Upon shaking an ethereal solution of the residue with 10% hydrochloric acid, a gelatinous precipitate formed. The hydrochloride was separated by centrifugation, washed three times with ether and decomposed in ethanol solution with 10% sodium hydroxide solution. The amine was extracted with ether and washed with water. The residue remaining after removal of solvent from the dried solution was crystallized from acetone yielding 3.4 g. (56.5%) of fine, white crystals melting at 115–117°. These gave no depression in melting point when mixed with a sample of benzylcholesterylamine.

The ether washings of the gelatinous hydrochloride gave 1.5 g. of unchanged benzyl-*i*-cholesterylamine hydrochloride melting at 216–218° (dec.).

Reaction of Benzyl-*i*-cholesterylamine Hydrochloride with Aniline.—A solution of 3.0 g. of benzyl-*i*-cholesterylamine hydrochloride in 15 ml. of aniline was refluxed for four hours. Upon cooling, the mixture set to a semi-solid mass. It was then digested with ethanol and chilled. The solid was separated, washed with ethanol and dried. The dry material, 2.3 g. (85%) of white plates, melted at 189–191°. A sample of the compound gave no depression in melting point when mixed with cholesterylaniline.[10]

In a similar experiment in which the free amine, benzyl-*i*-cholesterylamine, was employed, the amine was recovered unchanged.

Reaction of *i*-Cholesteryl Methyl Ether with Benzylamine.—A solution of 3.0 g. of *i*-cholesteryl methyl ether[1a] and 3.0 g. of benzylammonium *p*-toluenesulfonate in 20 ml. of benzylamine was refluxed for twenty-two hours. The solution was poured into water and extracted with ether. Upon shaking the ethereal layer with dilute hydrochloric acid an insoluble hydrochloride separated. The hydrochloride was centrifuged, washed three times with ether and then decomposed in ethanol with 10% sodium hydroxide. An ether extract of the free amine was washed with water, dried and concentrated. Upon crystallization from acetone, the yellow residue yielded 1.5 g. of white prisms melting at 115–118°. This material showed no depression in melting point when mixed with a sample of benzylcholesterylamine.

Upon heating a 1.0-g. sample of the *i*-ether with 5 ml. of benzylamine in a closed tube at 240° for eighteen hours, the *i*-ether was recovered unchanged.

Reaction of *i*-Cholesteryl Methyl Ether with Aniline.—A mixture of 0.6 g. of carefully purified *i*-cholesteryl methyl ether and 5 ml. of freshly distilled aniline containing a few mg. of *p*-toluenesulfonic acid was refluxed from an oil-bath at 190° for two hours and then allowed to cool. The semi-solid mass was slurried with 10 ml. of methanol, filtered, washed with methanol and dried. The resulting cholesterylaniline, 0.65 g. of white flakes, melted at 190°. This gave no depression in melting point when mixed with a sample of cholesterylaniline prepared in the known manner.[10]

In a similar experiment, in which the *p*-toluenesulfonic acid was omitted, the *i*-ether was recovered unchanged.

(10) Lieb, Winkelmann and Koeppl, *Ann.*, **509**, 214 (1934).

Summary

1. Cholesteryl *p*-toluenesulfonate reacts with ammonia and with primary aliphatic amines to give 6-amino-*i*-cholestenes accompanied by some 3-amino-5-cholestenes.

2. *i*-Cholesterylamine and benzyl-*i*-cholesterylamine are described and their structures proved by stepwise degradation to the known 3(β)-chlorocholestan-6-one.

3. Benzyl-*i*-cholesterylamine can be transformed into benzylcholesterylamine by treatment with benzylamine and benzylammonium toluenesulfonate. The necessity of the presence of the salt in this reaction points to an ionic mechanism for the conversion of the *i*-steroid into the normal steroid and further corroborates the known acid-catalyzed reactivity of the *i*-steroids.

CHICAGO, ILLINOIS RECEIVED NOVEMBER 28, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY OF THE UNIVERSITY OF CHICAGO]

Preparation of 17-Ketosteroids from Enol Acetates of 20-Ketosteroids[1a]

BY CHARLES W. MARSHALL, THEODORE H. KRITCHEVSKY, SEYMOUR LIEBERMAN[1b] AND T. F. GALLAGHER[1b]

The 20-ketosteroids are obtainable in good yield from accessible natural products. It appeared to us that oxidation of the enol acetates might offer a promising procedure for the preparation of 17-ketosteroids from these substances and we have accordingly investigated this problem using four different 20-ketosteroids. The general reactions are summarized in the partial formulations of Fig. 1. The enol acetates were prepared by the method of Bedoukian[2] and from the three pregnane derivatives studied, only one enol acetate was obtained. The structure of the product was proved by ozonolysis to the corresponding 17-ketosteroid. From 3(β)-hydroxy-20-ketoallopregnane, two stereoisomeric enol acetates were obtained which must be regarded as *cis* and *trans* isomers about the double bond from C-17 to C-20, since both compounds upon ozonolysis followed by saponification yielded isoandrosterone. The compound with higher melting point has been arbitrarily designated as the *trans*-form. For preparative purposes, isolation of the enol acetate is

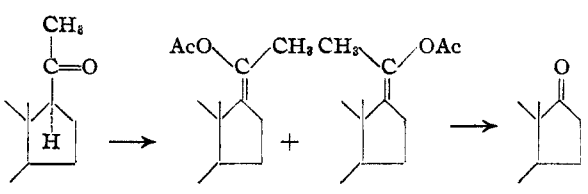

Fig. 1.

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(2) Bedoukian, THIS JOURNAL, **67**, 1430 (1945).

TABLE I

ENOL ACETATES OF 20-KETOSTEROIDS

No.	Derivatives of Δ^{17}-pregnene	Cryst. form	M. p.[a] °C.	$[\alpha]D^{b}$	Formula	Composition, % Calcd. C	Found C	Calcd. H	Found H
1	3(α),20-Diacetoxy	Prisms	141.5–142	+ 60	$C_{25}H_{38}O_4$	74.59	74.56	9.51	9.44
2	3(α),11(α),20-Triacetoxy	Needles	218 –220	− 19	$C_{27}H_{40}O_6$	70.40	70.65	8.75	8.61
3	3(α),12(α),20-Triacetoxy	Prisms	174 –175.5	+165[c]	$C_{27}H_{40}O_6$	70.40	70.47	8.75	8.73
4	3(α),12(α),20-Triacetoxy-21-benzal	Prisms	261 –263[d]	+118	$C_{34}H_{44}O_6$	74.42	74.41	8.08	8.07
5	3(β),20-Diacetoxy-Δ^{17}-allopregnene (*cis*)	Plates	121.5–122.5	+ 21	$C_{25}H_{38}O_4$	74.59	74.45	9.51	9.56
6	3(β),20-Diacetoxy-Δ^{17}-allopregnene (*trans*)	Ndls.	172.5–173.5	+ 12	$C_{25}H_{38}O_4$	74.59	74.53	9.51	9.47

[a] All melting points are corrected. [b] In $CHCl_3$. [c] +173° in acetone. [d] Sinter 257°.

unnecessary and the sirupy enol acetate can be directly ozonized without further purification.

Ozonolysis of the enol acetate proceeded smoothly and in satisfactory yield except with 3(α),12(α)-20-triacetoxy-Δ^{17}-pregnene. When this compound was ozonized in the same manner used for the other four substances, two products were obtained in approximately equal amounts. One was the anticipated 17-keto derivative and the other was a crystalline substance of melting point 217–218.5° and $[\alpha]^{25}D$ +40° ($CHCl_3$) which will be reported in detail at a later time. None of the other compounds investigated yielded a comparable by-product.

The enol acetate of 3(α),12(α)-dihydroxy-20-keto-21-benzalpregnane was prepared and the ultraviolet absorption spectrum of this compound is shown in Fig. 2. When this enol acetate was oxidized with O_3 or with CrO_3, no recognizable product was obtained. This experience is similar to that of Koechlin and Reichstein,[3] who oxidized the enol chloride of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane without obtaining any detectable amount of the 17-keto derivative, although 3(β)-acetoxy-20-keto-21-benzalallopregnane was converted to isoandrosterone in 45% yield by the same reactions. Since the preparation of 17-ketosteroids over the benzal derivatives appeared to be less advantageous than the method already described, further work on these compounds was abandoned.

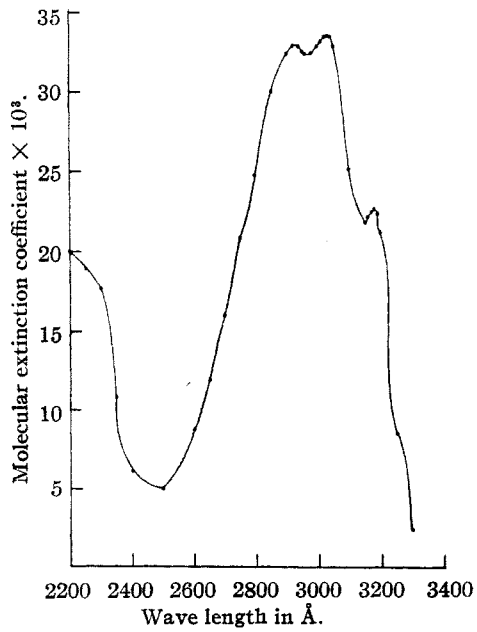

Fig. 2.—Absorption spectrum of the enol acetate of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane in 95% ethanol.

(3) Koechlin and Reichstein, *Helv. Chim. Acta*, **27**, 549 (1944).

Experimental

Preparation of Enol Acetates of 20-Ketopregnane Derivatives.—A solution of 2 millimoles of the ketone and 2 millimoles of *p*-toluenesulfonic acid in 75 cc. of acetic anhydride was distilled slowly through a short unpacked column until most of the acetic anhydride had been removed (four to five hours). The residual solution was chilled, water was added, and after a short interval the product was extracted with ether, which was in turn washed with sodium hydroxide solution and with water, dried over sodium sulfate and the ether removed. The dark residue was dissolved in petroleum ether and purified by passage through a column of aluminum oxide. The colorless enol acetates were recovered in the petroluem ether eluates and were recrystallized from this solvent. The characteristics of the products are recorded in Table I. The yield of crystalline enol acetate was between 60 and 70%. The isomers 5 and 6 required extensive chromatography to effect separation, and for this reason the yield was much lower.

Ozonolysis of the Enol Acetates.—The preparation of 3(α),11(α)-diacetoxy-17-ketoetiocholane is typical. A solution of 490 mg. of the enol acetate in 400 cc. of a 1:1 mixture of anhydrous methanol and ethyl acetate was chilled to −40° and five mole equivalents of ozone in a 6% stream were passed through the solution. A 5% palladium–calcium carbonate catalyst (2.5 g.) was added and the mixture was shaken in an atmosphere of hydrogen until there was no further uptake (less than fifteen minutes). After removal of the catalyst and solvent, the product was purified by chromatographic fractionation on aluminum oxide. The yield of analytically pure material based on the enol acetate was 51%. The characteristics of the products are recorded in Table II.

Hydrolysis of Acetylated 17-Ketosteroids.—Partial hydrolysis of compounds number 8 and 11 was accomplished at room temperature with 0.15 *N* sodium hydroxide in 85% ethanol. The monoacetate from 11 was amorphous.[4] The monoacetates obtained from the ozonolysis of compounds number 1, 5 and 6 were also hydrolyzed in this manner. Complete hydrolysis of the diacetate no. 8 was accomplished by heating under a reflux in an atmosphere of nitrogen with 0.5 *N* sodium hydroxide in 75% ethanol for one-half hour; the diacetate no. 11 required heating with 1.0 *N* sodium hydroxide in 75% ethanol for one hour. The constants are recorded in Table II.

(4) Reich, *Helv. Chim. Acta*, **28**, 863 (1945).

TABLE II

17-KETOSTEROIDS FROM THE OZONIZATION OF 20-ENOL ACETATES

No.	Derivatives of 17-ketoetiocholane	Obt. from	Cryst. form	Solvent	M. p.,[e] °C.	$[\alpha]D^{g}$	Formula	Composition, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
7	3(α)-Hydroxy[a]	1	Needles	C_6H_6-lig.	151 –152[f]	+109	$C_{19}H_{30}O_2$		[i]		
8	3(α),11(α)-Diacetoxy	2	Needles	Ligroin	170.5–172	+ 43	$C_{23}H_{34}O_5$	70.74	70.47	8.78	8.80
9	3(α)-Hydroxy-11(α)-acetoxy	8	Prisms	Ligroin	147 –148	+ 25	$C_{21}H_{32}O_4$	72.38	72.17	9.26	9.63
10	3(α),11(α)-Dihydroxy	8,9	Prisms	Et acet.	170.5–171	+ 80	$C_{19}H_{30}O_3$	74.47	74.43	9.87	9.55
11	3(α),12(α)-Diacetoxy[b]	3	Prisms	Acetone–lig.	156 –157	+193[h]	$C_{23}H_{34}O_5$	70.74	70.71	8.78	8.75
12	3(α),12(α)-Dihydroxy[c]	11	Needles	Et acet.	164.5–165	+167	$C_{19}H_{30}O_3$	74.47	74.50	9.87	9 54
13	3(β)-Hydroxy-allo[d]	5,6	Prisms	Et acet.-lig.	174 –175	+ 97	$C_{19}H_{30}O_2$		[i]		

[a] Reported values,[5] m. p. 150–151°;[6] m. p. 151–152°, transition point, 140–142°; $[\alpha]D$ +100°; $[\alpha]_{5461}$ +130° (ethanol). [b] Reported values,[7] m. p. 162–162.5°; $[\alpha]D$ +176°; $[\alpha]_{5461}$ +214° (acetone);[8] m. p. 157–158.5°; $[\alpha]D$ +179° (acetone). [c] Reported values,[4] m. p. 165.5–168°; m. p. 164–165°.[8] No rotation reported. [d] Reported values,[9] m. p. 174–174.5°; $[\alpha]D$ +87° (methanol). [e] All melting points are corrected. [f] Softens at 140°. [g] In $CHCl_3$. [h] +177° in acetone. [i] Identified by melting point of a mixture and comparison of the infrared spectrum with an authentic specimen. The infrared spectra were determined and compared by Dr. Konrad Dobriner, Sloan-Kettering Institute, New York 21, N. Y., to whom we extend our thanks.

Enol Acetate of 3(α),12(α)-Diacetoxy-20-keto-21-benzalpregnane.—This substance is obtained as one of the reaction products from the acetylation of the dihydroxy benzal derivative by heating twenty-four hours with acetic anhydride and pyridine. It is also obtained in small amounts from the acetylation catalyzed with perchloric acid according to the method of Whitman and Schwenk,[10] especially if the reaction mixture is permitted to stand at room temperature for forty-five minutes. It is most readily separated by chromatography upon aluminum oxide or by fractional crystallization of the acetylation product from acetone. It was recrystallized from glacial acetic acid, and its characteristics are recorded in Table I.

3(α)-Acetoxy-12(α)-hydroxy-20-keto-21-benzalpregnane.—When 3(α),12(α)-dihydroxy-20-keto-21-benzalpregnane is acetylated using milder conditions (pyridine-acetic anhydride at room temperature; acetic anhydride in the presence of low concentrations of perchloric acid at 5° for ten minutes), the 3-monoacetoxy derivative is obtained in good yield. The product was recrystallized from acetone as plates, m. p. 210–211°; $[\alpha]^{21}D$ +177° (ethanol).

Anal. Calcd. for $C_{30}H_{40}O_4$: C, 77.25; H, 8.69. Found: C, 77.57; H, 8.68.

Upon more vigorous acetylation with either pyridine and acetic anhydride or with acetic anhydride and sodium acetate, the monoacetate is converted to the known diacetate,[3] m. p. 123–126°.

Summary

1. The conversion of 20-ketosteroids to 17-ketosteroids was accomplished by preparation of the enol acetates followed by ozonolysis.

2. 3(α)-Hydroxy-17-ketoetiocholane, 3(β)-hydroxy - 17 - ketoetioallocholane, 3(α),12(α) - dihydroxy-17-ketoetiocholane, and 3(α),11(α)-dihydroxy-17-ketoetiocholane were prepared in this way.

3. The enol acetate of 3(β)-hydroxy-20-keto-allopregnane was obtained in two forms which were shown to be geometric isomers by ozonolysis to isoandrosterone.

4. The enol acetate of 3(α),12(α)-diacetoxy-20-keto-21-benzalpregnane was prepared and its ultraviolet absorption spectrum is described.

RECEIVED NOVEMBER 12, 1947

(5) Ruzicka, Goldberg, Meyer, Brüngger and Eichenberger, *Helv. Chim. Acta*, **17**, 1395 (1934).

(6) Callow, *Biochem. J.*, **33**, 559 (1939).

(7) Reich and Reichstein, *Helv. Chim. Acta*, **26**, 2102 (1943).

(8) Ettlinger and Fieser, *J. Biol. Chem.*, **164**, 451 (1946).

(9) Ruzicka, Goldberg and Brüngger, *Helv. Chim. Acta*, **17**, 1389 (1934).

(10) Whitman and Schwenk, THIS JOURNAL, **68**, 1865 (1946).

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY][1]

4,4'-Dichlorodibutyl Ether and its Derivatives from Tetrahydrofuran

BY KLIEM ALEXANDER AND L. E. SCHNIEPP

Cleavage of the tetrahydrofuran ring by acyl halides to give halogen-substituted butyl esters has been reported by Goldfarb and Smorgonskii,[2] Cloke and Pilgrim[3] and Manchen and Schmidt.[4] The reaction of tetrahydrofuran with acetyl chloride, catalyzed with a small amount of anhydrous zinc chloride, gives a good yield of δ-chlorobutyl acetate plus small amounts of compounds of the formulas: $CH_3COO(CH_2)_4O(CH_2)_4Cl$ and $CH_3COO(CH_2)_4O(CH_2)_4O(CH_2)_4Cl$.[3]

Because of the apparent ease with which acyl halides cleave the hydrogenated furan ring, an investigation was undertaken to determine whether or not inorganic acid chlorides react similarly. Preliminary experiments showed that phosphorus oxychloride, thionyl chloride and silicon tetrachloride, when catalyzed with zinc or zinc chloride, reacted vigorously with tetrahydrofuran. In no case was it found possible to isolate the phosphate, sulfite, or silicate esters; however, decomposition

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) Y. L. Goldfarb and L. M. Smorgonskii, *J. Gen. Chem. (USSR)*, **8**, 1516–1522 (1938).

(3) J. B. Cloke and F. J. Pilgrim, THIS JOURNAL, **61**, 2667 (1939).

(4) F. Manchen and W. Schmidt, U. S. Patent 2,314,454 (1943).