Piperidazine-3-carboxylic Acid, and the 5-Chloro- and 5-Hydroxy-derivatives—New Amino-acids derived from the Monamycins

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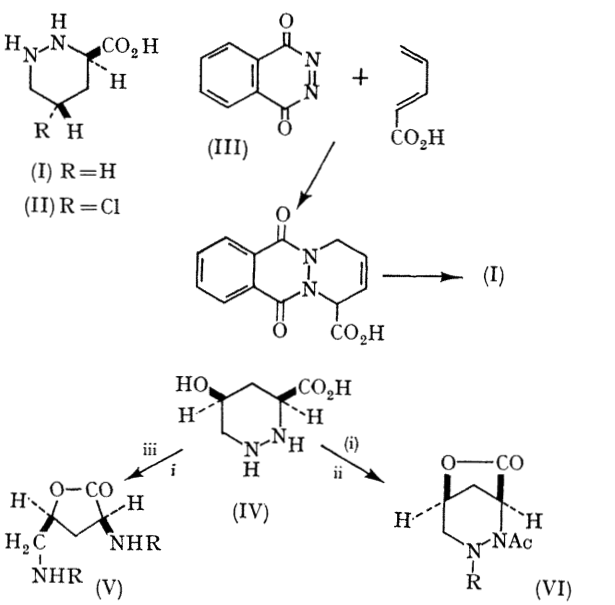
Summary The new amino-acids mentioned in the title have been isolated from acid hydrolysates of the monamycins.

FURTHER studies on monamycin, the crystalline antibacterial preparation obtained from cultures of *Streptomyces jamaicensis*[1] have established that it consists of a mixture of cyclohexadepsipeptides, each containing one α-hydroxy-carboxylic acid (either L-2-hydroxy-3-methylpentanoic or L-2-hydroxy-3-methylbutyric acid) and five amino-acid residues.[2] These include two piperidazine-3-carboxylic acid residues; one is 5-(*S*)-hydroxypiperidazine-3-(*S*) carboxylic acid (IV) and the other is either piperidazine-3-(*R*)-carboxylic acid (I), or 5-(S)-chloropiperidazine-3-(*R*)-carboxylic acid (II).

These new amino-acids have been isolated from the acid hydrolysates of the monamycins. The structure of piperidazine-3-(*R*)-carboxylic acid (I) was established by comparison with DL-piperidazine-3-carboxylic acid, an oil (2,4-dinitrophenyl derivative, m.p. 202° decomp.), which was synthesised through the interaction of phthalazine-1,4-dione (III), and buta-1,3-diene-4-carboxylic acid. Reduction of the natural product to D-ornithine defined the configuration.



R = $C_6H_3(NO_2)_2$-2,4; Reagents. (i) 2,4-Dinitrofluorobenzene; (ii) Ac_2O; (iii) H_2–Pt.

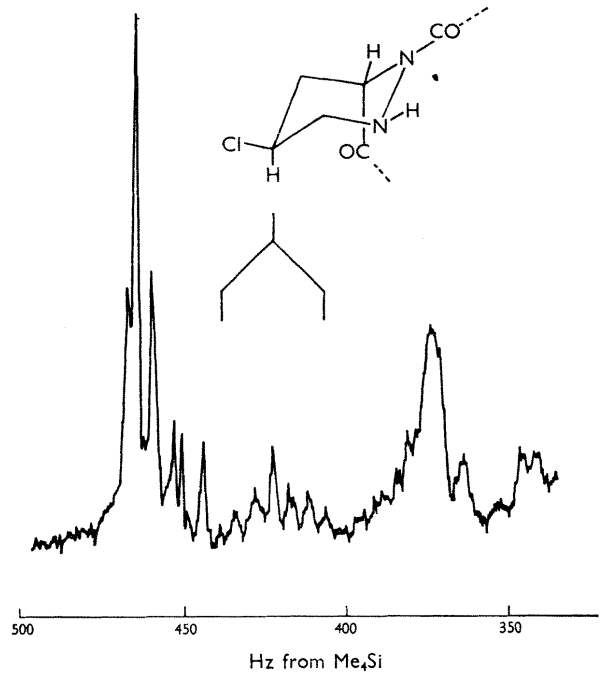


FIGURE. *Part of the* 100 *MHz spectrum of a monamycin compound containing the chlorinated residue with the conformation as shown.*

The structure and configuration of 5-(S)-hydroxypiperidazine-3-(*S*)-carboxylic acid (DNP-derivative, m.p. 201—202°) followed from reduction to the lactone (V)† by catalytic hydrogenation, reduction (P–HI) to a mixture of DL- and L- ornithine (*S*-configuration) and treatment of the 2,4-dinitrophenyl derivative of the acid (IV) with acetic anhydride to give the lactone (VI) (m.p. 258°; ν_{max} 1795 cm.$^{-1}$); the n.m.r. spectrum was in accord with this structure.

5-(*S*)-Chloropiperidazine-3-(*R*)-carboxylic acid, 2,4-dinitrophenyl derivative, m.p. 83—85°) was identified through reduction (H_2–Pt) to D-ornithine. The 100 MHz. n.m.r. spectrum of a compound of monamycin series containing this chlorinated residue, includes a multiplet (Figure), τ 5·79 ($CDCl_3$) which must be attributed to the >CHCl proton. This broad septet (band width, 32·5 Hz.) can only arise from coupling (*J ca.* 5 Hz.) of that proton with two neighbouring nuclei H_a,H_b), and two other neighbouring nuclei with the coupling constant approximately twice as large (*J ca.* 10 Hz.). This interpretation, which resembles that for 5-hydroxypipecolic acid,[3] defines the environment of the chlorine atom as in the Figure, and, with knowledge of the configuration (*R*) of the C-3 asymmetric centre, establishes the configuration at C-5 as (*S*).

The mode of biosynthesis of these novel amino-acids is being investigated.

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