Analogs of Steroid Hormones. I. 6-(4-Oxocyclohexenyl) and 6-(*p*-Hydroxyphenyl) Derivatives of 2-Naphthalenone[1]

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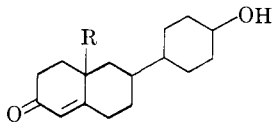
Starting with three different 6-methoxy-2(1H)-naphthalenones, a number of 4-oxocyclohexenyl and *p*-hydroxyphenyl derivatives of 2-naphthalenone have been prepared and tested for hormone and hormone-antagonist activity.

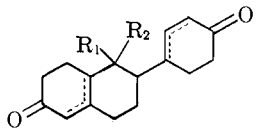
While compounds having steroid hormone activity have been found useful in cancer chemotherapy, their normal physiological activity is frequently responsible for undesirable side effects. For this reason, we became interested in synthesizing steroid analogs in order to study the relationship between structure and biological activity and to see if antineoplastic activity can be divorced from normal hormonal activity. Since much work has been done on estrogen analogs, it was decided to devote the initial effort, mainly, to androgen analogs.

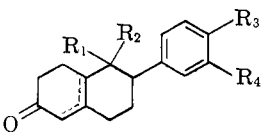
Since 2-phenylnaphthalene and 2-phenylindane derivatives have shown estrogenic activity, we decided to study first 6-cyclohexenyl and 6-phenyl derivatives of 2-naphthalenone. Wilds[2] and co-workers have previously synthesized and bioassayed compounds Ia and Ib starting with bicyclohexyl derivatives and using the method of du Feu, *et al.*,[3] to add the third ring. These compounds were found to be possibly weakly androgenic but they were not tested for hormone antagonist activity.



Ia, R = H
Ib, R = CH_3

We were interested in making the following compounds in order to study the effect of varying the C-5 alkyl substituent and the C-6 substituted ring on biological activity.

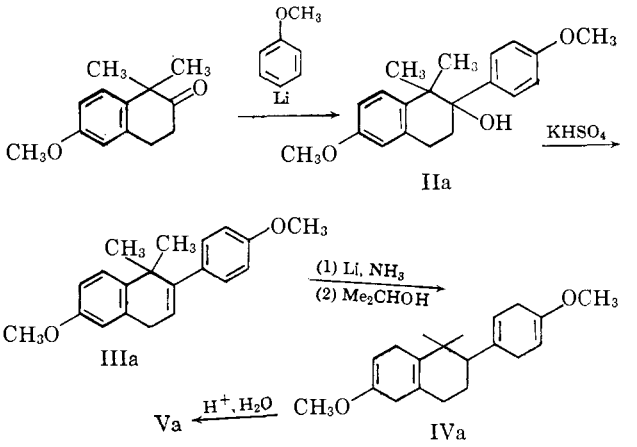




VI

Va, $R_1 = R_2 = CH_3$
b, R_1 = H; $R_2 = C_2H_5$
c, $R_1 = R_2$ = H
(mixtures of isomers)
VIa, $R_1 = R_2 = CH_3$; $R_3 = OCH_3$; $R_4 = CH_3$ (mixture of isomers)
b, $R_1 = C_2H_5$; R_2 = H; R_3 = OAc; R_4 = H (mixture of isomers)
c, $R_1 = R_2$ = H; R_3 = OH; R_4 = H (α,β-unsatd. ketone)
d, $R_2 = R_2$ = H; $R_3 = OCH_3$; R_4 = H (α,β-unsatd. ketone)
e, $R_1 = R_2$ = H; $R_3 = OCH_3$; $R_4 = CH_3$ (β,γ-unsatd. ketone)
f, $R_1 = R_2$ = H; $R_3 = OCH_3$; $R_4 = CH_3$ (α,β-unsatd. ketone)
g, $R_1 = R_2 = R_3 = R_4$ = H (β,γ-unsaturated ketone)
h, $R_1 = R_2 = R_3 = R_4$ = H (α,β-unsaturated ketone)

The syntheses started with suitably substituted 6-methoxy-2-tetralones, using the steps shown below for preparing Va. The principal difficulty encountered was in the reduction of IIIa–c. These compounds were insoluble in media using ether or tetrahydrofuran as



auxiliary solvents and thus failed to reduce. It was found that morpholine was a much more effective solvent in this reaction, although reduction was still not complete when there were two rings to reduce. It was also noted that a methyl *ortho* to the methoxyl in the benzene ring prevented reduction of that ring. To prepare VIb and c, the dihydropyran adduct of *p*-bromophenol was used instead of *p*-bromoanisole in making the lithium reagent to react with the tetralone. Dihydropyran was split off during the dehydration step and the resulting phenolic group was unaffected by the lithium–ammonia reduction.

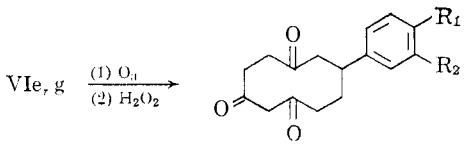
Except for VIc, which was a solid, the products submitted for bioassay were liquid mixtures of isomers, the double bonds being located either α,β or β,γ to the carbonyl as indicated. Thin layer chromatographic analysis of the products showed that at least four components were present in Va–c and two in VIa,b. The α,β-unsaturated isomers VIc, d, and f were solids and could be purified. Attempts to separate isomers of Va–c by preparative thin layer chromatography were unsuccessful as they were oxidized during the process. Judging from the relative sizes of the chromatographic spots and the ultraviolet extinction coefficient values of 8000–10,000, where 20,000 could be expected for the pure conjugated isomer, conjugation with the carbonyl was not particularly favored and the double bonds were randomly distributed.

(1) Supported by a research grant (CY-5077) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) A. L. Wilds, C. H. Hoffman, and T. H. Pearson, *J. Am. Chem. Soc.*, **77**, 647 (1955).

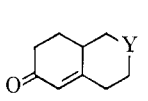
(3) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

The maxima of the ultraviolet absorption spectra of the ketones Va–c and VIa–d and f, but not VIh, showed an unexpected hypsochromic shift. According to Woodward's[4] rule as modified by Fieser,[5] the $\pi \rightarrow \pi^*$ transition of the above compounds should show absorption maxima at about 238 mμ in ethanol solution. Instead, they showed maxima at 229–234 mμ. On the other hand VIh and 4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone have the expected maxima at 238 mμ. Since a carbonyl conjugated with an endocyclic double bond would be expected to show a maximum at about 228 mμ,[5] the location of the double bonds in Va–c and VIa–f was left in doubt. However, the n.m.r. spectra of IIIe showed that 3 ethylenic protons were present and the n.m.r. spectrum of VId and f showed that one ethylenic proton was present, thus locating the double bonds in the indicated positions. As a further check samples of VIe and g were ozonized. The products isolated were ketones which showed strong ferric chloride tests. It thus appears that the abnormal ultraviolet spectra are due to hypsochromic shifts caused by the *p*-methoxyphenyl group in VIa–d and f and the cyclohexenone ring

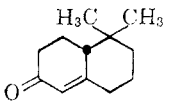


VIIa, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = R_2 = H$

in Va–c. This phenomenon is probably caused by an inductive removal of electrons from the chromophore resulting in a destabilization of the excited state. It has been shown previously[6a,b] that compounds such as IX show hypsochromic shifts of similar magnitude. Kharasch[7] and Brown[8] have shown that the *p*-methoxyphenyl group is more electronegative than phenyl.



IX



X

Y = NCH_3, S, or $N(CH_3)_2$[6]

It was observed that the proportions of ketone isomers formed from the hydrolysis of the enol ethers, IVa–h depended on the acid used as a catalyst. It was found that perchloric acid in aqueous dioxane hydrolyzed the enol ethers within 5 min. at room temperature to produce a product containing mostly β,γ-unsaturated ketones. When hydrochloric acid was used as catalyst, either on the product ketones from the perchloric acid treatment or on the enol ethers, products containing 50–65% of α,β-unsaturated ketones were produced, again in a few min. at room temperature. Prolonged standing in the acid medium did not produce any further shift toward conjugation. On the other hand, when VIg was refluxed for several hours in aqueous dioxane, it rearranged mostly to the conjugated isomer. It thus appears that the rearrangement of the double bond may be either prototropic or anionotropic in nature, the latter occurring more readily in this instance. 3,4,5,6,7,8-Hexahydro-2(1H)-naphthalenone did not exhibit this phenomenon. Both hydrochloric and perchloric acids catalyzed the rearrangement at about the same speed. The reaction was very slow at room temperature and required 3–4 hr. of heating at reflux temperatures before the extinction coefficient at 238 mμ reached a maximum value.

Concerning the steric relationships of these compounds, the n.m.r. spectra of VId and f showed axial benzylic protons. This indicates that the benzene ring is attached equatorially to the naphthalenone and this same conclusion most probably applied to Va–c and VIa–h. The naphthalenone ring is also probably attached equatorially to the cyclohexenone ring of the conjugated isomers of Va–c as the acid-catalyzed equilibration of the double bond would be expected to give the more stable product. The bridgehead hydrogens of Va–c, VIa–d, f, and h (conjugated isomers) are probably axial as it has been shown that the bridgehead hydrogens of 19-nortestosterone[9] and 4,4a,5,6,7,8-hexahydro-5,5-dimethyl-2(3H)-naphthalenone (X)[10], which were made by the same method from the corresponding phenol ether, are axial. The ethyl groups of Vb and VIb are probably attached equatorially as the metal–ammonia reduction of IIIb could be expected to favor the *trans* isomer.[11]

When bioassayed[12] IIId showed 35% inhibition of estrone in the antiuterotropic assay, but was not antiandrogenic: VIb was weakly uterotropic at the 9 mg. level. The following compounds showed no significant activity in the following assays: Va,b—androgenic, antiandrogenic, antiuterotropic; VIa—antiandrogenic, antiuterotropic; IIIe, VIe—uterotropic, antiuterotropic. Test results for the other compounds are not yet available and will be reported elsewhere.

It thus does not appear that the type of compound reported on here is a promising prototype for steroid hormone or hormone antagonist activity. The two compounds that did show some biological activity (IIId and VIb) possessed ethyl groups next to the phenol ring, while corresponding compounds lacking the ethyl group (IIIe and VIe) were inactive. This may indicate that such a group is essential *per se* for activity, or that its function, at least in part, is to change the over-all shape of the molecule by twisting the adjacent ring so that it no longer lies in the general plane of the rest of the molecule. Laarhoven, *et al.*,[13] have shown that alkyl substituents on methoxystilbenes cause twisting, the extent of which may be estimated from the degree of hypsochromic shift of an N → V band in the ultraviolet spectra of these compounds due to steric hindrance of coplanarity. This phenomenon was noted with these compounds, IIId absorbing at 254 mμ and IIIe at 314 mμ. If the data of the above authors is applied to these compounds, this corresponds to a twist angle of 35–40° in IIId. One would also expect

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(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 16–21.

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(7) M. S. Kharasch and R. Marker, *J. Am. Chem. Soc.*, **48**, 3130 (1926).

(8) H. C. Brown, *ibid.*, **61**, 1483 (1939).

(9) C. Djerassi, R. Riniker, and B. Riniker, *ibid.*, **78**, 6362 (1956).

(10) A. G. Armour, O. Buchi, A. Eschenmoser, and A. Storni, *Helv. Chim. Acta*, **42**, 2233 (1959).

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twisting to occur in octalone derivatives such as VIb, when the ethyl group and the ring both have equatorial conformations.

Experimental[14]

2,6-Naphthalenediol.—This compound was prepared using the method of Emmert.[15] A mixture of 375 g. of potassium hydroxide and 75 g. of sodium hydroxide was heated in a 1-l. 3-necked stainless steel flask, equipped with stirrer and thermocouple well, until the bulk of the water was driven off. The mixture was cooled to 250° and 165 g. of sodium 2-naphthol-6-sulfonate was added, with stirring. The mixture was then heated to 325° over a period of 1–1.5 hr., cooled, and dissolved in water. The solution was acidified with hydrochloric acid and ice. The product was filtered and recrystallized from water after decolorizing with Norit. The yields averaged 43 g. of tan product, m.p. 205–210°.

2,6-Dimethoxynaphthalene.—A solution of 25 g. (1.1 g.-atoms) of sodium in 500 ml. of absolute methanol was held at the boiling point while 80 g. (0.5 mole) of 2,6-naphthalenediol was added with stirring. The reaction was carried out in a 3-l. flask equipped with dropping funnel and gas inlet tube. After addition was complete, the bulk of the methanol was removed by vacuum evaporation, the flask was filled with argon, and 200 ml. of anhydrous dioxane was added. To the stirred mixture, 205 g. (1.1 mole) of methyl *p*-toluenesulfonate was added, and the mixture was heated at reflux until the reaction appeared to be complete. If the mixture became too thick to stir, more dioxane or benzene was added. Any residual alkalinity was removed by small additions of methyl sulfate. Water was then added to dissolve the salts and benzene was removed by vacuum evaporation until the product solidified. The product was washed with methanol and recrystallized from acetone to give yields of 50–55 g. (53–58%); m.p. 146–148°, lit.[16] m.p. 149°.

2,6-Dimethoxy-3,4-dihydronaphthalene.—The method of Robinson and Weygand[17] was used except that a smaller excess of sodium and a shorter reaction time were found to give satisfactory results. Starting with 69 g. (3 g.-atoms) of sodium and 69 g. (0.37 mole) of 2,6-dimethoxynaphthalene, and using isoamyl alcohol as the proton source, a yield of 56 g. (82%) of product was obtained, m.p. 82–83°, lit.[17] m.p. 83–84°.

3,4-Dihydro-6-methoxy-2(1H)-naphthalenenone.—2,6-Dimethoxy-3,4-dihydronaphthalene (45 g., 0.24 mole) was dissolved in 125 ml. of 88% formic acid at room temperature. The mixture was filtered through hardened filter paper to remove any insoluble material and allowed to stand 10 *min.* The solution was diluted with water and extracted with benzene. The benzene solution was washed free of acid, dried, and distilled. A yield of 40 g. (97%) of product distilling at 115–118° (0.1 mm.) was obtained, m.p. 33–35°, lit.[18] m.p. 36°.

3,4-Dihydro-6-methoxy-1,1-dimethyl-2(1H)-naphthalenone.—The method of Armour[19] was used except that the alkylation was run in a mixture of dioxane and ether instead of benzene. The product was obtained in 82% yield, $n^{20}D$ 1.5440. The infrared absorption maxima were identical with the literature values.[19]

1-Ethyl-3,4-dihydro-6-methoxy-2(1H)-naphthalenone.—Stork's enamine method,[20] as used by Murphy, *et al.*,[21] in the preparation of the 1-methyl analog was followed, except that a longer reflux (8 hr.) with the ethyl iodide was required; since the enamine product was resistant to hydrolysis, it was necessary to reflux with 5% sodium hydroxide rather than with water to obtain the product. Starting with 23.4 g. of 3,4-dihydro-6-methoxy-2(1H)-naphthalenone, a yield of 21.4 g. (79%) of product distilling at 115–118° (0.1 mm.) was obtained, $n^{20}D$ 1.5481. The infrared spectrum showed bands at 5.8 (C=O), 7.9, and 9.6 μ (aryl ether).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.62; H, 7.80.

3,4,5,6,7,8-Hexahydro-2(1H)-naphthalenone and 4,4a,5,6,7,8-Hexahydro-2(3H)-naphthalenone.—β-Naphthol was hydrogenated using the method of Stork,[22] and the phenolic fraction was alkylated with methyl sulfate. The resulting ether was reduced using the method of Wilds and Nelson,[23] except that redistilled ammonia[24] was used. The resulting enol ether was hydrolyzed in almost quantitative yield with 88% formic acid as outlined above for 6-methoxy-β-tetralone. The product distilled at 116–120° (10 mm.), $n^{20}D$ 1.5108, λ_{max} 237 mμ (ϵ 1600); lit.[25] $n^{26}D$ 1.5213, λ_{max} 238 mμ (ϵ 14,100) for the conjugated isomer. Thus the original product contained about 11% of the conjugated isomer.

Acid-Catalyzed Rearrangements.—A solution of 23.3 mg. of the above product in 10 ml. of 0.1 *M* hydrochloric acid and 20 ml. of ethanol was allowed to stand at room temperature, in the dark. At intervals, samples were withdrawn and ultraviolet spectra were taken. After 48 hr. the extinction coefficient had increased to 3200, after 6 days to 5350, and after 13 days to 8850. There was a tendency for the maximum to shift slightly from 237 to 240 mμ.

A 3.4-g. sample of the unconjugated ketone was refluxed with 20 ml. of ethanol and 10 ml. of 1.2 *M* hydrochloric acid for 30 min. The ultraviolet spectra of the product showed λ_{max} 238 mμ (ϵ 7400). The thin layer chromatogram showed two ketone spots. A gas chromatogram of the product also showed two peaks.

A 2.5-g. sample of the unconjugated ketone dissolved in 20 ml. of ethanol and 10 ml. of 0.35 *M* perchloric acid was refluxed for a total of 7 hr. After 2 hr., the extinction coefficient of the ultraviolet spectrum had increased to 9900, after 4 hr. to 12,300; there was no further increase after 4 hr. Again the maximum shifted to 240 mμ. Thin layer chromatograms of the products showed two ketone spots. The final product showed $n^{20}D$ 1.5232. The infrared spectra showed bands at 5.8 (C=O) and 5.95 μ (α,β-unsaturated C=O) of varying heights depending on the relative amounts of the isomers present.

1,2,3,4-Tetrahydro-2-hydroxy-6-methoxy-2-(*p*-methoxyphenyl)-1,1-dimethylnaphthalene (IIa).—Lithium (2.3 g., 0.33 g.-atom) was melted in a test tube containing 1–2 ml. of mineral oil, and sodium (0.1 g.)[26] was added and stirred into the lithium. The metal was then transferred to a 50-ml. flask containing about 35 ml. of heavy mineral oil, remelted, and stirred at high speed until the metal was dispersed into fine particles. After cooling, the oil was separated and the metal was washed twice with cyclohexane by decantation. The metal was then transferred to a 300-ml. 3-necked flask equipped with stirrer, dropping funnel, and thermometer with 50 ml. of dry ether. *n*-Butyl bromide (0.8 g.) was then added and the mixture was stirred for about 5 min. until the temperature of the mixture stopped rising. The mixture was cooled to −10° (argon atmosphere) and *p*-bromoanisole (10.1 g., 0.054 mole) in 20 ml. of dry ether was added over a 0.5-hr. period keeping the temperature at about −7°. After 5 min. of additional stirring, 3,4-dihydro-6-methoxy-1,1-dimethyl-2(1H)-naphthalenone (10.0 g., 0.049 mole), in 25 ml. of dry ether, was added over a 20-min. period, keeping the temperature at −5°. The mixture was stirred for 10 min. and then decanted through a layer of glass wool into a mixture of ice and ether. The ether layer was washed with water, dried, and evaporated *in vacuo*. The residual product was subjected to high-vacuum distillation to recover 3.2 g. of unreacted ketone, and the residue was recrystallized from acetone to give 7.5 g (71.6%) of product, m.p. 147–149°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.95; H, 7.69. Found: C, 77.05; H, 7.72.

1,2,3,4-Tetrahydro-2-hydroxy-6-methoxy-2-(4-methoxy-*m*-tolyl)-1,1-dimethylnaphthalene (IIb).—This compound was prepared as outlined for IIa. Starting with 3,4-dihydro-6-methoxy-1,1-dimethyl-2(1H)-naphthalenone (8.0 g.) and 4-bromo-3-methylanisole (12.0 g.), a yield of 6.0 g. (47%) of product, m.p. 143–145°, was obtained.

(14) Melting points are corrected. Microanalyses by Galbraith Laboratories. Ultraviolet spectra were taken in 95% ethanol (Beckman DU), infrared spectra in carbon tetrachloride, unless otherwise indicated (Beckman IR5). The n.m.r. spectra were run and interpreted by Dr. Donald P. Hollis of Varian Associates.

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(26) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 1807 (1960).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.30; H, 7.97. Found: C, 77.13; H, 7.98.

1,4-Dihydro-6-methoxy-2-(*p*-methoxyphenyl)-1,1-dimethylnaphthalene (IIIa).—A mixture of IIa (9.5 g.) and potassium bisulfate (1.0 g.) was heated to an oil bath temperature of 150° (0.5 mm.). After gas evolution had practically ceased, the mixture was cooled and the product was recrystallized from acetone. A yield of 6.5 g. (72%) of product was obtained, m.p. 127–128°. The infrared spectrum of the compound showed typical aryl ether bands at 8.0 and 9.6 μ.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.34; H, 7.23.

1,4-Dihydro-6-methoxy-2-(4-methoxy-*m*-tolyl)-1,1-dimethylnaphthalene (IIIb).—A solution of IIb (3.0 g.) in 10 ml. of toluene was heated with thionyl chloride (2.0 g.) at reflux for 5 min., and excess solvent and thionyl chloride were removed by vacuum evaporation. The residue was recrystallized from ethanol to give 2.3 g. (82%) of product, m.p. 108–110°. The infrared spectrum showed typical aryl ether bands at 8.0 and 9.6 μ.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.81; H, 7.79. Found: C, 81.82; H, 7.62.

1-Ethyl-3,4-dihydro-6-methoxy-2-(*p*-methoxyphenyl)naphthalene (IIIc).—The procedure used to make IIa and IIIa was employed except that the carbinol was not isolated. After removal of the unreacted ketone, the residue was dehydrated directly with potassium bisulfate. Starting with 1-ethyl-3,4-dihydro-6-methoxy-2(1H)-naphthalenone (10.0 g.) and recrystallizing the product from acetone, a yield of 7.5 g. (69% based on ketone consumed) of product was obtained, m.p. 91–94°; λ_{max} 230 mμ (ε 13,800), 254 mμ (13,600). The infrared spectrum showed typical aryl ether bands at 8 and 9.6 μ.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.84; H, 7.62.

***p*-(1-Ethyl-3,4-dihydro-6-methoxy-2-naphthyl)phenol (IIId).**—Using the same procedure as for IIIc, 1-ethyl-3,4-dihydro-6-methoxy-2(1H)-naphthalenone (10.0 g.) was reacted with the lithium reagent prepared from 15.2 g. of 2-(*p*-bromophenoxy)-tetrahydropyran[27] and lithium (2.3 g.). In this case, the dehydration of the carbinol with potassium bisulfate also caused the loss of the dihydropyran residue. After distilling the product at 166–176° (0.01 mm.) and recrystallizing twice from cyclohexane-benzene solution, a yield of 7.0 g. (69% based on ketone consumed) of product was obtained, m.p. 105.5–107°; λ_{max} 229 mμ (ε 12,300), 255 mμ (11,900); λ_{max}^{KBr} 2.8, 2.9 (OH), 8.0, 9.6 μ (aryl ether).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.42; H, 7.14. Found: C, 80.96; H, 7.43.

***p*-(3,4-Dihydro-6-methoxy-2-naphthyl)phenol (IIIe).**—Using the same procedure as for IIIc and d, and starting with 3,4-dihydro-6-methoxy-2(1H)-naphthalenone (10.0 g.) and recrystallizing the crude product from acetone, a yield of 3.5 g. (37.6% based on ketone consumed) of product, m.p. 185–187°, λ_{max}^{KBr} 2.9 (OH), 8.0, 9.6 μ (aryl ether), was obtained.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.79; H, 6.54.

3,4-Dihydro-6-methoxy-2-(*p*-methoxyphenyl)naphthalene (IIIf).—Using the same procedure as for IIIc, 3,4-dihydro-6-methoxy-2(1H)-naphthalenone (10.0 g.) was treated with the lithium reagent prepared from *p*-bromoanisole (11.8 g.) and lithium (2.3 g). The carbinol was dehydrated with potassium bisulfate to give, after recrystallizing the crude product from acetone, 7.1 g. (68.9% based on ketone consumed) of product, m.p. 150–152°; λ_{max} 233 mμ (ε 20,000), 314 mμ (24,200); λ_{max}^{KBr} 8.0, 9.65 μ (aryl ether).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.40; H, 6.71.

3,4-Dihydroxy-6-methoxy-2-(4-methoxy-*m*-tolyl)naphthalene (IIIg).—Using the same procedure as for IIIc, 3,4-dihydro-6-methoxy-2(1H)-naphthalenone (10.0 g.) was treated with the lithium reagent prepared from 4-bromo-2-methylanisole (12.0 g.) and lithium (2.0 g.). The carbinol was dehydrated with potassium bisulfate to give, after recrystallizing the crude product from butanone, 6.6 g. (61.1% based on ketone consumed) of product, m.p. 114–115°; λ_{max} 232 mμ (ε 13,300), 314 mμ (26,300); λ_{max} 8.0, 9.6 μ (aryl ether).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.42; H, 7.14. Found: C, 81.21; H, 7.12.

3,4-Dihydro-6-methoxy-2-phenylnaphthalene (IIIh).—3,4-Dihydro-6-methoxy-2-(1H)-naphthalenone (5.0 g.) was added at 4° to the Grignard reagent obtained from bromobenzene (6.6 g.) and magnesium (2.4 g.). After hydrolyzing with ammonium chloride solution, the reaction mixture was worked up using the same procedure as for IIIc. After recrystallizing from acetone, a yield of 3.0 g. (66.6% based on ketone consumed) of product was obtained, m.p. 105–107°; λ_{max} 233 mμ (ε 15,100), 313 mμ (22,400); λ_{max}^{KBr} 7.95, 9.55 μ (aryl ether).

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.44; H, 6.77. Found: C, 86.37; H, 6.90.

1,2,3,4,5,8-Hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)-1,1-dimethylnaphthalene (IVa).—1,4-Dihydro-6-methoxy-2-*p*-(methoxyphenyl)1,1-dimethylnaphthalene (IIIa) (3.2 g., 0.011 mole) was dissolved in 70 ml. of morpholine and added to a solution of lithium (5.0 g., 0.71 g.-atom) in 180 ml. of redistilled ammonia[23] contained in a 1-l. flask equipped with stirrer, thermometer, Dry Ice condenser, and dropping funnel. The mixture was stirred at −45° while 2-propanol (54 ml., 0.9 mole) was added over a 10-min. period. The reaction was then controlled by adjusting the temperature between −40 and −33°, the color of the lithium discharging in about 1 hr. The ammonia was then evaporated, water was added, and the product was taken up in benzene. The benzene layer was washed with water and dried, the solvent was removed by vacuum evaporation, and the crude product was recrystallized from alcohol to yield 1.4 g. (43.7%) of product, m.p. 90.5–92.5. The infrared spectrum showed the enol ether doublet at 5.90 and 6.00 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 80.00; H, 9.33. Found: C, 80.13; H, 9.41.

1,2,3,4,5,8-Hexahydro-6-methoxy-2-(4-methoxy-*m*-tolyl)-1,1-dimethylnaphthalene (IVb).—The procedure used to make IVa was followed. Starting with 1,4-dihydro-6-methoxy-2-(4-methoxy-*m*-tolyl)-1,1-dimethylnaphthalene (IIIb) (3.8 g., 0.012 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54 ml., 0.9 mole) and recrystallizing the crude product from alcohol, a yield of 2.8 g. (73.7%) of product was obtained, m.p. 127–129°. The infrared spectrum showed the enol ether doublet at 5.9 and 6.0 μ as well as the aryl ether band at 8.0 and 9.6 μ.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.77; H, 8.97. Found: C, 81.05; H, 8.65.

1-Ethyl-1,2,3,4,5,8-hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)naphthalene (IVc).—The procedure used to make IVa was used. Starting with 1-ethyl-3,4-dihydro-6-methoxy-2-(*p*-methoxyphenyl)naphthalene (IIIc) (5.0 g., 0.017 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54 ml., 0.9 mole) and recrystallizing the crude product from ethanol, a yield of 2.4 g. (47.3%) of product was obtained, m.p. 110–113°. The infrared spectrum showed the enol ether doublet at 5.9, 6.0 μ. The n.m.r. spectrum (CCl_4, 60 Mc.) showed a peak for two ethylenic protons at τ = 4.5 p.p.m. and for one at τ = 5.3 p.p.m., thus showing that the double bonds are located as indicated.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 80.00; H, 9.33. Found: C, 80.25; H, 9.22.

***p*-(1-Ethyl-1,2,3,4,5,8-hexahydro-6-methoxy-2-naphthyl)phenyl Acetate (IVd).**—The procedure used to make IVa was used except that, after evaporating the ammonia and adding water, the reaction mixture was made slightly acid with acetic acid before making the solvent extraction. Starting with *p*-(1-ethyl-3,4-dihydro-6-methoxy-2-naphthyl)phenol (IIId) (3.6 g., 0.013 mole), lithium (3 g., 0.43 g.-atom), and 2-propanol (35 ml., 0.58 mole) and acetylating the crude product with acetic anhydride in pyridine, a yield of 2.8 g. (66.7%) of product distilling at 162–165° (0.01 mm.) was obtained. The infrared spectrum showed a carbonyl band at 5.7 and an enol ether band at 6 μ.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.30; H, 7.98. Found: C, 77.09; H, 7.98.

***p*-(1,2,3,4,5,8-Hexahydro-6-methoxy-2-naphthyl)phenol (IVe).**—The procedure used to reduce IIId was used. Starting with *p*-(3,4-dihydro-6-methoxy-2-naphthyl)phenol (IIIe) (5.0 g., 0.02 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54 ml., 0.9 mole) and recrystallizing the crude product from benzene, a yield of 3.0 g. (59.4%) of product was obtained, m.p. 117–120°. The infrared spectrum showed bands at 2.8, 3.0 (OH) and 5.9, 6.0 μ (enol ether).

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 79.69; H, 7.81. Found: C, 79.79; H, 7.95.

1,2,3,4,5,8-Hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)naphthalene (IVf).—The procedure used to make IVa was followed. Starting with 3,4-dihydro-6-methoxy-2-(*p*-

(27) W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).

methoxyphenyl)naphthalene (IIIf) (5.0 g., 0.019 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54 ml., 0.9 mole) and recrystallizing the crude product from ethanol, a yield of 3.3 g. (64.7%) of product was obtained, m.p. 87–94°. After preparative thin layer chromatography on silica gel H, the melting point was raised to 108–112°, indicating that the original reduction was incomplete. The infrared spectrum showed the enol ether doublet at 5.9 and 6.0 μ, but also small aryl ether bands at 8.0 and 9.6 μ.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.61; H, 8.59.

1,2,3,4,5,8-Hexahydro-6-methoxy-2-(4-methoxy-*m*-tolyl)naphthalene (IVg).—The procedure used to make IVa was followed. Starting with 3,4-dihydro-6-methoxy-2-(4-methoxy-*m*-tolyl)naphthalene (IIIg) (5.0 g., 0.019 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54 ml., 0.9 mole) and recrystallizing the crude product from ethanol, a yield of 3.8 g. (74.5%) of product was obtained, m.p. 93–96°. The infrared spectrum showed the enol ether doublet at 5.9 and 6.0 μ as well as aryl ether bands at 8 and 9.6 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.28; H, 8.45. Found: C, 79.82; H, 8.92.

1,2,3,4,5,8-Hexahydro-6-methoxy-2-phenylnaphthalene (IVh).—The procedure used in making IVa was followed. Starting with 3,4-dihydro-6-methoxy-2-phenylnaphthalene (IIIh) (5.0 g., 0.021 mole), lithium (5.0 g., 0.71 g.-atom), and 2-propanol (54.0 ml., 0.9 mole) and recrystallizing the crude product from ethanol, a yield of 4.2 g. (83%) of product was obtained, m.p. 70–75°. The infrared spectrum showed the enol ether doublet at 5.9 and 6.0 μ.

Anal. Calcd. for $C_{17}H_{20}O$: C, 85.00; H, 8.33. Found: C, 85.09; H, 8.22.

4,4a,5,6,7,8-Hexahydro-5,5-dimethyl-6-(4-oxo-2-cyclohexen-1-yl)-2(3H)-naphthalenone (Va).[28]—1,2,3,4,5,8-Hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)-1,1-dimethyl naphthalene (IVa) (3.0 g.) was added to a solution of 0.5 ml. (0.006 mole) of 71% perchloric acid, diluted to 5 ml. with water, and 25 ml. of dioxane. The mixture was swirled until homogeneous and allowed to stand at room temperature for 15 min. The solution was then poured into 150 ml. of water containing enough sodium bicarbonate to neutralize the acid. The product was taken up in benzene. The benzene layer was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was distilled to give a yield of 2.4 g. (90%) of product distilling at 153–155° (0.01 mm.). The ultraviolet spectrum showed an absorbance maximum at 225 mμ (ϵ 4200) A further treatment with perchloric acid failed to change this value. The infrared spectrum showed a band at 5.8 (strong) (=O) and 5.95 μ (medium) (α,β-unsaturated C=O), a thin layer chromatogram of this product showed four spots with the leading one the largest and the last one the smallest.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.20; H, 8.67.

This product was treated with acid again, this time substituting 0.5 ml. (0.006 mole) of 38% hydrochloric acid for the perchloric acid. The solution was allowed to stand for 10 min., and the product was isolated as previously described. A yield of 2.0 g. of product distilling at 162–165° (0.01 mm.) was obtained. The ultraviolet spectrum showed a maximum at 232 mμ (ϵ 8800). The infrared spectrum again showed bands at 5.8 and 5.95 μ but this time the 5.95 band was almost as high as the one at 5.8 μ. The thin layer chromatogram of this product showed four ketone spots of about the same size. Another treatment with hydrochloric acid at room temperature produced no further change. The last product was the one submitted for bioassay.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.26; H, 8.63.

5-Ethyl-4,4a,5,6,7,8-hexahydro-6-(4-oxo-2-cyclohexen-1-yl)-2(3H)-naphthalenone (Vb).[28]—The procedure used to make Va was followed. Starting with 1-ethyl-1,2,3,4,5,8-hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)naphthalene (IVc) (4.7 g.) and an appropriate amount of perchloric acid solution, a yield of 3.6 g. (90%) of product distilling at 145–147° (0.01 mm.) was obtained; λ_{max} 226 mμ (ϵ 3800); λ_{max} 5.8 (strong) (C=O), 5.95 μ (weak) (α,β-unsaturated C=O).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.31; H, 9.13.

This product was then treated with hydrochloric acid as described for Va. A yield of 3.2 g. of material distilling at 153–155° (0.01 mm.) was obtained; λ_{max} 230 mμ (ϵ 8300); λ_{max} 5.8 (strong) (C=O), 5.95 μ (strong) (α,β-unsaturated C=O). This product was submitted for bioassay. The thin layer chromatograms for these products were similar to those for Va.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.18; H, 8.87.

4,4a,5,6,7,8-Hexahydro-6-(4-oxo-2-cyclohexen-1-yl)-2(3H)-naphthalenone (Vc).[28]—The procedure used to make Va was followed. Starting with (1,2,3,4,5,8-hexahydro-6-methoxy-2-(4-methoxy-1,4-cyclohexadien-1-yl)naphthalene (IVf) (5.7 g.) and an appropriate amount of the perchloric acid solution, a yield of 4.9 g. (96%) of product distilling at 146–147° (0.01 mm.) was obtained; λ_{max} 224 mμ (ϵ 6300); λ_{max} 5.8 (strong) (C=O), 5.95 μ (weak) (α,β-unsaturated C=O). A sample of this product was submitted for bioassay.

A part (3.3 g.) of this product was treated with hydrochloric acid as described for Va. A yield of 2.9 g. of material distilling at 155–158° (0.01 mm.) was obtained; λ_{max} 230 mμ (ϵ 14,500); λ_{max} 5.8 (strong) (C=O), 5.95 μ (strong) (α,β-unsaturated C=O). The thin layer chromatograms of these products were similar to those of Va.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.69; H, 8.19. Found: C, 78.61; H, 8.16.

4,4a,5,6,7,8,-Hexahydro-6-(4-methoxy-*m*-tolyl)-5,5-dimethyl-2(3H)-naphthalenone (VIa).[29]—The procedure used to make Va was followed except that hydrobromic acid was used instead of perchloric or hydrochloric acid. Starting with 1,2,3,4,5,8-hexahydro-6-methoxy-2-(4-methoxy-*m*-tolyl)-1,1-dimethylnaphthalene (IVb) (3.0 g.) and an appropriate amount of hydrobromic acid solution, a yield of 2.2 g. (77.1%) of product distilling at 148–151° (0.01 mm.) was obtained; λ_{max} 230 mμ (ϵ 12,400); λ_{max} (strong) (C=O), 5.95 (strong) (α,β-unsaturated C=O), 8 and 9.6 μ (aryl ether).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.54; H, 8.72. Found: C, 80.29; H, 8.63.

5-Ethyl-4,4a,5,6,7,8-hexahydro-6-(*p*-hydroxyphenyl)-2(3H)-naphthalenone Acetate (VIb).[29]—The procedure used to make Va was followed except that the treatment with perchloric acid was omitted and hydrochloric acid was used directly. Starting with *p*-(1-ethyl-1,2,3,4,5,8-hexahydro-6-methoxy-2-naphthyl)phenyl acetate (IVd) (2.0 g.) and an appropriate amount of hydrochloric acid solution, a yield of 1.5 g. (78.9%) of product distilling at 160–170° (0.01 mm.) was obtained; λ_{max} 230 mμ (ϵ 15,000); λ_{max} 5.65 (ester C=O), 5.8 (strong) (ketone C=O), 5.95 μ (strong) (α,β-unsaturated C=O). The thin layer chromatogram of the product exhibited two ketone spots.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.92; H, 7.69. Found: C, 76.58; H, 7.93.

4,4a,5,6,7,8-Hexahydro-6-(*p*-hydroxyphenyl)-2(3H)-naphthalenone (VIc).—The procedure used to make Va was followed, except that the treatment with perchloric acid was omitted. Starting with *p*-(1,2,3,4,5,8-hexahydro-6-methoxy-2-naphthyl)-phenol (IVe) (2.0 g.) and an appropriate amount of hydrochloric acid solution, and recrystallizing the crude product from acetone, a yield of 1.4 g. (70%) of product was obtained, m.p. 197–200° dec.; λ_{max} 230 mμ (ϵ 20,700); λ_{max}^{KBr} 6.1 μ (α,β-unsaturated C=O).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.34; H, 7.4. Found: C, 79.13; H, 7.50.

4,4a,5,6,7,8-Hexahydro-6-(*p*-anisyl)-2(3H)-naphthalenone (VId).—This product was recovered from the thin layer chromatographic purification on a preparative scale of Vc (silica gel H). Starting with a total of 1.5 g. of Vc and eluting the last band in each case with methanol, a yield of 100 mg. of product was obtained, m.p. 97–99.5°, λ_{max} 229 mμ (ϵ 23,100), λ_{max}^{KBr} 6.0 μ (α,β-unsaturated C=O). The thin layer chromatogram of this product exhibited one ketone spot.

The n.m.r. spectrum ($DCCl_3$, 60 Mc.) showed a peak for three aromatic protons at τ = 5.9 p.p.m. The proton at C-6 was shown to be axial, its resonance consisting of three triplets, the center one of which was located at τ = 2.8 p.p.m. This pattern results from the coupling of an axial proton with four other protons, two axial and two equatorial.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.69; H, 7.81. Found: C, 79.62; H, 7.90.

3,4,5,6,7,8-Hexahydro-6-(4-methoxy-*m*-tolyl)-2(1H)-naphthalenone (VIe).—The procedure used to make Va was followed

(28) This product is actually a mixture of four different isomers due to different locations of the double bonds whose positions were discussed previously.

(29) This product is actually a mixture of two different isomers due to different locations of the double bond whose position was discussed previously.

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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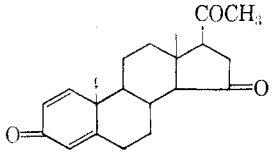
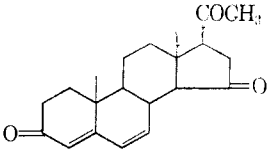
Various 15-oxygenated derivatives of progesterone and related structures were synthesized and their comparative efficacies as antimineralocorticoid agents assessed in adrenalectomized rats treated with deoxycorticosterone acetate. Incorporation of a 15-ketone augmented blocking properties of progesterone 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.

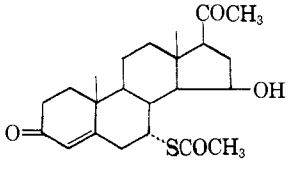
The usefulness of progesterone, a specific antagonist of mineralocorticoids in both laboratory and clinical studies,[1] for diuretic therapy in edematous patients has been well established.[2] We were interested to find that certain 15-oxygenated progesterone derivatives (*e.g.*, IIb, IIIb, and VIc) 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

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