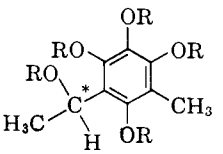
and CH_3 protons (type 1). Four weaker peaks at 2.0, 2.15, 2.25, and 2.34 p.p.m. are characteristic for methyl or methylene protons next to oxygen-bearing carbon and/or aromatic ring (type 2). A peak at 4.65 p.p.m. is ascribed to a hydroxyl proton. Integration indicates 46 protons of type 1, 12 of type 2, and 2 hydroxyl groups.

The compound does not react with diazomethane and does not give a coloration with ferric chloride. Hydrolysis with 10% aqueous ethanolic sodium hydroxide (1:1) resulted in darkening of the solution. The acidified hydrolysate gave a persistent purple color with ferric chloride. Three acids were obtained in equal molar ratios from the hydrolysate and were identified by gas–liquid chromatography of the methyl esters: 1-methylbutyric, capric, and lauric acids. This is consistent with the experimentally determined saponification equivalent for three ester functions. Subtracting the various functions indicated, a C_7H residue is left. This residue can be accommodated reasonably as a fully substituted benzene ring, and this is in agreement with the ultraviolet absorption and infrared spectra. The CH residue left constitutes then the center for optical activity. The high specific rotation suggests also that this optically active center contains a strongly hydrogen-bonded function.[9] The instability of the water-soluble phenolic residue indicated either a pyrogallol or a 1,2,3,5-tetrahydroxybenzene nucleus.

From the n.m.r. data the two remaining carbon–methyl groups must be attached either to a carbon atom which also carries oxygen or directly to an aromatic ring. The available information leads to a partial structure



where each R is one of the following: $-COCH(CH_3)-CH_2CH_3$; $CO(CH_2)_8CH_3$; $CO(CH_2)_{10}CH_3$; H(two).

Other closely related hydrogenation products have been isolated in crystalline form and these differ from the compound described in the nature of the acids and possibly also their relative positions.

Compounds B and D and the catalytic hydrogenation product (m.p. 96°) described here have not yet been tested for cocarcinogenic activity. However, the close similarity in infrared absorption spectra and chemical properties of A, B, C, D, and the hydrogenated compound leaves little doubt that they are all chemically closely related. The exact nature of the structural features required for activity are currently under examination.

It is expected that the biologically active material and the hydrogenation product described will exhibit both hydrophilic and lipophilic behavior which may play an important role in the biological activity of the material. It is of interest also that the partial structure proposed is similar to the long chain olefinic catechols which constitute the vesicant principles of poison ivy.[10]

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INSTITUTE OF INDUSTRIAL MEDICINE
NEW YORK UNIVERSITY MEDICAL CENTER
NEW YORK, N. Y.
B. L. VAN DUUREN
E. ARROYO
L. ORRIS

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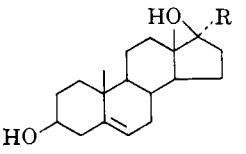
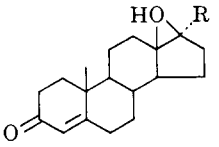
Aldosterone Antagonists. 2′3′α-Tetrahydrofuran-2′-spiro-17-(4-androsten-3-one) and Related Compounds

Sir:

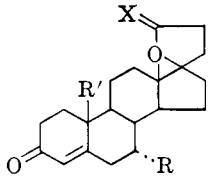
The spirolactones, *e.g.*, XVII, prepared by Cella and associates,[1] are effective aldosterone antagonists in animals[2] and in humans.[3] One series of spirolactone



I, R = $-C\equiv CCH_2OTHP$
II, R = $-CH_2CH_2CH_2OTHP$
XVIII, R = $CH_2CH_2CH_2OH$



III, R = $-CH_2CH_2CH_2OTHP$
IV, R = $-CH_2CH_2CH_2OH$
V, R = $-CH_2CH_2CH_2OTS$



VI, R′ = CH_3, R = H, X = H_2
VII, R′ = CH_3, R = $SCOCH_3$, X = H_2
XVI, R′ = H, R = H, X = H_2
XVII, R′ = CH_3, R = H, X = O
XXIX, R′ = CH_3, R = $SCOCH_3$, X = O

analogs, the spirolactams,[4] have marginal activity. Cella and co-workers[1b] showed that 3-keto-Δ^4 system in the A-ring of spirolactones was an activity-enhancing, although not an essential, function. Introduction of methyl groups [1d] and increased unsaturation,[1b] effective activity-enhancing devices in the antiinflammatory steroid series, have had relatively little effect on spirolactone activity. The 9-fluoro-11-oxygenated derivatives,[1c] however, are more active.

(1) (a) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959); (b) J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959); (c) E. A. Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960); (d) N. A. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *ibid.*, **26**, 3077 (1961).

(2) C. M. Kagawa, J. A. Cella, and C. C. Van Arman, *Science*, **126**, 1015 (1957).

(3) W. S. Coppage, Jr., and G. W. Liddle, *Ann. N. Y. Acad. Sci.*, **88**, 815 (1960).

(4) A. A. Patchett, F. Hoffman, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, **27**, 3822 (1962); R. R. Burtner and L. N. Nysted, U. S. Patent 3,001,986 (Sept. 26, 1961); L. N. Nysted and R. R. Burtner, *J. Org. Chem.*, **27**, 3175 (1962).

Among other possible variables associated with activity in the spirolactone series, it seemed desirable to determine the essentiality of the lactone carbonyl. A description of the synthesis of the compounds needed to establish this point is described herein. These compounds are highly active; therefore the lactone carbonyl is a nonessential function.

Condensation of the Grignard reagent prepared from the 2-tetrahydropyranyl (THP) ether of propargyl alcohol[5a] and dehydroepiandrosterone afforded, after chromatography, 17α-[3-(2-tetrahydropyranyloxy)propynyl]-5-androstene-3β,17-diol (I), an oil,[5b] which was hydrogenated catalytically (palladium-on-carbon) to 17α-[3-(2-tetrahydropyranyloxy)propyl]-5-androstene-3β,17-diol (II), noncrystalline. The latter was characterized by removal of the THP group,[5b] whence 17α-(3-hydroxypropyl)-5-androstene-3β,17-diol (XVIII) was obtained as a crystalline product, m.p. 267–269°.[6] By means of an Oppenauer oxidation, II was converted to 17α-[3-(2-tetrahydropyranyloxy)-propyl]-4-androsten-17β-ol-3-one (III), an oil after chromatography, which afforded 17α-(3-hydroxypropyl)-4-androsten-17β-ol-3-one (IV), m.p. 160–166°, $[\alpha]$ +53°, λ_{max} 241 mμ (ϵ 16,500) by employing standard THP reversal conditions.[5b] Ring closure of IV to 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-androsten-3-one) (VI),[7] m.p. 93–95°, $[\alpha]$ +41°, λ_{max} 241 mμ (ϵ 15,700), was effected with toluenesulfonyl chloride (TSCl) in pyridine at room temperature. This reaction undoubtedly proceeds by 17βO$^-$ displacement of the primary tosylate V, a compound which has never been isolated. Pyridine–CrO_3 converted IV to 3-(4-androsten-17-ol-3-one-17α-yl)propionic acid lactone (XVII), identical with an authentic sample.[1]

The action of chloranil[8] on VI gave 2′,3′α-tetrahydrofuran-2′-spiro-17-(4,6-androstadien-3-one) (6-dehydro VI), m.p. 98–100°, $[\alpha]$ −4°, λ_{max} 284 mμ (ϵ 26,300). The latter with thiolacetic acid[1] afforded 2′3′α-tetrahydrofuran-2′-spiro-17-(7α-acetylthio-4-androsten-3-one) (VII), m.p. 180–182°, $[\alpha]$ −54°, λ_{max} 238 mμ (ϵ 13,900).

The propargyl Grignard reagent with estrone methyl ether gave, after chromatography, oily 17α-[3-(2-tetrahydropyranyloxy)propynyl]-3-methoxy-1,3,5-estratrien-17-ol (VIII), the THP ether of which was cleaved in the usual manner, yielding 17α-(3-hydroxypropynyl)-3-methoxy-1,3,5-estratrien-17-ol (IX), m.p. 173–175°, $[\alpha]$ 0°. The latter was hydrogenated (palladium-on-carbon) yielding 17α-(3-hydroxypropyl)-3-methoxy-1,3,5-estratrien-17-ol (X), m.p. 159–160°, $[\alpha]$ +7° which with TSCl–pyridine gave 2′,3′α-tetrahydrofuran-2′-spiro-17-(3-methoxy-1,3,5-estratrien) (XI), m.p. 116–117°, $[\alpha]$ +6°. Reduction of XI with Li–NH_3 (Birch reduction[9]) proceeded normally giving, after an acid hydrolysis of the intermediate enol ether and rearrangement of the double bond, 2′,3′α-tetrahydrofuran-2′-spiro-17-(4-estraen-3-one) (XVI), m.p. 124–125°, $[\alpha]$ −10°, λ_{max} 240 mμ (ϵ 15,800).

Dehydration of 3-ethylenedioxy-5-androsten-11β-ol-17-one[10] (XIII), m.p. 213–218°, $[\alpha]$ −100°, was effected with methanesulfonyl chloride–collidine[11] leading to 3-ethylenedioxy-5,9(11)-androstadien-17-one (XIV), m.p. 196–198°, $[\alpha]$ +70°. This product with the propargyl Grignard reagent gave 17α-[3-(2-tetrahydropyranyloxy)propynyl]-3-ethylenedioxy-5,9(11)-androstadien-17-ol (XV) as an oil after chromatography. The usual hydrogenation conditions were then employed, affording 17α-[3-(2-tetrahydropyranyloxy)propyl]-3-ethylenedioxy-5,9(11)-androstadien-17-ol (XIX), m.p. 148–150°, $[\alpha]$ −41°. The THP and ethylenedioxy groups of the latter were removed simultaneously with methanol–toluenesulfonic acid, giving 17α-(3-hydroxypropyl)-4,9(11)-androstadien-17-ol-3-one (XX), m.p. 189–191, $[\alpha]$ +33°. Ring closure was effected as in the analogous cases previously mentioned, affording 2′,3′α-tetrahydrofuran-2′-spiro-17-[4,9(11)-androstadien-3-one] (XXI), m.p. 171–173°, $[\alpha]$ +9°, λ_{max} 239 mμ (ϵ 16,100).

The usual fluorohydrin elaboration sequence[12] was used with XXI providing, in order, 2′,3′-α-tetrahydrofuran-2′-spiro-17-(9α-bromo-4-androsten-11β-ol-3-one) (XXII), not characterized; 2′,3′α-tetrahydrofuran-2′-spiro-17-(9,11β-oxido-4-androsten-3-one) (XXIII), m.p. 142–144°, $[\alpha]$ −52°, λ_{max} 245 mμ (ϵ 14,700); and 2′,3′α-tetrahydrofuran-2′-spiro-17-(9α-fluoro-4-androsten-11β-ol-3-one) (XXIV), m.p. 246–254°, not further characterized. The latter with pyridine–CrO_3 gave 2′,3′α-tetrahydrofuran-2′-spiro-17-(9α-fluoro-4-androsten-3,11-dione) (XXV), m.p. 159–161°, $[\alpha]$ +96°, λ_{max} 236 mμ (ϵ 16,400).

The aldosterone antagonist activities of some of the products are shown in Table I. Highest activities are found in VII and XXV; indeed when administered orally to rats VII, *e.g.*, has about the same activity as the corresponding lactone.

TABLE I

ALDOSTERONE ANTAGONIST ACTIVITIES[a]

Compound	Mode of administration: Subcutaneous	Oral
XXIX	1.0	1.0
XXV	0.4–0.5	0.9–1.0
VII	0.6–0.7	0.9–1.1
XVI	0.3–0.4	0.6–0.7
VI	0.2–0.3	0.2–0.3

[a] The activities of the compounds were measured by their ability to reverse the effect of deoxycorticosterone acetate on the urinary excretion of Na^+ and K^+ of adrenalectomized rats. The detailed procedure will be published elsewhere.

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(6) Satisfactory elemental analyses were obtained for all of the crystalline compounds. Rotations (D line) were obtained in chloroform at $c \cong 1$ and 25°. Ultraviolet spectra were taken in methanol. Melting points were determined on the Kofler hot stage and are corrected.

(7) We are grateful to Mr. Paul Stecher of our Technical Information Department for suggesting the *Chemical Abstracts* nomenclature herein used.

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(9) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950).

(10) From the 3-ethylene ketal of cortisone acetate by reduction with $LiAlH_4$ followed by cleavage of the glycerol side chain with periodic acid.

(11) Unpublished procedure of Drs. R. Tull and J. Chemerda of these Laboratories.

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G. E. ARTH
HARVEY SCHWAM
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M. GLITZER

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