Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.18; H, 9.61.

1-Phenyl-3-octyn-2-ol.—A solution of 12 g. of 1-hexyne in 50 ml. of dry ether was added dropwise with stirring to the Grignard reagent prepared from 16.35 g. of ethyl bromide, 3 g. of magnesium turnings and 50 ml. of ether. The reaction mixture was then refluxed for 3 hours, cooled and 8.00 g. of phenylacetaldehyde in 50 ml. of ether was added over 1.5 hours with efficient stirring. The reaction mixture was allowed to stand overnight and then was decomposed by slowly adding it to a solution of 40 g. of ammonium chloride in 150 ml. of water, with external cooling. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried and concentrated *in vacuo*. Distillation of the residue through a short Vigreux column gave 5.37 g. (40%) of 1-phenyl-3-octyn-2-ol, b.p. 116–119° (0.6 mm.). Redistillation of a sample through a semi-micro column gave an analytical sample, b.p. 120–121° (0.77 mm.), $n^{28}D$ 1.5173; $\nu_{max}^{CCl_4}$ 3590(w), 3440(w) and 1030(s) cm.$^{-1}$ (hydroxyl function), and 2180(w) cm.$^{-1}$ (acetylenic bond).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.14; H, 9.00.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. III. Reaction of Dimethyl 3,4-*seco*-A-Homocholestanedicarboxylate with Sodium under Acyloin Conditions[1]

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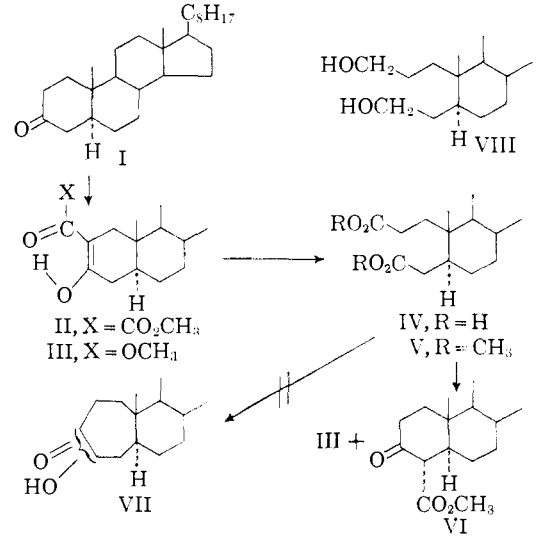
Acylation of cholestan-3-one with dimethyl oxalate gave 2-methoxalylcholestan-3-one which on decarbonylation afforded 2-carbomethoxycholestan-3-one. Treatment of this substance with sodium hydroxide gave 3,4-*seco*-A-homocholestanedicarboxylic acid which was converted to the dimethyl ester. The acyloin condensation of dimethyl 3,4-*seco*-A-homocholestanedicarboxylate using sodium in xylene gave 52% of 2- and 20% of 4-carbomethoxycholestan-3-one.

In connection with the recent work of Gardner, Haynes and Brandon[3] on the formation of Dieckmann reaction products under acyloin conditions, we wish to report our results on the attempted synthesis of a seven-membered ring acyloin in the steroid series. The work described in this paper was undertaken to prepare the cyclic acyloin VII. Similar acyloins in the 19-nor steroid family could serve as intermediates in the synthesis of steroidal tropolones.

Treatment of cholestan-3-one (I) with dimethyl oxalate and sodium methoxide gave, after acidification, 2-methoxalylcholestan-3-one (II) in 85% yield. The structure assigned to the oxalyl derivative II and consequently to the β-keto ester III is based upon the fact that 3-keto steroids belonging to the *trans* series (3-ketoallosteroids) give 2-substituted derivatives in reactions involving intermediate enol formation.[4] The absence of normal ketonic absorption (1700–1725 cm.$^{-1}$ region) in the infrared spectrum of II and the presence of strong bands at 1625 and 1575 cm.$^{-1}$ showed that this compound must be completely enolized.

Pyrolysis of the oxalyl derivative II in the presence of powdered soft glass resulted in the smooth elimination of carbon monoxide and the formation of 2-carbomethoxycholestan-3-one (III) in 66% yield. The infrared spectrum of III showed strong bands at 1660 and 1620 cm.$^{-1}$ characteristic of a chelate structure and also two weak bands at 1740 and 1715 cm.$^{-1}$ indicating[5] that the β-keto ester is not completely enolic. Attempts to prepare III either by direct acylation of cholestan-3-one using dimethyl carbonate and sodium hydride[6] or by acylation of 3-pyrrolidinyl-Δ^2-cholestene[7] using the method of Stork and co-workers[8] were unsuccessful.

Treatment of the β-keto ester III with concentrated sodium hydroxide in refluxing methanol followed by acidification of the reaction mixture gave 92% of 3,4-*seco*-A-homocholestanedicarboxylic acid (IV) which was converted to the dimethyl ester V with diazomethane.



When dimethyl 3,4-*seco*-A-homocholestanedicarboxylate (V) was subjected to the conditions of the

(1) Abstracted from the thesis submitted by Robert N. Schut to the Massachusetts Institute of Technology, 1958, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Public Health Service Research Fellow of the National Cancer Institute, 1955–1958.

(3) P. D. Gardner, G. R. Haynes and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).

(4) (a) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); (b) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938); (c) L. Ruzicka, V. Prelog and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948).

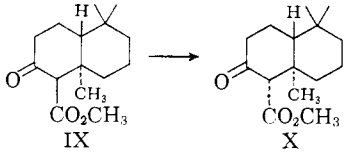
(5) (a) N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Peterson, THIS JOURNAL, **74**, 4070 (1952); (b) E. Wenkert and T. E. Stevens, *ibid.*, **78**, 5627 (1956); (c) O. L. Chapman and J. Meinwald, *J. Org. Chem.*, **23**, 162 (1958).

(6) J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta*, **40**, 1034 (1957).

(7) F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(8) G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).

acyloin reaction[9] (*i.e.*, dispersed sodium in refluxing xylene under high dilution conditions), only Dieckmann condensation products could be isolated. The results of a typical run are described below. The infrared spectrum of the crude mixture showed bands at 1750, 1715, 1660 and 1620 cm.$^{-1}$ indicating the presence of unenolized and enolized β-keto esters. When an ethereal solution of the reaction mixture was shaken with cold 8 *N* sodium hydroxide solution, the sodium salt of the enolized β-keto ester precipitated. Acidification of the salt regenerated the β-keto ester in 52% yield. The identity of this compound with 2-carbomethoxycholestan-3-one (III) obtained from the decarbonylation of II was established by mixed melting point and spectroscopic determinations. Following this separation, the ethereal filtrate was evaporated and the residue chromatographed. The β-keto ester VI was obtained in 20% yield along with a small amount of cholestan-3-one. The formulation of this β-keto ester as 4α-carbomethoxycholestan-3-one is based on the following considerations. The infrared spectrum of VI exhibited bands at 1750 and 1715 cm.$^{-1}$ characteristic of unenolized β-keto esters. The ferric chloride test with VI was negative in contrast with that of III which gave a purple color test. These facts are in keeping with the strong tendency of 3-ketoallosteroids to enolize toward C_2 rather than C_4.[10] When compound VI was treated with potassium *t*-amylate or sodium methoxide in benzene no isomerization occurred; only starting material was recovered. This indicates that the ester grouping is in the stable equatorial conformation and also that the unenolized β-keto ester is not a configurational isomer of 2-carbomethoxycholestan-3-one. Our results are in agreement with the work of Eschenmoser and coworkers[11] who found that the β-ketoester IX (ester group axial) could be isomerized in the presence of potassium *t*-amylate to X (ester group equatorial). Under the same conditions, the β-keto ester X was recovered unchanged. It is of interest



to compare the infrared spectra (Nujol mulls) of these compounds. Compound IX showed bands at 1722 and 1706 cm.$^{-1}$ while with isomer X carbonyl absorption occurred at 1745 and 1707 cm.$^{-1}$. The infrared spectrum of VI (stereochemistry corresponds to X) showed carbonyl absorption at 1740 and 1710 cm.$^{-1}$ in agreement with what would be predicted from Eschenmoser's data.

The reaction of dimethyl 3,4-*seco*-A-homocholestanedicarboxylate (V) with lithium or sodium in liquid ammonia[12] gave an oily product which resisted separation by chromatography and gave anomalous analytical results. In one run a small amount of a crystalline substance was obtained, the physical properties of which corresponded to 3,4-*seco*-A-homocholestane-3,4-diol (VIII). An authentic sample of VIII was prepared by the lithium aluminum hydride reduction of the corresponding diester V.

Experimental[13]

2-Methoxalylcholestan-3-one (II).—A solution of 31.0 g. of cholestan-3-one[14] and 19.2 g. of dimethyl oxalate in 1 l. of anhydrous *t*-butyl alcohol was added to a rapidly stirred solution of 5.6 g. of freshly prepared sodium methoxide in 40 ml. of absolute methanol under a nitrogen atmosphere. The yellow solution was stirred for 3 hours at room temperature and was then allowed to stand overnight. Acidification of the sodium enolate with 400 ml. of cold 5% hydrochloric acid gave 32.1 g. (85%) of a light yellow product, m.p. 104–106°. The material at this point is suitable for the decarbonylation reaction described below. Recrystallization of the product from methanol produced an analytical sample of 2-methoxalylcholestan-3-one, m.p. 106–107°; λ_{max}^{EtOH} 294 mμ (ϵ 8,000); $\nu_{max}^{CCl_4}$ 1740 (s, ester carbonyl), 1625 and 1575 cm.$^{-1}$ (s, conj. carbonyl, chelate structure). The product gives a deep red-brown color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.26; H, 10.56.

2-Carbomethoxycholestan-3-one (III).—The method of Bachmann, Cole and Wilds[15] was used. A 16.0-g. sample of 2-methoxalylcholestan-3-one (II) in a large Pyrex test-tube was placed in an oil-bath preheated to 180°. To the stirred melt was added 2 g. of powdered soft glass. After the initial vigorous evolution of gas, the mixture was heated at 180° for 30 minutes with occasional stirring. The cooled melt was dissolved in benzene and the powdered glass removed by filtration. The oily residue obtained on evaporation of the solvent was triturated with methanol to give 12.4 g. of a yellow amorphous solid which on recrystallization from methanol–acetone yielded 9.97 g. (66%) of III, m.p. 118–122°. Further recrystallization from methanol gave an analytical sample, m.p. 120–123°, $\nu_{max}^{CCl_4}$ 1660 and 1620 cm.$^{-1}$ (s, conj. carbonyl, chelate structure), λ_{max}^{EtOH} 257 mμ (ϵ 8,400). The β-keto ester gives a purple color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.37; H, 10.94.

3,4-*seco*-A-Homocholestanedicarboxylic Acid (IV).—The procedure for the synthesis of IV was adapted from the preparation of pimelic acid.[16] A mixture of 60 ml. of absolute methanol and 20 g. of sodium hydroxide was heated under reflux in an oil-bath and stirred efficiently for 1 hour in order to dissolve most of the base. Then 5.1 g. of 2-carbomethoxycholestan-3-one was added in small portions over a period of 1.5 hours. During this time, 8 g. of sodium hydroxide and 40 ml. of absolute methanol were added concurrently. The resulting mixture was stirred for 5 hours while the temperature of the oil-bath was kept at about 120°. It is important that efficient stirring be maintained in order to prevent the sodium hydroxide and sodium salts from caking on the side of the flask. After cooling the mixture,

(9) S. M. McElvain, "Organic Reactions," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 256.

(10) For an excellent review and discussion of this subject see R. B. Turner, W. R. Meador and R. E. Winkler, THIS JOURNAL, **79**, 4122 (1957).

(11) P. A. Stadler, A. Nechvatal, A. J. Frey and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957).

(12) Sodium in liquid ammonia has found considerable application for the synthesis of five- and six-membered ring acyloins. See, for example, J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, THIS JOURNAL, **75**, 6231 (1953); J. C. Sheehan and W. F. Erman, *ibid.*, **79**, 6050 (1957).

(13) Melting points are uncorrected. The infrared spectra were determined with a Baird or Perkin-Elmer (model 21) spectrophotometer fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m) medium and (w) weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11 MS). The microanalyses were performed by Dr. S. M. Nagy and his associates.

(14) Prepared by the method of L. F. Fieser and X. A. Dominguez, THIS JOURNAL, **75**, 1704 (1953).

(15) W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940).

(16) H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

it was diluted with 200 ml. of water and extracted with ether. The basic aqueous extract was heated on the steam-bath to remove the remaining organic solvents, cooled to 20° and acidified with concentrated hydrochloric acid giving 4.8 g. (92%) of a white powder, m.p. 237–238° dec. Recrystallization of the diacid from acetic acid–water (3:1) gave an analytical sample of 3,4-*seco*-A-homocholestanedicarboxylic acid, m.p. 234–235° dec.; ν_{max}^{KBr} 3400–2600 (m, hydroxyl of carboxylic acid), 1700 (s, carboxyl carbonyl) and 930 cm.$^{-1}$ (w, carboxylic acid dimer).

Anal. Calcd. for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.84; H, 10.63.

Treatment of the diacid with an excess of ethereal diazomethane gave 87% of the crude diester as a viscous oil. Chromatographic purification of this material on Merck acid-washed alumina using hexane–benzene (1:1) as the eluent gave 60% of **dimethyl 3,4-*seco*-A-homocholestanedicarboxylate (V)**, m.p. 55–57°. The analytical sample, obtained from methanol, melted at 56–57°, $\nu_{max}^{CCl_4}$ 1735 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{30}H_{52}O_4$: C, 75.58; H, 11.00. Found: C, 75.87; H, 10.95.

Reaction of Dimethyl 3,4-*seco*-A-Homocholestanedicarboxylate (V) under Acyloin Conditions.—To a 500-ml. Morton flask equipped with a Vibro-Mischer stainless steel stirrer, high dilution cycle and nitrogen system was added 10 ml. of a 1.8 *M* sodium dispersion in xylene. The dispersion was diluted with 125 ml. of anhydrous xylene and the mixture was heated under reflux while the sodium was kept dispersed by means of the Vibro-Mischer. When the xylene was refluxing efficiently through the high dilution cycle (aided by a stream of nitrogen passing through the system), a solution of 2.10 g. (4.4 mmoles) of dimethyl 3,4-*seco*-A-homocholestanedicarboxylate in 125 ml. of anhydrous xylene was added over an 11-hour period. Stirring was continued for 30 minutes after which the mixture was cooled and acidified slowly with a solution of 10 ml. of acetic acid in 40 ml. of anhydrous ether. The insoluble material was removed by filtration and washed with ether. After distillation of the solvents under reduced pressure, there was obtained 2.2 g. of yellow oil which partially solidified. The infrared spectrum of the material showed the presence of enolized and unenolized β-keto esters.

The crude mixture was dissolved in ether and shaken with cold 8 *N* sodium hydroxide solution. The precipitated yellow salt was collected and washed well with ether. The ether layer of the filtrate was separated and washed with water in order to remove traces of base. After drying and evaporation of the solvent there remained 0.80 g. of a yellow solid which was chromatographed on Merck acid-washed alumina. Elution with hexane–benzene (4:1) gave 0.04 g. (2%) of a white solid, m.p. 127–128° after one recrystallization from methanol. The material was identified as cholestan-3-one by a mixed melting point determination and comparison of infrared spectra. Further elution with hexane–benzene (1:1) gave 0.39 g. (20%) of the unenolized β-keto ester VI, m.p. 169–171°. Recrystallization of this material from ether produced an analytical sample, m.p. 170–172°, ν_{max}^{Nujol} 1740 (s, ester carbonyl) and 1710 cm.$^{-1}$ (s, ketone carbonyl). This β-keto ester showed no ultraviolet absorption and gave a negative ferric chloride test.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.52; H, 10.91.

The aforementioned sodium salt was suspended in ether and acidified with 5% hydrochloric acid. The ethereal solution was washed with water, dried and evaporated to give 1.02 g. (52%) of a light yellow solid which produced a purple color in alcoholic ferric chloride solution. After three recrystallizations from methanol–ethyl acetate, the product melted at 125–126°, $\nu_{max}^{CCl_4}$ 1660 and 1620 cm.$^{-1}$ with weak absorption at 1740 and 1715 cm.$^{-1}$ (normal ester and ketone carbonyls), λ_{max}^{EtOH} 257 mμ (ε 9,000).

Since the product from the decarbonylation of II had a different melting point (120–123°) when recrystallized from methanol, it was converted to the sodium salt and then regenerated according to the above procedure. Recrystallization of the product from methanol–ethyl acetate gave crystals, m.p. 125–126°, which showed no depression in melting point on admixture with a sample of the Dieckmann condensation product.

Isomerization Experiments.—To a solution of 10 ml. of anhydrous benzene and 2 ml. of anhydrous *t*-amyl alcohol under a nitrogen atmosphere was added 20 mg. of freshly cut potassium. When the reaction was complete, 21 mg. of the unenolized β-keto ester VI in 2 ml. of benzene was added and after 2 hours at room temperature, ether and water were added, the mixture was acidified with dilute hydrochloric acid, the ethereal extracts were washed with water, dried and concentrated. The residue (35 mg.) gave a negative ferric chloride test. Recrystallization of the material from ether yielded 6 mg. of white needles, m.p. 169–172°, which showed no depression in melting point on admixture with a sample of the starting material.

In a similar experiment 52 mg. of the β-keto ester VI was added to a suspension of 0.5 g. of freshly prepared sodium methoxide in 25 ml. of anhydrous benzene and the mixture was heated under reflux for 6 hours. After the usual work-up procedure, starting material was recovered in 87% yield.

Hydrolysis of the β-Keto Esters.—A mixture of 100 mg. (0.25 mmole) of 4α-carbomethoxycholestan-3-one (VI), 10 ml. of methanol and 2 ml. of 20% potassium hydroxide solution was heated under reflux for 5 hours. After removal of the methanol, water and ether were added, the ethereal extract was washed with water, dried and concentrated to give 60 mg. of a white solid. Recrystallization from methanol afforded 23 mg. of white powder, m.p. 127–128°. The mixed melting point with authentic cholestan-3-one was 127–129°. The basic extracts were acidified with concentrated hydrochloric acid and the resulting white precipitate was filtered, washed with water and dried. The white powder (27 mg.), m.p. 233–235° dec., was soluble in sodium bicarbonate solution and was shown by mixed melting point and spectroscopic determinations to be 3,4-*seco*-A-homocholestanedicarboxylic acid.

Under similar conditions 200 mg. of 2-carbomethoxycholestan-3-one (III) yielded 42 mg. of cholestan-3-one; no dicarboxylic acid was isolated.

3,4-*seco*-A-Homocholestane-3,4-diol (VIII).—A solution of 3.30 g. of dimethyl 3,4-*seco*-A-homocholestanedicarboxylate in 200 ml. of anhydrous ether was added with stirring over a 30-minute period to a slurry of 3 g. of lithium aluminum hydride and 100 ml. of ether. After stirring the mixture for an additional hour, water (50 ml.) was added cautiously followed by excess dilute sulfuric acid. A portion of the product which crystallized at this point was collected on a filter giving 1.12 g. of VIII, m.p. 158–159°. The ether solution, containing the remainder of the product, was washed with water, dried over magnesium sulfate and concentrated. Crystallization of the residue from methanol gave 0.48 g. of VIII, m.p. 158–161°, total yield 55%. The analytical sample was crystallized from benzene–petroleum ether, m.p. 161–162°.

Anal. Calcd. for $C_{28}H_{52}O_2$: C, 79.93; H, 12.46. Found: C, 79.66; H, 12.27.

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