2,8-Dimethyl-11-hydroxy-1,2,3,4,5,8,9,10-octahydro-5-oxo-9-*n*-pentylbenz[*d*]indeno[5,6-*b*]pyran (5) and 3,10-Dimethyl-1-hydroxy-3,4,5,7,7,8,9,10-octahydro-7-oxo-4-*n*-pentylbenz[*d*]indeno[4,5-*b*]pyran (6). Pechmann condensation of 4.68 g (0.02 mol) of 4 and 3.68 g (0.02 mol) of ethyl 4-methyl-2-cyclohexanone-1-carboxylate according to the procedure of Adams[8] after 1.5 h gave a creamy solid: 4 g (57%); mp 183–186° (ethyl acetate–petroleum ether). The material showed a single spot on TLC (1:4 ethyl acetate–hexane) but the NMR and GLC showed it to be a mixture of 5 and 6 (55:45 by GLC). Anal. ($C_{22}H_{30}O_3$) C, H.

11-Hydroxy-1,2,3,4,5,8,9,10-octahydro-9-*n*-pentyl-2,5,5,8-tetramethylbenz[*d*]indeno[5,6-*b*]pyran (8) and 1-Hydroxy-3,4,5,7,7,8,9,10-octahydro-4-*n*-pentyl-3,7,7,10-tetramethylbenz[*d*]indeno[4,5-*b*]pyran (9). Grignard addition with CH_3MgI was carried out according to the procedure described by us earlier.[9] It gave a purple gum which by TLC in 10% ether–petroleum ether showed the presence of two spots. The material was chromatographed on 150 g of Florisil in petroleum ether and eluted with graded ether (0.5–2%)–petroleum ether mixtures. Compound 8 was less polar and came off the column first. It was recrystallized from petroleum ether as colorless crystals, mp 101–103°, which on keeping become a semisolid. Anal. ($C_{25}H_{36}O_2$) C, H.

The later fractions from the chromatography column furnished 9 as colorless crystals (C_2H_5OH–H_2O), mp 104–106°. Anal. ($C_{25}H_{36}O_2$) C, H.

Both compounds 8 and 9 on treatment with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature gave a mixture containing 8 and 9 (1:1 by GLC).

Acknowledgment. We wish to thank Drs. N. P. Plotnikoff and J. Kyncl of Abbott Laboratories, North Chicago, Ill., for the biological test results.

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Preparation of 16α-Alkoxy and 16α-Acyloxy Derivatives of 21-Chloro-17-acyloxy Corticosteroids and Determination of Their Vasoconstrictor Activities in Humans

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A number of 16α-alkoxy and 16α-acyloxy derivatives of 21-chloro-17-acyloxy corticosteroids have been prepared. The synthetic routes used were (a) reaction of the 16α,17-disubstituted 21-mesylate with lithium chloride and (b) reaction of the 16α-substituted 17,21-cyclic ortho ester with triphenylmethyl chloride. The vasoconstrictor activities in humans exhibited by these compounds were significantly lower than that of a 16β-methyl analogue.

Replacement of the 21-hydroxyl group of certain corticosteroids with a Cl atom had led to the synthesis of clinically useful, topical antiinflammatory agents, for example, 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-17-(propanoyloxy)pregna-1,4-diene-3,20-dione (1, clobetasol propionate)[1] and 21-chloro-9-fluoro-11β-hydroxy-2',2'-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolane-3,20-dione (2, halcinonide).[2] In order to explore further the relationship between structure and topical antiinflammatory activity, we undertook to prepare 16α-acyloxy and 16α-alkoxy derivatives of 21-chloro-17-acyloxy corticoids. This note describes the preparation of such derivatives and the determination of their vasoconstrictor[3] activity in humans.

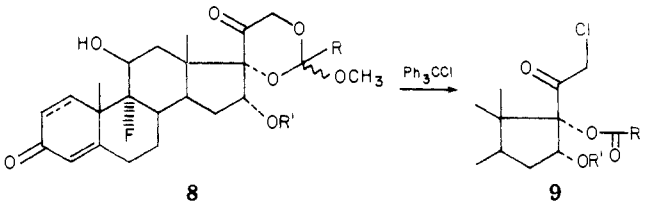
Chemistry. Hydrolysis of ortho ester **3a** (prepared from the known 16α-methoxy-17,21-diol[4] by the standard procedure[5]) to the 17-ester **4a** was complicated by the formation of by-products (21-ester and 17,21-diol). After chromatography and recrystallization, **4a** was obtained in 31.6% yield. Conversion of **4a** to the 21-chloro derivative **5a** was accomplished via the 21-mesylate.

Hydrolysis of ortho ester **3b** gave a mixture containing large amounts of the corresponding 17,21-diol 21-acetate (TLC analysis) and was not preparatively useful. Vitali and Gardi[5] noted a similar disparity between orthopentanoate and orthoacetate hydrolysis, but the effect here seems more pronounced.

Rather than explore alternate procedures[6] for hydrolysis, we chose to apply the elegant conversion of ortho esters to esters of chlorohydrins utilized by Newman and Chen.[7] Reaction of the 16-unsubstituted ortho ester **6a** with triphenylmethyl chloride in refluxing dichloromethane gave the 21-chloro-17-pentanoate **7a** in 27% yield. This material was identical with a sample prepared via the 21-mesylate.[8]

Application of this method to the ortho esters listed in Table I gave the desired 21-chloro 17-esters in the indicated yields (of analytically pure, TLC homogeneous material). Hydrolysis of **9d** with potassium carbonate in methanol at 0° gave the parent 21-chloro-11β,16α,17-triol, thus establishing unambiguously the assigned structure.

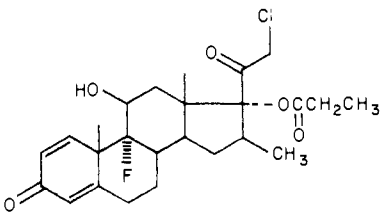
Table I. 16α-Substituted 21-Chloro 17-Esters



8 9

	8				9		
	Yield,[a] %	Mp, °C	R	R′	Yield,[b] %	Mp, °C	[α]D (CHCl3), deg
a	27.5	247-250	CH_3	CH_3	10.8	240-242	+92.5 (c 0.57)
b	43.9	240-241	CH_3	CH_3CH_2	37.7	229-230	+41.0 (c 0.63)
c	31.0	272-273	$CH_3(\Delta^{1,4})$	$CH_3C{=}O$	39.4	296-298	+08.3 (c 0.90)[c]
d	38.6	272-274	$CH_3CH_2(\Delta^{1,4})$	$CH_3C{=}O$	24.6	285-287	+08.8 (c 0.79)

[a] Yield of ortho ester after crystallization from acetone-hexane (prepared as described for 3a and purified by column chromatography on silica gel). [b] Combustion analyses (C, H, Cl, F) were within ±0.3% of the calculated value for these compounds. [c] Solvent, chloroform-methanol (9:1).



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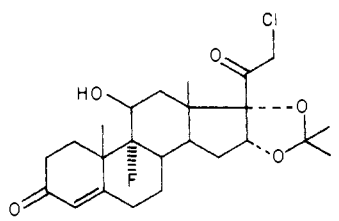

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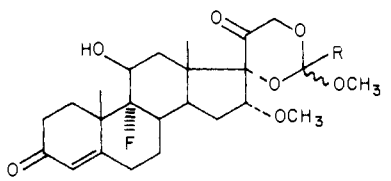

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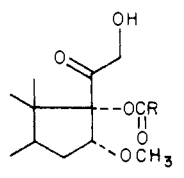

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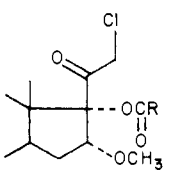

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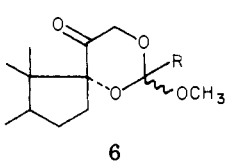

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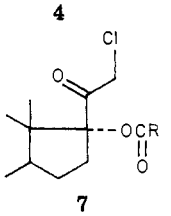

7

a, R = n-C_4H_9; b, R = CH_3

Although the yields are moderate, the Newman procedure allows the ready synthesis of steroids that are otherwise difficult to obtain.

Vasoconstrictor Assay. The 16α-substituted 21-chloro 17-esters **5a** and **9a-d** were compared with 9-fluoro-11β,21-dihydroxy-16β-methyl-17-(pentanoyloxy)pregna-1,4-diene-3,20-dione (betamethasone valerate, BMV) in the vasoconstrictor[3] and stripped-skin[9] assays in humans. These assays correlate well with the clinical efficacy of topical antiinflammatory steroids. All of these compounds were less active than BMV in both assays ($p < 0.001$). The most active (**9a**) exhibited ca. one-fifth the activity of BMV in these assays; the rest exhibited ca. one-tenth the activity of BMV or less. In contrast, both the 16β-methyl analogue 1[10] and halcinonide[2] exhibit activity at least equivalent to BMV in the vasoconstrictor assay.

The loss of vasoconstrictor activity that attends the replacement of a 16β-methyl group with a 16α-alkoxy or -acyloxy group in these compounds is dramatic. Since 21-chloro-16α,17-acetonides and 21-chloro-16-unsubstituted 17-esters, such as **7**,[11] also display good vasoconstrictor activity, this lack of activity is unexpected. Perhaps conformational restraints imposed by the 17-ester and 16α,17-acetonide moieties on the D ring and side chain are compatible with activity, whereas perturbation of such conformations by 16α-alkoxy or -acyloxy groups diminishes activity.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Infrared (mineral oil, Perkin-Elmer 137), NMR ($CDCl_3$, Perkin-Elmer R-12B), and mass spectra (70 eV, <150° source temperature, AEI-MS 902) were consistent with the assigned structures.

9-Fluoro-11β,21-dihydroxy-16α-methoxy-17-(pentanoyloxy)pregn-4-ene-3,20-dione (4a). A mixture of 2.6 g of 9-fluoro-11β,17,21-trihydroxy-16α-methoxypregn-4-ene-3,20-dione,[4] 5.2 ml of dimethylformamide, 5.2 ml of trimethyl orthovalerate, and 26 mg of p-toluenesulfonic acid was stirred at 125° for 9 h under nitrogen, cooled, and treated with 0.2 ml of pyridine. The resulting solution was poured into ice-water and extracted with chloroform to give the crude ortho ester **3a**. A solution of this material in 90 ml of methanol was refluxed for 1 h with 37.5 ml of a buffer solution[5] prepared by mixing 90 ml of 0.1 N acetic acid and 10 ml of 0.1 M sodium acetate. After cooling, the solution was diluted with ice-water and extracted with chloroform. The crude product (2.3 g) was chromatographed on a 55-g silica gel column. Elution with chloroform gave 900 mg (25%) of TLC-pure material in fractions 6-13 (125 ml each). Crystallization from acetone-hexane gave 800 mg of **4a**, mp 233-234°.

21-Chloro-9-fluoro-11β-hydroxy-16α-methoxy-17-(pentanoyloxy)pregn-4-ene-3,20-dione (5a). A solution of 700 mg of **4a** in 10 ml of pyridine was stirred at 0° for 150 min with 0.3 ml of methanesulfonyl chloride and then was poured into cold 5% hydrochloric acid. Extraction with chloroform gave 1.2 g of crude mesylate, which was refluxed with 1.2 g of lithium chloride in 65 ml of dimethylformamide for 90 min under nitrogen. The resulting solution was cooled and poured into 200 ml of ice-water; the precipitate thus formed was filtered and dried. The crude product was chromatographed on a 16-g silica gel column. Elution with chloroform-hexane (9:1) gave 400 mg (55%) of TLC-pure **5a** in fractions 3-7 (50 ml each). Crystallization from ether-hexane gave 200 mg of **5a**, mp 127-128°. Anal. ($C_{27}H_{38}ClFO_6$) C, H, Cl, F.

21-Chloro-9-fluoro-11β-hydroxy-17-(pentanoyloxy)-pregn-4-ene-3,20-dione (7a). A solution of 1.0 g (0.00215 mol) of ortho ester **6a** (prepared as described for **3a**) in 6 ml of di-

chloromethane was refluxed for 1 h under nitrogen with 0.6 g (0.00215 mol) of triphenylmethyl chloride. The solution was concentrated and applied to a 20 cm × 20 cm × 2 mm silica gel plate. After development with chloroform–ethyl acetate (1:1), the uv-active band of highest R_f was scraped off and eluted with chloroform–methanol. Recrystallization of the resulting solid from methanol gave 270 mg (26%), mp 209–211°, identical (ir, NMR, TLC) with a sample, mp 213–214°, prepared via the mesylate.[8] Anal. ($C_{26}H_{36}ClFO_5$) C, H, Cl, F.

Hydrolysis of 9d. A slurry of 150 mg of **9d** in 15 ml of methanol and 0.8 ml of 10% aqueous potassium carbonate solution was stirred at 0° for 90 min, neutralized with acetic acid, and diluted with cold water. The resulting solid was filtered and then dissolved in chloroform–methanol. The solution was dried and concentrated in vacuo to give 100 mg (91%) of 21-chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione, mp 265° dec, identical with an authentic sample prepared by hydrolysis of the corresponding acetonide.[12]

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Antimalarial Activity of Some Novel Derivatives of 2,4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine (Pyrimethamine)

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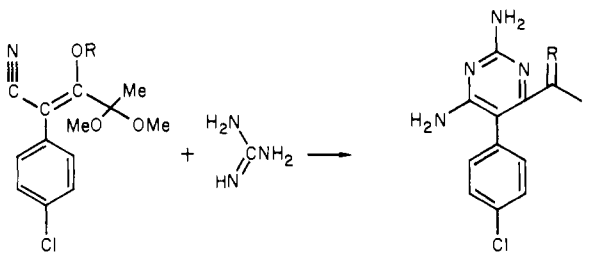
Thirteen new analogs of 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine (Daraprim, pyrimethamine) in which the α position of the 6-ethyl substituent was modified were prepared. The respective oxygen analogs (ketals, ketone, alcohol), the dimethyl hydrazone, and the nitrone displayed activities in the range of $^1/_4$ to $^1/_{16}$ that of pyrimethamine toward *Plasmodium berghei* in mice. The therapeutic ratios of some of these compounds may be slightly better than that of pyrimethamine.

Pellicularia f. sp. filamentosa sasakii 1F0 6675 hydroxylates and oxidizes the α position of the 6-ethyl substituent of pyrimethamine (**3**). The two products, 2,4-diamino-5-(*p*-chlorophenyl)-6-pyrimidinyl methyl ketone (**6**) and (+)-2,4-diamino-5-(*p*-chlorophenyl)-α-methyl-6-pyrimidinemethanol (dextro rotamer of **7**), were isolated and identified by Greenspan et al.[1] For confirmation of the structure and additional biological testing, we deemed it necessary to synthesize the ketone **6** and the racemic alcohol **7** by chemical means. Furthermore, these products provided ready access to the little explored derivatives of pyrimethamine in which the α position of the 6-ethyl side chain is functionalized.

Synthesis. The most attractive approach toward the synthesis of the 6-methyl ketone **6** was essentially the one originally described by Russell and Hitchings[2]; this method was also employed by Baker and Jordaan[3] for the preparation of the 6-formyl compound. *p*-Chlorophenylacetonitrile was allowed to react with ethyl 2,2-dimethoxypropanoate in basic medium to give the enol **1**, which, on treatment with diazomethane, furnished the enol ether **2**. Guanidine reacted readily with the enol ether **2** in ethanolic sodium ethoxide to give 2,4-diamino-5-(*p*-chlorophenyl)-6-pyrimidinyl methyl ketone dimethyl acetal (**4**) in high yield. The ketal-protecting group was hydrolyzed in acidic aqueous methanol giving the methyl ketone **6**, which was identical in all respects with material isolated by Greenspan et al.[1] Subsequent transformations of this ketone to the alcohol **7**, the oxime **8** (for the structure of **8** and subsequent numbers, see Table I), the hydrazones **11**, **12**, and **13**, and the nitrone **14** were conducted by standard methods and were unexceptional.



1, R = H
2, R = Me

3, R = H_2 (pyrimethamine)
4, R = $(OMe)_2$
5, R = $(OEt)_2$
6, R = O
7, R = H, OH

Raney nickel reduction of the oxime furnished the amine **9**, which on acylation gave the amide **10**. The guanidino compound **15** was prepared in the usual fashion. The physical constants of these compounds are listed in Table I. The racemic alcohol **7** had chromatographic mobilities and solution spectra identical with those of the resolved alcohol prepared by Greenspan.[1]

Antimalarial Activity. All compounds were tested for antimalarial activity against *Plasmodium berghei* (strain KBG 13) in mice, and the more potent ones were also tested against *Plasmodium gallinaceum* in a limited fashion by procedures described earlier.[4] Table II lists the activities of the various derivatives against *P. berghei*. The most potent compounds producing cures at relatively high levels were the acetals **4** and **5**, the methyl nitrone **14**, and the alcohol **7**. The ketone **6** and the dimethyl hydrazone **12** produced cures at 320 mg/kg but were found to be toxic