

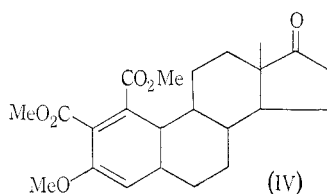
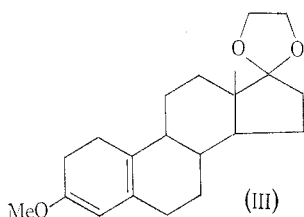
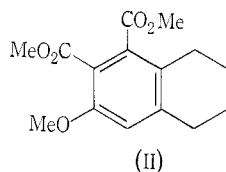
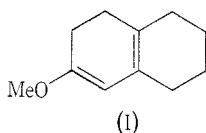
STEROID HORMONES

XX.* AN A-SUBSTITUTED OESTRONE DERIVATIVE

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An early application of the Diels–Alder reaction in synthesis was that of Alder and Rickert¹ in the production of phthalic esters by addition of acetylenedicarboxylic esters to cyclohexa-1,3-dienes, followed by thermal elimination of the bridge from the initial product. Such a process gives rise to methoxyphthalic esters from 1-methoxycyclohexa-1,3-dienes.²



The reaction of dimethyl acetylenedicarboxylate with 1-methoxycyclohexa-1,3-diene (I), in an equilibrium mixture with its unconjugated isomer,³ gave the diester (II) in 83% yield based on the amount of (I) present. Extending the reaction to the oestrone derivative (III), in admixture with its unconjugated isomer,³ gave rise to (IV) after final acid hydrolysis. This steroid represents a new type of substituted oestrone derivative and is an entry point to other 1- and 2-substituted derivatives. Compound (IV) has no oestrogenic or anti-fertility activity.⁴

* Part XIX, *J. chem. Soc. (C)*, 1967, 2509.

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¹ Alder, K., and Rickert, H. F., *Liebigs Ann.*, 1936, **524**, 180.

² Birch, A. J., and Hextall, P. J., *Aust. J. Chem.*, 1955, **8**, 96.

³ Birch, A. J., *J. chem. Soc.*, 1947, 1642.

⁴ Fried, J., Syntex Corporation, Palo Alto, personal communication.

Experimental

General experimental conditions will be reported elsewhere.⁵

Dimethyl 1,2,3,4-Tetrahydro-7-methoxynaphthalene-5,6-dicarboxylate

1,2,3,4,5,6-Hexahydro-7-methoxynaphthalene (3.0 g, 55%) in admixture with the 1,2,3,4,5,8-isomer³ (45%) and dimethyl acetylenedicarboxylate (1.42 g) were heated to 90° for 40 min, then further ester (0.2 g) added and heating continued for 1 hr, raising the temperature to 160°. After a further hour the product was left in a refrigerator and the crystalline solid isolated (2.31 g). The *dimethyl 1,2,3,4-tetrahydro-7-methoxynaphthalene-5,6-dicarboxylate* was recrystallized from acetone–light petroleum, m.p. 97.5–98.5°; ν_{\max} 1730, 1595 cm^{-1} ; λ_{\max} 213, 304 $\text{m}\mu$ ($\log \epsilon$ 4.36; 3.63); τ 3.26 (singlet, 1H, aromatic); 6.18, 6.20 (singlets, 9H, $2\text{CO}_2\text{Me}$ and OMe); 7.25 (multiplet, 4H, benzylic); 8.23 (multiplet, 4H, H 2 and H 3); m/e 278 (Found: C, 64.8; H, 6.1. $\text{C}_{15}\text{H}_{18}\text{O}_5$ requires C, 64.7; H, 6.5%).

1,2-Dimethoxycarbonyloestrone Methyl Ether (Dimethyl 3-Methoxy-7-oxoestra-1,3,5(10)-triene-1,2-dicarboxylate)

17-Ethylenedioxy-3-methoxyoestra-3,5(10)-diene (III) (in 56% admixture with the 1,4-dihydro compound)³ (1.0 g) and dimethyl acetylenedicarboxylate (290 mg) were heated to 95° under nitrogen for 1 hr. Further ester (100 mg) was added and heating continued at 165° for 2 hr. The gummy product was chromatographed on alumina (65 g, neutral, activity III). Elution with light petroleum–benzene (2:1) gave 17-ethylenedioxy-3-methoxyoestra-1,3,5(10)-triene, and later fractions with benzene and benzene–ether gave the desired product mixed with some gum, which was removed by trituration with a small amount of ether. Rechromatography yielded further material. The total product (213 mg) was crystallized from acetone–light petroleum to give the *17-ethylenedioxy derivative* of (IV), m.p. 206–206.5°; ν_{\max} 1735, 1595 cm^{-1} ; λ_{\max} 215, 302 $\text{m}\mu$ ($\log \epsilon$ 4.39, 3.57); τ 3.30 (singlet, 1H, aromatic); 6.18 (multiplet, 13H, $2\text{CO}_2\text{Me}$, OMe, $\text{OCH}_2\text{CH}_2\text{O}$); 9.12 (singlet, 3H, 18-Me); $[\alpha]_{\text{D}}^{28} +294^\circ$ (c , 0.83 in CHCl_3); m/e 444. After keeping at 100°/0.1 mm for 3 hr the m.p. was 210–212° and this material was analysed (Found: C, 67.35; H, 7.0. $\text{C}_{25}\text{H}_{32}\text{O}_7$ requires C, 67.55; H, 7.3%).

Toluene-*p*-sulphonic acid monohydrate (15 mg) was added to the acetal (150 mg) in acetone (25 ml) and left overnight. The product was crystallized from acetone–hexane to give *1,2-dimethoxycarbonyloestrone methyl ether* (108 mg), m.p. 202.5–203.5°; ν_{\max} 1735, 1595 cm^{-1} ; λ_{\max} 215, 301 $\text{m}\mu$ ($\log \epsilon$ 4.31, 3.51); τ 3.27 (singlet, 1H, aromatic); 6.16, 6.20 (singlets, 9H, OMe, $2\text{CO}_2\text{Me}$); 9.08 (singlet, 3H, 18-Me); $[\alpha]_{\text{D}}^{28} +400^\circ$ (c , 0.70 in CHCl_3); m/e 400 (Found: C, 70.0; H, 7.0. $\text{C}_{23}\text{H}_{28}\text{O}_6$ requires C, 70.0; H, 7.05%).

Acknowledgments

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⁵ Birch, A. J., McKague, B., and Someswara Rao, C., *Aust. J. Chem.*, 1969, **22**, in press.