The stereochemical purity of the two epoxides was shown to be greater than 99.5% by gas–liquid chromatography on a 30-ft. 20% Carbowax 20M on Chromosorb P column at 150°. The retention of the *cis* epoxide was 10.0 min. and that of the *trans* epoxide, 8.7 min.

Preparation of 1-Hexene Oxide.—A mixture of 24.4 g. (0.119 mole) of *m*-chloroperbenzoic acid (85%) and 10.0 g. (0.119 mole) of 1-hexene in 300 ml. of anhydrous diglyme was allowed to stand 24 hr. in a refrigerator. The mixture was subjected to distillation collecting the fraction up to 162°. This fraction was redistilled through a 2-ft. helices-packed column giving 7.05 g. (60%) of 1-hexene oxide, b.p. 116–119°, $n^{20}D$ 1.4051 (lit.[5] b.p. 117–119°, $n^{20}D$ 1.4060).

Acknowledgment.—The authors wish to thank the National Institutes of Health for a predoctoral fellowship to C. C. C. (No. 1-F1-GM-21, 333-01).

(5) W. D. Emmons and A. S. Pagaro, *J. Am. Chem. Soc.*, **77**, 89 (1955).

The Decarboxylation of 3-Carboxy-2-isoxazolines

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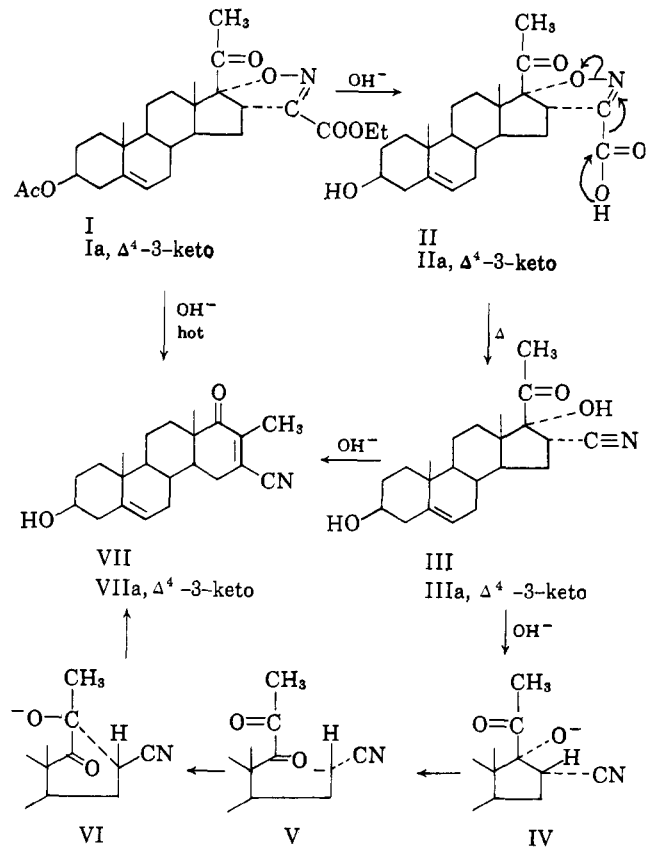
In the course of preparing a series of steroidal isoxazolines by the method of nitrile oxide addition to an olefin,[1] we found that pregna-5,16-dien-3β-ol-20-one acetate reacted smoothly in ether solution with carbethoxyformonitrile oxide[2] to yield (80%) the ethyl ester (I) of 16α,17α-[3-carboxy-3,1-(2-isoxazolino)]-pregn-5-en-3β-ol-20-one 3β-acetate ester.

Hydrolysis of this ester in methanol solution with aqueous sodium or potassium hydroxide at room temperature yielded the salt of the corresponding acid from which the free acid (II) was obtained by acidification with hydrochloric acid. The 3-acetate ester was removed simultaneously. When this hydrolysis was carried out by refluxing the ester in aqueous methanol with potassium carbonate, the acidic product (in 67% yield) was accompanied by a neutral product in 7% yield. This latter material showed infrared absorption at 2220 (cyano) and at 1680 cm.$^{-1}$ (conjugated carbonyl). The ultraviolet absorption, λ 247 mμ (ε 10,700), also indicated the presence of a conjugated ketone.

This same product (VII) was also obtained by a second process. When the free acid, 3β-hydroxy-16α,-17α-[3-carboxy-3,1-(2-isoxazolino)]-pregn-5-en-20-one (II) was heated on a hot plate at 250–280° to give a clear melt (with loss of CO_2 and initial foaming) and then cooled and crystallized, the product again showed cyano group absorption in the infrared but without conjugate absorption. Loss of the carboxyl group and isoxazoline ring opening produced the 16α-cyano-17α-hydroxy steroid (III) as a stable product. Treatment of this product (III) with base caused a dehydration and gave rise to VII. The structure of III was confirmed by analytical data, the presence of hydroxyl (3440 and 3240 cm.$^{-1}$), 20-carbonyl (1717 cm.$^{-1}$), and cyano (2267 cm.$^{-1}$) group absorption in the infrared,



and by the n.m.r. spectrum of the Δ⁴-3-keto analog (IIIa). The Δ⁴-3-keto series was obtained by the selective addition (55% yield) of carbethoxyformonitrile oxide to the Δ¹⁶ double bond of pregna-4,16-diene-3,20-dione to give Ia, followed by hydrolysis and pyrolysis to give IIa and IIIa, respectively. The Δ⁴-3-keto analog (IIIa) was sufficiently soluble in deuteriochloroform to obtain the n.m.r. spectrum, whereas the Δ⁵-3-hydroxy steroid (III) was not.

The n.m.r. spectrum of IIIa shows singlets in deuteriochloroform for the C-18 methyl (δ 0.68) and for the C-21 methyl (δ 2.28), both of which are characteristic of the normal steroid structure and which are not in accord with a D-homo structure.[3] The δ-value of 0.68 is also in better accord with a 17α-hydroxy-17β-acetyl configuration than with the "iso" structure, since the 17β-hydroxyl group tends to shift the resonance band of the C-18 methyl protons downfield in this type of structure.[4] The effects of the 16-cyano group cannot, however, be completely assessed. This interpretation of the n.m.r. data, together with the probable attack of the nitrile oxide from the α-face of the molecule, leads to the designation of III as 16α-cyano-3β,17α-dihydroxy-pregn-5-en-20-one.[4a]

(1) A. Quilico, in "Heterocyclic Compounds," R. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 99.

(2) G. S. Skinner, *J. Am. Chem. Soc.*, **46**, 731 (1924).

(3) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 215 (1961).

(4) Unpublished data from these laboratories. The C-18 methyl proton resonance in *epi*-testosterone has a value δ 0.70 compared with testosterone, δ 0.80. The C-18 methyl proton resonance in 3β-acetoxy-17α-hydroxy-pregn-5-en-20-one has a value δ 0.70 compared with 3β-acetoxy-17β-hydroxy-17-isopregn-5-en-20-one, δ 0.94.

(4a) NOTE ADDED IN PROOF.—The mass spectrum of compound IIIa gave additional evidence for the unrearranged steroid structure, showing a molecular ion peak at *m/e* 355 and fragments corresponding to the loss of acetyl at M − 312 and to acetyl at M − 43. The mass spectrum was determined with an Atlas CH4 mass spectrometer with an ionizing potential of 70 e.v. and an ionizing current of 18 μa. We wish to thank Dr. C. D. DeJongh of Wayne State University for determining and interpreting these results.

Treatment of III or IIIa with strong base readily yielded an α,β-unsaturated ketone VII or a bis α,β-unsaturated ketone VIIa, respectively. These were shown by n.m.r. to have a D-homo structure.[5] The C-18 methyl proton resonance is shifted downfield to δ 1.02 in VII and to δ 1.05 in VIIa, characteristic of a 17a-keto-D-homo steroid.[3] Instead of a singlet for the C-21 methyl protons, a split resonance (δ 2.08) is present which would be expected for a C-17 methyl in a D-homo steroid, split unequally through the 16,17 double bond by the C-15 protons.[7]

In the base-catalyzed D-homo rearrangement of a steroid with a 17α-hydroxy-17β-acetyl functionality, as in III, the predominant product in past experience has been the 17a-methyl-17a-hydroxy-17-one D-homo system corresponding to migration of the 13,17 bond.[8] Elimination of the elements of water from such a system in the present case would lead to a 17a-methylene group, a structure not allowed by the n.m.r. spectrum which shows no vinyl proton resonances and does show the D-homo 17-methyl proton resonance. The alternative possibility of C-18 methyl migration is precluded by the above considerations and the spectral requirement of an α,β-unsaturated carbonyl. Elimination thus removes the product VII from the equilibration mechanisms of the D-homo acyloin rearrangement in what corresponds to 16,17 bond migration.

The structures described above also fix the direction of addition of the nitrile oxide to the 16,17 double bond (as shown in I) analogous to the addition of diazomethane to this bond.[9]

The two 16α-cyano-17α-hydroxy steroids melt considerably higher (III, 275°; IIIa, 245°) than the corresponding 3-carboxy-2-isoxazolines (II, 213°; IIa, 210°) and this may explain the erratic melting points of these acids, which decarboxylate at their melting points and then exhibit a higher melting range.

Drefahl and Hörhold[6] have commented in a preliminary statement on the thermal instability of the 3-carboxy-2-isoxazolines during saponification of the esters, indicating the formation of an aldehyde (equivalent to loss of a carbon atom from the initial olefin), of carbon dioxide, and of an additional unidentified product. Whether this is a base catalyzed or only a thermal reaction is not clear from the description given.

Experimental

Melting points are corrected and were determined in a Thomas–Hoover (TH) apparatus (capillary tube) or on a Fisher-Johns (FJ) hot plate and are so labeled. The following measurements were made by Dr. J. M. Vandenbelt and his staff in our laboratories: rotations were measured at room temperature in chloroform solution in a 1-dm. tube; infrared spectra were determined in potassium bromide pressed disks in a Beckman IR-7 recording spectrophotometer; ultraviolet absorption spectra were determined in methanol in a Model 14 Cary recording spectrophotometer. Microanalyses were by Mr. C. E. Childs and his staff in our laboratories.

16α,17α-[3-Carboxy-3,1-(2-isoxazolino)]pregn-5-en-3β-ol-20-one 3β-Acetate, Ethyl Ester (I).—A solution of 3.56 g. (0.01 mole) of pregna-5,16-dien-3β-ol-20-one acetate and 4.58 g. (0.03 mole) of ethyl chloroximinoacetate[2] in 500 ml. of dry ether was treated with a solution of 4 ml. of triethylamine in 125 ml. of dry ether at 25° during 3 hr. with stirring. The reaction was then stirred for an additional 3 hr. and let stand at 25° overnight. The mixture was filtered and the filtrate was evaporated to a yellow oil which solidified on standing. Crystallization from methanol gave 3.8 g. of pearly white plates (80% yield): m.p. 168–170° (TH); λ_{max} 249 mμ (ϵ 5000); $[\alpha]^{23}D$ −14° (*c* 0.92, $CHCl_3$); ν_{max} 1728 (ester), 1717 (sh) (keto), 1588 (C=N) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{37}NO_5$ (471.6): C, 68.76; H, 7.89; N, 2.97. Found: C, 68.94; H, 7.99; N (Kjeldahl), 3.08.

16α,17α-[3-Carboxy-3,1-(2-isoxazolino)pregn-5-en-3β-ol-20-one (II).—A mixture of 0.5 g. of I with 30 ml. of methanol, 0.6 ml. of 50% aqueous sodium hydroxide, and 3 ml. of water was swirled to dissolve the steroid and was then let stand for 2 hr. at room temperature. A thick white precipitate formed. The mixture was cooled in ice and filtered. The solid was dissolved in 50 ml. of water and 1 ml. of methanol, diluted to 100 ml. with water, cooled, and acidified to pH 1 with 3 *N* hydrochloric acid. The mixture was chilled in ice and filtered. The product weighed 0.27 g., m.p. 224–230° (TH). Crystallization from 50% aqueous dioxane gave 0.21 g. of colorless needles: m.p. 213° (TH); 50% yield; ν_{max} 3405 (OH), 1730 (carboxyl), 1715 (keto), 1593 (C=N) cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{31}NO_5$ (401.5): C, 68.80; H, 7.78; N, 3.48. Found: C, 68.84; H, 7.80; N (Kjeldahl), 3.56.

3β-Hydroxy-17-methyl-17a-oxo-D-homo-pregna-5,16-diene-16-carbonitrile (VII).—A solution of 2.78 g. (5.9 mmoles) of I in 100 ml. of methanol with 2 g. of potassium carbonate and 25 ml. of water was refluxed for 2 hr. The methanol was evaporated under reduced pressure and the neutral solid was separated by filtration. The filtrate was acidified with acetic acid to yield 1.6 g. of acidic product (II).

The neutral product, 0.29 g., was crystallized from aqueous acetone to give VII: 0.14 g.; m.p. 260–262° (TH); λ_{max} 247 mμ (ϵ 10,700); ν_{max} 3470 (hydroxyl), 2220 (cyano), 1680 (keto) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}NO_2$: (339.5): C, 77.80; H, 8.61; N, 4.12. Found: C, 77.76; H, 8.61; N, 4.21.

Acetate.—VII with pyridine and acetic anhydride yielded white needles (from ethanol): m.p. 260°; λ_{max} 246 mμ (ϵ 10,600); ν_{max} 2210, 1728, 1678, 1640, 1623, 1259 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{31}NO_3$ (381.5): C, 75.55; H, 8.19; N, 3.68. Found: C, 75.54; H, 8.27; N, 3.77.

3β,17α-Dihydroxy-20-oxopregn-5-ene-16α-carbonitrile (III).—A sample (1.7 g., 4.2 mmoles) of II was heated on a hot plate in an erlenmeyer flask at 280° to give a clear yellow melt. On cooling, the product was taken into methanol and crystallized to yield 700 mg. (44%), m.p. 225–265°. Recrystallization from methanol and ether gave 350 mg.: m.p. 275–277° (FJ); no significant ultraviolet absorption; $[\alpha]^{23}D$ −98.3° (*c* 0.59, MeOH); ν_{max} 3440 and 3240 (hydroxyl), 1717 (keto), 2267 (cyano) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}NO_3$: (357.5); C, 73.91; H, 8.74; N, 3.92. Found: C, 73.74; H, 9.04; N, 4.31.

3β-Hydroxy-17-methyl-17a-oxo-D-homo-pregna-5,16-diene-16-carbonitrile (VII) from III.—A solution of 50 mg. of III and 500 mg. of potassium hydroxide in 15 ml. of methanol was heated on the steam bath for 10 min., cooled, and precipitated with water. The solid was filtered off, washed with water, and dried in air to yield 40 mg., m.p. 255° (FJ) of VII, infrared absorption curve identical with that of VII obtained by the carbonate hydrolysis of I (see above).

16α,17α-[3-Carboxy-3,1-(2-isoxazolino)]pregn-4-ene-3,20-dione, Ethyl Ester (Ia).—A solution of 1.6 g. of 16-dehydroprogesterone in diethyl ether, when treated with 2.3 g. of ethyl chloroximinoacetate by the same method as for I, yielded 1.2 g., 55% yield, m.p. 215–217° (FJ). Two crystallizations from methanol gave 1.0 g.; m.p. 218–220° (FJ); λ_{max} 240 mμ (ϵ 21,000); $[\alpha]^{23}D$ +89.3° (*c* 0.56, $CHCl_3$); ν_{max} 1727, 1676, 1625, 1597 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}NO_5$ (427.5): C, 70.23; H, 7.78. Found: C, 70.22; H, 7.65.

3,17a-Dioxo-17-methyl-D-homo-pregna-4,16-diene-16-carbonitrile (VIIa).—A solution of 1.5 g. of Ia in 100 ml. of methanol with 3 g. of potassium bicarbonate in 25 ml. of water was heated

(5) We are indebted to a referee of the original manuscript for valuable suggestions regarding a D-homo rearrangement reconciling our results with those of Drefahl and Hörhold.[6]

(6) G. Drefahl and H. H. Hörhold, *Chem. Ber.*, **97**, 159 (1964).

(7) We wish to thank Dr. Glenn Berchtold for discussions of the n.m.r. data.

(8) N. L. Wendler in "Molecular Rearrangement," Vol. II, P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p. 1116; N. L. Wendler, D. Taub, and R. Firestone, *Experientia*, **15**, 237 (1959).

(9) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962); D. Taub, R. D. Hofsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *ibid.*, **82**, 4012 (1960).

to boiling and then allowed to stand overnight at 25°. The mixture was filtered into excess dilute hydrochloric acid, diluted with water, and filtered; the product was washed with water. The wet acid IIa was melted in a 50-ml. erlenmeyer flask on a hot plate, cooled, taken into ether and filtered. The filtrate on evaporation gave an orange oil IIIa which was treated with 250 mg. of potassium hydroxide in 25 ml. of methanol and boiled for 15 min. The reaction was diluted with water to yield a crystalline solid, 400 mg., m.p. 170–174°. The product was purified by passing it over 10 g. of alumina in dichloromethane–ether. The first eluates gave white crystalline material which was crystallized from ether to give 180 mg. of VIIa: 15% yield; m.p. 190–193° (FJ); λ_{max} 240.5 mμ (ε 26,800); ν_{max} 2215 (cyano), 1688, 1624 cm.$^{-1}$; $[\alpha]^{23}D$ −18.5° (*c* 0.54, $CHCl_3$).

Anal. Calcd. for $C_{22}H_{27}NO_2$ (337.4): C, 78.30; H, 8.08. Found: C, 78.33; H, 8.22.

16α17α-[3-Carboxy-3,1-(2-isoxazolino)]pregn-4-ene-3,20-dione (IIa).—A solution of 4.0 g. (0.01 mole) of II in 1 l. of acetone (distilled over $KMnO_4$) was treated at ice-bath temperature and under nitrogen with 5 ml. of 8 *N* chromic acid (Jones reagent)[10] during 7 min., stirred for an additional 5 min., and quenched in 1.5 l. of ice–water. Most of the acetone was evaporated under reduced pressure, and the precipitated solid was separated by filtration, washed with water, and dried, 2.9 g., 72% crude. The crude product was refluxed for 25 min. in 200 ml. of 95% ethanol with 900 mg. of oxalic acid dihydrate. The mixture was evaporated under reduced pressure at 50–60° and crystallized from dioxane–water to give 2.37 g. (60% yield): m.p. 210–212° (TH); λ_{max} 240 mμ (ε 18,700); $[\alpha]^{24}D$ +102° (*c* 0.51, $CHCl_3$); ν_{max} 1741, 1719, 1675, 1633, 1587 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{29}NO_5$ (399.5): C, 69.15; H, 7.32; N, 3.51. Found: C, 69.05; H, 7.13; N, 3.60.

17α-Hydroxy-3,20-dioxopregn-4-ene-16α-carbonitrile (IIIa).—A sample (1.0 g.) of IIa was melted at 250° until all foaming ceased. The melt was cooled and stirred with methanol to yield 280 mg. of a solid product, m.p. 245° (FJ). Two crystallizations from methanol and ether gave 80 mg.: m.p. 245–247° (FJ); λ_{max} 240 mμ (ε 16,000); $[\alpha]^{23}D$ +92.2° (*c* 0.51, $CHCl_3$); ν_{max} 3440 (hydroxyl), 2250 (cyano), 1710 (keto), 1655 (keto), 1616 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}NO_3$ (355.5): C, 74.33; H, 8.22. Found: C, 74.14; H, 8.22.

(10) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon *J. Chem. Soc.*, 39 (1946).

A Novel 2.2.1-Bicyclic Elimination of a N-Tosylpyrazoline

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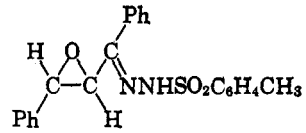
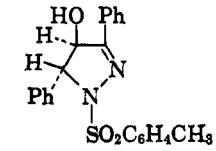
The pyrolytic decomposition of the alkali salts of tosylhydrazones of aldehydes and ketones in aprotic solvents has been reported to give products expected to arise from intermediate carbenes.[1,2] In view of our interest in heterocyclic small-ring compounds, we sought to define further the reactivity of a carbenoid center adjacent to a three-membered oxirane ring.

In an attempt to prepare the tosylhydrazone of *trans*-chalcone oxide (I), two different approaches were tried. Treatment of *trans*-chalcone oxide with tosylhydrazide in acidic ethanol for 5 min. at 50° gave a product identical with that obtained by treating benzalacetophenone tosylhydrazone with 10% sodium hydroxide and 30% hydrogen peroxide in methyl alcohol. That the product from both reactions was not the desired tosylhydrazone I was evidenced by a strong peak



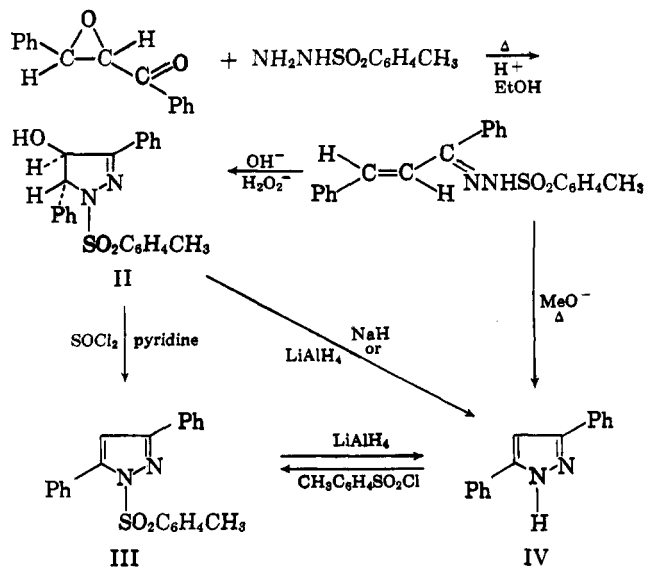
I



II

at 3.0 μ in its infrared spectrum. This material is instead assigned structure II on the basis of chemical and physical data cited below. The elemental analysis of II, m.p. 225–226°, indicates that it is an isomer of I. Dehydration with thionyl chloride–pyridine in benzene afforded in excellent yield 1-*p*-toluenesulfonyl-3,5-diphenylpyrazole (III). Treatment of III with lithium aluminum hydride in tetrahydrofuran readily gave rise to 3,5-diphenylpyrazole (IV). Structure III was further confirmed by its unequivocal synthesis from 3,5-diphenylpyrazole and *p*-toluenesulfonyl chloride. The various transformations leading to the products described above are outlined in Chart I.

CHART I



Even with the mildest conditions, 4-hydroxypyrazoline (II) resulted from the reaction of tosylhydrazide with the *trans* oxide of benzalacetophenone. The mechanism of its formation probably involves the intermediate formation of tosylhydrazone (I) which then undergoes an intramolecular ring opening and closure to form II. The configuration of II is such that the hydroxyl group on C-4 and the hydrogen on C-5 are on the same side of the pyrazoline ring. A related study of the reaction of hydrazine with an epoxy ketone[3] has shown that the epoxide ring is opened to give a similar intermediate, which, on heating, loses water to yield the corresponding pyrazole. It has also been reported[4] that the related *trans*-ethylenimine ketones and phenylhydrazine produce the analogous 4-aminotrialkylpyrazolines.

Treatment of II with sodium hydride in diglyme or tetrahydrofuran led to an unexpected result. Under the basic conditions employed, II was converted in almost quantitative yield to 3,5-diphenylpyrazole (IV)

(1) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).
(2) L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959).
(3) Jorlander, *Ber.*, **49**, 2782 (1916).
(4) N. H. Cromwell and H. Hoeksema, *J. Am. Chem. Soc.*, **71**, 716 (1949).