PHARMACEUTICAL BULLETIN

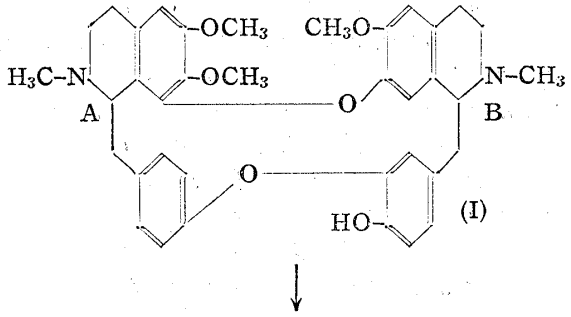
Vol. 1 No. 2 June 1953

24. Masao Tomita* and Eiichi Fujita**: Studies on the Alkaloids of Menispermaceous Plants. CV[1]. On the Structure of Biscoclaurine Alkaloids. (12)[2]. The Steric Configuration of two Asymmetric Centers in the Oxyacanthine-type Alkaloids.

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

It was previously reported that by cleaving O-methyloxyacanthine (II), obtained by the methylation of oxyacanthine (I), by means of metallic sodium in liquid ammonia, Fujita[3] obtained *d*-armepavine (III) on the one hand, and a phenolic bisected base on the other, and by the methylation of the latter he proved it to be *l*-O,O,N-trimethylcoclaurine (IV). Subsequently, the same cleavage reactions were carried out, after methylation, on repandine, an optical isomer of oxyacanthine, derived by allowing oxyacanthine (I) to react with 0.5 equivalent amount of hydrochloric acid, following the same procedure as employed by Bruchhausen, and on O-methylrepandine obtained above from which he obtained as the bisected bases *d*-armepavine (III) and a phenolic base, by the methylation of which he proved it as crystalline *d*-O,O,N-trimethylcoclaurine (IV)[2].

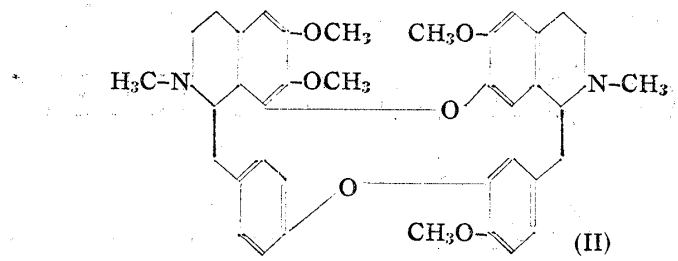
In regard to the optical isomers of the alkaloids of the berbamine type among the biscoclaurine-type alkaloids, Bruchhausen *et al.*[4] discussed the optical rotation of the compounds of this type, giving the following explanation. The molecules of this type have two asymmetric carbon atoms, and if one of the asymmetric centers is postulated to be A=±70° and the other B=±200°, then, in a series of tetrandrine, isotetrandrine (O-methylberbamine), and phaeanthine ((V) in all, $R_1=R_2=R_3=R_4=R_5=R_6=CH_3$),+A+B corresponds to tetrandrine



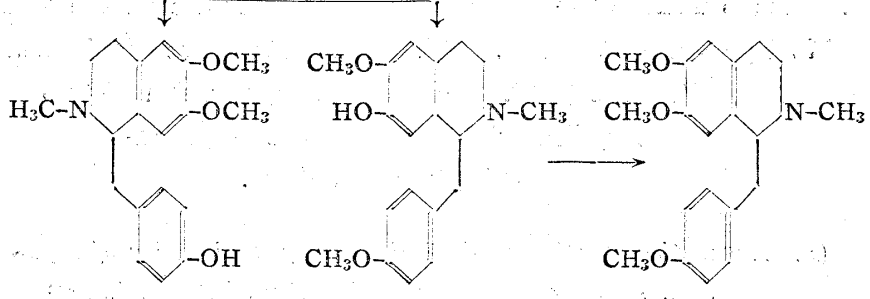
(I)

* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄).
** Minamijohsanjima-cho, Tokushima (藤田栄一).

1) Part CIV: This Bulletin, 1, 55 (1953).
2) Report (11): J. Pharm. Soc. Japan, 72, 1232 (1952).
3) E. Fujita: *Ibid.*, 72, 213, 217 (1952).
4) F.v. Bruchhausen, H. Oberembt, A. Feldhaus: Ann., 507, 144 (1933).

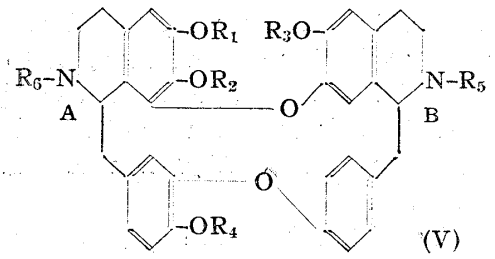


(II)

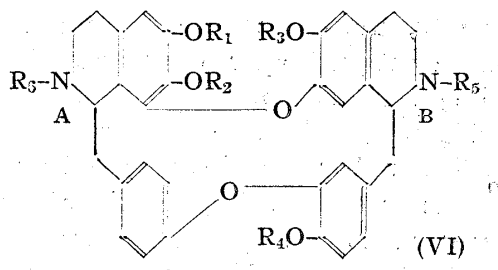


(III) (IV)

($[\alpha]_D$: +263°); −A+B to isotetrandrine ($[\alpha]_D$:+146°); and −A−B to phaeanthine ($[\alpha]_D$: −278°). An alkaloid corresponding to +A−B has not yet been discovered.



(V)



(VI)

On the other hand, in a series of oxyacanthine and repandine (each assigned (VI): $R_1=R_2=R_3=R_5=R_6=CH_3$; R_4=H), if +A+B corresponds to oxyacanthine ($[\alpha]_D$:+279°), and +A−B to repandine ($[\alpha]_D$:−106°), the explanation is well applicable.

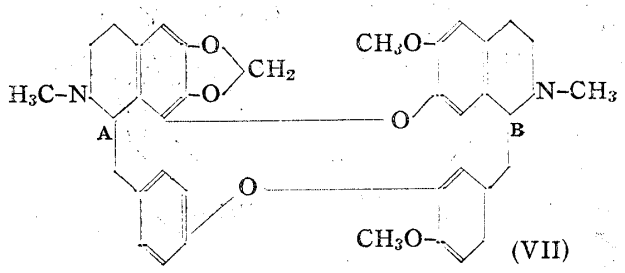
Recently, Tomita and Fujita revealed that when the same cleavage reaction was applied to various kinds of alkaloids belonging to the berbamine type, they were invariably bisected into two coclaurine-type molecules, and the bisected bases obtained show approximately the specific rotation of ±70°~±100°, thus giving an experimental evidence to the above hypothesis by Bruchhausen. Subsequently, regarding the specific rotation of the berbamine-type alkaloids, they deduced that the ±exaltation caused by the molecular asymmetry of the molecules of this type may be added to the specific rotation caused by each asymmetric carbon atom of the two coclaurine-type molecules. From the experimental results obtained by cleaving the alkaloids of the biscoclaurine group by means of metallic sodium in liquid ammonia, if A and B are postulated to be ±80°, respectively, in (V) of the berbamine type, a series of tetrandrine, isotetrandrine, and phaeanthine may be shown as follows:

	A	B	Exaltation	Calcd. $[\alpha]_D$	Found $[\alpha]_D$
Tetrandrine	+80°	+80°	+110°	+270°	+263°
Isotetrandrine	−80°	+80°	+110°	+110°	+146°
Phaeanthine	−80°	−80°	−110°	−270°	−278°

Also in (VI) of the oxyacanthine type, the following may well be analogized:

	A	B	Exaltation	Calcd. $[\alpha]_D$	Found $[\alpha]_D$
Oxyacanthine	+80°	+80°	+110°	+270°	+279°
Repandine	+80°	−80°	−110°	−110°	−106°

Considering the above experimental results on the basis of Bruchhausen's hypothesis, it should be concluded that when O-methyloxyacanthine (+,+) and O-methylrepandine (+, −) were reacted with metallic sodium in liquid ammonia, the steric configuration of the asymmetric center belonging to the right-hand tetrahydroisoquinoline nucleus in formula (II) underwent inversion from + to −, and from − to +, respectively. This is well in agreement with the fact, as Bruchhausen[5] has pointed out and which the authors reëxamined by the present experiments, that oxyacanthine changes to repandine when allowed to react with 0.5 equivalent amount of hydrochloric acid. In other words, the steric configuration of the asymmetric center beloging to the right-hand tetrahydroisoquinoline nucleus in oxyacanthine (I) has a tendency to undergo inversion readily.



(VII)

Consequently, the authors deduced that in the above two experiments, the Walden inversion also took place in an alkaline medium when employing metallic sodium in liquid ammonia, as in the case of oxyacanthine changing to repandine by hydrochloric acid.

As will be reported in the succeeding paper of this series[6], Tomita and Sasaki carried out the same cleavage reaction on cepharanthine (benzene adduct, $[\alpha]_D$:+300°) (VII), and by the methylation of the phenolic bases obtained as the decomposition products, proved the presence of substances corresponding to *d*-1-(4'-methoxybenzyl)-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline and *l*-O,O,N-trimethylcoclaurine (IV).

In addition to the two instances in the cleavage of O-methyloxyacanthine and O-methylrepandine, third instance has been discovered in that of cepharanthine, in which, according to the hypothesis by Bruchhausen, there is no way but to think that the steric configuration of the asymmetric center B in the right-hand tetrahydroisoquinoline nucleus underwent inversion by this reaction.

From the foregoing results, it necessarily follows that cepharanthine should have the structure belonging to the oxyacanthine type, not to the berbamine, and if this base has the structure of the berbamine type, *d*-type (IV) must naturally have been obtained, considering the value of its specific rotation.

However, when we think once more about the steric configuration of the two asymmetric centers in the molecules of the oxyacanthine-type alkaloids with the above three experimental results, the following may well be accepted, besides the view that, as stated above, the steric configuration of one of the two asymmetric centers underwent inversion by this reaction.

Since there exists an obvious difference in the structure of the alkaloids of the berbamine and of oxyacanthine types, it seems that the value of the exaltation of the rotation caused by their molecular asymmetry does not necessarily coincide in both types. On the assumption that the absolute configuration of the original bases underwent no inversion during the course of the reaction, from the signs of the rotations of their respective bi-

5) F. v. Bruchhausen, H. Schultze: Arch. Pharm., **267**, 623 (1929).
6) M. Tomita, Y. Sasaki: This Bulletin, **1**, 105 (1953).

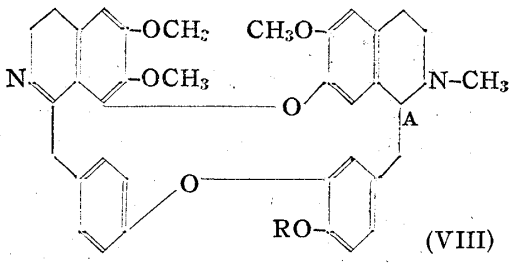
sected bases obtained, the steric configurations of the asymmetric carbon atoms (A, B) in oxyacanthine, repandine, and cepharanthine may be considered as (+, −), (+, +) and (+, −), respectively. If the value of the exaltation caused by the molecular asymmetry is given as ±270°, an illustration can be afforded, as shown in the following:

	A	B	Exaltation	Calcd. $[\alpha]_D$	Found $[\alpha]_D$
Oxyacanthine	+80°	−80°	+270°	+270°	+279°
Repandine	+80°	+80°	−270°	−110°	−106°
Cepharanthine	+80°	−80°	+270°	+270°	+300°

A discrimination is made in such a fashion that in the case of the oxyacanthine type, the value of the exaltation is given as ±270°, whereas in the case of the berbamine, as ±110°.

Previously, the structures of oxyacanthine and repandine were supposed to be (+A, +B) type, and (+A, −B) type, respectively, but the above consideration leads to the conclusion that this should be reversed, that of oxyacanthine being (+A, −B) type, and repandine, (+A, +B).

Another example is seen in the case of epistephanine[7] ($[\alpha]_D$: +180°) and hypoepistephanine[8] ($[\alpha]_D$: +186°). The structures of epistephanine (R=CH_3) and hypoepistephanine (R=H) are indicated by formula (VIII), and N-methylhydroepistephanine A corresponds to O-methyloxyacanthine. If the steric configuration of the asymmetric center A in formula (VIII) is postulated to have a negative sign, the value of its specific rotation becomes $[\alpha]_D$ (calcd.): −80°+270°=+190°, which agrees well with its observed value.



(VIII)

With regard to the question of whether the steric configuration of one of the two asymmetric centers in the oxyacanthine-type bases undergoes inversion by this cleavage reaction or whether the absolute configuration of that in their molecules suffers no change during the course of the reaction, the experimental data so far obtained are not sufficient enough to allow conclusion which of these two views is correct.

By carrying out the above cleavage reaction on the base corresponding to an isomer of oxyacanthine or repandine, whose steric configuration of the asymmetric center belonging to the left-hand tetrahydroisoquinoline nucleus has a negative sign, a more definite evidence may be given on this problem, but no base which may be regarded as such an isomer has yet been discovered. It is expected that by the occurrence of a new base of this type in the future, this problem may be settled in a short time.

The authors are indebted to Prof. Dr. S. Uyeo of the Osaka University and Dr. W. I. Taylor of the Cambridge University for their kind advices.

Summary

From the results of cleavage reactions previously carried out on O-methyloxyacanthine and O-methylrepandine (both being assigned (II)) by metallic sodium in liquid ammonia, it had been concluded that the steric configuration of the asymmetric center belonging to the right-hand tetrahydroisoquinoline nucleus in their molecules underwent the Walden inversion by this reaction. However, by discriminating the value of the exaltation of the rotation caused by the molecular asymmetry of the oxyacanthine-type bases from that of

7) H. Kondo, K. Tanaka: J. Pharm. Soc. Japan, 63, 267, 273 (1943); 64, 28 (1944); M. Tomita, S. Uyeo, K. Doi, T. Miwa: *Ibid.*, 69, 22 (1949); C. A., 44, 4476 (1950); M. Tomita, E. Fujita, F. Murai; J. Pharm. Soc. Japan, 71, 226 (1951); C. A., 46, 4554 (1952).

8) H. Kondo, T. Nozoe: J. Pharm. Soc. Japan, 63, 333 (1943); M. Tomita, E. Fujita, F. Murai: *Ibid.*, 71, 226 (1951); C. A., 46, 4554 (1952).

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)

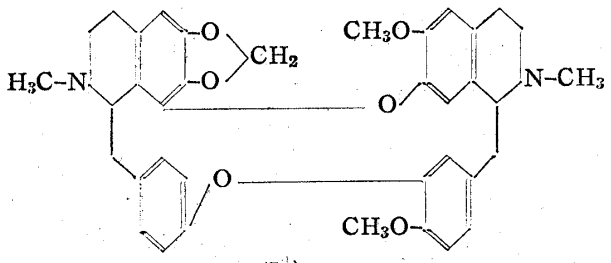
---

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.

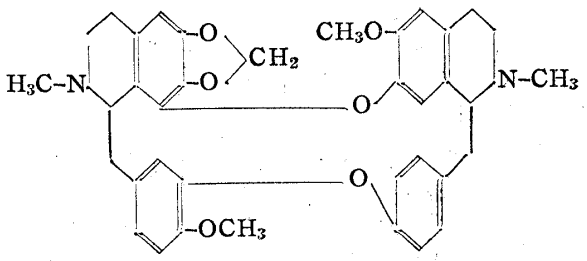
(Pharmaceutical Institute, Medical Faculty, University of Kyoto)*

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)

---

* 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).