using perchloric acid only. Starting with 1,2,3,4,5,8-hexahydro-6-methoxy-2-(4-methoxy-*m*-tolyl)naphthalene (IVg) (8.1 g.) and an appropriate amount of perchloric acid solution, and recrystallizing the crude product from acetone, a yield of 5.4 g. (70%) of product was obtained, m.p. 112–114°; λ_{max} 5.8 (C=O), 8.0 and 9.6 μ(aryl ether).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 79.96; H, 8.05.

8-(4-Methoxy-*m*-tolyl)-1,3,6-cyclodecanetrione (VIIa).—A solution of 3,4,5,6,7,8-hexahydro-6-(4-methoxy-*m*-tolyl)-2-(1H)-naphthalenone (VIe) (0.6 g.) in 25 ml. of ethyl acetate, 10 ml. of *t*-butyl alcohol, and 2 ml. of water was cooled to −30°. Ozone was passed through until no more was absorbed. The solution was evaporated to a volume of about 8 ml. and treated with 0.3 ml. of 90% hydrogen peroxide. The solution was allowed to stand 36 hr. at room temperature and the product which separated was removed and recrystallized from butanone. A yield of 0.3 g. of product was obtained, m.p. 143–148° dec. The product gave a strong ferric chloride test and the infrared spectrum showed a strong band of absorption between 5.8 and 5.9 μ(C=O).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.52; H, 7.28. Found: C, 71.24; H, 7.25.

4,4a,5,6,7,8-Hexahydro-6-(4-methoxy-*m*-tolyl)-2(3H)-naphthalenone (VIf).—3,4,5,6,7,8-Hexahydro-6-(4-methoxy-*m*-tolyl)-2-(1H)-naphthalenone (VIe) (1.6 g.) dissolved in a solution of 0.6 ml. of concentrated hydrochloric acid, 4.4 ml. of water, and 18 ml. of dioxane was refluxed 1.5 hr., and the product was isolated as described for Va. A yield of 1.3 g. of crude product was obtained which melted at 70–90° and could not be purified easily by recrystallization from its isomer, VIe. An analytical sample was obtained by use of preparative scale thin layer chromatography on silica gel H. Starting with 0.6 g. of crude material, 190 mg. of product melting at 90.5–92.5° was obtained, λ_{max} 231 mμ (ϵ 21,800), λ_{max}^{KBr} 6.0 μ(α,β-unsaturated C=O). Except for the aromatic methyl group, n.m.r. spectrum also showed the benzylic proton to be axial, as in VId.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 79.90; H, 8.22.

3,4,5,6,7,8-Hexahydro-6-phenyl-2(1H)-naphthalenone (VIg).—The procedure used to make Va was followed. (1,2,3,4,5,8-Hexahydro-6-methoxy-2-naphthyl)benzene (IVh) (4.9 g.) was hydrolyzed in a solution of perchloric acid in aqueous dioxane to produce 4.5 g. (97.9%) of material distilling at 143–144° (0.01 mm.), λ_{max} 5.8 μ(C=O). The thin layer chromatogram of this product showed two ketone spots, but the slow moving spot was very small.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.95; H, 7.96. Found: C, 85.01; H, 7.92.

8-Phenyl-1,3,6-cyclodecanetrione (VIIb).—3,4,5,6,7,8-Hexahydro-6-phenyl-2(1H)-naphthalenone (VIg) (1.0 g.) was ozonized using the same procedure as for VIe. A yield of 0.5 g. of product was obtained, m.p. 142–144°, λ_{max} 5.8–5.9 μ(C=O). The product gave a strong ferric chloride test.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.41; H, 6.98. Found: C, 74.52; H, 7.34.

4,4a,5,6,7,8-Hexahydro-6-phenyl-2(3H)-naphthalenone (VIh).—A solution of 3,4,5,6,7,8-hexahydro-6-phenyl-2(1H)-naphthalenone (VIg) (2.1 g.) in 25 ml. of ethanol, 9 ml. of water, and 1 ml. of 35% perchloric acid was refluxed 4 hr. The product was isolated using the same procedure as for Va. After recrystallizing the crude product from methanol, a yield of 1.7 g. of product was obtained, m.p. 68–72°, λ_{max} 238 mμ (ϵ 20,400), λ_{max} 5.95 μ(α,β-unsaturated C=O).

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.95; H, 7.96. Found: C, 85.04; H, 8.10.

15-Oxygenated Progesterones. A New Series of Synthetic Mineralocorticoid Antagonists

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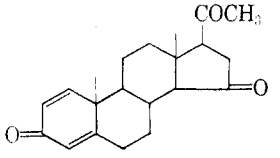
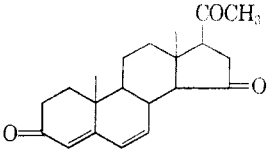
Various 15-oxygenated derivatives of progesterone and related structures were synthesized and their comparative efficacies as antimineralocorticoid agents assessed in adrenalectomized rats treated with deoxycorticosterone acetate. Incorporation of a 15-ketone augmented blocking properties of progesterone and its Δ^1-, Δ^6- and 7β-acetoxy derivatives; oral efficacy was increased in the case of the unsaturated compounds. β-Hydroxylation produced a favorable change in the parenteral properties of Δ^1-, Δ^6-, $\Delta^{1,6}$-, and 7α-acetylthioprogesterone, but orally only the acetylthio derivative demonstrated strong blocking properties. No significant antimineralocorticoid effects were found with the 15α-OH or 15α-acetoxy modifications of the same structures. Available data indicate that the 15-oxygenated steroids as mineralocorticoid antagonists lack progestational activity. In the n.m.r. spectra, a 15-ketone causes a downfield shift in the positions of the 18- and 21-methyl peaks, with further displacement following isomerization at 17. The 15-oxygen functions also affect the resonances due to the 6- and 7-protons of $\Delta^{4,6}$- and $\Delta^{1,4,6}$-3-oxosteroids.

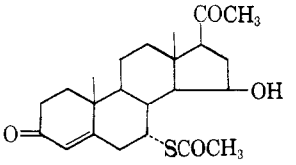
The usefulness of progesterone, a specific antagonist of mineralocorticoids in both laboratory and clinical studies,[1] for diuretic therapy in edematous patients has been well established.[2] We were interested to find that certain 15-oxygenated progesterone derivatives (*e.g.*, IIb, IIIb, and VIc) demonstrate an improved ability parenterally and orally to inhibit renal electrolyte effects of mineralocorticoids in laboratory animals. As synthetic antagonists, these compounds show



IIb



IIIb



VIc

(1) (a) R. L. Landau, D. M. Bergenstal, K. Lugibihl, and M. E. Kascht, *J. Clin. Endocrinol. Metab.*, **16**, 1194 (1955); (b) C. M. Kagawa, *Proc. Soc. Exptl. Biol. Med.*, **99**, 705 (1958); (c) W. B. Kessler and A. Borman, *Ann. N. Y. Acad. Sci.*, **71**, 486 (1958); (d) E. Rosemberg and I. Engel, *Endocrinology*, **69**, 496 (1961).

(2) (a) P. Ducommun and E. Engel, *Schweiz. Med. Wochschr.*, **90**, 561 (1960); (b) P. Hempel-Jørgensen and P. Eilersen, *Acta Med. Scand.*, **168**, 55 (1960); (c) P. P. Silva, R. Chiaverini, M. P. Netto, and A. L. M. Lourenco, *Am. J. Cardiol.*, **6**, 886 (1960); (d) D. F. Dimick, A. A. Dietz, and L. M. Bernstein, *J. Lab. Clin. Med.*, **58**, 812 (1961); (e) J. S. Jenkins, *Brit. Med. J.*, 861 (1961); (f) J. Sedlak and M. Pizl, *Klin. Wochschr.*, **40**, 360 (1962).

Table I

Relative Mineralocorticoid-Blocking Properties of Various 15-Oxygenated Derivatives of Progesterone and Related Steroids in Adrenalectomized Rats

Compd.	Median effective dose (MED)[a] (a)	15-Oxo (b)	15β-OH (c)	15α-OH (d)	15α-Acetoxy (e)
Progesterone (I)	1.30/>9.6	0.44/>2.4[b]	1.53/1.41[b]	>2.4[b]	>2.4[b]
Δ[1]-Progesterone (II)	>2.4[c]	0.23/0.25	0.12/1.60	>2.4	>2.4
Δ[6]-Progesterone (III)	>2.4/>2.4[d]	0.43/0.84[e]	0.25/>2.4[e]	>2.4	>2.4
Δ[1,6]-Progesterone (IV)	>2.4/>2.4[f]	2.4	0.55/2.4	>2.4	>2.4
1α-Acetylthioprogesterone (V)	>2.4[g]	>2.4	>2.4	>2.4	>2.4
7α-Acetylthioprogesterone (VI)	>2.4	>2.4/>2.4	0.43/0.24	...	...
7β-Acetoxyprogesterone (VII)	...	0.56/>2.4[e]	>2.4[e]	...	...
Testosterone (VIII)	1.6/>2.4	...	>2.4[h]	...	...

[a] Dosage in mg. per rat for 50% block of the urinary Na–K response to 12 γ of DCA, given as MED subcutaneously/orally. [b] See ref. 4. [c] F. Sondheimer, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **77**, 5673 (1955). [d] Ref. 19. [e] K. Tsuda, T. Asai, E. Ohki, A. Tanaka, and M. Hattori, *Chem. Pharm. Bull.* (Tokyo), **6**, 387 (1958); K. Tsuda, T. Asai, Y. Sato, T. Tanaka, T. Matsuhisa, and H. Hasegawa, *ibid.*, **8**, 626 (1960). [f] First synthesized by Dr. John S. Baran of these laboratories. [g] See ref. 6. [h] H. L. Herzog, M. J. Gentles, W. Charney, D. Sutter, E. Townley, M. Yudis, D. Kabasakalian, and E. B. Hershberg, *J. Org. Chem.*, **24**, 691 (1959).

structural characteristics distinct from those found in steroidal spirolactones.[3] The present paper will discuss the chemical synthesis and antimineralocorticoid activity of such 15-oxygenated progesterones and, also, data on n.m.r. spectra considered of interest for some of the compounds.

Chemistry.—The chemistry of these compounds is straightforward. The starting materials, 15α- and 15β-hydroxyprogesterone,[4] were converted to the Δ[1]-, Δ[6]-, and Δ[1,6]-derivatives by the usual methods,[5] after initial protection of the 15α-hydroxy group as the acetate.[4] From mother liquors obtained by hydrolysis of 15α-acetoxy-1,4-pregnadiene-3,20-dione (IIe), we isolated a small amount (2% yield) of 15α-hydroxy-17α-pregna-1,4-diene-3,20-dione (IX); oxidation of this compound gave 17α-pregna-1,4-diene-3,15,20-trione (X). The acetylthio compounds were prepared by the method described previously.[6]

Structure–Activity Relations.—Mineralocorticoid-blocking properties of the 15-oxygenated progesterones were assessed in 4-hr. tests using adrenalectomized rats according to published procedures.[7] The compounds were administered either by subcutaneous injection or orally in an oil solvent, and activity was determined by reversal of the urinary Na-retaining and K-dissipating actions of deoxycorticosterone acetate (DCA). Table I describes the approximate relative activities of a number of progesterone-like structures in terms of the dosage required for 50% inhibition of a standard dose of DCA (median effective dose or MED). Progesterone (Ia), the prototype of the 15-oxygenated derivatives, was effective by injections (MED 1.3 mg.), but relatively ineffective orally (MED >9.6 mg.). No significant blocking properties were noted in the derivatives with unsaturation in rings A and B (IIa, IIIa, and IVa) or acetylthio modifications at C-1 (Va) or 7 (VIa). The further incorporation of a 15-ketone into these structures produced variable changes of blocking efficacy (Ib–VIIb), but in some instances caused a favorable influence on activity. Most noteworthy was the increase of parenteral activity found in Ib–IIIb compared with their respective parent structures and, correspondingly, the strong oral efficacy associated with IIb and IIIb. Comparable activity parenterally was noted with VIIb, but not orally (MED >2.4 mg.). The triene derivative (IVb) with the combined unsaturation features of IIb and IIIb showed relatively poor properties parenterally (MED 2.4 mg.).

β-Hydroxylation at 15 gave a spectrum of activities in some respects unlike that found for the oxo modification. Thus, the data demonstrate the possibility of a reduction of parenteral efficacy (Ic *vs.* Ib, VIIc *vs.* VIIb) or an increase of activity parenterally (IVc *vs.* IVb, VIc *vs.* VIb) or orally (VIc *vs.* VIb), depending on the basic structure of the steroid. No significant antimineralocorticoid effects (MED >2.4 mg. subcutaneously) were noted with the tests of the 15α-OH cogeners (Id–Vd) or the 15α-acetoxy derivatives (Ie–Ve). Two additional compounds, IX and X (not included in Table I), were also inactive showing MED >2.4 mg. subcutaneously. Results of the present study indicate that the blocking activities of some of the 15-oxygenated compounds (Ib–IIIb, VIIb, IIc–IVc, VIc) are comparable to those of spironolactone,[8] a steroidal spirolactone[3b] and specific antagonist of mineralocorticoids,[7] with proven diuretic efficacy in clinical edema.[9]

The effect of modifying the antimineralocorticoid properties of another gonadal hormone, testosterone,[10] with 15β-hydroxylation was measured; the data demonstrate a loss of blocking efficacy with the structural change (VIIIc *vs.* VIIIa).

Of considerable parallel interest is the fact that the 15-oxo or 15β-OH derivatives (Ib–IVb, VIIb, Ic–IVc, VIc), effective as blocking agents, all failed to demonstrate progesterone-like changes in the uterine endometrium of immature rabbits primed with estra-

(3) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957); (b) J. A. Cella and R. C. Tweit, *J. Org. Chem.*, **24**, 1109 (1959); (c) J. A. Cella, E. A. Brown, and R. R. Burtner, *ibid.*, **24**, 743 (1959); (d) E. A. Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960); (e) N. W. Atwater, R. H. Bible, Jr., E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *ibid.*, **26**, 3077 (1961); (f) R. C. Tweit, F. B. Colton, N. L. McNiven, and W. Klyne, *ibid.*, **27**, 3325 (1962).

(4) J. Fried, R. W. Thoma, D. Perlman, and J. R. Gerke, U. S. Patents 2,879,280 and 2,879,277 (March 24, 1959).

(5) (a) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960); (b) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(6) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

(7) C. M. Kagawa, *Endocrinology*, **67**, 125 (1960).

(8) 3-(3-Oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (spironolactone, Aldactone-A®); by a similar comparison, spironolactone shows MED values of 0.33 and 0.48 mg. subcutaneously and orally, respectively.

(9) (a) C. L. Gantt, *N. Y. State J. Med.*, **61**, 756 (1961); (b) D. H. P. Streeten, *Clin. Pharmacol. Therap.*, **2**, 359 (1961).

(10) C. M. Kagawa and R. S. Jacobs, Jr., *Proc. Soc. Exptl. Biol. Med.*, **102**, 521 (1959).

TABLE II

D-RING CHANGES AND THE NUCLEAR MAGNETIC RESONANCE SPECTRA

Compd.	N.m.r. spectra (c.p.s.)[a] —position— 18-CH_3	21-CH_3
1,4-Pregnadiene-3,20-dione (IIa)	42	126
1,4-Pregnadiene-3,15,20,-trione (IIb)	46	133
17α-Pregna-1,4-diene-3,15,20-trione (X)	64	135

[a] At 60 Mc./sec.

diol-17β (Clauberg assay).[11] Altogether, therefore, these studies with the 15-oxygenated steroids illustrate that the antimineralocorticoid property of progesterone is separable from its endometrial effect.

N.m.r. Data.—The spectra[12] of the compounds exhibited some interesting effects. Since the results of introducing 15-hydroxyl groups have been already reported in the literature,[13] only the shifts caused by a 15-ketone are illustrated in Table II for a representative series of compounds. The 19-methyl resonance occurred at 74–75 c.p.s. in these three compounds. The displacement in the 18-methyl caused by the introduction of a 15-ketone into IIa is in the direction anticipated from the geometry of the D-ring,[14a] but the effect on the 21-methyl is surprising considering its greater distance. The drastic change in geometry resulting from isomerization at 17 causes only a small additional displacement of the 21-methyl, but substantially moves the 18-methyl signal. The deshielding of the 18-methyl caused by isomerization at 17 is similar in magnitude to the values reported by Slomp and Zürcher.[14b,c] The shifts caused by isomerization at 17 and presence of the 15-ketone are additive in this case, since the 18- and 21-methyl peaks in 15α-hydroxy-17α-pregna-1,4-diene-3,20-dione (IX) occur at the predicted positions, 60 and 129 c.p.s., respectively.

Another interesting effect of the 15-substituents is on the resonance due to the 6- and 7-hydrogens in the $\Delta^{1,4,6}$- and $\Delta^{4,6}$-3-oxosteroids. In 4,6-pregnadiene-3,20-dione (IIIa) these protons appear as a sharp singlet[15] which is virtually unaffected by the addition of a 15α-acetoxy group; contrastingly, the other 15-oxygen functions split the resonance into multiplets as shown in Table III. In the 4,6-dienones, the 7-hydrogen resonance is strongly displaced downfield by a 15-ketone (IIIb)[14a] or α-hydroxyl (IIId) which are in close proximity. This situation produces a typical AB pattern (J = 10 c.p.s.) with little additional splitting of the 6-proton signal (J = 1–2 c.p.s.) by the 4-proton.

In contrast to IIIa, the signals for the 6- and 7-hydrogens in the parent $\Delta^{1,4,6}$-3-oxosteroid (IVa) are shifted in opposite directions to produce an AB pattern. Acetoxylation in the 15α-position (IVe) has no effect on these peaks, while the introduction of a ketone (IVb) or 15α-hydroxyl (IVd) produces shifts similar to those obtained in IIIb and IIId. A single peak results in the 15β-hydroxy compound with the displacement downfield of the 6-proton to the 7-proton position. Otherwise, the vinyl hydrogen pattern is similar for the $\Delta^{1,4,6}$ (IVa–e) and the $\Delta^{1,4}$ (IIa–e) compounds. In the absence of nearby functions,[16] the positions of the 1-, 2-, and 4-proton signals are quite stable. The 4-hydrogen peak is displaced by a 1,2 (IIa *vs.* Ia), but not by a 6,7 (IIIa *vs.* Ia), double bond, providing thereby a method for distinguishing $\Delta^{1,4}$- and $\Delta^{4,6}$-3-ketones. Opposite effects on the 19-methyl peak are produced by these two systems. In progesterone, introduction of a 1,2 double bond causes a paramagnetic shift of 4 c.p.s., while a 6,7 double bond (IIIa) produces a diamagnetic displacement of 3 c.p.s. The two effects are additive in a compound containing both of these bonds (IVa).

Experimental

The seven acetylthio compounds (Vb–e and VIa–c) were prepared by method B of ref. 6. The physical constants and analytical data of all the new compounds are listed in Table IV. The ultraviolet spectra of IVa–e have three peaks.[17]

15β-Hydroxyl-1,4-pregnadiene-3,20-dione (IIc).—A solution of 15β-hydroxyprogesterone (Ic) (6.0 g.) in 0.33 l. of benzene, was azeotroped to remove traces of water and refluxed for 2 days with 5.0 g. of 2,3-dichloro-5,6-dicyanobenzoquinone. The benzene solution was decanted from a dark solid, concentrated, and the resulting residue recrystallized from methylene chloride–acetone to yield 2.05 g. of IIc, m.p. 226–229°. Recrystallization gave an analytical sample.

1,4-Pregnadiene-3,15,20-trione (IIb).—15β-Hydroxy-1,4-pregnadiene-3,20-dione (IIc) (0.16 g.) was dissolved in 25 ml. of C.P. acetone and oxidized with 0.15 ml. of Jones–Djerassi reagent.[18] The product was crystallized from acetone-ether to yield 0.10 g. of IIb.

15α-Acetoxy-1,4-pregnadiene-3,20-dione (IIe).—This compound was prepared from 15α-acetoxyprogesterone (Ie) by the method used for the 15β-hydroxy compound (IIc); the yield was similar.

15α-Hydroxy-1,4-pregnadiene-3,20-dione (IId).—15α-Acetoxy-1,4-pregnadiene-3,20-dione (IIe), 1.2 g., was hydrolyzed for 18 hr. with 0.5 g. of sodium hydroxide in 75 ml. of methanol. Neutralization with acetic acid followed by concentration under vacuum gave a residue which readily dissolved in methylene chloride–water. A crystalline solid was obtained by concentration of this methylene chloride solution, and recrystallized from methylene chloride–ether to yield 0.7 g. of IId.

15α-Acetoxy-4,6-pregnadiene-3,20-dione (IIIe).—15α-Acetoxyprogesterone (Ie) (18.5 g.) was dissolved in 0.5 l. of *t*-butyl alcohol with 18.5 g. of chloranil and 0.1 g. of *p*-toluenesulfonic acid monohydrate. The solution was refluxed for 3 hr. and concentrated *in vacuo*, and the residue was separated after trituration with chloroform and water. The chloroform layer, washed several times with base, was filtered through diatomaceous earth, and the filtrate was washed with water, dried, and con-

(11) Available data indicate a potency parenterally <5% that of the reference standard progesterone for each of the compounds; we are grateful to Drs. F. J. Saunders and E. F. Nutting of our Endocrinology Department for these results.

(12) Determined in deuteriochloroform on a Varian A-60 spectrometer; shifts measured from the tetramethylsilane resonance.

(13) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); Y. Kawazoe, Y. Sato, T. Okamoto, and K. Tsuda, *ibid.*, **11**, 328 (1963).

(14) (a) Protons in most orientations around a carbonyl group are deshielded by it. O. L. Chapman, H. G. Smith, and R. W. King, *J. Am. Chem. Soc.*, **85**, 806 (1963), have recently reported some of the rare examples of diamagnetic shifts due to a carbonyl group and have discussed the spacial requirements for this. See also L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959, pp. 121–125. (b) Quoted by W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963); see also G. Slomp, Abstracts, 13th Annual Mid-America Spectroscopy Symposium, Chicago, Ill., April 30–May 3, 1962, p. 30. (c) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(15) Dr. M. J. Kalm of these laboratories reports such a sharp singlet to be associated with the spectra of a number of $\Delta^{4,6}$-3-oxosteroids.

(16) We have observed that the position of the 1-proton doublet shifts about 25 c.p.s. to lower frequency with the introduction of an 11-ketone into a $\Delta^{1,4}$-3-ketone system, paralleling the effect on the 7-hydrogen of a 15-ketone.

(17) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

(18) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

Table III

Positions of Vinyl Protons in Nuclear Magnetic Resonance Spectra[a]

Compd.	Unsaturation	15-Oxygen function	1-H	2-H	4-H	6-H	7-H
Ia	Δ^4	...			344		
IIa	$\Delta^{1,4}$	...	429, 420	378, 369	365		
IIIa	$\Delta^{4,6}$	...			342	369	369
IVa	$\Delta^{1,4,6}$	...	433, 423	382, 372	364	368, 358	384, 374
Ib	Δ^4	C=O			343		
IIb	$\Delta^{1,4}$	C=O	429, 419	380, 370	366		
IIIb	$\Delta^{4,6}$	C=O			343	377, 367	424, 414
IVb	$\Delta^{1,4,6}$	C=O	431, 421	381, 371	363	383, 373	422, 412
Ic	Δ^4	β-OH			343		
IIc	$\Delta^{1,4}$	β-OH	432, 422	380, 370	368		
IIIc	$\Delta^{4,6}$	β-OH			343	374, 364	392, 382
IVc	$\Delta^{1,4,6}$	β-OH	433, 423	383, 373	364	381	381
Id	Δ^4	α-OH			344		
IId	$\Delta^{1,4}$	α-OH	427, 417	377, 367	364		
IIId	$\Delta^{4,6}$	α-OH			343	374, 364	412, 402
IVd	$\Delta^{1,4,6}$	α-OH	428, 418	379, 369	366	380, 370	403, 393
IIe	$\Delta^{1,4}$	α-$OCOCH_3$	428, 418	378, 368	365		
IIIe	$\Delta^{4,6}$	α-$OCOCH_3$			345	372	372
IVe	$\Delta^{1,4,6}$	α-$OCOCH_3$	428, 418	379, 369	363	365, 355	381, 371

[a] In c.p.s. at 60 Mc./sec.

Table IV

Physical and Analytical Data of 15-Oxygenated Progesterones

Compd.	M.p., °C.[a]	$\lambda_{max}^{CH_3OH}$, mμ	ε	$[\alpha]D^b$	Formula	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
IIb	208–210.5	243	15,200	+111 ± 4°	$C_{21}H_{26}O_3$	77.27	76.91	8.03	8.04
IIc	233–236.5	244	15,400		$C_{21}H_{28}O_3$	76.79	76.67	8.59	8.45
IId	227–230	244.5	16,000	+137 ± 1	$C_{21}H_{28}O_3$	76.79	76.78	8.59	8.52
IIe	193–196	243.5	16,600	+70	$C_{23}H_{30}O_4$	74.56	74.40	8.16	8.17
IIId	177–179	284	26,400	+220 ± 2	$C_{21}H_{28}O_3$	76.79	77.08	8.59	8.50
IIIe	169.5–172	282	27,000	+160 ± 1	$C_{23}H_{30}O_4$	74.56	74.44	8.16	8.24
IVa	147–148.5			+114	$C_{21}H_{26}O_2$	81.25	81.39	8.44	8.44
IVb	186–187.5			+102.5	$C_{21}H_{24}O_3$	77.75	77.52	7.46	7.57
IVc	242.5–245			+92 ± 1	$C_{21}H_{26}O_3$	77.27	77.03	8.03	8.23
IVd	176–178				$C_{21}H_{26}O_3$	77.27	76.80[c]	8.03	8.20[c]
IVe	171–172.5			+84 ± 1	$C_{23}H_{28}O_4$	74.97	75.16[c]	7.66	8.15[c]
Vb	166.5–167.5 dec.	240	16,600	+202 ± 2	$C_{23}H_{30}O_4S$	68.62	68.12[d]	7.51	7.59
Vc	188–189 dec.	241	15,400	+165 ± 1	$C_{23}H_{32}O_4S$	68.28	67.88	7.98	7.99
Vd	148–150 dec.	241.5	16,500		$C_{23}H_{32}O_4S$	68.28	68.31	7.98	8.13
Ve	177–178 dec.	240.5	16,100	+167 ± 2	$C_{25}H_{34}O_5S$	67.23	67.04	7.67	7.54
VIa	181–184.5	238	19,400		$C_{23}H_{32}O_3S$	71.09	71.25	8.30	8.25
VIb	187–189	237	22,200	+50 ± 1	$C_{23}H_{30}O_4S$	68.62	68.43	7.51	7.45
VIc	229.5–230.5 dec.	238	19,400	−13.5	$C_{23}H_{32}O_4S$	68.28	68.38	7.98	8.12
IX	178–180	244	15,400	−21 ± 1	$C_{21}H_{28}O_3$	76.79	76.54	8.59	8.28
X	167–169	243	15,500		$C_{21}H_{26}O_3$	77.27	77.12	8.03	8.01

[a] Determined in a bath and corrected. [b] Determined in chloroform at 25 ± 2°. [c] Careful chromatography and crystallization failed to remove the last traces of impurities remaining in these 2 compounds after dichlorodicyanobenzoquinone dehydrogenation. [d] Although the carbon analysis was poor, a sulfur determination checked theory. *Anal.* Calcd.: S, 7.97. Found: S, 7.83.

centrated. Benzene was added to the residue and distilled. The residue was crystallized from acetone–ether and recrystallized from methanol to yield 4.7 g. of IIIe.

15α-Hydroxy-4,6-pregnadiene-3,20-dione (IIId).—A solution of 4.65 g. of 15α-acetoxy-4,6-pregnadiene-3,20-dione (IIIe) and 2 g. of sodium hydroxide in 300 ml. of methanol was allowed to stand overnight, then neutralized with acetic acid, and diluted with 100 ml. of water. Distillation of the methanol under vacuum gave a solid which was readily separated by filtration and recrystallized from acetone to yield 2.75 g. of IIId.

1,4,6-Pregnatriene-3,20-dione (IVa).—A solution of IIIa[19] (12.5 g.) and 10 g. of dichlorodicyanoquinone in 120 ml. of purified dioxane was refluxed for 2 hr., then cooled; the dichlorodicyanohydroquinone was removed by filtration. The residue from the concentration of the filtrate was dissolved in benzene and chromatographed on 250 g. of silica gel. The column was washed with benzene and 2% ethyl acetate in benzene and eluted with 5% ethyl acetate in benzene. The 3rd through the 9th l. of eluate gave a residue which was crystallized 3 times from ether to yield 2.8 g. of IVa.

15β-Hydroxy-1,4,6-pregnatriene-3,20-dione (IVc).—15β-Hydroxy-4,6-pregnadiene-3,20-dione (IIIc) (5.17 g.) was refluxed for 4 hr. with 4.1 g. of 2,3-dichloro-5,6-dicyanobenzoquinone and 60 ml. of purified dioxane and, after cooling, the mixture was filtered to remove the hydroquinone. The residue obtained from concentration of the filtrate was triturated with acetone–ether and the resulting solid crystallized twice from methylene chloride–methanol–acetone to give 2.02 g. of IVc.

1,4,6-Pregnatriene-3,15,20-trione (IVb).—One gram of 15β-hydroxy-1,4,6-pregnatriene-3,20-dione (IVc) was partially dissolved in 130 ml. of acetone and oxidized with 0.89 ml. of Jones–Djerassi reagent.[18] After dilution with water, the mixture was concentrated under vacuum to remove the acetone; the solids thus obtained were separated and chromatographed on silica gel. The material eluted with 20% ethyl acetate in benzene was recrystallized from methylene chloride to give 0.42 g. of IVb.

(19) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

15α-Acetoxy-1,4,6-pregnatriene-3,20-dione (IVe).—15α-Acetoxy-4,6-pregnadiene-3,20-dione (IIIe) (4.15 g.) was dissolved in 40 ml. of purified dioxane together with 2.8 g. of dichlorodicyanoquinone. The solution was refluxed for 2 hr., cooled, and filtered. The residue obtained from the concentration of the filtrate was dissolved in benzene and chromatographed on silica gel. The residue from the combined eluates with 15 and 20% ethyl acetate–benzene was crystallized from acetone–ether to yield 1.95 g. of material. These crystals were dissolved in methylene chloride, washed with a basic solution, then recrystallized from acetone after removal of the solvent. One half of the material was rechromatographed; 0.3 g. of IVe, crystallized from acetone, was obtained from the 20% ethyl acetate–benzene eluates.

15α-Hydroxy-1,4,6-pregnatriene-3,20-dione (IVd).—15α-Acetoxy-1,4,6-pregnatriene-3,20-trione (IVe) (0.7 g.) was hydrolyzed by the method used for 15α-hydroxy-1,4-pregnadiene-3,20-dione. The product was chromatographed on silica gel and the residue from the 30% ethyl acetate–benzene eluates crystallized from acetone to yield 0.2 g. of IVd.

15α-Hydroxy-17α-pregna-1,4-diene-3,20-dione (IX).—The mother liquors from the hydrolysis of 49 g. of 15α-acetoxy-1,4-pregnadiene-3,20-dione (IIe) were concentrated, and the residue so obtained dissolved in benzene for chromatography on 400 g. of silica gel. A yield of 0.9 g. of IX, crystallized in acetone, was found in the combined fractions eluted with 35% ethyl acetate–benzene.

17α-Pregna-1,4-diene-3,15,20-trione (X).—This compound was crystallized in a yield of 0.14 g. from acetone–ether after oxidation[18] of 0.20 g. of the corresponding 15α-hydroxy compound (IX).

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Steroids. CCL.[1] The Synthesis of 2-Methylenehydrocortisone[2]

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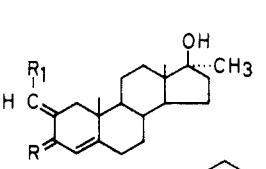
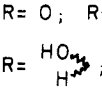
The synthesis of 17α,20;20,21-bismethylenedioxy-11β-hydroxy-2-N-piperidinomethylenepregn-4-en-3-one (IIf) and its conversion to 2-methylenehydrocortisone (IIi) are described. An improved preparation of the bismethylenedioxy derivative of hydrocortisone is reported.

Interest in C-2 substituted cortical hormones stems from the finding by an Upjohn group that introduction of a 2α-methyl substituent into hydrocortisone brought about a 4.5- and 2.6-fold increase, respectively, of its antiinflammatory and mineralocorticoid activities.[3] Subsequent studies in several laboratories have led to the preparation of cortical hormones substituted at C-2 by hydroxyl,[4] cyano,[5] fluoro,[6] hydroxymethylene,[7] and formyl[8] groups. However, none of these modifications were reported to enhance the activity of the parent hormone.

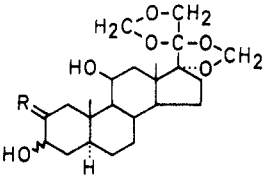
Our interest in hormone analogs having sp^2-hybridized carbon atoms at C-2 and C-3[9] together with our recent work[10] which led to the preparation of 2-methylene-Δ^4-3-ketoandrostenes prompted us to extend the latter study to the cortical hormone series. This communication describes the synthesis of 2-methylenehydrocortisone (IIi).[11]



Ia- R= O; R1= 

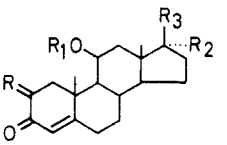
b- R=  ; R1= H

c- R= O; R1= H



IIIa- R= CH_2; with Δ^4 double bond

b- R= α CH_3, β H



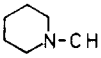
IIa- R= H_2; R1= H; R2= OH; R3= 

b- R= H_2; R1= H; R2,R3= bismethylenedioxy

c- R= H_2; R1= CH_3OCH_2 ; R2,R3= bismethylenedioxy

d- R= H_2; R1= $HOCH_2$; R2,R3= bismethylenedioxy

e- R= CHOH; R1= H; R2,R3= bismethylenedioxy

f- R=  ; R1= H; R2,R3= bismethylenedioxy

g- R= CH_2; R1= H; R2,R3= bismethylenedioxy

h- R= CH_2; R1= H; R2= OH; R3= 

i- R= CH_2; R1= H; R2= OH; R3= 

In our earlier work it was noted that the reduction of 17β-hydroxy-17α-methyl-2-N-piperidinomethylene-androst-4-en-3-one (Ia) with sodium borohydride afforded 17α-methyl-2-methyleneandrost-4-ene-3ξ,17β-

(1) Part CCXLIX: F. Alvarez, *Steroids*, submitted for publication.

(2) This paper constitutes Part VII in the series of ring A modified hormone analogs. Part VI: P. Crabbé, J. Revilla, and A. Bowers, *J. Med. Chem.*, **6**, 182 (1963).

(3) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955); W. W. Byrnes, L. E. Barnes, B. J. Bowman, W. E. Dulin, E. H. Morley, and R. O. Stafford, *Proc. Soc. Exptl. Biol. Med.*, **91**, 67 (1956).

(4) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 145 (1955).

(5) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961); J. C. Orr and A. Bowers, manuscript in preparation.

(6) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(7) H. M. Kissman, A. S. Hoffman, J. F. Poletto, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 950 (1962).

(8) J. A. Edwards, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **27**, 3378 (1962).

(9) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963), and subsequent papers.

(10) J. A. Edwards, M. C. Calzada, and A. Bowers, *ibid.*, **6**, 178 (1963).

(11) For an alternate route to 2-methylene cortical hormones which led to 2-methylenecortisone 21-acetate *cf.* T. R. Carrington, A. G. Long, and A. F. Turner, *J. Chem. Soc.*, 1572 (1962); see also U. S. Patent 2,847,430 (1958), and P. F. Beal, F. H. Lincoln, and J. A. Hogg, Abstracts, 132nd National Meeting of the American Chemical Society, New York, N. Y., Sept., 1957, p. 12-O.