atoms from glycinate rings of neighboring anions: Mn–O = 2.140–2.175, average, 2.165 Å. The acid hydrogens are used in extraordinarily strong hydrogen bonds, 2.460 Å. (with an estimated probable error of 0.015 Å.), which tie the complex anions into infinite strings parallel to *b*. The remaining eight water molecules of the cell are involved in the general pattern of hydrogen bonding which characterizes the crystal.

The over-all structural pattern of moderately strong bonding in three-dimensions leads to relatively subdued thermal motions as compared with $NH_4CoY\cdot 2H_2O$[5] or $RbFe(OH_2)Y\cdot H_2O$.[6] Indeed, we anticipate that extension of the Fourier synthesis to include all experimental amplitudes out to $(\sin\theta)/\lambda = 0.96$ will give atomic positions requiring little or no "back-shift" corrections.

The machine computations of this paper were carried out at the Cornell Computing Center through the courtesy of Mr. Richard C. Lesser, Director. Preparation and preliminary X-ray examination of the crystals were carried out by Dr. Gordon S. Smith.

(7) Fellow of the John Simon Guggenheim Memorial Foundation, 1960.

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REACTION OF 6-AMINOPENICILLANIC ACID WITH CARBON DIOXIDE

Sir:

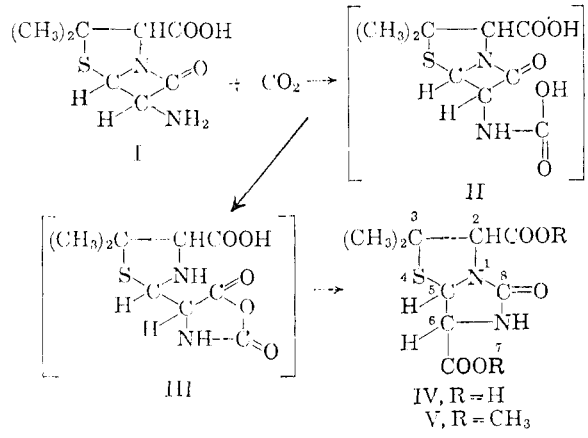
6-Aminopenicillanic acid has been prepared by fermentation of precursor-free penicillin broth,[1] by enzymatic cleavage of natural penicillins,[2–5] and by total synthesis.[6] Its availability has made possible the synthesis of many new, improved penicillins which are not amenable to preparation via fermentation. α-Phenoxyethylpenicillin[7,8] and 2,6-dimethoxyphenylpenicillin[9,10] are clinically important examples.

6-Aminopenicillanic acid (I) has now been found to react rapidly with carbon dioxide in neutral aqueous solution at room temperature to form 3,3-dimethyl - 8 - oxo - 4 - thia - 1,7 - diazabicyclo-[3.3.0]octane-2,6-dicarboxylic acid (IV). Solutions of 0.01 to 1 *M* 6-APA dissolved in 2 equivalents of sodium bicarbonate and placed under 1 atmosphere of carbon dioxide will react completely in 4 to 6 hours at room temperature. Increasing the carbon dioxide pressure increases the rate. The reaction rate is fastest in the *p*H range 5–7, which suggests that unprotonated amino groups and molecular carbon dioxide are the primary reactants.

When the reaction is completed, as indicated by a negative hydroxylamine assay for β-lactams, Compound IV can be isolated in 80–90% yields as the crystalline disodium salt, m.p. 250–251° (dec.), $[\alpha]^{25}D$ +277° (*c* 1, H_2O) (calcd. for $C_9H_{10}N_2O_5SNa_2$: C, 35.53; H, 3.31; N, 9.21. Found: C, 35.56; H, 3.76; N, 9.02). The microcrystalline free acid, m.p. 136–138°, decarboxylates readily.

Analytical and spectral data were consistent with Structure IV, which then was confirmed by conversion with methanolic HCl to the known[11] dimethyl ester (V), m.p. 170–171°, $[\alpha]^{25}D$ +238° (*c* 1, CH_3OH) (Calcd. for $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72. Found: C, 46.01; H, 5.67; N, 9.85). Identity with an authentic sample, prepared by reaction of methyl D-α-4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride[12] with phosgene, was established by comparison of optical rotations, melting points, mixed melting point, infrared spectra, and elemental analyses.

The ease with which this transformation occurs is surprising, but it is more easily understood if the course of the reaction is considered to involve intermediates II and III.



The sequence is analogous to that advanced for the penillic acid rearrangement of the natural penicillins.[13] Indeed, by writing the carbonyl group at position 8 in the enolic form, the complete nucleus of the penillic acids is obtained. Therefore, in order to simplify the nomenclature, Compound IV has been named 8-hydroxypenillic acid.

Since the reaction of 6-aminopenicillanic acid with carbon dioxide takes place so readily, it seemed probable that it might be occurring in *P. chrysogenum* fermentations in which 6-aminopenicillanic acid is an intermediate or end-product. Indeed,

(1) F. R. Batchelor, F. P. Doyle, J. H. C. Naylor and G. N. Rolinson, *Nature*, **183**, 257 (1959).
(2) G. N. Rolinson, *et al.*, *Nature*, **187**, 236 (1960).
(3) C. A. Claridge, A. Gourevitch and J. Lein, *ibid.*, **187**, 237 (1960).
(4) H. T. Huang, A. R. English, T. A. Seto, G. M. Shull and B. A. Sobin, *J. Am. Chem. Soc.*, **82**, 3790 (1960).
(5) W. Kaufmann and K. Bauer, *Naturwissenschaften*, **47**, 474 (1960).
(6) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **81**, 5838 (1959).
(7) Y. G. Perron, *et al.*, *ibid.*, **82**, 3934 (1960).
(8) The trade name of Bristol Laboratories for potassium α-phenoxyethylpenicillin is Syncillin.
(9) E. T. Knudsen and G. N. Rolinson, *Brit. Med. J.*, *ii*, 700 (1960).
(10) The trade name of Bristol Laboratories for sodium 2,6-dimethoxyphenylpenicillin is Staphcillin.
(11) H. T. Clarke, J. R. Johnson and R. Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 859, 891.
(12) J. C. Sheehan and J. P. Ferris, *J. Am. Chem. Soc.*, **81**, 2912 (1959).
(13) H. T. Clarke, J. R. Johnson and R. Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J. 1949, p. 453.

we have isolated 8-hydroxypenillic acid from such fermentations. When phenylacetic acid is omitted, relatively large quantities of both 6-aminopenicillanic acid and 8-hydroxypenillic can be isolated. When excess phenylacetic acid is present, both of these substances are produced but in much smaller concentrations.

The published literature reveals that 8-hydroxypenillic acid has been encountered but unrecognized by other investigators. In 1959, Tardrew and Johnson[14] reported the isolation of "Compound VI" from precursor-free *P. chrysogenum* fermentation broths. While they failed to identify the substance, they concluded that it was a stabilization product of a biosynthetic precursor of the penicillins. In the light of our findings, a review of their results leaves little doubt that "Compound VI" was 8-hydroxypenillic acid.

The fate of sulfur in *P. chrysogenum* fermentations can, therefore, be further defined

$$SO_4^{=} \longrightarrow \text{Cysteine} \longrightarrow \text{6-APA} \underset{}{\overset{RCH_2COOH}{\rightleftharpoons}} \text{Penicillins}$$

$$\text{6-APA} \xrightarrow{CO_2} \text{8-HPA}$$

The anomalous results reported recently by Steinman[15] using the manometric assay for studying the rate of 6-APA hydrolysis by penicillinase can be explained by reaction of some of the carbon dioxide with 6-APA to form 8-HPA.

It seems likely that nearly everyone working with 6-aminopenicillanic acid will, at some time, by chance or by design prepare 8-hydroxypenillic acid.

(14) P. L. Tardrew and M. J. Johnson, *J. Biol. Chem.*, **234**, 1850 (1959).

(15) H. G. Steinman, *Proc. Soc. Exptl. Biol. and Med.*, **106**, 227 (1961).

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A NEW GENERAL REACTION FOR PREPARING *gem* DINITRO COMPOUNDS: OXIDATIVE NITRATION

Sir:

The methods available for preparing *gem* dinitro compounds are of limited applicability or are very inefficient.[1] We wish to report a new general reaction, oxidative nitration, in which salts of primary and secondary nitro compounds are converted into the corresponding *gem* dinitro derivatives by reaction with silver nitrate and inorganic nitrites in alkaline or neutral aqueous media (Equations 1 and 2). Oxidation–reduction proceeds rapidly

$$RCH{=}NO_2^- + 2Ag^+ + NO_2^- \longrightarrow RCH(NO_2)_2 + 2Ag \quad (1)$$

$$R_2C{=}NO_2^- + 2Ag^+ + NO_2^- \longrightarrow R_2C(NO_2)_2 + 2Ag \quad (2)$$

(1) (a) G. Born, *Ber.*, **29**, 90 (1896), (b) E. ter Meer, *Ann.*, **181**, 1 (1876); J. S. Belew and L. G. Hepler, *J. Am. Chem. Soc.*, **78**, 4005 (1956); (c) W. I. Denton, R. B. Bishop, E. M. Nygaard and T. T. Noland, *Ind. Eng. Chem.*, **40**, 381 (1948); (d) C. T. Bahner, *ibid.*, **44**, 317 (1952); (e) M. G. Chancel, *Bull. soc. chim.*, **31**, 504 (1879); M. Fileti and G. Ponzio, *J. prakt. Chem.*, **55**, 195 (1897).

from homogeneous solution at 0–30° to yield an addition-complex which decomposes into *gem* dinitro compound and silver. Primary, secondary, and functionally-substituted dinitro compounds such as 1,1-dinitroethane, 1,1-dinitropropane, 2,2-dinitropropane, 2,2-dinitrobutane,[2a] 1,1-dinitrocyclohexane, 2,2,4,4-tetranitropentane,[2b] 2,3-dimethyl-2,4,4-trinitropentane,[2c] 2,2-dinitro-1-propanol, 1,1-dinitro-2-propanol, 2,2-dinitro-1,3-propanediol, 4,4-dinitropentanal and methyl 3,3-dinitropropionate may be prepared efficiently (60–95%) from their corresponding nitro derivatives. Sensitive or hindered compounds such as 3,3-dinitro-2-butanol,[2d] 2,2-dimethyl-1,1,3-trinitropropane[2e] and 1-cyclopropyl-1,1-dinitroethane,[2f] substances which cannot be prepared satisfactorily by other known methods, have been synthesized.

Dinitromethane has been obtained as its potassium salt from nitromethane[3] or much better from 1-nitro-2-propanol via base-catalyzed decomposition of 1,1-dinitro-2-propanol. The most practical method for preparing potassium dinitromethane (>53%) or potassium 2,2-dinitroethanol (99%) is by controlled alkaline demethylolation (Equations 3 and 4) of 2,2-dinitro-1,3-propanediol ob-

$$HO{-}CH_2{-}\underset{\displaystyle NO_2}{\overset{\displaystyle NO_2}{\overset{|}{\underset{|}{C}}}}{-}CH_2{-}OH \xrightarrow[-H_2O]{KOH} HO{-}CH_2{-}C(NO_2)_2K + CH_2{=}O \quad (3)$$

$$HO{-}CH_2{-}C(NO_2)_2K \longrightarrow CH(NO_2)_2K + CH_2{=}O \quad (4)$$

tained by oxidative nitration (70–80%) of 2-nitro-1,3-propanediol. Under different conditions 2,2-dinitro-1,3-propanediol is converted by potassium hydroxide to dipotassium 1,1,3,3-tetranitropropane[2g,4]; this salt apparently is formed by reaction of potassium dinitromethane and potassium hydroxide with 1,1-dinitroethylene[5] generated by decomposition of potassium 2,2-dinitroethanol.

Oxidative nitration of salts of 1,1-dinitro compounds does not give 1,1,1-trinitromethyl derivatives. α-Arylalkanenitronates yield *vicinal* dinitro compounds, $R_2C(NO_2)C(NO_2)R_2$, by oxidative dimerization along with carbonyl derivatives and *gem* dinitro compounds. Thus phenylnitromethane gives phenyldinitromethane (19%), benzaldehyde (36%) and *meso* and *d,l*-1,2-dinitro-1,2-diphenylethanes (12 and 25%, respectively); 9-nitrofluorene yields 9,9-dinitrofluorene (8%), fluorenone (8%), and 9,9′-dinitrodifluorenyl (76%). The effects of other functional groups on the oxidative nitration reaction are being studied.

The silver obtained may be separated easily and recovered essentially quantitatively as silver nitrate. Mercuric nitrate has been successfully sub-

(2) New compounds: (a) b.p. 78° (10 mm.): C, 32.18; H, 5.37. (b) M.p. 87.5°: C, 23.95; H, 3.18; N, 22.39. (c) M.p. 83°: C, 36.15; H, 5.86; N, 17.71. (d) B.p. 73–75° (2 mm.): C, 29.10; H, 4.75; N, 17.02. (e) M.p. 122°: C, 29.67; H, 4.15; neut. equiv., 207. (f) B.p. 99° (10 mm.): C, 38.08; H, 4.91; N, 17.45. (g) C, 11.77; H, 0.67; N, 18.11; K, 25.50.

(3) The yield is poor because alkaline solutions of nitromethane are rapidly converted to salts of methazonic acid and because the acid, dinitromethane, is unstable.

(4) This also has been observed independently by K. Klager, Aerojet-General Corporation, Azusa, California.

(5) See L. Zeldin and H. Shechter, *J. Am. Chem. Soc.*, **79**, 4708 (1957), and M. B. Frankel, *J. Org. Chem.*, **23**, 813 (1958).