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The Synthesis of a 13,14-Seco Steroid Analog[1]

MASATO TANABE AND DAVID F. CROWE

Life Sciences Research, Stanford Research Institute, Menlo Park, California

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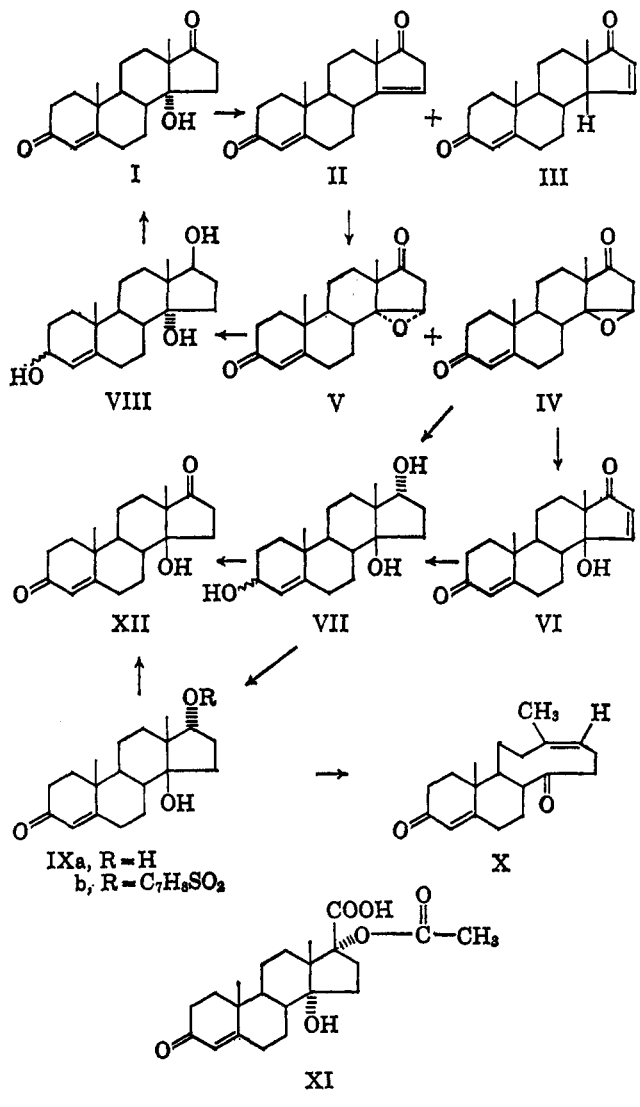
Reaction of 17α-tosyloxy-4-androsten-14β-ol-3-one (IXb) with sodium hydride in tetrahydrofuran yields 13,14-seco-4-*cis*-13(17)-androstadiene-3,14-dione (X). The preparation and reactions of 14β-hydroxyandrostanes are also described.

A previous attempt designed to obtain a 13,14-seco steroid by fragmentation of the C-13–C-14 bond in 3,5-cyclo-6β-methoxy-17β-tosyloxyandrostan-14α-ol under base-catalyzed conditions was unsuccessful. The only product isolated was 3,5-cyclo-6β-methoxy-14-androsten-17α-ol.[2] The origin of this alcohol was presumed to be *via* an intermediate 14α,17α-oxide, the product of the internal displacement reaction of the 14α-alkoxide ion with the 17β-tosylate function as the leaving group.

Placement of the participating C-14 hydroxyl group β or *cis* to the angular methyl group at C-18 should sterically prevent 14β,17β-oxide formation by the internal displacement reaction of the C-14 β-alkoxide ion. Corey[3] has recently reported on the formation of two bicyclononenone derivatives related to *dl*-caryophyllene and *dl*-isocaryophyllene by the fragmentation of tricyclic 1,3-diol monotosylate precursors. In these fragmentation reactions the participating hydroxyl groups were oriented *cis* to angular methyl groups.

The aim of the present investigation was to prepare and study the behavior of a 14β-hydroxy-17α-tosyloxyandrostane derivative under base-catalyzed conditions. A steroid derivative with this stereochemical arrangement of participating groups in the internal elimination reaction should lead to a 13,14-seco derivative. The method of Sondheimer[4] offered a convenient means for the inversion of a 14α-androstanol to its 14β epimer. Steroidal 14α-hydroxy derivatives are available by microbiological and chemical methods,[5] and the inversion process to a 14β-hydroxy derivative involved a four-step route (see Scheme I). The *p*-toluenesulfonic acid catalyzed dehydration of 4-androsten-14α-ol-3,17-dione (I) in toluene yielded 4,14-androstadiene-3,17-dione (II) and 4,15-androstadiene-3,17-dione (III). The origin of the latter 14-iso derivative III is similar to the reported formation of 14-iso-15-dehydroestrone 3-methyl ether from 15-dehydroestrone 3-methyl ether.[6] Treatment of the β,γ-unsaturated ketone II with *m*-chloroperbenzoic acid in chloroform yielded a mixture of approximately equal quantities of the 14β,15β- (IV) and 14α,15α-oxides (V).[7]

SCHEME I



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(2) M. Tanabe and D. F. Crowe, *J. Org. Chem.*, **28**, 3197 (1963).

(3) E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964).

(4) F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960).

(5) (a) A. F. St. Andre, *et al.*, *ibid.*, **74**, 5506 (1962); (b) S. H. Eppstein, *et al.*, *ibid.*, **80**, 3382 (1958).

(6) W. S. Johnson and W. F. Johns, *ibid.*, **79**, 2005 (1957).

(7) Sondheimer and co-workers[4] report only the isolation of the 14β,15β-oxide from perbenzoic acid treatment of 3β-acetoxy-14-androsten-17-one. Substituents at C-17 influence the stereochemical course of the peracid oxidation of Δ^{14} steroids. A cortical side-chain material blocked with bismethylenedioxy groups gives the 14α,15α-oxide: F. Bohlmann, V. Hint, and B. Diedrich, *Ber.*, **96**, 1316 (1963). Peracid treatment of 14-dehydroprogesterone is reported to yield the 14α,15α-oxide: H. Hasegawa, Y. Sato, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **9**, 409 (1961); H. Ishii, *ibid.*, **10**, 354 (1962). In the cardenolide series α oxidation is also reported: P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **45**, 1041 (1962).

Chromatographic behavior of this mixture of oxides on alumina indicated the lability of the 14β,15β-oxide IV toward β elimination to the isomeric 4,15-androstadien-14β-ol-3,17-dione (VI). In contrast, the 14α,15α-oxide V was eluted from the column unchanged. The stereochemistry of the oxides was established by reduction with lithium aluminum hydride to a mixture of epimeric 4-androstene-3,14,17-triols. Oxidation of this crude triol mixture with chromic acid yielded 4-androsten-14α-ol-3,17-dione (I) and 4-androsten-14β-ol-3,17-dione (XII).

The facile conjugate addition of nucleophiles to Δ^{15} 17-ketones previously noted by others[8] was observed in this work during the sodium borohydride reduction of the 14β-hydroxy-15-dehydro-17-keto derivative VI. This reduction in methanol led to a triol containing epimers at C-3 (VII). The disappearance of the C-15–C-16 double bond along with C-17 carbonyl reduction was indicated by chromic acid oxidation of the diol IXa to 4-androstene-14β-ol-3,17-dione.

The n.m.r. spectrum of the 14β-hydroxy derivative XII showed a single vinyl proton signal at τ 4.3, which is attributed to the C-4 hydrogen. The ultraviolet absorption maximum at 242 mμ (ϵ 16,000) and with this intensity is indicative of the presence of only the 3-keto-Δ^4 chromophore. Infrared absorption at 5.80 μ is in agreement with a cyclopentanone structure. The combined spectral characteristics of XII are in accord with the reduction of the C-15–C-16 double bond occurring during the sodium borohydride reduction of VI.

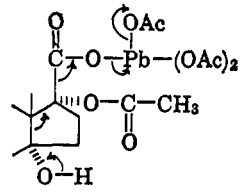
In order to retain the C-17 alcohol function in the triol VII for later conversion to a *p*-toluenesulfonate ester, VII was subjected to manganese dioxide oxidation in chloroform at room temperature.[9] These conditions were found to be suitable for selective oxidation of the C-3 allylic alcohol, and 4-androstene-14β,17α-diol-3-one (IXa) was isolated in good yield.

The stereochemistry in the diol IXa and also the triol VII at C-17 is assigned the α configuration. This assignment is based on the earlier observations made of the sodium borohydride reduction of 14-iso 17-ketones,[5] which are attacked from the β side to yield 17α-ols.

The diol IXa was converted to the 14β-hydroxy-17α-tosyloxy derivative under the usual conditions. Reaction of this 1,3-diol monotosylate with sodium hydride in tetrahydrofuran for conversion to the 14β-alkoxide ion yielded the 13,14-seco ketone X *via* the internal elimination reaction. The appearance of an additional carbonyl band at 5.92 μ in the infrared spectrum along with the disappearance of hydroxyl absorption is in accord with structure X. The n.m.r. spectrum of X shows the downfield shift of the C-18 methyl signal to τ 8.41 and a single vinyl proton at τ 4.5 characteristic of the grouping, H—C=C—CH_3.

Assignment of the stereochemistry of the endocyclic double bond in the nine-membered ring of X was made with knowledge of the original configurational relationships in the 1,3-diol monotosylate. Stereoelectronic considerations should favor the coplanar arrangement of the reacting centers in a concerted fragmentation reaction: the 17α-tosyloxy group and the C-13–C-14 bond in IXb fulfill this requirement. If it is assumed that the process used in the formation of X is concerted, then the original C-17 hydrogen and C-18 methyl stereochemical relationship is retained in the product.[10] The *cis*-cyclononene configuration is based, therefore, on the assignment of the C-17α stereochemistry in the diol IXa. The stereochemistry at C-8 in the seco ketone structure X is unassigned, since this hydrogen is now enolizable and base-catalyzed conditions were employed in its formation.

In the course of the preparation of 4-androsten-14α-ol-3,17-dione from the sodium bismuthate oxidation of 4-pregnene-14α,17α-21-triol-3,20-dione in acetic acid, moderate quantities of the etianic acid XI deriv-



ative were isolated.[11] The possibilities of fragmentation of this acid to a seco ketone[12] were apparent (arrows) by incipient generation of a carbonium ion at C-17[13] with lead tetraacetate. Treatment of the acetoxy acid XI with lead tetraacetate in benzene, however, led, by breaking of the C-17–C-20 bond, to the 17-ketone derivative I.

Experimental[14]

4-Androsten-14α-ol-3,17-dione (I) and 3-Keto-14α-hydroxy-17α-acetoxy-4-etiocholenic Acid (XI).—To a solution of 20 g. of 14α,17α,21-trihydroxy-4-pregnen-3-one[5b] in 1.5 l. of acetic acid and 500 ml. of water was added 300 g. of sodium bismuthate. This mixture was stirred for 24 hr. at room temperature and filtered. The filtrate was concentrated at reduced pressure and the residue was dissolved in 1.5 l. of chloroform. The chloroform was washed with 2 *N* hydrochloric acid and water and dried over sodium sulfate. Removal of the chloroform under re-

(8) The base-catalyzed addition of methanol to 15-dehydroestrone 3-methyl ether was observed by Johnson and Johns.[6] More recently the stereochemistry of the C-15 methoxyl group has been assigned the β configuration: E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964).

(9) For a review of selective steroid oxidations with manganese dioxide, see C. Djerassi, "Steroid Reactions," Holden-Day Inc., San Francisco, Calif., 1963, p. 104. Oxidation of a C-17 β-ol to the ketone has recently been reported using higher molar proportions of manganese dioxide: I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(10) C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkens [*Tetrahedron Letters*, 2901 (1964)] discuss the stereochemical requirements for synchronous fragmentation processes of this type. Stereospecific olefin formation was observed only with stereoelectronic control of the reaction. Corey, *et al.*,[3] and P. S. Wharton [*J. Org. Chem.*, **26**, 4781 (1961)] also report stereospecific olefin formation in fragmentation reactions.

(11) Isolation of the etianic acid derivative XI is apparently due to esterification to a 17α-acetoxy derivative prior to oxidation of the cortical side chain. The acetoxy acid XI resists further oxidation with sodium bismuthate.

(12) Since the completion of this work, two independent synthesis of 5,10-seco steroids have been reported. These seco ketones were prepared by lead tetraacetate fragmentation of steroid 5α-ols: M. L. Mihailovic, M. Stefanovic, L. Lorenc, and M. Gasic, *Tetrahedron Letters*, **No. 28**, 1867 (1964); M. Akhtar and S. Marsh, *ibid.*, **No. 36**, 2475 (1964). The preparation of a 13,14-seco steroid by periodic acid cleavage of 13,14-diols has been reported: W. F. Johns, *J. Org. Chem.*, **26**, 4503 (1961).

(13) The formation of carbonium ions by oxidative decarboxylation of carboxylic acids with lead tetraacetate has been reported: G. Büchi, R. E. Erickson, and N. Wakabayashi, *J. Am. Chem. Soc.*, **83**, 927 (1961); E. J. Corey and J. Casanova, Jr., *ibid.*, **85**, 165 (1963). Fragmentation to a medium-sized carbocyclic ring accompanying an anodic oxidative decarboxylation reaction has been published: P. S. Wharton, G. A. Hiegel, and R. V. Coombrige, *J. Org. Chem.*, **28**, 3217 (1963).

(14) Melting points were taken on a Fisher-Johns apparatus. A Perkin-Elmer Infracord was used to obtain infrared spectra. Rotations were determined in chloroform at 1% concentrations unless otherwise stated. T.l.c. data were obtained on Merck silica gel G. The n.m.r. spectra were obtained with 10% solutions in deuteriochloroform on a Varian A-60 spectrometer.

duced pressure left a residue which crystallized from acetone to yield 12 g. of I.[5b] Crystallization of the mother liquor residues from ethyl acetate yielded 2.8 g. of the etianic acid derivative XI. Crystallization from acetone yielded an analytical sample: m.p. 221–223°; $[\alpha]_D$ +35° (MeOH); λ_{max}^{Nujol} 2.1, 5.74, 6.1, and 6.2 μ; λ_{max}^{MeOH} 240 mμ (ϵ 16,000); n.m.r. τ 4.22 (C-4 H), 7.9 (acetate), 8.8 (C-19 3H), and 8.98 (C-18 3H).

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.45; H, 7.41.

The residue from the crystallization was chromatographed on Merck acid-washed alumina. The chloroform fractions yielded an additional 5 g. of I and the methanol fractions yielded a further 3.1 g. of XI.

Hydrolysis of 0.3 g. of the etianic acid XI in 30 ml. of methanol and 0.3 g. of sodium methoxide for 18 hr. followed by acidification with 2 *N* hydrochloric acid yielded 0.26 g. of 3-keto-14α,17α-dihydroxy-4-etiocholenic acid. An analytical sample was prepared by crystallization from methylene chloride–ether followed by another recrystallization from methanol: m.p. 201–203°; $[\alpha]_D$ +115° (methanol); λ_{max}^{Nujol} 3.0, 5.78, 6.0, and 6.2 μ; λ_{max}^{MeOH} 240 mμ (ϵ 16,500); n.m.r. τ 4.33 (C-4 H), 8.83 (C-19 3H), and 8.92 (C-18 3H).

Anal. Calcd. for $C_{20}H_{28}O_5$. C, 68.94; H, 8.10. Found: C, 69.11; H, 8.19.

The 3-keto-14α,17α-dihydroxy-4-etiocholenic acid was also prepared by treatment of 10 g. of 14α,17α,21-trihydroxy-4-pregnen-3-one dissolved in 600 ml. of methanol with a solution of 8 g. of periodic acid in 120 ml. of water. After 16 hr. at room temperature the solution was diluted with 400 ml. of water. The methanol was removed at reduced pressure and the solution was extracted with chloroform. The chloroform extract was washed with 10% sodium bisulfite solution and water. The acid was isolated by 5% sodium bicarbonate extraction and subsequent acidification to yield 6.5 g. of 3-keto-14α,17α-dihydroxy-4-etiocholenic acid. This acid was identical in all respects with the material prepared by saponification of XI.

4,14-Androstadiene-3,17-dione (II) and 14-Iso-4,15-androstadiene-3,17-dione (III).—To a slurry of 9 g. of 4-androsten-14α-ol-3,17-dione (I) in 270 ml. of toluene was added 0.270 g. of *p*-toluenesulfonic acid. The mixture was heated to 125° over the course of 0.5 hr., during which time complete solution was achieved. The solution was refluxed for an additional 3 hr. and then cooled to room temperature and 500 ml. of ethyl acetate was added. The solution was washed with 400 ml. of 5% sodium bicarbonate and twice with 400-ml. portions of water. After drying with sodium sulfate, evaporation of the solvent yielded a residue which was chromatographed on Merck acid-washed alumina. Elution with benzene gave 4 g. of II. An analytical sample was prepared by three crystallizations from methylene chloride–ether: m.p. 141–142°; $[\alpha]_D$ +248°; λ_{max}^{Nujol} 5.75, 6.0, and 6.2 μ; λ_{max}^{MeOH} 239 mμ (ϵ 16,900); n.m.r. τ 4.26 (C-4 H), 4.45 (C-15 H, multiplet), 7.12 (C-16 2H, multiplet), 8.77 (C-19 3H), and 8.86 (C-18 3H).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.18; H, 8.48.

Continued elution of the column with chloroform yielded 3 g. of III. Repeated crystallizations of a portion of this material from methylene chloride and ether afforded the analytical sample: m.p. 167–169°; $[\alpha]_D$ +569°; λ_{max}^{Nujol} 5.9, 6.0, 6.2, and 6.3 μ, $\lambda\lambda_{max}^{MeOH}$ 217 mμ (ϵ 12,500) and 239 mμ (ϵ 21,500).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.28.

14α,15α-Oxido-4-androstene-3,17-dione (V) and 4,15-Androstadien-14β-ol-3,17-dione (VI).—To a solution of 4 g. of II in 165 ml. of chloroform was added 2.7 g. of *m*-chloroperbenzoic acid and the solution was stored in the dark at room temperature for 18 hr. The solution was washed with 10% sodium bisulfite, 5% sodium bicarbonate solution, and water and dried over sodium sulfate. The chloroform was removed at reduced pressure to yield a colorless residue. Thin layer chromatographic (t.l.c.) analysis of the residue on Merck silica gel G plates (chloroform–ethyl acetate, 1:1) indicated the disappearance of the starting olefin II and the presence of the two oxides IV and V in nearly equivalent quantities. Attempts to separate those oxides by crystallization resulted in a mixture as judged by t.l.c. of the crystalline material.

Column chromatography on alumina indicated the lability of the 14β,15β-oxide IV and conversion to a more polar material resulted as determined by t.l.c. Complete conversion of the 14β,15β-oxide IV to the 14β-ol VI in the mixture was accomplished by adsorption of the residue on 35 g. of Merck basic alumina. After 10 min. the material was eluted with chloroform to give 3.1 g. of a mixture of V and VI. Crystallization of this mixture from methylene chloride gave 1.2 g. of VI. An analytical sample was prepared by crystallization from acetone–hexane: m.p. 234–236°; $[\alpha]_D$ +262° (dioxane); λ_{max}^{Nujol} 2.87, 5.88, 6.0, 6.2, and 6.3 μ; λ_{max}^{MeOH} 217 mμ (ϵ 12,200) and 239 mμ (ϵ 17,950); n.m.r. τ 3.8 (C-15 H, doublet, J = 2.9 c.p.s.), 4.23 (C-4 H), 4.53 (C-16H, doublet, J = 2.9 c.p.s.), 8.81 (C-19 3H), and 8.86 (C-18 3H).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.72; H, 8.00.

The mother liquor from the crystallization of VI was chromatographed on Merck acid-washed alumina. Elution with benzene–5% ether yielded 1.5 g. of V. An analytical sample was prepared by crystallization from acetone: m.p. 220–222°; $[\alpha]_D$ +107°; λ_{max}^{MeOH} 239 mμ (ϵ 14,500); λ_{max}^{Nujol} 5.74, 6.02, and 6.17 μ.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.16; H, 8.15.

4-Androstene-14β,17α-diol-3-one (IXa).—To a solution of 1.2 g. of VI in 140 ml. of methanol was added 2.4 g. of sodium borohydride and the solution was stirred for 2.0 hr. An additional 2.4 g. of sodium borohydride was added and the solution was stirred for an additional 16 hr. The excess sodium borohydride was decomposed with acetic acid and 200 ml. of water was added to the reaction mixture and the methanol was removed at reduced pressure. An additional 200 ml. of water was added and the solution was extracted with ethyl acetate. Removal of the ethyl acetate at reduced pressure afforded 1.0 g. of residue containing VII, λ_{max}^{Nujol} 2.9 μ. T.l.c. analysis indicated a mixture of two triols.

The residue was dissolved in 120 ml. of chloroform, 5.0 g. of Beacon Chemical Co. activated manganese dioxide was added, and the solution was stirred overnight. The solution was filtered through Celite and the filter cake was washed with hot chloroform. The chloroform was removed at reduced pressure, affording 800 mg. of residue. Crystallization from acetone–hexane gave 200 mg. of IXa. The mother liquor from the crystallization was dissolved in 72 ml. of chloroform and the manganese dioxide oxidation was repeated. Crystallization from acetone–hexane afforded another 137 mg. of IXa. An additional 80 mg. of IXa was obtained by separation of the residue left after the final acetone–hexane crystallization by preparative t.l.c. on two 8 × 8 in. × 2 mm. silica gel GF plates using a chloroform–5% methanol solvent system. An analytical sample was prepared by repeated crystallization from acetone: m.p. 243–245°; $[\alpha]_D$ +66° (dioxane); λ_{max}^{Nujol} 2.85, 6.0, and 6.2 μ; λ_{max}^{MeOH} 240 mμ (ϵ 14,800).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.03; H, 9.37.

17α-Acetoxy-4-androsten-14β-ol-3-one.—To a solution of 0.030 g. of IXa in 0.3 ml. of pyridine was added 0.3 ml. of acetic anhydride. The solution was allowed to stand for 16 hr. The pyridine and acetic anhydride were removed at reduced pressure. The oil that remained was dissolved in 20 ml. of chloroform. The chloroform was washed with 20 ml. of 2 *N* hydrochloric acid and 20 ml. of water and dried over sodium sulfate. The chloroform was removed at reduced pressure leaving 0.03 g. of a yellow oil. An analytical sample was prepared by sublimation at 100° (10^{-5} mm.): m.p. 149–153; λ_{max}^{Nujol} 2.83, 5.79, and 8.0 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.86; H, 8.98.

4-Androsten-14β-ol-3,17-dione (XII).—To a solution of 0.30 g. of IXa in 5 ml. of acetone Jones reagent[15] was added dropwise until a slight excess was present. The solution was filtered through Celite and 50 ml. of chloroform was added. The solution was washed with 25 ml. of 25% sodium bisulfite solution and three times with 25-ml. portions of water and dried over sodium sulfate, and the solvent was removed at reduced pressure affording 28 mg. of residue. An analytical sample was prepared by crystallization from methylene chloride–ether: m.p. 233–236°, $[\alpha]_D$ +124°; λ_{max}^{Nujol} 2.87, 5.80, 6.0, and 6.2 μ; λ_{max}^{MeOH} 238 mμ (ϵ 16,100); n.m.r. τ 4.26 (C-4 H), 8.80 (C-19 3H), and 8.92 (C-18 3H).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.60; H, 8.18.

(15) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1548 (1956); K. Bowden, I. N. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

4-Androsten-14α-ol-3,17-dione (I) and 4-Androsten-14β-ol-3,17-dione (XII) from 14α,15α-Oxido-4-androstene-3,17-dione (V) and 14β,15β-Oxido-4-androstene-3,17-dione (IV).—To a slurry of 7.5 g. of lithium aluminum hydride in 1200 ml. of tetrahydrofuran under a nitrogen atmosphere was added dropwise a solution of 4.5 g. of a mixture of the oxides IV and V (1:1) in 300 ml. of tetrahydrofuran. The mixture was refluxed for 2 hr. and cooled to room temperature and the excess lithium aluminum hydride was decomposed by dropwise addition of a saturated sodium sulfate solution. The solids were filtered and the solvent was removed at reduced pressure leaving 4.5 g. of residue. An infrared spectrum of the residue showed no carbonyl absorption.

To 1 g. of this residue dissolved in 100 ml. of acetone Jones reagent was added dropwise until a slight excess was present. Filtration through Celite, addition of water and chloroform extraction afforded 800 mg. of an oil. The oil was dissolved in benzene and chromatographed on silica gel. Elution with benzene–ether gave 300 mg. of recovered oxides IV and V and further elution with ether gave 350 mg. of an equal mixture of 14α- and 14β-ols I and XII. Separation of this alcohol mixture on an 8 × 8 in. × 2 mm. alumina G t.l.c. plate using a chloroform–ethyl acetate solvent system gave samples of the pure alcohols. One of the alcohols had a t.l.c. mobility and infrared spectrum identical with that of an authentic sample of 4-androsten-14α-ol-3,17-dione (I) and the other was identical with 4-androsten-14β-ol-3,17-dione (XII) obtained from the oxidation of 4-androstene-14β,17-diol-3-one (IXa).

17α-Tosyloxy-4-androsten-14β-ol-3-one (IXb).—To a solution of 0.26 g. of IXa in 6 ml. of pyridine under a nitrogen atmosphere at 0° was added 0.3 g. of *p*-toluenesulfonyl chloride. After 5 min. at 0° the solution was allowed to warm to room temperature. After 16 hr. a slurry of 25 ml. of ice–water was added to the reaction mixture and the product precipitated. The precipitate was extracted into 50 ml. of chloroform and the aqueous phase was extracted two more times with 50-ml. portions of chloroform. The chloroform washings were combined, washed with 75 ml. of 2 *N* hydrochloric acid, 75 ml. of 5% sodium bicarbonate, and two times with 75-ml. portions of water, and dried over sodium sulfate. The solvent was removed at reduced pressure leaving 377 mg. of residue: λ_{max}^{Nujol} 2.85, 6.0, 6.2, 6.23, 8.4, and 8.5 μ. This material was used without further purification.

13,14-Seco-4-*cis*-13(17)-androstadiene-3,14-dione (X).—To a slurry of 0.43 g. of sodium hydride in 20 ml. of dry tetrahydrofuran under a nitrogen atmosphere was added dropwise a solution of 0.35 g. of IXb in 20 ml. of dry tetrahydrofuran. The reaction mixture was refluxed for 28 hr. and cooled to room temperature and the excess sodium hydride was decomposed by dropwise addition of 2 ml. of water. An additional 50 ml. of water was added and the solution was extracted with 50 ml. of ethyl ether–20% chloroform and two times with chloroform–ether. The combined extracts were washed with 50 ml. of 5% sodium bicarbonate and three times with 75-ml. portions of water and dried over sodium sulfate. The solvent was removed at reduced pressure leaving 190 mg. of semisolid residue. An analytical sample was prepared by sublimation at 80° (10^{-5} mm.): m.p. 150–151; λ_{max}^{Nujol} 5.92, 6.0, and 6.2 μ; λ_{max}^{MeOH} 238 mμ (ε 14,900); n.m.r. τ 4.27 (C–4 H), 4.5 (C–17 H), 8.41 (C–18 3H), and 8.86 (C–19 3H).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 80.03; H, 9.33.

4-Androsten-14α-ol-3,17-dione (I) from 3-Keto-14α-hydroxy-17α-acetoxy-4-etiocholenic Acid (XI).—To a solution of 0.390 g. of XI in 0.125 ml. of pyridine and 4 ml. of benzene was added 0.40 g. of lead tetraacetate. The reaction mixture was refluxed for 4 hr. under a nitrogen atmosphere and then cooled to room temperature. An additional 10 ml. of benzene was added and the solid that had precipitated was filtered. The filter cake was washed with 10 ml. of benzene and 10 ml. of ethyl ether. The organic solution was washed with 25-ml. portions of 1 *N* sodium hydroxide, 1 *N* hydrochloric acid, saturated sodium chloride, and water and dried over sodium sulfate. The solvent was removed at reduced pressure leaving 0.2 g. of residue. Crystallization from methylene chloride afforded 50 mg. of a sample that had an infrared spectrum and thin layer chromatographic mobility identical with those of 4-androsten-14α-ol-3,17-dione (I).

The Reaction of 1,3-Disubstituted Ureas with Phosphorus Pentachloride[1]

HENRI ULRICH AND A. A. R. SAYIGH

Carwin Research Laboratories, The Upjohn Company, North Haven, Connecticut

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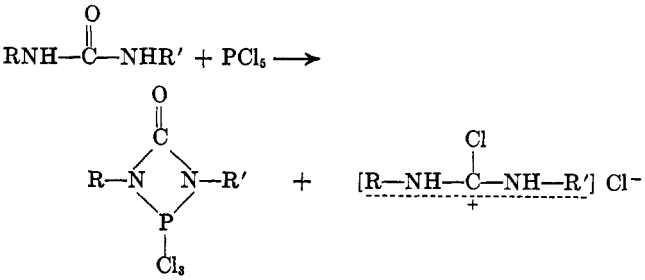
Nitrogen attack was observed in the reaction of phosphorus pentachloride with 1,3-disubstituted ureas in which at least one N-substituent was a primary alkyl group. Thus, 1,3-dialkyl- and 1-phenyl-3-alkylureas gave rise to the novel 2,4-disubstituted 1,1,1-trichloro-1,2,4-phosphadiazetidin-3-ones; 1-*p*-toluenesulfonyl-3-*n*-butylurea yielded *p*-toluenesulfonyltrichlorophosphazene and *n*-butyl isocyanate; and 1-benzoyl-3-*n*-butylurea gave benzonitrile, *n*-butyl isocyanate, and phosphorus oxychloride.

Earlier studies have shown that the reaction of 1,3-dialkylureas with either carbonyl[2] or oxalyl[3] chlorides gives rise to products formed *via* nitrogen attack. Recent studies show that the reaction of phosphorus pentachloride with 1,3-disubstituted ureas, in which at least one N-substituent is a primary alkyl group, gives rise to analogous products, *i.e.*, 1,1,1-trichloro-1,2,4-phosphadiazetidin-3-ones (I).

N,N′-Dialkylchloroformamidine hydrochlorides (II), formed in small amounts from the primary alkyl cases, are the main products obtained from the reaction of phosphorus pentachloride with 1,3-dialkylureas having secondary alkyl N substituents.[4]



Ia, R = R′ = Me
b, R = R′ = *n*-Bu
c, R = *n*-Bu; R′ = phenyl

Structural assignments for the trichloro-1,2,4-phosphadiazetidin-3-ones (I) were made on the basis of elementary analysis and infrared and n.m.r. spectroscopy. Absorption of the carbonyl group at 5.6 μ is in accord with the postulated four-membered ring. The H^1 n.m.r. spectra (Varian A-60) of compounds Ib and Ic showed the CH_2 groups adjacent to nitrogen to

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(3) H. Ulrich and A. A. R. Sayigh, in press.

(4) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).