cording to Haworth[27] or Zelinskii[28]) dissolved in 300 ml. of ether was added slowly to a stirred mixture of methylmagnesium bromide (3.1 g. of Mg in 200 ml. of ether) and 1 g. of freshly prepared cuprous chloride, so that no refluxing occurred. After twelve hours, the reaction products were treated with dilute sulfuric acid, the ether layer separated and distilled, yielding 9 ml. of saturated ketone, b. p. 86.8° (36 mm.), which was then purified through the semicarbazone, m. p. 172.5° (from 50% ethanol). *Anal.* Calcd. for $C_{10}H_{19}N_3O$: C, 60.9; H, 9.7; N, 21.3. Found: C, 60.9; H, 9.8; N, 21.3.[29] Regeneration by steam distillation from oxalic acid yielded the pure ketone with the boiling point unchanged.

2. **Dimethyl-2,2-dimethylcyclopentyl Carbinol, VI.**—16.8 g. of the above ketone was added slowly to 0.22 mole of methylmagnesium bromide solution so that no refluxing occurred. After twelve hours stirring, the products were treated with aqueous ammonium chloride, extracted with ether, and dried over anhydrous potassium carbonate. The material was then distilled directly therefrom at 0.5 mm., the bath temperature never exceeding 50°. The yield of crude carbinol was 90% or 16.8 g., d^{25}_4 0.9045, $n^{25}D$ 1.4580. *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.8; H, 12.9. Found: C, 78.1; H, 13.4.

3. **1,1-Dimethyl-2-isopropenyl- and -isopropylidenecyclopentane, VII and VIII.**—Thirty-one grams of biphenyl dissolved in dimethylcellosolve was treated with 3 g. of sliced sodium.[29] After the sodium biphenyl had been completely formed, the solution was drawn off into a dropping funnel, and added to 16.8 g. of the above carbinol, dissolved in 100 ml. of decalin, until a permanent color persisted.[31] Seventeen ml. of carbon disulfide was then added, followed two hours later by 16 ml. of methyl iodide. After standing overnight, the reaction products were distilled at 760 mm., until biphenyl began to distil over. The decomposition of the xanthate occurred readily, and was complete by the time the temperature reached 100°. The product was then distilled approximately 5 ml. of unsaturated material passing at about 152°, and 10 ml. at 165°; yield 80%.

4. **1,1-Dimethyl-2-isopropylcyclopentane, IX.**—The mixture of unsaturated products above was reduced in ethanol with Adams platinum catalyst. Unfortunately the reduction proceeded with great difficulty, and much material was lost by manipulations. Finally, the unreduced material was removed from the reduced by extraction with a 1:1 mixture of concentrated sulfuric acid and acetic anhydride. Thus one gram of completely saturated material was obtained (no color with tetranitromethane). On distillation, it had identical physical properties with AH_2. *Anal.* Calcd. for $C_{10}H_{20}$: C, 85.6; H, 14.4. Found: C, 84.9; H, 14.5.

(27) Haworth, *J. Chem. Soc.*, 1249 (1913).

(28) Zelinskii and Tarassowa, *Ann.*, **508**, 141 (1934).

(29) Thanks are due to Mr. James Fang of the Yale Graduate School for this analysis.

(30) Scott, Walker and Hinsley, THIS JOURNAL, **58**, 2442 (1936).

Summary

1. 2,7-Dimethyloctadiene-2,6 undergoes ring closure in the presence of phosphoric acid to 1,1-dimethyl-2-isopropenylcyclopentane.

2. A possible biological relationship between rarity in the terpene field of tail-to-tail isoprenic unions and of cyclopentanes has been suggested.

(31) Stevens and Deans, *Can. J. Research*, **17B**, 290 (1939).

NEW YORK, N. Y.
LOUISVILLE, KY.

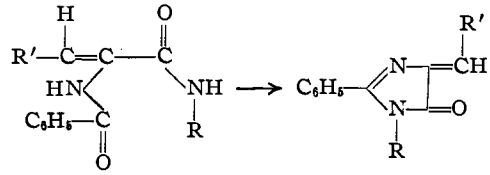
RECEIVED MAY 21, 1948

[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH

Analogs of Aspergillic Acid. III. Synthesis of Cyclic Hydroxamic Acids with a Five-membered Ring[1]

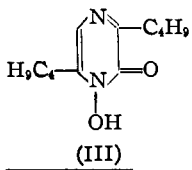
BY ELLIOTT SHAW AND JEAN MCDOWELL

Erlenmeyer[2] and Mohr and Geis[3] have observed the facile cyclization of certain α-acylamino amides to 5-imidazolones. For example, α-benzoylaminocinnamamide (I, R = H, R′ = C_6H_5) forms the imidazolone (II, R = H, R′ = C_6H_5) when heated a few minutes in aqueous alkali.[2]



(I) (II)

Similar changes have now been studied in the hydroxamic acid series and the goal of preparing II, R = OH, has been achieved by an acid cyclization of the open acid (V) to VII. This acid is a five-membered ring analog of the antibiotic, aspergillic acid (III).



(III)

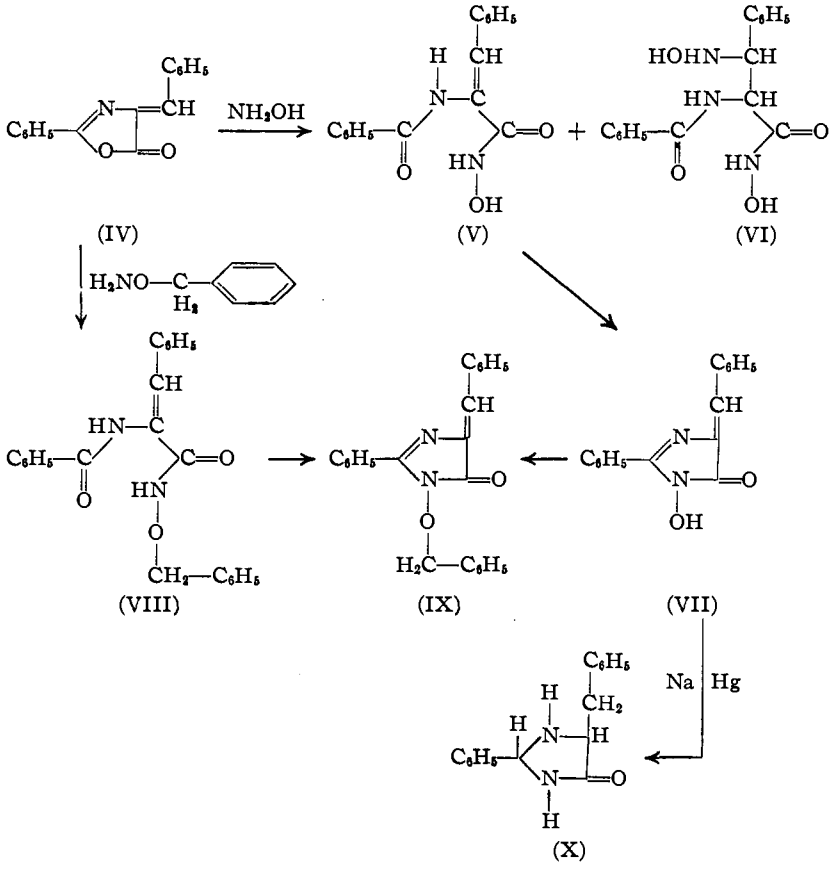
As the starting point of this synthesis, the reaction of the azlactone, 2-phenyl-4-benzylidene-5-oxazolone (IV), with methanolic hydroxylamine was undertaken. The course of the reaction was found to be dependent on the dryness of the methanolic hydroxylamine employed. When prepared from hydroxylamine hydrochloride and methanolic potassium hydroxide, methanolic hydroxylamine also contains the water of neutralization. Addition of the oxazolone (IV) to methanolic hydroxylamine prepared in this way resulted in gradual precipitation, over a period of several days, of the cyclic hydroxamic acid (VII) in low yields. If, however, methanolic sodium methylate was used to liberate hydroxylamine from its hydrochloride, the reaction of the resultant anhydrous solution with the oxazolone (IV) did not lead directly to the cyclic hydroxamic acid (VII). The initial product separating from the reaction mixture was identified as the β-hydroxylamino hydroxamic acid (VI) arising from both addition to the double bond and cleavage of the oxazolone ring. From the mother liquor of this material, the hydroxamic acid (V) was obtained.

Although the desired cyclic acid (VII) had been obtained in a single step from the oxazolone (IV)

(1) For the previous paper in this series see Lott and Shaw, THIS JOURNAL, **71**, 70 (1949).

(2) Erlenmeyer, *Ber.*, **33**, 2036 (1900).

(3) Mohr and Geis, *ibid.*, **41**, 798 (1908).

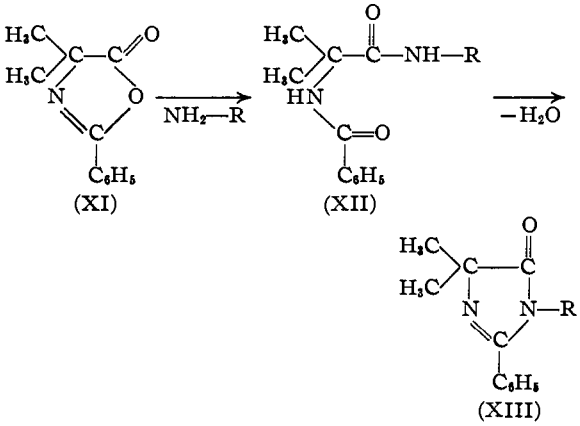


as described above, it was of interest to attempt its formation by cyclization of the open hydroxamic acid (V). Because of the ease of cyclization of the corresponding amide (I, R = H; R′ = C_6H_5) with hot aqueous alkali, the action of this agent on the hydroxamic acid was studied. A small amount of cyclic acid (VII) was formed along with an unidentified product. More remarkable was the ease with which boiling dilute hydrochloric acid effected the ring closure; in ten minutes, a conversion of about 50% was achieved. Under these conditions the amide does not cyclize. A derivative of VII containing a *p*-ethoxy substituent in the 4-benzylidene group was also successfully prepared from the corresponding azlactone through an acid cyclization of the intermediate open hydroxamic acid.

The cyclic acid (VII) was reduced with sodium amalgam to the dihydroimidazolone (X) previously described by Granacher and Gulbas,[4] confirming the absence of rearrangement in the intermediate steps.

Treatment of the sodium salt of the cyclic hydroxamic acid (VII) with benzyl chloride led to a benzyl ether (IX) identical with that obtained in a series of steps starting with O-benzylhydroxylamine. Reaction of the latter base with the oxazolone (IV) opened the ring to an O-benzylhydroxamic acid (VIII) which was then cyclized to the imidazolone (IX) by means of hot aqueous hydrochloric acid. This ring closure was also achieved through the action of heat and reduced pressure, conditions which have been used successfully in the conversion of a number of N-alkyl amides of α-benzamidocinnamic acid to imidazolones.[4,5] At the same time, part of the O-benzylhydroxamic acid (VIII) reverted to the azlactone (IV) with elimination of O-benzylhydroxylamine.

α-Benzamidoisobutyramide (XII, R = H) undergoes cyclization to XIII (R = H) readily when treated with hot aqueous alkali,[3] similarly to the cinnamamides as described above. For comparison, the corresponding hydroxamic acid (XII, R = OH) and O-benzylhydroxamic acid (XII, R = $O-CH_2-C_6H_5$) were prepared from the oxazolone (XI) by treatment with hydroxylamine and O-benzylhydroxylamine, respectively. However, ring closure of these to cyclic hydroxamic acids was not achieved.



Experimental[6]

Reaction of 2-Phenyl-4-benzylidene-5-oxazolone with Anhydrous Methanolic Hydroxylamine.—The oxazolone[7] (30 g., 0.12 mole) was added to *N* methanolic hydroxylamine prepared by mixing at room temperature a methanol solution of hydroxylamine hydrochloride (28 g., 0.41 mole) and an equivalent of methanolic sodium methylate, cooling, and filtering from the resultant sodium chloride. The

(4) Granacher and Gulbas, *Helv. Chim. Acta*, **10**, 819 (1927).

(5) Granacher and Mahler, *ibid.*, **10**, 246 (1927).

(6) Melting points are uncorrected. Analyses were carried out by Mr. J. F. Alicino.

(7) Williams and Ronzio, THIS JOURNAL, **68**, 647 (1946).

mixture was left standing in a stoppered flask; there was a slight heat evolution accompanied by gradual precipitation. After twenty-four hours, the solid was filtered off, 9 g., m. p. 129–130°, apparently the β-hydroxylamino hydroxamic acid (VI) described by Posner,[8] m. p. 128°. The material reduces Fehling solution in the cold.

Anal. Calcd. for $C_{16}H_{17}O_4N_3$: N, 13.33. Found: N, 13.08.

The filtrate from this product was concentrated under reduced pressure to a sirup. After crystallization had been induced, water was added gradually to increase the yield. There was obtained 16 g. of white crystals, m. p. 130° dec., a figure quite variable with the rate of heating. The hydroxamic acid (V) thus obtained is quite pure but was recrystallized from ethyl acetate for analysis; it gives a red color with ferric chloride.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: C, 68.10; H, 4.97; N, 9.93. Found: C, 68.58; H, 5.11; N, 9.74.

N-Hydroxy-2-phenyl-4-benzylidene-5-imidazolone (VII).—**(a) By Action of Hydroxylamine on the Oxazolone.**—2-Phenyl-4-benzylidene-5-oxazolone (24.9 g., 0.1 mole) was added to a methanol solution of hydroxylamine (0.1 mole in 125 ml.) prepared by treatment of hydroxylamine hydrochloride with an equivalent of potassium hydroxide in methanol solution and filtering off the potassium chloride. The suspension was left standing in a loosely stoppered flask. The oxazolone went into solution slowly. On the fourth day, golden needles of product began to separate; the solution was decanted from undissolved oxazolone and allowed to crystallize. After a few days more, the precipitate was filtered and, together with an additional crop obtained from the mother liquor, gave a 15% yield of the N-hydroxyimidazolone m. p. 206–207° (from ethanol). The acid gives a wine color with ferric chloride and forms a sparingly soluble, red sodium salt.

Anal. Calcd. for $C_{16}H_{12}O_3N_2$: C, 72.72; H, 4.55; N, 10.61. Found: C, 72.14; H, 4.77; N, 10.27.

(b) By Cyclization of α-Benzamidocinnamohydroxamic Acid.—The hydroxamic acid (1.0 g.) was refluxed for ten minutes with 3 *N* hydrochloric acid (20 ml.). The suspended solid became yellow in appearance. Filtration of the cooled mixture gave 0.5 g., 53%, of crude product, m. p. 202–203°, which, on recrystallization from ethanol, formed yellow needles, m. p. 206–207°, identical with the acid described above.

Action of Alkali on α-Benzamidocinnamohydroxamic Acid.—The acid (5 g.) was refluxed for six minutes with 1 *N* sodium hydroxide (50 ml.). The red solution was cooled and acidified with 10% hydrochloric acid. The precipitated gummy material was dissolved in ethanol, treated with charcoal, and concentrated. The first crop of yellow crystals, 0.38 g., m. p. 214° after recrystallization from ethanol, gave an amber color with ferric chloride and was alkali-soluble, acid-insoluble.

Anal. Found: C, 69.50; H, 4.81; N, 9.33.

This material depresses the m. p. of the cyclic hydroxamic acid (VII), which could be isolated, in this reaction, on concentration of the ethanol mother liquor of the above unknown product to yield 0.4 g., m. p. 206–207°.

Sodium Amalgam Reduction of N-Hydroxy-2-phenyl-4-benzylidene-5-imidazolone.—When the cyclic hydroxamic acid was treated in hot ethanol with sodium amalgam,[9] a 25% yield of 2-phenyl-4-benzyl-5-imidazolidone (X) was obtained m. p. 145–146°, no depression when mixed with an authentic sample.[4,9]

N-Hydroxy-2-phenyl-4-(*p*-ethoxybenzylidene)-5 imidazolone.—2-Phenyl-4-(*p*-ethoxybenzylidene)-5-oxazolone[10] (29 g., 0.1 mole) was added to *N* methanolic hydroxylamine (200 ml., 0.2 mole) prepared from sodium methylate and hydroxylamine hydrochloride as described above. After standing overnight, the solution was filtered free of an acid-soluble precipitate, apparently a β-hydroxylamino acid analogous to (VI). The filtrate was concentrated *in vacuo* to a sirup from which 10 g. of crude α-benzamido-*p*-ethoxycinnamohydroxamic acid, m. p. 195°, was crystallized. This acid was not purified but cyclized directly by refluxing for ten minutes in 3 *N* hydrochloric acid (200 ml.). The cooled mixture was filtered, and the yellow product recrystallized from ethanol, yielding 4 g., m. p. 231°.

Anal. Calcd.: for $C_{18}H_{16}O_3N_2$: C, 70.12; H, 5.19; N, 9.09. Found: C, 70.22; H, 5.04; N, 9.03.

α-Benzamido-O-benzylcinnamohydroxamic Acid (VIII).—2-Phenyl-4-benzylidene-5-oxazolone (5 g.) was refluxed in ether (300 ml.) and chloroform (30 ml.) for one hour with O-benzylhydroxylamine (2.5 ml.). The product separated from the cooled solution, 5.8 g., m. p. 164–165°, 78%; it is soluble in alkali from which it is precipitated by carbon dioxide, a property of O-alkylated hydroxamic acids.[11]

Anal. Calcd. for $C_{23}H_{20}O_3N_2$: C, 74.20; H, 5.38; N, 7.53. Found: C, 74.63; H, 5.46; N, 8.03.

1-Benzyloxy-2-phenyl-4-benzylidene-5-imidazolone (IX).—**(a) By Thermal Cyclization.**—In an apparatus assembled for a vacuum distillation, α-benzamido-O-benzylcinnamohydroxamic acid (5 g.) was heated in an oil-bath at 175° for fifteen minutes at a pressure of 2 mm. The residue in the still pot was triturated with methanol and filtered; 1.4 g. of crude 2-phenyl-4-benzylidene-5-oxazolone was obtained, identified by recrystallization from benzene and comparison with an authentic sample.

When the fusion was carried out at 190° and a pressure of 12 mm. for two hours, less azlactone formation was observed. From the methanol mother liquors there was obtained the desired imidazolone in a yield of 10%, m. p. 122° from methanol, a yellow solid insoluble in alkali.

Anal. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.99; H, 5.08; N, 7.92. Found: C, 77.99; H, 5.09; N, 8.05.

(b) By Hydrochloric Acid Cyclization.—α-Benzamido-O-benzylcinnamohydroxamic acid (VIII, 1 g.) was refluxed for ten minutes with 3 *N* hydrochloric acid (30 ml.) and dioxane (5 ml.). A red oil formed which solidified on cooling. The solid was washed free of acid by repeated decantation with water and recrystallized from alcohol, yielding yellow needles, m. p. 120°, 0.25 g., 26%.

(c) From the 1-Hydroxy-5-imidazolone.—1-Hydroxy-2-phenyl-4-benzylidene-5-oxazalone (0.44 g.) was added to a solution of sodium (0.038 g.) in absolute alcohol (125 ml.). The resultant suspension of red sodium salt was refluxed for two hours with benzyl chloride (0.25 g.). After the mixture had cooled, the solution was decanted from a residue of sodium chloride and concentrated, yielding 0.35 g., 60% of yellow needles, m. p. 119–20°. Recrystallized from ethanol, the product did not depress the m. p. of the benzyl ether obtained by the thermal cyclization described above (a) or the acid method (b).

α-Benzamido-N-benzyloxyisobutyramide (XII, R = $OCH_2C_6H_5$).—To 2-phenyl-4,4-dimethyl-5-oxazolone[3] (2.05 g.) in anhydrous ether (20 ml.) was added O-benzylhydroxylamine (2 ml.). Crystals appeared shortly, and the mass soon solidified. After two hours, the mixture was filtered with suction, 3 g., m. p. 203–204°, unchanged by recrystallization from chloroform. The product is soluble in dilute sodium hydroxide and is reprecipitated by carbon dioxide.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: N, 8.98. Found: N, 8.88.

α-Benzamidoisobutyrohydroxamic Acid (XII, R = OH).—**(a)** A suspension of the benzyl ether (6 g.) in 150 ml. of ethanol was shaken with palladium-on-charcoal (1 g.) at an initial hydrogen pressure of 50 pounds. After half an hour, the jelly-like mass was heated to dissolve the product and permit filtration of the catalyst. The hydroxamic acid was obtained on cooling the filtrate in a yield of 75% m. p. 163° dec.

(8) Posner, *Ann.*, **389**, 101 (1912).

(9) Williams, Symonds, Ekeley and Ronzio, THIS JOURNAL, **67**, 1157 (1945).

(10) Buck, Baltzly and Ide, *ibid.*, **60**, 1789 (1938).

(11) Yale, *Chem. Rev.*, **33**, 209 (1943).

(b) 2-Phenyl-4,4-dimethyl-5-oxazolone (23 g.) was added to *N* methanolic hydroxylamine (240 ml.) prepared from the hydrochloride and methanolic potassium hydroxide. There followed a slight temperature rise. The product crystallized out of solution. Recrystallization from methanol gave 6 g., m. p. 163° dec.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.30; N, 12.61. Found: C, 59.20; H, 6.45; N, 12.37.

Attempted Cyclizations of α-Benzamidoisobutyrohydroxamic Acid and Its O-Benzyl Ether.—The acid (XII, R = OH) was refluxed for fifteen minutes with *N* sodium hydroxide; acidification released carbon dioxide and led to the precipitation of a substance which did not contain the hydroxamic acid grouping (ferric chloride color test). When the O-benzyl derivative of the starting material (XII, R = $OCH_2C_6H_5$) was refluxed two hours in 2.5 *N* sodium hydroxide, no change took place.

Treatment of either the hydroxamic or its O-benzyl ether with hot aqueous hydrochloric acid led to a rapid hydrolysis to α-benzamidoisobutyric acid, m. p. 196–197°.[3]

Summary

The reaction of hydroxylamine with the azlactone, 2-phenyl-4-benzylidene-5-oxazolone, has been studied. The product obtained through opening of the ring, α-benzamidocinnamohydroxamic acid, on treatment with hot aqueous hydrochloric acid undergoes ring closure to the cyclic hydroxamic acid, 1-hydroxy-2-phenyl-4-benzylidene-5-imidazolone.

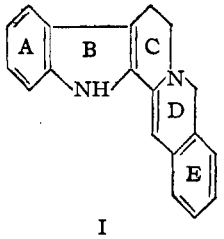
NEW BRUNSWICK, N. J. RECEIVED OCTOBER 6, 1948

[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF THE NATIONAL RESEARCH COUNCIL]

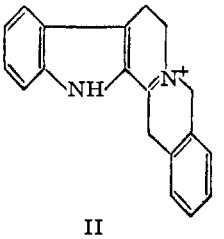
Concerning the Structure of Sempervirine[1]

BY O. E. EDWARDS AND LÉO MARION

Soon after an investigation of sempervirine ($C_{19}H_{16}N_2$) had been initiated in this Laboratory, it was shown by Prelog[2] that the alkaloid was degraded to yobyrine (2-(2′-methylbenzyl)-3-carboline) when heated with selenium and to the so-called "tetrahydroyobyrine" (2-[3′-(5′,6′,7′,8′-tetrahydroisoquinolyl)] - 3 - ethylindole) when heated in toluene with Raney nickel. The structures of these two compounds, first obtained from the degradation of yohimbine,[3] are definitely known and have been confirmed by synthesis.[4] Sempervirine, which is optically inactive, forms salts with one equivalent of acid and contains one active hydrogen atom (Zerewitinow), but contains no methylimino group.[2b] On the basis of these facts Prelog[2] suggested structure I to represent sem-



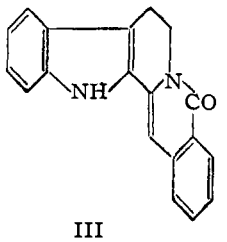
I



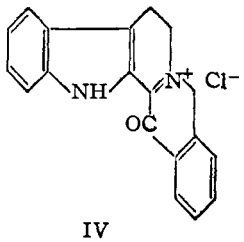
II

pervirine. The high basic strength of the alkaloid (pK = 10.6) is explained by assuming an equilibrium between I and the quaternary base II. In fact, the ultraviolet absorption spectra of the base and of its hydrochloride are identical at wave lengths shorter than 4100Å., which would be expected if II were the important form in both cases. In alkaline solution, however, the absorption is strikingly different,[2b] a change which could arise from a shift to structure I.

The compound represented by formula I has now been synthesized from the lactam III, prepared by a slight modification of the method of



III



IV

Schlittler and Allemann,[5] involving the condensation of tryptamine with homophthalic anhydride. This reaction gave rise to the two possible homophthalamic acids, but chiefly to the desired one (N-(*o*-carboxyphenylacetyl)-tryptamine) which was converted to the methyl ester and cyclized to III. The reported reduction of the lactamic group in oxysparteine with lithium aluminum hydride[6] seemed to be applicable to the reduction of the lactam III and indeed, the use of this reagent permitted the conversion of III into compound I in excellent yield. That the synthetic product has structure I follows from the fact that had the double bond been reduced as well as the CO in ring D, there would have resulted a compound which has already been synthesized[4a] and has properties different from those of the product. On the other hand, had the reaction produced a dihydroindole, the base would be diacidic whereas its hydrochloride contains only one equivalent of acid. The synthetic base, however, proved to be quite different from sempervirine and a much weaker base (pK = 5) as would be expected of a

(1) Published as National Research Council Bull. No. 1921.

(2) (a) R. Goutarel, M. M. Janot and V. Prelog, *Experientia*, **4**, 24 (1948); (b) V. Prelog, *Helv. Chim. Acta*, **31**, 588 (1948).

(3) F. Mendlik and J. P. Wibaut, *Rec. trav. chim.*, **48**, 191 (1929).

(4) (a) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 617 (1946); (b) P. L. Julian, W. J. Karpel, A. Magnani and E. W. Meyer, THIS JOURNAL, **70**, 180 (1948).

(5) E. Schlittler and T. Allemann, *Helv. Chim. Acta*, **31**, 128 (1948).

(6) G. R. Clemo, R. Raper and W. Short, *Nature*, **162**, 296 (1948).