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The Reaction of Dihydropyran with Steroidal Alcohols. Utility in the Syntheses of Testosterone Acyl Esters[1]

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Representative steroids have reacted with 2,3-dihydropyran to give the respective 2-tetrahydropyranyl ethers. These ethers or acetals are readily formed and cleaved, thus making them useful for protection of hydroxyl groups. This has been exemplified in the syntheses of various testosterone esters from dehydroepiandrosterone acetate in over-all yields of about 70%. The steroidal 2-tetrahydropyranyl ethers are stable to $LiAlH_4$ reduction and acylation conditions. Five new 17-acyl esters of 5-androsten-3β,17β-diol 3-(2'-tetrahydropyranyl) ether have been prepared.

In the syntheses of various steroids the necessity often arises for blocking one or more hydroxyl groups while another group is subjected to reaction.

The early syntheses of testosterone by Butenandt[2] and Ruzicka[3] depended upon the protection of the 3-hydroxyl group of dehydroepiandrosterone (II) with a labile acyl derivative, while the 17-carbonyl group was reduced to the respective epimeric mixture of alcohols. Protection of the 17-hydroxyl with a less labile acyl group then afforded access to the 3-hydroxyl by half-hydrolysis of the acyl moiety at the latter position. These blocking groups do not allow advantage to be taken of the asymmetric synthesis of the desired 17β-hydroxyl afforded by lithium aluminum hydride reduction of dehydroepiandrosterone acetate because the ester group is also subject to attack. We have previously reported[4] the conversion of dehydroepiandrosterone acetate to 5-androsten-3β,17β-diol in good yields by reduction with lithium aluminum hydride. The preparation of testosterone, or its esters, from this diol is difficult and the yields are low. If, however, the 3-hydroxyl group could be protected with an alkali-resistant acid-labile group while the reduction of the 17-ketone to an hydroxyl group is carried out, the 17-hydroxyl group could then be protected by an acid-resistant ester grouping while the group at the 3-position is removed by acid hydrolysis. Oppenauer oxidation of the 5-androsten-3β,17β-diol 17-ester so obtained would then give a testosterone acyl ester.

Lithium aluminum hydride has been used to reduce the 17-carbonyl group of 4-androsten-3,17-dione wherein the 3-oxygen was tied up as the benzylenol, or ethyl ether as described by Serini[5] or more recently *via* the benzylthioenol ether as reported by Rosenkranz.[6] The latter prepared testosterone from 4-androsten-3,17-dione *via* the benzylthioenol ether, lithium aluminum hydride reduction, and hydrochloric acid hydrolysis of the enol ether in an over-all yield of 25%.

This paper reports an efficient means of protecting non-phenolic hydroxyl groups in the steroid molecule through the use of the cyclic vinyl ether, 2,3-dihydropyran (III). This ether, which is a dehydration product of a hemiacetal, has been shown by Paul[7] and more recently by Woods and Kramer,[8] and Parham and Anderson[9] to combine with primary alcohols and various phenols in the presence of acidic catalysts to form alkali-resistant, acid-labile 2-tetrahydropyranyl ethers.

The ease of formation and cleavage of the 2-tetrahydropyranyl ether as a protecting group at the 3-position in dehydroepiandrosterone, together with its stability toward lithium aluminum hydride and acylating conditions, has afforded a most practical synthesis for testosterone acyl esters (VIII) in excellent yields. The stability of the above compound to alkylating conditions with alkyl lithiums has recently been shown by Greenhalgh, *et al.*[10]

Though cognizant of the formation of a new center of asymmetry in the pyran ring no effort was made in this work to separate the mixtures of stereoisomers since the ether was usually not isolated and purified in actual syntheses. And in addition, at least in the case of dehydroepiandrosterone, it was found that predominantly one isomer was obtained.

The syntheses of testosterone acyl esters from dehydroepiandrosterone acetate (I) employing (III) to protect the 3-position were carried out as follows.

The stability of the tetrahydropyranyl ether moiety under acylating conditions was established by the preparation of a number of 17-esters of V in excellent yields. A summary of the physical properties of these is given in Table I.

TABLE I

ESTERS OF 5-ANDROSTEN-3β,17β-DIOL 3-(2'-TETRAHYDROPYRANYL) ETHER

Ester	M.p., °C.	$[\alpha]^{25}D$ $CHCl_3$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Benzoate	192–194	−23.5	77.78	77.54	8.85	8.90
β-Cyclopentylpropionate	135–136	−40.4	77.06	77.05	10.12	9.80
Cyclohexylcarboxylate	159–161	−42.1	76.81	76.89	9.98	9.92
Propionate	128–129	−74.4	75.31	75.46	9.83	9.96
β-Phenylpropionate	114–115	−59.9	78.22	78.13	9.15	9.08

We have also treated III with the following steroids: cholesterol, stigmasterol, 5-pregnen-3β-ol-20-one, desoxycorticosterone, testosterone, and 3β-hydroxy-22,22-diphenyl-bisnor-5,20,(22)-choladiene. Results are summarized in Table II.

(1) Presented before the Division of Medicinal Chemistry at the Philadelphia Meeting of the American Chemical Society, April, 1950.

(2) A. Butenandt, *Ber.*, **68**, 1859 (1935).

(3) L. Ruzicka, *Helv. Chim. Acta*, **18**, 1478 (1935).

(4) A. C. Ott and M. F. Murray, Abstracts of 113th A.C.S. Meeting, **17K** (1948).

(5) A. Serini, *Ber.*, **71**, 1766 (1938).

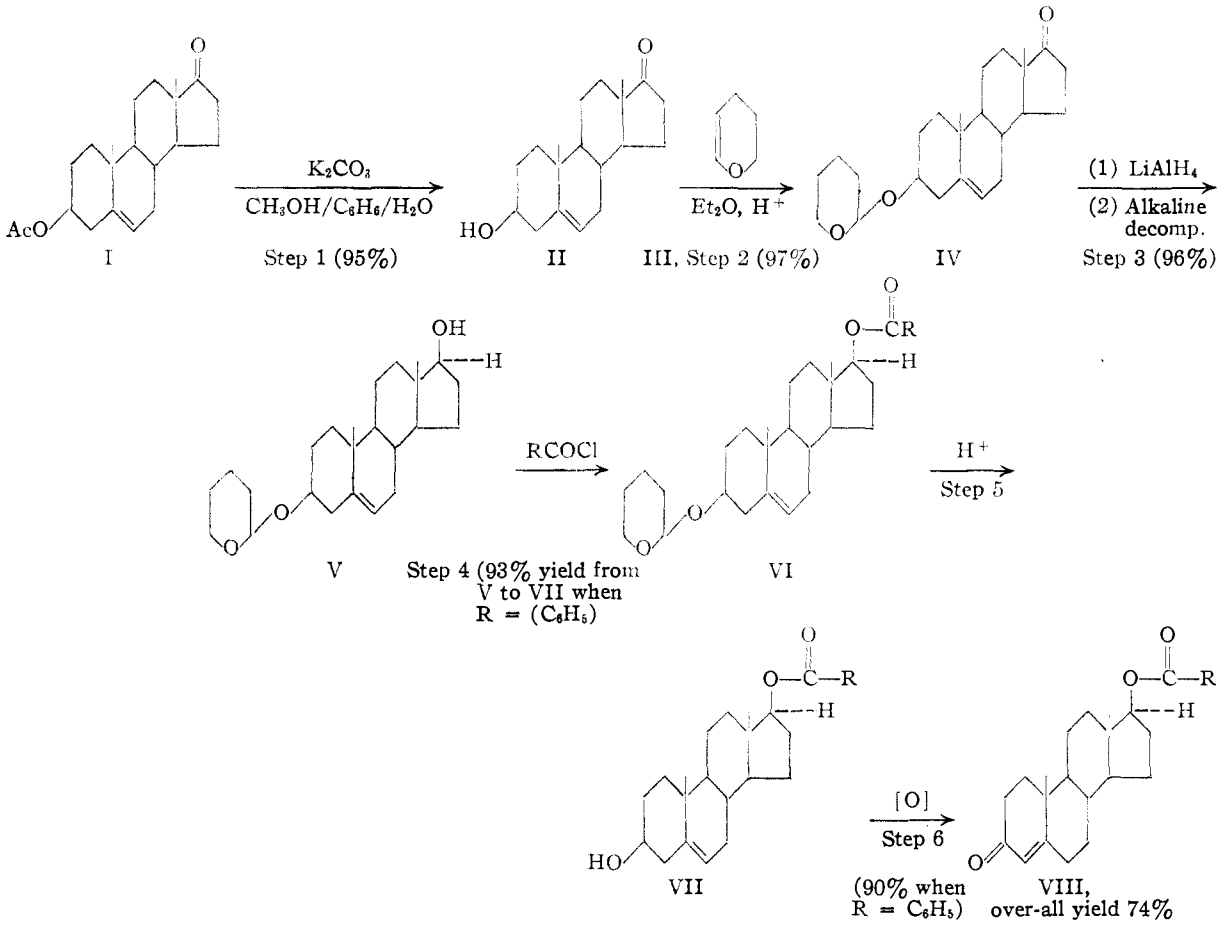
(6) G. Rosenkranz, THIS JOURNAL, **71**, 3689 (1949).

(7) R. Paul, *Bull. soc. chim.*, [5] **1**, 973 (1934).

(8) G. F. Woods and D. N. Kramer, THIS JOURNAL, **69**, 2246 (1947).

(9) W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948).

(10) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).



The respective 2-tetrahydropyranyl ethers were formed by simply dissolving the steroid in diethyl ether or ether–benzene solution of *III*, or in *III* alone as solvent, with subsequent addition of a trace of concentrated hydrochloric acid or *p*-toluenesulfonic acid.

TABLE II

REACTION OF 2,3-DIHYDROPYRAN WITH VARIOUS STEROIDS

Steroid	M.p., °C.	$[\alpha]^{25}D$[a]	2′-Tetrahydropyranyl ether M.p., °C.	$[\alpha]^{25}D$[a]	Yield, %	Analyses, % Carbon Calcd	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Cholesterol	149–150	− 41	154–155	− 23.5	92	81.64	81.50	11.54	11.44
Stigmasterol	168–170	− 50	162–163	− 54.5	85	82.19	82.03	11.36	11.29
5-Pregnen-3β-ol-20-one	188–189	+ 34	129–131	+ 16.7	51	77.96	77.97	10.06	10.08
Desoxycorticosterone	141–142	+ 78	111–112	+183	37	75.32	75.48	9.23	9.11
Dehydroepiandrosterone	144–145	+ 10	192–194	− 71.9	97	77.38	77.06	9.74	9.74
Testosterone	151–152	+109	98–100	+ 75.2	59	77.38	77.71	9.74	9.71
3β-Hydroxy-bisnor-5-cholenic acid, methyl ester	140–142	− 52	134–136	− 48.3	49	75.63	75.54	9.98	9.91
3β-Hydroxy-22,22-diphenyl-bisnor-5,20(22)-choladiene	110–112	+194	175–176	+224	57	85.04	85.27	9.15	9.01

[a] Optical rotations taken in chloroform.

Experimental[11]

Experimental for steps 2, 3, 4, 5 and 6; wherein R = C_6H_5–, illustrates the pertinent chemistry involved.

Preparation of Dehydroepiandrosterone 3-(2′-Tetrahydropyranyl) Ether (IV) (Step 2).—To a solution of 28.10 g. (0.0971 mole) of II in 900 cc. of anhydrous diethyl ether was added 41.2 g. (0.49 mole) of 2,3-dihydropyran (freshly distilled from sodium hydroxide pellets) followed by ten drops of concentrated hydrochloric acid. The contents of the flask were thoroughly mixed and the solution set aside for seven days.

Following this period several pellets of sodium hydroxide were added and the solution filtered. The ether was removed by distillation and the residue dried *in vacuo* overnight at 75°. (This residue or the ether solution thereof was entirely suitable for carrying out further reactions under neutral or basic conditions.) Weight of residue equaled 38.0 g.; theory, 36.5 g. After slurrying the residue with ether there were 35.4 g. (97%) (m.p. 172–174°) which was satisfactory for subsequent work. Recrystallization from acetone yielded beautiful colorless needles, m.p. 192–194°, $[\alpha]^{25}D$ −71.9. *Anal.* Calcd. for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.06; H, 9.74.

Preparation of 5-Androsten-3β,17β-diol 3-(2′-Tetrahydropyranyl) Ether (V) (Step 3).—To a solution of 0.56 g. (0.0148 mole) of lithium aluminum hydride in 75 cc. of an-

(11) All melting points were taken on a Fisher–Johns block. All rotations were taken in chloroform. Analyses and rotations were by Mr. William Struck and staff of our Microanalytical Laboratory.

hydrous diethyl ether was added a solution of 1.96 g. (0.0053 mole) of IV (m.p. 188–190°). After standing a short while the excess lithium aluminum hydride was decomposed by cautious dropwise addition of water. The mixture was then shaken out repeatedly with 5% NaOH, dried over sodium sulfate and filtered. The ether was removed by distillation. The residue weighed 2.03 g.; theory, 1.97 g., m.p. 156–160°. Recrystallization from ethyl alcohol raised the m.p. to 161–162°; yield 96%; $[\alpha]^{24}D$ −64.9. *Anal.* Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.56; H, 10.16.

Preparation of 5-Androsten-3β,17β-diol 3-(2′-Tetrahydropyranyl) Ether, 17-Benzoate (VI) (Step 4).—A solution of 1.87 g. (0.005 mole) of V (m.p. 161–162°) in 10 cc. of dry pyridine (freshly distilled) was cooled in an ice-bath and 0.85 g. (0.006 mole) of benzoyl chloride was added. After standing at room temperature the mixture was poured into ether–chloroform (3:2), and was shaken out with 10% ice-cold Na_2CO_3, cold dilute acetic acid, water, and 5% $NaHCO_3$ solution. The organic layer was then dried over anhydrous Na_2SO_4, treated with charcoal and filtered. The solvent was removed by distillation and the white crystalline residue weighed; wt. 2.5 g., theory, 2.4 g. Triturating with 95% ethyl alcohol gave 2.3 g. (96%) of a product melting at 186–188°. Recrystallization raised the m.p. to 191.5–194°; $[\alpha]^{26}D$ −23.5°. *Anal.* Calcd. for $C_{31}H_{42}O_4$: C, 77.78; H, 8.84. Found: C, 77.51; H, 8.89.

When the preparation of a known 17-acyl ester is desired and the properties of the intermediates are known, it is most practicable to pour the acylated mixture into a mineral acid solution and proceed as in Step 5.

Preparation of 5-Androsten-3β,17β-diol 17-Benzoate (VII) (Step 5).—To a solution of 11.81 g. (0.0247 mole) of VI in 750 cc. of 95% ethyl alcohol were added 40 cc. of water and 10 cc. of concentrated hydrochloric acid. The mixture was heated under reflux with stirring for 1.5 hours. The solution was refrigerated overnight, filtered, washed with cold alcohol and dried; wt. 7.02 g., m.p. 203–207°; yield 74%. From the mother liquors 2.17 g. more of VII, m.p. 196–200°, was obtained bringing the yield to 97%. Recrystallization of a portion from absolute ethyl alcohol raised the m.p. to 218–220° (lit. Butenandt, m.p. 220°). *Anal.* Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.26; H, 8.72.

Preparation of Testosterone Benzoate (VIII) (Step 6).—To a solution of 3.95 g. (0.010 mole) of VII in 300 cc. of toluene and 100 g. of cyclohexanone was added 3.40 g. of freshly distilled aluminum isopropoxide. After heating at 100° for 30 minutes the mixture was cooled, the *p*H adjusted to 7.0 with dilute hydrochloric acid, and then steam distilled until no more ketonic material came off. The mixture was then cooled to room temperature and extracted thoroughly with ether. The combined ether extracts were dried over sodium sulfate, filtered and reduced to dryness. The residue was recrystallized from methanol to give a total of 3.54 g. of testosterone benzoate melting at 191–193°; $[\alpha]^{25}D$ +162. *Anal.* Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.03; H, 8.55.

Cholesterol 3-(2′-Tetrahydropyranyl) Ether (IX).—To a solution of 1.10 g. (0.0028 mole) of cholesterol in 10 cc. of anhydrous, peroxide-free, diethyl ether was added 1.0 g. (0.0119 mole) of 2,3-dihydropyran (freshly distilled from sodium hydroxide pellets) followed by one drop of concentrated hydrochloric acid. The contents of the flask were thoroughly mixed and set aside three days.

The solution was worked up in the manner described for the preparation of IV and the residue recrystallized from isopropyl ether to yield 1.23 g. of VIII, m.p. 154–155°; yield 92%, $[\alpha]^{25}D$ −23.5. *Anal.* Calcd. for $C_{32}H_{54}O_2$: C, 81.64; H, 11.54. Found: C, 81.50; H, 11.44.

Stigmasterol 3-(2′-Tetrahydropyranyl) Ether (X).—Stigmasterol (1.31 g.) (0.00318 mole) was reacted with dihydropyran by the method described for cholesterol. After recrystallization from isopropyl ether, 1.35 g. (85%) of X was obtained, m.p. 162–163°. *Anal.* Calcd. for $C_{34}H_{56}O_2$: C, 82.19; H, 11.36. Found: C, 82.03; H, 11.29; $[\alpha]^{25}D$ −54.5.

3β-Hydroxy-bisnor-5-cholenic Acid Methyl Ester 3-(2′-Tetrahydropyranyl) Ether (XI).—To a solution of 3.60 g. (0.010 mole) of 3β-hydroxy-bisnor-5-cholenic acid, methyl ester in 100 cc. of anhydrous, peroxide-free, diethyl ether and 25 cc. benzene was added one drop concentrated hydrochloric acid, the solution shaken well and allowed to stand three days. After working up in the manner described for the preparation of IV, the residue was recrystallized from isopropyl ether to yield 2.16 g. of XI, m.p. 134–136°; yield 49%, $[\alpha]^{25}D$ −48.3. *Anal.* Calcd. for $C_{28}H_{46}O_4$: C, 75.32; H, 9.23. Found: C, 75.48; H, 9.11.

5-Pregnen-3β-ol-20-one 3-(2′-Tetrahydropyranyl) Ether (XII).—To a solution of 0.948 g. (0.003 mole) of 5-pregnen-3β-ol-20-one in 20 cc. of dihydropyran was added one drop of concentrated hydrochloric acid. After two days at room temperature the mixture was worked up in the usual manner. Recrystallization of the residue from isopropyl ether gave 0.59 g. of XII (51%), m.p. 127–129°. An analytical sample melted at 129–131°; $[\alpha]^{25}D$ +16.7. *Anal.* Calcd. for $C_{26}H_{40}O_3$: C, 77.96; H, 10.06. Found: C, 77.97; H, 10.08.

Desoxycorticosterone 21-(2′-Tetrahydropyranyl) Ether (XIII).—To a solution of 4.95 g. (0.015 mole) of desoxycorticosterone in 50 cc. of dihydropyran cooled to 5° was added four drops of concentrated hydrochloric acid in 6 cc. of diethyl ether. The solution was refrigerated for seven days and then the solvents removed by distillation under reduced pressure. Recrystallization of the resulting residue from isopropyl ether–hexane (2:1) gave 2.28 g. (37%) of XII, m.p. 108–111°. An analytical sample melted at 111–112°, $[\alpha]^{25}D$ +183. *Anal.* Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.23. Found: C, 75.48; H, 9.11.

3β-Hydroxy-22,22-diphenylbisnor-5,20(22)-choladiene 3-(2′-Tetrahydropyranyl) Ether (XIV).—Dihydropyran was treated with 0.912 g. (0.002 mole) of 3β-hydroxy-22,22-diphenyl-bisnor-5,20(22)-choladiene by the method used in the preparation of XIII. Recrystallization of the reaction residue gave 0.74 g. of XIV (57%), m.p. 165–170°. An analytical sample melted at 175–176° (from acetone), $[\alpha]^{25}D$ +224°. *Anal.* Calcd. for $C_{39}H_{50}O_2$: C, 85.04; H, 9.15. Found: C, 85.24; H, 9.04.

Testosterone 17-(2′-Tetrahydropyranyl) Ether (XV).—To a solution of 1.44 g. (0.005 mole) of testosterone in 65 cc. of peroxide-free ether and 1.26 g. (0.015 mole) of dihydropyran was added three drops of a solution prepared by shaking 1.0 g. of toluenesulfonic acid monohydrate in 100 cc. of diethyl ether and allowing to settle. The solution was allowed to stand a total of three weeks during which time 4.5 cc. of a 10% solution of dihydropyran in diethyl ether and three drops of the catalyst solution were added every three days. At the end of three weeks the ether solution was washed with 5% $NaHCO_3$, dried over sodium sulfate, and filtered. The solvent was removed by distillation and the residue recrystallized from isopropyl ether to yield 1.09 g. (58.6%) of XV, m.p. 94–96°. An analytical sample of the material melted at 98–100° (from isopropyl ether), $[\alpha]^{25}D$ +75.2°. *Anal.* Calcd. for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.71; H, 9.71.

5-Androsten-3β,17β-diol 3-(2′-Tetrahydropyranyl) Ether 17-Acyl Esters.—All of the 17-acyl derivatives of 5-androsten-3β,17β-diol 3-(2′-tetrahydropyranyl) ether (compound VI) listed in Table I, with the exception of the propionate were prepared by the method of Step 4.

5-Androsten-3β,17β-diol 3-(2-Tetrahydropyranyl) Ether 17-Propionate.—To a solution of 1.87 g. (0.05 mole) of 5-androsten-3β,17β-diol 3-(2′-tetrahydropyranyl) ether in 10 cc. of dry, freshly distilled pyridine was added 6.5 g. (0.05 mole) of propionic anhydride. The clear solution was allowed to stand six days at room temperature and worked up as in the method used for the preparation of the 17-benzoate. Recrystallization of the residue, obtained from the work-up, from ethyl alcohol gave 2.0 g. (93%) of product, m.p. 128–129°, $[\alpha]^{25}D$ −74.4. *Anal.* Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.46; H, 9.96.

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