(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°.[8]

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.

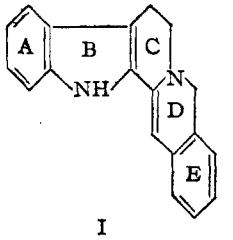
NEW BRUNSWICK, N. J. RECEIVED OCTOBER 6, 1948

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

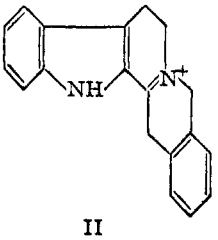
Concerning the Structure of Sempervirine[1]

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 sempervirine. 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.

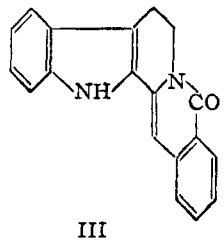


I

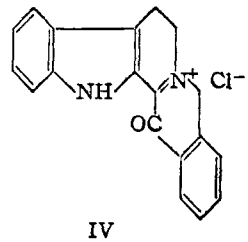


II

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



III



IV

(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).

compound of structure I. The ultraviolet absorption spectrum of the synthetic base is not strikingly different from that of sempervirine, but there is a marked change on salt formation (Fig. 1) which is undoubtedly attributable to association of the unshared pair of electrons on the basic nitrogen with a proton. The synthetic base is much less colored than sempervirine; unlike the latter, it forms an unstable hydrochloride which in solution in contact with air is readily transformed into a quaternary salt having the empirical formula $C_{19}H_{15}ON_2Cl \cdot H_2O$, probably represented by formula IV. The high basic strength of this substance (pK = 11.7) and the fact that the salt is not decomposed by hot dilute ammonia support such a structure (IV). The reported conversion of dihydroyobyrine to yobyrone by atmospheric oxygen[4b] also supports structure IV.

Unlike sempervirine, the synthetic base I shows no tendency to solvate. The infrared spectra of the synthetic base and of sempervirine were investigated in solution in chloroform containing traces of water and ethanol. The synthetic base showed a sharp band at ~3480 cm.$^{-1}$, indicating the presence of unassociated N–H groups,[7] while sempervirine showed a broad band extending approximately from 1350–3450 cm.$^{-1}$.[8]

Since sempervirine is a strong base (pK = 10.6), it is not likely to be represented by a structure such as formula I in which the double bond in ring D would be displaced to occupy in ring C the same relative position to the basic nitrogen, since such an alternative should also be a weak base. Consequently, it seemed possible that the empirical formula of the alkaloid might be greater than that hitherto accepted. However, all attempts to determine the molecular weight by measuring the difference in vapor pressure between ethanol and an ethanolic solution of sempervirine with the aid of the Puddington manometer[9] showed that the molecules were very highly associated in anhydrous solvent and that the degree of association decreased as the solvent was hydrated. Although no figure was obtained much smaller than twice $C_{19}H_{16}N_2$, the behavior of sempervirine in ethanol was such as to preclude a definite conclusion as to the magnitude of the molecular weight.[10]

Acknowledgments.—We are greatly indebted to Professor Raymond-Hamet, Ecole de Pharmacie, Paris, France, who kindly presented us with a generous sample of sempervirine hydrochloride; also, in these laboratories, to Drs. R. N. Jones and D. A. Ramsay for taking the absorption spectra and to Dr. I. E. Puddington for the use of his apparatus.

(7) V. Z. Williams, *Rev. Sci. Inst.*, **19**, 143 (1948).

(8) This broad band was first attributed to an NH bond in a state of hydrogen bonding. However, since this paper was submitted and after the appearance of the communications of Woodward and Witkop and of Woodward and McLamore (THIS JOURNAL, **71**, 379 (1949)) on this subject, the infrared absorption spectrum of sempervirine was again determined in spectroscopically pure chloroform as solvent. No absorption whatsoever could be detected in the NH region and, therefore, sempervirine does not contain an NH group.

(9) (a) I. E. Puddington, *Rev. Sci. Inst.*, **19**, 577 (1948); (b) I. E. Puddington, *Can. J. Research*, in press.

(10) Since submitting this paper we have found that the behavior of anhydrous sempervirine in absolute methanol is normal and that the molecular weight determination in that solvent indicates a single molecule, *i.e.*, $C_{19}H_{16}N_2$.

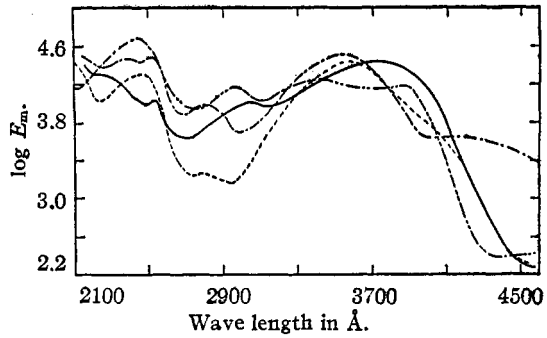


Fig. 1.—Ultraviolet absorption spectra in ethanol: ————, the synthetic base; - - - - - - -, the synthetic base hydrochloride; — - — - — the hydrochloride of the oxidized base; — - - — - -, sempervirine.

Experimental

N-(2-β-Indolylethyl)-homophthalimide.—A mixture of tryptamine (m. p. 117°,[11] 0.5 g.) and homophthalic acid (m. p. 185°, 0.56 g.) in a flask, previously flushed with nitrogen, was immersed in a bath at 180°. When the elimination of water had nearly stopped, the bath temperature was raised and maintained at 250° for five minutes. The melt was cooled while the flask was rotated to spread the mass which crystallized completely. After one crystallization from chloroform the product consisted of colorless needles, m. p. 214°, wt. 0.71 g. The mother liquors yielded a further 0.1 g. of product, m. p. 210°. The literature reports a melting point of 210°.[12] An attempt to cyclize the imide (0.29 g.) by refluxing with freshly distilled phosphorus oxychloride (5 cc.) for one hour yielded 0.16 g. of unchanged imide and a residue that proved intractable.

N-(*o*-Carboxymethylbenzoyl)-tryptamine.—N-(2-β-Indolylethyl)-homophthalimide (0.4 g.) was heated on the steam-bath for twelve and one-half hours with 0.5 *N* sodium hydroxide (5 cc.). The solution was cooled, saturated with carbon dioxide and filtered to remove a little suspended solid. The filtrate was acidified with hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and distilled to remove the solvent. An oily residue was left which was dissolved in methanol–ether. The solution, on seeding, deposited crystals, wt. 0.21 g. After three recrystallizations from methanol–ether the product consisted of colorless needles, m. p. 156° (dec.) when immersed at 145°.

Anal. Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.78; H, 5.63. Found: C, 70.65, 70.68; H, 5.70, 5.55.

N-(*o*-Carboxyphenylacetyl)-tryptamine.—Tryptamine (1.0 g.) and homophthalic anhydride (1.0 g.) were triturated together in a mortar and added to anhydrous benzene (125 cc.). The mixture was refluxed with occasional shaking. After 15 min. the solid had in part dissolved, in part become oily and crystals began to separate. After one hour the mixture was cooled. It consisted of crystals and an oily globule at the bottom of the flask. The thick globule was retained in the flask while the suspension of crystals in benzene was poured on a filter. The filtrate was poured back in the flask, refluxed for thirty minutes, cooled and the filtration repeated. This process was re-

(11) All melting points are corrected.

(12) C. Scholz, *Helv. Chim. Acta*, **18** 923, (1935).

peated (altogether six times) until most of the oil had been crystallized. The crystalline N-(*o*-carboxyphenylacetyl)-tryptamine thus obtained, after one crystallization from benzene, consisted of colorless needles, m. p. 146° (the literature[6] gives m. p. 143°). This reaction gave 77–84% yields.

The final benzene liquor obtained from the reaction, when concentrated, yielded small quantities of the isomeric homophthalamic acid, m. p. 156°, described above.

Cyclized Lactam (III).—An excess of diazomethane in ether was added to N-(*o*-carboxyphenylacetyl)-tryptamine (0.4 g.) dissolved in a little methanol and the solution allowed to stand for one hour. The solvent was then removed under diminished pressure and the residue refluxed for fifty minutes with freshly distilled phosphorus oxychloride (7 cc.). After twenty-five minutes crystals began to separate and at the end of the reaction time, the suspension was cooled and filtered. The crystalline filtered material weighed 0.17 g. The filtrate was concentrated under reduced pressure to a small volume, ice and water were added to the residue and the precipitate thus produced extracted with chloroform. The chloroform extract yielded a further 0.08 g. of product which was combined with the first crop and crystallized from methanol, wt. 0.18 g., yield, 50%. After two more recrystallizations from methanol–acetone, the lactam consisted of light yellow needles, m. p. 307° (vac.) when immersed at 302°. (The literature[5] reports m. p. 299° but the substance seems to oxidize when heated in the air and melting points taken in an open tube are unreliable.)

Anal. Calcd. for $C_{19}H_{14}ON_2$: C, 79.71; H, 4.90. Found: C, 79.75; H, 4.80.

Synthetic Base (I).—The lactam III (0.26 g.) was dissolved in boiling anhydrous dioxane (20 cc.) in a nitrogen atmosphere, the solution cooled and an excess (*ca.* 5%) of a solution of lithium aluminum hydride in anhydrous ether added. The resulting suspension was refluxed while a stream of nitrogen was swept through the apparatus until (20 min.) the bulk of the ether had evaporated through the condenser (warm water). The solution was refluxed ten minutes more, cooled and aqueous dioxane run in until the excess reagent and addition compound were decomposed. Water (100 cc.) was then added, the suspension chilled and filtered. The dry filter cake was extracted repeatedly with hot acetone. The combined acetone washings were filtered and concentrated to a small volume. This solution deposited the base as glistening, yellow plates, m. p. 247°, yield, 89%. The acetone mother liquor, on further concentration, yielded another 10 mg. of cruder material. Two more crystallizations from methanol brought the melting point to 248° when immersed at 243°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.60, 83.70; H, 5.57, 5.75; N, 10.47, 10.62.

The *pK* value was obtained by titrating the base in methanolic solution with 0.1 *N* hydrochloric acid and determining the *p*H at half titration. Found: *pK* 4.9, 5.1.

To a concentrated solution of the synthetic base in methanol, an excess of hydrochloric acid was added and the resulting solution concentrated under reduced pressure until the bulk of the hydrochloride had crystallized. After two recrystallizations from methanol–ether, the salt was obtained as yellowish-orange needles, m. p. 317°, when immersed at 313°.

Anal. Calcd. for $C_{19}H_{16}H_2 \cdot HCl \cdot 1.5H_2O$: C, 67.97; H, 6.00; N, 8.35. Found: C, 67.95, 68.06; H, 5.86, 5.86; N, 8.28, 8.16.

Oxidized Hydrochloride (IV).—Concentration of the mother liquor from the crystallization of the hydrochloride of the synthetic base yielded a higher melting salt. It was also observed that the base hydrochloride (m. p. 317°) in aqueous methanol or methanol–ether, left for several hours in contact with air, was transformed into the higher melting salt. This salt, after several recrystallizations from aqueous methanol, consisted of golden-orange needles, m. p. 354°, when immersed at 348°.

Anal. Calcd. for $C_{19}H_{16}ON_2Cl \cdot H_2O$: C, 66.95; H, 5.03; N, 8.22; Cl, 10.4. Found: C, 67.36, 67.37; H, 5.06, 5.13; N, 8.23, 8.36; Cl, 9.60, 10.04. Ionized chlorine (reaction with $AgNO_3$ at room temp.): 10.1. *pK* (determined from the *p*H at half titration with 0.05 N sodium hydroxide): 11.6, 11.7, 11.7.

The quaternary salt was dissolved in hot methanol and an excess of dilute ammonia added. The resulting solution, on cooling, deposited the unchanged salt. When a solution of the salt was made strongly alkaline with sodium hydroxide, a product separated that appeared to be a mixture of the quaternary salt and a base, but no homogeneous base could be obtained. The chloride did not react with hydroxylamine in the presence of sodium acetate, but was recovered unchanged.

Sempervirine.—The sempervirine hydrochloride after recrystallization from acetone–water, consisted of lemon-yellow needles, m. p. 352°, when immersed at 320°. The base liberated from this salt and recrystallized twice from aqueous methanol, was obtained as orange rhombic plates, m. p. 275° (vac.), when immersed at 272°; its *pK* value (half-titration of the hydrochloride in methanol with 0.05 *N* sodium hydroxide), 10.9. Attempts to determine the molecular weight of sempervirine by measuring the difference in vapor pressure between ethanol and ethanolic solutions of the base, with the aid of the Puddington differential manometer,[8] yielded anomalous results. Sempervirine (made anhydrous by heating *in vacuo* in a drying pistol) in absolute ethanol gave a molecular weight of 14,000 and > 40,000; sempervirine hydrate in absolute ethanol, 1200; sempervirine hydrate in 99.7% ethanol, 570, 520. In more dilute aqueous ethanol, fractionation of the solvent occurred with resultant change in vapor pressure, making the measurements unreliable.

Summary

1. The compound represented by the formula previously assigned to sempervirine has been synthesized and shown not to be identical with the alkaloid.

2. In the course of the synthesis, N-(*o*-carboxymethylbenzoyl)-tryptamine was obtained as a by-product and described for the first time.

3. The synthetic base forms a hydrochloride readily oxidized in solution by atmospheric oxygen to a substance of formula $C_{19}H_{15}ON_2Cl \cdot H_2O$, which is probably ketonic and is the salt of a much stronger base than the synthetic base.

4. Attempts to determine the molecular weight of sempervirine showed that the anhydrous molecules were very highly associated in anhydrous solvent and that the degree of association decreased as the solvent became hydrated.

OTTAWA, CANADA RECEIVED JANUARY 3, 1949