and flash distilled to give 37.17 g. of crude product, b.p. 82–103° at 0.8–1.7 mm. Distillation through a Podbielniak column with 13 in. of "Heli-pak" packing gave 3.73 g. of pure ethyl 6-cyanohexanoate, b.p. 99–100° at 1.3 mm., $n^{35}D$ 1.4292. The column holdup, 4.57 g., was 98% pure cyano ester and these two fractions represent a 16% yield. Other fractions contained considerable amounts of the cyano ester.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.13; H, 8.54; N, 8.26.

A more effective method of separating the hydroxy ester from the cyano ester was found to be chromatography on alumina. Thirty grams of a mixture of the hydroxy ester and cyano ester (64% cyano ester by infrared analysis[13]) in 100 ml. of benzene was passed over a 1 × 12 in. column of wet packed chromatographic alumina (Fisher 80–200 mesh) and eluted with benzene. Five 200-ml. fractions were collected. The first fraction gave 16.9 g. of ethyl 6-cyanohexanoate after evaporation of the benzene. Infrared analysis of the material showed it to be 90% pure cyano ester with trace impurities of benzene and the hydroxy ester. The other four fractions from the elution with benzene gave a total of 7.55 g. of residues which were mixtures of the hydroxy ester and the cyano ester. Elution of the column with 200 ml. of formula 30 ethanol gave an additional 6 g. of material, which by infrared analysis was shown to contain a maximum of 9% of the cyano ester and was predominately the hydroxy ester (some ethanol was present in the sample).

One gram (5.96 mmoles) of ethyl 6-cyanohexanoate was refluxed with 3 g. (54 mmoles) of potassium hydroxide in 15 ml. of water for 4.25 hr. The cooled hydrolysate was neutralized to pH 2 with concentrated hydrochloric acid and saturated with salt. The white solid which separated was filtered and the aqueous solution was extracted with three 30-ml. portions of ether. The residue from the evaporation of the ether was combined with the solid and recrystallized from benzene to give 0.3 g. of pimelic acid, m.p. 104.5–106.5°. A mixture melting point with authentic sample of pimelic acid, m.p. 105–106°, gave no depression.

Valeronitrile.—A mixture of 6.51 g. (0.1 mole) of dry, powdered potassium cyanide and 34.1 g. (0.1 mole) of *n*-butyl stearate in a 250-ml. reaction flask equipped with a stirrer, thermometer, nitrogen inlet, and side arm for distillation was heated by means of a Woods metal bath (at 260° initially) to 350° during 40 min. During the next 8 min. a liquid distilled from the reaction flask. Thirty-four minutes additional heating up to 397° yielded little more distillate. Infrared analysis showed the nitrile to be contaminated with alcohol. Redistillation of the distillate, 6.2 g., yielded 1.63 g. (19.7%) of valeronitrile, b.p. 139.8–140°, $n^{35}D$ 1.3908. The infrared spectrum of the product was identical with an authentic sample of valeronitrile (Eastman Kodak White Label).

(13) Infrared analyses were performed by H. J. Sloane and R. A. Nyquist.

Steroids. LXX.[1,2] The Preparation of Some Pentacyclic Steroid Derivatives

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A recent report[1b] from this laboratory describes the base-catalyzed condensation of acetone with steroidal Δ^{16}-20-ketones to produce pentacyclic products containing a 16,17-butanoandrostane ring system. We describe here an alternate approach to this class of compounds employing a Diels–Alder reaction[3] for the ring forming step.

3β,20-Diacetoxy-pregna-5,16,20-triene (I),[4] prepared by enol acetylation of 16-dehydropregnenolone acetate, reacted readily with dimethyl acetylene dicarboxylate to yield a mixture of epimeric (at C-16) adducts from which the major component, m.p. 197–198°, could be isolated by crystallization in 40–50% yield. The infrared spectrum of this compound contained bands at 1760 (enol acetate), 1730–1740 (esters), and 1640 cm.$^{-1}$ (olefin). These results as well as the elemental analysis, n.m.r. spectrum (see Experimental), and mode of formation are in agreement with structure II for the adduct; the 16β-H configuration proposed for the ring juncture is based solely on the known preference for 16α- attack shown by other addition reactions[5] of 16-dehydro steroids.

Dehydrogenation of the new cyclohexadiene ring of the adduct II was accomplished in 69% yield[6] by treatment with chloranil[7] in refluxing chlorobenzene or simply by boiling in nitrobenzene.[7] The aromatic product III could be crystallized from hexane, cyclohexane, or isopropyl alcohol. In each case, the product melted with evolution of gas within the range 120–130°. The crystals from isopropyl alcohol showed weak hydroxyl absorption in the infrared at 3600 cm.$^{-1}$ and gave an elemental analysis which checked well for one-half molecule of isopropyl alcohol of crystallization. Similarly, a n.m.r. spectrum[8] of the product from cyclohexane crystallization included a sharp singlet at 8.57 (6H) indicating a half mole of solvent of crystallization. Another noteworthy feature of this spectrum was evident in the high field methyl resonance region where two sharp singlets (3H each) were found at 8.91 and 8.98, respectively. The latter absorption peak, present also in the spectrum of the adduct II, may be assigned to the C-19 angular methyl group.[9] The C-18 methyl resonance which in most steroids appears at *higher* field[9] must, in this case, be identified with the *lower* field resonance line. This extreme deshielding of the C-18 methyl resonance is presumably caused by the magnetic anisotropy effect of the nearby aromatic ring.[10]

(1) (a) Presented in part at the American Chemical Society Southwest-Southeast Regional Meeting, December 7–9, 1961; (b) Paper LXIX, M. E. Wall, S. Serota, H. Kenney, and G. S. Abernethy, in press.

(2) This work was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(3) Maleic anhydride has already been reported to undergo diene addition reactions with 20-methylene-Δ^{16}-pregnenes and with 20-acetoxy-$\Delta^{16,20}$-pregnadiene derivatives; see F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959), and references therein cited.

(4) R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

(5) (a) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenberg, *ibid.*, **73**, 1528 (1951); (c) H. Hirschmann, E. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952); (d) D. Gould, F. Gruen, and E. B. Hershberg, *ibid.*, **75**, 2510 (1953); (e) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954); (f) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (g) J. Romo, *Tetrahedron*, **3**, 37 (1958); (h) R. H. Mazur and J. H. Cella, *ibid.*, **7**, 130 (1959); (i) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961).

(6) A reasonable yield of dehydrogenation product was also obtained from the amorphous epimer mixture remaining after crystallization of the adduct II (see Experimental).

(7) L. M. Jackman in "Advances in Organic Chemistry," Vol. II, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960.

(8) The n.m.r. spectra were taken in methylene chloride solution on a Varian Associates HR-60 spectrometer using tetramethylsilane as an internal standard (τ = 10.0). We thank Wallace Lawrence of the Chemstrand Research Laboratories for running these spectra.

(9) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chap. 7.

Treatment of the tetraester III with sodium methoxide in dry methanol resulted in the methanolysis of both acetyl groups and production of the phenolic diester 3-alcohol IV, m.p. 258–261°, in 77% yield. The infrared spectrum contained rather widely separated ester bands at 1720 and 1705 cm.$^{-1}$, respectively, as well as alcohol and phenol hydroxyl absorption. Well defined but different ultraviolet spectra were obtained by measurement in neutral solution ($\lambda_{max}^{CH_3OH}$ 220 and 261 mμ, 27,700 and ε 9650) and in alkaline solution ($\lambda_{max}^{1\ N\ NaOCH_3}$ 244 and 306 mμ, 22,600 and ε 11,000) in agreement with the presence of an ionizable phenolic chromophore.

The dihydroxy diester IV was found to react smoothly under conventional Oppenauer oxidation conditions producing the corresponding conjugated 3-ketone V in 88% yield. The presence of a conjugated ketone in this compound was confirmed by the infrared spectrum (ν_{max}^{Nujol} 1695 cm.$^{-1}$) but was not immediately evident in ultraviolet spectrum ($\lambda_{max}^{CH_3OH}$ 266 mμ, ε 34,500) (Fig. 2). It is apparent, however, that this spectrum represents the absorption contribution of the aromatic chromophore as well as the conjugated ketone chromophore. The absorption component due to the 3-keto-Δ^4 system was roughly assessed by running a "spectrum" of the conjugated ketone V against a solution of the 3-hydroxy compound IV (in identical concentration) as a "blank." This resulted in a symmetrical tracing in the region above 220 mμ (where isolated double bond absorption is negligible; the curve had a maximum at 242 mμ (ε 18,200) as expected for the Δ^4-3-ketone chromophore.

The pentacyclic steroid derivatives reported here have been submitted to the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, for biological evaluation.

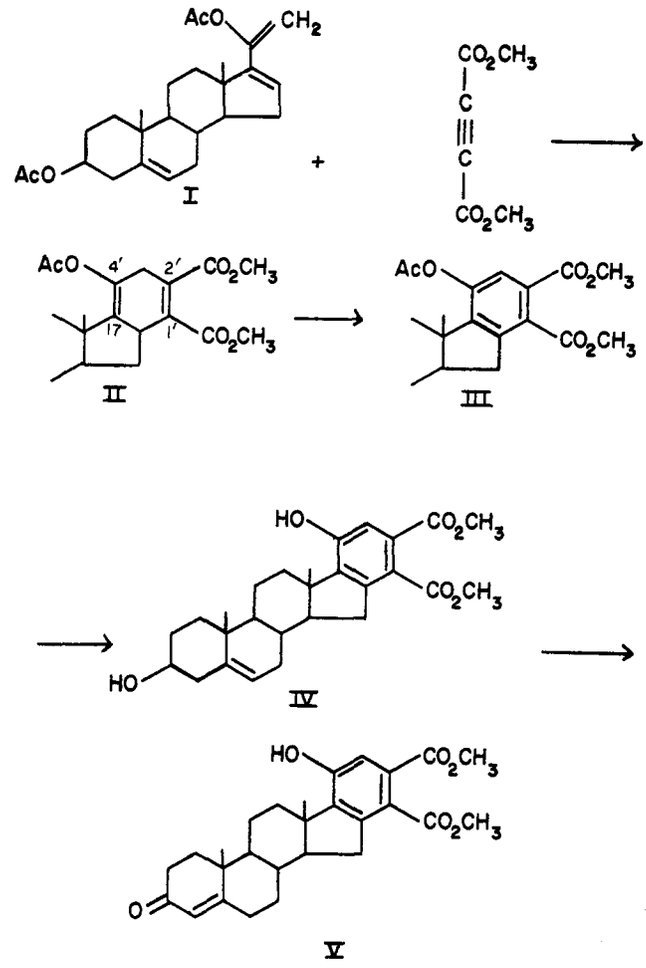

Figure 1

Experimental[11]

3β-20-Diacetoxypregna-5,16,20-triene (I).—The enol acetylation of 3β-acetoxypregna-5,16-dien-20-one was conveniently carried out on a large scale by a modification of Moffett and Weisblat's procedure.[4] A solution of 15 g. of *p*-toluenesulfonic acid monohydrate and 100 g. of the prior ketone in 2 l. of redistilled isopropenyl acetate was heated so as to cause slow distillation of solvent through an insulated Claisen head. Removal of acetone formed in the reaction was facilitated by passing a very slow stream of dry nitrogen through the system. The nitrogen flow was stopped after 6 hr., by which time 150 ml. of solvent had been collected and the temperature of the reaction mixture reached 100°. Slow distillation was continued for a final period of 1.5 hr. The acid catalyst was then neutralized by adding 8.0 ml. of pyridine, with swirling, to the cooled reaction mixture. Precipitated salt was removed by filtration through Celite. Evaporation of solvent at reduced pressure left a partly crystalline residue which was triturated with warm heptane and again freed of solvent. The resulting crystalline solid was dissolved in a minimum volume of benzene and passed slowly through a column containing 200 g. of Florisil. The early eluates (devoid of starting material by infrared determination) were freed of solvent and the solid residue was then recrystallized from methylene chloride–heptane, giving 74.3 g. (66%) of the enol acetate as colorless prisms, m.p. 137–142°. Further recrystallization from methylene chloride–methanol raised the m.p. to 143–145° without causing any change in the infrared spectrum; Moffett and Weisblat report m.p. 144–146° for this compound.[4]

Dimethyl 3β,4'-Dihydroxy-16α-(16,17-butanoandrosta-1',4',5-triene)-1',2'-dicarboxylate Diacetate[11] (II).—A solution of 8.50 g. (0.059 mole) of dimethylacetylene dicarboxylate and 23.23 g. (0.0583 mole) of 3β,20-diacetoxypregna-5,16,20-triene (I) in 350 ml. of dry benzene was heated under reflux for 16 hr. Removal of solvent at reduced pressure and crystallization of the residue from methanol gave 13.60 g. (43%) of the adduct II, m.p. 193–196°. An analytical sample, prepared by further crystallization from the same solvent, had m.p. 197–198°, $[\alpha]_D$ −85°; ν_{max} 1730–1740 (3-acetate and methyl esters), 1760 (enol acetate), and 1640 cm.$^{-1}$ (olefin). The n.m.r. spectrum showed singlet methyl resonances at 9.05 (C_{18}-CH_3), 8.96 (C_{10}-CH_3), 8.00 (C_2-OAc), 7.87 (C_4'-OAc), and 6.29 and 6.24 τ (methyl esters).

Anal. Calcd. for $C_{31}H_{40}O_8$: C, 68.86; H, 7.68. Found: C, 68.60; H, 7.45.

By concentrating original methanolic mother liquors, an additional crystalline but wide melting fraction (5.80 g., 18%, m.p. approx. 180–190°) could be obtained. This material, as well as the final amorphous residue (12.05 g.), gave an infrared spectrum which was nearly identical with that of the pure isomer (m.p. 197–198°) except in the region 1130–1150 cm.$^{-1}$.

Dimethyl 3β,4'-Dihydroxy-(16,17-butanoandrosta-1',3',5,16-tetraene)-1',2'-dicarboxylate Diacetate (III). A. Nitrobenzene Method.—A 5.9-g. sample of the adduct II, dissolved in 50 ml. of nitrobenzene, was heated to boiling and slowly distilled for 35 min. Most of the solvent was then removed at reduced pressure and below 55° using a rotary evaporator. The viscous, colored residue was dissolved in methylcyclohexane and adsorbed onto a column containing 100 g. of Florisil and prepared in the same solvent. The column was washed with 10% benzene in methylcyclohexane (200 ml.) and 20% benzene in methylcyclohexane (150 ml.) until elution of residual nitrobenzene was nearly complete. The reaction product was then eluted with benzene (500 ml.) and 10% ether in benzene (300 ml.). Crystallization from cyclohexane gave 4.44 g. (69%) of the aromatization product III, m.p. 120–125°, with evolution of gas. The n.m.r. spectrum included an intense, sharp singlet at 8.57 (C_4'-OAc) and 6.15 τ

(11) Melting points were obtained using a Kofler hot stage and are uncorrected. Optical rotations were measured at 25° in chloroform and infrared spectra were run in carbon disulfide except where noted. The pentacyclic derivatives are named as in paper LXIX (ref. 1b).

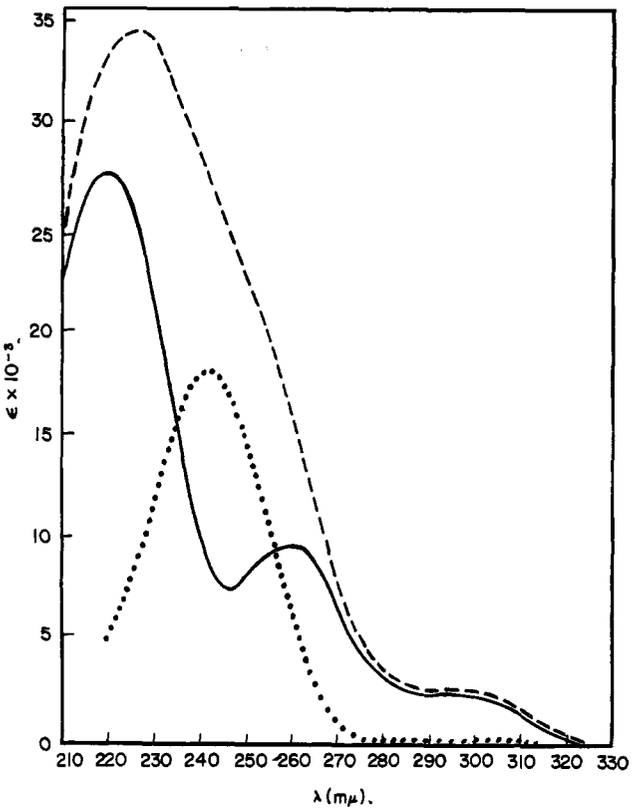

Fig. 2.—Absorption spectra of dimethyl 4'-hydroxy-(16,17-butanoandrosta - 1',3',4,16 - tetraene) - 3 - one - 1',2' - dicarboxylate (V), – – – –; dimethyl 3β,4'-dihydroxy-(16,17-butanoandrosta 1',3',5,16-tetraene)-1',2'-dicarboxylate (IV), ———; V, run against IV as a "blank", ...

(methyl esters). A sample was recrystallized from isopropyl alcohol giving colorless plates, m.p. 125–130°, with evolution of gas; $[\alpha]_D$ −88°; ν_{max} 1760 (phenolic acetate), 1735–1720 (3-acetate and methyl esters), 1583 (aromatic), and 3600 cm.$^{-1}$ (weak, isopropyl alcohol of crystallization).

Anal. Calcd. for $C_{31}H_{38}O_8 \cdot 0.5\ C_3H_8O$: C, 68.64; H, 7.45. Found: C, 68.77; H, 7.49.

B. Chloranil Method.—The amorphous C-16 epimer mixture remaining after crystallization of adduct II (see preceding) was freed carefully of solvent by conversion to a dry foam and warming *in vacuo*. A 9.80-g. sample of this material and 5.0 g. of chloranil were dissolved in 150 ml. of dry, redistilled chlorobenzene and heated under reflux for 16 hr. Solvent was then removed at reduced pressure; residue was taken up in benzene, washed with saturated aqueous sulfur dioxide, then with cold dilute sodium hydroxide, and finally with water until neutral. Dried (magnesium sulfate) benzene solution was decolorized by passage through 100 g. of Florisil. Benzene eluates were combined, concentrated, and the residue crystallized from isopropyl alcohol, yielding 5.72 g. (56%) of plates, m.p. 124–128° dec., identical with the aromatization product III prepared as described previously.

Dimethyl 3β,4'-Dihydroxy(16,17-butanoandrosta-1',3',5,16-tetraene)-1',2'-dicarboxylate (IV).—The aromatization product III (34.3 g.) was dissolved in 1300 ml. of methanol (freshly distilled from magnesium methoxide) containing sodium methoxide (from 3.57 g. of sodium). The solution was allowed to stand at 25° for 54 hr. under a nitrogen atmosphere. A 10-ml. portion of glacial acetic acid was then added followed by 200 ml. of water. About 1 l. of solvent was then removed at reduced pressure leaving a colorless crystalline sludge. The solid was collected and washed with 50% methanol–water; drying overnight at 50° *in vacuo* gave 21.0 (77%) of phenolic product, m.p. 250–255°. A sample of this material, further purified by two recrystallizations from acetone, had m.p. 258–261°, $[\alpha]_D^{CHCl_3}$ −107°; ν_{max}^{Nujol} 3460 (3-OH), 3150 (phenolic OH), 1720 and 1702 cm.$^{-1}$ (methyl esters); $\lambda\lambda_{max}^{CH_3OH}$ 219 (30,800), 258 (10,300), 294 mμ (inflection, ε 2810); $\lambda\lambda_{max}^{1\ N\ NaOCH_3}$ 244 (22,600), 306 mμ (ε 11,000).

Anal. Calcd. for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.16; H, 7.64.

Dimethyl 4'-Hydroxy-(16,17-butanoandrosta-1',3',4,16-tetraene)-3-one-1',2'-dicarboxylate (V).—A solution of 5.0 g. of the 3-alcohol IV and 50 ml. of cyclohexanone in 200 ml. of dry toluene was distilled until about 10 ml. of solvent was collected. A solution of 5.0 g. of aluminum isopropoxide in 50 ml. of toluene was added and the reaction mixture heated under reflux in a nitrogen atmosphere for 2 hr. About 100 ml. of toluene was then removed by distillation. The cooled reaction mixture was treated with ice (*ca.* 100 g.) and 150 ml. of cold 5% hydrochloric acid. The precipitated product was found to be very poorly soluble in the common organic solvents but could be extracted with three 200-ml. portions of 10% isopropyl alcohol in chloroform. The combined organic extracts were washed with dilute sodium bicarbonate, then water, and dried over sodium sulfate. The solution was concentrated, diluted with hot hexane, and the crystalline product collected. The conjugated ketone V (4.40 g., 88%) had m.p. 315–317°. The material was inserted in a Soxhlet thimble and continuously extracted with the solvent mixture toluene–chloroform–isopropyl alcohol (3:1:1); this resulted in recrystallization but caused no change in melting point. The product had $[\alpha]_D^{pyridine}$ −25°; ν_{max}^{Nujol} 1695 (conj. ketone), 1720 and 1730 (ester), and 3350 cm.$^{-1}$ (phenolic OH); $\lambda_{max}^{CH_3OH}$ 224 (35,900), 294 mμ (inflection, ε 2770); $\lambda\lambda\ 1_{max}^{1\ N\ NaOCH_3}$ 244 (38,300), and 306 mμ (ε 11,400). An ultraviolet spectrum of the conjugated ketone V was rerun in methanol using a solution of the 3-hydroxy compound IV (in identical concentration) as a "blank." The resulting tracing showed a single maximum at 241 mμ (ε 15,000).

Anal. Calcd. for $C_{27}H_{32}O_6$: C, 71.66; H, 7.13. Found: C, 71.40; H, 7.19.

Synthesis of Compounds Containing Carbon–Mercury and Carbon–Tin Bonds[1,2]

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The attempted preparation of compounds containing both carbon–tin and carbon–mercury bonds was reported in 1926.[3] Later investigation of the reaction indicated a stepwise degradation of the aryl or alkyl tin compound by the monosubstituted or inorganic mercury compound.[4] In the present investigation, the degradation of the substituted tin compounds was prevented by using disubstituted mercurials. This paper describes the synthesis of the tributyltin salt of

TABLE I

TRISUBSTITUTED TIN HALO ESTERS

Compound	M.p., °C.	Calcd. Sn	Found Sn	Yield,[a] %
Tri-*n*-butyl iodoacetate	68	25.1	25.5	50–60
Tri-*n*-propyltin iodoacetate	75	29.5	29.7	50–60
Tri-*n*-butyltin iodopropionate	61	24.3	24.3	50–60
Tri-*n*-butyltin bromoacetate	64	27.8	29.0	50–60
Tri-*n*-propyltin bromoacetate	73	30.8	30.9	50–60

[a] Crystallized from petroleum ether.

(1) Portions of this work were reported at the Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June, 1962. Scientific paper no. 2280, Washington Agricultural Experiment Stations, Pullman, Wash. Project 1525.

(2) Supported in part by medical and biological research funds, initiative 171, State of Washington.

(3) R. F. Chambers and P. C. Scherer, *J. Am. Chem. Soc.*, **48**, 1054 (1926).

(4) A. N. Nesmeyanov and K. H. Kocheshkov, *Ber.*, **67**, 317 (1934).