The acetone in the combined filtrates and washings was removed as completely as possible by distillation from a steam bath; the sirupy residue was dissolved in 100 ml. of water, the solution was gently warmed until the odor of acetone was no longer perceptible, and was then chilled at 0–1° for 2 days. The needle crystals of quinine L-β-hydroxybutyrate were collected with suction and washed with 10 ml. of ice water in small portions, and the adhering solution was largely displaced by washing with ether. The product was then recrystallized from 80 ml. of water as before, washed with 10 ml. of ice water and finally with ether.[4] After being dried in air, the crystals, which weighed 31.3 g., were dried *in vacuo* to constant weight, 26.1 g. These values correspond to 62 mmoles of the hydrated (4.5 H_2O) and anhydrous salts, respectively.

The free acids were liberated by the gradual addition of 45-ml. quantities of 45% H_2SO_4 to suspensions of the above products in 100 ml. of water. During this operation, quinine sulfate crystallized at first but later dissolved with the formation of the more soluble acid sulfate. The optically active β-hydroxybutyric acids were extracted in a continuous apparatus by a rapid current of ether during 8 hr. and after the removal of solvent the residues were dissolved in water. The solutions were cleared with Norit and aliquots taken for titration and measurement of rotation. The 81 mmoles of D salt yielded 75 mmoles of D acid, $[\alpha]_D^{25} = +23.9°$. The 62 mmoles of L salt yielded 58 mmoles of L acid, $[\alpha]_D^{25} = -24.5°$.

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(4) The yields of both salts could no doubt be materially increased by evaporation of the aqueous filtrates to dryness and repetition of the crystallizations from acetone and water.

α-Alkyloximino Aldehydes[1]

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Certain α-oximino acids, R—C(=NOH)—COOH, and α-alkyloximino acids, R—C(=NOR₁)—COOH, inhibit incorporation of glycine into tumor tissue and exhibit slight antitumor activity.[3] This activity, in experimental animals, even though not pronounced, suggests that modifications in the structure of these compounds be made for pharmacological testing.

Aldehydes are not only versatile intermediates for further syntheses but are frequently very active biologically. Accordingly, the preparation of two α-alkyloximino aldehydes, R—C(=NOCH₂C₆H₅)—CHO, is described, namely R = CH_3— and R = $C_6H_5CH_2$—.

The most promising route appeared to depend on the reduction of the corresponding acid chlorides. To accomplish this, it was necessary to avoid reagents or conditions that would also attack the sensitive alkyloximino groups. Since it is impossible to obtain the chlorides of α-oximino acids, R—C(=NOH)—COCl, by conventional procedures[4] the oxime intermediate is not available for this type of study. The reduction was accomplished with tri-*t*-butyl-oxyaluminohydride according to the procedure of Brown and McFarlin.[5] The yields of aldehydes were very low and because of comparative instability were characterized by reoxidation to the carboxylic acid and a derivative. Insufficient material was obtained to permit biological screening.

EXPERIMENTAL

The preparation of α-benzyloximino acids and the conversion to the corresponding acid chlorides has been previously described.[6,7] A typical reduction was carried out as follows.

Eighteen and seven-tenths g. (0.089 mole) of α-benzyloximinopropionyl chloride was placed in a 500 ml. three neck flask equipped with magnetic stirrer, dropping funnel, and thermometer. Fifty ml. of dry tetrahydrofuran was added, and the solution was cooled to −78° in an acetone–Dry Ice bath. An equivalent amount of lithium tri-*t*-butoxyaluminohydride prepared in tetrahydrofuran[5] was added through the dropping funnel slowly with stirring and continued cooling so that the temperature never went above −70°. When addition was completed, the reaction mixture was allowed to come to room temperature and poured over crushed ice. Since filtration of the precipitate was difficult, the procedure of Brown and McFarlin[6] which was followed to this point, was modified slightly. The reaction mixture was made acid to litmus with dilute HCl at 0°. The mixture was extracted with five 50-ml. portions of ether. The ether was evaporated and the remaining oil, which gave positive Tollens' and Schiff tests, was treated with sodium bisulfite. A precipitate formed instantly. The addition product was dried in air and repeatedly washed with ether until the washings were clear. A portion of the product was treated with dilute HCl and the liberated aldehyde was extracted with ether, the ether evaporated, and the residual oil used to prepare derivatives and a portion of the aldehyde was oxidized to the parent acid in alkaline permanganate after the procedure outlined in McElvain.[8] Melting point of product 75–76°.

Derivatives of α-benzyloximinopropionaldehyde. Semicarbazone, $CH_{14}N_4O_2$, m.p. 189°. Calcd.: C, 56.31%, H, 5.98%;

(1) Paper number 19 in amino acid series. For number 18 see K. L. Hoy and W. H. Hartung, *J. Org. Chem.*, **23**, 967 (1958).

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N, 23.93%. Found[9]: C, 56.64, 56.54%; H, 6.01, 6.06%; N, 23.14, 23.30%. 2,4-Dinitrophenylhydrazone, $C_{16}H_{18}N_5O_5$, m.p. 156–158°. Calcd.: C, 53.81%, H, 4.20%, N, 19.88%. Found: C, 53.84, 53.76%; H, 4.44, 4.43%; N, 18.80, 19.03%.[10]

Derivatives of α-benzyloximinohydrocinnamaldehyde. Semicarbazone, $C_{17}H_{18}N_4O_2$, m.p. 180°. Calcd.: C, 65.81%, H, 5.58%, N, 18.06%. Found[10]: C, 65.96, 65.68%; H, 6.27, 6.03%; N, 17.70%.

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(9) Analyses by Micro-Tech Laboratories, Skokie, Ill.

(10) Analyses by Messrs. Weiler and Strauss, Oxford, England.

Ring A Aromatization of a 19-Norsteroid

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The reactions of 4,5-epoxides of 3-ketosteroids have been studied, *inter alia*, by Camerino *et al.*,[1-3] who found that they led to 4-halo, 4-hydroxy, and 2α-hydroxy derivatives of 3-keto-Δ⁴-steroids. During the course of an investigation involving the preparation of some esters of 4-chloro-19-nortestosterone (Table I) in this laboratory, another reaction of such 4,5-epoxides was observed.

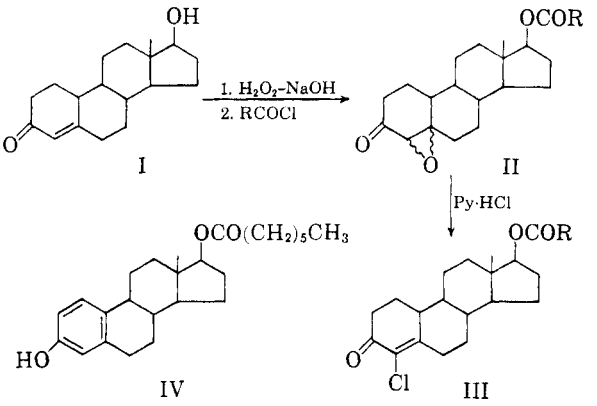
A synthetic scheme similar to that of the Italian workers[3] was employed. 19-Nortestosterone (I) was treated with alkaline peroxide and the oily epoxide was acylated with the appropriate acyl chloride. The crude esters (II) were boiled with pyridinium chloride in chloroform to give the desired 4-chloro compounds (III).

When this sequence was carried out in the case of the heptanoate derivative the expected ester (Table I, No. 1) was obtained as an oil and a second, crystalline, fraction was also isolated. This material had analyses, spectra, and melting point consistent with estradiol 17β-heptanoate (IV).

The mode of formation of IV is unknown. 3-Keto-4β,5-epoxides are known to rearrange under acid conditions to give stable 2α-hydroxy-3-keto-Δ⁴-steroids.[2]

The analogous 2β-hydroxy compounds, which could dehydrate to form a 1,4-diene-3-one, are not obtained under these conditions. The corresponding 4α,5-epoxides do not undergo such a rearrangement.

Apparently, in the case of the present 19-nor system, a rearrangement of the epoxide, perhaps involving C-10, followed by epoxide cleavage, elimination, and tautomerization, gives rise to the aromatic product. It is pertinent to note that 5β,10β-oxido-19-norandrostan-17β-ol-3-one furnishes 10β-hydroxy-19-nortestosterone on treatment with perchloric acid[4] and that the latter compound undergoes acid catalyzed conversion to estradiol.[5] A more detailed formulation of the mechanism cannot be given at this time since the oily intermediates could not be purified and, in particular, because it was necessary to use the oily, mixed 4α,5- and 4β,5-epoxides.



EXPERIMENTAL[6]

Esters of 4-chloro-19-nortestosterone (Table I). To a stirred solution of 5.0 g. (0.018 mole) of 19-nortestosterone[7] in 300 ml. of methanol maintained at −5° to 0° there were added, dropwise and simultaneously during 8–10 min., 10 ml. of 4*N* sodium hydroxide solution and 37.5 ml. of 30% hydrogen peroxide solution. The resulting solution was stirred at 0° for an additional 50 min., treated with 2.5 ml. of glacial acetic acid, and poured into 2 l. of brine. The resulting suspension was extracted with ethyl acetate (5 × 400 ml.) and the united extracts were dried with sodium sulfate, filtered, and concentrated *in vacuo* to give 6.1–6.6 g. of a gum with no selective ultraviolet absorption.

A stirred solution of the crude epoxide in 55 ml. of dry pyridine was chilled to below −5° and treated with 0.0549–0.0915 mole of the requisite acid chloride. The mixture was allowed to stand at 5–27° for 18 hr., cooled in ice, and then decomposed by cautious addition of 60 ml. of water. The resulting solution was poured into 1 l. of brine and extracted with chloroform (5 × 200 ml.). The combined organic extract was washed with 5% sodium bicarbonate solution and water, and then dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was a brown gum.

A solution of the crude ester in 120 ml. of chloroform containing 21.2 g. (0.183 mole) of distilled pyridinium chloride was refluxed for 18 hr. The cooled brown solution was diluted with 150 ml. of chloroform, washed with 1% hydrochloric acid and then with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by recrystallization or chromatography.

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(6) All melting points are corrected. Microanalyses were performed under the supervision of Mr. W. F. Ellenbogen, Analytical Section. Spectral determinations and interpretations were made by Dr. Walter Thompson.

(7) Purchased from Schering, A. G., m.p. 122.5–123.5°.