Steroidal Heterocycles. VI.[1] Formylation of A/B-*cis* 3-Ketosteroids.[2] Preparation of 5β-Steroidal[3,2-*c*]pyrazoles

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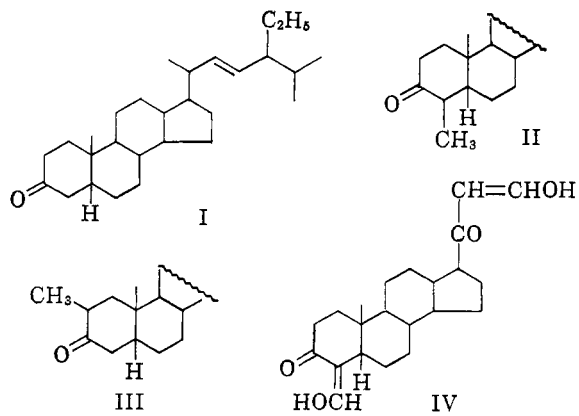
The formylation of 3-ketosteroids of the A/B-*cis* series has been shown to yield predominantly 2-hydroxymethylene-3-keto-5β-steroids rather than 4-hydroxymethylene derivatives. The structures of the formyl derivatives were proved by their conversion to the corresponding 5β-steroidal[3,2-*c*]pyrazoles and direct comparison of these with authentic samples prepared by catalytic hydrogenation of Δ⁴-steroidal[3,2-*c*]pyrazoles. Only in the 5β-stigmast-22-en-3-one series was evidence found for the formation of a 4-hydroxymethylene derivative as the minor product of formylation.

The 2-hydroxymethylene-3-ketosteroids obtained by the condensation of A/B-*trans*- and Δ⁴-3-ketosteroids with ethyl formate in the presence of base have been employed extensively in recent years as intermediates in the preparation of a variety of substituted steroids.[3] On the other hand, the preparation and use of hydroxymethylene derivatives of A/B-*cis* 3-ketosteroids have been reported in detail only by Tsuda and Nozoe.[3e,3f,4]

In work concerned with the methylation of 3-ketosteroids,[3e] 5β-stigmast-22-en-3-one (I) was formylated with ethyl formate and sodium methoxide in benzene, the derivative was methylated, and the formyl group then cleaved with acid. The resulting product was assigned the 4β-methyl structure II on the basis of its non-identity with the 2β-methyl analog III. The latter compound was prepared, in admixture with the 5α-isomer, by catalytic hydrogenation of 2α-methylstigmasta-4,22-dien-3-one in the presence of base. Since both methyl ketone II and methyl ketone III were prepared under apparently equilibrating conditions, they were assigned the stable conformations indicated, and their non-identity is strong presumptive evidence that the formylation of ketone I yields 4-hydroxymethylene-5β-stigmast-22-en-3-one. In connection with this work, 5β-ergost-22-en-3-one[3e] and 5β-pregnane-3,20-dione[3f] were also formylated; the entering group was assigned to the 4-position by analogy (*cf.* IV).



As part of a program concerned with the synthesis of steroidal heterocycles,[1-3b,3i,3j] the preparation of steroidal pyrazoles derived from A/B-*cis* 3-keto steroids *via* the intermediate hydroxymethylene derivatives has been investigated. The results obtained with simple 5β-androstan-3-ones, 5β-cholestan-3-one (coprostan-3-one), and 5β-pregnan-3-ones showed conclusively that formylation took place in the 2-position to at least a major extent. Because of the apparent discrepancy between our results and those of Tsuda and Nozoe,[3e] our work was extended to include the 5β-stigmast-22-en-3-one (I) series.

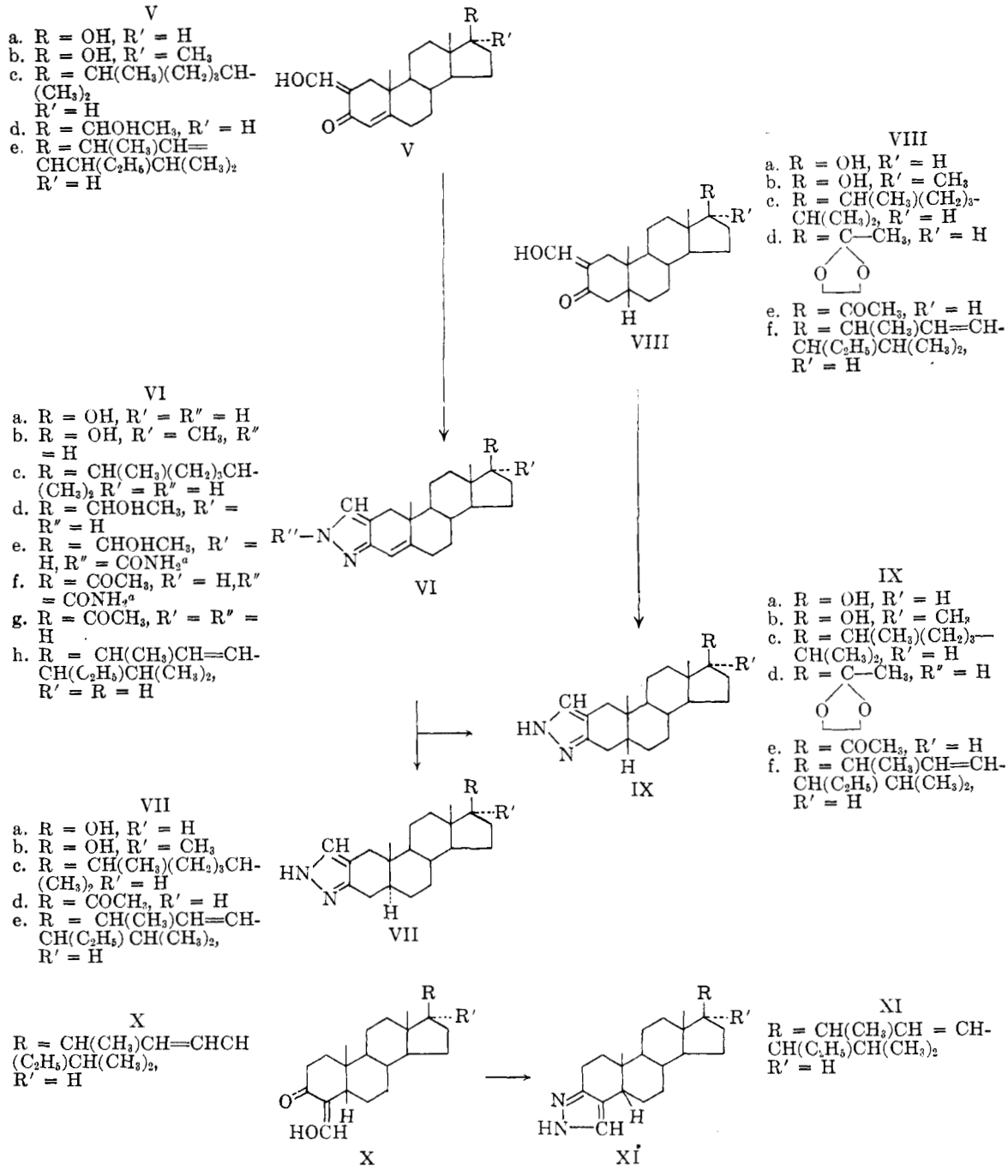
The formylation of 5β-androst-17β-ol-3-one gave an 86% yield of a crude, crystalline hydroxymethylene derivative, which was shown by fractional recrystallization and by several paper chromatographic systems to be a single compound. Condensation of the crude product with hydrazine hydrate

(1) Paper V, R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clarke, K. F. Jennings, and P. E. Shaw, *J. Org. Chem.*, **27**, 1148 (1962).

(2) For the preliminary communication see R. O. Clinton, R. L. Clarke, F. W. Stonner, D. K. Phillips, K. F. Jennings, and A. J. Manson, *Chem. Ind.* (London), 2099 (1961).

(3) *E.g.* (a) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 427 (1959); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *ibid.*, **81**, 1513 (1959); (c) F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959); (d) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959); (e) K. Tsuda and S. Nozoe, *Chem. Pharm. Bull.* (Tokyo), **7**, 232 (1959); (f) K. Tsuda and S. Nozoe, *ibid.*, **7**, 238 (1959); (g) Y. Urushibara and J. Iomata, *Bull. Chem. Soc. Japan*, **32**, 101 (1959); (h) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, J. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960); (i) 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); (j) 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); (k) G. deStevens and A. Halamandaris, *ibid.*, **26**, 1614 (1961); (l) J. C. Bloch, P. Crabbé, F. A. Kincl, G. Ourisson, J. Perez, and J. A. Zderic, *Bull. soc. chim. France*, 559 (1961).

(4) H. J. Ringold and G. Rosenkranz, U.S. Patent 2,981,743 (April 25, 1961) claimed, with little experimental detail, that 5β-pregnane-17α,21-diol-3,11,20-trione 20-ethylene ketal and 5β-pregnane-11β,17α,-21-triol-3,20-dione 20-ethylene ketal are formylated at C-4. In the related condensation of diethyl oxalate with A/B-*cis* steroidal-3-ketones, H. J. Ringold and G. Rosenkranz, U.S. Patent 2,844,602 (July 22, 1958), reported that 5β-androstan-17β-ol-3-one is ethoxalylated in the 4-position.



[a] Compounds VIe and VIf may have the alternate structures where R″ = $CONH_2$ is attached at the 2′-(rather than the 1′) position of the pyrazole ring.[3i]

afforded a 73% yield of one pure 5β-androstanopyrazole. Analysis of the total mother liquors by paper chromatography indicated the presence of only the same pyrazole.

The structure of the 5β-androstanopyrazole was proven by direct comparison with material prepared by an unequivocal route. 17β-Hydroxyandrost-4-eno[3,2-*c*]-pyrazole (VIa),[3i] prepared from 2-hydroxymethyleneandrost-4-en-17β-ol-3-one (Va) was hydrogenated over platinum oxide catalyst in acetic acid solution. Recrystallization of the crude product from the hydrogenation gave one of the two possible C-5 isomers, VIIa or IXa. A comparison by mixture melting points and infrared spectra proved conclusively that the product from the hydrogenation was identical with the above described 5β-androstanopyrazole, but different from 17β-hydroxy-5α-androstano[3,2-*c*]pyrazole (VIIa),[3i] prepared from 2-hydroxymethylene-5α-androstan-17β-ol-3-one.[3d,3i,5]

Since it has been shown[6] that the formylation of a Δ^4-3-ketosteroid yields exclusively the correspond-

ing 2-hydroxymethylene-Δ^4-3-ketosteroid, the 5β-androstanopyrazole must be 17β-hydroxy-5β-androstano[3,2-*c*]pyrazole (IXa) and the hydroxymethylene intermediate therefore has the structure VIIIa.

A similar series of reactions was carried out with 17α-methyl-5β-androstan-17β-ol-3-one. Formylation gave a good yield of a crude hydroxymethylene derivative, from which a single pure compound could be isolated. In turn, the crude hydroxymethylene-17α-methyl-5β-androstan-18-ol-3-one gave only one isolable pyrazole derivative, which was shown by mixture melting point and comparison of the infrared spectra to be identical with the major product obtained by the hydrogenation of 17β-hydroxy-17α-methylandrost-4-eno[3,2-*c*]pyrazole (VIb).[3b] Since the major product of hydrogenation differed markedly (mixture melting point and infrared spectrum) from 17β-hydroxy-17α-methyl-5α-androstano[3,2-*c*]-pyrazole (VIIb) and therefore has the structure IXb, the formylation of 17α-methyl-5β-androstan-17β-ol-3-one must give at least a preponderance of the 2-hydroxymethylene derivative VIIIb.

Formylation of 5β-cholestan-3-one in pyridine solution as well as in benzene solution gave comparable results. The hydroxymethylene-5β-cholstan-3-one was shown by careful recrystallization to be essentially a single pure compound. Its structure was proven as above by the demonstrated identity of the derived 5β-cholestano[3,2-*c*]pyrazole (IXc) with a sample prepared by catalytic reduction of cholest-4-eno[3,2-*c*]pyrazole (VIc). The compound prepared from hydroxymethylene derivative Vc, was further shown to be non-identical with 5α-cholestano[3,2-*c*]pyrazole (VIIc).

In the 5β-pregnane series, 5β-pregnan-3α-ol-20-one 20-ethylene ketal was oxidized with chromium trioxide–pyridine[7] to 5β-pregnane-3,20-dione 20-ethylene ketal. Formylation afforded a quantitative crude yield of 2-hydroxymethylene-5β-pregnane-3,20-dione 20-ethylene ketal (VIIId), which was characterized as the hydrolysis product, 2-hydroxymethylene-5β-pregnane-3,20-dione (VIIIe). The crude hydroxymethylene derivative VIIId was converted to the pyrazole IXd and the ketal group removed by acidic hydrolysis. Although a rather low over-all yield of 20-keto-5β-pregnano[3,2-*c*]-pyrazole (IXe) was obtained by this sequence, the losses were apparently due to manipulation rather than to the presence of an isomeric 5β-pregnanopyrazole.

The structure of pyrazole IXe (and thus of hydroxymethylene derivative VIIIe) was confirmed by direct comparison (mixture melting point and infrared spectra) with an authentic sample of 20-keto-5β-pregnano[3,2-*c*]pyrazole prepared by the following sequence: 2-hydroxymethylenepregn-4-20β-ol-3-one[3c] was converted to its corresponding pyrazole Id. The *N*-carbamyl derivative VIe of the latter was oxidized with chromic acid–pyridine[7] to 20-ketopregn-4-eno[3,2-*c*]-*N*-carbamylpyrazole (VIf). Hydrogenation of VIf over palladium–strontium carbonate catalyst,[8] followed by removal of the *N*-carbamyl group with boiling aqueous acetic acid afforded the 5β-pyrazole IXe, as well as some of the isomeric 20-keto-5α-pregnano[3,2-*c*]-pyrazole (VIId). Acidic hydrolysis of the *N*-carbamyl derivative VIf afforded 20-ketopregn-4-eno-[3,2-*c*]pyrazole (VIg), the steroidal [3,2-*c*]pyrazole analog of progesterone.

The formylation of 5β-stigmast-22-en-3-one (I), previously investigated by Tsuda and Nozoe,[3e] was re-examined using the method of structure proof employed above. In our hands, the reaction proved to be more complex than reported. The ketone I was treated with ethyl formate and sodium methoxide in benzene at room temperature (*ca.* 25°) to yield the crude hydroxymethylene ketone in 69% yield (24% of the starting ketone was recovered from the benzene filtrate). Several recrystallizations afforded an analytically pure hydroxymethylene-5β-stigmast-22-en-3-one, whose properties were similar to, but not identical with, those of the hydroxymethylene derivative described by Tsuda and Nozoe.[3e] Concentration of the mother liquors yielded a mixture of hydroxymethylene ketone and the methyl enol ether of a hydroxymethylene ketone (arising from the methanol used as recrystallization solvent and a trace of acid from the acidification).[9] Attempted purification of the mixture by chromatography on silica gel resulted in removal of the formyl group.[10]

Treatment of the crude product direct from the formylation with hydrazine hydrate gave a mixture of 5β-stigmast-22-enopyrazoles, which was difficult to resolve. Careful chromatography on Florisil yielded a pure 5β-stigmast-22-enopyrazole which was shown by mixture melting point, comparison of infrared and ultraviolet spectra, and optical rotation to be identical with 5β-stigmast-22-eno[3,2-*c*]-pyrazole (IXf), obtained together with 5α-stigmast-22-eno[3,2-*c*]pyrazole (VIIe) from the catalytic hydrogenation of stigmasta-4,22-dieno[3,2-*c*]pyrazole (VIh). In another run, repeated recrystallization of the mixture of 5β-stigmast-22-enopyrazoles afforded a pure, high-melting pyrazole which was not identical (mixture melting point, optical rotation) with either pyrazole VIIe or pyrazole IXf, and

(5) That the formylation of a 3-keto-5α-steroid gives the 2-hydroxymethylene derivative has been demonstrated by (a) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957); (b) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, ref. 3a; (c) Y. Urushibara and J. Inomata, ref. 3g.

(6) (a) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954); (b) J. A. K. Quartey, *J. Chem. Soc.*, 1710 (1958); (c) F. L. Weisenborn and H. E. Applegate, ref. 3c.

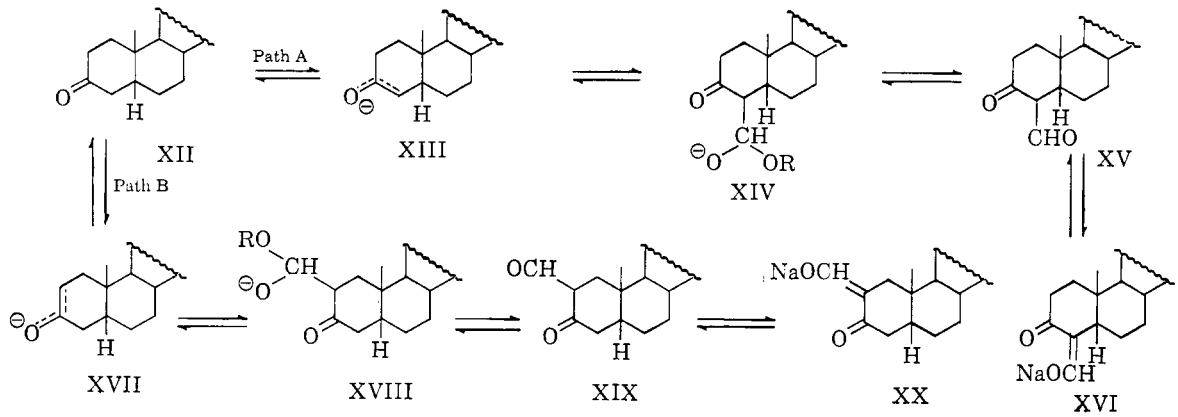
(7) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(8) The *N*-carbamyl group was partially removed during the hydrogenation, but there was no indication of reduction of the 20-ketone group.

(9) *Cf.*, footnote 3 of ref. 3j.

(10) In contrast, 2-hydroxymethylene-17α-methyl-5β-androstan-17β-ol-3-one (VIIIb) was recovered from a silica gel column unchanged (see Experimental).

therefore must be 5β-stigmast-22-eno[3,4-*c*]pyrazone (XI). Thus the formylation of 5β-stigmast-22-en-3-one (I) gave a mixture of 2-hydroxymethylene-5β-stigmast-22-en-3-one (VIIIf) and 4-hydroxymethylene-5β-stigmast-22-en-3-one (X), in a ratio of about three to two (estimated from the optical rotations of the crude pyrazole mixture and the two purified pyrazoles).

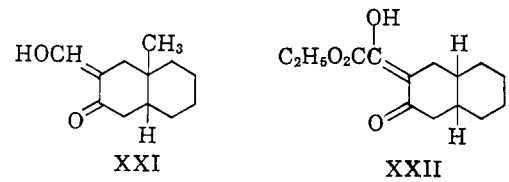


The experimental evidence reported here indicates that the formylation of an A/B-*cis* 3-keto steroid generally gives a preponderance of the 2-hydroxymethylene derivative. However, since base-catalyzed condensation of esters with ketones apparently proceeds by way of the enolate anion of the ketone,[11] and normal enolization of A/B-*cis*-3-ketosteroids is toward C-4,[12] the results appear superficially to be anomalous. The facts are best explained by assuming that ethyl formate first condenses at C-4.[13] Examination of the molecular models shows that the bulky intermediate XIV is sterically strained due to the closeness of the 6α-, 7α- and 9α-hydrogens to the group at C-4. As a result, the reverse reaction (XIV to XIII) would be favored and the ethyl formate would in time attack the minor enolate anion XVII forming intermediate XVIII which, with interference from only the 9α-hydrogen, would be more stable than intermediate XIV. Consequently, although the 3,4-enolate XIII is predominant over the 2,3-enolate XVII, the formylation reaction, being reversible, takes the path of least steric resistance (path B) to form the thermodynamically stable 2-substituted derivative. If, however, the sodium salt XVI of the more sterically strained hydroxymethylene derivative is extremely insoluble, as is apparently the case with 5β-stigmast-22-en-3-one, then the less stable kinetic product can be trapped as a precipitate, preventing, at least in part, the reverse reaction from occurring.

Evidence of the instability of the 4-hydroxymethylene derivatives of 3-keto-5β-steroids relative to the 2-hydroxymethylene derivatives has been cited above.[10]

Confirmation that the base-catalyzed formylation reaction is reversible (and therefore a dynamic equilibrium) and affected by steric factors has been reported by Roch,[14] who demonstrated that in several acyclic systems the position of formylation can be varied by a change of reaction solvent from ether to ethanol and by substitution beta to the carbonyl function.

Our results are supported by work in related bicyclic systems. For example, formylation of *cis*-9-methyl-3-decalone yields 2-hydroxymethylene-*cis*-9-methyl-3-decalone (XXI).[15] In the condensation



of diethyl oxalate with *cis*-2-decalone, ethoxylation occurs at C-3 (analogous to C-2 in steroids) to yield derivative XXII.[16]

On the basis of the present evidence, we confirm, in part, the results obtained by Tsuda and Nozoe in the formylation of 5β-stigmast-22-en-3-one (I). However, the structural assignments (substitution at C-4) given by Tsuda and Nozoe to the products of formylation of 5β-ergost-22-en-3-one[3e] and 5β-pregnane-3,20-dione[3f] by analogy with the 5β-stigmast-22-en-3-one system are in question and must await experimental proof.

Experimental[17]

2-Hydroxymethylene-5β-androstan-17β-ol-3-one (VIIIa).—To a suspension of 6.0 g. of sodium hydride in 300 ml. of dry benzene, under nitrogen, was added 8.0 ml. of absolute methanol. The mixture was stirred and heated briefly to

(11) C. R. Hauser, F. W. Swamer, and J. T. Adams, "Org. Reactions," Vol. 8, J. Wiley & Sons, Inc., New York, N. Y., 1954, p. 59.

(12) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957) and references cited therein.

(13) *Cf.* D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).

(14) (a) L. M. Roch and N. Boulay, *Compt. rend.*, **253**, 2375 (1961); (b) L. M. Roch, *Ann. chim.* (Paris), **6**, 105 (1961).

(15) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(16) (a) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 817 (1937); (b) G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 495 (1957).

boiling. After the mixture was cooled to room temperature, 38.5 g. of pure 5β-androstan-17β-ol-3-one [m.p. 142–144°, $[\alpha]_D$ +30.6° (1% in ethanol)] and 20 ml. of ethyl formate (distilled from phosphorus pentoxide) were added. The mixture was stirred at room temperature under nitrogen for 20 hr. After the careful addition of 60 ml. of water to destroy the excess sodium hydride, the mixture was diluted with 1 l. of water and 0.5 l. of ether. The ether–benzene layer was separated and re-extracted with water. The combined aqueous layers were washed once with ether and then neutralized with gaseous carbon dioxide to pH 7. The mixture was filtered and the collected solid washed thoroughly with water. After being air-dried for 3 days, 36.5 g. (86% crude yield) of material, m.p. 152–158° (evacuated sealed tube), was obtained. Recrystallization from acetonitrile furnished 30.6 g. of pure product, crystallizing in clusters of needles, m.p. 157–163° (evacuated sealed tube), $[\alpha]_D$ +26.9°, λ_{max} 284 mμ (7900).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.29; H, 9.54.

A chloroform solution of the initial crude hydroxymethylene derivative was spotted (40–150 γ) on Whatman No. 1 paper and the strips were developed in formamide–toluene, propylene glycol–toluene, and carbitol–methylcyclohexane systems. Location of the spots was determined by ultraviolet photography. All three of these systems indicated that only a single hydroxymethylene derivative was present in the crude product.

17β-Hydroxy-5β-androstano[3,2-*c*]pyrazole (IXa). A. From 17β-Hydroxyandrost-4-eno[3,2-*c*]pyrazole (VIa).—A solution of 3.00 g. of pure 17β-hydroxyandrost-4-eno[3,2-*c*]pyrazole (VIa)[3i] in 300 ml. of glacial acetic acid was hydrogenated in the presence of 1.5 g. of pre-reduced platinum oxide at room temperature and 3 atm. pressure. The uptake of hydrogen ceased after 1 hr., at which time 1.01 molecular equivalents of hydrogen had been absorbed. After filtration and washing of the catalyst, the combined filtrates were evaporated in vacuum and the solid residue was shaken with a mixture of methylene dichloride and aqueous ammonia. The insoluble material was combined with the residue obtained by evaporation of the organic layer and recrystallized from absolute ethanol. The pure compound crystallized in needles, m.p. 296.5–300° (uncor.). It gave a mixture melting point depression with 17β-hydroxy-5α-androstano[3,2-*c*]pyrazole (VIIa),[3i] m.p. 217–225°, and the infrared spectra were substantially different.

B. From 2-hydroxymethylene-5β-androstan-17β-ol-3-one (VIIIa).—A solution of 1.00 g. of the total crude product from the formylation of 5β-androstan-17β-ol-3-one in 10 ml. of ethanol was treated with 0.2 ml. of 100% hydrazine hydrate. The mixture was refluxed for 2 hr., cooled in ice, and filtered. The crystalline product was washed with two 2-ml. portions of ether and dried to 70° to yield 0.72 g. of material, m.p. 296–301.5° (uncor.). The combined filtrates and washings were evaporated to dryness under vacuum. The solid residue and the original crystalline fraction were each spotted on Whatman No. 1 paper and developed in Methyl Cellosolve–methylcyclohexane, or chloroform–toluene–formamide systems. The location of the steroidal pyrazole was shown by spraying with bromophenol blue; from both the original crystalline fraction and the combined residues a single spot was obtained, indicating the presence of only one steroidal pyrazole isomer.

The crystalline fraction was recrystallized once from absolute ethanol to give clusters of needles, m.p. 299–303° (uncor.), $[\alpha]_D$ +2.9° (1% in ethanol), λ_{max} 225 mμ (4800).

Anal. Calcd. for $C_{20}H_{30}N_2O$: C, 76.38; H, 9.62; N,[18] 4.46. Found: C, 76.34; H, 9.96; N,[18] 4.52.

The steroidal pyrazole obtained from hydroxymethylene-5β-androstan-17β-ol-3-one gave no melting point depression on admixture with the above product (IXa) obtained by the hydrogenation of 17β-hydroxyandrost-4-eno[3,2-*c*]pyrazole (VIa), and the infrared spectra were identical.

2-Hydroxymethylene-17α methyl-5β-androstan-17β-ol-3-one (VIIIb).—17α-Methyl-5β-androstan-17β-ol-3-one (20.8 g.) was formylated by the method outlined above for the lower homolog to yield 17.8 g. (79% crude yield) of the initial formylation product. A small sample of the crude hydroxymethylene derivative was chromatographed on 100 g. of silica gel pre-wet with 10% ether in pentane. Careful elution with 10% ether in pentane through 50% ether in pentane mixture gave a series of crystalline fractions at the latter level of ether concentration. These were combined and recrystallized from ether to give 1.6 g. of pure product as colorless needles, m.p. 205.6–211.6°, $[\alpha]_D$ +0.3°, λ_{max} 285 mμ (7200).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.69; H, 9.74.

There were no fractions from the chromatogram corresponding to a second hydroxymethylene derivative, nor to possible admixtures. (The second derivative, if formed, may have decomposed on the silica gel column.)

17β-Hydroxy-17α-methyl-5β-androstano[3,2-*c*]pyrazole (IXb). A. From 17β-Hydroxy-17α-methylandrost-4-eno-[3,2-*c*]pyrazole (VIb).—The catalytic hydrogenation of 2.0 g. of 17β-hydroxy-17α-methylandrost-4-eno[3,2-*c*]pyrazole (VIb)[3b] was carried out as outlined above. After the treatment with ammonium hydroxide, the crude product was recrystallized several times from ethyl acetate to give 0.7 g. of leaflets, m.p. 260–265° (uncor.). The compound gave a melting point depression with 17β-hydroxy-17α-methyl-5α-androstano[3,2-*c*]pyrazole (VIIb),[3b] m.p. 229.8–242.0°, and the infrared spectra were different.

B. From 2-Hydroxymethylene-17α-methyl-5β-androstan-17β-ol-3-one (VIIIb).—The condensation of 2.0 g. of the crude 2-hydroxymethylene-17α-methyl-5β-androstan-17β-ol-3-one with hydrazine hydrate in ethanol gave, after two recrystallizations from ethyl acetate, 0.85 g. of the pure steroidal pyrazole. The compound crystallized as leaflets, m.p. 271.4–279.6°, $[\alpha]_D$ −23°, λ_{max} 226 mμ (4900).

Anal. Calcd. for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.53. Found: C, 76.76; H, 9.87; N, 8.73.

Examination of the mother liquors from the above preparation did not indicate the presence of an isomeric steroidal pyrazole. The compound prepared by hydrogenation and that from the 2-hydroxymethylene derivative did not show a mixed melting point depression, and the infrared spectra were identical.

2-Hydroxymethylene-5β-cholestan-3-one (VIIIc).—Pure 5β-cholestan-3-one (coprostan-3-one) (m.p. 66.2–66.8°, $[\alpha]_D$ +36.5°) (5.03 g.) was formylated under the conditions outlined by Tsuda and Nozoe,[3e] using 1.40 g. of sodium methoxide, 6.35 ml. of dry ethyl formate, and 200 ml. of dry benzene. After isolation *via* the sodium salt,[19] 4.65 g. (86%) of crude product, m.p. 90–100° (uncor.), was obtained. Recrystallization of 4.50 g. of this crude product from isopropyl alcohol gave four fractions: 1.24 g., m.p. 101.4–103.2°; 1.69 g., m.p. 101–103°; 0.75 g., m.p. 99–102°; 0.80 g., m.p. 96–99°; total recovery, 4.48 g. The first three fractions had identical infrared spectra, and the last fraction differed only slightly in that it possessed an additional weak band at 5.90 μ. The first fraction had $[\alpha]_D$ +34.3°; λ_{max} 283 mμ (6400).

Anal. (first fraction): Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 80.64; H, 10.53.

Based on ultraviolet spectral assay, the last fraction was 84% pure (see below).

(17) All melting points are corrected except as noted. Optical rotations were determined in chloroform solution, $c \sim 1\%$, unless otherwise noted. Ultraviolet spectra (Cary) were determined in 95% ethanol and infrared spectra (Perkin-Elmer 21) in potassium bromide disks or carbon disulfide solution.

(18) "Basic" nitrogen, as determined by titration with perchloric acid in acetic acid solution. This is equivalent to the titration of one nitrogen in the pyrazole ring.

(19) 5β-Cholestan-3-one was isolated from the benzene–ether mother liquors; the material balance was 100%.

5β-Cholestan-3-one was also formylated in pyridine solution by means of sodium methoxide and ethyl formate.[3i] The crude 2-hydroxymethylene derivative was obtained in quantitative yield. Material prepared by this method was identical with that prepared above.

Cholest-4-eno[3,2-*c*]pyrazole (VIc).—A mixture of 14.7 g. of 2-hydroxymethylenecholest-4-en-3-one (Vc),[6a,6b] 3 g. of 100% hydrazine hydrate, and 75 ml. of ethanol was refluxed for 4 hr. The solution was evaporated to dryness under reduced pressure, and the residual solid was recrystallized from methanol and from acetone to yield 8.8 g. (60%) of the pyrazole derivative, m.p. 186.6–191.4°, $[\alpha]_D$ +113.0°, λ_{max} 261 mμ (10,100).

Anal. Calcd. for $C_{28}H_{44}N_2$: C, 82.28; H, 10.85; N^{18}, 3.43. Found: C, 81.96; H, 10.60; N^{18}, 3.48.

5α-Cholestano[3,2-*c*]pyrazole (VIIc).—The steroidal pyrazole was prepared by reaction of hydrazine hydrate with 2-hydroxymethylene-5α-cholestan-3-one[3g,5a] by the method described immediately above. The crude product precipitated in crystalline form on cooling the reaction mixture. Recrystallization from ethanol afforded a 63% yield of the pyrazole derivative, m.p. 220.2–228.6°, $[\alpha]_D$ +59.4°, λ_{max} 225 mμ (4800).

Anal. Calcd. for $C_{28}H_{46}N_2$: C, 81.89; H, 11.29; N, 6.82. Found: C, 82.22; H, 11.10; N, 6.93.

5β-Cholestano[3,2-*c*]pyrazole (IXc). A. From 2-Hydroxymethylene-5β-cholestan-3-one (VIIIc).—The condensation of 0.90 g. of 2-hydroxymethylene-5β-cholestan-3-one (IXc) with hydrazine hydrate in ethanol gave 0.87 g. (97%) of crude pyrazole, m.p. 239–244° (uncor.). Recrystallization from ether afforded 0.78 g. of pyrazole derivative, m.p. 242.6–245.4°, $[\alpha]_D$ +7.0°, λ_{max} 225 mμ (4700).

Anal. Calcd. for $C_{28}H_{46}N_2$: C, 81.89; H, 11.29: N^{18}, 3.41. Found: C, 81.97; H, 10.97; N^{18}, 3.49.

The last fraction (m.p. 96–99°) obtained in the recrystallization of 2-hydroxymethylene-5β-cholstan-3-one (VIIIc) was converted in the same manner to the pyrazole (IXc) in 63% yield.

B. From Cholest-4-eno[3,2-*c*]pyrazole (VIc).—A solution of 1.1 g. of cholest-4-eno[3,2-*c*]pyrazole (VIc) in 100 ml. of glacial acetic acid was hydrogenated under 50 p.s.i. at 25° in the presence of 0.40 g. of platinum oxide. After the hydrogenation was complete (4 hr.), the mixture was filtered and the filtrate concentrated to dryness under reduced pressure. The residue was taken up in a mixture of methylene dichloride and water. The organic layer was washed with saturated sodium bicarbonate solution and then concentrated to dryness under reduced pressure. Recrystallization from methanol and from ether gave the pure 5β-cholestano-[3,2-*c*]pyrazole (IXc), m.p. 248.8–250.8°, $[\alpha]_D$ +6.0°, λ_{max} 225 mμ (4700). The compound obtained in this manner did not depress the melting point of the material prepared from 2-hydroxymethylene-5β-cholest-3-one (VIIIc) and their infrared spectra were identical. On the other hand, there was a marked depression of melting point when pyrazole IXc was mixed with cholestano[3,2-*c*]pyrazole (VIIc) and the infrared spectrum of the latter differed substantially.

20β-Hydroxypregn-4-eno[3,2-*c*]pyrazole (VId).—A solution of 24.9 g. of pregn-4-en-20β-ol-3-one reacted with ethyl formate and sodium hydride in the manner described previously.[3c] A solution of the crude hydroxymethylene derivative and 7.5 ml. of hydrazine hydrate in 200 ml. of ethanol was refluxed for 30 min. Cooling of the solution afforded 15.55 g. of light yellow crystals, m.p. 253–260°. Several recrystallizations from methanol gave colorless rhomboids, m.p. 263–270°, $[\alpha]_D$ +114.9°, λ_{max} 260 mμ (11,000).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; O, 4.70. Found: C, 77.49; H, 9.43; O, 4.60.

20β-Hydroxypregn-4-eno[3,2-*c*]-N-carbamylpyrazole (VIe).—A solution of 15.5 g. of pyrazole VId in 600 ml. of methanol was mixed with a solution of 9.26 g. of potassium cyanate in 110 ml. of water. Concentrated hydrochloric acid was added slowly with stirring until the resultant solution was just acidic (10.5 ml.). After standing for 1 hr. at room temperature, the mixture was filtered to yield 15.1 g. of fine, colorless needles, m.p. 225–226° (uncor.). Recrystallization from acetone afforded colorless needles, m.p. 225–227° (uncor.), $[\alpha]_D$ +54.4°.

Anal. Calcd. for $C_{23}H_{33}N_3O_2$: C, 72.02: H, 8.67: N, 10.96. Found: C, 71.82: H, 8.51; N, 11.14.

20-Ketopregn-4-eno[3,2-*c*]pyrazole-N-carbamylpyrazole (VIf).—The pyrazole VIe (15.7 g.) in 275 ml. of pyridine was oxidized[7] with 15 g. of chromium trioxide in 175 ml. of pyridine. After 20 hr. the mixture was diluted with 500 ml. of water and 800 ml. of ethyl acetate. Concentration of the organic layer yielded a solid residue which, on recrystallization from methanol, yielded 14.5 g. of crystals, m.p. 222–226° (uncor.) An additional recrystallization from methanol afforded crystals, m.p. 226–234°, $[\alpha]_D$ +156.4°, λ_{max} 225 mμ (7150), 236 (8000), 242 (8000), 279 (21,700).

Anal. Calcd. for $C_{23}H_{31}N_3O_2$: C, 72.41; H, 8.19; N, 11.02. Found: C, 72.45; H, 8.24; N, 11.24.

20-Ketopregn-4-eno[3,2-*c*]pyrazole (VIg).—Acidic hydrolysis[3i] of 3.09 g. of 20-ketopregn-4-eno[3,2-*c*]-N-carbamylpyrazole (VIf) yielded 2.93 g. of crude product, m.p. 174–210°(uncor.). Two recrystallizations from methanol afforded 1.44 g. of crystals, m.p. 242–263° (uncor.). Several additional recrystallizations from methanol gave 20-ketopregn-4-eno[3,2-*c*]pyrazole (VIg) as colorless crystals, m.p. 259.6–269.6, $[\alpha]_D$ +233.9°, λ_{max} 261 mμ (13,000).

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.01; H, 8.66; N, 8.06.

5β-Pregnan-3α-ol-20-one 20-Ethylene Ketal.—A mixture of 30 g. of 5β-pregnan-3α-ol-20-one, 30 g. of ethylene glycol, 0.9 g. of *p*-toluenesulfonic acid monohydrate, and 700 ml. of benzene was refluxed under a water separator for 25 hr. The mixture was cooled, washed with dilute aqueous sodium hydroxide solution, and saturated sodium chloride solution, and then concentrated to dryness under reduced pressure. The residue was recrystallized twice from methanol containing a few drops of pyridine, to give 25.6 g. (75% yield) of colorless needles, m.p. 147.0–149.2, $[\alpha]_D$ +28.5°.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.13; H, 10.75.

5β-Pregnane-3,20-dione 20-Ethylene Ketal.—The above 3α-hydroxy compound (25.3 g.) was oxidized[7] by means of a solution of 33 g. of chromium trioxide in 330 ml. of pyridine. After 22 hr. the mixture was diluted with 1 l. of hot benzene and filtered. The filtrate was washed with water until the washings remained colorless. The benzene layer was concentrated to dryness under reduced pressure and the residual solid was recrystallized from 400 ml. of methanol with decolorization (Darco G-60) to yield 17.5 g. (69%) of product, m.p. 169–172° (uncor.). A further recrystallization from methanol gave pure material as leaflets, m.p. 169.8–172.8°, $[\alpha]_D$ +32.0°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.93; H, 10.08.

2-Hydroxymethylene-5β-pregnane-3,20-dione (VIIIe).—To a suspension of 1.6 g. of sodium methoxide in 100 ml. of pyridine was added 5.45 g. of 5β-pregnane-3,20-dione 20-ethylene ketal and 30 ml. of anhydrous ethyl formate. The mixture was stirred under nitrogen for 21 hr. and then concentrated to dryness under reduced pressure. The residue was dissolved in water and the clear aqueous solution was treated with gaseous carbon dioxide until the pH was 8. The precipitate was collected and washed thoroughly with water. After air-drying, there was obtained 5.9 g. (*ca.* 100% yield) of the crude 2-hydroxymethylene-5β-pregnane-3,20-dione 20-ethylene ketal (VIIId).

One and one-half grams of the crude formylated ketal was dissolved in 10 ml. of ethanol, 20 ml. of 2 *N* hydrochloric acid was added, and the solution was heated just to the boiling point. After standing for 1 hr. the solution was diluted with 6 ml. of water and the resulting precipitate was collected. Chromatography of the dried, crude solid (1.1 g.) on 25 g. of silica gel and elution with 25% ether in pentane furnished.

0.57 g. of the title compound. Recrystallization from ethanol afforded clusters of blades, m.p. 139.8–146.0°, $[\alpha]_D$ +114.2°, λ_{max} 285 mμ (7400).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.65; H, 9.62.

Although the yield of the pure hydroxymethylene derivative was low (probably due, in part at least, to deformylation during the acid hydrolysis of the ketal grouping) there was no indication of an isomeric formylation product.

20-Keto-5β-pregnane[3,2-*c*]pyrazole (IXe). A. From 2-Hydroxymethylenepregnane-3,20-dione 20-Ethylene Ketal (VIIId).—A mixture of 7.5 g. of the above crude 2-hydroxymethylene-5β-pregnane-3,20-dione 20-ethylene ketal (VIIId) 1.50 g. of 100% hydrazine hydrate, and 50 ml. of ethanol was refluxed for 3 hr. After the mixture was allowed to stand overnight at room temperature, the precipitated solid was collected, washed with water, and then stirred for 4 hr. with a mixture of 200 ml. of ethanol and 10 ml. of 2 *N* hydrochloric acid. During this period the suspended solid dissolved and a second solid precipitated. To the mixture was added 40 ml. of 2 *N* ammonium hydroxide solution and 60 ml. of water. The alcohol was removed in vacuum and the suspended solid was collected and washed with water. The air-dried, crude product weighed 5.7 g. The material was chromatographed on 200 g. of silica gel prewet with 1:2:2 methylene dichloride–ether–pentane. Elution with the same solvent mixture gave a series of crystalline fractions (2.85 g.). Recrystallization of the combined fractions from methanol and from methylene dichloride afforded the pure compound as massive prisms, m.p. 232–235°, $[\alpha]_D$ +91.6°, λ_{max} 225 mμ (4700).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.48; H, 9.63; N, 8.08.

B. From 20-Ketopregn-4-eno[3,2-*c*]-N-carbamylpyrazole (VIIf).—A mixture of 1.54 g. of 20-ketopregn-4-eno[3,2-*c*]-N-carbamylpyrazole (m.p. 226.4–234.4°), 400 mg. of 22% palladium hydroxide on strontium carbonate and 450 ml. of grain alcohol was hydrogenated under 3 atom. pressure and at room temperature. The reduction required 2 hr. After removal of the catalyst by filtration, the mixture was concentrated to dryness under reduced pressure. The residual solid had the m.p. 60–207° (uncor.) and λ_{max} 224 and 248 mμ (4500 and 2100, respectively), indicating about 90% cleavage of the carbamyl group. The crude material was dissolved in 50 ml. of 80% (v./v.) aqueous acetic acid, and the solution was refluxed for 1.5 hr. The solution was made alkaline with concentrated ammonium hydroxide solution, diluted with water, and filtered. The dried, crude solid (1.27 g.) was recrystallized twice from methanol to give 0.47 g. of 20-keto-5α-pregnano[3,2-*c*]pyrazole (VIId), m.p. 248–257° (uncor.), identical (mixed melting point and infrared spectrum) with an authentic sample prepared[20] from 5α-pregnane-3,20-dione 20-ethylene ketal. Recrystallization from ethanol afforded white blades, m.p. 250.0–263.8°, $[\alpha]_D$ +135.9°, λ_{max} 224 mμ (7100), 270 μ (110).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23. Found: C, 77.94; H, 9.44; N, 8.16.

The combined methanolic filtrates were concentrated to dryness in vacuum, and the residue was chromatographed (initially in benzene) on 50 g. of silica gel. Elution with 9:1 benzene–ether gave a series of crystalline fractions; the first few fractions were shown by infrared spectroscopy to consist of 20-keto-5α-pregnano[3,2-*c*]pyrazole (VIId) and the later fractions to correspond to the desired 5β-isomer. Recrystallization of the latter material from methanol and from methylene dichloride gave pure 20-keto-5β-pregnano-[3,2-*c*]pyrazole (IXe) m.p. 232–236°, undepressed on admixture with the compound prepared in part A above. The infrared spectra of the compounds prepared by the two methods were also identical.

Formylation of 5β-Stigmast-2-en-3-one (I).—To a mixture of 1.05 g. of ethyl formate (distilled from phosphorus pentoxide) and 0.766 g. of sodium methoxide (Matheson, Coleman and Bell) in 20 ml. of dry benzene was added a solution of 4.70 g. of 5β-stigmast-22-en-3-one [m.p. 110–112° (uncor.) $[\alpha]_D$ +10.8°[21]] in 20 ml. of dry benzene. The mixture was stirred for 1 hr.; a yellow gelatinous mixture was formed. The mixture was allowed to stand at room temperature (*ca.* 25°) overnight, filtered, and the collected solid was washed with ether. The solid was suspended in water–ether, 0.8 ml. of acetic acid was added, and the mixture was stirred (1 hr.) until the solid dissolved. The organic layer was washed with water and saturated sodium chloride solution, and filtered through anhydrous sodium sulfate. The solvent was evaporated to yield 3.47 g. (69% crude yield) of hydroxymethylene derivative as almost colorless crystals, m.p. 133–145° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +6.5°, λ_{max} 296 mμ (6980), λ_{max} 6.09 μ (ms), 6.32 (ms). From the original benzene filtrate was recovered 1.19 g. (24%) of the starting ketone.

The crude hydroxymethylene derivative (1.90 g.) was recrystallized three times from methanol and once from ether–pentane to yield 166 mg. of tan crystals, m.p. 151–155° (uncor.), $[\alpha]_D$ +23°, $\lambda_{max}^{CHCl_3}$ 298 mμ (7200), λ_{max} 6.10 μ (ms), 6.33 μ (ms).[22]

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.76; H, 11.28.

The purified sample was very sparingly soluble in methanol, in contrast to the solubility of the product obtained by Tsuda and Nozoe. This material was obviously a hydroxymethylene derivative, but its characteristics were sufficiently different from those of the reported[3e] hydroxymethylene derivative to indicate that one or both were mixtures.

Concentration of the mother liquors of the above sample afforded, after several recrystallizations from ether–pentane, 276 mg. of almost colorless crystals, m.p. 126–131°, $\lambda_{max}^{CHCl_3}$ 292 mμ (5600). This material was a hydroxymethylene ketone contaminated by *ca.* 17% of the methyl enol ether of the hydroxymethylene ketone (probably derived from the methanol solvent and residual acetic acid), as indicated by infrared and ultraviolet spectra and by methoxyl determination (Found: OCH_3, 1.21%). Attempted chromatography of the mother liquors on silica gel resulted in removal of the formyl group.

Formylation of 5β-stigmast-22-en-3-one (4.70 g.) at 17–18° afforded 2.00 g. of hydroxymethylene derivative as pale yellow crystals, $[\alpha]_D$ +6°, $\lambda_{max}^{CHCl_3}$ 297 mμ (3970), λ_{max}^{KBr} 5.85 μ (m), 6.13 μ (m).

Pyrazoles from the Mixture of Hydroxymethylene-5β-stigmast-22-en-3-ones.—A mixture of 3.36 g. of crude hydroxymethylene-5β-stigmast-22-en-3-ones (m.p. 133–145°), 2 ml. of 100% hydrazine hydrate and 100 ml. of tetrahydrofuran (distilled from calcium hydride) was refluxed for 4 hr. The crystalline product obtained after evaporation of the solvent was chromatographed on Florisil. Elution with 2% ether in benzene gave colorless crystals, which on recrystallization from ethyl acetate–hexane, afforded three crops: 1.03 g. of colorless leaflets, m.p. 262–265° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +2°, λ_{max} 224 mμ (4600), 0.63 g., m.p. 262–264°, $[\alpha]_D$ −13°; and 0.43 g., m.p. 263–264°, $[\alpha]_D$ −10°. The second and third crops were chromatographed on 200 g. of Florisil. Elution with 95% benzene–pentane afforded eighty-four 100 ml. crystalline fractions. The last thirteen fractions (73 mg.) were combined and recrystallized five times from ethyl acetate–hexane to yield 11 mg. of **5β-stigmast-22-eno[3,2-*c*]pyrazole (IXf)** as colorless crystals, m.p. 264–265° (evacuated sealed tube) (uncor.), $[\alpha]_D$ −21.7° (0.5% in $CHCl_3$), λ_{max} 226 mμ (4410). The mixture melting point of these crystals with the crystals,

(20) To be published.

(21) D. H. R. Barton and C. J. Brooks, *J. Am. Chem. Soc.*, **72**, 1633 (1950), report m.p. 107–108, $[\alpha]_D$ +13° (2–3% in $CHCl_3$). Our sample, prepared by the catalytic hydrogenation of stigmasta-4,22-dien-3-one over 10% palladium–carbon, was shown to be more than 99% pure by gas chromatography.

(22) Tsuda and Nozoe[3e] report m.p. 150–151°, $[\alpha]^{15}D$ +15.2° (1.2% in $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 291 mμ (8100).

m.p. 266–267°, obtained by the catalytic hydrogenation (see below) of stigmasta-4,22-dieno[3,2-*c*]pyrazole was 266–267°, and their infrared spectra were identical.

In another run, 1.50 g. of the crude hydroxymethylene ketones (obtained in the formylation at 17–18°) reacted with hydrazine hydrate to yield 1.60 g. of crude pyrazoles, m.p. 200–235°, $[\alpha]_D$ +8°. Chromatography on Florisil afforded first 0.15 g. of starting ketone (I), then 1.33 g. of colorless pyrazoles, $[\alpha]_D$ +3°, which on repeated recrystallization from ethyl acetate–hexane afforded 19 mg. of **5β-stigmast-22-[3,4-*c*]pyrazole (XI)** as fine needles, m.p. 300–301° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +37.0° (0.5% in $CHCl_3$), λ_{max} 225 mμ (4440).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08. Found: C, 82.29; H, 11.17.

The mixture melting point of these crystals with either pyrazole VIIe or pyrazole IXf (see below) was depressed and the infrared spectra were different.

Stigmasta-4,22-dieno[3,2-*c*]pyrazole (VIh).—To a mixture of 2.70 g. of sodium methoxide (Matheson, Coleman and Bell) and 3.70 g. of ethyl formate (distilled from phosphorus pentoxide) in 50 ml. of dry benzene was added a solution of 10.0 g. of stigmasta-4,22-dien-3-one (m.p. 128–130° (uncor.)] in 50 ml. of dry benzene and the mixture was refluxed with stirring for 30 min. The orange mixture was cooled and filtered. The collected solid was washed with ether and dried to yield 10.2 g. of yellow solid. The solid was suspended in a mixture of 100 ml. of water and 200 ml. of ether. Two milliliters of acetic acid was added and the mixture was stirred until the solid dissolved (3 hr.). The organic layer was separated, washed with water and saturated sodium chloride solution, and filtered through anhydrous sodium sulfate. Evaporation of the solvent afforded 8.08 g. of the yellow crystalline 2-hydroxymethylene derivative, m.p. 147–150° (uncor.), λ_{max} 250 mμ (11,500), 306 (4900), which was contaminated by water.[23]

A mixture of 7.10 g. of the crude 2-hydroxymethylene derivative, 3 ml. of hydrazine hydrate, and 200 ml. of ethanol was refluxed for 4 hr. The cooled mixture was diluted with benzene, treated with Darco, and concentrated to yield 5.55 g. (79% crude yield) of light yellow crystals, m.p. 206–230° (uncor.), 0.95 g. of yellow crystals, m.p. 145–205° (uncor.), and 0.94 g. of yellow-brown foam. Filtration of an ether solution of the first crop through 150 g. of Florisil, followed by two recrystallizations from benzene–ethanol afforded 4.93 g. (70%) of fine colorless needles, m.p. 232–234° (evacuated sealed tube) (uncor.), $[\alpha]_D$ +80.6°, λ_{max} 260 mμ (10,000).

Anal. Calcd. for $C_{30}H_{46}N_2$: C, 82.89; H, 10.67; N, 6.45. Found: C, 83.17; H, 10.73; N, 6.38.

Catalytic Hydrogenation of Stigmasta-4,22-dieno[3,2-*c*]-pyrazole (VIg).—A solution of 2.26 g. of stigmasta-4,22-dieno[3,2-*c*]pyrazole (m.p. 234–246°) in 150 ml. of benzene and 50 ml. of ethanol was hydrogenated in the presence of 3.60 g. of 10% palladium–carbon. The catalyst was added portionwise during the hydrogenation due to apparent poisoning of the catalyst by the products. The catalyst was separated and the filtrate concentrated to dryness. The crystalline residue was chromatographed on 90 g. of Florisil. Elution with benzene afforded 0.74 g. of colorless crystals, m.p. 259–265° (uncor.), and 0.79 g. of colorless crystals, m.p. 225–242° (uncor.). Recrystallization of the higher melting material from ethyl acetate afforded **5β-stigmas-22-eno-[3,2-*c*]pyrazole (IXf)** as colorless leaflets, m.p. 266–267° (evacuated sealed tube (uncor.), $[\alpha]_D$ −22.4° (0.5% in $CHCl_3$), λ_{max} 224 mμ (4760).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.42. Found: C, 82.58; H, 11.01; N, 6.52.

Recrystallization of the lower melting material from ethyl acetate afforded **5α-stigmast-22-eno[3,2-*c*]pyrazole (VIIe)** as fine colorless needles, m.p. 241–242° (evacuated sealed tube), $[\alpha]_D$ +40.8°, λ_{max} 224 mμ (4750).

Anal. Calcd. for $C_{30}H_{48}N_2$: C, 82.51; H, 11.08; N, 6.42. Found: C, 82.37; H, 11.21; N, 6.30.

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(23) Tsuda and Nozoe[33] report m.p. 162–163° and $\lambda_{max}^{CH_3OH}$ 253 mμ (14,300), 306 (7400) for the purified specimen.

Dehydration of Steroid 5,6-Halohydrins[1]

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The treatment of 5α-hydroxy-6β-halo steroids with potassium bisulfate or sulfuric acid in acetic anhydride led to the formation of 6β-halo-5β-methyl-19-norsteroids. Optical rotations and n.m.r. spectra data supported this conclusion. The crystallization liquors yielded additional dehydration products which could be explained as being derived from a common carbonium ion. The attempted rearrangement of compounds containing groups other than halogen in the 6β-position was unsuccessful. The biological activities of the rearranged products are presented.

Westphalen,[2] in 1915, was studying the acetylation of cholestane-3β,5α,6β-triol 3,6-diacetate using acetic anhydride and sulfuric acid. A compound was isolated which proved to be a dehydrated product. This product was shown by later workers[3] to have structure II.

The position of the double bond at C-9(10) and the β-methyl group at C-5 was substantiated by optical[4] and chemical[5] evidence. Compound II,

(1) Presented before the Division of Medicinal Chemistry, 140th Meeting of the American Chemical Society, Chicago, Illinois, September 3–8, 1961.

(2) T. Westphalen, *Chem. Ber.*, **48**, 1064 (1915).

(3) J. L. Dunn, I. M. Heilbron, R. F. Phipers, K. M. Samant, and F. S. Spring, *J. Chem. Soc.*, 1580 (1934); H. Lettre and M. Muller, *Chem. Ber.*, **70**, 1947 (1937); V. A. Petrow and M. Davis, *J. Chem. Soc.*, 2211 (1951).