Thermal Rearrangement of Cyclopropyl Imines. III. Total Synthesis of Pyridine Alkaloids[1,2]

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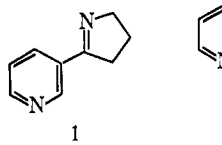
Abstract: The acid-catalyzed thermal rearrangement of cyclopropyl imines has been investigated and exploited as a general method of synthesis of Δ^1- or Δ^2-pyrrolines, which are in turn useful intermediates in alkaloid synthesis. The employment of this procedure for the synthesis of the pyridine alkaloids myosmine and apoferrorosamine is portrayed.

A large number of otherwise structurally diverse alkaloid skeletons incorporate various perturbations of the pyrrolidine ring system. Thus, the pyridine alkaloids myosmine (**1**) and apoferrorosamine (**2**) are obviously Δ^1-pyrrolines, whereas various *Senecio* bases such as laburnine (**3**) may be considered simply as trisubstituted pyrrolidines. According to this classification, certain *Aspidosperma* alkaloids such as aspidospermine (**4**) and various *Amaryllidaceae* bases structurally related to the *Aizoaceae* alkaloid mesembrine (**5a**) fall into a tetrasubstituted category.



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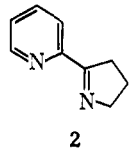

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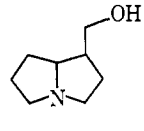

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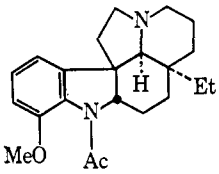

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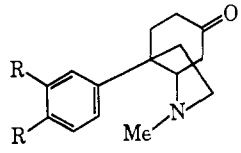
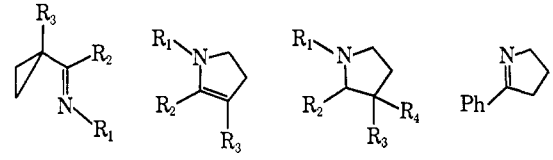


5a, R = OCH_3
b, R = H

We were intrigued by the possibility of employing Δ^2-pyrrolines **7** in a dual role as obvious precursors of various trisubstituted natural bases and as a general device for the elaboration of their tetrasubstituted counterparts **8**. In this latter plan we envisaged taking advantage of the nucleophilic properties associated with the β-carbon of the pyrroline to introduce further required structural variations. Among various methods of synthesis of Δ^2-pyrrolines which were considered, the thermally induced rearrangement of cyclopropyl imines **6** seemed admirably suited for this assignment, and we were pleased to discover that an example of the proposed rearrangement **6a** to **7a** had been reported by Cloke in 1929.[5] The novelty of this method of approach and its potentially broad base of utility prompted us to examine the crucial rearrangement step in some detail.



6 7 8 9

a, $R_1 = R_3 = H$; $R_2 = Ph$
b, $R_1 = R_3 = H$; $R_2 = 3$-pyridyl
c, $R_1 = R_3 = H$; $R_2 = 2$-pyridyl
d, $R_1 = H$; $R_2 = CH_3$; $R_3 = Ph$
e, $R_1 = CH_3$; $R_2 = H$; $R_3 = Ph$
f, $R_1 = CH_2Ph$; $R_2 = H$; $R_3 = Ph$
g, $R_1 = CH_3$; $R_2 = H$; $R_3 = 3,4\text{-}(CH_3)_2C_6H_3$

The original Coke procedure[5] involved reacting cyclopropanecarbonitrile with phenylmagnesium bromide and subsequent decomposition of the complex with water. Purification of the resulting ketimine **6a** was achieved by conversion to the hydrochloride from which the free base was regenerated by treating a hot chloroform solution of the salt with excess ammonia. Further purification of the imine was attempted by distillation. However, only pyrroline **7a** was obtained, in 90% yield. The product of this rearrangement was later[6] reformulated as the Δ^1-pyrroline **9** rather than the Δ^2 isomer **7a**, a fact in consonance with a growing body of information concerning these potentially tautomeric substances.[7] In order to gain experience with the proposed rearrangement we decided to repeat the Cloke experiment. The details of this process seemed unduly elaborate and we decided upon a rather more efficient method.[8] By employing phenyllithium and decomposing the intermediate lithium salt with $Na_2SO_4 \cdot 10H_2O$ we were able to isolate in good yield a water-white liquid which distilled at 56–58° (0.3 mm) and slowly decomposed upon standing. The appearance of a four-proton doublet at δ 0.94 in the pmr spectrum of this oil immediately informed us that in contrast to the Cloke experience we had succeeded in isolating ketimine **6a**. The remaining features of the pmr spectrum were entirely consistent with this formulation[8] as was the infrared spectrum wherein a strong imine stretching absorption at 1611 cm^{-1} and a 3265-cm^{-1} N–H band were prominent. Due to the fact that we

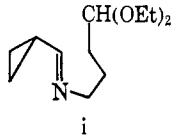
(1) A preliminary account of a portion of this work has appeared: R. V. Stevens and M. C. Ellis, *Tetrahedron Letters*, 5185 (1967).
(2) The material in this paper was first presented by R. V. S. at the 23rd Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 8, 1967.
(3) National Defense Education Act Research Fellow, 1966–1969.
(4) U. S. Public Health Service Predoctoral Research Fellow, 1967 to present.
(5) J. B. Cloke, *J. Am. Chem. Soc.*, 51, 1174 (1929); *cf.* also J. B. Cloke, L. H. Baer, J. M. Robbins, and G. E. Smith, *ibid.*, 67, 2155 (1945), and references cited therein.
(6) P. M. Maginnity and J. B. Cloke, *ibid.*, 73, 49 (1951).
(7) K. Blàha and O. Cervinka, *Advan. Heterocyclic Chem.*, 6, 149 (1966).
(8) *Cf.* Experimental Section.

had no information concerning the temperature at which Cloke attempted the distillation of this substance and in view of the rather low temperature and pressure we employed, a thermal study of the rearrangement step was initiated. This investigation was greatly facilitated when we discovered that pyrroline **9** exhibited a unique infrared absorption at 1340 cm^{-1}. Somewhat to our surprise we discovered that heating sealed samples of the ketimine at various temperatures and time periods did not readily induce rearrangement. Indeed, even after 2 hr at 200° only a weak 1340-cm^{-1} absorption was detected. Higher temperatures only increased resinification. *We have been unable in this and other work in our laboratory to induce smooth, purely thermal rearrangements of cyclopropyl imines.*[9,10]

Our inability to effect a purely thermal rearrangement of this ketimine was not a serious cause for concern in our synthetic efforts since it had previously been observed[5] that substitution of the corresponding hydrochloride in the thermal process provides a satisfactory solution. We find this result is completely reproducible. The additional observation that smooth rearrangement could be induced by employing catalytic amounts of the hydrochloride greatly facilitated our subsequent work.[12] Armed with this information we began a systematic program to exploit the rearrangement as a general device for alkaloid synthesis as outlined in the introduction to this paper. Quite naturally our initial goal was the simple pyridine alkaloids myosmine (**1**) and apoferrorosamine (**2**).

3-Lithiopyridine was prepared by metal–halogen exchange according to the method of Gilman[13] and treated with cyclopropanecarbonitrile at −78°. The intermediate lithio salt was decomposed with sodium sulfate decahydrate from which a 36% yield of pure but rather unstable ketimine **6b** was secured. An exceedingly hydroscopic hydrochloride of this base was precipitated from an ethereal solution. Admixture of a catalytic amount of this salt with the corresponding imine gave in 68% yield nearly pure myosmine (**1**) when maintained at 110° for 15 min. The natural product was distilled directly from the reaction flask, bp 77° (0.15 mm), and solidified upon standing. An analytical sample of **1** was secured by preparative layer chromatography and subsequent high vacuum sublimation. Myosmine obtained by this procedure melted at 45–46° (lit.[14] mp 44–45°) and displayed ir, uv, and pmr spectra which were identical with published[15] data.

(9) Cyclopropyl imine i, an obvious precursor of laburnine (**3**), was recovered unchanged at temperatures as high as 540° in the gas phase (W. L. Edmonson, 1967, unpublished data).



i

(10) The implication[11] that the thermally induced rearrangement of cyclopropyl imines is analogous to the well-documented vinylcyclopropane rearrangement appears on the basis of our experience to be subject to considerable doubt.

(11) R. Breslow in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, Chapter 4, *cf.* p 239.

(12) The most satisfactory explanation of the difference in behavior between our ketimine and that presumably obtained by Cloke rests upon the assumption that catalytic amounts of acid were carried along as a consequence of his unique method of purification.

(13) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).

(14) E. Späth and L. Mamoli, *Chem. Ber.*, **69**, 757 (1936).

The synthesis of unstable ketimine **6c** was accomplished in 35% yield in an analogous manner. Conversion of this base to its hydrochloride and subsequent admixture in a catalytic amount to freshly prepared **6c** prior to a 20-min heat treatment at 110° gave, upon direct distillation, nearly pure apoferrorosamine (**2**) in 75% yield. Preparative layer chromatography of the solidified distillate and high vacuum sublimation was again employed to obtain an analytical sample (mp 55–55.5°, lit.[16] mp 46–49°). The spectral features of the synthetic material were identical with those recorded[16] for the natural product.

In order to expand our base of support for further synthetic designs additional examples of the rearrangement were investigated. As will soon become clear the substrates and products of this study were also selected for potential deployment in the synthesis of *Amaryllidaceae* or *Aizoaceae* alkaloids. Thus, 1-phenylcyclopropanecarbonitrile[17] was exposed to an ethereal solution of methyllithium, and the resultant lithio salt decomposed *via* the sodium sulfate decahydrate procedure. Pure but somewhat unstable[18] ketimine **6d** was obtained in 73% yield. A purely thermal study of the rearrangement of this substrate was initiated but soon abandoned in view of previous results[9] coupled with the observation that only starting material was recovered from a 450° gas-phase thermolysis. In contrast, the thermal reorganization of ketimine **6d** to the pyrroline counterpart **10** proceeded with ease by prior conversion of the base to the hydrochloride salt.[19] The formulation of this pyrroline as the Δ^1 isomer is in agreement with the previously mentioned studies[7] and is corroborated by the infrared and pmr spectra in conjunction with a lack of significant absorption in the 305–315-mμ region characteristic of other 3-aryl-Δ^2-pyrrolines of this sort (*cf.* spectra table). Pyrroline **10** was conveniently converted to the very labile enamine **12** by quaternization with methyl iodide and subsequent basification. Alternatively, and perhaps more interestingly, the latter base could be secured by transformation of ketimine **6d** to the quaternary immonium salt **11**, which is also a hydroiodide and as such should be capable of catalyzing its own rearrangement to the acid salt of **12**. Indeed, when **6d** was refluxed in methyl iodide solvent followed by distillation of the excess methyl iodide, a brief 155° treatment, and subsequent basification, the Δ^2-pyrroline **12** was obtained in 54% yield.

Our interest in securing the cyclic enamine **12** was based upon its potential employment in the total synthesis of the mesembrine model **5b**. We had hoped that

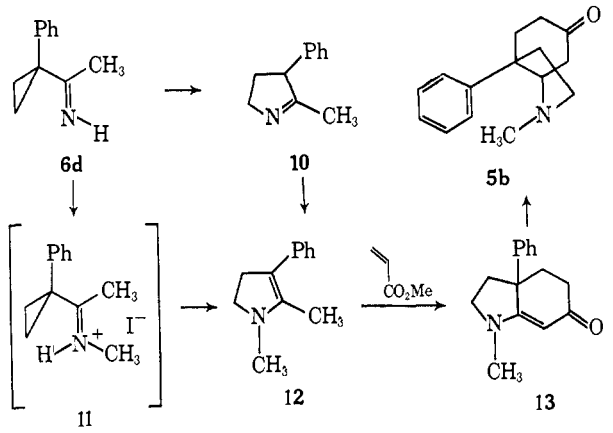
(15) Ir, C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954); uv, M. L. Swain, A. Eisner, C. F. Woodward, and B. A. Brice, *J. Am. Chem. Soc.*, **71**, 1341 (1949); pmr, J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 281.

(16) M. Pouteau-Thouvenot, A. Gaudemer, and M. Barbier, *Bull. Soc. Chim. Biol.*, **47**, 2085 (1965).

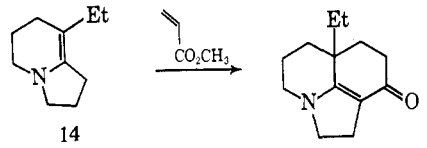
(17) C. Dupin and R. Fraisse-Jullien, *Bull. Soc. Chim. France*, 1993 (1964).

(18) The "instability" of ketimine **6d** and the others referred to throughout this study is not intended as an expression of their ability to rearrange, but rather to their behavior to external reagents, particularly to moisture. This "instability" is not unexpectedly increased by the preparation of acid salts and makes their elemental analysis in most cases practically impossible.

(19) Our initial studies in this series were performed on bases which had been entirely converted to hydrohalogen salts. We later discovered that only catalytic amounts of salt were required and generally provided better yields of pure rearranged materials.



this base could be invited to participate in a combination alkylation, intramolecular acylation with methyl acrylate. The product, **13**, of this transformation remains only a stereoselective reduction step way from the model **5b**. Considerable analogy for this proposal can be found in the recent literature[7,20,21] not the least interesting of which is the fate of bicyclic enamine **14** when exposed to methyl acrylate.[21] We were forced



to drop this method of approach when it was discovered that under a variety of conditions pyrroline **12** yielded only a complex mixture of products. The major components of this mixture were isolated by preparative layer chromatography, but inspection of their infrared spectra did not reveal the rather characteristic absorptions of the β-acyl enamine chromophore.[22] Although it is difficult to assign any one factor as being responsible for the failure of this experiment, we are inclined to believe that the extreme lability of this particular Δ^2-pyrroline is a major factor.[23] (See Table I for spectral data.)

Table I. Infrared and Ultraviolet Spectra of 3-Arylpyrrolines

Compd	Ir (solvent), cm^{-1}	$Uv_{max}^{95\%\ EtOH}$, mμ (ϵ)
7e[23]	1613 ($CHCl_3$)	306.5 (11,390)
7f	1613 ($CHCl_3$)	312 (18,280)
7g[23]	1619 ($CHCl_3$)	305 (14,270)
12	1623 (neat)	...
10	1648 (neat)	292 (1519)

In connection with another study, we had on hand a supply of cyclopropyl imine **6e** which was prepared by simply stirring a solution of 1-phenylcyclopropanecarboxaldehyde and methylamine in the presence of magnesium sulfate. This material was converted to the benzyl imine **6f** by refluxing with benzylamine and a trace of *p*-toluenesulfonic acid in benzene. Our subsequent work was greatly facilitated by the observation that only catalytic amounts of the hydrochloride salt were required to induce rearrangement of **6f** to the corresponding pyrroline **7f**[19] in 80% yield.

Although the mechanistic interpretation of the acid catalysis remains obscure, we are convinced that the employment of this method of approach to the synthesis of Δ^1- and Δ^2-pyrrolines is a useful one. Further examples of this rearrangement and exploitation of the products thereof for the total synthesis of mesembrine (**5a**) are described in the following article.

Experimental Section[24]

Cyclopropyl Phenyl Ketimine (6a) and Hydrochloride. A dry, 250-ml flask equipped with N_2 inlet, condenser, additional funnel, and magnetic stirring device was charged with 90 ml of a ~1 *N* ethereal solution of phenyllithium. Cyclopropanecarbonitrile (5.0 g, 75 mmol) in 5 ml of ether was added dropwise over a 5-min period, and when the exothermic reaction had ceased the brown solution was allowed to stir an additional 10 min, then 5.5 g (171 mmol of H_2O) of $Na_2SO_4 \cdot 10H_2O$ was added. After about 5 min the mixture started to reflux, and this was allowed to proceed until the solution turned yellow at which time it was filtered and the filter cake washed well with hexane. The combined filtrates were concentrated, and the resultant yellow oil was distilled yielding 7.55 g (70%) of **6a**: bp 56–58° (0.3 mm); ir (neat) 3265 and 1611 cm^{-1}; pmr δ 0.94 (d, 4 H, J = 7 cps), 2.05 (pentuplet, 1 H, J = 7 cps), and 7.77 ppm (m, 5 H).

Ketimine **6a** (1 g) was placed in a centrifuge tube and dissolved in 2 ml of ether and treated with dry HCl gas. The hydrochloride precipitated as a fine white hygroscopic powder and was dried *in vacuo*. The salt melted at 101–103° [lit.[5] mp 104–105°] but soon resolidified and remelted at 190–210°; ir (KBr) 1655 cm^{-1}.

2-Phenyl-1-pyrroline (9) and Hydrochloride.[5] Ketimine hydrochloride **6a** was placed in a small flask equipped with a N_2 flow system and immersed in an oil bath maintained at 108°. The salt rapidly melted and then resolidified. After cooling, the residue was leached with three portions of 0.1 *N* HCl and the acidic solution extracted with ether. Neutralization of the aqueous layer and ether extraction gave a yellow oil which was distilled in a bulb-to-bulb apparatus, bp 110–120° (bath temperature, 2.0 mm); ir (neat) 1613 cm^{-1}; pmr δ 2.01 (pentuplet, 2 H), 2.99 (t, 2 H), 4.19 (t, 2 H), 7.67 (m, 3 H), and 8.14 ppm (m, 2 H).

A hydrochloride was precipitated from ether and melted at 214–216°. A pure sample was secured by vacuum sublimation, mp 214–215° (lit.[25] mp 210–212.5°); ir (KBr) 1640 cm^{-1}.

Pyrolysis Study of Cyclopropyl Phenyl Ketimine (6a). 2-Phenyl-Δ^1-pyrroline (**9**) exhibited a unique infrared absorption at 1340 cm^{-1} not present in the corresponding ketimine **6a** and was therefore employed as a diagnostic tool. In each test two sealed samples were studied of which one contained a catalytic amount of the ketimine hydrochloride. Among various temperatures selected the 200° run was representative. At this temperature only the sample containing hydrochloride had rearranged after 10 min, and only after 2 hr could any 1340-cm^{-1} absorption be detected in the uncatalyzed sample and by then resinification was extensive.

Cyclopropyl 3-Pyridyl Ketimine (6b). In a 1 l., round-bottomed flask equipped with mechanical stirrer, nitrogen inlet, and addition funnel was placed 80 ml of 1.6 *N* *n*-butyllithium along with 300 ml of dry ether and the flask immersed in a Dry Ice–acetone bath at −72°. 3-Bromopyridine (20 g, 0.126 mol) in 100 ml of ether was added dropwise over a 20-min period resulting in the formation of a yellow precipitate. After the pyridine addition was complete the solution was stirred an additional minute then 7.0 g (0.104 mol) of cyclopropanecarbonitrile in 100 ml of ether was added as rapidly

(20) F. Bohlmann and O. Schmidt, *Chem. Ber.*, 97, 1354 (1964).
(21) M. E. Kuehne and C. Bayha, *Tetrahedron Letters*, 1311 (1966).
(22) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, 33, 747 (1968).
(23) The application of this general method of approach to the successful total synthesis of racemic mesembrine (**5a**) is outlined in the following paper.
(24) Proton magnetic resonance spectra were recorded in dilute deuteriochloroform solutions containing tetramethylsilane as internal standard except where indicated on a Varian A-56/60A spectrometer operating at 60 Mc. Infrared spectra were obtained on a Beckman IR-8 spectrophotometer; ultraviolet spectra are of 95% ethanol solutions and were taken on a Cary Model 14 spectrophotometer. Preparative layer operations employed Brinkmann precoated 20 × 20 cm plates of silica gel F-254, 2 mm thick. Melting and boiling points are uncorrected. Microanalyses were secured from the Elek Microanalytical Laboratory, Torrance, Calif.
(25) M. C. Kloetzel, J. L. Pinkus, and R. M. Washburn, *J. Am. Chem. Soc.*, 79, 4222 (1957).

as possible, and the solution turned golden brown. The cooling bath was removed and the mixture stirred an additional hour. $Na_2SO_4 \cdot 10H_2O$ (12 g) was then added and stirring continued for 0.5 hr during which a bright yellow color formed. The solution was then filtered and dried over Na_2SO_4 and the solvent removed *in vacuo* to give a red oil which was triturated with benzene further precipitating inorganic salts. After removal of the solvent the residue was distilled to give 5.5 g (36%) of the ketimine:[18] bp 80–86° (0.3 mm); ir (CCl_4) 1615 and 3275 cm^{-1}; pmr δ 1.78 and 2.02 (m, 5 H), 7.34 (m, 1 H), 8.10 (m, 1 H), 8.61 (m, 1 H), and 9.03 ppm (m, 1 H). Both the hydrochloride and hydrobromide of this ketimine were extremely hygroscopic.[18]

Myosmine [2-(3-Pyridyl)-1-pyrroline] (1). A 5-ml flask equipped with a still head for vacuum distillation was charged with 3.28 g of ketimine **6b** and a catalytic amount of hydrochloride as a freshly prepared ether suspension. The ether was removed under reduced pressure and the mixture maintained at 110° for 15 min under a pressure of 15–20 mm. The mixture darkened during the course of the reaction and was finally distilled to give 2.24 g (68%) of myosmine as a slightly yellow oil which solidified upon standing: bp 88.5–90° (0.1 mm). The infrared spectrum of the distillate revealed trace impurities of ketone. Preparative layer chromatography using ethyl acetate as developer gave pure myosmine from which an analytical sample was secured by vacuum sublimation, 40° (0.1 mm): mp 45–46° (lit.[14] mp 44–45°). The ir, uv, and pmr spectra were identical with those published for the natural base.[15] Although apparently not previously reported, we find that very pure myosmine is quite hygroscopic.

Cyclopropyl 2-Pyridyl Ketimine (6c). The procedure employed was essentially that employed for isomer **6b** using 20 g (0.126 mol) of 2-bromopyridine, 9 g (0.128 mol) of cyclopropanecarbonitrile, 80 ml of 1.6 *N n*-butyllithium (0.128 mol), and 20 g of $Na_2SO_4 \cdot 10H_2O$. The ketimine,[18] 6.28 g (34%), was secured by distillation: bp 69–70° (0.3 mm); ir (CCl_4) 3240 and 1620 cm^{-1}; pmr δ 1.14 (m, 4 H), 2.33 (m, 1 H), 7.28 (m, 1 H), 7.80 (m, 1 H), and 8.61 ppm (m, 1 H). The hydrochloride of this base was extremely hygroscopic.

Apoferrorosamine [2-(2-Pyridyl)-1-pyrroline] (2). The natural product was obtained in 75% yield from ketimine **6c** in a manner entirely analogous to that described above for myosmine: bp 65° (0.075 mm). Analytically pure base was prepared by sublimation, 45° (0.55 mm) and melted at 55–55.5° (lit.[16] mp 46–49°). The ir, uv, and pmr spectra agreed with those reported.[16]

1-Phenylcyclopropyl Methyl Ketimine (6d). 1-Phenylcyclopropanecarbonitrile,[17] 8.31 g (0.058 mol), was added dropwise under N_2 to 40 ml (0.064 mol) of 1.6 *M* methyllithium in ether. The reaction was mildly exothermic. The resultant yellow-orange solution was stirred at room temperature for 6 hr and then 8.5 g of $Na_2SO_4 \cdot 10H_2O$ was added. The reaction mixture refluxed slightly and inorganic salts were precipitated. After an additional 5 min of stirring the salts were filtered off and the filtrate was freed of solvent and distilled giving 6.78 g (73%) of ketimine **6d**: bp 58–60° (0.24 mm); ir (neat) 1629 and 3242 cm^{-1}; pmr δ 7.37 (broad singlet, 6 H), 1.83 (s, 3 H), and 1.18 ppm (m, 4 H). The instability of this base and various salt derivatives precluded its elemental analysis.

2-Methyl-3-phenyl-1-pyrroline (10). A saturated ethereal solution (30 ml) of hydrogen chloride was added dropwise under N_2 to a stirred solution of 4.15 g of **6d** in 10 ml of dry ether. The white hydrochloride precipitated immediately, and the suspension was heated to 60° to expel solvent. Without isolation the resultant salt was rapidly heated to 140° and stirred for 10 min. The yellow melt was then leached with dilute HCl and nonbasic materials extracted with ether. Basification of the acidic solution and ether extraction gave 2.32 g (56%) of pure pyrroline **10**: bp 58–60° (0.25 mm); ir (neat) 1648 cm^{-1}; pmr δ 7.34 (m, 5 H), 3.96 (m, 3 H), 2.20 (m, 2 H), and 1.88 ppm (s, 3 H); uv_{max} 292 mμ (ϵ 1519). Five recrystallizations (EtOH) of the picrate salt of **10** afforded an analytically pure sample, mp 141–142°.

Anal. Calcd for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.37; H, 4.25; N, 14.21.

1,2-Dimethyl-3-phenyl-2-pyrroline (12). Method A. To a flask containing 2.32 g (0.015 mol) of pyrroline **10** was added under N_2 and with stirring 25 ml of methyl iodide. An orange oil soon appeared and the mixture refluxed for 3.5 hr. The excess methyl iodide was removed *in vacuo* and the orange residue dissolved in 50 ml of hot water and basisified with 10% NaOH. Ether extraction, removal of solvent, and distillation gave 1.52 g (60%) of pure **12**: bp 83–85° (0.32 mm); ir (neat) 1623 cm^{-1}; pmr (CH_3CN) δ 7.15 (m, 5 H), pmr (PhH) δ 2.72 (m, 4 H), 1.71 (t, 3H, J = 1.6 cps), and 2.31 ppm (s, 3 H).

The pyrroline was extremely unstable and decomposed rapidly in chlorinated solvents. An analytically pure picrate of mp 135.5–137° was secured after three recrystallizations (EtOH).

Anal. Calcd for $C_{18}H_{18}N_4O_7$: C, 53.73; H, 4.51. Found: C, 53.70; H, 4.51.

Method B. Ketimine **6d** (2.33 g, 0.015 mol) was refluxed in 25 ml of methyl iodide under N_2. An orange oil began to separate after 0.5 hr. After 3 hr the methyl iodide was removed by distillation and the oily salt rapidly heated to 155° for 5 min to insure rearrangement. The resultant orange oil was dissolved in dilute acid and nonbasic materials extracted with ether. Basification of the acidic solution and ether extraction gave the crude product which was distilled to give 1.37 g (54%) of material identical with that prepared by method A.

N-Methyl-1-phenylcyclopropanecarboxaldimine (6e). A mixture of 0.321 g (2.19 mol) of 1-phenylcyclopropanecarboxaldehyde,[26] 6.8 ml of 1.55 *M* methylamine in benzene (4.38 mmol), 10 ml of dry benzene, and 1 g of anhydrous magnesium sulfate was stirred for 5 hr at room temperature and filtered. The solvent was removed at atmospheric pressure to give 0.336 g (96%) of the aldimine: bp 50–51° (0.13 mm); ir (neat) 1661 cm^{-1}; pmr δ 7.57 (quartet, 1 H, J = 1.5 cps), 7.21 (s, 5 H), 3.17 (d, 3 H, J = 1.5 cps), and 1.19 ppm (m, 4 H). The somewhat unstable aldimine was analyzed as its picrate (EtOH) whose sublimation provided a nicely crystalline substance of mp 167.5–168.5° dec.

Anal. Calcd for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43. Found: C, 52.40; H, 4.25; N, 14.26.

N-Benzyl-1-phenylcyclopropanecarboxaldimine (6f). A mixture of 16.0 g (0.10 mol) of **6e**, 11.3 g (0.11 mol) of benzylamine, 100 ml of dry benzene, and a catalytic amount of *p*-toluenesulfonic acid was refluxed under N_2 for 17 hr. The solvent was removed *in vacuo* and the residue distilled yielding 19.1 g (81%) of **6f**: bp 118–119° (0.17 mm); ir (neat) 1657 cm^{-1}; pmr δ 7.80 (t, 1 H, J = 1.2 cps), 7.23 (s, 5 H), 7.17 (s, 5 H), 4.51 (d, 2 H, J = 1.2 cps), and 1.26 ppm (m, 4 H).

Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.94; H, 7.48; N, 5.83. A somewhat unstable picrate (ethanol) had mp 199.5–201° dec.

1-Benzyl-3-phenyl-2-pyrroline (7f). To a flask containing 1.61 g of freshly distilled **6f** was added with stirring anhydrous HBr until a faint turbidity was noted. The flask and contents were placed under reduced pressure (15 mm) and heated for 4.25 hr between 104 and 127°. The resulting clear yellow oil was vacuum distilled yielding 1.29 g (80%) of **7f**, bp 140–150° (0.1 mm), which slowly crystallized upon standing. The solid residue was washed with a cold 50% methanol–water solution, and the washed crystals were subsequently sublimed at 90° (0.3 mm) in order to obtain analytically pure pyrroline: mp 59.5–60.5°; ir ($CHCl_2$) 1613 cm^{-1}; pmr δ 7.25 (s, 5 H), 7.11 (s, 5 H), 6.47 (t, 1 H, J = 1.3 cps), 3.91 (s, 2 H), and 2.91 ppm (m, 4 H); uv_{max} 312 mμ (ϵ 18,280).

Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.42; H, 7.27; N, 5.97.

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