Tetrahedron Letters No. 24, pp. 1133-1136, 1962. Pergamon Press Ltd.
Printed in Great Britain.

ON THE STRUCTURES OF TRILOBINE AND ISOTRILOBINE

Yasuo Inubushi

Faculty of Pharmacy, Osaka University, Toyonaka, Osaka-fu, Japan

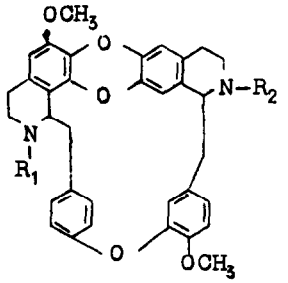
and

Kei-ichi Nomura

Faculty of Pharmacy, Kyoto University, Kyoto, Japan

(Received 13 August 1962)

STRUCTURES of trilobine and isotrilobine which were isolated from Cocculus trilobus DC. and two other Menispermaceous plants[1] have been reported to be represented by (Ia) and (Ib) respectively[2]. However, the stereochemical configurations at the asymmetric centers of these alkaloids and the location of the secondary nitrogen in trilobine have been undetermined.



(Ia) Trilobine

$R_1 = H$, $R_2 = CH_3$

or

vice versa

(Ib) Isotrilobine

$R_1 = R_2 = CH_3$

The reductive fission with sodium in liquid ammonia, by which steric configurations of most bisbenzylisoquinoline alkaloids have been decisively

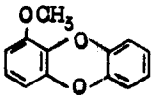
---

1 H. Kondo and T. Nakazato, J. Pharm. Soc. Japan 511, 691 (1924); Ibid 532, 461 (1926); H. Kondo and M. Tomita, Ibid. 542, 265 (1927); M. Tomita and F. Kusuda, Pharm. Bull. (Tokyo) 1, 1 (1953).

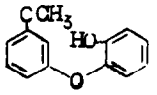
2 H. Kondo and M. Tomita, Ann. 497, 104 (1932); M. Tomita and C. Tani, J. Pharm. Soc. Japan. 62, 468, 481 (1942); M. Tomita and Y. Inubushi, Pharm. Bull. (Tokyo) 1, 360, 368 (1953); Ibid. 2, 1, 6, 215 (1954).

established, was applied to these alkaloids by one of the authors but this treatment gave unfavourable results because of the presence of the dibenzo-p-dioxin system[3].

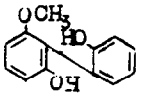
The results from preliminary experiments showed that 1-methoxydibenzo-p-dioxin (II) afforded hydroxybiphenyl derivative (IV) besides hydroxydiphenyl ether derivative (III) by this reductive fission and that the procedure adopted for the cleavage in order to obtain the maximum yield of the compound (III) should be carried out with addition of sodium hydride to the solution of sodium in liquid ammonia[4].



(II)



(III)



(IV)

Then, this improved procedure of cleavage was applied to isotrilobine, and the diphenyl ether derivative (VI) obtained from the first stage fission reaction was separated from biphenyl derivative, methylated with diazomethane and subjected to the second stage fission with sodium in liquid ammonia. The sole non-phenolic cleavage product (VIIa), mp 64-65°, $[\alpha]_D$ + 129.2 (95% EtoH), was identified with synthetic dl-1-(4'-methoxybenzyl)-2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline[5].

Phenolic products, (VIII) (R=H) and (IX) (R=H) which are with asymmetric center dextrorotatory were also obtained and their O-methyl ethers were

---

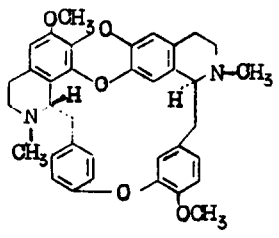
[3] M. Tomita, Y. Inubushi and H. Niwa, J. Pharm. Soc. Japan. 72, 206 (1952); Y. Inubushi, Pharm. Bull. (Tokyo) 2, 11 (1954).

[4] Y. Inubushi and K. Nomura, J. Pharm. Soc. Japan 79, 838 (1959): Ibid. in press.

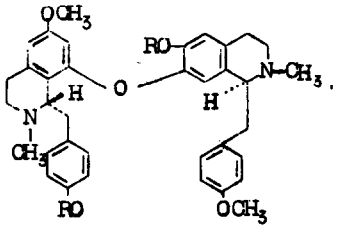
[5] Y. Sasaki, H. Ohnishi and N. Sato, Pharm. Bull. (Tokyo) 3, 178 (1955).

identified with authentic samples of (VIII) ($R=CH_3$)[6] and (IX) ($R=CH_3$)[7].

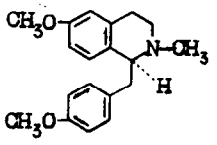
The absolute configuration of the compound (VIIb), which has levorotatory asymmetric center and is an antipode of (VIIa) has been recently established to be R configuration by Tomita and Kunitomo[8].



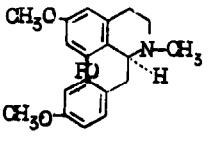
(V)



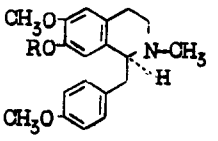
(VI)



(VIIa)



(VIII)



(IX)

(VIIa) mp 64-65° $[\alpha]_D$ + 129.2° (95%E+OH)

(VIIb) mp 64-65° $[\alpha]_D$ - 130.5° (95%E+OH)

Since it is clear that the absolute configuration of the compound (VIIa) is S configuration and also that (VIIa) originates from both benzyltetrahydroisoquinoline moiety of isotrilobine molecule when the mode of fission is taken into consideration, the structure of isotrilobine must be represented by (V) with the asymmetric centers both being S configurations.

Furthermore, the same treatment was applied to acetyltrilobine (X)*,

---

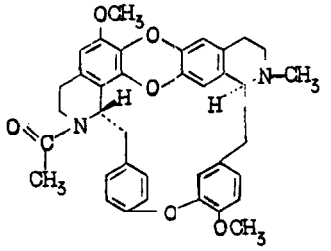
6 Y. Inubushi and K. Nomura, J. Pharm. Soc. Japan in press.

7 M. Tomita and J. Kunitomo have reported that the asymmetric center of (IX) ($R=CH_3$) is S configuration, J. Pharm. Soc. Japan 82, 734 (1962).

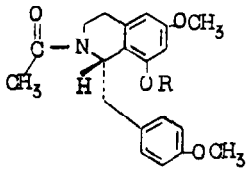
8 M. Tomita and J. Kunitomo, J. Pharm. Soc. Japan in press.

* As the preliminary experiment, dl-1-(4'-methoxybenzyl)-2-acetyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline was subjected to the same treatment, and 75% of recovery of the starting material was observed.

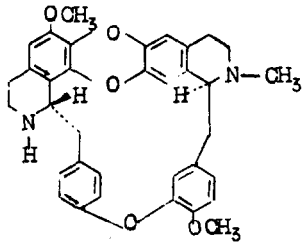
and the compound (VIIa) and (XI) were obtained, proved to be identical with authentic samples[5,6]. Since N-methyltrilobine has been reported to be identical with isotrilobine[9], the absolute configurations of two asymmetric centers of trilobine are the same as those of isotrilobine. From these results, it can be concluded that the structure of trilobine is represented by (XII), the nitrogen at the left being the secondary one.



(X)



(XI)



(XII)

Acknowledgement - we wish to express our deep gratitude to Professor M. Tomita for his hearty encouragement throughout this work.

9 M. Tomita and Y. Inubushi, Pharm. Bull (Tokyo) 3, 7 (1955).