ethyl-17-ethynylgon-5(10)-en-3-one, m.p. 177–184°, ν_{max}^{KBr} 3215, 3333, and 1704 cm^{-1}.

Biological Activities. The ketal (17), in a 10 day rat blood cholesterol depression test[15], had 80% of the blood cholesterol depressing potency of estrone, and in a mouse uterine growth test[16], had less than 0.01% of the feminizing potency of estrone. In the same two tests, the ketal (18) had 200 and 0.3% respectively, of the corresponding potencies of estrone. The decanoic ester (19) proved to be more potent and to have a longer duration of anabolic activity and a better separation of anabolic and androgenic activities than 19-nortestosterone β-phenyl propionate[17] in a $5^1/_2$-week study using a modified protocol[18] in the HERSHBERGER test[19]. In an acute study using the original HERSHBERGER protocol, the ketone (20) is at least four times as potent myotrophically than 17α-ethyl-19-nortestosterone[20] with approximately three times the myotrophic:androgenic ratio[21]. Extensive clinical trials have confirmed this behaviour in man. In the Clauberg test[22] the ketone (21) has approximately eighty times the potency of 17α-ethynyl-19-nortestosterone[18]. Full accounts of this work will be published elsewhere[23].

Zusammenfassung. Von mehreren (±) 3-Oxy- und (±) 3-Methoxy-13-alkylgona-1,3,5(10)trien-17-onen und verwandten Verbindungen, einschliesslich von Vertretern der (±) 13-Alkylgon-4-en-3-on-Reihe, werden Totalsynthese und biologische Wirksamkeit beschrieben.

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Oxidation of Steroidal Ketones II
Selenium Dioxide Catalyzed Hydrogen Peroxide Oxidation of 4-en-3-ones[1]

In the previous communication[2] we have shown that saturated steroidal 3-ketones undergo oxidation analogous to the Baeyer–Villiger process rather than ring contraction[3] when reacted with hydrogen peroxide in the presence of selenium dioxide. We now report observations with steroidal 4-en-3-ones and a 17-ketone.

The oxidation was carried out essentially as previously described[2]. The steroid was refluxed in tert.-butanol containing hydrogen peroxide and catalytic amounts of selenium dioxide. After refluxing for 7 h, water was added, and the steroids were recovered with a mixture of ethyl acetate-methylene chloride. The extract was then partitioned with an aqueous solution of sodium carbonate into neutral and acidic fractions.

PAYNE and SMITH[3a] have demonstrated the contractive oxidation of cyclopentanone to cyclobutane carboxylic acid. Under essentially similar conditions[2], however, 3β-acetoxy-5α-androstane-17-one gave 3β-acetoxy-17a-oxa-D-homo-5α-androstan-17-one[4] (I), m.p. 158–159° (reported[5] 158.5–159.5°) as the sole product of reaction.

The oxidation of 4-en-3-ones was more complex and apparently proceeded in several stages. Treatment of testosterone propionate as before[2] gave a syrupy acidic residue from which the ε-lactone acid IIa, m.p. 154–155°, was isolated. Upon saponification the unstable lactone acid IIb, m.p. 211–213°, was obtained which on attempted recrystallization changed to the γ-lactone acid IIIa, m.p. 211–212°. The product IIIa on propionation gave the 17β-propionate IIIb, m.p. 170–174°, different from IIa. Treatment of the ε-lactone IIb with etheral diazomethane converted it into the methyl ester-γ-lactone IIIc, m.p. 151–152°. Similarly propionation of IIb with pyridine-propionic anhydride gave IIIb. The compound IIa on diazomethane esterification gave IIId, m.p. 149–152°, also obtained from IIIb. Saponification of the mother liquor of IIa gave the γ-lactone IIIa directly.

Confirmation of the lactone structure IIa was obtained by an independent synthesis. Testosterone propionate on ozonization[6] gave the lactol IVa which on treatment with hydrogen peroxide-acetic acid[5a] yielded IIa.

The assignment of the structure IIa is based on the premise that the oxidation of the lactol IVa with peracetic acid proceeded via scission of the 5–10 bond. Support for this assumption is provided by the downfield shift of the 19-methyl (τ 8.69) consistent with a methyl group attached to a carbon bearing an oxygen. The infrared spectrum of this lactone had a band at 1750 cm^{-1} and the band extending from 1735 to 1720 cm^{-1} was unresolved.

[1] This work was supported by U.S. Public Health Grants CA-4663, and A-5326.
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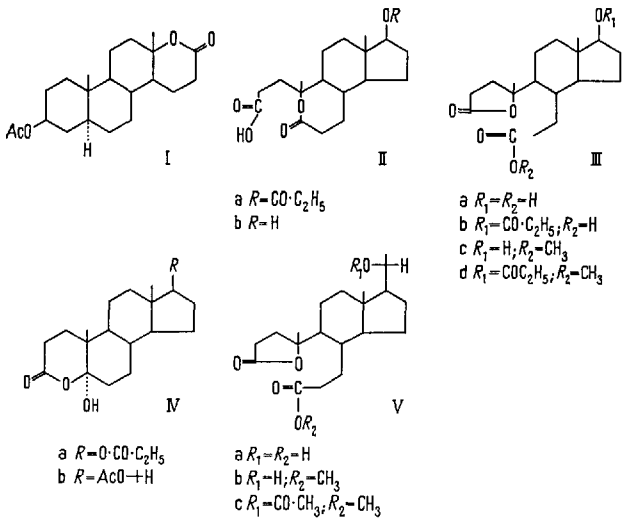
The unstable saponification product IIa had bands at 1750 and 1715 cm^{-1}. On the other hand the γ-lactone IIIa showed bands at 1770 and 1705 cm^{-1}. Again the 19-methyl exhibited the characteristic downfield shift (τ 8.64) in the NMR spectrum.



Similar results were obtained with 20β-acetoxypregn-4-en-3-one. The acidic syrupy reaction product was directly saponified to yield Va, m.p. 220–222°. Its structure was proved by alternative synthesis from IVb, m.p. 186–189°. Treatment of IVb with acetic acid-hydrogen peroxide followed by saponification, gave Va. Esterification with diazomethane gave Vb, m.p. 177–180°, which was acetylated to Vc, m.p. 164–165°.

It is reasonable to assume that the lactone II arises from the lactol IV. The mode of formation of IV is not immediately apparent. We have previously demonstrated that Baeyer-Villiger oxidation of Δ^4-3-ketones yields 7-membered enol-lactones (3-oxo-3a-oxa-4-enes) which can give 4,5-epoxides[7]. Similar enol-lactones have been shown to be formed from 4-ene-3-bis-hydroperoxides[8]. Formation of 4,5-diols from such enol-lactones (or epoxides), and loss of the elements of formic acid would lead to IV. Alternatively, 3-keto-4,5-glycol formation from 4-en-3-ones may be the initial step. A mode of action leading from 7-membered enol lactones to 3,5 lactones (3-oxo-4-oxa compounds)[9] will have to be ruled out since such lactones would be stable under the conditions employed by us.

The method described provides a means for the facile elimination of an α-carbon in a conjugated carbonyl system, and concomitant insertion of an oxygen function in the resulting ketonic product.

The utility of the procedure is further extended by the observation that an acetyl moiety, i.e. in progesterone is not being attacked, while the oxidation of ring A proceeds as described. Isolated double bonds give glycols as evidenced by the conversion of pregnenolone to the 3β,5α,6β-trihydroxypregnan-20-one.

Zusammenfassung. Oxydation von steroidalen Δ^4-3-Ketonen mit Wasserstoffsuperoxid in Anwesenheit von Selendioxid führt zu Verbindungen der allgemeinen Struktur II. Diese Methode erscheint besonders geeignet für eine oxydative Eliminierung des α-Kohlenstoffatoms in konjugierten Ketonen, sowie für die Synthese von Norsecosäurelactonen II. Ausgehend von 17-Ketonen erhält man Laktone I. Ein möglicher Reaktionsmechanismus wird diskutiert.

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d-Lysergyl-L-valin-methylester, ein neues, natürliches Mutterkornalkaloid[1]

Bei der Aufarbeitung von Alkaloidmutterlaugen aus Zuchtmutterkorn wurde ein neues, niedrigmolekulares Mutterkornalkaloid aufgefunden, das dann auch als Spurenalkaloid in vielen natürlichen Mutterkorndrogen nachgewiesen werden konnte. Diese neue Verbindung erwies sich als *d*-Lysergyl-L-valin-methylester. Sie stellt einen Mutterkornalkaloidtyp dar, von dem schon zahlreiche Vertreter auf partialsynthetischem Weg hergestellt worden waren[2] und der jetzt erstmals in der Natur beobachtet wurde. Das neue Alkaloid konnte aus den Alkaloidmutterlaugen durch wiederholtes Chromatographieren an neutralem Aluminiumoxid mit Benzol, dem steigende Mengen Methanol zugesetzt wurden, isoliert werden. Die freie Base ist in den meisten organischen Lösungsmitteln leicht löslich und konnte bisher nicht zur Kristallisation gebracht werden.

Amorphe Base Smp 80–85°. $[\alpha]_D^{20} = -103°$ ($\pm 2°$) (c = 1,6 in Chloroform), $[\alpha]_D^{20} = -65°$ ($\pm 2°$) (c = 1,4 in Pyridin). Für die Analyse wurde im Hochvakuum bei 100° getrocknet (Schmelze). $C_{22}H_{27}O_3N_3$ Ber. C 69,3 H 7,1 O 12,6 N 11,0%; Gef. C 69,0 H 7,2 O 12,6 N 11,2%. UV-Spektrum in Methanol: Maxima bei 225 mμ (4,34) und 311 mμ (3,94); Minimum bei 269 mμ (3,34). Titration mit 0,05*N* HCl: Mol-Gew. Ber. 381,5 Gef. 384/385. Gibt blaue Keller- und van Urk-Farbreaktion.

Das Hydrogenmaleinat kristallisiert aus Aceton in feinen Nadeln. Smp. 185° (Zers.). $[\alpha]_D^{20} = +38°$ (c = 1,2 in Alkohol/Wasser 1:1).

Das neue Alkaloid lässt sich durch Kochen der methanolischen, schwach essigsauren Lösung in *d*-Isolysergyl-L-valin-methylester umlagern. Aus dem Isomerengemisch lässt sich die Isoverbindung durch Chromatographieren an neutralem Aluminiumoxid (Aktivität I) mit Benzol + 0,2% Methanol als schneller wandernde Zone abtrennen.

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