

Studies in Terpenoids. Part XXX.¹ Synthesis of Pterosin E, a Sesquiterpenoid from Bracken

By **Mayara E. N. Nambudiry** and **G. S. Krishna Rao**,* Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

Pterosin E (2,5,7-trimethyl-1-oxoindan-6-ylacetic acid) (Ia), a naturally occurring sesquiterpenoid has been synthesized starting from α -bromomesitylene (IIIa). Alkylation of diethyl methylmalonate with (IIIa) gave the diester (IIIb) which was converted into the cyanomethyl diester (IVb). Hydrolysis of (IVb) to the dicarboxylic acid (V) followed by its cyclodehydration gave pterosin E.

PTEROSIN E (BH-4) is one of the several sesquiterpenoids with an indan-1-one nucleus, isolated by Natori *et al.*^{2a} from the leaves of bracken, *Pteridium aquilinum* var. *Latiusculum*. Based on spectral and chemical degradation evidence, pterosin E^{2b} was designated as 2,5,7-trimethyl-1-oxoindan-6-ylacetic acid (Ia).^{2a} Earlier Hikino *et al.*³ isolated a glucoside, named pteroside B from the same source and assigned to it and its aglycone structures (IIa and b). Natori *et al.*^{2a} also isolated from bracken an indanone which they coded BI-2 and established its identity with the aglycone of pteroside B of Hikino. However, by oxidation of BI-2^{2a} Natori obtained pterosin E (Ia), which led him to revise the structures of pteroside B and its aglycone (later named pterosin B^{2b}) to (IIc and d). In view of (i) the structural

controversy involving the nuclear location of the two carbon side chain [(IIb) *vs.* (IIc)] and (ii) the existence in bracken of a large number (24 to date) of related indanones,^{2a-c} we undertook the synthesis of pterosin E (Ia) which we report in this paper.

Our basic approach to the synthesis of pterosin E consisted of substituting one of the methyl groups of mesitylene with a bulky substituent, capable of serving a dual purpose, *viz.* (i) the regiospecific introduction of a function *para* to the bulky side chain and (ii) the use of the bulky chain for ring closure to the desired indanone. Accordingly alkylation of diethyl methylmalonate with α -bromomesitylene⁴ (IIIa) gave the disubstituted malonate (IIIb) in 70% yield. Of the several conditions⁵ tried for the chloromethylation of (IIIb) to (IVa), that using

¹ Part XXIX, R. B. Mane and G. S. Krishna Rao, submitted for publication.

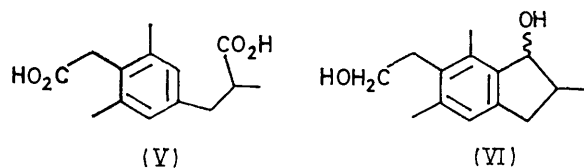
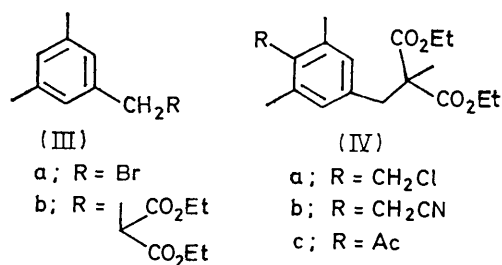
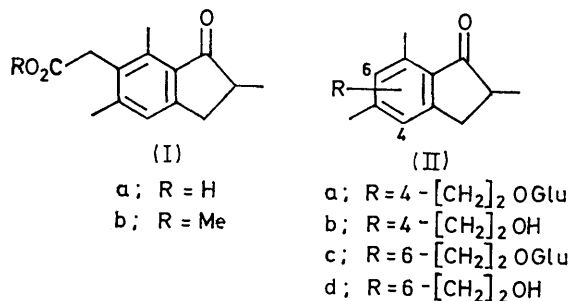
² (a) K. Yoshihira, M. Fukuoka, M. Kuroyanagi, and S. Natori, *Chem. Pharm. Bull. (Japan)*, 1971, **19**, 1491; (b) K. Yoshihira, M. Fukuoka, M. Kuroyanagi, and S. Natori, *ibid.*, 1972, **20**, 426; (c) M. Fukuoka, M. Kuroyanagi, M. Toyama, K. Yoshihira, and S. Natori, *ibid.*, p. 2282.

³ H. Hikino, T. Takahashi, S. Arihara, and T. Takemoto, *Chem. Pharm. Bull. (Japan)*, 1970, **18**, 1488.

⁴ R. R. Herr, T. Enkoji, and J. P. Dailey, *J. Amer. Chem. Soc.*, 1957, **79**, 4229.

⁵ G. A. Olah, 'Friedel-Crafts and Related Reactions,' Interscience, New York, 1963, vol. I, p. 52; 1964, vol. II, part II, p. 730.

paraformaldehyde and zinc chloride in tetrachloroethane was found to be the most satisfactory. The chloromethyl diester (IVa) exhibited a six proton singlet (δ 2.4) due to two aromatic methyl groups in identical environments, a chloromethyl methylene singlet (δ 4.57), and an aromatic two proton singlet (δ 6.7) also in identical environments, consistent with the structure assigned.



Treatment of (IVa) with sodium cyanide in refluxing dimethylformamide gave the cyanomethyl diethyl ester (IVb) which on vigorous acid hydrolysis furnished the dicarboxylic acid (V) whose n.m.r. spectrum also indicated identical environments for the two aromatic methyl groups (six proton singlet at δ 2.3) and the two aromatic protons (two proton singlet at δ 6.86), consistent with the structure assigned. Cyclodehydration of the dicarboxylic acid (V) with polyphosphoric acid gave in 66% yield the required 2,5,7-trimethyl-1-oxoindan-6-ylacetic acid (Ia), m.p. 151–153° (lit.^{2a} 160–162°, for the naturally occurring pterosin E), M^+ 232 (100%). Its i.r. spectrum showed the presence of the indanone carbonyl (1695 cm^{-1} in chloroform in the presence of triethylamine⁶), besides the carboxy-group (KBr pellet). The u.v. spectrum showed absorption bands identical with those reported^{2a} for pterosin E. Its n.m.r. spectrum tallied in all respects with that of an authentic spectrum of pterosin E.

In an attempt to introduce directly the required two carbon side chain at C-6, the diester (IIIb) was acetylated

⁶ K. Nakanishi, 'Infrared Absorption Spectroscopy, Practical,' Holden-Day, San Francisco, 1962, p. 44.

to (IVc), with the intention of subjecting it to a Willgerodt reaction⁷ ($\text{COMe} \rightarrow \text{CH}_2\text{CO}_2\text{H}$). Since success in this reaction depends mechanistically on the reactivity of the keto carbonyl group,^{7d} and as the mesityl keto-group of (IVc) was found to be extremely inert (towards the usual carbonyl reagents), the planned conversion of (IVc) was not pursued.

An attempted conversion of pterosin E (Ia) into pterosin B (IIId) the reverse of what was accomplished by Natori^{2a} on the natural sample, by lithium aluminium hydride reduction of (Ib) to the diol (VI), followed by preferential oxidation of the benzylic secondary alcohol failed owing to the pronounced instability of the secondary alcohol which exhibited a ready tendency to dehydrate. The hydride reduction product after alkaline work-up⁸ exhibited a vinyl methyl group (δ 2.12) and a vinyl proton (δ 6.54).

EXPERIMENTAL

I.r. spectra were recorded on Perkin-Elmer infracord 137 or Carl Zeiss UR-10 instruments and n.m.r. spectra on Varian HA-100D or T-60 machines. U.v. measurements were made on Unicam SP 700. Light petroleum refers to the fraction with b.p. 40–60°. Solvent extracts were appropriately washed and dried (Na_2SO_4) before evaporation.

Diethyl (3,5-Dimethylphenylmethyl)methylmalonate (IIIb). To a suspension of diethyl methylmalonate (3.1 g, 0.018 mol) and anhydrous potassium carbonate (1.8 g) in dimethylformamide (25 ml) maintained with stirring at 150°, α -bromomesitylene⁴ (3.55 g, 0.018 mol) in dimethylformamide (25 ml) was added during a period of 10 min and the reaction mixture was kept at 150° for 9 h with stirring. After removing most of the dimethylformamide by distillation *in vacuo*, water (30 ml) was added and the product was extracted with ether (3 \times 25 ml). Removal of the solvent and fractionation furnished the diester (IIIb) (3.6 g), b.p. 132° at 0.01 mmHg (Found: C, 69.5; H, 8.2. $\text{C}_{17}\text{H}_{24}\text{O}_4$ requires C, 69.9; H, 8.2%), ν_{max} (neat) 1720 cm^{-1} (ester C=O), δ (CCl_4) 1.23 (9H, t, $\text{CO}_2\text{CH}_2\text{CH}_3$ and α -Me), 2.27 (6H, s, Ar 3- and 5-Me), 3.07 (2H, s, ArCH₂), 4.17 (4H, q, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.77 (2H, s, Ar 2- and 6-H), and 6.85 (1H, s, Ar 4-H).

α -Methyl- β -(4-carboxymethyl-3,5-dimethylphenyl)propionic Acid (V).—Dry hydrogen chloride gas was bubbled for 4.5 h through a suspension of the foregoing diester (IIIb) (3.3 g), paraformaldehyde (0.8 g), and anhydrous zinc chloride (8 g) in tetrachloroethane (40 ml) maintained at 80°. The mixture was cooled and washed thoroughly with water to remove the zinc salts and the free mineral acid. After removal of the solvent the residue was sublimed (175–180° at 0.02 mmHg) to give a product (3 g), δ (CCl_4) 1.23 (9H, t, $\text{CO}_2\text{CH}_2\text{CH}_3$ and α -Me), 2.4 (6H, s, Ar 3- and 5-Me), 3.03 (2H, s, ArCH₂), 4.17 (4H, q, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.57 (0.9 \times 2H, s, ArCH₂Cl), and 6.7 (2H, s, Ar 2- and 6-H). From the integrated intensity of

⁷ (a) M. Carmack and M. A. Spielman in 'Organic Reactions,' ed. R. Adams, Wiley, New York, 1947, vol. 3, ch. 2; (b) F. Asinger, W. Schafer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem. Internat. Edn.*, 1964, 3, 19; (c) R. Mayer and J. Wehl, *ibid.*, 1964, 3, 705; (d) J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,' McGraw-Hill, New York, 1968, pp. 910–911.

⁸ V. M. Micovic and M. Lj. Mihailovic, *J. Org. Chem.*, 1953, 18, 1190.

the ArCH_2Cl signal, the required chloromethyl diester (IVa) in the product was estimated to be present to the extent of 90%. Since further purification of (IVa) was unsuccessful (t.l.c.), it was used directly in the next step.

The impure chloromethyl diester (IVa) (2.3 g) was refluxed with sodium cyanide (1.5 g) in dimethylformamide (75 ml) for 7 h. Most of the solvent was distilled off *in vacuo* and water (20 ml) added to the residue. The organic matter was extracted with ether (3×25 ml). Removal of solvent gave the crude arylacetonitrile diester (IVb) (2 g), ν_{max} (neat) 2292 ($\text{C}\equiv\text{N}$) and 1720 cm^{-1} (ester $\text{C}=\text{O}$). As t.l.c. (silica gel; various solvent combinations) did not give clear-cut zones, the crude nitrile diester (IVb) was hydrolysed directly.

The foregoing ester (IVb) (2 g) was refluxed for 24 h with glacial acetic acid (10 ml) and concentrated hydrochloric acid (60 ml). More of the mineral acid (20 ml) was then added and refluxing continued for a further period of 24 h. Acetic and hydrochloric acids were distilled off at atmospheric pressure and the organic residue was extracted with ether. Extraction of the ether layer with aqueous sodium carbonate (5%) followed by acidification (1:1 dilute hydrochloric acid) liberated a gummy acid which was re-extracted with ether (4×30 ml). Removal of the solvent furnished the dicarboxylic acid (V), m.p. 148–150° (after treatment with charcoal and crystallization from benzene) (0.9 g) (Found: C, 67.2; H, 6.9. $\text{C}_{14}\text{H}_{18}\text{O}_4$ requires C, 67.2; H, 7.2%), λ_{max} (ethanol) 219 ($\log \epsilon$ 3.93) and 265 nm (2.93), ν_{max} (CHCl_3) 3200–3700 (OH of CO_2H) and 1720 cm^{-1} ($\text{C}=\text{O}$ of CO_2H), δ (CCl_4), 1.17 (3H, d, J 7 Hz, α -Me), 2.3 (6H, s, Ar 3- and 5-Me), 2.3–3.2 (3H, α -H and β - CH_2), 3.67 (2H, s, $\text{CH}_2\text{CO}_2\text{H}$), 6.86 (2H, s, Ar 2- and 6-H), and 12.26 (2H, s, CO_2H).

2,5,7-Trimethyl-1-oxo-6-ylacetic Acid (Pterosin E) (Ia).—The foregoing dicarboxylic acid (V) (0.41 g) was stirred with polyphosphoric acid [prepared from phosphorous pentoxide (25 g) and syrupy phosphoric acid (15 ml)] at 100° for 2 h. The mixture was poured onto crushed ice (75 g) and water (75 ml). The indanone (Ia) which separated gradually was filtered off, m.p. 151–153° (after treatment with charcoal and crystallization from carbon tetrachloride) (0.25 g) (Found: C, 72.4; H, 7.0. $\text{C}_{14}\text{H}_{16}\text{O}_3$ requires C, 72.4;

H, 6.9%), λ_{max} (ethanol) 218 ($\log \epsilon$ 4.41), 260 (4.17), and 303 nm (3.48), ν_{max} (CHCl_3 and triethylamine) 1695 (indanone $\text{C}=\text{O}$), ν_{max} (KBr) 3200–3700 (OH of CO_2H) and 1700–1720 cm^{-1} (carboxy and ketone $\text{C}=\text{O}$), δ (CDCl_3) 1.27 (3H, d, J 7 Hz, HcMe), 2.39 (3H, s, Ar 5-Me), 2.65 (3H, s, Ar 7-Me), 2.4–2.7 (overlapping signals, m, 3- CH_2), 3–3.4 (1H, m, MeCH), 3.77 (2H, s, $\text{CH}_2\text{CO}_2\text{H}$), 7.12 (1H, s, Ar 4-H), and 10.55 (1H, s, CO_2H).

The indanone (Ia) (0.67 g) was refluxed for 6 h with absolute methanol (25 ml) and concentrated sulphuric acid (5 drops). Methanol was removed *in vacuo* and the residual organic matter was worked up as usual, when the neutral methyl ester (Ib) (0.6 g) was obtained, m.p. 84–86° (light petroleum) (Found: C, 72.7; H, 7.2. $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires C, 73.1; H, 7.3%), ν_{max} (Nujol) 1725 (ester $\text{C}=\text{O}$) and 1700 cm^{-1} (indanone $\text{C}=\text{O}$), δ (CDCl_3) 1.25 (3H, d, J 7 Hz, HcMe), 2.36 (3H, s, Ar 5-Me), 2.64 (3H, s, Ar 7-Me), 2.4–2.7 (overlapping signals, m, 3- CH_2), 3.1–3.4 (1H, m, MeCH), 3.66 (3H, s, CO_2Me), 3.72 (2H, s, $\text{CH}_2\text{CO}_2\text{Me}$), and 7.1 (1H, s, Ar 4-H).

Diethyl (4-Acetyl-3,5-dimethylphenylmethyl)methylmalonate (IVc).—To a cooled (ice-bath) suspension of the diester (IIIb) (2.9 g) and anhydrous aluminium chloride (4.3 g) in carbon disulphide (20 ml), acetyl chloride (1 g) in carbon disulphide (10 ml) was added over 45 min. The mixture was allowed to attain room temperature (1.5 h) and then left overnight. It was decomposed with dilute hydrochloric acid [acid-water (1:2); 30 ml]. The organic layer was separated. The aqueous portion was extracted with chloroform (3×25 ml). Removal of the solvent furnished diester (IVc) (2.9 g), b.p. 170° at 0.05 mmHg (Found: C, 68.0; H, 8.2. $\text{C}_{19}\text{H}_{26}\text{O}_5$ requires C, 68.3; H, 7.8%), δ (CCl_4) 1.22 (9H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$ and α -Me), 2.18 (6H, s, Ar 3- and 5-Me), 2.33 (3H, s, COMe), 3.03 (2H, s, ArCH_2), 4.12 (4H, q, $\text{CO}_2\text{CH}_2\text{CH}_3$), and 6.72 (2H, s, Ar 2- and 6-H).

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