Summary

p-Benzylbenzaldehyde and its oxime have been prepared. Both have a sweet taste, followed by a pungent or burning sensation. The influence of space orientation of groups upon taste in benzene and furan compounds is discussed in connection with the sweet taste of dulcin. Taste analogies are pointed out between benzene para compounds and 2,5-furan compounds.

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Synthesis and Physiological Action of Alpha Substituted N-Methylpyrrolidines

BY LYMAN C. CRAIG[1]

Introduction

Nicotine has long been recognized as a compound possessing unusual toxicity both to warm and to cold blooded animals. It is a compound of rather simple structure when compared to the other outstanding organic insecticides, the pyrethrins and rotenone. Accordingly it seems strange that with the exception of the recently synthesized Neonicotine[2] or Anabasine no other closely related compounds having high toxicity have been prepared or discovered.

Attempts to locate a specific atomic linkage or "Toxifore" grouping responsible for its unusual activity have been without result and have led previous investigators[3] to believe that such a grouping does not exist but that the make-up of the molecule as a whole is responsible for the physiological action. This is undoubtedly true in one sense as each atomic linkage must contribute something to the chemical behavior of the compound as a whole. However, the separate linkages must vary in the degree of their contribution to the chemical behavior and thus to the physiological action.

As part of a systematic study of structure and physiological action in the nitrogen heterocyclics it seemed desirable to prepare and study a series of α-substituted N-methylpyrrolidines. Such a study should establish whether or not the "Toxifore" grouping is contained in the pyrrolidine nucleus provided a series having the proper distribution of radicals could be obtained. From a structural standpoint nicotine may be considered as a member of the series. This paper reports the study mentioned.

(1) National Research Fellow.

(2) Smith, THIS JOURNAL, **54**, 39 (1932).

(3) LaForge, *ibid.*, **50**, 2471 (1928); Harlan, Ph.D. Dissertation, Iowa State College, 1928; Tattersfield, *J. Agr. Sci.*, **17**, 181–208; Tattersfield and Gimmingham, *Ann. Appl. Biol.*, **14**, 217 (1927); Richardson and Shepard, *J. Agr. Res.*, **40**, 1007 (1930).

A previous paper[4] reported a method of synthesis of α-substituted N-methylpyrrolines. Reduction by the appropriate means offers a suitable method of synthesis of α-substituted N-methylpyrrolidines. The method limits the series to those radicals of which a Grignard reagent can be prepared. While a pyrrole and thiophene Grignard can be prepared they could not be made to react with N-methyl-α-pyrrolidone and are not included in the series.

In a study of structure and physiological action complete data on the physical constants of the series are frequently worth while and instructive. However, data on the dissociation constants appeared especially pertinent to the present problem. Accordingly the dissociation constants of the series were measured.

Natural nicotine is optically active, being strongly levorotary. The other analogs of the series which were prepared synthetically are racemic mixtures. Resolution would be a long and tedious process. For comparative purposes nicotine was racemized and the inactive form as well as the active compared with the series.

Synthesis of Compounds

α-Phenyl-N-methylpyrrolidine.—The compound was first reported by LaForge[3] but Craig, Bulbrook and Hixon[5] were not able to isolate it by the same method.

The addition product of the Grignard reagent with N-methyl-α-pyrrolidone is prepared as previously described[4] from 10 g. of magnesium, 63 g. of bromobenzene, 150 cc. of anhydrous ether and 20 g. of N-methyl-α-pyrrolidone. It is hydrolyzed by addition of 65 cc. of concentrated hydrochloric acid in 120 cc. of water. The ether layer is removed and 10 g. of magnesium turnings added to the aqueous layer remaining in the flask. Hydrochloric acid is then added till the magnesium is all dissolved. The solution is made alkaline with sodium hydroxide and the volatile base recovered by steam distillation. The oil is dried over solid potassium hydroxide. It distils completely at a temperature of 106° (20 mm.) or 217.5° (uncorr.) at atmospheric pressure (LaForge, 225–227°). Reduction of the isolated α-phenyl-N-methylpyrroline was not attempted.

α-Phenyl-N-methylpyrrolidine is a colorless oil with rather a pleasant odor. It is soluble in approximately 500 parts of water and soluble in all organic solvents. An oxalate of the base is oily and cannot be crystallized but a picrate crystallizes nicely from 95% alcohol and melts at 146°. A chloroplatinate crystallizes nicely from hot water and melts at 122°. It was dried in a vacuum desiccator for analysis.

Anal. Calcd. for $(C_{11}H_{15}N)_2H_2PtCl_6$: Pt, 26.7. Calcd. for $(C_{11}H_{15}N)_2H_2PtCl_6 \cdot 3H_2O$: Pt, 24.9. Found: Pt, 25.0, 25.2.

α-(*p*-Chlorophenyl)-N-methylpyrrolidine.—*p*-Chlorobromobenzene is prepared according to the directions of Mouneyrat.[6] The synthesis from this point on is identical with the previous compound. A report of the compound could not be found in the literature.

The base is very similar in properties to the phenyl analog but less soluble in water. The oxalate could not be made to crystallize but the picrate crystallizes nicely from 95% alcohol. It melts sharply at 173°.

(4) Craig, THIS JOURNAL, **55**, 295 (1933).
(5) Craig, Bulbrook and Hixon, *ibid.*, **53**, 1831 (1931).
(6) Mouneyrat and Pouret, *Bull. soc. chim.*, [3] **19**, 801 (1898).

α-(*p*-Methoxyphenyl)-N-methylpyrrolidine.—*p*-Bromoanisole is prepared by bromination of anisole in chloroform. A Grignard reagent of it is prepared and the synthesis carried out as with the previous analog. It has not heretofore been prepared.

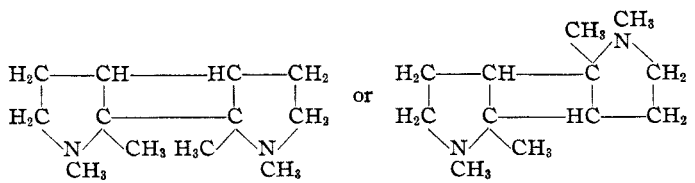
α-(*p*-Methoxyphenyl)-N-methylpyrrolidine is a colorless oil with an odor much like the phenyl analog. It is slightly more soluble in water. An oxalate cannot be crystallized. A picrate crystallized from alcohol melts at 155°.

α-(*p*-Hydroxyphenyl)-N-methylpyrrolidine.—A mixture of 5 g. of α-(*p*-methoxyphenyl)-N-methylpyrrolidine and 40 g. of hydriodic acid (sp. gr. 1.6) is heated for three hours under a reflux condenser by means of an oil-bath maintained at a temperature of 130–140°. The reaction products are cooled, diluted with water and excess potassium carbonate added. The solid which separates is washed with hot water and recrystallized from alcohol. The crude material weighs 4 g.

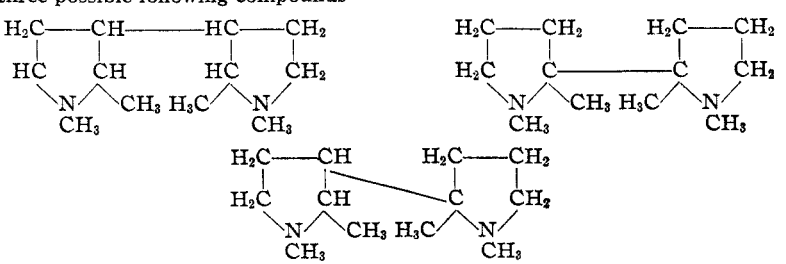
α-(*p*-Hydroxyphenyl)-N-methylpyrrolidine has about the same solubility as the *p*-methoxy derivative except that it is soluble in sodium hydroxide solution. A picrate recrystallized from hot water melts at 181°.

α-Methyl-N-methylpyrrolidine.—α-Methyl-N-methylpyrrolidine has been prepared previously by several different methods[7] although they are long and tedious. An attempt to prepare the base by the same procedure as with α-phenyl-N-methylpyrrolidine gives only the unreduced pyrroline. Apparently magnesium and hydrochloric acid will not reduce α-methyl-N-methylpyrroline or its hydrated intermediate.[8] Reduction of the pyrroline according to the method of Hielscher is very unsatisfactory. Electrolytic reduction in 15% sulfuric acid by the method of Tafel and Stern[9] gives satisfactory results. The base is recovered from the acid by adding excess sodium hydroxide and steam distilling. From 20 g. of α-methyl-N-methylpyrroline 9 g. of base distilling at 96–98° and 10 g. of a fraction boiling at 132–134° (20 mm.) are obtained. A picrate of the first fraction recrystallized from alcohol melts at 235°. Löffler reports 233.5° for the picrate of α-methyl-N-methylpyrrolidine.

α-Methyl-N-methylpyrroline has been shown to polymerize to either or both of the two isomers[4]



It is to be expected that the cyclobutane ring would rupture on reduction to give one of the three possible following compounds



(7) Löffler, *Ber.*, **43**, 2046 (1910); Hielscher, *ibid.*, **31**, 277 (1898); Merling, *Ann.*, **264**, 319 (1894).

(8) It is probable that in the reduction of the phenyl compounds the pyrroline is never formed but that the amino alcohol is directly reduced to the pyrrolidine (Lukes, *Collection Czechoslov. Chem. Comm.*, **2**, 531–44, also Ref. 4).

(9) Tafel and Stern, *Ber.*, **33**, 2224 (1900).

Anal. Calcd. for $C_{12}H_{24}N_2$: C, 73.4; H, 12.2; N, 14.3. Found: C, 73.1; H, 12.2; N, 14.2.

The compound is soluble in all proportions in water and organic solvents. It titrates as a diacidic base, giving a neutralization equivalent of 99.2.

α-Ethyl-, α-*n*-propyl- and α-*n*-butyl-N-methylpyrrolidine are prepared by the same procedure as is α-methyl-N-methylpyrrolidine. α-Ethyl- and α-*n*-propyl-N-methylpyrrolidine have been reported by Löffler.[7a] The properties and derivatives correspond with those reported by him. α-*n*-Butyl-N-methylpyrrolidine was first reported by Hess,[10] who prepared only a small amount of it by methylation of α-*n*-butylpyrrolidine. He reported a boiling point of 155–160°.

α-*n*-Butyl-N-methylpyrrolidine is slightly soluble in water (less than one part in 500) but soluble in organic solvents. The oxalate is oily. A picrate recrystallizes nicely from alcohol and melts at 114° (uncorr.).

N-Methylpyrrolidine was prepared as previously reported.[11] Nicotine ($[\alpha]_{20}^{D}$ −169°) was racemized according to the directions of Pictet.[12] It still retained a small rotation ($[\alpha]_{20}^{D}$ −2.71°).

Measurement of Dissociation Constants

The dissociation constants were determined by a method reported in a previous paper.[13] The values obtained are given in Table I. The purity of each sample was confirmed by direct titration. A sample was discarded if it varied more than 0.3% from the theoretical equivalent. All samples were one-half neutralized for measurement.

Insecticidal Action

The insecticidal studies were made in coöperation with an entomologist, Dr. C. H. Richardson of Iowa State College, and will be published in full in the entomological literature.

A relative measure of the insecticidal value was made by spraying various concentrations of solutions or emulsions on adult wingless aphids, *Aphis rumicis* L., each test animal receiving a constant amount of the total spray mixture. The relative measure was based on a 50% kill point as that has been shown to be the most valuable point for statistical comparisons. Each result given is determined statistically from a number of different trials using a large number of insects. A 0.25% solution of sodium oleate was used throughout the tests as a spreader. A summary of the data is given in Table I.

Pharmacological Studies

A study of the pharmacology of the series is being made in coöperation with Dr. D. I. Macht and will be reported elsewhere in full by him. Relative toxicity is based on the time required to kill. The test animals were goldfish, *Carassius aureus*, and tadpoles, *Rana sylvatica*. The effect of the series on the growth of the seedling *Lupinus albus* is also given. The index of growth is based on the percentage growth as compared to that of the

(10) Hess, *Ber.*, **52**, 1640 (1919).
(11) Craig and Hixon, THIS JOURNAL, **53**, 187 (1931).
(12) Pictet, *Ber.*, **33**, 1353 (1900).
(13) Craig and Hixon, *ibid.*, **53**, 4367 (1931).

TABLE I

	α-Substituted N-methylpyrrolidine	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	*l*-α-[β-Pyridyl]-(*l*-nicotine)	$C_{10}H_{14}N$				
2	*dl*-α-[β-Pyridyl]-(*dl*-nicotine)	$C_{10}H_{14}N$				
3	α-[*p*-Chlorophenyl]-	$C_{10}H_{14}NCl$	Cl = 18.2		18.3	18.1
4	α-[*p*-Methoxyphenyl]-	$C_{12}H_{17}NO$	75.2	9.00	75.1	9.08
5	α-[*p*-Hydroxyphenyl]-	$C_{11}H_{15}NO$	74.5	8.54	74.6	8.7
6	α-Phenyl	$C_{11}H_{15}N$	81.8	9.4	81.6	9.6
7	α-*n*-Butyl-	$C_8H_{19}N$				
8	α-*n*-Propyl-	$C_7H_{17}N$				
9	α-Ethyl-	$C_6H_{15}N$				
10	α-Methyl-	$C_5H_{13}N$				
11	α-Hydrogen	$C_4H_{11}N$				

	B. p., °C.	Yield, %	Dissociation constant	Nature of spray	Toxic concn. g. per 100 cc.
1	246		9×10^{-7}	Solution	0.038
2	246		9×10^{-7}	Solution	.11
3	118 (9 mm.)	50	5×10^{-6} [a]	Emulsion	.4
4	130–131 (9 mm.)	21	8×10^{-6}	Emulsion	.8
5	Solid, m. p., 157			Solution	No toxicity at 1
6	217.5	62	6.3×10^{-6} [b]	Emulsion	1.3
7	170	87	6×10^{-5}	Emulsion	1.7
8	147	92	6×10^{-5}	Emulsion	3.6
9	123	74	6×10^{-5}	Solution	No toxicity at 5
10	96	45	6×10^{-5}	Solution	No toxicity at 7.1
11	77		1.5×10^{-4}	Solution	No toxicity at 4

[a] This compound is very slightly soluble in water and an accurate dissociation constant therefore cannot be measured. The value given is estimated on the basis of theory presented under discussion of results. It is placed here for comparative purposes only.

[b] The author is indebted to Mr. Lyle D. Goodhue of Iowa State College for checking this value with the glass electrode.

seedling in physiological salt solution, a method previously reported by Dr. Macht in numerous publications. The results are summarized in Table II, in which the compounds are diluted 1–5000 with water.

TABLE II

α-Substituted-N-methylpyrrolidine (*l*-Nicotine)	Concentration	Time to kill goldfish: Free base	Time to kill goldfish: Hydrochloride	Time to kill tadpoles: Free base	Time to kill tadpoles: Hydrochloride	Index of growth of seedlings, %: Free base	Index of growth of seedlings, %: Hydrochloride
l-α-[β-Pyridyl]-	1–5000	5 min.	15 min.	2 min.[a]	5 min.[b]	46	69
dl-α-[β-Pyridyl]-	1–5000			5 min.[a]		49	
α-[*p*-Chlorophenyl]-	1–5000		40 min.	12 min.[a]	30 min.[b]		81
α-[*p*-Methoxyphenyl]-							
α-[*p*-Hydroxyphenyl]-							
α-Phenyl-	1–5000	12 min.	47 min.	5 min.	18 min.[b]	40[b]	73
α-*n*-Butyl-	1–5000	14 min.	105 min.	6 min.	78 min.[b]	54[b]	75
α-*n*-Propyl-	1–5000	15 min.	155 min.	7 min.	22 hrs.[b]	50[b]	82
α-Ethyl-	1–5000	34 min.	Alive after 18 hrs.	8 min.	Alive after 72 hrs.	64[b]	85
α-Methyl-	1–5000	68 min.	Alive after 18 hrs.	12 min.	60 hrs.[b]	66[b]	88
α-Hydrogen	1–5000	70 min.	Alive after 18 hrs.	9 min.	76 hrs.[b]	63[b]	61

[a] These values are at a dilution of 1–10,000. [b] These values are at a dilution of 1–1000. The tadpoles in testing the hydrochlorides were one week old. For the free bases they were two weeks old.

Other pharmacological studies to date have only included comparative studies of *l*-nicotine and α-phenyl-N-methylpyrrolidine. Both compounds produce a stimulation of uterine contractions, the nicotine being much more powerful. Neither of the compounds affected the contractions produced on smooth muscle organs by a subsequent dose of epinephrine. Intravenous injections were made on cats under ether anesthesia and the blood pressure and respiration studied. Although the toxicity was different (lethal dose for nicotine, 2 mg. per kg. of body weight; α-phenyl-N-methylpyrrolidine, 12 mg.), qualitatively the results were similar. Death was produced in both cases by primary paralysis of the respiration and secondary depression of the circulation with standstill of the heart.

Discussion of Results

In the series of compounds studied the only variable from a structural standpoint is the α-substituent of the pyrrolidine ring and the change in basicity is due entirely to the change in negativity or relative affinity of each radical. This difference in negativity can best be expressed according to the theory of "Electron Sharing Ability" of Hixon and Johns[14] which gives the different radicals a mathematical relationship. That the same relationship holds for the present series as has been shown to hold for numerous other series[13,14,15] is shown by the fact that in Fig. 1 a smooth curve can be plotted from the dissociation constants of the series when the various radicals are assigned values taken from an arbitrary primary amine series. For comparative purposes a curve of an α-substituted pyrrolidine series and also of an RCH_2NH_2 series are given. All three series are analogous in that the radical is one carbon atom removed from the basic group. The slope of the α-substituted pyrrolidine curve and that of the α-substituted N-methylpyrrolidine are almost identical, which indicates that the effect of methylation is constant. However, the slope of the RCH_2NH_2 series is slightly different but the ring structure present in both pyrrolidine series and not in the RCH_2NH_2 series may account for the slight difference in slope.

An examination of Table I will show that there is an apparent correlation between the dissociation constants or basicity and relative toxicity. It is doubtful whether hydroxyl-ion concentration or basicity in itself plays a major role as in the series toxicity increases as basicity decreases. Toxicity is more probably the result of some particular reactivity of the molecule which is correlated with the same effect that increases or decreases the basicity and can most conveniently be called the "Electron Sharing Ability" of the radical.

Such a correlation cannot be expected to hold quantitatively for each radical nor could a strictly linear relation be expected. Differences in

(14) Hixon and Johns, THIS JOURNAL, **49**, 1786 (1927).

(15) Johns, Peterson and Hixon, *J. Phys. Chem.*, **34**, 2218 (1930); Johns and Hixon, *ibid.*, **34**, 2226 (1930); Starr, Bulbrook and Hixon, THIS JOURNAL, **54**, 3871 (1932).

physical properties which largely affect penetration, etc., will play a considerable role. However, it is significant that the pharmacological studies place the compounds in the same order of toxicity as the insecticidal studies.

The relative toxicities of *l*-nicotine and *dl*-nicotine are of considerable interest aside from the series. If no toxic influence were exerted from the dextro half of the inactive form a toxic concentration should be 0.076 g. per 100 cc. as compared to that actually found which is 0.11 g., Macht[16] has shown that *dl*-nicotine exerts a synergistic effect on *l*-nicotine in toxicity

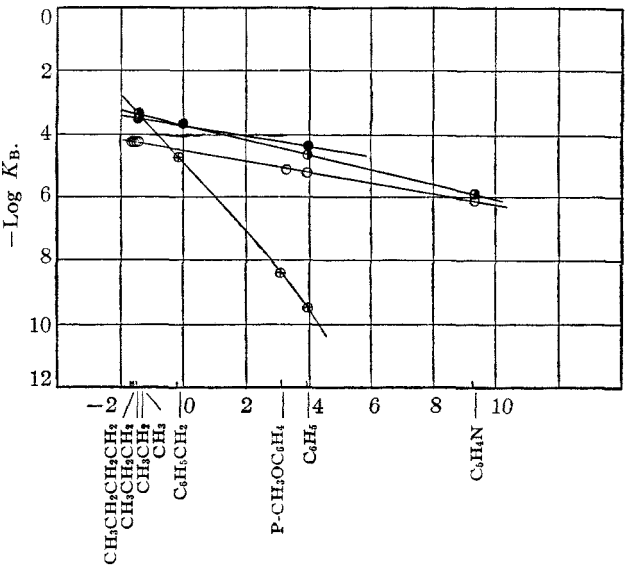


Fig. 1.—⊕, RNH_2 series; ◐, RCH_2NH_2 series; ⊙, α-substituted N-methylpyrrolidine series; ●, α-substituted pyrrolidine series.

to goldfish placed in a solution of the alkaloid, on rats studied by intraperitoneal injection and on cats and rabbits studied by intravenous injection. In all cases toxicity greater than the additive effect of the two preparations was noted. The results concerning toxicity to insects would indicate an antagonistic synergism with dextro and levo nicotine. However, these results are not strictly comparable to Macht's as his study was concerned with mixtures of *l*-nicotine and *dl*-nicotine. His mixtures contained 62.5% of levo and 37.5% of dextro nicotine.

A study of the insecticidal action of *d*-nicotine would be instructive. *d*-Nicotine has been shown to be one-half as toxic as *l*-nicotine to dogs and guinea pigs.[17] Its action was also found to be of a somewhat different nature.

(16) Macht, *Proc. Nat. Acad. Sci.*, **15**, 63–70 (1929).
(17) Mayor, *Ber.*, **37**, 1335 (1904).

The author wishes to express appreciation to Dr. E. Emmet Reid for his advice and encouragement during the progress of this work.

Summary

A series of α-substituted N-methylpyrrolidines has been prepared and their dissociation constants measured. The variation of toxicity with the different α-substituents has been studied. The most negative substituent is shown to be the most toxic.

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The Micro Estimation of Halogens in Organic Compounds

BY ADALBERT ELEK AND DOUGLAS W. HILL[1]

Numerous methods have been suggested for the estimation, on a micro scale, of halogens in organic compounds. Pregl[2] described two methods, the first involving combustion of the substance and the second an adaptation of the well-known Carius procedure. Although both methods give satisfactory results, they are open to criticism. Dieterle[3] and Nomura and Murai[4] have described methods based upon modifications of the macro procedure of Baubigny and Chavanne.[5] They used a mixture of concentrated sulfuric acid and potassium dichromate together with silver nitrate for the oxidation of the organic material before proceeding to the determination of the halide. Later, Willard and Thompson[6] described a method depending on the oxidation of the sample by means of fuming sulfuric acid to which, in certain instances, potassium persulfate was added. The halogen was distilled into alkaline arsenite and precipitated as silver halide. Zacherl and Krainick[7] modified the method of Nomura and Murai by employing a mixture of concentrated sulfuric acid, silver dichromate and potassium dichromate as the oxidizing agent and collected the halogen in a mixture of 0.01 *N* caustic soda with acid-free hydrogen peroxide, in which it was estimated by titration of the excess alkali. This method closely resembles the procedure of Viebock,[8] published a little earlier, in which the oxidizing agent consisted of a mixture of concentrated sulfuric acid and potassium dichromate with silver sulfate. Other methods

(1) Commonwealth Fund Fellow.
(2) Pregl, "Quantitative Organic Micro Analysis," 3d ed., 1930.
(3) Dieterle, *Arch. Pharm.*, **259**, 73 (1921).
(4) Nomura and Murai, *Bull. soc. chim.*, [4] **35**, 217 (1924).
(5) Baubigny and Chavanne, *Compt. rend.*, **136**, 1197 (1903).
(6) Willard and Thompson, THIS JOURNAL, **52**, 1893 (1930).
(7) Zacherl and Krainick, *Mikrochem.*, **11**, 61 (1932).
(8) Viebock, *Ber.*, **65**, 493 (1932).