Synthesis of Pregn-4-eno[3,2-*c*]pyrazoles Related to 9α-Fluoro-16α-methylcortisol[1]

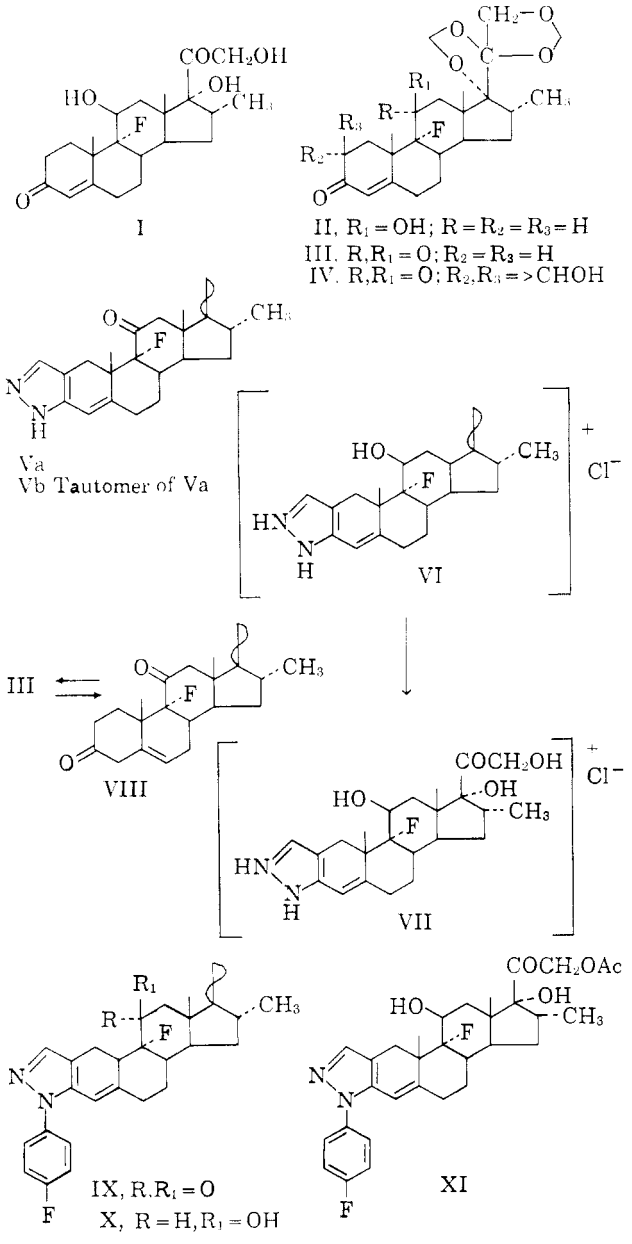
RALPH HIRSCHMANN, N. G. STEINBERG, E. F. SCHOENEWALDT, W. J. PALEVEDA, AND MAX TISHLER

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

Received October 8, 1963

The syntheses of 9α-fluoro-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole hydrochloride and of 9α-fluoro-2′-(4-fluorophenyl)-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole 21-acetate are described.

The synthesis of the steroidal 4-pregneno[3,2-*c*]-pyrazoles derived from cortisol,[2] 16α-methylcortisol,[2] allodihydrocortisol,[2] and from 6,16α-dimethyl-6-dehydrocortisol[3] has been reported. These compounds constitute a novel class of potent antiinflammatory steroids. In this paper we describe the synthesis of 9α-fluoro-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole hydrochloride (VII) and the 21-acetate of 9α-fluoro-2′-(4-fluorophenyl)-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole (XI).[1]



The conversion of 9α-fluoro-16α-methylcortisol (I) into the bismethylenedioxy[4] derivative (II) was effected in 60–75% yield. We then attempted to effect condensation of the fluorohydrin II with ethyl formate. Kissman and co-workers[5] have described the reaction of 9α-fluoro-11β-hydroxy-16α-isopropylidenedioxy-21-(tetrahydropyran-2′-yloxy)pregn-4-ene-3,20-dione with either diethyl oxalate or ethyl formate albeit in low yield. In our hands the Claisen condensation of II with ethyl formate in benzene in the presence of sodium hydride resulted in a crude product which gave a low fluorine analysis and which did not lend itself readily to purification. We circumvented this difficulty by converting II into the 11-ketone III with chromic oxide in pyridine[6] in 81% yield. When III was allowed to react with ethyl formate in benzene in the presence of sodium hydride or a mixture of sodium hydride and sodium methoxide, the desired 2-hydroxymethylene compound (IV) was obtained in about 40% yield. Use of sodium *t*-butoxide as the condensing agent gave IV in a yield of 60%.[7] With either condensing agent the β,γ-unsaturated ketone (VIII) was obtained as a by-product.[8] Compound VIII was shown to be isomeric with III by elemental analysis. The infrared spectrum revealed only the presence of saturated carbonyl groups. The absence of an α,β-unsaturated ketone was confirmed also by ultraviolet spectroscopy. In accordance with the proposed structure, the double bond was rapidly conjugated with the 3-ketone on treatment with dilute base.

(1) A preliminary announcement of this work has been published: R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963).

(2) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *ibid.*, **86**, 1520 (1964).

(3) (a) J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann, and S. L. Steelman, *ibid.*, **85**, 236 (1963); (b) R. Strachan, N. G. Steinberg, M. Tishler, and R. Hirschmann, *J. Med. Chem.*, **7**, 355 (1964).

(4) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

(5) H. M. Kissman, A. S. Hoffman, J. F. Poletto, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 950 (1962).

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) For an excellent study dealing with the formation of 2-hydroxymethylene-3-keto-steroids see R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *ibid.*, **83**, 1478 (1961).

(8) The deconjugation of Δ⁴-3-keto steroids with potassium *t*-butoxide in *t*-butyl alcohol has recently been discussed by H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, **No. 15**, 669 (1962).

The condensation of IV with hydrazine hydrate in refluxing ethanol afforded the pyrazole (V) in 89% yield. For reasons which were discussed in connection with the synthesis of the pyrazole of 16α-methylcortisol,[2] we tentatively assign structure Va rather than Vb to this pyrazole.

The reduction of the 11-ketone with an excess of sodium borohydride in a mixture of isopropyl alcohol and methylene chloride was carried out in the presence of triethylamine and/or water as suggested by Brown.[9] The reaction was slow and occasionally did not go to completion at room temperature overnight even when pure starting material was employed. Decomposition of excess hydride with cold dilute hydrochloric acid afforded a crystalline hydrochloride which was characterized by elemental analysis and by absorption bands in the infrared spectrum at 3.5–4.5 μ and at 6.1 and 6.27 μ. The free amine was obtained when the reduction and the decomposition with hydrochloric acid were carried out in dimethylformamide, the solvent of choice for the hydride reduction. The resulting free amine was readily converted into the hydrochloride salt by treating an acetone solution of the pyrazole with hydrogen chloride gas. The yield for the reduction and salt formation was 86%. The salt was not very soluble in either methylene chloride or water, but in the presence of both solvents the compound was hydrolyzed and passed into the organic layer as the free amine.

Treatment of the bismethylenedioxy compound (VI) with dilute aqueous formic acid gave the pyrazole (VII) as the free amine. Any 21-formate present in the crude reaction product was solvolyzed on treatment with a methanolic solution of sodium methoxide. The resulting pyrazole was converted into the crystalline hydrochloride (VII).

When IV was allowed to react with *p*-fluorophenylhydrazine in refluxing ethanol, a crystalline *p*-fluorophenylpyrazole was obtained. The latter was assigned the 2′-aryl structure (IX) because it had an absorption maximum at 261 mμ.[2] The reduction of IX with sodium borohydride gave the 11β-hydroxy compound (X), which was treated with aqueous formic acid to hydrolyze the BMD-protecting group. The resulting product was characterized as the 21-acetate (XI).

Biology.[10,11]—In the systemic granuloma assay,[12] VII was about 10–12 times as active as cortisol as an antiinflammatory agent, but unexpectedly it was only 3–4 times as active as cortisol in causing adrenal atrophy. Compound XI was about 500 times as active as cortisol both in inhibiting granuloma formation and in causing adrenal atrophy. Neither compound caused sodium retention in the adrenalectomized rat.[13]

Experimental

9α-Fluoro-16α-methyl-17,20:20,21-bis(methylenedioxy)pregn-4-ene-3,11-dione (III).—A 5-g. sample of I was dissolved in a mixture of 235 ml. of chloroform and 150 ml. of methylene chloride, cooled in an ice bath with stirring, and treated with 85 ml. of Merck Reagent formaldehyde (37%). An equal volume (85 ml.) of cold concentrated hydrochloric acid was added from a funnel over a 5-min. interval with stirring and cooling. The mixture was stirred at room temperature for 4 hr. The layers were separated and the organic layer was washed free of acid by successive washings with water and with a 5% solution of sodium bicarbonate. The organic layers were washed free of bicarbonate, dried over magnesium sulfate, and taken to dryness. The gummy residue was treated with enough hot methanol on a steam bath to effect trituration, and the resulting crystalline solid was separated by filtering the mixture while hot. The filtrate was set aside and it deposited more product on standing overnight. The crude product (3.76 g., 68.5%) was dissolved partially in 250 ml. of hot chloroform and diluted with an equal volume of hot benzene to complete solution. After cooling, the mixture was adsorbed on 100 g. of basic alumina and was eluted with the same solvent pair. The initial eluates, which were noncrystalline, were followed by the desired product. The crystalline fractions were combined, using methanol to complete the transfer to a sintered funnel. The yield was 3.25 g. of II (60%), m.p. 253–254° when inserted at 195°. This material was satisfactory for use in the oxidation step.

The fluorohydrin (II, 3.25 g.) was dissolved in 76 ml. of dry pyridine and added to a cold solution prepared by the cautious addition of 3.25 g. of chromium trioxide (in portions) to 34.7 ml. of cold pyridine. The mixture was allowed to stand at room temperature overnight. The mixture was poured into water and extracted three times with ethyl acetate, avoiding excessive shaking, especially during the third extraction. The combined ethyl acetate extracts were washed three times with *N* sulfuric acid and then with water until neutral. The combined ethyl acetate extracts were dried over magnesium sulfate and taken to dryness to give 2.94 g. of III. The product was dissolved in benzene, adsorbed in 90 g. of basic alumina, and eluted with benzene–chloroform (8:2). The eluate (2.63 g.) melted at 266–274° when inserted at 245°. An analytical sample prepared by two recrystallizations from ethyl acetate melted at 262–265°.

Anal. Calcd. for $C_{24}H_{31}FO_6$: C, 66.31; H, 7.13. Found: C, 65.85; H, 7.07.

9α-Fluoro-2-hydroxymethylene-16α-methyl-17,20:20,21-bis(methylenedioxy)pregn-4-ene-3,11-dione (IV).—Dry equipment was used in the following reaction. A 2.60-g. sample of the fluoro ketone (III) was dissolved in 95 ml. of dry benzene and treated with 2.43 ml. of freshly distilled ethyl formate. About 1.19 g. of a dispersion of sodium hydride in mineral oil (*ca.* 51%) was added, followed by about 1.19 g. of freshly prepared sodium methoxide (dried at about 175° for 4 hr.). The air in the system was again replaced with nitrogen, and the mixture, which turned yellow at once, was stirred at room temperature for 1.5 hr. At this point the color of the reaction mixture was dark orange. The mixture was chilled in an ice bath and a cold saturated solution of sodium dihydrogen phosphate was added gradually with care to decompose excess hydride and neutralize the alkoxide. Ether was added and the layers were separated. The aqueous layers were back-extracted with ether, and the combined organic layers were washed free of acid with water and then extracted three to four times with a 5% solution of sodium bicarbonate. These extracts were discarded. The desired hydroxymethylene compound was extracted (four to five times) with a cold solution of aqueous sodium hydroxide (2%). In order to avoid emulsification, the aqueous alkali was poured gently into the separatory funnel, and the layers were separated without shaking the funnel. The last two extracts were shaken with care. The dark alkaline extracts were back-extracted twice with ether and finally acidified in the cold with a solution of sodium dihydrogen phosphate. The neutral ether–benzene fraction was set aside and processed as described below. The hydroxymethylene compound was extracted into ether, and the ether extracts were washed free of acid with a saturated solution of sodium chloride. The solvent was evaporated and the amorphous product was crystallized from methanol to give 1.07 g. (39%) of IV, m.p. 230–232°, when inserted into the oil bath at 195°, λ_{max}[14] 239.5 mμ (log ε 4.20), 360 (4.00). This material was entirely satisfactory for use in the next step. The mother liquor gave product of lower purity.

(9) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(10) We are greatly indebted to Dr. S. L. Steelman for permission to include these results.

(11) S. L. Steelman, E. R. Morgan, M. A. Petraitis, M. E. Regn, and W. Worosila, *Federation Proc.*, **22**, 543 (1963).

(12) S. L. Steelman, E. R. Morgan, and R. H. Silber, *Steroids*, **1**, 163 (1963).

(13) Preliminary assay results indicate that the 16-unsubstituted pyrazole analog of VII causes sodium retention [R. Hirschmann and S. L. Steelman, unpublished observation.]

(14) Taken in methanol containing 2% of a 2.5 *N* solution of sodium hydroxide.

An analytical sample, obtained by recrystallization from ether and from methanol, had a lower melting point of 221–224°, but showed improved ultraviolet absorption, λ_{max}^{14} 239 mμ (log ε 4.29). 359.5 (4.08).

Anal. Calcd. for $C_{25}H_{36}FO_7$: C, 64.86; H, 6.70. Found: C, 65.04; H, 6.75.

The ether–benzene fraction containing the sodium hydroxide insolubles was washed free of base, dried over magnesium sulfate, and concentrated. Trituration with ether gave about 550 mg. of crystalline VIII, essentially devoid of selective ultraviolet absorption at 240 mμ. An analytical sample of **9α-fluoro-16α-methyl-17,20:20,21-bis(methylenedioxy)pregn-5-ene-3,11-dione,** obtained by recrystallization from acetone, melted at 227–231°.

Anal. Calcd. for $C_{25}H_{31}FO_6$: C, 66.35; H, 7.19. Found: C, 66.13; H, 7.45.

Addition of 1 drop of dilute alkali to a methanolic solution of VIII immediately regenerated an absorption maximum at 236 mμ.

In another experiment a suspension of 9 g. (0.198 mole) of a 52.7% sodium hydride–mineral oil dispersion in 750 ml. of dry benzene was treated with 18 ml. (0.192 mole) of dry *t*-butanol. The mixture was stirred in a nitrogen atmosphere for 1 hr., at which time hydrogen evolution had practically ceased. To the mixture was added 30.0 g. (0.0691 mole) of III and 42 ml. (0.52 mole) of freshly distilled ethyl formate. Stirring in a nitrogen atmosphere was continued for 2.5 hr. Any excess sodium hydride was decomposed with methanol. The red mixture was diluted with ether and cautiously extracted with a 2% solution of sodium hydroxide. The alkaline extract was acidified with glacial acetic acid. The resulting yellow, flocculent precipitate was extracted into methylene chloride. The organic extract was washed with water, dried, and the solvent was evaporated *in vacuo*. The crystalline residue was triturated with ether–Skellysolve B (1:1) and collected by filtration. The crystals were washed with ether–Skellysolve B (1:1), and with methanol containing a trace of pyridine. The dried, yellow hydroxymethylene compound weighed 16.27 g. (51%), m.p. 230–234° when inserted at 195°, λ_{max}^{14} 240 mμ (log ε 4.21), 360 (4.01). An additional 9% of IV may be obtained by reworking the mother liquors.

9α-Fluoro-16α-methyl-17,20:20,21-bis(methylenedioxy)-11-oxopregn-4-eno[3,2-*c*]pyrazole (V).—To a stirred mixture of 16.15 g. (0.0349 mole) of IV in 645 ml. of ethanol was added 6.45 ml. (0.133 mole) of hydrazine hydrate. The mixture was stirred at reflux in a nitrogen atmosphere for 1 hr. The starting material dissolved with a clear, amber color. After about 10 min. crystallization occurred. The mixture was concentrated *in vacuo* to a thick slurry. The crystals were separated by filtration and washed with ethanol. The yield of pyrazole V was 14.20 g. (89%), dec. above 300°, λ_{max}^{MeOH} 260 mμ (log ε 4.0), $\lambda_{max}^{pyridine}$ 3.15, 5.81 μ.

Anal. Calcd. for $C_{25}H_{31}FN_2O_5$: C, 65.51; H, 6.71. Found: C, 65.10; H, 6.90.

9α-Fluoro-11β-hydroxy-16α-methyl-17,20:20,21-bis(methylenedioxy)pregn-4-eno[3,2-*c*]pyrazole Hydrochloride (VI).—A 445-mg. aliquot of the fluoro ketone (V) was suspended in 75 ml. of a solution of sodium borohydride in 2-propanol, prepared by suspending an excess of sodium borohydride in 2-propanol, stirring vigorously for about 15 min., and filtering to separate the excess of sodium borohydride. To the mixture was added an 0.816-ml. aliquot of a solution of 0.55 ml. of triethylamine in 1.45 ml. of 2-propanol. The mixture was stirred and enough methylene chloride was added with cooling (about 30 ml.) to make the system homogeneous. One drop of water was added, and the mixture was stirred in a nitrogen atmosphere at room temperature overnight. The mixture was cooled and the excess sodium borohydride was decomposed by the cautious addition of cold 2.5 *N* hydrochloric acid. The solvent was evaporated *in vacuo*, and the residue was washed with water and dried to give 425 mg. of product devoid of saturated carbonyl absorption in the infrared. The compound was dissolved in a mixture of methanol and acetone and was crystallized by the addition of ether to give crystalline VI, m.p. 240° dec., λ_{max}^{MeOH} 267 mμ (log ε 4.02), λ_{max}^{Nujol} 3.5–4.5, 6.1 and 6.27 μ.

Anal. Calcd. for $C_{25}H_{33}FN_2O_5 \cdot HCl \cdot 0.5\ H_2O$: C, 59.34; H, 6.97; Cl, 7.0. Found: C, 59.80; H, 6.98; Cl, 7.14.

In another experiment 14.0 g. (0.0306 mole) of V was dissolved in 280 ml. of dimethylformamide and 6.5 ml. of water with warming. After cooling to 25°, 4.52 g. (0.199 mole) of sodium borohydride was added with stirring. A heavy, white precipitate was obtained. After 4 hr. the mixture was cooled in an ice bath, and the excess sodium borohydride was decomposed with *N* hydrochloric acid. The solution was poured into water to give a quantitative yield of crude free base. Conversion to the crystalline hydrochloride was accomplished by treatment of an acetone solution of the crude base with hydrogen chloride gas in the cold until crystallization was complete. The crystals were collected by filtration, washed with acetone, and dried to give 13.35 g. of VI (86.2%), λ_{max}^{MeOH} 270 mμ (log ε 4.06).

9α-Fluoro-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole Hydrochloride (VII).—A solution of 13.35 g. (26.4 mmoles) of VI in 134 ml. of 60% formic acid was heated at 99° for 15 min. in a nitrogen atmosphere. The reaction was quenched by the rapid addition of ice–water. The formic acid was neutralized by the addition of sodium carbonate solution. The resulting precipitate was removed by filtration, washed neutral with water, and dried. The crude material (12.08 g.) was dissolved in 121 ml. of methanol and treated with 5.35 ml. of 2.54 *N* sodium methoxide solution in a nitrogen atmosphere. After 10 min. the sodium alkoxide was neutralized with glacial acetic acid. The amber solution was decolorized with Darco G-60 and poured into water. The resulting amorphous solid was collected by filtration, washed with water, and dried. The yield of crude VII (free base) was 9.6 g. (86%), λ_{max}^{MeOH} 260 mμ (log ε 4.06). Paper chromatography[15] showed one spot, $R_f = 0.3$.

Crystalline hydrochloride was obtained by dissolving the free base (9.5 g.) in 57 ml. of acetone. The addition of 4.75 ml. of concentrated hydrochloric acid gave an oil which crystallized on standing. Dilution with 57 ml. of acetonitrile gave more crystalline material. The crystals were separated by filtration, washed with acetone–acetonitrile (1:1), and dried. The yield of analytically pure hydrochloride VII was 6.2 g. (60% from free base), dec. above 300°, $[\alpha]^{25}D$ +71° (*c* 1, pyridine), λ_{max}^{Nujol} 3–4.5, 5.87–5.91 μ; λ_{max}^{KBr} 3–3.1, 5.89, 6.13, 6.31 μ.

Anal. Calcd. for $C_{28}H_{32}ClFN_2O_7$: C, 60.72; H, 7.09; Cl^-, 7.79; N, 6.16. Found: C, 60.66; H, 7.40; Cl^-, 7.66; N, 6.45.

9α-Fluoro-2′-(4-fluorophenyl)-16α-methyl-17,20:20,21-bis(methylenedioxy)-11-oxopregn-4-eno[3,2-*c*]pyrazole (XI).—A mixture of 195 mg. of the hydroxymethylene compound (IV), 44 mg. of sodium acetate, and 76.8 mg. of *p*-fluorophenylhydrazine hydrochloride in 4.4 ml. of ethanol was refluxed in an atmosphere of nitrogen with constant stirring for 1 hr. The crystalline pyrazole, which had separated, amounted to 166 mg., m.p. 273–275° dec., λ_{max}^{MeOH} 262.5 mμ (log ε 4.16). A 106-mg. aliquot of the crude pyrazole was dissolved in benzene and was adsorbed on 10 g. of silica gel. The fractions eluted with benzene–ether (95:5) were combined (90.4 mg.) and crystallized from methanol to give 48.4 mg. of XI, m.p. 279–281°, and a second crop (12.3 mg.), m.p. 278–279.5°. An analytical specimen obtained by a further recrystallization of the combined fractions melted at 279.8–281°, λ_{max}^{MeOH} 261 mμ (log ε 4.20).

Anal. Calcd. for $C_{32}H_{31}FN_2O_5$: C, 67.37; H, 6.20. Found: C, 66.94; H, 6.29.

9α-Fluoro-2′-(4-fluorophenyl)-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole 21-Acetate (XI).—To a solution of 225.4 mg. of IX in 5.4 ml. of dimethylformamide and 0.18 ml. of water was added 84.0 mg. of sodium borohydride, and the mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath, and the excess of sodium borohydride was decomposed by the dropwise addition of 2.5 *N* hydrochloric acid. The final pH of the mixture was about 4. The solvent was evaporated *in vacuo*. The product was washed with water to afford 245 mg. of crude X. The product was adsorbed on 2.46 g. of silica gel and was eluted successively with ether–benzene (1:99; 5:95; 10:90). The latter system afforded 126 mg. of X, m.p. 217–222°, which was treated with 3 ml. of 60% formic acid in an atmosphere of nitrogen for 35 min. on a steam bath. The solvent was evaporated *in vacuo*, and the crude residue (66.9 mg.) was dissolved in 5 ml. of methanol and treated with 0.1 ml. of *N* sodium methoxide solution for 7 min. The sodium methoxide was neutralized with glacial acetic acid, and the solvent was evaporated. The crude product was acetylated with 0.5 ml. of acetic anhydride and 0.5 ml. of dry pyridine at room temperature overnight. The reaction mixture was concentrated to dryness. The yellow residue was adsorbed on acid-washed alumina and was eluted with chloroform, affording 59.8 mg. of XI. Four recrystallizations from acetone–Skellysolve B

(15) Methanol–formamide (2:1) as the stationary phase, chloroform as the mobile phase.

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.

Acknowledgment.—The authors wish to thank Dr. L. H. Sarett and Dr. A. A. Patchett for many stimulating discussions. We are indebted to Mr. R. Boos and his collaborators for analyses, to Mr. E. MacMullan for ultraviolet spectra, and to Mr. R. Walker and Mr. N. Allen for infrared spectra.

Notes

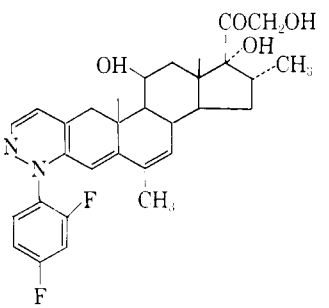
Synthesis of 2′-(2,4-Difluorophenyl)-11β,17,21-trihydroxy-6,16α-dimethyl-20-oxopregna-4,6-dieno[3,2-*c*]pyrazole

R. G. STRACHAN, N. G. STEINBERG, MAX TISHLER, AND RALPH HIRSCHMANN

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey

Received September 17, 1963

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.

(1) R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, 120 (1963).

(2) J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann, and S. L. Steelman, *ibid.*, **85**, 236 (1963).

(3) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *ibid.*, **86**, 1520 (1964).

(4) R. Hirschmann, N. G. Steinberg, E. Schoenewaldt, W. J. Paleveda, and M. Tishler, *J. Med. Chem.*, **7**, 352 (1964).

(5) R. Hirschmann and S. L. Steelman, unpublished observations.

(6) S. L. Steelman and E. R. Morgan, "Inflammation and Diseases of Connective Tissues," L. C. Mills and J. H. Moyer, Ed., W. B. Saunders Co., Philadelphia, Pa., 1961, p. 349.

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

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

DAVID J. MARSHALL, PETER F. MORAND, CLARA REVESZ, AND R. GAUDRY

Ayerst Research Laboratories, Montreal, Canada

Received November 27, 1963

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

(1) (a) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956); (b) S. Bernstein, S. M. Stolar, and M. Heller, *ibid.*, **22**, 472 (1957); (c) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959); (d) J. S. Baran, *J. Med. Chem.*, **6**, 329 (1963); (e) F. B. Colton and P. Klimstra, *Excerpta Med.*, Intern. Congr. Ser., No. 51, Intern. Congr. on Hormonal Steroids, Milan, 1962, p. 57; (f) B. Löken, M. Uskoković, M. Hagopian, R. I. Dorfman, and M. Gut, *Steroids*, **2**, 81 (1963).