

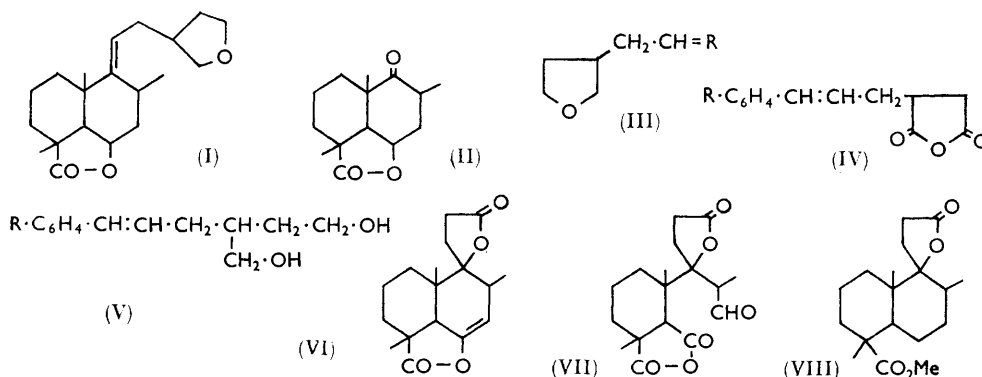
955. *The Constitution of Marrubiin. Part II.*¹ *Synthesis of 3-Tetrahydrofurylacetaldehyde.*

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The 2,4-dinitrophenylhydrazone of 3-tetrahydrofurylacetaldehyde has been synthesised. It is identical with a product derived from anhydrotetrahydromarrubiin, thus confirming the presence of a furan ring in the diterpene.

IN Part I¹ we showed that ozonolysis of anhydrotetrahydromarrubiin (I) gave the ketolactone (II). We also isolated the 2,4-dinitrophenylhydrazone of an aldehyde, which analysed correctly for the expected, but then unknown, 3-tetrahydrofurylacetaldehyde 2,4-dinitrophenylhydrazone [III; R = N·NH·C₆H₃·(NO₂)₂]. We did not describe this compound pending its synthesis, but it has been described,² though not identified by synthesis. We have now synthesised its racemic form and found it to be identical in melting point, mixed melting point, and infrared spectrum with, and to be inseparable chromatographically from, the natural product. The latter should be optically active but we found it to be either inactive or its specific rotation to be so low as to be within the accuracy of measurement.

The synthesis was as follows. γ -Phenylallylsuccinic anhydride (IV; R = H) obtained by the condensation of allylbenzene with maleic anhydride,³ was reduced with lithium aluminium hydride to 2-(γ -phenylallyl)butane-1,4-diol (V; R = H). The latter was



smoothly cyclised with toluene-*p*-sulphonic acid to 3-(γ -phenylallyl)tetrahydrofuran (III; R = CHPh). Ozonolysis of this compound gave a mixture of aldehydes whose 2,4-dinitrophenylhydrazones were separated on an alumina column giving the required compound [III; R = N·NH·C₆H₃·(NO₂)₂].

Condensation of *p*-allylanisole with maleic anhydride gave (γ -*p*-methoxyphenylallyl)succinic anhydride (IV; R = OMe) from which the diol (V; R = OMe) was obtained. We did not cyclise this compound. Hydrolysis of the anhydride (IV; R = OMe) gave (γ -*p*-methoxyphenylallyl)succinic acid which, on hydrogenation over palladised charcoal, gave (γ -*p*-methoxyphenylpropyl)succinic acid.

Several unsuccessful routes for the synthesis of the ketone (III; R = O) and its derivatives were explored. We hoped to prepare 3-allyltetrahydrofuran (III; R = CH₂) starting from dimethyl allylsuccinate, but the diol obtained from the reduction of this ester proved to be difficult to isolate.

We investigated the reactivity of 3-hydroxytetrahydrofuran,⁴ and derivatives which

¹ Part I, Cocker, Cross, Duff, Edward, and Holley, *J.*, 1953, 2540.

² Hardy, Rigby, and Moody, *J.*, 1957, 2955.

³ Rondestvedt, *Org. Synth.*, 1951, **31**, 85.

⁴ Wynberg, *J. Amer. Chem. Soc.*, 1958, **80**, 364.

could be useful intermediates in the construction of the side-chain of derivatives of (III). Reaction of the alcohol with phosphorus oxychloride or thionyl chloride, with or without pyridine, gave only small yields of 3-chlorotetrahydrofuran which were accompanied by tarry products. In any case, the halogen was found to be firmly bound. It did not react with ethyl sodiomalonate, and reaction with sodium iodide was negligible.

Some time ago⁵ we assigned structure (VI) to a compound obtained from marrubiin, since, on ozonolysis, it gave the aldehydo-anhydride (VII). We take this opportunity of giving experimental details of this and some related work.

EXPERIMENTAL

2-(γ -Phenylallyl)butane-1,4-diol (V; R = H).— γ -Phenylallylsuccinic anhydride³ (9.9 g.) was slowly added to a solution of lithium aluminium hydride (4.5 g.) in tetrahydrofuran (200 c.c.) and the mixture refluxed for 5.5 hr. After settlement of the solids, the supernatant liquor was decanted, the residue washed with tetrahydrofuran, and the mixture again decanted. The combined solutions were concentrated to 20 c.c., poured into ether (200 c.c.), and added to ice and 10% sulphuric acid. The ether layer was separated and the aqueous layer extracted several times with ether. The combined ethereal extracts gave the diol as a colourless oil (8.45 g.), b. p. 185°/1.2 mm., ν_{\max} . (liquid film) 3333 broad (OH), 1639 (C:O), 1600 cm.⁻¹ (Ar) (Found: C, 75.6; H, 9.0. C₁₃H₁₆O₂ requires C, 75.7; H, 8.8%).

3-(γ -Phenylallyl)tetrahydrofuran (III; R = CHPh).—The preceding diol (1.9 g.) was refluxed for 6 hr. in benzene (28 c.c.) with toluene-*p*-sulphonic acid (0.5 g.), the mixture was washed with sodium hydrogen carbonate, then with water, and dried. Removal of solvent and distillation of the residue (1.8 g.) gave 3-(γ -phenylallyl)tetrahydrofuran as an oil, b. p. 87°/0.2 mm., λ_{\max} . 2510 and 2840 Å (log ϵ 4.27 and 3.18) (Ar:C:C), ν_{\max} . 1647 (C:C), 1597, 1575, 1488 (Ar), 1067, 1024, and 980 cm.⁻¹ (tetrahydrofuran) (Found: C, 82.8; H, 8.9. C₁₃H₁₆O requires C, 82.9; H, 8.6%).

In one experiment γ -phenylallylsuccinic anhydride (21 g.) was refluxed for 4 hr. with lithium aluminium hydride (10 g.) in tetrahydrofuran (400 c.c.). After cooling, the supernatant liquor was decanted and concentrated to 100 c.c. Ether (300 c.c.) was added and the mixture was added to an excess of 15% sulphuric acid at 0°. The product was worked up directly, as described above, giving 3-(γ -phenylallyl)tetrahydrofuran (12.6 g.), b. p. 105°/0.3 mm., identical in all respects with the product described above.

Ozonolysis of 3-(γ -Phenylallyl)tetrahydrofuran.—A stream of ozonised oxygen was passed into a solution of this compound (0.63 g.) in ethyl acetate (40 c.c.) at -10° until no more ozone was absorbed. Freshly prepared palladised charcoal (0.5 g.) was carefully added and the mixture was hydrogenated at 0° until uptake of hydrogen ceased. Removal of catalyst and solvent gave a clear oil, which was treated with a solution of 2,4-dinitrophenylhydrazine (0.5 g.) in methanol (10 c.c.) containing sulphuric acid (2 c.c.). After 24 hr. the solution was diluted giving a solid (0.42 g.) which was chromatographed on a column of neutral alumina. Using mixtures of benzene and ether small amounts of a yellow oil were eluted, but chloroform gave a yellow solid (0.25 g.) which, after three crystallisations from light petroleum-benzene, gave 3-tetrahydrofurylacetaldehyde 2,4-dinitrophenylhydrazone as rhombs, m. p. 144–145°, λ_{\max} . (EtOH) 3570 Å (log ϵ 4.37), ν_{\max} . (Nujol) 1616, 1508 (Ar), 1590 (NO₂), 1131, and 1080 cm.⁻¹ (ether) (Found: C, 49.5; H, 5.1; N, 19.3. C₁₂H₁₄N₄O₆ requires C, 49.0; H, 4.8; N, 19.0%).

When the mixture of dinitrophenylhydrazones was submitted to thin-layer chromatography on Kieselgel G (Merck) using benzene-ether (70 : 30) as solvent, two spots were revealed, R_F 0.47 (3-tetrahydrofurylacetaldehyde 2,4-dinitrophenylhydrazone) and 0.98 (benzaldehyde 2,4-dinitrophenylhydrazone).

Ozonolysis of Anhydrotetrahromarrubiin (I).—This was carried out in a similar way to that described by Hardy *et al.*² The required 2,4-dinitrophenylhydrazone was obtained, m. p. and mixed m. p. 144–145° (ref. 2), $[\alpha]_D^{15}$ 0° (c 0.1 in CHCl₃) (Found: C, 48.9; H, 4.6; N, 19.6%).

(γ -*p*-Methoxyphenylallyl)succinic Anhydride (IV; R = OMe).—*p*-Allylanisole (22 g.), maleic anhydride (15 g.), and *o*-dichlorobenzene (40 c.c.) were refluxed for 6.5 hr. Distillation of the product gave the anhydride as a yellow solid (7.5 g.), b. p. 205°/0.3 mm., which crystallised from light petroleum as needles, m. p. 109°, ν_{\max} . 1855, 1767 (anhydride), 1605, 1504 (Ar), and 832 cm.⁻¹ (Ar) (Found: C, 68.2; H, 5.8. C₁₄H₁₄O₄ requires C, 68.3; H, 5.7%).

2-(γ -*p*-Methoxyphenylallyl)butane-1,4-diol (V; R = OMe).—The previous compound (2 g.)

⁵ Cocker, Edward, and Holley, *Chem. and Ind.*, 1955, 772.

was refluxed for 8 hr. with lithium aluminium hydride (1 g.) in ether (50 c.c.). The required diol (1 g.) crystallised from benzene–light petroleum as microneedles, m. p. 82–83°, ν_{\max} 3320 (bonded OH), 1608 cm^{-1} (Ar) (Found: C, 71.0; H, 8.25. $\text{C}_{14}\text{H}_{20}\text{O}_3$ requires C, 71.2; H, 8.5%).

(γ -*p*-Methoxyphenylallyl)succinic Acid.—The anhydride (2 g.) was refluxed for 2 hr. with sodium carbonate (0.9 g.) and water (20 c.c.) and the product was acidified, giving the required acid (1.7 g.) as plates, m. p. 138° (from water), ν_{\max} (Nujol) 2600 (CO_2H), 1701 (CO_2H), 1603, and 1506 cm^{-1} (Ar) (Found: C, 63.9; H, 6.5. $\text{C}_{14}\text{H}_{16}\text{O}_5$ requires C, 63.6; H, 6.1%).

(γ -*p*-Methoxyphenylpropyl)succinic Acid.—The unsaturated acid (0.5 g.) was hydrogenated for 2 hr. in ethanol (20 c.c.) over palladised charcoal (0.2 g.). The required acid formed micro-prisms (0.5 g.), m. p. 108° (from benzene–light petroleum) (Found: C, 63.4; H, 6.9. $\text{C}_{14}\text{H}_{18}\text{O}_5$ requires C, 63.1; H, 6.8%).

Dimethyl Allylsuccinate.—This ester (12 g.), prepared by refluxing allylsuccinic acid (29 g.) with methanol (380 c.c.) and sulphuric acid (20 c.c.) for 2 hr., formed an oil, b. p. 56–59°/0.07 mm., n_D^{21} 1.443, ν_{\max} (liq.) 1736 cm^{-1} (Found: C, 58.25; H, 7.9. $\text{C}_9\text{H}_{14}\text{O}_4$ requires C, 58.05; H, 7.6%).

3-Chlorotetrahydrofuran.—Thionyl chloride (6.3 g.) was slowly added at 0° to a stirred mixture of 3-hydroxytetrahydrofuran ⁴ (44 g.) and pyridine (44 g.). The mixture was stirred at 10° for 10 hr. and extracted several times with ether. The extract was washed with water and fractionated giving 3-chlorotetrahydrofuran (7 g.), b. p. 26°/10 mm. (lit.,⁶ 70–75°/17 mm.). Gas chromatography on a poly-*m*-phenyl ether) column revealed it to be pure.

Ozonolysis of the Butenolide (VI).^{1,5}—A stream of 5% ozonised oxygen was passed into a solution of the butenolide (2 g.) in ethyl acetate (200 c.c.) at –10° until no more ozone was absorbed (2 hr.). The mixture was shaken in hydrogen with palladised charcoal (0.5 g.) giving a solution from which a gum was obtained. This was dissolved in a minimum of boiling light petroleum–methanol and the solution was cooled, giving the aldehyde (VII) (0.35 g.) which crystallised from ethanol as needles, m. p. 155–156°, $[\alpha]_D +6.6^\circ$ (*c* 0.9 in CHCl_3), ν_{\max} (CHCl_3) 1835, 1783 (anhydride), 1767 (lactone), and 1720 cm^{-1} (aldehyde) (Found: C, 63.4; H, 7.0. $\text{C}_{17}\text{H}_{22}\text{O}_6$ requires C, 63.3; H, 6.8%). The aldehyde gave a positive Schiff's test.

Methyl Ester (VIII).—The acid ¹ (0.4 g.), obtained from the lactone (VI) by hydrogenation, in chloroform (10 c.c.) was set aside with an excess of diazomethane in ether. Removal of solvent gave a gum which solidified on treatment with light petroleum. Crystallisation of the solid from methanol gave the ester as needles (0.3 g.), m. p. 135–136°, ν_{\max} (CHCl_3), 1757 (lactone) 1718, and 1152 cm^{-1} (ester) (Found: C, 70.2; H, 9.2. $\text{C}_{18}\text{H}_{28}\text{O}_4$ requires C, 70.1; H, 9.15%).

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⁶ Reppe and Mitarbeiter, *Annalen*, 1955, **596**, 80.