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A NOVEL SYNTHESIS OF (+)-METHYL 6-BROMOPENICILLINATE*

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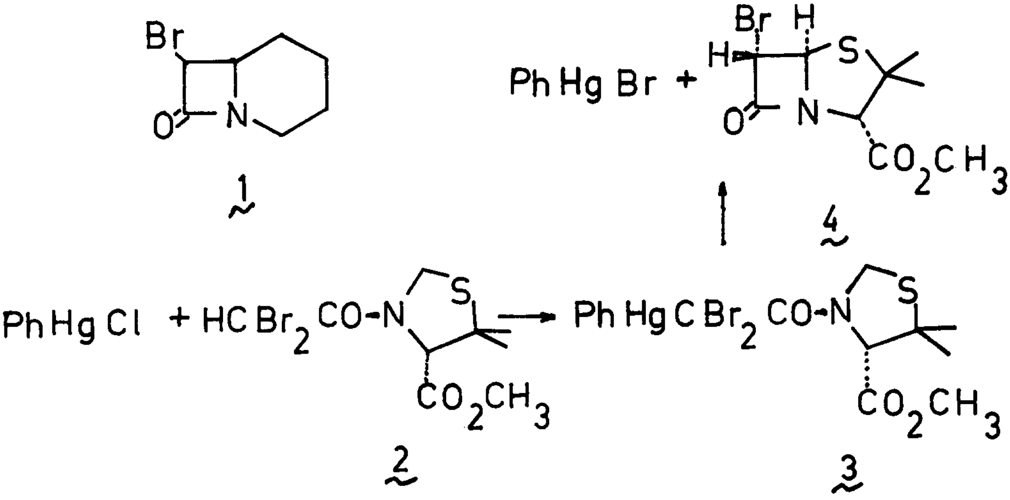
Some time ago we were able to synthesize the bromo-β-lactam 1 in high yield by a mercury induced carbene reaction (1, 2).

Unfortunately, considerable modification of this reaction was neccessary in order to make it applicable to systems more closely analogous to penicillin.

In this communication we wish to report the preparation of (+)-methyl 6-bromopenicillinate (3, 4).

Phenylmercuric chloride and (+)-methyl N-(dibromoacetyl)-5, 5-dimethylthiazolidine-4-carboxylate (2) were condensed at low temperature in tetrahydrofuran solution containing dry, alcohol free potassium t-butoxide. The crude mercury compound



1

4

2

3

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* Synthesis of strained heterocyclic compounds 3. Part 2: Ref. 1.

3 was formed in good yield. It contained small amounts of impurities which had to be removed by chromatography at low temperature prior to the next reaction step.

Thermal decomposition of the compound 3 in refluxing bromobenzene gave, per mole of starting material consumed, approximately 0.8 mole of phenylmercuric bromide, 0.3 mole of the ester 2 and 0.2 mole of the β-lactam 4. The reaction mixture was chromatographed at low temperature to give the crude β-lactam 4 which was sublimed and then recrystallized from light petroleum to give 10 % yield of (+)-methyl 6-bromopenicillinate (4), m.p. 48-49°. This material was identical in all respects (mixed m.p., IR, NMR, MS and optical rotation) with an authentic sample prepared from 6-aminopenicillanic acid (3) by diazotization followed by esterification (*cf.* 5).

The compound 4, obtained from penicillanic acid, has earlier been shown to have the configuration indicated (5). Displacement of the bromine atom at C-6 with an amine function in a reaction that proceeds with inversion, would therefore give penicillin derivatives with the correct configuration.

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1. B.Åkermark and N.G. Johansson, *Acta Chem.Scand.*, in press; accepted for publication June 1968. Publication delayed by request of the authors.

2. The reaction is most probably a carbene reaction, *cf.* D. Seyferth, J.Yick-Pui Mui and J.M.Burlitch, *J.Am.Chem.Soc.* **89**, 4953 (1967).

3. E.Evrard, M.Claesen, and H.Vanderhaeghe, *Nature* **201**, 1124 (1964).

4. Experimental details will be reported in a full paper:
N.G. Johansson, manuscript in preparation.

5. I. Mc Millan and R.J. Stoodley, *J.Chem.Soc.* (C) 2533 (1968).