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A SIMPLE ROUTE TO STEROID 17α,20α,21-TRIOLS

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REDUCTION of the 20-keto group in corticosteroids with the dihydroxyacetone side-chain (I) when carried out with $LiAlH_4$,[1] $LiBH_4$,[2] $NaBH_4$,[3] or catalytically with Adams' catalyst,[4] affords chiefly 17α,20β,21-triols. Preparation of the epimeric 17α,20α,21-triols, which are equally interesting from the point of view of corticosteroid metabolism,[5] is much more difficult; they may be obtained by inversion of 20β-epimers according to Fukushima et al.[6] or by microbiological reduction of the corresponding 20-keto derivatives.[7] We wish to report here a simple general procedure for preparing steroid 17α,20α,21-triols.

1a L.H. Sarett, M. Feurer and K. Folkers, J. Amer. Chem. Soc. 73, 1777 (1951);
b P.L. Julian, E.W. Meyer, W.J. Karpel and W. Cole, Ibid. 73, 1982 (1951).

2 N.L. Wendler, Huang-Minlon and M. Tishler, J. Amer. Chem. Soc. 73, 3818 (1951).

3 E.P. Oliveto and E.B. Hershberg, J. Amer. Chem. Soc. 75, 488 (1953).

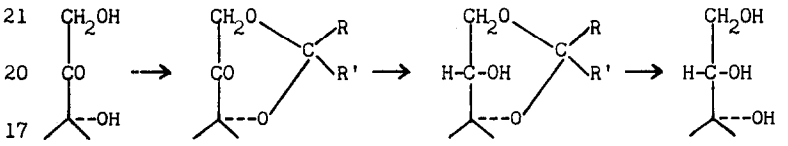
4 L.H. Sarett, J. Amer. Chem. Soc. 71, 1169 (1949).

5 L.F. Fieser and M. Fieser, Steroids p. 720. Reinhold, New York (1959).

6 D.K. Fukushima, N.S. Leeds, H.L. Bradlow, T.H. Kritchewsky, M.B. Stokem and T.F. Gallagher, J. Biol. Chem. 212, 449 (1955).

7a F. Carvajal, O.F. Vitale, M.J. Gentles, H.L. Herzog and E.B. Hershberg, J. Org. Chem. 24, 695 (1959);
b G. Leudemann, W. Charney, A. Mitchell and H.L. Herzog, Ibid. 24, 1385 (1959).

17α,21-Cyclic derivatives (II) of corticosteroids - e.g. acetonides,[8,9] acetals of other aldehydes and ketones[9] and cyclic orthoesters[10] - have been recently described by us and by other workers. We have now found that reduction of all these derivatives (II) with metal hydrides, followed by acid hydrolysis, affords in good yield 17α,20α,21-triols (IV), as practically the sole reaction products; this reaction is independent of the nature of the substituents R and R' (alkyl or alkoxy groups).



I II III IV

Thus, by reduction with $LiAlH_4$, cortexolone 17α,21-cyclopentanonide 3-ethyl enol-ether[9,11] afforded quantitatively a hydroxy-derivative, m.p. 172-175°, $[\alpha]_D$ -137,[12] which after acid hydrolysis yielded 17α,20α,21-trihydroxypregn-4-en-3-one, m.p. 226-229°, $[\alpha]_D$ +57; 20,21-diacetate, m.p. 251-253.5°, $[\alpha]_D$ +17, identical with the products prepared by Julian et al.[1b].

Similar results were obtained by reducing the 20-keto group selectively with $NaBH_4$ in methanol (Norymberski and Woods[13]), or in aqueous dimethylformamide (Taub et al.[14]). Prednisone 17α,21-cyclopentanonide[9] gave a

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8 M. Tanabe and B. Bigley, J. Amer. Chem. Soc. 83, 756 (1961). See also C.H. Robinson, L.E. Finkernor, R. Tiberi and E.P. Oliveto, J. Org. Chem. 26, 2863 (1961).

9 R. Gardi, R. Vitali and A. Ercoli J. Org. Chem. In press.

10 R. Gardi, R. Vitali and A. Ercoli, Tetrahedron Letters 448 (1961).

11 For the preparation of derivatives of this kind see also A.L. Nussbaum, E. Yuan, D. Dincer and E.P. Oliveto, J. Org. Chem. 26, 3925 (1961).

12 All melting points are uncorrected, all rotations are in dioxan. All new compounds gave satisfactory analytical results.

13 J.K. Norymberski and G.F. Woods, J. Chem. Soc. 3426 (1955). See also S.A. Szpilfogel, P.A. Van Hemert and M.S. De Winter, Rec. Trav. Chim. 75, 1227 (1956).

14 B. Taub, R.D. Hoffsommer and W.L. Wendler, J. Amer. Chem. Soc. 81, 3291 (1959).

20-hydroxyacetal, m.p. 275-280° $[\alpha]_D$ +97, which by brief refluxing with 2N-HCl in methanol furnished 17α,20α,21-trihydroxypregna-1,4-diene-3,11-dione, m.p. 239-241°, $[\alpha]_D$ +114; 20,21-diacetate, m.p 262-263°, $[\alpha]_D$ +71.[15]

17α,21-Benzylidenecortisone[9] likewise yielded the corresponding hydroxy-dioxan, m.p. 282-286°, $[\alpha]_D$ +88, which was hydrolyzed to 17α,20α,21-tri-hydroxypregn-4-ene-3,11-dione, m.p. 239-241°, $[\alpha]_D$ +143; 20,21-diacetate, m.p. 273-275°, $[\alpha]_D$ +98.[16]

With compounds carrying an 11β-hydroxyl group, our acetalization procedure may lead to the formation of 11β-mixed acetals, besides 17α,21-cyclic derivatives;[9] however, reduction of these compounds also gives 20α-alcohols. For example, prednisolone acetonide[8,9] yielded a hydroxy-derivative, m.p. 275-278°, $[\alpha]_D$ +25, which after hydrolysis gave 11β,17α, 20α,21-tetrahydroxypregna-1,4-dien-3-one, m.p. 240-243°, $[\alpha]_D$ +27.5; the corresponding 20,21-diacetate showed m.p. 227-229°, $[\alpha]_D$ -6.5, (ΔM_D for acetylation, -129). Similarly from 17α,21-benzylidenecortisol 11-(α-ethoxy) benzyl ether,[17] 11β,17α,20α,21-tetrahydroxypregn-4-en-3-one was obtained in satisfactory yield; m.p. 253-257°, $[\alpha]_D$ +84; 20,21-diacetate, m.p. 203-205°, $[\alpha]_D$ +39; (ΔM_D for acetylation, -131). The configuration of the new triols was allotted as 17α,20α,21 with confidence on the basis of the negative increment of molecular rotation after acetylation (ΔM_D).[18]

Using the aqueous dimethylformamide procedure we have also observed interesting differences in the reduction rates. The time required for the complete reduction of the 20-carbonyl group (disappearance of colour reaction with tetrazolium blue after acid treatment), is usually 10-20 min

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[15] R.E. Beyler, F. Hoffman and L.H. Sarett, J. Org. Chem. 24, 1386 (1959).

[16] R. Neher and A. Wettstein, Helv. Chim. Acta 39, 2062 (1956).

[17] We used, without isolation, the crude product obtained from the interchange reaction between cortisol and benzaldehyde diethylacetal.[9]

[18] L.F Fieser and M. Fieser, Steroids p. 612. Reinhold, New York (1959).

for 11-keto-derivatives, but is lengthened to about 24 hr for 11β-hydroxy compounds; for 11-mixed acetals, even in the presence of bulky substituents, the time is again 10-20 min.

Contrary to what might be expected, this new procedure does not allow the preparation of 17α,20α,21-triol 20-monoacetates; however, 21-monoacetates can be easily obtained. For example, 17α,20α,21-trihydroxypregna-1,4-diene-3,11-dione 17α,21-cyclopentanonide 20-acetate (as III; OAc at C-20), m.p. 209-214°, $[\alpha]_D$ +116, readily obtained by acetylation of the reduction product of prednisone cyclopentanonide, yielded by acid hydrolysis 17α,20α,21-trihydroxypregna-1,4-diene-3,11-dione 21-monoacetate, m.p. 233-235°, $[\alpha]_D$ +103; the structure of this 21-acetate was easily confirmed by acetylation to the 20,21-diacetate and by oxidation (CrO_3-pyridine) to prednisone acetate. Evidently the conditions of hydrolysis cause acetyl migration.[19,20]

17α,20α,21-Triols and derivatives were also obtained from reduction of corticosteroid 17α,21-cyclic orthoesters. Thus, for instance, both isomeric prednisone ethylorthoformates[10] after $NaBH_4$ reduction and acid hydrolysis gave the same 17α,20α,21-triol. Prednisone 17α,21-methylorthoacetate[10] yielded by reduction and hydrolysis 17α,20α,21-trihydroxypregna-1,4-diene-3,11-dione 21-monoacetate, identical with the product described above. In the same way, 11β,17α,20α,21-tetrahydroxypregna-1,4-dien-3-one 21-valerate, m.p. 190-192°, $[\alpha]_D$ +27 was readily obtained from prednisolone 17α,21-methylorthovalerate (m.p. 157-159°, $[\alpha]_D$ +65).

The spiro-ketal or spiro-ester ring E may exist theoretically in two chair conformations; study of optical rotatory dispersion curves of suitable

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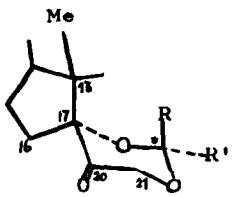
[19] Further details on this and related acyl migrations will be published elsewhere. For the rearrangement of corticosteroid 17α-monoesters, see ref. 10.

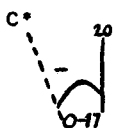
[20] In the 20β-series, Taub *et al.*[14] reported acyl migration between C_{20} and C_{21}, in both directions.

derivatives offers evidence regarding the preferred conformation. The two conformations (V, VI) may conveniently be described by the nomenclature of Klyne and Prelog[21], in terms of the partial conformation of C-20, C-17, O, C*; this is (-)-syn-skew and (+)-syn-skew for V and VI respectively (see VA, VIA).

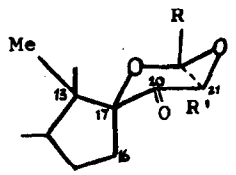
Optical rotatory dispersion curves of two 20-oxo-17,21-ethylorthoformates (epimeric at C*) both showed strong positive Cotton effects due to the 20-carbonyl group. Application of the Octant Rule (Moffitt et al.[22]) indicates that the preferred conformation of ring E is as shown in V (CO at C-20); the alternative conformation (as VI) would give a negative Cotton effect.



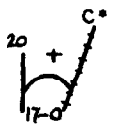
V
(20,17,O,C*; τ, -60)



VA



VI
(20,17,O,C*; τ, +60)



VIIA

In VI there would be severe non-bonded interactions between substituents at C-20 and the angular methyl group at C-13. These would be absent in V; hence, presumably, the preference for the latter conformation.

Conformational analysis of the reduction process suggests that apparently "steric approach control" is markedly less important than "product development control".[23] Inspection of models indicates that in the conformation (V) a 20α-hydroxyl group, although axial to the 1,3-dioxan ring, is

21 W. Klyne and V. Prelog, Experientia 16, 521 (1960).

22 W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, J. Amer. Chem. Soc. 83, 4013 (1961).

23 Cf. W.G. Dauben, G.J. Fonken and D.S. Noyce, J. Amer. Chem. Soc. 78, 2579 (1959); W.G. Dauben, E.J. Blanz, Jr., J. Jiu and N.A. Micheli, Ibid. 78, 3752 (1956).

probably more stable than the 20β-epimer, because in the latter we should have severe steric compression between 20β-hydroxyl and 13β-methyl groups.

The suggestion that the course of metal hydride reduction of these cyclic derivatives is determined by "product development control" is supported by the results of reduction with sodium and alcohol, which as a rule yields the thermodynamically more stable epimer.[24] In fact, the same 20α-hydroxy derivatives were obtained, although in yields less satisfactory than those obtained with metal hydrides.

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[24] Cf. D.H.R. Barton and C.H. Robinson, J. Chem. Soc. 3045 (1954).