In the case of the cyclization of Hevea and balata with sulfuric acid the band for the trisubstituted double bond at 1665 cm.$^{-1}$ shifts to a low intensity broad band at 1670 cm.$^{-1}$ and finally, upon the completion of cyclization, appears at 1653 cm.$^{-1}$. Simultaneously with the appearance of the band at 1653 cm.$^{-1}$, representing the vinylidene group, a new band appears at 885 cm.$^{-1}$.

In the cyclization of 3,4-polyisoprene the band at 1643 cm.$^{-1}$, characteristic of isopropenyl groups, is replaced by a band at 1650 cm.$^{-1}$ and finally, upon the completion of cyclization, by a band at 1665 cm.$^{-1}$. The original band at 1378 cm.$^{-1}$ due to the methyl group, during cyclization splits into a doublet at 1385 and 1370 cm.$^{-1}$, indicating the presence of two methyl groups on the quaternary carbon. This is the major difference between the spectra of the cyclopolyisoprene and the cyclized 3,4-polyisoprene and can be accounted for by a difference in the cyclization mechanism.

Further details of the syntheses of the ladder polymers and their detailed spectral analyses as well as of the cyclization of *cis*- and *trans*-1,4 and 3,4-polyisoprenes, will be published at a later date.

(2) It is recognized that the proposed reaction paths can lead to a number of different cyclopolymers. Cyclization of isotactic sequences (a,b) can lead to a product in which all 1,3-junctures are *cis* or diaxial and all 1,2-junctures are *trans* or axial-equatorial or to a product in which all 1,2-junctures are *cis*. Cyclization of syndiotactic sequences (c,d) can lead to 1,3-*trans*-1,2-*cis* or to 1,3-*trans*-1,2-*trans* products. The referee has pointed out that since both *cis* and *trans* structures are possible at the 1,2-junctures, the failure to remove the bridgehead chlorine atoms by *trans*-elimination involving α-hydrogen *cis* to the chlorine is insufficient evidence for structural differentiation.

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A NEW AND CONVENIENT ROUTE TO ORGANOFUNCTIONAL PHOSPHINE OXIDES AND SULFIDES

Sir:

Wittig and Rieber[1] have reported the preparation of tetraphenylphosphonium chloride by reaction of triphenylphosphine oxide with phenyllithium in ether, followed by treatment of the reaction mixture with hydrochloric acid. The possibility exists that this reaction proceeds *via* a pentacovalent phosphorus intermediate. Our interest in the possible intervention of pentacovalent phosphorus intermediates in the generation of phosphinealkylidenes[2] has prompted a more detailed study of this type of reaction. Of particular interest to us was the reaction occurring between triphenylphosphine oxide and methyllithium because of the possible kinetic instability of an intermediate $(C_6H_5)_3CH_3POLi$ species.

$$(C_6H_5)_3PO + C_6H_5Li \longrightarrow (C_6H_5)_4POLi \xrightarrow{HCl} [(C_6H_5)_4P]Cl$$

We have found that the action of methyllithium on triphenylphosphine oxide in diethyl ether produces benzene and a new organolithium reagent.

$$(C_6H_5)_3PO + CH_3Li \longrightarrow (C_6H_5)_2P(O)CH_2Li + C_6H_6$$

Thus in one experiment, 50 mmoles of 1.73 *M* methyllithium in ether was added at room temperature under nitrogen to a slurry of 50 mmoles of triphenylphosphine oxide in ether. The phosphine oxide dissolved, and an orange-red solution resulted. The latter was treated with 48% HBr. The organic layer was shown by gas chromatography to contain 43.7 mmoles of benzene (87.5%). Saturation of the aqueous layer with potassium bromide and extraction with chloroform gave 9.0 g. (83.5%) of methyldiphenylphosphine oxide, m.p. and mixed m.p. after recrystallization, 109–111° (lit.[3] m.p. 109–111°). In another experiment the ether solution produced was poured onto solid carbon dioxide to give $(C_6H_5)_2P(O)CH_2COOH$, m.p. 142–143° (lit.[4] m.p. 142–144°) in 47% yield. Benzene was formed in 86% yield in this reaction. The phosphinyl-substituted lithium reagent also was characterized by its reaction with triphenyltin chloride to give $(C_6H_5)_2P(O)CH_2Sn(C_6H_5)_3$ (76%)[5]; benzene was formed as before.

A similar reaction between ethyllithium and triphenylphosphine oxide resulted in $(C_6H_5)_2P(O)CHLiCH_3$, which was converted to $(C_6H_5)_2P(O)CH(COOH)CH_3$[6] and to $(C_6H_5)_2P(O)CH(CH_3)Sn(C_6H_5)_3$.[7]

The mechanism of these reactions appears to involve an exchange-metalation sequence

I. $(C_6H_5)_3PO + CH_3Li \longrightarrow CH_3(C_6H_5)_2PO + C_6H_5Li$

II. $CH_3(C_6H_5)_2PO + RLi \longrightarrow (C_6H_5)_2P(O)CH_2Li + RH$ ($R = C_6H_5$ or CH_3)

Experiments in which triphenylphosphine oxide was allowed to react with fresh, ethereal ethyllithium and the resulting mixture was quenched with D_2O demonstrated this. When the ratio of C_2H_5Li to $(C_6H_5)_3PO$ was 1:1, the benzene formed in the reaction (97%) (C_6H_6 from reaction II plus C_6H_5D from the reaction of C_6H_5Li present with D_2O) contained 14% C_6H_5D. When the $C_2H_5Li/(C_6H_5)_3PO$ ratio was increased to 3, the C_6H_5D content of the benzene formed (98%) rose to 50%. In a similar experiment the phenyllithium remaining in solution due to successful competition by ethyllithium in reaction II was characterized by its reaction with trimethylchlorosilane to give trimethylphenylsilane in 42% yield. A similar situation obtains in the methyllithium–triphenylphosphine oxide reaction. When these reagents were used in 1:1 molar ratio, quenching of the reaction mixture with D_2O gave benzene in 97% yield, which, however, contained only 2% C_6H_5D. The same experiment with the $CH_3Li/(C_6H_5)_3PO$ ratio increased to 3 gave benzene in 96% yield, which now contained 13% C_6H_5D. Separate experiments showed that methyl-, ethyl-, and phenyllithium metalate methyl- and ethyldiphenylphosphine oxides in good yield in diethyl ether solution, giving $(C_6H_5)_2P(O)CH_2Li$ and $(C_6H_5)_2P(O)CHLiCH_3$, respectively. Further experiments concerning the mechanism of this reaction will be presented when a full account of this work is published.

Triphenylphosphine sulfide also reacts in the same manner with methyllithium, but only in an ether–tetrahydrofuran medium. The $(C_6H_5)_2P(S)CH_2Li$ formed was converted to $(C_6H_5)_2P(S)CH_2COOH$[8] (39%) and to $(C_6H_5)_2P(S)CH_2Sn(C_6H_5)_3$[9] (74%). Preliminary experiments show that here also an exchange–metalation sequence is operative.

(1) G. Wittig and M. Rieber, *Ann.*, **562**, 187 (1949).

(2) D. Seyferth, J. K. Heeren and W. B. Hughes, *J. Am. Chem. Soc.*, **84**, 1764 (1962).

(3) H. Hoffmann, R. Grunewald and L. Horner, *Chem. Ber.*, **93**, 861 (1960).

(4) K. Issleib and G. Thomas, *ibid.*, **94**, 2244 (1961).

(5) M.p. 141–142°. *Anal.* Calcd. for $C_{31}H_{27}OPSn$: C, 65.87; H, 4.82, P, 5.48. Found: C, 65.52; H, 4.68, P, 5.68. N.m.r. in $DCCl_3$: CH_2 a doublet at 3.60 p.p.m. with J = 11 c.p.s., flanked by two satellite doublets due to splitting by the Sn nucleus with J = 29 c.p.s.; phenyl proton absorption at 8.90 p.p.m. (15 H) and 8.45 p.p.m. (10 H) downfield from tetramethylsilane.

(6) M.p. 138–140°. *Anal.* Calcd. for $C_{15}H_{15}O_3P$: C, 65.69; H, 5.51. Found: C, 65.61; H, 5.66.

(7) M.p. 176–177°. *Anal.* Calcd. for $C_{32}H_{29}OPSn$: C, 66.35; H, 5.05; P, 5.34; Sn, 20.60. Found: C, 66.20; H, 4.89; P, 5.27; Sn, 20.88.

(8) M.p. 193–195°; m.p. reported[4]: 188–190°. *Anal.* Calcd. for $C_{14}H_{15}O_2SP$: C, 60.86; H, 4.74. Found: C, 60.41; H, 5.19.

(9) M.p. 174–176°. *Anal.* Calcd. for $C_{31}H_{27}SPSn$: C, 64.05; H, 4.68; P, 5.33. Found: C, 63.84; H, 4.79; P, 5.53.

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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(10) (a) Alfred P. Sloan Research Fellow; (b) National Institutes of Health Predoctoral Fellow; (c) Fellow of the M.I.T. School for Advanced Study, 1961–1962.

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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, 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.

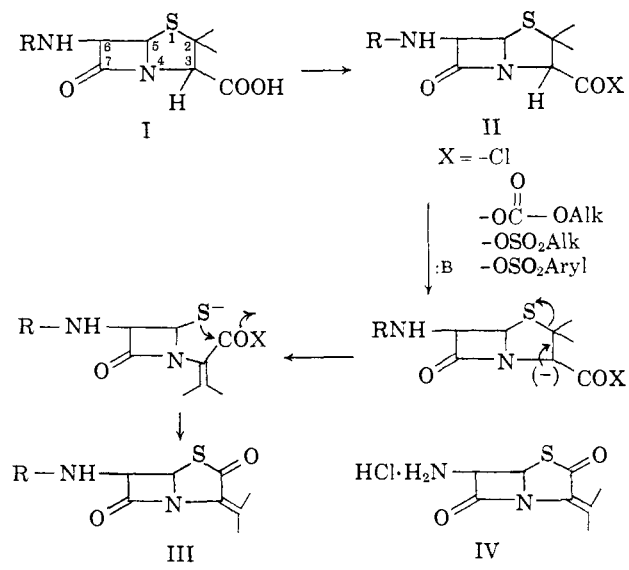

Fig. 1.—Conversion of a penicillin to an *anhydro*penicillin.

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

(1) D. C. Mortimer and M. J. Johnson, *J. Am. Chem. Soc.*, **74**, 4098 (1952); J. E. Philip, A. P. Saunders, A. F. DeRose, D. W. MacCorquodale, J. C. Sylvester and A. W. Weston, *J. Biol. Chem.*, **189**, 479 (1951); O. K. Behrens and M. J. Kingkade, *ibid.*, **176**, 1047 (1948), and references cited therein.

(2) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1262 (1957); **81**, 3089 (1959); J. C. Sheehan and D. R. Hoff, *ibid.*, **79**, 237 (1957); W. A. Bolhofer, J. C. Sheehan and E. L. A. Abrams, *ibid.*, **82**, 3437 (1960); J. C. Sheehan, Canadian Patents 610,096 (1960); 619,205 (1961).

(3) Y. G. Perron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel and L. C. Cheney, *J. Am. Chem. Soc.*, **82**, 3934 (1960); Y. G. Perron, W. F. Minor, L. B. Crast and L. C. Cheney, *J. Org. Chem.*, **26**, 3365 (1961); Y. G. Perron, W. F. Minor, L. B. Crast, A. Gourevitch, J. Lein and L. C. Cheney, *J. Med. Pharm. Chem.*, **5**, 1016 (1962); F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, U. S. Patent 2,951,839 (1960) [*C.A.*, **55**, 4535 (1961)]; F. P. Doyle and J. H. C. Nayler, U. S. Patent 2,996,501 (1961) [*C.A.*, **56**, 5971 (1962)]; F. P. Doyle, J. H. C. Nayler and H. Smith, U. S. Patent 2,985,648 (1961) [*C.A.*, **55**, 21472 (1961)]; F. P. Doyle, J. H. C. Nayler, H. Smith and E. R. Stove, *Nature*, **191**, 1091 (1961); F. P. Doyle, A. A. W. Long, J. H. C. Nayler and E. R. Stove, *ibid.*, **192**, 1183 (1961); D. C. Hobbs and A. R. English, *J. Med. Pharm. Chem.*, **4**, 207 (1961).

(4) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(5) G. N. Rolinson, F. R. Batchelor, D. Butterworth, J. Cameron-Wood, M. Cole, G. C. Eustace, M. V. Hart, M. Richards and E. B. Chain, *ibid.*, **187**, 236 (1960); C. A. Claridge, A. Gourevitch and J. Lein, *ibid.*, **187**, 237 (1960); H. T. Huang, A. R. English, T. A. Seto, G. M. Shull and B. A. Sobin, *J. Am. Chem. Soc.*, **82**, 3790 (1960); W. Kaufmann and K. Bauer, *Naturwissenschaften*, **47**, 474 (1960).

(6) Y. Villax, British Patent 758,653 (1956) [*C.A.*, **51**, 6957 (1957)].

(7) See, for example, D. A. Johnson, *J. Am. Chem. Soc.*, **75**, 3636 (1953); R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jansen, M. E. Trevett and G. B. Webb, *J. Chem. Soc.*, 3733 (1953).

(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.

(9) Y. G. Perron, W. F. Minor, L. B. Crast, A. Gourevitch, J. Lein and L. C. Cheney, *J. Med. Pharm. Chem.*, **5**, 1016 (1962); J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **84**, 2983 (1962).

(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.