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SYNTHETIC STUDIES RELATING TO ACETYLERGOSTEROL-(TRICARBONYL)IRON

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Summary

Acetylergosterol(tricarbonyl)iron has been prepared in good yield using benzylideneacetone(tricarbonyl)iron. The steroidal complex may be hydroborated or subject to osmolysis, to yield potential vitamin D precursors.

Acetylergosterol(tricarbonyl)iron was first prepared by the action of dodecacarbonyliron on the steroidal ester to give the complex in low yield [1]. In a later investigation, Cross [2] succeeded in catalytic reduction of the free double bond, and thus generated, after oxidation of the tricarbonyliron group, 22,23-dihydroergosterol acetate, a precursor to vitamin D_4. This reaction illustrates the ability of the tricarbonyliron moiety to act as a protecting group for the diene unit. However, no other reports have appeared which utilise this property to modify a steroidal system. This is surprising since ergosterol itself is a precursor to vitamin D_2 [3], while the acetate has been used to produce modified forms of the vitamin [4], in which currently there is so much interest [5].

We now wish to report a much improved synthesis of acetylergosterol(tricarbonyl)iron, and the reactions of this complex with diborane and osmium tetroxide.

The complex was prepared in yields of better than 70%*** by the use of benzylideneacetone(tricarbonyl)iron (cf. Howell et al. [6]). Separation of the required complex from free benzylideneacetone at first proved difficult, but was finally accomplished quite easily by filtration of a solution in toluene through 100 mesh silicic acid, which retained the chalcone. Osmolysis of the complex was readily accomplished. Consistent yields of around 85% were achieved by the use of anhydrous pyridine as solvent in the production of the osmate ester, which was cleaved with aqueous sodium metabisulphite. The free ligand, 22,23-

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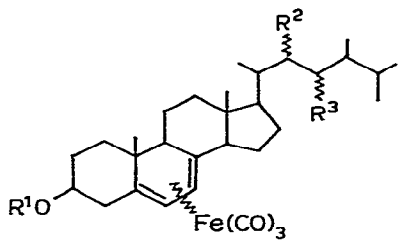
*** 20-30% unreacted steroid was also recovered.

dihydro-22,23-dihydroxyergosteryl acetate, was obtained by oxidation of the complex with alcoholic ferric chloride (cf. Alper and Edward [7]). Although the hydroxy groups must have added *cis*, the absolute configuration about C(22) and C(23) has not been ascertained.

Attempts to produce the diol with a variety of other agents proved unsuccessful. Unfortunately none of these exhibited that rapid attack on the double bond so characteristic of osmium tetroxide. Consequently much longer reaction times or higher temperatures were necessary, but these conditions caused competitive oxidation of the tricarbonyliron moiety. Hydroboration gives different results depending on the conditions. Thus generation of diborane in situ followed by



(Ia) R^1 = Ac; R^2 = H; R^3 = OH

(Ib) R^1 = Ac; R^2 = OH; R^3 = H

(IIa) R = H; R^2 = H; R^3 = OH

(IIb) R = H; R^2 = OH; R^3 = H

oxidation within one hour with alkaline hydrogen peroxide gave a mixture of the alcohols Ia and Ib, and the diols IIa and IIb; the ratio of ester to diol was about 1:4. However, when diborane was passed through a solution of the complex in tetrahydrofuran at 0°C and the resulting solution allowed to stand 60 hours before oxidation, the ratio of ester to diol fell to 1:10. This illustrates that attack at the carbon—carbon double bond proceeds more rapidly than reduction of the ester function; such different reactivities are not uncommon [8].

Hydration via hydroboration usually involves *anti*-Markonikov addition of the elements of water across a double bond. Since the 22,23 bond is in an approximately symmetric environment, it seems likely that a mixture of the 22 and 23 alcohols was formed. However, the selectivity has not been investigated.

Experimental

Ergosteryl acetate was prepared by the method of Stanbury [9].

Benzylideneacetone(tricarbonyl)iron. Two methods of preparation have been used. The first, a modification of the procedure of Howell et al. gave the complex in yields of 45-50%. The second was more suitable for large scale, continuous production of the complex; the yield was moderate.

Benzylideneacetone (5.1 g; 35 mmol) and nonacarbonyldiiron (13.8 g, 38 mmol) were heated under reflux in 40-60 petroleum ether (150 ml) for 5 h. The deep red reaction mixture was filtered and the filtrate stored 24 h at —30°C to give organe-red crystals (4.5 g; 45%).

Benzylideneacetone (20.4 g; 140 mmol) and pentacarbonyliron (25 ml; 190 mmol) in 30-40 petroleum ether (250 ml) were irradiated using a medium pressure mercury vapour lamp (Philips HPK 125) for 24 h. Nitrogen was bubbled through the solution to evaporate some of the solvent and precipitate the product as fine orange crystals (15 g), which were filtered off. The filtrate was topped up to 250 ml with petroleum ether and futher irradiated to give a

second or higher crop. Analysis found: C, 54.4; H, 3.6. $C_{13}H_{10}FeO_4$ calcd.: C, 54.5; H, 3.5%.

Acetylergosterol(tricarbonyl)iron. Ergosterol acetate (4.4 g; 10 mmol) and benzylideneacetone(tricarbonyl)iron (3.4 g; 12 mmol) were heated under reflux in toluene (70 ml) for 6 h. The resulting solution was filtered under reduced pressure through 100 mesh silicic acid with toluene as eluant to give a yellow band containing the product; a second yellow band eluted with ether was discarded. (The filtration column consisted of a sintered glass funnel, 5 cm diam., containing silicic acid to a depth of about 5 cm.) The solvent was removed under reduced pressure to give yellow gum, containing the required product and starting material. These were separated by digestion in cold methanol in which ergosteryl acetate was insoluble. The methanol soluble portion gave the product on evaporation as a yellow gum (4.1 g; 71%), or on standing as yellow crystals. Analysis found: C, 68.3; H, 8.2. $C_{33}H_{46}FeO_5$ calcd.: C, 68.5; H, 8.0%.

3β-Acetoxy-22,23-dihydro-22 (or 23)-hydroxyergosterol(tricarbonyl)iron (Ia and Ib); 22,23-dihydro-3β,22 (or 23)-hydroxyergosterol(tricarbonyl)iron (IIa and IIb). Boron trifluoride etherate (1 ml; 7 mmol) in THF (25 ml) was added with stirring over 20 min to a mixture of acetylergosterol(tricarbonyl)-iron (290 mg; 5 mmol) and sodium borohydride (320 mg; 8 mmol) in THF (25 ml). The mixture was allowed to stand 10 min before treatment with aqueous sodium hydroxide (0.5 *M*; 50 ml) and 50% hydrogen peroxide (2 ml). When evolution of oxygen had ceased, the product was extracted with dichloromethane (3 × 30 ml); the extracts washed with dilute sulphuric acid (twice) and water (twice); dried over anhydrous sodium sulphate; and the solvent removed under reduced pressure to give a yellow gum. PLC (silica gel) with toluene as eluant gave two slow moving bands; the upper band consisted of Ia and Ib (37 mg; 12.5%) and the lower band of Ia and IIb (121 mg; 45%).

Diborane (30 mmol), produced by the action of boron trifluoride etherate on sodium borohydride in THF, was slowly bubbled through acetylergosterol-(tricarbonyl)iron (700 mg; 12 mmol) in THF (50 ml) at 0°C over 30 min. The mixture was allowed to stand 60 h at room temperature before treatment with aqueous sodium hydroxide (0.5 *M*; 50 ml) and 50% hydrogen peroxide (6 ml). When evolution of oxygen had ceased, the product was extracted and purified in essentially the same manner as described above. Yield, IIa + IIb 554 mg (83%). Yield Ia + Ib, 61 mg (8.5%).

3β-Acetoxy-22,23-dihydro-22,23-dihydroxyergosterol(tricarbonyl)iron. Osmium tetroxide (1.0 g) in pyridine (10 ml) was added to acetylergosterol-(tricarbonyl)iron (2.2 g) in pyridine (10 ml) and the mixture allowed to stand 24 h. Water (100 ml) and a large excess of sodium metabisulphate were added and the mixture shaken. Within 5 min the yellow product began to appear on the surface of the mixture. After shaking for 24 h, the product was extracted with ether, and the extract washed with water (twice), dilute sulphuric acid (thrice), and water (twice) before drying over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a yellow glass. PLC (silica gel) with toluene as eluant gave two bands, the upper of which comprised starting material, and the lower the required product, obtained as a yellow glass (1.9 g; 82%). Analysis found: C, 64.9; H, 7.6. $C_{33}H_{48}FeO_7$ calcd.: C, 64.9; H, 7.9%.

3β-Acetoxy-22,23-dihydro-22,23-dihydroxyergosterol. 3β-Acetoxy-22,23-dihydroxyergosterol(tricarbonyl)iron (1.23 g; 2 mmol) and anhydrous ferric chloride (0.65 g; 4 mmol) in ethanol were stirred for 24 h at room temperature. Water was added and the product extracted with chloroform (3 × 50 ml). The extract was washed with water (5 times), and dried over anhydrous sodium sulphate. Removal of solvent gave a colourless gum, which was purified by re-crystallisation from ethanol/water to give transparent flakes, or by addition of water to a solution in ethanol to give a white powder (0.94 g; 99%). The product contained one mole ethanol of crystallisation.

Spectroscopic data

Acetylergosterol(tricarbonyl)iron

m/e 578 (M^+); τ ($CDCl_3$ soln.) 9.30, 9.23, 9.13, 9.10, 9.07 s (Me groups), 8.00 (acetate-H), 5.0-5.5 (broad, 3-H); 5.13d (J = 5 Hz) and 4.7-4.9m (J = 5 Hz) (6- and 7-H; 22- and 23-H).

Hydroboration products

I: *m/e* 596 (M^+); τ ($CDCl_3$ soln.) 8.00 (acetate-H), 6.2-6.6 (broad, 22- and 23-H), 5.2-5.5 (broad, 3-H); 5.10d (J = 5 Hz) and 4.76d (J = 5 Hz) (6- and 7-H).

II: *m/e* 554 (M^+); τ ($CDCl_3$ soln.) 6.0-6.6 (broad, 3-, and 22- or 23-H); 5.10 (J = 5 Hz) and 4.76d (J = 5 Hz) (6-H and 7-H).

Osmolysis products

Iron complex: m/e 612 (M^+); τ ($CDCl_3$ soln.) 9.27 (s, 18-H), 7.99 (s, acetate-H), 6.1-6.5 (broad, 22- and 23-H), 5.0-5.5 (broad, 3-H); 5.09d (J = 4 Hz) and 4.78d (J = 4 Hz) (6- and 7-H).

Free ligand: m/e 472 (M^+); τ ($CDCl_3$ soln.) 9.34 (s, 18-H), 7.97 (s, acetate-H), 6.2-6.6 (broad, 22- and 23-H), 5.2-5.6 (broad, 3-H); 4.61d (J = 5 Hz) and 4.45d (J = 5 Hz) (6- and 7-H).

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