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THE TRANSFORMATION OF D-HOMOSTEROIDS TO STEROIDS

A STEREOSPECIFIC BENZILIC ACID REARRANGEMENT[1,1a]

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Abstract—The D-homoannulation of some cortical hormones has been effected with a view toward transforming the products so obtained to D-homo-17,17a-diones. The latter, conveniently prepared by this means, were studied in the benzilic acid rearrangement mode of ring contraction back to steroids bearing a 17α-carboxyl and a 17β-hydroxyl. This rearrangement has been found to proceed in one steric sense, which may be accounted for on the basis of intermediates generated in compliance with the principles of conformational analysis.

THE transformation of suitable C(17)-substituted steroids into D-homosteroids has been found to occur readily under a variety of chemical[2] (acid and alkaline catalysis and heat) and microbiological[3] conditions. The direct reverse transformation, however, has been effected in only a few cases and was first reported by Prins and

[1] Portions of work reported in this publication have appeared as preliminary communications: *Chem. & Ind.* 1322 (1958); 431 (1954).

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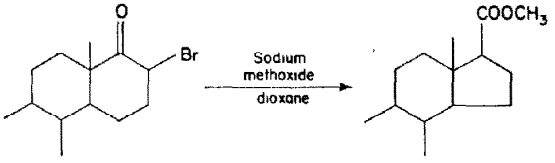
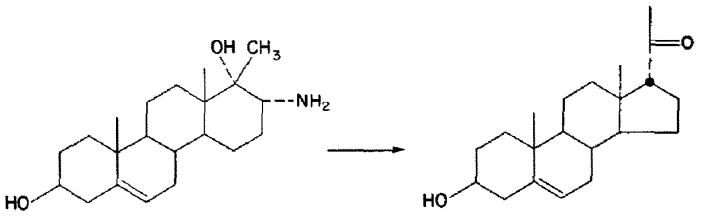
[2] For a representative list, though by no means all inclusive, of cases involving differing degrees of substitution, see: W. A. Yarnall and E. S. Wallis, *J. Amer. Chem. Soc.* **59,** 951 (1937); K. Miescher and H. Kägi, *Helv. Chim. Acta* **22,** 184 (1939); L. Ruzicka, K. Gätzi and T. Reichstein, *ibid.* **22,** 626 (1939); L. Ruzicka, M. W. Goldberg and F. Hunziker, *ibid.* **22,** 707 (1939); L. Ruzicka and H. F. Meldahl, *ibid.* **22,** 421 (1939); **23,** 364, 513 (1940); H. E. Stavely, *J. Amer. Chem. Soc.* **61,** 79 (1939); **62,** 489 (1940); **63,** 3127 (1941); M. W. Goldberg and R. Monnier, *Helv. Chim. Acta* **23,** 376, 840); M. W. Goldberg, J. Sice, H. Robert and P. A. Plattner, *ibid.* **30,** 1441 (1947); J. von Euw and T. Reichstein, *ibid.* **24,** 879 (1941); C. W. Shoppee and D. A. Prins, *ibid.* **26,** 185, 201, 1004 (1943); R. B. Turner, *J. Amer. Chem. Soc.* **75,** 3484 (1953); V. Georgian and N. Kundu, *Chem. & Ind.* 431 (1954); D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling and G. Roberts, *J. Amer. Chem. Soc.* **77,** 6585 (1955); N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *ibid.* **78,** 5027 (1956); R. B. Turner, M. Perelman and K. T. Park, Jr., *ibid.* **79,** 1108 (1957); F. Ramirez and S. Stafiej, *ibid.* **78,** 644 (1956); E. P. Oliveto, C. Gerold, R. Rausser and E. B. Hershberg, *ibid.* **79,** 3594 (1957); N. L. Wender, D. Taub and R. P. Graber, *Tetrahedron,* **7,** 173 (1959); H. Kuo, D. Taub and N. L. Wendler, *Chem. & Ind.* 1128 (1959); N. L. Wendler, D. Taub and H. Kuo, *J. Amer. Chem. Soc.* **82,** 5701 (1960); N. L. Wendler and D. Taub, *ibid.* **82,** 2836 (1960); N. L. Wendler, *Tetrahedron,* **11,** 213 (1960).

[3] J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *J. Amer. Chem. Soc.* **74,** 3962 (1952). See also L. F. Fieser and M. Fieser, "*Steroids*", Reinhold Publishing Corporation, New York, 1959, p. 584 for a summary of events leading to the classification of Marker's uranediol as a D-homosteroid.

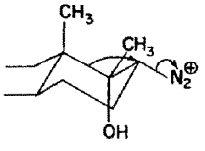
Shoppee.[4] These investigators applied the Favorski reaction to a 17-bromo-17a-keto-D-homoandrostane and obtained only a few per cent of a 5α-etianic ester.



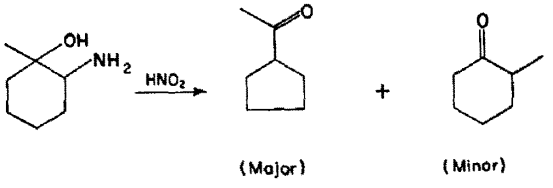
Pinacolic deamination of the 17α-amino-D-homoandrostene-diol (prepared by sodium–alcohol reduction of the 17-oxime) produced 17-isopregnenolone,[4,5] this



latter study demonstrating quite clearly the stereo-electronic limitations to this mode of ring contraction. The *trans*-antiparallelism of migrating and departing groups[6] necessary to ring contraction may be discerned in the conformational representation



of the diazonium form of the amine. On the basis of these considerations the 17,17a amino-carbinols epimeric to the one above at C-17 might be expected to, and indeed do, yield only D-homo derivatives.[4,5,7,8]



The transformation of D-homosteroid intermediates to steroids has been the subject of considerable study as a consequence of total synthesis activity in the steroid

[4] D. A. Prins and C. W. Shoppee, *J. Chem. Soc.* 494 (1946). See also D. E. Evans, A. C. de Paulet, C. W. Shoppee and F. Winternitz, *ibid.* 1451 (1957).

[5] R. J. W. Cremlyn, D. L. Garmaise and C. W. Shoppee, *ibid.* 1847 (1953).

[6] D. H. R. Barton and R. C. Cookson, *Quart. Revs.* **10**, 44 (1956).

[7] L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta* **24**, 1321 (1941); W. Klyne, *Nature*, **166**, 559 (1950); W. Klyne and C. W. Shoppee, *Chem. & Ind.* 470 (1952).

[8] For an instance of a conformationally less rigid monocyclic amino-carbinol pinacolic deamination germane to this discussion, in which ring contraction predominated, see M. Mousseron and L. Souche, *Bull. Soc. Chim. France.* (5), **2**, 1102 (1935); **4**, 1197 (1937).

field. The majority of total syntheses[9–12] have been directed via D-homo intermediates with subsequent D-homo-ring scission and recyclization to produce the normal steroid structure.

A direct reconversion to the regular steroid skeleton by means of a benzilic acid rearrangement could prove convenient and offer a D-homo-17,17a-dione as an alternative target for total synthesis.[13] In addition to ring contraction there would be generated also thereby a C-17 position functionalized so as to be transformable into other desired groupings. To establish the feasibility of this mode of ring contraction, especially as applied to steroids bearing a Δ^4-3-keto function and C-11 oxygen, as well as the stereo-chemical course of this rearrangement, D-homo-diones derived from cortisone, cortisol and Reichstein's Substance *S* were prepared and their rearrangement back to the normal steroid structure is reported herein.[14] The Δ^4-3-keto function in this series of transformations was preserved in order to ascertain whether it could be tolerated later during the alkaline rearrangement of the 17,17a-diones.

Reichstein's Substance *S* acetate (I) was caused to rearrange in acetic acid–acetic anhydride with boron trifluoride at ordinary temperatures. There were obtained two products; a diacetate, 17α-acetoxy-17β-acetoxymethyl-4-D-homoandrostene-3,17a-dione (IV), and a monoacetate recognized as 17α-hydroxy-17β-acetoxymethyl-4-D-homoandrostene-3,17a-dione (V).[15,16] The diol VI, from hydrolysis of the diacetate IV, on acetylation in pyridine-acetic anhydride produced the monoacetate V. The

[9] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **74,** 4223 (1952). See also L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.* **76,** 5014 (1954).

[10] W. S. Johnson, *ibid.* **78,** 6278 (1956) and following papers; W. S. Johnson, D. K. Banerjee, W. B. Schneider, C. D. Gutche, W. E. Shelberg and L. J. Chinn, *ibid.* **74,** 2832 (1952).

[11] G. Stork, H. J. E. Loewenthal and P. C. Mukharji, *ibid.* **78,** 501 (1956); G. Stork, N. H. Khastgir and A. J. Solo, *ibid.* **80,** 6457 (1958).

[12] P. Wieland, G. Anner, and K. Miescher, *Helv. Chim. Acta* **36,** 1803 (1953) and earlier papers.

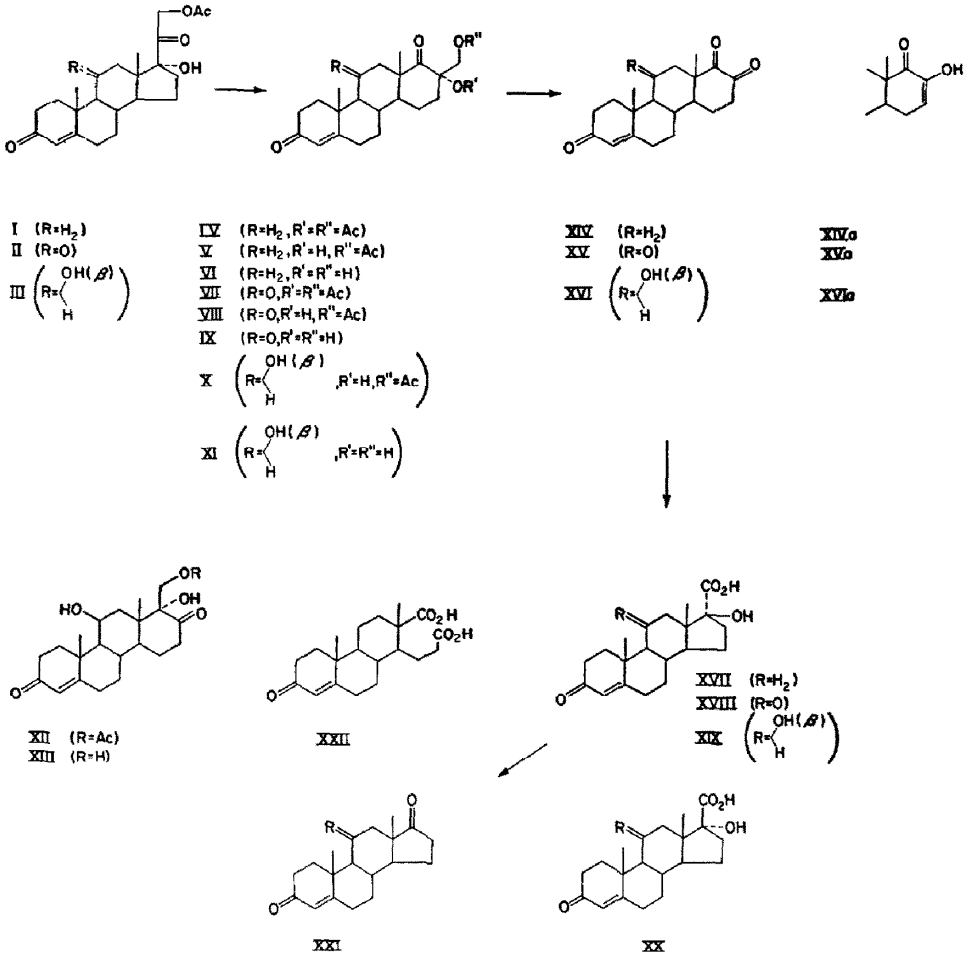
[13] Subsequent to the inception of this work a similar projection was communicated independently by R. G. Curtis and R. Schoenfeld, *Australian J. Chem.* **8,** 258 (1955).

[14] Following solution of this problem, a similar transformation in the D-homo-5β-androstane series was reported by N. L. Wendler and D. Taub, *Chem. & Ind.* 415 (1958); N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* **7,** 173 (1959). For application of the benzilic acid rearrangement to other portions of the steroid molecule, see ref. 13, and: L. S. Fieser and S. Rajagopalon, *J. Amer. Chem. Soc.* **71,** 3938 (1949); R. Hirschmann, G. A. Bailey, R. Walker and J. M. Chemerda, *ibid.*, **81,** 2822 (1959); T. Rull and G. Ourisson (with C. Eleftheriou, *Bull. Soc. Chim. France*, 1573 (1958); R. Hanna, C. Sandris and G. Ourisson, *ibid.* 1454 (1959); D. Lavie and D. Willner, *J. Amer. Chem. Soc.* **82,** 1668 (1960); N. L. Wendler and D. Taub, *ibid.* **82,** 2836 (1960); V. Georgian and Lupe T. deGeorgian: Benzilic acid rearrangement of 4-hydroxy-Δ^4-3-keto steroids. To be published.

[15] These homoannulation products as well as the corresponding ones from cortisone acetate (II) were previously erroneously formulated as the position isomers (17-keto-17a-hydroxy-hydroxymethyl) by analogy to earlier current thought, R. B. Turner, *J. Amer. Chem. Soc.* **75,** 3484 (1953). The subsequent meticulous work of N. L. Wendler and D. Taub, *Chem. & Ind.* 822 (1957), and N. L. Wendler and D. Taub, *J. Amer. Chem. Soc.* **80,** 3042 (1958), established the 17a-keto structures for these Lewis acid D-homoannulated products of 17α-hydroxy-20-keto steroids. See also R. B. Turner, M. Perelman and K. T. Park, *ibid.* **79,** 1108 (1957).

[16] [a] N. L. Wendler and D. Taub, *ibid.* **80,** 3402 (1958).

[b] E. Batres, G. Rosenkranz and F. Sondheimer, *ibid.* **76,** 5171 (1954). The formulations in this reference must be revised to the 17a-keto structures.



glycol VI was cleaved readily by means of periodic acid to formaldehyde and 4-D-homoandrostene-3,17,17a-trione (XIV), or more probably the diosphenol form XIVa. This substance produced a ferric chloride coloration, formed a quinoxaline derivative with *o*-phenylenediamine, was soluble in alkali and was isolable as a white monohydrate which showed I.R. absorption at 2·84 μ (OH), 5·82 μ (C=O) and 6·02 μ (Δ^4-3-keto). The U.V. absorption for this compound showed only a typical (λ_{max} 240 mμ, log ϵ, 4·20) absorption for the Δ^4-3-keto function and there was no indication of absorption by a diosphenol chromophore as observed with the C-11 oxygenated cases (*vide infra*). This data suggests that one of the carbonyl groups of the α-diketone is hydrated. On the basis of a conformational argument to be developed (*vide infra*) it is suggested that the C-17a carbonyl is the one that is hydrated. Excess periodic acid converted the glycol (VI) to a diacid XXII.

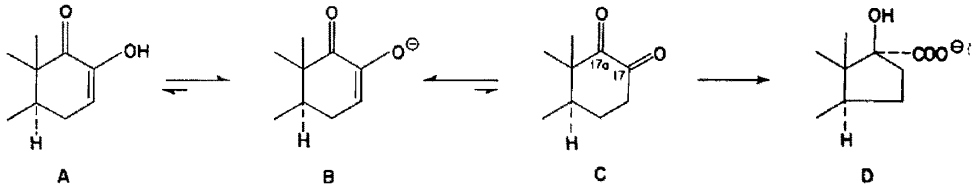
In analogous fashion cortisone acetate (II) was transformed to a diacetate, 17α-acetoxy-17β-acetoxymethyl-4-D-homoandrostene-3,11,17a-trione (VII) and a monoacetate 17α-hydroxy-17β-acetoxy-methyl-4-D-homoandrostene-3,11,17a-trione (VIII).[16] The glycol IX, obtained from the monoacetate VIII by mild basic hydrolysis, was oxidized by periodic acid to 4-D-homo-androstene-3,11,17,17a-tetraone (XV),

isolated as the colorless diosphenol XVa. This substance gave a ferric chloride coloration and showed U.V. absorption, λ_{max} 238 mμ, with considerable absorption in the 260–280 mμ range. No clear maximum developed but quite obviously diosphenol absorption was contributing to that of the Δ^4-3-keto system.

Finally, cortisol acetate (III) was caused to rearrange with aluminum isopropoxide to yield in addition to the previously reported[16b] major product X an isomeric monoacetate, which according to the study of Wendler *et al.*,[17] must be formulated as the 17-keto isomer XII. Methanolic bicarbonate hydrolysis of these monoacetates yielded isomeric triols XI and XIII, respectively, both of which were cleaved by periodic acid to 11β-hydroxy-4-D-homoandrostene-3,17,17a-trione XVI, or preferably XVIa. The diosphenol XVIa showed, as did XVa, a very intense U.V. maximum at λ_{max} 243 mμ (ϵ, 20,000) with a residual bulge in the range 260–280 mμ. This curve is clearly a composite of absorption of a Δ^4-3-keto chromophore and of a diosphenol (267 mμ).

The requisite α-diketones, or equivalents, in all three series in hand, their ring contraction to steroid C-17 hydroxy acids was studied and found to be effected readily by aqueous methanolic potassium hydroxide at 130° for two to three hours. In each of the cases (XIV → XVII, XV → XVIII), acids were obtained which proved to be epimeric with the 3-keto-Δ^4-17α-hydroxytienic acids (XX) derived from Substance *S*[18] and cortisone by periodic acid oxidation. The structure of the rearranged hydroxy-acid XIX from XVI is assigned by analogy to the C-17 configurations in XVII and XVIII. The rearranged product from XIV, 17β-hydroxy-3-keto-Δ^4-17-isoetienic acid (XVII), was oxidized to Δ^4-androstene-3,17-dione (XXI, R = H_2) with lead tetraacetate, and the methyl ester of XVII agreed in melting point previously reported for it.[18] The corresponding rearranged acids from XV and XVI, 17β hydroxy-3,11-diketo-Δ^4-17-isoetienic acid (XVIII) and 11β,17β-dihydroxy-3-keto-Δ^4-17-isoetienic acid (XIX), respectively, were convertible to adrenosterone (XXI, R = 0) by lead tetraacetate and by chromic acid oxidation respectively. The observed difference between XVIII and XX (R = 0) (and corresponding methyl esters) thus established the β orientation of the C-17 hydroxyl group in the former.

The stereochemical course of this benzilic acid rearrangement is noteworthy as



Scheme A

the study of this reaction and that of Wendler[19] represent the first cases in which the stereochemistry may be understood. Although no attempt was made to ascertain the maximum yield of the α-hydroxy acids produced in this reaction,[20] it is apparent that

[17] N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *ibid.* **78**, 5027 (1956).

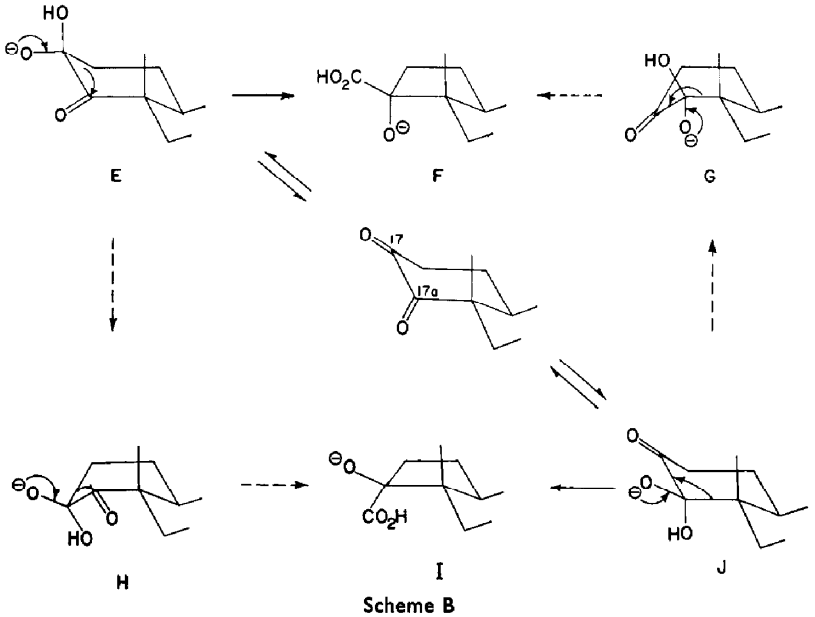
[18] T. Reichstein, C. Meystre and J. v Euw, *Helv. Chim. Acta* **22**, 1107 (1939).

[19] N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* **7**, 173 (1959).

[20] Recent studies (V. Georgian and Lupe T. deGeorgian) in the benzilic acid rearrangement of 3,4-diketosteroids indicate longer reaction times than those employed herein result in even higher yields of rearranged α-hydroxy acids.

within the limits of isolation technique the benzilic acid rearrangement of 17,17a-diketosteroids proceeds predominantly in one steric sense. Application of the established mechanism of this rearrangement[21] must be made necessarily to the diketo species *C*[22] (in equilibrium Scheme A) however small its concentration may be in the strongly alkaline reaction medium.

Attack by hydroxide ion on the α-diketo system at C(17) with the D-homo ring in a chair conformation followed by the necessary electronic displacements indicated in E (Scheme B) would lead to a 17α-hydroxy-17β-carboxy rearranged product *F*. Alternatively, the corresponding changes following initial attack on the C(17a)



Scheme B

carbonyl (chair conformation) would result in the epimeric 17α-carboxyl-17β-hydroxy arrangement (*J* → *I*, Scheme B). It may be seen readily that intermediates represented by part structure *J* are sterically preferred to those of the type *E* in which serious non-bonded interaction obtains between the C(18) methyl and a C(17) oxygen function,

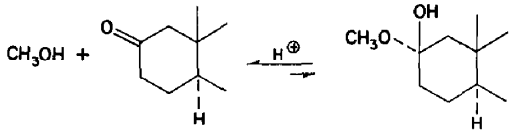
[21] cf. L. P. Hammett, "*Physical Organic Chemistry*", McGraw-Hill Book Company, Inc., New York, N.Y., 1940, pp. 321–322. See also, J. D. Roberts, D. R. Smith and C. C. Lee, *J. Amer. Chem. Soc.* **73**, 618 (1951).

[22] The scheme involving addition of hydroxide ion to the carbonyl of the diosphenolate ion (*B*, Scheme A) resulting in a doubly anionic species followed by protonation at C(16) to yield intermediate *J* (or *G*) in Scheme B seems energetically unattractive in requiring approach of the negative hydroxide to a species already negatively charged. The recent studies of C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.* **80**, 6360 (1958); **84**, 1750 (1962) on dicarbanions indicates that such are attainable but only under the most forcing conditions employing amide ion and on a molecular structure quite different from those encountered in the present case. This alternate scheme may not be rigorously ruled out and has been invoked[19] leading to the same stereo-chemical result as the scheme advanced in this paper.

hydroxyl or alkoxide.[23] Thus, the observed course of the reaction would appear to be controlled predominantly in one steric sense, that initiated by attack of hydroxide on the C(17a) carbonyl leading to intermediates of type *J*. Should conformational inversion to boat forms be postulated ($E \rightarrow H$, $J \rightarrow G$, Scheme B) prior to rearrangement, then as a direct result of this conformational control,[24] the products from *E* and *J* would be *I* and *F*, respectively, via routes ($F \rightarrow H \rightarrow I$; $J \rightarrow G \rightarrow F$). Boat form *G* appears entirely inadmissible in relation to *J* with the C(13) and C(17a) bonds bearing sizeable groups eclipsed. Boat form *H* would relieve the 1,3 steric interactions obtaining in *E* and might perhaps play a role in leading to the observed products of type *I* (Scheme B) should attack occur to some extent at C(17). Although a boat conformation has been invoked quite convincingly in explaining certain reactions of D-homo steroids bearing two firmly attached substitutents at C(17) thus making a chair form for this ring relatively unfavorable[25] (additional evidence against *E*), there would appear to be far less compelling reasons for postulating the boat form H as a reaction controlling species in our case. Rather, *E* could equilibrate to *J* and thence to *I*.

Additionally, it may be considered interesting that ring contraction has proceeded as well as it has. Although equilibria have been demonstrated involving the 17,17a-D-homo-ketols (C/D, *trans*-decalin) and the 17-hydroxy-20-ketosteroids (C/D, *trans*-hydrindane),[26] the latter forms are not favored in such equilibria, and except for transforming one D-homo ketol to another, it is impossible to utilize preparatively the reversal of the D-homoannulation of 17-hydroxy-20-ketones[27] as a steroid reconstitution means. Thus it would appear that the success of the benzilic acid mode of ring contraction in overcoming the C/D juncture strain in the return from a *trans*-hydrindane derives some driving force from the transformation of the diosphenolate

[23] An argument especially germane to the case in point is that provided by the optical rotatory studies of C. Djerassi, L. A. Mitscher and B. J. Mitscher, *J. Amer. Chem. Soc.* **81**, 947 (1959) on the hemiketal equilibrium obtaining with 2-keto-5α-steroids:



In methanol, the most favorable alcohol, the hemiketal form does not exceed 12% in the 2-keto cases and approximates 70% in the corresponding 3-keto-5α-steroids. Hemiketal formation is thus very sensitive to conformational factors and is profoundly affected by the generation of 1,3-diaxial interactions, of the same general type invoked in the discussion of our benzilic acid rearrangement mechanism.

[24] For interesting applications of the principle of conformational control of products see: (a) I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. Chim. France*, 1845 (1956); 742 (1959). (b) N. L. Wendler, D. Taub and R. Firestone, *Experientia*, **15**, 237 (1959); (c) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955).

[25] N. L. Wendler, *Chem. & Ind.* 1662 (1958); *Tetrahedron* **11**, 213 (1960).

[26] I. Elphimoff-Felkin and A Skrobek, *Comp. rend.* **246**, 2497 (1958); I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. Chim. France*, 742 (1959); N. L. Wendler, D. Taub and R. W. Walker, *Chem. & Ind.* 903 (1959); *Tetrahedron* **11**, 163 (1960); D. Taub and N. L. Wendler, *Chem. & Ind.* 902 (1959).

[27] Ref. 26 and R. B. Turner, private communication.

ion (*B*, Scheme A) to the much weaker base, carboxylate ion (*D*, Scheme A) (carboxylate resonance).[28]

Lastly, we would like to call attention to two small observations which are of some interest. A selective reduction of the 17a keto group was found to be possible with one equivalent of sodium borohydride in methanol on compound VI. The reduction product, m.p. 229–231°, showed I.R. absorption (6·00 6·20 μ), characteristic of the Δ^4-3-keto function and no non-conjugated carbonyl absorption indicating survival of the former and reduction at C-17a to the product 17α,17aξ-dihydroxy-17β-hydroxymethyl-4-D-homoandrosten-3-one. This reduction of a non-conjugated carbonyl, despite the somewhat hindered nature of same, in preference to a conjugated carbonyl is parallel to the situation reported previously[29] for similar selective reductions at C-17 and C-20 in Δ^4-3-keto steroids and in the case of a simpler bicyclic system.[30]

A second point of some interest was encountered in the periodic acid oxidation of Reichstein's compound *S* and cortisone where it was observed that oxidation of the ketol side chain conducted in methanol resulted in the production of 17α-hydroxy-etienic methyl esters directly. Since it was established that the esterification did not ensue following production of the free carboxylic acid, the indication is forced that the periodate acted on the methanol hemiketal at C-20 of the cortical side chain (see discussion in experimental section as well).

EXPERIMENTAL[31]

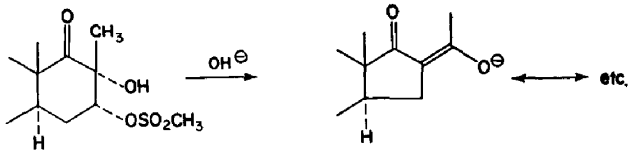
17α-Acetoxy-17β-acetoxymethyl-4-D-homoandrostene-3,17a-dione (IV) and *17α-Hydroxy-17β-acetoxymethyl-4-D-homoandrostene-3,17a-dione* (V)

To a solution of Reichstein's Substance *S* acetate (I) (6·00 g) in glacial acetic acid (500 ml) and acetic anhydride (10 ml) there was added 5 ml boron trifluoride-etherate and the reaction was allowed to stand at ordinary temp for 18 hr. The volatile matter was removed *in vacuo* with no external heating and the dark residual oil was taken up in chloroform, washed with water, bicarbonate solution, again with water and dried (Na_2SO_4). The chloroform was removed and the residue was taken up in benzene–hexane (5:3) and chromatographed on 180 g acid-washed activated alumina.

Benzene–ether (3:1) eluted material which could be fractionated by recrystallization from methanol into a head fraction (218 mg) m.p. 220–221° (proved to be Substance *S* diacetate by I.R. analysis and mixed m.p.) and a tail fraction (3·48 g), the diacetate IV, m.p. 127–129°. It was recrystallized from methanol, m.p. 127–129°, $[\alpha]_D^{25}$ +118° (*c* = 25 mg/ml, $CHCl_3$). (Found: C, 69·84; H, 7·93; Calc. for $C_{25}H_{34}O_6$: C, 69·76; H, 7·90%).

Elution of the column above with ether–ethyl acetate (1:1) afforded an oily fraction which crystallized on being triturated with ether. It was recrystallized twice from methanol and proved to be

[28] Strongly suggestive corroboration for this line of reasoning may be gleaned from the fact that a strongly enolic β-diketone results in the alkaline transformation and ring contraction:[25]



[29] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).

[30] J. D. Cocker and T. G. Halsall, *J. Chem. Soc.* 3441 (1957).

[31] All m.p.s and b.p.s are uncorrected. I.R. spectra were measured on a Baird Model AB-2 double-beam spectrophotometer. U.V. spectra were measured in 95% ethanol on a Beckman Model DK-2 spectrophotometer. Analyses were performed by Miss H. Beck, microanalytical laboratory, Northwestern University.

the monoacetate V (1·60 g), m.p. 197–198°, $[\alpha]_D^{25}$ +124° (c = 25 mg/ml, $CHCl_3$); (lit.[16b] m.p. 194–196°; $[\alpha]_D^{20}$ +134°). (Found: C, 70·82; H, 8·31; Calc. for $C_{23}H_{32}O_5$: C, 71·13; H, 8·24%).

17α-Hydroxy-17β-hydroxymethyl-4-D-homoandrostene-3,17a-dione (VI)

The D-homo diacetate IV, m.p. 127–129° (525 mg) was dissolved in 30 ml methanol and a solution of 700 mg sodium bicarbonate in 20 ml water added. The mixture was kept at ordinary temp for 24 hr, and the methanol then removed *in vacuo*. A little water was added and the precipitated solid was filtered and crystallized from methanol (Norite) to yield 372 mg VI, m.p. 197–198°, mixed m.p. with monoacetate V (of m.p. 197–198°) was 166–170°; $[\alpha]_D^{25}$ +110° ($CHCl_3$, c = 25 mg/ml); (lit.[16b] m.p. 193–194°; $[\alpha]_D^{20}$ +122°). (Found: C, 72·77; H, 8·96; Calc. for $C_{21}H_{30}O_4$: C, 72·83; H, 8·67%).

As a practical matter, it was found convenient to telescope the D-homoannulation reaction and the hydrolysis of the mixed acetates to the diol VI.

D-Homo-monoacetate V *from acetylation of D-homo-diol* VI

The D-homo diol VI, (m.p. 197–198°) when acetylated in the usual manner with acetic anhydride in pyridine overnight afforded the mono-acetate V, m.p. 197–198° (from methanol), mixed m.p. with VI 165–169°, no depression when mixed with sample of monoacetate V obtained above in the D-homoannulation reaction. I.R. corroborated the identity of these products.

Sodium borohydride reduction of D-homo-diol VI

17α,17aξ-Di-hydroxy-17β-hydroxymethyl-4-D-homoandrosten-3-one. To the D-homo-diol VI (173 mg) dissolved in 6 ml methanol, there was added a solution of 5 mg (one equivalent) sodium borohydride in 0·5 ml water and the solution was kept at room temp overnight. A small amount of precipitate was filtered off and the filtrate was concentrated *in vacuo*. Water (5 ml) was added and the semi-solid product solidified on being acidified with dilute HCl. It was filtered, washed and dried, 112 mg, m.p. 213–218°, and, when recrystallized from methanol, it had a m.p. 229–231°. The I.R. spectrum indicated the absence of non-conjugated carbonyl group and the presence of a conjugated carbonyl band at 6·00 μ, and 6·20 μ for conjugated double bond, thus establishing the controlled reduction of the 17a-carbonyl in preference to the conjugated carbonyl at C-3. (Found: C, 72·17; H, 8·93; Calc. for $C_{23}H_{32}O_4$: C, 72·41; H, 9·19%).

Periodic acid cleavage of glycol VI. *4-D-Homo-androstene-3,17,17a-trione* (XIV) *hydrate*

Isolation of formaldehyde. To a solution of the D-homo glycol VI (150 mg) in 10 ml methanol there was added 150 mg (1·5 equivalents) periodic acid dihydrate in 1 ml water. The solution was kept at room temp for 22 hr. Ten ml water, a pinch of zinc dust, a crystal of silver nitrate, and a trace of hydroquinone were added and the mixture was distilled. The distillate was collected in a solution of dimedon and the distillation was repeated with another 10 ml water. There was isolated 45 mg dimedon-foraldehyde complex, m.p. 190–193°, undepressed by an authentic sample.

Isolation of XIV-*hydrate.* To a solution of the D-homo glycol VI (500 mg) in 10 ml methanol there was added 330 mg (one equivalent) periodic acid dihydrate in 2 ml water. After standing at room temp overnight, the solution was concentrated *in vacuo*. The residue was treated with water and extracted with chloroform, which solution was then washed with water, bicarbonate solution (5%) and again with water. The chloroform was evaporated and the residual oily product was taken up in 5% sodium hydroxide solution, filtered, and the filtrate (cold) was acidified with dil. HCl. The colorless solid, 430 mg, m.p. 95–115°, was crystallized from methanol, m.p. 136–138°, $[\alpha]_D^{25}$ +25° (c = 21 mg/ml $CHCl_3$). Elemental analysis indicated a molecule of water of hydration. Thus this substance, which gives the characteristic deep red-violet coloration with $FeCl_3$, and which shows I.R. absorption at 2·84 μ (OH), 5·82 μ (normal carbonyl), 6·02 μ (Δ^4-3-keto) and U.V. λ_{max}^{EtOH} 240 mμ (log ε, 4·20) with no absorption in 260–280 mμ range, must be the trione XIV-(C-17a)-hydrate (Found: C, 71·93; H, 8·56; Calc. for $C_{20}H_{26}O_3 \cdot H_2O$: C, 72·28; H, 8·43%).

The *quinoxaline* derivative had m.p. 252–254° (dec) (from methanol). (Found: N, 7·59; Calc. for $C_{26}H_{30}ON_2$: N, 7·25%).

When the glycol VI was cleaved with 1·5 equivalents of periodic acid dihydrate as above, practically no α-diketone was obtained, but instead a carboxylic acid of m.p. 254–256°, analysis of which

agreed with a 17,17a-seco-17,17a-dioic acid of the formula XXII. (Found: C, 69·17; H, 7·83; Calc. for $C_{20}H_{28}O_5$: C, 68·93; H, 8·04%).

17β-Hydroxy-3-keto-Δ⁴-17-isoetienic acid XVII. *Benzilic acid ring contraction of* XIV

A solution of 500 mg XIV-hydrate 20 ml methanol, 30 ml water and 3 g potassium hydroxide was heated in a stainless steel bomb at 130–150° for 3 hr.[20] Excess methanol was removed *in vacuo*, the aqueous solution was acidified with dil. HCl and then made alkaline with bicarbonate and filtered. The clear filtrate on acidification yielded a solid, which on recrystallization from methanol (Norite) m.p. 228–230° depressed the m.p. of the acid obtained by periodic acid oxidation of Reichstein's Substance *S* XX (R = H_2) to 205–212°; yield of XVII 202 mg, $[\alpha]_D^{33}$ +89° (*c* = 25 mg/ml ethanol). (Found: C, 71·91; H, 8·31; Calc. for $C_{20}H_{28}O_4$: C, 72·28; H, 8·43%).

The *methyl ester* of acid XVII, prepared in the usual way by the action of an ethereal solution of diazomethane on a suspension of the acid, m.p. 184–186° (methanol–water); reported[18] 185–187°.

A better over-all yield of ring contraction was effected by converting the crude acid obtained as above directly into the methyl ester (diazomethane) and then purifying the crude ester by chromatography on acid-washed alumina. The benzene–ether (4:1) eluate afforded a 70% yield of methyl ester of XVII from XIV-hydrate.

Lead tetraacetate oxidation of isoetienic acid XVII *to androstenedione*

Lead tetraacetate (277 mg) was added in small portions to a solution of 200 mg hydroxy-isoetienic acid XVII in 30 ml dry benzene containing 1 ml glacial acetic acid and maintained at 50°. The solution at once turned yellow, but soon became colorless with the separation of lead diacetate. The mixture was heated at 50–60° for 1 hr. It was then treated with water and filtered. The organic layer was washed with bicarbonate solution and water and dried (Na_2SO_4). After evaporation of the solvent, the residue, androstenedione (XXI, R = H_2), was crystallized from methanol, 100 mg, m.p. 169–172°. This substance had an I.R. curve identical to, and was not depressed on being melted on admixture with a preparation of, androstenedione obtained from lead tetraacetate oxidation, as above, of 17α-hydroxy-Δ⁴-3-ketoetienic acid (XX, R = H_2), derived from periodic acid cleavage of Reichstein's Substance *S* as described below.

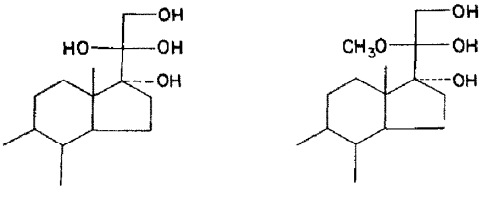
17α-Hydroxy-Δ⁴-3-ketoetienic acid (XX, R = H_2) *and methyl ester from periodic acid oxidation of Reichstein's Substance S*

A solution of 684 mg periodic acid in 5 ml water was added to a solution of 1·04 g Substance *S* dissolved in 30 ml methanol and maintained at ordinary temp 18 hr. The methanol was then removed *in vacuo* and the residue was taken up in chloroform, washed with water and extracted with bicarbonate solution. The bicarbonate extract gave on acidification a solid, 713 mg, m.p. 207–225°, which after two recrystallizations from methanol and vacuum drying had m.p. 238–240° (dec). Reported[18] 232–240°. (Found: C, 70·38; H, 8·20; Calc. for $C_{20}H_{28}O_4 \cdot \frac{1}{2}H_2O$: C, 70·55; H, 8·50%).

The *methyl ester* of XX (R = H_2) (diazomethane) had m.p. 213–215°. Reported[18] 216–218°.

From the chloroform solution above, after bicarbonate extraction, there was isolated, upon concentration and vacuum drying, 238 mg of a solid, m.p. 180–190°, after crystallization from methanol, m.p. 212–213°. This proved to be, by I.R. comparison and mixed m.p., identical to the methyl ester of XX (R = H_2).

The yield of methyl ester could be doubled with a corresponding decrease in the production of acid when the periodic acid cleavage of Substance *S* was carried out in absolute methanol. Since control experiments indicated that the quantities of methyl ester did not arise by esterification of acid produced as a precursor, it becomes necessary to postulate that acid and ester arise directly by periodic acid cleavage of the corresponding solvated forms of the ketol, *vis*:



an observation which bears on the mechanism of the cleavage of ketols (similarly cortisone, *vide infra*) in the Malaprade reaction.[32]

17α-*Acetoxy*-17β-*acetoxymethyl*-4-D-*homoandrostene*-3,11,17a-*trione* (VII) and 17α-*Hydroxy*-17β-*acetoxymethyl*-4-D-*homoandrostene*-3,11,17a-*trione* (VIII)

D-*Homoannulation by means of boron trifluoride etherate.* A solution of 2·00 g cortisone acetate (II) in 150 ml glacial acetic acid was treated with 4 ml acetic anhydride and 3 ml boron trifluoride-etherate at room temp for 18 hr. The reaction was worked up as in the analogous D-homoannulation of Reichstein's Substance *S*, the crude product being chromatographed on 60 g acid-washed activated alumina.

Elution with benzene–ether (1:1) gave an oily product, 619 mg, which could not be crystallized.

Elution with ether–ethyl acetate (1:1) afforded 500 mg of an oil which crystallized on trituration with ether and ethyl acetate. It was recrystallized from methanol, m.p. 227–228°, $[\alpha]_D^{25}$ + 128° (c = 25 mg/ml chloroform). Analysis corresponded to a diacetate VII. (Found: C, 67·60; H, 7·41; Calc. for $C_{25}H_{32}O_7$: C, 67·56; H, 7·20%).

Elution of the column above with pure ethyl acetate yielded the monoacetate VIII, 250 mg, which could be recrystallized from methanol, m.p. 206–207°, $[\alpha]_D^{25}$ + 175° (c = 25 mg/ml chloroform) (lit.[16b] 199–201°; 198–199·5°[16a]). (Found: C, 68·72; H, 7·45; Calc. for $C_{23}H_{30}O_6$: C, 68·65; H, 7·46%).

D-*Homoannulation by means of aluminum isopropylate* of cortisone acetate, 5·00 g, was effected essentially under conditions described by Batres *et al.*,[16b] employing 1·25 g aluminum isopropylate, 280 ml toluene, and 40 ml cyclohexanone. The crude product was taken up in benzene (100 ml) and hexane (30 ml) and was chromatographed on 250 g acid-washed activated alumina.

Ethyl acetate eluted 1·65 g which was recrystallized from methanol, 1·45 g, m.p. 199–202°, undepressed on admixture with monoacetate VIII obtained above.

17α-*Hydroxy*-17β-*hydroxymethyl*-4-D-*homoandrostene*-3,11,17a-*trione* (IX)

The monoacetate VIII was hydrolyzed with methanolic-aqueous sodium bicarbonate as in analogous cases above. The product, extracted with chloroform and recrystallized from dil. methanol, IX, had m.p. 195–196°, $[\alpha]_D^{25}$ + 184° (c = 25 mg/ml chloroform). (Found: C, 69·87; H, 7·44, Calc. for $C_{21}H_{28}O_5$: C, 70·00; H, 7·77%).

4-D-*Homoandrostene*-3,11,17,17a-*tetraone* (XV) or *corresponding diosphenol* XVa

The D-homoglycol IX (1·00 g) was cleaved by means of periodic acid dihydrate (600 mg) in dil. methanol and the product of reaction was isolated in a fashion analogous to the corresponding oxidation of glycol VI as above. The crude α-diketone (590 mg), or more likely the diosphenol XVa (colorless), was recrystallized thrice from methanol (Norite), m.p. 187–188°, $[\alpha]_D^{30}$ + 150° (c = 22 mg/ml chloroform). It gives a deep red-violet ferric chloride coloration. U.V. absorption: λ_{max}^{EtOH*} 238 mμ and considerable intensity in 260–280 mμ range indicative of diosphenol chromophore. (Found: C, 72·90; H, 7·48, Calc. for $C_{20}H_{24}O_4$: C, 73·17; H, 7·31%).

17β-*Hydroxy*-3,11-*diketo*-Δ^4-17-*isoetienic acid* (XVIII)

Benzilic acid ring contraction of XV. The diosphenol XVa (500 mg) was dissolved in 15 ml methanol and to this solution there was added a solution of 2 g potassium hydroxide in 50 ml water. The resultant clear yellow solution was heated at 130–140° for 3 hr in a stainless steel bomb[30] and was worked up as in the rearrangement above. There was obtained after recrystallization from dil. methanol (Norite) 160 mg XVIII, m.p. 221–223°, $[\alpha]_D^{33}$ + 165° (c = 12 mg/ml, ethanol). (Found: C, 69·19; H, 7·37, Calc. for $C_{20}H_{26}O_5$: C, 69·36; H, 7·51%).

The methyl ester of XVIII, prepared in the usual way (diazomethane), had m.p. 159–160°. (Found: C, 70·19; H, 7·76. Calc. for $C_{21}H_{28}O_5$: C, 70·00; H, 7·77%).

Lead tetraacetate oxidation of isoetienic acid XVIII *to adrenosterone* (XXI, R = O)

The oxidation of hydroxy acid XVIII (200 mg) with lead tetraacetate (267 mg) in dry benzene (40 ml) with 1 ml glacial acetic acid at 50° for 1–1·5 hr was conducted as in the above analogous case.

[32] L. Malaprade, *Bull. soc. chim. France* [5], **1**, 833 (1934).

The product, adrenosterone (XXI, R = O) was crystallized from methanol 106 mg, m.p. 223–224° and was undepressed by material prepared from cortisone and had identical I.R. absorption with such material.

17α-Hydroxy-Δ⁴-3,11-diketoetianic acid (XX, R = O) *and methyl ester from periodic acid oxidation of cortisone*

Cortisone (2·00 g) was oxidized with periodic acid dihydrate (1·26 g) in methanol (100 ml) and water (25 ml) under conditions similar to those described in the case of Substances *S* above. The activation (XX, R = O) (1·10 g) had m.p. 263–266° (dec); reported m.p. 263–265° (dec).

A neutral product (300 mg) was also obtained from this oxidation and corresponded to the methylester of XX (R = O), m.p. 228–229° (methanol), undepressed on admixture with methyl ester derived from acid XX (R = O) with diazomethane, both esters having identical I.R. spectra (cf. discussion of generation of esters in Malaprade reaction on Substance *S* above). (Found: C, 70·13; H, 7·54; Calc. $C_{21}H_{28}O_5$: O, 70·00; H, 7·7%).

11β,17α-Dihydroxy-17β-acetoxymethyl-4-D-homoandrostene-3,17a-dione (X) and *11β-17aα-Dihydroxy-17aβ-acetoxymethyl-4-D-homoandrostene-3,17-dione* (XII)

D-*Homoannulation of cortisol acetate* (III). Cortisol acetate (III, 5·00 g) was dissolved in 1·2 l. dry toluene and 60 ml cyclohexanone and to this solution there was added 1·25 g aluminum isopropylate. After being refluxed for 1 hr, the solution was cooled, water (70 ml) and conc HCl (30 ml) were added, and the whole was agitated. The organic layer was separated, washed with water, bicarbonate solution, and water, and it was dried (Na_2SO_4). The solvents were removed *in vacuo* and the oily residue was chromatographed on neutral activated alumina (150 g).

Elution with ether gave an oily product which was discarded. Elution with 750 ml ethyl acetate afforded 545 mg crystalline material XII, m.p. 224–227°, which was recrystallized from methanol, m.p. 229–231° (mixed m.p. with cortisol and cortisol acetate showed large depressions), $[\alpha]_D^{28}$ + 77° (*c* = 25 mg/ml chloroform). (Found: C, 68·36; H, 7·87; Calc. for $C_{23}H_{32}O_6$: C, 68·29; H, 7·98%).

Further elution with ethyl acetate yielded 1·80 g X, triturated with ether and crystallized from acetone–ether, m.p. 175–178°; reported[16b], m.p. 181–183°.

11β,17α-Dihydroxy-17β-hydroxymethyl-4-D-homoandrostene-3,17a-dione (XI)

The monoacetate X of m.p. 175–178° (500 mg) was hydrolyzed with dil. methanolic bicarbonate as in similar cases above. After evaporation of most of the methanol, the crude product was extracted with chloroform, washed with water and dried (Na_2SO_4) etc. Evaporation of this solution afforded the triol XI (390 mg), crystallized from methanol, m.p. 215–217°, $[\alpha]_D^{28}$ + 70° (*c* = 25 mg/ml dioxane). (Found: C, 69·40; H, 8·04; Calc. for $C_{21}H_{30}O_5$: C, 69·61; H, 8·28%).

11β,17aα-Dihydroxy-17aβ-hydroxymethyl-4-D-homoandrostene-3,17-dione (XIII)

The monoacetate XII m.p. 229–231° (1·23 g) was hydrolyzed as above with aqueous methanolic bicarbonate. There was obtained, after the usual work-up and crystallization from dil. methanol, the triol XIII, (900 mg), m.p. 117–118°, $[\alpha]_D^{27}$ + 104° (*c* = 25 mg/ml chloroform). (Found: C, 69·23; H, 8·48; Calc. for $C_{21}H_{30}O_5$: C, 69·61; H, 8·28%).

11β-Hydroxy-4-D-homoandrostene-3,17,17a-trione (XVI) or *corresponding diosphenol* (XVIa)

a. *Periodic acid oxidation of triol XI of m.p.* 215–217° (238 mg) was conducted with 150 mg periodic acid dihydrate as in the correlative oxidations above. There was obtained, after crystallization from methanol (Norite), 161 mg colorless crystals of diosphenol XVIa, m.p. 238–240°, $[\alpha]_D^{31}$ +130° (*c* = 18 mg/ml chloroform). It gave a deep red-violet coloration with ferric chloride; λ_{max}^{EtOH} 243 mμ (ε, 20,000) and intense absorption in 260–280 mμ range. (Found: C, 72·30; H, 7·84, Calc. for $C_{20}H_{26}O_4$: C, 72·72; H, 7·87%).

b. *Periodic acid oxidation of triol* XIII *of m.p.* 117–118° (362 mg) with 228 g periodic acid dihydrate, as above, produced 240 mg XVIa, m.p. 235–236° (from methanol). No depression in mixed m.p.

was produced between the products from preparations (a) and (b), and identical I.R. spectra were shown by both.

11β,17β-Dihydroxy-3-keto-Δ⁴-17-isoetienic acid (XIX).

Benzilic acid ring contraction of XVI. The diosphenol XVIa (400 mg) was rearranged in dil. methanol with 1·60 g potassium hydroxide as described for the corresponding benzilic acid rearrangements above. The cooled reaction solution was just neutralized with hydrochloric acid and evaporated under a nitrogen stream at ordinary temp nearly to dryness. Ethyl acetate extraction of the resdue followed by water washing and drying (Na_2SO_4) of the extract afforded, after due evaporation, a thick oil, which was triturated in the cold with a little ethyl acetate. The crystals of isoetienic acid XIX so obtained were recrystallized from ethyl acetate, 125 mg, m.p. 201–203°, $[\alpha]_D^{29}$ +116° (c = 21 mg/ml ethanol). (Found: C, 67·26; H, 7·96. Calc. for $C_{20}H_{28}O_5 \cdot \frac{1}{2}H_2O$: C, 67·22; H, 8·12%).

The *methyl ester* of XIX, prepared with diazomethane, had m.p. 204–206°. (Found: C, 69·61; H, 8·25; Calc. for $C_{21}H_{30}O_5$: C, 69·61; H, 8·28%).

Oxidation of hydroxyisoetienic acid XIX *to adrenosterone* (XXI, R = O)

The benzilic acid rearrangement product XIX of m.p. 201–203° (12 mg) was oxidized in glacial acetic acid (6 ml) with 100 mg chromium trioxide in 8 ml acetic acid at room temp for 1 hr. A little methanol was added to destroy the excess chromic acid and most of the acetic acid was taken off *in vacuo* with little or no external heat. The residue was diluted with water and extracted with chloroform, which was then washed with bicarbonate solution and dried (Na_2SO_4). There was obtained after evaporation and crystallization from methanol 60 mg adrenosterone of m.p. 219–221°, undepressed by authentic sample (also I.R. correspondence).

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