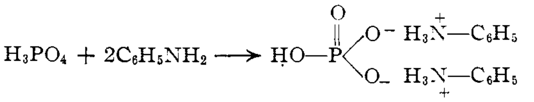
phosphate ion becomes positive, and phosphoric acid can be isolated as its dianilinium salt.

$$^{-}OP(O)(OR)_2 + 3HCl \longrightarrow H_3PO_4 + 2RCl + Cl^-$$



$$H_3PO_4 + 2C_6H_5NH_2 \longrightarrow HO-\overset{O}{\overset{\|}{P}}\begin{matrix}O^- \; H_3\overset{+}{N}-C_6H_5 \\ O^- \; H_3\underset{+}{N}-C_6H_5\end{matrix}$$

Experimental

The Preparation of the Esters.—Dimethyl and diethyl trichloromethylphosphonate were prepared by the interaction of carbon tetrachloride with the respective trialkyl phosphite.[2e]

Alkaline Hydrolysis of Diethyl Trichloromethylphosphonate.—A solution of the ester (2.5 g.) and potassium hydroxide (2.8 g.) in 30 ml. of ethanol was refluxed for two hours. Aliquot portions of the hydrolysate were treated as follows: (a) Aniline was added and the solution was heated. There was no odor of phenyl isonitrile. Heating a mixture of the original ester, potassium hydroxide and aniline, however, produces the isonitrile odor immediately.

(b) Hydrochloric acid was added, followed by magnesium metal. After the evolution of hydrogen had ceased, chromotropic acid (4,5-dihydroxy-2,7-naphthalenedisulfonic acid, disodium salt) and sulfuric acid were added. The formation of a pink-violet color indicated the presence of formaldehyde in the hydrolysate. The color was only observed if the hydrolysate was first reduced with the magnesium–acid combination (reduction of formic acid to formaldehyde).[11]

(c) Acidification with nitric acid, followed by silver nitrate, gave an immediate precipitate of silver chloride.

(d) Nitric acid and an ammonium molybdate solution were added. There was no evidence of precipitation.

The remaining alkaline hydrolysate was then refluxed with hydrochloric acid for six hours. The hot solution was treated with charcoal, filtered, and the filtrate was evaporated to dryness. The residual material, A, immediately gave a precipitate of yellow phosphomolybdate when it was treated as in (d) above.

Treatment of an ethereal extract of the above residue, A, with aniline, produced dianilinium phosphate (platelets from abs. ethanol, m.p. 182–183° dec.). The salt had the correct phosphorus content (10.8%) and neutralization equivalent (141) as compared to an authentic sample.[2e]

Saponification Equivalents.—Ten ml. of a standard ethanolic potassium hydroxide solution (3 g. of KOH in 100 ml. of 95% ethanol) were pipetted into an empty flask and into a flask containing the ester or chloroform (b.p. 61.5°). Both solutions were refluxed for two hours and then titrated with a standard hydrochloric acid solution. The difference between the two titration values was indicative of the actual base consumed.

TABLE I

SAPONIFICATION EQUIVALENTS (TWO HOURS AT 80°)

Compound	Mol. wt.	Saponification equivalent Calcd.	Saponification equivalent Observed
$CHCl_3$	119.4	34.12	35.01, 35.04
$(CH_3O)_2(O)PCCl_3$	227.4	50.54	53.5, 54.6, 56.0
$(C_2H_5O)_2(O)PCCl_3$	255.5	56.77	57.3, 58.6, 59.2

The observed values, in all cases, are greater than the calculated. This could be due to either (a) a slight loss of the volatile chloroform during the hydrolysis, or (b) an incomplete hydrolysis, or both. Plimmer and Burch,[6] for example, found that the hydrolysis of only one ethyl group is only 92% complete in triethyl phosphate after 30 hours treatment with 2 *N* alkali. This resistance of triethyl phosphate toward alkaline hydrolytic agents was confirmed by subjecting it to the same hydrolytic conditions as described in Table I; it was only 20% hydrolyzed.

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[11] F. Feigl, "Spot Tests," Vol. 2, 4th Ed., Elsevier Publishing Co., Houston, Texas, 1954, pp. 245–246.

Steroidal Cyclic Ketals. XVII.[1] The Synthesis of 6β-Hydroxyprogesterone

BY SEYMOUR BERNSTEIN, WILLIAM S. ALLEN, CARL E. LINDEN AND JASPER CLEMENTE

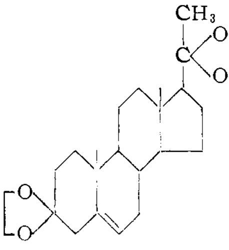
RECEIVED SEPTEMBER 2, 1955

Treatment of cholesterol with osmium tetroxide has been reported to produce an 81% yield of cholestane-3β,5,6α-triol.[2] Thus a stereospecific attack occurred on the rear-side of the molecule. No mention was made in this work of the possible formation of coprostane-3β,5,6β-triol. The formation of the latter would require a frontal attack. With this work in mind it was decided to study the reaction of a Δ⁵-3-ketal (in particular, the bis-ethylene ketal I of progesterone) with osmium tetroxide. The results obtained form the basis of this report.

The bis-ethylene ketal I of progesterone on reaction with osmium tetroxide gave in approximately 50% yield pregnane-5,6β-diol-3,20-dione 3,20-bis-ethylene ketal (II). (The structure of the latter was proven by a subsequent transformation (*vide infra*).) No allopregnane-5,6α-diol-3,20-dione 3,20-bis-ethylene ketal could be isolated. Nevertheless, it is apparent that a 3-ethylene ketal grouping has an important influence on the stereochemistry of osmylation of a Δ⁵-double bond.

Subsequent hydrolysis of the 5,6β-diol II with 90% (v./v.) acetic acid afforded in 65% yield the known Δ⁴-pregnene-6β-ol-3,20-dione (6β-hydroxyprogesterone) (III).[3] Hydrolysis with glacial acetic acid gave a 60% yield of III. These transformations represented a novel synthesis of the latter.

Hydrolysis of the 5,6β-diol II in methanol with 8% (v./v.) sulfuric acid resulted in the known allopregnane-3,6,20-trione (IV).[3] The rearrangement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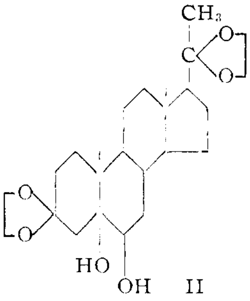
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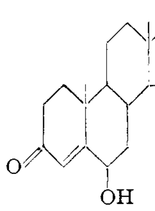
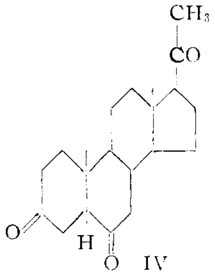

III


IV

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[1] Paper XVI, S. Bernstein, M. Heller and S. M. Stolar, THIS JOURNAL, **77**, 5327 (1955).

[2] V. Prelog and E. Tagmann, *Helv. Chim. Acta*, **27**, 1867 (1944); see also, M. I. Uschakow and A. I. Tjutenberg, *Chem. Zentr.*, **110, II**, 4489 (1939); R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 130 (1942).

[3] C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1587 (1952); C. Amendola, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954).

of a 6β-ol-Δ^4-3-one under acid conditions has been described.[3]

Acknowledgment.—We are indebted to Messrs. Louis M. Brancone and Samuel S. Modes for the microanalytical data, and to Messrs. William Fulmor and George Morton and Miss Anne Callaghan for the optical rotation data and the infrared absorption spectra.

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotation.—The rotations are for chloroform solution at 24–25°.

Absorption Spectra.—The ultraviolet absorption spectra were determined in absolute alcohol with a Beckman spectrophotometer (model DU). The infrared absorption spectra (pressed potassium bromide) were determined with a Perkin–Elmer spectrophotometer (model 21).

Petroleum Ether.—The fraction used had b.p. 60–70° (Skellysolve B).

All evaporations were carried out under reduced pressure.

Pregnane-5,6β-diol-3,20-dione 3,20-Bis-ethylene Ketal (II).—A solution of Δ^5-pregnene-3,20-dione 3,20-bis-ethylene ketal (I, 3 g. (7.46 millimoles)) in benzene (80 ml.) and pyridine (2.5 ml.) was treated with osmium tetroxide (2 g. (8.0 millimoles)), and the mixture was allowed to stand at room temperature for 36 hours. The osmate ester was then decomposed by being stirred for 4 hours with sodium sulfite (12.4 g.), potassium bicarbonate (12.4 g.), water (120 ml.) and methanol (40 ml.). The precipitate was separated by filtration, and washed with hot chloroform (1 liter). The filtrate and chloroform washings were combined, and the organic layer was separated. The extract was washed with saturated saline, dried and evaporated. The residue was crystallized from acetone–petroleum ether to furnish 1.59 g. (49%) of the diol, m.p. 195–196°. Recrystallization from the same solvent pair did not change the m.p.; $\lambda_{\max}$ none; $\nu_{\max}^{\mathrm{KBr}}$ 3700 and 1058 cm.$^{-1}$; $[\alpha]_D$ +28° (c 1.07).

Anal. Calcd. for $C_{25}H_{40}O_6$ (436.57): C, 68.77; H, 9.24. Found: C, 68.51; H, 9.40.

The mother liquor on concentration afforded two further fractions of solid, 0.55 g., m.p. 158–173°, and 0.48 g., m.p. 143–163°, which were combined. Attempts to purify this material by recrystallization were unsuccessful. Likewise chromatography (alumina or silica gel), and partition chromatography (Celite) failed to resolve the mixture. The latter afforded two fractions in order of increasing polarity; 0.44 g., m.p. 162.5–170°, $\nu_{\max}^{\mathrm{KBr}}$ 3597 and 1058 cm.$^{-1}$ (infrared spectrum very similar but not identical with that of the 5,6β-diol II); and 20 mg., m.p. 125–127°; $\nu_{\max}^{\mathrm{KBr}}$ 3610, 1718 (strong) and 1058 cm.$^{-1}$. Recrystallization of the less polar fraction did not sharpen the m.p. The presence of ketonic material in the more polar fraction may be ascribed to inadvertent hydrolysis, or may possibly have been a trace impurity in the starting material I.

Δ^4-Pregnene-6β-ol-3,20-dione (III).[4]—A solution of the 5,6β-diol II (0.35 g.) in 90% (v./v.) acetic acid (10 ml.) was heated on a steam-bath for 2 hours. Cold water was added, and the cloudy mixture was neutralized with a saturated potassium hydroxide solution. Chilling gave crystals which were collected, and washed well with water. This afforded 171 mg. (65%) of crude III, m.p. 162–168°. Recrystallization from acetone–petroleum ether raised the m.p. to 178.5–180.5°, $\lambda_{\max}$ 236–237 mμ (ε 13,500), $[\alpha]_D$ +103° (c 1.095). Its infrared absorption spectrum was identical to that of an authentic sample.[5]

Allopregnane-3,6,20-trione (IV).[6]—A solution of the 5,6β-diol II (0.5 g.) in methanol (30 ml.) containing 8% (v./v.) sulfuric acid (5 ml.) was refluxed for 2 hours. It was poured into ice-water, and the mixture was neutralized with solid sodium bicarbonate. The resulting crystalline product was collected by filtration. Recrystallization from acetone gave 193 mg., m.p. 237–240°. Concentration of the mother liquor furnished an additional 66 mg., m.p. 232–235°, for a total "crude" yield of 67%. Recrystallization of the first crop from acetone–petroleum ether raised the m.p. to 239.5–242°; $\lambda_{\max}$ none; $\nu_{\max}^{\mathrm{KBr}}$ 1710 and 1695 (shoulder) cm.$^{-1}$ $[\alpha]_D$ +62° (c 1.263).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 76.02; H, 9.24.

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[4] C. P. Balant and M. Ehrenstein, ref. 3, report m.p. 178–179°, $\lambda_{\max}^{\mathrm{alc.}}$ 235.5 mμ (ε 12,390), $[\alpha]^{28}\mathrm{D}$ +106.8° (chloroform); C. Amendola, G. Rosenkranz and F. Sondheimer, ref. 3, give m.p. 179–180°, $\lambda_{\max}^{\mathrm{alc.}}$ 236 mμ (ε 13,600), $[\alpha]^{20}\mathrm{D}$ +105° (chloroform).

[5] We are indebted to Dr. T. F. Gallagher of the Sloan–Kettering Institute for this spectral comparison.

[6] C. P. Balant and M. Ehrenstein, ref. 3, give m.p. 232.5–233°, $[\alpha]^{28}\mathrm{D}$ +61.0° (chloroform); C. Amendola, G. Rosenkranz and F. Sondheimer, ref. 3, found m.p. 231–233°. $[\alpha]$?D +65° (dioxane).

The Reaction of Dithiocarbamates with Acrylamide

By Charles M. Buess

Received August 29, 1955

In a study of Michael-type reactions, the action of substituted dithiocarbamates on acrylamide was investigated in an attempt to prepare a series of substituted carbamoylethyl dithiocarbamates (II, equation 2 below). The proposed sequence of reactions was

$$R_1R_2NH + CS_2 + B \longrightarrow R_1R_2NCS_2^{-}BH^{+}\ (I) \qquad (1)$$

$$I + CH_2{=}CHCONH_2 \longrightarrow R_1R_2NCS_2CH_2CH_2CONH_2\ (II) + B \qquad (2)$$

The dithiocarbamates were readily prepared according to equation 1. As the reaction of the second equation probably initially involves attack by the anion of the dithiocarbamate salt, I, on the β-carbon atom of acrylamide, the base, B, must be strong enough that the salts have sufficient ionic character. Pyridinium salts of the substituted dithiocarbamates, for example, react sluggishly if at all. On the other hand, when B is too strong a base, it can interact with the products, II, resulting in undesired side-reactions.

Triethylamine, which is a base of the proper strength, was chosen for this study. Being a tertiary amine, it cannot add to acrylamide, as some of the primary and secondary amines, R_1R_2NH, used in the preparation of the dithiocarbamates, were found to do under the conditions of the reaction. Triethylamine, therefore, may be used in excess so that the formation of the salts by equation 1 is essentially complete and there is no need for isolating these salts prior to the addition of acrylamide. Furthermore, triethylamine is a stronger base than most of the primary and secondary amines employed so that there is little tendency for the latter to function as the base B in the formation of the salts. With the exception of the experiments using aromatic amines as R_1R_2NH, the formation of the salts was observed to be rapid with the evolution of heat. If desired, most of the triethylammonium dithiocarbamates may be isolated (see Experimental, Triethylammonium Benzyldithiocarbamate). The dithiocarbamates from secondary amines, such as morpholinium morpholinodithioformate, may be heated in water or alcohol without inducing serious decomposition, but those from primary amines are less stable.

The amines, R_1R_2NH, used included aliphatic,