were most sensitive to the UV irradiation of their solutions.

The alternating-current oscillographic polarography means a new, very speedy and experimentally not very pretentious analytical method in the branch of photochemistry of biologically important substances and their closely related compounds. Besides decreases of investigated compounds caused by UV irradiation of their water solutions, this method permits the registration of some reaction products also in the photochemical reactions. It may therefore be assumed that it will be possible to extend in this way a knowledge of the course of some photochemical, and probably also radiation-chemical[10,12], reactions.

Zusammenfassung. Bei Anwendung der oszillographischen Polarographie mit Wechselstrom wurde der Einfluss der UV-Strahlung auf die wässrigen Lösungen einiger Bestandteile der Nukleinsäuren und Eiweißstoffe erforscht. Die oszillographischen Kurven der Funktion $dE/dt = f_1(E)$ wurden mit dem Polaroskop P 524 mit Hilfe der Quecksilbertropfelektrode verfolgt.

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Totally Synthetic (±)-13-Alkyl-3-hydroxy and Methoxy-gona-1,3,5(10)-trien-17-ones and Related Compounds

The flexibility of our recently described total synthesis of estrone[1,2] readily permits the preparation of numerous gona-1,3,5(10)-triene derivatives in which, in particular, the substituent attached to the 13-position and the size of ring D are varied. Expressed generally, the key reaction in these syntheses is a Michael condensation of a vinyl ketone (I) (or the corresponding 6-aryl-1-diethylaminohexan-3-one, or a mixture of the two) to give the adduct (III). We now report that this reaction can be carried out for cases in which X = hydroxyl and methoxyl, R = ethyl, *n*- and iso-propyl, *n*- and iso-butyl, isoamyl, and *n*-hexadecyl, and n = 1 and 2. The adducts (III) undergo double cyclodehydration under acidic conditions[2] to (±)-13-alkyl-3-hydroxy and methoxy-gona-1,3,5(10),8,14 pentaen-17 and 17a-ones (IV), readily convertible by selective hydrogenation over a 2% palladized calcium carbonate catalyst in benzene[2] to the corresponding gona-1,3,5(10),8-tetraenes. D-Cyclopentano members of this series (i.e. n = 1) are isomerized in boiling methanolic hydrochloric acid to (±)-13-alkyl-3-hydroxy and methoxy-gona-1,3,5(10),9(11)-tetraen-17-ones, converted by catalytic hydrogenation over 10% palladized charcoal in ethanol to (±) 13-alkyl-3-hydroxy and methoxy-gona-1,3,5(10)-trien-17-ones[3]. The (±)-13-alkyl-3-methoxy-gona-1,3,5(10),8-tetraenones are converted by lithium in aniline-liquid ammonia[4], with or without preliminary reduction by sodium borohydride in methanol, to (±)-13-alkyl-3-methoxygona-1,3,5(10)-trien-17 and 17a-ols, which may be oxidized by the Jones reagent[5] to the corresponding gonatrien-17 and 17a-ones[3a]. The metal-ammonia reduction of the 8,9-double bond is impeded in the 3-hydroxy series, possibly because delocalization of phenoxide charge hinders electron addition to the styrenoid system. The end products are assigned the 'natural' type stereochemistry by analogy with stereochemical

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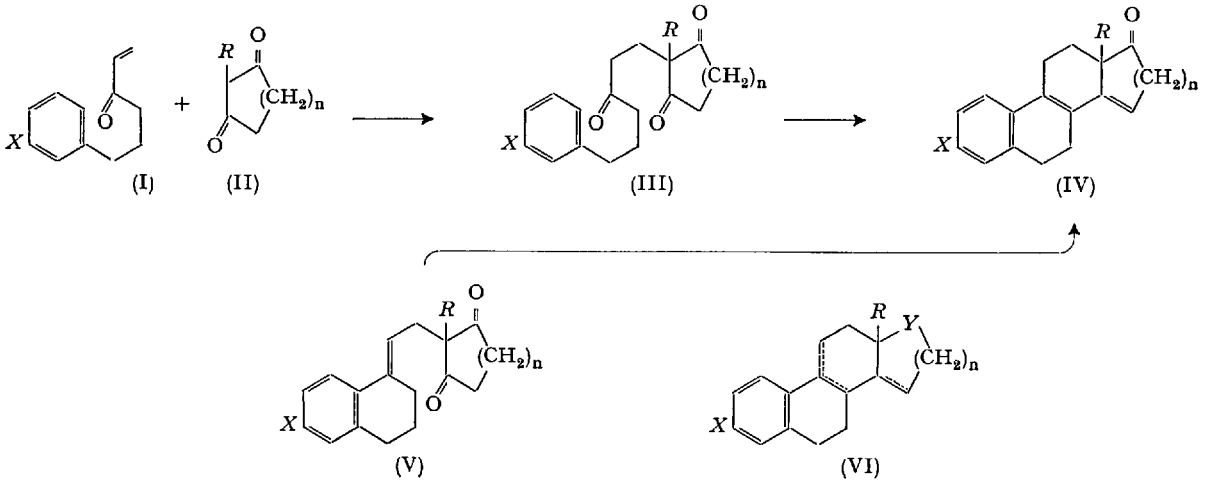

course of the same reactions carried out upon the 13-methyl homologues[6,7], and from the high degree of biological activity of various gonane derivatives made therefrom (below). The gonapentaenes (IV) may also be prepared by methanolic hydrochloric acid cyclodehydration of the diones (V) made by base-catalysed condensation of suitable 6-substituted-1-vinyl-1-tetralols with 2-alkylcycloalkane-1,3-diones (II)[7,8]. Compounds asterisked in the Table have been made by this route.

6-*m*-Methoxyphenyl-1-hexen-3-one (I; $X = OCH_3$)[9], b.p. 117° (0.4 mm) is prepared by fractionation of 1-diethylamino-6-*m*-methoxyphenylhexan-3-one[1]. 1-Diethylamino-6-*m*-hydroxyphenylhexan-3-one is prepared from 3-*m*-hydroxyphenylpropyl alcohol in an analogous manner to the methoxy analogue. Refluxing this alcohol with 48% hydrobromic acid gives 3-*m*-hydroxyphenylpropyl bromide, b.p. 122–124° (0.4 mm), n_D^{18} 1.5688, which, with sodium acetylide in liquid ammonia, followed by acetylation of the product in acetic anhydride-pyridine, gives 5-*m*-acetoxyphenyl-1-pentyne, b.p. 105–110° (0.1 mm). Treatment with diethylamine and formaldehyde under Mannich conditions[10] gives 1-diethylamino-6-*m*-acetoxyphenyl-2-hexyne, b.p. 150–152° (0.1 mm). Hydration of the triple bond under acidic conditions[10b] gives 1-diethylamino-6-*m*-acetoxyphenyl-3-hexanone, ν_{max} 1709 cm^{-1} suitable for direct use in condensation reactions with 2-alkylcycloalkane-1,3-diones. 2-Ethyl-, 2-*n*-propyl-, 2-isopropyl-, 2-*n*-butyl-, 2-isobutyl-, and 2-*n*-hexadecyl-cyclopentane-1,3-diones were prepared by modifications of the previously described method[11] for 2-methylcyclopentane-1,3-dione from the appropriate alkyl methyl ketones and had m.p.'s 180°, 175°, 146°, 149–151°, 194–196°, and 128–130°, respectively. 2-Ethyl- and 2-*n*- propyl-cyclohexane-1,3-diones were obtained by the literature methods[12].

The physical characteristics of a representative selection of gonapolyenes based on the general skeleton (VI) and made from appropriate pairs of the above starting materials are recorded in the Table.

The intermediate and end products have been used to prepare a number of steroid-like compounds for biological evaluation. This work is exemplified as follows. SALMI ketalization[13] of ketones (1) and (4) gives, respectively, (±) - 13 - ethyl - 17,17 - ethylenedioxy - 3 - methoxygona - 1,3,5(10),8,14-pentaene (17), m.p. 126.5–128°, λ_{max}^{EtOH} 312 mμ (ε 29,300) and (±)-13-ethyl-17,17-ethylenedioxy-3-methoxygona-1,3,5(10)-triene (18), m.p. 88.5–90° λ_{max}^{EtOH} (ε 2,100). Reduction with lithium and ethanol in tetrahydrofuran-liquid ammonia of the alcohol (5), followed by hydrolysis at room temperature with 0.7 *N* ethanolic hydrochloric acid, gives (±)-13-ethyl-17-hydroxygon-4-en-3-one[3b], m.p. 149.5–150°, λ_{max}^{EtOH} 242 mμ (ε 17,600) converted by *n*-decanoyl chloride in pyridine to the corresponding decanoate (19), m.p. 97–98.5° λ_{max}^{EtOH} 240 mμ (ε 17,800). The ketone (2) with lithium acetylide in dimethylacetamide-ethylenediamine gives (±)-13-ethyl-17-ethynyl-3-methoxygona-1,3,5(10),8-tetraen-17-ol, m.p. 101–103°, λ_{max}^{EtOH} 278 mμ (ε 16,100) hydrogenation of which, in benzene over palladised calcium carbonate, gives (±)-13,17-diethyl-3-methoxygona-1,3,5(10),8-tetraen-17-ol, m.p. 141.5–143°, λ_{max}^{EtOH} 278 mμ (ε 16,200). Reduction with lithium and aniline in liquid ammonia followed by Birch reduction and hydrolysis as before gives (±)-13,17-diethyl-17-hydroxygon-4-en-3-one (20), m.p. 144–145°, λ_{max}^{EtOH} 240 mμ (ε16,450). (±)-13-Ethyl-3-methoxygona-2,5(10)-dien-17-ol, m.p. 110–114°, ν_{max} 3279, 1701, 1669 cm^{-1}, from the usual Birch reduction of the alcohol (5), on Oppenauer oxidation with aluminium isopropylate and cyclohexanone in boiling toluene and reaction of the product with lithium acetylide as before, gives an ethynyl carbinol, converted by the usual acid hydrolysis to (±)-13-ethyl-17-ethynylgon-4-en-3-one (21), m.p. 203–206°, λ_{max}^{EtOH} 242 mμ (ε 16,900), and by mild acid hydrolysis[14] to (±)-13-

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Gonapolyenes of general structure (VI)

Compound	X	R	Y	Δ	n	m.p.°	λ_{max} (mμ)	ε × 10^{-3}
1*	CH_3O	C_2H_5	CO	8, 14	1	72–74	311	28.0
2	CH_3O	C_2H_5	CO	8	1	120.5–122.5	279	16.0
3	CH_3O	C_2H_5	CO	9 (11)	1	140–143	264	17.7
4	CH_3O	C_2H_5	CO	–	1	128–130	279	1.9
5	CH_3O	C_2H_5	CHOH	–	1	136–137	278	1.9
6	HO	C_2H_5	CO	8, 14	1	171.5–174	313	28.3
7	HO	C_2H_5	CO	8	1	266–270	279	15.8
8	HO	C_2H_5	CO	9 (11)	1	258	267.5	19.6
9	HO	C_2H_5	CO	–	1	223.5–226	280	2.2
10	CH_3O	*n*-C_3H_7	CO	8, 14	1	82–84	310	24.7
11	CH_3O	*n*-C_4H_9	CO	8, 14	1	53–55	312	29.2
12	CH_3O	iso-C_4H_9	CO	8, 14	1	57–60	312	26.5
13	CH_3O	*n*-$C_{16}H_{33}$	CO	8, 14	1	55–56.5	316	24.0
14	CH_3O	C_2H_5	CO	8, 14	2	90–92	311	28.5
15	CH_3O	*n*-C_3H_7	CO	8, 14	2	86–89	312	24.3
16*	$C_6H_5CH_2O$	C_2H_5	CO	8, 14	1	131–134	313	28.0

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.

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