155~188°. The crystals obtained from fractions 6~9 were crystallized from petroleum ether and melted at 116~119°, either alone or in admixture with diphenylene dioxide (XIX). The crystals from fractions 10~16, when recrystallized from methanol, showed m.p. 127~128°, identical with 1-methoxydiphenylene dioxide (XVIII). Yield, 0.25 g. *Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.67; OCH_3, 14.48. Found: C, 72.56; H, 4.82; OCH_3, 15.06. The crystals from fractions 17~25 showed m.p. 193.5~195.5 after recrystallization from ether, identical with 1,5-dimethoxydiphenylene dioxide (XX). Yield, 0.05 g.

Summary

Attempts to derive O-methyl-anhydro-demethylisotetrandrine (X), which possesses a diphenylene dioxide nucleus, belonging to the trilobine-isotrilobine series, from isotetrandrine (VII), one of the bases of the oxyacanthine-berbamine type, were found successful. It has thus been clarified that this substance is a new isomeride of trilobine or isotrilobine, (I) or (II).

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89. **Masao Tomita, Yasuo Inubushi, and Mutsuo Kozuka:** Studies on the Alkaloids of Menispermaceous Plants. CXII. On the Structure of Biscoclaurine Alkaloids. (15). Synthesis of Trilobine-Type Alkaloid from Isotetrandrine. (2). Hofmann Degradation.

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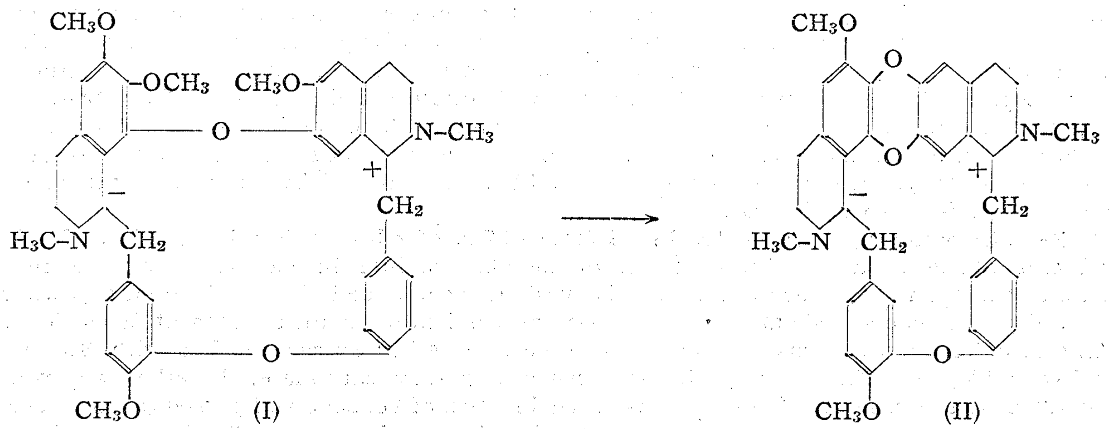
In the previous report[1] of this series, it was shown that O-methyl-anhydro-demethylisotetrandrine (II) was successfully derived from isotetrandrine (I) and that this substance (II) might be one of the isomers of trilobine ($[\alpha]^{9}_{D}$: +302.8° in chloroform) or isotrilobine ($[\alpha]^{8}_{D}$: +314.8° in chloroform), (III) or (IV), considering the steric configurations (−, +) of the two asymmetric centers in the molecule of isotetrandrine ($[\alpha]_D$: +146° in chloroform). It is natural, therefore, that this new base (II) cannot be compared directly with trilobine or isotrilobine but if this base (II) can be led to the optically inactive methine base with the elimination of its asymmetric centers by submitting to the first stage of Hofmann degradation, it seems possible to establish the structure of trilobine or isotrilobine (III or IV) by comparison with its corresponding inactive methine base derived from trilobine or isotrilobine. From such a point of view, the authors carried out the Hofmann degradation on O-methyl-anhydro-demethylisotetrandrine (II).



(I) (II)

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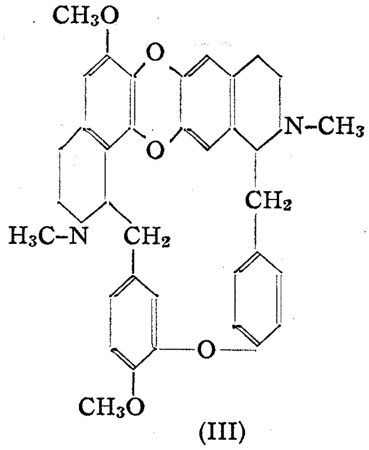
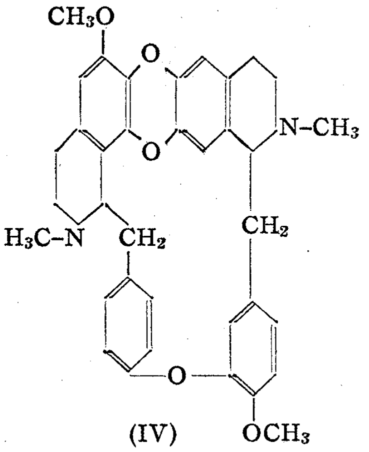
[1] M. Tomita, Y. Inubushi, M. Kozuka: Part CXI. This Bulletin, 1, 360(1953).



(III)



(IV)

Anhydro-demethylisotetrandrine (the two methoxyls in formula (II) replaced by two hydroxyl groups) derived from isotetrandrine (I) was first converted with dimethyl sulfate and alkali into the O-methyl ether methyl methosulfate, which in turn was subjected to the first stage of the Hofmann degradation and yielded two kinds of methine bases. The one crystallized readily from acetone in the form of microscopic pillars, m.p. 222°, and the other was isolated from the mother liquor of the former as a crystalline hydrobromide, m.p. 50~60° (hydrate), $[\alpha]_D$: −49.1°. The amount of the former, m.p. 222°, was too small to allow further examination, but the latter was transformed into the methiodide, which on the second stage of the degradation, afforded des-N base with liberation of trimethylamine. This substance crystallized in the form of needles, m.p. 207~208°, $[\alpha]_D^{10}$: +99.5° (in chloroform), and its analytical values correspond to the composition of $C_{34}H_{26}O_5$.

Meanwhile, the methiodide of O-methyl-anhydro-demethylisotetrandrine (II) was submitted to the first stage of the Hofmann degradation, and also gave two kinds of methines, one as microscopic pillars, m.p. 222°, and the other, as a crystalline hydrobromide, m.p. 50~60° (hydrate), $[\alpha]_D^{18}$: −50.5°, the identities of which were confirmed by admixture with the corresponding two methine bases obtained by the Hofmann degradation of the above methosulfate. The foregoing results revealed that the methine base as well as the des-N base, obtained by the Hofmann degradation of O-methyl-anhydro-demethylisotetrandrine (II), are optically active, and so it was impossible to compare with trilobine methyl methine (m.p. 106°[2], m.p. 105~107°[3]) or isotrilobine methyl methine (m.p. 115°[2], m.p. 110~114°[3]), which are both optically inactive. It should be noted, however, that although the des-N base derived from (II) has the composition of $C_{34}H_{26}O_5$, it is optically active and shows $[\alpha]_D^{10}$: +99.5° (chloroform).

Prior to this, Tomita and Uyeo[4] clarified that in spite of the absence of the asymmetric carbon atom, the des-N base, obtained through the two stages of the Hofmann degradation of insularine, is optically active ($[\alpha]_D^{22}$: +130.2° in acetone) and suggested that this might be due to the molecular asymmetry of the biscoclaurine type bases.

Although the majority of the biscoclaurine-type bases so far studied possess molecular asymmetry, the optical activity of the des-N base, obtained through the two processes of the Hofmann degradation, is a very rare example among the usual bases of the oxyacanthine-berbamine, or the cycleanine series, except that of insularine, as already pointed out by Faltis[5].

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[2] H. Kondo, M. Tomita: Ann., 497, 104(1932); J. Pharm. Soc. Japan, 52, 856(1932).

[3] M. Tomita, T. Tani: J. Pharm. Soc. Japan, 62, 468(1942).

[4] M. Tomita, S. Uyeo: J. Chem. Soc. Japan, 64, 68, 147(1943).

[5] F. Faltis, S. Wrann, E. Kuehas: Ann., 497, 69(1932).

The fact that the des-N base, which was obtained in this experiment is also optically active, may well be attributed to the asymmetry of its molecule and it can be said that this is the second example of such peculiarity following that of the degradation product of insularine.

The authors' thanks are due to the Ministry of Education for a grant from the Scientific Research Fund.

Experimental[6]

(1) **Hofmann Degradation of Anhydro-demethylisotetrandrine**—(i) **Methine Base**—1.5 g. of anhydro-demethylisotetrandrine was dissolved in 25 cc. of 5% aqueous sodium hydroxide, and 5 cc. dimethyl sulfate added with stirring. A further amount of dimethyl sulfate was added in 1 cc.-portions at room temperature at four successive intervals, the sodium hydroxide solution at a rate that maintained the reaction mixture slightly alkaline, and stirring was continued for further 40 minutes. The reation mixture was shaken with ether to remove the excess dimethyl sulfate, diluted to 100 cc. by the addition of water, and treated with 20 g. of potassium hydroxide. The mixture was heated for 30 minutes, and after the completion of the reaction, extracted with ether. The ether solution was dried with anhydrous potassium carbonate and the solvent distilled off, leaving 0.5 g. of an amorphous powder. Crystallization was induced by adding a small portion of acetone to this, but only a small amount of the crystals, m.p. 222°, was obtained. The mother liquor filtered from the above crystals was freed from the solvent, and on addition of dilute hydrobromic acid solution a crystalline hydrobromide, m.p. 50∼60°, $[\alpha]^{10}_{D}$: $-49.1°$ (in alcohol, $l=0.3$ dm., $c=0.81$), was obtained. The methine base obtained by liberation of this hydrobromide was an amorphous powder, which was difficult to crystallize.

(ii) **Des-N Base**—0.5 g. of the above amorphous methine base was heated with an excess of methyl iodide for 1 hr. and the excess methyl iodide was distilled off, yielding 0.5 g. of the methiodide. To this was added 20 cc. of 60% hydrous methanol and 5 g. of potassium hydroxide, and the mixture was heated in a water bath for 1 hr. The reaction proceeded with evolution of trimethylamine. After the reaction was complete, the depositing product was filtered and dissolved in chloroform. The chloroform solution was washed with 5% sulfuric acid solution and the chloroform removed. The residue was dissolved in benzene, and after filtering off insoluble materials, dried with anhydrous potassium carbonate. After removal of the solvent, a small quantity of acetone was added and on standing needle-shaped crystals appeared. After recrystallization from acetone, they showed m.p. 207∼208°. $[\alpha]^{10}_{D}$: $+99.5°$ (in chloroform, $l=0.3$ dm., $c=0.40$). *Anal.* Calcd. for $C_{34}H_{26}O_5$: C, 79.35; H, 5.10. Found: C, 78.86; H, 5.19.

(2) **Hofmann Degradation of O-Methyl-anhydro-demethylisotetrandrine** (II)—A mixture of 0.5 g. of O-methyl-anhydro-demethylisotetrandrine and an excess of methyl iodide was heated for 1.5 hrs., after which the excess methyl iodide was distilled off, leaving 0.5 g. of the methiodide, which decomposes at 277∼285°. This was dissolved in 30 cc. of 50% hydrous methanol and treated with 6 g. of potassium hydroxide. The mixture was heated in a boiling water bath for 1 hr., and after cooling, extracted with ether. The ether extract was dried with anhydrous potassium carbonate and the solvent removed, yielding 0.35 g. of an amorphous powder. Attempt to crystallize this by the addition of a small portion of acetone was made, but only a small amount of the crystals, m.p. 222°, was obtained. The crystals, m.p. 222°, so obtained gave no depression in m.p. when mixed with the crystals, m.p. 222°, obtained from the methyl methosulfate of anhydro-demethylisotetrandrine by the Hofmann method. The mother liquor left after the separation of the above crystals was freed from the solvent. Addition of dilute hydrobromic acid solution to the residue yielded the hydrobromide, m.p. 50∼60°, identical with the product obtained by degradation of the methosulfate. $[\alpha]^{8}_{D}$: $-50.5°$ (in alcohol, $l=0.3$ dm., $c=0.71$).

Summary

Since O-methyl-anhydro-demethylisotetrandrine (II) derived from isotetrandrine (I) was assumed to be isomeric with trilobine or isotrilobine (III or IV), Hofmann degradation was carried out on (II) with a view to comparing each of the inactive methine bases of (II), (III) or (IV). Experimental results revealed that the methine base and des-N base

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6) All melting points are uncorrected. The authors are indebted to Messrs. K. Hozumi and K. Imaeda, and Miss H. Iwata, who carried out the microanalyses.

obtained are both optically active. The example of des-N base being optically active in spite of the absence of asymmetric carbon atom, is rare among the biscoclaurine type bases, and is the second one following that of insularine. It has been surmised that this might be due to the molecular asymmetry, as in the case of insularine.

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90. Takeo Ueda, Kiyoshi Takahashi, Shigeshi Toyoshima, and Masasuke Ose: Researches on Chemotherapeutic Drugs against Viruses. XIV.1) Syntheses of several Quinolinium and Pyridinium Anionides.

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Antiviral chemotherapeutic drugs have hitherto been studied in our Institute and it has been made clear from the results obtained that the drugs possessing activities against neurotropic viruses were not effective against the influenza viruses. Accordingly alternate studies on chemotherapeutic drugs against the influenza viruses have been conducted.

As reported at the previous Annual Meeting of the Pharmaceutical Society2), it has been suggested from investigations on Hirst's phenomenon that some compounds of carbamic esters, capable of prohibiting cholinesterase, should exert remarkable activities on the influenza virus. Prompted by this interesting prediction, several quinolinium and pyridinium salts were synthesized in order to examine their effects against the virus.

This paper describes the syntheses of several compounds of the carbamyloxy-quinolinium and -pyridinium series, and their antiviral properties will be reported in the following paper.

Some compounds of the carbamyloxypyridinium series were already reported by Wuest3) while compounds of the carbamyloxyquinolinium series are not known yet.

Carbamyloxypyridinium halides are usually prepared by combining carbamic esters of pyridine with alkyl or aralkyl halides, and carbamic esters of pyridine, by condensing hydroxyl derivatives of pyridine with carbamination agents such as dimethylcarbamyl chloride and phenyl isocyanate.

According to these methods, carbamic esters of quinoline were synthesized by condensing hydroxyquinoline with carbamination agents, and carbamyloxyquinolinium salts, by combining the carbamic esters with alkyl and aralkyl halides. The methods of the syntheses of these compounds were somewhat improved in detail.

Dimethylcarbamic ester of quinoline and pyridine were prepared by refluxing the equimolar mixtures of hydroxyl derivatives of these bases and dimethylcarbamyl chloride in dehydrated pyridine for four to five hours. In contrast to employing dehydrochlorination agents such as triethylamine in benzene4) medium, this method of using pyridine was found to be successfull in all cases, which was employed throughout these studies.

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1) Part XIII: This Bulletin, 1, 278(1953).

2) T. Ueda, S. Toyoshima, M. Taniguchi, K. Takahashi: Papers read before the Annual Meetings of the Pharmaceutical Society of Japan (1951, 1952).

3) H. M. Wuest: C. A., 44, 3037(1950).

4) K. Nádor: C. A., 46, 7547(1952).