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.

LAWRENCE, KAN.

[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]

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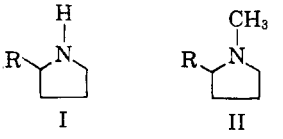
A number of 2-substituted pyrrolidines and *N*-methylpyrrolidines have been synthesized as possible antihypertensive agents.

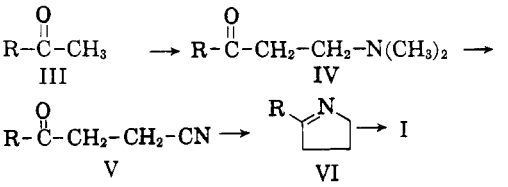
One of the many physiological effects of nicotine, 1-methyl-2-(3-pyridyl)pyrrolidine (II, R = 3-pyridyl), when administered in large doses, is a marked lowering of the blood pressure.[3] The toxicity of nicotine precludes its clinical use; however, it might be



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.

(5) Dr. Graham Chen, private communication.

(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).

TABLE I

β-ACYLPROPIONITRILES (V)

No.	Acyl Group	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Benzoyl[a]	A	43	75–76[h]					
2	*p*-Methoxybenzoyl[b]	B	81	95–96[h,i]					
3	*m*-Methoxybenzoyl[b]	B	88	52–53[j]					
4	*m*-Hydroxybenzoyl[c]	B	54	97–99[k]					
5	*p*-Phenylbenzoyl[d]	B	50	171–172[h]	$C_{16}H_{13}NO$	81.67	81.56	5.57	5.69
6	1-Naphthoyl[e]	A	45	60–61	$C_{14}H_{11}NO$	80.36	80.59	5.30	5.47
7	2-Naphthoyl[a,f]	B	51	117–118					
8	9-Phenanthroyl[g]	B	61	150–151[h]	$C_{18}H_{13}NO$	83.38	83.15	5.05	5.09

[a] Preparation described by Knott.[8] [b] Variation in Knott's procedure[8] increased yield. [c] No yield given by Knott.[8] [d] For intermediate β-dimethylamino-*p*-phenylpropiophenone, see W. L. Nobles and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, 47, 77 (1958). [e] The oil which separated during reflux period was extracted with ether and distilled, b.p. 179–184° (0.3 mm.), n_D^{25} 1.6204. It solidified when alcohol was added. Recrystallized from Skelly B. [f] Prepared by Dr. Robert Meyer of this laboratory.[4] Recrystallized from methanol. [g] For intermediate 3-dimethylamino-1-(9-phenanthryl)-1-propanone hydrochloride, see J. van de Kamp and E. Mosettig, *J. Am. Chem. Soc.*, **58**, 1568 (1936). [h] Recrystallized from alcohol. [i] B.p. 154–162° (0.4 mm.). [j] After distilling at 154–156° (0.5 mm.), the oil solidified. [k] Recrystallized from dilute alcohol.

thienyl)pyrrolidine (I, R = 2-thienyl) could not be obtained in this manner. Apparently, the sulfur of the thiophene ring poisoned the catalyst. Lithium aluminum hydride also failed to effect the desired reduction. The hydrogenation of β-9-phenanthroylbutyronitrile (V, R = 9-phenanthroyl) failed to yield any product. Since more than three moles of hydrogen was absorbed, it appeared that the phenanthrene ring was partially hydrogenated.

This method for the preparation of pyrrolines and pyrrolidines suffers from several limitations. It is, of course, limited to those ketones which undergo the Mannich reaction. The most serious drawback, however, is the small number of Mannich bases (IV) that may be used to alkylate potassium cyanide. Only Mannich bases possessing an aryl group adjacent to the carbonyl group appear to form β-keto nitriles (V), since no successful application of this reaction to wholly aliphatic ketonic Mannich bases has been reported.[10] Also, during the course of this work unsuccessful attempts were made to prepare the corresponding β-keto nitriles (V) from 2-diethylaminomethylcyclohexanone hydrochloride and 5-dimethylamino-1-phenyl-1-penten-3-one (the Mannich base from benzalacetone, IV, R = β-phenylvinyl).

Most of the keto nitriles (V, Table I) are low-melting solids, and some of them tended to separate as oils on recrystallization. This difficulty was circumvented by vacuum distillation of the crude products before recrystallization.

Knott prepared the isomeric β-naphthoylpropionitrile (V, R = 1-naphthoyl) and β-2-naphthoylpropionitrile (V, R = 2-naphthoyl) from the corresponding Mannich bases.[8] He reported melting points of 113–114° and 114°, respectively, for the two compounds. Burckhalter and Meyer[4] confirmed Knott's synthesis of the 2-isomer, but were unable to obtain the 1-isomer as a solid. Instead only an oil was isolated which was not characterized. Although Knott converted β-2-naphthoylpropionitrile to 2-(2-naphthyl)-Δ^1-pyrroline (VI, R = 2-naphthyl), he did not report any further transformations of his so-called β-1-naphthoylpropionitrile.[7] So, the preparation of the latter compound was repeated, and an oil, which could be purified by distillation, was obtained. When allowed to stand in alcohol at room temperature, it crystallized. The white solid obtained in this manner, after two recrystallizations from petroleum ether (60–70°), melted at 61° (Table I, Compound 6). That this compound, rather than Knott's melting at 113–114°, is β-1-naphthoylpropionitrile was proved by partial hydrogenation to 2-(1-naphthyl)-Δ^1-pyrroline (Table II, Compound 6), which has been prepared by Maginnity from 1-naphthylmagnesium bromide and γ-chlorobutyronitrile.[11] As a result of these observations, it seems likely that the compound assumed by Knott to be β-1-naphthoylpropionitrile is actually β-2-naphthoylpropionitrile, since he recorded the same melting point for both compounds. He did not report a mixed melting point.

2-(*m*-Hydroxyphenyl)-Δ^1-pyrroline (VI, R = *m*-hydroxyphenyl) has been obtained as a white, crystalline solid from the corresponding keto nitrile by the absorption of two moles of hydrogen.[7] Continued hydrogenation, however, failed to yield any of the desired 2-(*m*-hydroxyphenyl)pyrrolidine. The theoretical amount of hydrogen was absorbed, but the product appeared to be a resin. This material was soluble in both acid and base. It formed an oily picrate, and could not, according to Knott, be distilled. Repetition of this work resulted in a confirmation of Knott's observations except that the substance was found to distil over a wide range. The distillate solidified to a glassy solid.

(10) J. H. Brewster and E. L. Eliel, *Org. Reactions*, 7, 108 (1953).

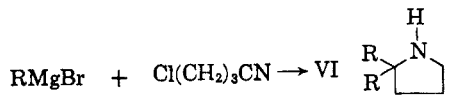
(11) P. M. Maginity and J. B. Cloke, *J. Am. Chem. Soc.*, 73, 49 (1951).

A different approach to 2-(*m*-hydroxyphenyl)pyrrolidine also failed. An attempt to demethylate 2-(*m*-methoxyphenyl)pyrrolidine (I, R = *m*-methoxyphenyl) by the action of hydriodic acid gave a resinous product similar to that obtained by the hydrogenation procedure. An attempt to methylate the crude reaction product to obtain 2-(*m*-hydroxyphenyl)-1-methylpyrrolidine (II, R = *m*-hydroxyphenyl) also failed.

The action of hydriodic acid on 2-(*m*-methoxyphenyl)-Δ^1-pyrroline (VI, R = *m*-methoxyphenyl) gave rise to a substance identical with Knott's 2-(*m*-hydroxyphenyl)-Δ^1-pyrroline (VI, R = *m*-hydroxyphenyl). Examination of the infrared absorption spectrum of the latter compound gave conclusive proof that the double bond was unaffected by the hydriodic acid.

Had the preparation of 2-(*m*-hydroxyphenyl)pyrrolidine been successful, it would have been interesting to see if this compound would undergo an internal Mannich reaction in the presence of formaldehyde to give a benzodehydropyrrolizidine ring system. Such an intramolecular Mannich reaction has apparently never been reported.

The second approach to pyrrolines, Procedure D, was first described by Cloke[12] and by Lipp and Seeles.[13] It involves the action of a Grignard reagent on γ-chlorobutyronitrile to give a pyrroline (VI). Apparently, any Grignard reagent may be used. Those pyrrolines (VI) which could not be

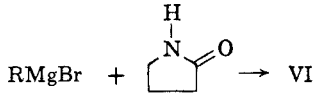


VII

prepared by Procedure C were obtained by this route (Table II). The only disadvantage of Procedure D is the low yields, which seldom exceed 50% and are frequently much lower.

When the crude product from the Grignard reaction was subjected to vacuum distillation, some high-boiling residue always remained in the still pot. The preparation of 2-benzyl-Δ^1-pyrroline (VI, R = benzyl) was run on a larger scale than usual in order to obtain enough of the higher boiling fraction to identify. It was considered to be either a polymer of 2-benzyl-Δ^1-pyrroline or else 2,2-dibenzylpyrrolidine (VII, R = benzyl). Analysis of the picrate indicated structure VII to be correct, and infrared spectrum of the free base confirmed the absence of a double bond.

The third approach to pyrrolines, Procedure E, involves the action of a Grignard reagent on 2-pyrrolidone. Only one example of this reaction has



been recorded in the literature. When Lukeš, Štorm, and Arnold[14] investigated the reaction of propylmagnesium bromide with 2-pyrrolidone, they found the main product to be 2-propylpyrrolidine (I, R = propyl), obtained in unstated yield. Their proof of structure rested on a comparison of the melting points of the picrate and benzenesulfonamide derivatives with those obtained from 2-propylpyrrolidine synthesized by another method. The alternate synthetic procedure was not stated. The melting points of the two derivatives do agree excellently with those reported by Gabriel[15] who synthesized 2-*n*-propylpyrrolidine by a ring closure reaction. In addition to the main product, Lukeš and co-workers obtained a small amount of a higher boiling fraction. This material consisted of a mixture of 2,2-di-*n*-propylpyrrolidine (VII, R = *n*-propyl) and an unidentified base, $C_{10}H_{25}N$, containing one double bond and three propyl groups.

On the basis of two examples studied, the third approach (Procedure E) proved to be unsatisfactory for the preparation of pyrrolines (VI). From phenylmagnesium bromide and 2-pyrrolidone, there was obtained only an 18% yield of 2-phenyl-Δ^1-pyrroline (VI, R = phenyl), while *p*-methoxyphenylmagnesium bromide gave only a 6% yield of 2-(*p*-methoxyphenyl)-Δ^1-pyrroline (VI, R = *p*-methoxyphenyl). These compounds were identical with those prepared by Procedure C. In both cases no other basic materials were obtained from the reaction mixtures. The yields could not be improved by means of various modifications of the experimental procedures.

Table II summarizes the data obtained on the pyrrolines, which were synthesized by Procedure C, D, or E of the Experimental section.

The pyrrolines (VI) obtained by the foregoing procedures were reduced to the corresponding pyrrolidines (I, Table III) by low pressure hydrogenation using Raney nickel catalyst according to Procedure F or H. Lithium aluminum hydride also proved capable of effecting the desired reduction (Procedure G).

The pyrrolidines (I) were converted to the 1-methyl derivatives (II, Table IV by the formaldehyde-formic acid method.[16]

PHARMACOLOGICAL RESULTS

Adrenergic blocking effect.[17] At a dose level of 10 mg./kg. I.V. in dogs, the following substances failed to reverse epinephrine-induced hypertension. Compounds 1, 3, 4, 7, 8, and 9 of Table III and

(12) J. B. Cloke, *J. Am. Chem. Soc.*, **51**, 1174 (1929).
(13) P. Lipp and H. Seeles, *Ber.*, **62**, 2456 (1929).
(14) R. Lukeš, F. Štorm, and Z. Arnold, *Collection Czechoslov. Chem. Comm.*, **12**, 641 (1947) [*Chem. Abstr.*, **42**, 5899 (1948)].
(15) S. Gabriel, *Ber.*, **42**, 1264 (1909).
(16) R. N. Icke, B. B. Wisegarver, and G. A. Alles, *Org. Syntheses*, **Coll. Vol. III**, 723 (1955).
(17) We wish to thank Dr. Graham Chen, Research Laboratories, Parke, Davis & Co., Detroit, Mich., for the test results.

TABLE II

2-SUBSTITUTED-Δ^1-PYRROLINES (VI)

No.	Substituent	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Phenyl[a]	C	83	44–45[l]					
		E	18						
	Picrate[a]			200–202[m]					
2	*p*-Methoxyphenyl[a]	C	76	77–78[n]					
		E	6						
	Picrate[a]			179–180[m]					
3	*m*-Methoxyphenyl	C	90[g]		$C_{11}H_{13}NO$	75.40	75.50	7.48	7.44
		D	46						
	Picrate			147–148[m]	$C_{17}H_{16}N_4O_8$	50.50	50.45	3.99	3.99
4	*m*-Hydroxyphenyl[a]		75[h]	158–160[o]					
	Picrate[a]			205–206[m]					
	Hydrochloride			252–253[p]	$C_{10}H_{12}ClNO$	60.76	61.06	6.12	6.22
5	Biphenylyl	D	76	159–160[m]	$C_{16}H_{15}N$	86.84	87.00	6.83	6.87
	Picrate			205–206[m]	$C_{22}H_{18}N_4O_7$	58.66	58.53	4.03	4.06
	Hydrochloride			236–237[p]	$C_{16}H_{16}ClN:{}^1/_2H_2O$	72.03	71.86	6.42	6.34
6	1-Naphthyl[b]	C	87	35–36[q]					
	Picrate[b]			176–177[m]					
7	9-Phenanthryl	D	28	123–124[m]	$C_{18}H_{15}N$	88.13	87.89	6.16	6.43
	Picrate			212–213[r]	$C_{24}H_{18}N_4O_7$	60.76	60.87	3.82	3.95
8	9-Anthryl	D	14	151–152[n]	$C_{18}H_{15}N$	88.13	88.61	6.16	6.35
	Picrate			214–215[m]	$C_{24}H_{18}N_4O_7$	60.76	60.89	3.82	3.92
9	2-Thienyl[a,c]	D	45	57.5–58.5[n]					
10	Benzyl[d]	D	39		$C_{11}H_{13}N[t]$	82.97	83.07	8.23	8.00
	Picrated[d]			114–115[m]					
11	1-Naphthylmethyl	D	22[i]						
	Picrate			195–196[m]	$C_{21}H_{18}N_4O_7$	57.53	57.61	4.14	4.07
12	2-Naphthylmethyl	D	26[j]		$C_{15}H_{15}N$	86.08	85.69	7.22	7.50
	Picrate			211–212[m]	$C_{21}H_{18}N_4O_7$	57.53	57.79	4.14	4.44
13	Methyl[e]	D	12[k]						
	Picrate[f]			123–124[m,s]					

[a] Described by Knott.[7] [b] Described by Maginnity and Cloke.[11] [c] Described by Kirchner and Johns.[21] [d] Described by D. F. Starr, H. Bulbrook and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932). [e] Described by R. Hielscher, *Ber.*, **31**, 277 (1898). [f] Described by G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951). [g] B.P. 95–96° (0.3 mm.), n_D^{25} 1.5692. [h] Made from compound 3 by demethylation with 47% hydriodic acid. [i] B.p. 135–139° (0.4 mm.), n_D^{25} 1.6144. [j] B.p. 135–136° (0.3 mm.), n_D^{20} 1.6228. Hydrochloride, m.p. 207° from isopropanol. [k] B.p. 99–101°, n_D^{20} 1.4296. [l] Recrystallized from Skelly A. [m] From alcohol. [n] From Skelly B. [o] From alcohol-benzene. [p] From isopropyl alcohol. [q] From Skelly A-B. [r] From alcohol-acetone. [s] Mixed m.p. with picric acid gave a marked depression. [t] Analyses by Clark Microanalytical Laboratories, Urbana, Ill. No active hydrogen was found at either 25 or 100° by the Zerevitinov procedure.

Compounds 1, 2, 3, 5, 6, and 9 of Table IV. At the same dose level, Compounds 5 of Table III and 8, 10, and 11 of Table IV effected a partial reversal of epinephrine-induced hypertension, and Compounds 4 and 7 of Table IV caused a complete reversal. It is of interest to note that the demethylated derivative of Compound 4, or 2-(*m*-hydroxyphenyl)-1-methylpyrrolidine (Compound 5 of Table IV), actually caused a rise in blood pressure above the level caused by epinephrine alone.

Nicotinolytic Activity.[18] Although 2-phenylpyrrolidine and 1-methyl-2-phenylpyrrolidine failed to show any adrenergic blocking activity, they both antagonized the hypertensive effect of small doses, 0.02–0.03 mg./kg., of nicotine in the dog.

1-Methyl-2-phenylpyrrolidine alone, caused an evanescent rise in blood pressure, its pressor potency being about $^1/_{25}$th that of nicotine. The nicotine pressor response was immediately reduced about 50% by 5 mg./kg. of 1-methyl-2-phenylpyrrolidine with return to normal in about one hour. At a dose level of 10–12 mg./kg., it immediately abolished, or nearly abolished, the nicotine pressor effect with return to 50–70% at 1 hr. and to normal at 2 hr. The effect of stimulation of the vagus nerve (causing a decrease in the heart rate) was markedly reduced by 10 mg./kg., but only slightly affected by 5 mg./kg. of the material.

2-Phenylpyrrolidine alone caused an initial evanescent rise in blood pressure, its pressor potency being about $^1/_{40}$th that of nicotine. The nicotine pressor response was immediately reduced about 20% by 1 mg./kg. of the substance, about 50% by 2.5 mg./kg., about 75% by 6 mg./kg., and about 90% by 10 mg./kg. The effect was more prolonged than that of 1-methyl-2-phenylpyrrolidine and persisted with lessening degree for 2–3 hr. This compound also blocked stimulation of the vagus nerve.

(18) The nicotinolytic tests were carried out by Dr. Paul S. Larson through the cooperation of Parke, Davis & Co., Detroit, Mich.

TABLE III

2-SUBSTITUTED-PYRROLIDINES (I)

No.	Substituent	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Phenyl[a]	F	82[e]						
	Picrate[a]			148–149[m]					
2	*p*-Methoxyphenyl[a]	F	91[f]						
	Picrate[a]			134–135[m,n]	$C_{17}H_{18}N_4O_8$	50.24	50.19	4.47	4.36
3	*m*-Methoxyphenyl	F	83[g]		$C_{11}H_{15}NO$	74.54	74.65	8.53	8.70
	Picrate			127–128[m]	$C_{17}H_{18}N_4O_8$	50.24	50.38	4.47	4.39
4	Biphenylyl	G	54[h]	58–59[o]	$C_{16}H_{17}N$	86.05	85.69	7.67	7.68
		H	85						
	Picrate			182–183[m]	$C_{22}H_{20}N_4O_7$	58.40	58.63	4.46	4.39
	Hydrochloride			177–178[p]	$C_{16}H_{18}ClN$	73.97	74.15	6.98	6.70
5	2-Naphthyl[b]	F	72[i]		$C_{14}H_{16}N$	85.24	85.22	7.67	8.38
	Picrate			174–175[m]					
	Hydrochloride			149–150[q]	$C_{14}H_{16}ClN$[t]				
6	9-Phenanthryl	G	94	94–95[o,r]	$C_{18}H_{17}N$	87.41	87.53	6.93	6.93
	Picrate			245–246[s]	$C_{24}H_{20}N_4O_7$	60.50	60.33	4.23	4.23
7	2-Thienyl[c]	G	88[j]						
	Picrate[c]			189–190[m]					
8	Benzyl[d]	H	92[k]						
	Picrate[d]			139–140[m]					
9	1-Naphthylmethyl	H	87[l]						
	Picrate			171–172[m]	$C_{21}H_{20}N_4O_7$	57.27	57.00	4.58	4.64
	Hydrochloride			167–168[s]	$C_{15}H_{18}ClN$	72.71	72.54	7.32	7.70

[a] Described by Knott.[7] [b] Prepared by Dr. Robert Meyer[2] from Compound 7, Table I. When that intermediate was prepared by the procedure of Knott (our Procedure A), it melted at 114°, and reduction stopped at the pyrroline stage (m.p. 95–96°), even when heat was applied. [c] Described by Kirchner and Johns.[21] [d] Footnote *d* of Table II. [e] B.p. 99–100° (4.5 mm.), n_D^{20} 1.5472. [f] B.p. 108–112° (1 mm.), n_D^{20} 1.5504. [g] B.p. 103–105° (1 mm.), n_D^{25} 1.5496. [h] B.p. 153–156° (0.2 mm.). [i] B.p. 139–141 (0.5 mm.). [j] B.p. 78–81° (1.5 mm.), n_D^{25} 1.5625. [k] B.p. 96–97° (2 mm.), n_D^{20} 1.6368. [l] B.p. 127–140° (0.7 mm.), n_D^{25} 1.5998. [m] Recrystallized from alcohol. [n] Knott[7] gave m.p. 172–173°. [o] From Skelly B. [p] From isopropyl alcohol. [q] From alcohol-ether. [r] From methyl alcohol. [s] From alcohol-acetone. [t] Anal. for Cl: Calcd. 15.17; found. 15.06.

EXPERIMENTAL[19]

β-Keto nitriles. Procedure A. According to Knott's procedure[8] the Mannich base and potassium cyanide were heated at reflux temperature in aqueous solution.

Some of the lower melting nitriles tended to precipitate as oils on recrystallization. This difficulty was obviated by vacuum distillation of the product before recrystallization.

Procedure B. To a solution of the Mannich base in water containing an equivalent of concentrated hydrochloric acid was added, beneath the surface of the liquid, an aqueous solution of potassium cyanide (hood.). The reaction mixture was then heated under reflux for 30 min. This is the procedure of Haggett and Archer.[20]

Pyrrolines.[21] *Procedure C.* The procedure described by Knott was followed.[7] A solution of the β-keto nitrile in ethanol was hydrogenated over Raney nickel catalyst at four atmospheres of hydrogen pressure. The reaction was interrupted when two moles of hydrogen had been consumed.

Procedure D. According to the procedure developed by Kirchner and Johns[22] for the preparation of 2-(2-thienyl)-Δ^1-pyrroline, a Grignard reagent was allowed to act upon γ-chlorobutyronitrile (Custom Chemical Lab.), and the reaction mixture was worked up as described.

Procedure E. Two moles of Grignard reagent was allowed to react with one mole of 2-pyrrolidone (Cliffs-Dow Co.), and the reaction mixture worked up according to Procedure D.

Pyrrolidines. Procedure F. According to the procedure described by Knott,[7] the β-keto nitriles were subjected to low pressure hydrogenation, according to Procedure C, until no more hydrogen was absorbed. The uptake corresponded to three moles.

Procedure G. The pyrrolines could be conveniently reduced to the pyrrolidines by lithium aluminum hydride (Metal Hydrides, Inc.) in ether by the usual procedure.[23] The reaction mixture was hydrolyzed with ammonium chloride solution and worked up in the usual manner.

Procedure H. Low pressure catalytic hydrogenation also proved to be a satisfactory method for the conversion of pyrrolines to pyrrolidines. The procedure followed was the same as described for the preparation of pyrrolidines directly from β-keto nitriles (Procedure F).

N-Methylpyrrolidines. The pyrrolidines were methylated by means of the formaldehyde-formic acid method. The procedure followed was that described by Icke, Wisegarver, and Alles[16] for the methylation of β-phenylethylamine.

2,2-Dibenzylpyrrolidine. Benzylmagnesium chloride, prepared from 127 g. (1 mole) of benzyl chloride, was allowed to react with 83 g. (0.8 mole) of γ-chlorobutyronitrile in the manner described for the preparation of 2-(2-thienyl)-Δ^1-pyrroline.[22] After removal of the drying agent and solvent, the residue was subjected to vacuum distillation to give 50 g. (39%) of 2-benzyl-Δ^1-pyrroline. After distillation of the pyrroline, considerable residue remained in the still pot. From

(18) Microanalyses were carried out by Mr. C. M. Beazley, Skokie, Ill. and by Drs. Strauss and Weiler, Oxford, England.

(19) E. Haggett and S. Archer, *J. Am. Chem. Soc.*, **71**, 2255 (1949).

(20) *Chem. Abstr.* names Δ^1-pyrrolines as derivatives of 3,4-dihydro-2H-pyrrolenine. For example, 2-phenyl-Δ'-pyrroline would be 3,4-dihydro-5-phenyl-2*H*-pyrrolenine.

(21) J. G. Kirchner and I. B. Johns, *J. Am. Chem. Soc.*, **62**, 2183 (1940).

(23) R. F. Nystrom and W. C. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

TABLE IV

2-SUBSTITUTED-1-METHYLPYRROLIDINES (II)

No.	Substituent	Yield, %	B.P. or M.P., °C.	Refractive Index (n_D)	Formula	Analysis C Calcd.	C Found	H Calcd.	H Found
1	Phenyl[a]	72	83–84 (6 mm.)	1.5242 (20°)					
	Picrate[a]		148–149[f,g]						
2	*p*-Methoxyphenyl[a]	71	87–90 (0.5 mm.)	1.5310 (20°)					
	Picrate[a]		155–156[f]						
3	*p*-Hydroxyphenyl[a,b]	50	158–159[h]						
	Picrate[a]		184–185[i]						
4	*m*-Methoxyphenyl	75	76–77 (0.6 mm.)	1.5290 (25°)	$C_{12}H_{17}NO$	75.35	75.22	8.96	9.24
	Picrate		143–144[f]		$C_{18}H_{20}N_4O_8$	51.42	51.70	4.80	4.89
5	*m*-Hydroxyphenyl[c] Hydrochloride	41	181–182[j]		$C_{11}H_{16}ClNO$	61.82	61.79	7.55	7.53
6	4-Biphenylyl	92	145–148 (0.3 mm.)[k]		$C_{17}H_{19}N$	86.03	85.40	8.07	8.30
	Picrate		182–183[f,g]		$C_{22}H_{22}N_4O_7$	59.22	59.48	4.75	5.02
	Hydrochloride		170–171[i]		$C_{17}H_{20}ClN$[o]	74.57	74.52	7.36	7.42
	Methiodide		212–214[m]		$C_{18}H_{22}IN$	57.00	56.97	5.85	5.81
7	2-Naphthyl[d]	80	102–103 (0.2 mm.)						
	Picrate		139–140[f]		$C_{21}H_{20}N_4O_7$	57.27	57.00	4.58	4.97
8	9-Phenanthryl	91	89–90[n]		$C_{19}H_{19}N$	87.31	87.21	7.33	7.32
	Picrate		160–161[f]		$C_{25}H_{22}N_4O_7$	61.22	61.47	4.52	4.54
	Hydrochloride		220–221[i]		$C_{19}H_{20}ClN$[p]	74.37	74.50	6.90	6.77
	Methiodide		245–246[m]		$C_{20}H_{22}IN$	59.56	59.72	5.50	5.66
9	2-Thienyl	63	47–48 (0.3 mm.)	1.5363 (25°)	$C_9H_{13}NS$	64.62	64.22	7.83	7.75
	Picrate		123–124[f]		$C_{15}H_{16}N_4O_7S$	45.45	46.23	4.07	4.13
10	Benzyl[e]	89	69–70 (0.3 mm.)	1.5186 (25°)	$C_{12}H_{17}N$	82.23	82.46	9.78	9.66
	Picrate		144–145[f]		$C_{18}H_{20}N_4O_7$	53.46	53.80	4.99	5.14
11	1-Naphthylmethyl	78	120–121 (0.5 mm.)	1.5828 (25°)	$C_{16}H_{19}N$	85.28	84.86	8.50	9.00
	Picrate		166–167[f]		$C_{22}H_{22}N_4O_7$	58.14	58.38	4.88	4.96

[a] Described by L. C. Craig, *J. Am. Chem. Soc.*, **55**, 2543 (1933). [b] Prepared from Compound 2 by demethylation with hydriodic acid. [c] Prepared from Compound 4 by demethylation with hydriodic acid, then isolated as the hydrochloride. [d] Prepared by Dr. Robert Meyer. [e] Described by R. Lukeš, *Chem. Listy*, **27**, 392, 409 (1933); *Chem. Abstr.*, **29**, 1720 (1935), but no physical constants are given. [f] From alcohol. [g] Showed a marked depression when mixed with the picrate of intermediate pyrrolidine. [h] From dilute alcohol. [i] From water. [j] From acetone-ether-methyl alcohol. [k] Crystallized by dissolving in Skelly A at room temperature and cooling in a Dry Ice bath. m.p. 40–41°. [l] From alcohol-ether. [m] From absolute alcohol. [n] From Skelly B or methanol. [o] 4.22% water was removed by analyst at 110° before C—H analysis. [p] Contains also 1.5% water.

this residue there was obtained 9 g. of 2,2-dibenzylpyrrolidine, b.p. 137–151° (1 mm.). The material was redistilled, and the fraction boiling over the range 169–172° (1.5 mm.) was collected, n_D^{25} 1.5878. The product was a light yellow oil.

A *picrate* was prepared and recrystallized five times from alcohol, once with the aid of decolorizing charcoal, m.p. 176.5–177.5°.

Anal. Calcd. for $C_{24}H_{24}N_4O_7$: C, 59.99; H, 5.04. Found: C, 60.03; H, 5.09.

LAWRENCE, KAN.