Grignard reagents (*e.g.*, methyl-, ethyl-, and n-propylmagnesium bromide) also undergo the exchange–metalation sequence with triphenylphosphine oxide in refluxing tetrahydrofuran solution to give species of the type $(C_6H_5)_2P(O)CHR\text{-}MgBr$ in 60–70% yield.

The very simply effected reactions described above provide a very convenient route to organofunctional phosphine oxides and sulfides based on the readily available triphenylphosphine oxide and sulfide. Application in the synthesis of phosphine oxides and sulfides of interest in inorganic and in organic chemistry chemistry is in progress.

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## ANHYDROPENICILLINS: A NOVEL REARRANGEMENT OF THE THIAZOLIDINE RING

*Sir:*

A variety of penicillins have been prepared by biosynthesis,[1] total synthesis[2] and partial synthesis[3] using 6-aminopenicillanic acid (6-APA) obtained by direct fermentation[4] or enzymatic hydrolysis of natural penicillins.[5] All these methods lead to penicillins which differ only in the nature of their side chains.

We now report a modification of the *nucleus* of penicillins which involves a novel rearrangement of the thiazolidine ring and provides a potentially valuable intermediate for further transformations. The rearrangement is effected by conversion of a penicillin (I) to the acid chloride[6] or mixed carboxylic-carbonic anhydride[7] (II) followed by treatment with base. The rearranged product (III) is then obtained directly, possibly *via* the route which we have outlined in Fig. 1.

The product of the rearrangement is formally derived from the parent penicillin by loss of water and we have,

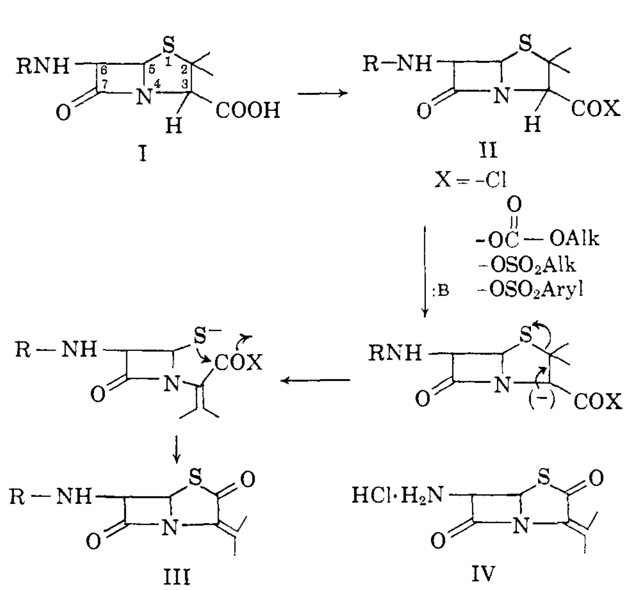

Fig. 1.—Conversion of a penicillin to an *anhydro*penicillin.

therefore, designated it as an *anhydro*penicillin. Thus potassium benzylpenicillin in methylene chloride containing a molar equivalent of pyridine was treated at −30° with a molar equivalent of thionyl chloride. Smooth conversion to the acid chloride was followed by disappearance of the carboxyl band in the infrared spectrum and appearance of a shoulder to the β-lactam absorption band at 5.6 μ. Treatment of the reaction mixture with a slight excess of triethylamine and direct crystallization from ethanol of the neutral product then afforded *anhydro*benzylpenicillin, m.p. 156–158° dec. *Anal.* Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.47; H, 5.02; N, 8.85. Found: C, 60.82; H, 5.17; N, 8.85.

In essentially the same manner were prepared the *anhydro* derivatives of α-phenoxyethylpenicillin,[3a,8] m.p. 150–151°. *Anal.* Calcd. for $C_{17}H_{18}N_2O_4S$: C, 59.0; H, 5.21; N, 8.10. Found: C, 59.16; H, 5.25; N, 8.31. N-Phthaloyl-6-aminopenicillanic acid,[9] m.p. 236–237°. *Anal.* Calcd. for $C_{16}H_{12}N_2O_4S$: C, 58.53; H, 3.66. Found: C, 58.84; H, 3.87. 6-(2-Hydroxy-1-naphthalamino)-penicillanic acid,[10] m.p. 219–221° dec. *Anal.* Calcd. for $C_{19}H_{16}N_2O_3S$: C, 64.77; H, 4.54. Found: C, 64.47; H, 4.71. 6-N-Tritylpenicillanic acid (two forms), m.p. 134–135°. *Anal.* Calcd. for $C_{27}H_{24}N_2O_2S\cdot 0.5H_2O$: C, 72.3; H, 5.58; N, 6.23. Found: C, 72.30; H, 5.61; N, 5.88, and m.p. 164–166°. *Anal.* Calcd. for $C_{27}H_{24}N_2O_2S$: C, 73.60; H, 5.45; N, 6.35; S, 7.28. Found: C, 73.55; H, 5.57; N, 6.00; S, 7.00.

The *anhydro* derivative of 6-aminopenicillanic acid IV was obtained as the rather unstable hydrochloride by treatment of the 6-N-trityl derivative (see above) with a slight excess of HCl in dioxane–ether. It was characterized by its infrared and ultraviolet spectra (see below).

The structure of *anhydro*penicillins may be deduced from these various facts: (1) microanalysis shows the

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(8) From this reaction we isolated a second crystalline product. It melts at 262° and microanalysis and molecular weight measurements indicate that it is a dimer. The same product can be obtained by thermal treatment or irradiation of *anhydro*-α-phenoxyethylpenicillin. The substance has a β-lactam (infrared maximum at 5.6 μ). The dimer with apparently analogous structure also has been isolated from the mother liquors of the *anhydro*benzylpenicillin preparation. The structure and chemistry of these dimers will be discussed in our full paper. We can, however, point out that the dimers are not the ketene dimers which might have been anticipated as by-products.

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(10) This Schiff base was prepared by treatment of 6-APA in methanol with 2-hydroxynaphthaldehyde, m.p. 174–176° dec. *Anal.* Calcd. for $C_{19}H_{18}N_2O_4S$: C, 61.60; H, 4.89. Found: C, 61.40; H, 4.95.

loss of water already mentioned; (2) the ultraviolet spectrum shows $\lambda_{max}^{CHCl_3}$ 269 m$\mu$ ($\epsilon$, 12000); (3) the infrared spectrum shows absorption at 5.52 $\mu$ (strained $\beta$-lactam), 5.9 $\mu$ (strained and conjugated $\gamma$-thiolactone), 6.0 $\mu$ (amide) and 6.1 $\mu$ (double bond); (4) the n.m.r. spectrum[11] shows absence of the tertiary hydrogen at carbon-3 and a doublet at $\tau$ = 7.83 and 7.92 for the isopropylidene group; (5) ozonolysis affords acetone in excellent yield; no acetone is obtained upon ozonolysis of the parent penicillin.

The *anhydro*penicillins possess extraordinary chemical stability as compared with the parent penicillins. This is surprising in view of the highly strained bicyclic system of these compounds (see infrared data above). Thus they are recovered unchanged after prolonged refluxing in ethyl alcohol, aqueous dioxane or xylene. The *anhydro*penicillins display only weak antibacterial activity.[12] However, their increased chemical stability and the activation of the methyl groups by the adjacent double bond makes the introduction of substituents on the methyl groups possible by allylic attack. Some of the products thus obtained show antibacterial activity *and* stability to penicillinase. Details of these and related experiments will be reported in a subsequent paper.

**Acknowledgments.**—We thank Professor B. Belleau of the University of Ottawa for stimulating discussions which led to the correct structure, D. L. Evans for valuable assistance with the infrared spectra and Dr. L. C. Cheney for his advice and encouragement.

(11) Obtained in methylene chloride on the Varian A60 N.M.R. spectrometer. We thank D. L. Whitehead for this spectrum.

(12) Whereas penicillin G. shows a minimum inhibitory concentration *versus Staph. aureus Smith* of 0.02–0.05 $\gamma$/ml., *anhydro*benzylpenicillin inhibits growth at 70 $\gamma$/ml.

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## SYNTHETIC PORPHYRINS RELATED TO CHLOROBIUM CHLOROPHYLLS

*Sir:*

Analytical evidence indicated that a tricarboxylic acid derived from fraction 5 of chlorobium phaeophorbide (660) degraded to a homolog of $\delta$-phylloporphyrin wherein the distribution of methyl and ethyl groups on the 5- and $\delta$-positions was uncertain.[1] This phylloporphyrin has since been isolated and characterized[2] as has a pyrroporphyrin[2] obtained in the same way from fraction 4 of chlorobium phaeophorbide (650).

We have synthesized the methyl ester of 1,3,8-trimethyl-2,4,5-triethylporphin-7-propionic acid (*Anal.* Calcd. for $C_{33}H_{38}O_2N_4$: C, 75.83; H, 7.33; N, 10.72. Found: C, 75.91; H, 7.48; N, 10.61) and of its $\delta$-methyl derivative (*Anal.* Calcd. for $C_{34}H_{40}O_2N_4$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.27; H, 7.21; N, 10.61). These syntheses were analogous to a synthesis of pyrroporphyrin XV[3] and utilized the pyrromethenes from 2-formyl-3-bromo-4-ethyl-pyrrole-5-carboxylic acid with 2-methyl- or 2-ethyl-3-methyl-pyrrole-4-propionic acid.

The identity of the methyl ester of the above chlorobium pyrroporphyrin and the first synthetic porphyrin seemed assured but not clear-cut because of their polymorphism. Their copper complexes, however, showed identical m.p. (220–226°), mixed m.p. and X-ray powder photographs. This proved the 5-ethyl group in fraction 4 of chlorobium phaeophorbide (650), also proved by degradation to ethylmaleimide.[2] It also proved that the pairs of substituents have the hitherto assumed arrangements on the pyrrole rings as in phaeophorbide-a; this was also proved in the case of chlorobium phaeophorbide (650) fraction 6 by conversion to pyrophaeophorbide-a.[2]

The methyl ester of the above phylloporphyrin homolog from chlorobium and the second synthetic porphyrin were identical in m.p. (214–215.5°), mixed m.p., and in their exceptionally well defined X-ray powder photographs. A difficulty in the analytical evidence was resolved when it was found that our synthetic porphyrin, like the analytical one[1] but not as reported for $\delta$-phylloporphyrin IV,[4] had bands II and III of its visible spectrum equal in intensity. The 5-ethyl group and the $\delta$-methyl group, the preferred alternative on general grounds,[2] as well as the hitherto assumed arrangement of the substituents are thus proved in chlorobium phaeophorbide (660) fraction 5; the proton magnetic resonance data is consistent with a $\delta$-alkyl group.[1]

We are also synthesizing porphyrins with the 4-*n*-propyl- and 4-isobutyl-substituents proved by the analytical work,[2] including 4-*n*-propyl-4-des-ethyl-desoxo-phylloerytherin methyl ester, m.p. 236–238° (*Anal.* Calcd. for $C_{35}H_{40}O_2N_4$: C, 76.61; H, 7.35; N, 10.21. Found: C, 77.02; H, 7.15; N, 10.55), copper complex, m.p. 244–246° (*Anal.* Calcd. for $C_{35}H_{38}O_2N_4$: C, 68.90; H, 6.28; CuO, 12.39. Found: C, 68.56; H, 6.34; residue, 12.39). This awaits analytical material for comparison.

The authors wish to thank Dr. A. S. Holt of the Division of Applied Biology for his generous coöperation.

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## INTRINSIC COTTON EFFECTS IN COLLAGEN AND POLY-L-PROLINE[1,2]

*Sir:*

Previous investigations of collagen solutions have shown that the optical rotation in the visible and near ultraviolet regions undergoes large changes from highly negative to less negative values upon denaturation.[3] Rotatory dispersion measurements, in spectral regions removed from absorption bands, on both native and denatured collagen solutions fit the one-term Drude equation as do dispersion data from random coil polypeptides and proteins with low helix contents.[4] Recently, acceptable models for the molecular structure of collagen have been proposed[5,6] which involve three left-handed polyglycine-poly-L-proline II type helices wound in a right-handed super helix. In this com-

(1) This is Polypeptides XLII. For the preceding paper in this series see reference 16.

(2) This work was supported in part by U. S. Public Health Service Grant A2558 and in part by the Office of the Surgeon General, Department of the Army.

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