spectrophotometer. The elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Preparation of Tetraphenyldiphosphine.—Following the procedure of Kuchen and Buchwald[7] a 70% yield of tetraphenyldiphosphine was obtained, mp 126–127°. The infrared spectrum (Nujol oil mull, 1430–670-cm^{-1} region) exhibited the following bands: 1430 m, 1380 m, 1325 w, 1300 w, 1183 vw, 1088 vw, 1065 m, 1020 m, 997 m, 919 w, 905 w, 744 m, 734 s, and 692 s cm^{-1}.

Anal. Calcd for $C_{24}H_{20}P_2$: C, 77.83; H, 5.44; P, 16.73; mol wt, 370.37. Found: C, 77.59; H, 5.60; P, 16.89; mol wt, 355 (cryoscopic in benzene).

Preparation of $(C_6H_5)_3SiN{=}P(C_6H_5)_2P(C_6H_5)_2{=}NSi(C_6H_5)_3$.—In a capsule was sealed *in vacuo* triphenylsilyl azide (6.02 g, 20 mmoles), benzene (50 ml), and tetraphenyldiphosphine (3.70 g, 10 mmoles). The mixture was heated at 80–115° (gradually raising the temperature) over the period of 14 days. On opening to a vacuum system only 17.13% of nitrogen was collected. Subsequently, benzene was removed *in vacuo* at room temperature, and the residue was heated at 140° for 3 days (until no additional increase in pressure was observed). Total amount of nitrogen collected was 18.57 mmoles (93% yield). The product was crystallized from benzene–heptane mixture followed by boiling with acetonitrile. This material was then dried overnight at 70° *in vacuo*, mp 236–238°. The infrared spectrum (Nujol mull, 1430–670-cm^{-1} region) exhibited the following bands: 1430 w, 1370 m, 1300 m, 1250 w, 1100 m, 740 w, 722 m, and 700 s cm^{-1}.

Anal. Calcd for $C_{60}H_{50}P_2Si_2N_2$: C, 78.56; H, 5.50; P, 6.76; Si, 6.13; N, 3.06; mol wt, 916.61. Found: C, 78.70; H, 5.59; P, 6.96; Si, 6.41; N, 3.18; mol wt, 847 (in chloroform, using a Mechrolab osmometer).

Treatment of $(C_6H_5)_2PH$ with $(C_6H_5)_3SiN_3$. A. Using Equimolar Quantities.—In a nitrogen atmosphere $(C_6H_5)_3SiN_3$ (9.04 g, 0.03 mole) in ether (90 ml) was treated with $(C_6H_5)_2PH$ (5.5 g, 0.03 mole) in ether (10 ml); the solution was then refluxed overnight. Subsequently, the ether was removed *in vacuo* and the residue was heated to 100° for 10 days. On cooling a solid mass was obtained. This material failed to show in its spectrum any absorption in the vicinity of 2130 cm^{-1}, indicating an absence of azido moieties. Repeated crystallization from heptane gave 4.67 g (45% yield, based on triphenylsilyl azide employed) of $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$: mp 161–162°; P^{31} nmr, a single peak at −43 ppm (in benzene solution, referenced to 85% H_3PO_4). The infrared spectrum (Nujol oil) exhibited the following bands: 3315 w (N–H), 2900 s, 2858 w (Nujol), 1587 w (C=C), 1460 s (Nujol), 1430 s (PC_6H_5), 1375 s (Nujol), 1290 s, 1250 s, 1180 m, 1155 w, 1105 s, 1025 m, 997 m, 935 s (PNH), 791 m, 744 s, 735 s, and 694 s cm^{-1}.

Anal. Calcd for $C_{48}H_{41}PSi_2N_2$: C, 78.65; H, 5.64; P, 4.23; Si, 7.41; N, 3.55; mol wt, 733.03. Found: C, 78.26; H, 5.72; P, 4.25; Si, 7.41; N, 3.55; mol wt, 670 (in benzene, using a Mechrolab osmometer).

The compound $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$ was heated in air above its melting point; no change resulted.

The mother liquors, from the recrystallization of $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$, were freed from solvent on the vacuum line. Unreacted $(C_6H_5)_2PH$ was removed *in vacuo* at *ca.* 95°; subsequent sublimation at 135° afforded $(C_6H_5)_3SiNHP(C_6H_5)_2$ (2.14 g, 19% yield). This sublimate was recrystallized from heptane: mp 148–149°; P^{31} nmr, a single peak at −26.6 ppm (in benzene solution, referenced to 85% H_3PO_4). The infrared spectrum (Nujol oil mull) exhibited the following bands: 3320 w (N–H), 2900 s, 2855 s (Nujol), 1460 s (Nujol), 1430 (PC_6H_5), 1380 m (Nujol), 1307 w, 1220 m, 1212 m, 1190 w, 1117 s, 1030 w, 1000 w, 905 s (P–NH), 741 s (shoulder), 733 s, and 698 s cm^{-1}.

Anal. Calcd for $C_{30}H_{26}PSiN$: C, 78.40; H, 5.70; P, 6.74; Si, 6.11; N, 3.05; mol wt, 459.61. Found: C, 78.62; H, 5.83; P, 6.63; Si, 5.75; N, 2.92; mol wt, 455 (in benzene, using a Mechrolab osmometer).

B. Excess $(C_6H_5)_3SiN_3$.—In a sealed, evacuated ampoule $(C_6H_5)_2PH$ (582.0 mg, 3.126 mmoles) was heated with $(C_6H_5)_3SiN_3$ (2.541 g, 8.430 mmoles) at 110–115° for 90 hr. On opening to the vacuum system, nitrogen (6.349 mmoles) was obtained, thus N_2:$(C_6H_5)_2PH$ = 2.03:1, showing that only the diadduct $(C_6H_5)_3SiNHP(C_6H_5)_2{=}NSi(C_6H_5)_3$ was formed. The reaction mixture on washing with ether, followed by crystallization of the ether-insoluble material from heptane, afforded 1.62 g (71% of the diadduct, mp 161–162°). Additional quantities of the product remained in ether and heptane mother liquors admixed with the excess of $(C_6H_5)_3SiN_3$.

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The Synthesis of 19-Oxygenated Cardenolides. I. A Convenient Preparation of 19-Hydroxydesoxycorticosterone

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In the recently described total synthesis of periplogenin[1] we took advantage, as an alternative and practical shortcut, of the microbiological hydroxylation in 14α of desoxycorticosterone as a means of introducing the 14,15 double bond and subsequently, by a sequence of steps well known in the steroid literature,[2] the 14β-hydroxyl group characteristic of this class of cardioactive substances.

It seemed attractive therefore to prepare by an efficient method 19-hydroxydesoxycorticosterone as a substrate for 14α-hydroxylation. By applying essentially the already disclosed synthetic sequence used for periplogenin,[1] 19-hydroxy-DOC could be considered a starting material for the synthesis of strophanthidol and related 19-oxygenated cardenolides.

It is of interest that 19-hydroxy-DOC was first obtained by degradation of strophanthidin itself.[12]

The commercially available 21-hydroxypregnenolone diacetate I was converted to the chlorohydrin II in 70% yield by allowing it to react with freshly prepared and chlorine-free hypochlorite solution in acetone. The 6,19-oxide III was obtained in 70% yield from chlorohydrin II by the iodine–lead tetraacetate reaction[13] and saponified to the diol IV with $KHCO_3$ in aqueous methanol in about 90% yield.

(1) R. Deghenghi, A. Philipp, and R. Gaudry, *Tetrahedron Letters*, 2045 (1963).

(2) A recent statement[3] claiming priority over a number of steps well documented in the previous literature (*e.g.*, for the addition of HOBr to a 14,15 double bond followed by Raney nickel debromination, *cf.* Ringold, *et al.*;[4] followed by β-epoxide formation, *cf.* Meister,[5] Bloom, *et al.*,[6] and Reichstein;[7] *cf.* also Meyer[8] and Bernstein;[9] for the hydride reduction of a 14,15β epoxide without epimerization of the 17β chain, *cf.* Meyer[10] and ref 5; also Kondo[11] and references cited therein), deserves little comment.

(3) C. R. Engel and G. Bach, *Steroids*, **3**, 593 (1964).

(4) H. J. Ringold, F. Sondheimer, and G. Rosenkrantz, U. S. Patent 2,889,346 (June 2, 1959; priority Dec 23, 1953).

(5) P. D. Meister, U. S. Patent 2,930,791 (March 29, 1960; applied June 7, 1955).

(6) B. M. Bloom, E. J. Angello, and G. D. Laubach, *Experientia*, **12**, 27 (1956).

(7) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **45**, 943 (1962).

(8) P. Hofer, H. Linde, and K. Meyer, *ibid.*, **45**, 1041 (1962).

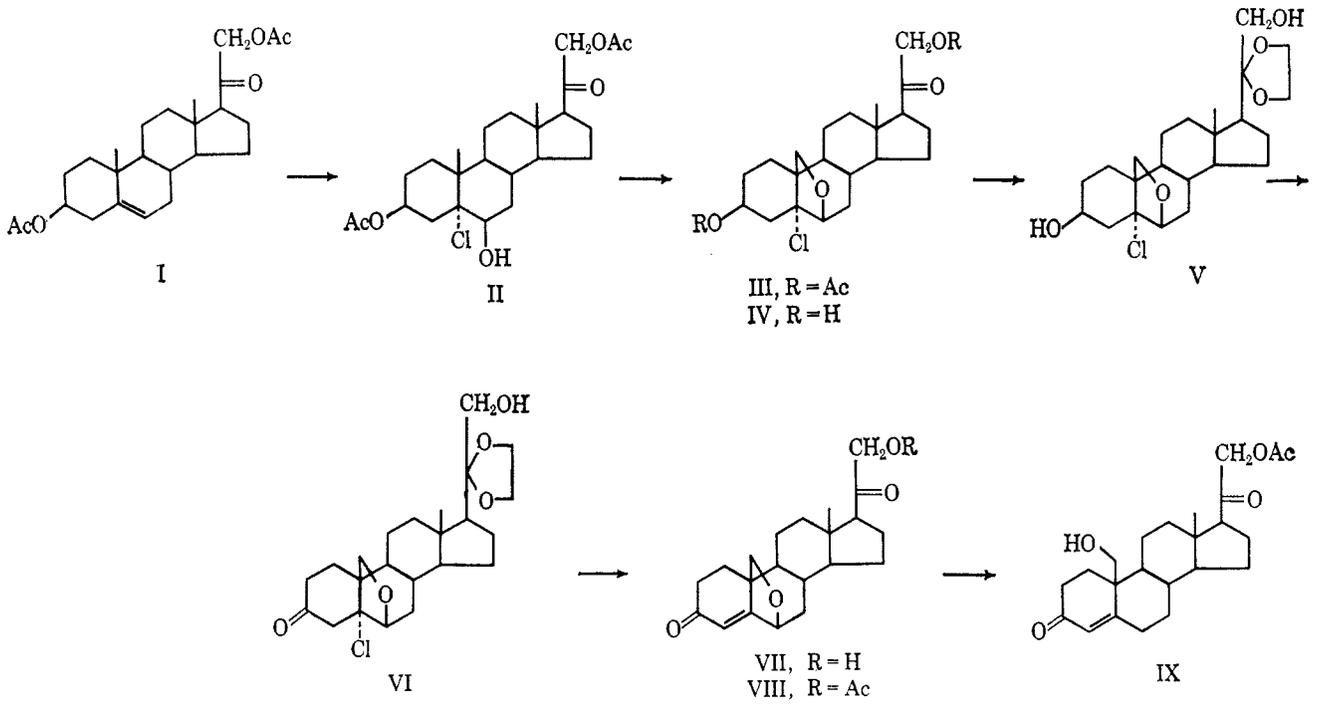
(9) M. Heller, F. J. McEvoy, and S. Bernstein, *Steroids*, **3**, 193 (1964).

(10) H. Linde and K. Meyer, *Helv. Chim. Acta*, **42**, 807 (1959).

(11) H. Kondo, U. S. Patent 3,134,772 (May 26, 1964; priority May 1, 1961).

(12) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954).

(13) J. Kalvoda, K. Heusler, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1017 (1963).



The procedure of selective oxidation of secondary *vs.* primary alcohol as described by Bernstein[14] was followed by preparing the 20-ketal V in about 70% yield from IV, and treating it with chromic anhydride in pyridine thus securing the 3-keto compound VI in about 50% yield. This route proved superior to the more obvious protection of the primary alcohol by a variety of selective esterifications. Acid treatment of crude VI provided in 80% yield 6,19-oxido-DOC (VII), characterized as the acetate VIII.

Reductive opening of the oxide bridge with zinc and acetic acid[13] gave 19-hydroxy-DOCA[12] (IX) in good yield.[15]

The microbiological hydroxylation of this compound and its application to the synthesis of 19-oxygenated cardenolides will be reported at a later date.

Experimental Section

5α-Chloro-3β,6β,21-trihydroxypregnan-20-one 3,21-Diacetate (II).—A solution of 160 g of sodium bicarbonate in 1.5 l. of water was saturated at 0° with a stream of chlorine for 15 min. Excess chlorine was removed by bubbling through the solution a stream of air and by repeated chloroform extraction until the organic and aqueous layers were colorless. This solution was found to contain 16.4 g of NaClO/l. by thiosulfate titration of an aliquot.[16]

To a solution of 21-hydroxypregnenolone diacetate (I, 110 g) in 3 l. of acetone was added 1320 ml of the hypochlorite solution (10% excess), and the mixture was stirred at room temperature for 30 min. Addition of a few milliliters of aqueous potassium iodide solution gave a weakly positive active chlorine reaction (iodine color), decolorized by addition of some thiosulfate solution. The bulk of the acetone was evaporated *in vacuo* at moderate temperature and the residue was extracted with ether and washed with thiosulfate and bicarbonate solution and water. Evaporation of the solvent afforded 70.0 g of crystalline II, mp 190–191.5°. Concentration of the mother liquor gave additional quantities of the chlorohydrin. A sample was recrystallized from acetone–hexane for analysis, mp 193–194°, $[\alpha]^{23}D$ +36.0° ($CHCl_3$). *Anal.* Calcd for $C_{25}H_{37}ClO_6$: C, 64.02; H, 7.95; Cl, 7.56. Found: C, 63.95; H, 8.03; Cl, 7.62.

5α-Chloro-3β,21-dihydroxy-6β,19-oxidopregnan-20-one 3,21-Diacetate (III).—Lead tetraacetate, 44 g, and 5.0 g of calcium carbonate were suspended in 1.8 l. of cyclohexane and refluxed for 30 min. A quantity of the chlorohydrin II, 10.0 g, and 13.0 g of iodine were subsequently added. The stirred mixture was refluxed and illuminated with photoflood lamp (750 w) for 2 hr. The cooled mixture was filtered through Celite and the filtrate was washed twice with thiosulfate solution and water. Evaporation of the dried solvent gave 11.8 g of a foamy residue which crystallized from acetone–ether–hexane to give 5.6 g of needles, mp 145–147°. The analytical sample melted at 146–147°, $[\alpha]^{23}D$ +73.5° ($CHCl_3$). *Anal.* Calcd for $C_{25}H_{35}ClO_6$: C, 64.30; H, 7.55; Cl, 7.59. Found: C, 64.42; H, 7.77; Cl, 7.66.

5α-Chloro-3β,21-dihydroxy-6β,19-oxidopregnan-20-one (IV).—The diacetate III, 1.0 g, was dissolved in 30 ml of methanol and refluxed in the presence of 470 mg of potassium bicarbonate in 10 ml of water for 1 hr. The solvent was removed *in vacuo* and the residue was extracted with ether. Evaporation of the solvent furnished 836 mg of a residue which crystallized from acetone–ether–hexane.

The analyzed sample had mp 166–168°, $[\alpha]^{23}D$ +57.8° ($CHCl_3$). *Anal.* Calcd for $C_{21}H_{31}ClO_4$: C, 65.87; H, 8.16; Cl, 9.26. Found: C, 66.07; H, 8.06; Cl, 9.21.

5α-Chloro-20-ethylenedioxy-6β,19-oxidopregnane-3β,21-diol (V).—The diol IV, 0.5 g, was dissolved in 25 ml of benzene and stirred and refluxed in presence of 25 ml of ethylene glycol and 75 mg of *p*-toluenesulfonic acid for 3.5 hr with a water separator. The cooled mixture was extracted with methylene dichloride, and the extract was washed with sodium bicarbonate and water. Evaporation of the solvent gave 0.526 g of a crystalline residue. One recrystallization from methylene dichloride–ether–hexane gave 0.374 g of needles, mp 225–227°.

The analyzed sample melted at 223.5–225°, $[\alpha]^{23}D$ +15.1° (dioxane). *Anal.* Calcd for $C_{23}H_{35}ClO_5$: C, 64.70; H, 8.26; Cl, 8.30. Found: C, 64.68; H, 8.20; Cl, 8.70.

21-Acetoxy-6β,19-oxido-4-pregnene-3,20-dione (VIII).—The diol V, 4.6 g, dissolved in 50 ml of pyridine was added to a slurry of 6.3 g of chromic oxide in 70 ml of pyridine and stirred at room temperature for 16 hr. The mixture was poured into water and extracted to give 2.2 g of amorphous residue, representing crude VI. This product was dissolved in 40 ml of acetone and treated at room temperature for 2 hr in the presence of concentrated sulfuric acid (6 drops). Extraction with methylene dichloride, washing with sodium bicarbonate solution and water, and evaporation of the dried solvent gave 1.830 g of crude

(14) S. Bernstein and R. Lenhard, *J. Am. Chem. Soc.*, **77**, 2331 (1955).

(15) 19-Hydroxylation of DOC by adrenal perfusion [*cf.* R. Neher and A. Wettstein, *Helv. Chim. Acta*, **39**, 2062 (1956)] and by fermentation in low yield [*cf.* M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull.* (Tokyo), **6**, 226 (1958)] has been described.

(16) Successive runs have shown that a reproducible hypochlorite content is difficult to obtain. This experiment describes the best yield in pure chlorohydrin.

VII, which was acetylated with acetic anhydride, 2.5 ml in 20 ml of pyridine, at room temperature for 16 hr. Usual work-up afforded 1.73 g of crystalline VIII (from acetone–hexane), mp 189–193°. The analyzed sample melted at 193–196°, $[\alpha]^{23}D$ +4.3° ($CHCl_3$). *Anal.* Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.48; H, 8.07.

19,21-Dihydroxy-4-pregnen-3,20-dione 21-Acetate (IX).—The oxide VIII, 0.675 g in 20 ml of acetic acid, was treated with 16.9 g of zinc powder prewashed with diluted acetic acid, with stirring on a steam bath for 10 min. The metal was filtered and washed with acetic acid; the filtrate taken to dryness *in vacuo* and the residue was dissolved in methylene dichloride and washed to neutrality with sodium bicarbonate and water. Evaporation of the solvent gave 0.578 g of amorphous IX, which crystallized from acetone: mp 196–198°, $[\alpha]^{23}D$ +176.5° ($CHCl_3$); lit.[12] mp 197–199°, $[\alpha]^{24}D$ +178°.

19,21-Dihydroxy-4-pregnene-3,20-dione (19-Hydroxydeoxycorticosterone).—Alkaline hydrolysis of the monoacetate IX according to the procedure described by Barber and Ehrenstein[12] gave the title compound: mp 160–162° (from acetone–ether), $[\alpha]^{23}D$ +179° ($CHCl_3$); lit.[12] mp 163–165°, $[\alpha]^{25}D$ +180°.

Acknowledgments.—The technical cooperation of Messrs. Heinz Haenni and Werner Wirz is gratefully acknowledged.

Carboxamidation of β-Dicarbonyl Compounds

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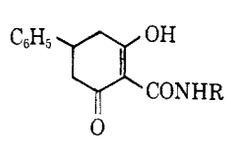
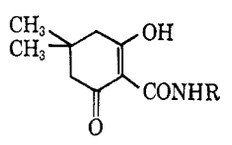
At the beginning of our work on the total synthesis of tetracycline antibiotics we were faced with the problem of constructing a 2-carboxamido 1,3-diketone moiety.[1] Although in the meantime the general synthetic approach has been changed[2] this Note describes some model experiments carried out previously in connection with this problem.

It has been known for a long time that organic isocyanates react with β-dicarbonyl compounds in the presence of catalytic amounts of base to yield N-substituted 2-carboxamido-1,3-dicarbonyl compounds. For instance, the reaction between 5-phenylcyclohexane-1,3-dione and phenyl isocyanate gave I.[3] Under the same conditions dimedon gave II.[3] Furthermore, dimedon reacts with acetyl isocyanate or carbomethoxy isocyanate to yield III and IV, respectively, which can be hydrolyzed with ammonia to V.[4,5]



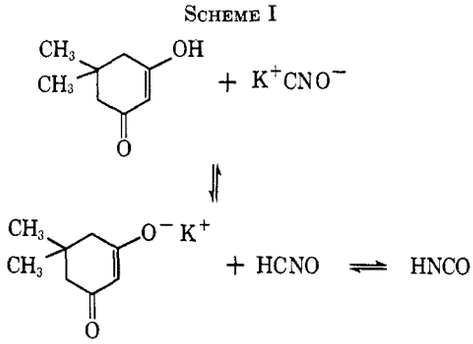
I, R = C_6H_5
VII, R = H



II, R = C_6H_5
III, R = $COCH_3$
IV, R = CO_2CH_3
V, R = H

At the outset of our work we tried to treat isocyanic acid with dimedon to form V. If dimedon was treated with isocyanic acid in chloroform–ether, a very slow reaction to V took place with most of the isocyanic acid polymerizing to cyamelide. However, if triethylamine was added to a chloroform–ether solution of dimedon and isocyanic acid, a faster reaction to V was observed. The fact that the polymerization of isocyanic acid is a main side reaction during these processes led to an attempt to find a system in which only a relatively low concentration of isocyanic acid would be available at a given time which might react in the wanted direction in preference to polymerization. Expecting that a solution of potassium cyanate and dimedon in water might establish the equilibrium outlined in Scheme I and that during and after establishment of this equilibrium V might be formed, dimedon and potassium cyanate were allowed to react in a mixture of dimethylformamide and water.[1b] The best

SCHEME I



results were obtained by dropping a water solution of potassium cyanate into a solution of dimedon in dimethylformamide. This way a 51% yield of V was obtained. If a greater amount of potassium cyanate was used or the reaction time was prolonged, the yields were lower. This may be due to the fact that potassium carbonate is formed by heating potassium cyanate in water and that potassium carbonate might degrade V. A control experiment showed that V is degraded by potassium carbonate in water.

In order to extent the potassium cyanate reaction to other systems, *trans*-decalin-1,3-dione[6] and 5-phenylcyclohexane-1,3-dione were used. In both cases the expected reaction took place and compounds VI and VII, respectively, were isolated. Furthermore, compound VIII, prepared during attempts to synthesize tetracycline antibiotics,[7] reacted with potassium cyanate to give IX.

In all the cases mentioned so far, carboxamidation also occurred with lead cyanate in acetonitrile, but no markedly better results were obtained.

The reaction products V–VII and IX could be isolated directly or *via* their crystalline, water-insoluble copper chelates. Compounds V–VII show, even in dilute solution, no infrared absorption maxima of carbonyl groups <6.2 μ and are therefore completely enolized and chelated. The same is true for IX,

(1) (a) For a general discussion of this problem, see H. Muxfeldt, *Angew. Chem.*, **74**, 443 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 372 (1962).
(2) H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).
(3) W. Dieckmann, J. Hoppe, and R. Stein, *Ber.*, **37**, 4627 (1904).
(4) M. M. Shemyakin, J. A. Arbuzow, M. N. Kolosov, G. A. Shatenshteyn, W. W. Onopienko, and J. V. Konnova, *Zh. Obshch. Khim.*, **30**, 542 (1960).
(5) Compound V was also prepared by fusing a mixture of dimedone and urea: H. C. Scarborough and W. A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).
(6) C.-K. Chuang and H.-L. Tien, *Ber.*, **69**, 25 (1936).
(7) H. Muxfeldt and W. Rogalski, *ibid.*, **95**, 2581 (1962).