crystallization of the product from ether–chloroform gave 0.388 g. (85%) of *dl-erythro*-2-amino-1,3-octadecanediol, m.p. 87–89°, lit.[1a] m.p. 84–86°; ν_{max}^{Nujol} 3310, 1595 (NH_2), ~3000, 1075, and 1015 cm.$^{-1}$ (hydroxy).

When the aminodiol was treated with ethyl acetate, the N-acetyl derivative was obtained, m.p. 125–125.5°, after recrystallization from hexane–ethyl acetate; ν_{max}^{Nujol} 3295 (N–H), ~3100 (hydroxy), 1645, and 1560 cm.$^{-1}$ (amide). This N-acetyl derivative showed negative reaction with the periodate oxidation reagent.[14]

In a usual way, tribenzoyl, m.p. 145.5–146°, lit.[1a] m.p. 144–145°, and triacetyl derivatives of the aminodiol, m.p. 91–92°, lit.[1a] m.p. 90–92°, were prepared in 72 and 69% yields, respectively.

Reactions of Steroidal Δ^4-3-Ketones in the Presence of Phosphorus Trihalides[1]

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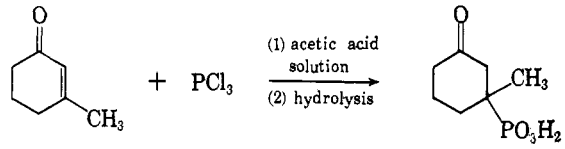
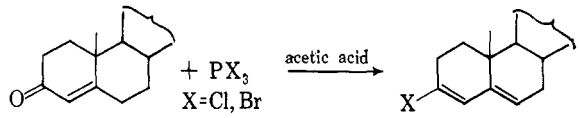
The preparation of steroidal 3-chloro-3,5-dienes from Δ^4-3-ketones has been the subject of two recent publications.[2,3] Oxalyl chloride[2] and phosphorus oxychloride[3] have been found to be effective reagents for causing this transformation. Other acid chlorides which have been used are acetyl chloride,[4] benzoyl chloride,[5] α-chloropropionyl chloride,[6] and phosphorus pentachloride.[7]

Phosphorus trichloride has not been used to effect this conversion. This reagent in fact would not be expected to cause this type of chlorination since the normal mode of reaction of phosphorus trihalides with ketones yields organophosphorus derivatives.[8] Saturated ketones give α-hydroxyphosphonic acids, and α,β-unsaturated ketones undergo Michael-type additions leading to γ-ketophosphonic acids. Thus, 3-methyl-2-cyclohexenone has been reported to react as follows with phosphorus trichloride in acetic acid.[9]



Phosphorus trihalides have been found in the present work, however, to convert steroidal Δ^4-3-ketones in acetic acid solutions to the corresponding 3-halo-3,5-dienes.

When an acetic acid solution of 4-cholesten-3-one and excess phosphorus trichloride is allowed to stand



at room temperature, 3-chloro-3,5-cholestadiene begins to precipitate after 1–2 hr. The conversion appears to be complete after 3–4 hr. The reaction has been extended to the preparation of 3-chloro-3,5-androstadien-17β-ol acetate from testosterone acetate. Phosphorus tribromide reacts equally well to give the previously unreported 3-bromo derivatives. The only other reported bromination of this type involves heating the steroid with α-bromopropionyl bromide.[6]

No similar halogenations of ketones with phosphorus trihalides are known except for the conversion of 1,3-cyclohexanediones to the corresponding 3-chloro-2-cyclohexenones.[10] This reaction is considered to proceed *via* the enol form of the diketone. The enol form of cholestenone or testosterone acetate, however, is probably not present in sufficient concentration to account for the very facile transformation reported here.

An alternate explanation for the ease of this reaction could be that the phosphorus trihalide reacts rapidly with the large excess of acetic acid used to dissolve the steroid. The acetyl chloride thus formed might then be the active halogenating agent. Acetyl chloride has indeed been found in the present investigation to convert cholestenone to the 3-chlorodiene under conditions similar to the phosphorus trichloride method, but this reaction is much slower and gives a lower yield than when the phosphorus reagent is used. The increased rate using phosphorus trihalides is possibly due to a catalytic effect of the phosphorous acid formed concurrently with acetyl chloride.

The influence of solvent is also shown when cholestenone is treated with phosphorus trichloride in acetic anhydride solution, conditions which also nor nally lead to the Michael-type addition. Cholestenone enol acetate results from this reaction. Phosphorus trichloride appears here to have the same function as the acid chloride in the preparation of steroidal enol acetates using acetyl chloride–acetic anhydride mixtures.

Experimental[11]

3-Halo-3,5-dienes. General Procedure.—Solutions of 3–5 g. of the Δ^4-3-ketones, 20–25 ml. of glacial acetic acid, and 2–3 ml. of the phosphorus trihalide were allowed to stand in stoppered flasks at room temperature for about 4 hr. The solutions turned bright yellow upon addition of the phosphorus trihalide, and crystallization of the product usually began after 1 hr. The mixtures were cooled and the crude products were obtained by filtration using sintered-glass funnels. The white, crystalline halodienes were washed with dilute sodium bicarbonate solution, dried, and recrystallized. The compounds as first isolated were pure white, but they decomposed on standing.

3-Chloro-3,5-cholestadiene.—The general procedure was followed using 3.53 g. (9.16 mmoles) of 4-cholesten-3-one, 25 ml. of glacial acetic acid, and 1.5 ml. (2.4 g., 17 mmoles) of phosphorus trichloride. The yield of crude product, m.p. 63–65°, was 3.09 g. (77%). Recrystallization from ether–95% ethanol gave large, colorless prisms, m.p. 65–66°, $[\alpha]^{29}D$ −125° (*c* 1.74, $CHCl_3$), λ_{max} 242 mμ (log ε 4.3); lit.[5,12] m.p. 62–63°, $[\alpha]^{23}D$ −117°, λ_{max} 243 mμ.

(1) This research was supported partially by Institutional Grant No. In. 82 of the American Cancer Society.

(2) R. Deghenghi and R. Gaudry, *Can. J. Chem.*, **40**, 818 (1962).

(3) G. W. Moersch and W. A. Neuklis, *ibid.* **41**, 1627 (1963).

(4) S. Kuwada, M. Miyasaki, and S. Yoshiki, *J. Pharm. Soc. Japan*, **57**, 234 (1937); *Chem. Abstr.*, **32**, 1275 (1938).

(5) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **19**, 806 (1936).

(6) F. Galinovsky, E. Kerschbaum, and H. Janisch, *Monatsh.*, **84**, 193 (1953).

(7) U. Westphal, Y.-L. Wang, and H. Hellmann, *Chem. Ber.*, **72**, 1233 (1939).

(8) J. B. Conant, V. H. Wallingford, and S. S. Gandheker, *J. Am. Chem. Soc.*, **45**, 762 (1923), and references herein.

(9) M. I. Kabachnick and T. Ya. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 540 (1952); *Chem. Abstr.*, **47**, 4848 (1953).

(10) R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950).

(11) All melting points were taken on a Kofler micro hot stage using calibrated thermometers. Ultraviolet spectra were obtained with a Beckman Model DB spectrophotometer using 95% ethanol as solvent.

(12) W. Bergmann and F. Hirschmann, *J. Org. Chem.*, **4**, 40 (1939).

3-Chloro-3,5-cholestadiene Using Acetyl Chloride.—As a comparison with the phosphorus trichloride reaction above, a similar procedure was followed using acetyl chloride. A solution of 3.53 g. (9.16 mmoles) of 4-cholesten-3-one, 25 ml. of glacial acetic acid, and 3.5 ml. (49 mmoles) of acetyl chloride was allowed to stand at room temperature in a stoppered flask. After 3 hr., the solution was seeded with 3-chloro-3,5-cholestadiene, but no crystallization occurred. After standing for 20 hr., the now brownish solution was again seeded with the chlorodiene, whereupon the product crystallized from the solution. Filtration of this mixture gave 1.14 g. (31%) of crude 3-chloro-3,5-cholestadiene, m.p. 61–63°.

3-Chloro-3,5-androstadien-17β-ol Acetate.—The general procedure was followed using 4.68 g. (14.2 mmoles) of testosterone acetate, 25 ml. of glacial acetic acid, and 2.0 ml. (3.2 g., 23 mmoles) of phosphorus trichloride. Two recrystallizations of the crude product from ether afforded 2.78 g. (53%) of 3-chloro-3,5-androstadien-17β-ol acetate, m.p. 143.5–152.5° (m.p. 163–165° in an evacuated capillary), $[\alpha]^{26}D$ −155° (*c* 2.76, $CHCl_3$), λ_{max} 242 mμ (log ε 4.5); lit.[2] m.p. 148–152°, $[\alpha]D$ −172° λ_{max} 242 mμ (log ε 4.4).

3-Bromo-3,5-cholestadiene.—The general procedure was followed using 5.02 g. (13.0 mmoles) of 4-cholesten-3-one, 25 ml. of glacial acetic acid, and 2.0 ml. (5.7 g., 21 mmoles) of phosphorus tribromide. A yield of 5.12 g. (88%) of crude 3-bromo-3,5-cholestadiene, m.p. 62–66°, $[\alpha]^{27}D$ −112°, was obtained. Recrystallization of this product from ether–methanol afforded material with m.p. 65–72°, $[\alpha]^{27}D$ −115° (*c* 1.84, $CHCl_3$), λ_{max} 240 mμ (log ε 4.6).

Anal. Calcd. for $C_{27}H_{43}Br$: C, 72.46; H, 9.68; Br, 17.86. Found[13]: C, 72.40; H, 9.78; Br, 17.95.

3-Bromo-3,5-androstadien-17β-ol Acetate.—The general procedure was followed using 5.01 g. (15.2 mmoles) of testosterone acetate, 25 ml. of glacial acetic acid, and 3.0 ml. (8.5 g., 32 mmoles) of phosphorus tribromide. Two recrystallizations of the crude product from acetone afforded 4.12 g. (69%) of 3-bromo-3,5-androstadien-17β-ol acetate, m.p. 162–168° (m.p. 178–179.5° in an evacuated capillary), $[\alpha]^{27}D$ −141° (*c* 2.86, $CHCl_3$), λ_{max} 240 mμ (log ε 4.4).

Anal. Calcd. for $C_{21}H_{29}BrO_2$: C, 64.09; H, 7.46; Br, 20.32. Found[14]: C, 63.96; H, 7.30; Br, 20.56.

3-Acetoxy-3,5-cholestadiene.—To a suspension of 0.82 g. (2.1 mmoles) of 4-cholesten-3-one in 8 ml. of acetic anhydride was added 0.4 ml. (0.6 g., 5 mmoles) of phosphorus trichloride. The steroid dissolved upon slight warming and swirling. The product began to precipitate after 10 min. The mixture was allowed to stand at room temperature for 1 hr., then it was cooled in an ice bath and filtered to give 0.69 g. (76%) of white crystals, m.p. 74–78°. Recrystallization of this material from 95% ethanol, then methanol afforded 0.30 g. (33%) of 3-acetoxy-3,5-cholestadiene, m.p. 80–81°, $[\alpha]^{27}D$ −99.9° (*c* 1.87, $CHCl_3$); lit.[15] m.p. 81°, $[\alpha]^{23}D$ −100.4°.

(13) Elemental analysis were performed by Weiler and Strauss Laboratories, Oxford, England.

(14) Elemental analysis were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(15) U. Westphal, *Chem. Ber.*, **70**, 2128 (1937).

Preparation of the γ-Lactone and γ-Lactam of 5-Methyl-4-oxo-2-hexenoic Acid

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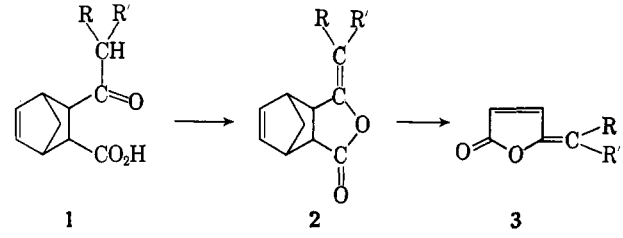
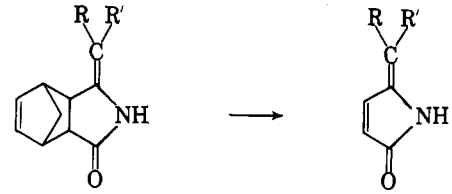
In a study of compounds related to the protoanemonin-type antibiotics, Walton[1] synthesized a number of 4-hydroxy-2,4-alkadienoic acid γ-lactones (**3**, R = alkyl, R′ = H) *via* cyclopentadiene Diels–Alder adducts (**1**). He was unable, though, to prepare the dialkyl unsaturated γ-lactones (**3**, R and R′ = alkyl). As an example, when R and R′ were methyl, the eno lactone **2** could not be formed using the usual methods (acetic anhydride and either sodium acetate or hydrochloric acid). Walton concluded, therefore, that branching in the position α to the carbonyl group interfered with lactonization. We have been able, by a change in reagents, to accomplish the lactonization and lactamization of **1** despite the α-branching.



1 **2** **3**

In our study we have found that when cyclopentadiene adduct **1** (R = R′ = CH_3) is treated with thionyl chloride followed by ammonium hydroxide, the product is not the expected ketoamide but rather the enol lactone **2**. Pyrolytic distillation of this lactone yields 5-methyl-4-hydroxy-2,4-hexadienoic acid γ-lactone (**3**, R = R′ = CH_3), characterized from its infrared, n.m.r., and mass spectra.

Since for our purposes we were interested not only in the γ-lactone but also in the γ-lactam (**5**), we set about to prepare it also. Ammonolysis of lactone **3** (R = R′ = CH_3) with aqueous ammonia or liquid ammonia failed to give the lactam; fusion of the lactone with ammonium carbonate also failed to give a new product. We were, however, able to prepare the desired lactam by a retro Diels–Alder decomposition of lactam **4**. Lactam **4** was prepared by fusion of keto acid **1** with ammonium carbonate, and this lactam was then pyrolyzed at 400° in a nitrogen atmosphere.



4 **5**

The product after purification by liquid chromatography was identified from its spectral properties as 5-methyl-4-amino-2,4-hexadienoic acid γ-lactam (**5**).

Experimental[2]

3-Isobutyryl-5-norbornene-2-carboxylic Acid (**1**).—Isopropylmagnesium bromide, prepared from 41 g. of isopropyl bromide, 7.3 g. of magnesium, and 250 ml. of ether, was added dropwise to 50 g. of 5-norbornene-2,3-dicarboxylic anhydride[3] dissolved in 100 ml. of benzene and 200 ml. of ether. After the addition was complete, the reaction mixture was stirred at room temperature for 2 hr., then hydrolyzed with 300 ml. of 3 *N* hydrochloric

(1) H. M. Walton, *J. Org. Chem.*, **22**, 312 (1957).

(2) All melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The n.m.r. spectra were run in deuterated chloroform solutions using a Varian Associates HR-60 instrument and are reported in τ-values with the number of protons in parenthesis. We are indebted to John J. Whalen and Johnnie L. Stewart for infrared spectra, to W. E. Walker, Jr., for n.m.r. spectra, to George W. Young for mass spectra, and to Richard F. Walsh for technical assistance.

(3) Nadic Anhydride, Allied Chemical Co.