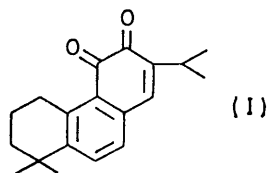


Synthetic Studies in the Diterpene Series. Part VIII.¹ Synthesis of Miltirone, a Diterpenoid Quinone

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Miltirone (I), a diterpenoid quinone has been synthesised from *p*-bromoanisole, the key intermediate being 6-isopropyl-7-methoxy-1-tetralone (VI). A Reformatsky reaction on compound (VI) with methyl γ -bromocrotonate, followed by aromatisation, treatment with methylmagnesium iodide, and cyclisation gave 1,2,3,4-tetrahydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthrene. The corresponding phenol was oxidised to a quinone, identical with miltirone, either by air or by Fremy's salt.

MILTIRONE is a tricyclic diterpenoid quinone isolated recently² from the roots of *Salvia miltiorrhiza* Bunge. On the basis of its spectroscopic properties and some chemical transformations, it has been assigned the structure (I) and is thus a new addition to naturally



occurring quinones related to tanshinones^{3,4} isolated from the same source. During the past few years, we have been interested in new methods for the synthesis of naturally occurring diterpenes¹ and the oxidation of some of the related phenols and phenolic ethers.⁵ As a part of this programme, we have confirmed the structure of this diterpenoid by an unambiguous synthesis (Scheme).

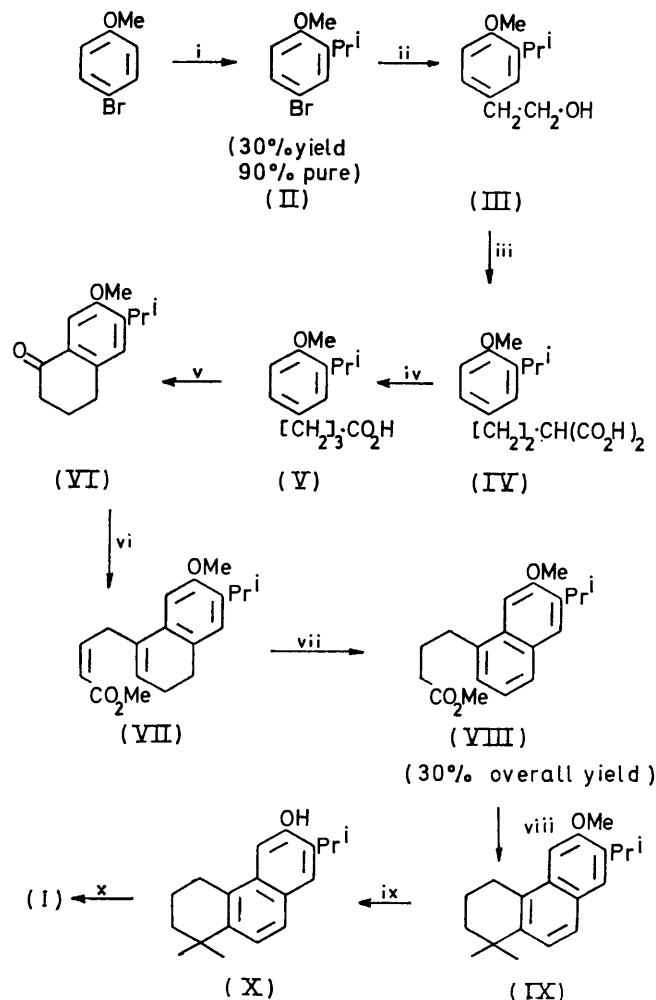
The identity of the synthetic compound (I) with natural miltirone was established by mixed m.p., i.r., and u.v. spectrometry. The n.m.r. spectrum is identical with that of miltirone² except that the isopropyl doublet in the latter is reported at τ 8.50 instead of 8.85.

EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 40–60°. T.l.c. was carried out on 20 × 10 cm plates, 0.1 mm thick, with silica gel G (Stahl). N.m.r. spectra were recorded with HA100, A60, or T60 spectrometers with [²H]chloroform as solvent and tetramethylsilane as internal reference. G.l.c. was carried out on a column (6 ft × 1/4 in) of 10% poly(diethylene glycol succinate) on Gaschrom Z (60–80 mesh) with nitrogen (40 ml min⁻¹ at 20 lb in⁻²) as carrier gas at 120°. Solutions were dried over anhydrous sodium sulphate.

4-Bromo-2-isopropylanisole (II).⁶—*p*-Bromoanisole (83 g, 0.44 mol), isopropyl alcohol (20.6 g, 0.34 mol), and 80% sulphuric acid (300 g) was heated in an oil-bath at 75–80° with stirring for 3 h. The cooled product was decomposed with ice-water and worked-up. G.l.c. analysis of the crude product showed it to be a mixture of *p*-bromoanisole (56%), 4-bromo-2-isopropylanisole (34%), and di-isopropyl-

bromoanisole (10%). This was submitted to fractional distillation through a packed column, monitored by g.l.c.



SCHEME Reagents and conditions: i, PrⁱOH-H₂SO₄ at 80°; ii, Grignard reagent of (II) + CH₂-CH₂-O; iii, derived bromo-

compound with (EtO₂C)₂CH₂ and hydrolysis; iv, decarboxylation; v, Friedel-Crafts reaction (AlCl₃) on the derived acid chloride; vi, Reformatsky reaction with methyl γ -bromocrotonate; vii, heating with palladium black; viii, treatment with methylmagnesium iodide and heating with polyphosphoric acid; ix, pyridine hydrochloride at 220°; x, aerial oxidation or Fremy's salt

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The fractions with boiling range 110—125° at 9 mmHg were refractionated and a middle fraction (30 g), b.p. 120° at 9 mmHg; n_D^{30} 1.5395 (Found: C, 52.8; H, 5.8. Calc. for $C_{10}H_{13}BrO$: C, 52.5; H, 5.7%) was taken. G.l.c. showed the presence of a trace (<10%) of dialkylated product but the material was good enough for subsequent use; τ ($CDCl_3$; 100 MHz) 2.82 (2H, m, ArH *meta* to OMe), 3.41 (d, J 8 Hz, ArH *ortho* to OMe), 6.25 (3H, s, OMe), 6.75 (1H, m, J 7 Hz, 1H, $CHMe_2$), and 8.82 (6H, d, J 7 Hz, CMe_2). Recently, Russian workers⁷ reported the alkylation of *p*-bromoanisole using propene and isobutene with preponderant *o*-alkylation.

3-Isopropyl-4-methoxyphenethyl Alcohol (III).⁸—The alcohol (III) was prepared from the bromo-compound (II) essentially following the procedure of Bachmann.⁹ From the bromide (50 g), magnesium (6 g), ethylene oxide (15 g), and dry ether (150 ml) was obtained the alcohol (III) (25 g, 50%), b.p. 115—118° at 0.4 mmHg; n_D^{30} 1.5205 (Found: C, 74.1; H, 9.1. Calc. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3%) (lit.,⁶ n_D^{33} 1.5180).

3-Isopropyl-4-methoxyphenethyl Bromide.—The preceding alcohol was treated with phosphorus tribromide in carbon tetrachloride¹⁰ at 60° and the bromide was obtained as an oil, b.p. 120° at 1 mmHg; n_D^{30} 1.5355 (Found: C, 56.1; H, 6.8. $C_{17}H_{17}BrO$ requires C, 56.0; H, 6.6%).

4-(3-Isopropyl-4-methoxyphenyl)butyric Acid (V).—A mixture of the above bromide (37.6 g), diethyl malonate (48 g), and sodium ethoxide [from sodium (4.3 g) and absolute ethanol (110 ml)] was heated under reflux for 8 h. After removal of ethanol, the residue was cooled, acidified, and extracted with ether. The organic matter after removal of solvent was distilled to furnish diethyl 3-isopropyl-4-methoxyphenethylmalonate (41 g), b.p. 180—185° at 0.5 mmHg; n_D^{34} 1.4880 (Found: C, 68.0; H, 8.5. $C_{19}H_{28}O_5$ requires C, 67.8; H, 8.3%). The ester (41 g) was hydrolysed with refluxing 20% alcoholic potassium hydroxide solution (150 ml) and the substituted malonic acid (IV) (35 g) was liberated from the aqueous solution by acidification. The acid crystallised from benzene in flakes, m.p. 122—123° (Found: C, 50.8; H, 7.5. $C_{15}H_{20}O_5$ requires C, 51.0; H, 7.1%).

The above malonic acid (29.6 g) was heated at 170° for 1 h and then distilled *in vacuo* to furnish the acid (V) (21.5 g), b.p. 168—170° at 0.4 mmHg (Found: C, 71.2; H, 8.6%; equiv., 233. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%; equiv., 236). On being chilled, the acid solidified but became liquid again at room temperature.

6-Isopropyl-7-methoxy-1-tetralone (VI).—The acid (V) (20 g) was converted into the acid chloride by treatment with phosphorus pentachloride (20 g) in dry benzene (15 ml). Phosphoryl chloride was removed completely under vacuum after addition of some dry benzene, the process being repeated twice. The residue was taken up in dry benzene (30 ml) and added gradually¹¹ to a cooled solution of anhydrous aluminium chloride (16.8 g) in benzene (50 ml). After the reaction was over (4 h at room temperature), the mixture was decomposed with hydrochloric acid and the product was worked-up in the usual way. The tetralone

(VI) was obtained as an oil (15 g), b.p. 145—150° at 0.2 mmHg; n_D^{35} 1.5515 (Found: C, 76.9; H, 8.1. $C_{14}H_{18}O_2$ requires C, 77.0; H, 8.2%); τ ($CDCl_3$; 100 MHz) 2.65 (1H, s, 5-H), 3.07 (1H, s, 8-H), 6.17 (3H, s, OMe), 6.72 (1H, m, J 7 Hz, $CHMe_2$), 7.18 (2H, t, J 6 Hz, 4-H₂), 7.50 (2H, t, J 6 Hz, 2-H₂), 7.93 (2H, m, J 6 Hz, 3-H₂), and 8.83 (6H, d, J 7 Hz, CMe_2). The dinitrophenylhydrazone had m.p. 193° (from benzene-methanol) (Found: C, 60.0; H, 5.4; N, 14.2. $C_{20}H_{22}N_4O_5$ requires C, 60.3; H, 5.5; N, 14.1%).

Methyl 4-(3,4-Dihydro-6-isopropyl-7-methoxy-1-naphthyl)-but-2-enoate (VII).—A mixture of amalgamated zinc wool (4.2 g), methyl γ -bromocrotonate (9.5 g), the tetralone (VI) (6 g), and dry benzene (25 ml) was heated under reflux^{12,13} in a steam-bath for 1 h and then decomposed with crushed ice and hydrochloric acid. The benzene layer was separated, washed with aqueous sodium carbonate solution and water, dried, and evaporated. The residue on distillation afforded the ester (VII) (4.5 g), b.p. 190—210°, which was used directly in the next operation.

Methyl 4-(6-Isopropyl-7-methoxy-1-naphthyl)butyrate (VIII).—The ester (VII) (4.5 g) and palladium black¹⁴ (300 mg) were heated at 280—300° under carbon dioxide for 3 h. The mixture was extracted with hot benzene to afford the ester (VIII) (4.3 g) as a viscous oil. This was hydrolysed to the corresponding acid (as VIII) which crystallised from aqueous methanol as needles (3 g), m.p. 116° (Found: C, 73.4; H, 6.7. $C_{15}H_{18}O_3$ requires C, 73.7; H, 6.5%); τ (60 MHz) —0.6 (CO_2H), 2.4 and 2.75 (5H, m, ArH), 6.03 (3H, s, OMe), 6.6 (1H, m, $CHMe_2$), 6.9, 7.5, and 7.9 (6H, m, 3 \times CH_2), and 8.7 (6H, d, J 7 Hz, 2 \times Me). The acid was re-esterified with diazomethane to the methyl ester (VIII), a viscous oil, b.p. 180—182° at 0.2 mmHg (Found: C, 74.0; H, 7.3. $C_{16}H_{18}O_3$ requires C, 74.4; H, 6.9%).

1,2,3,4-Tetrahydro-1,1-dimethyl-6-methoxy-7-isopropylphenanthrene (IX).—The ester (VIII) (2 g) was treated with an excess of methylmagnesium iodide and the crude alcohol so obtained was cyclised^{15,16} by polyphosphoric acid (30 g) at 170° for 3 h. The tetrahydrophenanthrene derivative thus obtained was purified by elution through activated alumina and finally crystallised from methanol as plates (1.2 g), m.p. 83—85° (Found: C, 85.4; H, 9.5. $C_{20}H_{26}O$ requires C, 85.1; H, 9.2%); τ ($CDCl_3$; 60 MHz) 2.5—3.0 (4H, m, ArH), 6.15 (3H, s, OMe), 6.70 (1H, m, $CHMe_2$), 7.05 (2H, t, J 6 Hz, 2H, benzylic CH_2), 8.25 (4H, m, 2 \times CH_2), and 8.7—8.8 (12H, m, 12H, 4 \times Me).

The corresponding phenol (X) was prepared by heating the above methyl ether (0.8 g) with freshly prepared pyridine hydrochloride¹⁷ at 210—220° for 3 h under carbon dioxide. The product was worked-up in the usual way and the resulting gum (0.8 g) was chromatographed over a column of silica gel (30 g). The unconverted methyl ether (200 mg) was eluted with petroleum and the phenol (X) (500 mg) with 2% ether in petroleum. The latter on crystallisation from light petroleum had m.p. 94—95° (Found: C, 84.7; H, 9.3. $C_{19}H_{24}O$ requires C, 85.0; H, 8.9%); ν_{max} (Nujol) 3260 cm^{-1} (OH).

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Synthesis of Miltirone (I).—(a) In the preceding chromatograph, after the phenol (X) was removed from the column, a deep red zone remained behind. This was eluted with 10% ether-petroleum and a red solid (30 mg), m.p. 92–95°, was obtained. One further crystallisation from light petroleum afforded scarlet red crystals, m.p. 100° (Found: C, 80.6; H, 8.0. Calc. for C₁₅H₂₂O: C, 80.8; H, 7.8%) which was found to be identical (i.r. and u.v.) with natural miltirone (*vide infra*). Aerial oxidation converting phenol into quinone is already well known.¹⁸

(b) The phenol (X) (100 mg) in acetone (20 ml) was mixed with a solution of potassium nitrosodisulphonate (350 mg) in water (18 ml) and aqueous m/6-potassium dihydrogen phosphate (13 ml).^{19,20} The solution was stirred at 20° for 45 min and then left overnight. The red oil was extracted with ether, the ethereal solution was washed with water, dried, and solvent evaporated. The residue gave two spots in t.l.c. and was chromatographed over silica gel. The red fraction obtained by elution with 5% ether in petroleum was rechromatographed to afford miltirone (I) (35 mg) which solidified on scratching. It

afforded red plates, m.p. 100–101° (from light petroleum) (Found: C, 80.7; H, 7.9%); λ_{max} (EtOH) 256, 362, and 436 nm (log ϵ 4.53, 3.34, and 3.50); ν_{max} (KBr) 3440, 2950, 2870, 1680, 1660, 1635, 1580, 1565, 1485, 1455, 1415, 1390, 1370, 1334, 1300, 1258, 1230, 1212, 1200, 1145, 1015, 960, 937, 922, and 853 cm⁻¹. The u.v. and i.r. spectra of the natural and synthetic samples were identical. The mixed m.p. of the two samples remained undepressed. They were indistinguishable by t.l.c. in three different solvent systems. The n.m.r. spectrum (CDCl₃; 60 MHz) showed τ 2.63 (2H, ABq, *J* 8 Hz, ArH), 2.93 (1H, d, *J* 1 Hz, 7-H), 6.81br (2H, t, benzylic), 8.30 (4H, m, 2- and 3-H₂), 8.70 (6H, s, 1-Me₂), and 8.85 (6H, d, *J* 7 Hz, CHMe₂). The methine proton was presumably obscured by the benzylic protons.

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