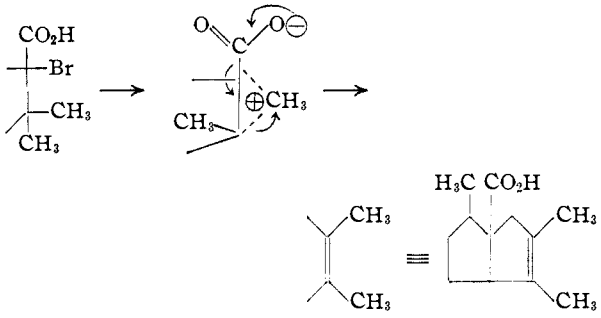
THE REARRANGEMENT OF BROMONORCEDRENEDICARBOXYLIC ACID

Sir:

It was first noted by Ruzicka and van Melsen that treatment of bromonorcedrenedicarboxylic acid (bromoNCDA) with base leads to the loss of the elements of hydrobromic acid and carbon dioxide and the formation of an unsaturated bicyclic monobasic acid, $C_{12}H_{18}O_2$.[1] On the (incorrect) assumption that bromoNCDA is a bromosuccinic acid[2] the reaction is unexceptional and has many precedents.[3] It was eventually recognized however that the C_{12} acid is not an α,β unsaturated acid and that apparently bromide ion and carbon dioxide are lost from the same carbon atom.[1,2] Little further progress was made in the elucidation of the structure of the C_{12} acid, and the rearrangement which leads to it has remained one of the arcana of cedrene chemistry.[4]

An entirely new light was shed on the reaction when it was demonstrated that NCDA is a glutaric acid derivative,[5] and the problem of the base decomposition of bromoNCDA was re-examined. It seemed to us likely that the reaction was essentially one of solvolysis of a neopentyl bromide type, undoubtedly facilitated in the present case by the cancellation of the positive charge on the relevant carboxyl group by formation of a carboxylate anion:



The correctness of this assumption was proved in the following manner: The monomethyl ester of NCDA, m.p. 131°,[2] was converted into the methyl ketone, dinitrophenylhydrazone m.p. 138°, by reaction of the acid chloride with dimethyl cadmium. Perbenzoic acid cleavage, followed by base hydrolysis of the resulting acetate gave the anticipated *hydroxy acid* $C_{12}H_{20}O_3$, m.p. 195–196°; which was then heated with phosphorus tribromide. After hydrolysis with water a crystalline acid was obtained which infrared comparison showed to be *identical* with the C_{12} acid of Ruzicka and van Melsen.

An attractive hypothesis was that the quaternary grouping involved in the rearrangement of bromoNCDA included the *gem* dimethyl group of cedrene.[6] This hypothesis received support from our observation that the characteristic *gem* dimethyl split peak at about 7.3 μ,[7] which is clearly evident in the infrared spectra of practically all the cedrene degradation products which we have examined, is changed to the usual C-methyl band in the rearranged C_{12} acid. Conclusive proof of the involvement of the *gem* dimethyl group was obtained by taking advantage of the fact that a rearranged acid in which the original *gem* dimethyl grouping had changed to two separate methyl groups must show between one and two more C-methyls than the parent compound. Experimental results were in agreement with predictions: NCDA monomethyl ester showed C-methyl: Calcd. for one C-methyl, 6.4. Found: 5.9%. The C_{12} acid showed C-methyl: Calcd. for three C-methyls, 23.2. Found: 22.6%.

The rearrangement of bromonorcedrenedicarboxylic acid, which incidentally finds a striking parallel in the transformation of bromocamphoric acid into laurolenic acid,[8] thus serves to locate the *gem* dimethyl group in cedrene.

(1) L. Ruzicka and J. A. van Melsen, *Ann.*, **471**, 40 (1929).

(2) L. Ruzicka, Pl. A. Plattner and G. W. Kusserow, *Helv. Chim. Acta*, **25**, 85 (1942); Pl. A. Plattner, G. W. Kusserow and H. Kläui, *ibid.*, **25**, 1345 (1942).

(3) See for instance R. Fittig and A. Landolt, *Ann.*, **188**, 71 (1877); S. J. Cristol and W. P. Norris, THIS JOURNAL, **75**, 632 (1953).

(4) The last published investigation of the C_{12} acid is by W. Treibs, *Ber.*, **76**, 160 (1943).

(5) G. Stork and R. Breslow, THIS JOURNAL, **75**, 3291 (1953).

(6) J. Simonsen and D. H. R. Barton, The Terpenes, Vol. III, Cambridge University Press, London, 1952.

(7) A. W. Thompson and P. Torkington, *Trans. Faraday Soc.*, **41**, 246 (1945).

(8) O. Aschan, *Ber.*, **27**, 2112 (1894); A. Lapworth and W. H. Lenton, *J. Chem. Soc.*, **79**, 1284 (1901).

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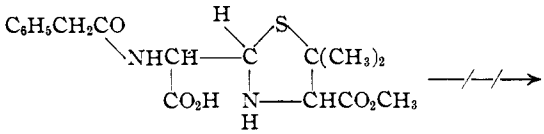
THE SYNTHESIS OF SUBSTITUTED PENICILLINS AND SIMPLER STRUCTURAL ANALOGS. VII. THE CYCLIZATION OF A PENICILLOATE DERIVATIVE TO METHYL PHTHALIMIDOPENICILLANATE

Sir:

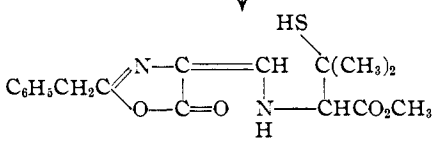
In the very intensive efforts made to cyclize β-methyl penicilloates (I) and related compounds to penicillin derivatives (II), the typical reaction products definitely identified were penicillenates (III), in which azlactonization has occurred and the thiazolidine ring has been disrupted.[1] It is not surprising that the five-membered oxazolone (azlactone) ring is formed in preference to a fused four-membered β-lactam ring whenever that possibility exists. However, of the very large number of recorded attempts[1] to effect a ring-closure of a penicilloate, none was conducted on a structure which could not azlactonize.

By a cyclization procedure we have synthesized a β-lactamthiazolidine (VI), which has the complete structure (configuration unassigned) of the natural penicillins, except for the substitution of a phthalimido group for the acylamino side chain. We have chosen to call this compound methyl phthal-

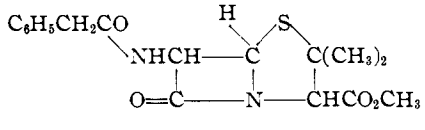
(1) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 851.



β-Methyl benzylpenicilloate (I)

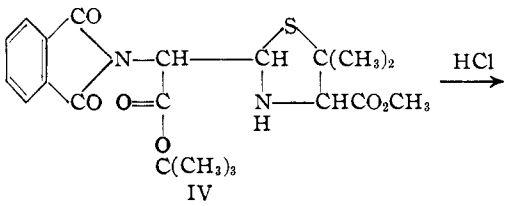


Methyl benzylpenicillenate (III)

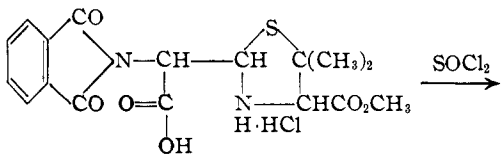


Methyl benzylpenicillinate (II)

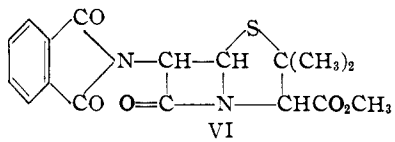
imidopenicillanate.[2] The key intermediate is V, a penicilloic acid derivative structurally incapable of azlactonization.



IV



V



VI

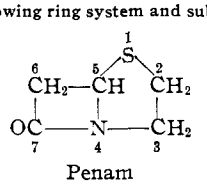
Condensation of *t*-butyl phthalimidoacetate with *t*-butyl formate in the presence of sodium hydride led to 31% of *t*-butyl α-phthalimidomalonaldehydrate, m.p. 155–156° (dec.).[3] *Anal.* Calcd. for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.23; N, 4.84. Found: C, 62.48; H, 5.29; N, 4.70. A crystalline, stereoisomeric mixture of *t*-butyl 4-carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetates was obtained in 84% yield by condensation of this aldehyde-ester with DL-penicillamine. Several recrystallizations from acetone-water afforded a homogeneous sample, m.p. 179.5–180.5° (dec.). *Anal.* Calcd. for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.20; H, 5.79; N, 6.35. Treatment with diazomethane generated the corresponding methyl ester IV (90% yield), m.p. 121–122°. *Anal.* Calcd. for $C_{21}H_{26}N_2O_6S$: C, 58.05; H, 6.03; N, 6.45. Found: C, 58.02; H, 6.09; N, 6.52.

By cleavage of the *t*-butyl ester with dry hydrogen chloride, an 85% yield of 4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiozalidineacetic acid hydrochloride (V) was formed, m.p. 160–161° (dec.). *Anal.* Calcd. for $C_{17}H_{19}N_2O_6SCl$: C, 49.21; H, 4.62; N, 6.75. Found: C, 48.99; H, 4.86; N, 7.07. Treatment of V with thionyl chloride, followed by oxidation with potassium permanganate in acetic acid solution gave the sulfone of VI in 13% yield; m.p. 200–201° (dec.). *Anal.* Calcd. for $C_{17}H_{16}N_2O_7S$: C, 52.03; H, 4.11; N, 7.14. Found: C, 52.18; H, 4.05; N, 7.27. From a similar reaction mixture before oxidation there was isolated by chromatography over alumina the pure β-lactam-thiazolidine VI,[4] m.p. 171–172° (dec.). *Anal.* Calcd. for $C_{17}H_{16}O_5N_2S$: C, 56.67; H, 4.47; N, 7.78. Found: C, 56.64; H, 4.56; N, 8.04.

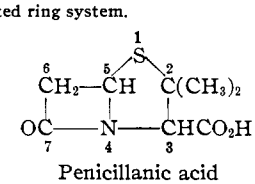
The infrared spectrum of methyl phthalimidopencillanate (VI) has the intense band at 5.62 μ which is associated with the β-lactam carbonyl in natural pencillins[5] and in synthetic β-lactam-thiazolidines. Conversion to the sulfone causes the expected shift[6] of this band to about 5.57 μ; in the spectrum of both VI and VI sulfone the characteristic phthalimido bands at 5.65 μ and 5.82 μ are observed.

We are indebted to Bristol Laboratories of Syracuse, N. Y., for generous financial support of this work.

(2) As a convenience in naming VI and similar analogs of the penicillins we suggest the terms "penam" and "penicillanic acid" for the following ring system and substituted ring system.



Penam



Penicillanic acid

As in the case of the penicilloic acids, these terms carry no stereochemical implications. Thus methyl benzylpenicillinate (penicillin G methyl ester) is one of the stereoisomers of methyl phenylacetamidopenicillanate. The numbering is that generally accepted for the penicillins, and the point of attachment of the side chain is understood to be 6 unless otherwise stated.

(3) All melting points are corrected.

(4) This lactam is inactive when tested by routine penicillin assay procedures (Bristol Laboratories, Syracuse, N. Y.).

(5) Ref. 1, p. 404.

(6) J. C. Sheehan, H. W. Hill, Jr., and E. L. Buhle, THIS JOURNAL, **73**, 4374 (1951); Ref. 1, p. 411.

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FORMATION OF THE ISONICOTINIC ACID HYDRAZIDE ANALOG OF DPN[1]

Sirs:

In a previous paper from this laboratory[2], diphosphopyridine nucleotidase (DPNase) of beef spleen was shown to catalyse the exchange of added C^{14}-labeled nicotinamide with the nicotinamide moiety of DPN resulting in the isolation of C^{14}-labeled DPN. The speculation that structural analogs of nicotinamide might take part in a similar

(1) Contribution No. 53 of the McCollum-Pratt Institute. Aided by grants from the American Tuberculosis Association, the American Cancer Society as recommended by the Committee on Growth of the National Research Council, the Williams-Waterman Fund and the Rockefeller Foundation.

(2) L. J. Zatman, N. O. Kaplan and S. P. Colowick, *J. Biol. Chem.*, **200**, 197 (1953).