Summary

Of the two forms of *dl*-2,5-diphenyl-4-methyloxazolines, the *ψ*-form has been obtained, but not the regular form. Therefore, the formation of the latter was studied and was successfully obtained by two ways, the one being based on the reaction between *dl*-norephedrine and benzimidoethyl ether hydrochloride, and the other on the treatment of *dl*-*ψ*-1-phenyl-1-chloro-2-benzoylaminopropane with boiling absolute ethanol containing anhydrous sodium carbonate. Further, the regular oxazoline was reacted with methyl tosylate and yielded *dl*-O-benzoylephedrine tosylate. The purpose of the reaction was to find an example of the new method of N-monoalkylation of *β*-amino-alcohols, which was reported in the previous papers.[1,3,4]

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3. Masao Tomita and Yasuo Inubushi: Studies on the Alkaloids of Menispermaceous Plants. CXXII.[1] Structure of Trilobine and Isotrilobine. (12).[2]

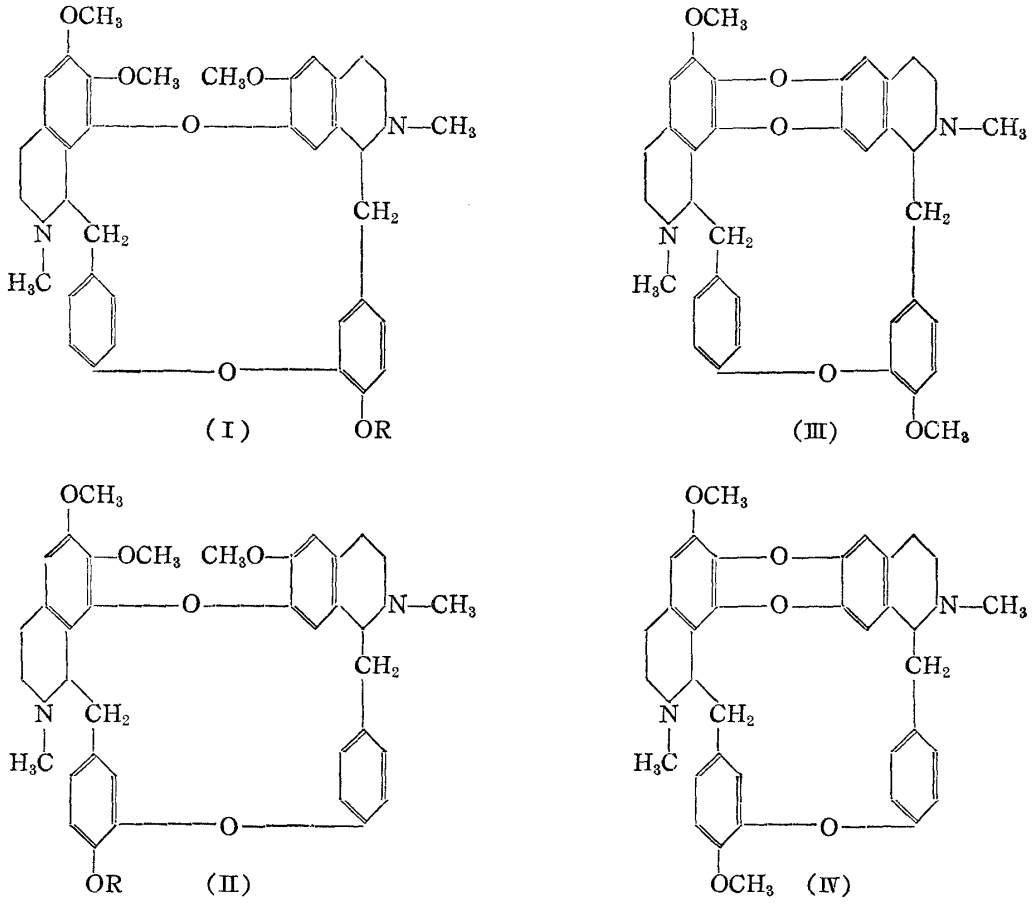
(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

Until recently, it was considered that trilobine stood in the same structural relation[3] to isotrilobine as oxyacanthine (I, R=H) did to berbamine (II, R=H), which indicated that if (III) was assumed to represent trilobine, then (IV) would correspond to isotrilobine, and *vice versa*. However, this ambiguity was removed by the recent work of the same authors[4] who succeeded in deriving some of the trilobine-isotrilobine type bases from the oxyacanthine-berbamine series. In a series of these studies, it was found that in spite of the fact that O-methylanhydrodemethyloxyacanthine[2] of the trilobine type derived from oxyacanthine possesses a structure represented by (III), it did not agree with any of trilobine or isotrilobine, and unexpectedly, O-methylanhydrodemethyloxyacanthine methyl methine, trilobine methyl methine, and isotrilobine methyl methine were all found to be identical. This fact suggested that trilobine and isotrilobine must have an identical structure (III) and that they are stereoisomers of each other, the stereochemical arrangements about the two asymmetric centers differing from those of oxyacanthine.

On the other hand, by a previous work by Tomita and his co-workers of applying the sodium-liquid ammonia fission to the oxyacanthine-berbamine type bases and by determining the constitutions and the specific rotations of the bisected bases of the coclaurine type thereby obtained, the chemical structure of the original bases, as well as the configurations of the two asymmetric centers in them, have been elucidated. As regards the stereochemical configurations of the two asymmetric centers of some of the oxyacanthine series including O-methyloxyacanthine,[5] O-methylrepandine,[6] cepharanthine,[7] and epistephanine,[1] it was considered for a time by comparison of the values of

* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 犬伏康夫).

1) Part CXXI. M. Tomita, E. Fujita: This Bulletin, **2**, 378(1954).
2) Part (11). Y. Inubushi, M. Kozuka: This Bulletin, **2**, 215(1954).
3) M. Tomita: Fortschr. Chem. org. Naturstoffe, **9**, 203(1952).
4) M. Tomita, Y. Inubushi, M. Kozuka: This Bulletin, **1**, 360, 368(1953); Y. Inubushi: *Ibid.*, **2**, 1(1954); M. Tomita, Y. Inubushi: *Ibid.*, **2**, 6(1954); Y. Inubushi: *Ibid.*, **2**, 11, 215(1954).
5) E. Fujita: J. Pharm. Soc. Japan, **72**, 213, 217(1952).
6) E. Fujita, T. Saijoh: *Ibid.*, **72**, 1232(1952).
7) M. Tomita, Y. Sasaki: This Bulletin, **1**, 105(1953); *ibid.*, **2**, 89, 375(1954).



specific rotations of their bisected bases with those of the original bases, that the configuration of the asymmetric center at the right hand isoquinoline residue in these bases underwent Walden inversion during cleavage reactions. Later, however, it became more valid to assume that the configuration of the concerned asymmetric center remained unchanged[8] in this reaction. On the basis of this speculation it follows that the stereochemical configurations of the two asymmetric centers in oxyacanthine (I, R=H) and its optical isomer, repandine (I, R=H), are (+,−) and (+,+), respectively. Also, in an attempt to convert the oxyacanthine-berbamine type bases into the trilobine series, made by Tomita and Inubushi, *et al.*, no evidence was obtained that the configuration of their asymmetric centers had undergone inversion in this reaction. These facts indicate that the configurations of the two asymmetric centers in O-methylanhydrodemethyloxyacanthine (III) must be (+,−). Accordingly, there is a reason to consider that in trilobine and isotrilobine, differing from this substance in the configurations of the two asymmetric centers, their centers of asymmetry may correspond to any of (−,+), (+,+) and (−,−). However, judging from the fact that both trilobine and isotrilobine have $[\alpha]_D$: +ca. 300°, and from the experimental results so far obtained in the related investigations of the biscoclaurine bases, it seems inconceivable that trilobine and isotrilobine have the asymmetric centers of either (+,+) or (−,−) type. These considerations suggest that trilobine and isotrilobine (III) must have the same configuration of (−,+) type. This is inconsistent with the hitherto derived conclusion that trilobine and isotrilobine have identical structure (III) and the only difference between them lies in the stereochemical arrangements about the two asymmetric centers.

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

If, on the other hand, trilobine and isotrilobine are not stereoisomers, it may be suggested that they are polymorphic, but on comparing the physical and chemical properties of both bases, no evidence supporting this view was provided.

Under these circumstances, it became necessary to reinvestigate the experimental data previously obtained regarding trilobine and isotrilobine. On detailed investigation of the data in the Hofmann degradation of trilobine, there was found a slight but appreciable difference between the basicity of the two nitrogen atoms in trilobine. Thus, a suspicion has arisen that of the two nitrogen atoms, one may be present as NH group, although the values corresponding to the two N-CH_3 groups were obtained in the N-CH_3 determination of trilobine, and the Liebermann's nitroso reaction was also found to be negative. In this connection, it is to be noted that one of the authors (Tomita) encountered a similar example in trilobamine[3,9] which, in spite of having an NH group, gave no typical Liebermann's nitroso reaction.

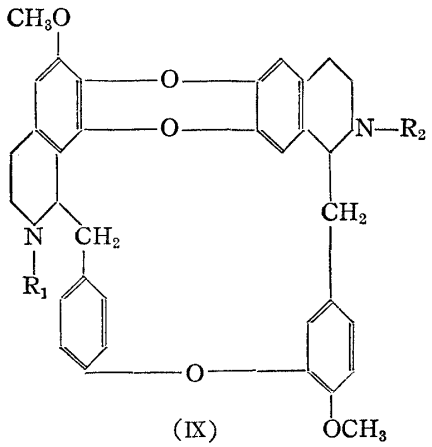
As a result of examination of the infrared spectra of trilobine and isotrilobine, trilobine was found to exhibit a weak but detectable absorption at 3.025 μ, thus suggesting the presence of an NH group. For the sake of confirmation, the infrared spectra of tetrahydropapaverine (V), laudanosine (N-methyltetrahydropapaverine) (VI), O,O-dimethylcoclaurine (VII), and O,O,N-trimethylcoclaurine (VIII) were compared, and there was also observed a weak absorption in those of (V) and (VII), which was in good accord with that of trilobine. Naturally, it seems conceivable that in the case of trilobine, which consists of a large molecule and whose two nitrogen atoms are in N-CH_3 and NH groups, the infrared absorption of NH band is feeble.

When trilobine and isotrilobine were each heated with formaldehyde and formic acid, the reaction proceeded with evolution of carbon dioxide gas in the case of trilobine, whereas no evolution of carbon dioxide gas was observed in the case of the latter, during the course of the reaction. On treatment of their reaction products, it was found that trilobine (m.p. 237°) underwent conversion into isotrilobine (m.p. 215°), whereas isotrilobine was recovered unreacted. Heating trilobine with formic acid resulted in recovering the unreacted material. These experimental results revealed that trilobine underwent N-methylation to form isotrilobine.

The elemental analyses, N-CH_3 groups, and the specific rotations of trilobine and isotrilobine were again submitted to measurements and the results are shown in Table I.

Table I.

	Formula	m.p.(C°)	OCH_3	NCH_3	$[\alpha]_D$(in $CHCl_3$)
Trilobine	$C_{35}H_{34}O_5N_2$	237	2	1	+307.9°
Isotrilobine	$C_{36}H_{36}O_5N_2$	215	2	2	+312.6°



(IX)

9) I. R. C. Bick, E. S. Ewen, A. R. Todd: J. Chem. Soc., **1949**, 2767.

From these experimental results, it has become clear that the hitherto accepted view that trilobine and isotrilobine are optically isomeric with each other must be denied, and that since isotrilobine is none other than N-methyltrilobine, the structure of isotrilobine should be represented by formula (IX, $R_1=R_2=CH_3$), and that of trilobine, by formula (IX, $R_1=H$, $R_2=CH_3$ or $R_1=CH_3$, $R_2=H$).

Furtheremore, it is certain that these two bases have the same stereochemical configurations of the two asymmetric centers, and judging from the experimental results so far obtained regarding the specific rotations of the biscoclaurine bases and their bisected bases by the sodium-liquid ammonia fission, both are considered to be of (−,+) type.

The authors wish to thank Messrs. Y. Matsui and A. Narisada of the Research Laboratory, Shionogi & Co. Ltd., for the measurement of the infrared spectra. This work was helped by a Grant in Aid for Scientific Research from the Ministry of Education, to which the authors are also indebted.

Experimental[10]

Trilobine—The analytical data of trilobine showing m.p. 237° after recrystallization from benzene were reëxamined. $[\alpha]_D^{31}$: +307.9°(in $CHCl_3$, $l=0.5$ dm., $c=0.77$). *Anal.* Calcd. for $C_{35}H_{34}O_5N_2$: C, 74.73; H, 6.05; OCH_3, 11.03; (N)-CH_3, 2.66. Found: C, 74.48; H, 6.10; OCH_3, 10.68; (N)-CH_3, 2.68. A sample of trilobine was chromatographed on Toyo filter paper No. 50 in BuOH-AcOH-H_2O (5:1:4). The paper was dried and sprayed with an EtOH solution of the potassium salt of tetrabromophenolphthalein ethyl ester (0.1%) and dried again. After spraying with aq. oxalic acid (0.1%) the position of trilobine was shown by a deep blue spot, the Rf value of which was 0.68. In the Liebermann's nitroso test, this base caused a slightly yellow precipitate immediately after the addition of aq. $NaNO_2$, which did not transfer to ether and gave no coloration with phenol and conc. H_2SO_4.

Isotrilobine—A sample of isotrilobine showing m.p. 215° after recrystallization from acetone gave the following results in analyses. $[\alpha]_D^{31}$: +312.6°(in $CHCl_3$, $l=0.5$ dm., $c=0.69$). *Anal.* Calcd. for $C_{36}H_{36}O_5N_2$: C, 74.96; H, 6.30; OCH_3, 10.76; (N)-CH_3, 5.21. Found: C, 75.03; H, 6.29; OCH_3, 9.91; (N)-CH_3, 4.77. The paper chromatography in the same way as above gave the Rf value of 0.73. The Liebermann's nitroso reaction was negative; in this case, very little amount of precipitate formed by the addition of aq. $NaNO_2$.

Action of Formaldehyde-Formic Acid upon Trilobine—A solution of 0.15 g. of trilobine in 0.38 cc. of formic acid (83%) was heated with 0.45 cc. of formaldehyde solution (37%) on a boiling water bath, during which the evolution of carbon dioxide gas occurred. After heating was continued for 4 hrs., 20 cc. of water was added and the mixture was shaken up once with ether to remove any neutral substance. Subsequently, the aqueous solution was made alkaline with aq. NaOH, and the depositing base taken up in a large amount of ether. The ethereal solution was dried over anhyd. K_2CO_3 and the ether concentrated until crystals began to separate out. After standing, the deposited crystals were filtered with suction and recrystallized from acetone, yielding 0.08 g. of colorless pillars, m.p. 213~215°, undepressed on admixture with isotrilobine (m.p. 213~215°). $[\alpha]_D^{31}$: +320.3°(in $CHCl_3$, $l=0.5$ dm., $c=0.71$). *Anal.* Calcd. for $C_{36}H_{36}O_5N_2$: C, 74.96; H, 6.30. Found: C, 74.58; H, 6.56.

0.05 g. of trilobine was heated with 0.18 cc. of formic acid on a water bath for 4 hrs., after which the reaction mixture was treated as above. In this case, crystals were obtained from benzene in the form of colorless pillars, m.p. 237°, undepressed on admixture with the original trilobine (m.p. 237°).

Action of Formaldehyde-Formic Acid upon Isotrilobine—0.15 g. of isotrilobine was treated in a similar manner with 0.38 cc. of formic acid and 0.45 cc. of formaldehyde solution and the product thus obtained formed colorless pillars, m.p. 213~215°, which was confirmed to be the original isotrilobine (m.p. 213~215°) by the mixed melting point determination.

Summary

In an earlier paper[2] of this series, experimental evidence was presented that the methine base obtained by the Hofmann degradation of O-methylanhydrodemethyloxyacanthine (III), a trilobine-type base derived from oxyacanthine (I, R=H), was identical with trilobine methyl methine or isotrilobine methyl methine. On this basis it was suggested that trilobine and isotrilobine are optical isomers, both having the common

10) All melting points are uncorrected. The authors' thanks are due to Messrs. Hozumi and Imaeda for carrying out the microanalyses.

structure (III). In the present series of experiments, it was confirmed that although so far trilobine was considered to possess two N-CH_3 groups, actually one of the two nitrogen atoms is present as N-CH_3, and the other, as an NH group (see Table I). It follows, therefore, that isotrilobine should be represented by the structure of (IX, $R_1=R_2=CH_3$), whereas trilobine by (IX, $R_1=H$, $R_2=CH_3$ or $R_1=CH_3$, $R_2=H$). Furthermore, it was suggested that the stereochemical arrangments about the two asymmetric centers in these bases are both of (−,+) type.

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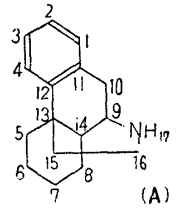
4. **Norio Sugimoto and Hiroshi Kugita** : Studies on the Syntheses of Hydrogenated Quinolines and Isoquinolines as Analgesics. IV.[1] Synthesis of 3-Hydroxy-9-azamorphinan.

(*Osaka Research Laboratory, Gohei Tanabe & Co., Ltd.**)

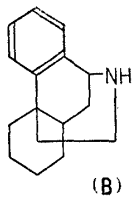
In 1946, Grewe[2] succeeded in synthesizing the parent nucleus of morphine and designated this structure as morphinan (A). Later, various improved methods for the synthesis of morphinan were published and, according to the reports of Gross, Fromberg, Isbell, and Böni,[3] there is no analgesic action in *d*-3-hydroxy-N-methylmorphinan or N-ethylmorphinan while their administration in large doses is effective against rheumatism.

It has, however, been found that *l*-3-hydroxy-N-methylmorphinan causes a marked analgesic action, which is lasting and is about three times stronger than that of morphine. This action is antagonistic to morphine.

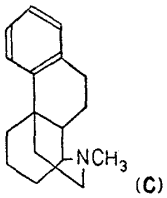
Following the synthesis of morphinan, studies on the syntheses of its allied compounds have been published but these were all allied compounds with identical compositions but with entirely different skeleton. For example, Newmann and others[4] synthesized, in 1947, 1,3,4,9,10,10a-hexahydro-9,4a-2*H*-iminoethanophenanthrene (B) but failed to give its pharmacological effect. Recently, May and others[5] reported on the synthesis of 1,2,3,9,10,10a-hexahydro-11-methyl-1,4a-4*H*-iminoethanophenanthrene (C) but there seemed to be no marked analgesic action in this compound.



(A)



(B)



(C)

The compound which was taken up as the object of our attempt to synthesize the isomers of morphinan is 9-azamorphinan and as can be known from such a designation, it is an isomer of morphinan in which the nitrogen in its skeleton has shifted from 17-

* Honjo-Kawasaki-cho, Ohyodo-ku, Osaka (杉本典夫, 釘田博至).

1) Part III : J. Pharm. Soc. Japan, **75**(1955), in press.
2) R. Grewe : Naturwissenschaften, **33**, 333(1946).
3) E. Goss, K. Fromberg, H. Isbell, A. Böni : Feder. Proc., 8, Part I, 297(1949); Arch. Int. Pharm. Therap., **85**, 3871(1952); Experientia, 8, 394(1952); J. Pharmacol. Exptl. Therap., **107**, 524(1953); Zeitsch. Rheumaforschung, **12**, 23(1953).
4) M. S. Newmann, *et al.* : J. Am. Chem. Soc., **69**, 942(1947).
5) E. L. May, *et al.* : J. Org. Chem., **19**, 618(1954).