at 0° the oily residue partially crystallized. By rapid manipulation with methanol, the crystals could be washed free of oil on a filter, and in this way 135 mg. of crystalline product was obtained, m. p. 55–70°. The material was again leached with methanol and the colorless product was recrystallized from aqueous methanol, giving plates, m. p. 87–88.5°; $[\alpha]^{25.5}D$ −30.8° (±2°, c = 0.287 in 95% ethanol).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 83.99, 84.55; H, 9.74, 9.56.

The substance showed no depression when mixed with a sample of $\Delta^{3,5}$-androstadienone-17 (m. p. 88–89°) prepared by the dehydration of dehydroisoandrosterone according to Burrows, *et al.*[2]

The oxime was prepared by warming 6.5 mg. of the ketone with 20 mg. of hydroxylamine hydrochloride and 20 mg. of anhydrous sodium acetate in 3 cc. of methanol at 60° for two hours and diluting with water. Recrystallized from aqueous methanol, the substance melted at 164–166°, which agrees with the value previously reported.[2]

Anal. Calcd. for $C_{19}H_{27}ON$: C, 79.80; H, 9.55. Found: C, 79.00; H, 9.56.

Summary

Five substances, and a transformation product of one of them, have been isolated from the neutral 17-ketosteroid fraction from the acid-hydrolyzed urine of a girl with a corticoadrenal tumor. Androsterone was found present in small amounts (0.3 mg./l.) corresponding to the level in normal female urine, while the quantity of 3α-hydroxyaetiocholanone-17 isolated (13 mg./l.) is about 10 times the normal amount, and the dehydroisoandrosterone encountered (88 mg./l.) represents approximately a 100-fold increase above normal. About one-third of the total dehydroisoandrosterone had been transformed into 3-chloro-Δ^5-androstenone-17 in the acid hydrolysis. The other two steroids isolated have not been encountered in the urine of normal males or females. One has been identified as $\Delta^{3,5}$-androstadienone-17 (25 mg./l.), which Burrows, Cook, Roe and Warren had isolated from the urine of a male patient having an adrenal tumor. It is suggested that the substance may have been produced in the acid hydrolysis from a precursor of the allylic alcohol type, namely, Δ^4-dehydroisoandrosterone or Δ^4-dehydroandrosterone. The other substance, found present to the extent of 8 mg./l., is a new steroid which has been characterized as a 3α-hydroxyandrostenone-17 with the double bond at either the 6,7-, 7,8-, 9,11-, or 11,12-position. It may arise from an easily dehydrated precursor, for example one with a hydroxyl group at C_{11}.

These and other observations regarding excretory steroids associated with pathological conditions suggest certain tentative inferences concerning steroid metabolism and the possible metabolic production of carcinogens in the body.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS

RECEIVED DECEMBER 21, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 236]

Identification of Organic Compounds. IV. Trityl Ethers of Cellosolves, Carbitols and Related Glycols[1,2]

BY MARGARET K. SEIKEL[3] AND ERNEST H. HUNTRESS

The studies of this Laboratory on the systematic identification of organic compounds have now been extended to the preparation of trityl (*i. e.*, triphenylmethyl) ethers of certain important organic solvents of the classes commonly called "Cellosolves" and Carbitols" and also of related glycols. Previous work on the preparation of solid derivatives of these classes is well summarized and new instances reported in two papers[4] published while the present paper was being written.

The general method of tritylation has here been greatly simplified in comparison with that previously suggested for ethylene glycol,[5,6] methyl cellosolve[7] and cellosolve.[6] For example, ordinary rather than especially dehydrated reagents can be used, the reaction time is shortened to a few minutes, and one recrystallization of the initially crystallized products often suffices for purification.

Detailed methods of procedure are as follows.

(1) For Article II, see THIS JOURNAL, **62**, 750 (1940).

(2) Presented at the Detroit Meeting of the American Chemical Society, September, 1940.

(3) Research Associate in Organic Chemistry, M. I. T.; present address, Wellesley College, Wellesley, Mass.

(4) Mason and Manning, THIS JOURNAL, **62**, 1635–1640, 3136–3169 (1940).

(5) Helferich, Speidel and Toeldte, *Ber.*, **56**, 766–770 (1923).

(6) Hurd and Filachione, THIS JOURNAL, **59**, 1949–1952 (1937).

(7) Nierenstein, *Ber.*, **60** 1821 (1927).

TABLE I

Ether	M. p., °C.	Solvent per g.	Yield, %	Crystal form[i]	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
-trityl ether									
β-Methoxyethyl ("Methyl cellosolve")	105.5–106.0[a]	20 cc. MeOH or 2 cc. 95% alc.	80–85	Hexagons					
β-Ethoxyethyl ("Cellosolve")	79.0–79.5[b]	2–3 cc. MeOH or alc.	80–85	Flat ndls.					
β-Isopropoxyethyl ("Isopropyl cellosolve")	71.0–71.5	5 cc. MeOH	50–60	1–1.5 cm. needles	$C_{24}H_{26}O_2$	83.2	83.0	7.56	7.90
β-Benzyloxyethyl ("Benzyl cellosolve")	76–77	20 cc. MeOH or 10 cc. alc.	50–70	Stocky ndls.	$C_{28}H_{26}O_2$	85.2	85.1	6.64	6.92
β-Phenoxyethyl ("Phenyl cellosolve")	123.5–124	150 cc. MeOH or 50 cc. alc. or 3 cc. acetone	75–85	1.5 cm. thin ndls.	$C_{27}H_{24}O_2$	85.2	84.8	6.36	6.70
β-(*p*-*t*-Butylphenoxy)-ethyl	121.0–121.5	150–200 cc. MeOH or 50–60 cc. alc.	65–70	2.5 cm. ndls.	$C_{31}H_{32}O_2$	85.3	85.5	7.39	7.78
"Methyl carbitol"	58–59	3 cc. MeOH or 5 cc. alc.	55–60	Tiny ndls. or leaflets	$C_{24}H_{28}O_3$	79.5	79.5	7.23	7.46
Ethylene glycol	105.0–105.5[c]		50	Rect. prisms, cubes	$C_{21}H_{20}O_2$	82.9	82.8	6.62	6.68
Diethylene glycol	112.5–113.5		40–60	Granules	$C_{23}H_{24}O_3$	79.3	78.8	6.94	7.17
-ditrityl ether									
Ethylene glycol	187–188[d]	[e]	60–70	Hex. tablets	$C_{40}H_{34}O_2$	87.9	88.0	6.27	6.64
Diethylene glycol	157.5–158	[f]	60–70	Stocky ndls.	$C_{42}H_{38}O_3$	85.4	85.3	6.48	6.82
Triethylene glycol[g]	142.0–142.5	[h]	45–60	Granules	$C_{44}H_{42}O_4$	83.2	82.8	6.67	7.08

[a] 104° recorded in ref. (7). [b] 77–78° recorded in ref. (6). [c] 102–103° recorded in ref. (6). [d] 185–186° recorded in ref. (5). [e] Solubility in 100 cc. 95% alc. is 0.020 g. cold, 0.17 g. hot. [f] Solubility in 100 cc. 95% alc. is 0.031 g. cold, 0.33 g. hot. [g] This ditrityl ether exists in two forms, the stable form melting at 142.0–142.5° and also a labile modification, m. p. 130.5–131.0°, the melting point of the ordinary reaction product depending upon their ratio. The labile low-melting form is converted to the stable higher melting form by heating at 125° and rubbing the gummy residue with acetone; any products with broad melting range (*e. g.* 125–137°) should be so treated. No method of converting the stable form to the labile form has been found, nor can conditions deliberately be controlled to produce only the latter. [h] Solubility in 100 cc. 95% alc. is 0.050 g. cold, 0.41 g. hot. [i] All of the compounds are colorless.

Tritylation of the Ether-Alcohols.—In a 15-cm. test-tube heat for five minutes on a steam-bath a mixture of 0.5 cc. of the ether-alcohol, 0.5 equivalent of trityl chloride, and 1.0 cc. of pyridine. Cool, add water, and induce crystallization of the precipitated oil by scratching, icing, or washing with fresh water. Recrystallize the crude product from the minimum volume of methanol or 95% ethanol using about 2–3 cc./g. if the material is completely miscible.

The tritylation is practically complete after heating for one minute but somewhat longer treatment does no harm. Derivatives of ordinary commercial samples of the cellosolves may thus be obtained but preliminary purification of methyl carbitol is essential.[8] Ordinary pyridine may be used in most cases with only slight diminution of yields. For methyl carbitol, however, anhydrous reagent is imperative, and anhydrous pyridine was used for the work reported in Table I. The crude products from phenyl- and benzyl-cellosolve must be thoroughly washed with water; the gummy crude from β-(*p*-*t*-butylphenoxy)-ethyl alcohol preferably should be extracted with 5 cc. of methanol.

Ditritylation of the Glycols.—Heat 0.10 cc. of ethylene glycol or 0.25 cc. of diethylene glycol or triethylene glycol with *exactly* two equivalents of trityl chloride and 1–2 cc. of pyridine in a 15-cm. test-tube (protected by a calcium chloride tube) for either fifteen minutes in the case of the ethylene and triethylene glycol, or for one hour in the case of the diethylene glycol on a steam-bath. Isolate the product in the usual way and recrystallize the crude directly from acetone (15–30 cc./g.), evaporating the solution to one-half volume before cooling.

(8) For the determination and removal of ethylene glycol from commercial carbitols see Seikel, *Ind. Eng. Chem., Anal. Ed.*, **13**, in press (1941).

Monotritylation of the Glycols.—Heat 0.25 cc. of ethylene glycol or 0.5 cc. of diethylene glycol with 0.5 equivalent of trityl chloride and 1.0 cc. of anhydrous pyridine for five minutes on a steam-bath. Extract the crude products with 95% alcohol (5 cc. for ethylene or 10–15 cc. for diethylene glycol), leaving the insoluble residue of ditrityl ethers (20–30%). After evaporating in an air stream the alcohol solution of monotrityl ethers, recrystallize from methyl or ethyl alcohol (2–3 cc. solvent per gram crude solid) and allow several hours for separation of products.

Impure reactants adversely affect this reaction. Anhydrous pyridine must be employed as otherwise the resultant triphenylcarbinol prevents separation of products. The yields of accompanying ditrityl ethers were peculiarly constant and apparently independent of time, temperature or purity of reactants.

The properties of these trityl ethers, analytical data regarding them, and details as to their methods of preparation are given in Table I. All melting points were taken by the method described in Mulliken's "Identification of Pure Organic Compounds," Vol. I, page 218, on a 360° rod form melting point thermometer immersed in sulfuric acid to the zero point, and are uncorrected.

These trityl ethers exhibit a tendency toward alcoholysis or hydrolysis when their alcohol or dilute alcohol solutions are boiled for a protracted period. In this respect the derivatives of diethylene glycol are much more unstable than those of ethylene glycol.

Alcoholysis Experiments.[9] **"Methyl Cellosolve" Trityl Ether.**—This compound was refluxed for sixteen hours

(9) All products were purified and identified by mixed melting points.

with absolute ethyl alcohol. After evaporation of the solvent and recrystallization of the residue from methanol, 56% of the original material was recovered. From the mother liquors a small amount of triphenylcarbinol ethyl ether was isolated.

"Phenyl Cellosolve" Trityl Ether.—This compound was suspended in absolute ethyl alcohol and refluxed for twenty-two hours. After cooling, 78% of the original material was recovered. From the residue obtained from the mother liquor, a trace of triphenylcarbinol ethyl ether was finally isolated.

"Methyl Carbinol" Trityl Ether.—This product was refluxed for twenty-two hours with absolute ethyl alcohol, the solution evaporated to dryness and the residue extracted with 3–4 drops of cold methanol; the residue represented an 81% yield of triphenylcarbinol ethyl ether. However, when a sample of the derivative was refluxed overnight with 95% alcohol, there was fractionally crystallized from the reaction mixture both triphenylcarbinol (39% yield) and triphenylcarbinol ethyl ether (18% yield). Finally, when refluxed for sixteen hours with 65% alcohol, the solution evaporated to dryness and the residue recrystallized, a 47% yield of triphenylcarbinol was obtained.

Summary

1. The trityl ethers of the cellosolves and the ditrityl ethers of the glycols represent easily prepared, nicely crystalline derivatives for their identification.

2. No purification or dehydration of the reactants is necessary in most cases.

CAMBRIDGE, MASSACHUSETTS RECEIVED OCTOBER 7, 1940

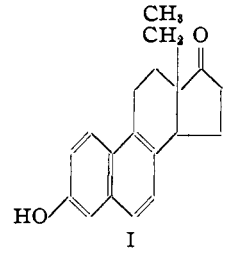
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of Compounds Related to the Sex Hormones. A Homolog of Equilenin Containing an Angular Ethyl Group

BY W. E. BACHMANN AND D. W. HOLMES

All of the sex hormones and apparently all of the other steroids possess an angular methyl group at C_{13} between the C and D rings. We have now replaced the angular methyl group of the sex hormone equilenin by an angular ethyl group in order to determine what effect such a structural change would have on the estrogenic activity of the molecule. Previous studies have demonstrated that changes in the configuration or structure of the equilenin molecule may result in loss of estrogenic activity. Thus, the diastereoisomers[1] of the hormone possess little activity, and removal[2] of the C_3-OH or shifting[3] it to C_6 is accompanied by loss of the estrogenic property.

3-Hydroxy-19-methyl-17-equilenone[4] (I), the homolog of equilenin containing an angular ethyl group, was prepared in *cis* and *trans* forms, both of which are racemic mixtures. For the synthesis of these compounds, the methyl ester of 7-methoxy-1-keto-1,2,3,4-tetrahydro-2-phenanthroic acid (II), an intermediate in the synthesis of equilenin, was used as starting material. The sodio derivative of this compound reacted with ethyl iodide to give III, which was allowed to react with zinc and methyl bromoacetate.



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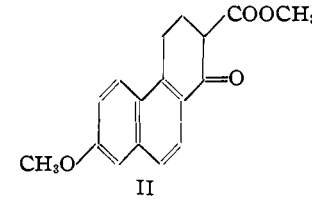

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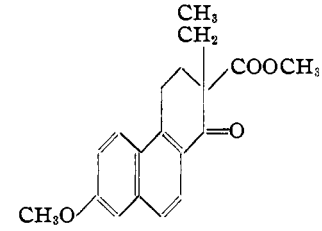
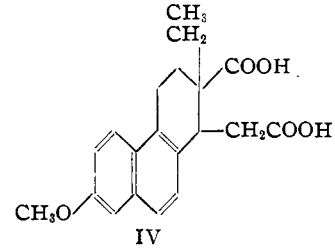


III



IV

The resulting hydroxy ester was dehydrated and hydrolyzed to give the unsaturated acids which were reduced to a mixture of the *cis* and *trans* forms of 7-methoxy-2-ethyl-2-carboxy-1,2,3,4-tet-

(1) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).
(2) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940).
(3) Bachmann and Holmes, *ibid.*, **62**, 2750 (1940).
(4) For the nomenclature employed for these compounds see Reference (2).