gave XI, m.p. 241–243°, λ_{max}^{MeOH} 260 mμ (log ε 4.20), $\lambda_{max}^{CHCl_3}$ 2.74, 2.8–2.95 (OH), 5.73, 8.08 (acetate), 5.77μ (20 C=O).

Anal. Calcd. for $C_{31}H_{36}F_2N_2O_5$: C, 67.07; H, 6.49. Found: C, 67.06; H, 6.66.

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Notes

Synthesis of 2′-(2,4-Difluorophenyl)-11β,17,21-trihydroxy-6,16α-dimethyl-20-oxopregna-4,6-dieno[3,2-*c*]pyrazole

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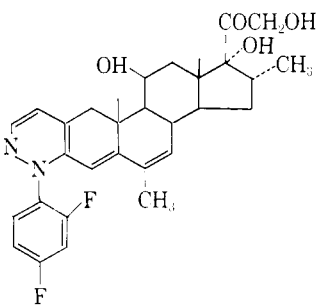
It has been shown that 2′-phenylpregn-4-eno[3,2-*c*]-pyrazoles derived from cortisol or other glucocorticoids are more potent antiinflammatory agents than the parent 3-keto-Δ^4-steroids.[1–4] A variety of compounds carrying substituents in the aromatic ring were also prepared and tested, but these were less active than the unsubstituted phenylpyrazole.[5] The only exception proved to be the *p*-fluorophenyl derivative[1,3] which was about 1.65 times as active as the phenylpyrazole and 6.5 times as active as the *p*-chlorophenylpyrazole[3] in the 16α-methylcortisol series. Since a small, electron-withdrawing group in the *para* position was thus activity enhancing, it appeared of interest to prepare the *o,p*-difluorophenylpyrazole (III). In the oral granuloma inhibition assay[6] III proved to be about 115[7] times as active as cortisol, whereas its *ortho*-unsubstituted analog[2] was 600 times as active as cortisol.



III

Experimental

2′-(2,4-Difluorophenyl)-11β-hydroxy-6,16α-dimethyl-17,20:20,21-bis(methylenedioxy)pregna-4,6-dieno[3,2-*c*]pyrazole (II).—To 500 mg. (1.09 mmoles) of 11β-hydroxy-2-hydroxymethylene-6,16α-dimethyl-17,20:20,21-bis(methylenedioxy)-pregna-4,6-dien-3-one (I),[2] in 5 ml. of glacial acetic acid was added 108 mg. (1.31 mmoles) of sodium acetate and 238 mg. (1.31 mmoles) of 2,4-difluorophenylhydrazine hydrochloride. The solution was stirred for 30 min. in an atmosphere of nitrogen and then was filtered to remove a small amount of insoluble material. Water was added and a flocculent precipitate formed which was extracted into methylene chloride. The methylene chloride layer was washed successively with a cold solution of dilute hydrochloric acid, water, a dilute solution of sodium hydroxide, water, and saturated sodium chloride solution, and was dried over magnesium sulfate. The solution was concentrated to dryness to yield 627 mg. of a light yellow foam. The crude product was dissolved in a minimum amount of benzene and chromatographed on 17.5 g. of neutral alumina. Benzene–methylene chloride mixtures (9:1 and 7:3) eluted 420 mg. of II. Crystallization from acetone–hexane afforded 100 mg. of crystalline II, m.p. 215–217°, $\lambda\lambda_{max}^{MeOH}$ 312 mμ (log ε 4.31), 269 (4.15). The ultraviolet spectrum is in accord with the assigned structure.[1–3] An analytical sample prepared by repeated recrystallization from acetone–hexane melted at 216–217°.

Anal. Calcd. for $C_{32}H_{36}F_2N_2O_5$: C, 67.75; H, 6.41. Found: C, 67.56; H, 6.28.

2′-(2,4-Difluorophenyl)-11β,17,21-trihydroxy-6,16α-dimethyl-20-oxopregna-4,6-dieno[3,2-*c*]pyrazole (III).—A mixture of 320 mg. of II and 25 ml. of 60% aqueous formic acid was heated under nitrogen on a steam bath for 35 min. and was concentrated *in vacuo* to dryness. Addition of 3 ml. of water followed by vigorous agitation of the mixture gave 268 mg. of a noncrystalline solid. The crude product was dissolved in 7 ml. of methanol, 0.07 ml. of a 2.3 *N* solution of sodium methoxide was added, and the solution was stirred in an atmosphere of nitrogen for 10 min. The base was neutralized with glacial acetic acid, and the solution was concentrated to dryness. The residue was dissolved in methylene chloride, washed with water, and dried over magnesium sulfate. After concentrating the solution to dryness, the residue was dissolved in hot acetone and hexane was added to afford crystalline III. Recrystallization from acetone gave an analytical sample, m.p. 224–226.5°, $\lambda\lambda_{max}^{MeOH}$ 312.5 mμ (log ε 4.30), 270 (4.14).

Anal. Calcd. for $C_{30}H_{34}F_2N_2O_4 \cdot 0.5C_3H_6O$: C, 68.35; H, 6.72. Found: C, 68.30; H, 6.58.

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(7) We are greatly indebted to Dr. S. L. Steelman for permission to report this result.

17-Substituted 3β-Hydroxy-4-pregnen-20-ones

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A number of communications have appeared on the synthesis of 3β-hydroxy-Δ^4-pregnenes and -androstenes,[1] and some compounds of this class have shown physiological activity. For example, 3β-hydroxy-4-pregnen-20-one[1a] and its 6α-methyl derivative[1f] are

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