Total Syntheses of Racemic Aspergillic Acid and Neoaspergillic Acid

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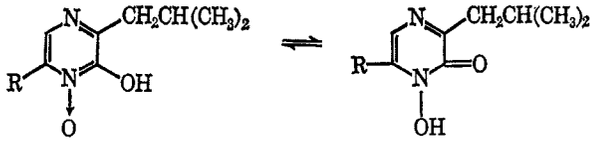
Treatment of 1-chloro-3-methyl-2-oximinopentane with N-leucyl-O-benzylhydroxylamine, followed by hydrolysis of the product, gave N-[4-methyl-2-(3-methyl-2-oxopentylamino)valeryl]-O-benzylhydroxylamine, which was reductively debenzylated to give 4-methyl-2-(3-methyl-2-oxopentylamino)valerohydroxamic acid. On treatment with ammonia in methanol the hydroxamic acid was cyclized to yield racemic 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine 1-oxide, whose spectroscopic properties were essentially identical with those of the optically active aspergillic acid. A similar technique starting from 1-chloro-4-methyl-2-oximinopentane and N-leucyl-O-benzylhydroxylamine yielded 3,6-diisobutyl-2-hydroxypyrazine 1-oxide, whose properties were identical in all respects with those of neoaspergillic acid. During the course of the synthetic reactions, it was found that an initial dehydration of 4-methyl-2-(2-oxoalkylamino)valerohydroxamic acid or its benzyl ester giving the dihydropyrazine was followed or accompanied not only by dehydrogenation to yield 2-hydroxypyrazine 1-oxides, but also by loss of water or benzyl alcohol to yield 2-hydroxypyrazines.

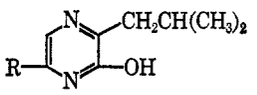
Aspergillic acid was isolated in 1943 by White and Hill from the culture filtrate of *Aspergillus flavus* grown on a medium containing trypton,[1] and it has been shown to be bactericidal for some Gram-negative as well as Gram-positive bacteria.[1,2,4b] Glister reported that a mold, probably belonging to the *Aspergillus* genus, produces a powerful antibacterial agent with a range considerably greater than that of penicillin.[3] Thereafter Menzel and co-workers concluded that the active substance described by Glister is unquestionably identical with aspergillic acid, although the mold seems to be different from *A. flavus*.[4]

The structural investigation of aspergillic acid was made by Dutcher and Spring and his co-workers. Dutcher suggested that it is a cyclic hydroxamic acid related to pyrazine.[5] Aspergillic acid can be reduced to a neutral deoxyaspergillic acid, the racemization product of which was found by Newbold, *et al.*, to be identical with synthetic 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (**2a**).[6] Thus, aspergillic acid has been assigned the corresponding 1-oxide or the tautomeric pyrazine hydroxamic acid structure (**1a**).



1a, R =	$C_2H_5CH(CH_3)$	aspergillic acid
b, R =	$C_2H_5C(OH)(CH_3)$	hydroxyaspergillic acid
c, R =	$(CH_3)_2CHCH(OH)$	neohydroxyaspergillic acid
d, R =	$(CH_3)_2C(OH)$	mutaaspergillic acid
e, R =	$(CH_3)_2CHCH_2$	neoaspergillic acid

Analogous antibiotics, hydroxyaspergillic acid (**1b**),[4] neohydroxyaspergillic acid (**1c**),[7] and mutaaspergillic acid (**1d**),[8] were isolated from *Aspergillus* species and have been suggested to possess the analogous pyrazine cyclic hydroxamic acid structures. Recently, another antibacterial substance was isolated by Micetich and MacDonald from the culture filtrate of *Aspergillus sclerotiorum*[9] and they have proposed the name neoaspergillic acid,[10] for which the structure **1e** was suggested on the basis of the spectral data and the identity of the reduction product with authentic 3,6-diisobutyl-2-hydroxypyrazine (**2e**).



2a, R = *sec*-C_4H_9
e, R = *i*-C_4H_9
g, R = C_6H_5

In two preliminary communications[11] we have reported on the total syntheses of racemic aspergillic acid and neoaspergillic acid. The present paper deals with the detailed information concerning the syntheses and structural assignments for racemic aspergillic acid and neoaspergillic acid.

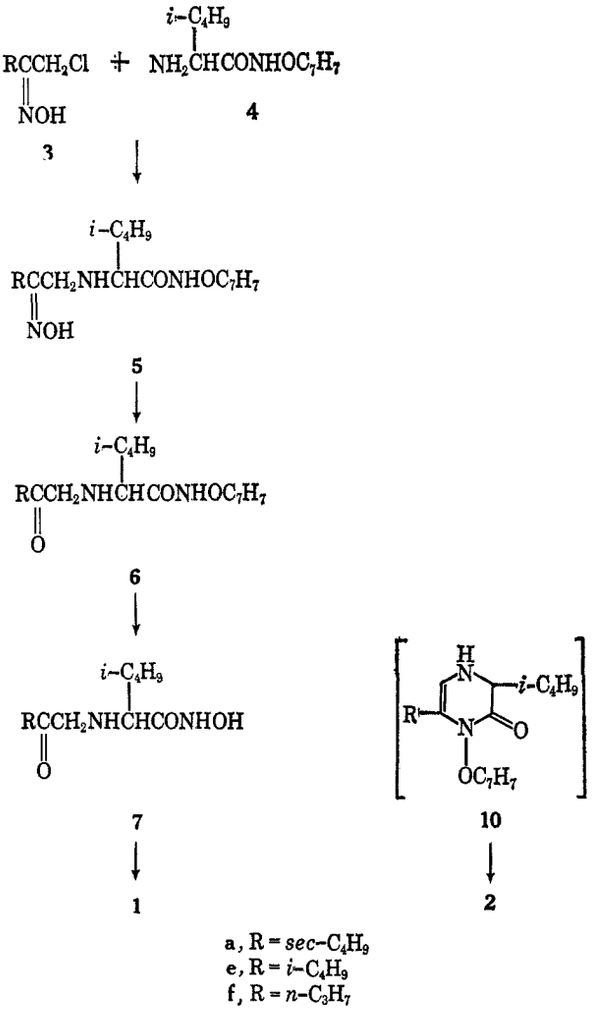
A new method for the synthesis of a pyrazine cyclic hydroxamic acid has been developed in our laboratory.[12] The method consists in the treatment of 1-chloro-2-oximinopentane (**3f**) with N-leucyl-O-benzylhydroxylamine (**4**) followed by interoximation of the product with benzaldehyde to give N-[4-methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine (**6f**) which was, after debenzylation, cyclized to 3-isobutyl-6-propyl-2-hydroxypyrazine 1-oxide.

In an analogous fashion, 1-chloro-3-methyl-2-oximinopentane (**3a**) was treated with the hydroxylamine **4** to give N-[4-methyl-2-(3-methyl-2-oximinopentylamino)valeryl]-O-benzylhydroxylamine (**5a**). After many unsuccessful attempts to transform the oximino group of **5a** to the corresponding carbonyl group, N-[4-methyl-2-(3-methyl-2-oxopentylamino)valeryl]-O-benzylhydroxylamine (**6a**) was obtained by heating **5a** in 3 *N* hydrochloric acid–methanol at 41–43°, whereby 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (**2a**) was isolated as a by-product. The hydrochloride of **6a** could not be crystallized, while the hydrochloride of **6f** was obtained in the form of needles, mp 141–142°. The infrared spectrum of **6a** exhibited two carbonyl bands at 1710 and 1650 cm^{-1}. This absorption pattern was essentially identical with that of **6f**,

(1) E. C. White and T. H. Hill, *J. Bacteriol.*, **45**, 433 (1943).
(2) E. C. White, *Science*, **92**, 127 (1940).
(3) A. Glister, *Nature*, **148**, 470 (1941).
(4) (a) A. E. O. Menzel, O. Wintersteiner, and G. Rake, *J. Bacteriol.*, **46**, 109 (1943); (b) J. D. Dutcher, *J. Biol. Chem.*, **232**, 785 (1958).
(5) J. D. Dutcher, *ibid.*, **171**, 321, 341 (1947).
(6) (a) G. Dunn, J. J. Gallagher, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, S126 (1949); (b) G. T. Newbold, W. Sharp, and F. S. Spring, *ibid.*, 2679 (1951).
(7) U. Weiss, F. Strelitz, H. Flow, and I. N. Asheshov, *Arch. Biochem. Biophys.*, **74**, 150 (1958).
(8) S. Nakamura, *Bull. Agr. Chem. Soc.* (Japan), **23**, 65 (1959), **24**, 629 (1960); S. Nakamura, *Agr. Biol. Chem.*, **25**, 658 (1961).
(9) R. G. Micetich and J. C. MacDonald, *J. Chem. Soc.*, 1507 (1964).
(10) J. C. MacDonald, R. G. Micetich, and R. H. Haskins, *Can. J. Microbiol.*, **10**, 90 (1964).
(11) M. Masaki, Y. Chigira, M. Sugiyama, and M. Ohta, *Tetrahedron Letters*, 4837 (1965); Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Japan*, **39**, 632 (1966).
(12) M. Masaki and M. Ohta, *J. Org. Chem.*, **29**, 3165 (1964).

and the band at 1710 cm^{-1} was ascribed to the ketonic carbonyl group. (See Scheme I.)

SCHEME I

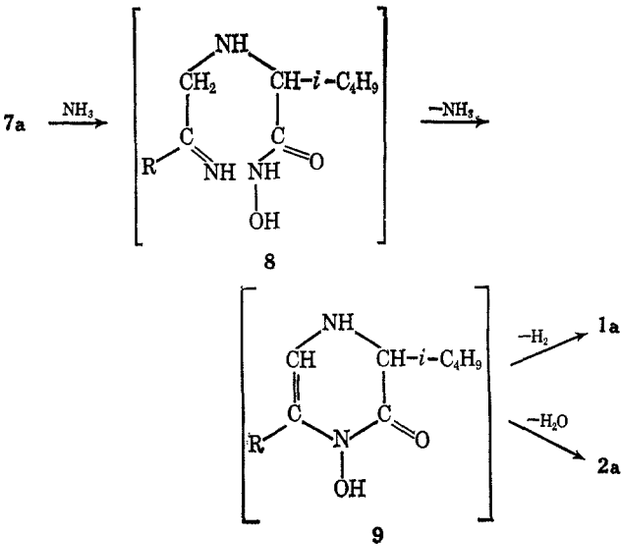


Catalytic hydrogenation of **6a** gave a 45% yield of 4-methyl-2-(3-methyl-2-oxopentylamino)valerohydroxamic acid (**7a**), which gave a red color with a methanolic solution of ferric chloride and was characterized by elemental analysis and its infrared spectrum. Treatment of **7a** with ammonia in methanol at room temperature gave the required 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine 1-oxide, *i.e.*, racemic aspergillic acid (**1a**).

After the ammonia treatment, 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (**2a**) was also isolated as a by-product. A probable pathway for the ring closure would involve an initial reaction of the carbonyl group with ammonia followed by cyclization of the resultant ketimine (**8**) with elimination of ammonia to yield the corresponding dihydropyrazine (**9**). The unstable dihydropyrazine would yield the racemic aspergillic acid upon dehydrogenation by air oxidation, a feature common to most pyrazine syntheses.[13] It is possible, however, that **9** might be transformed to the stable pyrazine system not only with dehydrogenation but also with dehydration, and, in fact, the formation of **2a** in this transformation might be due to the latter reaction course. (See Scheme II.)

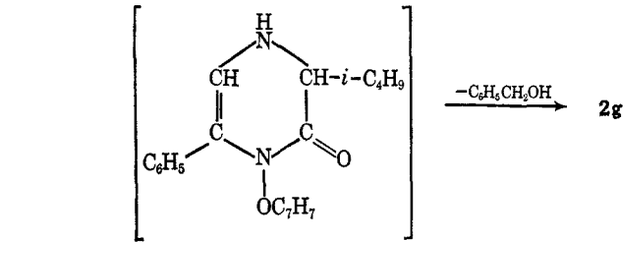
(13) See ref 12 and 15, and the literatures cited therein.

SCHEME II



The formation of a trace of **2a** isolated from the hydrolysis of **5a** may be reasonably explained as follows. A cyclization occurred to small extent to yield 3-isobutyl-6-*sec*-butyl-1-benzyloxy-2-oxo-3,4-dihydropyrazine (**10a**) from which benzyl alcohol was eliminated to form **2a**. In fact, when phenacyl bromide was treated with **4** in a saturated methanolic solution of ammonia, 3-isobutyl-6-phenyl-2-hydroxypyrazine (**2g**) was, as expected, obtained in a 27% yield together with a 51% yield of diphenylpyrazine. (See Scheme III.)

SCHEME III



The synthesized racemic aspergillic acid gave a wine-red ferric reaction like natural aspergillic acid, and was characterized by elemental analysis as well as infrared, ultraviolet, and nmr spectroscopy. The spectra obtained are essentially identical with those of aspergillic acid (see Table I), and showed that the structure proposed for aspergillic acid was correct.

The synthesis of neoaspergillic acid was carried out in an analogous manner to the case of aspergillic acid. 1-Chloro-4-methyl-2-pentanone was directly oximated using the technique mentioned previously[14] to give the corresponding oxime in a 45% yield. The oxime showed bp 80–84° (2.5 mm), while the oxime prepared by the reduction of 4-methyl-2-nitro-1-pentene had bp 85–89° (7.5 mm). The difference might be ascribed to the configuration of the oximes, because an identical ketone (**6e**) was obtained by treatment of both oximes with **4** followed by interoximation of the product with benzaldehyde in the presence of 3 *N* hydrochloric acid. In the oxime interchange

(14) Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Japan*, **39**, 1014 (1966).

TABLE I

Acid	Form	Mp, °C	Ultraviolet,[a] λ_{max}, mμ (log ε)	Infrared,[b] ν_{max}, cm^{-1}	Nmr,[c] τ (no. of protons)
Aspergillic acid	Synthesized	97.5–98.5	233 (3.88)	3120, 2940, 2850,	8.90 (9)
	Racemic		328 (3.94)	2800–2250 (broad),	8.45, 8.55 (3)
				2040, 1640, 1585,	8.12 (3)
				1150, 710	6.85, 6.97 (2)
					6.67, 6.55, 6.45, 6.35 (1)
					2.30 (1)
	Natural	96[d]	234 (3.81)[e]		8.98, 8.85 (9)[f]
		97–99[e]	328 (3.92)		8.55, 8.43 (3)
					8.21–7.48 (3)
					6.90, 6.79 (2)
					6.62, 6.50, 6.38, 6.27 (1)
					2.17 (1)
Neoaspergillic acid	Synthesized	127.5–128.5	234 (3.86)	3100, 2950, 2860,	8.93, 8.83 (12)
			328 (3.97)	2800–2200 (broad),	7.65 (2)
				2060, 1640, 1585,	7.08, 6.96, 6.83 (4)
				1150, 710	2.30 (1)
	Natural[f]	125–126	236 (3.96)	3140, 2980, 2880,	8.93, 8.83 (12)
			328 (4.02)	2450 (broad, centered at), 2050	7.61 (2)
					7.03, 6.90, 6.80 (4)
					2.15 (1)

[a] In EtOH. [b] In KBr. [c] In trifluoroacetic acid with tetramethylsilane as internal reference. [d] Reference 1. [e] Reference 6a. [f] Reference 9.

reaction, 3,6-diisobutyl-2-hydroxypyrazine, *i.e.*, flavacol (**2e**), was obtained as a by-product in a poor yield.

Reductive debenzylation of **6e** gave 4-methyl-2-(4-methyl-2-oxopentylamino)valerohydroxamic acid (**7e**), which on treatment with ammonia in methanol gave the expected 3,6-diisobutyl-2-hydroxypyrazine 1-oxide, *i.e.*, neoaspergillic acid (**1e**). This product gives a wine-red color with ferric chloride and was characterized by elemental analysis as well as infrared, ultraviolet, and nmr spectroscopy. The properties and the spectral data indicate the identity of the product to be the natural neoaspergillic acid, as shown in Table I.

Experimental Section

N-[4-Methyl-2-(3-methyl-2-oximinopentylamino)valeryl]-O-benzylhydroxylamine (5a).—To a solution of N-leucyl-O-benzylhydroxylamine (**4**,[12] 14 g, 59 mmoles) in tetrahydrofuran (300 ml) was added 1-chloro-3-methyl-2-oximinopentane (**3a**,[14] 4.3 g, 29 mmoles) and the resultant solution was kept at room temperature for 1 week. The solvent was evaporated under reduced pressure, and ether (200 ml) and water (170 ml) were added to the residue. After insoluble material had been removed by filtration, the ethereal layer was washed with water and extracted with 1 *N* aqueous sodium hydroxide. The aqueous extract was treated with activated charcoal and saturated with carbon dioxide to separate **5a** as a pale yellow solid (5.2 g). As this solid could be refined neither by crystallization nor by distillation, it was directly used for the next step. The infrared spectrum (liquid film) had bands at 3200, 2960, 1665, 1590, 750, and 700 cm^{-1}.

The insoluble material (5.8 g) obtained in the above treatment with ether and water could be recrystallized from ethyl acetate to give colorless needles, mp 131–132°. The substance is not the hydrochloride of **4** and the elemental analysis showed a probable molecular formula, $C_{13}H_{21}ClN_2O$ (Calcd: C, 60.82; H, 8.19; N, 10.92. Found: C, 60.61; H, 8.55; N, 10.98.). The unidentified substance could, however, be transformed by treatment of the solution in 1 *N* sodium hydroxide with carbon dioxide to **4**.

N-[4-Methyl-2-(3-methyl-2-oxopentylamino)valeryl]-O-benzylhydroxylamine (6a).—To a solution of crude **5a** (2.5 g, 7.2 mmoles) in methanol (20 ml), 3 *N* hydrochloric acid (20 ml) was added and the mixture was kept at 41–43° on a water bath for 5 hr. The solution was concentrated to dryness under reduced pressure and the pale brown, oily residue was washed three times with ether and then treated with a mixture of ether and ethyl acetate. The insoluble crystalline substance (A) was collected by filtration. The filtrate was concentrated and the residue was dissolved in 1 *N* aqueous sodium hydroxide. After washing with ether and treatment with activated charcoal, the aqueous solution was saturated with carbon dioxide to separate a yellow oil, which was extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and concentrated to give **6a** as a yellow oil (1.5 g, yield 63%), the structure of which was confirmed by comparison of the infrared spectrum with that of a lower homolog,[12] N-[4-methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine (**6f**): 3200, 2960, 1710, 1650, 750, and 700 cm^{-1} (liquid film).

The crystalline substance (A) described above was recrystallized from methanol to give 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine hydrochloride (0.1 g), mp 135°.

Anal. Calcd for $C_{12}H_{21}N_2ClO$: C, 58.80; H, 8.59; N, 11.45. Found: C, 58.94; H, 8.49; N, 11.71.

4-Methyl-2-(3-methyl-2-oxopentylamino)valerohydroxamic Acid (7a).—A solution of crude **6a** (1.5 g, 4.5 mmoles) in methanol (60 ml) was shaken with 5% palladium on charcoal (0.5 g) at an initial pressure of 40 kg/cm^2 of hydrogen. After hydrogen absorption had ceased, the catalyst was removed and the solution was concentrated under reduced pressure. The crystalline residue was washed with ether and recrystallized from methanol to yield 0.5 g of colorless clusters of microscopic needles (yield 45%), mp 134° dec. The infrared spectrum (KBr) had a broad band at 2700–2300 and sharp bands at 3260, 2960, and 1620 cm^{-1}.

Anal. Calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47. Found: C, 59.25; H, 10.15; N, 11.65.

3-Isobutyl-6-*sec*-butyl-2-hydroxypyrazine 1-Oxide (Racemic Aspergillic Acid, 1a).—A suspension of **7a** (0.7 g) in methanol (20 ml) was saturated with gaseous ammonia under cooling. The resultant solution was allowed to stand at room temperature for 4 days, and then was concentrated under reduced pressure to dryness. The residue was dissolved in a mixture of methanol (10 ml) and 1 *N* aqueous sodium hydroxide (10 ml). The solution was again concentrated under reduced pressure to dryness and the residue was dissolved in water (10 ml) and treated with activated charcoal. The aqueous solution was saturated with carbon dioxide to separate a waxy product, which was collected by filtration. The filtrate was treated with activated charcoal and then acidified to pH 1.2 with 3 *N* hydrochloric acid. The crystalline solid was collected and recrystallized from 60% aqueous methanol to yield 60 mg of **1a** as yellow needles, mp 97.5–98.0°.

Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.21; H, 9.17; N, 12.56.

The waxy product collected above was dissolved in benzene and the solution was chromatographed on unactivated alumina. Elution with benzene followed by concentration of the eluate gave a crystalline substance. Recrystallization from methanol

yielded 3-isobutyl-6-*sec*-butyl-2-hydroxypyrazine (0.2 g) as colorless needles, mp 99–100°, whose structure was confirmed by comparison (mixture melting point determination and identity of infrared spectra) with an authentic sample.[14]

1-Chloro-4-methyl-2-oximinopentane (3e). A. From 4-Methyl-2-nitro-1-pentene.—The reduction with stannous chloride and hydrogen chloride was performed in the manner reported previously,[15] bp 84–87° (7.5 mm).

B. From 1-Chloro-4-methyl-2-pentanone.—An aqueous solution of hydroxylamine from the hydrochloride (8.0 g, 175 mmoles) in water (10 ml) and sodium carbonate decahydrate (16 g, 56 mmoles) in water (10 ml) was added dropwise, with stirring, to 1-chloro-4-methyl-2-pentanone (8.0 g, 59 mmoles) at 0°. After the addition was complete, stirring was continued for 4 hr. The mixture was extracted with ether and the extract was washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the residue was distilled to give a colorless oil (3.9 g, yield 45%), bp 80–84° (2.5 mm).

Both oximes obtained by A and B methods gave an identical product (**6e**) in the following reactions.

N-[4-Methyl-2-(4-methyl-2-oxopentylamino)valeryl]-O-benzylhydroxylamine (6e) Hydrochloride.—To a solution of **4** (15 g, 63 mmoles) in methanol (170 ml) was added 1-chloro-4-methyl-2-oximinopentane (**3e**, 4.5 g, 30 mmoles). After 6 days the solution was concentrated under reduced pressure and the residue was treated with ether (150 ml). After removal of the insoluble, crystalline product, the ethereal solution was washed twice with water and dried over anhydrous sodium sulfate. The ether was evaporated and the residue was dissolved in a mixture of methanol (65 ml), 3 *N* hydrochloric acid (40 ml), and benzaldehyde (5 g, 47 mmoles). The resultant solution was left to stand at room temperature for 90 hr. The solution was concentrated under reduced pressure to 20–30 ml, to which ether (100 ml) and water (10 ml) were added, whereupon colorless crystals separated gradually. The mixture was kept in a refrigerator overnight, and then the crystals (3.3 g) were collected and washed with ether and ethyl acetate. Recrystallization from 30% aqueous methanol gave two products. As the first crop, a small quantity of colorless needles was obtained, mp 147–147.5°. The product was confirmed to be 3,6-diisobutyl-2-hydroxypyrazine by comparison (mixture melting point determination and identity of infrared spectra) with an authentic sample.[16]

After removal of the first crop, the filtrate was left to stand overnight to separate clusters of colorless small needles as the main product, mp 134–135° dec. The infrared spectrum (KBr) had a complex series of absorptions between 2800 and 2300 cm^{-1} and sharp bands at 3220, 2950, 1690, 750, and 700 cm^{-1}.

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.

4-Methyl-2-(4-methyl-2-oxopentylamino)valerohydroxamic Acid (7e).—The hydrochloride of **6e** (2.5 g) was dissolved in 1 *N* aqueous sodium hydroxide (30 ml) and treated with activated charcoal. The clear solution was saturated with carbon dioxide to give an oil, which was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether gave the oily free base (1.5 g), which was reduced under the same conditions as in **7a**. After removal of the catalyst, the methanol was evaporated and the residual crystals were washed with ether, yield 0.5 g, 45%. An analytical sample was obtained by recrystallizing twice from 80% aqueous methanol as clusters of colorless needles, mp 141–142° dec. The infrared spectrum (KBr) had a broad band at 2700–2200 and sharp bands at 3160, 2950, 1725, and 1610 cm^{-1}.

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.

3,6-Diisobutyl-2-hydroxypyrazine 1-Oxide (Neoaspergillic Acid, 1e).—A suspension of **7e** (1.1 g, 4.5 mmoles) in methanol (30 ml) was saturated with gaseous ammonia. After 3 days the resultant solution was concentrated under reduced pressure and the residue was dissolved in a mixture of methanol (20 ml) and 1 *N* aqueous sodium hydroxide (10 ml). The solution was treated with activated charcoal and then again concentrated under reduced pressure. A solution of the residue in water (20 ml) was saturated with carbon doxide. After removal of an oily material (all attempts to crystallize it were unsuccessful), the solution was acidified to pH 1.5 with 3 *N* hydrochloric acid, whereupon crystals separated gradually. The mixture was left to stand in a refrigerator for 3 hr and the crystals were collected. Recrystallization from 80% aqueous methanol yielded neoaspergillic acid (0.1 g, yield 9.9%) as yellow needles, mp 127.5–128.5°.

Anal. 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.

3-Isobutyl-6-phenyl-2-hydroxypyrazine (2g).—A solution of **4** (2.4 g, 10 mmoles) in methanol (30 ml) was saturated with gaseous ammonia, and phenacyl bromide (1.9 g, 9.5 mmoles) was added to the solution, which was then left to stand in a refrigerator for 4 days. The crystalline solid (0.6 g) was removed by filtration. [Recrystallization from methanol gave 3,6-diphenylpyrazine, mp 196° (lit. mp 196°,[17a] 195–196°[17b]).] The filtrate was concentrated under reduced pressure and the residue was extracted with 1 *N* aqueous sodium hydroxide. After treatment with activated charcoal, the extract was saturated with carbon dioxide to separate hydroxypyrazine **2g** (0.6 g, 2.6 mmoles). Recrystallization from ethyl acetate gave yellow, long needles, mp 167°.

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 15.27. Found: C, 73.42; H, 7.63; N, 15.21.

(15) M. Masaki and M. Ohta, *Bull. Chem. Soc. Japan*, **36**, 922 (1963).
(16) M. Masaki and M. Ohta, *ibid.*, **36**, 1177 (1963).
(17) (a) L. Wolff, *Ber.*, **20**, 432 (1887); (b) E. Braun and V. Meyer, *ibid.*, **21**, 1278 (1888).

The Decarboxylation of α-Nitrophenylcinnamic Acids

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The decarboxylation of α-nitrophenylcinnamic acids in the presence of piperidine was found to proceed *via* the Michael addition of the piperidine to the double bond of the cinnamic acid derivative and the loss of carbon dioxide from the Michael adduct, with and without the regeneration of piperidine, to afford *trans*-4-nitrostilbenes and tertiary amines, respectively.

The decarboxylation of α-4-nitrophenyl-*trans*-cinnamic acid in the presence of piperidine at 150–160° was first reported in 1911.[1] Earlier studies had shown that decarboxylation did not occur in the absence of piperidine, decomposition of the cinnamic acid derivative taking place at 260°.[2] In view of these results Pfeiffer and Sergiewskaja attempted the condensation of benzaldehyde with 4-nitrophenylacetic acid in the presence of piperidine at 150–160° and found *trans*-4-nitrostilbene to be afforded in good yield.[1] Although this decarboxylation procedure has been successfully used in the synthesis of substituted stilbenes,[3] no mechanistic studies were reported until 1963.

(1) P. Pfeiffer and S. Sergiewskaja, *Ber.*, **44**, 1107 (1911).
(2) R. Walther and A. Wetzlich, *J. Prakt. Chem.*, [2] **61**, 181 (1900).
(3) (a) H. Kaufmann, *Ber.*, **54**, 795 (1921); (b) N. Cullinane, *J. Chem. Soc.*, 2060 (1923); (c) H. Harrison and H. Wood, *ibid.*, 580 (1926); (d) R. Ketcham and D. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963).