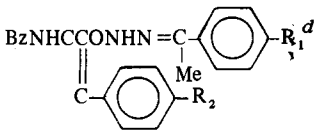
Table III. Cytotoxicity of Hydrazide Derivatives against KB Strain of Human Carcinoma of the Nasopharynx

No.	R_1	R_2	Mp, °C	ED_{50}, μg/ml
				
1	2,4-$(OH)_2$[a]	3-NO_2-4-(OCH_3)	265	>10
2	2,4-$(OH)_2$-5-NO_2[b]	3-NO_2-4-(OCH_3)	160	22
3	2-$(OH)_4$-Me-5-Cl[c]	3-NO_2-4-(OCH_3)	187	18
4	3-Me-4-OH[c]	3-NO_2-4-(OCH_3)	278	84
5	2-OH-5-Cl[c]	3-NO_2-4-(OCH_3)	188	>100
6	4-OH[c]	3-NO_2-4-(OCH_3)	270	>100
7	2-OH-3-Me[c]	3-NO_2-4-(OCH_3)	280	>100
8	2-OH[c]	3-NO_2-4-(OCH_3)	260	>100
9	2-OH[b]	3,4-(OCH_2O)	173	93
10	4-OH[b]	3,4-(OCH_2O)	197	24
11	2-(OH)-3-Me[b]	3,4-(OCH_2O)	225	>100
12	3-Me-4-(OH)[b]	3,4-(OCH_2O)	192	23
13	2-(OH)-5-Cl[b]	3,4-(OCH_2O)	183	19
14	2,4-$(OH)_2$[b]	3,4-(OCH_2O)	215	23
15	2,4-$(OH)_2$-5-Br[b]	3,4-(OCH_2O)	240	47
16	2,4-$(OH)_2$-5-NO_2[b]	3,4-(OCH_2O)	225	24
17	2-(OH)-4-Me-5-Cl[b]	3,4-(OCH_2O)	200	59
18	2-(OH)-4,6-Me_2-5-Cl[b]	3,4-(OCH_2O)	221	59

[a]DMF. [b]Alkali diluted with saline. [c]Saline. [d]Supplied by R. P. Mahesh.

contg H_2SO_4 (2 ml) was added to 2,3,4-pentanetrione 3-arylhydrazone (0.01 mole) in a mixt of EtOH–AcOH on a steam bath for several hr. It was left overnight at room temp, when crystals sepd. This was recrystd from DMF–EtOH (Table I).

Acknowledgments. The authors thank Dr. H. B. Wood, H. W. Bond of Cancer Chemotherapy, NIH, Bethesda, Md., and Dr. W. C. McGuire of Phillips Roxane, Inc., for their cooperation and for the screening data.

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Preparation and Progestational Activity of 6-Cyano-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate and Related Compounds

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In recent years considerable attention has been given to the preparation of 6-substituted-6-dehydroprogestagens among which 6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**1**, chlormadinone acetate) and 6-methyl-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**2**, megestrol acetate) have found use in contraceptives. The progestational potentiating effect of the 16-methylene moiety has been demonstrated sometime ago.[1]

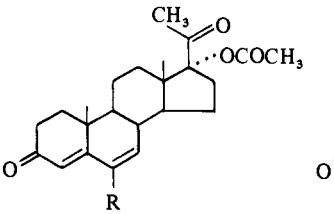
As an extension of our investigations[2] on the progestational activity of 6-dehydro-16-methylene-17α-acetoxyprogesterone derivatives in the present communcation, we wish to report the synthesis of 6-formyl-6-dehydro-16-methylene-17α-acetoxyprogesterone (**3**) and of 6-cyano-6-dehydro-16-methylene-17α-acetoxyprogesterone (**4**).

Table I. Progestational Activity[a,b]

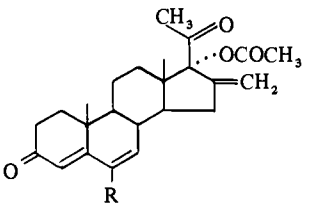
Compd	Activity
3	1[c]
4	5.8
7	0.45
8	2.1
11	1.8

[a]Progesterone = 1. [b]Progestational activity was detd in immature rabbits by the method of McPhail.[7] The compounds were dissolved in sesame oil for im administration. Progesterone in sesame oil was given im. The statistical analysis for the progestational assays utilized the randomized Bloch analysis of variance with Dunnett's and Duncan's multiple comparison procedure (see ref 8). [c]Approximate value.

The preparation of the 6-formyl **3** was carried out by converting the ethyl enol ether **5**[3] by the Vilsmeier reaction† to the 6-formyl enol ether **6**. On treatment with dichlorodicyanobenzoquinone (DDQ) in 95% aqueous acetone[5] **6** afforded the desired **3** in 45% yield.



1, R = Cl
2, R = CH_3

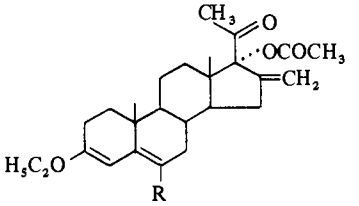


3, R = CHO
4, R = CN
9, R = CH=NOH
11, R = $CH=NOCH_3$

In order to prepare the 6-cyano derivative **4** the 6-formyl enol ether **6** was used as starting material. Reaction of **6** with NH_2OH gave the oximinomethyl compound **7** which when treated with NaOAc in refluxing Ac_2O afforded the 6-cyano enol ether **8**.‡

In contrast to the 6-formyl enol ether **6**, the 6-cyano enol ether **8** was completely inert toward DDQ. Even forcing conditions (large excess of DDQ in refluxing dioxane for 48 hr) failed to give any of the desired **4**. Only small amounts of the 6-cyano-$\Delta^{1,4,6}$-trienone and highly colored materials (probably DDQ adducts) could be isolated.

In order to overcome the difficulties in the dehydrogenation of **8**, the oximinomethyl enol ether **7** was treated with DDQ in 95% aqueous acetone. Rapid conversion to the corresponding dienone **9** occurred and the latter compound was isolated in 68% yield. Reaction of **9** with $POCl_3$ in pyridine afforded the desired 6-cyano dienone **4** in 70% yield.



5, R = H
6, R = CHO
7, R = CH=NOH
8, R = CN
10, R = $CH=NOCH_3$

†Burn, *et al.*,[4] described the prepn of the analogous 3-methoxy-$\Delta^{3,5}$-6-formyl compd from the corresponding 3-methyl enol ether.

‡A British patent[6] describes the preparation of the analogous 3-methoxy-$\Delta^{3,5}$-6-cyano compound.

The methoxime **10**, prepared by the reaction of **6** with methoxamine, was also rapidly dehydrogenated with DDQ yielding the 6-methoximinomethyl dienone **11**.

Biology.§ Table I lists the intramuscular progestational activities of **3**, **4**, **11**, and several of the intermediates.

Experimental Section#

3-Ethoxy-6-formyl-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-Acetate (6). A soln of $POCl_3$ (9.7 ml) in DMF (81.5 ml) was added dropwise to a suspension of 3-ethoxy-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-acetate (**5**) (16.3 g) in DMF (163 ml) at 20°. The reaction mixt was stirred for 2.5 hr, then added to H_2O (4 l.) contg KOAc (100 g). After stirring for 1 hr the ppt was collected by filtration. Crystn from EtOH afforded 13 g (75%) of **6**: mp 170–174°; [α]D −255° ($CHCl_3$); λ_{max} 219 mμ (ε 11,300), 325 (15,300). *Anal.* ($C_{27}H_{36}O_5$) C, H.

6-Formyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (3). A soln of **6** (353 mg) in 95% aqueous Me_2CO (7.5 ml) was stirred with DDQ (187 mg) at 20° for 105 min. The reaction mixt was passed through a short column of neutral alumina (Woelm, act. 1). Elution with $CHCl_3$–MeOH (1:1) followed by crystn from Me_2CO–C_6H_{14} gave 152 mg (45%) of **3**: mp 210–212°; [α]D −152° ($CHCl_3$); λ_{max} 278 mμ (ε 22,000); ν_{max} 1725, 1700, 1685, 1645 cm^{-1}; nmr, δ 5.43 and 5.62 (C_{16}=CH_2), 9.63 (C_6CHO) ppm. *Anal.* ($C_{25}H_{30}O_5$) C, H.

3-Ethoxy-6-oximinomethyl-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-acetate (7) was prepd from **6** by the method described in ref 6 in 63% yield after crystn from EtOH–H_2O: mp 135–140°; [α]D −286°; λ_{max} 296 mμ (ε 21,000). *Anal.* ($C_{27}H_{37}O_5N \cdot 0.5H_2O$) C, H, N.

3-Ethoxy-6-cyano-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-acetate (8) was prepd from **7** by the method described in ref 6 in 66% yield after crystn from EtOH–*i*-Pr_2O: mp 120–125°; [α]D −250°; λ_{max} 284 mμ (ε 19,700). *Anal.* ($C_{27}H_{35}O_4N$) C, H, N.

6-Oximinomethyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (9). A soln of **7** (3.48 g) in 95% aqueous Me_2CO (80 ml) was stirred with DDQ (3 g) at 20° for 45 min. The reaction mixt was passed through a column of neutral alumina (Woelm, act. 1). Elution with $CHCl_3$ gave 2.21 g (68.6%) of homogeneous **9**. A small part was crystd from EtOAc affording an EtOAc solvate: mp 140–145°; [α]D −103°; λ_{max} 245 mμ (ε 11,620) 287 (16,000). *Anal.* ($C_{25}H_{31}NO_5 \cdot 0.5$EtOAc) C, H, N.

6-Cyano-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (4). A soln of **9** (488 mg) in pyridine (5 ml) was stirred with $POCl_3$ (2.2 ml) under N_2 for 2 hr. The soln was added to H_2O, and the ppt collected and dried. Crystn from EtOAc gave (in 2 crops) 329 mg (70%) of **4**: mp 221–223°; [α]D −141°; λ_{max} 275 mμ (ε 23,800); ν_{max} 2237, 1750, 1721, 1670, and 1638 cm^{-1}; nmr, δ 0.80 ($C_{13}CH_3$), 1.15 ($C_{10}CH_3$), 2.04 ($C_{17}OCOCH_3$), 2.17 ($C_{20}CH_3$), 5.52 and 5.67 (C_{16}=CH_2), 6.24 (C_4H), and 6.89 (C_7H) ppm. *Anal.* ($C_{25}H_{29}O_4N$) C, H, N.

3-Ethoxy-6-methoximinomethyl-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-Acetate (10). A soln of **6** (500 mg), methoxamine·HCl (95 mg), and NaOAc (186 mg) in EtOH (10 ml) and H_2O (2 ml) was heated at reflux for 30 min, then allowed to stand at 20° for 16 hr. The soln was added to H_2O, extd with CH_2Cl_2, and dried. The solvent was evapd *in vacuo* and the residue crystd from MeOH–H_2O affording 423 mg (79%) of **10**: mp 95–98°; [α]D −271°; λ_{max} 222 mμ (ε 9900), 302 (21,400). *Anal.* ($C_{28}H_{39}O_5N$) C, H, N.

6-Methoximinomethyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (11). A soln of **10** (100 mg) in 95% aqueous Me_2CO (10 ml) was stirred with DDQ (100 mg) at 20° for 30 min. Most of the solvent was removed *in vacuo* and the residue chromatogd over neutral alumina (Woelm, act. 1). Elution with $CHCl_3$–EtOAc (1:1) afforded after crystn from Me_2CO–H_2O 52 mg (55.7%) of **11**: mp 185–191°; [α]D −88°; λ_{max} 260 mμ (ε 15,000), 283 (16,500); nmr, δ 3.90 (=$NOCH_3$), 5.49 and 5.64 (C_{16}=CH_2), 6.27 (C_4H), 6.42 (C_7H), and 7.88 (C_6CH=$NOCH_3$) ppm. *Anal.* ($C_{26}H_{33}O_5N$) C, H, N.

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#Melting points are uncorrected. Rotations are in dioxane at 25° at about 1% concentration, uv spectra are of MeOH solutions, and ir spectra are in Nujol unless otherwise stated. The nmr spectra were measured on a Varian A 60-A spectrometer in $CDCl_3$ (Me_4Si). Solns were dried over anhyd Na_2SO_4. Analyses were determined by the Physical Organic Department of the Schering Corp. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Antiinflammatory Activities of 17,21-Methyl Ortho Esters, 17-Mono- and 17,21-Diesters of 6α,9α-Difluorocorticosteroids

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Corticosteroid 17,21-alkyl ortho esters were prepared some years ago in our laboratory.[1] Their acid-catalyzed hydrolysis gave rise to corticosteroid 17-monoesters, which were conventionally acylated to the corresponding 17,21-diesters.[2,3] Several derivatives of the above 3 classes, obtained from various parent corticoids, proved to display extremely interesting antiinflammatory activity, mainly after local treatment.[4-8]

This paper reports the synthesis and some biological properties of 17,21-alkyl ortho esters, 17-monoesters, and 17,21-diesters of 6α,9α-difluorocortisol and 6α,9α-difluoroprednisolone, known potent antiinflammatory steroids.[9,10]

Chemistry. 17,21-Alkyl ortho esters were prepared from 6α,9α-difluorocortisol and 6α,9α-difluoroprednisolone by exchange reaction with trimethyl ortho esters according to the already published procedure.[1] Hydrolysis of alkyl ortho esters was performed in buffered solution at pH near 5. In these conditions both direct hydrolysis to 21-ester and acyl migration 17-O → 21-O were minimized and 17-monoesters were obtained in optimum yield.[11,12]

Acylation of 17-monoesters, although performed in conventional manner, required a careful control of the temperature below 0° in order to avoid extensive formation of triesters, since the presence of an acyloxy group in 17α position was found to significantly enhance reactivity of 11β-OH.†

†This matter will be discussed in a forthcoming paper.