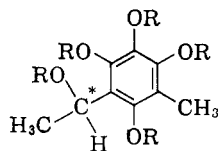


and CH_3 protons (type 1). Four weaker peaks at 2.0, 2.15, 2.25, and 2.34 p.p.m. are characteristic for methyl or methylene protons next to oxygen-bearing carbon and/or aromatic ring (type 2). A peak at 4.65 p.p.m. is ascribed to a hydroxyl proton. Integration indicates 46 protons of type 1, 12 of type 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: $-\text{COCH}(\text{CH}_3)-\text{CH}_2\text{CH}_3$; $\text{CO}(\text{CH}_2)_8\text{CH}_3$; $\text{CO}(\text{CH}_2)_{10}\text{CH}_3$; 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

Acknowledgment.—This work was supported by

(9) C. Robinson and M. J. Bott, *Nature*, **168**, 325 (1951).

(10) W. F. Symes and C. R. Dawson, *J. Am. Chem. Soc.*, **76**, 2959 (1954).

Grant C-5946 from the Department of Health, Education and Welfare, U.S. Public Health Service, National Cancer Institute.

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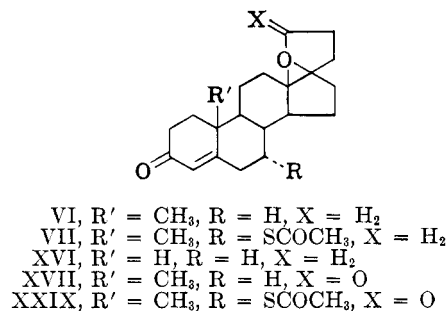
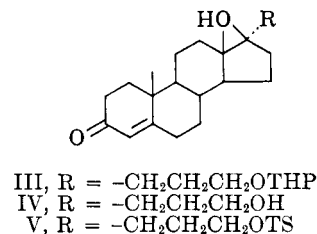
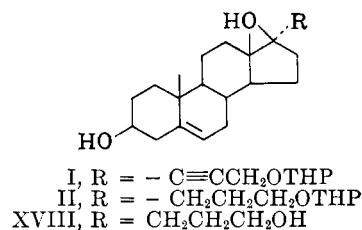
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RECEIVED JUNE 11, 1963

Aldosterone Antagonists. 2'3'-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 animals² and in humans.³ One series of spirolactone



analogues, 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, 17 α -[3-(2-tetrahydropyranyloxy)propynyl]-5-androstene-3 β ,17-diol (I), an oil,^{5b} which was hydrogenated catalytically (palladium-on-carbon) to 17 α -[3-(2-tetrahydropyranyloxy)propyl]-5-androstene-3 β ,17-diol (II), noncrystalline. The latter was characterized by removal of the THP group,^{5b} whence 17 α -(3-hydroxypropyl)-5-androstene-3 β ,17-diol (XVIII) was obtained as a crystalline product, m.p. 267–269°. By means of an Oppenauer oxidation, II was converted to 17 α -[3-(2-tetrahydropyranyloxy)propyl]-4-androstene-17 β -ol-3-one (III), an oil after chromatography, which afforded 17 α -(3-hydroxypropyl)-4-androstene-17 β -ol-3-one (IV), m.p. 160–166°, [α] +53°, λ_{\max} 241 m μ (ϵ 16,500) by employing standard THP reversal conditions.^{5b} Ring closure of IV to 2',3' α -tetrahydrofuran-2'-spiro-17-(4-androstene-3-one) (VI),⁷ m.p. 93–95°, [α] +41°, λ_{\max} 241 m μ (ϵ 15,700), was effected with toluenesulfonyl chloride (TSCl) in pyridine at room temperature. This reaction undoubtedly proceeds by 17 β O[–] displacement of the primary tosylate V, a compound which has never been isolated. Pyridine–CrO₃ converted IV to 3-(4-androstene-17-ol-3-one-17 α -yl)propionic acid lactone (XVII), identical with an authentic sample.¹

The action of chloranil⁸ on VI gave 2',3' α -tetrahydrofuran-2'-spiro-17-(4,6-androstadiene-3-one) (6-dehydro VI), m.p. 98–100°, [α] –4°, λ_{\max} 284 m μ (ϵ 26,300). The latter with thiolacetic acid¹ afforded 2',3' α -tetrahydrofuran-2'-spiro-17-(7 α -acetylthio-4-androstene-3-one) (VII), m.p. 180–182°, [α] –54°, λ_{\max} 238 m μ (ϵ 13,900).

The propargyl Grignard reagent with estrone methyl ether gave, after chromatography, oily 17 α -[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 17 α -(3-hydroxypropynyl)-3-methoxy-1,3,5-estratrien-17-ol (IX), m.p. 173–175°, [α] 0°. The latter was hydrogenated (palladium-on-carbon) yielding 17 α -(3-hydroxypropyl)-3-methoxy-1,3,5-estratrien-17-ol (X), m.p. 159–160°, [α] +7° which with TSCl–pyridine gave 2',3' α -tetrahydrofuran-2'-spiro-17-(3-methoxy-1,3,5-estratrien) (XI), m.p. 116–117°, [α] +6°. Reduction of XI with Li–NH₃ (Birch reduction⁹) 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°, [α] –10°, λ_{\max} 240 m μ (ϵ 15,800).

Dehydration of 3-ethylenedioxy-5-androstene-11 β -ol-17-one¹⁰ (XIII), m.p. 213–218°, [α] –100°, was effected with methanesulfonyl chloride–collidine¹¹ leading to

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.

3-ethylenedioxy-5,9(11)-androstadien-17-one (XIV), m.p. 196–198°, [α] +70°. This product with the propargyl Grignard reagent gave 17 α -[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 17 α -[3-(2-tetrahydropyranyloxy)propyl]-3-ethylenedioxy-5,9(11)-androstadien-17-ol (XIX), m.p. 148–150°, [α] –41°. The THP and ethylenedioxy groups of the latter were removed simultaneously with methanol–toluenesulfonic acid, giving 17 α -(3-hydroxypropyl)-4,9(11)-androstadien-17-ol-3-one (XX), m.p. 189–191, [α] +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°, [α] +9°, λ_{\max} 239 m μ (ϵ 16,100).

The usual fluorohydrin elaboration sequence¹² was used with XXI providing, in order, 2',3' α -tetrahydrofuran-2'-spiro-17-(9 α -bromo-4-androstene-11 β -ol-3-one) (XXII), not characterized; 2',3' α -tetrahydrofuran-2'-spiro-17-(9,11 β -oxido-4-androstene-3-one) (XXIII), m.p. 142–144°, [α] –52°, λ_{\max} 245 m μ (ϵ 14,700); and 2',3' α -tetrahydrofuran-2'-spiro-17-(9 α -fluoro-4-androstene-11 β -ol-3-one) (XXIV), m.p. 246–254°, not further characterized. The latter with pyridine–CrO₃ gave 2',3' α -tetrahydrofuran-2'-spiro-17-(9 α -fluoro-4-androstene-3,11-dione) (XXV), m.p. 159–161°, [α] +96°, λ_{\max} 236 m μ (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.

(10) From the 3-ethylene ketal of cortisone acetate by reduction with LiAlH₄ followed by cleavage of the glycerol side chain with periodic acid.

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

(12) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954); **79**, 1130 (1957); R. F. Hirschmann, R. Miller, J. Wood, and E. R. Jones, *ibid.*, **78**, 4956 (1956).

(5) (a) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, *J. Chem. Soc.*, 3646 (1950); (b) S. P. Barton, G. Cooley, B. Ellis, and V. Petrov, *ibid.*, 5094 (1957).

(6) Satisfactory elemental analyses were obtained for all of the crystalline compounds. Rotations (D line) were obtained in chloroform at *c* \approx 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.

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957).

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

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RECEIVED JUNE 21, 1963