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STUDIES IN THE BIOCHEMISTRY OF MICRO-ORGANISMS - IV.

SYNTHESIS OF 0,0-DIMETHYLCURVULINIC ACID.

A. Kamal and M. Akram Sandhu,

West Regional Laboratories, Pakistan Council of Scientific and
Industrial Research, Ferozepur Road, Lahore-16.

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In part II[1] the constitution of curvulinic acid was established as 2-acetyl-3,5-dihydroxyphenylacetic acid from which curvulin could be obtained by esterification with ethyl-alcohol.

In this paper the synthesis of 0,0-dimethylcurvulinic acid which is obtained by alkaline hydrolyses of 0,0-dimethylcurvulin, is reported as a synthetic proof of the structure of curvulinic acid and consequently of curvulin.

The intermediate: 3,5-dimethoxyphenylacetic acid was prepared in accordance with the method of Musgrave[2] but with slight modification since in our hands, this acid was obtained in low yields. The diazoketone as prepared by Musgrave[2], was reacted with methylalcohol, methyl 3,5-dimethoxyphenylacetate being obtained in 84% yield. The acid: 3,5-dimethoxyphenylacetic acid was obtained on alkaline hydrolysis of the ester. This acid when subjected to Burton & Praills' reaction[3] with acetic anhydride and perchloric acid gave 2-acetyl-3,5-dimethoxyphenylacetic acid identical to 0,0-dimethylcurvulinic acid.

EXPERIMENTAL

All melting points are corrected.

<u>Methyl 3,5-dimethoxyphenylacetate:</u>

To the suspension of the crystalline diazoketone prepared in accordance with the method of Musgrave[2] from 3,5-dimethoxybenzoic acid (5.46; 0.03 mole) in absolute methyl alcohol (60 ml.), was added a slurry of freshly prepared silveroxide (Ca. 8.2 g.) in portions. The contents were refluxed (4 hrs.)

and then filtered. The filtrate was treated with charcoal and again filtered. Removal of the solvent gave methyl 3,5-dimethoxy-phenyl-acetate, b.p. 125-130°C./0.3 mm.; 5.3 g. (84%); $[\eta]_D^{16^{\circ}C.}$; = 1.55.

The ester is soluble in ethylacetate, ether, chloroform, acetone, ethyl and methyl alcohols and insoluble in light-petroleum. It was characterised through its hydrolysis to the acid described below:-

3,5-Dimethoxyphenylacetic acid:

Methyl 3,5-dimethoxyphenylacetate (5.3 g; 0.025 mole) was taken up in ethanolic/KoH (10%; 25 ml.) and refluxed (3 hrs.). Removal of solvent and acidification with dil. H_2SO_4 gave 3,5-dimethoxyphenylacetic acid; 4.52 g; (92%); m.p. 98-99°C. Crystallized from hot water; prismatic needles; 4.42 g; (90%); m.p. 101-102°C. (Lit. 101-102°C[2]; 100-102[4]).

2-Acetyl-3,5-dimethoxyphenylacetic acid: (O,O-Dimethylcurvulinic acid).

3,5-Dimethoxyphenylacetic acid (0.45 g; 0.0025 mole) dissolved in acetic anhydride (0.53 g;) was cooled in ice-cold water and treated with perchloric acid (72%; 0.1 ml.). The clear solution was kept at 0°C. for 15 minutes and then allowed to stand at room temperature. After some time the product started crystallizing out. The contents were allowed to stand (24 hrs.), ice (10 g.) added and the product isolated with ethylacetate. The extract was dried (Na_2SO_4), treated with charcoal and filtered. Removal of the solvent gave 2-Acetyl-3,5-dimethoxylphenylacetic acid, m.p. 115°C., 0.41 g. (69%). Crystallized from ethyl-acetate; microscopic needles; 0.39 g; (65%), m.p. 120°C., undepressed on admixture with O,O-dimethylcurvulin acid. It also gave I.R. and U.V. absorption spectra identical to those of O,O-dimethylcurvulinic acid[1].

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