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A SIMPLE ROUTE TO STEROID 17α,20α,21-TRIOLS AND THEIR 21-MONOESTERS*

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Abstract—Metal hydride reduction of corticosteroid 20-oxo-17,21-cyclic acetals yields 17α,20α,21-troils after acid hydrolysis. The same reactions on 17,21-alkyl orthoesters yield the corresponding 17α,20α,21-triol 21-monoesters, also obtainable by acid-catalysed intramolecular transesterification from 20α-acyloxy 17,21-cyclic acetals.

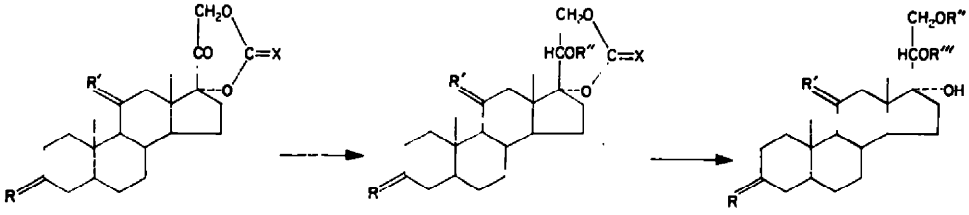
METAL hydride reduction of the carbonyl group in 20-oxopregnanes is known to afford chiefly the 20β-ol,[1] although reduction of certain derivatives, as for instance Δ^{16}-20-ketones[2] may give rise to a mixture of 20β and 20α alcohols in variable ratio. Reduction of the 20-ketone function in corticosteroids with the dihydroxyacetone side chain also affords chiefly 17α,20β,21-triols and the stereochemical course of the reduction is practically the same when it is carried out with $LiAlH_4$,[3] $LiBH_4$,[4] $NaBH_4$,[5] or with Adams's PtO_2 catalyst and hydrogen.[6] Since reduction *in vivo* of the 20-ketogroup in cortical hormones is reported to yield both possible epimers,[7] the interest of a simple route to 17α,20α,21-triols, mainly for metabolic researches, is quite evident. In this connection it had been found that metal hydride reduction of 16α,17α-oxido-20-ketones gave rise to greater amounts of 20α-epimers.[3b] A more definite stereospecific reduction of 20-oxo-17α,21-diols to 17α,20α,21-triols was accomplished by microbiological methods.[8] Inversion of 17α,20β,21-triols at C_{20}, *via* the 17α-acetate 20β-tosylate, was described by Fukushima *et al.*[9] but this method is somewhat tedious.

* This paper is Part VI in the series on *Condensation derivatives in corticosteroid side chains* from Vister Research Laboratories. For preceding paper see Ref. 22. This paper is also Part 12 in the series on optical rotary dispersion from Westfield College; for preceding paper see *Tetrahedron Letters* 1443 (1964).

[1] L. F. Fieser and M. Fieser, *Steroids* p. 567. Reinhold, New York (1959).
[2] Cf. W. R. Benn, *J. Org. Chem.* **28**, 3557 (1963). Formation of 20α-alcohols also occurs in the reduction of 12-substituted 20-ketones (G. Just and R. Nagarajan, *Canad. J. Chem.* **39**, 548 (1961)).
[3] [a] L. H. Sarett, M. Fener 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).
[4] N. L. Wendler, Huang-Minlon and M. Tishler, *J. Amer. Chem. Soc.* **73**, 3818 (1951).
[5] E. P. Oliveto and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 488 (1953).
[6] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1169 (1949).
[7] Ref. 1, p. 720.
[8] [a] F. Carvajal, O. F. Vitale, M. J. Gentles, H. L. Herzog and E. B. Hershberg, *J. Org. Chem.* **24**, 695 (1959);
[b] G. Lendemann, W. Charney, A. Mitchell and H. L. Herzog, *Ibid.* **24**, 1385 (1959).
[9] D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. N. Kritchewsky, M. B. Stokem and T. F. Gallagher, *J. Biol. Chem.* **212**, 449 (1955).

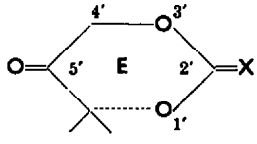
Recently, it has been reported that transacetalation reactions in proper conditions and with suitable reagents on corticosteroids with the dihydroxyacetone side chain yielded 17α,21-cyclic derivatives such as acetals[10,11] and alkyl orthoesters.[12] The availability of compounds of this kind, bearing a spiroacetal ring E, suggested an investigation of the reduction of the 20-carbonyl group in view of a possible change of its stereochemical course owing to the new cyclic nature of the ketone.

As we had hoped, metal hydride reduction of all 17,21-cyclic acetals and orthoesters (I) afforded, practically as the sole reaction products, 20-hydroxyderivatives (II) which were immediately recognized as 20α-alcohols, because their acid hydrolysis gave rise to 17α,20α,21-triols (III).[13]



I II III

The stereochemical course of the reduction proved to be independent of the nature of the substituents (=X) at carbon atom C_2' in the 5'-keto-1',3'-dioxane ring (IV). Also in the case of the pairs of 17,21-alkyl orthoformates epimeric at the new asymmetric carbon atom C_2',[12] the reduction of both epimers gave the same 20α-hydroxy derivative after acid hydrolysis, as was verified, e.g. for the prednisone ethylorthoformates.



IV

The reductions have been carried out according to the following procedures. Reduction with $LiAlH_4$ in ether (method A) or with $NaBH_4$ in tetrahydrofuran (method B) on products bearing the other ketogroups suitably protected, e.g. on 3-ethyl enolether of I (Δ^4, R=O).[14] In the absence of protective groups, all the carbonyls present in the molecule are reduced at the same time. Selective reduction of 20-ketones in the presence of Δ^4 or $\Delta^{1,4}$-3-ketones with $NaBH_4$ in aqueous dimethylformamide

[10] M. Tanabe and B. Bigley, *J. Amer. Chem. Soc.* **83**, 756 (1961); See also C. H. Robinson, L. E. Finkenor, R. Tiberi and E. P. Oliveto, *J. Org. Chem.* **26**, 2863 (1961).

[11] R. Gardi, R. Vitali and A. Ercoli, *J. Org. Chem.* **27**, 668 (1962).

[12] R. Gardi, R. Vitali and A. Ercoli, *Tetrahedron Letters* 448 (1961); *Gazz. Chim. Ital.* **93**, 413 (1963).

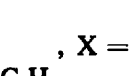
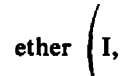
[13] For a preliminary communication of these results see R. Gardi, R. Vitali, A. Ercoli and W. Klyne, *Tetrahedron Letters* 189 (1962).

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

(method C) according to Taub *et al.*[15] or in methanol (method D) according to Norymberski and Woods.[16]

Remarkable differences in reduction rates have been observed according to the nature of the substituent at C_{11}, chiefly if the aqueous dimethylformamide procedure (method C) is used. Thus, reduction of the 20-oxo group in the 17,21-cyclic derivatives of 11-ketocorticosteroids usually required 10 to 20 minutes for completion. The required time was much longer (about 24 hr) for 11β-hydroxyderivatives and was even greater for 11-desoxycompounds. Such a behaviour is noteworthy only for the dramatic increase of the ratio between the reduction rates, since the same order of reactivity has been observed during the reduction of 20-ketones with free side chain. Moreover it has to be pointed out that similar relationships have been noted for the rates of other nucleophilic displacements in the corticosteroid side chain, such as hydrolysis[17] and methanolysis[18] of 21-acetates.

The low reactivity of the 20-carbonyl group in compounds lacking an 11-carbonyl may often make it difficult to prepare the corresponding 20α-derivatives by selective reduction in the presence of the conjugated 3-ketone function. However in the case of 11β-alcohols this difficulty was easily overcome by employing suitable starting materials.

As reported earlier,[11] transacetalation on corticosteroids bearing a 11β-hydroxyl, carried out in proper conditions and with a suitable acetal, e.g. benzaldehyde dimethyl acetal, gives rise to 17,21-cyclic acetals having a mixed acetal in 11β position (e.g. I, R′ =  , X = ). Compounds of this kind undergo reduction according to the procedure C in a very brief time, as short as that necessary to reduce the 11-oxocorticosteroid at C_{20}. Accordingly, the most useful route for preparing e.g. 11β,17α,20α,21-tetrahydroxypregn-4-en-3-one (III, Δ^4, R = O, R′ =  , R″, R‴ = H) proved to be the selective reduction of 17,21-benzylidencortisol 11β-(α-methoxy)-benzyl ether (I, Δ^4, R = O, R′ =  , X = ). After reduction of 17,21-acetals, the 17α,20α,21-triols can be obtained by acid hydrolysis in mild conditions. Also in the case of 17,21-alkylorthoformates, hydrolysis with mineral acids, after reduction, affords free 17α,20α,21-triols. Hydrolysis in the same conditions of higher 20α-hydroxy-17α,21-orthoesters yields the corresponding 21-monoesters. Orthoformates give 21-monoformates after milder treatment with oxalic acid.

Thus, prednisone 17,21-methylorthaocetate yielded by reduction and acid hydrolysis a product recognized as 17α,20α,21-trihydroxypregna-1,4-diene-3,11-dione

[15] B. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **81**, 3291 (1959).

[16] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955); See also S. A. Szpilfogel, P. A. Van Hennert and M. S. De Winter, *Rec. Trav. Chim.* **75**, 1227 (1956).

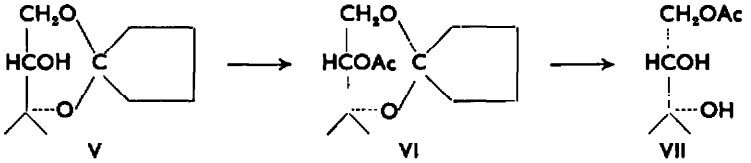
[17] V. Delaroff, R. Smalig, M. Legrand and J. Mathieu, *Bull. Soc. Chim.* 725 (1963).

[18] R. Gardi and R. Vitali, *Gazz. Chim. Ital.* **93**, 1520 (1963).

21-monoacetate. Acetylation of this gave the corresponding 20,21-diacetate, identical with the product prepared by Beyler *et al.*,[19] while oxidation with CrO_3 in pyridine led to prednisone acetate.

It is noteworthy that acid hydrolysis of 20-hydroxy 17,21-orthoesters follows a course quite different from that of orthoesters of corticosteroids with the dihydroxyacetone side-chain; the latter as a rule afford chiefly 17α-monoesters.[12,20] Evidently, the 20-ketone function plays an important role in promoting protonation of the 21-oxygen. Reduction and hydrolysis of orthoesters thus appears to be useful procedure for preparing 17α,20α,21-triol 21-monoesters.

An alternate route, which does not involve the corresponding orthoesters, arises from the easy intramolecular transesterification of 20-monoesters. For instance, prednisone cyclopentanonide was reduced selectively and the product (V) acetylated in



pyridine to give 20α-acetoxy-17α,21-cyclopentylidenedioxypregna-1,4-diene-3,11-dione (VI). Alkaline saponification of the latter regenerated the free hydroxy acetal, thus excluding structural change during acetylation. However, acid hydrolysis gave rise to 17α,20α-dihydroxy-21-acetoxypregna-1,4-diene-3,11-dione (VII), identical with the product obtained as above. Acyl migration from 20- to 21-oxygen evidently occurs during acid hydrolysis. In a similar manner the 21-monoesters of all 17α,20α,21-triols can be easily prepared.[21]

Experiments with suitable mixed 20,21-diesters showed that the same intramolecular transesterification takes place also by basic catalysis. Furthermore 20-monoesters of 17α,20β,21-triols also rearrange to 21-monoesters by the action of both acids and bases.[22]

However, in the 20β series it was possible to isolate 20-monoacetates. Reduction of a suitable prednisone 21-(α-alkoxy)-ether, acetylation and removal of the protective group from the 21-hydroxyl by careful hydrolysis with oxalic acid afforded 17α,20β,21-trihydroxy-pregna-1,4-diene-3,11-dione 20-monoacetate. On the contrary, hydrolysis of 20α-acyloxy-17α,21-cyclic acetals (VI) even in very mild conditions directly yielded 21-monoesters (VII) in all instances.

In view of the behaviour of 20β-acyloxy-21-ethers, it might be suggested that the failure to isolate 20α-monoesters in this manner is due to the initial protonation of the 21-oxygen in the cyclic acetal, namely to the initial cleavage of the C_{21}—O—C bond at C_{21}.

The α-configuration at C_{20} of the new 17α,20α,21-triols was confirmed by the negative increment of molecular rotation after acetylation of the 20,21-diacetates.[23]

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

[20] R. Gardi, R. Vitali and A. Ercoli, *Gazz. Chim. Ital.* **93**, 431 (1963).

[21] In the case of 11β-hydroxy-17α,21-benzylidenedioxy-20α-acetoxy-pregn-4-en-3-one 11-(α-methoxy-)benzyl ether while hydrolysis with H_2SO_4 yielded the 21-acetate of the tetraol, treatment with HCl or oxalic acid permitted the selective hydrolysis of the C_{11}-acetal group alone.

[22] R. Gardi, R. Vitali and A. Ercoli, *Gazz. Chim. Ital.* **93**, 1642 (1963).

[23] Ref. 1, p. 612.

The values for all the 17α,20α,21-triols prepared are reported in Table 1. For cortolone the increment (M_D triacetate—M_D tetraol) is reported; the value is within the normal limits, taking in account the M_D contribution (+82) of acetylation of the 3-hydroxy.[24] The value for the 5-ene-3β-ol is also that for triacetylation, and should be corrected for the contribution (−35) of 3-acetylation.[24]

TABLE 1

Compound	M_D 20,21-Diol	M_D' 20,21-Diacetate	ΔM_D for acetylation
17α,20α,21-Trihydroxypregn-4-en-3-one	+199	+ 74	−125
17α,20α,21-Trihydroxypregn-4-en-3,11-dione	+518	+438	− 80
17α,20α,21-Trihydroxypregna-1,4-dien-3,11-dione	+411	+316	− 95
11β,17α,20α,21-Tetrahydroxypregn-4-en-3-one	+306	+175	−131
11β,17α,20α,21-Tetrahydroxypregna-1,4-dien-3-one	+100	− 29	−129
3β,17α,20α,21-Tetrahydroxypregn-5-ene	−251	−379†	−128‡
3β,17α,20α,21-Tetrahydroxy-5β-pregnan-11-one	+125	+ 99†	-- 26‡

† M_D for 3,20,21-triacetate

‡ −93, −108 respectively after correction for acetylation at C_3.

As might be expected, the same molecular rotation relationships do not apply to 20α-hydroxy-17,21-cyclic acetals, all of which showed positive values ΔM_D for (acetylation).

Conformational analysis

Spiro-ring E. The spiro-ketal or spiro-ester ring E may exist theoretically in two chair conformations (cf. the discussion by Fieser and Fieser[25] on the conformations of ring F in the spiroketal system of the sapogenins).

Study of optical rotatory dispersion curves of suitable derivatives offers evidence regarding the preferred conformation. The two conformations (VIII, IX) may conveniently be described by the nomenclature of Klyne and Prelog,[26] in terms of the partial conformation of C-20, C-17, O, C*; this is (−)-*syn-clinal* and (+)-*syn-clinal* for VIII and IX, respectively (see VIIIA, IXA).

Optical rotatory dispersion curves of six 20-oxo-17,21-orthoesters all showed strong positive Cotton effects due to the 20-carbonyl group (Table 2). Application of the Octant Rule (Moffitt *et al.*[27]) indicates that the preferred conformation of ring E must therefore be shown in VIII (CO at C-20); the alternative conformation (as IX) would give a negative Cotton effect. (Any effect of the two heterocyclic oxygen atoms in the Octant treatment can be neglected, because they are symmetrically disposed with reference to the carbonyl group.)

Since the orthoester carbon atom C* is *opposite* to the carbonyl C-20 of the six-membered ring E (i.e. in 1,4-position) it would be expected that the configuration at C* would not significantly effect the amplitude; this is found to be the case experimentally.

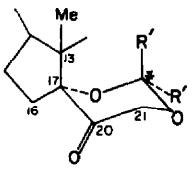
In IX there would be severe non-bonded interactions between substituents at C-20

[24] W. Klyne in E. A. Braude and F. C. Nachod *Determination of Organic Structures by Physical Methods*. Academic Press (1955).

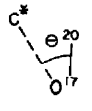
[25] Cf. Fieser L. F. and M. Fieser, Ref. 1, p. 824.

[26] W. Klyne and V. Prelog, *Experientia* **16**, 521 (1960).

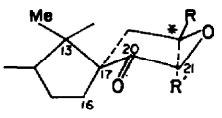
[27] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).



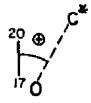
VIII
(20,17,0,C*; τ,-60)



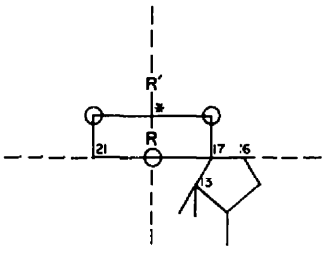
VIII a



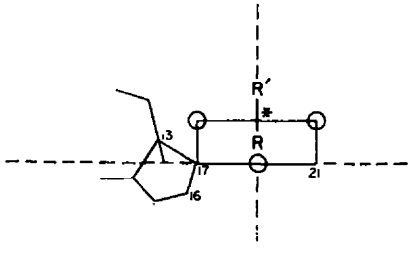
IX
(20,17,0,C*; τ,+60)



IX a



VIII b



IX b

and the angular methyl group at C-13. These would be absent in VIII; hence, presumably, the preference for the latter conformation.

Reduction progress. Conformational analysis of the reduction process suggests that apparently "steric approach control" is markedly less important than "product development control".[28] Inspection of models indicates that in the conformation (VIII) a 20α-hydroxyl group, although axial to the 1,3-dioxan ring, is probably more

TABLE 2. OPTICAL ROTATORY DISPERSION OF 17α,21-ORTHOESTERS[12]

Compound (as VIII)			Cotton effect Amplitude (a)	
Substituents in ring A	Orthoester group	m.p.	MeOH	Dioxan
3β-Benzoyloxy,5-ene	Et orthoformate	153–6	+137	+125
3β-Benzoyloxy,5-ene	Et orthoformate	174–6	+ 83!	+124!
3β-Benzoyloxy,5-ene	Me orthovalerate		+139!	+130!
3β-Ethoxy,5α(H)	Et orthoformate	80–3	+127	+132
3β-Ethoxy,5α(H)	Et orthoformate	155–8	+145	+146
3β-Ethoxy,5α(H)	Me orthoacetate		+171	+166

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

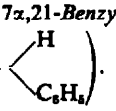
[28] Cf. W. G. Dauben, G. J. Fonken and D. S. Noyce, *J. Amer. Chem. Soc.* **78**, 2579 (1959); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, N. A. Micheli, *Ibid.* **78**, 3752 (1956).

stable epimer.[29] Reduction by this procedure of cortexolone 3-ethyl enol ether 17,21-cyclopentanonide afforded, after hydrolysis and acetylation, 20α,21-diacetoxy-17α-hydroxy-pregn-4-en-3-one. The yield was low, since extensive cleavage of the ether linkages occurred,[30] but thin-layer chromatography indicated that the 20α epimer was the only 17α,20,21-triol present.

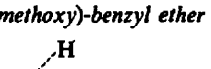
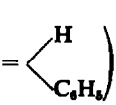
EXPERIMENTAL

M.ps are uncorrected. Unless stated otherwise, optical rotations at the sodium D line were taken in 0·5% dioxan solution at 24° ± 1°. UV spectra were determined in 95% ethanol with an Optica CF_4 spectrophotometer. The IR spectra were measured in Nujol mull on the Perkin–Elmer 21 instrument (PE-21). Optical rotatory dispersion curves were measured in methanol or dioxan solution (conc. approx. 0·1 mg/ml) at 18–22° on a Rudolph spectropolarimeter.

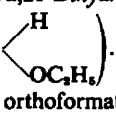
Preparation of some hitherto undescribed starting products (I)

17α,21-*Benzylidenecortisol* 11-(α-*methoxy*)-*benzyl ether* (I, Δ^4, R = O, R′ =  , X = ). Transacetylation of cortisol (15 g) with benzaldehyde dimethyl acetal (30 ml) carried out by the conventional method,[11] gave a crystalline product (18·4 g) m.p. 196–198°. An analytical sample had m.p. 205–208°;[31] $[\alpha]_D$ +107°; λ_{max} 241 mμ (ε 16,000); ν_{max}^{nujol} 1718, 1666, 1626, 1501, 1106, 1070, 1033 and 970 cm^{-1} (Found: C, 75·56; H, 7·44. $C_{36}H_{42}O_6$ requires: C, 75·76; H, 7·42%).

17α,21-*Benzylideneprednisolone* 11-(α-*methoxy*)-*benzyl ether*

(I, $\Delta^{1,4}$, R = O, R′ =  , X = ).

Prednisolone (10 g), treated as above described gave a crystalline product (14·37 g) m.p. 195–208°. An analytical sample had m.p. 206–212°; $[\alpha]_D$ +106·8°; λ_{max} 243 mμ (ε 15,700); ν_{max}^{nujol} 1714, 1658, 1621, 1604, 1123, 1058, 1005, 968 and 943 cm^{-1}. (Found: C, 76·10; H, 7·18. $C_{36}H_{40}O_6$ requires: C, 76·03; H, 7·09%).

17α,21-*Dihydroxy*-5β-*pregnan*-3,11,20-*trione* 17α,21-*ethyl orthoformate* (I, 5β, R = R′ = O, X = ). The interchange reaction of 17α,21-dihydroxy-5β-pregnan-3,11,20-trione (5 g) and ethyl orthoformate (10 ml), with pyridine hydrochloride (0·1 g) as catalyst,[12] gave the title compound (3·3 g) m.p. 198–201°; $[\alpha]_D$ +108°; ν_{max}^{nujol} 1734, 1703, 1130, 1078, 1042 and 939 cm^{-1}. (Found: C, 68·71; H, 8·07. $C_{24}H_{34}O_6$ requires: C, 68·87; H, 8·19%).

General Procedures for the Reduction of 20-*oxo*-17,21-*Cyclic Derivatives*

Method A

17α,20α,21-*Trihydroxypregn*-4-*en*-3-*one* 17α,21-*cyclopentanonide* 3-*ethyl enol ether* (3-ethyl enol ether of II, Δ^4, R = O, R′ = H_2, R″ = H, X = $(CH_2)_4$). To a suspension of $LiAlH_4$ (4 g) in anhydrous ether (150 ml) was added a solution of cortexolone cyclopentanonide 3-ethyl enol ether[11] (3-ethyl enol ether of I, Δ^4, R = O, R′ = H_2, X = $(CH_2)_4$). The mixture was refluxed with stirring for 45 min. After decomposition of the excess hydride with ethyl acetate, saturated Na_2SO_4 solution was added; the organic layer was then separated and washed with water. The dried extract was evaporated and the residue crystallized from methylene chloride–methanol to give a product (8·6 g), m.p. 168–173°. An analytical sample had m.p. 172–175°; $[\alpha]_D$ −136°; λ_{max} 241 mμ (ε = 19,500); ν_{max}^{nujol}

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

[30] For the cleavage and rearrangement of 17,21-cyclic derivatives in alkaline medium at high temp. see R. Gardi and R. Vitali, *Gazz. Chim. Ital.* 93, 1961 (1963).

[31] The broad m.p. range exhibited by this benzylidene derivative and by other related compounds may be ascribed to the existence of an unresolved epimeric mixture.

3490, 1654, 1632, 1116 and 1054 cm^{-1}. (Found: C, 75·76; H, 9·51. $C_{26}H_{42}O_6$ requires: C, 75·97; H, 9·56%).

20-*Acetate* (3-ethyl enol ether of II, Δ^4, R = O, R′ = H_2, R″ = $COCH_3$, X = $(CH_2)_4$). A solution of the above described 20α-hydroxy-derivative (3 g) in pyridine (30 ml) and acetic anhydride (15 ml) was allowed to react for 90 min on a boiling water bath. The mixture was then poured into ice-water. The solid which precipitated was collected by filtration and crystallized from methanol giving a substance (2·97 g) m.p. 97–101°. An analytical sample had m.p. 98–101°; $[\alpha]_D$ −91°; λ_{max} 241 mμ (ε 18,900); ν_{max}^{nujol} 1739, 1654, 1630, 1238, 1125 and 1049 cm^{-1}. (Found: C, 74·18; H, 9·16. $C_{30}H_{44}O_6$ requires: C, 74·34; H, 9·15%).

Method B

3α,17α,20α,21-*Tetrahydroxy-5β-pregnan*-11-*one* 17α,21-*ethyl-orthoformate* (II, 5β, R =  , R′ = O, R″ = H, X = ). A solution of $NaBH_4$ (0·6 g) in water (3 ml) was added to I (R = R′ = O, X = ; 3 g) in tetrahydrofuran (50 ml) and the mixture was kept at room temp. overnight. After removing the solvent *in vacuo*, water was added and the solid collected by filtration. Crystallization from acetone–hexane yielded a product (2·1 g), m.p. 192–195°. The analytical sample recrystallized from methanol showed m.p. 193–195°; $[\alpha]_D$ +41°; ν_{max}^{nujol} 3340, 1699, 1248, 1128, 1073, 1024, 945 and 878 cm^{-1}. (Found: C, 68·14; H, 8·95. $C_{24}H_{38}O_6$ requires: C, 68·22; H, 9·07%).

Method C

17α,21-*Benzylidenedioxy*-20α-*hydroxypregn*-4-*en*-3,11-*dione* (II, Δ^4, R = R′ = O, R″ = H, X = ). To a solution of I[11] (Δ^4, R = R′ = O, X  ; 5 g) in dimethylformamide (200 ml), $NaBH_4$ (1 g) in water (50 ml) was added. The mixture was kept at room temp. with stirring for 15 min, then water (1,500 ml) was added and the solid was collected by filtration. Crystallization from methylene chloride–methanol gave the pure product (4·28 g) m.p. 284–286°; $[\alpha]_D$ +28°; λ_{max} 239 mμ (ε 15,000); ν_{max}^{nujol} 3420, 1693, 1644, 1598, 1116, 1058 and 1040 cm^{-1}. (Found: C, 74·65; H, 7·78. $C_{28}H_{34}O_6$ requires: C, 74·64; H, 7·61%).

20-*Acetate* (II, Δ^4, R = R′ = O, R″ = $COCH_3$, X = ): m.p. 207–209°; $[\alpha]_D$ = +89°; λ_{max} 238–239 mμ (ε 15,000); ν_{max}^{nujol} 1725, 1700, 1685, 1610, 1228, 1165, 1080 and 1038 cm^{-1}. (Found: C, 73·32; H, 7·45. $C_{30}H_{36}O_6$ requires: C, 73·14; H, 7·37%).

According to the above procedure the following compounds were prepared starting from the corresponding 20-*ketones*[11,12]

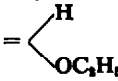
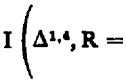
17α,20α,21-*Trihydroxypregna*-1,4-*dien*-3,11-*dione* 17α,21-*acetonide* (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = ): m.p. 220–225°; $[\alpha]_D$ +107°; λ_{max} 239–240 mμ (ε 14,500); ν_{max}^{nujol} 3440, 1704, 1660 1621, 1605, 1150, 1063 and 1039 cm^{-1}. (Found: C, 72·24; H, 8·05. $C_{24}H_{32}O_6$ requires: C, 71·97; H, 7·98%).

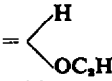
17α,20α,21-*Trihydroxypregna*-1,4-*dien*-3,11-*dione* 17α,21-*cyclopentanonide* (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = $(CH_2)_4$): m.p. 275–280°; $[\alpha]_D$ +97°; λ_{max} 239–240 mμ (ε 14,500); ν_{max}^{nujol} 3440, 1715, 1667, 1627, 1609, 1125 and 1044 cm^{-1}. (Found: C, 73·33; H, 8·13. $C_{26}H_{34}O_6$ requires: C, 73·21; H, 8·04%).

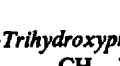
20-*Acetate* (II, $\Delta^{1,4}$, R = R′ = O, R″ = $COCH_3$, X = $(CH_2)_4$): m.p. 209–214°; $[\alpha]_D$ +116°; λ_{max} 240 mμ (ε 14,500); ν_{max}^{nujol} 1738, 1705, 1668, 1625, 1606, 1238, 1132, 1054, 1024 and 988 cm^{-1}. (Found: C, 71·49; H, 7·54. $C_{28}H_{36}O_6$ requires: C, 71·77; H, 7·74%). Alkaline hydrolysis: A

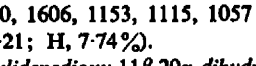
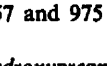
solution of the above 20-acetate (0·25 g) in methanol (15 ml) and 10% K_2CO_3 aqueous solution (1·75 ml) was refluxed for 5 hr. Evaporation of part of the solvent and dilution with water afforded a product (0·2 g) m.p. 270–275°; this proved to be identical with the 20α-hydroxy-derivative submitted to the acetylation.

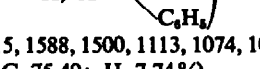
20-Benzoate (II, $\Delta^{1,4}$, R = R′ = O, R″ = COC_6H_5, X = $(CH_2)_4$). The 20α-hydroxy-cyclopentanonide (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = $(CH_2)_4$; 2 g) in pyridine (20 ml) was treated at 0° with benzoyl chloride (2 ml) and allowed to stand overnight at room temp. Crystallization from methanol gave a product m.p. 224–227°; $[\alpha]_D$ +149°; λ_{max} 234 mμ (ε 27,000; ν_{max}^{nujol} 1712, 1671, 1634, 1607, 1588, 1273, 1126, 1071 and 1041 cm^{-1}. (Found: C, 74·68; H, 7·13. $C_{33}H_{38}O_6$ requires: C, 74·69; H, 7·22%).

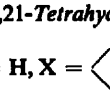
17α,20α,21-Trihydroxypregna-1,4-dien-3,11-dione 17α,21-ethyl-orthoformates (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = ). (a) From I ($\Delta^{1,4}$, R = R′ = O, X = ) epimer $[\alpha]_D$ +184°;[12] m.p. 213–215°; $[\alpha]_D$ +92·5°; λ_{max} 240–241 mμ (ε 13,700); ν_{max}^{nujol} 3350, 1698, 1650, 1607, 1597, 1180, 1132, 1098, 1039 and 890 cm^{-1}. (Found: C, 69·04; H, 7·73. $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%).

(b) From I ($\Delta^{1,4}$, R = R′ = O, X = ) epimer $[\alpha]_D$ +157°;[12] m.p. 186–188°; $[\alpha]_D$ +86·5°; λ_{max} 240–241 mμ (ε 14,000); ν_{max}^{nujol} 3520, 3280, 1692, 1653, 1610, 1597, 1159, 1057, 1012 and 886 cm^{-1}. (Found: C, 69·06; H, 7·67. $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%).

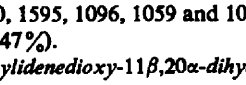
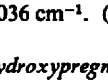
17α,20α,21-Trihydroxypregna-1,4-dien-3,11-dione 17α,21-methyl orthoacetate (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = ): m.p. 190–192°; $[\alpha]_D$ +67°; λ_{max} 239–240 mμ (ε 14,100); ν_{max}^{nujol} 3560, 1692, 1668, 1630, 1606, 1153, 1115, 1057 and 975 cm^{-1}. (Found: C, 69·01; H, 7·77. $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%).

17α,21-Benzylidenedioxy-11β,20α-dihydroxypregn-4-en-3-one 11-(α-methoxy)-benzyl ether (II, Δ^4, R = O, R′ =  , R″ = H, X = ): m.p. 235–237°; $[\alpha]_D$ +90°; λ_{max} 243 mμ (ε 14,500); ν_{max}^{nujol} 3460, 1660, 1615, 1588, 1500, 1113, 1074, 1044, 1023 and 982 cm^{-1}. (Found: C, 75·53; H, 7·70. $C_{36}H_{44}O_6$ requires: C, 75·49; H, 7·74%).

20-Acetate (II, Δ^4, R = O, R′ =  , R″ = $COCH_3$, X =): m.p. 175–176°; $[\alpha]_D$ +122·5°; λ_{max} 242–243 mμ (ε 15,800): ν_{max}^{nujol} 1731, 1670, 1611, 1226, 1096, 1060 and 978 cm^{-1}. (Found: C, 74·29; H, 7·59. $C_{26}H_{46}O_7$ requires: C, 74·24; H, 7·54%).

11β,17α,20α,21-Tetrahydroxypregna-1,4-diene-3-one 17α,21-acetonide (II, $\Delta^{1,4}$, R = O, R′ =  , R″ = H, X =): m.p. 275–278°; $[\alpha]_D$ +25°; λ_{max} 244–245 mμ (ε 14,300); ν_{max}^{nujol} 3440, 1655, 1596, 1080 and 1032 cm^{-1}. (Found: C, 71·69; H, 8·69. $C_{24}H_{34}O_5$ requires: C, 71·61; H, 8.5%).

11β,17α,20α,21-Tetrahydroxypregna-1,4-dien-3-one 17α,21-cyclopentanonide (II, $\Delta^{1,4}$, R = O, R′ =  , R″ = H, X = $(CH_2)_4$): m.p. 270–273°; $[\alpha]_D$ +27°; λ_{max} 244 mμ (ε 14, 200); ν_{max}^{nujol} 3440, 1652, 1600, 1595, 1096, 1059 and 1036 cm^{-1}. (Found: C, 72·65; H, 8·52. $C_{26}H_{36}O_5$ requires: C, 72·86; H, 8·47%).

17α,21-Benzylidenedioxy-11β,20α-dihydroxypregna-1,4-dien-3-one 11-(α-methoxy)-benzyl ether (II, $\Delta^{1,4}$, R = O, R′ =  , R″ = H, X = ): m.p. 228–232°; $[\alpha]_D$ +82°;

λ_{max} 244 mμ (ε 14,600); ν_{max}^{nujol} 3400, 1650, 1614, 1597, 1112, 1074, 1024, 982 and 955 cm^{-1}. (Found: C, 75·66; H, 7·38. $C_{36}H_{42}O_6$ requires: C, 75·76; H, 7·42%).

20-*Acetate* (II, $\Delta^{1,4}$, R = O, R′ =  , R″ = $COCH_3$, X = ): m.p. 202–206°; $[\alpha]_D$ +106°; λ_{max} 243–244 mμ (ε 15,250); ν_{max}^{nujol} 1743, 1661, 1622, 1604, 1499, 1238, 1097, 1049 and 951 cm^{-1}. (Found: C, 74·49; H, 7·23. $C_{38}H_{44}O_7$ requires: C, 74·48; H, 7·24%).

Method D

Almost all the above reported compounds were prepared with comparable results by the procedure of Norymberski.[16] As an example, to a solution of I ($\Delta^{1,4}$, R = R′ = O, X = $(CH_2)_4$; 1 g) in methanol (200 ml) kept at 0° in a N_2 atm. $NaBH_4$ (145 mg) in methanol (20 ml) was added with stirring. After 30 min the solvent was partially evaporated *in vacuo*. Then the reaction mixture was poured into water and the precipitate collected by filtration.

Crystallization from methylene chloride–methanol gave a material (0·5 g) m.p. 267–270° which showed no depression of the m.p. upon admixture with a sample of II ($\Delta^{1,4}$, R = R′ = O, R″ = H, X = $(CH_2)_4$) prepared by method C.

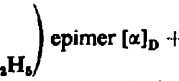
Reduction with sodium and alcohol

To a boiling solution of the 3-ethyl enol ether of I (Δ^4, R = O, R′ = H_2, X = $(CH_2)_4$) (1 g) in n-propanol (50 ml) in which a small quantity of Na had been previously dissolved, Na (2 g) was added in portions during 30 min. The mixture was refluxed for an additional 30 min, then diluted with water and extracted with ether. After removal of the solvents, the oily residue was submitted to hydrolysis with HCl as reported below. The residue obtained by extraction in chloroform was then acetylated with acetic anhydride in pyridine. Compound II (Δ^4, R = O, R′ = H_2, R″ = R‴ = $COCH_3$; 0·140 g) was obtained; m.p. 247–251°; $[\alpha]_D$ +17·4°; no depression of m.p. in admixture with an authentic sample.[30] Thin layer chromatography of the whole product before the acetylation showed that the 20α epimer was the sole 17,20,21-trihydroxycompound.

17α,20α,21-*Triols*

17α,20α,21-*Trihydroxypregna*-1,4-*dien* 3,11-*dione* (III, R = R′ = O, R″ = R‴ = H). (a) A mixture of II ($\Delta^{1,4}$, R = R′ = O, R″ = H, X = $(CH_2)_4$; 0·3 g) and methanol (5 ml) containing dil HCl (1 ml) was boiled on the water bath until the solid dissolved and it was then warmed for an additional 5 min. After evaporation of part of the solvent, water (2 ml) was added and the solid (0·24 g) collected by filtration, washed and dried (m.p. 235–238°, with a phase change at 222°). Crystallization from methanol gave the product with m.p. 239–241° (226°); $[\alpha]_D$ +114°; λ_{max} 240 mμ (ε 14,600); ν_{max}^{nujol} 3380, 1704, 1664, 1626, 1605, 1058 and 1045 cm^{-1}. (Reported: m.p. 240–242° (225–227°), $[\alpha]_D$ +132 ± 2°;[19] m.p. 238–240° (225°), $[\alpha]_D$ +117°[8a]).

20,21-*Diacetate* (III, $\Delta^{1,4}$, R = R′ = O, R″ = R‴ = $COCH_3$). The diacetate prepared in the usual manner with pyridine and acetic anhydride overnight, and recrystallized from acetone had m.p. 262–263°, $[\alpha]_D$ −71°; λ_{max} 239–240 mμ (ε 14,500); ν_{max}^{nujol} 3470, 1737, 1718, 1704, 1674, 1636, 1609, 1266, 1237, 1069 and 1050 cm^{-1}. (Reported: m.p. 255–259°, $[\alpha]_D$ +71 ± 2°;[19] m.p. 250–251° (sample at 267–270°), $[\alpha]_D$ +75°[8a]).

(b) Acid hydrolysis as above described of the orthoformate (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = ) epimer $[\alpha]_D$ +92·5° (0·2 g), yielded the same trihydroxyderivative (0·12 g) m.p. 233–235° (226°), which gave the identical diacetate; m.p. 261–263°; $[\alpha]_D$ +70°.

(c) Hydrochloric acid hydrolysis as above of the orthoformate (II, $\Delta^{1,4}$, R = R′ = O, R″ = H, X = ) epimer $[\alpha]_D$ +68·5° (0·2 g), yielded the same product m.p. 236–238° (227°) which gave the same diacetate m.p. 259–262°, $[\alpha]_D$ +70°.

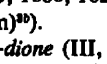
According to the above procedure the following compounds were prepared from the corresponding 17,21-acetals:

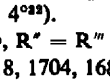
17α,20α,21-*Trihydroxypregn-4-en-3-one* (III, Δ^4, R = O, R′ = H_2, R″ = R‴ = H): m.p. 226–229°; $[\alpha]_D$ +74·5°; λ_{max} 242 mμ (ε 15,550); ν_{max}^{nujol} 3530, 3470, 3380, 1660, 1618, 1080, 1072 and 1056 cm^{-1}. (Reported m.p. 225–227·5°, $[\alpha]_D$ +76·2° (chloroform)[35]).

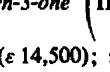
20,21-*Diacetate* (III, Δ^4, R = O, R′ = H_2, R″ = R‴ = $COCH_3$): m.p. 251–253·5°; $[\alpha]_D$ +17°; λ_{max} 242 mμ (ε 15,900); ν_{max}^{nujol} 3450, 1715, 1680, 1621, 1264, 1237, 1063 and 1030 cm^{-1}. (Reported: m.p. 251–253·5°, $[\alpha]_D$ +31·5° (chloroform)[35]).

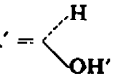
17α,20α,21-*Trihydroxypregn-4-en-3,11-dione* (III, Δ^4, R = R′ = O, R″ = R‴ = H): m.p. 239–241°; $[\alpha]_D$ −143°; λ_{max} 239 mμ (ε 14,500); ν_{max}^{nujol} 3560, 3400, 1706, 1663, 1620 and 1054 cm^{-1}. (Reported: m.p. 240–243°, $[\alpha]_D$ +141 ± 4°[22]).

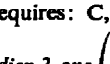
20,21-*Diacetate* (III, Δ^4, R = R′ = O, R″ = R‴ = $COCH_3$): m.p. 273–275°; $[\alpha]_D$ +98°; λ_{max} 239 mμ (ε 14,100); ν_{max}^{nujol} 3480, 1730, 1718, 1704, 1681, 1623, 1255, 1237, 1067 and 1053 cm^{-1}. (Reported: m.p. 277–280°, $[\alpha]_D$ +99 ± 4°[22]).

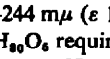
11β,17α,20α,21-*Tetrahydroxypregn-4-en-3-one* (III, Δ^4, R = O, R′ =  ; R″ = R‴ = H): m.p. 253–257°; $[\alpha]_D$ −84°; λ_{max} 243 mμ (ε 14,500); ν_{max}^{nujol} 3470, 3350, 1639, and 1044 cm^{-1}. (Found: C, 69·24; H, 8·84. $C_{21}H_{32}O_5$ requires: C, 69·20; H, 8·85%).

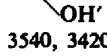
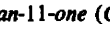
20,21-*Diacetate* (III, Δ^4, R = O, R′ =  ; R″ = R‴ = $COCH_3$): m.p. 203–205°; $[\alpha]_D$ +39°; λ_{max} 243 mμ (ε 15,000); ν_{max}^{nujol} 3550, 3460, 1728, 1648, 1614, 1254, 1234 and 1054 cm^{-1}. (Found: C, 66·99; H, 8·07. $C_{25}H_{36}O_7$ requires: C, 66·94; H, 8·09%).

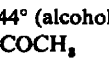
11β,17α,20α-*Tetrahydroxypregna-1,4-dien-3-one* (III, $\Delta^{1,4}$, R = O, R′ =  ; R″ = R‴ = H): m.p. 240–243°; $[\alpha]_D$ +27·5°; λ_{max} 243–244 mμ (ε 13,750); ν_{max}^{nujol} 3450, 3300, 1660, 1594 and 1040 cm^{-1}. (Found: C, 69·43; H, 8·31. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%).

20,21-*Diacetate* (III, $\Delta^{1,4}$, R = O, R′ =  ; R″ = R‴ = $COCH_3$): m.p. 227–229°; $[\alpha]_D$ −6·5°; λ_{max} 244 mμ (ε 14,750); ν_{max}^{nujol} 3540, 3420, 1748, 1724, 1659, 1617, 1601, 1260, 1236 and 1043 cm^{-1}. (Found: C, 67·25; H, 7·69. $C_{25}H_{34}O_7$ requires: C, 67·24; H, 7·68%).

3α,17α,20α,21-*Tetrahydroxy-5β-pregnan-11-one* (*Cortolone*) (III, 5β, R =  , R′ = O, R″ = R‴ = H): m.p. 208–210°; $[\alpha]_D$ +34° (EtOH); ν_{max}^{nujol} 3640, 3430, 3280, 1688, 1081, 1057 and 1040 cm^{-1}. (Reported m.p. 208–209°, $[\alpha]_D$ +44° (alcohol);[33] m.p. 208–209°, $[\alpha]_D$ +34·2° (EtOH)[9].)

3,20,21-*Triacetate* (III, 5β, R =  , R′ = O, R″ = R‴ = $COCH_3$): m.p. 216–217°; $[\alpha]_D$ +28·5°, +20° (EtOH); ν_{max}^{nujol} 3485, 1740, 1726, 1702, 1245, 1234 and 1060 cm^{-1}. (Reported: m.p. 213–214°, $[\alpha]_D$ +18 (acetone);[33] m.p. 214–216°, $[\alpha]_D$ +28°[9]).

3β,17α,20α,21-*Tetrahydroxypregn-5-ene* (III, Δ^5, R =  , R′ = H_2, R″ = R‴ = H). Reduction with $LiAlH_4$, according to the *method* A, of I (R =  , R′ = H_2, X = $(CH_2)_4$);[30] (2 g), followed by HCl hydrolysis of the not purified intermediate, gave a product (1·2 g) m.p. 250–255°. Two crystallizations from methanol raised the m.p. to 261–264°; $[\alpha]_D$ −71·5°; ν_{max}^{nujol} 3320, 1670 and 1064 cm^{-1}. (Found: C, 71·73; H, 9·79. $C_{21}H_{34}O_4$ requires: C, 71·96; H, 9·78%).

3,20,21-*Triacetate* (III, Δ^5, R =  , R′ = H_2, R″ = R‴ = $COCH_3$): m.p. 195–197°;

[33] R. Neher and A. Wettstein, *Helv. Chim. Acta* **39**, 2062 (1956).
[35] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1169 (1949).

$[\alpha]_D$ −79·5°; ν_{max}^{nujol} 3510, 1738, 1277, 1243 and 1029 cm^{-1}. (Found: C, 67·98; H, 8·38. $C_{27}H_{40}O_7$ requires: C, 68·04; H, 8·46%).

17α,20α,21-Triol 21-monoesters

17α,20α,21-Trihydroxy-pregna-1,4-diene-3,11-dione 21-acetate (III, $\Delta^{1,4}$, R = R′ = O, R″ = $COCH_3$, R‴ = H). (a) The usual hydrolysis with HCl–methanol of II ($\Delta^{1,4}$, R = R′ = O, R″ = H, X = $\begin{matrix}CH_3\\OCH_3\end{matrix}$) (0·25 g) yielded a product (0·184 g) m.p. 230–233°. A sample recrystallized from methanol had m.p. 233–235°; $[\alpha]_D$ +103°; λ_{max} 239–240 mμ (ε 15,000); ν_{max}^{nujol} 3550, 3260, 1742, 1071, 1658, 1615, 1602, 1231 and 1046 cm^{-1}. (Found: C, 68·43; H, 7·51. $C_{25}H_{30}O_6$ requires: C, 68·63; H, 7·51%). The acetylation of this compound gave III ($\Delta^{1,4}$, R = R′ = O, R″ = R‴ = $COCH_3$) m.p. 262–263°; $[\alpha]_D$ +71°. Oxidation: to the complex prepared from chromic anhydride (0·1 g) and pyridine (1 ml) a solution of the above 21-monoacetate (0·1 g) in pyridine (1 ml) was added. The mixture was kept overnight at room temp., then filtered to separate the precipitated salts. The filtrate was diluted with saturated NaCl solution and the crystalline product collected by filtration. After crystallization from methanol it had m.p. 228–232°. There was no depression of the m.p. upon admixture with a sample of authentic prednisone 21-acetate.

(b) Hydrochloric acid hydrolysis of the above described II ($\Delta^{1,4}$, R = R′ = O, R″ = $COCH_3$, X = $(CH_2)_4$; 0·5 g) yielded the 21-monoacetate (0·33 g) m.p. 228–232°. Crystallization from methanol gave the product 233–235°.

The following products were prepared according to both the above procedures

17α,20α,21-Trihydroxypregn-4-en-3-one 21-acetate (III, Δ^4, R = O, R′ = H_2, R″ = $COCH_3$, R‴ = H): m.p. 219–221°; $[\alpha]_D$ +44°; λ_{max} 241 mμ (ε 15,600); ν_{max}^{nujol} 3540, 3400, 1725, 1656, 1618, 1227 and 1047 cm^{-1}. (Found: C, 70·70; H, 8·87. $C_{23}H_{34}O_6$ requires: C, 70·74; H, 8·78%).

17α,20α,21-Trihydroxypregna-1,4-dien-3,11-dione 21-benzoate (III, $\Delta^{1,4}$, R = R′ = O, R″ = COC_6H_5, R‴ = H): m.p. 224–226°; $[\alpha]_D$ +122°; λ_{max} 233 mμ (ε 26,250); ν_{max}^{nujol} 3460, 1707, 1668, 1624, 1605, 1591, 1285, 1246 and 1050 cm^{-1}. (Found: C, 72·13; H, 6·87. $C_{28}H_{32}O_6$ requires: C, 72·39; H, 6·94%).

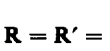
20-Acetate (III, $\Delta^{1,4}$, R = R′ = O, R″ = COC_6H_5, R‴ = $COCH_3$): m.p. 201–203°; $[\alpha]_D$ +82·5°; λ_{max} 233 mμ (ε 26,500); ν_{max}^{nujol} 3470, 1752, 1713, 1668, 1626, 1608, 1593, 1282, 1229 and 1114 cm^{-1}. (Found: C, 70·99; H, 6·77. $C_{30}H_{34}O_7$ requires: C, 71·13; H, 6·77%).

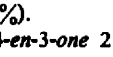
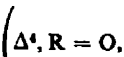
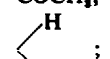
11β,17α,20α,21-Tetrahydroxypregna-1,4-dien-3-one 21-acetate (III, $\Delta^{1,4}$, R = O, R′ = $\begin{matrix}H\\OH\end{matrix}$, R″ = $COCH_3$, R‴ = H): m.p. 256–258°, $[\alpha]_D$ +25°; λ_{max} 244–245 mμ (ε 14,000); ν_{max}^{nujol} 3440, 1720, 1652, 1605, 1592, 1266, 1245 and 1039 cm^{-1}. (Found: C, 68·08; H, 8·02. $C_{23}H_{28}O_6$ requires: C, 68·29; H, 7·97).

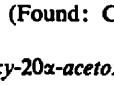
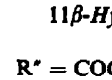
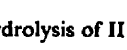
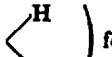
11β,17α,20α,21-Tetrahydroxypregna-1,4-dien-3-one 21-propionate (III, $\Delta^{1,4}$, R = O, R′ = $\begin{matrix}H\\OH\end{matrix}$, R″ = COC_6H_5, R‴ = H). This compound was prepared by reaction of II ($\Delta^{1,4}$, R = O, R′ = $\begin{matrix}H\\OH\end{matrix}$, R′ = H, X = $\begin{matrix}CH_3\\CH_3\end{matrix}$) with propionic anhydride in pyridine and acid hydrolysis of the crude product, without isolation of the intermediate 20-ester. Crystallization from acetone–hexane gave a pure material with m.p. 184–187°; $[\alpha]_D$ +24°; λ_{max} 244 mμ (ε 14,000); ν_{max}^{nujol} 3400, 1723, 1710, 1646, 1598, 1586, 1271, 1242 and 1036 cm^{-1}. (Found: C, 68·58; H, 8·29. $C_{24}H_{30}O_6$ requires: C, 68·87; H, 8·19%).

11β,17α,20α,21-Tetrahydroxypregna-1,4-dien-3-one 21-valerate (III, $\Delta^{1,4}$, R = O, R′ = $\begin{matrix}H\\OH\end{matrix}$, R″ = COC_4H_9, R‴ = H). This compound was prepared by reduction according to the *method* C of the prednisolone 17,21-methyl orthovalerate,[12] followed by acid hydrolysis, without isolation of the

intermediates. The product isolated by chromatography on Florisil and crystallized from methanol had m.p. 190–192°; $[\alpha]_D$ +27°; λ_{max} 244 mμ (ε 14,100); ν_{max}^{nujol} 3450, 1737, 1664, 1618, 1600, 1268, 1241 and 1033 cm^{-1}. (Found: C, 70·24; H, 8·46. $C_{26}H_{38}O_6$ requires: C, 69·93; H, 8·58%).

17α,20α,21-*Trihydroxypregna*-1,4-*dien*-3,11-*dione* 21-*formate* (III, $\Delta^{1,4}$, R = R′ = O, R″ = COH, R‴ = H). To a suspension of II ($\Delta^{1,4}$, R = R′ = O, R″ = H, X =  , $[\alpha]_D$ +68·5°; 0·5 g) in methanol (5 ml) 2N oxalic acid (1 ml) was added. The mixture was refluxed on a water-bath until the solid dissolved and kept warm for an additional 5 min. After evaporation of part of the solvent, water was added. The precipitated solid collected by filtration and crystallized from methanol gave a product (0·25 g) m.p. 194–197°; $[\alpha]_D$ +100°; λ_{max} 240–241 mμ (ε 14,150); ν_{max}^{nujol} 3380, 1698, 1654, 1600, 1245, 1173, 1050 and 970 cm^{-1}. (Found: C, 66·85; H, 7·28; O, 25·75. $C_{22}H_{28}O_6$. 1/2 CH_3OH requires: C, 66·81; H, 7·47; O, 25·72%).

11β,17α,20α,21-*Tetrahydroxypregn*-4-*en*-3-*one* 21-*acetate* (III, Δ^4, R = O, R′ =  , R″ = $COCH_3$, R‴ = H). A mixture of II (Δ^4, R = O, R′ =  , R″ = $COCH_3$, X =  ; 1 g) in methanol (15 ml) containing dil H_2SO_4 (0·5 ml) was boiled on a water bath until the solid dissolved and then kept warm for 30 min. After evaporation of part of the solvent water was added and the solid (0·12 g), m.p. 207–211°, collected by filtration. Crystallization from methanol gave the product with m.p. 214–216°; $[\alpha]_D$ +71°; λ_{max} 243–244 mμ (ε 15,000); ν_{max}^{nujol} 3450, 1717, 1698, 1634, 1260, 1235 and 1040 cm^{-1}. (Found: C, 67·69; H, 8·43. $C_{23}H_{34}O_6$ requires: C, 67·95; H, 8·43%).

11β-*Hydroxy*-17α,21-*benzylidenedioxy*-20α-*acetoxy*-*pregn*-4-*en*-3-*one* (II, Δ^4, R = O, R′ =  , R″ = $COCH_3$, X = ). The hydrolysis of II (Δ^4, R = O, R′ =  , R″ = $COCH_3$, X =), carried out either with HCl or with 2N oxalic acid solution allowed us to isolate the title compound as a product of partial hydrolysis, with m.p. 258–262°, $[\alpha]_D$ +59·5°; λ_{max} 243 mμ (ε 14,500); ν_{max}^{nujol} 3440, 1732, 1650, 1607, 1502, 1234, 1121, 1095, 1043 and 984 cm^{-1}. (Found: C, 72·81; H, 7·69. $C_{30}H_{38}O_6$ requires: C, 72·87; H, 7·69%). Oxidation: to the complex prepared from chromic anhydride (0·35 g) and pyridine (3·5 ml) a solution of the above compound (0·35 g) in pyridine (3·5 g) was added. The mixture was kept overnight at room temp, then filtered to separate the precipitated salts. The filtrate was diluted with water and the crystalline product (0·21 g) collected by filtration had m.p. 203–206°. There was no depression of the m.p. upon admixture with a sample of II (Δ^4, R = R′ = O, R″ = $COCH_3$, X = ) formerly described.

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