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CORTICOSTEROID 17α-MONOESTERS FROM 17α,21-CYCLIC ORTHOESTERS

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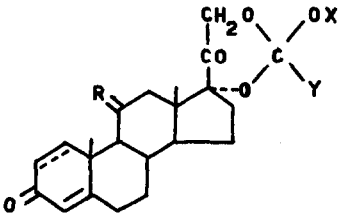
IN pursuing our work concerned with the preparation, by an interchange reaction, of 17α,21-cyclic derivatives of corticosteroids with dihydroxy acetone side chain,[1] we have prepared a great number of 17α,21-orthoesters of corticosteroids, including cortisone, cortisol, cortexolone and their 1-dehydro derivatives.[2]

These compounds were obtained from the 17α,21-diol and a lower alkyl orthoester by brief distillation in benzene in the presence of a small



R = H_2, = O, =  **; X = lower alkyl; Y = H or alkyl**

[1] R. Gardi, R. Vitali and A. Ercoli, In press; see also M. Tanabe and B. Bigley, J.Amer.Chem.Soc. 83, 756 (1961).

[2] 16α,17α-Cyclic orthoesters of triamcinolone have been prepared recentl by L.L. Smith and M. Marx, J.Amer.Chem.Soc. 82, 4625 (1960).

amount of an acid catalyst;[3] the yields varied between 45 and 80%.

Two isomers are possible owing to the new asymmetric carbon atom. At least in the case of orthoformates, we have been able not only to isolate the two epimers, but also to obtain their stereospecific synthesis by a proper choice of the acid catalyst. Thus, as briefly exemplified in the table, the use of pyridine hydrochloride leads to the formation of the more dextro rotatory epimer, whereas a reaction catalysed by p-toluenesulphonic acid furnishes the epimer with negative M_D contribution.

Compound	Catalyst	M.p.	$[\alpha]_D$	ΔM_D (M_D orthoester-M_D parent diol)
R = O; Y = H; X = C_2H_5	Py.HCl	164-166°	+198°	+111
	TsOH	187-189°	+162°	- 39
R = O; Y = H; X = C_2H_5; Δ^1	Py.HCl	157-159°	+184°	+146
	TsOH	210-211°	+140°	- 35
R =  ;Y=H; X = C_2H_5; Δ^1	Py.HCl	140-142°	+126°	+157
	TsOH	198-200°	+ 85°	- 13

The 17α,21-orthoesters are quite stable to base, remaining unchanged after refluxing for 2 hr in methanolic N KOH; they are hydrolysed in various manners by acids. Thus, by heating for 10 min in methanol with a few drops of N HCl, the cyclic orthoformates regenerate the starting free alcohols in high yield. By carrying out the hydrolysis with HCl at room temperature or with oxalic acid by heating, a mixture of 17α-monoformate and 21-monoformate is obtained, which can be resolved by fractionated crystallization. For instance, we have thus prepared prednisolone 17α-monoformate, m.p. 244-245°, $[\alpha]_D$ +20°.[4]

[3] By this procedure we did not observe formation of 3-enol ethers.

[4] Melting points uncorrected, rotations in dioxane. Satisfactory analyses have been obtained for all compounds mentioned.

By a similar procedure prednisolone 17α,21-methylorthoacetate, m.p. 214-216°, $[\alpha]_D$ +61°, furnishes, as a major product, the 17α-monoacetate, m.p. 240-242°, $[\alpha]_D$ +10°, in addition to small amounts of 21-ester. Accordingly, cortisol 17α-monoacetate, m.p. 234-237°, $[\alpha]_D$ +50°, was easily prepared.

Prednisone 17α-monovalerate, m.p. 198-201°, $[\alpha]_D$ +69°, is virtually the sole product of the hydrolysis of prednisone 17α,21-methylorthovalerate, m.p. 200-203°, $[\alpha]_D$ +114°, even if carried out with HCl by heating. Similarly, prednisolone 17-monovalerate, m.p. 210-213°, $[\alpha]_D$ +3,5°, was quantitatively obtained.

The structure of these esters was assigned on the basis of elemental analyses, papergram mobilities and infrared spectra, and also confirmed by acylation to 17α,21-diesters, identical with the products prepared, when possible, by a different route.[5]

Up to now, the 21-oxygenated 17-monoesters have been inaccessible, since one can not selectively acylate the 17α-hydroxyl in the presence of 21-oxygen and means are not known for selectively hydrolysing at 21 in a 17α,21-diester.[6]

A tentative explanation for the formation of the 21-monoester beside the 17α-monoester after the hydrolysis of 17α,21-orthoesters might be found in another unexpected finding: by refluxing in benzene in the presence of p-toluenesulphonic acid, corticosteroid 17α-monoesters readily rearrange to the corresponding 21-monoesters in quantitative yield. The isomerization rate decreases, as a rule, by increasing the acylic chain length. Therefore we could assume that hydrolysis of 17α,21-orthoesters affords, at first, the 17α-monoester only, which can partially rearrange to the 21-monoester.

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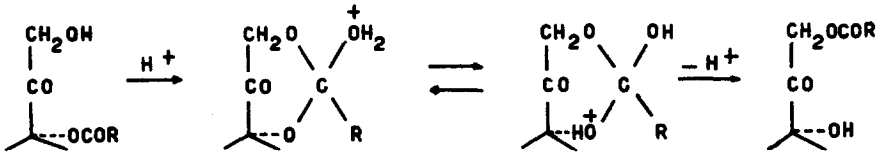
[5] R.B. Turner, J.Amer.Chem.Soc. 75, 3489 (1953).

[6] Cf. H.J. Ringold, G. Rosenkranz and F. Sondheimer, J.Amer.Chem.Soc. 78, 820 (1956).

Seemingly, hydrolysis of 17α, 21-orthoesters to 17α-monoesters occurs with the initial split of the C-O-C bond at C-21.[7] This is also indirectly supported by the assumption of a mechanism via an ortho form for the rearrangement of the 17α-monoester, as reported for other acyl migrations.[8]



This rearrangement might also account for the impossibility to hydrolyse selectively a 17α,21-diester, since conditions for hydrolysis could effect the acyl migration. Others have postulated this kind of rearrangement in basic medium and proposed a cyclic orthoester as an intermediate.[6,9]

According to our previous findings on acetal formation,[1] we have also obtained, as a side-product of the interchange reaction between prednisolone and ethyl orthoformate, a bis-orthoester, the 11-diethoxymethyl ether of 17α, 21-ethylorthoformate, m.p. 144-146°, $[\alpha]_D$ +116°. Its hydrolysis afforded prednisolone 11-monoformate, m.p. 225-228°, $[\alpha]_D$ +127°.

Studies on further acid-catalysed transformation products of steroidal 17α,21-orthoesters are in progress.

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[7] Cf. S. Winstein and B.E. Buckles, J.Amer.Chem.Soc. 65, 613 (1943).

[8] H. Gillman, Organic Chemistry Vol. II, pp. 1610-1611. John Wiley, New York (1947).

[9] L.F. Fieser and M. Fieser, Steroids p. 680. Reinhold, New York (1959).