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SYNTHESIS OF CYCLIC HYDROXAMIC ACID DERIVATIVES OF PYRAZINE

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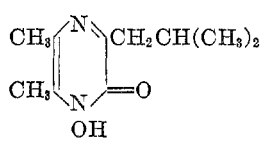
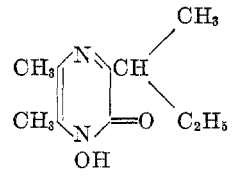
Since 1944, when Dutcher and Wintersteiner (1) concluded that aspergillic acid is a pyrazine cyclic hydroxamic acid, interest has been stimulated in the virtually unexplored field of cyclic hydroxamic acids. Thus, cyclic hydroxamic acids have been prepared in the pyridine (2–5), quinoline (4, 5), pyrimidine (3), and imidazole (6) series. Attempts to prepare pyrazine cyclic hydroxamic acids by oxidation of 2-chloro- and 2-ethoxy-pyrazine derivatives failed, the 4-oxides rather than the 1-oxides always being obtained (7).

By condensing α-aminohydroxamic acids with 1,2-dicarbonyl compounds under alkaline conditions, Spring, *et al.* (8, 9) obtained pyrazine cyclic hydroxamic acid derivatives. This condensation has been under investigation in these laboratories under conditions differing from those of the English group, and the findings are herewith reported.

Diacetyl condenses readily at room temperature in aqueous suspension with L-leucinehydroxamic acid, DL-isoleucinehydroxamic acid, and aminomalonohydroxamic acid to yield the pyrazine cyclic hydroxamic acids I, II, and III, respectively. Glyoxal, in aqueous solution, also reacts spontaneously with aminomalonohydroxamic acid to give IV.



I



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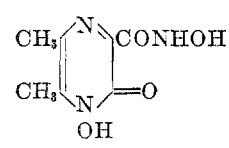

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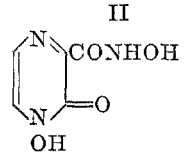
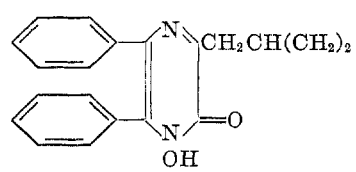


IV

Even a less reactive diketone such as benzil gives, on refluxing with L-leucinehydroxamic acid in aqueous alcohol without an alkaline catalyst, the corresponding cyclic hydroxamic acid V.



V

It was also found that the starting α-aminohydroxamic acids can be more conveniently prepared in an aqueous medium.

Table I contains the results of the antibacterial tests of two of the new cyclic hydroxamic acids and of aspergillic acid. These data were determined by Dr. John N. Porter of these laboratories by the streak plate method.

Acknowledgment. The authors express their appreciation to Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

Glycinehydroxamic acid. This compound, previously repared by Jones and Sneed (10) in anhydrous ethanol at −10°, was conveniently prepared as follows: to an ice-cold stirred solution of 14 g. (0.1 mole) of glycine ethyl ester hydrochloride and 7 g. (0.1 mole) of hydroxylamine hydrochloride in 17 cc. of water, was added, during one-half hour, 26.4 cc.

TABLE I

MINIMUM CONCENTRATION IN MICROGRAMS PER CC. REQUIRED FOR INHIBITION

TEST ORGANISM	ASPERGILLIC ACID	1-HYDROXY-2-KETO-3-ISOBUTYL-5,6-DIMETHYL-1,2-DIHYDROPYRAZINE	1-HYDROXY-2-KETO-3-*sec*-BUTYL-5,6-DIMETHYL-1,2-DIHYDROPYRAZINE
E. typhosa	30	63	30
S. pullorum	15	30	15–30
B. subtilis	10	63	30
B. cereus	<8	63	15
E. coli	63	63	30
Ps. aeruginosa	500	>1000	1000
P. vulgaris	15	63	30
K. pneumoniae	15	30	30
T.B. #607	<8	30	30
S. gallinarum	15–30	63	30
P.C.I.-3	15	63	30
S. lutea	8	15	15
S. marcescens	250	500	125
S. aureus	30	125	60
M. phlei	<8	63	15

(0.33 mole) of 12.5 *N* sodium hydroxide. The resulting solution was acidified with 8.5 cc. of 12 *N* hydrochloric acid. On cooling in ice, the product crystallized as a white solid; it was filtered and washed with a little cold water; yield 3.5 g. (39%); m.p. 142–143° (dec.). Jones and Sneed (10) report m.p. 140° (dec.).

Aminomalonohydroxamic acid. This dihydroxamic acid was prepared in a similar manner to glycinehydroxamic acid. From 50.9 g. (0.29 mole) of aminomalonic ester (11), 45.2 g. (0.65 mole) of hydroxylamine hydrochloride, 57 cc. of water, and 99 cc. (1.2 moles) of 12.5 *N* sodium hydroxide, was isolated 31.8 g. (43%) of a white product. Aminomalonohydroxamic acid is somewhat unstable to hot water. For analysis a sample was recrystallized rapidly from water; m.p. 142–143° (sudden dec.).

Anal. Calc'd for $C_3H_7N_3O_4$: C, 24.2; H, 4.7; N, 28.2.

Found: C, 25.2; H, 4.9; N, 27.4.

All of the α-aminohydroxamic acids give dark red colors with ferric chloride solution and green salts on treatment with cupric acetate. Aminomalonohydroxamic acid is soluble in dilute sodium carbonate solution and in dilute hydrochloric acid.

L-*Leucinehydroxamic acid* was obtained in a 55% yield by the same procedure in the form of sparkling cyrstals, m.p. 195–200° (dec.) after recrystallization from water.

Anal. Calc'd for $C_6H_{14}N_2O_2$: C, 49.3; H, 9.6; N, 19.2.

Found: C, 49.4; H, 10.0; N, 19.5.

DL-*Isoleucinehydroxamic acid*, prepared by the general procedure, melted at 180–182° (dec.) after recrystallization from water; yield 73%.

Anal. Calc'd for $C_6H_{14}N_2O_2$: C, 49.3; H, 9.6; N, 19.2.

Found: C, 49.3; H, 10.0; N, 19.3.

Cunningham, *et al.* (5) report m.p. 171–172° (dec.).

1-Hydroxy-2-keto-3-isobutyl-5,6-dimethyl-1,2-dihydropyrazine (I). A mixture of 5 g. (0.034 mole) of L-leucinehydroxamic acid, 4.7 g. (0.055 mole) of diacetyl, and 30 cc. of water was shaken for a few minutes whereupon a clear solution resulted, accompanied by a slight evolution of heat. After having been stored for two days at room temperature, a light yellow solid crystallized and was filtered; yield 2.5 g. (44%); m.p. 94–97°.

After one recrystallization from ethanol, yellow crystals were obtained; m.p. 95–96°.

Anal. Calc'd for $C_{10}H_{16}N_2O_2$: C, 61.3; H, 8.2; N, 14.3.

Found: C, 61.0; H, 8.3; N, 14.2.

The product is soluble in hot water and fairly insoluble in cold water. It is soluble in dilute sodium carbonate solution and in 3 *N* hydrochloric acid.

The product may be obtained in a second, colorless modification melting at 69–71° by vacuum sublimation of the higher-melting form.

Anal. Found: C, 61.6; H, 8.4; N, 14.2.

The lower-melting form can be converted into the higher-melting form by seeding a melt of the former at about 75° with a crystal of the latter. Also, on prolonged standing, the colorless form becomes yellow and the m.p. rises to 96°. Whether or not the compounds differ only in crystalline form or are tautomeric has not been established.

All of the pyrazine cyclic hydroxamic acids described below give dark red colors with ferric chloride.

1-Hydroxy-2-keto-3-sec-butyl-5,6-dimethyl-1,2-dihydropyrazine (II). A mixture of 3 g. (0.021 mole) of DL-isoleucinehydroxamic acid, 2.6 g. (0.03 mole) of diacetyl, and 10 cc. of water was shaken for 15 minutes. Some undissolved solid remained which was removed after about one hour. Upon standing overnight, light tan crystals separated and were filtered and washed with ice-water; yield 1.2 g. (29%); m.p. 78–81°. The crude product was purified by vacuum sublimation at 110°/0.5 mm. A white sublimate, m.p. 83–85°, with previous softening, was obtained.

Anal. Calc'd for $C_{10}H_{16}N_2O_2$: C, 61.3; H, 8.2; N, 14.3.

Found: C, 61.0; H, 8.7; N, 14.3.

The cyclic hydroxamic acid is difficultly soluble in cold water; soluble in hot water, methanol, and ethanol. It is also soluble in dilute mineral acid, carbonate solution, and stronger alkalies.

1-Hydroxy-2-keto-5,6-dimethyl-1,2-dihydropyrazinohydroxamic acid (III). A mixture of 5.7 g. (0.038 mole) of aminomalonodihydroxamic acid, 5.1 g. (0.059 mole) of diacetyl, and 57 cc. of water was shaken vigorously, whereupon the temperature rose to about 40° and an almost clear solution was obtained. A light yellow solid then separated rapidly and was filtered and washed with water; yield 6.4 g. (84%); m.p. 220–222° (sudden dec.). The m.p. was unchanged after one recrystallization from water.

Anal. Calc'd for $C_7H_9N_3O_4$: C, 42.3; H, 4.5; N, 21.1.

Found: C, 42.3; H, 4.8; N, 21.1.

The product is soluble in dilute sodium carbonate solution.

1-Hydroxy-2-keto-1,2-dihydropyrazino-3-hydroxamic acid (IV). A mixture of 6 g. (0.040 mole) of aminomalonohydroxamic acid and 8.5 g. (0.044 mole) of 30% aqueous glyoxal was shaken vigorously for five minutes. The resulting clear brown, acidic solution was brought to *p*H 5 with 10% sodium bicarbonate solution and the resulting sodium salt of the product was filtered, suspended in water, and heated to the b.p.; 7 cc. of 6 *N* hydrochloric

acid was added. The clear solution was treated with Norit, filtered, and cooled. The product crystallized in the form of sparkling yellow-orange crystals; m.p. 185–186° (dec.); yield 2.7 g. (38%).

Anal. Calc'd for $C_5H_5N_3O_4$: C, 35.1; H, 2.9; N, 24.6.
Found: C, 35.2; H, 3.3; N, 24.8.

In subsequent runs the free hydroxamic acid was found to crystallize directly from the reaction mixture.

1-Hydroxy-2-keto-3-isobutyl-5,6-diphenyl-1,2-dihydropyrazine (V). A mixture of 4.2 g. (0.020 mole) of benzil, 3.45 g. (0.024 mole) of L-leucinehydroxamic acid, and 100 cc. of 50% ethanol was refluxed 17 hours. The product, a light brown solid, was filtered and washed with 1 *N* hydrochloric acid; yield 4.3 g. (67%); m.p. 203–210° (dec.).

After one recrystallization from benzene white needles were obtained; m.p. 217–220° (dec.).

Anal. Calc'd for $C_{20}H_{20}N_2O_2$: C, 75.1; H, 6.3; N, 8.8.
Found: C, 75.2; H, 6.7; N, 8.9.

The product forms a sparingly soluble sodium salt.

SUMMARY

The preparation of a number of new pyrazine cyclic hydroxamic acids is described.

PEARL RIVER, NEW YORK

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