

TOTAL SYNTHESIS OF (+)-DAURICINE

Tetsuji Kametani and Keiichiro Fukumoto

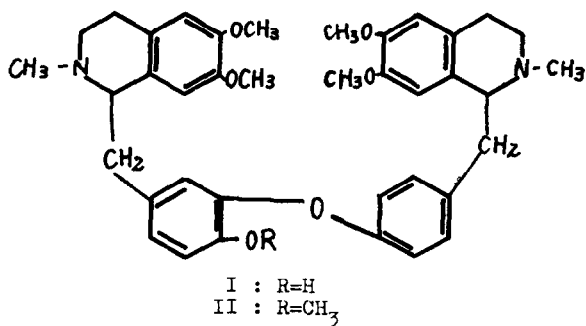
Pharmaceutical Institute, School of Medicine

Tohoku University

No. 85, Kitayobancho, Sendai, Japan

(Received 5 August 1964)

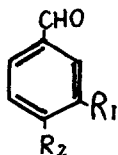
DAURICINE, $C_{38}H_{44}O_6N_2$, m.p. 115° , one of the alkaloids of Menispermaceous plants, was isolated from Menispermum dauricum DC. by Kondo and Narita (1) in 1927, and also from Menispermum canadense L. by Manske (2). The structure of dauricine was assigned as (I) by chemical methods (3,4,5) and a synthesis of O-methylauricine has already been described (5,6), confirming Kondo's structure (I) for the alkaloid. Tomita, et al (6) stated that O-methylauricine (II) was synthesized by the Ullmann reaction of (-)-armepavine and (-)-3'-bromo-O-methylarmepavine. However, a total synthesis of dauricine (I) has not yet been achieved.



The purpose of the present investigation was to study the cyclization of the diamide (X) in order to obtain the corresponding isoquinoline (XI) and its methiodide (XII) as possible intermediates for the synthesis of dauricine (I). A study of the reduction of (XII) eventually led to a synthesis of (\pm)-dauricine that supports the structure (I).

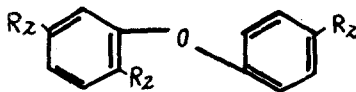
Ullmann reaction of 4-bromobenzaldehyde (III) with 4-benzyl-protocatechualdehyde (IV) (5) gave 2-benzyloxy-4',5-diformylbiphenyl ether (V) as pale yellow prisms, m.p. 77 - 78° (Found: C, 75.84; H, 4.94. $C_{21}H_{16}O_4$ requires C, 75.89; H, 4.85%), which was also obtained by benzylation of 2-hydroxy-4',5-diformylbiphenyl ether (VI), m.p. 136° (Found: C, 69.30; H, 4.49. $C_{14}H_{10}O_4$ requires C, 69.42; H, 4.16%), prepared by demethylation of 2-methoxy-4',5-diformylbiphenyl ether (VII) (7).

Oxidation of the biphenyl ether (V) gave the corresponding dicarboxylic acid (VIII) as colourless prisms, m.p. 248 - 249° (Found: C, 69.31; H, 4.65. $C_{21}H_{16}O_6$ requires C, 69.22; H, 4.93%).



III : $R_1=H$; $R_2=Br$

IV : $R_1=OH$; $R_2=OCH_2C_6H_5$



V : $R_1=OCH_2C_6H_5$; $R_2=CHO$

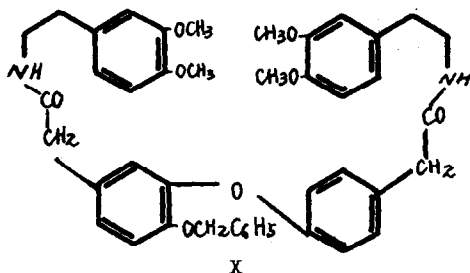
VI : $R_1=OH$; $R_2=CHO$

VII : $R_1=OMe$; $R_2=CHO$

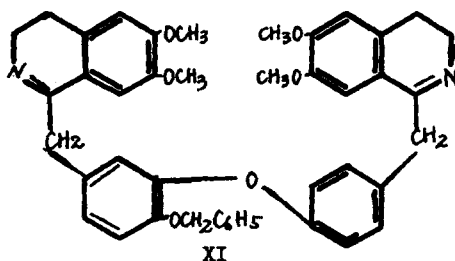
VIII : $R_1=OCH_2C_6H_5$; $R_2=CO_2H$

IX : $R_1=OCH_2C_6H_5$; $R_2=COCl$

Arndt-Eistert reaction (8) of homoveratrylamine with the acid chloride (IX), which was obtained by chlorination of the above acid (VIII) with thionyl chloride, afforded the amide (X) as a yellowish-brown amorphous powder.

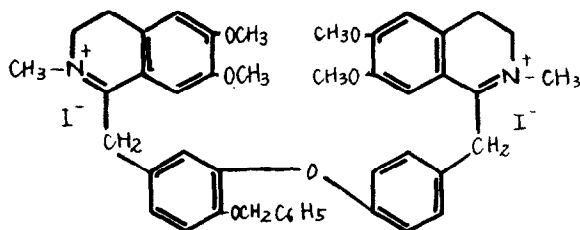


Bischler-Napieralski cyclization of the above amide (X) with phosphoryl chloride in benzene afforded the isoquinoline derivative (XI) as a brown syrup, whose distyphnate crystallized from acetone-ether as a yellow powder, m.p. 138 - 139^o (Found: C, 56.41; H, 4.62. $C_{43}H_{42}O_6N_2 \cdot 2C_6H_5O_8N_3$ requires C, 56.31; H, 4.13%).



Reduction of the amorphous methiodide (XII), which could not be purified by recrystallization, with zinc dust and ethanol-concentrated hydrochloric acid (1:1) afforded a mixture of (\pm)-dauricine (I) and its diastereoisomer as a yellow-orange syrup which

formed a yellow amorphous solid on being triturated with hexane.



Repeated alumina-chromatography of this product and precipitation with benzene and hexane resulted in formation of a pale yellowish-green powder, m.p. 122 - 124°, which gave analytical data in accord with the formula (I). However, neither specimen or synthetic and natural dauricine could be obtained crystalline.

The infrared spectra (in chloroform) of the picrate, m.p. 140 - 142° and the styphnate, m.p. 146 - 149°, of the racemate (I) were superimposable on those of natural dauricine picrate and styphnate, prepared from a natural dauricine donated by Professor Manske. PFC (Toyo Roshi, No. 51): R_F 0.64 (BuOH-AcOH-H₂O=4:1:5) (Synthetic racemate of I), R_F 0.64 (natural dauricine). The spots were detected by their fluorescence under UV light (short wave 2536A, cycle 50).

We express our deep gratitude to Prof. M. Tomita for the gift of natural dauricine and its derivatives. We are indebted also to Dr. R. H. F. Manske for a gift of natural dauricine.

REFERENCES

1. H. Kondo and Z. Narita, J. Pharm. Soc. Japan (Yakugaku Zasshi), No. 542, 279 (1927).
2. R. H. F. Manske, Canad. J. Research, 21B, 17 (1943).
3. H. Kondo and Z. Narita, J. Pharm. Soc. Japan (Yakugaku Zasshi), 49, 688 (1929).
4. H. Kondo and Z. Narita, Ber., 63, 2420 (1930).
5. H. Kondo, Z. Narita, and S. Uyeo, J. Pharm. Soc. Japan (Yakugaku Zasshi), 55, 369 (1935).
6. M. Tomita, K. Ito, and H. Yamaguchi, Chem. Pharm. Bull., 3, 449 (1955).
7. Chem. Fabr. Schering, D.R.P. 82,816; Frdl., 4, 1283.
8. M. S. Newman and R. F. Beal, J. Amer. Chem. Soc., 72, 5163 (1950).