22. *Compounds Related to the Steroid Hormones. Part XI.*[1] *Conversion of* 4,5α-*Dihydrocortisone* 21-*Acetate into* 16α-*Acetoxyprednisone* 21-*Acetate.*

By S. Eardley and A. G. Long.

Thionyl chloride and pyridine cause elimination of the 17α-hydroxy-group from 17α,21-dihydroxy-20-methoxyimino-steroids. The 3,3-ethylenedioxy-20-methoxyimine (III; R = O·CH_2·CH_2·O·, R′ = N·OMe, R″ = Ac) was converted in this way into a Δ^{16}-derivative, from which the trione (IV; R = R′ = O, R″ = Ac) was generated by acid hydrolysis and subsequent acetylation. Osmium tetroxide in pyridine then gave the 16α,17α-diol (VII; R = H, R′ = Ac) which, with acetone, gave a ketal. Quantitative studies of the oxidation (with alkaline tetrazolium solutions) of both the diol and ketal established that they were not D-homo-compounds. The 16,17-diol gave a diacetate (VII; R = R′ = Ac, from which (16α,21-diacetoxy-17-hydroxypregna-1,4-diene-3,11,20-trione was made by bromination and dehydrobromination in ring A.

Hydrolysis of the 16,21-diacetoxy-ketols with only 1 equivalent of alkali yielded the respective 16,17,21-trihydroxy-20-ketones (VII; R = R′ = H) and (IX; R = R′ = H).

This Paper describes methods for making 16α-hydroxyl corticosteroids [2] from the diacetate (VII; R = R′ = Ac), which was prepared from a Δ^{16}-20-ketone derived from 4,5α-dihydrocortisone acetate (21-acetoxy-17-hydroxy-5α-pregnane-3,11,20-trione) (III; R = R′ = O, R″ = Ac), an intermediate in the manufacture of cortisone.[3] Attempts to eliminate the 17α-hydroxy-group from this trione failed to yield the corresponding Δ^{16}-20-ketone (IV; R = R′ = O, R = Ac), so we had recourse to the ketal (III; R = R′ = O·$[CH_2]_2$·O, R″ = Ac),[4] the semicarbazone (III; R = R′ = N·NH·CO·NH_2, R″ = Ac),[5] and, with the best results, to the oxime methyl ethers; the oximes themselves were passed over, as we expected they would rearrange or fragment under the conditions needed for the eliminations.[6]

Examples of the utility of such oximes and their ethers have been demonstrated in the conversion of cortisone into cortisol;[7] in particular, the efficiency of formation and

[1] (*a*) Part X, *J.*, 1962, 4729; (*b*) Glaxo Laboratories Ltd., B.P. 866,730.

[2] (*a*) Allen, Bernstein, *et al.*, *J. Amer. Chem. Soc.*, 1956, **78**, 1909, 5693; 1959, **81**, 1689; Bernstein, *Recent Progr. Hormone Res.*, 1958, **14**, 1; (*b*) cf. Ellis, Hartley, Petrow, and Wedlake, *J.*, 1955, 4383.

[3] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356; Glaxo Laboratories Ltd., B.P. 788,307.

[4] Bernstein, *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 1028; *J. Org. Chem.*, 1959, **24**, 429; cf. Szpilfogel and Gerris, *Rec. Trav. chim.*, 1955, **74**, 1462.

[5] Wendler, *et al.*, *J. Org. Chem.*, 1957, **22**, 498; 1960, **25**, 2258; *J. Amer. Chem. Soc.*, 1960, **82**, 4012.

[6] (*a*) Theilacker, Gerstenkorn, and Gruner, *Annalen*, 1949, **563**, 104; Hudlicky and Hokr, *Coll. Czech. Chem. Comm.*, 1949, **14**, 561; Donaruma, *J. Org. Chem.*, 1957, **22**, 1024; Stephen and Staskun, *J.*, 1956, 980; cf. Schmidt-Thomé, *Chem. Ber.*, 1955, **88**, 895; Glidden Co. Inc., U.S.P. 2,531,441; (*b*) *e.g.*, Fischer, Grob, and Renk, *Helv. Chim. Acta*, 1962, **45**, 2539; Conley, *Experientia*, 1962, **18**, 497.

[7] (*a*) Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614; (*b*) cf. Fried and Nutile, *J. Org. Chem.*, 1962, **27**, 914; Heller, McEvoy, and Bernstein, *ibid.*, 1963, **28**, 1523.

hydrolysis of the 20-methoxyimines suited them to our purpose. The 3β,21-diacetoxy-*O*-methyloxime (V; R = N·OMe) is converted by thionyl chloride in pyridine at −30° into the Δ^{16}-20-*O*-methyloxime (VI; R = N·OMe), which is recognizable by its ultraviolet absorption at 246 mμ (this corresponds to a bathochromic shift of 10 mμ accompanying methoximation of an unsaturated ketone; oximation causes a much smaller shift in the same direction [3]). Hydrolysis with hydrochloric acid and acetone, with subsequent acetylation, converted this compound into the Δ^{16}-20-ketone (VI; R = O). Evidence from paper chromatography suggests that hydrolysis of the 21-acetate occurs prior to removal of the methoxyimino-group.

Ketalization offered the best means of protecting the 3-oxo-group, as the 3-methoxyimines are hydrolysed with difficulty; [7b] methoximation of the 21-acetoxy-17α-hydroxy-20-oxo-ketals, being base-catalysed, does not disturb the group at the 3-position. Acid-catalysed hydrolysis removed both protecting groups in one operation, provided that steps (such as the addition of acetone) were taken to prevent transfer of the methoxyimino-group to the 3-position: the methoxyimino-ketal (II; R = N·OMe) was hydrolysed to the 3-methoxyimine (I; R = N·OMe, R′ = O, R″ = H), unless such precautions were observed.

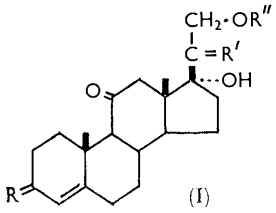
Paper chromatography served in the assessment of reactions with reducing ketol derivatives such as the 20-methoxyimines. Whereas the primary and secondary ketols and their esters are revealed on the papers by reduction of alkaline tetrazolium solutions,[7] the non-reducing derivatives are detected with this reagent only after hydrolysis by exposure to the fumes arising from hydrochloric acid; in this way compounds of the two types may be both detected and differentiated.[8] Evidence from paper chromatography of interactions between groups in the side-chain is presented in the Experimental section: it shows, for instance, that the 21-hydroxy-group contends the more successfully in bonding with the carbonyl group in a 20-oxo-17,21-diol, although the 17-hydroxyl group is known to form the bond when the 21-position bears non-hydroxylic substituents.[9]

We converted the trione (III; R = R′ = O, R″ = Ac) into its 3-ketal (III; R = O·$[CH_2]_2$·O, R′ = O, R″ = Ac) and further into the 20-methoxyimine (III; R = O·$[CH_2]_2$·O, R′ = N·OMe, R″ = Ac). The action of thionyl chloride and pyridine on the latter product yielded the Δ^{16}-derivative (IV; R = O·$[CH_2]_2$·O, R′ = N·OMe, R″ = Ac), acid-catalysed hydrolysis and reacetylation of which gave the required enone (IV; R = R′ = O, R″ = Ac). The yield (50%) was nearly twice that obtained by other methods (involving 3,20-bisketals and 3,20-bissemicarbazones) for converting the 17-hydroxy-compound (III; R = R′ = O, R″ = Ac) into this enone.

Hydroxylation of Δ^{16}-20-ketones with osmium tetroxide gives different products, according to the conditions of the experiment, since formation of 16,17-diols may be accompanied or superseded by production of D-homo-compounds.[10–12] Wendler and his collaborators [12] studied the D-homo-compounds, and we relied on their information in interpreting our findings. The best agents for hydroxylating the Δ^{16}-20-ketone (IV; R = R′ = O, R″ = Ac) were osmium tetroxide and pyridine,[2] with subsequent decomposition of the complex by means of sodium sulphite and potassium hydrogen carbonate. In this way we obtained an acetoxy-diol in about 60% yield and a little of a triol, both products giving the same hydroxy-diacetate. Omission of pyridine reduced the yield from the hydroxylation to 3%, and the reaction then gave other (unidentified) products. The properties of the acetoxy-diol corresponded to structure (VII; R = H, R′ = Ac),

[8] Cf. Sensi and Lancini, *Gazzetta*, 1959, **89**, 1965.
[9] Cf. Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.
[10] Smith, Garbarini, Goodman, Marx, *et al.*, *J. Amer. Chem. Soc.*, 1960, **82**, 1437, 4616; Kupchan, Slade, and Young, *Tetrahedron Letters*, 1960, No. 24, p. 22.
[11] Georgian and Kundu, *Tetrahedron*, 1963, **19**, 1037; Schätzle, Urheim, Thürkauf, and Rottenberg, *Helv. Chim. Acta*, 1963, **46**, 2418.
[12] Wendler, Taub, *et al.*, *Tetrahedron*, 1959, **7**, 173; 1960, **11**, 163, 213; *J. Amer. Chem. Soc.*, 1960, **82**, 2837; Wendler, *Chem. and Ind.*, 1959, 20; see Bernstein, *et al.*, ref. 23.

inasmuch as the spectra lacked absorption due to an αβ-unsaturated carbonyl group, and only one hydroxyl group was acetylable under mild conditions; moreover, the compound behaved on paper chromatography as a hydrogen-bonded (and therefore *cis*) diol [9] and its molecular rotation (in relation to that of the 16,21-diacetate) [2b] befitted a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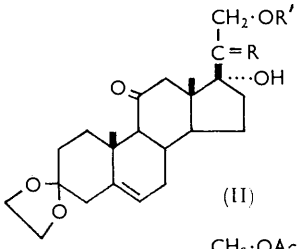
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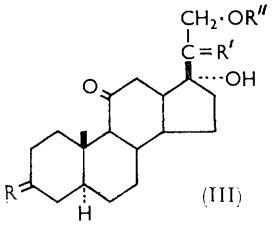
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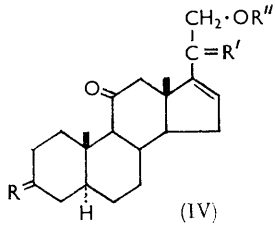
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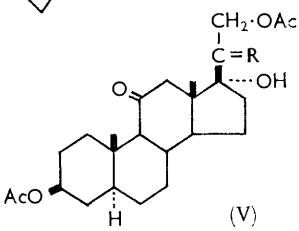
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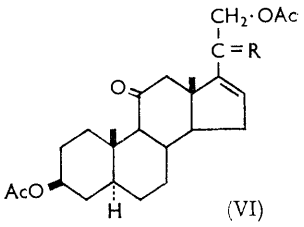
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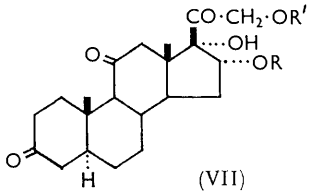
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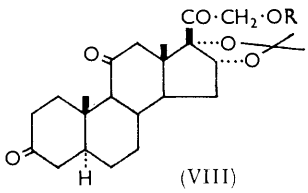
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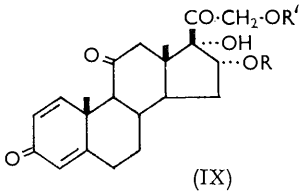
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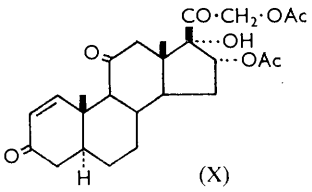
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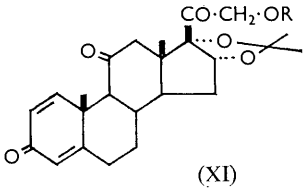
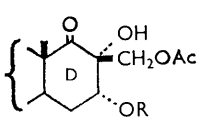
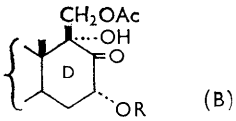

(XI)

16α,17α-dihydroxy-21-acetate. The formation of an isopropylidene derivative (VIII; R = Ac) from the acetoxy-diol (VII; R = H, R′ = Ac) was in keeping with this evidence for a vicinal diol.[2,12,13]

These properties and their similarity to those of congeners [2] did not exclude D-homo-structures, the likeliest [12] of which would be (A) and (B).


(A)


(B)

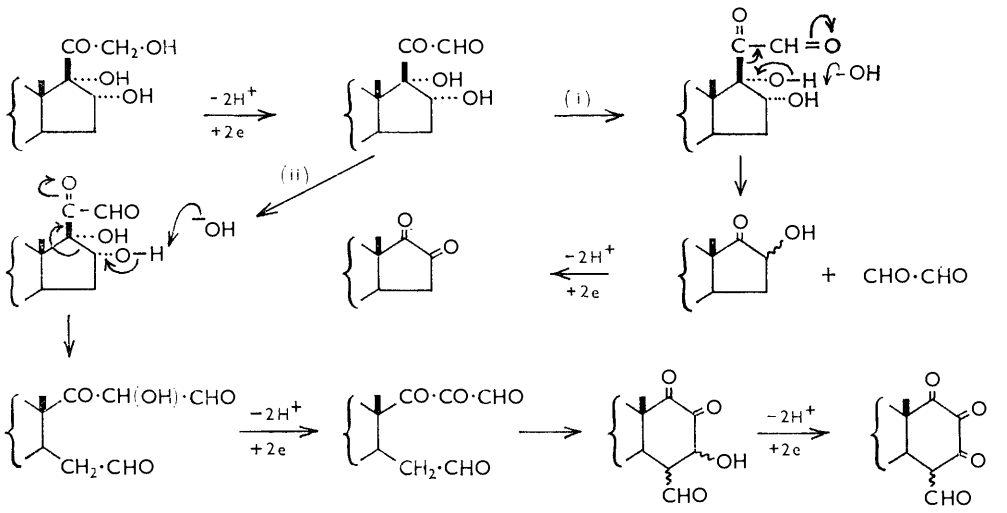
The infrared spectra of the isopropylidene derivative indicate the presence of a primary acetate group adjacent to a carbonyl, provided that the latter group is immune from hydrogen-bonding.[14] These conditions are met only in the unrearranged structure (VIII; R = Ac). [Compounds with structure (B) might give derivatives implicating the

[13] Cooley, Ellis, Hartley, and Petrow, *J.*, 1955, 4373; Fried, Borman, Kessler, Grabowich, and Sabo, *J. Amer. Chem. Soc.*, 1958, **80**, 2338; Bernstein, Littell, Brown, and Ringler, *ibid.*, 1959, **81**, 4573.

[14] Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820; Dickson and Page, *J.*, 1955, 447.

groups at the 16- and 17aα-positions, but they would still fail to meet the requirements just described.]

Alkaline tetrazolium solutions gave coloured formazans with our triol and its esters. This agent oxidizes primary and secondary ketols to oxo-aldehydes and diketones,[2,15–17] and might be expected to distinguish reducing ketol systems, such as those in (VII) and

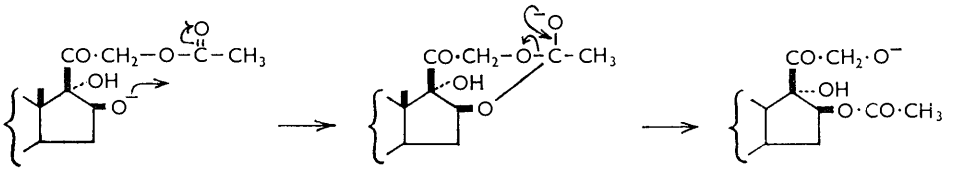


(B), from the tertiary system in (A). However, form (A) may undergo, under the conditions of the test, a reversed aldol reaction resulting in a reducing ketol (see below).[18] On the basis of a modified test to distinguish reductions delayed by prior reactions of this type, we have sounder grounds for rejecting structure (A) for our compound.

Further evidence accrued from quantitative assessments of the tetrazolium reaction.[15,19] If the amount of formazan generated by cortisone acetate is reckoned as 1 equivalent, the yields from the acetoxy-isopropylidene derivative (1 equivalent) and from the triol and its esters (2 equivalents) confirm the other evidence that ring D in our compounds is 5-membered. Generation of 2 equivalents of formazan from the triol and esters, although alone it does not distinguish any one of the 3 structures, attests to the prevalence of reversed aldol or cognate reactions,[12] as shown. The results indicate that course (i) is followed, as (ii) would generate more than 2 equivalents of formazan.

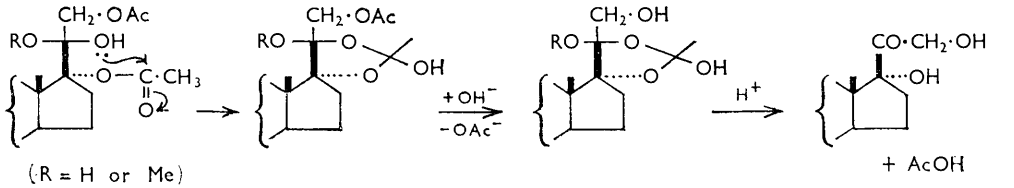
Alkaline hydrolysis of the acetate (VII; R = H, R′ = Ac) and of the diacetate (VII; R = R′ = Ac) gave the triol (VII; R = R′ = H). One equivalent of potassium hydroxide sufficed for the diester. With 1 equivalent of potassium hydrogen carbonate the diester yielded the triol (VII; R = R′ = H) and the 21-acetate (VII; R = H, R′ = Ac). The latter conditions promote conversion [12] of a 21-acetoxy-16β-formyloxy-17α-hydroxy-20-ketone into a 16β-acetoxy-17α,21-dihydroxy-20-ketone, presumably by an internally catalysed exchange (cf. ref. 10).
with 1 equivalent of base, since neither of the mono-esters (VII; R = Ac, R′ = H or R = H, R′ = Ac) nor a 17,21-ortho-ester would be expected to hydrolyse spontaneously to the triol.[12]

[15] Mader and Buck, *Analyt. Chem.*, 1952, **24**, 666.
[16] Stoll, Stauffacher, and Seebeck, *Helv. Chim. Acta*, 1953, **36**, 2027; Auterhoff, *Arch. Pharm.*, 1953, **286**, 319; Auterhoff and Zeisner, *ibid.*, p. 525; 1954, **287**, 541.
[17] Cf. Meyer and Lindberg, *Analyt. Chem.*, 1955, **27**, 813; McAleer, Kozlowski, Stoudt, and Chemerda, *J. Org. Chem.*, 1958, **23**, 958; Tweit, Goldkamp, and Dodson, *ibid.*, 1961, **26**, 2856.
[18] Cf. Wendler and Taub, *J. Amer. Chem. Soc.*, 1958, **80**, 3402.
[19] Cf. Smith, *et al.*, *J. Amer. Pharmaceut. Assoc.* (*Sci. Edn.*), 1959, **48**, 348; *J. Amer. Chem. Soc.*, 1960, **82**, 4625.



This mechanism, or an elaboration implicating the 17-hydroxy-group, does not offer a complete explanation of the hydrolysis of the 16α,21-diacetate (VII; R = R′ = Ac).

One equivalent of alkali completes the hydrolysis of 17α,21-diacetoxy-20-ketones.[3,20] Internal participation is manifest in this reaction, but the evidence does not reveal the acceptor of the second acetate function; we conclude that it is transferred, in the fashion of a Zemplén saponification, to the alcohol in the solvent, or that the solvated 20-oxo-group is implicated in a process of the type in the accompanying diagrams (cf. ref. 11).



Bromination of the diacetate (VII; R = R′ = Ac) yielded a dibromo-ketone that was converted [21] with calcium carbonate in dimethylacetamide mainly into 16α-acetoxyprednisone acetate (IX; R = R′ = Ac). One by-product was the Δ^1-3-ketone (X), which was extracted as its water-soluble Girard derivative ($\Delta^{1,4}$-3-ketones do not give such derivatives under the conditions used [3,22]).

The groups in ring D and the side-chain of the 1,4-diene reproduced the behaviour already described for these groups in the saturated ketone (VII; R = R′ = Ac), so that appropriate conditions could be chosen for making the monoacetate (IX; R = H; R′ = Ac), the triol (IX; R = R′ = H), and the 21-hydroxy-ketal (XI; R = H) and its acetate (XI; R = Ac). As the 16,17-isopropylidene derivatives are stable to acid [13] (and therefore might be expected to survive the conditions for acid-catalysed bromination), we tried to convert the 3-oxo-ketal (VIII; R = Ac) into the corresponding 1,4-dien-3-one (XI; R = Ac). No pure product could be isolated, notwithstanding evidence from paper chromatography and spectroscopy of the presence of the required ketone (XI; R = Ac).

To confirm that no rearrangement of ring D had occurred during the bromination and dehydrobromination of ring A, we submitted our specimens of 16α-hydroxyprednisone (IX; R = R′ = H) and the 21-acetoxy-ketal (XI; R = Ac) to assays by tetrazolium solutions, as described above for the corresponding saturated 3-ketones. Again the results confirmed the structures: the triol (IX; R = Ac) reduced 2 equivalents of the reagent, the cyclic ketal (XI; R = Ac) only one. Further, Dr. Milton Heller found no significant differences between the infrared spectra of our specimen of 16α-acetoxyprednisone acetate and these of another made in a different way.[23a]

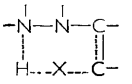
[20] Ringold, *et al.*, *J. Amer. Chem. Soc.*, 1956, **78**, 820; *J. Org. Chem.*, 1957, **22**, 1090; 1963, **28**, 575; Gardi, Vitali, and Ercoli, *Tetrahedron Letters*, 1961, No. 13, p. 448; cf. Wieland, Heusler, Ueberwasser, and Wettstein, *Helv. Chim. Acta*, 1958, **41**, 74; Elks and Phillipps, *J.*, 1961, 4573.

[21] Carrington, Eardley, Elks, Green, Gregory, Long, and Sly, *J.*, 1961, 4560; cf. Pelc, Hermanek, and Holubek, *Coll. Czech. Chem. Comm.*, 1961, **26**, 1852.

[22] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.

[23] (*a*) See also Bernstein, Heller, *et al.*, *J. Amer. Chem. Soc.*, 1959, **81**, 1256; *J. Org. Chem.*, 1961, **26**, 5036; Searle and Co. Inc., U.S.P. 2,727,909; Ellis, Hall, Petrow, and Waddington-Feather, *J.*, 1961, 4111; (*b*) Wendler, in "Molecular Rearrangements" ed. de Mayo, Interscience, New York, 1963, **2**, p. 1019; (*c*) McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811; Ellis *et al.*, ref. 23*a*; (*d*) Djerassi, *ibid.*, 1949, **71**, 1003; (*e*) Grob, Fischer, Randenbach, and Zerganyi, *Helv. Chim. Acta*, 1964, **47**, 1003; ref. 6.

[*Added in proof.*—Acetic anhydride in acetic acid converted an 11β,17-dihydroxy-20-semicarbazonopregnane into a $\Delta^{14(18)}$-17α-acyl-17β-methyl-steroid.[23b] We have not observed such complications in eliminations from 17-hydroxy-20-methoxyimines and -20-ketals (the latter in the presence of a base). Semicarbazono-[23c] and arylhydrozono-groups[23d] can facilitate expulsion of adjacent groups either by processes[23b] possible in the methoxyimines or by special mechanisms, involving general base catalysis or transition states such as (i) or intermediates derived from a 2-amino-6*H*-1,3,4-oxadiazinium cation. The evidence suggests the operation of special mechanisms; elimination from the hydroxy-ketals and methoxyimines probably suffers little interference from neighbouring groups. Concerted reactions with the methoxyimines, if they occur, are likelier to cause fragmentation.[23e]]



(i)

Experimental

Melting points were measured with a Kofler hot-stage apparatus. Solutions for determinations of infrared and ultraviolet absorption and of optical rotations were made up in bromoform, ethanol, and chloroform, respectively (all at 18—23°, the last at concentrations of 0·25—1·0%), unless otherwise described. Charcoal was Nuchar G-190 (unground) (The Pulp and Paper Co., 230 Park Avenue, New York 17); Florisil was manufactured by the Floridin Co., Tallahassee, Florida, U.S.A.; alumina (Grade O) was bought from P. Spence and Sons, Widnes, Lancs.; calcium carbonate was Calofort U.[21] Commercial batches of *O*-methylhydroxylamine hydrochloride may contain up to 8% of a solid insoluble in pyridine (probably ammonium chloride). This was filtered off. Solutions in organic solvents were dried with magnesium sulphate or sodium sulphate. Identity of one specimen with another was confirmed by mixed m. p., infrared spectroscopy, and paper chromatography (see below).

Purified thionyl chloride was used.[24] The D-homo-isomers of some 17,21-dihydroxy-20-ketones and their esters reduce TSTZ [7] (after prior reversed aldol reactions) in solution in alcoholic solvents.[18] We found that addition of the steroid in chloroform to the reagent solution results in reduction (and colouring) only if the compound is a 20-oxo-17,21-diol or an ester thereof; D-homo-isomers that react with the reagent are not detected unless ethanol is added to the two-phase system.

" Ketol content " was measured by the method of Mader and Buck; [15] cortisone acetate was assigned a value of 100%, the content of other compounds being related to this (with allowance for differences in m.wt.). Formaldehyde and glyoxal gave no colour in these circumstances. Owing to differences from compound to compound in the rate of oxidation, Mr. J. Jefferies measured for us the intensities of colour at their maxima.

Acetylations were carried out with cold acetic anhydride and pyridine, so that the 17-hydroxy-group was not affected.[25]

Paper Chromatography.—Results were obtained with solvent mixture L and the TSTZ spray, as described before.[7] 21-Hydroxy-20-methoxyimines, -oximes, and -semicarbazones did not reduce the TSTZ spray, unless they were first hydrolysed on the paper by hanging it for 1 hr. over a pool of concentrated hydrochloric acid in a closed glass tank. ΔR_M values are calculated from R_F values obtained in conditions designed for reproducibility and for absence of adsorption.[9]

Effect of Hydrating the 16,17-*Double Bond.*—(This value is very nearly the increment due to the 17-hydroxy-group.) In 21-acetoxy-20-ketones, ΔR_M + 0·40 [Calc. from (III; R = R′ = O, R″ = Ac), R_F 0·69, and (IV; R = R′ = O, R″ = Ac), R_F 0·85]. In 21-hydroxy-20-ketones, ΔR_M + 0·75 [Calc. from (III; R = R′ = O, R″ = H), R_F 0·25, and (IV; R = R′ = O, R″ = H), R_F 0·65] (The increment calculated from the values for cortisol, R_F 0·08, and corticosterone, R_F 0·46, is ΔR_M + 0·90; the discrepancy with the value given above is attributed to the slightly polar contribution of the 16,17-double bond). In 21-acetoxy-20-methoxyimines, ΔR_M + 0·25 [Calc. from (III; R = O·[CH_2]$_2$·O, R′ = N·OMe, R″ = Ac), R_F 0·90, and (IV; R = O·[CH_2]$_2$·O, R′ = N·OMe, R″ = Ac), R_F 0·94].

[24] *Org. Synth.*, 1943, Coll. Vol. 2, p. 570.
[25] Fox, Origoni, and Smith, *J. Amer. Chem. Soc.*, 1960, **82**, 2581.

Effect of Acetylating the 21-*Hydroxy-group*.—In a series of 20-oxo-17α,21-diols this conversion is accompanied by ΔR_M −0·91. For the Δ^{16}-compounds (IV; R = R′ = O, R″ = H), R_F 0·65, and (IV; R = R′ = O, R″ = Ac), R_F 0·85, ΔR_M −0·48. The results given above confirm that the 17- and 21-hydroxy-groups form hydrogen bonds with the 20-ketones, the latter ousting the former when they are in competition (footnotes *c* and *d* in Table 2 in ref. 9 are transposed).

Effect of 20-*Methoximation*.—For the 21-acetoxy-17-hydroxy-compounds (I; R = O, R′ = N·OMe, R″ = Ac), R_F 0·79, and (I; R = R′ = O, R″ = Ac), R_F 0·62, ΔR_M −0·37; and for (III; R = O·$[CH_2]_2$·O, R′ = N·OMe, R″ = Ac), R_F 0·90, and (III; R = O·$[CH_2]_2$·O, R′ = O, R″ = Ac), R_F 0·79, ΔR_M = −0·37.

3β,21-*Diacetoxy*-20-*methoxyimino*-5α-*pregn*-16-*en*-11-*one* (VI; R = N·OMe).—To a stirred solution of the 20-methoxyimine (V; R = N·OMe) (1·0 g.)[7] in pyridine (10 ml.) at −40° was added quickly thionyl chloride (0·4 ml.) in pyridine (10 ml.), this solution being mixed and kept at −40° under nitrogen. The mixture became orange and cloudy; after 1 hr. it was poured into ice and water. The tarry precipitate was rubbed with ethanol, which rendered it into a powder (0·72 g.). Two crystallizations from ethanol gave the Δ^{16}-*methoxyimine* (0·41 g., 42%), m. p. (cap.) 142—144°. Two more crystallizations gave the sample (0·33 g.) for analysis as chunks, m. p. 145·5—147°, $[\alpha]_D$ +36°, $\lambda_{max.}$ 246·5 mμ (ε 14,400), R_F 0·96, $\nu_{max.}$ (CS_2) 1735 and 1240 (acetates), 1703 (ketone), and 878 cm.$^{-1}$ (>C=CH−) (Found: C, 67·8; H, 8·0; N, 3·2. $C_{26}H_{37}NO_6$ requires C, 67·95; H, 8·1; N, 3·05%).

3β,21-*Diacetoxy*-5α-*pregn*-16-*ene*-11,20-*dione* (VI; R = O).—A solution of the Δ^{16}-20-methoxyimine (VI; R = N·OMe) (0·43 g.) in warm acetone (42 ml.) was cooled and diluted with 2N-hydrochloric acid (22 ml.). Crystals separated and then dissolved when the solution was swirled; after 3 days at room temperature the solution was neutralized with sodium hydrogen carbonate solution, which precipitated a powder. Extraction into ethyl acetate and evaporation of the resulting solution left a solid (0·35 g.), $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1\,cm.}$ 378), R_F 0·06, 0·32, 0·63, and 0·89. (Only the second spot appeared without treatment of the paper with acid before the TSTZ spray; the other spots were weak, except for that at R_F 0·63, which is probably due to the 21-hydroxy-Δ^{16}-20-methoxyimine. Paper chromatography suggests that hydrolysis of the methoxyimino-group in Δ^{16}- and 17-hydroxy-21-acetoxy-20-methoxyimines depends on prior hydrolysis of the ester group.) This product was treated again for 3 days at room temperature with acetone and 2N-hydrochloric acid. Extraction as before gave a residue (0·30 g.), $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 193), R_F 0·07 (weak), 0·29, and 0·64 (weak) (all reduced TSTZ without prior exposure to acid fumes). Acetylation at 20° for 18 hr. with acetic anhydride (5 ml.) and pyridine (5 ml.) gave, on evaporation, a gum (0·42 g.). Chromatography on Florisil afforded, in the benzene to benzene–ethyl acetate (3 : 1) eluates, material (0·38 g.) that gave the Δ^{16}-*diketone* (0·10 g.), birefringent chunks, m. p.s 65 and 118° (from ethyl acetate–hexane), $[\alpha]_D$ +46°, $\lambda_{max.}$ 235 mμ (ε 8,600), $\nu_{max.}$ (CS_2) 1752 and 1234 (21-acetate), 1732 and 1244 (3-acetate), 1710 (ketone), and 1690 and 820 cm.$^{-1}$ (Δ^{16}-20-ketone) (Found: C, 70·1; H, 8·4. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%).

21-*Acetoxy*-3,3-*ethylenedioxy*-17-*hydroxy*-20-*methoxyiminopregn*-5-*en*-11-*one* (II; R = N·OMe, R′ = Ac).—A solution of the ketal (II; R = O, R′ = Ac) (7·0 g.)[7a] in pyridine (140 ml.) was treated with a solution of *O*-methylhydroxylamine hydrochloride (7·0 g., 5·3 mol.) in pyridine (75 ml.); α_D (1 dm. tube) + 1·29° ⟶ +0·65° (73 hr.) (constant). After a week the solution was evaporated *in vacuo* almost to dryness, and diluted with water, when the *methoxyimino-ketal* (6·6 g., 89%) was precipitated. Two crystallizations from aqueous pyridine gave the pure compound, m. p. 204·5—205·5°, $[\alpha]_D^{25}$ +13° (dioxan), R_F 0·89, $\nu_{max.}$ (Nujol) 3430 (OH), 1754 and 1218 (21-acetate), 1700 (ketone), and 1106 and 1048 cm.$^{-1}$ (>C−O−C<) (Found: C, 65·6; H, 7·6; N, 3·2. $C_{26}H_{37}NO_7$ requires C, 65·7; H, 7·8; N, 2·95%). The compound did not reduce TSTZ and showed no maximum with $E^{1\%}_{1\,cm.}$ >10 between 220 and 300 mμ.

21-*Acetoxy*-17-*hydroxy*-20-*methoxyiminopregn*-4-*ene*-3,11-*dione* (I; R = O, R′ = N·OMe, R″ = Ac).—A solution of the methoxyimino-ketal (II; R = N·OMe, R′ = Ac) (1·0 g.) in acetone (50 ml.) and 2N-hydrochloric acid (50 ml.) was kept for 2 hr. at room temperature, and poured into sodium hydrogen carbonate solution. Part (0·51 g.) of the precipitate (0·75 g.) was acetylated with acetic anhydride (2·5 ml.) and pyridine (2·5 ml.); dilution with water gave a solid (0·50 g.), part (0·20 g.) of which was crystallized from cyclohexane–ethyl acetate (*ca.* 3 : 1) as birefringent needles (0·13 g., 52%) of the 20-*methoxyimine*, m. p. 178·5—179·5°, $[\alpha]_D^{26}$ +184° ($CHCl_3$), +154° (dioxan), $\lambda_{max.}$ 236 mμ (ε 17,600), R_F 0·79, $\nu_{max.}$ 3580 and 3450 (OH),

1733 and 1244 (acetate), 1700 (ketone), and 1663 and 866 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 67·0; H, 7·4; N, 3·4. $C_{24}H_{33}NO_6$ requires C, 66·8; H, 7·7; N, 3·25%). The compound did not reduce TSTZ.

Treatment of the methoxyimino-ketal (II; R = N·OMe, R′ = Ac) (0·20 g.) in ethyl acetate (5 ml.) and acetone (10 ml.) for 66 hr. with 2N-hydrochloric acid gave, after the operations described above, slightly impure cortisone acetate (I; R = R′ = O, R″ = Ac) (0·135 g., 80%), m. p. 226—234°, $[\alpha]_D$ +169° (acetone), R_F 0·60 and 0·79 (weak); crystallization from ethyl acetate yielded the pure compound,[3] m. p. 230—242°, $[\alpha]_D$ +180° (acetone), $\lambda_{max.}$ 236 mμ (ε 16,000), R_F 0·60.

21-*Acetoxy*-17-*hydroxy*-3-*methoxyiminopregn*-4-*ene*-11,20-*dione* (I; R = N·OMe, R′ = O, R″ = Ac).—(*a*) A solution of the methoxyimino-ketal (II; R = N·OMe, R′ = Ac) (1·0 g.) in ethanol (50 ml.) was treated with 2N-hydrochloric acid (50 ml.). After 48 hr. at room temperature the solution was neutralized with sodium hydrogen carbonate, and the steroid isolated with methylene dichloride, and acetylated (see above). Part (0·85 g.) of this material (0·86 g.), R_F 0·64 and 0·87, was chromatographed on Florisil (30 g.). The fractions were eluted with ethyl acetate–benzene. The less polar fraction (0·455 g.) crystallized from ethyl acetate as prisms (0·405 g., 45%), m. p. 199—213°; recrystallization from pyridine gave the 3-methoxyimine as leaflets, m. p. 209—212° (cap.), 218—219° (Kofler), $[\alpha]_D$ +258°, $\lambda_{max.}$ 248 mμ (ε 19,300), R_F 0·85, identified with the specimen described below. The more polar fraction crystallized from ethyl acetate as prisms (0·13 g., 15%) of cortisone acetate (I; R = R′ = O, R″ = Ac),[3] m. p. 249—252°, $[\alpha]_D$ +223°, $\lambda_{max.}$ 237·5 mμ (ε 16,000).

(*b*) A solution of the acetate (I; R = R′ = O, R″ = Ac) (1·0 g.) in ethanol (75 ml.) was treated with *O*-methylhydroxylamine hydrochloride (1·0 g.) and crystalline sodium acetate (1·63 g.) in water (5 ml.) and set aside for 24 hr. at room temperature. Crystals (soluble in water) separated. Addition of water precipitated more crystals (1·02 g.), which separated from ethyl acetate as blades (0·58 g., 54%), m. p. 213—214°, R_F 0·84; recrystallization from aqueous pyridine gave the 3-*methoxyimine* as leaflets, m. p. 218—219°, $[\alpha]_D$ +256°, $\lambda_{max.}$ 247·5 mμ (ε 21,000), R_F 0·86, $\nu_{max.}$ 3600 (OH), 1742 and 1248 (21-acetate), 1724 (20-ketone), and 1704 cm.$^{-1}$ (ketone) (Found: C, 67·0; H, 7·7; N, 3·6. $C_{24}H_{33}NO_6$ requires C, 66·8; H, 7·7; N, 3·25%).

21-*Acetoxy*-3,3-*ethylenedioxy*-17-*hydroxy*-5α-*pregnane*-11,20-*dione* (III; R = O·$[CH_2]_2$·O, R′ = O, R″ = Ac).—A suspension of 4,5α-dihydrocortisone acetate (III; R = R′ = O, R″ = Ac) (10 g.)[3] in benzene (360 ml.) and ethylene glycol (80 ml.) containing toluene-*p*-sulphonic acid (50 mg.) was stirred and refluxed for 5·5 hr., with separation of the denser components of the azeotrope. The solid changed from a powder to leaflets. The mixture was neutralized with saturated sodium hydrogen carbonate. The precipitate (9·96 g.) was crystallized from 50% aqueous pyridine to give the ketal (9·60 g., 87%), m. p. 275—278°, $[\alpha]_D$ +84°, R_F 0·79, identified with a specimen made by another method.[26] Second crops yielded more (0·42 g.) of the material.

21-*Acetoxy*-3,3-*ethylenedioxy*-17-*hydroxy*-20-*methoxyimino*-5α-*pregnan*-11-*one* (III; R = O·$[CH_2]_2$·O, R′ = N·OMe, R″ = Ac).—The above ketal (9·5 g.) in pyridine (94 ml.) was treated with *O*-methylhydroxylamine hydrochloride (9·5 g.) in pyridine (94 ml.) for 6 days; the optical rotation was constant after 60 hr. and the solution did not then reduce TSTZ. Addition of water precipitated the *methoxyimine* as prisms (9·55 g., 94%), m. p. 204—205° (from acetone), $[\alpha]_D$ +42°, R_F 0·90 (Found: C, 65·6; H, 8·3; N, 3·2. $C_{26}H_{39}NO_7$ requires C, 65·4; H, 8·2; N, 2·9%).

21-*Acetoxy*-3,3-*ethylenedioxy*-17-*hydroxy*-20-*semicarbazono*-5α-*pregnan*-11-*one* (III; R = O·$[CH_2]_2$·O, R′ = N·NH·CO·NH_2, R″ = Ac).—A solution of semicarbazide hydrochloride (21·2 g.) in water (30 ml.), concentrated hydrochloric acid (60 ml.), and pyridine (100 ml.) was added[7] to a stirred solution of the ketal (III; R = O·$[CH_2]_2$·O, R′ = O, R″ = Ac) (10·6 g.) in pyridine (200 ml.). Some crystals separated; they dissolved subsequently. After 72 hr. crystalline sodium acetate (110 g.) was added, the solution was concentrated *in vacuo* to about 200 ml., and poured on to ice. The white precipitate (10·3 g., 83%) was crystallized from aqueous pyridine to give the *semicarbazone* as leaflets, m. p. 207—210° (sweating at 168°), $[\alpha]_D$ +54° ($CHCl_3$ with trace of pyridine), $\lambda_{max.}$ 237·5 mμ (ε 12,000), $\nu_{max.}$ 3500 and 3400 (OH), 1735 and 1230 (acetate), 1702 (ketone), 1702 and 1560 cm.$^{-1}$ (CONH) (Found: C, 59·8; H, 8·1; N, 7·9. $C_{26}H_{39}N_3O_7,H_2O$ requires C, 59·6; H, 7·9; N, 8·0%).

21-*Acetoxy*-3,3-*ethylenedioxy*-20-*methoxyimino*-5α-*pregn*-16-*en*-11-*one* (IV; R = O·$[CH_2]_2$·O,

[26] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.

R′ = N·OMe, R″ = Ac).—A stirred solution of the methoxyimine (III; R = O·[CH_2]$_2$·O, R′ = N·OMe, R″ = Ac) (5·0 g.) at −40° under nitrogen was treated with a solution of thionyl chloride (2 ml.) in pyridine, prepared at −40° under nitrogen. After 1 hr. the light brown solution was poured on to ice. The white precipitate, crystallized from aqueous pyridine, then ether, gave the Δ^{16}-*methoxyimine* (3·9 g., 81%), m. p. 149—150° (crystal change at 136·5°), $[\alpha]_D$ +49°, $\lambda_{max.}$ 246 mμ (ε 14,500), R_F 0·94, $\nu_{max.}$ 1733 and 1246 (acetate), 1698 (ketone), and 1057 cm.$^{-1}$ (>C–O–C<) (Found: C, 68·2; H, 8·1; N, 3·4. $C_{26}H_{37}NO_6$ requires C, 68·0; H, 8·1; N, 3·05%).

21-*Acetoxy*-5α-*pregn*-16-*ene*-3,11,20-*trione* (IV; R = R′ = O, R″ = Ac).—(*a*) 2N-Hydrochloric acid (215 ml.) was added to a solution of the above methoxyimine (4·3 g.) in acetone (215 ml.). 3 Days later the product was isolated with chloroform and washed therein with sodium hydrogen carbonate solution. Evaporation to dryness and acetylation of the residue with acetic anhydride (15 ml.) and pyridine (20 ml.) gave a solution that, when poured on to ice, yielded the *trione*, blades (2·57 g., 71%), m. p. 197—199° (from ethyl acetate), $[\alpha]_D$ +85°, R_F 0·85, $\lambda_{max.}$ 235·5 mμ (ε 9,100), $\nu_{max.}$ 1744, 1235 and 1212 (acetate), 1704 (ketones), and 1690 and 820 cm.$^{-1}$ (Δ^{16}-20-ketone) (Found: C, 70·9; H, 7·7. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

(*b*) Thionyl chloride (0·4 ml.) was dissolved in pyridine (10 ml.) at −40° and the solution added to the semicarbazone (III; R = ·O·CH_2·CH_2·O·, R′ = N·NH·CO·NH_2, R″ = Ac) (1·0 g.) in pyridine (10 ml.), also at −40°. The mixture was kept for 15 hr. at −5° (all the operations up to this point were carried out in an atmosphere of nitrogen), and poured into a stirred mixture of concentrated hydrochloric acid (75 ml.) and water (25 ml.). After 15 min. chloroform (50 ml.) was run in and the stirring continued for 1 hr., after which the chloroform layer was separated. This procedure was repeated five times. The combined extracts were washed with sodium hydrogen carbonate solution. The residue (0·58 g.) obtained by evaporation was acetylated with acetic anhydride (4 ml.) and pyridine (6 ml.). A solid, probably the trione (III; R = R′ = O, R″ = Ac) (0·08 g.),[3] m. p. 230—233°, separated. Evaporation of the filtrate gave a brown gum, a benzene solution of which was percolated through charcoal (20 g.). The eluted material (0·24 g.) was nearly white and crystallized from ethanol to give prisms of the trione (46 mg., 6%), m. p. 188—190°, $[\alpha]_D$ +83°, $\lambda_{max.}$ 236 mμ (ε 8,200), R_F 0·0 (weak) and 0·89, identical with the specimen described above.

Application of this procedure to the bis-semicarbazone (III; R = R′ = N·NH·CO·NH_2, R″ = Ac) [7] gave poor yields of products containing <30% of the Δ^{16}-20-ketone (IV; R = R′ = O, R″ = Ac) (estimated by ultraviolet spectroscopy and paper chromatography). Similarly, poor results were obtained with the acetate (III; R = R′ = O, R″ = Ac); treatment of both the methoxyimine (III; R = O·[CH_2]$_2$·O, R′ = N·OMe, R″ = Ac) and the bis-semicarbazone (III; R = R′ = N·NH·CO·NH_2, R″ = Ac) with acetic acid and acetic anhydride [5] gave very low yields of αβ-unsaturated ketones. We thank Dr. J. Elks and Mr. W. Wall for this information and for the results of experiments (*c*) and (*d*).

(*c*) The bis-semicarbazone (III; R = R′ = N·NH·CO·NH_2, R″ = Ac) (3·0 g.) in *NN*-dimethylformamide (30 ml.) containing hydrogen chloride (0·42 g., 2 mol.) was heated under nitrogen for 2 hr. Pouring of the solution into water precipitated a solid (1·54 g.), which was treated with redistilled pyruvic acid [27] (5 ml.) in acetic acid (70 ml.) [5] and water (35 ml.) at room temperature for 40 hr., and then at 60° for 2 hr. The solution was poured into water, the steroid extracted with methylene dichloride, and washed therein with potassium hydrogen carbonate solution. Acetylation of the extracted material with acetic anhydride (7·5 ml.) and pyridine (7·5 ml.) at room temperature overnight gave a solid (1·23 g.), chromatography of which on acid-washed alumina (40 g.; Brockmann grade II and III) [28] in benzene yielded a fraction (0·27 g.) that gave the Δ^{16}-ketone (0·10 g., 4%), m. p. 193—195°.

(*d*) The bisketal (III; R = R′ = O·[CH_2]$_2$·O, R″ = Ac) [26] (1·0 g.) in pyridine (20 ml.) kept at −20° was treated with thionyl chloride (4 ml.), added dropwise.[4] The dark solution was left overnight at 0° and poured on to ice and sodium hydrogen carbonate. The yellow gum (0·98 g.) extracted with ether was heated for 30 min. in refluxing 2% ethanolic sodium hydroxide (30 ml.); the solution was concentrated and poured into water. The precipitate was heated for 1 hr. in refluxing 8·5% (v/v) sulphuric acid (8 ml.) and methanol (80 ml.); neutralization of the cooled solution with sodium hydrogen carbonate, evaporation, and dilution with water gave a crude solid (0·35 g.), which was acetylated as described in (*c*) above. The product

[27] Green and Long, *J.*, 1961, 2532.
[28] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.

(0·39 g.) m. p. 188—191°, was crystallized from ethyl acetate to give the Δ^{16}-ketone (0·21 g., 28%), m. p. 190—195°.

21-*Acetoxy*-16α,17-*dihydroxy*-5α-*pregnane*-3,11-20-*trione* (VII; R = H, R′ = Ac).—Osmium tetroxide (1·0 g.) in benzene (10 ml.) was added [2] to a solution of the above Δ^{16}-ketone (0·81 g.) in benzene (20 ml.) containing pyridine (0·7 ml.). The mixture darkened and slowly deposited brown crystals. After 5 days the mixture was stirred for 5 hr. with water (68 ml.), methanol (25 ml.), crystalline sodium sulphite (7·2 g.), and potassium hydrogen carbonate (7·2 g.). More of the last two substances (7·2 g. of each) was added and the stirring continued for 18 hr. Chloroform (200 ml.) was run in, the mixture stirred for 45 min., filtered through kieselguhr, and the denser phase segregated; further extractions with chloroform of the aqueous solution were carried out to remove all the material that reduced TSTZ. The brown-red crystals on the kieselguhr pad were leached with hot chloroform (2 l.). The extracts were washed sparingly with brine and evaporated. The residual white solid (1·01 g.) crystallized from acetone as plates (0·52 g.) of the *diol*; further crops gave a total yield of 0·55 g. (63%). Recrystallization of the first crop from ethyl acetate furnished birefringent blades, m. p. 233—237°, $[\alpha]_D$ +96°, R_F 0·58, $\nu_{max.}$ (Nujol) 3470 and 3400 (OH), 1740 and 1242 (21-acetate), 1728 (20-ketone), and 1704 cm.$^{-1}$ (ketones) (Found: C, 65·6; H, 7·5. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·7%). The mother-liquor from the original crystallizations contained the triol (VII; R = R′ = H), R_F 0·08, acetylation of which with acetic anhydride (2 ml.) and pyridine (3 ml.) gave the crude 16,21-diacetate (VII; R = R′ = Ac) (0·10 g.), m. p. 245—249°, R_F 0·70 and 0·85 (weak).

16α,21-*Diacetoxy*-17-*hydroxy*-5α-*pregnane*-3,11,20-*trione* (VII; R = R′ = Ac).—(*a*) Acetic anhydride (2 ml.) was added to a solution of the above diol (0·30 g.) in pyridine (10 ml.). The solution was set aside overnight, then poured on to ice. The precipitate (0·30 g.) gave rods of the *diacetate* (0·155 g., 47%), m. p. 262—266° (from ethyl acetate), $[\alpha]_D$ +45°, R_F 0·70, $\nu_{max.}$ 3560 (OH), 1746—1732 and 1230 (acetates), and 1705 cm.$^{-1}$ (ketones) (Found: C, 64·6; H, 7·4. $C_{25}H_{34}O_8$ requires C, 64·9; H, 7·4%), ketol content, 202%. The triol (VII; R = R′ = H) was acetylated likewise to this diacetate.

(*b*) The preparation of the diol (VII; R = H, R′ = Ac) was repeated on the Δ^{16}-ketone (IV; R = R′ = O, R″ = Ac) (1·0 g.) up to the chloroform extractions. The total steroidal extract was acetylated with acetic anhydride (12 ml.) and pyridine (20 ml.). In this way the crystalline diacetate (VII; R = R′ = Ac) (0·79 g., 66%), m. p. 262—265°, $[\alpha]_D$ +46°, was most easily obtained. Omission of pyridine from the oxidation mixture reduced the yield of this diacetate to 3%. Another product, m. p. 187—188°, $[\alpha]_D$ +31°, R_F 0·72, $\nu_{max.}$ 3480 (OH), 1738 and 1228 (acetates), and 1708 cm.$^{-1}$ (ketones), was isolated in 6% yield (after chromatography on Florisil). An α-ketol content of 115% and the inability to reduce TSTZ in the two-phase system, unless ethanol were added, suggested that this was a D-homo-isomer of the diacetate (VII; R = R′ = Ac); the other properties agree with this supposition. Decomposition with refluxing aqueous alcoholic sodium sulphite of the osmium complex obtained in presence of pyridine also gave very poor yields: after chromatography, a product, m. p. 215—240°, $[\alpha]_D$ −39°, R_F 0·89, $\nu_{max.}$ 1756 and 1215 [enol acetate (?)], 1740 and 1225 (21-acetate), and 1705 cm.$^{-1}$ (ketones), was obtained in $<2\%$ yield.

The 16,21-diacetate (VII; R = R′ = Ac) could be chromatographed without change on Grade O alumina in methylene dichloride–ethanol (9 : 1).

16α,17,21-*Trihydroxy*-5α-*pregnane*-3,11,20-*trione* (VII; R = R′ = H).—Potassium hydroxide (3·025 g.) was dissolved in oxygen-free anhydrous methanol (250 ml.); [29] part (5 ml., 2·16 mmol.) of this solution was added to the diacetate (VII; R = R′ = Ac) (0·500 g., 2·16 mmol.) in a mixture of anhydrous methanol (12·5 ml.) and methylene dichloride (8 ml.) under nitrogen. After 4 min. water (2·16 mmole) was added in solution in methanol (0·5 ml.) [prepared from water (3·89 ml.) made up to 100 ml. with anhydrous methanol]. The solution was swirled all this time and for another 3 min. Water (12·5 ml.) at 0° and, 1 min. later, acetic acid solution (0·75 ml.) [prepared from acetic acid (12·36 ml.) made up to 100 ml. with water] were added. Evaporation at $<40°$ *in vacuo* of the two-phase system (pH 5—6) led to the separation of crystals (0·231 g.), m. p. 228—232°. These were combined with a second crop (0·04 g.) and the material extracted with methylene dichloride (0·13 g.) and crystallized from ethyl acetate–methylene dichloride, giving the triol as plates (0·267 g., 65%), m. p. 223—226°. Recrystallization from aqueous methanol gave plates (0·192 g.), m. p. 210—216°, $[\alpha]_D$ +55° (MeOH), with the same infrared absorption (see below).

[29] Merck and Co. Inc., U.S.P. 2,634,277.

(*b*) A stirred solution of the diacetate (VII; R = R′ = Ac) (100 mg.) in methanol (15 ml.) under nitrogen was treated with potassium hydrogen carbonate (100 mg.) in water (3 ml.). The suspension cleared in 50 min.; after another 3 hr. the colourless solution was poured on to ice containing acetic acid (0·1 ml.), and the pH adjusted to 7 with sodium hydrogen carbonate. Kept overnight at 0°, this solution deposited birefringent plates and blades of the *triol* (19·8 mg., 24%), m. p. 215—217°, R_F 0·09, $\nu_{max.}$ (Nujol) 3350 (OH) and 1710 cm.$^{-1}$ (ketones) (Found: C, 66·9; H, 7·9. $C_{21}H_{30}O_6$ requires C, 66·6; H, 8·0%). Material extracted with methylene dichloride from the mother-liquors crystallized from aqueous methanol as plates (14 mg.), m. p. 210—215°.

21-*Acetoxy*-16α,17-*isopropylidenedioxy*-5α-*pregnane*-3,11,20-*trione* (VIII; R = Ac).—Concentrated hydrochloric acid (2 drops) was added to a hot solution of the acetoxy-diol (VII; R = H, R′ = Ac) (0·20 g.) in acetone (10 ml.).[2,13] The solution was kept overnight at room temperature and poured on to ice. A white solid (0·20 g.), R_F 0·58 (weak) and 0·91, crystallized out. It was acetylated for 4 hr. with acetic anhydride (2 ml.) and pyridine (2 ml.). Pouring of this solution on to ice precipitated a white solid (0·19 g.), R_F 0·70 (weak) and 0·91, which was leached with warm carbon disulphide; the insoluble part (0·02 g.), m. p. 259—264°, R_F 0·70, consisted of the diacetate (VII; R = R′ = Ac), and the filtrate gave plates (0·17 g., 85%), of the *cyclic ketal* which recrystallized from benzene–hexane as spikes (0·12 g.), m. p. 214—217°, $[\alpha]_D$ +102°, R_F 0·91, $\nu_{max.}$ (CS_2) 1758 and 1230 (21-acetate), 1730 (20-ketones), 1712 (ketone), and 1230 and 1085 cm.$^{-1}$ (>C–O–C<) (Found: C, 67·8; H, 8·0. $C_{26}H_{36}O_7$ requires C, 67·8; H, 7·9%), α-ketol content, 96%.

16α,21-*Diacetoxy*-17-*hydroxypregna*-1,4-*diene*-3,11,20-*trione* (IX; R = R′ = Ac).—A stirred suspension of the trione (VII; R = R′ = Ac) (15 g.) in acetic acid (167 ml.) containing 5M-hydrogen bromide in acetic acid (13·55 ml.) was treated [3] with 0·53M-bromine in acetic acid (127·5 ml., 2·06 mol.), added in 10 min. at <20° (solution was achieved after addition of half of the halogen). After a further 15 min. the solution was poured into an excess of sodium acetate solution, and the steroidal dibromide (21·5 g.) extracted with methylene dichloride, evaporation being carried out at <20°. This crude product was mixed [21,27] with calcium carbonate (7·5 g.) and added to refluxing *NN*-dimethylacetamide (210 ml.) containing calcium carbonate (7·5 g.) under nitrogen. After 10 min. most of the solvent was distilled off *in vacuo*; the remaining solution was poured into 2N-hydrochloric acid (300 ml.), and the product extracted with methylene dichloride, in which it was washed with sodium hydrogen carbonate solution. The residue obtained on evaporation was treated for 15 min. with Girard's reagent P (3·75 g.) in refluxing methanol (225 ml.) containing glacial acetic acid (12 ml.).[3] The brown solution, when cool, was poured into a mixture of sodium hydrogen carbonate and ethyl acetate; extraction with the latter removed a brown solid (12·3 g.), which was decolorized by percolation of a benzene solution successively through charcoal and Florisil (for further work on the aqueous layer, see below); crystallization from methanol of the product (9·36 g.) gave the diene as rods (2·95 g., 19%), m. p. 151—152°, forming at 160° blades, m. p. 213—214°, $[\alpha]_D$ +136° (MeOH), +96° ($CHCl_3$), R_F 0·57, $\lambda_{max.}$ 237·5 mμ (ε 14,100), $\nu_{max.}$ 1748—1732 and 1230 (acetates), 1708 (ketone), 1660 and 890 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 63·0; H, 6·6. $C_{25}H_{30}O_8,H_2O$ requires C, 63·0; H, 6·8%). Further crops (3·0 g.) of material similar to that described above were obtained. Recrystallization from ethyl acetate–hexane gave the *anhydrous compound*, m. p. 216—218°, $[\alpha]_D$ +137° (MeOH), $\lambda_{max.}$ 237·5 mμ (ε 15,700), with infrared absorption in solution similar to the above (Found: C, 65·7; H, 6·7. Calc. for $C_{25}H_{30}O_8$; C, 65·5; H, 6·6%). The optical rotations of the solutions used for polarimetry decreased on keeping. Dr. Milton Heller of Lederle Laboratories compared our product with his [30] by infrared spectrophotometry and found them essentially the same (letter to Dr. B. A. Hems, dated 12th August, 1958). Crystallization from solvents containing ethyl acetate, methanol, and benzene gave products with different spectra as Nujol mulls, but similar in solution.

16α,21-*Diacetoxy*-17-*hydroxy*-5α-*pregn*-1-*ene*-3,11,20-*trione* (X).—The aqueous layers from the above Girard separation were stirred with ethyl acetate (250 ml.) and adjusted to pH 1 with concentrated hydrochloric acid. After 1 hr. all the steroid material had been segregated into ethyl acetate, and it was washed therein with sodium carbonate solution; the product, a brown solid (2·36 g.) obtained by evaporation, was chromatographed in benzene on Florisil. The main fraction (1·95 g.) in the eluates crystallized from methanol as rods of the Δ^1-*trione* (0·91 g.), m. p. 248—250° (sweating above 230°), $[\alpha]_D$ +87°, R_F 0·61, $\lambda_{max.}$ 226·5 mμ (ε 11,000),

[30] American Cyanamid Co. Inc., U.S.P. 2,806,043.

$\nu_{max.}$ 1745—1730 and 1230 (acetates), 1708 (ketones), 1668 and 782 (Δ^1-3-ketone), and 1600 cm.$^{-1}$ (H_2O) (Found: C, 62·8; H, 7·2. $C_{25}H_{32}O_8,H_2O$ requires C, 62·75, H, 7·2%).

16α,17,21-*Trihydroxypregna*-1,4-*diene*-3,11,20-*trione* (IX; R = R′ = H).—The diacetate (IX; R = R′ = Ac) (3·0 g.) was hydrolysed with potassium hydroxide (1 mol.) in an oxygen-free solvent composed of methanol and methylene chloride,[29] as described above for the preparation of the triol (VII; R = R′ = H). The product formed birefringent rods (1·99 g., 81%); recrystallization of this material from methanol gave prisms of the *triol*, m. p. 255—258° (sweats above 250°), $[\alpha]_D$ +117° (MeOH), R_F 0·06, $\lambda_{max.}$ 237·5 mμ (ε 15,400), $\nu_{max.}$ (Nujol) 1725 and 1706 (ketones), 1654 and 906 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 67·5; H, 7·1. $C_{21}H_{26}O_6$ requires C, 67·4; H, 7·0%), α-ketol content, 190%.

21-*Acetoxy*-16α,17-*dihydroxypregna*-1,4-*diene*-3,11,20-*trione* (IX; R = H, R′ = Ac).—An oxygen-free solution of the diacetate (IX; R = R′ = Ac) (0·50 g.) in methanol (15 ml.) was treated with potassium hydrogen carbonate (0·25 g., 2·3 mol.) under nitrogen, and stirred for 90 min. at 20°. After 15 min. a white solid began to precipitate. The suspension was poured into ice-cold water (50 ml.), acetic acid added to bring the pH to 7, and the mixture left for 18 hr. at 0°. The insoluble material (0·28 g.), m. p. 225—233°, was kept separate from the steroid extracted with chloroform; the former furnished the *ketol acetate* (IX; R = H, R′ = Ac) as birefringent rods (0·16 g., 35%), m. p. 243—246° (sweating from 230°) (from methanol–methylene dichloride), $[\alpha]_D$ +168°, and recrystallization from the same solvent gave birefringent spears, m. p. 254—257°, $[\alpha]_D$ +167° (*c* 0·19), R_F 0·06 (weak) and 0·41, $\lambda_{max.}$ 237·5 mμ (ε 16,000), $\nu_{max.}$ (Nujol) 1750 and 1235 (21-acetate), 1730 (20-ketone), 1700 (ketone), and 1650 and 888 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 66·4; H, 7·0. $C_{23}H_{28}O_7$ requires C, 66·3; H, 6·8%). [The compound, R_F 0·06, was probably the triol (IX; R = R′ = H), possibly produced during the chromatography.]

The chloroform extract contained a solid (0·10 g.), m. p. 222—230°, consisting mainly of the triol (IX; R = R′ = H).

21-*Hydroxy*-16α,17-*isopropylidenedioxypregna*-1,4-*diene*-3,11,20-*trione* (XI; R = H).—A suspension of the triol (IX; R = R′ = H) (1·5 g.) in acetone (60 ml.)[2,13] containing concentrated hydrochloric acid (4 drops) was stirred for 40 hr. at 20° under nitrogen. [Acetone (5 ml.) containing hydrochloric acid (4 drops) was added from time to time to replace losses.] The resulting yellow solution was diluted with water (10 ml.) and the pH brought to 7 with sodium hydrogen carbonate solution. The solution was concentrated to 30 ml., water (30 ml.) added, and the steroid extracted with methylene dichloride. The extract (1·7 g.) yielded the cyclic ketal (XI; R = H) as birefringent rods (1·10 g., 66%) from ethyl acetate. Crystallization from this solvent caused yellowing; the crystals were therefore purified by chromatography in benzene–ethyl acetate (100 : 0 to 94 : 6) on charcoal. The eluted material crystallized as colourless rods (0·56 g.), m. p. 270—285°, $[\alpha]_D$ +175°; subsequent crops (0·33 g.) were nearly the same. Recrystallization of the first crop from ethyl acetate gave the *ketal* (XI; R = H) as birefringent prisms, m. p. 292—296° (sweating above 285°), $[\alpha]_D$ +187°, R_F 0·70, $\lambda_{max.}$ 237 mμ (ε 15,400), $\nu_{max.}$ 1710 (ketone), and 1660 and 890 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 69·2; H, 7·2. $C_{24}H_{30}O_6$ requires C, 69·5; H, 7·3%).

21-*Acetoxy*-16α,17-*isopropylidenedioxypregna*-1,4-*diene*-3,11,20-*trione* (XI; R = Ac).—(*a*) The 21-hydroxy-compound (XI; R = H) (0·51 g.) in pyridine (5 ml.) was acetylated with acetic anhydride (3 ml.), addition of which caused yellowing, but the colour had almost disappeared in 10 min. After 4 hr. the solution was poured on to ice. The precipitate (0·47 g.) yielded spears of the *acetate* (0·27 g., 48%), m. p. 182—184° (from acetone–hexane), $[\alpha]_D$ +171°, R_F 0·91, $\lambda_{max.}$ 237·5 mμ (ε 15,300), $\nu_{max.}$ (CS_2) 1754 and 1228 (21-acetate), 1730 (20-ketone), 1712 (ketone), and 1660 and 890 cm.$^{-1}$ ($\Delta^{1,4}$-3-ketone) (Found: C, 68·1; H, 7·1. $C_{26}H_{32}O_7$ requires C, 68·4; H, 7·1%), α-ketol content, 90%.

(*b*) A suspension of the ketol acetate (IX; R = H, R′ = Ac) (50 mg.) in acetone (7 ml.) containing concentrated hydrochloric acid (2 drops) was shaken overnight at 20°. Then a similar quantity of acid was added, and in a further 2 hr. shaking solution had been achieved. The solution was poured on to ice; the precipitated solid and material extracted with methylene dichloride (57 mg. in all) gave a product that separated from acetone–hexane as clumped crystals (14 mg.) of the ketal (XI; R = Ac), m. p. 176—180°, after a first crop (4 mg.) containing the starting material had been removed.

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