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SYNTHESIS OF 1-HYDROXY-3-ISOBUTYL-6-(1-HYDROXY-1-METHYLETHYL)-2-PYRAZINONE AND THE STRUCTURE OF MUTA-ASPERGILLIC ACID

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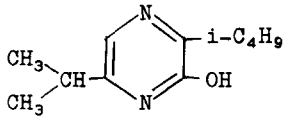
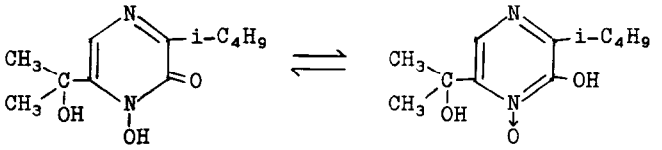
In 1960 Nakamura isolated a new growth inhibitant against hiochi-bacteria from the culture filtrates of Aspergillus Oryzae as pale yellow needles and proposed to designate the antibiotic as muta-aspergillic acid (2). The acid is reduced with hydroiodic acid in phosphoric acid to yield deoxy-muta-aspergillic acid, which has been shown to be identical with the synthetic 3-isobutyl-6-isopropyl-2-hydroxypyrazine (I) (3). In view of this result as well as other chemical and physical properties, muta-aspergillic acid has been assigned 1-hydroxy-3-isobutyl-6-(1-hydroxy-1-methylethyl)-2-pyrazinone or its tautomeric 1-oxide of the 2-hydroxypyrazine structure (II) (3,4).



(I)

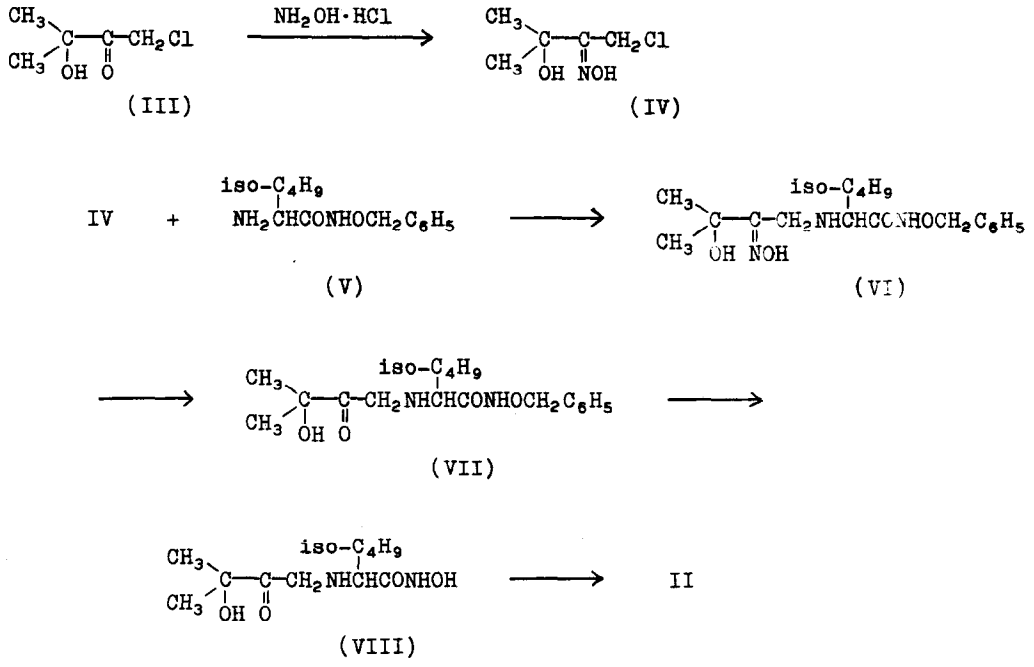


(II)

Masaki and Ohta have found a novel method for synthesizing pyrazine cyclic hydroxamic acid (5), and recently it has been shown that 1-hydroxy-3,6-diisobutyl-2-pyrazinone and 1-hydroxy-3-isobutyl-6-sec-butyl-2-pyrazinone could be synthesized by this method and the chemical and physical properties of the synthesized products were essentially identical with those of neoaspergillic

acid and aspergillic acid, respectively (6).

In the present communication, we wish to report a synthesis of 1-hydroxy-3-isobutyl-6-(1-hydroxy-1-methylethyl)-2-pyrazinone and a comparison of its chemical and physical properties with those of muta-aspergillic acid. The synthesis was performed, as illustrated in Scheme I, by using an analogous technique to that used in the total synthesis of neoaspergillic acid or racemic aspergillic acid.



Scheme I

1-Chloro-3-hydroxy-3-methyl-2-butanone (III) (7) was converted by treatment with hydroxylamine hydrochloride into 1-chloro-3-hydroxy-3-methyl-2-butanone oxime (IV) (8), which was characterized as its piperidino derivative (8). Treatment of the oxime (IV) with N-L-leucyl-O-benzylhydroxylamine (V) (5) in methanol at room temperature gave a 74% yield of N-[4-methyl-2-(3-hydroxy-3-methyl-2-hydroxyiminobutylamino)valeryl]-O-benzylhydroxylamine (VI) as an oily product (9), which was hydrolyzed in the presence of benzaldehyde

in 3 N hydrochloric acid-methanol to give N-[4-methyl-2-(3-hydroxy-3-methyl-2-oxobutylamino)valeryl]-O-benzylhydroxylamine (VII) (9) in a 52% yield.

The catalytic reduction of VII afforded 4-methyl-2-(3-hydroxy-3-methyl-2-oxobutylamino)valerohydroxamic acid (VIII) (8) as colorless amorphous powder (from tetrahydrofuran-n-hexane), which gives a positive ferric chloride reaction and decomposes at 120-121°. When VIII (1 g) was treated with methanolic ammonia at room temperature for 90 hrs, the cyclization reaction and the subsequent air oxidation occured and II (20 mg) was obtained as pale yellow microscopic needles of mp 167-168° (decomp.) (10).

The product shows a wine red color with a methanolic solution of ferric chloride, and the structure was confirmed by elementary analysis (Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.28; H, 7.92; N, 12.64.) and by its infrared spectrum [3340 (broad), 3140, 2960, 2870, 2800-2300 (broad), 2060, 1640, 1590, 1180, 1120 and 675 cm^{-1} (in KBr)], which is very similar to that of neoaspergillic acid or aspergillic acid (6,11), except for the absorption bands attributable to the hydroxyl group of the side chain in 6-position of II at 3340 and 1120 cm^{-1}. The ultraviolet spectrum of II showed absorption maxima at 232 mμ (ϵ =12500) and 332 (7300) in methanol and at 233 mμ (ϵ =6100) and 334 (7200) in ethanol (12), which are also very similar to those of neoaspergillic acid [λ_{max}^{EtOH} 236 mμ (ϵ =9150) and 328 (10500)] (6,11), aspergillic acid [λ_{max}^{EtOH} 234 mμ (ϵ =6500) and 328 (8300)] (6,13) or hydroxyaspergillic acid [λ_{max}^{EtOH} 232 mμ (ϵ =7900) and 330 (7500)] (14).

Although the above data of ferric chloride reaction, melting point and infrared spectrum for the synthesized II are essentially identical with those for the natural muta-aspergillic acid (4), the ultraviolet absorption maxima observed for II are shifted toward shorter wave lengths than those recorded for muta-aspergillic acid [λ_{max}^{MeOH} 242 mμ (ϵ =5100) and 335 (8600)] (4). The difference in ultraviolet spectrum between the synthesized II and the natural muta-aspergillic acid may be due to a recording error for muta-aspergillic acid, or may suggest an alternative structure for muta-aspergillic acid. A further investigation on these points and an examination in the biological activity of the synthesized product (II) are now in progress.

References

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(7) This compound was prepared by the procedures modified from the methods described in the following references: H. Meister, German Patent 1,138,-791 and 1,142,350 (cf. Chem. Abstr., 58, 9090 (1963) and 59, 9837 (1963); M. Julia and J. M. Surzur, Bull. soc. chim. France, 1615 (1956).

(8) A satisfactory elemental analytical result was obtained for this new compound.

(9) Either distillation or crystallization of this oily product was unsuccessful, but the structure was well suported by its infrared spectrum.

(10) The melting point was recorded in a liquid bath and uncorrected, but another melting point of 172-173° (decomp.) was observed when measured on a Yanagimoto micro hot stage. Nakamura has recorded a melting point of 173-174° (uncorrected) for the natural muta-aspergillic acid (3).

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(12) The ultraviolet spectra were determined using a Beckmann type (EPU-2 type) Hitachi photo-electric spectrophotometer.

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