free hydroxyl band; found: C, 73.24; H, 8.88). The presently described procedure is equally applicable to the steroidal sapogenins as exemplified by the performic acid oxidation of $\Delta^{7,9(11)}$-22-isoallospirostadien-3β-ol acetate[3] to 9α,11α-oxido-22-isoallospirostan-3β-ol-7-one acetate (m.p. 295–297°, $[\alpha]^{20}D$ −128° ($CHCl_3$), $\lambda_{max.}^{nujol}$ 1736 and 1718 cm.$^{-1}$; found: C, 71.74; H, 8.94). Analogous transformations of this oxidoketone to 11-oxygenated 22-isoallospirostan-3β-ols have already been completed and will be reported shortly in a detailed paper.

Since the starting diol (I)[5] has been prepared from both diosgenin[3,4] and Δ^5-pregnen-3β-ol-20-one[4] (which is also available from stigmasterol), the above described experiments constitute the conversion of the two most abundant plant steroids into 11-oxygenated pregnane derivatives.

RESEARCH LABORATORIES
SYNTEX, S. A.
LAGUNA MAYRAN 413
MEXICO CITY 17, D. F.
GILBERT STORK[9]
J. ROMO
G. ROSENKRANZ
CARL DJERASSI

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(9) Department of Chemistry, Harvard University, Cambridge, Massachusetts.

ACYLALKYLCARBONATES AS ACYLATING AGENTS FOR THE SYNTHESIS OF PEPTIDES

Sir:

Mixed anhydrides of carbonic with carboxylic acids have been found to be excellent acylating agents for the preparation of amides. In particular, anhydrides between branched chain alkyl carbonic acids and N-substituted amino acids or peptides react readily at low temperature with amino acid or peptide esters, or with a salt of an amino acid, to give the corresponding peptide or higher peptide in good yield. The by-products of the reaction, carbon dioxide and an alcohol, are readily removed and the peptide is obtained initially in a very high state of purity.

For peptide synthesis, the over-all reaction is given by

$$\text{X-NHCH(R)COOCOOR}''' + \text{H}_2\text{NCH(R')COOR}'' \longrightarrow \text{X-NHCH(R)CONHCH(R')COOR}'' + \text{R}'''\text{OH} + \text{CO}_2\uparrow$$

where X is a blocking group, R and R′ are amino-acid residues and R″ is an esterifying or salt forming group. Best results have been obtained when R‴ is a *s*- or isobutyl radical.

The mixed anhydrides are formed by treating *s*- or isobutylchlorocarbonate with a solution of the triethylamine salt of an N-substituted aminoacid or peptide in an inert solvent as toluene or chloroform at 0 to −10°. The reaction is complete in 25–30 minutes. A solution of the amino acid or peptide ester to be acylated, also in an inert solvent, is then added and the reaction mixture is allowed to warm to room temperature and stand overnight. Carbon dioxide evolution begins immediately upon addition of the base and is substantially complete after several hours. In some cases, the formed N-substituted peptide ester crystallizes directly from the reaction mixture and is essentially pure after washing with water to remove triethylamine hydrochloride. More generally, the reaction mixture is washed with water and with dilute sodium bicarbonate solution, dried and diluted with petroleum ether to crystallize the product.

Amino acids may be used in this procedure by preparing a solution in one equivalent of 2 *N* alkali and adding this to the preformed mixed anhydride. The heterogeneous mixture is then stirred rapidly for 1–2 hours and the aqueous phase is separated, extracted with ether and acidified to precipitate the formed peptide acid.

In general, *s*-butylchlorocarbonate gave slightly higher yields than the isobutyl isomer. Peptide ethyl esters prepared using these reagents to form the reactive mixed anhydrides include those of carbobenzoxyglycyl-L-tyrosine[1] (68%); m.p. 129–130°, $[\alpha]^{24}D$ +19.3° (*c* = 10, ethanol); dicarbobenzoxy-L-lysylglycine[2] (64%), m.p. 89–90°, $[\alpha]^{24}D$ −12.0° (*c* = 4, ethanol); carbobenzoxy-L-leucyl-L-tyrosine[3] (63%), m.p. 116–118°, $[\alpha]^{24}D$ −14.9° (*c* = 10, ethanol); phthalylglycyl-L-leucine[3] (61%), m.p. 142–143°, $[\alpha]^{24}D$ −23.2° (*c* = 5, ethanol); carbobenzoxyglycyl-DL-phenylalanylglycine[3] (83%), m.p. 134–135° (from carbobenzoxyglycyl-DL-phenylalanine and ethyl glycinate); phthalyl-DL-phenylalanylglycylglycine[3] (67%), m.p. 164–165° (from phthalyl-DL-phenylalanine and ethyl glycylglycinate) and carbobenzoxyglycyl-DL-phenylalanyl-DL-phenylalanylglycylglycine[3] (59%), m.p. 188–193° (from carbobenzoxyglycyl-DL-phenylalanine and ethyl DL-phenylalanylglycylglycinate).

Peptide acids prepared by the free aminoacid procedure include carbobenzoxyglycyl-DL-phenylalanine[4] (63%), m.p. 160–162°; carbobenzoxyglycyl-DL-valine[5] (49%), m.p. 127–128° and 146–147° and carbobenzoxy-DL-alanyl-DL-phenylalanine[5] (50%), m.p. 145–146°.

ADDED IN PROOF. We have just received a publication by R. A. Boissonnas (*Helv. Chim. Acta*, **34**, 874 (1951)) on this same general subject matter.

(1) M. Bergmann and J. S. Fruton, *J. Biol. Chem.*, **118**, 405 (1937).
(2) M. Bergmann, *et al.*, *Z. physiol. Chem.*, **224**, 26 (1934).
(3) Carbon, hydrogen and nitrogen analysis was satisfactory.
(4) H. Neurath, *et al.*, *J. Biol. Chem.*, **170**, 221 (1947).
(5) T. Wieland and R. Sehring, *Ann.*, **519**, 122 (1950).

CHEMOTHERAPY DIVISION
STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY
STAMFORD, CONNECTICUT
JAMES R. VAUGHAN, JR.

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THE TOTAL SYNTHESIS OF SOME NATURALLY OCCURRING STEROIDS

Sir:

We have resolved methyl *dl*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate[1] by the following method. Reduction of the keto-ester with sodium borohydride in ethanol gave a mixture of the corresponding 3-α and 3-β-hydroxy-esters. Treatment with excess digitonin,[2] followed by decomposition of the precipitated complex, gave material enriched in the desired *d*-3-β-hydroxy-ester. Further resolution was achieved by two repetitions of this procedure, and

(1) Woodward, Sondheimer, Taub, Heusler and McLamore, THIS JOURNAL, **73**, 2403 (1951).
(2) *Cf.* Windaus, Klänhardt and Weinhold, *Z. physiol. Chem.*, **126**, 308 (1923).

the product was oxidized by the Oppenauer method. Chromatographic purification of the resulting impure keto-ester, followed by several crystallizations, then furnished pure methyl *d*-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate, m.p. 188–191°, $[\alpha]_D$ + 182° ±5° ($CHCl_3$). This keto-ester has been obtained by the degradation of Compound F[1], and had m.p. 187–191°, $[\alpha]_D$ +177 ±5° ($CHCl_3$); mixed m.p. showed no depression.

Hydrogenation of the *d*-keto-ester with platinum in acetic acid, and oxidation of the resulting saturated product with chromium trioxide in acetic acid, gave a mixture from which methyl 3-ketoetioallocholanate (I), m.p. 177–180°, was isolated after chromatography and crystallization. An authentic sample of (I)[3,4] had m.p. 178–180°, and there was no depression in m.p. on admixture. The infrared spectra of the two samples were also identical.

The saturated keto-ester (I) has previously been converted to the Δ^4-compound,[4] which we have now hydrolyzed to the free acid, 3-keto-Δ^4-etiocholenic acid, m.p. 240–243°. In view of the conversion of the latter to desoxycorticosterone,[5] and progesterone,[6] this reaction sequence constitutes a total synthesis of these hormones.

Alkaline hydrolysis of the keto-ester (I) has given us the corresponding acid, 3-ketoetioallocholanic acid, m.p. 256–259°, which has previously been transformed into methyl 3-α-acetoxyetiallocholanate.[7] This compound has been converted to androsterone,[8] which in turn has been transformed *via* androstanedione[9] into androstenedione,[10] and thence into testosterone.[11] The conversion of progesterone to androstanedione has also been described,[12] and this constitutes another route to testosterone.

(3) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

(4) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

(5) Wilds and Shunk, *ibid.*, **70**, 2427 (1948).

(6) Riegel and Prout, *J. Org. Chem.*, **13**, 933 (1948); Reichstein and Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(7) Plattner and Fürst, *ibid.*, **26**, 2266 (1943).

(8) Dalmer, v. Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935).

(9) Butenandt and Tscherning, *Z. physiol. Chem.*, **229**, 185 (1934).

(10) Djerassi and Scholz, *J. Org. Chem.*, **13**, 697 (1948); Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(11) *Inter al.*, Miescher and Fischer, *Helv. Chim. Acta*, **22**, 158 (1939).

(12) Marker, Kamm, Jones and Oakwood, THIS JOURNAL, **59**, 614 (1937).

CONVERSE MEMORIAL LABORATORY R. B. WOODWARD
HARVARD UNIVERSITY FRANZ SONDHEIMER
CAMBRIDGE 38, MASSACHUSETTS DAVID TAUB

RECEIVED MAY 27, 1951

THE TOTAL SYNTHESIS OF CHOLESTEROL

Sir:

Cholesterol is the characteristic sterol of higher animals. It was isolated from gall stones by Conradi in 1775 and thus was the first member of the steroid family to be discovered. However it was not until 1932 that its correct structure (apart from stereochemical refinements) was proposed, mainly due to the brilliant researches of Windaus dating from 1903, and to those of Wieland dating from 1912. We now wish to record the total synthesis of cholesterol.

Methyl 3-ketoetio*allo*cholanate (I) has been obtained previously by total synthesis.[1] In view of conversions already described,[2] essentially the only remaining stage in a synthetic route from (I) to cholesterol is the homologation of 3-β-acetoxy*nor*-Δ^5-cholenic acid to 3-β-acetoxy-Δ^5-cholenic acid. The rather cumbersome nature of this scheme however led us to employ a more direct approach. Reduction of (I) with sodium borohydride in ethanol gave crude methyl 3-β-hydroxyetio*allo*cholanate, purified through the digitonide. The pure ester, m.p. 168–170° (undepressed on admixture with an authentic sample), was hydrolyzed to the corresponding hydroxy-acid, m.p. 249–251°, which was then acetylated. Treatment with thionyl chloride gave the acid chloride, m.p. 134–136°, which with excess cadmium-methyl yielded crude 3-β-acetoxy*allo*pregnanone-20, m.p. 139–144°. The latter reacted with excess isohexylmagnesium bromide,[3] and the gummy product, containing 20-hydroxycholestanol-3 and probably the C-20 epimer, was dehydrated (at C-20) and acetylated (at C-3) by boiling with acetic acid and then with acetic acid–acetic anhydride.[3] The reaction mixture was hydrogenated in the presence of a platinum catalyst. Chromatographic purification of the saturated material gave crude cholestanol-3 acetate, which on crystallization readily yielded the pure ester, m.p. 109–110°,[4] undepressed on admixture with an authentic sample (m.p. 110°). The infrared spectra of the two samples were also identical. Alkaline hydrolysis of the synthetic acetate furnished cholestanol-3, m. p. 142–142.5°,[4] undepressed on admixture with an authentic specimen (m.p. 142–143°). Cholestanol-3 has already been oxidized to cholestanone-3,[5] which in turn has been converted *via* Δ^4-cholestenone-3[6] into cholesterol[8]; the total synthesis of the latter is therefore complete.

Cholesterol has previously been converted into a number of other compounds of interest, the most important of which perhaps is vitamin D_3.

CONVERSE MEMORIAL LABORATORY R. B. WOODWARD
HARVARD UNIVERSITY FRANZ SONDHEIMER
CAMBRIDGE 38, MASSACHUSETTS DAVID TAUB

RECEIVED JUNE 20, 1951

(1) Woodward, Sondheimer and Taub, THIS JOURNAL, **73**, 3547 (1951).

(2) Djerassi and Scholz, *ibid.*, **69**, 2404 (1947); Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937); MacPhillamy and Scholz, *J. Biol. Chem.*, **178**, 37 (1949); Ruzicka, Plattner and Pataki, *Helv. Chim. Acta*, **25**, 425 (1942); Plattner and Pataki, *ibid.*, **26**, 1241 (1943); Kuwada and Yogo, *J. Pharm. Soc. (Japan)*, **57**, 963 (1937); Riegel and Kaye, THIS JOURNAL, **66**, 723 (1944).

(3) *Cf.* Butenandt and Cobler, *Z. physiol. Chem.*, **234**, 218 (1935).

(4) These m.p's. were taken in a capillary. All others were taken on a Kofler micro hot-stage.

(5) *Inter al.* Bruce, *Organic Syntheses*, Coll. Vol. II, 139 (1943).

(6) Butenandt and Wolff, *Ber.*, **68**, 2091 (1935); Ruzicka, Plattner and Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938). This transformation could probably be more conveniently carried out by use of the general method for converting *allo*steroids to Δ^4-3-ketosteroids recently developed (Ref. 7).

(7) Rosenkranz, Mancera, Gatica and Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(8) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); Dauben and Eastham, THIS JOURNAL, **72**, 2305 (1950); Birch, *J. Chem. Soc.*, 2325 (1950).