However, if one selects a larger D and consequently a steeper slope, the more difficult the comparison will be. In comparing the slopes, the sensibility of high frequency titrator must be maintained constant throughout all titrations.

The authors are indebted to Prof. M. Ishidate of the University of Tokyo and Prof. K. Takiura of the University of Osaka for valuable suggestions and encouragements. The authors also wish to thank Messrs. K. Kawaguchi, K. Koizumi, I. Nakagawa, and Y. Tamura for gifts of samples of some of the acids used in the present series of experiments.

Summary

A new simple estimation method of the distance r between the two carboxyl groups of a dicarboxylic acid by high frequency titration in nonaqueous medium is described. This method is based on the Coulomb's force between the two groups. In spite of its being very simple, relatively good results were obtained.

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88. Masao Tomita, Kazuo Itō, and Hideo Yamaguchi: Studies on the Alkaloids of Menispermaceous Plants. CXXX.[1] Synthesis of O-Methyldauricine by Ullmann Reaction.

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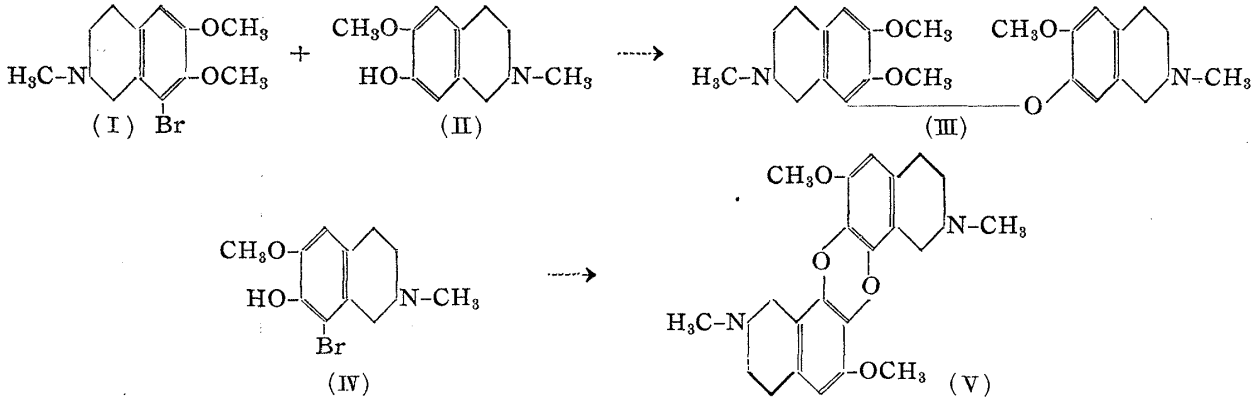
One of the authors, Tomita,[2] had previously performed some preliminary experiments with the intention of synthesizing the biscoclaurine alkaloids. Among his projected syntheses was included the Ullmann reaction of 6,7-dimethoxy-8-bromo-N-methyl-1,2,3,4-tetrahydroisoquinoline (I) and 6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (corypalline) (II). In this reaction, however, debromination of (I) occurred as a side reaction, only to yield 6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (O-methylcorypalline), and no trace of the desired product (III) was found. A similar attempt to synthesize the diphenylene dioxide derivative (V) by the condensation of two molecules of 8-bromocorypalline (IV) by the Ullmann method was also found unsuccessful, since debromination of (IV) occurred, merely yielding corypalline (II) and O-methylcorypalline. The observation during these experiments was that the bromine at 8-position of the

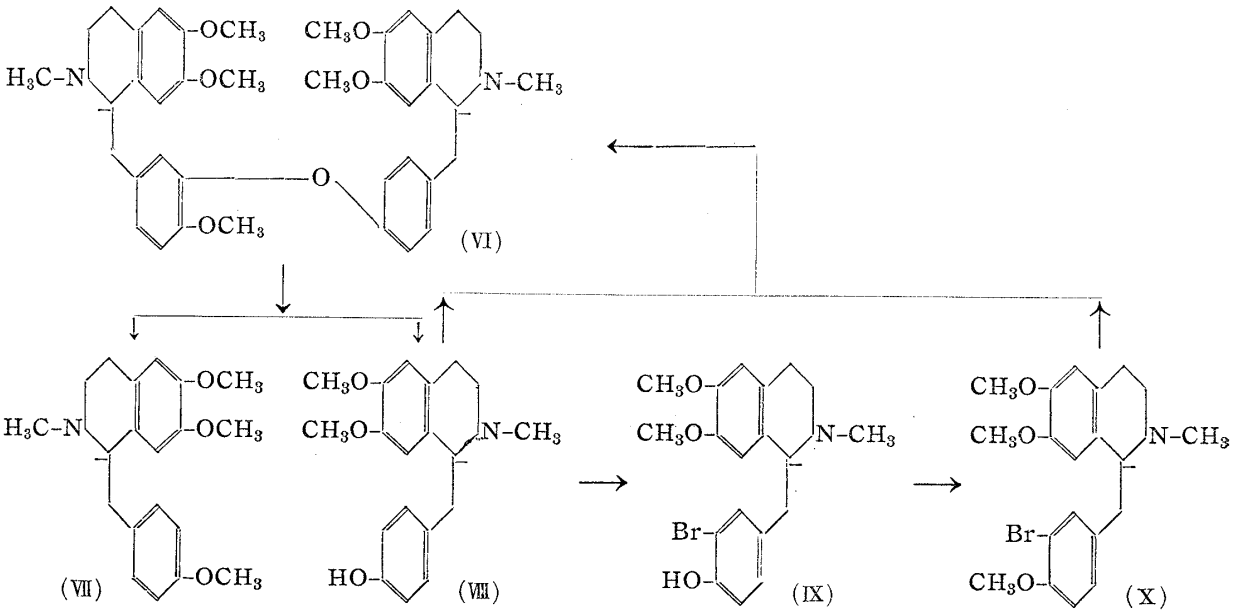


* Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 伊藤一男, 山口秀夫).

1) Part CXXIX. H. Kondo, K. Takeda: Ann. Rept. ITSUU Lab. (Tokyo), **6**, 34(1955).
2) M. Tomita, H. Watanabe: J. Pharm. Soc. Japan, **58**, 783(1938).

tetrahydroisoquinoline ring tends to separate unfavorably readily in the Ullmann reaction.

The work reported here is concerned with the initial step in projected syntheses of the biscoclaurine alkaloids from the tetrahydroisoquinoline units possessing a brominated benzyl residue, and this paper describes the synthesis of O-methyldauricine.



As the starting material for this synthesis, one of the bisected bases obtained by the fission[3] of the O-methyl compound (VI) of natural dauricine with sodium in liquid ammonia, viz., *l*-1-(4′-hydroxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (*l*-armepavine) (VIII) was used. The action of one mole of bromine upon *l*-armepavine (VIII) gave rise to the monobromo derivative. This substance was difficult to crystallize, but gave a well-crystallizing oxalate forming colorless needles, m.p. 197~198°(decomp.). The proof that the bromination took place in the position adjacent to the phenolic hydroxyl group was not provided in this case, but considering the fact that, as shown later, the objective O-methyldauricine could be derived from this substance, it is certain that it corresponds to *l*-1-(3′-bromo-4′-hydroxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (IX). On subsequent methylation with diazomethane, (IX) furnished the O-methyl ether (X) which, because of difficulty of crystallization, was characterized as the oxalate forming colorless needles, m.p. 166~167°(decomp.).

The condensation of *l*-O-methyl ether (X) with *l*-armepavine (VIII) was effected by the Ullmann reaction as described in the experimental section. The treatment of the reaction product yielded a mixture of non-phenolic bases showing a feeble halogen reaction, which in spite of various attempts, could not be induced to crystallize. In order to confirm whether or not any desired product was formed, this amorphous mixture was submitted to paper chromatography. The Rf values of the chromatograms obtained revealed that the objective O-methyldauricine (VI) was present together with small amounts of 3′-bromo-O-methylarmepavine (X) and *l*-O-methylarmepavine (VII), a debromination product of (X).

Since the literature also records the difficulty of crystallization of free O-methyldauricine, it was attempted to identify it as the dimethiodide. The mixture of

3) Y. Inubushi, H. Niwa : J. Pharm. Soc. Japan, **72**, 762(1952).

non-phenolic bases obtained by the Ullmann reaction was treated with methyl iodide, and the resulting crystalline dimethiodide was purified by chromatography using alumina, whereby it was obtained as beautiful crystals, though in a poor yield. H. Kondo and Narita first described O-methyldauricine dimethiodide as a slightly yellowish powder, decomposing at 181°,[4] but they later corrected it as hexahedral pillars, m. p. 152°(decomp.),[5] $[\alpha]_D^{22}$: −80.1°(acetone). However, when we derived it from dauricine, it showed the same m.p. as reported in their former paper.[4]

The data of synthetic O-methyldauricine dimethiodide agree closly with those of the O-methyl-dimethiodide derived from natural dauricine, as shown in Table I.

Table I.

	O-Methyldauricine dimethiodide	
	Natural	Synthetic
m.p.(decomp.)°C	181~182	181~182
Crystal form	Colorless plates	Colorless plates
$[\alpha]_D$(in MeOH)	−142.9°(29°)	−151.4°(30°)

Their infrared spectra are given in Fig. 1.

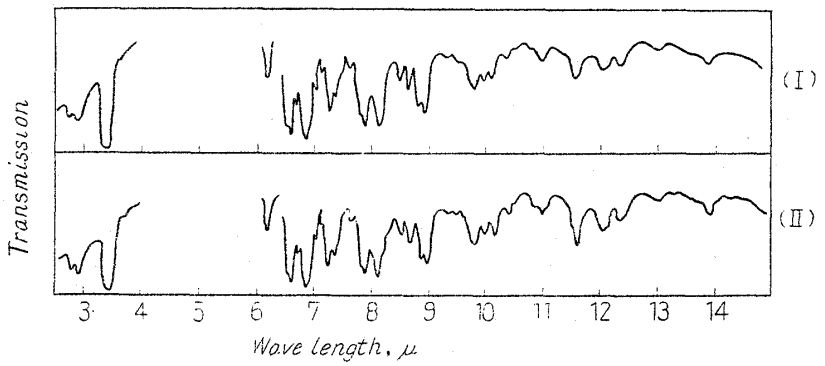


Fig. 1. O-Methyldauricine Dimethiodide
(I) Synthetic, m.p. 181~182°(decomp.)
(II) Natural, m.p. 181~182°(decomp.)
Perkin-Elmer Model 12-C (NaCl prism), Nujol mull.

The synthesis of optically active O-methyldauricine is the first successful instance of the optically active biscoclaurine alkaloids synthesized by the Ullmann reaction.

The cost of this work was supported partly by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which we are indebted. Our thanks are also offered to Messrs. Matsui and Narisada of the Research Laboratory, Shionogi & Co., Ltd. for the infrared determinations, and to Messrs. Kikuchi, Ishii, and Fujitani for their cooperation in the preparation of dauricine.

Experimental[6]

8-Bromocorypalline (IV)—To 5.4 g. of 10% (w/w) CS_2 solution of Br_2 at room temp. was added dropwise with stirring a suspension of 0.5 g. of corypalline in 30 cc. of CS_2. After completion of the addition the mixture was heated on a water bath at 50° for some time. The cooled mixture was treated with a small amount of aq. $NaHSO_3$ to decompose the excess Br_2, and the solvent distilled off. The residue was dissolved in water, washed with ether, made alkaline with Na_2CO_3, and extracted with ether. The ether extract was dried over anhyd. K_2CO_3, and

4) H. Kondo, Z. Narita : J. Pharm. Soc. Japan, 47, 279(1927).
5) H. Kondo, Z. Narita : *Ibid.*, 49, 688(1929).
6) All melting points are uncorrected. We are indebted to Mr. K. Hozumi and the members of the Central Analysis Room of this Institute for microanalytical data.

the ether evaporated, leaving 0.45 g. of the crude crystals. The aq. layer after the ether extraction was saturated with NaCl and again extracted with ether. Similar treatment of the ether extract furnished an additional amount of 0.04 g. of the crystals. Overall yield, 0.49 g. (69.4%). By recrystallization from EtOH they showed m.p. 189~190°.

Ullmann Reaction of 8-Bromocorypalline (IV)—(a) At a Lower Temperature: 0.1 g. of 8-bromocorypalline was dissolved in a solution of 0.015 g. of potassium in abs. MeOH, and the solution was evaporated to dryness *in vacuo* below 40°. The residue was mixed well with 0.01 g. of Cu powder, and the mixture was heated at 190° (bath temp.) for 3 hrs. After cooling the content was dissolved in 5% HCl and the Cu powder filtered off. The filtrate, after being washed with ether, was made alkaline with aq. NaOH and extracted with ether. The ether extract was dried over anhyd. K_2CO_3 and the ether removed, yielding no trace of the desired product. Subsequent extraction with benzene and $CHCl_3$ also gave no product. On the other hand, the alkaline aq. layer after extraction by the above solvents was acidified with HCl, then basified with Na_2CO_3, and extracted with ether. The ether extract was dried over anhyd. K_2CO_3, and the ether removed. After recrystallization of the residue from EtOH, 0.05 g. of the unreacted material, m.p. 189~190°, was recovered.

(b) At a Higher Temperature: (i) The potassium salt of (IV) was prepared as above from 0.2 g. of 8-bromocorypalline and 0.03 g. of K. It was mixed well with 0.02 g. of Cu powder, and the mixture was gradually heated in an oil bath. As soon as the temperature (oil bath temp.) reached 210°, vigorous reaction took place with evolution of white vapor. The mixture was kept at 210~220° (bath temp.) for 2 hrs. Then the content was extracted with 5% HCl under warming, and the soluble portion was treated accroding to the procedure described in (a). From the non-phenolic portion there was obtained a small quantity of oily product which gave negative tests for a diphenylene dioxide ring (H_2SO_4–HNO_3) and for halogen (Cu). Because of the small amount this was not examined further. From the phenolic portion, a product showing m.p. 168° after recrystallization from $CHCl_3$ and giving a negative halogen test was obtained, which was found to be identical with corypalline by mixed melting point determination.

(ii) The K salt of (IV) obtained from 1 g. of 8-bromocorypalline and 0.16 g. of potassium was treated with 0.1 g. Cu powder in the same manner as described in (i). The reaction product was extracted repeatedly with ether under warming and the ether extract was separated into phenolic and non-phenolic portions as described previously. The oily product obtained from the non-phenolic portion was dissolved in a small amount of ether, and after addition of petroleum ether the solution was allowed to stand in an ice chest, whereafter needles appeared. Upon recrystallization from ether-petroleum ether they showed m.p. 79~80°, gave negative tests for a diphenylene dioxide ring and for halogen, and were found to be identical with O-methylcorypalline.

Meanwhile, the phenolic portion, after being treated as described in (i), gave 20 mg. of corypalline. The black resinous residue left after the initial ether extraction was extracted with 5% HCl under warming, and treated as before. The non-phenolic portion yielded a very small amount of an oily product, which gave negative diphenylene dioxide and halogen reactions. This product was assumed to be identical with the product, m.p. 79~80°, obtained above, but because of the very small amount available, it was not examined further. From the phenolic portion a small amount of corypalline was recovered.

***l*-Armepavine (VIII)**—4.24 g. of O-methyldauricine (VI) obtained by methylation of dauricine with CH_2N_2 was cleaved in liquid NH_3 with Na according to that described in literature.[3] As the bisected bases, 2.10 g. of *l*-O-methylarmepavine (VII) and 2.05 g. of *l*-armepavine (VIII) were obtained. The latter, after recrsytallization from acetone-ether, formed colorless plates, m.p. 145~146°, weighing 2.0 g.

***l*-3′-Bromoarmepavine (IX)**—To a solution of 2.0 g. of *l*-armepavine (VIII) in 8 cc. of glacial HOAc at room temp. was added dropwise with stirring 10.9 g. of 10% Br_2–HOAc solution. White precipitates which immediately resulted dissolved, and, after all the Br_2 was added, stirring was continued for some time, and then the solvent removed *in vacuo*. The residue was dissolved in water, made weakly alkaline with NH_4OH, and the depositing base extracted several times with ether. The ether extracts were combined, dried over anhyd. Na_2SO_4, and the ether distilled off, yielding a pink glutinous product (*l*-3′-bromoarmepavine (IX)). This was dissolved in a small amount of EtOH and treated with the calculated amount of saturated EtOH solution of oxalic acid, yielding crystals of the oxalate. Recrystallization from MeOH afforded 2.46 g. of colorless needles, m.p. 197~198° (efferv.). *Anal.* Calcd. for $C_{19}H_{22}O_3NBr \cdot C_2H_2O_4 \cdot 1^1/_2H_2O$: C, 49.51; H, 5.30. Found: C, 49.45, 49.18; H, 4.92, 4.75. The oxalate was dissolved in a little water, made weakly alkaline with NH_4OH, and the depositing free base taken up in ether. The ether extract was dried over anhyd. Na_2SO_4 and the ether removed, leaving 2.15 g. of white glutinous base. This was difficult to crystallize and gave a positive halogen test.

***l*-3′-Bromo-O-methylarmepavine (X)**—To a solution of 2.15 g. of *l*-3′-bromoarmepavine (IX) in MeOH was added an ethereal CH_2N_2 prepared from 8 g. of nitrosomethylurea, and the mixture set aside over night. The solvent was removed, and the residue was dissolved in dil. HCl, made alkaline with NaOH, and the depositing base taken up in ether. The ether extract was washed with dil. NaOH, dried over anhyd. K_2CO_3, and the ether evaporated, leaving 1.82 g. of yellowish oily O-methyl product. This was in like manner converted into the oxalate which after recrystallization from acetone formed colorless needles, m.p. 166~167°(decomp.); yield, 1.96 g. *Anal.* Calcd. for $C_{29}H_{24}O_3NBr \cdot C_2H_2O_4$: C, 53.02; H, 5.31. Found: C, 53.03, 52.88; H, 5.37, 5.10. The free base from the oxalate was obtained as a slightly yellowish oil which was also difficult to crystallize. Yield, 1.56 g.

Ullmann Reaction of *l*-Armepavine (VIII) and *l*-3′-Bromo-O-methylarmepavine (X) (Formation of O-Methyldauricine (VI))—0.231 g. of *l*-armepavine (VIII) was dissolved by warming in a solution of 0.03 g. of K in approx. 3 cc. of anhyd. MeOH, and the solution evaporated *in vacuo* to dryness. The residue was mixed well with 0.3 g. of *l*-3′-bromo-O-methylarmepavine (X), 0.05 g. of Cu powder, and 0.03 g. of anhyd. $Cu(OAc)_2$. The mixture was heated first at 185~195° (oil bath temp.) for 2 hrs., and then at 195~200° for 1 hr. After completion of the reaction the content was extracted with 10 successive portions of ether, and the ether extracts were combined and filtered. The concentrated ether solution was washed with 2 successive portions of 3% aq. NaOH to remove the phenolic base. Treatment of the washings gave 0.056 g. of recovered *l*-armepavine oxalate (m.p. 207°(efferv.)). On the other hand, the ether layer was shaken with 3% HCl, the aq. acid layer was made alkaline with aq. NaOH, and the depositing base extracted several times with ether. The ether extract was washed once with 3% aq. NaOH, subsequently with water, and dried over anhyd. K_2CO_3. Removal of the ether left 0.27 g. of slighlty yellowish glutinous non-phenolic portion giving a positive halogen test. The mixture of non-phenolic bases thus obtained was submitted to paper chromatography as follows: Toyo Filter Paper No. 50 was used, and development was effected by the ascending technique with a mixture of BuOH (67 cc.), H_2O (27 cc.), and HOAc (10 cc.). For the detection of alkaloidal spots, the Dragendorff reagent was used along with fluorescence in the ultraviolet light. The Rf values obtained are given below.

	Rf values		
Mixture of non-phenolic bases obtained by Ullmann reaction	0.60	0.83	0.88
O-Methyldauricine (VI)	0.60		
l-O-Methylarmepavine (VII)		0.84	
l-3′-Bromo-O-methylarmepavine (X)			0.87

The chromatograms revealed that the fraction of non-phenolic bases contained mainly the desired O-methyldauricine (VI), accompanied by a small amount of unreacted materials, *l*-O-methylarmepavine (VII) and *l*-3′-bromo-O-methylarmepavine (X).

In order to characterize the objective product, the above non-phenolic portion was treated with MeI in MeOH, when the methiodide was obtained as an orange red oil. This was chromatographed[7] on alumina using a 1 : 5 mixture of MeOH and acetone as a solvent, whereby the methiodide was isolated as white crystals. Recrystallization from EtOH yielded 18 mg. of colorless plates, m.p. 181~182°(decomp.)(sint. at 178°), undpressed on admixture with O-methyldauricine dimethiodide (m.p. 181~182°(decomp.)) prepared from natural dauricine. They also gave identical infrared spectra. $[\alpha]_D^{29}$: -142.9°(in MeOH, l=0.5 dm., c=0.5035). *Anal.* Calcd. for $C_{39}H_{46}O_6N_2 \cdot 2CH_3I \cdot 2^1/_2H_2O$: C, 50.80; H, 5.89. Found: C, 50.47; H, 6.02.

O-Methyldauricine Dimethiodide—0.15 g. of O-methyldauricine obtained by methylation of natural dauricine was treated with MeI by the usual method. The product obtained was purified by chromatography in the same manner as previously described, whereby O-methyldauricine dimethiodide was obtained as colorless plates, which after recrystallization from EtOH showed m.p. 181~182°(decomp.). Yield, 0.11 g. $[\alpha]_D^{30}$: −151.4°(in MeOH, l=0.5 dm., c=0.4754). *Anal.* Calcd. for $C_{39}H_{46}O_6N_2 \cdot 2CH_3I \cdot 2^1/_2H_2O$: C, 50.80; H, 5.89. Found: C, 50.30; H, 6.11.

Summary

O-Methyldauricine (VI) was synthesized by the Ullmann reaction of *l*-armepavine (VIII) and *l*-3′-bromo-O-methylarmepavine (X). It was characterized as the dimethiodide, which was confirmed to be identical with that of natural dauricine.

(Received September 7, 1955)

7) The chromatography was effected by the procedure described by J. D. Dutcher in J. Am. Chem. Soc., **74**, 2225(1952).