described in Table II. The n.m.r. spectrum is shown in Fig. 4. The 2,4-DNP derivative was prepared as described previously, m.p. 221–222° (lit.[11] m.p. 221–222° for the 2,4-DNP of benzalacetone).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92; CH_3O, 15.20. Found: C, 70.20; H, 5.70; CH_3O, 14.93.

In an attempt to prevent ring opening, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate was added to a suspension of 0.12 mole of lithium amide in 300 ml. of anhydrous liquid ammonia. The mixture was stirred for 0.5 min., followed by the addition of 10.6 g. (0.1 mole) of freshly distilled benzaldehyde. Stirring was continued for 5 min., 6.5 g. (0.12 mole) of solid ammonium chloride was added, and the work-up was the same as for the preparation of (IVb). After one recrystallization from alcohol water, 6 g. (30%) of the dienoic acid (IVa) was obtained, m.p. 157.5–158° dec. This crystalline material gave an infrared spectrum identical with that of the dienoic acid (IVa).

3-Methoxy-7-phenyl-*cis*-2-*trans*-4,6-heptatrienoic Acid (IVc, Kavaic Acid).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous ammonia, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate, and 13.2 g. (0.1 mole) of freshly distilled *trans*-cinnamaldehyde. After two recrystallization from 95% alcohol, 12 g. (52%) of kavaic acid (IVc) was obtained, m.p. 178–178.5° dec. (lit.[13] m.p. 184° dec.).

The yellow crystalline material was soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test. The 2,4-DNP derivative was prepared as described previously, m.p. 217–217.5 (lit.[14] m.p. 218–220°, cinnamal-acetone). The infrared spectrum (Nujol mull) exhibited absorption at 5.95 (conjugated acid) and 14.6 μ (monosubstituted benzene). The ultraviolet absorption is described in Table II.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13; CH_3O, 13.48. Found: C, 72.84; H, 5.91; CH_3O, 14.52.

An authentic sample of kavaic acid was prepared by adding 0.23 g. (0.001 mole) of kavain[15] to a suspension of 0.002 mole of lithium amide in 50 ml. of anhydrous liquid ammonia. The kavaic acid was isolated as described above and recrystallized twice from absolute methanol, m.p. 184° dec. (lit.[13] m.p. 184° dec.). The admixture melting point of authentic kavaic acid 184° dec.) and kavaic acid (IVc, m.p. 178–178.5° dec.) was 179° dec. This authentic sample of kavaic acid exhibited absorption in the ultraviolet at the following wave lengths: λ_{max}^{EtOH} 244 (ε 8320), 251 (9570), and 332 mμ (41,900) [lit.[13] λ_{max}^{EtOH} 251 (ε 9500) and 332 mμ (40,000)].

5,5-Diphenyl-3-ethoxy-4-*cis*-2-pentadienoic Acid (IVd).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia, 15.8 g. (0.1 mole) of ethyl β-ethoxy-*cis*-crotonate, and 18.2 g. (0.1 mole) of benzophenone. After two recrystallizations from alcohol–water, 12 g. (41%) of the dienoic acid IVd was obtained, m.p. 149.5° dec. The long, white crystalline rods were soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.27; H, 6.17.

3-Methoxy-7-*cis*-2-*trans*-4-heptadienoic Acid (IVe, Dihydrokavaic Acid).—The procedure for the preparation of 3-ethoxy-5-phenyl-*cis*-2-*trans*-4-pentadienoic acid (IVb) was followed using 0.2 mole of lithium amide in 300 ml. of anhydrous liquid ammonia, 14.4 g. (0.1 mole) of crude ethyl β-methoxy-*cis*-crotonate, and 13.4 g. (0.1 mole) of hydrocinnamaldehyde. After two recrystallizations from alcohol–water, 1.4 g. (6%) of the trienoic acid IVe was obtained, m.p. 137.5–138° dec. (lit.[14] m.p. 139–140° dec.). This crystalline material was soluble in dilute sodium carbonate solution and gave a negative ferric chloride (enol) test. The infrared spectrum (chloroform) exhibited absorption at 5.98 (C=O) and 6.1 μ (C=C).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.40; H, 6.94. Found: C, 72.46; H, 7.09.

Acknowledgment.—The authors gratefully acknowledge the support of this project by the National Institutes of Health Grant NB 02733.

(13) See Table II, footnote *c*.

(14) W. Brosche and W. Peitzsch, *Ber.*, **62**, 368 (1929).

(15) The authors are grateful to Smith, Kline and French Laboratories for generously providing a sample of kavain.

Synthesis of a Homolog of Aspergillic Acid

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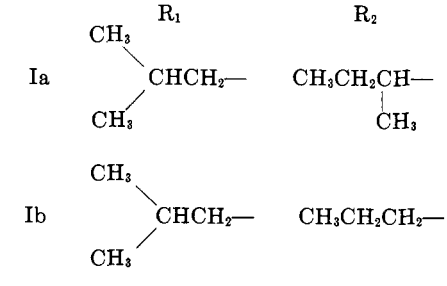
The 6-propyl homolog of aspergillic acid was synthesized. N-Leucyl-O-benzylhydroxylamine, prepared by reaction of phthalylleucyl chloride with O-benzylhydroxylamine, followed by treatment with hydrazine hydrate, was treated with 1-chloro-2-pentanone oxime; the product was hydrolyzed to give N-[4-methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine, which was catalytically hydrogenated to give the corresponding hydroxamic acid. The open-chain hydroxamic acid was cyclized by means of treatment with ammonia to yield 1-hydroxy-3-isobutyl-6-propyl-2-pyrazinone.

Aspergillic acid, an antibiotic isolated by White and Hill[1] from the culture filtrates of *Aspergillus flavus*, has been concluded by Dutcher[2] and Newbold, *et al.*,[3] to be 1-hydroxy-3-isobutyl-6-*sec*-butyl-2-pyrazinone or its tautomeric 1-oxide of the 2-hydroxypyrazine (Ia). Hydroxyaspergillic acid isolated by Menzel[4] and mutaaspergillic acid isolated recently by Nakamura[5] have



been shown to be also 3,6-disubstituted 1-hydroxy-2-pyrazinones.

(1) E. C. White and T. H. Hill, *J. Bacteriol.*, **45**, 433 (1943).

(2) J. D. Dutcher, *J. Biol. Chem.*, **171**, 321, 341 (1947).

(3) G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 2679 (1951).

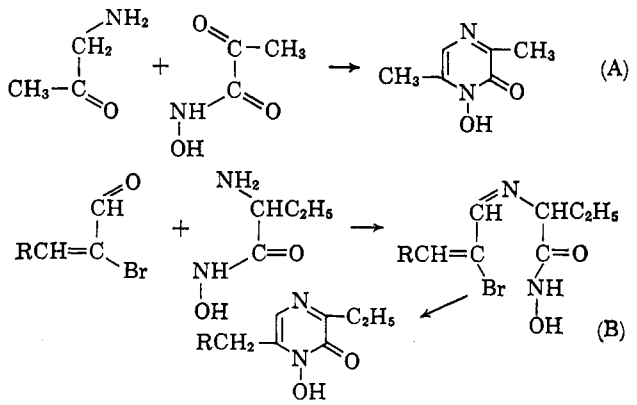
(4) A. E. O. Menzel, O. Wintersteiner, and G. Rake, *J. Bacteriol.*, **46**, 109 (1943); *cf.* J. D. Dutcher, *J. Biol. Chem.*, **232**, 785 (1958).

(5) S. Nakamura, *Bull. Agr. Chem. Soc. Japan*, **24**, 629 (1960); *cf.* S. Nakamura, *Agr. Biol. Chem.*, **25**, 74, 658 (1961).

Results and Discussion

Two syntheses of 3,6-disubstituted cyclic pyrazine-hydroxamic acids have been described. Reaction of aminoacetone with the bisulphite derivative of pyruvohydroxamic acid gave 1-hydroxy-3,6-dimethyl-2-pyr-

azinone[6] (A). The second synthesis (B) consists of the reaction of 2-aminobutyrohydroxamic acid with 2-bromocinnamaldehyde or 2-bromocrotonaldehyde to yield 2-(2-bromocinnamylideneamino)- or 2-(2-bromocrotonylideneamino)butyrohydroxamic acid which, when treated with potassium *t*-butoxide, gave 3-ethyl-6-benzyl-[7] or 3,6-diethylpyrazine[6] cyclic hydroxamic acid. These methods, however, have limitations,[6] and the synthesis of a pyrazine cyclic hydroxamic acid by the direct oxidation of a pyrazine derivative is impracticable, because in the peroxidation of hydroxypyrazines the oxygen atom enters at the nitrogen atom remote from the hydroxyl group.[8]



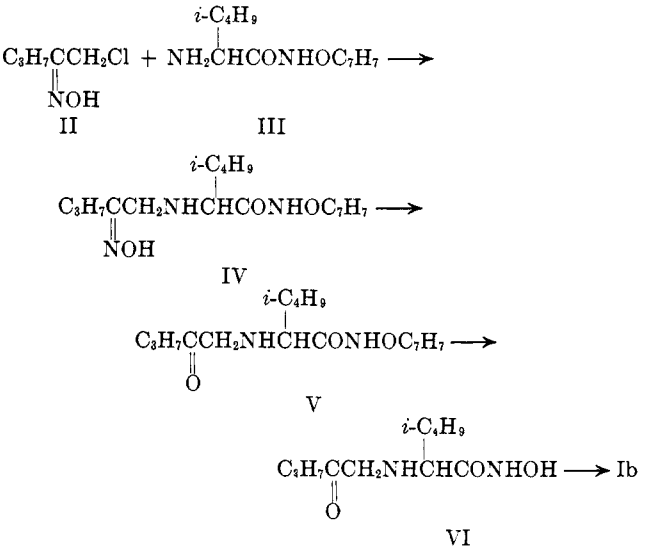
(A)

(B)

A new synthesis of a 3,6-disubstituted pyrazinehydroxamic acid was therefore sought. The present paper describes the synthesis of a homolog of aspergillic acid, 1-hydroxy-3-isobutyl-6-propyl-2-pyrazinone (Ib) by a new method, which involves the reaction of 1-chloro-2-pentanone oxime (II) with N-leucyl-O-benzylhydroxylamine (III), followed by hydrolysis of the product (IV) to yield N-[4-methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine (V), which after catalytic debenzylation was treated with ammonia in methanol.

N-Leucyl-O-benzylhydroxylamine (III) was prepared by the reaction of O-benzylhydroxylamine with phthalylleucyl chloride followed by treatment of the product with hydrazine. In an attempt to obtain III by benzylation of leucinehydroxamic acid (VII), the sodium salt of VII was treated in ethanol with benzyl chloride, but this reaction gave an unidentified crystalline compound, $C_{18}H_{28}N_2O_2$, m.p. 93°, instead of III. As alkylation or acylation of aminohydroxamic acid has been hitherto scarcely known, benzoylation of VII was also studied, in order to compare it with the benzylation described above. In this case, however, only the dibenzoyl derivative was obtained, even when less than 1 equiv. of benzoyl chloride was added dropwise (at −5°) to an aqueous solution of the potassium salt of VII.

It has been shown in our laboratory[9] that the reaction of α-halo oximes with the esters of amino acids yields N-(2-hydroxyiminoalkyl)amino acids, which are easily hydrolyzed to give N-(2-oxoalkyl)amino acids. In an analogous manner, when III was treated with II in methanol at room temperature, the α-aminoketoxime (IV) was obtained as an oily product. The crude product was hydrolyzed in the presence of benzaldehyde in hydrochloric acid–methanol to give the corresponding α-amino ketone (V), which was characterized as the hydrochloride. The same treatment of III with phenacyl bromide oxime yielded N-(4-methyl-2-phenacylaminovaleryl)-O-benzylhydroxylamine.



Catalytic hydrogenation of cyclic O-benzylhydroxamic acid derivatives in the pyridine series[10] has been known to yield the corresponding hydroxamic acids. When this method is applied to the open-chain N-acyl-O-benzylhydroxylamine, debenzylation might give the amide and benzyl alcohol or the desired hydroxamic acid and toluene or a mixture of all these products. Catalytic reduction of III at room temperature yielded exclusively leucinehydroxamic acid. In a similar manner, V was reductively debenzylated to give a 70% yield of the corresponding hydroxamic acid (VI), which gave a red color with a methanolic solution of ferric chloride and was characterized by elementary analysis.

Shaw and McDowell[11] have observed, by boiling for 10 min. in dilute hydrochloric acid, the ring closure of α-benzamidocinnamohydroxamic acid to the cyclic hydroxamic acid. Cyclization of VI was attempted by refluxing in dilute hydrochloric acid, by refluxing in benzene in the presence or absence of BF_3, and by treating with aqueous alkali, but the desired product was not obtained under these conditions.

A new method for cyclization was then examined in which the ketonic group was converted to the less stable imino group, which might cyclize more easily than the former.[12] Treatment of VI with ammonia in methanol at room temperature gave the required 1-hydroxy-3-isobutyl-6-propyl-2-pyrazinone (Ib). The last stage in this reaction involves the air oxidation, which is common to most pyrazine syntheses.[9b,13]

The cyclic hydroxamic acid (Ib) is soluble in sodium bicarbonate solution, gives a positive ferric chloride

(6) D. W. C. Ramsay and F. S. Spring, *J. Chem. Soc.*, 3409 (1950).

(7) G. Dunn, J. A. Elvidge, G. T. Newbold, D. W. C. Ramsay, F. S. Spring, and W. Sweeny, *ibid.*, 2707 (1949).

(8) R. A. Baxter, G. T. Newbold, and F. S. Spring, *ibid.*, 1859 (1948).

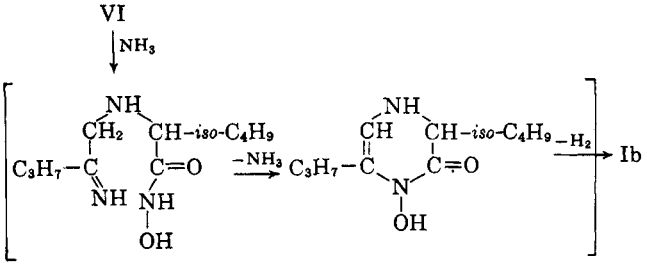
(9) (a) M. Masaki and M. Ohta, *Bull. Chem. Soc. Japan*, **36**, 922 (1963); (b) M. Masaki and M. Ohta, *ibid.*, **36**, 1177 (1963).

(10) E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949); D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631 (1955).

(11) E. Shaw and J. McDowell, *J. Am. Chem. Soc.*, **71**, 1691 (1949).

(12) After this work was performed, we became aware that G. Charles [*Bull. soc. chim. France*, 1539 (1963)] has found a new alkylidenation reaction of the active methylene compound with the imino component which was used in place of the less reactive carbonyl component in the Knoevenagel reaction.

(13) Y. A. Tota and R. C. Elderfield, *J. Org. Chem.*, **7**, 313 (1942); R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 370 (1947).



reaction like aspergillic acid, and was characterized by elementary analysis as well as its ultraviolet spectrum, which is very similar to that[14] of aspergillic acid.

Experimental

Starting Materials.—O-Benzylhydroxylamine was obtained by neutralizing the hydrochloride,[15] suspended in ether, with an aqueous solution of potassium carbonate, b.p. 117–119° (30 mm). Phthalyl-L-leucyl chloride was prepared by the method of King, *et al.*,[16] and the crude product was used without purification.

L-Leucinehydroxamic acid (VII) was prepared by the use of the procedure of Cunningham, *et al.*[17] A solution of hydroxylamine [from the hydrochloride (13.9 g.) and sodium (4.6 g.) in methanol (300 ml.)] was added to a solution of L-leucine ethyl ester [from the hydrochloride (19.4 g.) in methanol (50 ml.) and sodium (2.3 g.) in methanol (50 ml.)] at 0°. The mixture was kept at 0° for 4 days. The solid (16 g.) was collected and recrystallized from DMF to give a colorless cluster of very small needles, m.p. 203–204° (begins to sublime about 190°).

Anal. Calcd. for $C_6H_{14}N_2O_2$: C, 49.30; H, 9.65; N, 19.17. Found: C, 49.37; H, 9.77; N, 19.39.

Reaction of VII with Benzyl Chloride.—Sodium (2.13 g.) was dissolved in ethanol (80 ml.), and L-leucinehydroxamic acid (13.5 g.) was added to the sodium ethoxide solution. The mixture was heated at 70° with stirring, and benzyl chloride (11.2 g.) was added dropwise to the resultant solution. After 3 hr. the mixture was cooled to room temperature and poured into water (400 ml.). The oily product slowly solidified and was recrystallized from petroleum ether (b.p. 30–60°) to give colorless needles (5.2 g.), m.p. 93°.

Anal. Calcd. for $C_{18}H_{28}N_2O_2$: C, 71.01; H, 9.27; N, 9.20. Found: C, 71.00; H, 9.49; N, 9.27.

Reaction of VII with Benzoyl Chloride.—L-Leucinehydroxamic acid (5.2 g.) was dissolved in a solution of potassium hydroxide (2 g.) in water (20 ml.), and benzoyl chloride (5 g.) was added dropwise, with stirring, to the solution at −5°. From the mixture a solid soon began to separate. After the addition was complete, stirring was continued for 30 min. The solid was collected, dissolved in ether (20 ml.), treated with activated charcoal, and then reprecipitated by the addition of ligroin (80 ml.). The product (3.9 g.) was washed with hot ligroin and recrystallized from aqueous ethanol (1:1.25) to give the dibenzoyl derivative of VII as colorless needles, m.p. 143°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 68.08; H, 6.08; N, 8.19.

N-(4-Methyl-2-phthalimidovaleryl)-O-benzylhydroxylamine (VIII).—A solution of phthalyl-L-leucyl chloride (prepared from 85 g. of phthalyl-L-leucine) in absolute ether (300 ml.) was added dropwise with vigorous stirring at −10° to a solution of O-benzylhydroxylamine (40 g.) and pyridine (26.5 g.) in absolute ether (300 ml.). To maintain this temperature, the addition took about 3 hr., and stirring was continued until the temperature of the solution reached room temperature. The mixture was then poured into water, and the organic layer was washed successively with water, aqueous sodium bicarbonate, twice with water, 1 *N* hydrochloric acid, and finally once with water, and dried over anhydrous sodium sulfate. Evaporation of the ether yielded the product (105 g.) as a sirup, a portion of which was dissolved in benzene, reprecipitated by the addition of ligroin, and allowed to stand in a refrigerator. After about a month, the product crystallized and was recrystallized from benzene–ligroin to give colorless prisms, m.p. 97°.

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.79; H, 6.31; N, 7.91.

N-Leucyl-O-benzylhydroxylamine (III).—A solution of crude VIII (33 g.) and 80% hydrazine hydrate (6 g.) in methanol (150 ml.) was heated at 40–50°. Phthaloyl hydrazine began to separate in approximately 1 hr. After 5 hr. the mixture was cooled to room temperature and 6 *N* hydrochloric acid (20 ml.) was added. The phthaloyl hydrazine was filtered off and the filtrate was concentrated to 40–50 ml. under reduced pressure. The residue was dissolved in water (300 ml.) and treated with activated charcoal. When neutralized with an aqueous solution of sodium carbonate, the solution gave a colorless solid. It was collected, dried, and washed with ethyl acetate, m.p. 97–99°, yield 18 g. A portion of the product was recrystallized from water and analyzed, m.p. 102–103°.

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.51; H, 9.05; N, 12.03.

N-(4-Methyl-2-phenylureidovaleryl)-O-benzylhydroxylamine.—III was treated with phenyl isocyanate yielding the phenylureido derivative. It was recrystallized from 1-butanol to give colorless prisms, m.p. 192°.

Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.40; H, 7.18; N, 12.07.

N-[4-Methyl-2-(2-oxopentylamino)valeryl]-O-benzylhydroxylamine (V) Hydrochloride.—To a solution of crude III (22 g., 0.93 mole) in methanol (220 ml.) was added 1-chloro-2-pentanone oxime (6.3 g., 0.465 mole),[9a] and the clear solution was allowed to stand at room temperature. After 6 days the methanol was evaporated under reduced pressure, the residue was dissolved in ether (250 ml.), and the ether solution shaken twice with water (120, 80 ml.). The combined aqueous extracts were treated with activated charcoal and neutralized with an aqueous solution of sodium carbonate; thereby the half mole of III was recovered. The above ether solution was evaporated to give N-[2-(2-hydroxyiminopentylamino)-4-methylvaleryl]-O-benzylhydroxylamine (IV) as an oil, which was used directly in the next step.

To a solution of the product (IV) in methanol (60 ml.) were added benzaldehyde (6 g.) and 3 *N* hydrochloric acid (40 ml.). The mixture was kept for 90 hr. at room temperature, after which it was concentrated under reduced pressure. Ether (100 ml.) was added to the residue; thereby small needles (6.3 g.) crystallized out, which were washed with ethyl acetate. This material was satisfactory for the next step. An analytical sample was obtained by recrystallization from methanol–ethyl acetate as colorless very small needles, m.p. 141–142°.

Anal. Calcd. for $C_{18}H_{28}N_2O_3 \cdot HCl$: C, 60.50; H, 8.12; N, 7.84. Found: C, 60.96; H, 8.51; N, 8.12.

N-(4-Methyl-2-phenacylaminovaleryl)-O-benzylhydroxylamine Hydrochloride.—Phenacyl bromide oxime (1.36 g.) was added to a solution of III (3 g.) in absolute tetrahydrofuran (100 ml.) and the resultant solution was allowed to stand at room temperature for 4 days, after which it was evaporated and the residue was dissolved in ether. The solution was shaken with water. By neutralizing the aqueous extract with a solution of sodium carbonate, 1 g. of III was recovered. The ethereal layer was evaporated to afford N-[2-(2-hydroxyimino-2-phenylethylamino)-4-methylvaleryl]-O-benzylhydroxylamine, which was dissolved in methanol (10 ml.). To the solution were added 3 *N* hydrochloric acid (10 ml.) and benzaldehyde (0.8 g.), and the mixture was left at room temperature (23–28°). After 3 days the solution was boiled under reflux for 20 min. and concentrated under reduced pressure. Ether was added to the residue; thereby small needles slowly crystallized out. They were collected and washed with ethyl acetate to yield 0.5 g. Recrystallization from ethanol–ether afforded colorless very small needles, m.p. 151–153°.

Anal. Calcd. for $C_{21}H_{26}N_3O_3 \cdot HCl$: C, 64.45; H, 6.91; N, 7.16. Found: C, 64.09; H, 7.03; N, 7.45.

Catalytic Hydrogenation of III.—A solution of III (1 g.) in ethanol (50 ml.) was shaken with 5% palladium on charcoal (0.5 g.) at an initial pressure of 40 kg./cm.^{2} of hydrogen. The product crystallized out and was separated from the catalyst by solution in 1 *N* hydrochloric acid and reprecipitated with a

(14) G. Dunn, J. J. Gallagher, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, S126 (1949).

(15) R. Behrend and K. Leuchs, *Ann.*, 257, 205 (1890).

(16) F. E. King, J. W. Clark-Lewis, R. Wade, and W. A. Swindin, *J. Chem. Soc.*, 877 (1957).

(17) K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *ibid.*, 2091 (1949).

solution of sodium bicarbonate, yielding 0.44 g. Recrystallization from DMF gave the product of m.p. 201–203°, which was identified as L-leucinehydroxamic acid by mixture melting point with the specimen described above.

4-Methyl-2-(2-oxopentylamino)valerohydroxamic Acid (VI).—The hydrochloride of V (5.8 g.) was dissolved in 1 *N* sodium hydroxide (40 ml.) and treated with activated charcoal. The solution was neutralized with carbon dioxide to afford an oil, which was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 4.8 g. of the oily free base (V), and it was reduced with hydrogen–5% palladium on charcoal (0.5 g.) at 40-kg./cm.^{2} initial pressure in ethanol (60 ml.). A portion of the product crystallized out and was collected together with the catalyst by filtration. The product was separated from the catalyst by solution in 1 *N* sodium hydroxide (20 ml.) followed by immediate reprecipitation with 1 *N* hydrochloric acid, yielding 1.4 g. The ethanolic filtrate obtained above was concentrated under reduced pressure to dryness. The crystalline residue was thinned with ether for filtration, yielding 1 g. of product. Total yield was 2.4 g. (70%). This product was practically pure for use in the next step. An analytical sample was obtained by recrystallization from methanol, m.p. 170–175°.

Anal. Calcd. for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.13. Found: C, 57.13; H, 9.88; N, 12.38.

1-Hydroxy-3-isobutyl-6-propyl-2-pyrazinone (Ib).—A suspension of VI (0.8 g.) in methanol (30 ml.) was saturated with ammonia under cooling. The resultant clear solution was allowed to stand at room temperature for 2 days, and concentrated to dryness under reduced pressure. The residue was dissolved in a mixture of methanol (10 ml.) and 1 *N* sodium hydroxide (8 ml.), and again concentrated to dryness under reduced pressure. The dark brown oily residue was dissolved in water (20 ml.) and treated with activated charcoal. The solution was saturated with carbon dioxide to separate an oily or crystalline by-product, which was removed by treatment with activated charcoal. The clear solution was acidified to pH 2 with 3 *N* hydrochloric acid and kept at 0° overnight. The crystalline solid was collected and recrystallized from a small amount of acetone to yield a cluster of very small yellowish needles (0.1 g.), m.p. 129–131°. The product is soluble in sodium bicarbonate solution and gives a deep red color with a methanolic ferric chloride solution; it showed ultraviolet absorption at λ_{max}^{EtOH} 235 mμ (ε 6100) and 326 (7800).

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.65; N, 13.32. Found: C, 62.66; H, 8.91; N, 13.53.

Synthesis of *ortho* and *meta* Analogs of Thyropropionic Acid and of Their Iodinated Derivatives[1]

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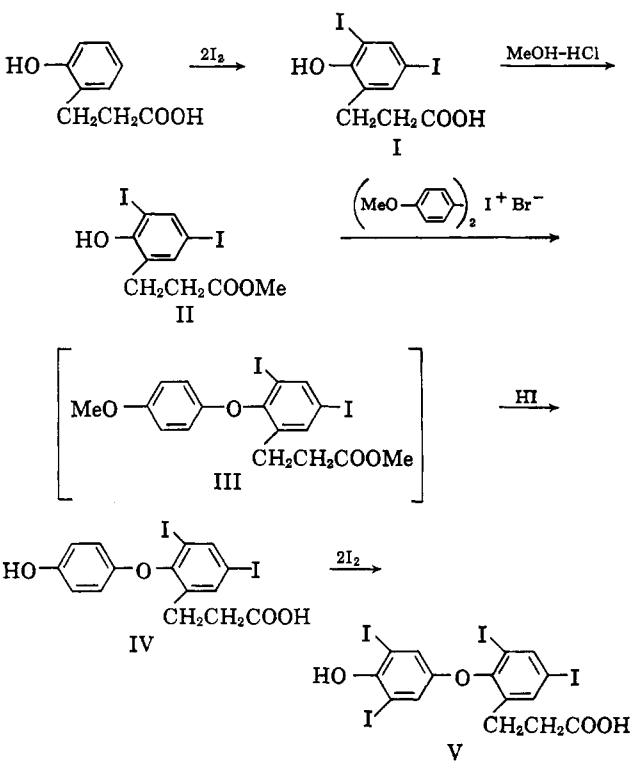
Received March 31, 1964

The synthesis of various analogs of desaminothyronine in which the aliphatic side chain is in *ortho* or *meta* position with respect to the ether bridge is described.

Niemann, *et al.*, reported the synthesis of two analogs of thyroxine, *o*- and *m*-thyroxine, in which the phenolic hydroxyl is in the *ortho* or *meta* position with respect to the ether bridge.[3–5] Attempts to synthesize another analog of thyroxine, in which the aliphatic side chain is in the *meta* position with respect to the ether bridge, were reported by Jackson.[6,7] The present paper describes the synthesis of various desamino analogs of thyroxine (V, IX, and XIV) in which the propionic acid side chain is either in the *ortho* or in *meta* position with respect to the ether bridge. These analogs were needed as reference substances for the identification of reaction products obtained in the earlier reported reactions[8] between 4-hydroxy-3,5-diiodophenylpyruvic acid and the acids I, VI, and X.

The *ortho* analog V of thyropropionic acid was synthesized according to the sequence of reactions shown in Scheme I. Conversion of the phenol II to the diphenyl ether IV was carried out essentially according to the method of Ziegler and Maar.[9] The *ortho* analog V was obtained in good yield.

SCHEME I



The *meta* analogs IX and XIV were synthesized in a similar manner as shown in Scheme II.

Depending on the amount of iodine used in the iodination of *m*-hydroxyphenylpropionic acid, either the diiodo acid VI or the triiodo acid X was obtained.

(1) This work was supported by U. S. Public Health Service Research Grant AM 07955 from the National Institute of Arthritis and Metabolic Diseases.

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