[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE, NEWARK, DEL., AND RESEARCH LABORATORIES, PARKE, DAVIS AND CO., ANN ARBOR, MICH.]

The Formation of 1,2-Diazabicyclo[3.2.0]heptenone Derivatives from Steroidal 21-Diazo-16α,17α-pyrazolines[1a]

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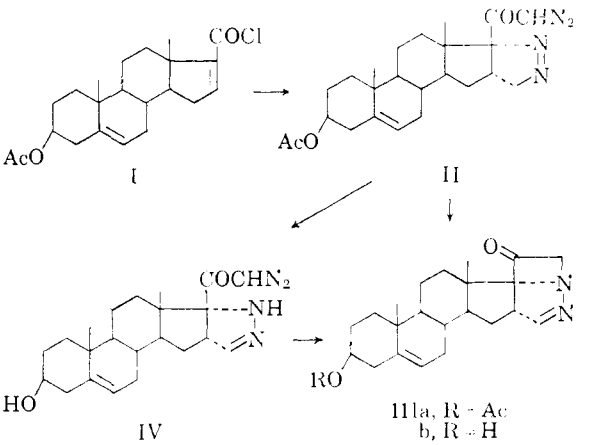
The reaction of 3β-acetoxy-5,16-etiadienyl chloride with diazomethane at 0° gives 21-diazo-16α,17α-[3,1-(1-pyrazolino)]-5-pregnen-3β-ol-20-one acetate, which with acid undergoes cyclization to the steroidal diazabicyclo[3.2.0]heptenone III. The cyclic ketone is also obtained by ring closure of the 21-iodopyrazoline; the mechanism of the ring closure is discussed. Several related 21-substituted pyrazolines and a number of transformation products of the bicyclic ketone, including 11-oxygenated derivatives, are described.

Pyrazolines obtained by the addition of diazomethane to Δ^{16}-20-ketopregnenes have been known for many years, and recently have come into prominence as intermediates in the synthesis of therapeutically active 16β-methylsteroids.[2] In this paper are described the preparation and reactions of several 21-substituted pyrazolines, including the 21-diazoketone, which have led to some novel steroids with a fused heterocyclic ring attached to ring D.

The relatively rapid addition of diazomethane to the trisubstituted Δ^{16}-double bond is noteworthy, since an α-alkyl substituent usually suppresses or completely inhibits pyrazoline formation from α,β-unsaturated carbonyl systems.[3] The marked susceptibility of Δ^{16}-20-ketones to conjugate addition is also observed in reactions with many other nucleophiles such as alcohols,[4] cyanide ion[5] and carbanions.[6] The exceptional electrophilic character of the Δ^{16}-20-carbonyl system was further demonstrated in this work by the reaction of diazomethane with 3β-acetoxy-5,16-etiadienyl chloride(I). In an attempt to prepare the Δ^{16}-unsaturated diazoketone, the acid chloride was treated briefly with excess diazomethane at 0°, conditions which do not normally affect a Δ^{16}-20-ketone. The product isolated in high yield was found to be the 21-diazopyrazoline II, evidently arising from very rapid addition of diazomethane to the unsaturated diazomethyl ketone. The enhanced reactivity of the diazomethyl ketone as compared to other α,β-unsaturated carbonyl derivatives has been noted previously.[3a] The 17β-diazoacetyl-16α,17α-pyrazoline structure for the product follows from the infrared spectrum, with bands at 4.75, 6.1 ($COCHN_2$) and 6.4 μ (N=N), and the well known rearward attack of nucleophiles at the 16,17-double bond.[7]

The reaction of the diazoketone with warm acetic acid furnished a product whose composition corresponded to the loss of nitrogen without incorporation of other elements. The same product was obtained with propionic acid or hydriodic acid, and it was evident that cyclization had occurred. The compound exhibited a strong infrared absorption band at 5.58 μ, indicating a small-ring carbonyl, and gave an oxime under the usual conditions. The most probable structure of the product was considered to be the 16α,17α,21-[3,1,1-(2-pyrazolino)]-5-pregnen-20-one (III), and this assignment is substantiated by the formation of the same product, in low yield, by cyclization of the 21-iodo-17α-pyrazoline as described below. The similar ring closure of a steroidal 21-diazo-17α-hydroxy-20-ketone to the 17α,21-oxidoketone has been reported.[8]



Subsequent to the initial work with this steroidal pyrazoline, the diazoacetylpyrazolines(V) and (VI) were prepared from α-methylcinnamoyl chloride and found to undergo the same ring closure reaction.[9] The more stable Δ^2-pyrazoline VI, obtained by base-catalyzed isomerization of the initially-formed Δ^1-isomer V, was converted by very mild acid treatment to the bicyclic ketone VII. On warming this product or the Δ^1-pyrazoline with acetic acid to 80° the diazepinone VIII was formed by valence tautomerization of VII.

The parallel course of the ring closure reaction in the two series was confirmed by the difference in reactivity of the two steroidal pyrazoline isomers. Alkaline hydrolysis of the 3β-acetoxy-pyrazoline II

(1) (a) Heterocyclic Studies. VIII. Paper VII, *J. Am. Chem. Soc.*, **81**, 6049 (1959). Taken in part from the Ph.D. dissertation of W. F. Holton, University of Delaware, June, 1961. Supported in part by PHS Grant A-3629 from the National Institute of Arthritis and Metabolic Diseases. (b) Parke, Davis and Co.

(2) D. Taub, R. D. Hofsommer, H. L. Slates, C. H. Kuo and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

(3) (a) J. A. Moore, *J. Org. Chem.*, **20**, 1607 (1955); (b) R. J. Landborg, Ph.D. Thesis, Iowa University, 1960.

(4) T. F. Gallagher and D. K. Fukushima, *J. Am. Chem. Soc.*, **73**, 196 (1951).

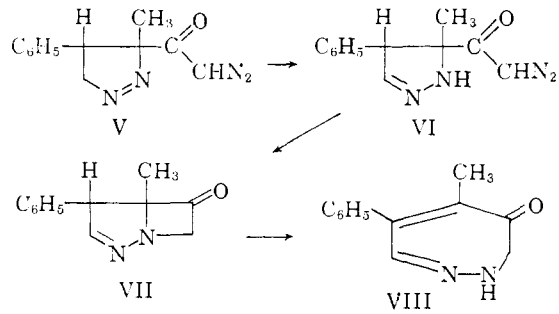
(5) J. Romo, *Tetrahedron*, **3**, 37 (1958); B. Ellis, V. Petrow and D. Wedlake, *J. Chem. Soc.*, 3748 (1958).

(6) P. Bladon, *ibid.*, 3723 (1958).

(7) T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).

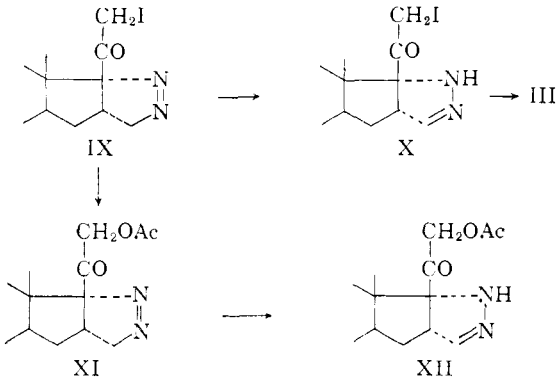
(8) B. G. Christensen, N. G. Steinberg and R. Hirschmann, *Chemistry & Industry*, 1259 (1958).

(9) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959).



in methanol at room temperature gave the 3-alcohol and the infrared and ultraviolet spectra showed that isomerization of the pyrazoline ring had also taken place, with formation of IV. The infrared spectrum contained bands at 2.86 (O—H), 3.08 (N–H), 4.70 and 6.1–6.2 μ ($COCHN_2$ and C=N), and the ultraviolet maximum was displaced from 274 mμ (ϵ 10,200) in II to 261 mμ (ϵ 13,600) in IV. A very similar change is observed on going from V (λ_{max}^{EtOH} 271 mμ, ϵ 11,200) to VI (λ_{max}^{EtOH} 254 mμ, ϵ 14,900).[9] This isomerization is a normal reaction under these conditions,[9] although the basic hydrolysis of a 3α-acetoxy-11-keto-16α, 17α-(1-pyrazoline) has been accomplished in tetrahydrofuran solution without concomitant isomerization.[10] The 3-hydroxy-21-diazo-16α,17α-(2-pyrazoline) (IV), like VI, was found to liberate nitrogen on simply dissolving in acetic acid at room temperature, and about 90% of the theoretical amount of nitrogen was obtained in 1 hour at 30°. Nitrogen evolution with the 1-pyrazoline isomer (II) was negligible below 60° and 0.7 hour was required for complete nitrogen evolution at 72°.

To obtain further information on the nature and mechanism of the ring closure reaction the iodoacetylpyrazoline IX was prepared from the readily available[11] 21-iodo-5,16-pregnadien-3β-ol-20-one acetate. The 21-iodo-16α,17α-(2-pyrazoline) (X) was obtained by isomerization of IX with acid in a two-phase system as originally described by v. Auwers and König.[12] The iodopyrazolines were rather unstable and neither was obtained in analytical purity. Both of these compounds were reduced to 3β-acetoxy-16α,17α-[3,1-(2-pyrazolino)]-5-pregnen-20-one by treatment with hydriodic acid. Reaction of the iodopyrazolines with potassium acetate in acetone furnished the respective 21-acetoxypyrazolines XI and XII, in good yields. The acid-catalyzed isomerization was also found to be very suitable for the conversion of XI to XII without hydrolysis of the 21-acetyl group. The pyrazoline isomers in three series, 21-iodo, 21-acetoxy and 21-unsubstituted, showed characteristic and consistent differences in physical properties. The infrared spectra of all of the 1-pyrazolines showed a weak but distinctive band in the region 6.40–6.45 μ, characteristic of the unsymmetrical N=N bond, which disappeared on isomerization. The spectra of the 2-pyrazolines all showed a sharp band of medium intensity at 3.0–3.10 μ (N—H) and a weak band at 6.28–6.35 μ (C=N). The pyrazoline isomerization is also accompanied by a large positive change in rotation. The ΔM_D value for the double bond shift in the 21-iodo and 21-acetoxy series was +590°, for the 21-unsubstituted compounds +370 and for the 21-diazo pair +220°



Solvolysis of the 21-iodo-2-pyrazoline in ethanolic silver nitrate solution furnished a small amount of the cyclic ketone III. The major product was non-crystalline and presumably consisted of the 21-ethoxy derivative. The corresponding formation of the four-membered cyclic oxidoketone, in unspecified yield, together with the 21-phosphate ester was observed in the reaction of a 21-iodo-17α-hydroxy-20-ketone with silver dihydrogen phosphate.[13]

The rapid ring closure of the 21-diazo-2-pyrazoline IV in acetic acid evidently proceeds by attack of the pyrazoline nitrogen on the protonated diazoketone rather than by a prior dissociation of the diazonium cation. This mechanism is suggested by the low yield of the cyclization product obtained in the solvolysis of the iodoketone and the absence of detectable amounts of the 21-acetoxypyrazoline XII in the product obtained from the diazoketone in acetic acid even when excess acetate ion was added as an external nucleophile. In the latter case the product was not the cyclic ketone III, but the infrared spectrum contained the characteristic strained carbonyl band at 5.58 μ, together with additional carbonyl bands suggesting concomitant reaction at the —C=N— bond. The structure of this product is uncertain, but the same compound was obtained from IIIa under these conditions, and it is evident that the reaction of the diazoketone must have involved ring closure. A similar situation has been encountered in the reactions of a 21-diazoethyl-17α-hydroxy-20-ketone,[14] which furnishes the cyclic oxide with acids in heavily buffered media.

The much faster rate of cyclization of the 2-pyrazoline isomers IV and VI in both series compared to the respective 1-pyrazolines II and V suggests that the reaction is accelerated by participation of the —NH—N= group in IV and VI but not by the azo linkage in II and V. The rate of nitrogen evolution with the latter is comparable to that of unsubstituted diazoketones such as 21-diazopregnenolone. The rate of acid-catalyzed decomposition of

(10) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

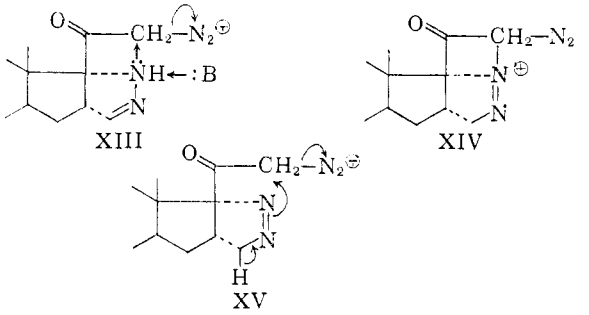
(11) C. Djerassi and C. T. Lenk, *ibid.*, **76**, 1724 (1954).

(12) K. v. Auwers and U. König, *Ann.*, **496**, 27 (1932).

(13) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker and J. M. Chemerda, *J. Am. Chem. Soc.*, **78**, 4814 (1956).

(14) Private communication from Dr. E. J. Agnello, Chas. Pfizer and Co.

diazoacetic esters has been shown[15] to depend upon the nature and concentration of the nucleophilic partner, and the effect of the —NH— group in the ring closure of the 2-pyrazolines is presumably due to concerted displacement of nitrogen from the diazonium ion, as in XIII. A similar participation of the —N̈=N̈— group in the 1-pyrazolines would be less important because of the lesser nucleophilic character of the unsaturated nitrogen. Moreover, the intermediacy of a form such as XIV appears unlikely because of steric strain,[16] so that the formation of the four-membered ring from the 1-pyrazoline probably occurs either concurrently with the shift of the double bond as in XV, or in a subsequent step, with the 2-pyrazoline as an intermediate. The pyrazoline isomerization (with 16α,17α-[3,1-(1-pyrazolino)]-5-pregnen-3β-ol-20-one) can be effected in glacial acetic acid at 70°, and the ring closure of II may therefore proceed *via* IV.

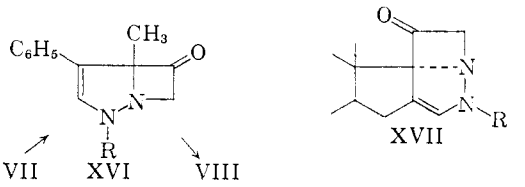


Although the formation of the steroidal 16α,17α-21-[3,1,1-(2-pyrazolino)]-20-one (III) and the diazabicyclo[3.2.0]hepten-6-one (VII) are completely parallel, the two systems differ markedly in chemical properties. The phenyl-substituted compound VII is exceptionally labile. Isomerization to the diazepinone VIII occurs under mild acidic or basic conditions; acylation furnishes derivatives of the Δ^3-tautomer XVI which in turn undergo a wide spectrum of rearrangements including reversion to the diazepinone VIII.[17] Attempts to effect parallel reactions with the steroidal bicyclic ketone have so far been unsuccessful. The cyclic ketone system is unaffected by acidic or basic hydrolytic conditions; vigorous acetylation leads to products involving a change in the —C=N— bond which are not yet well-defined, but no products involving the isomer XVII or a seven-membered ring have been recognized. This contrasting behavior can be ascribed to the opposite effects of the phenyl substituent in the case of VII and the fused five-membered ring in III. The transformation of VII to the Δ^3-tautomer XVI or the diazepinone VIII results in loss in energy with formation of a conjugated system with the benzene ring. A similar isomerization of the steroidal bicyclic ketone III to XVII would require the formation of an energetically unfavorable double bond exocyclic to the already strained five-membered D ring.

(15) The data are summarized by R. Huisgen, *Angew. Chem.*, **67**, 442 (1955).

(16) This type of intermediate was erroneously depicted in the cyclization of V in the first communication of this series, J. A. Moore, *J. Am. Chem. Soc.*, **77**, 3417 (1955).

(17) F. J. Marascia, Ph.D. Thesis, University of Delaware, 1958.



The stability of the diazabicycloketone system permitted a number of further transformations of III. Oppenauer oxidation of IIIb furnished the Δ^4-3-ketone XVIII, and microbial oxidation of this derivative with *Metarrhizium* sp. M 2313 led in good yield to a monohydroxylated product which by analogy[18] and chemical behavior is assigned the 11α-hydroxy structure XIX.[19] Chromic acid oxidation of this product provided the 11-ketone XX. The attempted conversion of the 3,11,20-triketone to the 3,20-bisketal, which was desired as intermediate in the preparation of the 11β alcohol, resulted in monoketalization to give the Δ^5-3-ethylene ketal XXI, with infrared bands at 5.58 and 5.86 μ. Reduction of this compound with sodium borohydride in methanol gave a product which, from the infrared (C.11 carbonyl 5.86 μ), was assigned the 11-keto-20-alcohol structure XXII. Experiments directed to the preparation, reduction and cleavage of the 3,20-bis-semicarbazone[20] of XX were erratic and largely unproductive, but a very small amount of product was obtained which from infrared data corresponded well with the 11β-alcohol XXIII. This derivative was obtained in larger quantities by microbial oxidation of XVIII with a *Cunninghamella* species (M 2047).[19,21]

The failure of XVIII to form a cyclic ketal at C.20 is noteworthy, since the carbonyl group displayed the expected high reactivity of cyclobutanones in other reactions. The facile hydride reduction and oxime formation have been mentioned, and a particularly characteristic reaction was the formation of stable addition products with methanol. Crystallization of the ketones III (a or b) from methanol under the usual conditions furnished very sparingly soluble compounds which from analysis and infrared (complete disappearance of the 5.58 μ carbonyl absorption and appearance of an OH band at 3.1–3.2 μ and ketal bands in the 8–9 μ region) are formulated as the 20β-methoxy hemiketals. The ketones were regenerated by treatment with acetic acid or prolonged refluxing in ethanol. Wheeler[22] has studied the hemiketal formation of cyclanones with alcohols, and has observed that the product from methanol and cyclobutanone is more stable than that with cyclohexanone, possibly due to the relief of I-strain in the former. The reverse

(18) 11α-Hydroxylation with organisms of this genus has been demonstration by Y. Kurosawa, *J. Agri. Soc. Japan*, **32**, 515 (1958), and the species *Metarrhizium* M 2313 has been found in unpublished work from these laboratories by O. D. Bird, F. E. Peterson, J. J. Pfiffner and G. French to convert compound S to 11-epicortisol.

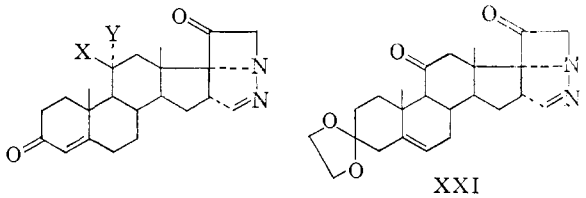
(19) We are indebted to O. D. Bird and F. E. Peterson, Parke, Davis and Co., for carrying out these microbiological oxidations.

(20) E. P. Oliveto, R. Rausser, L. Weber, E. Shapiro, D. Gould and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1736 (1956).

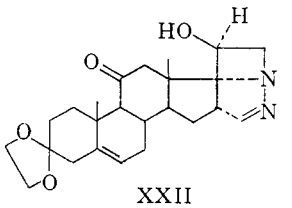
(21) This species has been shown in unpublished work to convert compound S to cortisol; other 11β-hydroxylations with this genus have been reported by K. M. Mann, F. R. Hanson and P. W. O'Connell, *Fed. Proc.*, **14**, 251 (1955).

(22) O. H. Wheeler, *J. Am. Chem. Soc.*, **79**, 4191 (1957).

relationship, however, obtains with these two ketones and ethanol because of the steric interaction of the larger alkyl group and the rigid four-membered ring. The results with the bicyclic ketones III and XVIII are consistent with these data, and indicate that while attack of nucleophiles such as borohydride, methanol and hydroxylamine at the rear (upper) face of the four-membered ring is rapid, the small ring size, together with the restriction imposed by the fused pyrazoline ring, combine to prevent dioxolane formation.



XXI



XXII

XVIII, X = Y = H
XIX, X = H, Y = OH
XX, X and Y = O
XXIII, X = OH, Y = H

Acknowledgment.—We are indebted to Mrs. M. Creger and Miss C. Klein for technical assistance, to Mr. E. Schoeb for infrared data, to Mrs. C. Spurlock and Mrs. V. Lee for the rotations and ultraviolet curves and to Mr. C. Childs and associates for microanalytical results.

Experimental[23]

3β-Hydroxy-5,16-etiadienic Acid.—Using the procedure of King[24] a solution of 25 g. of 5,16-pregnadien-3β-ol-20-one and 20.5 g. of iodine in 200 ml. of pyridine was warmed overnight on the steam-bath, cooled, and the tan pyridinium salt collected and washed with methanol–ether; 30 g. A suspension of this salt in 400 ml. of ethanol containing 20 g. of potassium hydroxide and 50 ml. of water was refluxed for 2 hours and then cooled, diluted with water and acidified. Extraction with ether furnished 12 g. (48%) of the 3-hydroxy acid, which was acetylated without further purification. In some runs a large amount of dark amorphous resin was obtained and the yield of acid was very low. A completely reliable, but much more laborious procedure, involved the conversion of the 16-dehydropregnenolone to the 21-iodo ketone *via* the 16,21-dienol acetate[11] and treatment with pyridine. In this way a light yellow pyridinium salt was obtained in 95% yield, and the over-all yield of acid after alkaline degradation was 72% based on 16-dehydropregnenolone.

3β-Acetoxy-5,16-etiadienic acid was prepared by refluxing the hydroxy acid, 18 g., in 250 ml. of glacial acetic acid for 20 hours. After removing the acetic acid, the residue was crystallized from methanol to give 16.9 g. (88%) of white prisms, m.p. 256–258°.[25]

(23) Infrared spectra were obtained in KBr disks. Only the more significant bands are recorded; in a few cases when different band positions were obtained on different instruments, both values are given, one in parentheses. Rotations are in $CHCl_3$ solution, about 1%, unless otherwise noted. Melting points were run on a Fisher-Johns block and are uncorrected.

(24) L. C. King, *J. Am. Chem. Soc.*, **66**, 1612 (1944).

(25) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **71**, 1487 (1938), report m.p. 253–254°.

16α,17α-[3,1-(1-Pyrazolino)]-21-diazo-5-pregnen-3β-ol-20-one Acetate (II).—A solution of 13.2 g. of the acetoxy acid and 20 ml. of thionyl chloride in 50 ml. of benzene was refluxed for 3 hours and then evaporated to a sirup. This was dissolved in benzene and the solution was again evaporated, and the treatment was repeated to remove traces of thionyl chloride. The pale yellow residue was dissolved in a little benzene plus 200 ml. of ether and the solution added to ethereal diazomethane prepared from 60 g. of nitrosomethylurea. Crystallization began in a few minutes, and after 30 min. the precipitate was collected; 8.3 g., m.p. 162–164° dec. Concentration of the ether solution gave an additional 5.57 g. (total yield 89%), m.p. 160–162°. Crystallization from methanol furnished cream-colored prisms, m.p. 162–164° dec., $[\alpha]_D$ +135°, λ_{max}^{ETOH} 274 mμ (ε 10,200); λ^{KBr} 4.75, 5.8, 6.1–6.15, 6.45 μ.

Anal. Calcd. for $C_{24}H_{32}O_3N_4$(424.5): C, 67.90; H, 7.60. Found: C, 67.93; H, 7.80.

16α,17α-[3,1-(2-Pyrazolino)]-21-diazo-5-pregnen-3β-ol-20-one (IV).—A solution of 500 mg. of II and 400 mg. of potassium hydroxide in 30 ml. of methanol containing 2 ml. of water was allowed to stand at room temperature for 6 hours. The pale green solution was then evaporated at reduced pressure, diluted with water and again evaporated until crystals were obtained; 200 mg. (45%). Recrystallization from methanol gave tiny needles, m.p. 215–225° dec., $[\alpha]_D$ +197° (MeOH), λ_{max}^{ETOH} 261 mμ (ε 13,600); λ^{KBr} 2.86, 3.10, 4.75, 6.1–6.2 μ.

Anal. Calcd. for $C_{22}H_{30}O_2N_4$ (382.5): C, 69.08; H, 7.91. Found: C, 69.12; H, 7.79.

16α,17α,21-[3,1,1-(2-Pyrazolino)]-5-pregnen-3β-ol-20-one Acetate (IIIa).—A solution of 3 g. of the acetoxy-1-pyrazoline II in 15 ml. of acetic acid was warmed for 30 min. on the steam-bath and was then boiled for 2–3 min. After cooling, water was added and the solution extracted with ether. After washing the ether solution with dilute potassium hydroxide solution and water it was dried and evaporated to give 2.3 g. (82%) of colorless crystals, m.p. 186–192°. Recrystallization from ethanol gave prisms, m.p. 194–195°, $[\alpha]_D$ +219°; λ^{KBr} 5.58 (5.61), 5.77, 6.25 μ.

Anal. Calcd. for $C_{24}H_{32}O_3N_2$ (396.5): C, 72.69; H, 8.14; N, 7.07. Found: C, 72.68; H, 8.16; N, 7.16.

Methyl Hemiketal of IIIa.—A solution of 25 mg. of the acetoxy ketone IIIa in 5 ml. of methanol was heated at 50° for 6 hours. During this period colorless crystals of the hemiketal separated. This material was collected; m.p. 194–195°, practically no depression on m.m.p. with starting material; λ^{KBr} 3.20, 5.77, 6.25, 7.80, 8.3, 8.4, 8.5, 8.6, 8.8 μ.

Anal. Calcd. for $C_{25}H_{36}N_2O_4$ (428.5): C, 70.06; H, 8.47; N, 6.54. Found: C, 69.95; H, 8.27; N, 6.56.

After prolonged heating in a relatively large volume of ethanol this compound dissolved, and on concentration and cooling, the ketone IIIa crystallized, m.p. 193–195°, infrared spectrum identical with that of IIIa.

Oxime of IIIa.—A solution of 200 mg. of IIIa and 200 mg. of hydroxylamine hydrochloride in 50 ml. of ethanol containing 2 ml. of pyridine was refluxed for 1 hr. After concentrating the solution, the oxime crystallized in very small white needles. Recrystallization from ethyl acetate furnished 120 mg. (58%), 267–271° dec.

Anal. Calcd. for $C_{24}H_{33}O_3N_3$ (411.5): C, 70.04; H, 8.08; N, 10.21. Found: C, 70.32; H, 8.17; N, 10.14.

16α,17α,21-[3,1,1-(2-Pyrazolino)]-5-pregnen-3β,20β-diol-3-Acetate.—To a solution of 100 mg. of the ketone IIIa in 15 ml. of ethanol at 25° was a solution of 50 mg. of sodium borohydride in 10 ml. of ethanol. Very small crystals began to separate after a few seconds; after standing for 1 hour excess hydride was destroyed with dilute acetic acid and the carbinol was collected. The tiny plates, 95 mg. (95%), m.p. 292–298°, were recrystallized from hot ethanol; m.p. 293–298°; λ^{KBr} 3.1, 5.80, 6.25 μ.

Anal. Calcd. for $C_{24}H_{34}O_3N_2$ (398.5): C, 72.33; H, 8.62; N, 7.03. Found: C, 72.05; H, 8.82; N, 6.99.

Oxidation of 80 mg. of the 20-alcohol with chromic anhydride–pyridine gave, after the usual work-up, 80 mg. of yellow crystals, m.p. 185–190°. After two recrystallizations from ethanol, colorless crystals of the ketone IIIa were obtained, m.p. and m.m.p. 190–192°, infrared identical with that of IIIa.

16α,17α,21-[3,1,1-(2-Pyrazolino)]-5-pregnen-3β-ol-20-one (IIIb). A. From IV.—A solution of 115 mg. of the hydroxy-2-pyrazoline (IV) in 1.5 ml. of glacial acetic acid was allowed to stand at room temperature for 1 hour (gas evolution was nearly complete after 20 min.). The solution was diluted with water, extracted with ether, and the ether solution washed with bicarbonate and water. Concentration of the dried ether solution gave 83 mg. (78%) of fine white needles, m.p. 234–236°.

B. From IIIa.—A solution of 175 mg. of the acetoxy ketone IIIa in 25 ml. of ethanol containing 250 mg. of potassium hydroxide and 2 ml. of water was warmed at 50° for 1.5 hours and then evaporated to dryness at reduced pressure. The residue was washed with water and then crystallized from ethanol to give 100 mg. (64%) of colorless needles, m.p. 229–236°. Recrystallization from ethanol gave white needles, m.p. 235–237°, mixed m.p. with material from A undepressed, $[\alpha]_D$ +233°; λ^{KBr} 3.0, 5.60, 6.25 μ.

Anal. Calcd. for $C_{22}H_{30}N_2O_2$ (354.5): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.52; H, 8.50; N, 7.85.

The methyl hemiketal was obtained by crystallization of the above material from methanol; m.p. 234–239°, $[\alpha]_D$ +185° (pyr.); λ^{KBr} 2.9–3.2, 6.25, 7.8 μ.

Anal. Calcd. for $C_{23}H_{34}N_2O_3$ (386.5): C, 71.47; H, 8.87; N, 7.25. OCH_3, 8.02. Found: C, 71.84; H, 8.67; N, 7.31; OCH_3, 7.73, 8.07.

16α,17α-[3,1-(1-Pyrazolino)]-21-iodo-5-pregnen-3β-ol-20-one (IX) Acetate.—A solution of 4.82 g. of 21-iodo-5,16-pregnadien-3β-ol-20-one[11] in 400 ml. of 0.1 *M* ethereal diazomethane was allowed to stand for 3 days at room temperature. The filtered solution was evaporated and the residue was crystallized from ether to give 4.25 g. (81%) of pale yellow powder, m.p. 148–153° dec. Recrystallization from ether gave nearly colorless needles, m.p. 154–155° dec., $[\alpha]_D$ +23°. A different crystalline form, m.p. 163–164°, was isolated on one occasion from an attempted acid isomerization. Recrystallization of the lower-melting form from ether on a seed of this material gave plates, m.p. 162–163° dec.; λ^{KBr} 5.85, 6.45 μ.

Anal. Calcd. for $C_{24}H_{33}O_3N_2I$ (524.4): C, 54.96; H, 6.34; N, 5.34. Found: C, 56.12; H, 6.46; N, 6.09.

16α,17α-[3,1-(2-Pyrazolino)]-21-iodo-5-pregnen-3β-ol-20-one Acetate (X).—A solution of 500 mg. of the 21-iodo-1-pyrazoline IX in 250 ml. of ether was shaken with 5 ml. of 6 *N* hydrochloric acid for 3 minutes. After washing with water and bicarbonate, the ether solution was concentrated and 300 mg. (60% conversion, 93% yield) of nearly colorless crystals of X, m.p. 165–168° dec., was obtained. From the mother liquor was isolated 178 mg. of unchanged IX, m.p. 154–155°. Recrystallization of the 300 mg. of first crop material from ether gave fine needles, m.p. 166–168° dec., $[\alpha]_D$ +114°; λ^{KBr} 3.00, 5.81, 5.91 (shld), 6.25 μ.

Anal. Calcd. for $C_{24}H_{33}N_2O_3I$ (524.4): C, 54.96; H, 6.34. Found: C, 55.53; H, 6.65.

16α,17α-[3,1-(2-Pyrazolino)]-5-pregnen-3β-ol-20-one Acetate.—A solution of 500 mg. of the 21-iodo-1-pyrazoline (IX) in 90 ml. of chloroform was shaken for 2 min. with 10 ml. of 47% hydriodic acid. The organic layer was then treated with 25 ml. of saturated aqueous potassium iodide solution and then diluted with ether. The ether solution was washed with thiosulfate solution and water and then dried and evaporated. The concentrated solution deposited 332 mg. (87%) of white prisms, m.p. 151–156°. Recrystallization from ether raised the m.p. to 154–158°; further recrystallization from methanol furnished small blocks, m.p. 142–144°, $[\alpha]_D$ +107°; λ^{KBr} 2.95, 5.85, 5.95, 6.32 μ.

Anal. Calcd. for $C_{24}H_{34}N_2O_3$ (398.5): C, 72.33; H, 8.60; N, 7.03. Found: C, 72.21; H, 9.16; N, 7.07.

For comparison the 1-pyrazolines were prepared from 16-dehydropregnenolone and the acetate by treatment of the respective ketones with excess diazomethane for 40 hr., and the previously unrecorded rotations were determined: **16α,17α-[3,1-(1-pyrazolino)]-5-pregnen-3β-ol-20-one**, m.p. 177–179° (lit. 178–179°[26]), $[\alpha]_D$ +22°; **acetate**, m.p. 164–166° (lit. 168–169°[26]), $[\alpha]_D$ +13°. Isomerization of the acetate in ether solution with 6 *N* hydrochloric acid as described for the conversion of IX to X furnished the 3β-acetoxy-2-pyrazoline, m.p. and mixed m.p. with material from the hydriodic acid reduction of IX, 141–144°.

(26) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

Cyclization of X.—A solution of the 21-iodo-2-pyrazoline (X) (155 mg.) in 40 ml. of ethanol was treated with a solution of 0.18 g. of silver nitrate in 10 ml. of 90% ethanol. A colloidal precipitate began to separate within a few minutes. After standing at room temperature for 3 hours the alcohol was removed and the residue was taken up in water and ether. The ether solution furnished 122 mg. of a colorless glass. Crystals were obtained after prolonged standing in ether, then after several recrystallizations from ether and then ethanol, 8 mg. (7%) of the cyclic ketone III, m.p. and mixed m.p. 192–193.5°, was obtained. The infrared spectrum was identical with that of a sample prepared from II. No other crystalline material was obtained.

16α,17α-[3,1-(1-Pyrazolino)]-5-pregnen-3β,21-diol-20-one Diacetate (XI).—Potassium acetate prepared by grinding together 1.00 g. of anhydrous potassium carbonate and 0.6 ml. of glacial acetic acid was added to a solution of 100 mg. of the iodopyrazoline IX in 40 ml. of acetone. After standing overnight at room temperature the mixture was diluted with water and filtered. Recrystallization of the resulting solid from ether gave 43 mg. (50%) of white needles, m.p. 166–168° dec., $[\alpha]_D$ −29°; λ^{KBr} 5.72, 5.85, 6.45 μ.

Anal. Calcd. for $C_{26}H_{36}N_2O_5$ (456.6): C, 68.39; H, 7.95; N, 6.14. Found: C, 68.32; H, 8.00; N, 6.07.

16α,17α-[3,1-(2-Pyrazolino)]-5-pregnen-3β,21-diol-20-one Diacetate (XII).—To a solution of 100 mg. of the 21-iodo-2-pyrazoline (X) in 30 ml. of acetone was added potassium acetate prepared as described above and the mixture was allowed to stand 40 hr. The product was isolated by dilution with water; recrystallization from ether gave 53 mg. (61%) of colorless needles, m.p. 163–164° dec., $[\alpha]_D$ +100°; λ^{KBr} 3.05, 5.73, 5.85, 6.30 μ.

Anal. Calcd. for $C_{26}H_{36}N_2O_5$ (456.6): C, 68.39; H, 7.95. Found: C, 68.06; H, 7.97.

Isomerization of 40 mg. of the 1-pyrazoline isomer XI with hydrochloric acid as described above furnished 30 mg. (75%) of XII, crystallized from ether, m.p. and mixed m.p. 163–164°, identical infrared spectra.

16α,17α,21-[3,1,1-(2-Pyrazolino)]-4-pregnen-3,20-dione (XVIII).—To a solution of 7.4 g. of 16α,17α,21-[3,1,1-(2-pyrazolino)]-5-pregnen-3β-ol-20-one in 250 ml. of cyclohexanone and 750 ml. of toluene was added 15 g. of aluminum isopropylate and the solution was heated to reflux for 45 minutes. The solution was cooled, washed with a dilute solution of sodium potassium tartrate and then twice with water and evaporated to dryness *in vacuo* at 60°. The residue was evaporated with water several times *in vacuo* to remove cyclohexanone polymers and then chromatographed over 20 g. of alumina in petroleum ether–methylene chloride. The fractions were crystallized from petroleum ether and combined and recrystallized from methylene chloride–petroleum ether to yield 4.3 g. (58%) of XVIII, m.p. 188–191°, $[\alpha]_D$ + 350° (0.61 EtOH), λ_{max}^{MeOH} 240 mμ (ε 17,000); λ^{KBr} 5.58 (20 C=O), 5.95 (3 C=O), 6.16 (Δ⁴) 6.29 μ (—C=N—).

Anal. Calcd. for $C_{22}H_{28}O_2N_2$ (352.4): C, 74.96; H, 8.01, N, 7.95. Found: C, 74.65; H, 7.83; N, 8.01.

16α,17α,21[3,1,1-(2-Pyrazolino)]-4-pregnen-11α-ol-3,20-dione (XIX).—Spores from 4 agar slants of *Metarrhizium* sp. M 2313 were suspended in 40 ml. of water and 5% by volume of the suspension was used to inoculate 600 ml. of the following medium: malt extract 50 g., sucrose 30 g., $NaNO_3$ 2 g., KCl 0.5 g., $MgSO_4 \cdot 7H_2O$ 0.5 g., $FeSO_4 \cdot 7H_2O$ 0.01 g., K_2HPO_4 1 g., pH 6.5. The inoculated medium was incubated at 25° for 72 hours on a rotary shaker at 240 r.p.m. Three per cent by volume of this vegetative culture was used to inoculate 24 flasks of the above medium (600 ml. each) and after 48 hours of incubation on the shaker, 300 mg. of 16α,17α,21-[3,1,1-(2-pyrazolino)]-4-pregnen-3,20-dione in 7.5 ml. of acetone was added to each flask. They were incubated at 25° on the shaker for 72 hours and then the whole culture was extracted 3 times with one-half volume of ethyl acetate each. The combined ethyl acetate solutions were evaporated to a small volume at 60° *in vacuo*. The residue was dissolved in 50 ml. of methylene chloride and diluted slowly with portions of dry ether to give two tarry fractions which were filtered off; on further dilution 2.9 g. of crystalline solid, m.p. 243–244°, was obtained. The tarry fractions were dissolved in methylene chloride and reprecipitated with ether and the mother liquor solids were chromatographed on alumina in ether–methylene chloride. The product was crystallized from methylene chloride–ether to give

5 g. (67%) of XIX, m.p. 245–247°, $[\alpha]_D$ +392°, λ_{max}^{EtOH} 240 mμ (16,730); λ^{KBr} 2.94 (-OH), 5.58, 6.07, 6.24, 6.32 μ.

Anal. Calcd. for $C_{22}H_{28}O_3N_2$ (368.4): C, 71.71; H, 7.66; N, 7.60. Found: C, 71.55; H, 7.88; N, 7.35.

16α,17α,21-[3,1,1-(2-Pyrazolino)]-4-pregnen-3,11,20-trione (XX).—A solution of 2 g. of 16α,17α,21-[3,1,1-(2-pyrazolino]-4-pregnen-11α-ol-3,20-dione in 30 ml. of glacial acetic acid was cooled in ice and mixed with a cold solution of 750 mg. of chromic anhydride in 5 ml. of water and 15 ml. of acetic acid. The mixture was kept at 0° for 10 min. and then at 25° for 3 hours. The solution was poured into 500 ml. of water, 500 ml. of ethyl acetate was added and the aqueous layer was made slightly alkaline by adding a strong solution of sodium hydroxide while cooling with ice. The ethyl acetate layer was separated and the water layer was again extracted with ether–ethyl acetate 1:1. The combined organic extracts were washed with water, dried over magnesium sulfate and evaporated. The residue was crystallized from methylene chloride–ether to yield 1.3 g. (65%) of XX, m.p. 229–230°. After passage over a column of alumina, crystallization from ether gave prisms, m.p. 230–233°, $[\alpha]_D$ +440°, λ_{max}^{MeOH} 237 mμ (17,000); λ^{KBr} 5.60, 5.86, 6.0, 6.16, 6.31 μ.

Anal. Calcd. for $C_{22}H_{26}O_3N_2$ (366.4): C, 72.10; H, 7.15; N, 7.65. Found: C, 71.80; H, 7.13; N, 7.77.

16α,17α,21-[(3,1,1-(2-Pyrazolino)]-4-pregnen-11β-ol-3,20-dione (XXIII).—A 5% by volume aqueous spore suspension of *Cunninghamella* sp. M 2047 was used to inoculate three 100-ml. portions of medium as described above for XIX, and the medium was incubated for 72 hours at 27° on a rotary shaker at 240 r.p.m. Eight 600-ml. portions of this same medium were each inoculated with 3% by volume of the vegetative culture and were incubated for 48 hours. To each of the flasks was added 300 mg. of XVI dissolved in 7.5 ml. of acetone and incubation was continued on the shaker for an additional 24 hours. The whole culture was extracted 3 times with 0.5 volumes of methylene chloride and the combined extracts were concentrated under reduced pressure to dryness. The residue was chromatographed over a column of 30 g. of alumina. Fractions 16 through 18 (ether–methylene chloride 3:2) were collected and recrystallized from ether–methylene chloride to give 140 mg. (6%) of XXIII, m.p. 255–258°, $[\alpha]_D$ +450°, λ_{max}^{EtOH} 240 mμ (17,600); λ^{KBr} 2.94, 5.58, 6.00, 6.20, 6.29 μ.

Anal. Calcd. for $C_{22}H_{28}O_3N_2$(368.4): C, 71.71; H, 7.66; N, 7.60. Found: C, 71.61; H, 7.40; N, 7.92.

In the preparation of XXIII from XX, 500 mg. of the triketone was dissolved in a mixture of 750 mg. of pyridine, 5 ml. of water and 30 ml. of methanol containing 1.0 g. of semicarbazide hydrochloride. The solution was refluxed for 18 hours, and then evaporated to one-half volume and slowly diluted with water. The white precipitate was filtered, washed and dried to give 620 mg. of semicarbazone, m.p. < 200°. Without purification this material was dissolved in 18 ml. of tetrahydrofuran and 9 ml. of water and treated with 400 mg. of potassium borohydride. The solution was refluxed for 7 hr. during which an additional 100 mg. of hydride was added. After acidification with acetic acid the solution was concentrated, diluted with water and the precipitate collected; 500 mg. This product was hydrolyzed by refluxing for 6 hr. with a mixture of 7.5 ml. of acetic acid, 2.5 ml. of water, 1.5 ml. of pyruvic acid and 5 ml. of tetrahydrofuran. The solution was evaporated to dryness at 60° and the residue was washed with water and dried, giving 200 mg. of pale tan powder. Chromatography on 4 g. of alumina in methylene chloride–ether gave 10 mg. of colorless crystals of XXIII, m.p. 245–247°, infrared spectrum identical with material obtained from microbiological oxidation.

3-Ethylenedioxy-16α,17α,21-[3,1,1-(2-Pyrazolino)]-5-pregnene-11,20-dione (XXI).—A solution of 500 mg. of XX in 10 ml. of ethylene glycol, 65 ml. of benzene and 50 mg. of *p*-toluenesulfonic acid was heated for 6 hr. under a reflux condenser fitted with a tube for water removal. The solution was cooled, made alkaline with 20% sodium hydroxide solution and extracted with 50 ml. of methylene chloride and 50 ml. of ether. The organic layer was washed with water, dried, evaporated to dryness *in vacuo* and the residue was chromatographed over 10 g. of alumina using ether and methylene chloride. The crystalline fractions were combined and crystallized from ether to yield 250 mg. (45%) of XXI, m.p. 238–240°, $[\alpha]_D$ + 202°; λ^{KBr} 5.59, 5.87, 5.89 (weak, Δ^5), 6.30.

Anal. Calcd. for $C_{24}H_{30}O_4N_2$ (410.5): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.32; H, 7.41; N, 6.67.

3-Ethylenedioxy-16α,17α,21-[3,1,1-(2-pyrazolino)]-5-pregnen-20β,ol-11-one (XXII).—To a solution of 100 mg. of XIX dissolved in 50 ml. of methanol was added a solution of 100 mg. of sodium borohydride in 3 ml. of water. An additional 10 ml. of methanol was added and the solution was warmed to 50° until all the solid had dissolved and then was allowed to stand at 25° for 7 hr. After concentrating on the steam-bath the solution was diluted with water and the crystalline precipitate was collected, washed with water and dried, giving 70 mg. (70%) of colorless fine needles, m.p. 305–310° dec., $[\alpha]_D$ + 195°; λ^{KBr} 3.05, 5.86, 6.29 μ.

Anal. Calcd. for $C_{24}H_{32}O_4N_2$ (412.5): C, 69.87; H, 7.82; N, 6.79. Found: C, 69.68; H, 7.75; N, 6.69.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

π-Complexes. II.[1] Charge Transfer Spectra of π-Complexes Formed by Tetracyanoethylene with Polycyclic Aromatic Hydrocarbons and with Heteroaromatic Boron Compounds[2]

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The charge transfer spectra of the π-complexes formed by tetracyanoethylene with a number of polycyclic aromatic hydrocarbons and with various heteroaromatic compounds of boron have been measured in chloroform solution. The results for the hydrocarbons were consistent with the molecular orbital treatment given in Part I.[1] The results for the boron compounds lead to estimates of the molecular orbital parameters for boron.

In the first paper[1] of this series a simple molecular orbital treatment was given of the charge transfer spectra of the complexes formed between aromatic compounds and acceptors such as trinitrobenzene, picric acid or chloranil. Complexes of this kind are treated as weak π-complexes formed by mutual interaction of the π-orbitals of the donor (A) and acceptor (B). Since the interaction is weak it should lead to only relatively minor changes in the energies of the individual orbitals; the absorption bands of A and B should consequently appear almost unchanged in the spectrum of the complex. However there is the additional possibility in the complex of charge transfer transitions in which an electron initially occupying an orbital i of A jumps into one of the empty orbitals j of *B*. The transition energy ΔE_{ij} for this process should be given by

$$\Delta E_{ij} = B_j - A_i \qquad (1)$$

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