m.p. 266–267°, obtained by the catalytic hydrogenation (see below) of stigmasta-4,22-dieno[3,2-*c*]pyrazole was 266–267°, and their infrared spectra were identical.

In another run, 1.50 g. of the crude hydroxymethylene ketones (obtained in the formylation at 17–18°) reacted with hydrazine hydrate to yield 1.60 g. of crude pyrazoles, m.p. 200–235°, $[\alpha]_D$ +8°. Chromatography on Florisil afforded first 0.15 g. of starting ketone (I), then 1.33 g. of colorless pyrazoles, $[\alpha]_D$ +3°, which on repeated recrystallization from ethyl acetate–hexane afforded 19 mg. of **5β-stigmast-22-[3,4-*c*]pyrazole (XI)** as fine needles, m.p. 300–301° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +37.0° (0.5% in $CHCl_3$), λ_{max} 225 mμ (4440).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08. Found: C, 82.29; H, 11.17.

The mixture melting point of these crystals with either pyrazole VIIe or pyrazole IXf (see below) was depressed and the infrared spectra were different.

Stigmasta-4,22-dieno[3,2-*c*]pyrazole (VIh).—To a mixture of 2.70 g. of sodium methoxide (Matheson, Coleman and Bell) and 3.70 g. of ethyl formate (distilled from phosphorus pentoxide) in 50 ml. of dry benzene was added a solution of 10.0 g. of stigmasta-4,22-dien-3-one (m.p. 128–130° (uncor.)] in 50 ml. of dry benzene and the mixture was refluxed with stirring for 30 min. The orange mixture was cooled and filtered. The collected solid was washed with ether and dried to yield 10.2 g. of yellow solid. The solid was suspended in a mixture of 100 ml. of water and 200 ml. of ether. Two milliliters of acetic acid was added and the mixture was stirred until the solid dissolved (3 hr.). The organic layer was separated, washed with water and saturated sodium chloride solution, and filtered through anhydrous sodium sulfate. Evaporation of the solvent afforded 8.08 g. of the yellow crystalline 2-hydroxymethylene derivative, m.p. 147–150° (uncor.), λ_{max} 250 mμ (11,500), 306 (4900), which was contaminated by water.[23]

A mixture of 7.10 g. of the crude 2-hydroxymethylene derivative, 3 ml. of hydrazine hydrate, and 200 ml. of ethanol was refluxed for 4 hr. The cooled mixture was diluted with benzene, treated with Darco, and concentrated to yield 5.55 g. (79% crude yield) of light yellow crystals, m.p. 206–230° (uncor.), 0.95 g. of yellow crystals, m.p. 145–205° (uncor.), and 0.94 g. of yellow-brown foam. Filtration of an ether solution of the first crop through 150 g. of Florisil, followed by two recrystallizations from benzene–ethanol afforded 4.93 g. (70%) of fine colorless needles, m.p. 232–234° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +80.6°, λ_{max} 260 mμ (10,000).

Anal. Calcd. for $C_{30}H_{46}N_2$: C, 82.89; H, 10.67; N, 6.45. Found: C, 83.17; H, 10.73; N, 6.38.

Catalytic Hydrogenation of Stigmasta-4,22-dieno[3,2-*c*]-pyrazole (VIg).—A solution of 2.26 g. of stigmasta-4,22-dieno[3,2-*c*]pyrazole (m.p. 234–246°) in 150 ml. of benzene and 50 ml. of ethanol was hydrogenated in the presence of 3.60 g. of 10% palladium–carbon. The catalyst was added portionwise during the hydrogenation due to apparent poisoning of the catalyst by the products. The catalyst was separated and the filtrate concentrated to dryness. The crystalline residue was chromatographed on 90 g. of Florisil. Elution with benzene afforded 0.74 g. of colorless crystals, m.p. 259–265° (uncor.), and 0.79 g. of colorless crystals, m.p. 225–242° (uncor.). Recrystallization of the higher melting material from ethyl acetate afforded **5β-stigmas-22-eno-[3,2-*c*]pyrazole (IXf)** as colorless leaflets, m.p. 266–267° (evacuated sealed tube (uncor.), $[\alpha]_D$ −22.4° (0.5% in $CHCl_3$), λ_{max} 224 mμ (4760).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.42. Found: C, 82.58; H, 11.01; N, 6.52.

Recrystallization of the lower melting material from ethyl acetate afforded **5α-stigmast-22-eno[3,2-*c*]pyrazole (VIIe)** as fine colorless needles, m.p. 241–242° (evacuated sealed tube), $[\alpha]_D$ +40.8°, λ_{max} 224 mμ (4750).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.42. Found: C, 82.37; H, 11.21; N, 6.30.

Acknowledgment.—The authors express their appreciation to Mrs. Gabrielle Snyder for technical assistance, to Dr. F. C. Nachod and Miss Catherine Martini and staff for spectra data, to Mr. K. D. Fleischer and staff for analytical service, and to Dr. E. D. Nielson and Mr. A. V. R. Crain, Jr., for the paper chromatographic studies.

(23) Tsuda and Nozoe[33] report m.p. 162–163° and $\lambda_{max}^{CH_3OH}$ 253 mμ (14,300), 306 (7400) for the purified specimen.

Dehydration of Steroid 5,6-Halohydrins[1]

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Received January 15, 1962

The treatment of 5α-hydroxy-6β-halo steroids with potassium bisulfate or sulfuric acid in acetic anhydride led to the formation of 6β-halo-5β-methyl-19-norsteroids. Optical rotations and n.m.r. spectra data supported this conclusion. The crystallization liquors yielded additional dehydration products which could be explained as being derived from a common carbonium ion. The attempted rearrangement of compounds containing groups other than halogen in the 6β-position was unsuccessful. The biological activities of the rearranged products are presented.

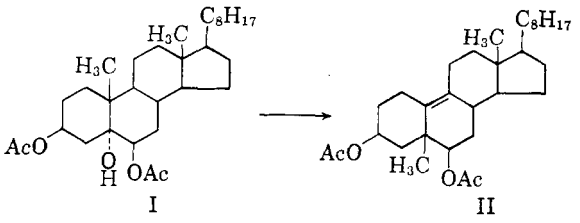
Westphalen,[2] in 1915, was studying the acetylation of cholestane-3β,5α,6β-triol 3,6-diacetate using acetic anhydride and sulfuric acid. A compound was isolated which proved to be a dehydrated product. This product was shown by later workers[3] to have structure II.

The position of the double bond at C-9(10) and the β-methyl group at C-5 was substantiated by optical[4] and chemical[5] evidence. Compound II,

(1) Presented before the Division of Medicinal Chemistry, 140th Meeting of the American Chemical Society, Chicago, Illinois, September 3–8, 1961.

(2) T. Westphalen, *Chem. Ber.*, **48**, 1064 (1915).

(3) J. L. Dunn, I. M. Heilbron, R. F. Phipers, K. M. Samant, and F. S. Spring, *J. Chem. Soc.*, 1580 (1934); H. Lettre and M. Muller, *Chem. Ber.*, **70**, 1947 (1937); V. A. Petrow and M. Davis, *J. Chem. Soc.*, 2211 (1951).



which became known as "Westphalen's diol" diacetate, has a high dextrarotation characteristic of the rearranged structure and proved to be a useful way to follow the course of reaction.

The rearrangement was initially studied in the cholestane[6] series with the yields being improved by using potassium bisulfate[7] in place of sulfuric acid. Many other rearranged products were prepared substituted at C-17.[8] These were tested for androgenic or progestational activity but showed only a very low order of activity or none at all. The attempted rearrangement of cholestane-3β,5α,6α-triol 3,6-diacetate,[9] 6-oxocholestane-3β,5α-diol 3-acetate[9] and cholestane-3β,5α-diol 3-acetate[4] was unsuccessful, seeming to indicate that a β-hydroxy or acetoxy group was necessary at C-6 in order to have the rearrangement proceed.

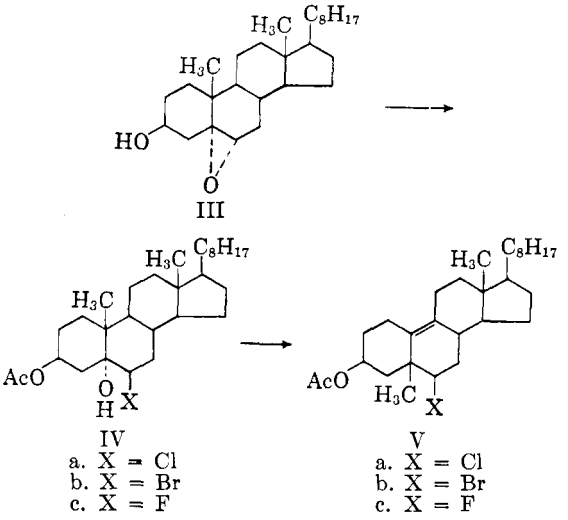
We became interested in the compounds that could be obtained by this type of Wagner-Meerwein rearrangement with the belief that the compounds would show some interesting biology. The evidence, as presented by the previous workers in the field, was not encouraging. It was felt, however, that if the hydroxy group at the C-6 position were eliminated or replaced by another group, the compounds would show good activity since it is known that a hydroxy or keto group on the C-6 carbon of steroids reduces activity.[10]

The first attempt was to prepare a 6-desoxy compound by treating cholestane-3β,5α-diol 3-acetate[11] with potassium bisulfate and acetic anhydride. This reaction had not been reported at this time and when attempted was unsuccessful, yielding starting material, cholesteryl acetate and some uncrystallizable resins. Shortly thereafter, Schumacher[4] published his results on the same reaction isolating cholesta-3,5-diene in addition to cholesteryl acetate. This confirmed the belief that a 6β-substituent was necessary for the rearrangement to proceed.

Following this line of reasoning, it was decided that introducing halogens on the C-6 carbon could be accomplished with little difficulty, also, that the halogens would not reduce the activity of the molecule, in fact, might even enhance it.

The introduction of the halogens was accomplished through the use of the 5α,6α-epoxides which when treated with acidic reagents gave the correct 5α-hydroxy-6β-halo steroids.

Cholesterol when treated with peracetic acid[12] gave the 5α,6α-epoxycholestan-3β-ol (III). This when treated with 37% hydrochloric acid or 48% hydrobromic acid gave the corresponding 6β-chloro-[13] (IVa) and 6β-bromocholestane-3β,5α-diol[14] (IVb). The 6β-fluorohydrin (IVc) was obtained by treating the oxide with boron trifluoride etherate.[15] The 3-acetates of these halohydrins when treated with potassium bisulfate and acetic anhydride yielded the corresponding 6β-halo-5β-methyl-19-nor-9-cholesten-3β-ol 3-acetate (V).



Treating Va with sodium hydroxide and methanol gave the free 3β-ol which could be oxidized to the noncrystalline 3-keto compound.

The crystallization liquors of Va upon chromatography over silica gel gave, in addition to some starting material, 6-chloro-5-cholesten-3β-ol 3-acetate,[13,16] 6β-chlorocholestane-3β,5α-diol 3,5-diacetate, and a product which had an analysis corresponding to a cholestenediol monoacetate. This latter compound was proven to be 5-cholestene-3β,4β-diol 3-acetate by direct comparison.[17]

(4) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952); H. Aebli, C. A. Grob, and E. Schumacher, *Helv. Chim. Acta*, **41**, 774 (1958).

(5) B. Ellis and V. Petrow, *J. Chem. Soc.*, 2246 (1952).

(6) V. A. Petrow, *ibid.*, 1077 (1937); V. A. Petrow, O. Rosenheim, and W. W. Starling, *ibid.*, 677 (1938).

(7) V. A. Petrow, *ibid.*, 998 (1939).

(8) V. A. Petrow and M. Davis, *ibid.*, 2973 (1949); V. A. Petrow and M. Davis, *ibid.*, 1185 (1950).

(9) B. Ellis and V. A. Petrow, *ibid.*, 1078 (1939); Y. Fulmer Shealy and R. Dodson, *J. Org. Chem.*, **16**, 1427 (1951).

(10) A. Butenandt and B. Riegel, *Chem. Ber.*, **69**, 1163 (1936); M. Ehrenstein, *J. Org. Chem.*, **4**, 506 (1939); M. Ehrenstein and T. O. Stevens, *ibid.*, **5**, 318 (1940); C. P. Balant and M. Ehrenstein, *ibid.*, **17**, 1487 (1952).

(11) P. A. Plattner, T. Petrzilka, and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).

(12) E. J. Becker and E. S. Wallis, *J. Org. Chem.*, **20**, 353 (1955).

(13) L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, **20**, 244 (1937); D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950).

(14) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950); Y. Ueno, *J. Pharm. Soc. Japan*, **72**, 1622 (1952); *Chem. Abstr.*, **47**, 8765[b].

(15) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(16) C. J. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 683 (1946).

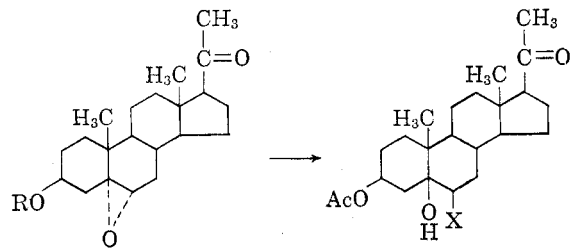
(17) B. Pelc, *Chem. Listy*, **51**, 946 (1957); *Chem. Zentr.*, **33**, 9228 (1958); V. A. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 135 (1943).

Pregnenolone or its acetate on treatment with peracetic acid gave the corresponding 5α,6α-epoxy-3β-hydroxy-pregnan-20-one or its 3-acetate (VI).[18]

Treating VIb with boron trifluoride etherate gave the fluorohydrin[15] (VIIa) while with 37% hydrochloric acid and 48% hydrobromic acid the corresponding chlorohydrin (VIIb) and bromohydrin (VIIc) were obtained.

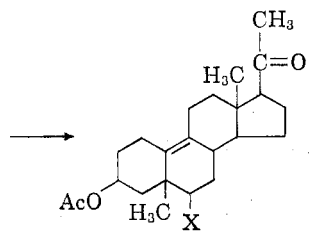
The fluorohydrin (VIIa) on treatment with potassium bisulfate and acetic anhydride gave 6β-fluoro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-acetate (VIIIa). In addition, some 3β,5α-dihydroxy-6β-fluoropregnan-20-one 3,5-diacetate was isolated.

The chlorohydrin (VIIb) with potassium bisulfate and acetic anhydride gave the 6β-chloro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-acetate even though the solution turned a very dark color indicating extensive decomposition.



VI
a. R = H
b. R = Ac

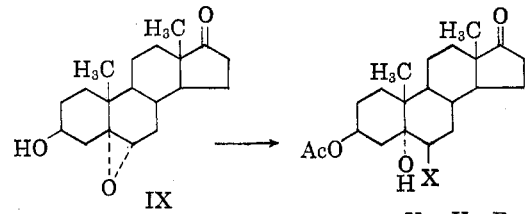
VII
a. X = F
b. X = Cl
c. X = Br



VIII
a. X = F
b. X = Cl

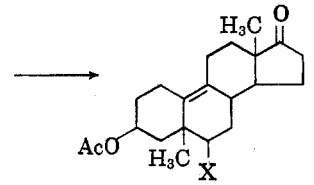
When the bromohydrin (VIIc) was warmed with acetic anhydride and potassium bisulfate, the mixture turned completely dark and no crystalline material was obtained. When VIIIb is warmed with aqueous methanolic potassium carbonate, the 3-hydroxy compound is obtained. This on oxidation with chromic acid in benzene and aqueous acetic acid yields the 3-keto compound. Sodium borohydride reduction of VIIIb in aqueous *t*-butyl alcohol gives the 6β-chloro-5β-methyl-19-nor-9-pregnene-3β,20β-diol 3-acetate.

The peracetic oxidation of 3β-hydroxy-5-androsten-17-one gave the corresponding 5α,6α-epoxy compound (IX).[19]



IX

Xa. X = F
b. X = Cl



XIa. X = F
b. X = Cl

The treatment of IX with 48% hydrofluoric acid led to a mixture of 6β-fluoro-3β,5α-dihydroxy-androstan-17-one and 3β,5α,6β-trihydroxy-androstan-17-one. The chlorohydrin[20] was prepared from IX by treatment with 37% hydrochloric acid.

When Xa was warmed with potassium bisulfate and acetic anhydride, the rearranged compound (XIa), 6β - fluoro - 3β - hydroxy - 5β - methyl - 19 - nor-9-androsten-17-one 3-acetate was formed.

Similarly warming the chlorohydrin (Xb) with potassium bisulfate or sulfuric acid and acetic anhydride caused dehydration forming 6β-chloro-3β - hydroxy - 5β - methyl - 19 - nor - 9 - androsten-17-one 3-acetate (XIb). From the mother liquors by direct crystallization and chromatography there was obtained 6β-chloro-3β,5α-dihydroxyandrostan-17-one 3,5-diacetate, 6β-chloro-3β-hydroxy-4-androsten-17-one 3-acetate, 6-chloro-3β-hydroxy-5-androsten - 17 - one 3 - acetate, 4 - androstene - 3,17-dione, and 4-methyl-1,3,5(10)-estratrien-17-one.[21] These compounds were not formed by the possible decomposition of the halohydrin on the silica gel column since the halohydrin was isolated unchanged from a chromatogram using silica gel.

The 6β-chloro-5β-methyl-19-nor-9-androstene-3β,17β-diol diacetate is prepared from 5-androstene-3β,17β-diol by epoxidation[19] with peracetic acid, cleaving the oxide with 37% hydrochloric acid and rearranging with potassium bisulfate and acetic anhydride.

The treatment of 3β,17α-dihydroxy-5-pregnen-20-one 17-acetate with perbenzoic acid in benzene yielded the 5α,6α-epoxy compound (XII).[22]

When XII is treated with 37% hydrochloric acid, the chlorohydrin is obtained, which is then con-

(18) S. A. Julia, *Ann. Chim.* (Paris), **8**, 410 (1953); *Chem. Abstr.*, **49**, 1765[b]; Y. Urshibara, M. Chuman, and S. Wada, *Bull. Chem. Soc. Japan*, **24**, 83 (1951); *Chem. Abstr.*, **47**, 5857[a].

(19) L. Ruzicka and A. C. Muhr. *Helv. Chim. Acta*, **27**, 503 (1944).

(20) G. Sala, G. Baldratti, R. Ronchi, V. Clini, and C. Betrazzoli, *Sperimentale*, **106**, 490 (1956); *Chem. Zentr.*, **48**, 13400 (1957).

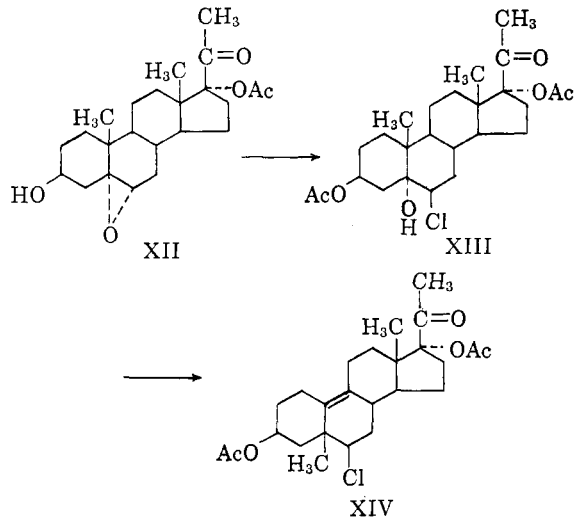
(21) Private communication, Dr. W. Hoehn; M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958).

(22) A. Bowers, L. C. Ibanez, and H. J. Ringold, *ibid.*, **81**, 5991 (1959).

TABLE I
MOLECULAR ROTATION DIFFERENCES[a,b]

Halohydrin	M_D^s	Rearranged product	M_D^p	ΔM_D ($M_D^p - M_D^s$)
IVc	−83.1	Vc	+423.5	+506.6
VIIa	+223.0	VIIIa	+654.0	+431.0
Xa (R = H)	+166.2 (MeOH)	XIa	+609.0	+442.8
IVa	−145.0	Va	+610.0	+755.0
VIIb	+32.9	VIIIb	+862.0	+829.1
Xb	+134.0	XIb	+860.0	+726.0
XIII (3-OAc)	−214.8	XIV	+598.0	+812.8
6β-Chloroandrostane-3β,5α,17β-triol 3,17-diacetate	−244.0	6β-Chloro-5β-methyl-19-norandrost-9(10)-ene 3β,17β-diol diacetate	+621.0	+865.0
IVb	−181.5	Vb	+677.0	+858.0
Cholestane-3β,5α,6β-triol 3,6-diacetate	−257.0	I	+443.0	+680.0

[a] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 204–210. [b] All rotations in chloroform except as noted.



verted into XIV with potassium bisulfate and acetic anhydride.

An infrared spectrum was run on each crystalline compound to aid in the identification of the products. All spectra were in accord with the structures assigned.

XIV is converted into 6β-chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one on standing with aqueous methanolic potassium hydroxide and into 6β-chloro-17α-hydroxy-5β-methyl-19-nor-9-pregnene-3,20-dione with chromic acid in benzene and aqueous acetic acid.

Attempts to reduce the 20-keto group in XIV with sodium borohydride were unsuccessful. However, lithium aluminum hydride in tetrahydrofuran was able to reduce XIV to yield 6α-chloro-5β-methyl-19-nor-9-pregnene-3β,17α,20β-triol.

The crystallization liquors of XIV were chromatographed over silica gel from which was obtained 6β-chloro-3β,17α-dihydroxy-4-pregnen-20-one 3,17-diacetate, 6-chloro-3β,17α-dihydroxy-5-pregnen-20-one 3,17-diacetate, 17α-hydroxy-4-pregnene-3,20-dione 17-acetate, and 17α-hydroxy-4-methyl-19-nor-1,3,5(10)-pregnatrien-20-one 17-acetate.

The main evidence to show that a rearrangement has occurred was through the use of optical rotations. Petrow[3,5–7] and associates showed that the rearrangement is accompanied by a strong dextrorotatory shift as compared to the starting material. This holds true with the halo compounds as shown in Table I where M_D^p are all over +400. This compares with Westphalen's diol diacetate which has a molecular rotation of +443. These rotations were used to identify the crystalline rearranged products obtained since all other compounds isolated exhibited smaller positive rotations or were negative.

An interesting fact can be observed in Table I in that the molecular rotation differences calculated from starting halohydrin in which fluorine was the halogen fell in the range of +431 to +506. The compounds containing chlorine had ΔM_D's of +726 to +865. The only bromine containing compound (IVb, Vb) had a ΔM_D of +858.

Further evidence that the rearrangement occurred was through the use of n.m.r. spectra. The disappearance of the C-19 methyl group and the appearance of the C-5 methyl group could be detected through the shift of group frequencies reported as τ values.[23] It can be seen in Table II that the τ values for the C-18 methyl groups are 9.200–9.250 compared to 9.10–9.375 reported by Shoolery and Rogers[24] for similar compounds showing that no disturbance of this angular group had occurred.

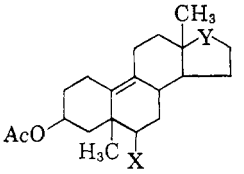
However, the C-19 methyl group has τ values ranging from 8.775–9.000 while the methyl group in the listed compounds are 8.733 to 8.792 which are attributed to the C-5 methyl.

The agreement between the τ values of Westphalen's diol diacetate and the corresponding chlorinated compound is such that they must have the same rearranged structure.

A number of attempts were made to expand the

(23) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).
(24) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

TABLE II
NUCLEAR MAGNETIC RESONANCE SPECTRA[a]
TAU VALUES[b]



X	Y	3αH	6αH	5 Methyl	18 Methyl
OAc	H, C—C_8H_{17}	4.950	5.2225 5.3375	8.792	9.208
Cl	H, C—C_8H_{17}	4.957	6.133	8.758	9.200
Cl	OAc, C—$COCH_3$	4.850 4.917	5.933 6.067 6.133	8.742	9.250
Cl	H, C—$COCH_3$	4.917	5.958 6.150	8.750	9.250
Cl	C=O	4.933	5.992 6.083 6.167	8.733	9.000

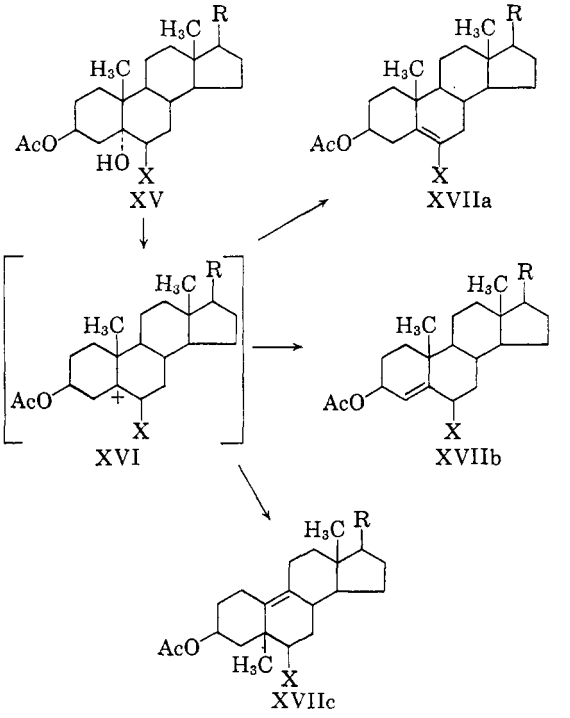
[a] Spectra were run and interpreted by Dr. N. McNiven of Worcester Foundation. Steroids were dissolved in deuterochloroform using tetramethylsilane as internal standard. The frequency was 60 Mc. [b] The τ values for other methyl groups which appear in the molecules are: 3β-acetoxy, 7.917 (XIb, XIV) and 7.933 (I, Va, VIIIb); 6β-acetoxy, 7.958 (I); 17α-acetoxy, 7.967 (XIV); 17β-acetyl, 7.908 (VIIIb) and 7.967 (XIV); and cholesterol side chain, 9.022 (I) and 9.092 (Va).

scope of the reaction. When 5α,6α-epoxy-cholestan-3β-ol 3-acetate was treated with pyrrolidine, the 6β-pyrrolidyl-cholestane-3β,5α-diol 3-acetate was formed. This when treated with potassium bisulfate or sulfuric acid in acetic anhydride led to intractable resins or starting material.

Another example was the formation of 6β-dimethylamino-3β,5α-dihydroxy-pregnan-20-one 3-acetate from 5α,6α-epoxy-3β-hydroxypregnan-20-one 3-acetate and dimethylamine which when treated with potassium bisulfate and acetic anhydride gave no reaction. However, using sulfuric acid in place of potassium bisulfate 3β-hydroxy-5β-pregnane-6,20-dione 3-acetate was formed. The reaction probably proceeds by the elimination of dimethylamine and isomerization of the 5,6-epoxide.[25]

If 6β-methylspirostane-3β,5α-diol 3-acetate is treated with potassium bisulfate or sulfuric acid in acetic anhydride, 6β-methyl-5-spirosten-3β-ol 3-acetate is obtained.

Thus it is seen that when 5,6-halohydrins (XV) are treated with potassium bisulfate and acetic anhydride, dehydration can occur by three paths all stemming from the carbonium ion XVI.



If the 6α-hydrogen is lost the double bond appears between C-5 and C-6 (XVIIa). However, if the proton is lost from the C-4 position a Δ^4 compound is formed. Finally migration of the C-19 methyl group to the C-5 carbon with the loss of a proton from C-10 gives the desired rearranged product. From the previous work on this rearrangement and our observations, the group at C-6 must be of such a nature and in such a position (β) that the tendency of the steroid molecule to lose a proton from C-4 or C-6 is reduced permitting the migration to proceed.

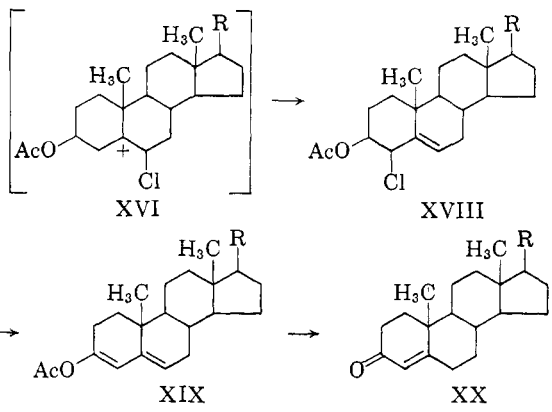
In order to explain the formation of a 3-keto-Δ^4 system and the A-ring 4-methyl benzene the halogen at the 6-position must be removed. It is not likely that the Δ^5-6-chloro compound would be reactive since it is a vinyl chloride and is therefore relatively inactive. It may be thought that the Δ^4-6-chloro compound, since it is allylic, could react and possibly form an intermediate to a Δ^4-3-ketone. However, treating 6β-chloro-3β-hydroxy-4-androsten-17-one 3-acetate with sulfuric acid and acetic anhydride yielded only starting material.

The possible route could be by an allylic shift of the halogen after the formation of the carbonium ion XVI. The formation of 4β-chloro-5-cholesten-3β-ol 3-acetate (XVIII) has been reported[17] by treating 6β-chlorocholestane-3β,5α-diol 3-acetate with pyridine and thionyl chloride.

If this occurs when XV is treated with acetic anhydride and sulfuric acid or potassium bisulfate, the reaction scheme would be the halohydrin forming the ion XVI with a shift of the chlorine to posi-

(25) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957); F. S. Spring and G. Swain, *ibid.*, 1356 (1939).

tion 4 (XVIII). This can dehydrohalogenate to the enol acetate XIX which in the acidic work-up of the reaction hydrolyzes to XX.



Similarly the 4-methyl-A-aromatic system would be formed from the carbonium ion XVI, and through an intermediate such as 17-alkyl-1,4-androstadiene-3-ol acetate can rearrange[26] to the 4-methyl-1,3,5(10)-triene steroid.

Va, b, and c were found to inhibit the conversion of mevalonic acid into cholesterol[27] to the extent of 77, 73, and 144%, respectively, that of the standard, Liosol.

VIIIa and VIIIb were inactive as progestational agents in the Clauberg assay.[28] VIIIb was shown to be a DCA blocker to the extent of 27% that of the standard, SC-5233.[29]

XIa and XIb were inactive in the androgen assay.[30] XIb was found to be a DCA blocker to the extent of 28% that of the standard.

XIV was inactive in the Clauberg assay but showed a 61% inhibition of the conversion of mevalonic acid into cholesterol.

Experimental[31]

Dehydration of Cholestane-3β,5α-diol 3-Acetate.—A mixture of 4.9 g. of cholestane-3β,5α-diol 3-acetate, 25 ml. of acetic anhydride, and 1.2 g. of potassium bisulfate was heated with stirring for 20 min. on a steam bath. The mixture was poured into 400 ml. of saturated sodium chloride solution and after standing for 5 hr. it was extracted with a total of 1 l. of ether. The ether solution was washed with water, 5% sodium bicarbonate solution, and water until neutral. The solution was dried over anhydrous sodium sulfate and then concentrated to a small volume. A crude crop of crystals weighing 2.9 g. was obtained. This was recrystallized from absolute alcohol yielding a material melting at 111–113°. A mixed melting point with cholesterol acetate showed no depression. The infrared spectra of product and authentic cholesterol acetate were identical. By chromatographing the residue over silica gel some starting material was obtained but no other crystalline products.

(26) H. Dannenberg and C. H. Doering, *Ann.*, **311**, 84 (1958).
(27) N. L. R. Bucher, *J. Am. Chem. Soc.*, **75**, 498 (1953).
(28) M. K. McPhail, *J. Physiol.*, **83**, 145 (1934).
(29) C. M. Kagawa, *Endocrinology*, **67**, 125 (1960).
(30) E. Eisenberg and G. S. Gordan, *J. Pharmacol. Exp. Therap.*, **99**, 38 (1950).
(31) All melting points are corrected and were determined by the capillary tube method. Optical rotations are in chloroform except as noted.

6β-Fluoro-5β-methyl-19-nor-9-cholesten-3β-ol 3-Acetate (Vc).—A mixture of 6.6 g. of 6β-fluorocholestane-3β,5α-diol 3-acetate,[15] 165 ml. of acetic anhydride, 82 ml. of acetic acid, and 4.1 g. of powdered potassium bisulfate was heated with stirring on a steam bath for 45 min., and then poured into 500 ml. of saturated sodium chloride solution and 1 l. of water. After standing for 1.5 hr. the aqueous mixture was extracted with a total of 800 ml. of methylene chloride. This solution was washed with water, 10% sodium bicarbonate solution, and water, and dried over anhydrous sodium sulfate. The solvent was then removed under a vacuum leaving a residue weighing 5.9 g. This was chromatographed over 200 g. of Davison 923 silica gel. The 1:1 petroleum ether (b.p. 60–71°)–benzene eluate gave 4.1 g. of material which when crystallized from absolute alcohol and ethyl acetate (8:10) yielded 2.6 g. of 6β-fluoro-5β-methyl-19-nor-9-cholesten-3β-ol 3-acetate, m.p. 92.5–93°, $[\alpha]^{26}D$ +93.3°.

Anal. Calcd. for $C_{29}H_{47}O_2F$: C, 77.97; H, 10.61. Found: C, 77.52; H, 10.47.

6β-Chloro-5β-methyl-19-nor-9-cholesten-3β-ol 3-Acetate (Va.)—A mixture of 100 g. of 6β-chlorocholestane-3β,5α-diol[13] and of 910 ml. of acetic anhydride was heated 0.5 hr. at 130°. The solution was cooled and 25.2 g. of powdered potassium bisulfate was added. This was heated with stirring for 20 min. at 80–100° and then poured into 1 l. of water and 700 ml. of saturated sodium chloride solution. Ice was added to keep the temperature below 50°. After standing 2 hr. a total of 6 l. of isopropyl acetate was used for extraction. The ester solution was washed with water, 10% sodium bicarbonate solution, and water until neutral. The solvent was removed, after drying over anhydrous sodium sulfate, by vacuum distillation. The residue was dissolved and crystallized from 250 ml. of ethyl acetate to yield 35.5 g. of 6β-chloro-5β-methyl-19-nor-9-cholestene-3β-ol 3-acetate, m.p. 139–141, $[\alpha]^{26}D$ +131.9°.

Anal. Calcd. for $C_{29}H_{47}ClO_2$: C, 75.21; H, 10.23; Cl, 7.65. Found: C, 75.30; H, 10.05; Cl, 7.47.

The residue from the crystallization liquors was chromatographed on 1700 g. Florisil. The petroleum ether–benzene (1:1) eluates gave 6.2 g. of material which when crystallized from methanol gave crystals, m.p. 131–133°, $[\alpha]^{26}D$ −57.2° (lit.,[14] for 6β-chloro-5-cholesten-3β-ol 3-acetate, m.p. 131°, $[\alpha]$ −50°).

Anal. Calcd. for $C_{29}H_{47}ClO_2$: C, 75.21; H, 10.23; Cl, 7.65. Found: C, 74.89; H, 9.96; Cl, 7.39.

The sixth, seventh, and eighth fractions of the benzene eluate gave 2.6 g. of material which on crystallization from methanol gave needles of 6β-chlorocholestane-3β,5α-diol diacetate, m.p. 165–167°, $[\alpha]^{26}D$ −17.3°.

Anal. Calcd. for $C_{31}H_{51}ClO_4$: C, 71.16; H, 9.82; Cl, 6.78. Found: C, 71.21; H, 9.96; Cl, 6.62.

The seventh and eighth fractions of the benzene–ethyl acetate (19:1) eluate yielded 5.9 g. of material which crystallized from benzene melted at 189–190°, and proved to be starting material as shown by its infrared spectrum and mixed melting point.

Fractions 10, 11, and 12 of the benzene–ethyl acetate (19:1) eluate when combined and crystallized gave a material, m.p. 186–188°, $[\alpha]^{26}D$ −61.2°. The infrared spectrum shows a hydroxyl and an acetate group. An n.m.r. spectrum shows that the molecule is not rearranged, has a hydrogen attached to an ethylenic group, the hydrogens on the carbons attached to the oxygens are α. It proved to be 5-cholestene-3β,4β-diol 3-acetate.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.37; H, 11.01.

5-Cholestene-3β,4β-diol 3-acetate was prepared from 10 g. of cholesteryl acetate following V. Petrow's[17] method. The product was crystallized successively from 95% alcohol, methanol, ethyl acetate, and acetone yielding 600 mg. (plates) melting at 185–186°, $[\alpha]^{25}D$ −62° (lit., m.p. 187–190°, $[\alpha]^{29}D$ −60°).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88. Found: C, 78.81; H, 10.74.

This material and the cholestenediol monoacetate from the above chromatogram exhibited no depression on taking a mixed melting point and their infrared spectra were identical in all respects.

6β-Chloro-5β-methyl-19-nor-9-cholesten-3β-ol.—There was dissolved in 500 ml. of methanol, 6.4 g. of 6β-chloro-5β-methyl-19-nor-9-cholesten-3β-ol 3-acetate. A solution of 1 g. of sodium hydroxide in 50 ml. of methanol was added and the solution refluxed 0.5 hr. On cooling the solution was diluted with 6 l. of water and neutralized with Dry Ice. The suspension was filtered, washed four times with water, and air-dried on the filter. Crystallization from either acetone or ethyl acetate led to a gel. However, 2.6 g. was obtained from petroleum ether, m.p. 144–146°, $[\alpha]^{26}D$ +140°.

Anal. Calcd. for $C_{27}H_{45}ClO$: C, 77.00; H, 10.77; Cl, 8.42. Found: C, 76.54; H, 10.75; Cl, 8.58.

6β-Chloro-5β-methyl-19-nor-9-cholesten-3-one.—A solution of 1.6 g. of 6β-chloro-5β-methyl-19-nor-9-cholesten-3β-ol in 60 ml. of benzene was stirred for 5 hr. at room temperature with a solution of 0.5 g. chromic acid in 7.6 ml. of water and 3.8 ml. of acetic acid. The excess chromic acid was decomposed with a solution of 800 mg. of sodium sulfite in 25 ml. of water. The mixture was extracted three times with ethyl acetate and then washed with 10% sodium bicarbonate solution and water until neutral. After drying and removing solvent under vacuum the residue was chromatographed over 62 g. of 923 Davison silica gel. The 100% benzene eluate yielded 547 mg. of a material that would not crystallize. However, it is believed to be 6β-chloro-5β-methyl-19-nor-9-cholesten-3-one, $[\alpha]^{26}D$ +66.1°. The infrared spectrum shows an absorption band at 5.80 μ characteristic of six-membered ring ketones.

6β-Bromo-5β-methyl-19-nor-9-cholesten-3β-ol 3-Acetate (Vb).—A mixture of 15 g. of 6β-bromocholestane-3β,5α-diol[14] in 150 ml. of acetic anhydride was heated at reflux for 0.5 hour and allowed to cool to room temperature. The solution had 4.5 g. of powdered potassium bisulfate added to it and then was heated at 40° for 1 hr. during which time it turned a dark greenish brown. It was poured into 300 ml. of saturated sodium chloride solution and 300 ml. of water and allowed to stand 2 hr. The aqueous chloride solution was extracted with a total of 400 ml. of isopropyl acetate, followed by washing with 10% sodium bicarbonate solution, and water until neutral. After drying, the solvent was removed and the residue crystallized from 45 ml. of petroleum ether and ethyl acetate (5:4). There was obtained 1.6 g. (needles) of 6β-bromo-5β-methyl-19-nor-9-cholesten-3β-ol 3-acetate, m.p. 140–142°, $[\alpha]^{26}D$ +133.5°.

Anal. Calcd. for $C_{29}H_{47}O_2Br$: C, 68.62; H, 9.33; Br, 15.24. Found: C, 68.99; H, 9.31; Br, 15.07.

6β-Fluoro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-Acetate (VIIIa).—A mixture of 8.0 g. of 3β,5α-dihydroxy-6β-fluoropregnan-20-one 3-acetate[15] in 125 ml. of acetic anhydride and 2.3 g. of powdered potassium bisulfate was heated at 65–90° for 20 min., poured into 300 ml. of water and 300 ml. of saturated sodium chloride, and allowed to stand for 2 hr. The aqueous solution was extracted with isopropyl acetate, washed with water, 10% sodium bicarbonate solution, and water until neutral. After drying and removing the solvent the residue was chromatographed over 185 g. of 923 Davison silica gel. Fraction 1 of the benzene: ethyl acetate (19:1) eluate weighing 3.6 g. was rechromatographed over 60 g. of 923 Davison silica gel and the first fraction of the benzene–ethyl acetate (19:1) eluate, weighing 2.8 g., was crystallized from 95% ethyl alcohol yielding 750 mg. of 6β-fluoro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-acetate, m.p. 102–104°, $[\alpha]^{26}D$ +173.5°.

Anal. Calcd. for $C_{23}H_{33}FO_3$: C, 73.37; H, 8.83. Found: C, 73.10; H, 8.72.

The second fraction of the benzene: ethyl acetate (19:1) eluate weighing 865 mg. on recrystallization from ethyl acetate gave 236 mg. of 3β,5α-dihydroxy-6β-fluoropregnan-20-one diacetate, m.p. 187–188°, $[\alpha]D$ +41.8°.

Anal. Calcd. for $C_{25}H_{37}FO_4$: C, 68.77; H, 8.54. Found: C, 69.01; H, 8.68.

6β-Chloro-3β,5α-dihydroxypregnan-20-one 3-Acetate (VIIb).—There was dissolved in 3.9 l. of methylene chloride 64 g. of 5α,6α-epoxy-3β-hydroxypregnan-20-one 3-acetate.[18] This was stirred vigorously while adding rapidly 3.2 l. of 37% hydrochloric acid. After 15 min., 1.5 l. of water was added and the methylene chloride solution separated. The aqueous solution was extracted with a total of 1 l. of methylene chloride. The combined methylene chloride solutions were washed with water, 10% sodium bicarbonate solution, and water until neutral. The solvent, after drying over anhydrous sodium sulfate, was removed under a vacuum. The residue was crystallized from 1500 ml. of 95% alcohol yielding 59 g. of 6β-chloro-3β-5α-dihydroxypregnan-20-one 3-acetate, m.p. 237–238°, $[\alpha]^{26}D$ +8.0°.

Anal. Calcd. for $C_{23}H_{35}ClO_4$: C, 67.21; H, 8.58; Cl, 8.63. Found: C, 67.24; H, 8.58; Cl, 8.60.

6β-Chloro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-Acetate (VIIIb).—There was obtained, following the procedure in making VIIIa, from 95.8 g. of 6β-chloro-3β,5α-dihydroxypregnan-20-one 3-acetate and 27.0 g. of powdered potassium bisulfate in 900 ml. of acetic anhydride and 460 ml. of glacial acetic acid at 60° for 30 min., 25 g. (ethanol) of 6β-chloro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-acetate, m.p. 115–116°, $[\alpha]^{26}D$ +211.6°.

Anal. Calcd. for $C_{23}H_{33}ClO_3$: C, 70.30; H, 8.46; Cl, 9.03. Found: C, 70.71; H, 8.69; Cl, 9.17.

6β-Chloro-5β-methyl-19-nor-9-pregnene-3β,20β-diol 3-Acetate.—There was added to 10.6 g. of 6β-chloro-3β-hydroxy-5β-methyl-19-nor-9-pregnen-20-one 3-acetate in 530 ml. of 80% *t*-butyl alcohol, 5.0 g. of sodium borohydride. After 3 hr. at room temperature an additional 2.7 g. of sodium borohydride was added. The solution was poured, after 2 additional hours, into 3000 ml. of 5% sodium chloride solution containing 40 ml. of glacial acetic acid. The precipitate was filtered, washed with water, and air-dried. The solid was crystallized from 70 ml. of ethyl acetate yielding 6.2 g. of 6β-chloro-5β-methyl-19-nor-9-pregnene-3β,20β-diol 3-acetate, m.p. 171–174°, $[\alpha]^{26}D$ +163.8°.

Anal. Calcd. for $C_{23}H_{35}ClO_3$: C, 69.94; H, 8.93; Cl, 8.97. Found: C, 69.74; H, 9.06; Cl, 9.11.

6β-Bromo-3β,5α-dihydroxypregnan-20-one 3-Acetate (VIIc).—From a solution of 8.3 g. of 5α,6α-epoxy-3β-hydroxypregnan-20-one 3-acetate in 500 ml. of methylene chloride and 350 ml. of 48% hydrobromic acid, following the procedure for making VIIb, there was obtained from acetone 5.2 g. of 6β-bromo-3β,5α-dihydroxypregnan-20-one 3-acetate, m.p. 193–194°, $[\alpha]^{26}D$ −9.8°.

Anal. Calcd. for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.75; Br, 17.55. Found: C, 60.98; H, 7.95; Br, 17.48.

This compound with acetic anhydride and potassium bisulfate yielded tars.

6β-Chloro-3β,5α-dihydroxyandrostan-17-one.—Following the procedure for making VIIb, 85 g. of 5α,6α-epoxy-3β-hydroxyandrostane-17-one was converted into 69 g. of 6β-chloro-3β,5α-dihydroxyandrostan-17-one (crystallized from ethyl acetate), m.p. 216–217°, $[\alpha]^{26}D$ +38.4°.

Anal. Calcd. for $C_{19}H_{29}ClO_3$: C, 66.93; H, 8.57; Cl, 10.40. Found: C, 66.97; H, 8.75; Cl, 10.59.

6β-Chloro-3β,5α-dihydroxyandrostan-17-one 3-Acetate (Xb) and 6β-Chloro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one 3-Acetate(XIb).—6β-Chloro-3β,5α-dihydroxyandrostan-17-one (48.3 g.) and 250 ml. of acetic anhydride were refluxed 0.5 hr. After cooling, an 11-ml. sample was removed and decomposed in 300 ml. of 15% salt solution. The aqueous mixture was extracted with ethyl acetate which, in turn, was washed with sodium bicarbonate solution and water until neutral. After drying over anhydrous sodium sulfate, the ethyl acetate was removed by vacuum distillation. The residue was crystallized from ethyl acetate–

methanol (1:1) to give 6β-chloro-3β,5α-dihydroxyandrostan-17-one 3-acetate, m.p. 204–205°, $[\alpha]^{26}D$ +3.5°.

Anal. Calcd. for $C_{21}H_{31}ClO_4$: C, 65.86; H, 8.16; Cl, 9.13. Found: C, 65.92; H, 7.98; Cl, 8.97.

With the temperature at 35°, 12 drops of concentrated sulfuric acid was added to the balance of the reaction. This temperature was maintained for 30 min. The solution was then poured into 1300 ml. of 15% brine and allowed to stand for 2 hr. The aqueous mixture was extracted with a total of 1000 ml. of isopropyl acetate which was washed with 10% sodium bicarbonate solution and water until neutral. After drying over anhydrous sodium sulfate the isopropyl acetate was concentrated by vacuum distillation to approximately 80 ml. from which 18.1 g. of 6β-chloro-5β-methyl-3β-hydroxy-19-nor-9-androsten-17-one 3-acetate was obtained, m.p. 189–190°, $[\alpha]^{26}D$ +230°.

Anal. Calcd. for $C_{21}H_{29}ClO_4$: C, 69.12; H, 8.01; Cl, 9.71. Found: C, 69.06; H, 7.96; Cl, 9.71.

The crystallization liquors were chromatographed over silica gel. There was eluted with benzene–ethyl acetate (49:1) and crystallized from 95% alcohol 4.2 g. of 4-methyl 1,3,5(10)-estratrien-17-one, m.p. 184–185°, $[\alpha]^{25}D$ +148°, λ_{max}^{MeOH} 262.5 mμ, ε 350, 269 mμ, ε 304 (lit.,[21] m.p. 184.5–186°, $[\alpha]^{25}D$ +146°).

A mixed melting point taken with an authentic sample provided by Dr. Willard Hoehn of these laboratories exhibited no depression. Their infrared spectra were identical. The infrared spectrum has absorption peaks at 6.32, 12.86, and 13.50 μ which could be attributed to an aromatic 1,2,3-substitution.[32]

The benzene–ethyl acetate (19:1) eluate yielded from 95% alcohol 3.6 g. of 6-chloro-3β-hydroxy-5-androsten-17-one,[33] m.p. 192–193°, $[\alpha]^{26}D$ −20°.

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.11; H, 8.01; Cl, 9.72. Found: C, 69.36; H, 8.04; Cl, 9.50.

Also crystallized from this eluate using 95% alcohol was 2.0 g. of 6β-chloro-3β-hydroxy-4-androstene-17-one 3-acetate,[33] m.p. 204–206°, $[\alpha]^{26}D$ +63°.

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.11; H, 8.01; Cl, 9.72. Found: C, 68.93; H, 8.28; Cl, 9.75.

A paper chromatogram on these two compounds shows discrete spots with different running times. When tested for androgenic activity the Δ^4 compound was active at 5 mg. while the Δ^5 compound was inactive.

Further elution with benzene–ethyl acetate (9:1) yielded from 95% alcohol, 7.3 g. of 6β-chloro-3β,5α-dihydroxyandrostane-17-one 3,5-diacetate, m.p. 204–205°, $[\alpha]^{26}D$ +19°.

Anal. Calcd. for $C_{23}H_{33}ClO_5$: C, 65.03; H, 7.83; Cl, 8.34. Found: C, 65.14; H, 8.16; Cl, 8.45.

The only other crystalline product that was obtained was eluted with benzene ethyl acetate (5:1). It was 580 mg. of 4-androstene-3,17-dione on the basis of its infrared spectrum and mixed melting point with an authentic sample.

6β-Chloro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one.—6β-Chloro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one 3-acetate (4.4 g.) in 240 ml. of methanol, 12 g. of potassium carbonate, and 110 ml. of water was refluxed 1 hr. and poured into 1200 ml. of 10% brine solution. After standing for 2 hr. the solution was filtered and the precipitate washed with water and air-dried. Crystallization from ethyl acetate gave 1 g. of 6β-chloro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one, m.p. 186–187°, $[\alpha]^{26}D$ +255°.

Anal. Calcd. for $C_{19}H_{27}ClO_2$: C, 70.68; H, 8.43; Cl, 10.98. Found: C, 71.04; H, 8.30; Cl, 10.99.

6β-Chloro-5β-methyl-19-nor-9-androstene-3,17-dione.—There was added to 2.3 g. of 6β-chloro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one in 88 ml. of benzene, a solution of 1.1 g. of chromic acid in 7.5 ml. of water, and 15.8 ml. of acetic acid. This mixture was stirred at room temperature for 4 hr. upon which 1 g. of sodium sulfite in 40 ml. of water was added. The benzene layer was separated and the aqueous layer extracted with a total of 500 ml. of ethyl acetate. The combined organic solutions were washed with water and 10% sodium bicarbonate solution until neutral. After drying over anhydrous sodium sulfate, the organic solvents were removed by vacuum distillation. The residue on being crystallized from 20 ml. of ethyl acetate gave 1.3 g. of 6β-chloro-5β-methyl-19-nor-9-androstene-3,17-dione, m.p. 179–181°, $[\alpha]^{26}D$ +191°.

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.12; H, 7.85; Cl, 11.05. Found: C, 70.94; H, 7.58; Cl, 10.81.

3β,5α-Dihydroxy-6β-fluoroandrostan-17-one.—From 10 g. of 5α,6α-epoxy-3β-hydroxyandrostan-17-one in 200 ml. methylene chloride and 100 ml. of 48% hydrofluoric acid, following the procedure for making VIIb, there crystallized from ethyl acetate 2.4 g. of 3β,5α-dihydroxy-6β-fluoroandrostan-17-one,[34] m.p. 275–280° dec., $[\alpha]^{26}D$ +51.2° (1.018% MeOH).

Anal. Calcd. for $C_{19}H_{29}FO_3$: C, 70.35; H, 9.01. Found: C, 69.90; H, 9.02.

The aqueous acid solution after 1 hr. yielded 1.5 g. of androstane-3β,5α,6β-triol,[35] m.p. 295–297°.

6β-Fluoro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one 3-Acetate (XIa).—Two grams of 3β,5α-dihydroxy-6β-fluoroandrostan-17-one in 50 ml. of acetic anhydride was heated at 100–110° for 1 hr. After cooling to 32°, 0.3 g. of powdered potassium bisulfate was added and heating with stirring was resumed for 15 min. at 90–100°. The mixture was poured into 450 ml. of 15% brine and allowed to stand for 2 hr. After extracting with ethyl acetate, washing with water and 10% sodium bicarbonate, the ethyl acetate was removed by vacuum distillation, and the residue crystallized from 95% ethyl alcohol yielding 0.3 g. of 6β-fluoro-3β-hydroxy-5β-methyl-19-nor-9-androsten-17-one 3-acetate, m.p. 157–159°, $[\alpha]^{26}D$ +175°.

Anal. Calcd. for $C_{21}H_{29}FO_3$: C, 72.38; H, 8.36. Found: C, 72.32; H, 8.11.

5α,6α-Epoxyandrostane-3β,17β-diol.—A solution of 50 g. of 5-androstene-3β,17β-diol in 920 ml. of benzene was mixed with 216 ml. of peracetic acid.[12] After standing overnight the solution was poured into 2 l. of water and the benzene layer separated. The aqueous layer was extracted twice with isopropyl acetate, the combined benzene and ester solutions were washed with 5% sodium hydroxide solution and water until neutral. After drying over anhydrous sodium sulfate and removing the solvent under a vacuum, the residue was crystallized from ethyl acetate to give 35.3 g. of 5α,6α-epoxyandrostane-3β,17β-diol monohydrate, m.p. 194–195°, $[\alpha]^{26}D$ −66.6° (1.006% EtOH). The anhydrous material is obtained by drying in a vacuum for 2 hr. at 110°.

Anal. Calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.40; H, 10.45.

6β-Chloroandrostane-3β,5α,17β-triol.—5α,6α-Epoxyandrostane-3β,17β-diol (28.7 g.) was treated as in the preparation of VIIb. The residue, 23.2 g., was recrystallized from 100 ml. of ethyl acetate to give a solvate containing a half a molecule of ethyl acetate as solvent of crystallization, m.p. 125–126°, and from acetone to give a monoacetone solvate, $[\alpha]^{26}D$ −23° (1.000% MeOH). Crystallization from methylene chloride gave 6β-chloroandrostane-3β,5α,17β-triol monoacetonate, m.p. 172–175°.

Anal. Calcd. for $C_{22}H_{37}ClO_4$: C, 65.89; H, 9.30; Cl, 8.84. Found: C, 65.64; H, 9.59; Cl, 8.90.

6β-Chloroandrostane-3β,5α,17β-triol 3,17-Diacetate.—Following the procedure to make Xb, 21.5 g. of 6β-chloroandrostane-3β,5α,17β-triol monoacetonate was converted into 6β-chloroandrostane-3β,5α,17β-triol 3,17-diacetate, crystallized from acetone, m.p. 197–198°, $[\alpha]^{26}D$ −57°.

Anal. Calcd. for $C_{23}H_{35}ClO_5$: C, 64.69; H, 8.26; Cl, 8.30. Found: C, 64.63; H, 8.13; Cl, 8.34.

(32) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1954.

(33) The assignment of the position of the ethylenic groups was based on optical rotations. See, W. Klyne, "The Chemistry of the Steroids," John Wiley and Sons, New York, N. Y., 1957, p. 53ff.

(34) A qualitative analysis for the presence of fluorine was run through the kindness of Dr. Clarence Bergstrom.

(35) M. Ehrenstein, *J. Org. Chem.*, **4**, 506 (1939).

6β-Chloro-5β-methyl-19-nor-9-androstene-3β,17β-diol 3,17-Diacetate.—Maintaining the above solution at 55–65°, 4.0 g. of powdered potassium bisulfate was added. Then following the procedure for Va there was crystallized from ethyl acetate 9.6 g. of 6β-chloro-5β-methyl-19-nor-9-androstene-3β,17β-diol 3,17-diacetate, m.p. 143–144°, $[\alpha]^{26}D$ +152°.

Anal. Calcd. for $C_{23}H_{33}ClO_4$: C, 67.54; H, 8.13; Cl, 8.67. Found: C, 67.94; H, 8.74; Cl, 8.56.

6β-Chloro-3β,5α,17α-trihydroxypregnan-20-one 3,17-Diacetate (XIII).—Fifty-six grams of XII was transformed using the procedures for making VIIb and Xb into 60 g. of 6β-chloro-3β,5α,17α-trihydroxypregnan-20-one 3,17-diacetate (from ethyl acetate), m.p. 200–202°, $[\alpha]^{26}D$ −45.8°.

Anal. Calcd. for $C_{25}H_{37}ClO_6$: C, 64.02; H, 7.95; Cl, 7.56. Found: C, 63.67; H, 8.06; Cl, 7.56.

3β,17α-Dihydroxy-6β-chloro-5β-methyl-19-nor-9-pregnen-17-one 3,17-Diacetate (XIV).—From 60 g. of 6β-chloro-3β,5α,17α-trihydroxypregnan-20-one 3,17-diacetate following the procedure for VIIIa but holding the temperature at 40–50°, there crystallized from ethyl acetate 21.3 g. of 3β,17α-dihydroxy-6β-chloro-5β-methyl-19-nor-9-pregnen-17-one 3,17-diacetate, m.p. 186–187°, $[\alpha]^{25}D$ +132.8°.

Anal. Calcd. for $C_{25}H_{35}ClO_5$: C, 66.57; H, 7.82; Cl, 7.86. Found: C, 66.53; H, 8.19; Cl, 7.91.

The residue from crystallization on chromatography over silica gel yielded from the benzene–ethyl acetate (19:1) eluate 350 mg. of 17α-hydroxy-4-methyl-19-nor-1,3,5(10)-pregnatrien-20-one 17-acetate (from alcohol), m.p. 187–188°, $[\alpha]^{26}D$ +23°. The infrared spectrum exhibited absorption peaks at 6.30, 12.78, and 13.50 μ. These can be attributed to an aromatic 1,2,3-substitution.[32]

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.06; H, 8.59.

The second material isolated from this eluate and crystallized from 95% alcohol was 400 mg. of 6-chloro-3β,17α-dihydroxy-5-pregnen-20-one 3,17-diacetate, m.p. 208–209°, $[\alpha]^{26}D$ −79°.

Anal. Calcd. for $C_{25}H_{35}ClO_5$: C, 66.43; H, 7.81; Cl, 7.81. Found: C, 66.43; H, 7.83; Cl, 7.81.

The third material crystallized from 95% alcohol was 700 mg. of 3α,17α-dihydroxy-4-pregnen-20-one 3,17-diacetate, m.p. 159–161°, $[\alpha]^{26}D$ +27°.

Anal. Calcd. for $C_{25}H_{35}ClO_5$: C, 66.43; H, 7.81; Cl, 7.81. Found: C, 66.55; H, 7.85; Cl, 7.75.

The above two compounds were tested for progestational activity using the Clauberg assay. The Δ^5 compound showed an activity of 50% that of progesterone, while the Δ^4 compound showed an activity of 10%.

A material from the benzene–ethyl acetate (20:3) eluate which had a m.p. 221–223°, an ultraviolet spectrum with a maximum absorption at 240.5 mμ and an infrared spectrum showing the presence of an acetate group and a conjugated ketone was thought to be impure 17α-acetoxyprogesterone.[36] There was not enough material to obtain a pure sample.

6β-Chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-17-one.—There was added to 4 g. of 6β-chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one diacetate in 125 ml. of methanol, 4.6 g. of potassium hydroxide in 15 ml. of water. After standing at room temperature for 4 hr., 10 ml. of 37% hydrochloric acid in 2000 ml. of water was added. The precipitate was filtered, washed with water, and air-dried. Recrystallization from 35 ml. of methanol gave 2.8 g. of 6β-chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one, m.p. 187–189°, $[\alpha]^{26}D$ +154°.

Anal. Calcd. for $C_{21}H_{31}ClO_3$: C, 68.74; H, 8.51; Cl, 9.66. Found: C, 68.78; H, 8.39; Cl, 9.73.

6β-Chloro-17α-hydroxy-5β-methyl-19-nor-9-pregnene-3,20-dione.—To 1.8 g. of 6β-chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one in 80 ml. of benzene and 80 ml. of acetic acid was added 1.1 g. of chromic acid in 10 ml. of water. After stirring at room temperature for 5 hr., 1 g. of sodium sulfite was added. The benzene layer was separated and washed with water and 10% sodium bicarbonate solution till neutral. After drying over anhydrous sodium sulfate the benzene was removed under vacuum distillation and the residue crystallized from 95% ethyl alcohol yielding 0.5 g. of 6β-chloro-17α-hydroxy-5β-methyl-19-nor-9-pregnene-3,20-dione, m.p. 193–195°, $[\alpha]^{26}D$ +91°.

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.10; H, 8.01; Cl, 9.71. Found: C, 68.54; H, 7.77; Cl, 9.72.

6β-Chloro-5β-methyl-19-nor-9-pregnene-3β,17α,20β-triol.—Two grams of 6β-chloro-3β,17α-dihydroxy-5β-methyl-19-nor-9-pregnen-20-one 3,17-diacetate was dissolved in 50 ml. of tetrahydrofuran and added to this was 1 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The reaction was refluxed for 1.5 hr. After cooling in an ice bath, chips of ice were added to decompose the excess lithium aluminum hydride and then 60 ml. of 6 *N* hydrochloric acid. The solution was extracted with 800 ml. of isopropyl acetate after adding 200 ml. of water. The isopropyl acetate solution was washed with water until neutral, dried over anhydrous sodium sulfate, and taken to dryness by vacuum distillation. The residue was crystallized from ethyl acetate yielding 0.7 g. of 6β-chloro-5β-methyl-19-nor-9-pregnene-3β,17α,20β-triol, m.p. 174–175°, $[\alpha]^{26}D$ +142°.

Anal. Calcd. for $C_{21}H_{33}ClO_3$: C, 68.36; H, 9.02; Cl, 9.61. Found: C, 68.54; H, 8.80; Cl, 9.58.

6β-Pyrrolidylcholestane-3β,5α-diol 3-Acetate.—5α,6α-Epoxycholestan-3β-ol (10 g.) was dissolved in 200 ml. of methanol and 100 ml. of pyrrolidine. The solution was refluxed for 24 hr. and vacuum stripped to dryness. The residue was dissolved in 60 ml. of pyridine and 10 ml. of acetic anhydride and allowed to stand overnight at room temperature. The solution was poured into 1 l. of water and made acid with hydrochloric acid. This was extracted with a total of 900 ml. of methylene chloride. The methylene chloride was washed with sodium bicarbonate solution and water until neutral. After drying over anhydrous sodium sulfate, this solvent was removed under vacuum and the residue crystallized from acetone to give a 6 g. of 6β-pyrrolidylcholestane-3β,5α-diol 3-acetate, m.p. 151–154°, $[\alpha]^{26}D$ −39.5°.

Anal. Calcd. for $C_{33}H_{57}NO_3$: C, 76.84; H, 11.14; N, 2.72. Found: C, 77.01; H, 11.07; N, 3.06.

This material led only to resins when treated with acetic anhydride and potassium bisulfate or sulfuric acid.

6β-Methylspirostane-3β,5α-diol 3-Acetate.—There was dissolved in 250 ml. of pyridine 50 g. of 6β-methylspirostane-3β,5α-diol to which was added 12 ml. of acetic anhydride. After standing overnight at room temperature the volume was reduced to approximately 50 ml. by vacuum distillation; 700 ml. of methylene chloride was added and the solution washed with water, dilute hydrochloric acid, water, sodium bicarbonate solution, and water until neutral. After drying over anhydrous sodium sulfate the methylene chloride was removed by vacuum distillation. The residue was crystallized from ethyl acetate giving 42.9 g. of 6β-methylspirostane-3β,5α-diol 3-acetate, m.p. 176–179°, $[\alpha]^{26}D$ −75.0°.

Anal. Calcd. for $C_{30}H_{48}O_5$: C, 74.06; H, 10.03. Found: C, 74.04; H, 9.96.

If the above acetate is treated with acetic anhydride and potassium bisulfate or sulfuric acid to cause rearrangement only 6-methyl-5-spirosten-3β-ol 3-acetate is formed.[37]

3β,5α-Dihydroxy-6β-dimethylaminopregnan-20-one.—There was placed in a pressure bottle 20 g. of 3β-hydroxy-5α,6α epoxypregnan-20-one, 150 ml. of methanol, and 100 ml. of dimethylamine. This was heated in a steam cabinet (50–60°) for 3 days. The solvent was blown off with nitrogen and the residue crystallized from ethyl acetate yielding 8.0 g. of

(36) H. J. Ringold, B. Loken, G. Rosenkrantz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 816 (1956).

(37) Compared with an authentic sample obtained from Productos Esteroids, S.A., Mexico City.

3β,5α-dihydroxy-6β-dimethylaminopregnan-20-one, m.p. 217–221°, $[\alpha]^{26}D$ −9°.

Anal. Calcd. for $C_{23}H_{39}NO_3$: C, 73.16; H, 10.41; N, 3.73. Found: C, 72.90; H, 10.16; N, 3.87.

3β,5α-Dihydroxy-6β-dimethylaminopregnan-20-one 3-Acetate.—3β,5α-Dihydroxy-6β-dimethylaminopregnan-20-one (7.0 g.) and 40 ml. of acetic anhydride were heated at 130° for 0.5 hr. After cooling to 40°, a 3-ml. sample was removed and decomposed with 200 ml. of 10% brine. The solution was neutralized with sodium bicarbonate and extracted with a total of 200 ml. of isopropyl acetate. This was washed twice with water, dried over anhydrous sodium sulfate, and blown to dryness with nitrogen. The residue was crystallized from acetone to give 3β,5α-dihydroxy-6β-dimethylaminopregnan-20-one 3-acetate, m.p. 187–189°, $[\alpha]^{26}D$ −22°.

Anal. Calcd. for $C_{25}H_{41}NO_4$: C, 71.56; H, 9.85; N, 3.34. Found: C, 71.27; H, 9.81; N, 3.62.

3β-Hydroxy-5β-pregnane-6,20-dione 3-Acetate.—With the above solution at 40°, and precipitation beginning, concentrated sulfuric acid was added dropwise until the solution cleared (25 drops). The temperature was maintained at 36–40° with stirring for 15 min. The reaction was poured into 1 l. of 10% brine, allowed to stand for 2 hr., and neutralized with 20% sodium hydroxide solution. The mixture was extracted with a total of 1.2 l. of isopropyl acetate, washed with water until neutral, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue split into two parts. One part was hydrolyzed and the other part crystallized twice from ethyl acetate to give a product, m.p. 152–154°, which contained no nitrogen. The infrared spectrum showed the presence of three carbonyls. The compound is believed to be 3β-hydroxy-5β-pregnane-6,20-dione 3-acetate, $[\alpha]^{26}D$ +26.5°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.62; H, 8.83.

3β-Hydroxy-5β-pregnane-6,20-dione.—A solution of 3.1 g. of residue from above in 40 ml. of methanol was treated with 1 g. of potassium carbonate in 10 ml. of water. After standing overnight the solution was poured into 1 l. of water and extracted with a total of 900 ml. of isopropyl acetate. After washing with water, drying over anhydrous sodium sulfate, the solvent was removed by vacuum distillation. The residue was crystallized from ethyl acetate to give 3β-hydroxy-5β-pregnane-6,20-dione, m.p. 186–187°, $[\alpha]D$ + 39.5°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.50; H, 9.50.

The Oxidative Rearrangement of Vinylic Sulfides[1,2]

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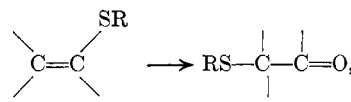
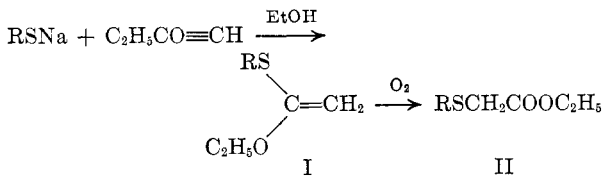
Received March 26, 1962

A variety of vinylic sulfides were prepared and the oxygen-induced rearrangement,  , was investigated. A mechanism for this reaction and facts supporting it are presented.

On investigating the nucleophilic addition of thiols to ethoxyacetylene, the resulting adducts [CH_2=C(OEt)SR, where R is *t*-C_4H_9, C_6H_5, and *p*-$CH_3C_6H_4$] were found to be unstable to air.[3] The major product of this autoxidation was the responding ethyl arylmercapto- or alkylmercaptoacetate (II). Similar oxidative rearrangements[4f]



I II

(1) Presented at the 17th National Organic Chemistry Symposium of the American Chemical Society, June 29, 1961, Bloomington, Indiana.

(2) Abstracted from the Ph.D. thesis of Robert J. Steltenkamp, Purdue University, 1962.

(3) W. E. Truce and R. J. Steltenkamp, *J. Am. Chem. Soc.*, **82**, 6427 (1960).

(4) (a) E. Demole, *Ber.*, **11**, 315, 1302, 1307, 1710 (1878); **12**, 2245 (1879); *Bull. soc. chim.*, [ii] **34**, 201 (1880); (b) F. Swarts, *Bull. acad. roy. Belg.*, [3] **34**, 307–326 (1897); [3] **35**, 849 (1898); [3] **36**, 532 (1898); (c) L. Henry, *ibid.*, [3] **36**, 497 (1899); *Ber.*, **12**, 1839 (1879); (d) J. Foster, *J. Am. Chem. Soc.*, **31**, 596 (1909); (e) R. A. Dickinson and J. A. Leermakers, *ibid.*, **54**, 3852 (1932); (f) G. B. Bachman, *ibid.*, **55**, 4279 (1933); **57**, 1088 (1935); (g) K. L. Muller and H. J. Schumacker, *Z. physik. Chem.*, **B37**, 365 (1937); (h) R. S. Corley, J. Lal, and M. W. Kane, *J. Am. Chem. Soc.*, **78**, 3489 (1956).

have previously been reported only for various halogenated ethylenes and halogenated vinyl ethers,[4] *e.g.*, CH_2=CBr_2 $\xrightarrow{O_2}$ $BrCH_2COBr$.

The autoxidation of the 1,1-adducts[5] (I) proceeded rapidly when oxygen was passed into the pure liquid and the exothermic reaction was generally performed in an ice water bath. In each case the major product, II, was formed in yields of 47 to 54%. Other products isolated were free thiol, the corresponding disulfide, ethoxyacetylene, and the saturated compound, resulting from the addition of mercaptan to the 1,1-adduct.

The autoxidation of 1-ethoxy-1-(phenylmercapto)propene, prepared by the nucleophilic addition of benzenethiol to 1-ethoxy-1-propyne, proceeded readily, affording ethyl α-phenylmercaptopropionate in a 54% yield. The products were examined by vapor phase chromatography and the structure confirmed by independent synthesis.

Ketene mercaptals autoxidize to thiol esters. The reaction occurs with both aromatic and ali-

(5) The nucleophilic addition of thiols to ethoxyacetylene yielded the 1,1-disubstituted ethenes, whereas free radical addition produced the 1,2-adduct. [H. J. Alkema and J. F. Arens, *Rec. trav. chim.*, **79**, 1257 (1960); see also ref. 3.]