THE SYNTHESIS OF (3S,5S)-5-HYDROXYHEXAHYDROPYRIDAZINE-3-CARBOXYLIC ACID

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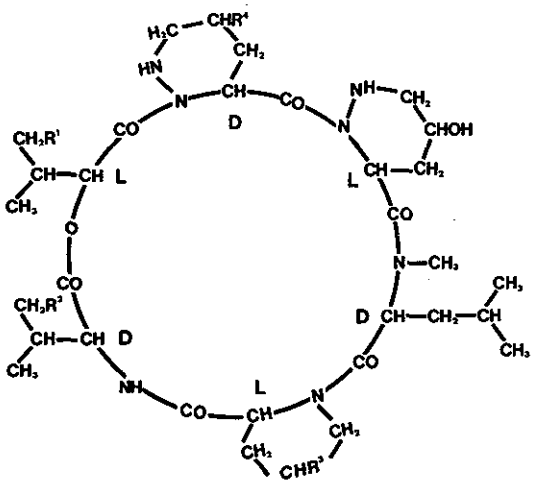
The compound named in the title, a naturally occurring amino acid, has been synthesised from the Diels-Alder adduct of penta-2,4-dienoic acid to phthalazinedione, through successive oxidation with mercuric acetate, hydrogenation with Rh-Al_2O_3 catalyst, acid hydrolysis, resolution with quinine, and hydrazinolysis.

Each of the monamycins (I)[1], members of a family of cyclohexadepsipeptide antibiotics produced by Streptomyces Jamaicensis, contains a single residue of the amino acid, (3S,5S)-5-hydroxyhexahydropyridazine-3-carboxylic acid (IX), with the trivial name, 5-hydroxypiperazic acid(5HyPip). This acid of the L-configuration and the corresponding piperazic, and chloropiperazic acids of D-configuration, were isolated for the first time from hydrolysates of the monamycins.

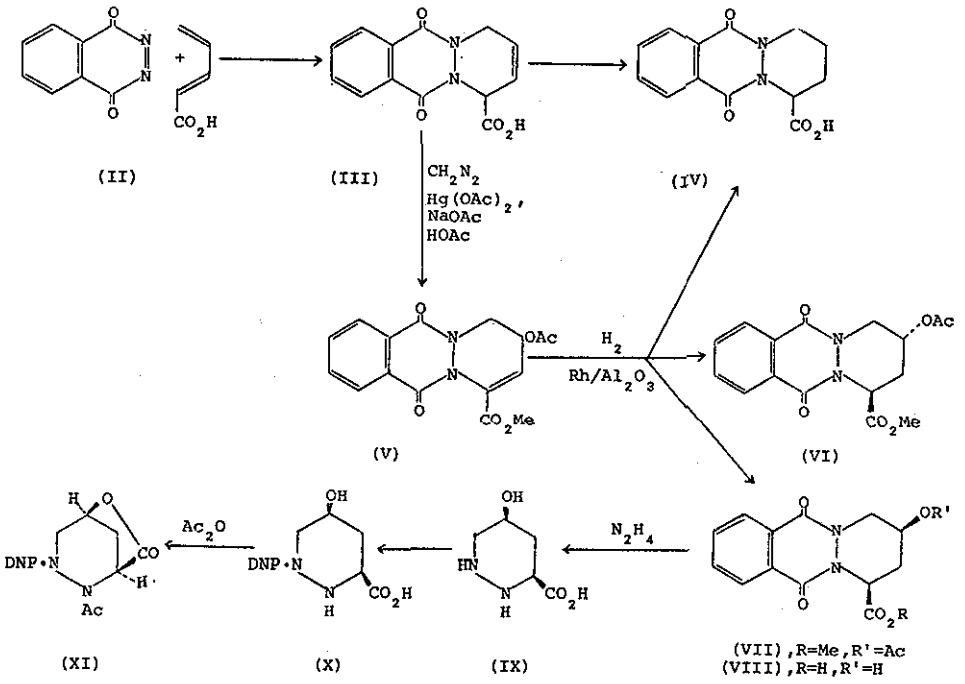


Monamycin	R^1	R^2	R^3	R^4
A	H	H	Me	H
B_1	H	H	Me	H
B_2	H	Me	H	H
B_3	Me	H	H	H
C	Me	H	Me	H
D_1	Me	H	Me	H
D_2	H	Me	Me	H
E	Me	Me	Me	H
F	Me	Me	Me	H
G_1	H	H	Me	Cl
G_2	H	Me	H	Cl
G_3	Me	H	H	Cl
H_1	Me	H	Me	Cl
H_2	H	Me	Me	Cl
I	Me	Me	Me	Cl

(I)

We have undertaken a synthesis of (3S,5S)-5-hydroxypiperazic acid to enable the total synthesis of congeners of the monamycins. DL-Piperazic acid has been prepared, readily, by successive catalytic hydrogenation, and acid-catalysed hydrolysis of 1,4,9,10-tetrahydro-9,10-dioxopyridazino[1,2-b]phthalazine-1-carboxylic acid (III), the product of Diels-Alder addition of penta-2,4-dienoic acid to the strong dienophile, phthalazine-dione (II).[2] The synthesis of racemic 5-hydroxypiperazic acid was attempted initially using 4-benzyloxypenta-2,4-dienoic acid in a similar sequence.[3] This did not prove practicable. We turned then to a synthesis based on oxidation of the methyl ester of the adduct (III). It was found that when this unsaturated ester was heated with 1.5 mole mercuric acetate in the presence of sodium acetate and glacial acetic acid for 5h., oxidation occurred. Purification of the reaction mixture gave methyl 3-acetoxy-3,4,9,10-tetrahydro-9,10-dioxopyridazino[1,2-b]phthalazine-1-carboxylate (V), m.p. 203-205°; $\upsilon(CHCl_3)$ 1750,1660,1610 cm^{-1}, $\delta(CDCl_3)$ 2.1

(s,3H,OCOC$\underline{H}_3$), 3.9(s,3H,$CO_2C\underline{H}_3$), 4.0-4.2(q,1H,H-4'), 4.7-4.9 (q,1H,H-4), 5.0-6.0(m,1H,H-3), 6.22(d,1H,H-2), 7.8-8.4 (m,4H,ar); m/e 330(M^+).



After investigating various hydrogenation conditions it was found that formation of the cis form of methyl 3-acetoxy-1,2,3,4,9,10-hexahydro-9,10-dioxopyridazino[1,2-b]phthalazine-1-carboxylate (VII) was favoured by reduction of the enamine (V) with 5% rhodium on alumina in glacial acetic acid. Under these conditions, approximately 10% of the trans isomer (VI) and less than 10% of the ester of the acid (IV) were formed. The major cis ester (VII) had m.p. 167-169°; $\upsilon(CHCl_3)$ 1750,1655 cm^{-1}; $\delta(CHCl_3)$ 2.02(s,3H,OCOC$\underline{H}_3$), 2.2-2.4(m,1H,H-2), 2.8-3.0

(m,1H,H-2'), 3.3-3.5(q,1H,H-4), 3.7(s,3H,$CO_2\underline{CH}_3$), 5.06-5.3 (m,2H,H-3,H-4'), 5.7-5.8(q,1H,H-1), 7.8-8.4(m,4H,ar); m/e 332(M^+). It was converted to the corresponding hydroxy-acid (VIII) by hydrolysis at 100° for 1h. using 6N-hydrochloric acid. This product had m.p. 228-230°, and the anticipated i.r. and ^1H n.m.r. spectra. It was resolved into its enantiomers with quinine. The laevo isomer, m.p. 210-212°, $[\alpha]_D^{20}$-294° (c,0.5% in MeOH) crystallised as the less soluble quinine salt form.

The (3S,5S)-5-hydroxyhexahydropyridazine-3-carboxylic acid (IX) was prepared from the phthaloyl derivative by treatment with excess hydrazine hydrate (60% in water) at 100° for 2h. The product, an oil, was obtained after removing hydrazine by distillation and phthalhydrazide by filtration from the acidified (pH 2.0) solution. It was characterised as the dinitrophenyl derivative (X), m.p. and mixed m.p. with authentic material 213-214°,[4] $[\alpha]_D^{25}$-223(c,0.24% in Me_2CO); DNP-lactone (XI), m.p. and mixed m.p. 258-260°; the i.r. and ^1H n.m.r. spectra of the natural and synthetic DNP-derivatives were identical.

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