excess of calcium hydroxide, which tends to rule out the possibility of heterogeneous catalysis. While this favorable yield shift was demonstrated for cyanide oxidation only, a dependence of this effect on the nature of the substrate seems highly unlikely considering that manganate(VII) is usually the primary oxidant[1,3] in alkaline aqueous systems. In light of these evidences it becomes apparent that the reaction is of considerable interest to the field of organic synthesis.

It should further be noted that the observed effect is probably limited to calcium among the alkaline earth metals, because the higher members of this group (Sr^{2+}, Ba^{2+}) tend to form insoluble salts with the transient manganate(VI) ion.

Since the observed phenomena discussed in this paper promise to lead to more and deeper insights into the chemistry of oxyanions of manganese, the author hopes to encourage further investigations of these reactions.

Experimental Section

Potassium Manganate(VI).—Pure crystalline potassium manganate(VI) was prepared according to the method described by Scholder and Waterstradt[9] as follows. Powdered reagent grade potassium permanganate (20 g) was slowly added to a 1000-ml round flask containing a cold solution of 250 g of KOH in 250 ml of distilled water. The solution was heated to boiling for 20 min under a reflux condenser, which was attached to an absorption tube containing "Ascarite" to prevent back-diffusion of carbon dioxide. After cooling to ambient temperature and crystallization, the reaction product was separated by filtration through a Gooch filtering crucible of medium pore size. The following solutions were employed for further purification of the raw product: I, 50 ml of 40% KOH (filtered); II, 50 ml of CH_3OH and 5 g of KOH (filtered); III, 100 ml of CH_3OH and 3 g of KOH (filtered); IV, 50 ml of CH_3OH and 0.5 g of KOH (filtered); V, 100 ml of ethyl ether (water free). Solutions II–V were precooled to −15°. The crystals were first washed with 50 ml of I at room temperature, then with 50 ml of II, and finally with 40 ml of III, both at −15°. Further removal of adhering KOH was accomplished by resuspension and shaking of the crystals in 50 ml of III, followed by filtration and successive washing with 50 ml of IV, and four times each with 25 ml of ether (V). The temperature was kept below −10° during each of the latter operations. The crystals were then vacuum dried over P_2O_5 for a minimum period of 3 hr.

Differential spectrophotometric analysis at 526 and 603 mμ of a solution of a weighed amount of the product in 2 *N* KOH revealed a purity of 100 ± 0.2% as K_2MnO_4 with no detectable trace of permanganate present. The assay of K_2MnO_4 prepared by this method is usually in the order of 99.8%.

Disproportionation of K_2MnO_4 in Aqueous KOH.—A quantity of 0.44 g of K_2MnO_4 was dissolved under magnetic stirring in 500 ml of 0.025 *N* KOH, which was preadjusted to pH 12.4 employing a pH meter. Control of pH throughout the duration of the experiment was accomplished by addition of small increments of 0.5 *N* nitric acid delivered from a microburette and by simultaneous pH monitoring. The solution was kept agitated with a magnetic stirrer. The temperature was maintained at 23 ± 1°.

The reaction was arrested by addition of 5 ml of a saturated solution of $Ba(OH)_2$ to 20-ml aliquots followed by rapid mixing for 10 min in order to facilitate the agglomeration of manganese(IV) and barium manganate. After filtration of this mixture through a fine Gooch crucible, the concentration of permanganate in the filtrate was determined by spectrophotometric analysis[7] at 526 mμ, with appropriate volume corrections taken into account.

Disproportionation of K_2MnO_4 in Aqueous $Ca(OH)_2$.—The disproportionation reaction in systems saturated with calcium hydroxide was conducted under conditions identical with those described for aqueous KOH with the following exceptions.

K_2MnO_4 was dissolved in 500 ml of distilled water containing 1 g of $Ca(OH)_2$. The pH of this solution remained at a constant value of 12.4 without necessitating adjustments throughout the duration of the experiment.

Oxidation of Cyanide.—The alkaline oxidation of cyanide with permanganate was investigated under a variety of experimental conditions and over a wide range of reactant concentrations.[10] A description of the experimental details of those studies relevant to this paper is given below.

Standardized solutions of KCN and $KMnO_4$ were employed. The reaction was initiated by addition of permanganate solution to solutions saturated with $Ca(OH)_2$ and containing KCN under conditions of rapid mixing and at room temperature. Initial concentrations varied for cyanide and permanganate between 10^{-3} and 10^{-2} *M* and between 3×10^{-4} and 3×10^{-3} *M*, respectively. An excess of each individual reactant was applied in some of the cases. The stoichiometric relationship postulated for the reaction in the presence of calcium hydroxide was established during advanced stages and after completion of the reaction, usually no later than 30 min after initiation. Quenching of the reaction, *i.e.* reduction of excess permanganate to manganese dioxide, was accomplished by dropwise addition of hydrogen peroxide or manganese nitrate. Manganese dioxide was separated by filtration through membrane filters (220 mμ); its removal by this method was readily accomplished by virtue of its precipitation in the presence of calcium ions. The concentration of cyanide was determined argentometrically by the Liebig method,[8] whereas permanganate was measured spectrophotometrically[7] in those cases in which an excess of the oxidant had been applied.

Registry No.—K_2MnO_4, 10294-64-1; KOH, 1310-58-3; $Ca(OH)_2$, 1305-62-0; KCN, 151-50-8.

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(10) Unpublished research, Carus Chemical Co., LaSalle, Ill.

Conversion of Hetacillin into Cephalexin

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In 1963 Morin and collaborators[1] showed that thermal treatment of esters of penicillin V sulfoxide in acidic media gave rise to the corresponding esters of 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid.[2] Later, when cephalexin[3] was shown to be of commercial importance, Chauvette and coworkers[4] reported the synthesis of cephalexin in a multistep sequence from penicillin V sulfoxide ester. We wish to report the synthesis of cephalexin from commercial hetacillin[5] by a four-step series of reactions. Hetacillin (**1**) was nitrosated[6,7] to block its secondary amino function and subsequently oxidized to the sulfoxide **3** with sodium metaperiodate.[8] The sulfoxide **3** was thermally rearranged as the free acid in the presence of *p*-toluenesulfonic acid to the cephalosporin derivative **4**, de-

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(5) G. A. Hardcastle, Jr., D. A. Johnson, C. A. Panetta, A. I. Scott, and S. A. Sutherland, *ibid.*, **31**, 897 (1966).

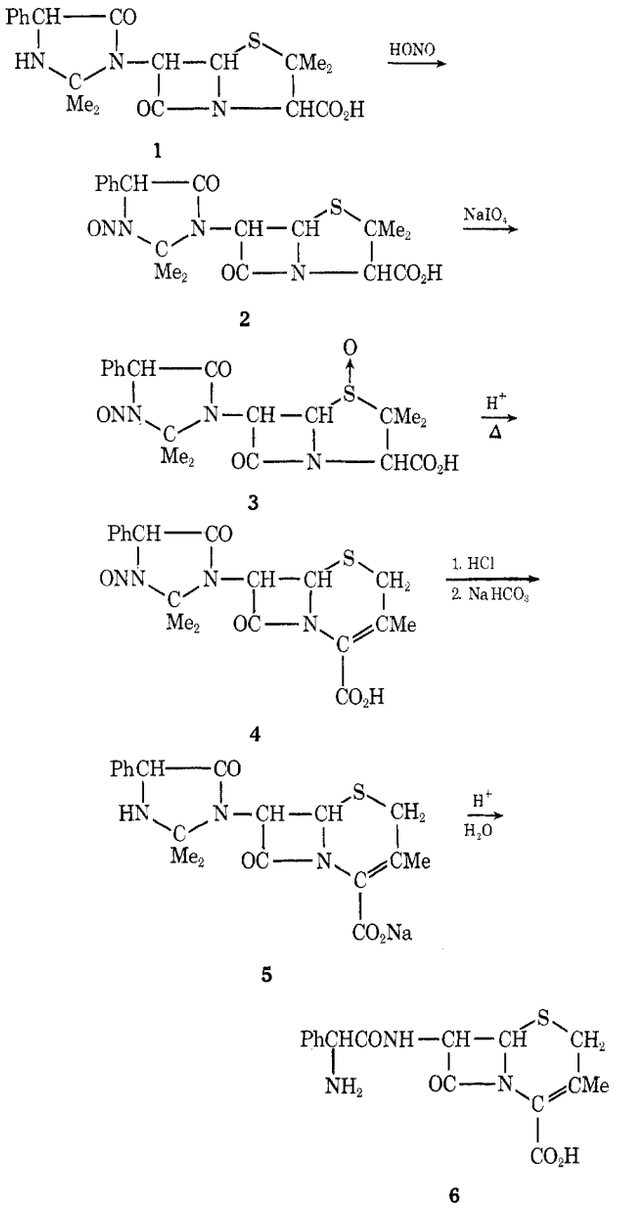
(6) P. Quitt, R. O. Studer, and K. Vogler, *Helv. Chim. Acta*, **47**, 166 (1964).

(7) F. H. C. Stewart, *Aust. J. Chem.*, **22**, 2451 (1969).

(8) J. M. Essery, K. Dadabo, W. J. Gottstein, A. Hallstrand, and L. C. Cheney, *J. Org. Chem.*, **30**, 4388 (1965).

nitrosated with dry hydrogen chloride, and hydrolyzed to cephalexin (6).

The nitrosation of hetacillin (1) proceeded readily in 70% yield to "nitrosohetacillin" (2). Oxidation of 2 to the sulfoxide 3 in 90% yield was attained with sodium metaperiodate. However, it was found that one main contaminant of 3 was its C_6 epimer. The production



of this unwanted isomer was obviated by carefully controlling the acidity of the oxidation reaction. When the reaction mixture was kept at pH 5 or below, the α isomer was reduced to less than 5%. The sulfoxide 3 was thermally rearranged to 4, which was isolated as its *N,N'*-dibenzylethylenediammonium (DBED) salt. Conversion of this salt to "nitrosohetacephalexin" (4) afforded an average yield of 32%. The final denitrosation of 4 to "hetacephalexin" (5) was accomplished in yields averaging 60%. Hydrolysis of 5 afforded cephalexin (6) in 70% yield.

However, when cephalexin was the desired product, "nitrosohetacephalexin" (4) could be advantageously denitrosated and hydrolyzed without isolation of 5 to obtain cephalexin in a yield of 30%.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. The ir spectra were recorded on a Beckman IR-9 spectrometer. The nmr spectra were run on a Varian A-60 spectrometer at a sweep width of 500 cps using dimethyl sulfoxide as a solvent. The authors wish to thank Mr. R. M. Downing and Miss Elizabeth A. Ragan for the microanalyses, and Mr. D. F. Whitehead and Mr. A. L. Vulcano for the spectral data.

6β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic Acid (2).—To a suspension of 142 g (0.37 mol) of commercial hetacillin (1) in 2 l. of water at room temperature was added 69 g (0.41 mol) of sodium nitrite. The mixture was layered with 1.5 l. of ethyl acetate, and with vigorous stirring 6 *N* hydrochloric acid was added dropwise until both layers were clear (pH of aqueous layer 1.9). The addition took 15 min. Stirring was continued for an additional 15 min, and the ethyl acetate was separated, washed with water, and evaporated at 40° (15 mm). The crystalline solid was collected, washed with ether, and recrystallized from methanol–water to yield 110 g (71%): mp 195° dec; ir (KBr) 2800–3600 (carboxyl OH), 1803–1790 (β-lactam C=O), 1750 and 1730 (carboxyl C=O and imidazolidinyl C=O), 700 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.30 (s, 5, C_6H_5–), 5.64 (s, 1, C_6H_5CHN), 5.60 (d, 1, J = 4 cps, NCHCO), 5.45 (d, 1, J = 4 cps, NCHS), 4.35 (s, 1, $NCHCO_2$), 2.00 (s, 6, CH_3CH_3CN), 1.48 (s, 6, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_5S$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.55; H, 5.58; N, 13.33.

6β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic Acid Sulfoxide (3).—To a mixture of 110 g (0.263 mol) of 6β-(D-2,2-dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid (2) in 2.5 l. of water was added with vigorous stirring 66 g (0.31 mol) of sodium metaperiodate. The solution was adjusted to pH 5 with 10% sodium hydroxide, and the mixture was stirred at room temperature for 3 hr with periodic adjustment of the pH. When the mixture became clear, the solution was stirred for an additional 1 hr. The final pH of this solution was 4.1. The sulfoxide was precipitated by addition of 40% H_3PO_4 to pH 2, collected, washed well with water, air dried to constant weight, and finally dried *in vacuo* over P_2O_5 to yield 103 g (91%) of white crystals. An analytical sample was obtained by recrystallization from dimethylformamide and water: mp 160° slow dec; ir (KBr) 3540 (hydrate OH), 2400–3400 (carboxyl OH), 1804 (β-lactam C=O), 1720–1750 (imidazolidinyl C=O and carboxyl C=O), 1050 (SO), 705 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.32 (s, 5, C_6H_5–), 5.77 (s, 1, C_6H_5CHN), 5.72 (d, 1, J = 4.5 cps, NCHCO), 4.83 (d, 1, J = 4.5 cps, NCHS), 4.30 (s, 1, $NCHCO_2$), 2.12 and 2.05 (2 s, 6, CH_3CH_3CN), 1.47 and 1.20 (2 s, 3, 3, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_6S$: C, 52.52; H, 5.11; N, 12.92. Found: C, 52.66; H, 5.37; N, 13.45.

7β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-3-methyl-3-cephem-4-carboxylic Acid (4).—A stirred solution of 10 g (0.022 mol) of 6β-(D-2,2-dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid sulfoxide monohydrate (3) and 2.5 g of anhydrous *p*-toluenesulfonic acid (prepared by azeotropic drying of the monohydrate with ethyl acetate) in 250 ml of tetramethylurea was heated in a preheated bath at 135° for 2 hr. The solvent was removed at 40° (0.1 mm) to obtain an oil which was dissolved in 100 ml of ethyl acetate. The ethyl acetate solution was washed twice with 100-ml portions of water and extracted twice with 100 ml of saturated aqueous sodium bicarbonate solution (final pH 6.7). The aqueous layers were separated, combined, and stirred with 100 ml of ethyl acetate. The aqueous solution was adjusted to pH 2 with 40% H_3PO_4 and the organic extract was separated. The solution was extracted twice more with 100-ml portions of ethyl acetate and the extracts were combined and azeotroped to obtain an oil at 35° (15 mm). The residue was slurried with Skellysolve B and collected as a tan, amorphous powder which weighed 6.2 g. The solids were suspended in 80 ml of water, and saturated sodium bicarbonate solution was added until all the material dissolved (final pH 7.5). A solution of 4 g (0.011 mol) of *N,N'*-dibenzylethylenediammonium diacetate (DBED) in 75 ml of water was added, and the mixture was stirred for 0.5 hr with 150 ml of MIBK in a two-phase system. The mixture was stored at 25° for 5 days. The crystalline DBED salt of 4 was collected and washed with water and finally with acetone. After air drying the salt weighed 4 g: mp 150–152° dec; ir

(KBr) 3200–3600 (water OH), 2200–3200 (NH_2^+), 1770 (β-lactam C=O), 1730 (imidazolidinyl C=O), 1600 (COO^-), 760, 705 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.0–7.6 (m, 20, C_6H_5–), 5.3–6.0 (m, 15, NH_2^+, H_2O, NCHCO), 5.0 (d, 2, NCHS), 3.9 (s, 4, $C_6H_5CH_2N$), 2.6–3.4 (m, 8, $SCH_2C{=}C$, NCH_2CH_2N), 1.9 (s, 18, $CH_3C{=}C$, CH_3CH_3C).

Anal. Calcd for $C_{54}H_{60}N_{10}O_{10}S_2 \cdot 3H_2O$: C, 57.53; H, 5.90; N, 12.43. Found: C, 57.54; H, 6.21; N, 12.71.

The 4 g of the DBED salt of **4** was suspended in 75 ml of water, and 25 ml of 40% H_3PO_4 was added. The mixture was layered with 50 ml of ethyl acetate and shaken vigorously until all the salt dissolved. A final extraction was made with 50 ml of ethyl acetate and the organic layers were collected, washed with water, and evaporated at 40° (15 mm) to obtain a crystalline solid which weighed 2.95 g (32%), mp 175–180°. The ir and nmr spectra were identical with the spectra of authentic **4** prepared from cephalexin.

7β-(D-α-Aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic Acid (Cephalexin) (6) *via* Hetacephalexin (5).—Into a solution of 1 g (0.0025 mol) of **4** in 50 ml of dioxane (purified by running through a column of aluminum oxide) was introduced a stream of dry hydrogen chloride for 5 min at room temperature. The solution was evaporated at 30° (15 mm) to a gum, which was slurried with ethyl acetate and collected. The solid was then dissolved in water (50 ml) and made basic with aqueous sodium bicarbonate solution to pH 4.8. The mixture was filtered, and the filtrate was evaporated at 30° (15 mm) to a glass which was further dried by azeotropic distillation with ethyl acetate. The yield of the sodium salt was 600 mg (63%). The nmr and ir spectra were consistent with the spectra of the acetone condensation product of cephalexin (**5**).

A solution of 1 g (0.0024 mol) of sodium hetacephalexin (**5**) in 5 ml of water was adjusted to pH 3.5 with 6 *N* hydrochloric acid and stirred at room temperature overnight while a stream of nitrogen was bubbled through the solution to remove the acetone formed during the reaction. The white crystalline cephalexin was collected, the filtrate was adjusted to pH 3.5 again and made up to a volume of 5 ml, and the procedure was repeated. The initial crop weighed 350 mg after drying *in vacuo* over P_2O_5. The second crop weighed 240 mg, giving a total yield of 590 mg (70%). The nmr and ir spectra were identical with those of authentic cephalexin.

Cephalexin (6) Prepared Directly from 4.—A solution of 2 g (0.0048 mol) of **4** in 100 ml of peroxide-free dioxane was treated with dry hydrogen chloride for 10 min at room temperature. The solution was evaporated at 35° (15 mm) to a gummy solid. The solid was dissolved in 10 ml of water and filtered, and the pH was raised to 4.5 by the addition of 10% sodium hydroxide solution. The solution was stirred for 48 hr at 30° while a stream of nitrogen was bubbled through the mixture. The white solid was collected and washed with cold water and finally with acetone to yield 550 mg (30%) of pure **6**.

7β-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-3-methyl-3-cephem-4-carboxylic Acid (4) from Cephalexin.—To a mixture of 10 g (0.03 mol) of (7-D-α-aminophenylacetamido)-3-methyl-3-cephem-4-carboxylic acid in 100 ml of water was added 10% sodium hydroxide solution until pH 7.8 was attained. To this solution was added 40 ml of acetone, and the reaction mixture was stored overnight. The solvent was evaporated, leaving behind a frothy, amorphous solid which was dissolved in 200 ml of water and acidified to pH 2 with 6 *N* hydrochloric acid, and layered with 200 ml of ethyl acetate. The solution was cooled in an ice bath to 5°, and 2.1 g (0.03 mol) of sodium nitrite was added. After stirring for 0.5 hr, the ethyl acetate was separated, washed with water, and evaporated under reduced pressure to an oil. The oil solidified on slurrying with ether to give 2.5 g of an amorphous solid. During storage overnight, a second crop separated, which was crystalline and weighed 1.2 g. The crops were combined and recrystallized from ethyl acetate and ether to obtain 3.2 g (26%). The analytical sample was recrystallized from boiling methanol: mp 175–180° dec; ir (KBr) 2500–3500 (carboxyl OH), 1780 (β-lactam C=O), 1720 and 1730 (imidazolidinyl C=O and carboxyl C=O), 700 cm^{-1} (C_6H_5–); nmr (DMSO-d_6) δ 7.31 (s, 5, C_6H_5), 5.68 (s, 1, C_6H_5CHN), 5.55 (d, 1, J = 4.5 cps, NCHCO), 5.15 (d, 1, J = 4.5 cps, NCHS), 2.9–3.6 (m, 2, SCH_2), 1.8–2.3 (m, 9, CH_3CH_3CN and $CH_3C{=}$).

Anal. Calcd for $C_{19}H_{20}N_4O_5S \cdot {}^1/_2H_2O$: C, 53.73; H, 4.74; N, 13.17. Found: C, 53.90; H, 4.96; N, 13.48.

6α-(D-2,2-Dimethyl-3-nitroso-5-oxo-4-phenyl-1-imidazolidinyl)-penicillanic Acid Sulfoxide (6 Epimer of 2).—To a solution of 20 g (0.048 mol) of **2** in 500 ml of water made basic to pH 9 by the addition of 10% sodium hydroxide was added 12 g (0.056 mol) of sodium metaperiodate. After stirring for 2 hr at pH 7, the solution was acidified to pH 2 with 40% H_3PO_4 and the crystalline solid was collected, washed with water, and dried *in vacuo* over P_2O_5 to yield 14 g (67%): mp 201° dec; ir (KBr) 2990 and 2950 (CH_3), 1795 (β-lactam C=O), 1735 (imidazolidinyl C=O and carboxyl C=O), 705 (monosubstituted phenyl); nmr ($CDCl_3$ and DMSO-d_6) δ 7.0–7.76 (m, 5, C_6H_5), 5.7 (d, J = 2 Hz, 1, C_6H), 5.6 (s, 1, C_6H_5CH), 4.9 (d, J = 2 Hz, 1, C_5H), 4.3 (s, 1, C_3H), 1.9–2.2 (m, CH_3CH_3CN), 1.65 and 1.3 (2 s, 3, 3, CH_3CH_3CS).

Anal. Calcd for $C_{19}H_{22}N_4O_6S \cdot 2H_2O$: C, 48.51; H, 5.57; N, 11.91. Found: C, 48.47; H, 5.23; N, 11.79.

Registry No.—**1**, 14537-96-3; **2**, 34959-70-1; **2** (6 epimer), 34959-71-2; **3**, 34982-12-2; **4**, 34959-72-3; **4** DBED salt, 34959-73-4; **6**, 15686-71-2.

Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. V.[1a] A Novel Synthesis of 3-*n*-(1′,2′-Dehydro)pentadecylcatechol (3β-Alkylvinylcatechols) *via* Dehydration of a Bis(trimethylsilyl) Intermediate[1b]

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In connection with recent studies[1a] of the role of the side chain in the dermatological activity of 3-alkylcatechols, it became necessary to develop a practical synthesis of 3-*n*-(1′,2′-dehydro)pentadecylcatechol (**1a**), the styrenic analog of the saturated component of poison ivy urushiol, 3-*n*-pentadecylcatechol (3-PDC). A search of the literature revealed that no efficient synthesis of compounds of the general type, 3β-alkylvinylcatechol, had previously been reported.

While the dimethyl (**1b**) and dibenzyl (**1c**) ethers of **1a** can easily be prepared by conventional routes from, respectively, 2,3-dimethoxybenzaldehyde and 2,3-dibenzyloxybenzaldehyde,[2] neither **1b** nor **1c** can be converted to the free dihydroxybenzene derivative, **1a**.[3]

Exploratory experimentation confirmed the results of earlier studies in which it had been found that 3-*n*-

(1) (a) Previous paper in the series (IV): A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 733 (1971). (b) These investigations were supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health. (c) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) (a) H. J. Backer and N. H. Haack, *Recl. Trav. Chim. Pays-Bas*, **57**, 225 (1938); (b) B. Loev and C. R. Dawson, *J. Amer. Chem. Soc.*, **78**, 6095 (1956).

(3) Prior to the development of the synthetic route with which this report is concerned, a series of experiments were conducted testing methods of cleavage of **1b** and **1c** to **1a**. Use of a variety of agents, including $AlCl_3$–chlorobenzene, HBr–HOAc, pyridinium chloride, and others for the cleavage of **1b** gave high yields of polymer when conditions vigorous enough to effect cleavage were employed. Reductive cleavage of **1c** using either Na–1-butanol or hydrogenolysis (10% Pd/C) yielded only the saturated 3-PDC.