ammonium chloride and 25 mL of water and benzene. The organic layer was washed with water and brine and taken to dryness. The residual oil was distilled at 0.2 mm to give 2.37 g (88%) of product, bp 116–124 °C. Anal. ($C_{16}H_{26}O_4$) C, H.

4-Carboxy-4-cyclopentylcyclohexanone Ethylene Ketal (16). A mixture of 10.0 g (0.035 mol) of the ester and 2.10 g of NaOH in 80 mL of ethylene glycol was heated at reflux for 18 h. The mixture was worked up exactly as above and the product recrystallized (SSB) to give 7.22 g (51%) of acid, mp 110–113 °C. Anal. ($C_{14}H_{22}O_4$) C, H.

4-Cyclopentyl-4-(methylamino)cyclohexanone Ethylene Acetal Hydrochloride (18). The acid (16) obtained above was rearranged to the isocyanate exactly as above [7.81 g, $(C_6H_5O)_2POH_3$; 3.95 mL of THF]. The isocyanate (oil, ν_{max} 2280) obtained on chromatography was reduced by means of $LiAlH_4$ (1.0 g). The basic product obtained after the usual workup was recrystallized as the HCl salt to give 2.50 g (32%) of crystals, mp 179–182 °C. Anal. ($C_{14}H_{26}ClNO_2$) C, H, N.

4-Cyclopentyl-4-(dimethylamino)cyclohexanone Ethylene Ketal Hydrochloride (19). The free base from the above secondary amine hydrochloride was subjected to the standard methylation procedure (CH_2O, $NaBH_4$) twice. The product was recrystallized (CH_2Cl_2–EtOAc) as the HCl salt to give 0.62 g (24%) of salt, mp 200–203 °C. Anal. ($C_{15}H_{28}ClNO_2$) C, H, N.

4-Cyclopentyl-4-(dimethylamino))cyclohexanone Hydrochloride (20). Hydrolysis of 1.14 g of the acetal as above afforded on crystallization (CH_2Cl_2–EtOAc) 0.63 g (66%) of the ketone, hydrochloride salt. Anal. ($C_{13}H_{24}ClNO$) C, H, N.

Biology. Methods. The biological testing consisted of a battery of standard assays.[8] Briefly, CF-1 female mice were dosed sc with a suspension (or solution) of the test compound in 0.25% aqueous methylcellulose and 15 min later subjected to a series of procedures to detect analgesia, sedation, and narcotic antagonism. The tail-flick, tail-pinch, and HCl writhing procedures were used to detect analgesia, whereas the inclined screen test was used to measure sedation. After the completion of the tests (about 45 min postinjection), 6.3 mg/kg morphine sulfate was given subcutaneously and 15 min later the mice were retested on the tail-flick procedure to determine if the compound might have narcotic antagonist properties. Blockade of morphine-induced elevation of tail-flick latency was scored as antagonism. Six mice were tested at each dose in this battery of assays. When multiple doses were examined, the ED_{50} values were calculated by the method of Spearman and Karber.[10]

(10) D. J. Finney, "Statistical Method in Biological Assay", Hafner Publishing Co., New York, 1952.

Synthesis and Structure–Activity Studies of a Series of 7α-Halogeno Corticosteroids[1]

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The preparation and topical antiinflammatory potencies of a series of 7α-halogeno-16-substituted-prednisolone derivatives are described. The 7α-chloro, 7α-bromo, and 7α-iodo corticosteroids were obtained by addition of hydrogen halide to the 6,7-dehydro compounds. The extent of addition of HCl varied with substitution at C-11, while no addition of HF was observed at all. The 7α-fluoro corticosteroids were prepared by reaction of the appropriate 7β-hydroxy compounds with *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine. The 7β-hydroxy steroids were obtained, in turn, from the 6,7-dehydro compounds via the 6β,7β-dihydroxy derivatives. Antiinflammatory potencies were measured in mice by the Tonelli croton oil ear assay. The greatest effect of a 7α-halogen was observed in the 16α-methylprednisolone series, where 7α-chloro and 7α-bromo substitution increased potency 2.5- to 3.5-fold. Compounds **4b** and **5b** were equipotent to betamethasone dipropionate. 7α-Halogen substitution in other series produced more variable effects and sometimes led to a reduction of antiinflammatory potency.

Since the pioneering efforts of Sulzberger and co-workers in the dermatological use of topical hydrocortisone,[2,3] many chemical modifications of the natural hormones have been made in attempts to improve existing therapy. Most of the important structural changes have involved halogenation at C_6 and/or C_9,[4,5] methylation[6,7] or hydroxylation[8] at C_{16}, and introduction of a 1,2 double bond.[9] Furthermore, it was shown that topical activity could be enhanced

(1) Part of this material was presented in preliminary form at the 5th International Congress on Hormonal Steroids, New Delhi, India, Nov 1978, by M. J. Green, J. Berkenkoph, X. Fernandez, M. Monahan, H.-J. Shue, R. L. Tiberi, and B. N. Lutsky, abstract S. 1 (2); *J. Steroid Biochem.*, 11, 61 (1979).

(2) Trivial names employed are hydrocortisone (11β,17α,21-trihydroxy-4-pregnene-3,20-dione), betamethasone valerate (9α-fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-valerate), betamethasone dipropionate (9α-fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate).

(3) M. Sulzberger and V. H. Witten, *J. Invest. Dermatol.*, **19**, 101 (1952); M. Sulzberger, V. H. Witten, and C. C. Smith, *J. Am. Med. Assoc.*, **151**, 468 (1953).

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(6) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958); G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958).

(7) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *ibid.*, **80**, 4435 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, **82**, 4012 (1960).

(8) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(9) S. Tolksdorf, M. L. Battin, J. W. Cassidy, R. M. McLeod, F. H. Warren, and P. L. Perlman, *Proc. Soc. Exp. Biol. Med.*, **92**, 207 (1956).

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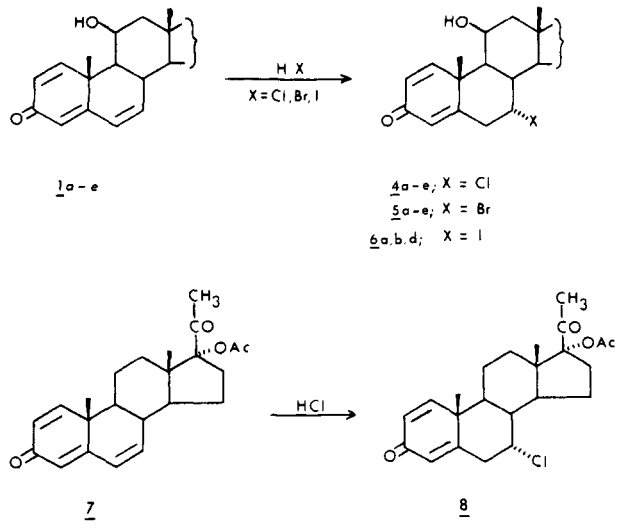
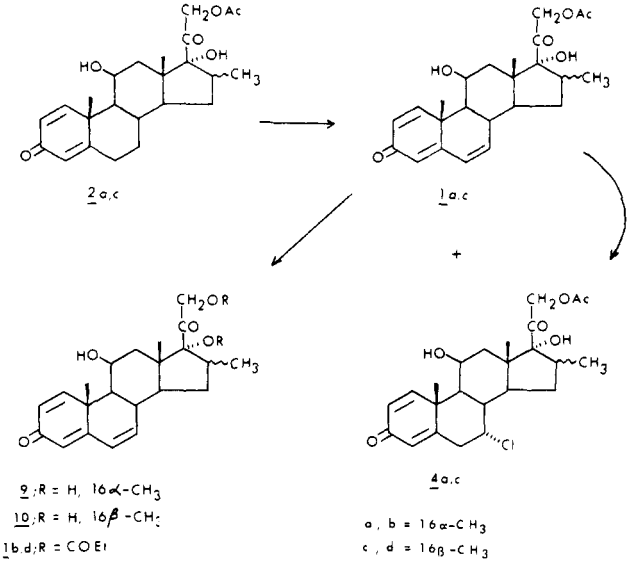
Scheme I



Scheme II



by increasing the lipophilicity of the parent molecule, through esterification of the 17- and/or 21-hydroxyl groups,[10] or by formation of a 16α,17-acetonide grouping.[11]

Until now, the influence of the 7 position on the biological activities of corticosteroids had not been extensively investigated, although early reports indicated that 7α-hydroxy,[12] 7α-methyl,[13] 7α-(acetylthio),[14] 7α-(alkylthio),[14] and 7α-(thiocyano)[14] groups all substantially reduced systemic activity of the parent molecule. We now report the surprising observation that substitution with halogen in the 7α position can yield corticosteroids with exceptional topical potency. Moreover, this activity does not appear to be due to the loss of hydrogen halide and the generation of a 6,7-dehydro steroid.

Chemistry. a. 7α-Chloro, 7α-Bromo, and 7α-Iodo Corticosteroids. Addition of hydrogen halides (HX; X = Cl, Br, I) to α,β-unsaturated ketones is a useful and well-known[15] synthetic reaction related to the Michael reaction of carbanions. However, for steroidal 4-en-3-ones, 1,4-dien-3-ones, 4,6-dien-3-ones, and 1,4,6-trien-3-ones, such addition products have not been reported. Indeed, for 4,6-dien-3-ones it has been stated that they are formed in solution but are too unstable to isolate.[14,16] In contrast, 6,7-dehydro-*A*-nortestosterone is reported[16] to form an adduct, the 7α-chloro compound, with HCl. Its stability is attributed[16] to the difficulty in forming the 7α-chloro-3,5-dien-3-ol necessary for elimination to the 6,7-dehydro compound. However, we have found that such adducts are not limited to unusual ring-contracted steroids but are also formed with normal steroids; the 7α-chloro-, 7α-bromo- and 7α-iodo-1,4-dien-3-ones which are formed are stable and easily isolable compounds.

Treatment of the 11β-hydroxy-1,4,6-trien-3-ones **1a–e** with a solution of dry HBr gas in glacial AcOH (30%, w/v) at 5 °C for 20 min gave almost total conversion to the 7α-bromo products **5a–e** (Scheme I).[17] Similarly, dry HI in glacial AcOH (30%, w/v) gave complete conversion to the 7α-iodo compounds **6a,b,d** in less than a minute at 5 °C.[17] Surprisingly, treatment of **1b** with a saturated solution of dry HCl gas in glacial AcOH gave only 25% of the corresponding 7α-chloro compound **4b**. Since HCl is only sparingly soluble in AcOH (a saturated solution is approximately 7%, w/v), other solvents were tried in attempts to increase the effective concentration of HCl. However, solutions of HCl in THF (45.5%, w/v) or dioxane (16.5%, w/v) gave only minor improvements in the yield of the 7α-Cl compound, 35 and 30%, respectively. In practice, it was found most convenient to use a solution of HCl in dioxane (16.5%, w/v) for the preparation of the 7α-chloro compounds **4b,d,e** and to separate the desired 7α-Cl compounds from the starting trienones by thick-layer chromatography.[18] In contrast, reaction of the 11-unsubstituted 1,4,6-trien-3-one **7**[19] with HCl/AcOH or HCl/THF gave greater than 90% conversion to the 7α-chloro compound **8** (Scheme I). HF did not add to either trienone **1b** or **7** through reaction with HF/AcOH (28%, w/v).

The structures of these addition products were assigned from both spectral data and chemical evidence. In particular, the UV spectra showed the change of the three absorption maxima at about 220, 250, and 300 nm of the 1,4,6-trien-3-one to the single peak at 240 nm due to a 1,4-dien-3-one.[20] Also, the NMR spectra showed the appearance of a one proton multiplet at 4.66 ppm for the 7α-Cl compounds and at 4.90 ppm for the 7α-Br and 7α-I

(10) A. W. McKenzie and R. H. Atkinson, *Arch. Dermatol.*, **89**, 741 (1964).
(11) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).
(12) A. L. Nussbaum, G. Brabazon, T. L. Popper, and E. P. Oliveto, *J. Am. Chem. Soc.*, **80**, 2722 (1958).
(13) R. E. Beylor, A. E. Oberster, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 170 (1960).
(14) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 3915 (1961).
(15) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 451, and references cited therein.
(16) P. A. Diassi, S. D. Levine, and R. M. Palmere, *J. Med. Chem.*, **10**, 551 (1967).

(17) The yield of purified material which we obtained were, however, considerably less than quantitative (see Experimental Section). This is due in part to the difficulty with which some of these compounds crystallized and in part to the workup procedure we employed (pouring into water and filtering off the precipitated solids). This process sometimes gave low material recoveries, especially when working with small quantities—extraction of the aqueous phase with EtOAc gave added material but it was found to have undergone extensive decomposition (TLC).

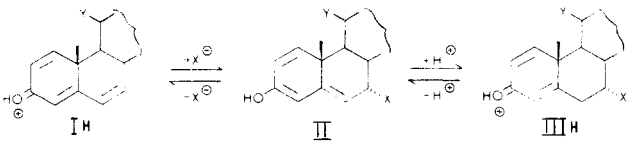
(18) In the preparation of **4a** and **4c**, separation was achieved after conversion of the bulk of the starting material to the 6β,7β-dihydroxy compound by reaction with osmium tetroxide.

(19) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **28**, 92 (1963).
(20) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, Oxford, 1964, p 406.

compounds with $W_{1/2}$ = 7–9 Hz, attributable to the geminal, equatorial 7β-H, in place of the peaks due to the C-6 and C-7 vinyl protons. Treatment of **4b**, **5b**, and **6b** with dilute HCl/dioxane gave back the 6,7-dehydro starting materials, showing that no rearrangement had occurred in ring D or with the dihydroxyacetone side chain. Finally, reaction of the 7β-hydroxy compound **14** with $Et_2NCClCCl_2$[21] gave a 70% yield of the 7α-chloro compound **4a**, identical by NMR and MS to **4a** formed by addition of HCl to the trienone. This reagent converts hydroxyl groups to chlorides with inversion of configuration.[21] These 7α-chloro, 7α-bromo and 7α-iodo products could be purified by thick-layer chromatography and crystallized without decomposition; however, it proved exceedingly difficult to get correct elemental analyses for the 7α-iodo compounds even though the UV spectra of these compounds showed the complete absence of trienone.

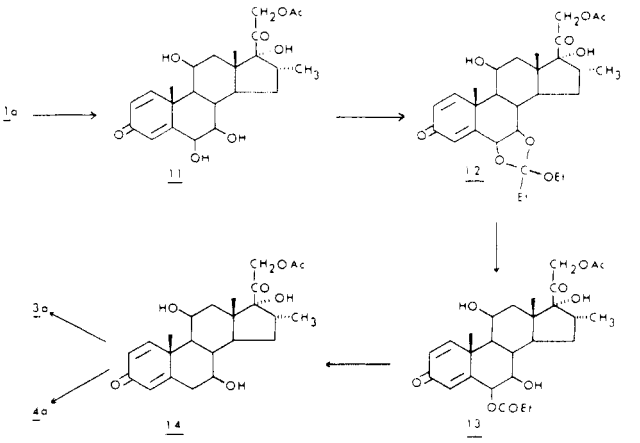
The starting 1,4,6-trien-3-one 21-acetates were prepared from the 1,4-dien-3-ones by reaction with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) under acidic conditions[22] (Scheme II). For example, treatment of 16α-methylprednisolone 21-acetate[6] (**2a**) with 1.2 equiv of DDQ in HCl/dioxane (3.33%, w/v) gave a 21% yield of the 6,7-dehydro compound **1a**, which was purified by crystallization. The crude product was contaminated with a small quantity of the 7α-chloro addition product **4a**. In a similar manner, 16β-methylprednisolone 21-acetate[7] (**2c**) gave 6,7-dehydro-16β-methylprednisolone 21-acetate (**1c**) in 36% yield. The low yields of these DDQ dehydrogenations are puzzling, since no other products are recovered from the workup procedure (evaporation of the dioxane/HCl and alumina column chromatography of the EtOAc-soluble portion of the residue to remove dihydro-DDQ and unreacted DDQ). It is possible that a trienone/dihydro-DDQ adduct is formed,[23] which is then held on the alumina column, but we have not been able to isolate it. The 17,21-dipropionate 1,4,6-trien-3-ones **1b,d** were prepared from the 21-acetate analogues **1a,c** by base hydrolysis to the 17,21-diols **9** and **10**, followed by dipropionylation via the 17α,21-ethylorthopropionate procedure of Gardi et al.[24]

Hydrogen halide additions to α,β-unsaturated carbonyl compounds have been most often interpreted[15,25] in terms of a 1,4 addition, followed by ketonization of the resulting enol. Thus, initial protonation of the carbonyl oxygen of the trienone is followed by axial attack of X^- at C_7 to give the intermediate II, which reketonizes to give the pro-



tonated product IIIH. All steps are, of course, reversible, such that an equilibrium is set up. For the reaction with HBr and HI, this equilibrium lies almost completely to the right, yielding almost all 7α-bromo and 7α-iodo adducts. This is also true for HCl when Y is H, but when Y is an 11β-OH this equilibrium must lie mainly with protonated trienone IH[25] to give the observed product ratio, I/III, of 75:25. It appears, therefore, that for HCl the equilibrium can be shifted to the left or right by conformational changes caused by substituent alterations at C-11. For the

Scheme III



reaction with HF, the equilibrium apparently lies totally to the left, since we observe no addition product at all.[26]

The stability of these 7α-halo-1,4-dien-3-ones after workup is in direct contrast to the reported instability of the 1,2-dihydro analogues.[27] This must, in part, be due to the relative difficulty with which the 1,4-dien-3-one system enolizes in comparison to the 4-en-3-ones, since any low-temperature elimination must proceed through enol intermediates. For example, 1,4-dien-3-ones form enol ethers,[28,29] enol esters,[29,30] and enamines[31] only under extreme forcing conditions, whereas these derivatives are readily produced from 4-en-3-ones under normal conditions.[32] However, treatment of the 7α-fluoro-, 7α-chloro-, 7α-bromo-, and 7α-iodo-1,4-dien-3-ones **3b**, **4b**, **5b**, and **6b** with dilute acid readily gave the elimination product **1b**, and the relative rates of these eliminations are in the order I ≃ Br > Cl > F. Thus, reaction of the 7α-bromo and 7α-iodo compounds, **5b** and **6b**, with HCl/dioxane (3%, w/v) gave almost complete conversion to the 6,7-dehydro compound **1b** after 40 min at room temperature. The 7α-chloro compound **4b** required 5 h for complete elimination, while the 7α-fluoro analogue **3b** had only undergone 50% elimination after this time.

b. 7α-Fluoro Corticosteroids. Since the 7α-fluoro compounds could not be produced by addition of HF to the trienone system, we attempted to synthesize them from the corresponding 7β-hydroxy derivatives. However, the required starting 7β-hydroxy corticosteroids have not been reported,[33] even though the epimeric 7α-hydroxy compounds were first synthesized many years ago.[12] The re-

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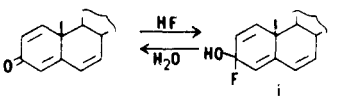
(23) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).
(24) R. Gardi, R. Vitali, G. Falconi, and A. Ercoli, *J. Med. Chem.*, **15**, 556 (1972).
(25) J. N. Marx, *Tetrahedron Lett.*, 4957 (1971).

(26) An alternative explanation is that F^- would prefer to react with the carbonyl carbon to form the fluorohydrin i which, on workup, regenerates the carbonyl.



(27) References 14 and 16 and unpublished work from these laboratories by M. J. Gentles and E. L. Shapiro.
(28) D. H. R. Barton, L. J. Danks, R. H. Hesse, M. M. Pechet, and C. Wilshire, *Nouv. J. Chim.*, 1, 315 (1977).
(29) Reference 32 p 394; U.S. Patent 3 047 596.
(30) H. Reinmann and R. S. Jaret, *Can. J. Chem.*, **48**, 1478 (1970).
(31) R. Bucourt and J. Dube, *Bull. Soc. Chim. Fr.*, **II-33** (1978).
(32) R. Gardi and A. Ercoli in "Organic Reactions in Steroid Chemistry", Vol. 1, J. Fried and J. Edwards, Eds., Van Nostrand Reinhold, New York, 1972, p 391.
(33) 7β-Hydroxy derivatives of 4-pregnen-3-ones have been reported from microbiological reactions, e.g., V. Schwarz, J. Protiva, and J. Martinkova, *Collect. Czech. Chem. Commun.*, **36**, 3455 (1971).

ported[12] 7α-hydroxy syntheses involve either the reduction of the 6α,7α-epoxide with $Cr(OAc)_2$ or reductive debromination of the 6β-Br, 7α-OH compound with Zn/EtOH. Unfortunately, such reactions cannot be applied to the synthesis of 7β-OH compounds, since neither the epimeric epoxide nor 6ζ-Br, 7β-OH steroids are known compounds.

We recently reported[34] that the reaction of OsO_4 with 1,4,6-trien-3-one systems gave only products of β attack at the 6,7 double bond. Thus, reaction of **1a** with 1 equiv of OsO_4 gave the 6β,7β-diol **11** which, on reaction with triethylorthopropionate in Me_2SO with a catalytic quantity of p-TsOH·H_2O, gave the 6β,7β-ethylorthopropionate **12** (Scheme III). Acid hydrolysis of **12** led exclusively to the 6β-(propionyloxy)-7β-hydroxy compound **13**. This acid-catalyzed opening to give only the axial propionate is consistent with the hydrolysis results obtained by King and Allbutt[35] for ortho esters anchored to a *trans*-decalin system and is predicted by the principles of stereoelectronic control.[36]

Reduction of **13** with $Cr(OAc)_2$ in buffered aqueous Me_2CO[12,37,38] then gave the desired 7β-hydroxy compound **14** in 41% yield. A similar sequence of reactions converted the 6,7-dehydro-17,21-dipropionates **1b** and **1d** into the 16α-methyl- and 16β-methyl-7β-hydroxyprednisolone 17,21-dipropionates (**15** and **16**), respectively. Reaction of **14** with *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine[39] in CH_2Cl_2 at 0 °C gave the desired 7α-fluoro-16α-methylprednisolone 21-acetate (**3a**), with only minor amounts of the elimination product **1a**. In a similar manner, the dipropionate derivative **15** gave the 7α-fluoro compound **3b**. However, reaction of the 16β-methyl analogue **16** with the fluorinating reagent proceeded much more slowly and, on warming the reaction mixture to room temperature, a considerable quantity of the 7α-fluoro-9,11-olefin was formed along with the desired **3d**.

Biological Results and Discussion

Topical antiinflammatory activity was measured in mice by a modification[1,40] of the croton oil ear assay of Tonelli et al.[41] The topical potencies of the 7α-halogeno corticosteroids, their 7α-unsubstituted parent compounds, and their 6,7-dehydro derivatives are listed in Table I relative to betamethasone valerate (**20**). For comparison purposes, the relative potencies of hydrocortisone (**19**) and betamethasone 17,21-dipropionate (**21**) are also listed.

In the 16α- and 16β-methylprednisolone series, esterification of both C-17 and C-21 hydroxyl groups resulted in compounds which were consistently more potent than those compounds with C-21 acetoxy substitution alone. This is not surprising, since the effect of increased lipophilicity on topical antiinflammatory activity has been described.[42]

The most profound influence of 7α-halogeno substitution is found in the 16α-methylprednisolone series, where both 7α-chloro and 7α-bromo substitution significantly increases topical potency over the 7α-hydrogen parent. 7α-Iodo substitution has a lesser effect, while introduction of a 7α-fluorine atom leaves the potency unchanged. The potency increases for chloro and bromo substitution range from 2.5-fold, for the 17,21-dipropionates, to 3- to 3.5-fold for the 21-acetates, and for iodo substitution from 1.5- to 2-fold. The 7α-chloro- and 7α-bromo-16α-methylprednisolone 17,21-dipropionates (**4b** and **5b**) are nearly twice as potent as the standard, betamethasone valerate (**20**), and are somewhat more potent than, although not statistically different from, betamethasone dipropionate (**21**). The high potencies are all the more exceptional in light of the nonfluorinated nature of these compounds, since the presence of a 9α- and/or 6α-fluorine atom has hitherto been considered important for optimum topical antiinflammatory potency.

Interestingly, the influence of 7α-halogeno substitution is less clear cut in other series, suggesting that such substitution is exquisitely sensitive to structural manipulation at sites rather remote from the 7 position. For example, among the 16β-methyl corticosteroids only the 7α-chloro compound **4c** shows a potency greater than that of the parent **2c** as the 21-acetate derivative, while as the 17,21-dipropionate only the 7α-bromo compound **5d** is more potent than **2d**. All of the 7α-halogeno-16β-methyl compounds are less potent than their 16α-methyl congeners.

In both the 16α- and 16β-methylprednisolone series, introduction of a 6,7 double bond consistently reduced potency below that observed for the 7α-chloro-, 7α-bromo-, and 7α-iodo-substituted corticosteroids. For this reason, it seems unlikely that elimination of the elements of HX (X = Cl, Br, I) is a necessary prerequisite for, or occurs prior to, production of the antiinflammatory effect of 7α-halogeno-substituted corticosteroids.

In the 16,17-acetonide series, a marked difference in the effect of 7α-halogeno substitution on topical activity was observed. Thus, the 7α-chloro compound **4e** was approximately one-third as potent and the 7α-bromo compound **5e** was as potent as the parent **2e**. The reasons for this difference, and for the overall inconsistency of topical antiinflammatory potency, are not presently understood.

Experimental Section

Melting points were taken on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Optical rotations were determined at 26 °C as 0.3% DMF solutions (unless otherwise specified). NMR spectra were obtained at 60 or 100 MHz on either a Varian A60-A or an XL-100-15 spectrometer, and chemical shifts are reported in parts per million downfield from an internal $Si(CH_3)_4$ standard. Mass spectra were recorded on a Varian MAT CH5 spectrometer using a 70-eV source. Silica gel preparative (1000 μm) and analytical (250 μm) thin-layer chromatography (TLC) plates were obtained from Analtech, Inc., and the silica gel used for column chromatography was the TLC grade (silica gel G type 60) supplied by E. Merck.

1,4,6-Pregnatriene-3,20-diones. 16α-Methyl- and 16β-Methyl-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione 21-Acetate (1a and 1c). To a solution of dry HCl gas (22 g) in dioxane (660 mL) was added 16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate[6] (**2a**; 10 g, 24.1 mmol) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; 6.55 g, 28.9 mmol) at room temperature. After the reaction mixture was stirred for 24 h, the solids were removed by filtration and the filtrate was concentrated to a gummy residue under reduced pressure at 40 °C. The residue was dissolved in $CHCl_3$/EtOAc (1:1) and filtered through a short column of neutral alumina (Woelm activity V, 200 g) to remove excess DDQ. Concentration of the eluates gave a crude residue (3.5 g) of **1a** contaminated with

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(37) We have found from related work (unpublished) that neither a 6β,7β-dihydroxy-1,4-dien-3-one nor its 6,7-acetonide can be reduced to the 7β-hydroxy compound with $Cr(OAc)_2$.
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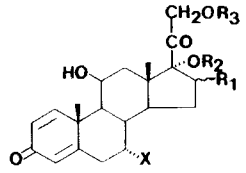
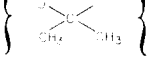
Table I. 7α-Halogeno Corticosteroids and the Associated 7α-Hydrogen and 6,7-Dehydro Compounds



no.	X	R_1	R_2	R_3	mp, °C	$[\alpha]^{26}_D$, deg (DMF)	formula	anal.	UV, λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)	NMR (Me_2SO-d_6), δ: 7β H	NMR: C_{10} CH_3	NMR: C_{13} CH_3	topical potency[n]
1a	H[r]	α-CH_3	H	$COCH_3$	227-229	+59.6	$C_{24}H_{30}O_6$	C, H	300 (11.9), 252 (10.1), 220 (12.9)		1.36	0.94	29 (15-43)[p]
2a	H	α-CH_3	H	$COCH_3$[a]							1.40	0.91	26 (18-34)[p]
3a	F	α-CH_3	H	$COCH_3$	139-143	+58.6[f]	$C_{24}H_{31}O_6F$	C, H[g]	241 (13.0)	4.90 (J = 50 Hz)	1.40	0.90	16 (0-34)[p]
4a	Cl	α-CH_3	H	$COCH_3$	197-203	+50	$C_{24}H_{31}O_6Cl$	C, H, Cl	242 (14.3)	4.65	1.41	0.92	81 (65-97)[o]
5a	Br	α-CH_3	H	$COCH_3$	169-175	+40.3	$C_{24}H_{31}O_6Br$	C, H, Br	242 (15.3)	4.79	1.41	0.93	94 (48-142)[o]
6a	I	α-CH_3	H	$COCH_3$	154-156	+22.3	$C_{24}H_{31}O_6I$	H; C, I[h]	242 (15.4)	4.88	1.40	0.95	54 (6-102)
1b	H[r]	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	*d*	+24.0	$C_{28}H_{36}O_7$	C, H	298 (11.9), 253 (9.3) 220 (12.1)		1.35	1.01	57 (35-79)[p]
2b	H	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	161-164	+61.7	$C_{28}H_{38}O_7$	C, H	243 (15.2)		1.40	1.00	76 (65-98)
3b	F	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	157-161	+33	$C_{28}H_{37}O_7F$	C, H, F	240 (15.9)	4.86 (J = 50 Hz)	1.41	1.01	69 (57-81)[p]
4b	Cl	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	212-216	+42.5	$C_{28}H_{37}O_7Cl$	C, H, Cl	242 (15.6)	4.66	1.42	1.02	176 (150-202)[q]
5b	Br	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	>295	+37.3	$C_{28}H_{37}O_7Br$	C, H, Br	242 (15.4)	4.90	1.43	1.03	186 (134-238)[q]
6b	I	α-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	150[e]	+22.0	$C_{28}H_{37}O_7I$	C; H, I[i]	241 (14.5)	4.91	1.43	1.08	103 (79-127)
1c	H[r]	β-CH_3	H	$COCH_3$	192-194	+87.1	$C_{24}H_{30}O_6$	C, H	299 (12.0), 252 (10.0), 220 (12.6)		1.36	0.97	4 (0-8)[p]
2c	H	β-CH_3	H	$COCH_3$[b]							1.38	0.93	10 (7-13)[p]
4c	Cl	β-CH_3	H	$COCH_3$	228-230	+78.3	$C_{24}H_{31}O_6Cl$	C, H, Cl	241 (15.5)	4.70	1.43	0.95	32 (24-48)[p]
5c	Br	β-CH_3	H	$COCH_3$	165[e]	+64.6	$C_{24}H_{31}O_6Br$	C, H	242 (15.6)	4.90	1.43	0.96	20 (12-28)[p]
1d	H[r]	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	*d*	+93.1	$C_{28}H_{36}O_7$		298 (8.2), 250 (7.9), 220 (10.5)		1.44	1.03	27 (21-33)[q]
2d	H	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	*d*	+75.1	$C_{28}H_{38}O_7$	C, H			1.41	0.88	74 (46-102)
3d	F	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	109-113	+50[f]	$C_{28}H_{37}O_7F$	*j*	240 (15.0)	4.98 (J = 50 Hz)	1.43	0.89	78 (58-98)
4d	Cl	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	125[e]	+74.4	$C_{28}H_{37}O_7Cl$	C, H; Cl[k]	241 (15.2)	4.74	1.44	0.91	88 (60-116)
5d	Br	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	135-137	+66.4	$C_{28}H_{37}O_7Br$	C, H, Br	242 (15.5)	4.89	1.44	0.92	120 (104-136)[o]
6d	I	β-CH_3	$COCH_2CH_3$	$COCH_2CH_3$	145-148	+52.0	$C_{28}H_{37}O_7I$	H; C, I[l]	241 (14.7)	5.00	1.44	0.95	36 (24-48)[q]
1e	H[r]			$COCH_3$	250-252	+101.7	$C_{26}H_{32}O_7$	C, H	300 (12.2), 254 (9.6), 222 (11.8)		1.43	0.88	25 (11-39)[q]
2e	H			$COCH_3$[c]	247-252	+122.3					1.37	0.82	91 (90-92)
4e	Cl			$COCH_3$	255-257	+104.9	$C_{26}H_{33}O_7Cl$	C, H, Cl	241 (16.2)	4.75	1.37	0.87	31 (13-49)[p]
5e	Br			$COCH_3$	197-200	+91.9	$C_{26}H_{33}O_7Br$	C, H; Br[m]	242 (15.2)	4.83	1.37	0.87	100 (50-150)
19 (hydrocortisone)													3 (1-5)[p]
20 (betamethasone 17-valerate)													100 (standard)
21 (betamethasone 17,21-dipropionate)													165 (137-193)[p]

[a] See ref 6. [b] See ref 7. [c] M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, 1, 331 (1963). [d] Noncrystalline. [e] Decomposition. [f] For $CHCl_3$ solution (0.1%). [g] 0.5 H_2O as solvent of crystallization. [h] C: calcd, 53.14; found, 54.46. I: calcd, 23.39; found 21.56. [i] H: calcd, 6.09; found 6.52. I: calcd, 20.72; found 20.12. [j] Insufficient for complete characterization (see text). [k] Cl: calcd, 6.80; found 6.05. [l] C: calcd, 54.90; found 53.98. I: calcd, 20.71; found, 19.20. [m] Br: calcd, 14.87; found 14.04. [n] Statistically derived estimated cumulative potencies relative to betamethasone valerate (100). Numbers in parentheses are estimated 95% level confidence intervals of the pooled estimates. [o] Statistically different from 7α-hydrogen parent compound at $p \leq 0.01$. [p] Statistically different from betamethasone 17-valerate at $p \leq 0.01$. [q] Statistically different from both 7α-hydrogen parent and betamethasone 17-valerate at $p \leq 0.01$. [r] 6,7-Dehydro.

the 7α-chloro adduct **4a**. Crystallization from MeOH/hexane gave **1a** (2.1 g, 21%), mp 227–229 °C.

In a similar manner, treatment of 16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-acetate[7] (**2c**; 10 g, 20.6 mmol) with DDQ (6.53 g, 28.8 mmol) in HCl/dioxane (3.33%, w/v, 600 mL) gave **1c** (3.6 g, 36%), mp 192–194 °C, after crystallization from EtOAc/hexane.

11β,16α,17α,21-Tetrahydroxy-1,4,6-pregnatriene-3,20-dione 16,17-Acetonide 21-Acetate (1e). Similarly, treatment of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide 21-acetate[8] (**2e**; 10.6 g, 23.2 mmol) with DDQ (6.5 g, 28.9 mmol) in HCl/dioxane (3.33%, w/v, 720 mL) gave crude **1e** (5.07 g) which was purified by crystallization from Me_2CO/hexane to yield **1e** (1.9 g, 18%), mp 250–252 °C.

16α-Methyl- and 16β-Methyl-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione (9 and 10). **1a** (1.5 g, 3.12 mmol) in MeOH (360 mL) was treated with saturated aqueous $NaHCO_3$ solution (40 mL) at room temperature. After the solution was stirred for 2 h, the solids were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was taken up in EtOAc. The organic solution was washed with water and dried ($MgSO_4$), and the solvent was evaporated to give a white solid (1.13 g). Crystallization from Me_2CO gave **9** (0.72 g, 53%): mp 229–232 °C; $[\alpha]_D$ +46.1°; UV λ_{max} (MeOH) 300 nm (ε 11 900), 252 (10 100), 220 (12 900); ^1H NMR (Me_2SO-d_6) δ 0.79 (C_{16}-CH_3, d, J = 7 Hz), 0.92 (C_{13}-CH_3, s), 1.35 (C_{10}-CH_3, s). Anal. ($C_{22}H_{30}O_5$) C, H.

Similar treatment of **1c** (1.75 g, 4.2 mmol) gave **10** (0.813 g, 52%) after crystallization from EtOAc and then Me_2CO/hexane: mp 188–191 °C; $[\alpha]_D$ +65.7°; UV λ_{max} (MeOH) 299 nm (ε 10 600), 250 (9000), 220 (11 100); ^1H NMR (Me_2SO-d_6) δ 1.03 (C_{13}-CH_3, s), 1.06 (C_{16}-CH_3, d, J = 7 Hz), 1.35 (C_{10}-CH_3, s). Anal. ($C_{22}H_{30}O_5$) C, H.

16α-Methyl- and 16β-Methyl-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione 17,21-Dipropionate (1b and 1d). A mixture of **9** (1.9 g, 5.1 mmol), *p*-TsOH·H_2O (0.142 g 0.75 mmol), triethylorthopropionate (3.8 mL), and Me_2SO (9.5 mL) was stirred at room temperature. After 2 h the reaction mixture was poured into aqueous $NaHCO_3$ solution, and the product was extracted into EtOAc. The organic solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give a gummy residue of the 17α,21-ethylorthopropionate. This residue was dissolved in 2% aqueous AcOH (15 mL) and after 1 h at room temperature it was poured into water (350 mL) containing 8% NaOH solution (50 mL). The solids formed were filtered off, washed with water, air dried, and without further purification treated with propionic anhydride (4.6 mL) and pyridine (23 mL). After 3.5 h at room temperature, the reaction mixture was poured into water (750 mL) containing 1 N HCl (150 mL) and the product extracted into EtOAc. The organic solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give crude **1b**. Chromatography of this product on silica gel (200 g) and elution with $CHCl_3$/EtOAc (1:1) gave pure **1b** (2.1 g, 85%) which could not be induced to crystallize. A portion (0.18 g) was further purified on a preparative reverse-phase high-pressure LC column (Whatman Magnum 9 ODS-2), eluting with MeOH/H_2O (7:3) to give **1b** as a white amorphous powder.

In a similar manner **10** (1.64 g, 4.4 mmol) gave **1d** (0.9 g, 42%), after chromatography on silica gel (150 g, eluting with 4:1 $CHCl_3$/EtOAc), which could not be crystallized.

1,4-Pregnadiene-3,20-diones. 16α-Methyl- and 16β-Methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (2b and 2d). In a sequence of reactions analogous to that used for the 6,7-dehydro compounds **1b** and **1d** above, 16α-methyl- and 16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-diones gave the corresponding 17,21-dipropionates. Thus, 16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione[6] (3 g, 8 mmol) gave crude **2b** as a white solid (2 g), a portion of which (0.2 g) was purified on preparative TLC (development solvent $CHCl_3$/EtOAc, 4:1) to give **2b** (0.15 g), mp 161–164 °C from Et_2O/hexane. Similarly 16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione[7] gave **2d**, which could not be induced to crystallize.

7α-Chloro-1,4-pregnadiene-3,20-diones. 7α-Chloro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (4b). A solution of **1b** (2.1 g, 4 mmol) in dry HCl/dioxane (16.5%, w/v, 25 mL) was kept at room temperature for 16 h and then poured into a rapidly stirred mixture of ice–water (400 mL). The resulting precipitate was filtered off, washed thoroughly with water, and air dried to give crude product (1.8 g). The filtrate was extracted with EtOAc, the organic extract was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give further product (0.1 g). Separation of the combined product by preparative TLC (development solvent: Et_2O/hexane, 2:1) gave starting material **1b** (0.78 g, 37%) and **4b**, which was purified by trituration with Me_2CO/Et_2O to give **4b** (0.347 g, 15%); crystallization from Me_2CO/MeOH gave the analytical sample, mp 212–216 °C.

In a comparative experiment, 50-mg samples of **1b** were dissolved in HCl/AcOH (7%, w/v, 1 mL) and HCl/dioxane (16.5%, w/v, 1 mL) at room temperature and in HCl/THF (45%, w/v, 1 mL) at 0 °C. Samples were taken after 4 and 8 h and quenched with water. The precipitates were filtered off, washed with water, and air dried. Analysis of the UV spectra of these samples (ratio of the maxima at 240–250 and 300 nm) gave 25, 30, and 35% conversion to the 7α-chloro compound, respectively. Examination of artificial mixtures by this method gave agreement between actual and calculated values within ±2%.

7α-Chloro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (4d). Treatment of **1d** (0.9 g, 1.86 mmol) with HCl/dioxane solution (16.5%, w/v, 15 mL) in the manner described above and separation of the product on preparative TLC (development solvent: Et_2O/hexane, 2:1) gave, after crystallization from EtOAc, **4d** (0.15 g, 15%).

7α-Chloro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-Acetonide 21-Acetate (4e). In a similar manner to that described above, reaction of **1e** (0.68 g, 1.5 mmol) with HCl/dioxane (16.5%, w/v, 35 mL) gave a crude product, of which a portion (0.2 g) was separated on preparative TLC (development solvent: Et_2O/hexane, 2:1) to give **4e** (0.037 g, 17%); crystallation from Me_2CO/hexane gave **4e**, mp 255–257 °C.

7α-Chloro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (4a) and 16α-Methyl-6β,7β,11β,17α,21-pentahydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (11). a. Isolation from Crude 1a. The crude product from the preparation of **1a** (3.4 g, 0.82 mmol) and OsO_4 (2 g, 0.78 mmol) was dissolved in dioxane (200 mL) and pyridine (2 mL) and stirred at room temperature. After 5 days, the solution was saturated with H_2S and filtered through a pad of Hi-Flo Supercel. The filtrate was concentrated under reduced pressure to a black residue, which was chromatographed on a column of silica gel (300 g). Elution with EtOAc/$CHCl_3$ (1:1) gave **4a** (0.298 g, 9%), mp 197–203 °C from Me_2CO/hexane, and then **11** (0.81 g, 23%), crystallized from MeOH/Et_2O to give the analytical sample: mp >250 °C; $[\alpha]_D$ + 42.4°; UV λ_{max} (MeOH) 243 nm (ε 14 200); ^1H NMR (Me_2SO-d_6) δ 0.78 (C_{16}-CH_3, d, J = 6 Hz), 0.90 (C_{13}-CH_3, s), 1.50 (C_{10}-CH_3, s), 3.08 (7α-H, m), 4.18 (6α-H, d, J = 3 Hz), 4.22 (11α-H, m), 4.70 and 5.05 (C_{21}-H's, d, J = 18 Hz), 6.00 (C_4-H, d, J = 2 Hz), 6.10 (C_2-H, dd, J = 10 and 2 Hz), 7.27 (C_1-H, d, J = 10 Hz). Anal. ($C_{24}H_{32}O_8$) C, H.

b. From 7β-Hydroxy Compound. A suspension of **14** (0.05 g, 0.116 mmol) in CH_2Cl_2 (3 mL) was treated with *N,N*-diethyl-1,2,2-trichlorovinylamine (0.031 mL, 0.037 g, 0.127 mmol) for 1 h. A further portion of the reagent (0.056 mL, 0.23 mmol) was added, and after a further 5 h the reaction mixture was evaporated to dryness under reduced pressure. Preparative TLC (development solvent: $CHCl_3$/EtOAc, 3:1) gave starting material (25 mg, 50%) and **4a** (19 mg, 35%), the NMR and MS of which were identical with that of **4a** produced above.

7α-Chloro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (4c). The crude product from the preparation of **1c** (0.5 g) was treated in the above manner (a) with OsO_4 (0.278 g), and the product was separated on preparative TLC (development solvent: $CHCl_3$/EtOAc, 4:1) to give **4c** (0.035 g), mp 228–230 °C, from Me_2CO/hexane.

7α-Chloro-17α-hydroxy-1,4-pregnadiene-3,20-dione 17-Acetate (8). A solution of **7** (2 g, 5.44 mmol) in HCl/THF (45%, w/v, 40 mL) was stirred at 0 °C for 1 h. The reaction mixture was poured into efficiently stirred ice–water, and the resultant precipitate was filtered off, washed with water, and air dried to give crude **8** (1.9 g). Examination of this material by TLC showed almost complete absence of starting material, and the UV spec-

trum indicated there was at least a 90% conversion, as judged by the ratio of the absorption maxima at ~250 and 300 nm. Crystallization from Me_2CO gave **8** (1 g, 45%): mp 200–206 °C; $[\alpha]_D$ +4.8°; UV λ_{max} (MeOH) 242 nm (ϵ 16100); ^1H NMR (Me_2SO-d_6) δ 0.65 (C_{13}-CH_3, s), 1.23 (C_{10}-CH_3, s), 2.06 and 1.97 (C_{20}-CH_3, $OCOCH_3$, s), 4.54 (7β-H, m), 6.00 (C_4-H, d, J = 2 Hz), 6.13 (C_2-H, dd, J = 10 and 2 Hz), 7.21 (C_1-H, d, J = 10 Hz). Anal. ($C_{23}H_{29}O_4Cl$) C, H, Cl.

Similarly a solution of **7** (0.1 g) in HCl/AcOH solution (7%, w/v, 1 mL) for 4 h gave a product with the same TLC and UV spectrum as in the above experiment, indicating a better than 90% conversion to **8**. Also, an NMR spectrum of the reaction mixture after 1 h showed only signals due to **8** and the absence of any signals due to the starting material.

7α-Bromo-1,4-pregnadiene-3,20-diones. 7α-Bromo-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (5b). **1b** (0.29 g, 0.6 mmol) was dissolved in a freshly prepared solution of dry HBr/AcOH (30%, w/v, 5.8 mL) at approximately 5 °C. After 1 h at this temperature, the reaction mixture was poured into ice–water (400 mL) with efficient mixing. The solids were filtered, washed thoroughly with water, and air dried to give a crude product (0.23 g). TLC examination of this product showed only a trace of starting material. Trituration of the product with Me_2CO/Et_2O gave pure **5b** (0.19 g, 56%) and crystallization from Me_2CO/Et_2O/hexane gave the analytical sample, mp >295 °C.

7α-Bromo-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (5a). In a similar manner, **1a** (0.1 g, 0.24 mmol) in HBr/AcOH (30%, w/v, 2 mL) for 1 h at 5 °C gave crude **5a** (0.064 g), which was purified on preparative TLC (development solvent: $CHCl_3$/EtOAc, 5:2) to give **5a** (0.038 g, 32%). Crystallization from Me_2CO/Et_2O gave the analytical sample, mp 169–175 °C.

7α-Bromo-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (5d). Similarly, **1d** (0.3 g, 0.62 mmol) in HBr/AcOH (30%, w/v, 6 mL) gave crude **5d**, which was purified on preparative TLC (development solvent: Et_2O/hexane, 2:1) to yield pure **5d** (0.13 g, 37%). Crystallization from i-Pr_2O/Me_2CO gave the analytical sample, mp 135–137 °C.

7α-Bromo-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (5c). Similar treatment of **1c** (0.16 g, 0.39 mmol) with HBr/AcOH (30%, w/v, 3 mL) gave crude **5c**, which was purified on preparative TLC (development solvent: EtOAc/hexane, 1:1). Trituration with Et_2O and crystallization from EtOAc gave pure **5c** (0.031 g, 20%), mp 165 °C with decomposition.

7α-Bromo-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-Acetonide 21-Acetate (5e). Reaction of **1e** (0.8 g, 1.75 mmol) with HBr/AcOH (30%, w/v, 20 mL) gave crude **5e** (0.88 g). A portion of this product (0.4 g) was purified on preparative TLC (development solvent: Et_2O/hexane, 2:1). Crystallization from Me_2CO gave **5e** (0.176 g, 37%), mp 197–200 °C.

7α-Iodo-1,4-pregnadiene-3,20-diones. 7α-Iodo-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (6b). **1b** (0.2 g, 0.41 mmol) was dissolved in a freshly prepared solution of dry HI gas in glacial AcOH (30%, w/v, 4 mL) at approximately 5 °C. After 20 min, a 5% $Na_2S_2O_3$ solution (80 mL) was added to the reaction mixture. The precipitate which formed was filtered off, washed with water, and added to an EtOAc extract of the filtrate. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure at 0 °C to a yellow solid. TLC examination of this product showed the complete absence of starting material. Preparative TLC purification of this product (development solvent: EtOAc/hexane, 42:58) gave **6b** (0.105 g, 42%), which was crystallized from EtOAc to give **6b**, mp 150 °C dec. This material did not give acceptable elemental analyses and neither did a sample that was further purified on a reverse-phase high-pressure LC column (Whatman Magnum 9 ODS-2, eluting with MeOH/H_2O, 7:3) and then crystallized from EtOAc.

7α-Iodo-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (6a). In a similar manner, treatment of **1a** (0.6 g, 1.45 mmol) with HI/AcOH (30%, w/v, 10 mL) and purification by preparative TLC (development solvent: EtOAc/$CHCl_3$, 1:4) gave **6a** (0.27 g, 35%). Crystallization from Me_2CO/Et_2O gave **6a** (0.17 g), mp 154–156 °C, which gave poor elemental analyses that were not improved on recrystallization.

7α-Iodo-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (6d). Similar treatment of **1d** (0.25 g, 0.52 mmol) with HI/AcOH (30%, w/v, 5 mL) for 0.75 h at 5 °C and quenching with 5% $NaHSO_3$ solution gave a yellow solid. A portion of this product was purified on a preparative reverse-phase high-pressure LC column (Whatman Magnum 9 ODS-2, eluting with MeOH/H_2O, 7:3) to give a white solid (0.085 g), which was crystallized from Et_2O to give **6d**, mp 145–148 °C.

Attempted Addition of HF to 1,4,6-Pregnatriene-3,20-diones. A solution of **7** (0.2 g) in HF/AcOH (28%, w/v, 2 mL) was kept at 0 °C. Samples were removed and quenched with saturated $NaHCO_3$ solution, and the product was extracted into EtOAc. The organic solution was washed with water, dried, and evaporated to dryness under a stream of N_2. Examination of samples taken at 1, 2, 3.5, and 20 h by UV spectroscopy showed that no 7α-fluoro product was formed. Similar treatment of **1b** (0.2 g) with HF/AcOH (28%, w/v, 2 mL) at 0 °C and sampling of the reaction mixture as above also showed the absence of any addition of HF.

7α-Fluoro-1,4-pregnadiene-3,20-diones. 6β,7β,11β,17α,21-Pentahydroxy-1,4-pregnadiene-3,20-diones. A mixture of **1b** (2 g, 4.13 mmol), OsO_4 (1 g, 3.94 mmol), pyridine (3 mL), and dioxane (75 mL) was stirred at room temperature for 6 days. The reaction mixture was saturated with H_2S, stirred for a further 0.5 h, and then filtered through Hi-Flo supercel. The filtrate was concentrated under reduced pressure to a black gum, which was taken up into $CHCl_3$ and applied to a column of silica gel (150 g). Elution with $CHCl_3$/EtOAc (1:1) gave unreacted starting material (0.645 g, 32%), and elution with $CHCl_3$/EtOAc (1:3) gave 16α-methyl-6β,7β,11β,17α,21-pentahydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate (**17**; 0.89 g, 42%) as a noncrystallizable foam: ^1H NMR (Me_2SO-d_6) δ 0.83 (C_{16}-CH_3, d, J = 6 Hz), 1.00 (C_{13}-CH_3, s), 1.54 (C_{10}-CH_3, s), 3.16 (7α-H, dd, J = 10 and 3 Hz), 4.22 (6α-H, d, J = 3 Hz), 4.30 (11α-H, m), 4.70 and 4.97 (C_{21}-H's, d, J = 17 Hz), 6.05 (C_4-H, d, J = 2 Hz), 6.17 (C_2-H, dd, J = 10 and 2 Hz), 7.30 (C_1-H, d, J = 10 Hz).

In a similar manner, **1d** (0.8 g, 0.165 mmol) gave 16β-methyl-6β,7β,11β,17α,21-pentahydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate (**18**; 0.447 g, 52%) as a noncrystallizable foam: ^1H NMR (Me_2SO-d_6) δ 0.86 (C_{13}-CH_3, s), 1.20 (C_{16}-CH_3, d, J = 6 Hz), 1.52 (C_{10}-CH_3, s), 3.18 (7α-H, dd, J = 12 and 3 Hz), 4.22 (6α-H, d, J = 3 Hz), 6.04 (C_4-H, d, J = 2 Hz), 6.18 (C_2-H, dd, J = 10 and 2 Hz), 7.30 (C_1-H, d, J = 10 Hz).

7β,11β,17α,21-Tetrahydroxy-1,4-pregnadiene-3,20-diones. A mixture of **11** (1.2 g, 2.68 mmol), triethylorthopropionate (2.4 mL), p-TsOH·H_2O (0.09 g), and Me_2SO (5 mL) was stirred at room temperature. After 1.5 h, the reaction mixture was poured into water and the product extracted into EtOAc. The organic solution was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to give the 6β,7β-ethylorthopropionate **12** as a gum. This product proved to be unstable during attempts to purify it, so it was immediately hydrolyzed with 2% H_2O/98% AcOH (5 mL). After 1 h at room temperature, the solution was poured into water and the product extracted into EtOAc. The organic solution was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated under reduced pressure to give **13** as a gum. A portion of this product (0.1 g) was purified by preparative TLC (development solvent: EtOAc/$CHCl_3$, 1:1) and crystallized from EtOAc/Et_2O to give **13**: mp 208–212 °C; $[\alpha]_D$ +25.6°; UV λ_{max} (MeOH) 244 nm (ϵ 13600); ^1H NMR (Me_2SO-d_6) δ 0.78 (C_{16}-CH_3, d, J = 7 Hz), 0.90 (C_{13}-CH_3, s), 1.39 (C_{10}-CH_3, s), 3.26 (7α-H, dd, J = 10 and 4 Hz), 4.30 (11α-H, m), 4.71 and 5.03 (C_{21}-H's, d, J = 18 Hz), 5.31 (6α-H, d, J = 4 Hz), 6.00 (C_4-H, s), 6.15 (C_2-H, dd, J = 10 and 2 Hz), 7.30 (C_1-H, d, J = 10 Hz). Anal. ($C_{27}H_{36}O_9$·H_2O) C, H. The remainder of crude **13** was dissolved in Me_2CO (250 mL), and a solution of water (24 mL), AcOH (6 mL), and NaOAc (8.4 g) was added followed by freshly prepared $Cr(OAc)_2$ (the wet cake prepared from 10 g of $CrCl_2$). The reaction mixture was stirred for 2.5 h at room temperature and filtered, and the filtrate was concentrated under reduced pressure. The residue was taken up into EtOAc, washed with water, and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a gum, which was chromatographed on silica gel (100 g). Elution with $CHCl_3$/EtOAc (1:1) containing

1% MeOH gave **14** (0.48 g, 41%), which was crystallized from Me_2CO/MeOH/hexane: mp 204–207 °C; $[\alpha]_D$ +47.5°; UV λ_{max} (MeOH) 242 nm (ϵ 13 600); ^1H NMR (Me_2SO-d_6) δ 0.76 (C_{16}-CH_3, d, J = 7 Hz), 1.08 (C_{13}-CH_3, s), 1.40 (C_{10}-CH_3, s), 3.22 (7α-H, m), 4.24 (11α-H, m), 4.75 and 5.07 (C_{21}-H's, d, J = 18 Hz), 5.94 (C_4-H, d, J = 2 Hz), 6.18 (C_2-H, dd, J = 10 and 2 Hz), 7.34 (C_1-H, d, J = 10 Hz). Anal. ($C_{24}H_{32}O_7$·CH_3OH) C, H.

Similar treatment of **17** (0.87 g, 1.56 mmol) gave 16α-methyl-7β,11β,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate (**15**; 0.24 g, 31%) as white crystals: mp 125–133 °C; $[\alpha]_D$ +32.4°; UV λ_{max} (MeOH) 243 nm (ϵ 13 600); ^1H NMR (Me_2SO-d_6) δ 0.81 (C_{16}-CH_3, d, J = 6 Hz), 1.01 (C_{13}-CH_3, s), 1.38 (C_{10}-CH_3, s), 3.12 (7α-H, m), 4.22 (11α-H, m), 5.87 (C_4-H, d, J = 2 Hz), 6.10 (C_2-H, dd, J = 10 and 2 Hz), 7.26 (C_1-H, d, J = 10 Hz). Anal. ($C_{28}H_{38}O_8$) C, H.

In a similar manner, **18** (0.447 g, 0.86 mmol) gave 16β-methyl-7β,11β,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 17,21-dipropionate (**16**; 0.167 g, 38%) as a noncrystallizable foam.

7α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (3b). To a solution of **15** (0.22 g, 0.44 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine (0.385 mL, 0.455 g, 2.4 mmol). After 1.75 h at 0 °C, the solvent was removed under reduced pressure at 0 °C and the gummy product was purified by preparative TLC (development solvent: Et_2O/hexane, 2:1) to give **3b** (0.095 g, 43%). Crystallization from EtOAc/hexane gave **3b** (0.069 g), mp 157–161 °C.

7α-Fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 21-Acetate (3a). **14** (0.130 g, 0.3 mmol) in CH_2Cl_2 (75 mL) was treated with *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine (0.286 mL, 0.34 g, 1.8 mmol) for 18 h at 0 °C. The solvent was removed under reduced pressure at 0 °C, and the solid product was purified on preparative TLC (development solvent: EtOAc/$CHCl_3$, 2:5). The product **3a** (0.088 g, 67%) was contaminated with a small amount of the 6,7-dehydro compound **1a**, as shown by the UV spectrum. Further purification on a preparative reverse-phase high-pressure LC column (Whatman Magnum-9 ODS-2), eluting with MeOH/H_2O (3:2), gave, on removal of the MeOH under reduced pressure, **3a** as white crystals, mp 139–143 °C.

7α-Fluoro-16β-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17,21-Dipropionate (3d). To a solution of **16** (0.167 g, 0.33 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *N,N*-diethyl(2-chloro-1,1,2-trifluoroethyl)amine (0.292 mL, 0.346 g, 1.83 mmol). After 2 h at 0 °C, another portion of the fluorinating agent (0.292 mL) was added, and the reaction mixture stirred for a further 2 h at 0 °C. TLC examination showed very little reaction had occurred, so the reaction mixture was allowed to stand at room temperature for 2 h and then evaporated to dryness under reduced pressure. Separation of this product on preparative TLC (development solvent: $CHCl_3$/EtOAc, 5:1) gave **3d** (0.022 g, 13%), which was crystallized from Me_2CO/hexane to give **3d**, mp 109–113 °C, and 7α-fluoro-16β-methyl-17α,21-dihydroxy-1,4,9-(11)-pregnatriene-3,20-dione 17,21-dipropionate (0.045 g, 28%) as a gum: ^1H NMR ($CDCl_3$) δ 0.73 (C_{13}-CH_3, s), 1.40 (C_{10}-CH_3, s), 4.28 and 4.86 (C_{21}-H's, d, J = 17 Hz), 4.86 (7β-H, d, J = 50 Hz), 5.73 (C_{11}-H, d, J = 6 Hz), 6.10 (C_4-H), 6.23 (C_2-H, dd, J = 10 and 2 Hz), 7.16 (C_1-H, d, J = 10 Hz).

Acid-Catalyzed Elimination of 7α-Halogeno-1,4-pregnadiene-3,20-diones. A solution of **4b** (1 g, 1.92 mmol) in HCl/dioxane (1.45%, w/v, 100 mL) was stirred at room temperature for 20 h and the solvent was removed under reduced pressure. The resulting gum was chromatographed on a column of silica gel (100 g), eluting with EtOAc/hexane (42:58) to give **1b** (0.8 g, 86%) as a noncrystallizable foam.

In a comparative experiment, approximately 0.05 M solutions of the 7α-halo compounds **3b**, **4b**, **5b**, and **6b** in HCl/dioxane (3% w/v) were kept at room temperature and were sampled by removing aliquots and rapidly removing the solvent under a stream of N_2. The resulting gum was examined by TLC and UV spectroscopy and, after no further change was detected, by NMR spectroscopy. Thus, the 7α-iodo and 7α-bromo compounds, **6b** and **5b**, reached equilibrium (approximately 90% **1b** as judged from the UV maxima at 300 and 250 nm) after 2 h, the 7α-chloro compound **4b** after 5 h, and the 7α-fluoro compound **3b** was still 50% unchanged after 5 h.

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Structure–Activity Study of Antiulcerous and Antiinflammatory Drugs by Discriminant Analysis

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Discriminant analysis was used in the structure–activity study of antiulcerous benzoguanamines, antiinflammatory phenylacetic acids, and aminouracils. The usual discriminant analysis requires the equality of covariance matrix for the multivariate normal distribution between observation groups. When this condition is not fulfilled for some pairs of groups, a modified procedure, the "admissible" discriminant analysis after Anderson and Bahadur, was applied. In this procedure, the model of equal covariance is not the prerequisite for the analysis. As the primary criterion for selecting the best combination of variables in the discriminant functions, we used the number of misclassified compounds which is minimum. The discriminant variables were selected from the physicochemical parameters used to analyze the variation in hydrophobicity due to structural modifications. The potency scores divided into three groups for each of the three series of compounds were predicted with more than 80% accuracy, when the two-group analysis was performed for the most potent and least potent groups omitting the intermediary group.

Discriminant analysis was first applied to structure–activity studies by Martin et al.[1] They demonstrated its usefulness when the potency of a series of drugs is roughly presented, in terms of the response level at a fixed dose or the screening ratings instead of generating a dose–response relationship for each drug. Recently, this procedure has been used with considerable success in structure–ac-

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