Heterocyclic Studies. XVIII.[1] Some Reactions of a Steroidal 1,2-Diazabicyclo[3.2.0]heptenone[2]

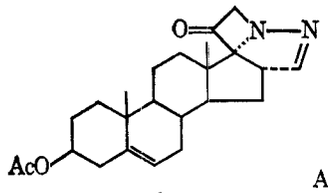
TATSUO YAMAUCHI[3] AND JAMES A. MOORE

Department of Chemistry, University of Delaware, Newark, Delaware

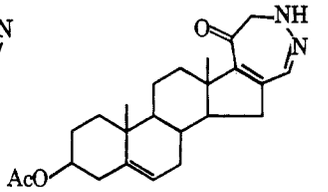
Received February 25, 1965

The addition of acetyl chloride to the ketone 1 followed by treatment with water or alcohols leads to the 2′-acetyl-3′β-hydroxy 20-ketone 4 or the 3′-alkoxy derivatives 8. These compounds are interconvertible under acid conditions. The corresponding 20-alcohols were also prepared. The oximes of 1 and 2′-acetyl-3′-methoxy ketone undergo fission under conditions of the Beckmann rearrangement to give 2′-cyanomethylandrosteno-[16,17:3′,4′]-2′H-pyrazole 11. Both 1′H- and 2′H-pyrazoleacetonitriles were obtained by alkylation of the unsubstituted pyrazole 15. Characteristic ultraviolet and n.m.r. differences of the ring-D pyrazoles were correlated with those in the androstano[3,2:3′,4′]pyrazole series.

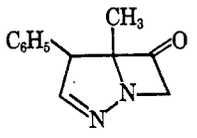
The preparation and some nuclear transformations of compound 1, with the 1,2-diazabicyclo[3.2.0]heptenone system fused to the steroid D ring, were reported earlier.[4] In preliminary studies of the heterocyclic chemistry of 1, conversion to the diazepinone 2 was accomplished, and the acylation of 1 was studied briefly.[5] We now report some further reactions of 1 which were surveyed in an effort to effect useful transformations to other heterocyclic steroids by rearrangements paralleling those that have been observed with the versatile methylphenyl-substituted counterpart 3.[1,6]



1

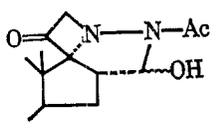


2

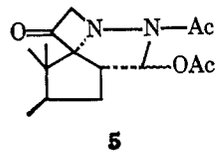


3

Acetylation Products.—As discussed previously,[5] the heterocyclic system of 1, in contrast to 3, is quite resistant to the action of acid or base, but reaction with acylating agents proceeds quite readily. Acetyl chloride and acetic anhydride were both reported to give the addition products 4 and 5. It has now been found that the reaction of 1 with acetyl chloride in pyridine followed by the addition of water gives, as expected, mainly 4; contrary to the earlier report, the diacetyl derivative 5 is produced in trace amounts at most. The major product with acetic anhydride is 5, but 4 was also isolated. In addition to 4, a by-product was obtained in the reaction of 1 with acetyl chloride in low and erratic yield. This compound was of considerable interest since it contained only a single nitrogen atom, but structural information could not be obtained owing to the lack of a reproducible method of preparation.



4



5

The formation of the carbinol 4 clearly involves the hydrolysis of an intermediate addition product, as observed[1] with the diazoacetylpyrazoline precursor of 3; this might be either a pyridinium salt or the 3′-chloro compound. Addition of alcohols to the reaction mixture of 1 and acetyl chloride–pyridine gave the respective 3′-alkoxy derivatives. Attempts to detect a chloro compound by t.l.c. were not successful, since the reaction mixture was ultimately exposed to moisture and 4 was obtained. Treatment of the alcohol 4 with phosphorus oxychloride in pyridine gave a reaction mixture which behaved like that obtained from 1 and acetyl chloride, but again only solvolysis products were isolated.

The reaction of 1 with acetyl chloride in benzene, without pyridine, gave two other products. The major component was a sparingly soluble, high-melting compound which was very similar to the 3′-hydroxy compound 4 in infrared and n.m.r. spectra except for the absence of the OH group. This product on hydrolysis led to 4, and was formed when 4 was refluxed in benzene saturated with hydrogen chloride. These properties are consistent with the bimolecular ether 9, and the composition agreed well with this structure, which represents simply another product of adventitious hydrolysis. The other product from the reaction, isolated after hydrolysis, was the diazepinone 7,[5] obtained in the same yield (16%) as in the reaction of 1 with acetic acid–sodium acetate.

Some additional transformations in this 2′-acetyl series are summarized in Chart I. The alkoxy derivatives 8 were readily obtained by treatment of the 3′-hydroxy compound with the alcohol in the presence of sulfuric acid; acid hydrolysis of the ethers gave the alcohol. These reactions parallel those observed in the methylphenyl series (3)[1] and are presumably SN1 displacements facilitated by the adjacent nitrogen function. In the derivatives of 3, the *endo* configuration, corresponding to that shown in 4–8 (Chart I) was assigned[1] to the oxygen substituents on the basis of steric factors and the absence of spin coupling in

(1) Part XVII: J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org.* Chem., **31**, 34 (1966).

(2) Supported by Grant A-3629 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

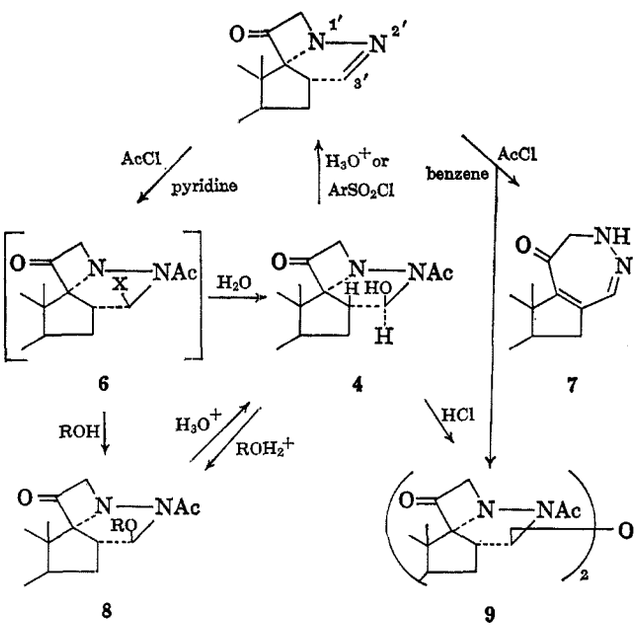
(3) On leave from the Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.

(4) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962).

(5) J. A. Moore and L. J. Pandya, *J. Org. Chem.*, **29**, 336 (1964).

(6) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *J. Am. Chem. Soc.*, **84**, 3022 (1962).

CHART I



the protons corresponding to H-3′ and H-16β in **4**. A similar absence of splitting in the H-3′ peak (δ = 5.7–5.9 p.p.m.) in the spectra of **4** and the ethers **8** leads us to a tentative conclusion of the same *endo* configuration (steroid β configuration in projection).

A characteristic feature of the n.m.r. spectra of all of the 3′-substituted compounds (**4**, **8**, and **9**) was the appearance of the C-21 methylene proton signal as a *single* two-proton peak (δ = 4.37 p.p.m.). The H-21 peak in the unsaturated ketone **1** was a well-defined AB pattern, δ_A = 4.44 p.p.m., δ_B = 4.02 p.p.m., J_{gem} = |17| c.p.s.; there was further splitting of these lines ($J \cong 1$ c.p.s.) with the H-3′ peak (7.05 p.p.m.). The collapse of the splitting pattern in the spectra of the 3′-substituted compounds, which was observed only with the hydroxy compound in the methylphenyl series, must be caused by equivalence of the chemical shifts ($\delta_A = \delta_B$) induced in some manner by the *endo* oxygen functions. The C-20 carbonyl stretching frequency was essentially the same (1800 ± 5 cm.$^{-1}$) in **1** and all of the C-3′-substituted compounds.

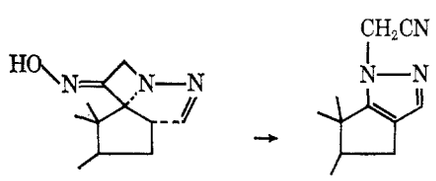
Although the methylphenyl and steroid compounds exhibited similar properties in these solvolytic reactions, there is a fundamental difference with respect to elimination in the C-3′,16β system of **4** and other derivatives. Acylation of the methylphenyl ketone **3** leads directly to the 2-acetyl-Δ^3 compound, and all of the bicyclic ketones related to **3** can be transformed to 1,2-diazepine or 1-aminopyridine derivatives by elimination.[1] As noted previously,[5] the introduction of a 3′,16 double bond in the rigid skeleton of **4** would present an insurmountable steric requirement in the conversion of C-16 to an sp^2 center. The resistance to elimination in this sense is seen in the regeneration of the Δ^2 double bond on vigorous acid hydrolysis of **4** and, remarkably, also on treatment with *p*-toluenesulfonyl chloride in pyridine, presumably by elimination of acetyl chloride.

Several other reactions were explored in an effort to delineate the chemical properties of the 2′-acetyl-3′-hydroxy system of **4**. No products were isolated from attempted oxidations. The alcohol was readily attacked by base, and a low yield of an acidic product was obtained. On exposure to air the reaction mixture became bright red and a trace of violet product, λ_{max} 517, 552 mμ, was isolated. Analysis of the acid indicated the presence of only one nitrogen atom, but the small amount of material precluded adequate characterization.

Reduction of the 3′ alcohol **4** with sodium borohydride resulted in a complex mixture. A very small amount of the 3′,20-diol was obtained, but the other products were not identified. The same diol was prepared by treatment of the $\Delta^{2'}$-20 alcohol[4] with acetyl chloride, followed by hydrolysis, and the 3′-methoxy-20-ξ-ol was obtained by addition of methanol to the acetylation reaction. The 20-hydroxyl group was previously found to be resistant also to acetylation with acetic anhydride.[4]

Fission of Bicyclic Oximes.—Reactions of the oximes presented another possibility for obtaining different functional derivatives and ring systems from the bicyclic ketones. The $\Delta^{2'}$-oxime **10**[4] and the 2′-acetyl-3′-methoxy derivative **12** are readily prepared under the usual conditions. Attempts to reduce **10** to a 20-amine with lithium aluminum hydride led to mixtures of five or six components (t.l.c.) which were not further explored.

The reaction of **10** with either phosphorus oxychloride or thionyl chloride gave in 70% yield a single product whose composition corresponded to a dehydration product. The loss of water from an oxime under Beckmann rearrangement conditions suggested a "second-order" rearrangement or fission[7] to a nitrile, a reaction which is well known with oximes of α-amino ketones.[8] In the case of **10**, the product of a



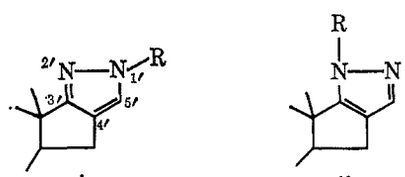
10 **11**

Beckmann fission would be the androsteno[17,16:-3′,4′]-2′H-pyrazole-2-acetonitrile **11**.[9] This interpretation was initially suspect because of the absence of any detectable C≡N absorption in the infrared spec-

(7) P. A. S. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 501.

(8) C. A. Grob, *Bull. soc. chim. France*, 1360 (1960.)

(9) The name androsteno[17,16-*c*]pyrazole has been used previously.[10] The genetic numbering adopted here, *e.g.*, [17,16:3′,4′], seems preferable for such heterocyclic steroids, since it provides a systematic basis for numbering the heterocyclic component. The isomers i and ii are designated 1′H and



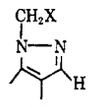
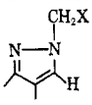
i ii

2′H in order to retain the same numbering throughout the series rather than reversing the direction to keep the substituted nitrogen numbered 1′ as is done with monocyclic pyrazoles.

(10) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Med. Chem.*, **6**, 793 (1963).

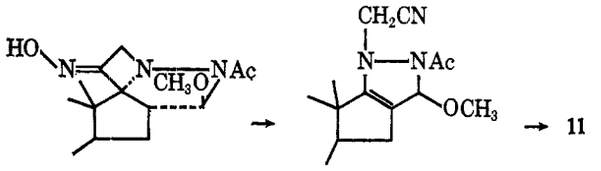
TABLE I

SPECTRAL DATA ON ANDROSTENO[16,17:4′,3′]PYRAZOLES

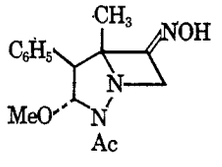
	X	δ, p.p.m. C-18 CH_3	δ, p.p.m. -N- CH_2-X	δ, p.p.m. C-5′ H	λ_{max}^{EtOH}, mμ (ε)
2′-H series	-CN	1.10	4.95	7.22	229.5 (5700)
	$-CO_2CH_3$	1.01	4.78	7.20	
	$-CO_2C_2H_5$	1.02	4.77	7.20	
1′-H series	-CN	1.03	5.00	7.12	231.5 (9000)
	$-CO_2CH_3$	1.03	4.85	7.07	

trum,[11] but n.m.r. data (Table I) and the synthesis described below confirmed structure **11**.

The fission of α-amino ketones is a typical fragmentation reaction and is facilitated by an antiparallel geometry such as obtains in acyclic *anti*-oxime derivatives.[8] This steric situation would not be realized with either geometrical isomer of the oxime **10** because of the constraint of the four-membered ring, but the lack of "frangomeric assistance"[8] is evidently compensated by the relief of strain as well as the gain of pyrazole resonance in the product. The methoxyacetyl oxime **12** was also converted to the pyrazole **11** with thionyl chloride; since the ketone **8** (R = CH_3) was not affected by similar treatment with thionyl chloride, the fission of **12** presumably proceeds through the methoxyacetylpyrazoline **13**. The corresponding methoxyacetyl bicyclic oxime **14**[1] gave no detectable pyrazole.



12 **13** **11**

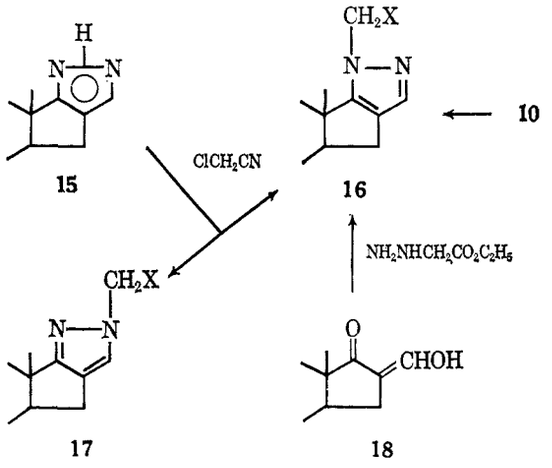


14

The formation of the pyrazole **11** from **10** opened the possibility of definite structural assignments of N-substituted androsteno[17,16:3′,4′]pyrazoles prepared by other methods. A parallel situation has been exploited in the 3(5)-methyl-4-phenylpyrazole series.[12] As discussed in the latter case, the structures of pyrazoles obtained in alkylations or ring closures with unsymmetrical hydrazines cannot be specified with assurance from the course of such reactions.

The alkylation of 3β-hydroxy-5-androsteno[17,16:-3′,4′]pyrazole (**15**) with chloroacetonitrile, with or without the addition of base, gave a mixture of the two nitriles **11** and **17**, each in about 30% yield. Although the isomers were readily separated by crystallization of the 3-acetates, no resolution was observed in thin layer or alumina chromatography, and quantitative estimation of the isomer ratio was not possible. In several experiments there appeared to be no significant excess of one over the other. The lower melting nitrile was identical with the product obtained from the oximes **10** and **12**.

From the condensation of 16-hydroxymethylenedehydroepiandrosterone with ethyl hydrazinoacetate, the ethyl ester **16** (X = $CO_2C_2H_5$) was isolated in low yield. After saponification of the remaining material, only the 2′-acetic acid **16** (X = CO_2H) was obtained. While a minor amount of the 1′ isomer might have gone undetected, this condensation appears to give predominately the 2′-substituted pyrazole. This result coincides with the previous finding[13] in the condensation of hydrazinoacetic ester with α-ethoxymethylene-α-phenylacetone, in which the major product arose from attack of the NH_2 group of this hydrazine at the aldehyde carbonyl group.



15 **16** **10** **17** **18**

N.m.r. and ultraviolet data in the two series of substituted pyrazoles are summarized in Table I. The difference in the peak positions of the 5′-pyrazole proton in the two series, 6 c.p.s. with the nitriles and 8 c.p.s. with the esters, is in the same direction and is precisely the same magnitude (8 c.p.s. for the methyl esters) as that observed in the pyrazole proton peaks of the 3- and 5-methyl-4-phenylpyrazole-1-acetic acids.[12] It may be noted that the position of substitution in the pyrazole ring has little effect on the chemical shift of the C-18 methyl group.

The preparation of N-methyl derivatives of the [17,16:3′,4′]pyrazole system in the estratriene series has recently been reported.[10] The same N-methylpyrazole was obtained by alkylation with dimethyl sulfate or condensation of 16-formylestrone 3-methyl ether with methyl hydrazine. This product was tentatively assigned the N-1′ methyl structure (corresponding to **17**) by comparison of the ultraviolet maximum with those of the N-methylandrostano-[3,2:3′,4′]pyrazoles **19** and **20**.[14] The value for **19** used in this comparison was not correct, however, and the 223-mμ maximum reported for the 1′-methylestratrieno[17,16:3′,4′]pyrazole is evidently that of the ring-A chromophore and is not characteristic for this

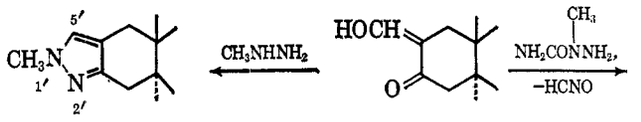
(11) The intensity of C≡N bands varies widely and may be depressed markedly by neighboring heteroatoms. C≡N absorption is reported to be completely lacking in the structurally similar Reissert compounds: W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(12) C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30**, 1892 (1965).

(13) J. A. Moore and C. L. Habraken, *ibid.*, **30**, 1889 (1965).

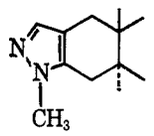
(14) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

pyrazole system. The aromatic A ring in the estrone derivative obscures the pyrazole n.m.r. signal as well as the ultraviolet maximum, and no comparison with the data in Table I can be made.



19

λ_{max} 231 mμ (ε 7100)
δ (5'H) = 7.37 p.p.m.[15]



20

λ_{max} 229 mμ (ε 4900)
δ (5'H) = 7.55 p.p.m.[15]

In the N-methylandrostano[3,2:3',4']pyrazole series, both N-methyl derivatives **19** and **20** were prepared as indicated[14]; the structural assignment was based on the formation of **20** by pyrolysis of the N-methylsemicarbazone, with the usual assumption of attack of the more reactive nitrogen in the substituted hydrazine at the aldehyde carbonyl. It was later found, however, that the product obtained from the semicarbazone was a mixture of isomers[16]; a pure sample was obtained by reduction of the Δ^4-pyrazole.

The ultraviolet and n.m.r. data for the 1'- and 2'-substituted pyrazole in the ring-D series (Table I) and the ring-A series (see formulas) are completely consistent with the previous structural assignments in the latter series. The 2-mμ difference in ultraviolet maxima is evidently quite characteristic for pairs of 1,3,4- and 1,4,5-trialkylpyrazoles, but the n.m.r. data provide a more emphatic distinction. From the data reported here and related values for 4-phenylpyrazoles,[12] it appears to be a general rule that the 3-proton in a 1-alkyl 5-substituted pyrazole is less shielded than the 5-proton in the isomeric 1-alkyl 3-substituted pyrazole.

Experimental Section[17]

Acylation of Bicyclic Ketone 1.—To a solution of 2.0 g. of **1** in 80 ml. of pyridine at 0° was added 1.5 ml. of acetyl chloride in one portion. A white precipitate formed immediately and the suspension was stirred for 1.5 hr. at 0°. The mixture was poured into 400 ml. of ice–water, and, after standing several hours, the milky suspension was extracted with ether and then with chloroform. After washing with water, the ether solution was evaporated to a semisolid residue; crystallization of this material from ethyl acetate gave 600 mg. of crystalline **4**, m.p. 200–203°, identical (infrared) with material previously prepared,[5] and 556 mg. of amorphous solid. Chromatography of the latter material gave an additional 160 mg. of **4** (total 760 mg., 36%).

Evaporation of the chloroform extract furnished 700 mg. of residue which was crystallized from methanol to give 160 mg. of crystals, m.p. 252–254° dec., designated as substance B. Recrystallization from methanol gave prisms: m.p. 255–258° dec.; ν^{KBr} 3450 (OH), 2980 (C–H), 1770, 1720 (OAc), 1660 (N–Ac), 1500, 1450, 1360, 1250 (ester C=O), 1195, 1032, 927 cm.$^{-1}$; n.m.r. δ = 0.90 (C-18), 1.05 (C-19), 2.03, 2.07 (two CH_3CO), 5.42 (two protons, C-6 H and ?), 6.48 p.p.m. (one proton).

Anal. Calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13; O, 21.45. Found: C, 66.69, 66.79; H, 7.82, 7.83; N, 3.37; O, 21.41.

Acetylation of substance B with acetic anhydride or acetyl chloride and pyridine in the usual way gave a monoacetyl derivative which was crystallized from ethyl acetate–hexane: m.p. 275–278° dec.; ν^{KBr} 3500 (sharp, NH?), 1785, 1740, 1680, 1500 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_7$: C, 66.23; H, 8.03; N, 2.96. Found: C, 66.42; H, 7.73; N, 2.86.

3β-Acetoxy-2'-acetyl-3'β-methoxy-16α,17α,21-(3',1',1'-pyrazolidino)-5-pregnen-20-one (8, R = CH_3). A. From 4.—A solution of 100 mg. of the 3'-hydroxy ketone **4** in 10 ml. of methanol containing 5 drops of concentrated sulfuric acid was stored at 25° for 1 hr., neutralized with sodium bicarbonate, and evaporated to dryness. The residue was acetylated with acetic anhydride–pyridine and the crude product was chromatographed on alumina. The first fractions eluted with benzene were crystallized from acetone to give 36 mg. of prisms: m.p. 194–197°; ν^{KBr} 1800, 1745, 1670–1680 (split) (C=O) cm.$^{-1}$; n.m.r. 0.97 (C-18), 1.03 (C-19), 2.03 (OAc), 2.30 (N–Ac), 3.35 (–OCH_3), 4.37 (C-21), 5.37 (C-6), 5.68 (C-3') p.p.m. See Table II for analysis.

B. From 1.—To a solution of 100 mg. of the $\Delta^{2'}$-bicyclic ketone **1** in 4 ml. of pyridine was added 0.8 ml. of acetyl chloride. The solution was stirred at 0° for 2 hr. with exclusion of moisture and then 2 ml. of methanol was added. The solution was then evaporated *in vacuo* and the solid residue was washed with water and then extracted with ether. Concentration of the ether solution and dilution with hexane gave 60 mg. of colorless crystals of **8** (R = CH_3), m.p. 190–193°. Recrystallization from ether–hexane gave prisms, m.p. 193–196°, identical (infrared) with material prepared by method A.

By substitution of other alcohols for methanol, the foregoing procedure was used, with minor modifications in detail and recrystallization solvents, to prepare the other 3'-alkoxy derivatives summarized in Table II.

Anal. Calcd.: N, 5.95. Found: N, 5.88.

Reaction of 4 with Phosphorus Oxychloride.—A solution of 200 mg. of **4** in 9 ml. of pyridine containing 0.4 ml. of $POCl_3$ was allowed to stand at 0° for 4 hr. After pouring into water, the mixture was extracted with butanol; the butanol solutions were washed with water and evaporated *in vacuo* to give 188 mg. of solid residue. On chromatography on alumina, 70 mg. of colorless solid was obtained from the first benzene eluates. Crystallization from ethyl acetate–hexane gave fine needles: m.p. 202–204°; $\nu^{KBr}_{C=O}$ 1800, 1745, 1670 cm.$^{-1}$. This product was identified as the 3'-butoxy derivative **8** (R = Bu) by the correspondence of the infrared spectrum in all details with a sample prepared as described above (Table II, R = *n*-Bu).

Later fractions eluted from the chromatogram with benzene gave mixtures of **8** (R = Bu) and another product which was not present in large enough amounts to permit characterization.

Acetylation of 1 with Acetyl Chloride in Benzene. Formation of 7 and 9.—A solution of 1.00 g. of **1** in 200 ml. of benzene containing 10 ml. of acetyl chloride was refluxed for 7.5 hr. and was then evaporated *in vacuo* to dryness. Crystallization of the yellow residue from benzene–ether gave 276 mg. of nearly colorless needles of the **bimolecular ether 9**, m.p. 251–253° dec. Further recrystallization from benzene–ether and acetone gave colorless crystals: m.p. 259–263° dec.; $\nu^{KBr}_{C=O}$ 1800, 1745, 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{52}H_{70}N_4O_3$: C, 69.77; H, 7.88; N, 6.26. Found: C, 69.71; H, 8.05; N, 6.56.

The solid residue (850 mg.) from the crystallization of **9** could not be separated cleanly by crystallization of chromatography and was therefore subjected to hydrolysis by refluxing for 3 hr. in 500 ml. of ethanol–water (4:1) containing 2% sulfuric acid. After evaporation and addition of water, the precipitated yellow solid was collected (500 mg.) and the filtrate was extracted with chloro-

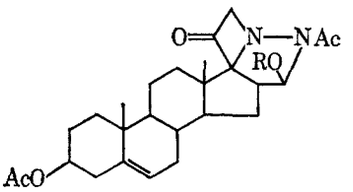
(15) We are indebted to Dr. A. J. Manson for communicating these values.

(16) D. K. Phillips and A. J. Manson, *J. Org. Chem.*, **26**, 2886 (1963).

(17) Melting points were observed with a Fisher-Johns apparatus with a calibrated thermometer. Alumina for chromatography was Woehlm neutral grade, activity IV, unless otherwise specified; 20–30 times the weight of sample was used. All reaction mixtures were initially examined by thin layer chromatography using 5 × 20 cm. plates coated with silica gel G (E. Merck), nominal thickness 0.5 mm., dried at 100° for 1 hr. Plates were developed with chloroform–isopropyl alcohol (25:1 or 25:3), sprayed with 10% H_2SO_4 or $SbCl_3$ in chloroform, and then charred. After chromatography, crystallization was in general carried out only with fractions which gave a single spot. All substances indicated as single compounds were homogeneous by t.l.c. Infrared spectra were recorded in KBr pellets with a Perkin-Elmer Infrared Model 137. N.m.r. spectra were run in $CDCl_3$ solutions (30 mg./0.4 ml.) with internal tetramethylsilane (δ = 0 p.p.m.) with a Varian A-60 spectrometer.

TABLE II

3β-ACETOXY-2′-ACETYL-3′β-ALKOXY-16α,17α,21-(3′,1′,1′-PYRAZOLIDINO)-5-PREGNEN-20-ONES



R	M.p., °C.	δ (H-3′), p.p.m.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
CH_3	194–197	5.68	$C_{27}H_{38}N_2O_5$[a]	68.91	8.14	68.73	8.28
C_2H_5	198–202	5.75	$C_{28}H_{40}N_2O_5$	69.39	8.32	69.55	8.38
i-C_3H_7	202–205	5.82	$C_{29}H_{42}N_2O_5$	69.85	8.49	69.68	8.45
n-Bu	203–205	5.73	$C_{30}H_{44}N_2O_5$	70.28	8.65	69.97	8.66
Cyclo-C_6H_{11}	255–257	5.88	$C_{32}H_{46}N_2O_5$	71.34	8.61	71.20	8.66

[a] *Anal.* Calcd.: N, 5.95; Found: N, 5.88.

form, giving 118 mg. of solid on evaporation. Fractional crystallization of the 500 mg. of precipitate from chloroform–methanol gave 160 mg. of 3β-hydroxy-1′,7′-dihydro-5,16-androstadieno-[16,17:4′,5′]-6′H-1′,2′-diazepine-6′-one (**7**), as yellow crystals, m.p. 249–254°, identical with an authentic specimen[5] by infrared, mixture melting point, and t.l.c. From the more soluble fraction was obtained 66 mg. of the 3β-hydroxy-3′-ethoxy bicyclic ketone **8**, R = Et, identified by t.l.c. with material described below obtained by hydrolysis of pure **9**. Chromatography of the remaining material from the fractional crystallization combined with the solid from the chloroform extract gave an additional 13 mg. of **8** (R = Et) and 27 mg. of impure **7** together with mixed fractions.

Hydrolysis of 9.—A solution of 200 mg. of the bimolecular ether **9** in aqueous ethanolic sulfuric acid was refluxed for 3 hr. and evaporated. Water was added and the precipitated solid was collected, dried, and chromatographed on alumina. The solid eluted with benzene–chloroform (10:1) was crystallized from ethyl acetate to give 56 mg. of needles, m.p. 228–230°, identical (mixture melting point and infrared spectrum) with material isolated in the above reaction. The infrared spectrum, ν_{OH}^{KBr} 1800, 1660 cm.$^{-1}$, was consistent with the 3β-hydroxy-3′-ethoxy bicyclic structure, but satisfactory analytical data were not obtained. For characterization, the compound was acetylated to give the acetate (Table II, R = Et), m.p. 192–196°, identical with material obtained by addition of ethanol to the acetylation mixture of **1**.

Formation of Bimolecular Ether 9 from 3′-Hydroxybicyclic Ketone 4.—A solution of 170 mg. of **4** in 17 ml. of benzene was saturated with hydrogen chloride at room temperature and then refluxed for 3 hr. After evaporating to dryness, the solid residue was chromatographed on 8 g. of alumina. Elution with benzene gave 15 mg. of a mixture; further elution with benzene–chloroform (10:1) gave 70 mg. of solid (mostly **9** by t.l.c.) which was recrystallized from benzene–hexane and then acetone–hexane to give colorless crystals of the ether **9**, m.p. 255–258° dec., identical with material described above by mixture melting point and infrared spectrum.

Hydrolysis of 4.—A solution of 300 mg. of **4** in 40 ml. of dioxane plus 10 ml. of 2% sulfuric acid was heated for 2 hr. on the steam bath. After diluting with water, dioxane was evaporated *in vacuo* and the aqueous solution was extracted with chloroform. The residue obtained on evaporation of the chloroform gave 71 mg. of crystals; the remaining amorphous material, 183 mg., was chromatographed on alumina. The first fractions, eluted with benzene–chloroform (1:1) contained 73 mg. of solid, which on crystallization from ethyl acetate–hexane furnished needles of the 3β-hydroxy-Δ$^{2'}$ bicyclic ketone **1** (3β-OH), m.p. 254–257°, infrared spectrum identical with that of an authentic sample.[4]

Later fractions eluted with chloroform gave 40 mg. of crystalline material which was combined with the 71 mg. of crystals initially obtained and recrystallized from ethanol to yield 88 mg. of the 3β,3′β-dihydroxy-2′-acetyl bicyclic ketone: m.p. 235–240°; ν_{OH}^{KBr} 3340 cm.$^{-1}$, $\nu_{C=O}$ 1800, 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}N_2O_4$: C, 69.53; H, 8.27. Found: C, 69.49; H, 8.44.

Conversion of 4 to 1 with *p*-Toluenesulfonyl Chloride.—A solution of 100 mg. of **4** and 100 mg. of tosyl chloride in 8 ml. of pyridine was heated for 12 hr. on the steam bath and then poured into water. The resulting precipitate (50 mg.) was collected and recrystallized from ether to give needles of **1**, m.p. 190–195°, identical by infrared spectrum and mixture melting point with an authentic sample.

3β-Acetoxy-2′-acetyl-16α,17α,21-(3′,1′,1′-pyrazolidino)-5-pregnene-3′β,20β-diol. A.—A solution of 200 mg. of the 3β-acetoxy 20-alcohol **4** in 20 ml. of pyridine at 0° was treated with 0.6 ml. of acetyl chloride. After stirring for 4 hr., the mixture was poured into water and extracted with ether. The residue, 210 mg., from the ether layer was chromatographed on alumina. The first fractions eluted with benzene–chloroform (3:1) gave 96 mg. of solid which contained at least three components. Later fractions gave 95 mg. of solid which was chromatographed again. Crystallization of these fractions from ethyl acetate–hexane gave 71 mg. of the diol: m.p. 238–240° (recrystallization raised the melting point to 240–243°); ν^{KBr} 3500 (broad OH), 1745, 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}N_2O_5$: C, 68.09; H, 8.35. Found: C, 67.71; H, 8.35.

B. From 4.—To a solution of 150 mg. of **4** in 25 ml. of ethanol was added 90 mg. of sodium borohydride. After standing for 3 hr., the solution was diluted with water and neutralized with acetic acid, and the precipitate (117 mg.) was collected. Chromatography on alumina gave three groups of fractions. The first group, eluted with benzene–chloroform (5:1 and 2:1), gave 20 mg. of a mixture; the second, eluted with chloroform, gave 49 mg. of a single substance; and the final fractions, eluted with chloroform–methanol, gave 48 mg. of a mixture.

The solid from the second fractions was recrystallized from ethyl acetate–hexane to give needles, m.p. 195–198°. This product was not identified.

Further chromatography of the mixed fractions gave an additional 35 mg. of the above compound and from the last fractions, eluted with chloroform, 13 mg. of the diol described in A, m.p. 242–245°, infrared spectrum identical with material from A.

3β-Acetoxy-2′-acetyl-3′β-methoxy-16α,17α,21-(3′,1′,1′-pyrazolidino)-5-pregnen-20β-ol.—A solution of 200 mg. of the alcohol in 20 ml. of pyridine was treated with 0.4 ml. of acetyl chloride; after standing at 0° for 2 hr., 8 ml. of methanol was added, the solution was evaporated, and the solid residue was washed with water and chromatographed on alumina. Elution with benzene gave a mixture, then elution with benzene–$CHCl_3$ (10:1) gave 120 mg. of a single substance which on crystallization furnished 50 mg. of colorless needles: m.p. 202–205°; ν^{KBr} 3000, 1745, 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}N_2O_5$: C, 68.61; H, 8.53. Found: C, 68.46; H, 8.67.

3β-Acetoxy-5-androsteno[17,16:3′,4′]-2′H-pyrazole-2′-acetonitrile (11).—A solution of 180 mg. of the oxime **10**[4] in 30 ml. of benzene was treated with 0.3 ml. of thionyl chloride and heated for 1 hr. The cooled solution was washed thoroughly with water, the water washes were extracted with ether, and the combined organic layers were dried and evaporated. The solid residue was crystallized from ethanol to give 127 mg. of colorless needles of **11**, m.p. 214–218°. Recrystallization from methanol furnished prisms, m.p. 220–223°. The infrared spectrum contained no bands in the 2000–2400-cm.$^{-1}$ region; strong bands

were present at ν^{KBr} 1740 (OAc), 1370, 1260, 1080, 860, and 809 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94; N, 10.68. Found: C, 72.78; H, 8.03; N, 10.87.

The same product was obtained by treatment of the oxime in pyridine solution at 0° with $POCl_3$; after 3 hr. at 0°, the solution was poured into water and the solid was collected and recrystallized from methanol, m.p. and m.m.p. 219–223°.

3β-Acetoxy-2′-acetyl-3′β-methoxy-16α,17α,21-(3′,1′,1′-pyrazolidino)-5-pregnen-20-one Oxime (12).—A solution of 300 mg. of the 3′-methoxy ketone **8** (R = CH_3), 300 mg. of hydroxylamine hydrochloride, and 600 mg. of potassium acetate in 60 ml. of methanol was refluxed for 22 hr. The solution was then evaporated and the residue was crystallized from aqueous methanol to give 100 mg. of colorless crystals. An additional 80 mg. of the same product was obtained by chromatography of the mother liquor. The combined material was recrystallized from acetone–hexane and then methanol–water to give colorless needles, m.p. 235–238°.

Anal. Calcd. for $C_{27}H_{39}N_3O_5$: C, 66.78; H, 8.10; N, 8.65. Found: C, 66.66; H, 8.25; N, 8.66.

Nitrile 11 from 3′-Acetyl-3′-methoxy Oxime.—A solution of 314 mg. of the above oxime in benzene containing 0.1 ml. of thionyl chloride was refluxed for 1 hr. After washing with water and evaporation, the residue was crystallized from ethanol to give 114 mg. of nitrile **11**, m.p. 219–223°, identical with material described above (mixture melting point and infrared spectrum).

2′-Carboxymethyl-3β-hydroxy-5-androsteno[16,17:4′,5′]-2′H-pyrazole (16, X = CO_2H).—A solution of 100 mg. of the nitrile **11** in 50 ml. of 5% ethanolic KOH was refluxed for 4 hr. and then concentrated. After dilution with water, the solution was extracted with ether; evaporation of the ether gave 8 mg. of noncrystalline residue. The aqueous layer was then acidified with HCl and extracted with chloroform. The residue from evaporation of the chloroform solution was crystallized from acetone–hexane to give 25 mg. of the acid, m.p. 266–271° dec., and 20 mg. of a lower melting second crop. Two recrystallizations from acetone–hexane gave prisms: m.p. 273–277° dec.; ν^{KBr} 2400–3400 (broad), 1745, 1210, 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.13; H, 8.31; N, 7.92.

The **methyl ester 16** (**X = CO_2CH_3**) was prepared from the acid with methanolic diazomethane. After 5 hr. the solution was evaporated and the residue was crystallized from acetone–hexane and then methanol–water to give needles: m.p. 186–187°; ν^{KBr} 3500, 1760 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39. Found: C, 71.71; H, 8.31.

Alkylation of 3β-Hydroxy-5-androsteno[16,17:4′,5′]pyrazole with Chloroacetonitrile.—A mixture of 200 mg. of the pyrazole **15**,[18,19] 55 mg. of sodium iodide, 55 mg. of sodium methoxide (very similar results were obtained in another experiment without sodium methoxide), and 5 ml. of chloroacetonitrile, without solvent, was heated on the steam bath for 1 hr. The steroid slowly dissolved, giving a brown solution with some insoluble inorganic salt. After addition of water, the mixture was extracted with chloroform, and after washing with water, drying, and evaporation, the residue (210 mg.) from the chloroform solution was chromatographed on alumina. The main fraction, eluted with benzene–chloroform (10:1 and 5:1) gave 97 mg. of solid which showed only a single spot on the t.l.c. plate. After acetylation with acetic anhydride, the material was recrystallized from ethanol. The first crop was 36 mg. of the 1′-nitrile **17** (X = CN) as a crystalline powder; further crystallization from ethanol gave colorless plates, m.p. 255–260° and finally 265–270° dec. The infrared spectrum contained no –C≡N band; the major differences with the spectrum of **11** were in the 830–1000-cm.$^{-1}$ region, particularly the presence of sharp peaks at 905 and 975 cm.$^{-1}$ in the spectrum of **17** (X = CN).

Anal. Calcd. for $C_{24}H_{31}N_3O_2$: C, 73.25; H, 7.94. Found: C, 73.53; H, 8.01.

Further crystallization from the ethanol mother liquor of **17** gave 38 mg. of needles of **11**, m.p. 216–221°, identical (mixture melting point and infrared spectrum) with material obtained from the oxime.

Condensation of 16-Formyldehydroepiandrosterone and Ethyl Hydrazinoacetate.—A solution of 500 mg. of the 16-hydroxymethylene ketone **18**,[20] 250 mg. of ethyl hydrazinoacetate hydrochloride (Aldrich Chemical), and 0.5 ml. of 10% aqueous NaOH in 75 ml. of tetrahydrofuran was refluxed for 10 hr. The solution was then evaporated and the residue was extracted with hot benzene. The residue from the benzene solution was eluted from alumina with benzene–chloroform, and the total solid obtained, 300 mg., was rechromatographed on alumina to give a main fraction of 210 mg. which was crystallized repeatedly from acetone–water to give 15 mg. of prisms of ethyl 3β-hydroxy-5-androsteno-[16,17:4′,5′]-2′H-pyrazole-2′-acetate (**16**, X = $CO_2C_2H_5$): m.p. 105–107°; ν^{KBr} 3500, 1760 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.24. Found: C, 70.77; H, 8.89.

The mother liquors from the above crystallization were evaporated and hydrolyzed with 10 ml. of 10% ethanolic KOH for 1 hr. at 80°. After acidification, 42 mg. of acid, m.p. 272–274° was obtained, identical (infrared spectrum) with material obtained by hydrolysis of nitrile **11**.

Carboxymethyl-3β-hydroxy-5-androsteno[16,17:4′,5′]-1′H-pyrazole (17, X = CO_2CH_3).—A solution of 155 mg. of nitrile **17** (X = CN) in 60 ml. of 5% ethanolic KOH was refluxed for 5 hr. and then evaporated. The residue was dissolved in water and the solution was washed with ether and then acidified. The crystalline precipitate was recrystallized from acetone to give 70 mg. of the acid **17** (X = CO_2H) as needles, m.p. 250–253°.

The **methyl ester** was prepared with diazomethane in methanol solution and was recrystallized from methanol–water to give needles, m.p. 160–163°.

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39. Found: C, 71.31; H, 8.39.

Acknowledgment.—We thank Dr. J. M. Vandenbelt and Mrs. Carola N. H. Spurlock, Parke, Davis & Company, for the ultraviolet spectra and Dr. William Theuer for the n.m.r. data. T. Y. expresses appreciation to the Ministry of Education, Tokyo, for a travel grant.

(18) K. Brückner, K. Irmscher, F. v. Werder, K.-H. Bork, and H. Metz, *Chem. Ber.*, **94**, 2897 (1961).

(19) We wish to thank Dr. Hershel Herzog, Schering Corp., for providing a sample of this pyrazole.

(20) We wish to thank Dr. E. L. Wittle, Parke, Davis & Co., for providing a sample of this ketone.