logarithm, and the reciprocal, of the concentration of intermediate *vs.* time. The first relation was nearly linear while the second was not, indicating that the second step of the reaction is a first-order process. The data are shown in Table II.

TABLE II
TEST FOR A FIRST-ORDER CONSTANT—LATTER STAGE RATE DATA

$10^5/t$, sec.$^{-1}$[a]	Specific[b] conductance $\times 10^6$	$[C_2H_5P(OC_4H_9)_3I]$	k, sec.$^{-1}$, $\times 10^5$
9.60	21.8	0.152	2.4
9.17	21.3	.149	2.5
8.93	20.8	.145	2.7
8.48	20.5	.143	2.6
8.20	20.4	.142	2.6
8.06	20.2	.141	2.6
7.70	19.9	.139	2.6
6.71	19.2	.134	2.5
6.10	18.8	.131	2.4
5.72	18.6	.130	2.3
2.92	14.2	.099	2.0
1.24	5.4	.038	2.1
1.21	5.3	.037	2.0
1.19	5.2	.036	2.0
1.05	4.6	.032	1.9
		Mean	2.3

[a] Uncorrected for time required for initial build-up of the conducting intermediate. [b] Corrected for initial conductance.

While a more rigorous mathematical treatment of the rate data for these consecutive reactions would be possible, such a treatment does not seem justified in terms of the precision of the experimental data and particularly the approximations made in relating conductance to concentration. The value of the work lies in its confirmation of the existence of a phosphonium ion intermediate in the Arbuzov rearrangement of simple aliphatic tertiary phosphites and its indication of the relative rates of the two steps.

It might be thought that when different alkyl groups are present in the halide and phosphite starting materials a mixture of products would be obtained since a second alkyl halide is generated in the course of the reaction.[5] It now appears that the first step of the reaction is so much faster than the second that by the time appreciable amounts of the second alkyl halide are formed in the reaction mixture, the phosphite ester has been largely converted to the phosphonium intermediate and is no longer available. This is in accord with work showing that in one example of such a system only a single product was obtained, in 95% yield.[6]

Acknowledgment.—We thank Dr. John P. Schaefer for making the conductivity bridge available.

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(6) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

16β-Methyldesoxycorticosterone Acetate (16β-Methyl DOCA)

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Two different syntheses of 16α-methyldesoxycorticosterone acetate have been reported some years ago by one of the authors and his co-workers[1,2] and by Petrow and Williamson.[3] The lack of any mineralcorticoid activity of this methylated DOCA derivative prompted us to advance the hypothesis that the 16α-methyl group is responsible for abolishing the sodium retention activity of 16α-methyl-9α-fluoroprednisolone (dexamethasone) when compared with the nonmethylated parent compound. This hypothesis was also supported by the results of Wieland and co-workers[4] in the case of aldosterone, which by 16α-methylation completely lost its typical mineralcorticoid activity.

In prosecution of the work in this field it seemed interesting to investigate whether the 16β-methylation of DOCA would also be accompanied by the loss of the sodium retention activity. In this case the former hypothesis should also be valuable to explain the absence of activity on the electrolyte balance of the new 16β-methylcorticoids (16β-methylprednisolone[5,6] and 16β-methylprednisone[7]).

The attempts to prepare 16β-methyl-DOCA according to both procedures previously described for the preparation of the 16α-methyl isomer failed; the 21-iodo intermediate seems to be very unstable and could not be converted by usual methods into the 21-acetate. Therefore we started from the known[8] pregna-5,16-diene-3β,21-diol-20-one 21-acetate (I), in which the 21-acetoxy group was already present. Compound I was converted with diazomethane to the 16α,17-diazomethylene derivative II.

Pyrolysis of this compound afforded 16-methylpregna - 5,16 - diene - 3β,21 - diol - 20 - one 21-acetate (III), which was reduced with hydrogen (Raney nickel catalyst) to 16β-methylpregn-5-ene-3β,21-diol-20-one 21-acetate (IV). It is well known that this hydrogenation gives preferentially

(1) British Patent Application No. 39037/58, December 3, 1958.
(2) G. Maffii, L. Fontanella, P. Schiatti, and E. Testa, *Experientia* (Basel), **16**, 422 (1960).
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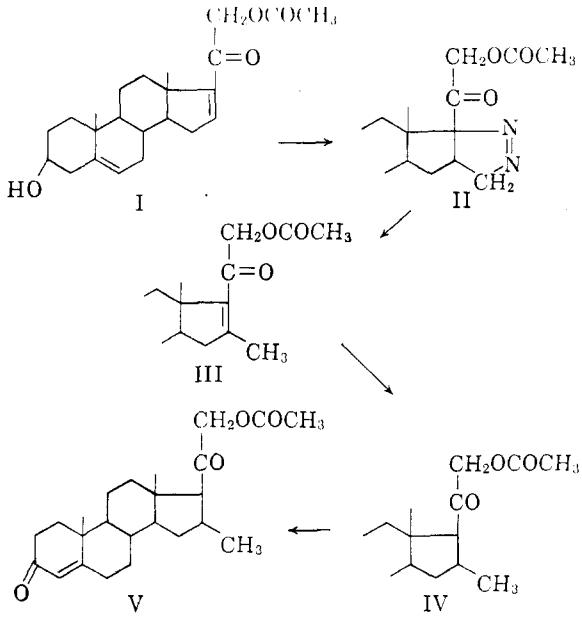
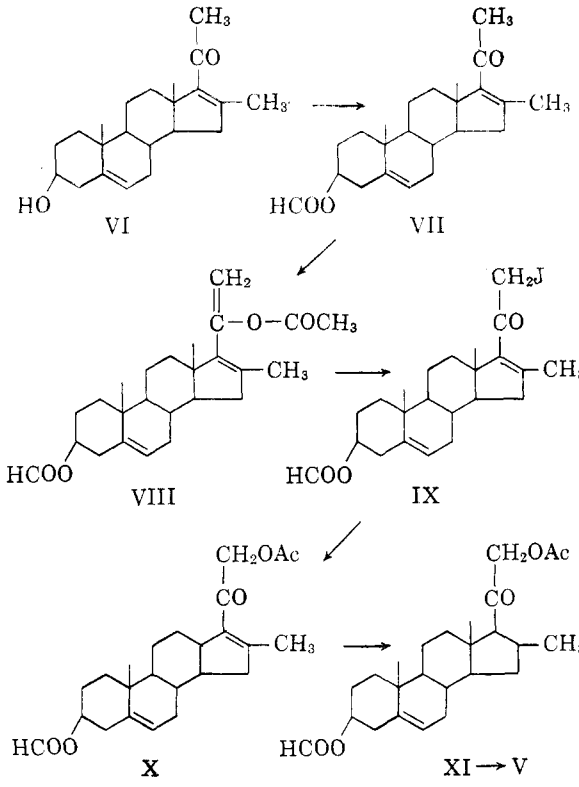
the 16β derivatives[9-11]: The stereospecificity of this reaction seems to be enhanced by the presence of a C-21-acetoxy group.[12] The transformation of IV to the 16β-methyl DOCA (V) was eventually performed through an Oppenauer oxidation.



In an alternate synthesis the introduction of the methyl group in the 16-position before the 21-acetoxylation was carried out starting from 16-methylpregnadienolone[11] (VI). This compound was formylated and converted into 16-methylpregna-5,16-diene-3β,21-diol-20-one 3-formate 21-acetate (X) through the 20-enol acetate (VIII) and the 21-iodo derivate (IX). The selective hydrogenation of the Δ-16 double bond with Raney nickel and the direct oxidation of the formyl ester (XI) by the Oppenauer[13] method led to 16-methyldesoxycorticosterone acetate identical with that obtained by the other process. This synthesis is an extension of a known method for the preparation of DOCA[8]; in this case it was expected that X would be more soluble than the corresponding free alcohol and that XI could be more easily purified. In both cases the desired solubility was not reached; moreover, compound X was largely hydrolyzed, as shown by the presence of a band near 3340 cm.$^{-1}$ in the infrared spectrum.

The easy isomerization of the 16β-methylpregnane-20-one derivatives to the 16β-methyl-17α-pregnane-20-one analogs has been noted by many authors.[9,11,14] Some consideration of this



should also be made for our compounds. In analogy with the observations of Wettstein on 16-methylpregnane derivatives,[11] the formation of the 17α-isomer during the Raney nickel hydrogenation may be excluded. The values of the molecular rotatory power in dioxane of desoxycorticosterone acetate (M_D = +630) and of the two methyl derivatives (16α-methyl; M_D = +525°; 16β-methyl; M_D = +570°) are so close that the 17α-configuration in the case of 16β-methyldesoxycorticosterone acetate is to be excluded; otherwise, a ΔM about ten times greater would be observed.

An additional and complete proof of the proposed structure was given hydrolyzing the 16β-methyldesoxycorticosterone acetate with ethanolic potassium hydroxide and reacetylating the product obtained. In this way it was possible to obtain the isomer 16β-methyl-17α-pregna-4-ene-21-ol-3,20-dione 21-acetate (XII); M_D^{chlf} +77. Compound V shows in the same solvent a M_D^{chlf} +620; therefore the ΔM_D (17α−17β) = −543 is in good accordance with the data reported in literature for analogous cases.[15] It was interesting to note that 16α-methyl DOCA, when submitted to an identical alkaline treatment, led to the recovery of unchanged starting compound in almost quantitative yield, emphasizing that the 16β-methyl group may be considered as responsible for this isomerization. These results have therefore to be considered as an exception to the Lardon[16]

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(10) P. De Ruggieri, *Farmaco* (Parvia), *Ed. Sci.*, **16**, 583 (1961).
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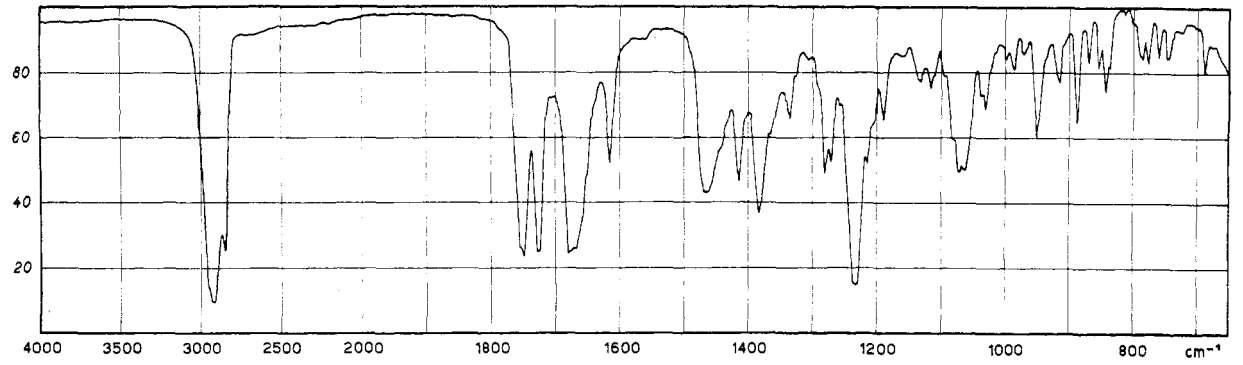

Figure 1

rule on the relative stability of the side chain in C-14 alpha steroids.

16β-Methyldesoxycorticosterone acetate has been submitted to biological investigations by Maffii and co-workers. The results will be published elsewhere; however, it can be reported in advance that the compound lacks any mineralcorticoid activity, in analogy with the results obtained with the 16α-methyldesoxycorticosterone acetate.

Experimental

16α,17α-Diazomethylenepregn-5-ene-3β,21-diol-20-one 21-Acetate (II).—To a solution of 25 g. of pregna-5,16-diene-3β,21-diol-20-one 21-acetate (I)[8] in 300 ml. of tetrahydrofuran, chilled at −10°, an anhydrous ether solution of diazomethane, prepared from 100 g. of nitrosomethylurea, was slowly added. After 1 hr. the temperature was allowed to rise to +5° and the solution stored overnight at 5°. Evaporation to dryness gave 27.7 g. of the crystalline compound II, m.p. 165–169°, which was sufficiently pure for the next step. A small amount was purified through a crystallization from acetone and gave an analytically pure sample; m.p. 179–180°; $[\alpha]^{20}D$ −24.3 (*c* 0.946, $CHCl_3$). Infrared (Nujol mull); 3465 (OH), 1753, (C_{20}=O), 1556 (N=N) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4N_2$: C, 69.55; H, 8.27; N, 6.76. Found: C, 69.70; H, 8.48; N, 6.86.

16-Methylpregna-5,16-diene-3β,21-diol-20-one 21-Acetate (III).—A suspension of 25.7 g. of II (m.p. 165–169°) in 130 ml. of paraffin oil was slowly heated under effective stirring to 160°. At this temperature nitrogen evolution took place and continued spontaneously without any additional heating; the temperature reached 165°. As soon as the gas evolution stopped, the solution was cooled to 90° under stirring and treated with 190 ml. of hexane. The product which separated on cooling was collected, washed once more with hexane, and dried. Yield 28.7 g., m.p. 160–172°. The raw material was recrystallized up to constant m.p. Yield 14.5 g. (63%), m.p. 187–190°; $[\alpha]^{20}D$ −85° (*c* 0.954, $CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 252 mμ; ε 8400; infrared (Nujol mull): 3465 (OH), 1753 (O.$COCH_3$), 1660 (C_{20}=O), 1596 (C_{16}=C_{17}) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.82; H, 8.88. Found: C, 74.66; H, 8.96.

16β-Methylpregna-5-ene-3β,21-diol-20-one 21-Acetate (IV).—A solution of 10.8 g. of III in 2200 ml. of methanol was treated with 20 g. of Raney nickel and shaken with hydrogen at room temperature and normal pressure til gas adsorption stopped. The catalyst was filtered off and the solution evaporated to dryness: the crude oil was dissolved in acetone and evaporated to dryness *in vacuo*. The white solid product was dissolved in 100 ml. of ether, filtered, and evaporated till the solution became cloudy. After storage at 5°, 7.2 g. of compound IV was collected, m.p. 135–142°. A small sample was recrystallized several times until analytically pure m.p. 150–152°; $[\alpha]^{20}D$ +0.2 (*c* 0.5, $CHCl_3$). Infrared (Nujol mull): 3540 broad (OH), 1747 (O$COCH_3$), 1720 (C_{20}=O) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.21; H, 9.34. Found: C, 73.95; H, 9.78.

16β-Methylpregna-4-ene-21-ol-3,20-dione 21-Acetate (16β-Methyl DOCA) (V).—To a solution of 5.2 g. of IV in 145 ml. of toluene and 43 ml. of cyclohexanone, after removing 15 ml. of toluene by distillation, a solution of 2 g. aluminum isopropoxide in 16 ml. of toluene was added. The mixture was refluxed 5 hr., then cooled and washed with a saturated solution of Seignette salt, then with diluted sodium hydroxide solution, and eventually with water. The organic phase was dried over sodium sulfate, evaporated to dryness, and extracted several times with hot petroleum ether. After drying *in vacuo* the oily residue was slurried with ether; 466 mg. of V, m.p. 133–140°, could be separated. The remaining oil was dissolved in benzene, percolated on alumina (50 g.), and eluted with benzene. The first 200-ml. fraction was evaporated and the oily residue (3.2 g.) slurried with petroleum ether. An additional crop of V, 894 mg., m.p. 130–138°, was obtained. Both crops (1.3 g.) were crystallized from methanol. Yield: 1.2 g.; m.p. 142–144°; $[\alpha]^{20}D$ +148° (*c* 0.925, dioxane); +161 (*c* 0.947, chloroform) λ_{max} 241 mμ (CH_3OH); $E_{max}^{1\%}$ 435 (CH_3OH). The infrared spectrum (Nujol mull) is reported in Fig. 1; λ_{max}^{chf} (C_{20}=O), 1743 (C=O acetate), 1660 (C_3=O) 1613 (C_4=C_5) cm.$^{-1}$).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.81. Found: C, 74.51; H, 8.71.

16β-Methylpregna-5,16-diene-3β-ol-20-one 3-Formate (VII).—A solution of 125 g. of 16-methylpregna-5,16-diene-3β-ol-20-one[11] in 1550 ml. of 85% formic acid was heated for 1 hr. at 80°. The solution was poured into 15 l. of ice water, the separated product was collected, washed to neutrality, and dried. One hundred and thirty-two grams of a crude product melting at 143–155° was recovered and repeatedly recrystallized from acetone to give 93 g. of VII, m.p. 160–162°; $[\alpha]D$ −107.7° (*c* 0.5, $CHCl_3$); λ_{max} = 251 (CH_3OH); $E_{max}^{1\%}$ 261 (CH_3OH). Infrared (Nujol mull): 1710 (C=O formate), 1645 (C_{20}=O), 1594 (C_{16}=C_{17}) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.04. Found: C, 77.73; H, 9.22.

16-Methylpregna-5,16,20-triene-3β,20-diol 3-Formate 20-Acetate (VIII).—A solution of 45 g. of VII in 570 ml. of isopropenyl acetate was heated at the boiling point for 12 hr. under stirring in the presence of 6 g. of *p*-toluenesulfonic acid. The isopropenyl acetate mixed with acetone, formed during the reaction, was removed on boiling by slow continuous distillation. The distillate of the first 6 hr. (83 ml.) was replaced by adding to the reaction solution an equal volume of fresh isopropenyl acetate; during the following 6 hr., 180 ml. of distillate were collected without

addition of further isopropenyl acetate. The mixture was cooled to 10°, diluted with 600 ml. of ethyl ether, the organic solution was washed with 250 ml. of a cold 3% sodium bicarbonate solution, and with water to neutrality. The solution was dried over sodium sulfate, concentrated to dryness, and the residue was taken up with 800 ml. of hexane. The solution was passed through a column containing 80 g. of Florisil (the column had been washed with fresh hexane). The eluate was concentrated to a volume of 150 ml., then 15 ml. of methanol was added, the resulting white crystalline product was filtered, dried (19 g., m.p. 103–113°), and recrystallized from methanol giving 14.5 g. of VIII, m.p. 111–116°, which was used for the next step. The product, further recrystallized from CH_3OH, melted at 115–119°; $[\alpha]^{22}D$ −99.8° (*c* 0.5, $CHCl_3$); λ_{max} 239 (CH_3OH); $E_{1\,cm.}^{1\%}$ 182.2 (CH_3OH). Infrared (Nujol mull) 1762 (C=O acetate), 1720 (C=O formate), 1645 (C_{20}=C_{21}), 1597 (C_{16}=C_{17}) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_4$ (m.w. 398.54): C, 75.35; H, 8.60. Found: C, 74.99; H, 8.67.

16-Methyl-21-iodo-pregna-5,16-diene-3β-ol-20-one 3-Formate (IX).—To a suspension of 24 g. of VIII (m.p. 111–116°) in 85 ml. of dioxane 15.6 g. of N-iodosuccinimide was added under stirring. The mixture was heated for 45 min. at 80 ± 5° under a nitrogen stream, then poured into 200 ml. or a cold aqueous solution of 10% sodium metabisulfite. A solid product separated and after a short stirring was collected; 28.5 g. of crude 21-iodo derivative melting at 112–120° was obtained and used for the next step.

The product repeatedly crystallized from chloroform–methanol melted at 142–144°. $[\alpha]D$ −106 ± 2° (*c* 0.5, $CHCl_3$); λ_{max} 265 (CH_3OH); $E_{max}^{1\%}$ 124.2 (CH_3OH). Infrared (Nujol mull): 1700 (C=O formate), 1637 (C_{20}=O), 1595 (C_{16}=C_{17}).

Anal. Calcd. for $C_{23}H_{31}O_3J$: J, 26.31. Found: J, 26.18.

16-Methylpregna-5,16-diene-3β,21-diol-20-one 3-Formate 21-Acetate (X).—To a solution of 19 g. of IX in 240 ml. of acetone 88 ml. of glacial acetic acid was added, followed, after cooling to 10–15°, by 140 ml. of triethylamine.[17] The mixture was refluxed for 45 min., diluted with 2300 ml. of water, and allowed to stand for 1 hr. Then 20 g. of Celite was added and the solid was collected. The cake was carefully washed with water, dried, and extracted many times with a total volume of 500 ml. of warm acetone. The extracts were concentrated to a small volume giving a crystalline compound; 12 g.; m.p. 155–160°. From the mother liquors, by concentration and addition of ether, a further crop of 2.3 g. of product melting at 155–160° was obtained. The combined crops were recrystallized from 95% ethanol giving 11.4 g. of X; m.p. 150–162°. This product was used as such for the following step. A sample, after many crystallisations from ethanol, melted at 161–162°. $[\alpha]D$ −88° (*c* 1, $CHCl_3$); λ_{max} 252 (95% EtOH); $E_{1\,cm.}^{1\%}$ 212 (95% EtOH). Infrared (Nujol mull), 1742 (C=O acetate), 1708 (C=O formate), 1658 (C_{20}=O), 1600 (C_{16}=C_{17}) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.44; H, 8.26. Found: C, 72.26; H, 7.99.

16β-Methylpregna-5-ene-3β,21-diol-20-one 3-Formate 21-Acetate (XI).—A solution obtained by dissolving 8.5 g. of X in 4000 ml.[18] of hot ethanol was rapidly cooled to 30°. Then 25 g. of Raney nickel was added and the mixture was hydrogenated under atmospheric pressure at room temperature until a sample, filtered and diluted with methanol, showed no more absorbance at 252 mμ (disappearance of =C=O conjugated with a double bond). This required 3–4 hr. The catalyst was removed by filtration and the resulting solution was concentrated under reduced pressure. The dry white solid residue (9 g.; m.p. 131–135°) was recrystallized from isopropyl ether giving 6 g. of a product melting at 139–142°. During the hydrogenation a partial hydrolysis of the formyl ester at position 3 occurred. The resulting product was used as such for the next step.

16β-Methylpregna-4-ene-21-ol-3,20-dione 21-Acetate (16β-Methyl DOCA) (V).—A solution of 6 g. of crude XI in 240 ml. of anhydrous toluene and 96 ml. of cyclohexanone was distilled until 40 ml. of toluene was removed. To the resulting completely anhydrous solution 6 g. of aluminum isopropoxide dissolved in 48 ml. of anhydrous toluene was added in 5 min. The reaction mixture was heated at reflux under stirring for 2 hr. The working up of the product was carried out as described above for V and gave 1.9 g. of 16β-methyl DOCA, which was found identical with the product previously obtained.

16β-Methyl-17α-pregna-4-ene-21-ol-3,20-dione 21-Acetate (XII).—To a solution of 300 mg. of V in 30 ml. of methanol 0.3 g. of potassium hydroxide dissolved in 1 ml. of water was added with stirring under a nitrogen atmosphere and the mixture was refluxed for 1 hr. After dilution with 40 ml. of water, the methanol was removed *in vacuo*. The resulting crystalline product which was collected, washed with water, and dried (220 mg.) was dissolved in 2 ml. of pyridine and mixed with 2 ml. of acetic anhydride.[1] After standing overnight the solution was poured into 25 ml. of water previously acidified with hydrochloric acid. After 30 min. stirring the mixture was extracted three times with a total of 60 ml. of methylene chloride. The organic extract was washed with 0.1 *N* hydrochloric acid, 2% sodium bicarbonate solution, and water; then it was dried over sodium sulfate and evaporated to dryness. The residue was taken up with benzene and filtered through 4 g. of neutral aluminum oxide. The filtered benzene (about 200 ml.) was evaporated to dryness and the residue (150 mg.) recrystallized from methanol. Eighty milligrams of XII melting at 161–162° was recovered. $[\alpha]D$ +20 (*c* 0.802, $CHCl_3$); $[\alpha]D$ +2.3 (*c* 0.789, dioxane). Infrared (chloroform solution *c* 2.5) 1743 (C=O acetate), 1718 (C_{20}=O), 1660 (C_3=O), 1613 (C_4=C_5) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$ (386.5): C, 74.58; H, 8.81; Found: C, 74.37; H, 8.96.

A sample of 16α-methyl DOCA, when subjected to a similar treatment, did not give raise to isomerization in detectable extent. Most of the starting material was therefore recovered unchanged.

Acknowledgment.—We are gratefully indebted to Dr. G. G. Gallo and Dr. R. Pasqualucci for the physico-chemical determinations, to Dr. G. Pelizza and Mr. Restelli for the analytical determination and to Dr. A. Wittgens for the assistance in the preparation of the manuscript.

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(18) Since the product has a low solubility, it was advisable to hydrogenate rapidly to avoid the separation of crystals.

The Preparation of Fluorinated Anthraquinones and Fluorinated Substituted Anthraquinones[1]

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The first fluorinated anthraquinones to be made were those by Hahn and Reid,[2] who have re-