reed electrometer and a Cary multi-range recorder. This procedure has been described in detail by Neville[14] and by Raaen and Ropp.[15]

Spectrophotometric Analysis of the Rearrangement Products of N-Nitro-N-methylaniline.—*o*- and *p*-nitro-N-methylaniline were determined directly and nitrous acid was estimated by conversion to a diazonium salt and the coupling of the latter with N,N-dimethyl-α-naphthylamine. To carry out these analyses the following solutions were used.

Solutions.—N-nitro-N-methylaniline (81.5 mg. in 50.00 cc. of purified dioxane), *o*-nitro-N-methylaniline (48.6 mg. in 25.00 cc. of purified dioxane), *p*-nitro-N-methylaniline (24.1 mg. in 25.00 cc. of purified dioxane), N-methylaniline (18.6 mg. in 25.00 cc. of purified dioxane), sodium nitrite (16.5 mg. in 25.00 cc. of water), perchloric acid (5.03 *N*), ammonium sulfamate (5.0 g. in 100 cc. of water), acetate buffer (to a solution of 15.0 g. of sodium acetate trihydrate in 50.0 cc. of water was added 50.0 cc. of glacial acetic acid), nitrous acid reagent (to a solution of 0.2 g. of *p*-nitroaniline and 0.2 g. of N,N-dimethyl-α-naphthylamine in 45.0 cc. of glacial acetic acid was added 5.0 cc. of 60% perchloric acid).

Determination of *o*- and *p*-Nitro-N-methylaniline.—Two-cc. aliquots of purified dioxane and of the *o*-, *p*- and N-nitro-N-methylaniline solutions were separately treated according to the following procedure.

A 2.00-cc. aliquot of dioxane or one of the nitro-N-methylaniline solutions was added to a thermostated (40.0 ± 0.5°) solution of 5.00 cc. of 5.03 *N* perchloric acid and about 40 cc. of water in a 50.0-cc. volumetric flask. The contents of the flask were made up to volume with water at 40° and the mixture was shaken and thermostated at 40.0 ± 0.5° for 60 min. A 5.00-cc. aliquot of the resulting solution was added to 5.00 cc. of 5% ammonium sulfamate solution in a 25.0-cc. volumetric flask. The flask was then heated on a steam bath for 30 min. and cooled. Acetate buffer was added to bring the volume to 25.0 cc. and the mixture was shaken. The final solution from the dioxane run was used as a spectral blank. The solutions made up from the *o*- and *p*-nitro-N-methylaniline solutions were employed as standards for evaluating the extinction coefficients of these compounds so that the ultimate solution obtained from N-nitro-N-methylaniline could be analyzed for these components using Beer's law. The absorptions of these final solutions were determined at 390, 410, 430, 450, and 470 mμ using a Beckman DU spectrophotometer.

The method of least squares was used to compute the concentrations of *o*- and *p*-nitro-N-methylaniline that best reproduced the optical densities at the five wave lengths.

Nitrous Acid Determination.—The procedure described below was carried out simultaneously on three different original mixtures to obtain blanks, standards, and unknowns.

To a solution of 5.00 cc. of 5.03 *N* perchloric acid and about 40 cc. of water at 40.0 ± 0.5° in a 50.0-cc. volumetric flask were added accurately measured aliquots of the standard solutions (*vide infra*). The solution was brought to the mark with water at 40°, shaken, and thermostated at 40.0 ± 0.5° for 60 min.

One 5.00-cc. aliquot of this reaction mixture was treated as described above under "Determination of *o*- and *p*-Nitro-N-methyl-aniline" (*i.e.*, it was added to 5.00 cc. of 5% ammonium sulfamate solution, heated at 100° for 30 min., and diluted to 25.0 cc. with acetate buffer) with the exception that the absorption of the final solution was determined at 500, 520, 540, and 560 mμ.

Another 5.00-cc. aliquot was added to 5.00 cc. of nitrous acid reagent in a 25.0-cc. volumetric flask. This mixture was kept for 24 hr. at 25° and was then diluted to the mark with acetate buffer. The spectrum of the resulting solution was determined at 500, 520, 540, and 560 mμ.

For the blanks a 2.00-cc. aliquot of purified dioxane was carried through the procedure outlined above. The sulfamate-treated solution was used as a spectral blank for all the other solutions and the nitrous acid reagent-treated portion (designated B) was used to determine the absorption characteristics of the reagent.

The standards were prepared by adding 1.00 cc. each of the *o*- and *p*-nitro-N-methylaniline, N-methylaniline, and sodium nitrite solutions to the warm perchloric acid solution (the nitrite was added last). This mixture approximates that resulting from rearrangement. The final solution containing sulfamate was called S′ and that containing nitrous acid reagent, S.

The rearrangement was carried out using a 2.00-cc. portion of the N-nitro-N-methylaniline solution. The solution subjected to nitrous acid reagent was termed R and that treated with sulfamate solution as R′.

The concentration of the nitrous acid formed in the rearrangement was found from the expression

$$C = M(D_R - D_{R'} - D_B)/50(D_S - D_{S'} - D_B)$$

where M is the concentration of $NaNO_2$ in the original standard and the D's are the optical densities of the solutions referred to above. Since all solutions were examined at four wave lengths, four separate values of C resulted from each determination. The average deviation of these values from the mean was always less than 1%.

(14) O. K. Neville, *J. Am. Chem. Soc.*, **70**, 3501 (1948).

(15) V. F. Raaen and G. A. Ropp, *Anal. Chem.*, **25**, 174 (1953).

[CONTRIBUTION FROM MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N. J.]

Synthesis and Structure of Steroidal Pregn-4-eno- and 5α-Pregnano[3,2-*c*]pyrazoles. A Novel Class of Potent Anti-Inflammatory Steroids[1,2]

BY RALPH HIRSCHMANN, PAUL BUCHSCHACHER, N. G. STEINBERG, J. H. FRIED, R. ELLIS, G. J. KENT, AND MAX TISHLER

RECEIVED SEPTEMBER 23, 1963

The preparation of several [3,2-*c*]pyrazoles related to cortisol, to 16α-methylcortisol, and to 4,5α-dihydrocortisol is described. The novel observation that a carbonyl function at C-3 is not required for anti-inflammatory activity is discussed. The 2′-phenyl and especially the 2′-*p*-fluorophenyl[3,2-*c*]pyrazole functions have the greatest enhancing effect on anti-inflammatory activity known to date. The [3,2-*c*]pyrazole function, unlike the 2α-methyl substituent, does not enhance mineralocorticoid activity. The structure assignment for the isomeric 1′- and 2′-alkyl- and arylpyrazoles is discussed. In the 4,5α-dihydro series the ratio of the isomeric pyrazoles obtained was markedly dependent on the reaction temperature.

Since the synthesis of cortisone by Sarett[3,4] and the discovery of the dramatic success of that compound in the treatment of rheumatoid arthritis by Hench and Kendall,[5] much has been learned about structural changes which enhance the activity of the anti-inflammatory steroids.[6] In 1959, Clinton and his co-workers[7] and more recently de Ruggieri, *et al.*,[8] reported that androst-4-eno- and androstano-[3,2-*c*]pyrazoles are potent anabolic agents. These results were consistent with other reports that an oxygen at C-3 is not required for anabolic-androgenic[9] or pro-

(1) For preliminary announcements concerning this class of compounds see: 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) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(4) L. H. Sarett, *ibid.*, **71**, 2443 (1949).

(5) P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley, *Proc. Staff Meetings Mayo Clinic*, **24**, 181 (1949).

(6) For recent reviews see: L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959; L. H. Sarett, A. A. Patchett and S. L. Steelman, "Fortschritte der Arzneimittelforschung," Vol. 5, E. Jucker, Ed., Birkhäuser Verlag, Basel and Stuttgart, 1963.

(7) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, **81**, 1513 (1959); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clark, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *ibid.*, **83**, 1478 (1961); (c) G. O. Potts, A. L. Beyler, and D. F. Burnham, *Proc. Soc. Exptl. Biol. Med.*, **103**, 383 (1960).

(8) P. de Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. chim. ital.*, **92**, 768 (1962).

gestational[10] activity. On the other hand, a C-3 carbonyl group seemed to be required for the anti-inflammatory effect.[11] For example, 17β-hydroxy-17α-methyl-5α-androstano[2,3-d]isoxazole proved to be a potent anabolic agent[9] but the pregn-4-eno[2,3-d]isoxazoles derived from cortisone,[9a] or from 16α-methylcortisol,[12] were inactive as anti-inflammatory agents.[13] Furthermore, other structural changes in the environment of the A-ring which enhance the biological activities of androgens or progestins diminished anti-inflammatory potency, as illustrated by the 19-nor,[14] 2-oxa-,[15] or the 4,5-dihydro[6] analogs of cortisol.

This paper describes the synthesis of certain 5α-pregnano- and pregn-4-eno[3,2-c]pyrazoles related to cortisol and reports their biological activities. It was found that the N-unsubstituted and N-alkylated pyrazoles displayed biological activity of the same order of magnitude as the parent steroid. Even more surprising was the observation that the 2′-phenyl- and especially the 2′-*p*-fluorophenyl derivatives are in fact the most powerful activity-enhancing functions so far disclosed in the anti-inflammatory area.[1,16] These results, moreover, strongly suggest that the pyrazoles are active as such and not as a result of a biological regeneration of the 3-keto group.

Our first objective was the synthesis of the pyrazole related to 16α-methylcortisol. While the Claisen condensation at C-2 of cortisone acetate with ethyl formate has been described in the patent literature,[17] we elected to protect the cortical side chain by formation of the bismethylenedioxy (BMD)[18] derivative II. The latter was then allowed to react with ethyl formate in benzene in the presence of sodium hydride to give the hydroxymethylene derivative III which was purified *via* its sodium salt. Occasionally the condensation of II with ethyl formate afforded as the major base-soluble product the 11β-formate IV, characterized by absorption bands at 5.82 and 8.5 μ not found in the 11β-hydroxy compound III. The conversion of β-dicarbonyl compounds into pyrazoles is frequently carried out[19] in hot acetic acid, but we preferred to use ethanol as the solvent because of the sensitivity of the BMD protecting group to hot acid. It was recognized[20] only later that pyrazole formation may be effectively carried out in acetic acid at room temperature overnight. The crystalline condensation product from the reaction of III with hydrazine hydrate in hot ethanol exhibited an absorption maximum at 261 mμ (log ε 4.01) in good agreement with the spectral data reported by Clinton, *et al.*,[7b] for the same chromophore in the androgen series. We feel that at this point an unambiguous structure assignment cannot be made for the N-unsubstituted pyrazole. Physical measurements to be discussed below favor structure V over VI.

When III was allowed to react with phenylhydrazine, a crystalline phenylpyrazole (VII) was obtained in good yield which absorbed at the same wave length as V but exhibited a significantly higher molecular extinction (log ε 4.23). To our knowledge phenylpyrazoles of 4,5-unsaturated steroids had not heretofore been described.

Careful chromatography on alumina of the crude product from the condensation of III with phenylhydrazine in refluxing ethanol afforded in at least one instance a minor product which, on the basis of infrared spectroscopy and elemental analyses, appeared to be an isomeric pyrazole (X). It differed markedly from VII in its ultraviolet spectrum, exhibiting a maximum at 298 mμ (log ε 4.47). We believe that the higher molecular extinction of X relative to VII reflects steric inhibition of resonance in the latter case, resulting from the interaction of the *o*-hydrogen with the C-4 hydrogen of the steroid nucleus. This interpretation is in agreement with the fact that n.m.r. shows the phenyl protons in X to be split as in aniline, but not in the case of VII, suggesting resonance interaction between N and the phenyl group only for X.[21] The structure assignment is consistent also with the following mechanistic considerations. The reaction of the 4-unsaturated 2-hydroxymethylene- 3-ketones with hydroxylamine to yield pregn-4-eno[2,3-d]isoxazoles[9,12] demonstrated that Schiff base formation involved the aldehydic rather than the ketonic carbonyl function.[22] If it is assumed that the primary amino group of phenylhydrazine is the more reactive one, one predicts structure VII for the major condensation product.[23] It is known[19] that a β-ketoaldehyde and its enol ether can lead to different pyrazoles on treatment with substituted hydrazones. One would, therefore, predict a higher yield of the 1′-pyrazole X from the enol ether IX than from III. This proved indeed to be the case.

It was initially attempted to effect separation of the isomeric pyrazoles in the 11-keto rather than in the 11β-hydroxy series. Therefore the 2-methoxymethylene derivative XIV was allowed to react with phenylhydrazine in ethanol at room temperature. Chromatography afforded XV and XVI in nearly equal yield. The former was converted into X by reduction with lithium aluminum hydride in refluxing tetrahydrofuran.

We found that the 2-hydroxymethylene 3-ketones readily afforded the corresponding enol ethers under acid conditions. Indeed, IX was first prepared inadvertently during a recrystallization from methanol of a sample of III presumed to have contained traces of residual mineral acid. Since the reaction of III with phenylhydrazine was carried out in refluxing ethanol, it is possible that X, obtained as a by-product in this reaction, was in fact formed *via* the 2-ethoxymethylene compound.

(9) See, *e.g.* (a) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Simon, L. Magana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960); (b) J. A. Edwards and A. Bowers, *ibid.*, 1962 (1961); (c) R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(10) M. S. de Winter, C. M. Siegman, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959); Z. Madjerek, J. de Visser, J. Vander, and G. A. Overbeek, *Acta Endocrinol.*, **35**, 8 (1960).

(11) E. W. Boland, *Am. J. Med.*, **31**, 581 (1961).

(12) R. Hirschmann and S. L. Steelman, unpublished observation. The assay result with the isoxazole of 16-methylcortisol is more significant than that with the corresponding 11-ketone because the latter—like 2-methylcortisone—might be resistant to *in vivo* reduction at C-11 [I. E. Bush and V. B. Mahesh, *Biochem. J.*, **71**, 718 (1959)].

(13) While certain derivatives of the carbonyl group at C-3 such as the oxime, semicarbazone, and methoxime displayed some measure of anti-inflammatory activity [unpublished results from the Merck Institute for Therapeutic Research, Rahway, N. J.; see also, U. S. Patent 3,074,979, January 22, 1963], these results could be rationalized by assuming *in vivo* regeneration of the pregn-4-en-3-one structure. The excellent oral activity of the 3-enol ether of cortisone [A. Ercoli and R. Gardi, *J. Am. Chem. Soc.*, **82**, 746 (1960)] could be similarly explained.

(14) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas, and C. Djerassi, *ibid.*, **76**, 6210 (1954); B. J. Magerlein and J. H. Hogg, *ibid.*, **79**, 1508 (1957).

(15) R. Hirschmann, N. G. Steinberg, and R. Walker, *ibid.*, **84**, 1270 (1962).

(16) S. L. Steelman, E. R. Morgan, M. A. Petraitis, M. E. Regn, and W. Worosila, *Federation Proc.*, **22**, 543, Abstract No. 2288 (1963).

(17) Australian Patent Application 2,759,50409, July 1, 1959.

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

(19) T. L. Jacobs, "Heterocyclic Compounds," Vol. 5, R. E. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957.

(20) E. F. Schoenewaldt and M. J. Paleveda, private communication.

(21) B. Arison and N. Trenner, private communication.

(22) This conclusion is also consistent with the findings of R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clark, K. F. Jennings, and P. E. Shaw, *J. Org. Chem.*, **27**, 1148 (1962).

(23) The same conclusion was reached by Clinton, *et al.*,[7b] who assigned the 2′-phenyl structure to the pyrazole derived from a 2-hydroxymethylene-3-keto-5α-steroid. (See, however, our results with the 4,5-saturated steroids, below.)

CHART I

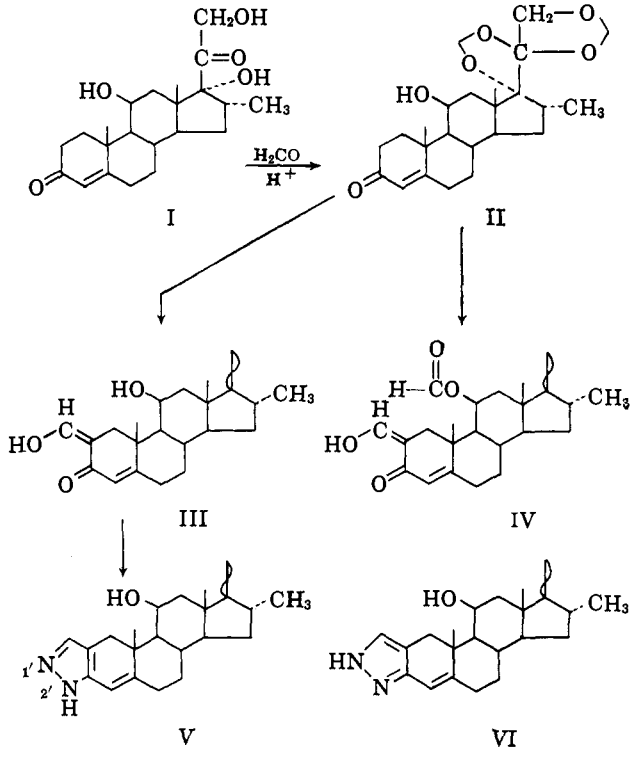


CHART II

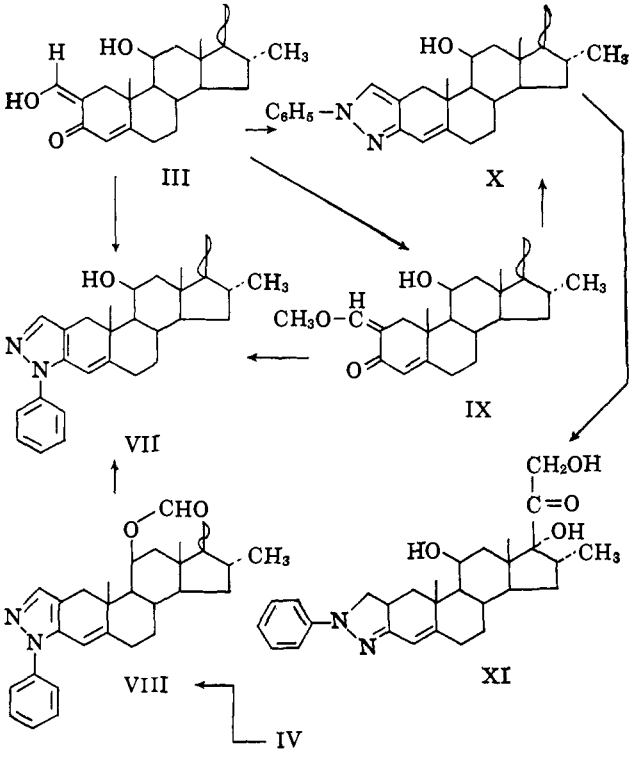
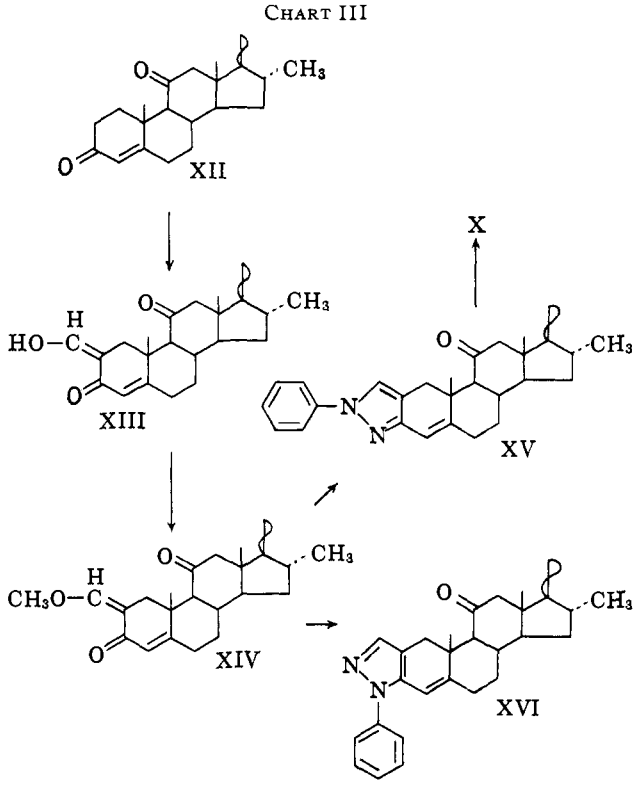


CHART III



Pyrazole formation also was used to provide further support for the structure of the 11-formate IV which was occasionally obtained in the Claisen condensation. Condensation of IV with phenylhydrazine gave the crystalline 2′-phenylpyrazole VIII which could be saponified at C-11 to give VII.

Consideration of the inductive effect of the methyl group leads one to predict that condensation of III with methylhydrazine should result in the formation of a greater proportion of the 1′-substituted pyrazole than was obtained with phenylhydrazine. This prediction could be verified experimentally. The structure assignment of the methylpyrazoles rests on the following consideration.

Compound XVII may be considered to contain a longer conjugated chromophore than XVIII and should, therefore, absorb at longer wave length. On the other hand, the distance separating the charges in the polarized form XVIIIa is greater than in XVIIa and it is reasonable, therefore, that XVII should exhibit lower molecular extinction[24] but an absorption maximum at longer wave length than XVIII. The structural assignments derive further support from the fact that XVIII, like the 1′-phenylpyrazoles X and XV, is the isomer which is eluted first from acid-washed alumina, exhibits significantly more absorption in the 7.2 μ region in the infrared, is more levorotatory, and—like XI—exhibits less anti-anflammatory potency.

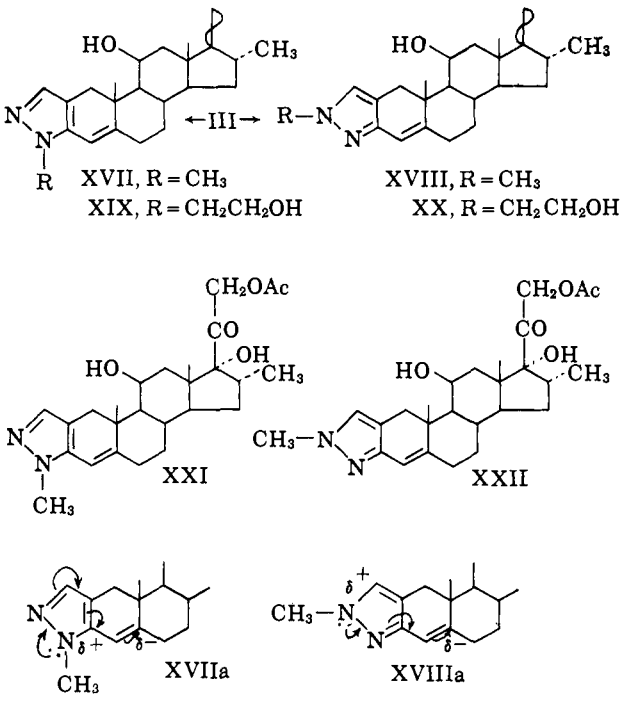
When the hydroxymethylene compound was allowed to react with β-hydroxyethylhydrazine in acetic acid at room temperature, a mixture of the 1′- and 2′-alkylpyrazoles, XX and XIX, was obtained. The latter compound was obtained pure.

The structure assignment in the case of the unsubstituted pyrazole (V or VI) is less definitive than that for the N-alkyl- and N-arylpyrazoles. We prefer formula V, however, on the basis of the molecular extinction in the ultraviolet (log ϵ 4.0 rather than 4.10) and lack of absorption in the 7.2 ϵ region in the infrared.

Hydrolysis of the bismethylenedioxy-protecting groups was effected with dilute formic acid but somewhat longer reaction times were required than in the case of the 3-ketosteroids, presumably because of the presence of a basic nitrogen in the molecule. In view of the interesting biological results obtained with the 2′-phenylpyrazole (see below), several monosubstituted aromatic 2′-phenylpyrazoles were prepared as well. Of these the *p*-fluoro- and the *p*-chlorophenylpyrazoles were more potent than the N-unsubstituted steroid and

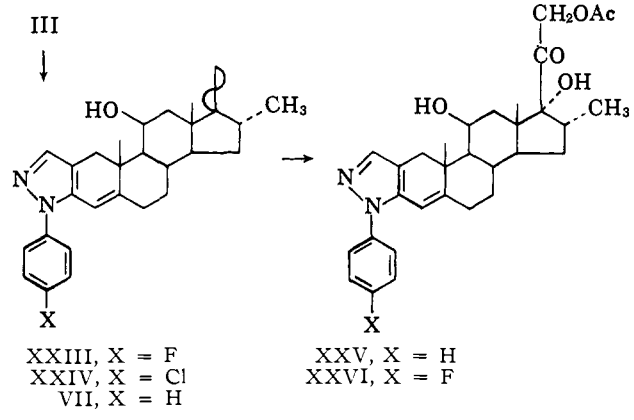
(24) *Cf.* R. B. Turner and D. M. Boitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

CHART IV



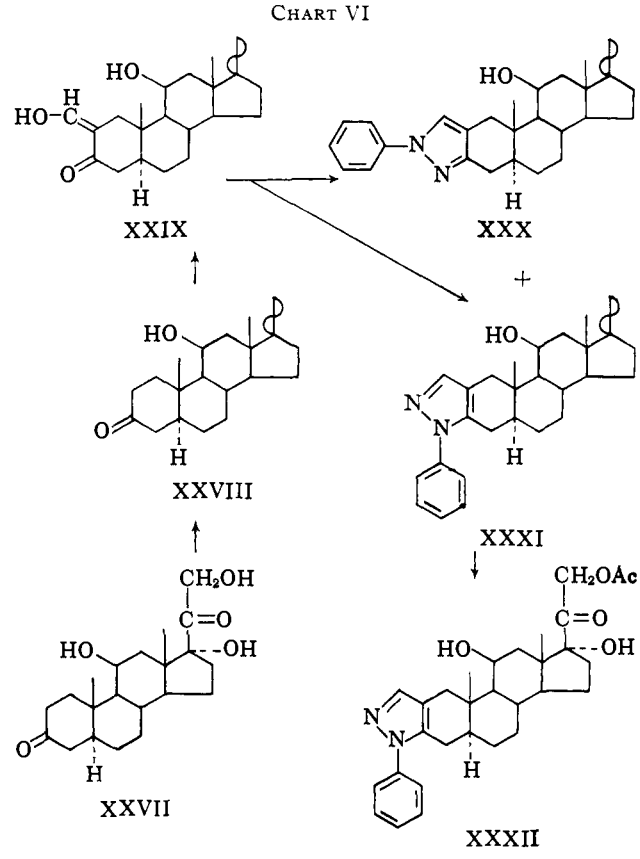
the preparation of these compounds is described in this paper.

CHART V



It is known that anti-inflammatory steroids such as cortisol lose their systemic activity upon reduction of the 4,5-double bond.[6] In view of the extremely high order of anti-inflammatory potency shown by the 2′-phenylpyrazole, it was of interest to prepare also the 2′-phenylpyrazole in the 5α-pregnane series to study its efficacy systemically and locally. To this end, 4,5α-dihydrocortisol XXVII was converted into the BMD derivative XXVIII and then allowed to react with ethyl formate to give XXIX. The reaction of 17β-hydroxy-2-hydroxymethylene-17α-methylandrostan-3-one with phenylhydrazine was reported by Clinton, *et al.*,[7b] to yield a single product, formulated as the 2′-phenylpyrazole, λ_{max} 262 mμ. In our hands the condensation of XXV with phenylhydrazine gave a mixture which was separated by chromatography into two isomeric pyrazoles XXX and XXXI, showing absorption maxima at 269 mμ (log ε 4.30) and at 251 mμ (log ε 4.04), respectively. Structure assignment is based on the same considerations as in the pregnene series. It is noteworthy that the proportion of the 1′-phenylpyrazole formed was greater in the 5α-pregnane than in the pregnene series. This indicates that the 3-carbonyl group is more reactive in the 4,5-saturated series and this is consistent with the observation[9a] in the androgen series that only the 4,5α-saturated but not the pregn-4-ene-β-ketoaldehydes give two isomeric isoxazoles on treatment with hydroxylamine. The ratio of the isomers was dramatically affected by the reaction temperature, heating favoring the formation of the 2′-phenylpyrazole.

CHART VI



We obtained additional evidence that XXXI is structurally related to the 2′-phenylpyrazole VII by reducing the latter catalytically. The noncrystalline product exhibited an absorption maximum at 251 mμ as expected (and not at 269 mμ). The reduction is presumed to have led preponderantly to the 5β-isomer by analogy with the β-side reduction of androst-4-eno-[3,2-c]pyrazoles.[25]

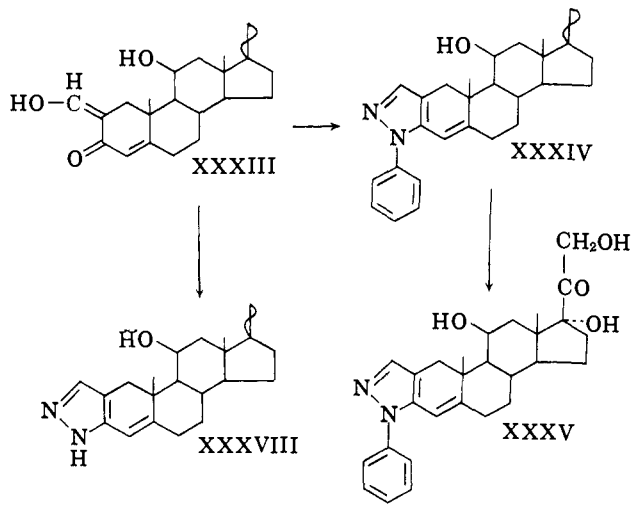
It is known[6] that the 2α-methyl substituent greatly potentiates mineralocorticoid activity of the anti-inflammatory steroids. On the other hand,[6] the 16α-methyl substituent eliminates salt retention. Since our pyrazoles contain a carbon substituent at position 2, it was of interest to learn whether such compounds would possess significant mineralocorticoid activity in the absence of a 16α-methyl substituent. As indicated in the summary of biological results, this was not the case.

We, therefore, undertook the preparation of the 2′-phenylpyrazole derived from cortisol as shown in Chart VII.

Biology.[1,16]—The 16α-methyl-2′-phenylpyrazole XXV and the *p*-fluorophenyl analog XXVI were 60 and 100 times as active as cortisol in the oral granuloma assay,[16] whereas the isomeric 1′-phenylpyrazole XI was less than 2 times cortisol. Unlike the *p*-fluoro compound, a variety of other *o*-, *m*-, and *p*-substituents decreased the activity of the 2′-phenylpyrazole.[12] The *p*-chloro analog of XXVI was about 15 times as active as cortisol.

(25) R. O. Clinton, R. L. Clark, F. W. Stonner, A. J. Manson, and K. F. Jennings, *J. Org. Chem.*, **27**, 2800 (1962).

CHART VII



These results are particularly noteworthy because the highly potent 2′-phenylpyrazole resembles the biologically inactive isoxazole in its double bond structure, whereas the nearly inactive 1′-phenylpyrazole—like the natural corticoids—has an exocyclic double bond at C-3. The isomeric 1′- and 2′-methylpyrazoles XXII and XXI were found to be 1.5 and 5.9 times as active as cortisol, respectively, in the oral granuloma assay. The 4,5α-dihydrophenylpyrazole XXXII was about 8 times as active as cortisol in the local granuloma inhibition test and equipotent with cortisol systemically. The 16-unsubstituted 2′-phenylpyrazole derived from hydrocortisone (XXXV) was about 25 times as active as cortisol in the granuloma-pellet assay. In the adrenalectomized rat, which had been given an oral load of sodium chloride, 250 μg. of XXXV produced a significant increase in the *output* of sodium, whereas 2500 μg. of cortisol had no effect on the excretion of sodium.

Experimental[26]

11β-Hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-en-3-one (II).—To a stirred solution of 25.0 g. of 16α-methylcortisol (I) in 1.5 l. of ethanol-free chloroform was added with cooling 750 ml. of formaldehyde (Merck, low methanol content) and 750 ml. of a cold solution of concentrated hydrochloric acid. After stirring for 7 hr. at room temperature, the layers were separated, and the organic fraction was washed with water, with a 5% solution of sodium bicarbonate, and again with water. The solution was dried over magnesium sulfate. Removal of the solvent *in vacuo* gave an oil which was triturated with hot methanol to afford 22.7 g. of crude II.

The crystalline solid was dissolved in 250 ml. of a mixture of benzene and chloroform (9:1), adsorbed on 690 g. of acid-washed alumina, and eluted successively with benzene–chloroform (9:1, 4:1, and 7:3). The last-named mixture afforded an oil, which was triturated with hot methanol to give 14.8 g. of II, m.p. 253–257°. Material of this purity was satisfactory for use in the next step. An analytical sample, obtained by several recrystallizations from acetone, melted at 277–279°, λ_{max}^{MeOH} 242 mμ (log ε 4.20); λ_{max}^{Nujol} 2.9–3.0 (OH), 6.0–6.1 (3-keto-Δ^4), 6.2 (C=C), 9–9.2 μ (BMD).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.95; H, 7.98.

11β-Hydroxy-2-hydroxymethylene-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-en-3-one (III).—A solution of 2.7 g. of 11β-hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-en-3-one (II), m.p. 253–257°, in 10 ml. of benzene, was stirred with 1.92 ml. of freshly distilled ethyl formate and 1.12 g. of a dispersion in oil (*ca.* 51%) of sodium hydride in a nitrogen atmosphere for 2 hr. The reaction mixture turned from yellow to red during this period. The reaction mixture was chilled, and a solution of potassium dihydrogen phosphate was added to decompose the excess of hydride and to liberate the free hydroxymethylene compound. The layers were separated, and the benzene layer was extracted several times with a 5% solution of sodium bicarbonate, followed by several extractions with a 2% solution of sodium hydroxide.

(26) All melting points are uncorrected.

The bicarbonate extracts were discarded. The combined sodium hydroxide extracts were acidified with 2.5 *N* hydrochloric acid, and extracted with methylene chloride. The organic layer was washed several times with water and dried over magnesium sulfate. Evaporation of the solvent afford 1.5 g. of the crude hydroxymethylene compound which showed λ_{max}^{27} 242.5 mμ (log ε 4.15), 355 mμ (log ε 3.98).

An analytical sample was obtained by recrystallizing 50 mg. of the above product twice from ether to give 20 mg. of III, m.p. 201–203°, $[\alpha]^{26}D$ −27° ($CHCl_3$); λ_{max}^{27} 242 mμ (log ε 4.17, 4.20), 357 mμ (log ε 4.00, 4.02).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.20; H, 7.58.

11β-Hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-*c*]pyrazole (V).—A solution of 315 mg. of III, m.p. 201–203°, in 13.8 ml. of absolute alcohol, was treated with 0.12 ml. of hydrazine hydrate on a steam bath for 45 min. in a nitrogen atmosphere. The reaction mixture was taken to dryness *in vacuo*, the residue was washed with water, and then dried *in vacuo*. The product, 159 mg., λ_{max}^{MeOH} 261 mμ (log ε 4.00), was crystallized twice from methanol to give an analytical sample, m.p. 295–301.5°,[28] λ_{max}^{MeOH} 261 mμ (log ε 4.01).

Anal. Calcd. for $C_{25}H_{34}O_5N_2 \cdot {}^1/_2CH_3OH$[29]: C, 66.82; H, 7.81. Found: C, 67.00; H, 7.70.

11β-Hydroxy-1′-phenyl-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-*c*]pyrazole (X) **from** III.—A solution of 1.02 g. of III, m.p. 198–200°, and 0.5 ml. of phenylhydrazine in 30 ml. of ethanol was refluxed for 1 hr. under nitrogen. The reaction mixture was taken to dryness *in vacuo*. The residue was dissolved in methylene chloride–ether (1:5) and washed once with water, six times with 2.5 *N* hydrochloric acid, twice with a solution of 2 *N* potassium hydroxide, and finally with water until the washings remained neutral. The organic layer was dried over sodium sulfate and taken to dryness. The crude product (1.25 g.) was dissolved in 10 ml. of benzene and chromatographed on 42 g. of acid-washed alumina. Benzene–ether mixtures (50:1–20:1) eluted 135 mg. of the crude 1′-phenylpyrazole. Crystallization from methylene chloride–ether afforded 35 mg. of crystalline X, m.p. 219–222°, λ_{max}^{MeOH} 298 mμ (log ε 4.47). The preparation of an analytical specimen is described below.

11β-Hydroxy-2′-phenyl-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-*c*]pyrazole VII from III.—Further elution of the column described immediately above with solvents ranging from benzene–ether (10:1) to ether yielded 924 mg. of crude VII. One single crystallization from methylene chloride–methanol afforded 706 mg., m.p. 258–260°. An analytical specimen melted at 260–260.5°, $[\alpha]^{25}D$ +25° ($CHCl_3$), λ_{max}^{MeOH} 261 mμ (log ε 4.23).

Anal. Calcd. for $C_{31}H_{38}O_5N_2$: C, 71.79; H, 7.39. Found: C, 72.09; H, 7.30.

11β-Formyloxy-2′-phenyl-16α-methyl-17,20:20,21-bis(methylenedioxy)-pregn-4-eno[3,2-*c*]pyrazole (VIII) *via* **IV**.—In one experiment the condensation of II with ethyl formate in anhydrous benzene catalyzed by freshly prepared sodium methoxide afforded a crude base-soluble product IV; λ_{max}^{27} 357 (log ε 4.00), 242 mμ (log ε 4.18); λ_{max} 5.84–5.85, 8.5 (formate), 5.99, 6.14 μ. Compound IV was allowed to react with phenylhydrazine as described above to afford crude VIII, m.p. 258.5–262°, λ_{max}^{MeOH} 261 mμ (log ε 4.21); $\lambda_{max}^{CHCl_3}$ 5.82, 5.85 (formate), 6.19, 6.6 (aromatic), 9.05 μ (BMD); λ_{max}^{Nujol} 5.82, 6.2, 6.6, 9.1–9.3 μ. The product was treated with charcoal (Nuchar C-1000N) and recrystallized twice from ethanol–benzene to give an analytical specimen of VIII, m.p. 268–269.5°.

Anal. Calcd. for $C_{32}H_{38}O_6N_2$: C, 70.31; H, 7.01. Found: C, 69.74; H, 6.80.

Deacylation of VIII (625 mg.) was initially attempted by dissolving the compound in 7.5 ml. of ethanol containing 45 mg. of potassium hydroxide and refluxing in an atmosphere of nitrogen for 75 min. The infrared spectrum of the product indicated the presence of significant amounts of residual 11-formate. The alcoholysis was, therefore, repeated as above but using 135 mg. of potassium hydroxide. The mixture was taken to dryness and the product was distributed between ether–methylene chloride and water. The organic layer was dried and taken to dryness to afford an oil which was triturated with acetone to give VII, m.p. 256–260.5°. A mixture melting point with material prepared directly from III was undepressed.

2′-Phenyl-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-*c*]pyrazole 21-Acetate Hydrochloride (XXV).—A solution of 350 mg. of VII in 30 ml. of 60% formic acid was heated on a steam bath in an inert atmosphere for 35 min. The solution was taken to dryness and water was added. The crude product

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

(28) This melting point was taken on a micro hot stage.

(29) The tendency of some steroidal pyrazoles to crystallize as "stable, reproducible solvates" was first pointed out by R. O. Clinton, *et al.*[7] See also R. G. Strachan, N. G. Steinberg, M. Tishler, and R. Hirschmann, *J. Med. Chem.*, in press.

was removed by filtration to afford 300 mg., which was dissolved in 7.5 ml. of methanol containing about 50 mg. of sodium methoxide. The mixture was allowed to stand at room temperature in an atmosphere of nitrogen for 10 min. The alkoxide was neutralized with acetic acid and the mixture was taken to dryness. After the addition of water, the product (285 mg.) was removed by filtration. A 150-mg. aliquot was acetylated with 3.0 ml. of a mixture of pyridine and acetic anhydride (1:1) at room temperature overnight. The solvents were removed *in vacuo*, water was added, and the product was removed by filtration. The compound was dissolved in acetone and treated with 2.5 *N* hydrochloric acid. Removal of the solvent afforded a hydrochloride which was crystallized from acetone–ether to give an analytical sample, m.p. 143–145°.[28]

Anal. Calcd. for $C_{31}H_{39}O_5N_2Cl \cdot C_3H_6O$[29]: C, 66.59; H, 7.40. Found: C, 66.63; H, 7.67.

2-Methoxymethylene-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-ene-3,11-dione (XIV).—A mixture consisting of 1.0 g. of 2-hydroxymethylene-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-ene-3,11-dione,[30] 200 ml. of methanol, and 200 mg. of *p*-toluenesulfonic acid was brought to reflux and allowed to stand for 2 hr. at room temperature. The solution was diluted with water and extracted with ethyl acetate. The ethyl acetate phase was washed with sodium hydroxide, dried, and concentrated *in vacuo*. Crystallization from ethyl acetate afforded 0.50 g. of XIV. A sample for analysis was crystallized from ethyl acetate and ether, m.p. 290–302° dec., $[\alpha]^{24}D$ +19° ($CHCl_3$), λ_{max}^{MeOH} 252 (log ε 4.08), 301 mμ (log ε 3.91).

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.86; H, 7.45.

11-Oxo-2′-phenyl-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole (XVI) and 11-Oxo-1′-phenyl-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno-[3,2-c]pyrazole (XV).—A mixture consisting of 0.40 g. of XIV, 80 ml. of ethanol, and 0.8 ml. of phenylhydrazine was heated to effect solution and allowed to stand for 16 hr. at room temperature under nitrogen. After addition of 1.6 ml. of acetic acid the solution was allowed to stand for an additional 4 hr. and was worked up as above. Chromatography on acid-washed alumina and elution with benzene afforded 0.22 g. of XV. A sample for analysis was crystallized from benzene and ethyl acetate, m.p. 268–275°, $[\alpha]^{25}D$ −15° ($CHCl_3$), λ_{max}^{MeOH} 297 mμ (log ε 4.49).

Anal. Calcd. for $C_{31}H_{36}O_5N_2$: C, 72.07; H, 7.02. Found: C, 71.78; H, 6.44.

Further elution with ether–Skellysolve B (1:1) afforded 0.22 g. of XVI. A sample for analysis was crystallized twice from benzene, m.p. 304–312°, $[\alpha]^{24}D$ +81° ($CHCl_3$), λ_{max}^{MeOH} 262 mμ (log ε 4.22).

Anal. Calcd. for $C_{31}H_{36}O_5N_2$: C, 72.07; H, 7.02. Found: C, 71.52; H, 7.13.

Lithium Aluminum Hydride Reduction of XV.—A suspension consisting of 0.20 g. of XV, 0.30 g. of lithium aluminum hydride, and 20 ml. of tetrahydrofuran was refluxed for 75 min. The reaction mixture was distributed between ethyl acetate and water. Chromatography on acid-washed alumina and elution with benzene–ether (1:1) afforded 0.15 g. of X, which was identical with the pyrazole prepared from III. An analytical specimen prepared by repeated recrystallization from ether melted at 223–224°, λ_{max}^{MeOH} 298 mμ (log ε 4.50).

Anal. Calcd. for $C_{31}H_{38}O_5N$: C, 71.79; H, 7.39. Found: C, 71.86; H, 7.22.

11β-Hydroxy-2-methoxymethylene-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-en-3-one (IX).—In one experiment the crude hydroxymethylene compound III prepared from II by a Claisen condensation was purified *via* its sodium salt as described above. The resulting alkaline extracts were made acid to congo red and the crude product was removed by filtration and washed with water. The solid was dissolved in refluxing methanol and allowed to crystallize to afford a product, which now gave a negative ferric chloride test and which exhibited the same ultraviolet spectrum in methanol and in methanol containing dilute aqueous sodium hydroxide. An analytical specimen melted at 257° dec., λ_{max}^{MeOH} 255 (log ε 4.10), 298 mμ (log ε 3.94).

Anal. Calcd. for $C_{26}H_{36}O_7 \cdot {}^1/_2CH_3OH$: C, 66.81; H, 8.04. Found: C, 66.88; H, 8.15.

Treatment of IX with phenylhydrazine as described above for the 11-ketone XIV afforded after chromatography a mixture of the isomeric 1′- and 2′-phenylpyrazoles X and VII, identical with the respective pyrazoles derived from III and phenylhydrazine.

1′-Phenyl-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-c]pyrazole (XI).—A mixture of 130 mg. of X and 20 ml. of 60% aqueous formic acid was heated on a steam bath for 30 min. The solution was diluted with water and extracted with methylene chloride. The methylene chloride extract was washed with water, aqueous sodium bicarbonate solution, dried, and concentrated *in vacuo*. The crude product in 10 ml. of methanol was treated with 0.25 ml. of 0.5 *N* sodium methoxide in methanol for 30 min. under nitrogen. The base was neutralized with acetic acid and the product was isolated as above to yield XI. A sample for analysis was crystallized twice from ethyl acetate, m.p. 209–214°, $[\alpha]^{24}D$ +50° ($CHCl_3$), λ_{max}^{MeOH} 298 mμ (log ε 4.50).

Anal. Calcd. for $C_{29}H_{36}O_4N_2$: C, 73.08; H, 7.61. Found: C, 72.26; H, 7.66.

2′-(4-Fluorophenyl)-11β-hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole (XXIII).—To a solution of 446 mg. of the 2-hydroxymethylene 3-ketone III (m.p. 195–197°) in 10 ml. of absolute ethanol was added 59.0 mg. of sodium acetate and 194 mg. of *p*-fluorophenylhydrazine hydrochloride. The reaction mixture was refluxed for 1 hr. in a nitrogen atmosphere.

The solvent was removed *in vacuo*, and the residue was dissolved in ether. The ethereal solution was extracted successively with a 2.5 *N* solution of hydrochloric acid, a 2.5 *N* solution of sodium hydroxide, and water. The ethereal layer was then dried over magnesium sulfate and taken to dryness. Removal of the solvent followed by crystallization from methanol afforded 288 mg. of the *p*-fluorophenylpyrazole XXIII, m.p. 147–152°. Two further recrystallizations from 90% ethanol raised the m.p. to 155–155.5°, λ_{max}^{MeOH} 261.5 mμ (log ε 4.20); λ_{max}[31] 288.5 (log ε 4.14), 252 mμ (log ε 4.07).

Anal. Calcd. for $C_{31}H_{37}O_5N_2F$: C, 69.38; H, 6.95. Found: C, 69.82; H, 7.17.

2′-(4-Fluorophenyl)-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-c]pyrazole 21-Acetate (XXVI).—The above pyrazole (188.7 mg., m.p. 147–152°) was treated with 5 ml. of 60% aqueous formic acid for 0.5 hr. on a steam bath under nitrogen. The reaction mixture was taken to dryness *in vacuo*, affording 135 mg. of a colorless oil.

The crude product was dissolved in 3 ml. of methanol and allowed to react with 0.27 ml. of a solution of sodium methoxide (0.96 *N*) for 7 min. in an inert atmosphere at room temperature. The alkoxide was then neutralized with glacial acetic acid, and the solvent was removed *in vacuo* giving 137 mg. of an oil. The crude pyrazole was acetylated by treatment with an equal mixture of pyridine and acetic anhydride (8 ml.) at room temperature overnight. The solvent was evaporated *in vacuo*, affording 120 mg. of an oil. The crude product was dissolved in 5 ml. of benzene, adsorbed on 12.0 g. of silica gel, and eluted successively with benzene, benzene–ether (97:3, 95:5, 90:10, 4:1). The last-named system afforded, after crystallization from methanol, 17.8 mg. of XXVI, m.p. 178–184°.

An analytical sample, m.p. 186–188°, $[\alpha]^{25}D$ +38° ($CHCl_3$), was prepared by further crystallization from methanol.

Anal. Calcd. for $C_{31}O_5H_{37}N_2F$: C, 69.37; H, 6.95. Found: C, 69.66; H, 7.24.

2′-(4-Chlorophenyl)-11β-hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole(XXIV).—A suspension of 223 mg. of III, 49 mg. of sodium acetate, and 107 mg. of *p*-chlorophenylhydrazine hydrochloride in 5 ml. of ethanol was refluxed in an inert atmosphere for 70 min. The mixture was cooled, filtered to remove small amounts of insolubles and the filtrate was taken to dryness. Addition of water gave a dark yellow solid which was removed by filtration and washed successively with dilute acid and with water. The solid was triturated with acetone to afford crystalline XXIV, m.p. 155° dec. One further recrystallization from methanol gave 31 mg., m.p. 155–157° dec., λ_{max}^{MeOH} 262 (log ε 4.31), 231 mμ (log ε 4.05).

Anal. Calcd. for $C_{31}H_{37}O_5N_2Cl$: C, 67.31; H, 6.74. Found: C, 67.27; H, 6.73.

In another experiment 446 mg. of III was allowed to react with the *p*-chlorophenylhydrazine as described above, but the crude product was crystallized directly from methanol to give 308 mg. of XXIV, m.p. 153–155° dec. A 200-mg. aliquot was heated with 25 ml. of 60% formic acid for 40 min. The mixture was taken to dryness, dissolved in 18 ml. of methanol, and treated with 0.53 ml. of a solution of 1 *N* sodium methoxide in the usual manner. The product was allowed to react with pyridine and acetic anhydride and after the usual work-up the 21-acetate (115 mg.) was adsorbed on 3.5 g. of acid-washed alumina and eluted with benzene. The initial 18 ml. of eluate was discarded, but the remaining benzene fraction (37 ml.) and the fractions eluted with methanol chloroform (1:99, 2:98) were crystallized from methanol to give **2′-(4-chlorophenyl)-11β,17,21-trihydroxy-16α-methyl-20-oxopregn-4-eno[3,2-c]pyrazole 21-acetate**, m.p. 135–140°; λ_{max} 2.8–3.0 (OH), 5.75 (shoulder), 8.08 (acetate), 5.80 (20-carbonyl), 6.15, 6.21, 6.63 μ (phenyl). The compound did not give a satisfactory carbon and hydrogen analysis.

1′,16α- and 2′,16α-Dimethyl-11β-hydroxy-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazoles (XVIII and XVII).—A mixture of 368 mg. of the 2-hydroxymethylene derivative III (m.p. 199–201.0°), 17 ml. of dry ethanol, 260 mg. of sodium acetate, and 370 mg. of methylhydrazine sulfate was stirred for 1 hr. under reflux under nitrogen. The solvent was removed

(30) Prepared essentially as described for the 11β-hydroxy analog. The preparation of this compound by Dr. H. Mrozik will be described in a forthcoming publication.

(31) Taken in methanol containing 2.5 *N* hydrochloric acid.

in vacuo and the residue was dissolved in methylene chloride–ether (*ca.* 5:1), washed successively with a solution of 0.5 *N* hydrochloric acid (four times), 2 *N* potassium hydroxide solution (twice), and with water, and dried over sodium sulfate. The solvent was evaporated to give 409 mg. of a tan foam, λ_{max}^{MeOH} 271 mμ (log ε 4.02). This material plus 61 mg. of a mixture of the methylpyrazoles XVIII and XVII (from an earlier chromatogram) were dissolved in 10 ml. of benzene, adsorbed on 17 g. of basic alumina and eluted with mixtures of benzene–ether (30:1 to 20:1). These eluates (XVIII, λ_{max}^{MeOH} 268–269 mμ) were combined and yielded 139 mg. Two fractional crystallizations from a very small volume of methanol separated a small amount of the less soluble 2′-methylpyrazole XVII (λ_{max}^{MeOH} 275 mμ). The resulting mother liquor was taken to dryness, dissolved in ether containing a trace of methylene chloride, and the 1′-methylpyrazole XVIII was crystallized by the addition of Skellysolve B. White needles (115 mg.), m.p. 232°, λ_{max}^{MeOH} 267 mμ, were thus obtained. For analysis, a comparable sample (m.p. 227–229°) was crystallized three times from ether–Skellysolve B to give the 1′-methylpyrazole XVIII, m.p. 240.5–242°, $[\alpha]^{25}D$ +14° ($CHCl_3$), λ_{max}^{MeOH} 266.5 mμ (log ε 4.12), λ_{max}^{31} 283 mμ (log ε 4.19).

Anal. Calcd. for $C_{26}H_{36}O_5N_2$: C, 68.39; H, 7.95; N, 6.14. Found: C, 68.26; H, 7.88; N, 6.18.

The isomeric 2′-methylpyrazole (λ_{max}^{MeOH} 273–276.5 mμ, 275 mg.) was eluted with benzene–ether mixtures (15:1 and 10:1) and finally with ether. This product was twice crystallized from methylene chloride–methanol to give 148 mg. of XVII as white needles, m.p. 259–260°.

Two further recrystallizations of a 30-mg. aliquot from methylene chloride–ether–Skelly B gave 17 mg. of the 2′-methylpyrazole XVII, m.p. 260–260.5°, $[\alpha]^{25}D$ +34° ($CHCl_3$), λ_{max}^{MeOH} 277.5 mμ (log ε 4.01), λ_{max}^{36} 282.5 mμ (log ε 4.12).

Anal. Calcd. for $C_{26}H_{36}O_5N_2$: C, 68.39; H, 7.95; N, 6.14. Found: C, 68.24; H, 7.93; N, 6.07.

11β,17,21-Trihydroxy-1′,16α-dimethyl-20-oxo-pregn-4-eno-[3,2-*c*]pyrazole 21-Acetate (XXII).—A solution of 130 mg. of the 1′-methylpyrazole XVIII, m.p. 234°, λ_{max}^{MeOH} 267 mμ (log ε 4.09), in 6 ml. of 60% formic acid was heated for 35 min. on a steam bath under nitrogen. The mixture was taken to dryness and the residue was repeatedly suspended in benzene and in benzene–Skellysolve D and taken to dryness. The residual white foam was dissolved in 15 ml. of pure methanol and treated at room temperature for 10 min. with 40 mg. of sodium methoxide. Glacial acetic acid was added to bring the pH of the solution to *ca.* 6. The methanol was removed *in vacuo*, benzene was added to the residue, and evaporated *in vacuo*. The residue was then dissolved in methylene chloride–ether (*ca.* 1:5). The resulting solution was washed three times with a saturated solution of sodium chloride, dried over sodium sulfate, and taken to dryness *in vacuo* to give 114 mg. of a white foam, λ_{max}^{MeOH} 266 mμ (log ε 4.08). The intensity of a quantitative tetrazolium assay was about 70% that of 16α-methylcortisol (w./w.).

The above 1′-methylpyrazole (103 mg.) was acetylated with 0.9 ml. of pyridine–acetic anhydride (1:1) at room temperature overnight. The solution was concentrated *in vacuo*, suspended in benzene, and taken to dryness. The residue was dissolved in methylene chloride, washed successively with a solution of dilute hydrochloric acid, saturated sodium bicarbonate solution, and with a saturated salt solution. Evaporation of the solvent gave 87 mg. of a slightly tan foam (λ_{max}^{MeOH} 267 mμ, log ε 4.05) which was purified by means of a short chromatogram on 1.7 g. of neutral alumina. Benzene, benzene–ether mixtures, and ether eluted a total of 67 mg. of semicrystalline material, which could not be crystallized; 44 mg. of this material, dissolved in methylene chloride, was filtered again through a small amount of neutral alumina. The first 30 ml. of methylene chloride eluates afforded 44 mg. of a white foam, λ_{max}^{MeOH} 267 mμ (log ε 4.05), which gave a satisfactory elemental analysis for XXII.

Anal. Calcd. for $C_{26}H_{36}O_5N_2$: C, 68.39; H, 7.95. Found: C, 68.39; H, 7.88.

11β,17,21-Trihydroxy-2′,16α-dimethyl-20-oxo-pregn-4-eno-[3,2-*c*]pyrazole 21-Acetate (XXI).—A solution of 160 mg. of 2′-methylpyrazole XVII (m.p. 257°; λ_{max}^{MeOH} 277 mμ (log ε 4.01) in 10 ml. of 60% formic acid was treated and isolated as described for the 1′-isomer. The resulting foam was treated with sodium methoxide (30 mg.) as described above. The product afforded 147 mg. of a tan foam, λ_{max}^{MeOH} 277 mμ (log ε 4.01).

The 2′-methylpyrazole (146 mg.) was acetylated in 1.6 ml. of a mixture of pyridine and acetic anhydride (1:1) at room temperature. After 14 hr. the reaction mixture was concentrated *in vacuo* to a thick oil. The residue was successively treated with benzene, methanol, benzene, and finally with Skellysolve B and each solvent was evaporated *in vacuo*. The residue was taken up in methylene chloride and washed successively with 0.25 *N* hydrochloric acid, with a saturated solution of sodium bicarbonate, and with a saturated salt solution. Removal of the solvent gave a tan foam (152 mg.) which was dissolved in methylene chloride and filtered through 1.5 g. of neutral alumina. The first 40 ml. of methylene chloride eluted 119 mg. of a white foam, λ_{max}^{MeOH} 276.5 (log ε 4.03), λ_{max}^{31} 282.5 mμ (log ε 4.15), which resisted crystallization, even as the hydrochloride.

Anal. Calcd. for $C_{26}H_{36}O_5N_2$: C, 68.39; H, 7.95; N, 6.14. Found: C, 68.93; H, 8.16; N, 5.61.

11β-Hydroxy-17,20:20,21-bis-(methylenedioxy)-5α-pregnan-3-one (XXVIII).—A suspension of 12.0 g. of 4,5α-dihydrocortisol in 735 ml. of methylene chloride was added to a cold mixture of 240 ml. each of concentrated hydrochloric acid and of formaldehyde (Merck, low methanol content). The mixture was stirred at room temperature overnight and was worked up essentially as described for II. Chromatography on alumina, followed by crystallization from ethyl acetate, afforded 6.2 g. of XXVIII, m.p. 223–224°. The compound was identical with a specimen which had been prepared by Dr. D. Hoff of these laboratories by lithium–ammonia reduction of the bismethylenedioxy derivative of cortisol. An analytical sample melted at 224–225°.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.14; H, 8.47.

11β-Hydroxy-2-hydroxymethylene-17,20:20,21-bis-(methylenedioxy)-5α-pregnan-3-one (XXIX).—A mixture of 1.2 g. of a 53% suspension of sodium hydride in mineral oil, 40 ml. of dry benzene, and 1.2 ml. of dry *t*-butyl alcohol was stirred at room temperature under nitrogen for 20 min. This mixture was added to a solution of 3.800 g. of XXVIII in 150 ml. of dry benzene and 7 ml. of freshly distilled ethyl formate. The reaction mixture turned yellow within 30 sec. and was magnetically stirred at room temperature under nitrogen overnight. The suspension was poured into water and extracted successively with benzene–ether (1:1) and with ether. The organic layers were extracted once with a 2 *N* solution of potassium hydroxide. The ice-cooled, basic extract was covered with a layer of ether and acidified with 18% hydrochloric acid. The hydroxymethylene compound XXIX was extracted with ethyl acetate. Removal of the washed and dried solvent left 3.751 g. of a semicrystalline product, which was once crystallized from ether to give 3.040 g. (76.5%) of fine crystals, m.p. 251–253°, λ_{max} 314 mμ[33] (log ε 4.24). An aliquot (130 mg.) of this material was crystallized three times from methylene chloride–ether and finally once from methylene chloride–ether containing a trace of petroleum ether to give an analytical sample (74 mg.), m.p. 253.5–255°, $[\alpha]^{24}D$ −40° ($CHCl_3$), λ_{max} 314.5[27] (log ε 4.30), λ_{max}^{MeOH} 288 mμ (log ε 3.87).

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.89. Found: C, 66.22; H, 7.71.

1′-Phenyl- and 2′-Phenyl-11β-hydroxy-17,20:20,21-bis-(methylenedioxy)-5α-pregnano[3,2-*c*]pyrazoles (XXX and XXXI).

A. In Refluxing Propanol.—The allodihydroformyl derivative XXIX (1.900 g., m.p. 251–253°) was dissolved in 50 ml. of chloroform and 200 ml. of 1-propanol (solution A). Phenylhydrazine (2 ml.) was dissolved in 25 ml. of 1-propanol (solution B); 20 ml. of 1-propanol and 2.5 ml. of solution B were heated to reflux under nitrogen. Solution A and B were added dropwise (ratio A:B *ca.* 10:1) over a period of 45 min. The reaction mixture was stirred magnetically and the bath temperature was kept at 155°. After a total reaction time of 1.25 hr., the 1-propanol was evaporated to dryness *in vacuo*. The residue was dissolved in methylene chloride–ether (*ca.* 1:8) and was washed consecutively with a solution of 2.5 *N* hydrochloric acid (four times), 2 *N* potassium hydroxide (three times), and water. Removal of the solvent under reduced pressure gave 2.632 g. of a brown amorphous material (λ_{max}^{MeOH} 264 mμ) which was added in 40 ml. of benzene to 75 g. of acid-washed alumina. Benzene–ether mixtures, varying from 250:1 to 10:1, eluted a total of 861 mg. of the 1′-phenyl isomer XXX (λ_{max}^{MeOH} 269 mμ). One crystallization from methylene chloride–methanol furnished 735 mg. (33.1%) of fine needles, m.p. 241–243°. On gradually changing the composition of the eluent from benzene–ether 10:1 to ether, 1.059 g. of the 2′-phenyl isomer XXXI (λ_{max}^{MeOH} 251.5 mμ) was eluted. This material was once crystallized from methylene chloride–methanol to give 845 mg. of needles, m.p. 280–282°. The mother liquor yielded another 120 mg. of crystals, m.p. 281–283°. The combined material furnished after three crystallizations from methylene chloride–methanol 603 mg. of pure XXXII, m.p. 284–285°. From the combined mother liquors an additional 292 mg. of needles, m.p. 282–284°, was obtained, giving XXXI in a total yield of 40%.

For analysis the 2′-phenylpyrazole II (60 mg.) was recrystallized three times from the same solvent pair to give 39 mg. of fine needles, m.p. 285–286°, $[\alpha]^{27}D$ −10° ($CHCl_3$), λ_{max}^{MeOH} 251 mμ (log ε 4.04).

Anal. Calcd. for $C_{30}H_{38}O_5N_2$: C, 71.12; H, 7.56; N, 5.53 Found: C, 70.99; H, 7.38; N, 5.38.

The 1′-phenylpyrazole XXX (100 mg.) was twice crystallized from methylene chloride–methanol giving 76 mg. of analytically pure needles, m.p. 247–247.5°, $[\alpha]^{24}D$ −16° ($CHCl_3$), λ_{max}^{MeOH} 269.5 mμ (log ε 4.30).

Anal. Calcd. for $C_{30}H_{38}O_5N_2 \cdot {}^1/_2CH_3OH$[29]: C, 70.20; H, 7.36; N, 5.35. Found: C, 70.12; H, 7.38; N, 5.29.

B. In Ethanol–Acetic Acid at Room Temperature.—A solution of 283 mg. of the 2-formyl derivative XXIX, m.p. 248–251°,

30 ml. of ethanol, 500 mg. of phenylhydrazine, and 100 mg. of glacial acetic acid was stirred at room temperature for 23 hr. under nitrogen. An additional 500 mg. of phenylhydrazine and 100 mg. of glacial acetic acid was added. After a total reaction time of 3.5 days, the reaction mixture was concentrated *in vacuo* at room temperature to a small volume. Methylene chloride and ether were added and the organic solution was washed successively with water (once), a solution of 2.5 *N* hydrochloric acid (three times), 2 *N* potassium hydroxide (four times), and finally water. The organic phase was dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 336 mg. of brown amorphous product (λ_{max}^{MeOH} 266 mμ, log ε 4.20). This material was added in 10 ml. of benzene to 11 g. of acid-washed alumina. Benzene–ether mixtures (ratio increasing from 100:1 to 15:1) eluted a total of 301 mg. of XXX (λ_{max}^{MeOH} 268–269 mμ), while only 22 mg. of XXXI (λ_{max}^{MeOH} 253 mμ) was isolated in crystalline form. The combined fractions of the major product XXX were once crystallized from methylene chloride–methanol to give 172 mg. of fine needles, m.p. 242–243°.

C. In Ethanol at Room Temperature.—A solution of 80 mg. of XXIX, 20 ml. of ethanol, 2 ml. of methylene chloride, and 100 mg. of phenylhydrazine was stirred for 2.5 days at room temperature (under nitrogen). Isolation essentially as described under B led to 92 mg. of a brown amorphous product (λ_{max}^{MeOH} 267 mμ, log ε 4.22) which was chromatographed on 3.5 g. of neutral alumina. Benzene, benzene–ether, 100:1 and 50:1, eluted 65 mg. of the 1′-phenylpyrazole XXX. One crystallization from methylene chloride–methanol furnished 43 mg. of white needles, m.p. 241–242°, λ_{max}^{MeOH} 269 mμ. Benzene–ether 20:1 and 5:1 eluted 5.5 mg. of the 2′-isomer XXXI absorbing at 252.5 mμ, which was once crystallized from methylene chloride–carbon tetrachloride to give 3 mg. of white needles, m.p. 284–285°.

11β,17,21-Trihydroxy-2′-phenyl-20-oxo-5α-pregnano[3,2-c]-pyrazole 21-Acetate (XXXII).—A suspension of 500 mg. of XXXI, m.p. 284–285°, in 50 ml. of 60% formic acid was heated on the steam bath under nitrogen. Eventually all material went into solution. After 30 min., the formic acid was evaporated to dryness *in vacuo*. The residue (495 mg.) was flushed twice with benzene and then taken up in 30 ml. of pure methanol. Sodium methoxide (27 mg.) was added and the solution stirred at room temperature for 15 min. After addition of a few drops of glacial acetic acid (pH of the solution *ca.* 6.5), the slightly yellow solution was taken to dryness *in vacuo*. Benzene was added and evaporated to dryness to afford 535 mg. An aliquot of the crude product (280 mg.) was taken up in methylene chloride–ether (1:10) and was washed twice with a saturated solution of sodium chloride and once with water. The solution was dried over sodium sulfate and evaporated to dryness.

This product (225 mg., λ_{max}^{MeOH} 250.5 mμ, log ε 4.02) was acetylated at room temperature overnight with pyridine–acetic anhydride (1:1). The solvents were removed *in vacuo* and the residue was flushed several times with benzene and ligroin. The material was taken up in methylene chloride–benzene and washed successively with water (once), a solution of 2.5 *N* hydrochloric acid (twice), saturated sodium bicarbonate solution (twice), and water (twice). Removal of the solvent gave 226 mg. of slightly tan material, which was filtered through 7.5 g. of neutral alumina. The eluate was crystallized twice from methylene chloride–isopropyl alcohol and yielded 128 mg. of white heavy crystals, m.p. 247–249°. The analytical sample melted at 248.5–250°, λ_{max}^{MeOH} 251 mμ (log ε 3.96).

Anal. Calcd. for $C_{30}H_{38}O_5N_2$: C, 71.12; H, 7.56. Found: C, 71.41; H, 7.65.

Catalytic Hydrogenation of 11β-Hydroxy-2′-phenyl-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole (VII).—A solution of 100 mg. of the 2′-phenylpyrazole VII (m.p. 258.5–261°) in 70 ml. of methanol was stirred for 16 hr. with 200 mg. of 10% palladium-on-charcoal in a hydrogen atmosphere (pressure *ca.* 50 mm.) at 26°. Ultraviolet spectroscopy of an aliquot showed that most of the material had been reduced. New catalyst (100 mg.) was added and the hydrogenation was continued for another 4 hr. The catalyst was removed and the solution was evaporated to dryness *in vacuo*. A white foam (82 mg.) was obtained (λ_{max}^{MeOH} 251 mμ), which failed to crystallize. The product is believed to have the 5β-configuration.[25]

11β-Hydroxy-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno-[3,2-c]pyrazole (XXXVIII).—To a solution of 300 mg. of XXXIII[32] in 13.1 ml. of absolute alcohol was added 0.12 ml. of hydrazine hydrate. The reaction mixture was refluxed for 1 hr. in an atmosphere of nitrogen. The reaction mixture was taken to dryness *in vacuo* to give 285 mg. of an amorphous solid. Several recrystallizations from methanol afforded 102 mg. of XXXVIII, m.p. 251–255°, λ_{max}^{MeOH} 261 mμ (log ε 4.02).

Anal. Calcd. for $C_{24}H_{32}O_5N_2$: C, 67.27; H, 7.53. Found: C, 67.40; H, 7.48.

11β-Hydroxy-2′-phenyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole (XXXIV).—A suspension of 3.85 g. of slightly impure[33] XXXIII, m.p. 235–240°, was suspended in 38 ml. of acetic acid. After the addition of 1.1 ml. of phenylhydrazine, the mixture was stirred at room temperature for 35 min. in an atmosphere of nitrogen. The resulting deep red solution was poured into 100 ml. of ice–water and the mixture was extracted several times with methylene chloride. The combined organic layers were washed successively with dilute base, dilute acid, and a saturated solution of sodium chloride. Removal of the solvent afforded a product[33] (λ_{max}^{MeOH} 260 mμ) which was refluxed with 60 ml. of a solution containing 1.8 g. of potassium hydroxide in 100 ml. of ethanol in an inert atmosphere. The bulk of the solvent was removed *in vacuo* and the product was distributed between methylene chloride and a saturated solution of sodium chloride. The neutral organic layer was taken to dryness to afford a foam which was free of saturated carbonyl absorption in the infrared. Trituration with acetone gave 2.35 g. of a crystalline solid, m.p. *ca.* 210°. A 200-mg. aliquot was recrystallized from acetone and then from methanol to give an analytical sample, m.p. 290.5–293°, λ_{max} 261 mμ (log ε 4.22), $[\alpha]^{25}D$ +35.4 ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{36}O_5N_2$: C, 71.40; H, 7.19. Found: C, 71.92; H, 7.25.

The crude product was used in the following step.

11β,17,21-Trihydroxy-2′-phenyl-20-oxo-pregn-4-eno[3,2-c]pyrazole (XXXV).—The bulk of XXXIV (2.15 g., m.p. 210°) was dissolved in 90 ml. of a 60% solution of aqueous formic acid and heated on a steam bath for 30 min. The solution was concentrated to dryness and the residue was taken up in methylene chloride–ether and with a solution of sodium bicarbonate and with a saturated solution of sodium chloride. The residue was dissolved in 100 ml. of methanol and allowed to react with 2.4 ml. of a 0.95 *N* solution of sodium methoxide in methanol under nitrogen for 10 min. After neutralization with acetic acid, the solution was concentrated and the residue was distributed between methylene chloride–ether and water. Concentrating the dried organic layer afforded an amorphous solid which was crystallized from the same solvent pair. Crystallization from methanol afforded an analytical specimen, m.p. 172.5–176°, λ_{max}^{MeOH} 260 mμ (log ε 4.20).

Anal. Calcd. for $C_{28}H_{34}O_4N_2$: C, 72.70; H, 7.41. Found: C, 72.69; H, 7.43.

2′-(β-Hydroxyethyl)-11β-hydroxy-16α-methyl-17,20:20,21-bis-(methylenedioxy)-pregn-4-eno[3,2-c]pyrazole (XIX).—A mixture of 7 g. of III was dissolved in 80 ml. of acetic acid and treated with 1.45 g. of β-hydroxyethylhydrazine in 10 ml. of acetic acid. The reaction mixture was stirred in an atmosphere of nitrogen for 1 hr. The reaction color changed from yellow to red-orange. The reaction mixture was diluted with 1 l. of water. Salt was added to prevent emulsification during the subsequent extractions. The product was extracted five times with 125 ml. of methylene chloride. The organic layer was washed successively with water, 1.25 *N* hydrochloric acid, water, a 1 *N* sodium hydroxide solution, water, and finally a saturated sodium chloride solution. The organic layer was dried over magnesium sulfate and taken to dryness *in vacuo* to yield 7.0 g. of a yellow-orange foam. A 6-g. aliquot in methylene chloride was chromatographed on 180 g. of acid-washed alumina, taking 200-ml. solvent cuts. Elution with 1.6 l. of methanol–methylene chloride (1:200) yielded 1.58 g. of a mixture, λ_{max}^{MeOH} 269–273 mμ (fraction A). Two liters of methanol–methylene chloride (1:100) yielded 3.00 g. of impure XIX, λ_{max}^{MeOH} 273–276 mμ (fraction B). Further elution with 1.2 l. of methanol–methylene chloride (1:50) yielded 850 mg. of crude XIX, λ_{max}^{MeOH} 277 mμ (fraction C). Finally, elution with 600 ml. of methanol–methylene chloride (1:33) yielded an additional 290 mg. of XIX, λ_{max}^{MeOH} 276–277 mμ (fraction D). Adsorption of fraction B on 60 parts of acid-washed alumina and elution with methanol–methylene chloride (1:100, 1:50) yielded 285 mg. of crystalline XIX, m.p. 169–174°. A further recrystallization afforded analytically pure material, m.p. 184–186°, $[\alpha]^{25}D$ +30° ($CHCl_3$), λ_{max}^{MeOH} 277 mμ (log ε 4.01).

Anal. Calcd. for $C_{27}H_{38}N_2O_6$: C, 66.64; H, 7.87; N, 5.76. Found: C, 66.67; H, 7.70; N, 5.50.

Acknowledgment.—We are grateful to Dr. L. H. Sarett and to Dr. A. A. Patchett for helpful discussions throughout the course of this investigation. We are indebted to Mr. R. Boos and his associates for elemental analyses, to Mr. MacMullan and collaborators for ultraviolet spectra, and to Messrs. R. Walker and N. Allan for infrared spectra. We should like to thank Messrs. B. Arison and N. Trenner for the interpretation of the n.m.r. spectra of compounds VII and X. We are greatly indebted to Dr. S. L. Steelman for permission to include the biological results.

(32) J. A. Edwards, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **27**, 3378 (1962).

(33) This material was contaminated by some 11β-formate as indicated by infrared spectroscopy (see also preparation of IV).