precipitated solid was filtered out and recrystallized from benzene or hexane–benzene mixture. The products obtained are indicated in Table IV.

1-Phenoxy-2,4,4-trichlorocyclopentene-3,5-dione (XXV).—A mixture of 117 g. of tetrachlorocyclopentene-3,5-dione, 51 g. of methylmorpholine, and 250 g. of phenol was heated on the steam bath for 48 hr. The excess phenol was then stripped under vacuum and the remaining material dissolved in benzene. Insoluble salts were filtered out, the mother liquor evaporated, and the remaining liquid distilled to obtain a yellowish liquid, b.p. 129–132° (0.25 mm.). After recrystallization from hexane and aqueous acetic acid, there was obtained 45 g. (31%) of a yellowish solid, m.p. 62–63°.

Anal. Calcd. for $C_{11}H_5Cl_3O_3$: C, 45.32; H, 1.73. Found: C, 45.23; H, 1.69.

Reaction of 1-Phenoxy-2,4,4-trichlorocyclopentene-3,5-dione (XXV) with Methanol.—A solution of 4 g. of XXV in 25 ml. of methanol was refluxed for 36 hr. Titration of an aliquot of the solution to a congo red end point followed by a Volhard titration showed that one molar equivalent of strong acid had been formed, but negligible hydrogen chloride. The reaction mixture was evaporated free of methanol, the residual oil taken up in water, insolubles removed by hexane extraction, and the water solution evaporated under aspirator vacuum on the steam bath. The residual 2 g. of crystalline solid was found by infrared to be identical to the enol III.

Acknowledgment.—The authors wish to acknowledge the assistance of Mr. Abram Davis and Mr. John Michalovic in obtaining and interpreting the spectral data presented herein.

Epimerization of Axial Steroid Alcohols Accompanying Lead Tetraacetate Oxidative Coupling

GEORGE B. SPERO, JOHN L. THOMPSON, WILLIAM P. SCHNEIDER, AND FRED KAGAN

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

Received January 18, 1963

Reaction of lead tetraacetate with 11β (axial) steroid alcohols results in formation of the same 1α,11α-epoxides as are obtained from the corresponding 11α (equatorial) epimers. Deuterium labeling experiments show that this unusual epimerization occurs with quantitative retention of the C-11 hydrogen.

A recent communication[1a] reporting the striking epimerization of a secondary alcohol through photolysis of its nitrite ester prompts us to report our experience in epimerization of steroid alcohols with lead tetraacetate.[1b] The reaction of steroid secondary alcohols with lead tetraacetate to effect substitution of an unactivated δ carbon atom which is favorably situated in respect to the hydroxyl, was first reported by Jeger and co-workers.[2] Subsequently additional reports from that group and from others[3a,b,4] followed. With C-11 hydroxylated steroids the 1,11α-epoxides have been obtained from the 11α-epimers.[5] The 11β-epimers have been reported by various investigators to give only oxidation to the 11-ketone,[6] and 11β,18-epoxide,[7] or, in the presence of iodine, the 11β,19-epoxide.[3]

Our experience with the lead tetraacetate reaction on steroid C-11 alcohols differs from the above reports with respect to the 11β-epimers, in that epimerization accompanies oxidative coupling.

Reaction of either 11β-hydroxyprogesterone bisethylene ketal (Ia) or 11α-hydroxyprogesterone bisethylene ketal (IIa) with lead tetraacetate in boiling cyclohexane gave the same 1α,11α-epoxide IIIa. The structure of the epoxide was determined by its n.m.r. spectrum and by its conversion to the known 11α-hydroxy-1,4-pregnadiene-3,20-dione (Va)[8a,b] through ketal removal followed by base-catalyzed β-elimination of epoxide bond at C-1.[9] The previous series of conversions was done separately on 1α,11α-epoxide material derived from both the 11α- and 11β-hydroxy epimers. At all stages, the products (III, IV, and V) were demonstrated to be identical by mixture melting point, rotation, and infrared spectra comparisons. These conversions, in addition to locating the position of the epoxy oxygen, served to establish the α-configuration of the oxygen bond at C-11. A study of models suggested the preferred attachment at C-1 to be on the α side. This is substantiated by the Swiss work.[5] The 1α,11α-oxygen bridge constrains the A-ring to the boat form providing a rigid A,B,C ring system. This rigidity may explain the failure of the double bond to isomerize from the C-5 to the C-4 position on acid-catalyzed removal of the ketal group as in III → IV.

The yield of epoxide III from the 11α-epimer was about double (50–60%) that obtained from the 11β-epimer (25–30%). A major side reaction of the 11β-epimer was oxidation to 11-ketoprogesterone bisethylene ketal. With both epimers some loss of ketal at C-20 occurred.

In addition to Ia and IIa, a second pair of epimeric steroid C-11 alcohols, 11α- and 11β-hydroxypregnenolone 3-acetate,[10] was similarly treated with lead tetraacetate. Only one epoxide was obtained from both and was designated as 1α,11α-epoxypregnenolone acetate by analogy with the results obtained from I and II and

(1) (a) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961); (b) After submission of our manuscript, a paper by K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963), appeared, which also describes the epimerization of steroid hydroxyl groups with lead tetraacetate.

(2) G. Cainelli, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *ibid.*, **42**, 1124 (1959).

(3) (a) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); (b) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 1317 (1962), and references cited therein.

(4) A. Bowers, E. Denot, L. Cuéllar Ibáñez, Ma. Elena Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962).

(5) J. Kalvoda, G. Anner, D. Arigoni, K. Heusler, H. Immer, O. Jeger, M. Lj. Mihailović, K. Schaffner, and A. Wettstein, *Helv. Chim. Acta*, **44**, 186 (1961).

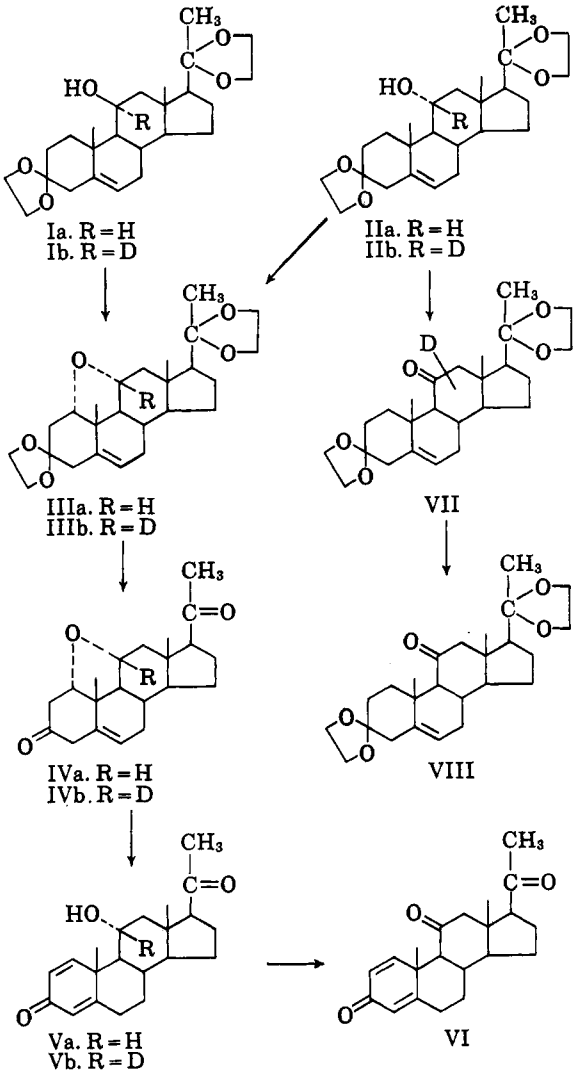
(6) A. Bowers and E. Denot, *J. Am. Chem. Soc.*, **82**, 4956 (1960).

(7) P. F. Beal and J. E. Pike, *Chem. Ind.*, 1505 (1960).

(8) (a) H. A. Kroll, J. F. Pagano, and R. W. Thoma, U. S. Patent 2,822,318 (February 4, 1958); (b) S. E. Eppstein, P. D. Meister, and A. Weintraub, U. S. Patent 2,883,400 (April 21, 1959).

(9) The publication by Jeger and co-workers[5] on the preparation and structure proof of IIIa appeared subsequent to completion of our work and followed essentially the same path. Our physical constants for IIIa and IVa are in agreement with those reported by them. The melting point given by Jeger, *et al.*, for Va seems to be in error and does not correspond with ours which is in agreement with that given in ref. 8a,b.

(10) W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963).



by its n.m.r. spectrum which showed the angular methyl groups still intact.

From the previous results it becomes apparent that an inversion of the 11β-hydroxyl to sterically preferred α (equatorial) configuration must take place at some stage of the reaction, the mechanism of which remains obscure. If the first step is formation of the lead alkoxide[11] followed by homolytic fission to the alkoxy radical, then this epimerization and that reported by Nickon, *et al.*,[1] may go by the same mechanism. One might have expected the 11β-alkoxy radical formed to attack the C-18 or C-19 methyl groups as has been reported when an 11β-nitrite ester is photolyzed.[12] However, we did not isolate any predicted products from such a reaction. The 11-ketone can be eliminated as an intermediate since 11-ketoprogesterone bisethylene ketal, either alone or in the presence of cyclohexanol, was recovered unchanged when treated with lead tetraacetate.[13] If inversion of the 11β-epimer takes place at some stage prior to ring closure, any such intermediate must be short lived. Papergram studies of aliquots worked up at intervals during the reaction failed to show the presence of any 11α-hydroxyprogesterone bisethylene ketal.

To gain further insight into the mechanism of the reaction, the C-11 hydrogens in I and II were replaced with deuterium, and the fate of the deuterium was investigated. Conceivably, this hydrogen might have undergone isotopic exchange during the reaction either by a free radical or an ionic mechanism, and either before or after formation of a lead alkoxide intermediate.

11α - Deuterio - 11β - hydroxyprogesterone bisethylene ketal (Ib) and 11β-deuterio-11α-hydroxyprogesterone bisethylene ketal (IIb) were prepared by reduction of 11-ketoprogesterone bisethylene ketal with lithium aluminum deuteride and with sodium in the presence of deuterioethanol, respectively. The lithium aluminum deuteride reduction gave a product containing one atom of deuterium per molecule as expected. The sodium and deuterated alcohol reduction gave a product containing 2.23 atoms of deuterium per molecule. Excess deuterium entered the molecule in ring C in positions 9 and/or 12, probably through enolization of the 11-ketone. This was established by analysis of the 11-ketone (VII) prepared by oxidation of the deuterated alcohol. Compound VII still contained 1.56 atoms of deuterium per molecule but on equilibration with base for nineteen hours nearly all of the deuterium was lost to give compound VIII containing 0.25 atom of deuterium per molecule.[14]

Treatment of the two deuterated epimers Ib and IIb with lead tetraacetate resulted in formation of the 1α,11α-epoxide with *no loss of deuterium in either case.* That the deuterium was still at position C-11 was established by conversion of the deuterated epoxide derived from Ib to 1-dehydro-11-ketoprogesterone (VI) using the sequence of steps IIIb → IVb → Vb → VI. The deuterium remained in the molecule during the ketal removal and epoxide opening steps but was lost in the oxidation step, giving VI essentially deuterium free (D = 0.06 atom per molecule).

While these results are not sufficient to establish a mechanism for the epimerization, they show that any mechanism proposed must not involve more than a transient breaking of the C-11 hydrogen bond. A "cage" type[15] mechanism might be involved in which the 11-hydrogen is temporarily detached, and returns to the opposite face of the C-11 carbon, resulting in epimerization.[16] On the other hand, if the reaction proceeds *via* an 11-alkoxy radical, the relative bond strengths of the groups attached to such alkoxy radicals[17] would not seem to favor C–H bond breakage, but rather C–C bond breakage,[18,19] as, for example, the

(11) R. Criegee, L. Kraft, and B. Rank, *Ann.*, **507**, 159 (1933).

(12) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962).

(13) We consider an oxidation–reduction scheme of the Oppenauer–Meerwein–Pondorff type between an 11β-lead alkoxide and traces of 11-ketone impurity as highly unlikely to account for the observed amounts of epimerization. The sterically hindered nature of the 11-position in steroids makes oxidation–reduction reactions of this type very unsatisfactory under the best conditions.

(14) This small amount of deuterium still remaining is probably due to incomplete exchange. We believe this could be reduced or eliminated by a longer reaction period.

(15) L. Herk, M. Feld, and M. Szwarc, *J. Am. Chem. Soc.*, **83**, 2998 (1961).

(16) A "cage" loose enough to account for epimerization of this type might be expected to lose permanently a portion of the 11-hydrogens, thus accounting for the production of the 11-ketone observed as a by-product.

(17) P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

(18) A. L. Nussbaum, E. P. Yuan, C. H. Robinson, A. Mitchell, E. P. Oliveto, J. M. Beaton, and D. H. R. Barton, *J. Org. Chem.*, **27**, 20 (1962).

(19) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein (ref. 3b, footnote 38) visualize the epimerization reaction observed by Nickon, *et al.*, as going through the alkoxy radical and C–C bond cleavage to an aldehyde and a C-radical. This is followed by intramolecular recombination of the aldehyde and C-radical in such a way as to produce the epimeric alkoxy radical. No details or references are given for this unusual recombination.

C-9(11) bond. We have no evidence that would bear on this possibility, or the other alternative, C-11 oxygen bond breaking *via* a displacement reaction.

Whatever the mechanism for the epimerization, the possibility of this transformation might be considered in other lead tetraacetate reactions. For example, in the slow cleavage of some *vic*-glycols, which for steric reasons cannot form the most generally accepted[20] cyclic lead alkoxide intermediates, epimerization might precede cleavage.

Experimental[21]

Materials.—3,20-Bisethylenedioxy-11β-hydroxy-5-pregnene (Ia) was prepared by reduction of the corresponding ketone[22] with lithium aluminum hydride and was purified until free of any 11α-epimer as shown by paper chromatography.

Lead tetraacetate (Matheson Coleman and Bell), which was wet with acetic acid as purchased, was triturated three or four times with anhydrous ether, briefly air dried until free flowing, and the light brown product used at once.

Cyclohexane was washed with concentrated sulfuric acid and water, dried, and distilled.

1α,11α-Epoxy-3,20-bisethylenedioxy-5-pregnene (IIIa). From Ia.—A suspension of 5.0 g. of 3,20-bisethylenedioxy-11β-hydroxy-5-pregnene (Ia) and 15.0 g. of lead tetraacetate in 1500 ml. of cyclohexane was allowed to stir and reflux for 4.5 hr., during which time the initially brownish mixture gradually became white. The mixture was cooled, filtered, and the filtrate was washed with 300 ml. of 5% solution of potassium iodide, 300 ml. of 5% solution of sodium thiosulfate, and water. After drying the washed solution over anhydrous sodium sulfate, it was evaporated to dryness and the residue was crystallized from 30 ml. of acetone to give 1.33 g. of product, m.p. 195–215°. The analytical sample had m.p. 212–217°, $[\alpha]_D$ −31° (dioxane).

Anal. Calcd. for $C_{26}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.06; H, 8.83.

From IIa.—Five grams of 3,20-bisethylenedioxy-11α-hydroxy-5-pregnene (IIa)[23] was treated with 15 g. of lead tetraacetate in 1200 ml. of cyclohexane as given previously for the 11β-hydroxy epimer. Crystallization from acetone gave 2.75 g. of product, m.p. 195–215°. The analytical sample had m.p. 209–215°, $[\alpha]_D$ −29° (dioxane).

Anal. Found: C, 71.93; H, 8.58.

Both products had identical infrared curves (Nujol mulls) and a mixture of the two showed no depression in melting point. The n.m.r. spectrum corresponded to that reported.[5]

1α,11α-Epoxy-5-pregnene-3,20-dione (IVa).—A solution of 730 mg. of 1α,11α-epoxy-3,20-bisethylenedioxy-5-pregnene (IIIa) and 5 ml. of 1 *N* sulfuric acid in 100 ml. of acetone was gently boiled on the steam bath 10 min. After concentrating the solution under a stream of nitrogen to about 25 ml., 100 ml. of water was added and the resulting precipitate was isolated and crystallized from acetone to give 377 mg. of IVa, m.p. 203–208°. The analytical sample had m.p. 205–208°, $[\alpha]_D$ +176° (dioxane).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.75; H, 8.89.

11α-Hydroxy-1,4-pregnadiene-3,20-dione (Va).[8]—To a solution of 225 mg. of 1α,11α-epoxy-5-pregnene-3,20-dione (IVa) in 45 ml. of absolute alcohol was added 225 mg. of potassium acetate and the mixture was allowed to stir and reflux for 16 hr. Water (20 ml.) was added and the solution was cooled to give 217 mg. of Va, m.p. 220–233°. Recrystallization from ethyl acetate raised the melting point to 233–234°. This was identical to an authentic sample.[8b]

3,20-Bisethylenedioxy-11α-deuterio-11β-hydroxy-5-pregnene (Ib).—To a suspension of 0.8 g. of lithium aluminum deuteride in 180 ml. of anhydrous ether was added, dropwise over 5 min., a solution of 4.1 g. of 3,20-bisethylenedioxy-5-pregnen-11-one in 60 ml. of benzene. The mixture was allowed to stir and reflux for 1 hr. and was then cooled and the excess deuteride decomposed by the careful addition of water (100 ml.). The organic phase was separated, washed with water, dried, and evaporated to dryness. Crystallization of the residue from isopropyl ether afforded 2.97 g. of Ib, m.p. 146–148°. The analytical sample had m.p. 148–150°, $[\alpha]_D$ −3° (acetone).

Anal. Calcd. for $C_{25}H_{37}DO_5$: C, 71.56; H, 8.89; D, 1 atom/molecule. Found: C, 71.44; H, 9.22; D, 1.00 atom/molecule.

3,20-Bisethylenedioxy-11β-deuterio-11α-hydroxy-5-pregnene (IIb).—In an atmosphere of nitrogen and with efficient stirring, to 50 ml. of xylene was added 2.0 g. of sodium in portions followed by 2.0 g. of 3,20-bisethylenedioxy-5-pregnen-11-one and the mixture was heated at reflux for 10 min. While refluxing, 10 ml. of deuterioethanol in 20 ml. of xylene was added dropwise over a period of 30 min. After refluxing for an additional 30 min., the mixture was cooled and 20 ml. of methanol was added dropwise followed by 100 ml. of water. The mixture was then extracted with ether (300 ml.) and ethyl acetate (100 ml.) and the extracts were washed with water, dried, and evaporated to dryness to give 2.0 g. of IIb, m.p. 218–220°. The analytical sample, recrystallized from acetone, had m.p. 220–223°, $[\alpha]_D$ −7° (acetone).

Anal. Calcd. for $C_{25}H_{37}DO_5$: C, 71.56; H, 8.89; D, 1 atom/molecule. Found: C, 71.27; H, 9.12; D, 2.23 atoms/molecule.

1α,11α-Epoxy-11β-deuterio-3,20-bisethylenedioxy-5-pregnene (IIIb). From Ib.—Reaction of 1.0 g. of 3,20-bisethylenedioxy-11α-deuterio-11β-hydroxy-5-pregnene (Ib) with 3.0 g. of lead tetraacetate according to the procedure given for the non-deuterated compound gave 200 mg. of IIIb, m.p. 196–215°. The analytical sample, recrystallized from methanol, had m.p. 209–214°, $[\alpha]_D$ −44° (chloroform).

Anal. Calcd. for $C_{26}H_{35}DO_5$: C, 71.91; H, 8.45; D, 1 atom/molecule. Found: C, 71.96; H, 8.95; D, 1.00 atom/molecule.

From IIb.—Similarly, reaction of 1.0 g. of 3,20-bisethylenedioxy-11β-deuterio-11α-hydroxy-5-pregnene (IIb) with 3.0 g. of lead tetraacetate gave 655 mg. of IIIb, m.p. 210–215°. The analytical sample, recrystallized from ethyl acetate, had m.p. 210–218°, $[\alpha]_D$ −41° (chloroform).

Anal. Found: C, 71.66; H, 8.77; D, 2.27 atoms/molecule.

1α,11α-Epoxy-11β-deuterio-5-pregnene-3,20-dione (IVb).—Treatment of 1.08 g. of IIIb with sulfuric acid as in the preparation of IVa gave 611 mg. of IVb, m.p. 188–198°. The analytical sample, recrystallized from acetone, had m.p. 203–207°.

Anal. Calcd. for $C_{21}H_{27}DO_3$: C, 76.55; H, 8.26; D, 1 atom/molecule. Found: C, 76.63; H, 8.58; D, 1.00 atom/molecule.

11α-Hydroxy-11β-deuterio-1,4-pregnadiene-3,20-dione (Vb).—Treatment of 538 mg. of IVb with sodium acetate in absolute alcohol as in the preparation of Va, gave 482 mg. of Vb, m.p. 220–225°. The analytical sample, recrystallized from ethyl acetate, had m.p. 231–233°.

Anal. Calcd. for $C_{21}H_{27}DO_3$: C, 76.55; H, 8.26; D, 1 atom/molecule. Found: C, 76.56; H, 8.49; D, 1.01 atom/molecule.

1-Dehydro-11-ketoprogesterone (VI).[8]—Chromium trioxide (150 mg.) was added in portions to 1.5 ml. to pyridine while the temperature was maintained at 20–25°. A solution of 150 mg. of Vb in 25 ml. of pyridine was added to the chromium trioxide–pyridine complex and the mixture was allowed to stand for 20 hr. The mixture was then poured into ice–water and extracted with ether–benzene (1:1). The extract was washed with water, dried, and evaporated to dryness to give 150 mg. of solid which was crystallized from ethyl acetate–petroleum ether to give 120 mg. of VI, m.p. 175–180°. The analytical sample, recrystallized from acetone–petroleum ether, had m.p. 178–180° and contained 0.06 atom of deuterium per molecule.

Oxidation of IIb.—Oxidation of 300 mg. of IIb with chromium trioxide–pyridine complex in essentially the same manner as described for compound VI gave 228 g. of VII, m.p. 180–184°. The analytical sample, recrystallized from ethyl acetate, had m.p. 182–185° and contained 1.56 atoms of deuterium per molecule.

Base Equilibration of VII.—One hundred milligrams of VII was dissolved in 20 ml. of methanol and 0.2 ml. of 25% solution of sodium methoxide in methanol was added. The reaction solution was heated at reflux for 19 hr. and was then poured into ice–water and the resulting solid (90 mg., m.p. 180–185°) was

(20) E. J. Moriconi, W. F. O'Connor, E. A. Kenneally, and F. T. Wallenberger, *J. Am. Chem. Soc.*, **82**, 3122 (1960), and references therein.

(21) Melting points were determined on a Fisher-Johns block and are uncorrected. Deuterium analysis were done by Josef Nemeth, Urbana, Ill.

(22) B. J. Magerlein and R. H. Levin, *J. Am. Chem. Soc.*, **75**, 3654 (1953).

(23) E. J. Corey and G. A. Gregoriou, *ibid.*, **81**, 3124 (1959).

crystallized from ethyl acetate and from methanol to give 69 mg. of VIII, m.p. 180–185°. This material contained 0.25 atom of deuterium per molecule.

1α,11α-Epoxypregnenolone Acetate. From 11α-Hydroxypregnenolone 3-Acetate.—To a hot solution of 0.75 g. of 11α-hydroxypregnenolone 3-acetate in 300 ml. of cyclohexane was added 4.0 g. of lead tetraacetate. The mixture was allowed to stir and reflux for 4 hr. and was then cooled and filtered. The filtrate was washed with 5% potassium iodide solution, 5% sodium thiosulfate solution, and water, and was dried over anhydrous sodium sulfate. Chromatography of the solution over Florisil resulted in the product fraction being eluted with 7.5% acetone in petroleum ether (b.p. 60–70°). Crystallization of this material from acetone gave 240 mg. product, m.p. 150–157°. The analytical sample had m.p. 152–157°, $[\alpha]_D$ −20° (chloroform).

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 74.16; H, 8.66. Found: C, 73.55; H, 8.62.

From 11β-Hydroxypregnenolone 3-Acetate.—Reaction of 0.96 g. of 11β-hydroxypregnenolone 3-acetate with 7.0 g. of lead tetraacetate for 15 hr. as described previously for the 11α-hydroxy epimer, resulted in 113 mg., m.p. 142–155°, of epoxide being obtained. The analytical sample had m.p. 149–155°, $[\alpha]_D$ −17° (chloroform).

Anal. Found: C, 74.36; H, 9.06.

There was no depression in melting point when the two epoxide samples were mixed and the infrared curves of the two were identical.

Acknowledgment.—The authors gratefully acknowledge the services of J. L. Johnson and W. A. Struck and associates for analysis, rotations, and infrared spectra; G. Slomp and F. A. MacKellar for n.m.r. interpretations; and L. M. Reineke for papergram analysis.

Steroids with Functional Sulfur Groups. III.[1] The Reaction of Some Thiocyano Steroids

ISAO KITAGAWA,[2] YO UEDA,[2] TOSHIO KAWASAKI,[2] AND ERICH MOSETTIG[3]

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland

Received March 6, 1963

The reaction of 9α-thiocyano-Δ⁴-androstene-3,11,17-trione with aqueous methanolic potassium carbonate gave 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androsten-11β-ol-3,17-dione (VIa). The latter was isomerized to 2′-methoxy-5′,6′-dihydro-4′H-1′,3′-thiazino[4′,5′,6′:5α,10,9α]androstane-3,11,17-trione (Xa) and could be transformed to 9α-methylthio-Δ⁴-androstene-3,11,17-trione (VIIa). Similar reactions were carried out on cortisone and testosterone derivatives.

In a previous paper[1a] we reported that treatment of 9α-thiocyanocortisone acetate (Ia) with aqueous methanolic potassium carbonate at room temperature gave a crystalline compound which was thought to be 9α-thiocarboxamidocortisone (Ib). The absence of an 11-carbonyl band in the infrared spectrum of this compound, however, made such a formulation (Ib) improbable, but unfortunately all attempts at structural elucidation by further chemical transformations failed.

It could be expected that analogous reactions with appropriate compounds lacking the sensitive ketol side chain would give more favorable results. A suitable starting material appeared to be 9α-thiocyano-Δ⁴-androstene-3,11,17-trione (Va), obtained by treatment of the known[4] 9β,11β-epoxy-Δ⁴-androstene-3,17-dione (III) with thiocyanic acid and subsequent oxidation of the resulting 9α-thiocyano-Δ⁴-androsten-11β-ol-3,17-dione (IV) with chromic acid. Treatment of Va with aqueous methanolic potassium carbonate at room temperature gave in a good yield, a product exhibiting absorption maxima at 3.01 μ (hydroxyl), 5.73 μ (C-17 carbonyl), 5.99 μ (Δ⁴-C-3 carbonyl), 6.07 μ (C=N),[5] 6.11 (Δ⁴ C=C), but lacking the absorption bands ascribed to the C-11 carbonyl (5.86 μ) and the thiocyano groups (4.64 μ). The hydroxyl moiety of this compound could not be acetylated with pyridine–acetic anhydride. Furthermore, analytical data agreed with the empirical formula $C_{21}H_{27}O_4NS$ (Va + CH_3OH) rather than $C_{20}H_{25}O_4NS$ (Va + H_2O) and indicated the presence of a methoxyl group. The appearance of a singlet peak at τ 6.15[6] in the n.m.r. spectrum also supported the above observation. In view of this evidence, we are assigning to this product the provisional structure 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-androsten-11β-ol-3,17-dione (VIa), and by analogy ascribing the formulation 2′-methoxythiazolino[4′,5′:11α,9α]-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (IIa) to the reaction product of Ia. If aqueous ethanolic potassium carbonate is used in place of methanolic potassium carbonate, the corresponding 2′-ethoxythiazolino derivative, VIc,[7] is formed. The presence of the ethoxyl function was shown by elementary analysis as well as n.m.r. data [τ 5.78 (quartet) and τ 8.70 (triplet)].[6]

Treatment of VIa in aqueous ethanolic potassium carbonate at reflux afforded, instead of the expected 9α-thiol derivative, an easily sublimable product which gave a negative sodium nitroprusside test. The infrared spectrum of this compound exhibited bands at 5.73, 5.91, and 6.03 μ, attributable to C-17, C-11, and Δ⁴-C-3-carbonyls, respectively, and lacked the SH absorption,[8] as would be expected of 9α-methylthio-Δ⁴-

(1) (a) Part I, T. Kawasaki and E. Mosettig, *J. Org. Chem.*, **27**, 1374 (1962); (b) Part II, Y. Ueda and E. Mosettig, to be published.

(2) Visiting Scientists, National Institutes of Health, under the sponsorship of the Cancer Chemotherapy National Service Center, National Cancer Institute.

(3) Deceased on May 31, 1962.

(4) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(5) L. C. King, L. A. Subluskey, and E. W. Stern, *J. Org. Chem.*, **21**, 1232 (1956); A. I. Meyers, *ibid.*, **24**, 1233 (1959); **26**, 218 (1961).

(6) A singlet peak at τ 6.17–6.20 is observed for the CH_3O function in a similar environment, *i.e.* —C≡C—OCH_3. Two peaks at 8.70 (triplet) and 5.73 (quartet) are observed with C_2H_5O function in CH_3CH_2O—C(=O)—. N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, no. 105, 291, 107, 181, etc.

(7) Further transformation of the ethoxythiazolino compound is now under study.

(8) At 2000–2550 cm.⁻¹: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 350.