1-(4′-hydroxybenzyl)-6,7-methylenedioxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XVIII) may well be considered, and this, by the fission of the methylenedioxy group, must presumably give rise to the A-base. With a view to providing a positive evidence for this supposition, the sodium-liquid ammonia fission was applied to *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII) corresponding to the O-methyl ether of (XVIII). If the above assumption is not

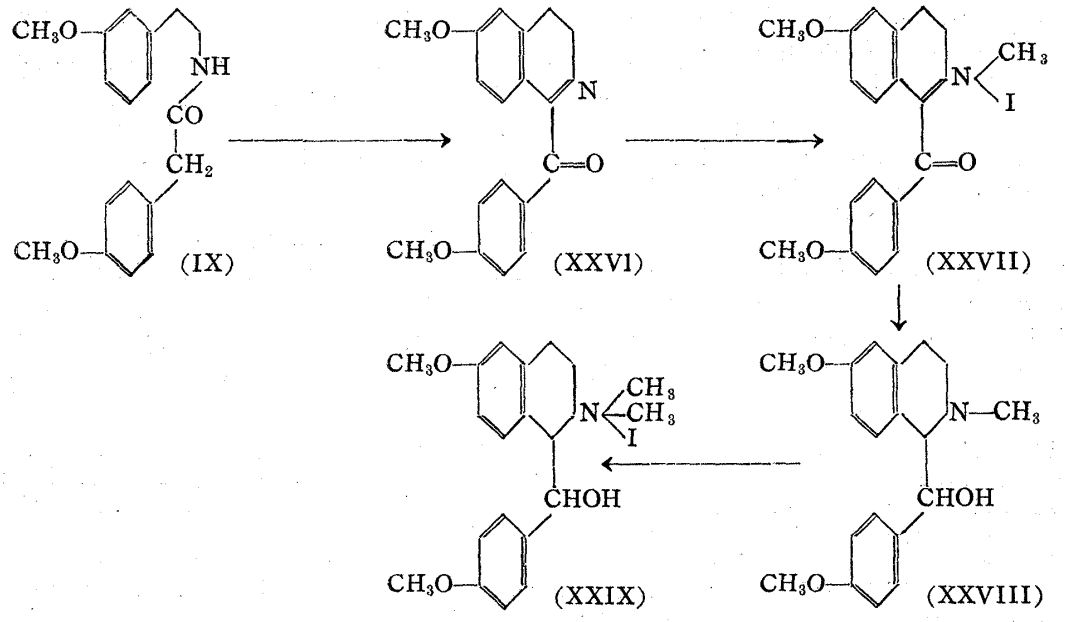
erroneous, it is quite conceivable that the base (XXIV), whose methylenedioxy group underwent fission, when degraded by the Hofmann procedure, would yield an optically inactive O-methyl ether methyl-methine (XXV), identical with O,O-dimethyl ether methyl-methine of the A-base.

As a preliminary experiment to this end, *dl*-1-benzyl-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline[11] (XXI) was first subjected to a similar mode of cleavage, yielding only one phenolic base (XXII). Furthermore, the paper chromatography revealed a single spot, which showed that the fission of the methylenedioxy group had occurred only in one direction. As the next step, this technique was applied to *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII), prepared from *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline,[11] and in this case it was also found that as a result of the one-sided cleavage of the methylenedioxy group, only one phenolic base (XXIV) was obtained. In this connection, it is of interest to note that while in the fission of hydrohydrastinine, Clayson[3] obtained two kinds of bases, viz. 6-hydroxy- and 7-hydroxy-N-methyltetrahydroisoquinolines, only a single base was produced in that of the 1-benzyl derivation.

(XXIV) thus obtained, on being degraded by the Hofmann method, yielded O-methyl ether methyl-methine (XXV) which was isolated as the picrate, m.p. 158°, the identity of which was confirmed by admixture with O,O-dimethyl ether methyl-methine picrate, m.p. 158°, of the A-base obtained from cepharanthine. These two picrates also gave identical infrared spectra, thus proving them to be identical. Since it has become clear that O,O-dimethyl ether methyl-methine of the A-base is not identical with any of the methines (XIII and XIV) obtained by the first-stage Hofmann degradation of *dl*-1-(4′-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XI) or *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XII), but with O-methyl ether methyl-methine (XXV) derived from *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII) via (XXIV), it is suggested that the A-base should be *d*-1-(4′-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XIX), and the fission of cepharanthine must have proceeded according to the following scheme: (I)→(XVIII)+(III)→(XIX)+(III). At the same time, it is also suggested that a phenolic base produced by the fission of *dl*-1-(4′-methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII) should be *dl*-1-(4′-methoxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIV). The final proof on this point must await the synthetic work which is now in progress.

It is now known that in the Bischler-Napieralsky reaction,[6,12] the objective substituted 1-benzyl-3,4-dihydroisoquinoline undergoes oxidation to form 1-benzoyl-3,4-dihydroisoquinoline derivative during the treatment of the reaction products. Similar facts were also encountered with the ring-closing process of the acid amide (IX) to 1-(4′-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (X). In this case, the product obtained, contrary to the expectation, was found to be 1-(4′-methoxybenzoyl)-6-methoxy-3,4-dihydroisoquinoline (XXVI), an oxidized product of (X). The infrared spectrum also showed the presence of a C=O band. The methochloride derived from the methiodide (XXVII) of (XXVI), on catalytic hydrogenation, yielded *dl*-1-(6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4′-methoxyphenyl)carbinol (XXVIII) showing the presence of a C-OH band in the infrared spectrum. Hofmann degradation of *dl*-1-(6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4′-methoxyphenyl)carbinol methiodide (XXIX) obtained from (XXVIII) gave a product having an odor like anisaldehyde.

11) M. Tomita, M. Satomi: J. Pharm. Soc. Japan, 58, 617(1938).
12) Lindenmann: Helv. Chim. Acta, **32**, 69(1949).



We are indebted to Prof. M. Tomita for his continuing interest and counsel in this work, and to Messrs. Matsui and Narisada of the Research Laboratory, Shionogi & Co., Ltd., for the measurment of the infrared spectra. Our thanks are also offered to the Ministry of Education for financial aids.

Experimental*

(I) Degradation of the A-base by the Hofmann Method:

(1) O,O-Dimethyl Ether Methiodide of the A-Base—0.1 g. of O,O-dimethyl ether[5] of the A-base was refluxed with MeI in 5 cc. MeOH for 30 mins. Removal of MeOH and the excess MeI deposited colorless needles which upon recrystallization from MeOH melted at 170~172°. *Anal.* Calcd. for $C_{19}H_{23}O_2N \cdot CH_3I$: C, 54.68; H, 5.92. Found: C, 55.14, 54.71; H, 6.06, 6.02.

(2) First-Stage Hofmann Degradation of O,O-Dimethyl Ether Methiodide of the A-Base—0.1 g. of the methiodide was heated in a boiling water bath with 10 cc. of 20% KOH solution for 30 mins., and the deposited oily product was taken up in ether. After five such repetitions of this process, the ether extracts were combined and treated with 1% HCl. The acid solution was then basified with conc. aq. NH_4OH and the depositing methine base extracted with ether. The ether extract was dried over anhyd. K_2CO_3 and the solvent removed, leaving a slightly yellowish oil. This was chromatographed in benzene on alumina, and adsorbed on the column with a light purple band (by the ultraviolet ray). The band was developed with abs. EtOH, and the eluate treated with a sat. EtOH solution of picric acid. The picrate thus obtained was recrystallized from EtOH and formed orange red needles, m.p. 158°. *Anal.* Calcd. for $C_{20}H_{25}O_2N \cdot C_6H_3O_7N_3$: C, 57.77; H, 5.22. Found: C, 57.83, 57.51; H, 5.01, 5.17.

(3) First-Stage Hofmann Degradation of O,O-Dimethyl Ether Methosulfate of the A-Base—To a solution of 0.1 g. of A-base in 5 cc. of 5% KOH was added dropwise with vigorous stirring 1 cc. of Me_2SO_4. After the reaction mixture had become clear, it was extracted with ether to remove the excess Me_2SO_4. Then 4 g. of KOH and water were added to make this solution 20 cc. The resulting solution was boiled in an oil bath for 30 mins., and the oily product which separated out was taken up in ether. This was treated in a manner similar to that described in (2), and then converted to its picrate which crystallized in orange red needles, m.p. 158°, undepressed by admixture with the picrate, m.p. 158°, obtained in (2).

(4) O,O-Dimethyl Ether Methyl-Methine Methiodide of the A-Base—0.1 g. of the methine base picrate obtained in (2) and (3) was dissolved in the minimum amount of acetone and the solution passed through an alumina column wetted with acetone, whereby the free base was readily obtained due to the tenacious adsorption of the picric acid in the column. This, however, did not crystallize in spite of various attempts. Consequently, this was treated with MeI in benzene and converted to its crystalline methiodide. Recrystallization from EtOH gave prisms, m.p. 169~170°. *Anal.* Calcd. for $C_{20}H_{25}O_2N \cdot CH_3I$: C, 55.64; H, 6.18. Found: C, 55.12, 54.94; H, 5.45, 5.71. $[\alpha]_D^{19}$: ±0° (4.382 mg. subst. in 2 cc. MeOH).

* All melting points are uncorrected. We are indebted to Mr. K. Hozumi and the members of the Microanalytical Laboratory of this Institute for microanalyses.

(II) Synthesis of *dl*-1-(4′-Methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline and Its Hofmann Degradation:

(1) ***m*-Methoxy-ω-nitrostyrene (VII)**—A mixture of 0.9 g. of methylamine hydrochloride, 0.4 g. of Na_2CO_3, and MeOH was stirred well, filtered, and added to a solution of 22.5 g. of *m*-methoxybenzaldehyde[8] and 10.9 g. of nitromethane in MeOH. The solution was kept in a room temperature for 4 days and the ω-nitrostyrene which crystallized out was collected and had m.p. 91~92° (reported m.p. 91~92°[9]). After standing for about 2 weeks there was obtained an additional amount of crystals from the mother liquor; overall yield, 18.3 g. (62%).

(2) ***m*-Methoxyphenethylamine (VIII)**—3.6 g. of *m*-methoxy-ω-nitrostyrene was reacted with 3 g. $LiAlH_4$ in 250 cc. of dry ether. After the reaction, 6 cc. of water and 10 cc. of 20% NaOH were added slowly to decompose the excess reagent. The ether layer was dried over anhyd. K_2CO_3 and the ether removed, yielding a slightly yellowish oil. This, on treatment with EtOH solution of oxalic acid, gave a white crystalline oxalate. By recrystallization from EtOH it showed m.p. 164~165°; yield, 3.7 g. (76.4%). *Anal.* Calcd. for $C_9H_{13}ON \cdot C_2H_2O_4$: C, 54.77; H, 6.22. Found: C, 54.89; H, 6.48.

(3) **N-(3-Methoxyphenethyl)(4′-methoxyphenyl)acetamide (IX)**—2 g. of *p*-methoxyphenylacetic acid was heated with 3.3 g. of $SOCl_2$ on a water bath, when a uniformly yellow solution resulted immediately with effervescence. Removal of the excess $SOCl_2$ *in vacuo* left the acid chloride as an oil. To a well-stirred solution of the free base from 2.8 g. of *m*-methoxyphenethlymine oxalate in 200 cc. of ether were added dropwise an ether solution of the above acid chloride and 5% aq. NaOH alternately, during which period the reaction mixture was kept weakly alkaline. After the addition was completed, stirring was continued for a further 40 mins. Then the ether solution was dried over anhyd. K_2CO_3, and the ether removed, yielding the acid amide as a yellowish oil. Recrystallization from $CHCl_3$ afforded prisms, m.p. 80° (reported m.p. 80°[6,7]); yield, 2.3 g. (66.5%).

(4) **1-(4′-Methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (X)**—One g. of the acid amide was boiled with 9 g. of $POCl_3$ in an oil bath for 1 hr. After standing the content was treated three times with a large amount of petroleum ether to remove the petroleum ether-soluble portion. The brownish oily product which remained was induced to crystallize by adding EtOH and standing, whereupon microscopic crystals of the base hydrochloride appeared. Recrystallization from EtOH yielded 0.7 g. of white needles, m.p. 210~212°. *Anal.* Calcd. for $C_{18}H_{19}O_2N \cdot HCl$: C, 68.03; H, 6.29. Found: C, 67.84, 67.77; H, 6.46, 6.47.

(5) ***dl*-1-(4′-Methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XI)**—One g. of the above 3,4-dihydroisoquinoline hydrochloride was dissolved in 20 cc. of 50% AcOH and 3 g. of Zn dust added. The mixture was boiled in an oil bath for 3 hrs., after which the reaction mixture was basified by conc. NH_4OH, and the depositing product was taken up in ether. The ether solution was dried over anhyd. K_2CO_3, and the solvent distilled off, leaving a slightly yellowish glutionus residue. Addition of conc. HCl to this gave needles of the hydrochloride; yield, 0.9 g., m.p. 193~195° (repoted m.p. 196°[7]). *Anal.* Calcd. for $C_{18}H_{21}O_2N \cdot HCl$: C, 67.61; H, 6.88. Found: C, 67.57; H, 6.66.

This substance also furnished a picrate crystallizing from EtOH in yellow needles, m.p. 195~196° (reported m.p. 197°[7]). *Anal.* Calcd. for $C_{18}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 56.25; H, 4.69. Found: C, 56.16; H, 4.90. The Liebermann nitroso reaction was positive.

(6) ***dl*-1-(4′-Methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XII)**—A solution of 0.4 g. of (XI) in 5 cc. of 83% HCO_2H was heated in a water bath with 1.2 cc. of 37% HCHO for 3 hrs. The mixture was cooled, diluted with water, and extracted with ether to remove the ether-soluble portion. The acid layer was basified by conc. NH_4OH and the resulting product was taken up in ether. The ether solution was dried over anhyd. K_2CO_3 and the ether removed, yielding a slightly yellowish oil. This, which gave a negative Liebemann nitroso reaction, did not crystallize in spite of various treatments. However, this afforded the methiodide crystallizing from EtOH in white prisms, m.p. 187~188° (reported m.p. 185~185°[6]) and the picrate forming from EtOH in yellow needles, m.p. 185° (decomp.) (reported m.p. 176°[6]). *Anal.* Calcd. for $C_{19}H_{23}O_2N \cdot CH_3I$: C, 54.67; H, 5.92. Found: C, 54.60, 54.45; H, 5.82, 6.00. *Anal.* Calcd. for $C_{19}H_{23}O_2N \cdot C_6H_3O_7N_3$: C, 57.03; H, 4.94. Found: C, 57.03; H, 4.76.

(7) **First-Stage Hofmann Degradation of *dl*-1-(4′-Methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline Methyl Methosulfate [(XI) → (XIII + XIV)]**—To a suspension of 0.1 g. of (XI) in 5 cc. of 5% NaOH was added dropwise with vigorous stirring 0.6 cc. of Me_2SO_4. After completion of the addition, the mixture was warmed on a water bath for a while, and after cooling the excess Me_2SO_4 was removed by means of ether. Then 5 g. of NaOH and water were added to make the whole 20 cc. This was heated in a boiling water bath for 30 mins. and the depositing oily product was extracted with ether. After three such repetitions of this process, the combined ether extracts was shaken up with 1% HCl, the acid layer was made alkaline with conc. NH_4OH, and the methine base taken up in ether. The ether extract was dried over anhyd. K_2CO_3 and the ether expelled, leaving a colorless glutinous product. By chromatography using alumina and benzene, this

was separated into crystallizable portion (a) and amorphous glutionus portion (b). The former (a) crystallized from petr. ether in white needles, m.p. 64°, and its picrate, from MeOH in orange red needles, m.p. 175°. The latter (b) did not crystallize in spite of various attempts, but its picrate formed yellow needles, m.p. 146°. Thus the former (a) was named α-methine (XIII), and the latter (b), β-methine (XIV). These α- and β-methine picrates depressed the m.p. of the methine picrate derived from A-base to 140~145° and 128~132°, respectively. α-Methine—*Anal.* Calcd. for $C_{20}H_{25}O_2N$: C, 77.17; H, 8.04. Found: C, 77.26; H, 8.21. α-Methine picrate—*Anal.* Calcd. for $C_{20}H_{25}O_2N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 55.91; H, 5.38. Found: C, 56.09; H, 5.26. β-Methine picrate—*Anal.* Calcd. for $C_{20}H_{25}O_2N \cdot C_6H_3O_7N_3$: C, 57.77; H, 5.37. Found: C, 57.73, 57.90; H, 5.15, 5.03.

In the ether extraction after Hofmann degradation, it was also observed that a considerable amount of ether-insoluble material formed. This was soluble in $CHCl_3$, and $CHCl_3$ extract, after drying over anhyd. K_2CO_3 and evaporating, left a yellowish oil which soon solidified to a crystalline mass. By recrystallization from $CHCl_3$-benzene, it formed colorless needles, m.p. 167°, and its analytical values correspond to a composition of *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline methyl methosulfate. *Anal.* Calcd. for $C_{21}H_{29}O_6NS$: C, 59.57; H, 6.86. Found: C, 59.82; H, 7.03.

(8) **First-Stage Hofmann Degradation of *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3-4-tetrahydroisoquinoline** [(XII) → (XIII + XIV)]—0.2 g. of *dl*-1-(4′-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline methiodide was boiled with 10 cc. of 20% KOH in an oil bath. Treatment of the reaction mixture by the same procedure as in (7) yielded α-methine (XIII) and β-methine (XIV), whose picrates were found to be identical with those obtained in (7).

(9) **α-Methine (XIII) and β-Methine (XIV) Methiodides**—(a) α-Methine (XIII) Methiodide: 0.5 g. of α-methine picrate was decomposed, as before, by running its acetone solution through the alumina column, and the oily methine base thus obtained was treated in acetone with MeI to give the methiodide which upon recrystallization from EtOH formed colorless pillars, m.p. 189~190°. *Anal.* Calcd. for $C_{20}H_{25}O_2N \cdot CH_3I$: C, 55.64; H, 6.18. Found: C, 55.18, 54.90; H, 6.08, 6.40.

(b) β-Methine (XIV) Methiodide: β-Methine picrate was likewise treated, but this methine base did not give any crystalline methiodide.

(10) **Second-Stage Hofmann Degradation of α- and β-Methine Methiodide** [(XIII) → (XV); (XIV) → (XV)]—(a) Des-N α-Methine (XV): 0.2 g. of α-methine methiodide was added to 10 cc. of 20% KOH solution and the mixture was heated in a boiling water bath for 30 mins. After cooling the depositing oily product was extracted with ether. Heating and the ether extraction was repeated 5 times. The ether extracts were combined, washed first with 1% HCl and then with water, and dried over anhyd. K_2CO_3. Upon removal of the solvent the oily residue soon solidified. Recrystallization from ether yielded colorless pillars, m.p. 70°. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.26; H, 6.76. Found: C, 80.98; H, 6.93.

(b) Des-N β-Methine (XV): 0.1 g. of β-methine methiodide was treated in the same manner as above, giving des-N-β-methine, m.p. 70°, either alone or mixed with des-N-α-methine, m.p. 70°.

(11) **Oxidation of Methine Base with Potassium Permanganate**—(a) *p*-Methoxybenzoic Acid (XVI): To a mixture of a solution of 0.15 g. of α-methine in 12 cc. of 50% aq. acetone and 5 cc of 0.5% H_2SO_4 was added with stirring during 30 mins., 28 cc. of 5% $KMnO_4$, the reaction temperature being kept between 5° and 10°. Stirring was continued for a further 40 mins. and the resultant MnO_2 was decomposed by passage of SO_2. The clear solution obtained deposited white crystals which were taken up in ether, and the ether extract was washed with water and dried over anhyd. Na_2SO_4. Removal of the ether yielded white needles. After sublimation *in vacuo*, they showed m.p. 182~183°, undepressed by admixture with *p*-methoxybenzoic acid, m.p. 181~182°.

(b) 4-Methoxyphthalic Acid (XVII): The aq. mother liquor left after the ether extraction described in (a) was almost neutralized by Na_2CO_3, the depositing $MnCO_3$ filtered, and the filtrate concentrated to almost 10 cc. To this solution was added dropwise during about 5 hrs., 15 cc. of saturated aq. $KMnO_4$, after which the mixture was allowed to stand at room temperature overnight. Then, the mixture was warmed at 50° to ensure the completion of the reaction, and after passage of SO_2, treated in the same manner as before. The crystals obtained were purified by vacuum sublimation, and then recrystallized from ether-petr. ether to form white needles, m.p. 92~93°, undepressed by admixture with 4-methoxyphthalic anhydride, m.p. 92~93°. For the sake of confirmation, on admixture with 3-methoxyphthalic anhydride, m.p. 160~161°, the melting point depressed to 83~89°.

(III) Fissions of *dl*-1-Benzyl-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXI) and *dl*-1-(4′-Methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII) with Metallic Sodium in Liquid Ammonia:

(1) **Fission of *dl*-1-Benzyl-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline** [(XXI) → (XXII)]—A solution of 0.5 g. (XXI) in 20 cc. of toluene was added dropwise to stirred 300 cc. of liquid NH_3 containing 0.5 g. of Na. After permitting evaporation of NH_3, the residue was treated with water and extracted with ether to remove non-phenolic portion. The alkaline layer was treated with NH_4Cl and the depositing base was taken up in ether. The ether solution was shaken with

3% HCl, the aq. layer was made alkaline with $NaHCO_3$ and extracted with ether. The ether extract was dried over anhyd. K_2CO_3, and the ether eliminated, yielding a yellow glutinous residue of a phenolic portion. This gave a simple spot at Rf 0.75 in paper chromatography (ascending technique) using Toyo Roshi No. 50 and the solvent mixture of BuOH (30 cc.), H_2O (30 cc.), and AcOH (1 cc.). The picrate formed from EtOH yellow needles, m.p. 172~174°. *Anal.* Calcd. for $C_{17}H_{19}ON \cdot C_6H_3O_7N_3$: C, 57.26; H, 4.56. Found: C, 57.27; H, 4.64.

(2) ***dl*-1-(4'-Methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline**—One g. of *dl*-1-(4'-methoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride prepared by Tomita, *et al.*[11] was dissolved in water and extracted with ether to remove ether-soluble impurities. The aqueous solution was basidified by conc. NH_4OH and the deposited base taken up in ether. The ether solution was dried over anhyd. K_2CO_3 and the ether removed. The colorless oily residue soon solidified to a crystalline mass. Upon recrystallization from EtOH it formed white needles, m.p. 80~81°. *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 72.73; H, 6.30. Found: C, 72.53; H, 6.59.

(3) ***dl*-1-(4'-Methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XXIII)**—One g. of the above compound was dissolved in 2.5 cc. of 83% HCOOH, followed by 3 cc. of 37% HCHO. The mixture was heated in a water bath for 3 hrs., then diluted with 20 cc. of water, and extracted with ether to remove ether-soluble material. The aqueous layer was made alkaline with conc. NH_4OH and the depositing product was taken up in ether. The ether solution, after being dried over anhyd. K_2CO_3, was evaporated, leaving a yellow sticky residue. Because of the difficulty of crystallization this was converted into its picrate which crystallized from acetone in orange red needles, m.p. 179~180°. *Anal.* Calcd. for $C_{19}H_{21}O_3N \cdot C_6H_3O_7N_3$: C, 55.55; H, 4.44. Found: C, 55.21, 55.22; H, 4.76, 4.73.

(4) **Fission of *dl*-1-(4'-Methoxybenzyl)-6,7-methylenedioxy-N-methyl-1,2,3,4-tetrahydroisoquinoline [(XXIII)→(XXIV)]**—The cleavage of 0.8 g. of (XXIII) was effected by dissolving it in 20 cc. of toluene and adding its solution to 300 cc. of liquid NH_3 containing 0.8 g. of Na. On treatment by the same manner as described in (1), the phenolic product was obtained as white prisms, m.p. 151~152°, after recrystallization from acetone. *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.33; H, 7.42. Found: C, 76.52; H, 7.53. The phenolic portion obtained by this fission gave a single spot at Rf 0.65 in paper chromatography (ascending technique). Solvent mixture: BuOH (50 cc.), H_2O (50 cc.), and AcOH (1 cc.). Indicator: Dragendorff's reagent.

(5) **First-Stage Hofmann Degradation of the Base (XXIV), m.p. 151~152° [(XXIV)→(XXV)]**—0.1 g. of (XXIV) was methylated with 5 cc. of 5% KOH and 1 cc. of Me_2SO_4. After removing Me_2SO_4, 5 g. of KOH and water were added to this solution to make 20 cc. After boiling the excess mixture in an oil bath for 30 mins., the depositing oil was taken up in ether, and this process was repeated five times. O-Methyl ether methyl-methine obtained after the same treatment as described in (1) (2) did not crystallize in spite of various attempts, but it also gave a picrate crystallizing from EtOH in orange yellow needles, m.p. 158~159°, undepressed by admixture with O,O-dimethyl ether methyl-methine picrate, m.p. 158°, of the A-base obtained by the fission of cepharanthine. Also these picrates gave identical infrared spectra. The methiodide was readily obtained by passing the picrate through alumina and treating the resulting free base with CH_3I. By recrystallization from abs. EtOH, it melted at 169~170°, undepressed by admixture with O,O-dimethyl ether methyl-methine methiodide of the A-base.

(IV) Peculier Behavior of N-(3-Methoxyphenethyl)(4'-methoxyphenyl)acetamide toward Bischler-Napieralsky Reaction:

(1) **1-(4'-Methoxybenzoyl)-6-methoxy-3,4-dihydroisoquinoline (XXVI)**—One g. of the acetamide (IX) was boiled with 9 g. of $POCl_3$ in an oil bath for 1 hr. After cooling a large amount of petr. ether was added to the mixture to remove petr. ether-soluble portion. The yellowish brown sticky residue left after three such extractions by petroleum ether was dissolved in water, treated with 50% NaOH, and the depositing product was taken up in ether. The ether solution was dried over anhyd. K_2CO_3 and the ether removed, yielding yellow needles. Upon recrystallization from EtOH they showed m.p. 161~162°; yield, 0.7 g. (71.4%). The infrared spectrum showed a C=O band at 6.06 μ and a C=N band at 6.37 μ. *Anal.* Calcd. for $C_{18}H_{17}O_3N$: C, 73.22; H, 5.76. Found: C, 73.38, 73.04; H, 6.00, 6.09.

(2) **1-(4'-Methoxybenzoyl)-6-methoxy-3,4-dihydroisoquinoline Methiodide (XXVII)**—One g. of the above compound was refluxed in acetone with MeI for some time. Evaporation of the solvent and the excess MeI deposited yellow crystals. After recrystallization from abs. EtOH, they showed m.p. 186~187°. The infrared spectrum showed a C=O band at 6.04 μ and a C=N band at 6.40 μ. *Anal.* Calcd. for $C_{18}H_{17}O_3N \cdot CH_3I$: C, 52.18; H, 4.57. Found: C, 52.34, 51.78; H, 4.58, 4.47.

(3) ***dl*-(6-Methoxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinolyl)(4'-methoxyphenyl)carbinol (XXVIII)**—0.5 g. of the methiodide was dissolved in MeOH and shaken with freshly prepared AgCl. The methochloride thus obtained was reduced with Pd-C catalyst prepared from 20 cc. of 1% $PdCl_2$ and 0.2 g. of carbon, 74.8 cc. H_2 being absorbed. After filtering off the catalyst, a slightly reddish oil was obtained which solidified on standing. After recrystallization from EtOH it crystallized into

white silky needles, m.p. 104~105°. *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.84; H, 7.35. Found: C, 72.99; H, 7.4.

(4) *dl*-(6-Methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4'-methoxyphenyl)carbinol Methiodide (XXIX)—0.1 g. of the above carbinol was methylated in MeOH with MeI, and the methiodide was obtained as white plates, m.p. 160~161°. The infrared spectrum showed the presence of OH bands at 3.04 and 2.95 μ. *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot CH_3I$: C, 52.76; H, 5.72. Found: C, 52.38, 52.34; H, 5.84, 5.78.

(5) First-Stage Hofmann Degradation of *dl*-(6-Methoxy-N-methyl-1,2,3,4-tetrahydroisoquinolyl)(4'-methoxyphenyl)carbinol Methiodide—0.1 g. of the methiodide was boiled with 10 cc. of 30% KOH. The depositing oil was extracted with ether, and the ether extract, after being dried over K_2CO_3, evaporated, yielding a residue having an odor like anisaldehyde.

Summary

Another one of the fragments obtained by the fission of cepharanthine with sodium in liquid ammonia, which has a composition of $C_{17}H_{19}O_2N$, m.p. 205~207°(decomp.), with two phenolic hydroxyl groups, was proved to be *d*-1-(4'-hydroxybenzyl)-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline.

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35. Shigehiko Sugasawa and Makoto Kirisawa: Oxidation of 3-Substituted 1-Alkylpyridinium Salts. II.[1] Oxidation of 1-Methyl- and 1-Phenethyl-3-phenylpyridinium Salts.

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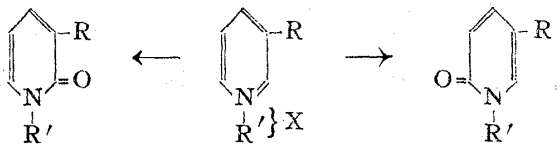
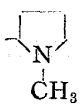
When oxidized with alkaline potassium ferricyanide, 3-substituted 1-alkylpyridinium salt (I) gives the corresponding 6- (II) and/or 2-pyridone (III). The orientation of this oxidation is exclusively governed by the nature of the substituent R in the 3-position, whereas that of R' seems to have scarcely any influence.

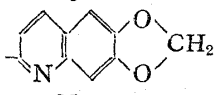


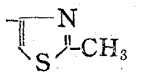
(III) (I) (II)

a: R'=-COOEt or $-CONH_2$

b: 

c: 

d: 

e: 

When R is an alkoxycarbonyl or a carbamyl[2], 3-pyridyl-,[3] N-methyl-2-pyrrolidyl-,[4] 6,7-methylenedioxy-2-quinolyl-,[5] or 2-methyl-4-thiazolyl-,[5] the corresponding 6-pyridone (II: a, b, c, d and e, respectively) is obtained as the main, if not the sole,

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