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SYNTHESIS OF NEOASPERGILLIC ACID

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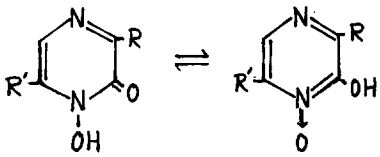
The antibiotic aspergillic acid, for which a pyrazine cyclic hydroxamic acid of structure Ia has been concluded,[1] was isolated in 1943 by White and Hill.[2] Thereafter, hydroxyaspergillic acid (Ib),[3] neohydroxyaspergillic acid (Ic)[4], and muta-aspergillic acid (Id)[5] have been isolated and those have been shown to be analogous pyrazine cyclic hydroxamic acids and to possess antibacterial properties. More recently, Micetich and MacDonald[6] have isolated another antibacterial pyrazine cyclic hydroxamic acid from the culture filtrate of Aspergillus sclerotiorum, for which a structure



(I)

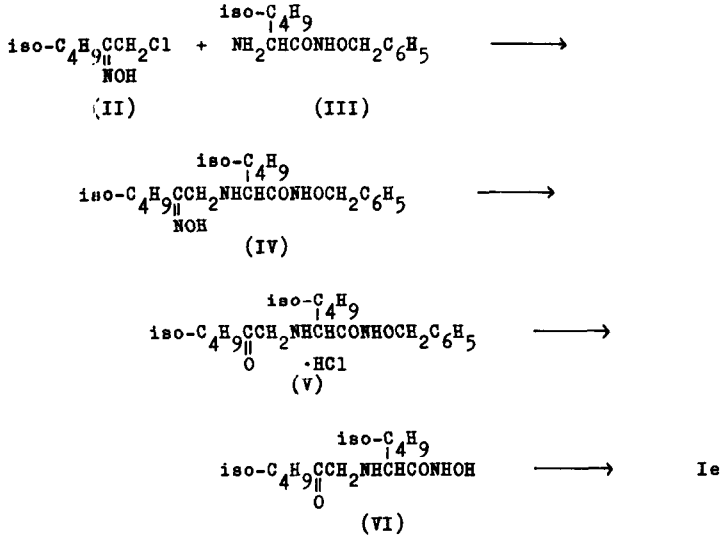
R = CH_2Pr^i

R' = a CHMeEt
b C(OH)MeEt
c $CH(OH)Pr^i$
d C(OH)MeMe
e CH_2Pr^i

of 1-hydroxy-3,6-diisobutyl-2-pyrazinone or its tautomeric 1-oxide of the 2-hydroxypyrazine (Ie) has been suggested and the name

neoaspergillic acid has been proposed.[7]

Although many synthetic studies of cyclic hydroxamic acids related to pyrazine have been made, none of these natural products have been hitherto synthesized. This paper describes a total synthesis of neoaspergillic acid and the essential identity of the natural product with the synthetic substance. The synthesis was performed by using the method which has been shown in our laboratory[8] for synthesizing pyrazine cyclic hydroxamic acid.



Treatment of 1-chloro-4-methylpentanone oxime (II)[9] with N-L-leucyl-O-benzylhydroxylamine (III)[8] in methanol at room temperature yielded N-[4-methyl-2-(4-methyl-2-oximinopentylamino)valeryl]-O-benzylhydroxylamine (IV) as an oily product, which was hydrolyzed in the presence of benzaldehyde in hydrochloric acid-methanol to

give N-[4-methyl-2-(4-methyl-2-oxopentylamino)valeryl]-O-benzylhydroxylamine hydrochloride (V) in a 29.6% yield (calcd. from II), m.p. 134-135° (Anal. Calcd. for $C_{19}H_{30}N_2O_3 \cdot HCl$: C, 61.46; H, 8.36; N, 7.55. Found: C, 61.47; H, 8.51; N, 7.82).

The catalytic reduction of 6 g. of the free base of V gave 1.4 g. of 4-methyl-2-(4-methyl-2-oxopentylamino)valerohydroxamic acid (VI), m.p. 141-142° (decomp.) (Anal. Calcd. for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47. Found: C, 58.72; H, 9.87; N, 11.64), 1.1 g. of which was treated with ammonia in methanol yielded 0.1 g. of Ie, clusters of small yellowish needles from 80% aqueous methanol, m.p. 127.5-128.5°. The product gives a wine red color with a methanolic solution of ferric chloride and was characterized by elementary analysis (Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.31; H, 9.08; N, 12.67.) and ultraviolet spectrum [λ_{max}^{EtOH} 234 mμ (ε 7200) and 328 (9300)] as well as infrared spectrum (Fig. 1).

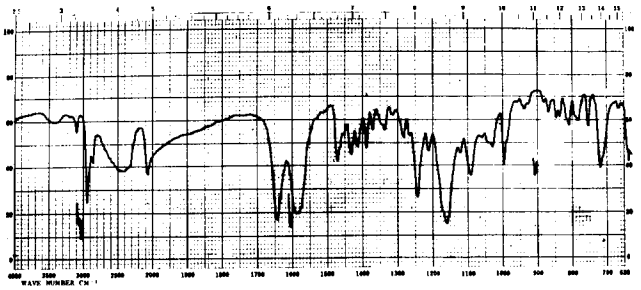


Fig. 1. Infrared Spectrum of Synthesized Neoaspergillic Acid

These constants and properties are essentially identical with those of the natural product [m.p. 125-126°, λ_{max}^{EtOH} 236 mμ (ε 9150) and 328 (10500), infrared sharp bands at 2030, 2880, 2980 and

3140 cm^{-1} with broad bands centered at ca. 3340 and 2450 cm^{-1}].[6]

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