3. **Yasuo Inubushi:** Studies on the Alkaloids of Menispermaceous Plants. CXV. On the Structure of Biscoclaurine Alkaloids. (17). Cleavage of Trilobine by Metallic Sodium in Liquid Ammonia.*

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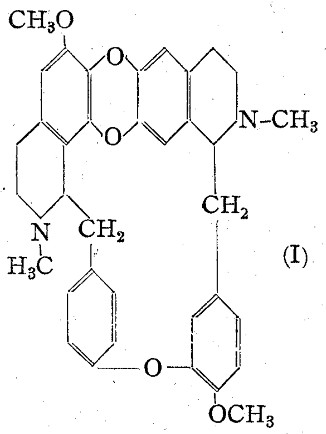
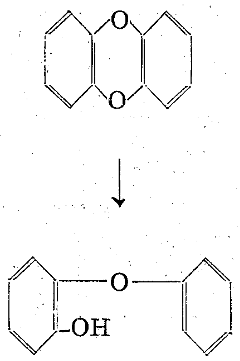
Several years ago, M. Tomita and Fujita¹⁾ carried out a series of cleavage reactions upon several bases of the oxyacanthine-berbamine and the cycleanine series by metallic sodium in liquid ammonia, and, as a result of examining the coclaurine type bisected bases thereby obtained, determined the chemical constitution of the original bases. Also, M. Tomita and Inubushi²⁾ demonstrated that in this reaction, when any phenolic hydroxyl group was present in the position *ortho* to that of ethereal oxygen linkage forming diphenyl ether, the ethereal oxygen linkage could not be bisected owing to the hindrance of its phenolic hydroxyl group. For example, when diphenylene dioxide (II) constituting the fundamental skeleton of the trilobine-isotrilobine type of bases (I) was subjected to the same mode of degradation, 2-hydroxydiphenyl ether (III) was formed and the reaction did not proceed any further. The same investigation further clarified that the biscoclaurine type of bases possessing phenolic hydroxyl group, such as berbamine³⁾, etc., could be bisected successfully by the two stages of this cleavage reaction.



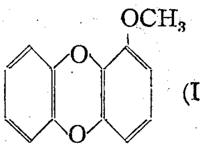
(I)



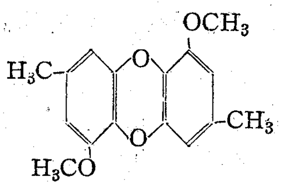
(II)

(III)

At that time, the author applied, as fundamental experiments, the same reactions to some of the diphenylene dioxide derivatives, including 1-methoxydiphenylene dioxide (IV) and 1,5-dimethoxy-3,7-dimethyldiphenylene dioxide (V), and subsequently, to trilobine, but without favorable results.



(IV)



(V)

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*) Masao Tomita: Studies on the Alkaloids of Menispermaceous Plants. CXV.

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

1) M. Tomita, E. Fujita, F. Murai: J. Pharm. Soc. Japan, 71, 226, 301, 1035, 1039 (1951); M. Tomita, E. Fujita: *Ibid.*, 72, 213, 217, 1232 (1952); This Bulletin, 1, 101 (1953); M. Tomita: "Fortschr. Chem. org. Naturstoffe," 9, 175 (1952).

2) M. Tomita, Y. Inubushi, H. Niwa: J. Pharm. Soc. Japan, 72, 206 (1952).

3) M. Tomita, Y. Inubushi: *Ibid.*, 72, 220 (1952).

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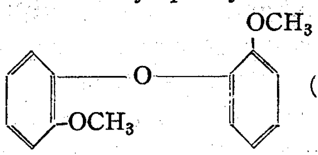
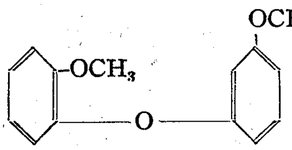
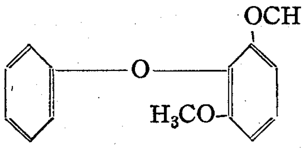
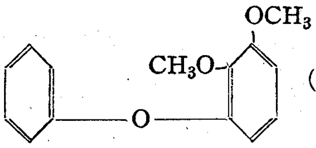
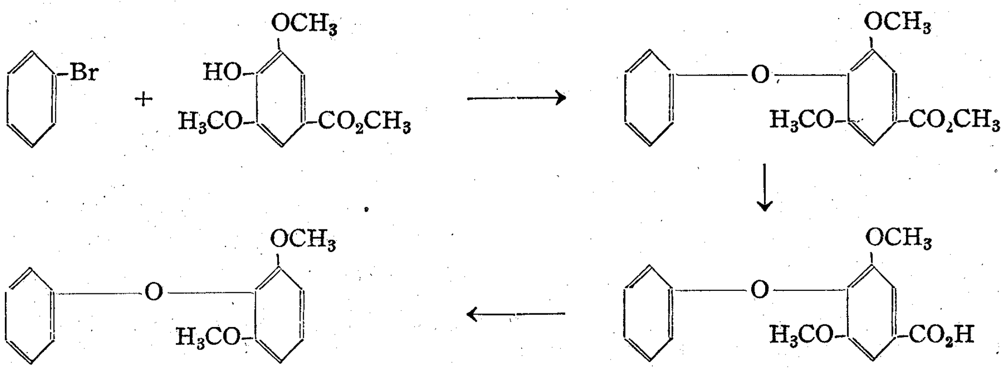
1-Methoxydiphenylene dioxide (IV), when allowed to react with metallic sodium in liquid ammonia by the same procedure as described in the experimental section, yielded a phenolic product which crystallized in the form of colorless pillars, m.p. 132°. The analytical values correspond to $C_{13}H_{12}O_3$, the composition of monomethoxymonohydroxydiphenyl ether. This substance gave a negative test for diphenylene dioxide group with sulfuric-nitric acid reagent. Methylation of this substance with diazomethane gave a methyl ether which crystallized in the form of pillars, m.p. 112°.

Every conceivable hydroxydiphenyl ether derivatives which can be formed by the cleavage of 1-methoxydiphenylene dioxide (IV), after methylation with diazomethane, is expected to accord with any one of the four kinds of the dimethoxydiphenyl ether derivatives (VI to IX), shown in Table I but the above methyl ether, m.p. 112°, obtained by this reaction was not identical with any of them.

TABLE I.

Dimethoxydiphenyl ether	m.p.	Source
 (VI)	78°	Tomita[4]
 (VII)	54°[5] 51~52°[6]	Keimatsu[5] Noyce, *et al.*[6]
 (VIII)	106~107°	
 (IX)	oil	

Of these compounds, (VIII) and (IX), which have not hitherto been reported in literature, were prepared by the following route.


(VIII)

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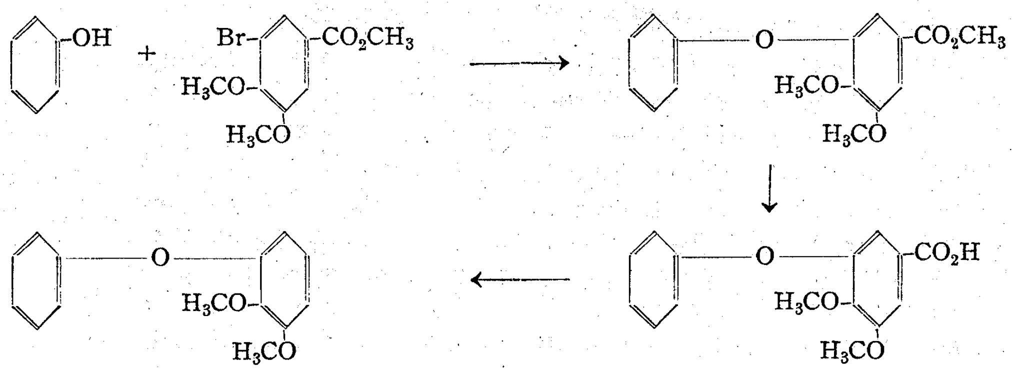
4) M. Tomita: J. Pharm. Soc. Japan, 53, 775 (1933).
5) I. Keimatsu: *Ibid.*, 56, 682 (1936).
6) S. Noyce, W. Weldon: J. Am. Chem. Soc. 74, 5146 (1952).

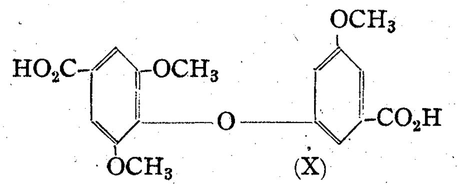
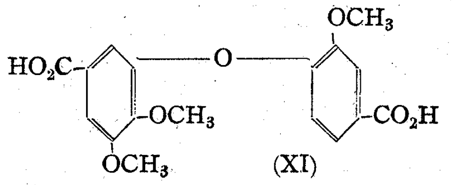


(IX)

Subsequently, 1,5-dimethoxy-3,7-dimethyldiphenylene dioxide (V) was submitted to the same mode of reaction and furnished a phenolic product which crystallized in the form of colorless needles, m.p. 188°. This substance gave a negative reaction for diphenylene dioxide group with sulfuric-nitric acid reagent. The analytical values correspond to $C_{16}H_{18}O_4$, the composition of monohydroxydimethoxydimethyldiphenyl ether. This, on methylation with diazomethane followed by oxidation with potassium permanganate, afforded a crystalline acid, m.p. 315~320° (decomp.). Its methyl ester forms clusters of rhombs, m.p. 209~211°.

Every possible hydroxydiphenyl ether derivatives which may reasonably be produced by the cleavage of 1,5-dimethoxy-3,7-dimethyldiphenylene dioxide (V), is to be expected, by methylation followed by oxidation, to conform to any of two kinds of diphenyl ether derivatives (X and XI) given in Table II, but the above acid, m.p. 315~320°, and its methyl ester, m.p. 209~211°, were not identical with any of them.

TABLE II.

Trimethoxydiphenyl ether dicarboxylic acid	Acid, m.p.	Dimethyl ester, m.p.
 (X)	283~284°[7]	114.5~116°[7]
 (XI)	243°[8] 250~251°[9]	108.5~110°[7]

In the case of trilobine (I), when allowed to react with metallic sodium in liquid ammonia, it was bisected mostly into a phenolic base. After ethylation with diazoethane, this was subjected to the second stage of the cleavage reaction, but the cleavage hardly proceeded, only yielding a small amount of needle crystals, m.p. 173~175°.

It seems hardly likely that as a result of the cleavage reactions of methoxydiphenylene dioxide derivatives, constituting the fundamental skeleton of trilobine (I), the

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[7] Y. Inubushi, T. Amano: J. Pharm. Soc. Japan, 72, 1459 (1952).

[8] H. Kondo, M. Satomi, T. Ikeda: Ann. Repts. ITSUU Lab. Japan, 2, 13 (1951).

[9] W. M. Whaley, L. Starker, M. Meadow: J. Org. Chem., 18, 833 (1953).

original substance was bisected into two benzene derivatives by its two ether linkages both undergoing scission, considering from the physical constants, such as melting point, boiling point, etc., of the products obtained. It seems incorrect to consider that they are, such products, whose benzene nuclei underwent hydrogenation instead of scission, since their analytical values correspond perfectly to the compositions of the hydroxydiphenyl ether derivatives at first expected. This reaction must have followed some abnormal, complicated process or other. Concerning this cleavage reaction of the trilobine-isotrilobine type of bases and diphenylene dioxide derivatives, a further research is needed.

The author gratefully acknowledges Prof. Dr. M. Tomita for his continued guidance during the course of this study. The author is also grateful to the Ministry of Education for a Grant from the Scientific Research Fund.

Experimental[10]

(1) **Cleavage Reaction of 1-Methoxydiphenylene Dioxide (IV) by Metallic Sodium in Liquid Ammonia**—To a well-stirred 200 cc. of liquid ammonia, chilled to between −60° to −65°, were added dropwise a solution of 0.5 g. of the substance (IV) in 50 cc. of ether, and simultaneously metallic sodium in small portions, until the blue color of the reaction mixture persisted for 20 minutes. The quantity of metallic sodium required was 0.3 g. After the completion of the reaction, the content was allowed to stand overnight to volatilize ammonia. The residue was treated with 50 cc. of water and extracted with ether. The water layer was acidified with sulfuric acid and the depositing white precipitate was taken up in ether. The ether extract was dried over anhydrous sodium sulfate and the solvent removed, leaving 0.4 g. of phenolic brownish oil. Distillation of this oil gave 0.3 g. of the fraction with b.p$_{0.5}$ 128°. On addition of petroleum ether to the above fraction and on standing, it crystallized; m.p. 132°. It gave a dark brownish color with ferric chloride, and the test for diphenylene dioxide nucleus with sulfuric-nitric acid was negative. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.22; H, 5.55. Found: C, 72.32; H, 5.80. Subsequently, the crystals, m.p. 132°, were methylated with diazomethane in the usual manner and gave an oil which distilled at b.p$_{0.9}$ 160∼170° (bath temp.). On addition of petroleum ether to this and on standing, it solidified and gave a crystalline methyl ether, m.p. 112°.

(2) **2,6-Dimethoxydiphenyl Ether (VIII)**—This compound was prepared by the Ullmann method. A mixture of 1.4 g. of methyl 4-hydroxy-3,5-dimethoxybenzoate, 1.03 g. of bromobenzene, 0.1 g. of copper powder, and 0.1 g. of anhydrous copper acetate was heated at 210∼220° (bath temp.) for 6 hrs. After cooling, the reaction product was extracted with ether. The ether extract was washed with 5% aqueous sodium hydroxide and subsequently with water, and dried over anhydrous sodium sulfate. Removal of the ether and distillation yielded the fraction with b.p$_2$ 140∼155°. On addition of petroleum ether to this fraction, and on standing, it solidified, and after recrystallization from a mixture of ether and a small portion of petroleum ether, crystallized in the form of needles, m.p. 123∼124°. The yield of methyl 2,6-dimethoxydiphenyl ether-4-carboxylate was 0.56 g. This compound was then saponified by *N* potassium hydroxide solution, and gave 0.4 g. of 2,6-dimethoxydiphenyl ether-4-carboxylic acid crystallizing in needles, m.p. 205∼207°. This was decarboxylated by copper powder in quinoline, and the product so obtained was recrystallized from methanol, yielding 0.1 g. of rectangular pillars, m.p. 106∼107° (2,6-dimethoxydiphenyl ether (VIII)). *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.04; H, 6.08. Found: C, 72.85; H, 6.14. Admixture with the product, m.p. 112°, obtained by cleavage of the substance (IV), followed by methylation, showed a depression in the m.p. of 36°.

(3) **2,3-Dimethoxydiphenyl Ether (IX)**—The Ullmann reaction was effected with 0.3 g. of metallic potassium, 0.71 g. of phenol, 2.07 g. of methyl 5-bromoveratrate, 0.1 g. of copper powder, and 0.1 g. of anhydrous copper acetate, in the same manner as described in (2). Distillation of the reaction product yielded 0.6 g. of the fraction (a), b.p$_6$ 132° and 0.5 g. of the fraction (b), b.p$_{0.5}$ 162°. Saponification of the fraction (b) furnished 2,3-dimethoxydiphenyl ether-5-carboxylic acid as needles, m.p. 158∼160°[11]. Yield, 0.4 g. Decarboxylation of this with quinoline and copper powder led to the desired (IX) as a colorless oil, which distilled at b.p$_{0.5}$ 160∼180° (bath temp.).

(4) **Cleavage Reaction of 1,5-Dimethoxy-3,7-dimethyldiphenylene Dioxide (V) by Metallic Sodium in Liquid Ammonia**—Following the same procedure as described in (1), 0.54 g. of the substance (V) was allowed to react with 1.0 g. of metallic sodium in liquid ammonia.

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[10] All melting points are uncorrected. The author's thanks are due to Messrs. Hozumi and Imaeda for carrying out the microanalyses.

[11] F. Faltis, H. Dieterich: Ber., 67, 237 (1934).

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After the completing of the reaction, the phenolic portion furnished 0.3 g. of needle-shaped crystals, m.p. 188°, which could be recrystallized from ether. This substance gave a negative test for diphenylene dioxide nucleus with sulfuric-nitric acid. *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.77; H, 6.56. Found: C, 70.69; H, 6.05.

Subsequently, this substance was methylated with diazomethane by the usual method and afforded 0.15 g. of slightly yellowish oil, which was suspended in 60 cc. of water and oxidized with 1.4 g. of potassium permanganate. The reaction mixture was filtered from manganese dioxide, made acid with hydrochloric acid, and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and the solvent removed. The residue was induced to crystallize by adding methanol. Recrystallization from aqueous methanol gave 0.01 g. of an acid, m.p. 315~320° (decomp.). Methylation of the acid, m.p. 315~320°, with diazomethane yielded methyl ether, m.p. 209~211°, which crystallized in the form of rhombs.

(5) **Cleavage Reaction of Trilobine (I) by Metallic Sodium in Liquid Ammonia**—To 300 cc. of liquid ammonia was added dropwise with stirring a solution of 1.2 g. of trilobine in 50 cc. of toluene, followed by 0.5 g. of metallic sodium in small portions. Then, a cleavage recation took place, and after the reaction, ammonia was allowed to volatilize by standing. Subsequently, water was added to the remainder and toluene layer separated from water layer. The former layer was shaken several times with aqueous sodium hydroxide, and the aqueous alkaline solution so obatined was combined with the above water layer. The combined aqueous solution was then acidified by sulfuric acid, washed with ether, and the ether layer discarded. The aqueous layer was made alkaline by ammonia and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and the solvent distilled off, leaving 1.2 g. of amorphous powder. This was ethylated with diazoethene prepared from nitrosoethylurethane and gave 1.1 g. of amorphous non-phenolic product. This ethylated product was submitted to the second stage of the same mode of cleavage reaction, but it required very little amount of metallic sodium. After the completion of the reaction, the phenolic portion was extracted with chloroform, and dried over anhydrous potassium carbonate. Removal of the solvent yielded minute amount of needles, m.p. 173~175°.

Summary

A series of cleavage reactions was carried out on 1-methoxydiphenylene dioxide (IV), 1,5-dimethoxy-3,7-dimethyldiphenylene dioxide (V), and trilobine (I) by metallic sodium in liquid ammonia, as the result of which no such bisected product as considered from the result obtained by the same mode of reaction being applied to diphenylene dioxide itself, was obtained. It is suggested, therefore, that the reactions in the former case must have followed some complicated process or other, differing from that in the latter case.

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