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The Synthesis of Deoxyaspergillic Acid and Tetrahydrodeoxyaspergillic Acid

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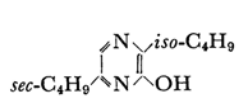
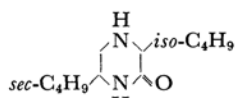
Deoxyaspergillic acid (I) and tetrahydrodeoxyaspergillic acid (II) were synthesized. 1-Chloro-3-methyl-2-pentanone was directly oximinated with hydroxylamine, and then the oxime was treated with L-leucine ethyl ester to yield *N*-(3-methyl-2-oximinopentyl)-L-leucine ethyl ester (III), which, on alkali-hydrolysis, followed by acid-hydrolysis, gave *N*-(3-methyl-2-oxopentyl)-L-leucine (IV). The treatment of the methyl ester of IV with ammonia gave I, and the hydrogenation of III on Raney nickel gave II.

The antibiotic aspergillic acid has been concluded to be 1-hydroxy-3-isobutyl-6-*sec*-butyl-2-pyrazinone or its tautomeric 1-oxide of the 2-hydroxypyrazine.[1] The reduction of aspergillic acid with hydrazine yields deoxyaspergillic acid, i. e., 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (I), while reduction with zinc in acetic acid gives tetrahydrodeoxyaspergillic acid, i. e., 3-isobutyl-6-*sec*-butyl-2-piperazinone (II).[2]



(I)



(II)

Two routes for the synthesis of racemic deoxyaspergillic acid have been reported. The first, reported by Newbold et al.,[1] consists of the reaction of 3-methyl-2-oximinovaleraldehyde with leucine nitrile to give 2-aminopyrazine-1-oxide derivative, which is then converted into I by treatment with sodium dithionite, followed by hydrolysis. The second synthesis consists of the treatment of DL-leucyl-DL-isoleucine anhydride with phosphoryl chloride.[3] On the other hand, tetrahydrodeoxyaspergillic acid has never been synthesized. The present paper will describe an alternative route for the synthesis of racemic deoxyaspergillic acid and the synthesis of racemic tetrahydrodeoxyaspergillic acid.

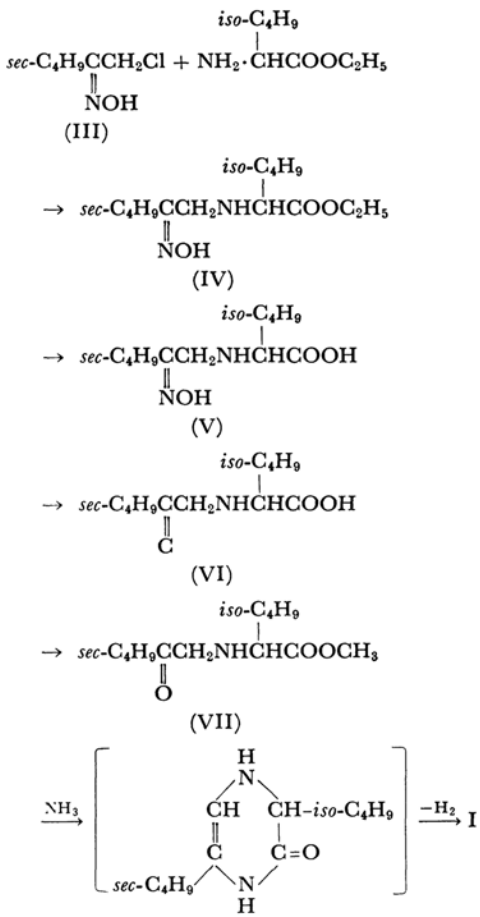
It has been previously reported in our laboratory that 3, 6-disubstituted 2-hydroxypyrazines[4] and 2-piperazinones[5] can be synthesized starting from

1) G. T. Newbold, W. Sharp and F. S. Spring, *J. Chem. Soc.*, **1951**, 2679.
2) J. D. Dutcher, *J. Biol. Chem.*, **171**, 321 (1947).
3) J. J. Gallagher, G. T. Newbold, W. Sharp and F. S. Spring, *J. Chem. Soc.*, **1952**, 4870.
4) M. Masaki and M. Ohta, This Bulletin, **36**, 1177 (1963).
5) M. Masaki and M. Ohta, ibid., **36**, 922 (1963).

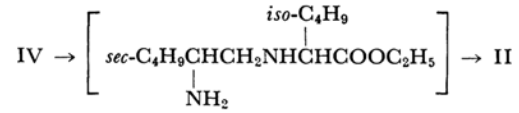
N-(2-oximinoalkyl)-amino acid esters. In an application of this method to the synthesis of I and II, however, 1-chloro-3-methyl-2-pentanone oxime (III) is required. Aliphatic α-halooxime is generally prepared by the reduction of nitroolefine with stannous chloride.[6] The direct oximination of aliphatic α-haloketones with hydroxylamine has been successfully reported only in the case of α-bromo- and α-chloro-acetone,[7] because the reaction of α-haloketone with amines is very complex.[8]

The reaction of 1-chloro-2-pentanone with hydroxylamine was, therefore, studied under various conditions; finally a 43% yield of 1-chloro-2-pentanone oxime was obtained by stirring a suspension of the ketone in an aqueous hydroxylamine solution at 0°C for 4 hr. In a similar manner, 1-chloro-3-methyl-2-pentanone was converted into the corresponding oxime (III) in a 50% yield.

The treatment of 1-chloro-3-methyl-2-pentanone oxime (III) with L-leucine ethyl ester in ether at room temperature yielded *N*-(3-methyl-2-oximinopentyl)-L-leucine ethyl ester (IV) as a yellow oil which was characterized by saponifying it to the corresponding carboxylic acid (V). *N*-(3-Methyl-2-oximinopentyl)-L-leucine (V) was treated with benzaldehyde in hydrochloric acid - methanol to give *N*-(3-methyl-2-oxopentyl)-L-leucine (VI), which was then converted into the methyl ester hydrochloride (VII) by esterification with methanol and hydrogen chloride. When treated with ammonia in methanol, this ester hydrochloride yielded 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (I). The last stage of this reaction involves air oxidation, which is common to most pyrazine syntheses.[4] The product was confirmed by a comparison of its melting point, as well as its infrared and ultraviolet absorption spectra, with those of the deoxyaspergillic acid derived from aspergillic acid[2] or that synthesized by Newbold et al.[1,3]



The oximino ester (IV) was hydrogenated in the presence of Raney nickel at 80°C in an autoclave; thereby the initially-produced amino ester cyclized spontaneously to yield 3-isobutyl-6-*sec*-butyl-2-piperazinone (II), which was isolated as its hydrochloride. The hydrochloride showed the same melting point as that of tetrahydrodeoxyaspergillic acid hydrochloride and showed the absorption bands at 3200, 1660 and 1470 cm^{-1} characteristic of 3, 6-disubstituted 2-piperazinones.[5] These data, as well as the results of the elementary analysis, support the assigned structure.



Experimental

The Oximination of 1-Chloro-2-pentanone.— An aqueous solution of hydroxylamine [from the hydrochloride (3 g.) in water (2.5 g.) and sodium carbonate decahydrate (6 g.) in water (10 ml.)] was stirred, drop by drop, into 1-chloro-2-pentanone (5.0 g.) at 0°C; then, after the addition was complete, the stirring was continued for another 4 hr. The mixture was extracted with ether, and the ethereal layer was washed twice with water and dried over anhydrous sodium sulfate. The evaporation of the ether and the distillation of the residue yielded 2.3 g. of 1-chloro-2-pentanone oxime, b. p. 62—70°C/3 mmHg (lit.[5] 78—82°C/7 mmHg.)

Found: N, 10.32. Calcd. for $C_5H_{10}NOCl$: N, 10.33%.

1-Chloro-3-methyl-2-pentanone Oxime (III).— In an analogous manner to that used for 1-chloro-2-pentanone, 1-chloro-3-methyl-2-pentanone[9] (20 g.) was treated with an aqueous solution of hydroxylamine hydrochloride (10 g.) and sodium carbonate decahydrate (20 g.); 1-chloro-3-methyl-2-pentanone oxime (12 g.) was thus obtained as a colorless oil, b. p. 74—78°C/2.5 mmHg.

Found: C, 48.06; H, 8.19; N, 9.20. Calcd. for $C_6H_{12}NOCl$: C, 48.16; H, 8.13; N, 9.36%.

6) A. Dornow, H. D. Jordan and A. Müller, *Chem. Ber.*, **94**, 67 (1961).
7) R. Scholl and G. Matthaiopoilos, ibid., **29**, 1552 (1896).
8) C. L. Stevens, P. Blumbergs and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).
9) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, **1947**, 375.

The reaction of the product with piperidine afforded 1-piperidino-3-methyl-2-pentanone oxime as a colorless oil, b. p. 108—110°C/0.15 mmHg.

Found: N, 14.41. Calcd. for $C_{11}H_{22}N_2O$: N, 14.14%.

***N*-(3-Methyl-2-oximinopentyl)-L-leucine Ethyl Ester (IV).**—To a solution of leucine ethyl ester (15.5 g.) in absolute ether (50 ml.) there was added a solution of 1-chloro-3-methyl-2-pentanone oxime (6.4 g.) in absolute ether (25 ml.); the mixture was then allowed to stand at room temperature for a week. After the crystals of leucine ethyl ester hydrochloride (4.5 g.) had been removed, the ethereal solution was washed several times with water and extracted with 3 N hydrochloric acid (3×50 ml.). The combined extracts were neutralized with an aqueous solution of sodium carbonate to give a yellow oil, which was then extracted with ether. The ethereal extracts were washed twice with water and dried over anhydrous sodium sulfate. The evaporation of the ether yielded IV as a yellow oil (10 g.), which was characterized by saponifying it to the corresponding carboxylic acid (V), as is shown below.

***N*-(3-Methyl-2-oximinopentyl)-L-leucine (V).**—The crude IV (4.5 g.) was added to a solution of potassium hydroxide (4.5 g.) in water (20 ml.). When the mixture was allowed to stand at room temperature overnight, the mixture became nearly clear. The solution was diluted with water (20 ml.), treated with activated charcoal, and then neutralized with a 20% aqueous acetic acid to give colorless needles, which were recrystallized from methanol, m. p. 168—169°C (decomp.). Yield, 2.2 g.

Found: N, 11.18. Calcd. for $C_{12}H_{24}N_2O_3$: N, 11.47%.

***N*-(3-Methyl-2-oxopentyl)-L-leucine (VI).**—To a mixture of V (2 g.) and 3 N hydrochloric acid (20 ml.), benzaldehyde (2 g.) and methanol (20 ml.) were added the resultant clear solution was allowed to stand at room temperature. After a week the mixture was concentrated to about 20 ml. under reduced pressure. The residue was washed three times with ether and neutralized with a saturated solution of sodium carbonate. The precipitated crystals (0.9 g.) were recrystallized from methanol to yield colorless microscopic needles, m. p. 164.5—165.5°C (decomp.).

Found: N, 6.41. Calcd. for $C_{12}H_{23}NO_3$: N, 6.11%.

***N*-(3-Methyl-2-oxopentyl)-L-leucine Methyl Ester Hydrochloride (VII).**—A suspension of VI (0.8 g.) in methanol was refluxed for 2 hr., while dry hydrogen chloride was passed continuously through the mixture; then the mixture was allowed to stand overnight. The solution was evaporated under reduced pressure to give an oily residue, which was dried in a desiccator over potassium hydroxide under reduced pressure. Crystallization from ethyl acetate afforded colorless plates, m. p. 145°C (after half melting at 134°C). Yield, 0.4 g.

Found: N, 5.24. Calcd. for $C_{13}H_{25}NO_3 \cdot HCl$: N, 5.01%.

3-Isobutyl-6-*sec*-butyl-2-hydroxypyrazine (I).—A solution of VII (0.3 g.) in methanol (20 ml.) was saturated with ammonia. After three days the solution was evaporated to afford a brown oily residue, to which ethyl acetate (5 ml.) was then added. After the insoluble ammonium chloride had been removed, the filtrate was again concentrated under reduced pressure, and the residue was extracted with 6 N hydrochloric acid. After treatment with activated charcoal, the solution was neutralized with 2 N sodium hydroxide, yielding pale brown crystals (0.1 g.). Recrystallization from aqueous methanol gave colorless needles with a m. p. of 99.5—100.5°C. λ_{max}^{EtOH} 228 mμ (ε=7900) and 325 (8400). (Found: C, 69.22; H, 9.98; N, 13.68).

These constants are essentially identical with those of the racemic deoxyaspergillic acid derived from aspergillic acid [m. p. 103—104°C, λ_{max}^{EtOH} 228 mμ (ε=7000) and 325 (8400)][2] or that synthesized by Newbold et al. [m. p. 100.5—101.5°C, λ_{max}^{EtOH} 227 mμ (ε=8000) and 324 (8000)].[1] The infrared spectrum of the product was also essentially identical with that[10] of deoxyaspergillic acid.

3-Isobutyl-6-*sec*-butyl-2-piperazinone (II) Hydrochloride.—A solution of crude IV (4 g.) in ethanol (150 ml.) was shaken with Raney nickel (2 g.) at an initial pressure of 90 kg./cm² of hydrogen at 80°C. After the hydrogen absorption had ceased, the catalyst was removed and the solution was concentrated under reduced pressure. The residue was dissolved in ether (100 ml.) and treated with dry hydrogen chloride to give a yellow oil, which was, after being washed several times with ether, left in absolute ether in a refrigerator. After two days, small needles crystallized out. They were collected and recrystallized twice from *n*-butanol to yield 0.5 g. of colorless needles, which melted at 260°C (decomp.) after darkening at 230°C. ν_{max}^{KBr} 3200, 2950, 1660, 1470, 1280 and 1000 cm^{-1}. (Found: C, 58.15; H, 9.95; N, 11.26.)

According to Dutcher,[2] the tetrahydrodeoxyaspergillic acid hydrochloride derived from aspergillic acid by reduction with zinc and acetic acid melts at 260°C after darkening at 235°C.

10) S. Nakamura, *Agr. Biol. Chem.*, **25**, 658 (1961).