The Synthesis and Stereochemistry of Isomeric 16-Hydroxy-17(20)-pregnenes

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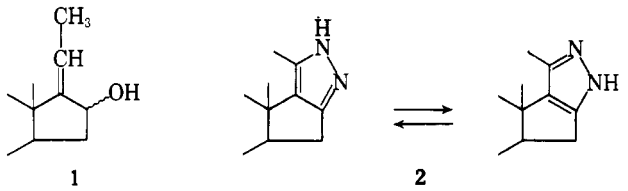
The hydrazine reduction of 16α,17-epoxypregnenolone (**5**) afforded a pyrazole (**9**) and two isomeric allylic alcohols, 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8**) and 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7**). The acid-catalyzed equilibration of 5,16-pregnadiene-3β,20(α or β)-diol also afforded two isomeric allylic alcohols, compound **7**, identical with the product of the hydrazine reaction, and 5,17(20)-(*trans*)-pregnadiene-3β,16β-diol (**6**). Assignments of structure were made on the basis of the methods of preparations, conversions of the isomers to identical products, n.m.r. spectra of the compounds, and molecular rotations.

Several years ago we observed that the Kishner reduction–elimination of the steroidal 16α,17-epoxy-20-keto system afforded two isomeric unsaturated alcohols together with a steroidal pyrazole.[1] The stereochemistry of the isomeric alcohols remained in question until recently. The investigation of the prototropic equilibration of the steroidal allylic Δ^{16}-20-hydroxy system also afforded two isomeric alcohols, one of which was identical with one of the alcohols obtained in the previously mentioned Kishner reduction–elimination. The three alcohols represented three of four possible isomeric 5,17(20)-pregnadiene-3β,16-diols having the partial structure **1**, while the pyrazole isolated in the hydrazine reduction had the partial structure **2**.

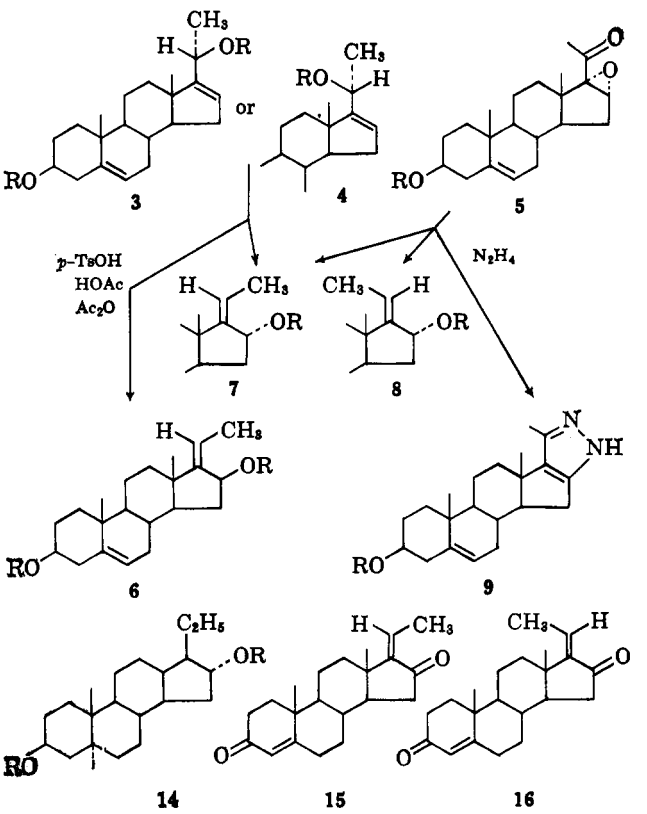


1 **2**

These structural assignments are supported by the recent work of Wharton and Bohlen[2] wherein α,β-epoxy ketones also were shown to react with hydrazine to afford allylic alcohols.[3,4]

The Hydrazine Reduction of 16α,17-Epoxypregnenolone (5).—The Kishner reduction–elimination of 16α,-17-epoxypregnenolone (**5**), under Huang-Minlon conditions,[5] yielded 3β-hydroxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (**9a**), and a mixture of difficultly separable 5,17(20)-pregnadiene-3β,16-diols (**7a** and **8a**). The steroidal pyrazole (**9a**) was readily identified by its analysis, its infrared and ultraviolet spectra [λ_{max} 225 mμ (ϵ 6100)],[6] and by analogy with previous reactions of α,β-epoxy ketones with hydrazine.[7]

CHART I



Series a, R = H
Series b, R = Ac

The isomeric 5,17(20)-pregnadiene-3β,16-diols (**7a** and **8a**), which also could be made more simply by heating 16α,17-epoxypregnenolone (**5a**) with hydrazine hydrate under reflux, could be separated with difficulty into pure 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7a**), m.p. 219–222°, and 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**), m.p. 190–191.5°, by careful chromatography on silica gel, followed by fractional crystallization of the intermediate fractions. The evidence for these assignments of structure is presented later in this paper. From reactions run either at the high or low temperature, the *cis* isomer (**8a**) was isolated in slightly higher yield than the *trans* compound (**7a**).

The course of this reaction can be most readily rationalized as another example of the Kishner reduction–elimination reaction, which has been investigated most competently by Leonard and Gelfand.[8] The partial stereoselectivity of the reaction also can be rationalized

(1) R. M. Dodson, U. S. Patent 2,937,168 (May 17, 1960).

(2) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(3) Since this work was completed, a communication has appeared describing the hydrazine reduction of the same 16α,17-epoxy 20-ketone described herein. However, only a single alcohol was isolated and the stereochemistry was not assigned. See Huang-Minlon and Chung-Tungshun, *Tetrahedron Letters*, **No. 19**, 666 (1961).

(4) The formation of both isomers is shown by C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, p. 256. No physical properties or evidence for the assigned configurations are given. NOTE ADDED IN PROOF.—Two recent publications describing the hydrazine reduction of 16,17-epoxy 20-ketones have appeared since the submission of this manuscript: R. Sciaky and F. Facciano, *Gazz. chim. ital.*, **93**, 1028 (1963); and C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 269 (1964).

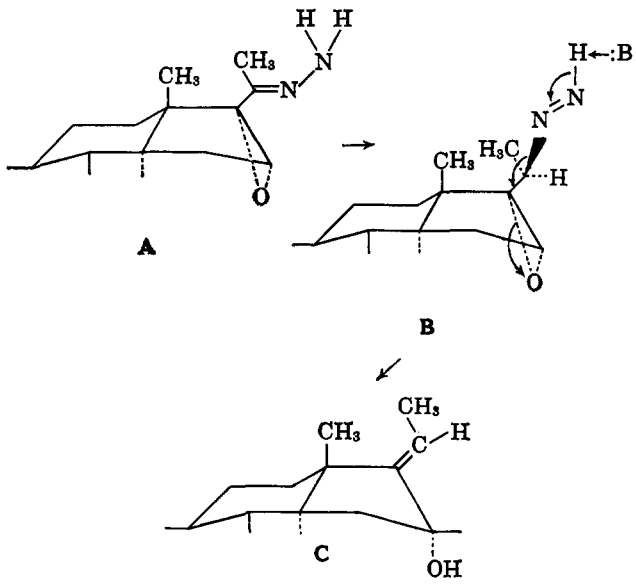
(5) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(6) 3,4,5-Trimethylpyrazole has λ_{max}^{EtOH} 223 mμ (ϵ 4900). D. Dal Monte Casoni, A. Mangini, and P. Passerini, *Boll. sci. fac. chim. ind. Bolongna*, **12**, 147 (1954). For the infrared spectrum of 3,4,5-trimethylpyrazole see v. R. Hüttel, H. Wagner, and P. Jochum, *Ann. Chem.*, **593**, 179 (1955).

(7) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 5, Chapter 2 (T. L. Jacobs), p. 68.

(8) N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3272 (1955). For other examples of the Kishner reduction-elimination reaction, see the many references in this paper.

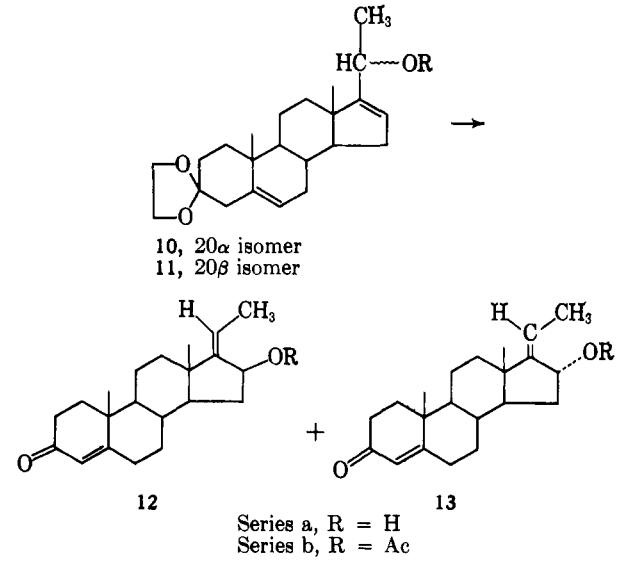
on the basis of the mechanisms contained in that paper. Thus, if it is assumed that the preferred conformation of the 20-hydrazone (**A**) is similar to that of the 20-ketone in pregnan-20-one[9] or in 3β-acetoxy-17α-bromo-5α-pregnan-20-one,[9] then protonation at C-20, either of the hydrazone, or of a negative ion obtained from it, should occur preferentially from the α side and result in the formation of **B**. *trans* elimination from **B** should lead to the formation of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**C**, **8a**).



The Acid Equilibration of 20-Hydroxy-16-pregnenes.—In an attempt to synthesize the other isomeric 16-hydroxy-17(20)-pregnenes and in an attempt to determine the relative stability of the various isomeric endocyclic (Δ^{16}-20-ols) and exocyclic ($\Delta^{17(20)}$-16-ols) allylic alcohols, the acid-catalyzed isomerization of the 20-hydroxy-16-pregnenes was studied. Initially, we had intended to study the equilibration in acid of *pure* 20α- and 20β-hydroxy-Δ^{16}-pregnenes. However, in the preparation of these starting materials we observed[10] a marked tendency for the epimeric 20-hydroxy-5,16-pregnadienes to form molecular complexes. Indeed, because of the extreme difficulty encountered in separating these epimers, the following rearrangement studies were made: (a) in the 3-hydroxy-Δ^5 series, rearrangements were run on the pure 20β-hydroxy compound (**4a**) and on a 1:1 mixture of 20α- and 20β-hydroxy compounds (**3a** and **4a**); (b) in the 3-ethylene ketal-Δ^5 series, rearrangements were run on the pure 20α-hydroxy ketal (**10a**) and on a 1:1 mixture of 20α- and 20β-hydroxy ketals (**10a** and **11a**). This potentially complicating factor proved to be of no consequence as to the position of the equilibrium. Thus the stereochemistry at C-20 did not appear to alter the position of the *exo–endo* equilibrium nor the ratio of the geometric isomers in the products under the reaction conditions employed. The equilibrations were run at room temperature in acetic acid–acetic anhydride medium in the presence of 0.01 to 0.02 *N* *p*-toluenesulfonic acid for at least 24 hr.[11] The resulting mixture of products resisted several attempts at precise quantitation by thin layer, vapor phase, or paper chromatographic techniques. Nevertheless, sufficient resolution was attained by column chromatography to indicate quite clearly that the position of the equilibrium lay well in the direction of the *exo*-unsaturated compound.

The mixture resulting from the previously described acid-catalyzed equilibration of 5,16-pregnadiene-3β,20β-diol[12] was partly resolved by chromatography on alumina. The major components, isolated in a ratio of about 3:1, were 3β,16β- and 3β,16α-diacetoxy-5,17(20)-(*trans*)-pregnadiene (**6b** and **7b**), respectively, accompanied by a small amount of the unrearranged epimeric 20β- and/or 20α-acetoxy-Δ^{16}-pregnenes (**3b** and **4b**). As far as we could determine the same ratio of products resulted from the equilibration of a 1:1 mixture of the C-20 epimers[10] as from the 20β-diol. Equilibration of the corresponding diacetates gave the same ratio of products.

In the 3-ethylene ketal[10] series, the results of equilibration were strictly analogous to the 3-hydroxy compounds. Thus the pure 20α-hydroxy compound, which was the more readily purified of this pair of epimers, gave the same ratio of products as resulted from a 1:1 mixture of C-20 epimers, namely the analogous 3-keto-Δ^4 structures **12** and **13**. In this series also, the 16β isomer was the preponderant product.



Stereochemistry of the 5,17(20)-Pregnadiene-3,16-diols.—The assignment of configuration of the hydroxyl group as well as the geometry about the 17(20) double bond in each of the isomeric products was based largely on n.m.r. spectral evidence. Various chemical transformations as well as an analysis of the molecular rotations of the compounds provided additional evidence for the assignments given. As seen in Table I the two 17(20)-(*trans*)-diols (**6** and **7**) and their diacetates exhibited the expected molecular rotatory contributions for 16β and 16α substitution. The single

(9) N. L. Allinger and M. A. DeRooge, *J. Am. Chem. Soc.*, **83**, 4256 (1961); C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 128.

(10) W. R. Benn, *J. Org. Chem.*, **28**, 3557 (1963).

(11) This system was chosen to avoid competing etherification, dehydration, or rearrangement to a ketone. In preliminary experiments, attempts to study the equilibrium of the alcohols rather than their esters, *e.g.*, treatment with perchloric acid in acetone, led to polymeric products.

(12) R. E. Marker, D. L. Turner, R. B. Wagner, P. R. Ulshafer, H. M. Crooks, Jr., and E. L. Wittle, *J. Am. Chem. Soc.*, **63**, 779 (1941).

TABLE I
ROTATIONAL VALUES

Isomer	Configuration 16-OR	Configuration $\Delta^{17(20)}$	$[\alpha]_D$	M_D	ΔM_D (16-OR) Obsd.[a]	ΔM_D (16-OR) Lit.[b]	ΔM_D (OAc-OH) Obsd.	ΔM_D (OAc-OH) Lit.[b]	ΔM_D (*cis-trans*)[c]
6a	β-OH	*trans*	−32	−101	121	38			
6b	β-OAc	*trans*	−17	−68	175	102	54	64	
7a	α-OH	*trans*	−73	−231	−9	−59			
7b	α-OAc	*trans*	−116	−465	−222	−298	−213	−239	
8a	α-OH	*cis*	−89	−282					−51
8b	α-OAc	*cis*	−89.5	−359			−56	−239	106
15	=O	*trans*	−61	−191	−542	−490			
16	=O	*cis*	−30	−94					97

[a] The observed values of ΔM_D are calculated from reported molecular rotational values for the 16-desoxy analogs believed to have the more stable *trans* configuration at the 17(20) double bond. This assignment is most reasonable in light of the several methods reported for the preparation of the reference compounds: L. Ruzicka, M. W. Goldberg, E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); **25**, 1297 (1942); and R. Fischer, G. Lardelli, and O. Jeger, *ibid.*, **33**, 1335 (1950). [b] Literature values are taken from L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179, and from W. Klyne, "The Chemistry of the Steroids," Methuen and Co. Ltd., London, 1957, p. 55. [c] Hogg and co-workers report positive values for ΔM_D (*cis–trans*) in a series of $\Delta^{17(20)}$-C_{21} compounds; J. A. Hogg, *et al.*, *J. Am. Chem. Soc.*, **77**, 4436 (1955).

cis compound (**8**) showed a molecular rotatory contribution for the acetylation of a 16α-hydroxy group different from those previously recorded. This may reflect distortion in the *cis* isomer that is not present in the other two compounds.

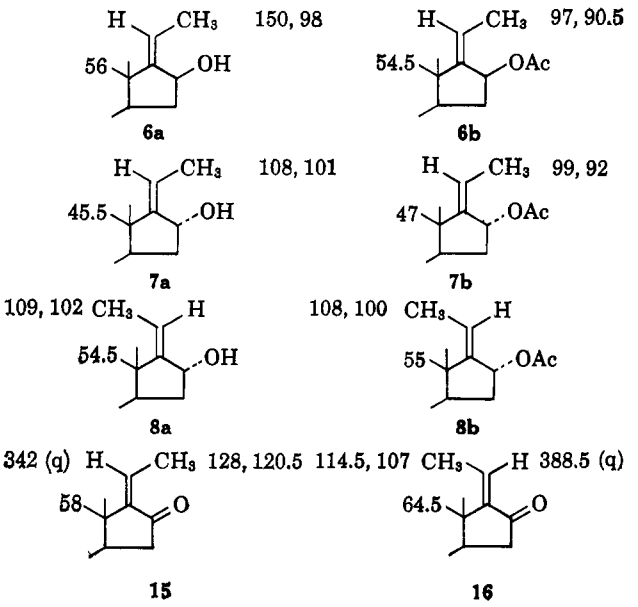
Tsuda and co-workers[13a] and Tweit, Dodson, and Muir[13b] have observed that a β-hydroxy or β-acyloxy substituent at C-14[13a] or C-15 causes a marked downfield shift in the position of the C-18 methyl resonance in the n.m.r. spectrum of pregnane derivatives, whereas the corresponding α isomer results in a much smaller displacement. We have observed a similar downfield shift in the position of the C-18 methyl resonance in two of the three diols and their diacetates relative to the position of this absorption in the third isomer (Table II). This might suggest that these two isomers had the β configuration at C-16 and the remaining isomer the α configuration. However, an explanation that is more in agreement with the other data is that in one of the two isomers (**6**) the downfield shift results from the deshielding effect of a β-oxygen function at C-16, while in the second compound (**8**) a corresponding shift of the *same magnitude* is produced by interaction between the C-18 angular methyl group and the C-21 methyl group of a *cis*-oriented ethylidene side chain, a situation that is precluded by the geometry of a *trans* conformation.[14]

In further support of the assignments shown, a comparison of the n.m.r. spectra of the 16-acetylated diols with their respective alcohols reveals a long-range effect on the position of the doublet produced by the C-21 methyl proton resonance in two of the isomers and not in the third. As can be seen from molecular models, a *trans*-oriented $\Delta^{17(20)}$-pregnene forces the C-21 methyl group into close proximity to a substituent at C-16. Thus in the two isomers assigned the *trans* structure (**6** and **7**), replacement of the proton of the hydroxyl function with an electron-withdrawing acetyl group results in less deshielding of the protons of the C-21 methyl group by the electrons of the C-16 oxygen,

(13) (a) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); (b) R. C. Tweit, R. M. Dodson, and R. D. Muir, *J. Org. Chem.*, **27**, 3654 (1962).

(14) The principle of additivity of effects would predict a downfield shift of about 20 c.p.s. for the missing 16β-*cis* isomer. *Cf.* J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958). NOTE ADDED IN PROOF.—B. J. Magerlein, *et al.*, *J. Org. Chem.*, **28**, 3474 (1963), recently have observed the same deshielding influence on the C-18 protons by *cis*-$\Delta^{17(20)}$-21-hydroxy compounds relative to the *trans* isomers.

TABLE II[a]
C-18 AND C-21 METHYL PROTON RESONANCE FREQUENCIES OF ISOMERIC 5,17(20)-PREGNADIENE-3β,16-DIOLS AND THEIR DERIVATIVES



[a] N.m.r. spectra were determined in deuteriochloroform using a Varian Associates A-60 spectrometer operating at 60 Mc.p.s. The numbers adjacent to the protons at C-18, C-20, and C-21 indicate their resonance frequencies expressed in cycles per second in the direction of decreasing field strength relative to an internal tetramethylsilane standard.

i.e., an upfield shift in the C-21 absorption upon acetylation. Tsuda[13a] also has observed an upfield shift in the position of angular methyl resonance upon acetylation of a hydroxyl function so situated as to permit a spatial interaction of the two groups. In the *cis* isomer (**8**) the C-21 methyl group is physically remote from the long-range influence of functionality at C-16 and thus there is essentially no change in the position of this band upon acetylation.

The configurations of the two isomeric 16-hydroxy-4,17(20)-pregnadiene-3-ones (**12** and **13**) isolated from the acid-catalyzed equilibration of the 3-ethylene ketals (**10** or **11**) were assigned using the same line of reasoning. Thus the major product was assigned the 16β-$\Delta^{17(20)}$-*trans* structure, and the minor component the 16α-$\Delta^{17(20)}$-*trans* configuration.

The products of reduction and oxidation of the diols **6**, **7**, and **8** showed properties in agreement with those expected on the basis of the structural assignments given. Thus isomers **7** and **8** and their respective diacetates are shown to differ only in geometry about the 17(20) double bond by virtue of their reduction in the presence of palladium on carbon to a common saturated 5α-pregnane-3β,16α-diol (**14**). Reduction of the third isomer assigned the 16β-*trans* configuration (**6**) gave a mixture of a hydrogenolysis product together with what appears to be, on the basis of spectral evidence, a 16-keto-17ξ-ethyl derivative resulting from isomerization of the double bond through the enol intermediate.[15]

The allylic 16-hydroxy-$\Delta^{17(20)}$ system was very unreactive toward selective oxidation by either manganese dioxide or dichlorodicyanobenzoquinone. Room temperature treatment resulted in recovery of considerable starting material. Use of elevated temperatures resulted in appreciable oxidation of the 3-hydroxyl group to a 3-keto-4,6-diene system as evidenced by the appearance of a band in the ultraviolet spectrum at 283 mμ. In light of these observations the experiments were not pursued.[16]

Oxidation under Oppenauer conditions proceeded smoothly; however, there invariably was an appreciable amount of isomerization of the resulting dienedione about the 17(20) double bond even under these mild conditions. Nevertheless, the predominant isomer in each case was that expected on the basis of the previous assignment of geometry about the 17(20) double bond.

The n.m.r. spectra of the two isomeric 4,17(20)-pregnadiene-3,16-diones afforded an unequivocal assignment of the configuration of the ethylidene side chain. The substituent at C-20 adjacent to the carbonyl function at C-16 is subject to the magnetic anisotrophic influence of that group resulting in a deshielding or downfield shift. Thus the spectrum for one isomer assigned the *trans* configuration (**15**) displayed a doublet for the C-21 methyl proton centered 13.5 c.p.s. downfield from the corresponding absorption of the other isomer, assigned the *cis* structure (**16**). The spectrum for the latter compound exhibited a quartet for the C-20 vinyl proton centered 46.5 c.p.s. downfield relative to the first.[17] The comparable deshielding of the C-18 methyl protons by the C-21 methyl group in the *cis* compounds (**8a** and **16**) when compared with the *trans* compounds (**7a** and **15**) also should be noted.

Discussion

The question of the relative stability of a double bond exocyclic or endocyclic to a five-membered ring has been discussed by several authors.[18] Turner's[18c] studies on the heats of hydrogenation of the isomeric *exo–endo* pairs of five-, six-, and seven-membered ring compounds showed that in each case the *endo* isomer was the more stable member of the pair. Dreiding and Hartman[19] have observed that either 2-methylenecyclopentanol or 1-cyclopentenyl methanol in the presence of 1% sulfuric acid at reflux temperature underwent rearrangement to 2-methylcyclopentanone. However, from these experiments no conclusions could be drawn concerning the relative stability of the isomers.

The steroidal Δ^{16}-20-acetoxy system offers one advantage in the study of *exo–endo* equilibria involving a five-membered ring in that each of the isomeric olefins are trisubstituted. However, the rigidity of the steroid nucleus (the *trans* C:D ring juncture), the steric effects of the neighboring ring, and the C-18 angular methyl group impose such limiting features on this system that generalization to other systems would of necessity be limited.

From the lack of stereospecificity of this anionotropic rearrangement, it is reasonable to conclude that thermodynamic equilibrium has been approached among the products formed. Thus, in this system (1) only the *trans*-olefin was isolated; (2) the trisubstituted exocyclic [$\Delta^{17(20)}$] double bond was favored over the trisubstituted endocyclic [$\Delta^{16,17}$] double bond; and (3) the more stable 16β-acetoxy isomer was favored over the less stable 16α-acetoxy compound. That the 16β configuration is more stable than the 16α in certain 16-substituted steroids possessing an exocyclic double bond at C-17 can be seen from the work of Fajkos,[20] Bowers,[21] and others.

Experimental[22]

The Reaction of 16,17-Epoxypregnenolone with Hydrazine. Method A. 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7α).—A solution of 10.0 g. of 3β-hydroxy-16α,17-oxido-5-pregnen-20-one in 200 ml. of hydrazine hydrate (85%) was brought slowly to reflux temperature over 0.75 hr. and allowed to reflux for 15 min. The reaction mixture was cooled and the grey precipitate separated by filtration and washed thoroughly with water. The dried solids were dissolved in a 5% ethyl acetate–benzene solution and placed on a column of 400 g. of silica gel. From the early fractions eluted by 20% ethyl acetate–benzene there crystallized prisms melting 213–218°. Recrystallization from ethyl acetate afforded the 16α-*trans* isomer (**7a**) as blades melting 219–222°, $[\alpha]_D$ −73°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.70; H, 10.07 (MT).

5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—From later fractions of the previous chromatogram the major product was eluted with 20% ethyl acetate–benzene and crystallized to give the 16α-*cis* isomer (**8a**) as needles having m.p. 185–190°. An analytical sample was obtained by recrystallization from ethyl acetate, m.p. 190–191.5°, $[\alpha]_D$ −89°.[23]

(15) *Cf.* R. Delaby and J. Dumoulin, *Bull. soc. chim. France*, **39**, 1578 (1926), for analogous isomerization of allylic alcohols to ketones on palladium catalysts.

(16) P. N. Rao, *J. Org. Chem.*, **26**, 2149 (1961). See, however, ref. 4.

(17) Other recent examples of the use of n.m.r. spectroscopy in distinguishing between isomeric ethylidenes adjacent to a five-membered ring carbonyl are reported by G. Albers-Schönberg and H. Schmid, *Helv. Chim. Acta*, **44**, 1447 (1961), in the elucidation of the structures of plumericin and isoplumericin, and by K. S. Brown, Jr., and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590 (1962), working with derivatives of cyclobuxine. *Cf.* also L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960).

(18) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957). (b) B. R. Fleck, *ibid.*, **22**, 439 (1957), and references cited therein. (c) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

(19) A. S. Dreiding and J. A. Hartman, *ibid.*, **78**, 1216 (1956).

(20) J. Fajkos, *J. Chem. Soc.*, 3966 (1959), and references cited therein.

(21) A. Bowers, P. G. Holton, E. Necoechea, and F. A. Kinel [*ibid.*, 4057 (1961)] have shown that 16α-methyl-4-androstene-3,17-dione is converted by acid or alkali completely to the 16β-methyl isomer.

(22) Melting points were taken on a Fisher melting point apparatus. Rotations were taken in chloroform at about 1% concentration at 26 ± 2° and the ultraviolet spectra were determined in methanol. Analyses marked by MT were carried out by Micro-Tech Laboratories, Skokie, Ill. All other spectra and analytical results were carried out under the direction of Dr. R. T. Dillon of the Analytical Department of G. D. Searle and Co. We wish to acknowledge the assistance of Dr. E. G. Daskalakis and his associates for some of the chromatographic separations.

(23) In their communication Huang-Minlon and Chung-Tungshun[3] describe a single 16-hydroxy-$\Delta^{17(20)}$ compound from the hydrazine reaction, m.p. 182–183°, $[\alpha]^{27}_D$ −89° (ethanol), and its diacetate, m.p. 158–160°, $[\alpha]^{27}_D$ −67° (ethanol). These physical constants are more nearly in agreement with our *cis* compound (**8**), isolated as the major product, than with the *trans* isomer.

The diol fraction was eluted with 20% ethyl acetate in benzene as a pair of incompletely resolved bands. The total yield of diol material was 51% with the *cis* isomer (**8a**) somewhat predominant over the *trans* (**7a**).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 80.09; H, 9.97.

5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol Diacetate (7b).—The diacetate was prepared by treatment of the diol **7a** with acetic anhydride in pyridine at room temperature overnight. It crystallized as prisms from methanol, m.p. 149–151.5°, $[\alpha]_D$ −116°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.82; H, 8.93.

5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol Diacetate (8b).—The diacetate was prepared in the same manner as described for the *trans* isomer. It crystallized from methanol as plates, m.p. 163–165°, $[\alpha]_D$ −89.5°.[23]

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.15; H, 8.76.

The Reaction of 16,17-Epoxypregnenolone with Hydrazine. Method B.—The first reaction in this series was run under the usual conditions for the Huang-Minlon modification of the Wolff–Kishner reduction.[5] From the reaction of 2.00 g. of 16,17-epoxypregnenolone with 2.00 g. of potassium hydroxide and 2.0 ml. of hydrazine hydrate (85%) in 20 ml. of diethylene glycol (195° for 5.5 hr.) was isolated, by chromatography on silica gel, 140 mg. of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol (**7a**), m.p. 217.5–218.5°, and 277 mg. of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**), m.p. 190–191.5°, $[\alpha]_D$ −88°.

3β-Hydroxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (9a).—**9a** was obtained from the preceding reaction on elution of the chromatographic column with ethyl acetate. Crystallization of the material so obtained from acetone–cyclohexane yielded 92 mg. of the steroid pyrazole, m.p. 305–307° dec., with rapid heating; $[\alpha]_D$ −73°; λ_{max} 225 mμ (ε 6100); λ_{max}^{KBr} 2.70, 3.02, 6.20, 7.23, 7.82, 9.19, 9.48, 9.58, and 9.82 μ; lit.[3] m.p. 302–304°; $[\alpha]^{27}D$ −76° (chloroform) (see also ref. 1).

Anal. Calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58. Found: C, 77.12, 76.89; H, 8.85, 8.96; N, 8.68, 8.86.

3β-Acetoxyandrost-5-ena-[16,17-*c*]-5′-methylpyrazole (9b).—**9b**, m.p. 268–273°, λ_{max} 225 mμ (ε 6650), was obtained by the acetylation of **9a** with acetic anhydride in pyridine and crystallization of the resulting material from aqueous methanol containing a little ammonium hydroxide.

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.97; H, 8.76. Found: C, 75.04; H, 8.71.

Acid-Catalyzed Rearrangement of 5,16-Pregnadiene-3β,20-diols. 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol Diacetate (7b).—To a solution of 12.3 g. of a 1:1 molecular mixture of 5,16-pregnadiene-3β,20α- and -3β,20β-diol[10] in 180 ml. of acetic acid and 30 ml. of acetic anhydride was added 800 mg. of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand under nitrogen at room temperature for 48 hr. A green color slowly developed over the reaction period. The reaction was diluted with warm water and extracted with benzene; the organic phase was washed with sodium carbonate solution, then with water, and finally dried and concentrated under vacuum to an amber gum. Crystallization from methylcyclohexane afforded 3.8 g. of light yellow crystals, m.p. 149–163°. Further recrystallization did not result in narrowing the melting range. On the basis of the infrared spectrum the material was judged to be predominantly the 16β-acetoxy *trans* isomer (**6b**) described subsequently.

The filtrates from the crystallization were chromatographed on neutral alumina. The band of material eluted by benzene was clearly not homogeneous. From the early fractions of this band there was obtained, by crystallization from methanol, prisms melting at 145–148°, amounting to about 13% of the total product. Further recrystallization afforded a pure sample of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol diacetate (**7b**) having melting point and spectra identical with the diacetate, m.p. 149–151.5°, derived from the hydrazine reaction.

Later fractions from the benzene eluted band, amounting to about 10% of the total product, crystallized poorly. However, on the basis of the infrared spectra these fractions were shown to be predominantly the 3,20-diacetoxy starting material.

5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol Diacetate (6b).—A second very broad band was collected from eluates of 1 to 2% ethyl ether in benzene. From these fractions there was isolated by crystallization from methanol the pure 16β-acetoxy *trans* isomer (**6b**), m.p. 173–175.5°, $[\alpha]_D$ −17°. This material together with the solids collected by direct crystallization from the crude reaction product accounted for about 40% of the total product.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.07; H, 9.02.

From the more polar eluates of the previous chromatogram there were obtained only gummy products that resisted crystallization and characterization. These fractions amounted to some 30% of the total and appeared to be mixtures of monoacetates of the previously described diols, probably resulting from partial hydrolysis of the allylic acetates during the work-up or during chromatography by traces of moisture, together with some polymeric products of the reaction.

5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol (6a).—A sample of the 3β,16β-diacetate (**6b**) was hydrolyzed by refluxing with 5% methanolic potassium hydroxide for 2.5 hr. The product was crystallized from ethyl acetate–methylcyclohexane and finally from acetone to give an analytical sample, m.p. 182–188°, $[\alpha]_D$ −32°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.80; H, 10.11.

Of the three isomeric diols described, this one proved to be the most unstable and difficult to purify. In one instance the compound crystallized as plates from methanol and had m.p. 186.5–188.5°. However, this solvent generally was avoided as it led to contamination by impurities resulting from methyl ether formation as shown by the appearance of a band at 206 c.p.s. in the n.m.r. spectrum. After having stood for a few months, this compound had a much broader melting point range. The infrared spectrum of the resulting material showed absorption in the carbonyl region, suggesting that some oxidation of the allylic hydroxyl group had occurred.

Rearrangement of a 1:1 Mixture of 5,16-Pregnadiene-3β,20α-diol and -3β,20β-diol Diacetates (3b:4b).—A solution containing 3.0 g. of a 1:1 complex of **3b**:**4b**,[10] m.p. 142–143°, was allowed to stand in the presence of 100 mg. of *p*-toluenesulfonic acid in 45 ml. of acetic acid and 7.5 ml. of acetic anhydride at room temperature for 60 hr. The reaction mixture was then poured into 400 ml. of water water and allowed to cool to room temperature and then extracted with ether. The organic phase was washed with sodium carbonate solution, dried, and evaporated under vacuum to give 2.93 g. of gummy solid material, $[\alpha]_D$ −51°. Vapor phase chromatography[24] indicated that the product consisted of about 60% of the 16β-*trans* isomer (**6b**) and about 30% of a mixture of the 16α-*trans* isomer (**7b**) and the 20-acetoxy-Δ^{16} starting material as a second unresolved band. A third, less polar band of variable intensity (10–20% of the total) appeared in each of the chromatographic studies and is most likely a triene resulting from pyrolytic elimination of an allylic acetoxy function occurring in the preheater of the instrument. Thin layer chromatography on silica gel did not show sufficient resolution to permit estimation of quantities. Chromatography on alumina afforded a partial separation and isolation of the two isomeric 16α- and 16β-acetoxy compounds in the same proportions as described in the preceding experiment.

A pure sample of 5,16-pregnadiene-3β,20β-diol[12] was subjected to the identical acid-catalyzed equilibration conditions with essentially the same results as were obtained from the 1:1 mixture of C-20 epimers. The predominant product isolated by column chromatography was the 16β-(*trans*)-diacetate (**6b**) together with lesser amounts of the 16α epimer (**7b**).

5-Pregnene-3β,16α-diol.[3]—A solution containing 150 mg. of 5,17(20)-(*cis*)-pregnadiene-3β,16α-diol (**8a**) in 20 ml. of ethyl alcohol was stirred in a hydrogen atmosphere in the presence of 30 mg. of 5% palladium on carbon. After a period of 50 min. 1 molar equiv. of hydrogen had been consumed and the reduction was discontinued. Removal of the catalyst by filtration, followed by evaporation of the solvent under vacuum, afforded 109 mg. of amorphous solid melting 230–245°. Crystallization from ethyl acetate gave 76 mg. of needles, m.p. 247–250°. The analytical sample had m.p. 249–250°, $[\alpha]_D$ −62°; lit.[3] m.p. 240–251°, $[\alpha]_D$ −73° (ethanol); Δν 38.5 (18-H), 61.5 (19-H) c.p.s. (CD_3COOD).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.40; H, 10.79.

5α-Pregnane-3β,16α-diol (14a). From 5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—The reduction of the 16α-(*cis*)-diene (**8a**) was carried out as in the preceding experiment but allowed

(24) A gas chromatography column packed with β-cyanoethylmethylpolysilane suspended on Chromosorb W was employed.

to continued until uptake of hydrogen ceased. After 2.25 hr. approximately 2 moles of hydrogen had been absorbed. Following removal of the catalyst, the ethanol was evaporated under vacuum and the product crystallized as fine needles from ethyl acetate in 90% yield, m.p. 259.5–260°, $[\alpha]_D$ −12.5° (0.5%).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.61; H, 11.42 (MT).

From 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7a).—The reduction of the 16α-(*trans*)-diene (**7a**) was carried out under identical conditions as described before. After 3.75 hr. about 2 moles of hydrogen had been absorbed and the catalyst was removed, the ethanol evaporated and the product crystallized from ethyl acetate. The saturated diol (**14a**) isolated in 87% yield was shown to be identical with the product of the reduction of the previous *cis* isomer by melting point and infrared spectral identity.

5α-Pregnane-3β,16α-diol Diacetate (14b). Method A.—The diacetate was prepared from the saturated diol (**14a**) by treatment with acetic anhydride in pyridine. A sample crystallized from methanol had m.p. 152.5–153.5°; $[\alpha]_D$ −78°; ΔM_D (16-OAc–16-OH) −246, −259; $\Delta\nu$ 37 (18-H), 49 (19-H) c.p.s.

Method B.—A solution of 5,17(20)-(*trans*)-pregnadiene-3β,16α-diol diacetate (**7b**) in ethanol was shaken in an atmosphere of hydrogen together with 5% palladium on carbon until 2 molar equiv. of hydrogen had been absorbed. The saturated diacetate was identical with that prepared by method A.

Reduction of 5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol and Its Diacetate (6a and 6b).—Reduction of the diol **6a** in the presence of palladium on calcium carbonate in ethyl alcohol was very sluggish. After 5 hr. only about 0.2 molar equiv. of hydrogen had been taken up and the reduction was discontinued. The crude product was largely starting diol. However, the appearance of a band at 5.76 μ in the infrared spectrum suggested formation of a five-membered ring ketone by isomerization of the allylic 16-hydroxyl function into the keto form.

In the presence of palladium on carbon the uptake of hydrogen was more rapid. After an interval of 40 min. 1 molar equiv. had been absorbed but only impure solids were isolated. The material gave a yellow 2,4-dinitrophenylhydrazone and had a band at 5.75 μ in the infrared. When the reduction was allowed to continue for 3.75 hr. approximately 2 molar equiv. of hydrogen had been absorbed. A solid was isolated in low yield having m.p. 137–139°. This was shown to be the product resulting from hydrogenolysis of the 16-hydroxy group and reduction of both double bonds. Mixture melting point determination and a comparison of the infrared spectra with an authentic sample showed this to be 5α-pregnan-3β-ol (lit.[25a] m.p. 137–138°). The crude residue from crystallization of the product had a band in its infrared spectrum at 5.74 μ, again indicating isomerization to a ketone.

Treatment of the 5α-pregnan-3β-ol with acetic anhydride in pyridine afforded the acetate as leaflets having m.p. 113–114° (lit.[25c] m.p. 113–114°).

Reduction of 0.2 g. of the 16β-(*trans*)-diacetate (**6b**) in the presence of palladium on carbon proceeded rapidly with the uptake of 2 molar equiv. of hydrogen in 1 hr. and 10 min. The product was a mixture from which could be isolated in somewhat impure form two hydrogenolysis products. From methanol there was obtained as first crop 73 mg. of prisms having m.p. 143–152°, $[\alpha]_D$ −55°. A comparison of infrared spectra and mixture melting point determination showed this to be slightly impure 3β-acetoxy-5-pregnene (lit.[26] m.p. 151–152°, $[\alpha]_D$ −60°).

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.82; H, 10.66.

The second crop from the preceding reduction crystallized as leaflets from methanol, 51 mg., m.p. 109–110°. Mixture melting point determination with an authentic sample of 3β-acetoxy-5α-pregnane,[25c] m.p. 113–114°, showed no depression. The infrared spectra of the two samples were virtually identical.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.78; H, 11.00.

Later crops appeared to be mixtures of these two compounds.

***trans*- and *cis*-4,17(20)-Pregnadiene-3,16-dione (15 and 16). From 5,17(20)-(*trans*)-Pregnadiene-3β,16β-diol (6a).**—A solution of 1.0 g. of the 16β-*trans* isomer (**6a**) and 1.0 g. of aluminum isopropoxide in 100 ml. of toluene and 14 ml. of cyclohexanone was maintained at reflux for 1 hr. during which time a total of 37 ml. of solvent was removed by distillation. Following this period the solution was diluted with Rochelle salt solution and steam distilled for 2 hr. Solids were collected by filtration, and dried to constant weight, 0.78 g., m.p. 172–190°. This material was taken up in benzene and placed on a column of 45 g. of alumina. Elution with 3 to 5% ethyl acetate in benzene afforded 336 mg. of crystalline solids melting at 180–190°. Recrystallization from aqueous methanol afforded an analytical sample of 4,17(20)-(*trans*)-pregnadiene-3,16-dione (**15**), m.p. 188–190°; $[\alpha]_D$ −61°; λ_{max} 241 mμ (25,000); λ_{max}^{KBr} 5.82, 5.96, 6.07, 6.17 μ; $\Delta\nu$ 58 (18-H), 73.5 (19-H), 120.5, 128 (21-H), 331.5, 338.5, 345.5, 353 (20-H) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.41.

Further elution of the product from the column with 10% ethyl acetate–benzene yielded as a minor component 143 mg. of the *cis* isomer (**16**) as prisms from aqueous methanol, m.p. 170–171.5°; $[\alpha]_D$ −30°; ΔM_D (*cis*–*trans*) +97.5°; λ_{max} 241 mμ (ε 27,600); λ_{max}^{KBr} 5.80, 5.95, 6.06, 6.16 μ; $\Delta\nu$ 64.5 (18-H), 74 (19-H), 107, 114.5 (21-H), 377, 384.5, 392, 399.5 (20-H) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.48; H, 8.87.

Paper chromatography indicated that the oxidation of the 16β-(*trans*)-diol afforded the mixture of *trans*-*cis* diones in the ratio of about 4:1, respectively.

From 5,17(20)-(*cis*)-Pregnadiene-3β,16α-diol (8a).—An Oppenauer oxidation of the 16α-*cis* isomer carried out in the same fashion as described before afforded the *cis*-dienedione (**16**) and *trans*-dienedione (**15**) in a ratio of about 2:1 as determined by paper chromatography.

From 5,17(20)-(*trans*)-Pregnadiene-3β,16α-diol (7a).—This isomer upon Oppenauer oxidation gave the *trans*-dienedione (**15**) in 57% yield by direct crystallization. The filtrates were shown by paper chromatography to contain additional quantities of this product accompanied by lesser amounts of the *cis* isomer.

Acid-Catalyzed Rearrangement of the Epimeric 20-Hydroxy-5,16-pregnadiene-3-one Ethylene Ketals. 16α-Acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (13b).—A solution of 5 g. of 20α-hydroxy-5,16-pregnadiene-3-one ethylene ketal[10] in 110 ml. of acetic acid and 15 ml. of acetic anhydride together with 250 mg. of *p*-toluenesulfonic acid monohydrate was allowed to stand at room temperature for 60 hr. The reaction mixture was poured into warm water and then extracted with benzene. The organic layer was washed with sodium carbonate solution, dried, and concentrated to a sirup. The ultraviolet spectrum showed a maximum at 239 mμ (ε 14,320).

The crude product was placed on a column of alumina and, using a gradient elution technique, eluted by gradually varying the solvent from pure benzene to 3% ethyl acetate–benzene. The products were not cleanly separated but were eluted as a single rather broad band. From the early fractions, eluted by 1% ethyl acetate in benzene there was obtained as long rods from methanol 16α-acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (**13b**), m.p. 133–133.5°. An analytical sample had m.p. 133–134°; $[\alpha]_D$ +5°; λ_{max} 240.5 mμ (ε 17,050); $\Delta\nu$ 49 (18-H), 72.2 (19-H), 92.2, 99 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.39; H, 8.96.

16β-Acetoxy-4,17(20)-(*trans*)-pregnadien-3-one (12b).—From the fractions obtained as the trailing edge of the band of eluents containing 1.5 to 2.5% ethyl acetate in benzene the major component in the reaction mixture was isolated. Crystallization of this material from methanol yielded the 16β-acetoxy-*trans* isomer (**12b**), m.p. 157–159.5°; $[\alpha]_D$ +114°; λ_{max} 241 mμ (ε 17,050); $\Delta\nu$ 57 (18-H), 72.4 (19-H), 91.5, 98.5 (21-H) c.p.s.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.45; H, 8.89.

The intermediate fractions could not be induced to crystallize. In one experiment these fractions were pooled and rechromatographed on alumina using the same gradient elution procedure as employed in the initial separation. By this operation additional quantities of the isomeric 16-hydroxy compounds **12b** and **13b** were isolated. Nevertheless, the separation was incomplete and intermediate fractions again were not crystalline. By analogy with the results obtained in the 3-acetoxy series, the

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presence of a small amount of Δ^{16}-20-acetoxy material may account, in part, for the difficulties encountered in obtaining crystalline material.

A similar acid-catalyzed equilibration of a 1:1 mixture of 20α- and 20β-hydroxy-Δ^{16}-3-ethylene ketals[10] afforded the same mixture of products in the same relative proportions as were isolated from the pure 20α isomer.

16α-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (13a).—The treatment of the 16α-acetate **13b** with alcoholic potassium hydroxide at reflux for 1.5 hr. afforded the 16α-hydroxy compound (**13a**). The product crystallized as needles from ether–petroleum ether (b.p. 66–69°) and had m.p. 173.5–175.5°; $[\alpha]_D$ +104.5°; ΔM_D (16-OAc–16-OH) −311°; λ_{max} 240 mμ (ϵ 16,700); $\Delta\nu$ 47.5 (18-H), 72.5 (19-H), 105, 112 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.21; H, 9.54.

16β-Hydroxy-4,17(20)-(*trans*)-pregnadien-3-one (12a).—Alkaline hydrolysis of the 16β-acetate (**12b**) afforded the 16β-hydroxy compound (**12a**) as blades from ether–petroleum ether, m.p. 172–175°; $[\alpha]_D$ +141.5°; ΔM_D (16-OAc–16-OH) −39°; λ_{max} 240.5 mμ (ϵ 16,850); $\Delta\nu$ 58.4 (18-H), 72.2 (19-H) 100, 106 (21-H) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.55; H, 9.70.

Preparation of Amino Acids from Trichloromethylcarbinols[1]

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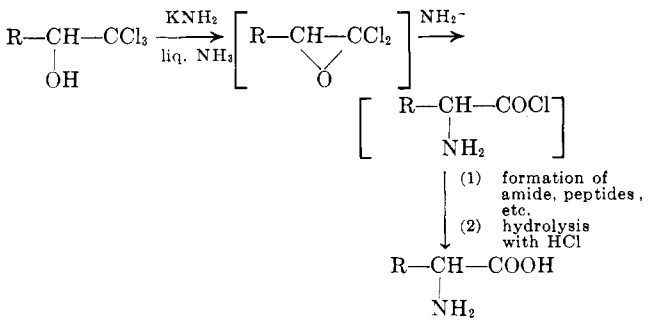
The conversion of four trichloromethylcarbinols to amino acids by treatment with potassium amide in liquid ammonia at −33° has been studied. The reaction occurs in 29 to 48% yields, and is believed to involve the formation of an intermediate epoxide followed by the opening of the epoxide ring by amide ion. The amino acids prepared were α-aminobutyric acid, valine, 2-methyl-2-aminopropionic acid, and phenylglycine. Methods of preparing alkyl and aryl trichloromethylcarbinols are reviewed and discussed.

Alkyl and aryl trichloromethylcarbinols are potentially useful intermediates for the synthesis of α-substituted carboxylic acids. It is known that phenyltrichloromethylcarbinol reacts with a concentrated aqueous potassium hydroxide solution to form α-chlorophenylacetic acid in 26% yield,[3] with methanolic potassium hydroxide to form α-methoxyphenylacetic acid in 72% yield,[4] and with ethanolic sodium ethoxide to form α-ethoxyphenylacetic acid in 33% yield.[5] The mechanism proposed for these reactions involves the intermediate formation of an epoxide and the subsequent opening of the epoxide ring by a nucleophilic reagent.[6] In the present work, amide ion was used as the nucleophilic reagent to obtain α-amino acids.



The conversion of four trichloromethylcarbinols to amino acids was studied (Table I). The R group in the above equation was ethyl, isopropyl, and phenyl. In addition, 1,1,1-trichloro-2-methyl-2-propanol (chlorobutanol) was studied. In all cases, the reaction was carried out by adding the carbinol to a solution of potassium amide in liquid ammonia at −33°. The mixture was stirred for 8 to 12 hr. the ammonia was allowed to evaporate, and the final amino acid was obtained by hydrolyzing the initially formed products with ethanolic hydrochloric acid.

Attempts were made to isolate the α-amino amide, a postulated intermediate prior to acid hydrolysis, but positive identification could not be made. It appears that a mixture of products are formed at this stage of the reaction. Thus, if the excess potassium amide is decomposed under mild conditions, *e.g.*, by the use of 95% ethanol, and the hydrolysis step with hydrochloric acid is omitted, phenylglycine is still obtained in 5 to 12% yield. When hydrolyzed with hydrochloric acid, the yield is 48%. Apparently, there are both readily hydrolyzable and difficultly hydrolyzable species in the reaction mixture. The former probably includes the amino acid amide; the latter may include the diketopiperazine, peptides, and Schiff bases. Even under what appeared to be optimum conditions, a red, viscous nonhydrolyzable oil accounted for about half of the reaction product. Infrared spectroscopy and v.p.c. showed benzaldehyde and unchanged starting materials to be two of the major components of this oil.

Optimum reaction conditions were determined with phenyltrichloromethylcarbinol. With potassium amide the reaction did occur, whereas sodamide was ineffective, presumably because of its insolubility in the liquid ammonia solvent. Even powdered potassium hydroxide slurried in liquid ammonia was almost as effective (39% yield) as the potassium amide. With no base present there was no reaction. Using potassium hydroxide as the base, attempts to carry out the reaction at 30 and at 100° in a steel hydrogenation vessel gave only 15% yields, probably because the rocking autoclave provided insufficient agitation. The reaction was also carried out at 48° in a methanolic potassium hydroxide solution saturated with ammonia, and a 34% yield of phenylglycine was obtained.

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