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13. Bisbenzylisoquinoline Alkaloids and Related Compounds. VI.*3 A Modified Total Synthesis of the Stereoisomeric Mixture of Dauricine.*4

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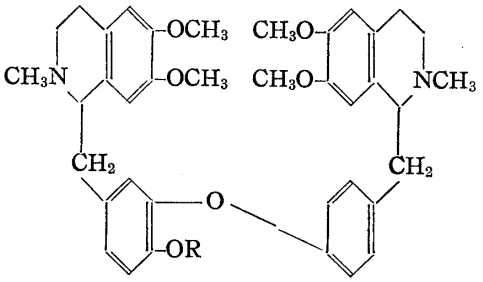
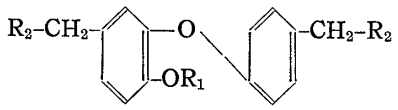
A total synthesis of racemic dauricine has already been described,[1,2] confirming Kondo's structure (I) for the alkaloid. Tomita, *et al.*[3] also reported the synthesis of O-methyldauricine (II).

The purpose of the present investigation was to study an alternative synthesis of the diamide (X) in order to obtain the corresponding dihydroisoquinoline (XI) and its methiodide (XII) as possible intermediates for the synthesis of stereoisomeric mixture of O-benzyldauricine (III), and to investigate the Ullmann reaction of (±)-armepavine (XIII) with 1-(4-benzyloxy-3-bromobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIV) for the synthesis of III, leading eventually to a total synthesis of the stereoisomeric mixture of dauricine (I).[1,2]

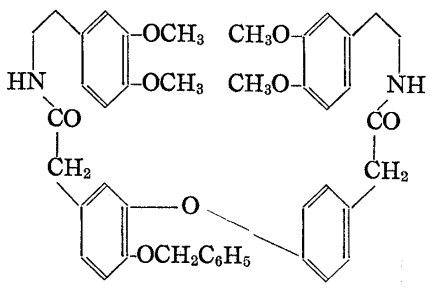


I : R=H
II : R=CH_3
III : R=$CH_2C_6H_5$

Demethylation of the diacid[4] (IV) gave the hydroxy compound (V), which was converted into diethyl 4-hydroxy-3,4′-oxydiphenyldiacetate (VI) by esterification. Hydrolysis of the compound (VIIa), which was obtained by benzylation of VI, yielded the diacid (VIII). Schotten-Baumann reaction of 3,4-dimethoxyphenethylamine with the acid chloride (IX) afforded the diamide (X) as a colorless amorphous powder. This compound (X) was also obtained by fusion of 3,4-dimethoxyphenethylamine with dimethyl 4-benzyloxy-3,4′-oxydiphenyldiacetate (VIIb).



IV : R_1=CH_3; R_2=CO_2H
V : R_1=H; R_2=CO_2H
VI : R_1=H; R_2=$CO_2C_2H_5$
VIIa : R_1=$CH_2C_6H_5$; R_2=$CO_2C_2H_5$
VIIb : R_1=$CH_2C_6H_5$; R_2=CO_2CH_3
VIII : R_1=$CH_2C_6H_5$; R_2=CO_2H
IX : R_1=$CH_2C_6H_5$; R_2=COCl



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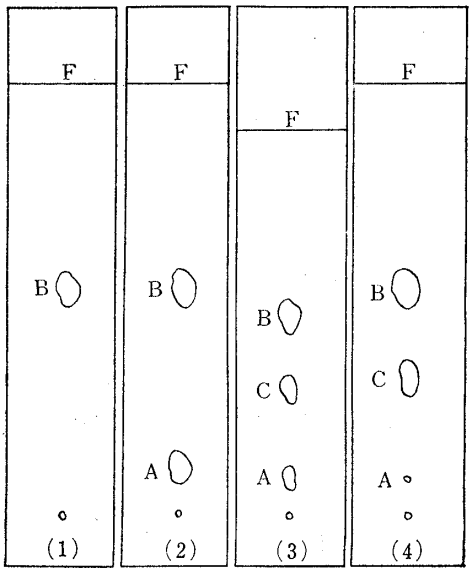
*3 Part V. T. Kametani, S. Takano, K. Masuko, F. Sasaki : This Bulletin, **14**, 67 (1966).
*4 This forms part CXXXIII of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.

1) T. Kametani, K. Fukumoto : Tetrahedron Letters, **1964**, 2771.
2) *Idem* : J. Chem. Soc., **1964**, 6141.
3) M. Tomita, K. Ito, H. Yamaguchi : This Bulletin, **3**, 449 (1955).
4) H. Kondo, H. Kataoka, G. Ito, K. Nagasawa, S. Iketomo: Ann. Rept. ITSUU Lab. (Tokyo), **1**, 15 (1950).



A : (±)-Armepavine (XIII).
Rf=0.082~0.101
B : 1-(3-Bromo-4-benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIV).
Rf=0.494~0.513
C : O-Benzyldauricine (III).
Rf=0.297~0.328
F : The line of the liquid front
1 : Pure compd. (XIV)
2 : Reaction time : 0 hr.
3 : " : 5 hr.
4 : " : 15 hr.

Fig. 1. Thin-layer Chromatography of the Products during the Ullmann Reaction

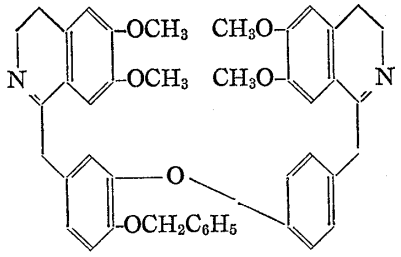
Silica gel B. (Wako) activated at 120° for 2 hr. (0.25 mm.) and chloroform-methanol (5:4) as solvent were used at 21.5°; and the spots were detected by their fluorescence under UV light and by vapor iodine.

Bischler-Napieralski cyclization of the above diamide (X) with phosphoryl chloride in benzene afforded the dihydroisoquinoline derivative (XI), which was converted into the dimethiodide (XII). Reduction of XII with sodium borohydride afforded O-benzyldauricine (III). Repeated alumina-chromatography resulted in formation of an oily syrup, whose distyphnate was identical with an authentic sample.[2]

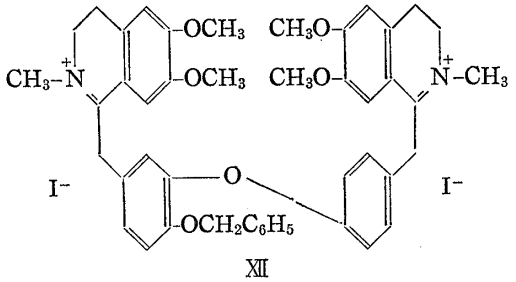
Furthermore, the Ullmann reaction between 1-(4-hydroxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIII)[5] ((±)-armepavine) and 1-(3-bromo-4-benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline*3 (XVI) afforded the mixture including O-benzyldauricine (III), whose alumina-chromatography and thin-layer chromatography gave the same compound (III) mentioned above. Both specimens were found to be identical with infrared spectrum and paper chromatography.

With regards to the synthesis of the compound[5] (XIII), a modified synthesis was carried out, to give the amide (XV) in better yield by heating a mixture of 3,4-dimethoxyphenethylamine and methyl 4-benzyloxyphenylacetate. Furthermore, Bischler-Napieralski reaction of XV under mild conditions gave the dihydroisoquinoline derivative (XVI) in an excellent yield. Reduction of the methiodide (XVII) with sodium borohydride, followed by hydrolysis of XVIII with concentrated hydrochloric acid, gave (±)-armepavine (XIII).

Since conversion of III into the synthetic dauricine (I) with hydrochloric acid had already



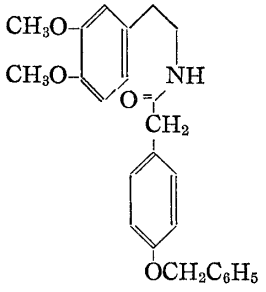
XI



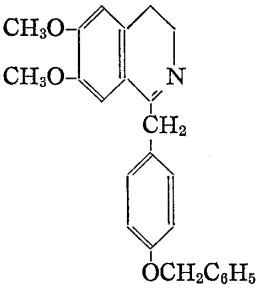
XII

been achieved in a previous paper,[2] an alternative synthesis of I was completed. Since the synthetic dauricine (I) showed the infrared and ultraviolet spectra superimposable on those of natural dauricine and behaved similarly on paper and thin-layer chromatography, it was taken for as racemic base.[1,2] However nuclear magnetic resonance spectra of both specimen do not agree as shown in Fig. 2. Therefore,

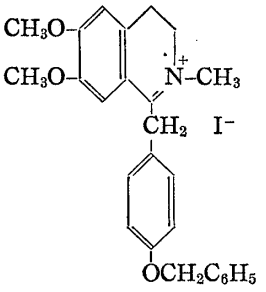
5) M. Tomita, H. Yamaguchi : This Bulletin, **1**, 10 (1953).



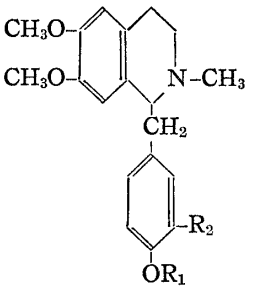
XV



XVI



XVII



XIII : $R_1=R_2=H$
XIV : $R_1=CH_2C_6H_5$; $R_2=Br$
XVIII : $R_1=CH_2C_6H_5$; $R_2=H$

we came to the revised conclusion that synthetic dauricine must be a diastereoisomeric mixture, on which point Fujitani, *et al.*[6] recently reported.

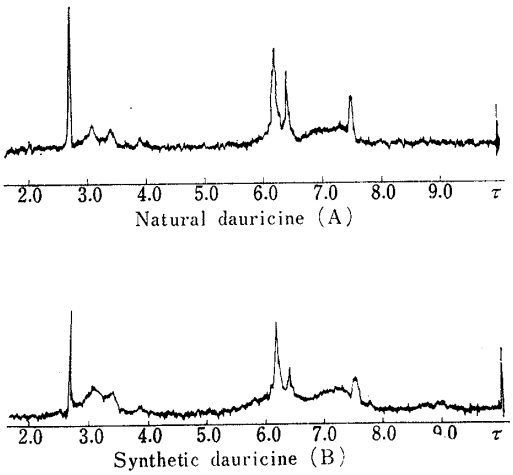


Fig. 2. Nuclear Magnetic Resonance Spectra of Natural Dauricine (A) and Synthetic Dauricine (B) at 60 mc. in Deuterochloroform

Experimental*5

4-Hydroxy-3,4′-oxydiphenyldiacetic Acid (V)——A mixture of 3 g. of 4-methoxy-3,4′-oxydiphenyldiacetic acid[7] (IV) (m.p. 174~176°), 25 ml. of AcOH and 25 ml. of 48% of HBr was refluxed for 7 hr., and the solvent was removed by distillation *in vacuo* to give a black resinous substance. Recrystallization of the residue from hot H_2O gave 1.5 g. of the hydroxy compound (V) as colorless needles, m.p. 166~167°. *Anal.* Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found : C, 63.60; H, 4.48.

4-Benzyloxy-3,4′-oxydiphenyldiacetic Acid (VIII)——a) HCl gas was introduced into a solution of 1 g. of the preceding acid (V) in 10 ml. of dry EtOH, and the mixture was refluxed on a water-bath for 7 hr., and distilled *in vacuo*. To the residue was added 20 ml. of H_2O, and an oily substance separated was extracted with ether. The solvent was washed with 5% $NaHCO_3$ and saturated NaCl solution, and dried on Na_2SO_4. Removal of the solvent gave 0.7 g. of the ester (VI) as a pale yellow oil.

b) To 0.7 g. of the above ester (VI) in EtOH was added a mixture of 0.3 g. of benzyl chloride and 0.4 g. of K_2CO_3, and the mixture was refluxed on a water-bath for 7 hr. A hot solution was, while warm, filtered and an inorganic substance was washed with hot EtOH. The above mother liquor was admixed with the washing. Removal of the solvent gave 1.3 g. of a pale brown oil (VIIa), which solidified on being allowed to stand. Recrystallization of the residue from EtOH gave the benzyl-derivative (VIIa) as colorless needles, m.p. 55~57.5°. *Anal.* Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29. Found : C, 72.04; H, 6.64.

c) A mixture of 10 ml. of 15% NaOH and 10 ml. of EtOH was added to the preceding ester (VIIa). The mixture was refluxed on a water-bath for 5 hr., and distilled. The residue was taken up in H_2O, filtered, and neutralized with 10% HCl. The colorless precipitate which separated was recrystallized from dilute MeOH to afford the acid (VIII) (0.8 g.) as a colorless powder, m.p. 141~144°. *Anal.* Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found : C, 70.14; H, 5.38.

Dimethyl 2-Benzyloxy-3,4′-oxydiphenyldiacetate (VIIb)——To the ethereal solution of diazomethane [prepared from 14 g. of N-methyl-N-nitroso-*p*-toluenesulfonamide, 10 g. of KOH, 16 ml. of H_2O, and 50 ml. of MeOH] was added to a solution of 3 g. of the above acid (VIII) in 300 ml. of MeOH on cooling, and the mixture was set aside overnight in a refrigerator for 3 days. Removal of the solvent gave a viscous oil, which was dissolved in ether. The solvent was washed with 5% NaOH and water, dried

*5 Infrared and nuclear magnetic resonance spectra were measured on a Type EPI-2 Hitachi infrared spectrophotometer and Varian A-60 Spectrometer in deuterochloroform with tetramethylsilane as an internal standard, respectively. Melting points were determined on a Kofler block and uncorrected.

6) K. Fujitani, Y. Aoyagi, Y. Masaki : Yakugaku Zasshi, **84**, 1234 (1964).
7) H. Kondo, S. Uyeo : *Ibid.*, **53**, 557 (1933).

on $CaCl_2$, and distilled off, to afford 2.3 g. of the ester (Ⅶb) as colorless scales, m.p. 69~72°, which were recrystallized from dilute EtOH to give colorless needles, m.p. 71~72°. *Anal.* Calcd. for $C_{25}H_{24}O_6$: C, 71.41; H, 5.75. Found: C, 71.13; H, 5.83.

N,N'-Bis(3,4-dimethoxyphenethyl)-2,2'-(4-benzyloxy-3,4'-oxydiphenyl)bisacetamide (X)——a) Schotten-Baumann reaction. The preceding acid (Ⅷ) (1 g.) was added in small portions to 2.1 ml. (3.5 g.) of $SOCl_2$ containing 2 drops of pyridine, and the mixture was kept at 40° overnight. Removal of an excess of the reagent *in vacuo* gave pale yellow crystals (Ⅸ) which were extracted with 50 ml. of dry benzene.

The above acid chloride (Ⅸ) in benzene was added drop by drop to a cooled and stirred solution of 2 g. of 3,4-dimethoxyphenethylamine in 20 ml. of dry benzene at 0~5° during 30 min., from which a pale yellow precipitate separated. The mixture was stirred for an additional 1 hr., and after the addition of H_2O, extracted with $CHCl_3$. The extract was washed with 5% HCl, 5% KOH and H_2O, dried on K_2CO_3, and distilled off, to afford 1.9 g. of a viscous syrup, which solidified on being triturated with hexane. Filtration of the crystals yielded 1.3 g. of the diamide (X) as an amorphous powder, m.p. 79~97°. Recrystallization from MeOH-ether and then from benzene-ether gave a colorless powder, m.p. 84~86°. *Anal.* Calcd. for $C_{43}H_{46}O_8N_2$: C, 71.85; H, 6.45; N, 3.90. Found: C, 71.87; H, 6.15; N, 3.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3043 (NH), 1660 (C:O).

b) Fusion method. A mixture of 0.7 g. of the above ester (Ⅶb) and 0.6 g. of 3,4-dimethoxyphenethylamine was kept at 180° in an oil-bath for 1 hr. in a current of N_2 and then heated at 180~190° for 7 hr. On cooling, the mixture was extracted with $CHCl_3$, washed with 5% HCl, 5% NaOH and H_2O, and dried on $CaCl_2$. Removal of the solvent yielded 0.93 g. of a brown viscous syrup, and the residue was recrystallized from AcOEt-ether afforded 0.7 g. of the diamide (X) as a colorless powder, whose infrared spectrum was identical with those of the above amide obtained by the procedure (a) and an authentic sample.[2]

N-(3,4-Dimethoxyphenethyl)-2-(4-benzyloxyphenyl)acetamide (XV)——A mixture of 4.4 g. of 3,4-dimethoxyphenethylamine and 5.6 g. of methyl 4-benzyloxyphenylacetate[8] was heated in an oil-bath at 180~190° in a current of N_2 for 3 hr., an evolution of MeOH being observed. After cooling the reaction mixture which solidified was dissolved in $CHCl_3$, and the solvent was washed with 3% HCl and H_2O, dried on K_2CO_3, and distilled off, to yield 8.8 g. of a colorless solid. Recrystallization from MeOH gave the amide (XV) as colorless needles, m.p. 114~115° (lit.,[8] 116°).

1-(4-Benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (XVI)——A mixture of 9.5 g. of the above amide (XV), 50 ml. of dry toluene, and 5 ml. of $POCl_3$ was heated under reflux in a current of N_2 for 0.5 hr. The hot reaction mixture was poured into 300 ml. of petroleum ether, and an oil was soon precipitated. An upper layer was removed by decantation, and the oily residue was washed with petroleum ether repeatedly. The oil which solidified on being allowed to stand for a while was extracted with $CHCl_3$, which was poured into a large excess of 10% Na_2CO_3 solution. The solvent layer was washed with H_2O, dried on K_2CO_3, and distilled off, to give the dihydroisoquinoline (XVI) as a pale brown viscous syrup (8.8 g., 97%), which could not be obtained crystalline. This was characterized as methiodide (XVII).

Preparation of the Methiodide (XVII)——A mixture of 8.8 g. of the above dihydroisoquinoline (XVI) in 10 ml. of methyl iodide was allowed to stand at room temperature (18°) for 1 hr., giving a yellow solid to which 20 ml. of dry benzene was added.

The crystals were filtered and dried on a filter to give a pale yellow powder (XVII) (9.2 g., 76%), m.p. 199~200° (decomp.) (lit.,[9] 199°), which was a little labile on exposure in the air and too easy to become resinous during recrystallization.

1-(4-Benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVIII)——To a suspension of 9 g. of the above methiodide (XVII) in 100 ml. of MeOH was added in small portions with shaking 4 g. of sodium borohydride, giving a colorless clear solution. After the reaction, the solvent was distilled off in a current of N_2, the residue treated with H_2O, and extracted with $CHCl_3$. The solvent was washed with H_2O, dried on K_2CO_3, and distilled off, to afford a pale yellow viscous syrup (XVIII) (6.7 g., 98%), which was characterized as the perchlorate. Recrystallization from EtOH gave colorless needles, m.p. 185.5~186° (decomp.). *Anal.* Calcd. for $C_{26}H_{29}O_3N \cdot HClO_4$: C, 61.95; H, 6.00; N, 2.78. Found: C, 61.67; H, 6.00; N, 2.70.

1-(4-Hydroxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[(±)-Armepavine] (XIII)——A mixture of 5.5 g. of the above tetrahydroisoquinoline (XVIII), 25 ml. of conc. HCl, and 30 ml. of benzene was heated at 70° in a current of N_2 for 1.5 hr. After 50 ml. of water was added to the above mixture, an aqueous layer was separated from benzene, washed with benzene, and evaporated to dryness *in vacuo* in a current of N_2. The residue was basified with 10% NaOH and extracted with 50 ml. of ether. An alkaline solution was once filtered, and crystalline NH_4Cl was added in small portions to the filtrate, giving a yellow precipitate, which was extracted with $CHCl_3$. The solvent was washed with

8) P. Weiss: J. Am. Chem. Soc., **70**, 4263 (1948).
9) M. Tomita, H. Yamaguchi: This Bulletin, **1**, 10 (1953).

H_2O, dried on Na_2SO_4, and distilled off, to yield a pale brown viscous syrup, which solidified on being triturated with acetone–ether. Filtration and recrystallization from acetone–ether afforded (±)-armepavine (XIII) (3.3 g., 77%) as colorless prisms, m.p. 164~165° (lit.,[9] 165°).

Stereoisomeric Mixture of O-Benzyldauricine (III)——A mixture of 1.2 g. of (±)-armepavine (XIII), 1.6 g. of 1-(3-bromo-4-benzyloxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XIV), 715 mg. of K_2CO_3, 212 mg. of Cu powder, 72 mg. of KI, and 7.2 ml. of dry pyridine was heated, with stirring, at 150~160° in an oil-bath in a current of N_2 for 15 hr. During the reaction, the sample from the reaction mixture was taken up, and the formation of O-benzyldauricine was inspected by thin-layer chromatography, whose data were shown in Fig. 1.

A new spot (C) was identical with that of an authentic sample[2] on thin-layer chromatography (Fig. 1), and it revealed that the debrominated substance of XIV and diphenyl derivative which would be formed by bimolecular Ullmann reaction of XIV were not detected. After 15 hours' heating, the reaction mixture was treated as usual, and non-phenolic substance was collected. Namely, the reaction mixture was extracted with benzene and filtered. The solvent was washed with H_2O, dried on Na_2SO_4, and distilled off, to give a brown viscous syrup, which was chromatographed on alumina (diam., 2.5 cm.; length, 25 cm.). The first benzene eluate (4.7 L.) (F_1~F_{47} : each fraction, 100 ml.) showed positive Beilstein test, and removal of the benzene eluate (F_2~F_7) gave the compound (XIV) whose perchlorate was identified by mixed melting point and IR spectrum.

Removal of the second $CHCl_3$–benzene eluate (1:1) (F_{53}~F_{54}) (200 ml.) gave O-benzyldauricine (III) as a pale yellow viscous syrup (110 mg.), which was characterized as the styphnate. Recrystallization of the styphnate from EtOH–ether gave a yellow powder, m.p. 136~140°, whose IR spectrum was superimposable on that of an authentic sample.[2]

The above O-benzyldauricine was hydrolyzed with ethanolic HCl as described in the preceding paper[2] to give synthetic dauricine whose picrate and styphnate were identical with corresponding derivatives of the natural dauricine gifted by Prof. M. Tomita in IR spectra.

Nuclear Magnetic Resonance of Synthetic Dauricine (I)——NMR (τ) spectrum of synthetic dauricine in $CDCl_3$ showed 6.17 (singlet) and 6.39 (singlet) ($4OCH_3$, 12H), 7.48 (singlet) and 7.51 (singlet) ($2:NCH_3$, 6H) as was shown in Fig. 2. Manske's sample which was recrystallized from $CHCl_3$–hexane showed 6.19 (singlet), 6.21 (singlet) and 6.39 (singlet) ($4OCH_3$, 12H) and 7.49 (singlet) and 7.52 ($2:NCH_3$, 6H). A slight difference in the region of methoxyl signal was observed.

We thank Dr. Richard H. F. Manske, Dominion Rubber Company, Ltd., Research Laboratories (Guelph, Ontario, Canada) for a gift of natural dauricine. We are also grateful to Prof. Masao Tomita, Kyoto University for a gift of natural dauricine and Dr. Y. Murayama, President of Tokyo College of Pharmacy for his support and encouragement throughout the course of this work.

Summary

The diamide (X) was prepared from 3,4-dimethoxyphenethylamine and acid chloride (IX). This compound (X) was also obtained by condensation of dimethyl 4-benzyloxy-3,4′-oxydiphenyldiacetate (VIIb) with the above amine. Cyclization of the diamide (X), followed by the reduction of the methiodide of XI, gave the stereoisomeric mixture of O-benzyldauricine (III), which was also obtained by Ullmann reaction of XIII with XIV.

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