It is also readily soluble in ether, an observation in marked contrast to the insolubility of the hydrochloride. The m.p. was 148–149°. The sample for analysis was purified by sublimation; m.p. 151–152°, mixed m.p. with II was 123–131°. The product gave a green color with ferric chloride.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.26; H, 5.87.

The ultraviolet spectrum of III showed λ_{max} 310 mμ, log ε 4.17. The important infrared bands were: 3.10, 3.40w, 3.46w, 6.03, 6.12, 6.21, 6.32, 6.84, 6.93, 7.18, 7.39, 7.58, 8.07, 8.20, 8.44, 9.50, 10.00, 10.29, 10.43, 10.90, 11.40, 12.95, and a broad band around 14.70 μ.

6-Propyl-α-deoxykojic acid (IV). To crude II (5.0 g.), dissolved in 150 cc. of methanol, was added 25 mg. of 10% palladium-on-carbon and the suspension was shaken in a Parr apparatus at about 30 lbs./inch.[2] The uptake of hydrogen ceased after 5 min. The suspension was filtered, the solvent was removed, and the residue was recrystallized from a mixture of methanol and ethyl acetate. The product separated in creamy crystals, yield 3.5 g. (70%), m.p. 128–131°. Sublimation afforded pure IV, m.p. 132.5–133.5°. From the yellow mother liquor 1.5 g. of less pure material was recovered, from which some pure IV could be obtained on sublimation, the rest decomposing.

The product was considerably more soluble in ethyl acetate, acetone, and methanol than I, but it was less soluble in water. It gave a deep violet color with ferric chloride.

When 0.3 g. of crude III was hydrogenated analogously, 0.28 g. of cream colored crystals was obtained, m.p. 131–132.5°. The mixed m.p. with the above crystals also was 132–133.5°. The infrared spectra of the compound from the two sources were identical, with these bands: 3.09, 3.39, 3.41, 3.49, 6.04, 6.18, 6.28, 6.85, 6.97, 7.20, 7.37 with shoulders at 7.43 and 7.48, 7.74, 8.06, 8.18, 8.35, 9.08 with shoulders at 9.11 and 9.20, 9.50 with shoulder at 9.65, 10.19, 10.29, 10.29, 10.43, 11.35, 11.63, 12.60w, 13.01, and a broad band around 14.20μ.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 64.39; H, 7.29.

3,5-Dinitrobenzoates of I, II, III, IV. About 0.2 g. of I, II, III, or IV was dissolved in 5 cc. of dry pyridine at room temperature, mixed with 0.35 g. of 3,5-dinitrobenzoyl chloride, and stirred for 5 min. The solution of I remained clear, that of II turned deep red-brown, that of III became a thick slurry, and that of IV yielded a thin slurry. Each reaction mixture was then heated on a hot plate for 30 sec. and the flasks were then cooled under tap water. Then 10 cc. of ice water was added to each mixture and the resulting precipitate was collected on a filter, washed with water, and dried over calcium chloride at room temperature and 10 mm. Yields were between 0.3 and 0.4 g.

The products were recrystallized from chloroform-ligroin with the use of Norit, and then from benzene-hexane. Fine, colorless crystals were obtained for each product. These melting points were observed for the several dinitrobenzoates: from I, 215–216°; from II, 96.5°; from III, 234–235°; from IV, 125°. The infrared spectra of the derivatives had the following peaks in common: 3.27 (aromatic CH), 5.72 (benzoate carbonyl), 5.97 (pyrone carbonyl), 6.47 and 7.44 (nitro), 12.58 (sym. trisubstituted benzene), and the four spectra were generally similar up to about 9.55μ. A good region for differentiation of the derivatives was 9.55–11.90μ where the individual compounds exhibited the following bands: I. 9.75, 9.92, 10.47, 10.73, 10.96, 11.25, 11.90. II. 10.10, 10.34, 10.59, 10.85, 10.94, 11.23, 11.39, 11.90. III. 9.99, 10.23 (shoulder 10.43), 10.66, 10.85, 10.92, 11.30, 11.90. IV. 9.94, 10.49, 10.65, 10.84, 10.92, 11.29, 11.60, 11.90μ.

Explosions were encountered in analyzing all of the dinitrobenzoates but they seemed not to affect the values for the esters from I, III, IV. The explosion with the dinitrobenzoate of II, however, did make analysis unrealizable, for duplicate analyses (C, H, N) were inconsistent and varied widely. These and other microanalyses were performed by Miss Hilda Beck.

Anal. of dinitrobenzoates.

From I. Calcd. for $C_{13}H_8N_2O_8$: C, 48.76; H, 2.52. Found: C, 48.37; H, 2.54.

From III. Calcd. for $C_{16}H_{12}N_2O_8$: C, 53.33; H, 3.36. Found: C, 53.71; H, 3.10.

From IV. Calcd. for $C_{16}H_{14}N_2O_8$: N, 7.73. Found: N, 7.57.

EVANSTON, ILL.

[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF KANSAS]

The Structure of 2-Substituted Pyrrolines[1,2]

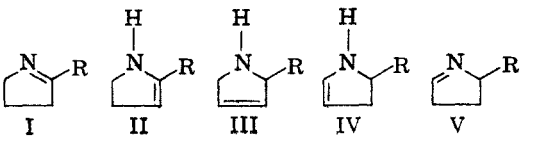
J. H. BURCKHALTER AND J. H. SHORT[4]

Received January 24, 1958

Of the five possible structures which may be written for 2-substituted pyrrolines upon the basis of the location of the double bond, only the Δ^1- and Δ^3-pyrrolines have been shown conclusively to exist. The present work confirms the existence of the former rather than a Δ^2 structure. An attempt to synthesize 2-phenyl-Δ^4-pyrroline resulted in failure.

While employing a number of 2-substituted pyrrolines in the synthesis of a group of desired 2-substituted pyrrolidines,[5] it became apparent from a survey of the literature that much confusion existed concerning the structures of the intermediate 2-substituted pyrrolines, and a determination of the structures of these pyrrolines became an objective.

Five 2-substituted pyrrolines are structurally possible, depending upon the location of the double bond (I–V). There appears to be no controversy



(1) Based upon a portion of the Ph.D. Thesis of J. H. Short, University of Kansas, 1954.

(2) During the preparation of this manuscript, a recent report on the structure of 2-phenylpyrrolines was noted.[3]

(3) M. C. Kloetzel, J. Z. Pinkus, and R. M. Washburn, *J. Am. Chem. Soc.*, **79**, 4222 (1957).

(4) Parke, Davis & Co., Fellow. Present address, Abbott Laboratories, North Chicago, Ill.

(5) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1281 (1958).

concerning the existence and identity of Δ^3-pyrrolines (III); compounds of this structure are the usual[6] but not the exclusive[7,8] products obtained from the partial reduction of substituted pyrroles. However, confusion has centered around the existence of Δ^1-pyrrolines (I and V) and Δ^2-pyrrolines (II and IV). Several workers have arbitrarily assigned a Δ^2 structure to their compounds,[9,10] while Cloke and colleagues suggest either the Δ^1- or Δ^2-pyrroline form or a tautomeric mixture of the two.[11]

It is surprising that so many workers have accepted the Δ^2-pyrroline structure without question since analogous open chained vinyl amines have been considered to exist in only a few special cases where conjugated systems are involved.[12] But using infrared spectral data, Witkop has recently challenged even some of these assignments as vinyl amines (eneamines).[13] Further, by the same means, Witkop has come to the conclusion that there are probably no authentic secondary Δ^2-pyrrolines.[14] Of course, tertiary Δ^2-pyrrolines, such as 1-methyl-2-substituted-Δ^2-pyrrolines are well known.[15]

Maginnity and Cloke, using the Zerevitinov method of determining active hydrogen, apparently were the first workers to choose the Δ^1-pyrroline (I) over the Δ^2-pyrroline (II) structure upon a rational basis.[16] Since none of the pyrrolines tested liberated appreciable quantities of active hydrogen, Δ^1-pyrrolines were indicated.

The following pyrrolines were synthesized as described in the publication which follows,[5] and their infrared spectra were determined: 2-phenyl-, 2-(p-methoxyphenyl)-, 2-(2-thienyl)-, 2-(4-biphenylyl)-, 2-(9-phenanthryl) and 2-(1-naphthyl)-. All show a strong absorption peak at about 6.20μ which may be attributed to C=N bonding, and none show absorption in the 3.00μ region where the NH group is known to absorb.[17] The infrared spectra, therefore, confirm the Δ^1-pyrroline (I) structure for these substances.

Two different methods of preparation, as illustrated by schemes C and D for 2-(*m*-methoxyphenyl)pyrroline,[5] gave rise to the same pyrroline. The samples had identical boiling points and refractive indices. The picrates had the same melting points, and there was no depression upon admixture. Sizable portions of the two picrates were combined and recrystallized with no change in melting point. Further, the two pyrrolines gave identical infrared and ultraviolet absorption spectra. Both gave infrared peaks at 6.26 μ, while neither absorbed in the 3.00 region in confirmation of the absence of the NH group. Thus, the Δ^1-pyrroline structure is indicated.

Although the active hydrogen determinations of Maginnity and Cloke imply that 2-benzylpyrroline exists solely in the Δ^1-pyrroline form,[16] the infrared spectrum of this substance suggests a tautomeric equilibrium, with the Δ^1-pyrroline form predominating. If 2-benzylpyrroline actually exists as a tautomeric mixture, then three structures must be considered. In addition to the normal Δ^1-pyrroline (I), there is the Δ^2-pyrroline formulation (II), and the structure with an exocyclic double bond. It can be seen that the double bonds of I and II are not in positions of conjugation with the phenyl group. If 2-benzylpyrroline actually exists as a tautomeric equilibrium between I and a structure possessing the vinylamine group, then the exocyclic structure would appear to be a more logical choice than II since the former would be favored by the conjugation of the phenyl group with the double bond.

Samples of 2-benzylpyrroline from several different runs were subjected to infrared analysis. Strong absorption was observed at about 6.10μ, which represents the absorption of the C=N group. It will be noticed that the C=N absorption of this compound is at a slightly shorter wavelength than the C=N absorption of the compounds already discussed. This shift in wavelength presumably occurs because the C=N group of 2-benzyl-Δ^1-pyrroline (I) is not in conjugation with the phenyl group (or other aryl group), as is the case with other 2-substituted pyrrolines. The absorption peak of a double bond such as is under consideration here is displaced to a slightly longer wave length when in a position of conjugation as compared to a position of nonconjugation.[17] Also, ultraviolet absorption spectra of these substances confirmed the conclusion that the double bond of 2-benzylpyrroline is not conjugated with the phenyl group, while the double

(6) H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 319.

(7) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

(8) A. Sonn, *Ber.*, **68**, 148 (1935); **72**, 2150 (1939).

(9) S. Gabriel, *Ber.*, **42**, 1238 (1909); R. Hielscher, *Ber.*, **31**, 277 (1898); J. Dhont and J. P. Wibant, *Rec. trav. chim.*, **63**, 81 (1944); H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

(10) E. B. Knott, *J. Chem. Soc.*, 186 (1948); J. B. Cloke, *J. Am. Chem. Soc.*, **51**, 1174 (1929); P. Lipp and H. Seeles, *Ber.* **62**, 2456 (1929); L. C. Craig, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, **53**, 1931; D. F. Starr, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932).

(11) J. B. Cloke and T. S. Leary, *J. Am. Chem. Soc.*, **67**, 1249 (1945); J. B. Cloke *et al.*, *J. Am. Chem. Soc.*, **67**, 1587 (1945); 2155 (1945).

(12) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945); A. Seher, *Arch. Pharm.*, **284**, 371 (1951); S. Kanao and K. Shinozuka, *J. Pharm. Soc., Japan*, **50**, 148 (1930) [*Chem. Zentr.*, **102**, I, 1743 (1931)]; Krabbe and Schmidt, *Ber.*, **72**, 381 (1939).

(13) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(14) B. Witkop, *J. Am. Chem. Soc.*, **76**, 5597 (1954).

(15) L. C. Craig, *J. Am. Chem. Soc.*, **55**, 295, 2543 (1933); R. Lukeš, *Collection Czechoslov. Chem. Comm.*, **2**, 531 (1930) [*Chem. Abstr.*, **25**, 102 (1931)].

(16) P. M. Maginnity and J. B. Cloke, *J. Am. Chem. Soc.*, **73**, 49 (1951).

(17) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Compounds*, D. Van Nostrand Co., Inc., New York, N. Y., 1949; and F. A. Miller in H. Gilman, *Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1953, Vol. 3, pp. 122–157

bond of the 2-phenyl analogs, for example, is in a position of conjugation.

Close inspection of the infrared spectrum of 2-benzylpyrroline shows weak absorption in the 3.05–3.10μ region which is presumably due to the NH group. However, active hydrogen determinations were negative in confirmation of Maginnity's observation.[16] Since the only groups with which we are concerned here are known to absorb in the 3.00μ region are NH and OH, absorption in this region and the absence of active hydrogen must be considered to be anomalous.

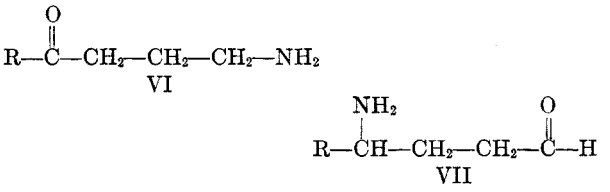
In order to determine if this anomalous result also obtains in the naphthalene series, 2-(2-naphthylmethyl)pyrroline was prepared and its infrared spectrum determined. Unlike that of 2-benzylpyrroline, the spectrum of this compound is entirely in agreement with a Δ^1-pyrroline structure, since no adsorption was observed in the 3.00μ region.

Other anomalous results, however, have been observed with 2-methylpyrroline by Evans, who found weak absorption at 3.02μ.[18] This observation was confirmed; our 2-methylpyrroline shows absorption at 3.07μ which is apparently due to the presence of an NH group. The C=N group absorbs at 6.11μ. Since there is no other double bond in the compound, the 2-pyrroline structure (II) cannot be rationalized on the basis of conjugation. Again Maginnity found no active hydrogen in 2-methylpyrroline,[16] so the absorption at 3.07μ must also be considered anomalous in agreement with the results of Evans.

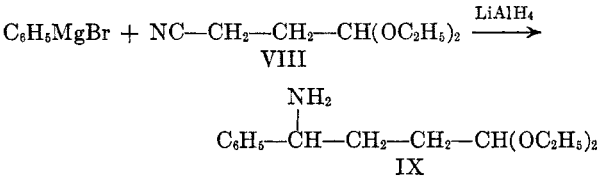
For purposes of comparison, the infrared spectra of the saturated 2-phenylpyrrolidine and 1-methyl-2-phenylpyrrolidine[5] were determined. The former substance has a strong absorption peak at 3.02μ which is attributed to the NH group, and double bond absorption in the 6.20 region is absent. The latter compound, as expected, shows no absorption in either the 3.00 or 6.20μ region.

The evidence at hand in regard to the structure of pyrrolines obtained by Procedures C, D, and E,[5] as well as from other ring closure reactions,[8,9] indicates that these compounds exist chiefly, if not exclusively, as Δ^1-pyrrolines (I). Thus, it has not yet been demonstrated that Δ^2-pyrrolines (II) can exist as such.

Although five isomeric structures (I–V) may be written for any given substituent (*e.g.*, phenyl), no more than two isomers (I and III) are known actually to exist. Examples of the fifth isomer (V) are unknown at the present time, although it should be capable of separate existence from I by analogy with such isomeric pairs as *N*-methylenebenzylamine and *N*-benzylidinemethylamine.[19] Further, if Δ^1-pyrrolines are considered to arise from an intramolecular condensation involving an amino group and a carbonyl group, it can be seen that I and V differ in the relative position of the substituent to the two functional groups in the intermediate amino carbonyl compound. The ring closure of a γ-aminopropyl ketone (VI) gives rise to pyrrolines of type I. Cyclization of γ-amino-γ-substituted-butyraldehydes (VII), on the other hand, would be expected to lead to the isomeric Δ^1-pyrrolines (V).



In attempting the synthesis of a type V compound through an aldehyde (VII, R = phenyl), phenylmagnesium bromide was allowed to react with diethyl β-cyanopropionacetal (VIII), and the Grignard complex was subjected to the reducing action of lithium aluminum hydride. The compound isolated from the reaction proved to be the desired diethyl γ-amino-γ-phenylbutyracetal (IX). Under



the influence of mineral acid, it was hoped IX could be converted to the corresponding amino aldehyde which might then undergo intramolecular condensation to the desired 5-phenyl-Δ^1-pyrroline (V, R = phenyl). However, V was not obtained since the aldehyde seemed to have a greater tendency to polymerize than to undergo the desired reaction. A similar attempt using model compound X (IX, where phenyl is replaced with hydrogen) also failed.

EXPERIMENTAL

Diethyl γ-aminobutyracetal X. A mixture of 16 g. (0.1 mole) of diethyl β-cyanopropionacetal,[20] 100 ml. of ethanol saturated with ammonia, and about 5 g. of Raney nickel catalyst (Davison and Co., water slurry) was shaken at room temperature at an initial hydrogen pressure of 60 p.s.i. The theoretical amount of hydrogen was absorbed in 10 hr. After removal of the catalyst and solvent, the residue was subjected to vacuum distillation to obtain 15 g. (91%) of colorless oil, b.p. 79–81° (10 mm.), n_D^{25} 1.4290. The recorded boiling points are 84° (11 mm.) and 93° (15 mm.).[20]

Diethyl γ-amino-γ-phenylbutyracetal (IX). According to the procedure of Pohland and Sullivan,[21] 110 ml. (0.33 mole) of a 3*N* ether solution of phenylmagnesium bromide (Arapahoe Special Products) was allowed to react with 47 g. (0.3

(18) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).
(19) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1199 (1929).
(20) R. H. F. Manske, *Can. J. Research*, **5**, 598 (1931).
(21) A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **75**, 5898 (1953).

mole) of diethyl β-cyanopropionacetal.[20] The Grignard adduct was reduced with 14 g. (0.37 mole) of lithium aluminum hydride. After hydrolysis of the reaction mixture with 400 ml. of 10% ammonium chloride solution the reaction was worked up as described[21] to give a colorless oil, b.p. 90–107° (0.3 mm.). The material was redistilled and a middle cut, 37 g. (53%), was collected, b.p. 103–107° (0.3 mm.), n_D^{25} 1.5026.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.47; H, 9.45.

Acknowledgment: Appreciation is expressed to Parke, Davis & Co. for fellowship funds, and to Mr. R. Bruce Scott and Dr. George Moersch of the Research Division of that Company and to Dr. Calvin Stevens of Wayne State University for the determination and interpretation of the early infrared spectra.

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[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF KANSAS]

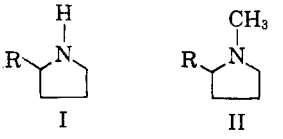
Synthesis of Nicotine Analogs[1]

J. H. BURCKHALTER AND J. H. SHORT[2]

Received January 24, 1958

A number of 2-substituted pyrrolidines and *N*-methylpyrrolidines have been synthesized as possible antihypertensive agents.

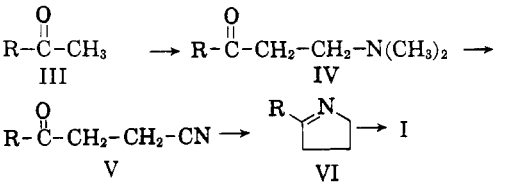
One of the many physiological effects of nicotine, 1-methyl-2-(3-pyridyl)pyrrolidine (II, R = 3-pyridyl), when administered in large doses, is a marked lowering of the blood pressure.[3] The toxicity of nicotine precludes its clinical use; however, it might be



I II

possible, by incorporating groups other than 3-pyridyl in the pyrrolidine nucleus, to obtain substances useful for the treatment of hypertension. With this objective in mind, 2-(2-naphthyl) pyrrolidine (I, R = 2-naphthyl) and its *N*-methyl derivative (II, R = 2-naphthyl) have already been prepared.[4] These compounds were found to reverse epinephrine-induced hypertension in the dog, with the latter the more effective of the two.[5] In view of these results, it seemed worthwhile to synthesize a number of compounds represented by I and II.

The preparation of the pyrrolines and pyrrolidines was undertaken by three different synthetic procedures. The first method, described as Procedures C and F in the Experimental section, has been used by Rupe and Gisiger[6] and by Knott.[7] It depends upon the reductive cyclization of a β-aroylpropionitrile (V) to a pyrroline (VI) or pyrrolidine (I).



III IV V VI

The starting material for this series of reactions was a substituted acetophenone (III) or a similar aryl methyl ketone. The ketone was allowed to react with paraformaldehyde and dimethylamine hydrochloride in the manner of the Mannich reaction to give an aryl β-dimethylaminoethyl ketone (IV). The Mannich base was then used to alkylate potassium cyanide to give a β-aroylpropionitrile (V).[8] The nitrile, in turn, was subjected to low pressure hydrogenation in the presence of Raney nickel catalyst. If the reaction mixture was shaken until no more hydrogen was absorbed, the uptake corresponded to three moles and the product isolated was a 2-arylpyrrolidine (I). When the hydrogenation was interrupted after two moles of hydrogen had been absorbed, the substance obtained was a 2-aryl-Δ^1-pyrroline (VI).[9] Since the first two moles of hydrogen were absorbed much faster than the third mole, the isolation of the pyrrolines offered no difficulty.

This series of reactions was successful for the synthesis of I, where R = phenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, and 1-naphthyl. Also, a small amount of 2-(4-biphenylyl)pyrrolidine (I, R = 4-biphenylyl) was isolated as the hydrochloride by this procedure. Because of the failure of the intermediate keto nitrile to absorb hydrogen, 2-(2-

(1) Based upon a portion of the Ph.D. Thesis of J. H. Short, University of Kansas, 1954.

(2) Parke, Davis & Co. Fellow. Present address, Abbott Laboratories, North Chicago, Ill.

(3) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 622.

(4) J. H. Burckhalter and R. Meyer, unpublished results.

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(6) H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

(7) E. B. Knott, *J. Chem. Soc.*, 186 (1948).

(8) E. B. Knott, *J. Chem. Soc.*, 1190 (1947).

(9) For structure studies, see J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1278 (1958).