A description of the entire DEAE-cellulose chromatogram of the supernatant was presented earlier,[4] and will be reported in detail elsewhere.

(4) B. W. Moore, *Fed. Proc.*, **18**, 289 (1959).

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A GENERAL SYNTHESIS OF THE PENICILLINS

Sir:

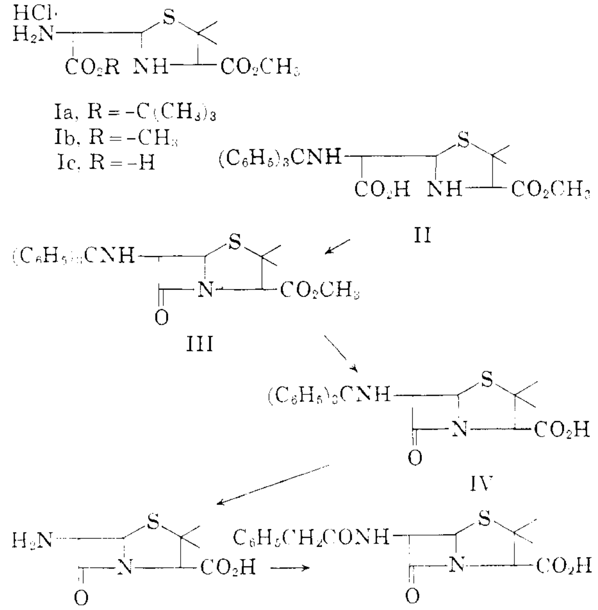
This Communication describes both a partial (from penicillin G) and a total general synthesis of the penicillins. The key intermediate in the two routes is 6-aminopenicillanic acid (V),[1] which we have acylated to form both "natural" penicillins and penicillins not obtainable directly by fermentation.[2]

In the total synthesis series, removal of the phthaloyl group from t-butyl D-α-4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetate[3] as described for the corresponding DL-isomer[4] produced t-butyl D-α-4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (Ia), $C_{13}H_{25}N_2O_4SCl$, in 68% yield; m.p. 183–184° (dec.), α^{31}D + 91° (c 1.2 in methanol) [found: C, 45.65; H, 7.61; N, 8.31]. Cleavage of the t-butyl ester with hydrogen chloride led to a 92% yield of the dihydrochloride of D-α-4-carbomethoxy-5,5-dimethyl-α-amino-2-thiazolidineacetic acid (Ic), $C_9H_{18}N_2O_4SCl_2$; m.p. 94–97° (dec.), α^{29}D + 82° (c 0.5 in 6 N hydrochloric acid) [found: C, 33.72, H, 5.88; N, 8.93]. Trityl chloride and diethylamine[5] converted Ic into D-α-4-carbomethoxy-5,5-dimethyl-α-tritylamino-2-thiazolidineacetic acid (II). Treatment of II with N,N′-diisopropylcarbodiimide in dioxane–water, followed by chromatography over neutral alumina, afforded crystalline methyl 6-tritylaminopenicillanate (III) in 25% yield, $C_{28}H_{28}N_2O_3S$; m.p. 165–166°, α^{31}D + 96° (c 1.1 in n-butyl acetate), λ_{max}^{KBr} at 5.63(vs)μ [found: C, 71.29; H, 6.07; N, 5.73].

By the partial synthesis route, saponification of the α-methyl ester grouping of Ib (obtained from penicillin G[6]) with one equivalent of sodium hydroxide and tritylation[5] of this product formed II in 20% over-all yield as a non-crystalline solid, $C_{28}H_{30}N_2O_4S$; m.p. 87–89° (dec.), α^{31}D + 45° (c 1.3 in n-butyl acetate) [found: C, 68.74; H, 6.28; N, 5.55]. Cyclization of II with diisopropylcarbodiimide gave crystalline III, in 22% yield, m.p. 165–166°.

Compound III also was prepared in 25% over-all yield by tritylation of natural 6-aminopenicillanic acid followed by esterification with diazomethane, m.p. 165–166°, undepressed upon admixture with the corresponding samples made by total synthesis and from penicillin G and having an identical infrared spectrum (KBr) and optical rotation.

The methyl ester of III was saponified selectively[7] to afford 6-tritylaminopenicillanic acid (IV) as the crystalline diethylamine salt in 17% yield, $C_{31}H_{37}N_3O_3S$; m.p. 166–168° (dec.), α^{29}D + 89° (c 1 in dioxane), λ_{max}^{KBr} at 5.66(vs)μ [found: C, 69.71; H, 7.00; N, 7.90]. The salt responded to the quantitative hydroxylamine assay for penicillins.[8] Tritylation[5] of V gave the diethylamine salt of IV in 26% yield, m.p. 164–166° (dec.). Identity of samples of IV prepared from III and V, respectively, was established by undepressed mixed m.p., identical infrared spectra (KBr) and rotations.



V, 6-aminopenicillanic acid VI, penicillin G

Detritylation of IV with dilute hydrochloric acid gave 32% of crystalline 6-aminopenicillanic acid (V), $C_8H_{12}N_2O_3S$; m.p. 207–208° (dec.), [natural,[2] 208–209° (dec.)], undepressed mixed m.p. with natural, α^{31}D + 273° (c 1.2 in 0.1 N hydrochloric acid) [found: C, 44.43; H, 5.54; N, 12.86]. The infrared spectra (KBr) of natural and synthetic V were identical. Synthetic V was compared to natural V, in parallel determinations involving phenoxyacetylation followed by microbiological assay of the penicillin V formed, and shown to contain 107 ± 10% of 6-aminopenicillanic acid.

Acylation of V with phenylacetyl chloride in aqueous acetone containing sodium bicarbonate

(1) J. C. Sheehan, K. R. Henery-Logan and D. A. Johnson, THIS JOURNAL, **75**, 3292 (1953), footnote 2.

(2) In a Ciba Foundation Symposium held in London, England, in March, 1958, J. C. S. stated that ". . . we have prepared this compound [6-aminopenicillanic acid] via a totally synthetic route. . . . We have shown that one can acylate with various acid chlorides and obtain the corresponding penicillin" ("Amino Acids and Peptides with Antimetabolic Activity," G. E. W. Wolstenholme and C. M. O'Connor, Editors, J. A. Churchill Ltd., London, England, 1958, p. 258). More recently the isolation of 6-aminopenicillanic acid directly from penicillin fermentation broths has been reported by F. R. Batchelor, F. P. Doyle, J. H. C. Nayler and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(3) J. C. Sheehan and K. R. Henery-Logan, THIS JOURNAL, **81**, 3089 (1959).

(4) J. C. Sheehan and P. A. Cruickshank, *ibid.*, **78**, 3677 (1956).

(5) L. Zervas and D. M. Theodoropoulos, *ibid.*, **78**, 1359 (1956).

(6) J. C. Sheehan and J. P. Ferris, *ibid.*, **81**, 2912 (1959).

(7) H. T. Clarke, J. R. Johnson and R. Robinson, Editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 94.

(8) J. H. Ford, *Anal. Chem.*, **19**, 1004 (1947).

gave penicillin G in 77% isolated yield as the crystalline *N*-ethylpiperidine salt,[9] m.p. 153–155° (dec.). Penicillin V, prepared in 79% yield by phenoxyacetylation of compound V, was isolated as the potassium salt. Identity of these synthetic samples with the corresponding penicillin salts obtained directly by fermentation was established rigorously by infrared spectra (KBr), m.p. and mixed m.p., optical rotation and microbiological assay. Treatment of V with benzylsulfonyl chloride led to 6-benzylsulfonamidopenicillanic acid.[10] These acylation experiments demonstrate the generality of these synthetic routes for the preparation of both "natural" and "unnatural" penicillins.

We are indebted to Bristol Laboratories of Syracuse, N. Y., for financial support, for bioassays, and for a sample of natural 6-aminopenicillanic acid, and to Mr. Edward J. Hessler for technical assistance.

(9) J. C. Sheehan, W. J. Mader and D. J. Cram, THIS JOURNAL, **68**, 2407 (1946).

(10) J. C. Sheehan and D. R. Hoff, *ibid.*, **79**, 237 (1957).

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FREE-RADICAL-INITIATED *CIS-TRANS* ISOMERIZATION OF DECAHYDRONAPHTHALENE

Sir:

We wish to report *cis–trans* isomerization of decahydronaphthalene (I) by a free radical chain reaction. Di-*tert*-butyl peroxide (0.002 mole) was added over a period of one hour to pure *cis*-I (0.131 mole) refluxing at 195°. After one hour the *trans*-I content had increased from 0.1 to 7.8%, based on total I. Assuming the generation of two free radicals by each peroxide molecule, 2.6 moles of *trans*-I were formed per mole of free radical, clearly demonstrating that the isomerization proceeds by a free radical chain process. No isomerization took place at 195° in the absence of initiator.

We wish to suggest a mechanism for this free radical chain isomerization. The weakest bonds in I, those on the 9 or 10 carbon atoms, are preferentially attacked by a free radical, removing a hydrogen atom from one of those carbon atoms. The resulting free radical, 9-decahydronaphthyl (II), is assumed to have a planar arrangement of C–C bonds around the 9 carbon atom. *cis–trans* Isomerization then occurs by hydrogen atom exchange between I and II, since the hydrogen atom would add to II with equal probability at either side of the plane referred to, producing either *cis-* or *trans*-I. A chain reaction, II + I → I + II, proceeds until radical II is removed by reaction with another free radical.

cis–trans Isomerization of I also was found to occur thermally in the gas phase in the temperature range 440 to 460°, at a rate increasing with pressure. Thus, with one hour time of reaction at 450°, and initial *cis*-I concentrations of 0.0117, 1.53, and 2.66 moles/liter, the I in the product contained 0.9, 31.5, and 43.5% *trans*-I, respectively.[1] It appears not unlikely that the thermal isomerization and the peroxide-initiated isomerization proceed by the same free radical chain mechanism.

(1) Calculations by T. Miyakawa and K. S. Pitzer, THIS JOURNAL, **80**, 61 (1958), give 86.6% *trans*-I, 13.4% *cis*-I at equilibrium at 450°.

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BOOK REVIEWS

The Determination of Molecular Structure. By P. J. WHEATLEY. Oxford University Press, 417 Fifth Avenue, New York 16, N. Y. 1959. vi + 263 pp. 14.5 × 22 cm. Price, $5.60.

Since all of chemistry ultimately depends on the details of the structure of molecules and atoms, it behooves every chemist to know something of the methods by which molecular structure may be determined. This book should provide a reasonably complete introduction to this broad field. It is written strictly for the non-specialist and contains neither extensive details of experimental techniques nor elaborate mathematical discussions. To quote the author, "... the emphasis throughout has been placed on the scope and limitations of the various methods."

Following a lucid introduction to molecular symmetry, the book is divided into three main sections: I. Spectroscopic Methods, II. Diffraction Methods, and III. Miscellaneous Methods, the latter including such topics as stereochemistry, electric and magnetic moments, and nuclear magnetic resonance. Each section contains a general description of the method as well as several real examples from the literature illustrating the way in which molecular *size* and *shape* may be determined from the experimental data. Chemical behavior, of course, also depends intimately on the detailed *electronic* structures of molecules, and an amplification of the few references to this aspect of structural chemistry would have greatly increased the usefulness of the book.

Active workers in the fields discussed will find both omissions and statements with which they are not in complete sympathy, but this should not detract seriously from the usefulness of the book to the general reader.

The section on x-ray diffraction, the author's specialty, is perhaps the best written, although it is somewhat surprising that no mention is made of the least squares method, which is in at least as common use as are Fourier methods in the final stages of a structure refinement. Furthermore, the estimate of six man-years as the time required to determine molecular parameters to an accuracy of 0.015 Å. for a ten atom problem is unduly pessimistic, particularly in the light of modern computing methods. An error of fact appears on p. 121; the structure of NaCl is *not* uniquely determined by the observations that it is face-centered cubic and that there are four formulae units per unit cell.

The section on electron diffraction in its emphasis on the radial distribution method and on the positions of diffraction maxima and minima seems to reflect a certain unfamiliarity with some of the better work in the field. In addition,