

1178. *Bisbenzylisoquinoline Alkaloids and Related Compounds.*
*Part IV.*¹ *A Total Synthesis of (±)-Dauricine.*²

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The diamide (IX) was prepared from the diacid chloride (VIII) and 2-(3,4-dimethoxyphenyl)ethylamine by an Arndt–Eistert reaction. Cyclisation gave the bisdihydroisoquinoline (X), the dimethiodide of which, on reduction, gave (±)-dauricine (I).

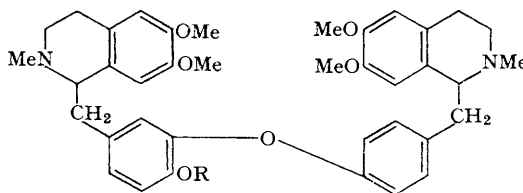
DAURICINE, C₃₈H₄₄N₂O₆, one of the alkaloids of Menispermaceous plants, was isolated from *Menispermum dauricum* DC. by Kondo and Narita³ in 1927, and also from *Menispermum*

¹ Kametani, Ro, and Iwabuchi, Part II, *J. Pharm. Soc. Japan*, in the press; Part III, *Tetrahedron Letters*, 1964, 2771.

² This forms Part CXIV of "Studies on the Syntheses of Heterocyclic Compounds" by T. Kametani.

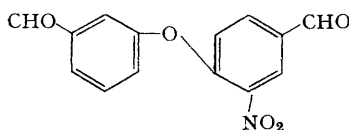
³ Kondo and Narita, *J. Pharm. Soc. Japan*, 1927, No. 542, 279.

canadense L. by Manske.⁴ The structure (I) proposed³ for dauricine was established by chemical methods^{3, 5, 6} and by a synthesis of *O*-methyldauricine methyl methine.⁷ Tomita *et al.*⁸ have synthesised *O*-methyldauricine (II) by an Ullmann reaction between (–)-armepavine and (–)-3'-bromo-*O*-methylarmepavine. In this Paper we describe a synthesis of (±)-dauricine which confirms the structure (I).

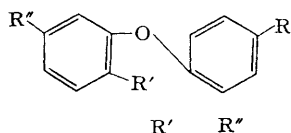


I: R = H
II: R = Me

An Ullmann reaction between isovanillin and 4-bromobenzaldehyde gave the ether (VI),⁷ demethylation of which gave the phenol (V). This was converted by benzylation into 2-benzyloxy-4',5-diformyldiphenyl ether (IV), which was also obtained by an Ullmann reaction between 4-bromobenzaldehyde and 4-benzyloxy-3-hydroxybenzaldehyde.⁹ Attempts to prepare the ether (IV) by alternative routes were unsuccessful. Thus, a Vilsmeier reaction on 2-hydroxydiphenyl ether¹⁰ did not give the expected product (V), and an Ullmann reaction between 4-benzyloxy-3-bromobenzaldehyde and 4-hydroxybenzaldehyde gave only the debromination product, 4-benzyloxybenzaldehyde. An attempt to remove the nitro-group of the ether (III), prepared by an Ullmann reaction between 4-benzyloxy-3-bromotoluene and *p*-cresol, was also unsuccessful.



(III)



(IV: OCH₂Ph CHO)
(V: OH CHO)
(VI: OMe CHO)
(VII: OCH₂Ph CO₂H)
(VIII: OCH₂Ph COCl)

Oxidation of the diphenyl ether (IV) with potassium permanganate in acetone gave the dicarboxylic acid (VII) which with thionyl chloride gave the diacid chloride (VIII). An Arndt-Eistert reaction¹¹ with the corresponding diazoketone, which was prepared in the usual manner, and 2-(3,4-dimethoxyphenyl)ethylamine afforded the diamide (IX) as an amorphous powder. Cyclization of the diamide with phosphoryl chloride in benzene afforded the bisdihydroisoquinoline (X), characterised as the distyphnate.

Reduction of the dimethiodide (XI), which could not be obtained crystalline, with zinc and hydrochloric acid in ethanol afforded crude (±)-dauricine (I) as a yellow amorphous solid. Chromatography on alumina followed by crystallisation from benzene-hexane gave

⁴ Manske, *Canad. J. Res.*, 1943, **21b**, 17.

⁵ Kondo and Narita, *J. Pharm. Soc. Japan*, 1929, **49**, 688.

⁶ Kondo and Narita, *Ber.*, 1930, **63**, 2420.

⁷ Kondo, Narita, and Uyeo, *J. Pharm. Soc. Japan*, 1935, **55**, 369.

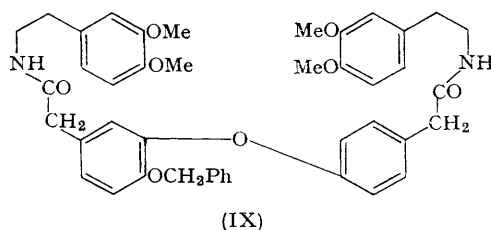
⁸ Tomita, Ito, and Yamaguchi, *Chem. and Pharm. Bull. (Japan)*, 1955, **3**, 449.

⁹ Chem. Fabr. Schering, D.R.P., 82,816; (*Frdl.*, **4**, 1283).

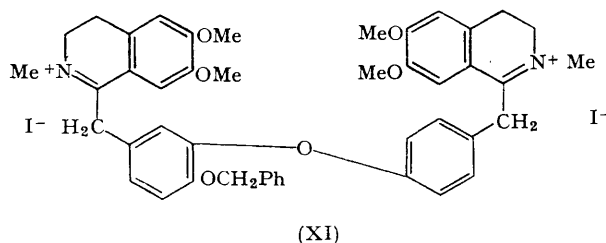
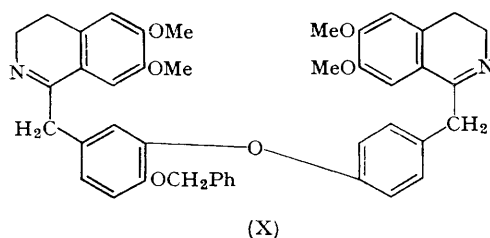
¹⁰ Ungnade and Zilchi, *J. Org. Chem.*, 1950, **15**, 1108.

¹¹ Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

both the pure alkaloid as a pale yellowish-green powder, m. p. 122—124°, and its monohydrate as a pale greyish-yellow powder, m. p. 109—110°; the latter was converted into the anhydrous material by desiccation. The synthetic dauricine was identical (paper chromatography, infrared and ultraviolet spectra) with a natural sample, kindly supplied by Professor R. H. F. Manske, and both gave the same dipicrates and the same distyphnates.



The distyphnate prepared from the synthetic material was identical with that prepared from the monohydrate, confirming that the monohydrate was not a diastereoisomer of the anhydrous material.



Dauricine was also obtained from the methiodide (XI) by reduction with sodium borohydride to give *O*-benzylauricine, the benzyl group of which was removed by treatment with hydrochloric acid in ethanol. The samples of dauricine prepared by the two synthetic routes were identical.

EXPERIMENTAL

Ultraviolet and infrared spectra were determined on a Type EPS-3 Hitachi recording spectrophotometer and a Type EPI-2 Hitachi infrared spectrophotometer, respectively. Melting points were determined on a Kofler block.

4-Benzylloxy-3-bromotoluene.—A mixture of 3-bromo-4-hydroxytoluene (147 g.), benzyl chloride (111.1 g.), anhydrous potassium carbonate (88 g.), and methanol (300 ml.) was refluxed for 10 hr. The potassium chloride formed was filtered off, the organic solvent was removed by distillation, and the residue was extracted with benzene. The benzene extract was washed successively with 10% aqueous sodium hydroxide, water, saturated aqueous calcium chloride, and water, and then dried (Na₂SO₄). Removal of the solvent afforded the *O*-benzyl derivative as a pale yellow solid (180 g., 75%), which crystallised from methanol as colourless needles, m. p. 36—37° (Found: C, 60.6; H, 4.5. C₁₄H₁₃BrO requires C, 60.7; H, 4.7%).

4',5-Diformyl-2-methoxydiphenyl Ether (VI).—A mixture of isovanillin (34.5 g.), 4-bromobenzaldehyde (42 g.), copper powder (14.5 g.), potassium carbonate (16 g.), and pyridine (1 ml.) was gradually heated in an oil-bath for 1.5 hr. until the temperature of the mixture reached 160–170° (a vigorous gas evolution was observed at 140–150°), and then cooled and extracted with benzene. The extract was filtered to remove copper powder, washed with 10% aqueous sodium hydroxide and water, dried (Na₂SO₄), and evaporated to give a dark brown oil (39.2 g.) which solidified to give yellow crystals when triturated with ether. Recrystallisation from ether yielded the diphenyl ether (28.1 g., 49.1%) as colourless needles, m. p. 79° (lit.,⁷ 80–83°).

4',5-Diformyl-2-hydroxydiphenyl Ether (V).—(a) A mixture of the ether (VI) (13 g.), acetic acid (100 g.), and 48% hydrobromic acid (20 g.) was refluxed for 7 hr. and then the solvent was removed by distillation *in vacuo* to give a black resinous substance which was extracted with warm chloroform. The extract was washed with water and then extracted with 10% aqueous sodium hydroxide. The alkaline extract was acidified with 10% hydrochloric acid to afford an oil which was extracted with chloroform. The chloroform extract was washed with water and dried (Na₂SO₄), and the solvent was removed to give the *diphenyl ether* as brown crystals (5.6 g.), m. p. 108–112°. Recrystallisation from aqueous ethanol afforded colourless silky crystals, m. p. 136° (Found: C, 69.3; H, 4.5. C₁₄H₁₀O₄ requires C, 69.4; H, 4.2%), ν_{\max} . (CHCl₃) 3520 (OH) and 1690 cm.⁻¹ (C=O).

(b) A mixture of 2-benzyloxy-4',5-diformyldiphenyl ether (IV) (70 mg.), ethanol (4 ml.), and 48% hydrobromic acid (2 ml.) was refluxed on a water-bath for 2 hr. Removal of the solvent gave a residue which was basified with 10% aqueous sodium hydroxide. The mixture was extracted with benzene and the aqueous layer was acidified with 10% hydrochloric acid. The organic material was extracted with benzene, and the extract was washed with water, dried (Na₂SO₄), and evaporated to leave a yellowish-orange viscous gum which was crystallised from ethanol to give the diphenyl ether (V) (33 mg.), which was identical with the sample described above.

2-Benzyloxy-4',5-diformyldiphenyl Ether (IV).—(a) A mixture of 4-benzyloxy-3-hydroxybenzaldehyde (21.4 g.), 4-bromobenzaldehyde (17.4 g.), copper powder (6 g.), potassium carbonate (6.5 g.), and pyridine (10 drops) was gradually heated in an oil-bath at 130–140° for 15 min. and then at 100° for 2 hr. (a vigorous gas evolution was observed). The mixture was cooled and extracted with benzene and the extract was washed successively with 10% aqueous sodium hydroxide, 10% hydrochloric acid, and water, and then dried (Na₂SO₄). Removal of the solvent gave a reddish-brown viscous oil (20.7 g.) which was chromatographed in ether on alumina to give the *diphenyl ether* (16.3 g., 51.9%) as yellow prisms, m. p. 69–71° raised to 77–78° by recrystallisation from ether or methanol (Found: C, 75.8; H, 4.9. C₂₁H₁₆O₄ requires C, 75.9; H, 4.85%), ν_{\max} . (CHCl₃) 1678 cm.⁻¹ (CHO).

(b) The ether (V) (3.0 g.) was dissolved in hot methanol (50 ml.), and a mixture of benzyl chloride (1.6 g.) and potassium carbonate (0.85 g.) was added. The mixture was refluxed on a water-bath for 5 hr., the solvent was removed and 10% aqueous sodium hydroxide (10 ml.) was added to the residue. A brown oil separated which was extracted with benzene, and the extract was washed with water, and dried (Na₂SO₄). Removal of the solvent gave a yellow syrup (3 g.), which solidified when triturated with ether. Crystallisation from ether afforded the diphenyl ether (IV), which was identical with the sample described above.

2-Benzyloxy-4',5-diformyl-2'-nitrodiphenyl Ether (III).—A mixture of 4-benzyloxy-3-hydroxybenzaldehyde (6 g.), 4-bromo-3-nitrobenzaldehyde (6 g.), and pyridine (50 ml.) was refluxed in an oil-bath for 2.5 hr.* The pyridine was removed *in vacuo* to leave a brown syrup which was extracted with hot chloroform. The extract was washed with 10% hydrochloric acid, 10% aqueous sodium hydroxide, and water, and then dried (Na₂SO₄). Removal of the solvent gave the *diphenyl ether* (6.3 g., 66%) as pale yellow prisms, m. p. 110–110.5° after crystallisation from benzene (Found: C, 66.7; H, 4.1; N, 3.8. C₂₁H₁₅NO₆ requires C, 66.8; H, 4.0; N, 3.7%), ν_{\max} . (KBr) 1689 cm.⁻¹ (CHO).

Ullman Reaction of 4-Benzyloxy-3-bromobenzaldehyde with 4-Hydroxybenzaldehyde.—A mixture of 4-benzyloxy-3-bromobenzaldehyde (5 g.), 4-hydroxybenzaldehyde (2.5 g.), copper powder (1.6 g.), and potassium carbonate (2.4 g.) was heated at 180–190° for 1 hr. and then at 195–200° for an additional 30 min. The mixture was extracted with hot benzene, and the extract was washed with 10% aqueous sodium hydroxide and water, and then dried (Na₂SO₄). Removal of the solvent gave orange crystals (3.8 g.) which were crystallised from methanol to give 4-benzyloxybenzaldehyde.

* This reaction proceeded easily without copper powder, possibly due to the influence of the nitro-group.

hyde as yellowish-orange needles, m. p. and mixed m. p. with an authentic sample 68—70° (lit.,¹² 72°).

2-Benzylloxy-4',5-dicarboxydiphenyl Ether (VII).—Potassium permanganate (3.7 g.), in water (150 ml.), was added dropwise to a hot, stirred solution of the aldehyde (IV) (4 g.) in acetone (40 ml.). After the addition, the mixture was refluxed for 1 hr. and then the solvent was removed by distillation *in vacuo*. The residue was cooled, and the manganese dioxide was filtered off, and washed with 10% aqueous sodium carbonate. The filtrate and washings were combined and acidified with 10% hydrochloric acid. The precipitate was crystallised from aqueous acetone to give the *diacid* as colourless prisms (3.2 g., 76.2%), m. p. 248—249° (Found: C, 69.3; H, 4.65. C₂₁H₁₆O₆ requires C, 69.2; H, 4.4%), ν_{\max} . (KBr) 1688 cm.⁻¹ (C=O).

2-Benzylloxy-4',5-di-(3,4-dimethoxyphenethylaminocarbonylmethyl)diphenyl Ether (IX).—The acid (VII) (2 g.) was refluxed for 1 hr. with thionyl chloride (20 g.) containing dried pyridine (3 drops), and then the excess of thionyl chloride was removed by distillation. The residue of crude acid chloride (VIII) was dissolved in ether, and the solution added to diazomethane [from toluene-*p*-sulphonyl-*N*-methyl-*N*-nitrosoamide (25 g.), potassium hydroxide (7 g.), and ethanol (50 ml.)] in ether (300 ml.). The mixture was kept in an ice-box and then concentrated and cooled to give the diazoketone [2.3 g., 98.5% based on the acid (VII)] as yellow scales, m. p. 146—147° (decomp.).

A solution of silver benzoate¹¹ (2.2 g.), prepared from silver nitrate and sodium benzoate according to Newman's procedure, in triethylamine (22 ml.) was added in small portions during 2 hr. to a mixture of the diazoketone (2.3 g.), 2-(3,4-dimethoxyphenyl)ethylamine (2.8 g.), and dry benzene (100 ml.). After the addition the mixture was refluxed on a water-bath for 1 hr., and then filtered. The filtrate was washed with 10% hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water, and then dried (K₂CO₃). Removal of the solvent afforded a viscous oil which was chromatographed on alumina to give a yellowish-orange solid (3.3 g.). This was crystallised from benzene-ether to give the *diamide* as a colourless powder, m. p. 83—85° (Found: C, 71.4; H, 6.2; N, 3.6. C₄₃H₄₆N₂O₈ requires C, 71.85; H, 6.45; N, 3.9%), ν_{\max} . (CHCl₃) 3403 (NH) and 1660 cm.⁻¹ (C=O).

2-Benzylloxy-4',5-bis-(3,4-dihydro-6,7-dimethoxy-1-isoquinolylmethyl)diphenyl Ether (X).—A mixture of the diamide (IX) (3.3 g.), dry benzene (60 ml.), and phosphoryl chloride (10 g.) was refluxed for 2 hr. An excess of hexane was added to the reaction mixture and the upper layer was removed by decantation. The residue was repeatedly washed with hot benzene and hexane and then basified with 10% ammonium hydroxide. The organic material was extracted with benzene, and the extract was washed with water and dried (K₂CO₃). Evaporation of the solvent in a current of nitrogen afforded the *bisdihydroisoquinoline* (2.8 g., 90.3%) as a reddish-pink syrup, ν_{\max} . (CHCl₃) 1623 cm.⁻¹ (C=N). The *distyphmate* crystallised from acetone-ether as a yellow powder, m. p. 138—139° (Found: C, 56.4; H, 4.6. C₄₃H₄₂N₂O₆.2C₆H₃N₃O₈ requires C, 56.3; H, 4.1%).

O-Benzylauricine.—A mixture of the above *bisdihydroisoquinoline* (0.9 g.), methyl iodide (4 g.), and methanol (9 ml.) was refluxed on a water-bath for 3 hr. The solvent was removed by distillation and the residue was triturated with hot ether to leave a brown powder (0.9 g.). Crystallisation from chloroform-hexane gave the dimethiodide (XI) as an amorphous powder, m. p. 154—156° (sintered at 144°).

Sodium borohydride (1.2 g.) was added in small portions with shaking to a solution of the dimethiodide (0.9 g.) in methanol (30 ml.). The mixture was refluxed for 1½ hr. and then the solvent was distilled off and the residue treated with water (30 ml.). The mixture was extracted with benzene and the extract was washed with water, dried (K₂CO₃), and evaporated to leave a reddish-pink viscous syrup (0.4 g.). This was chromatographed on alumina to give *O-benzylauricine* as a reddish glass (0.3 g., 32.3%), ν_{\max} . (CHCl₃) 2755 cm.⁻¹ (N-Me). The *distyphmate* crystallised from acetone-ether as a yellow powder, m. p. 136—138° (Found: C, 56.5; H, 5.0. C₄₅H₅₀N₂O₆.2C₆H₃N₃O₈ requires C, 56.8; H, 4.7%).

(±)-*Dauricine* (I).—(a) A mixture of concentrated hydrochloric acid (20 ml.), ethanol (20 ml.), the dimethiodide (XI) (3.2 g.), and zinc powder was refluxed on a water-bath for 4 hr., and then more zinc dust (20 g.) and concentrated hydrochloric acid (30 ml.) were added, and the refluxing was continued for a further 7 hr. An additional portion (20 ml.) of the acid was then added, and the mixture was refluxed for a further 4 hr. The excess of zinc was filtered off, and the bulk of the solvent was removed by distillation. The residual solution was extracted with benzene to remove impurities, and then basified with 10% aqueous sodium hydroxide. The organic material was

¹² Wörner, *Ber.*, 1896, **29**, 142.

extracted with benzene, and the aqueous layer was saturated with ammonium chloride and extracted with chloroform. The chloroform extract was washed, dried (K_2CO_3), and concentrated to give a pale brown syrup (1.5 g., which was chromatographed on a column of alumina. The column was eluted with benzene to give a brown solid (50 mg.), which was triturated with hexane and then recrystallised from benzene-hexane to give (\pm)-*dauricine monohydrate* as a pale greyish-yellow powder, m. p. 109–110° (Found: C, 71.1; H, 7.2; N, 4.3; H_2O , 2.5.† $C_{38}H_{44}N_2O_6 \cdot H_2O$ requires C, 71.0; H, 7.2; N, 4.4; H_2O , 2.8%), ν_{max} . (CCl_4) 3530 (phenolic OH) and 3400 cm^{-1} (OH, water of crystallisation). Desiccation of the monohydrate for many days afforded *dauricine* (I) which was identical with the sample described below. The column was eluted with chloroform, giving a dark grey resinous powder (0.7 g.), which was not identified. Elution of the column with ethanol gave a yellowish-brown syrup, which afforded a yellowish-green powder (0.3 g.), m. p. 119–120°. Crystallisation from benzene-hexane yielded (\pm)-*dauricine* as a pale yellowish-green powder, m. p. 122–124°, which was extremely hygroscopic and formed the monohydrate, m. p. 110°, on exposure to the air for a while. Since an elemental analysis of this compound was very difficult, it was identified by paper chromatography: PPC (Toyo Roshi No. 51) R_F (synthetic) 0.64, (natural) 0.64 [butanol-acetic acid-water (4:1:5) as solvent; the spots were detected by their fluorescence under u.v. light]. The i.r. spectrum of synthetic dauricine in carbon tetrachloride was superimposable on that of natural dauricine. The u.v. spectra of the synthetic and the natural base [in EtOH: λ_{max} . 279 $m\mu$ ($\log \epsilon$ 4.29) and λ_{max} . 279 $m\mu$ ($\log \epsilon$ 4.23), respectively] were also identical.

The *distyphmate* of synthetic dauricine crystallised from acetone-ether as a yellow powder, m. p. 146–149° (Found: C, 53.4; H, 4.0; N, 9.55. $C_{38}H_{44}N_2O_6 \cdot 2C_6H_3N_3O_8$ requires C, 53.85; H, 4.5; N, 10.3%). This derivative was identical (m. p. and i.r. spectrum) with that prepared from dauricine monohydrate. The *dipicrate* of synthetic dauricine was obtained as a yellow powder, m. p. 140–142° (from acetone-ether) (Found: C, 55.0; H, 4.0; N, 9.8. $C_{38}H_{44}O_6N_2 \cdot 2C_6H_3O_7N_3$ requires C, 55.4; H, 4.65; N, 10.3%). The i.r. spectra of these derivatives were superimposable on those of the corresponding derivatives prepared from natural dauricine. The *dipicrate* of natural dauricine had m. p. 139–141° (from acetone-ether) (Found: C, 54.9; H, 5.0; N, 9.8. $C_{38}H_{44}O_6N_2 \cdot 2C_6H_3O_7N_3$ requires C, 55.4; H, 4.65; N, 10.3%), and the *distyphmate* had m. p. 152–153° (from acetone-ether) (Found: C, 54.0; H, 4.7. $C_{38}H_{44}N_2O_6 \cdot 2C_6H_3N_3O_8$ requires C, 53.9; H, 4.5%).

(b) A mixture of *O*-benzylauricine (0.6 g.), ethanol (10 ml.), and concentrated hydrochloric acid (10 ml.) was refluxed for 2.5 hr. The bulk of the ethanol was removed by distillation, and the residual solution was extracted with ether, and basified with 10% ammonium hydroxide. The organic material was extracted with chloroform, and the extract was washed with water and dried (K_2CO_3). The solvent was removed and the residue was crystallised from benzene-hexane to give dauricine as a yellowish-green powder, m. p. 122–124°, which was identical (infrared and ultraviolet spectra) with a natural sample. The compound formed a dipicrate, m. p. 140–142° undepressed on admixture with the dipicrate of the synthetic dauricine described above.

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

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† The determination of water of crystallisation was carried out by desiccation over P_2O_5 at 60° (5 mm.) for 3 days.