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Insecticidal action in the nitrogen heterocyclics

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INSECTICIDAL ACTION IN THE NITROGEN HETEROCYCLICS

by

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INTRODUCTION

In the field of organic insecticides nicotine has long stood as one of the few compounds having marked insecticidal properties. The active principles of the other important organic insecticides which are extracts of pyrethrins from pyrethrum flowers and rotenone from derris root do not contain nitrogen. Nicotine is accordingly the only compound in the nitrogen heterocyclics that has been widely used as an insecticide.

Studies undertaken to determine the atomic linkage responsible for the high toxicity of nicotine have been without success and chemists as well as entomologists have come to believe that the high toxicity of nicotine is due to the peculiar molecular structure of the compound as a whole rather than to any single atomic linkage or grouping. This idea is based on the fact that the few compounds closely related to nicotine which have been investigated for insecticidal properties and which appear from a purely structural standpoint to be only slightly different from nicotine, have been of a low order of toxicity.

Even if this concept were correct one would expect the existence of a series of compounds of gradient toxicity approaching and even surpassing that of nicotine. Up to the

present time such a series has not been found but the compounds tested have been relatively few due to the difficulty of synthesis in this field. It seems improbable that such a series cannot be synthesized and that the toxicity of nicotine cannot be equalled by other nitrogen heterocyclics when the classical studies on the correlation between structure and physiological action in the field of local anesthetics and of arsenic compounds used in the treatment of trypanosomiasis is considered. While these studies have been made on warm blooded animals yet they have a general biological significance and as has been previously expressed[1] tend to show that the change in physiological action in any homologous series is not qualitative in nature but quantitative.

If it is considered that nicotine is a member of a gradient series all showing more or less toxicity and an investigation of such a probable series proposed, it will be necessary to choose a single atomic linkage or grouping in the molecule which is basicly responsible for the toxicity. Such a choice is difficult from the existing data.

Metanicotine showed a much lower degree of toxi-

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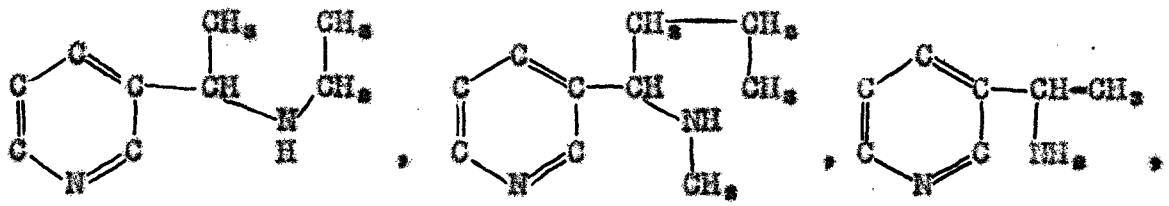
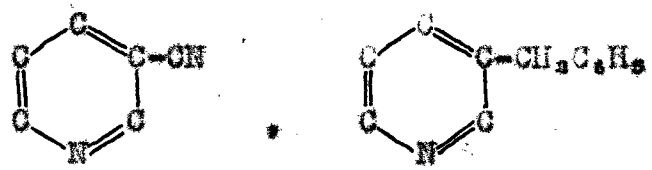
1 Oswald, Chemische Konstitution und Pharmakologische Wirkung, 277.(1929).

city than nicotine as tested by C. H. Richardson and Shepard[2] but a higher toxicity than other simple pyridine homologs. Harlan[3] was not able to ascribe as high a relative toxicity to this compound when extreme care was taken to remove all unchanged nicotine from the metanicotine. The following pyridine derivatives were prepared by La Forge[4] and tested by Richardson and Shepard.





They were all found to have a relatively low order of toxicity which indicated that the pyridine nucleus was not the main grouping responsible for the toxicity in nicotine. The same authors prepared and tested the following pyrrolidine derivatives:

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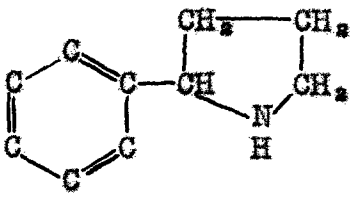
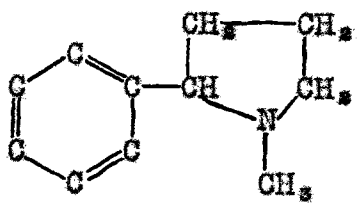
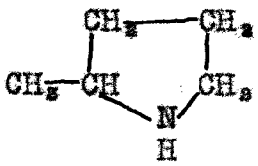
2 C. H. Richardson and H. H. Shepard, J. Agr. Res., 40, 1007 (1930).

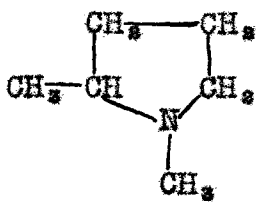
3 Harlan, Studies on Nicotine (Ph.D. thesis) Iowa State College. Unpublished M.S.

4 LaForge, J. Am. Chem. Soc., 50, 2471 (1928).









finding them of a low order of toxicity although tests on these compounds were made on the hydrochlorides. Harlan and also Richardson and Smith[5] found hexahydronicotine to be of a low order of toxicity. This evidence would support the conclusion that the seat of toxicity in nicotine does not lie in the pyrrolidine ring.

From these studies Harlan suggested that the high toxicity might be due to an accumulation of toxicities from the pyridine ring and the pyrrolidine ring as both are known to have a certain degree of toxicity although he believed a greater part of the toxicity to lie in the pyrrolidine nucleus.

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5 Richardson and Smith, United States Dept. of Agriculture Bulletin No. 1160. (1923).

The conclusions drawn from the two series of compounds studied are in agreement with Tattersfields'[6] idea that the whole makeup of the nicotine molecule including its spatial arrangement contribute to its potency.

The following investigation was undertaken on the assumption that if a series of pyrrolidine derivatives were prepared and their dissociation constants measured as well as their toxicity to insects, a gradient correlation would be found between the two sets of data. The dissociation constants would be expected to correlate with the former relationship reported by Hixon and Johns[7] between the organic amines and acids and would be a distinct contribution in the chemical field even if it failed to throw light on the cause of the high toxicity in nicotine since the majority of the compounds have heretofore not been prepared.

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6 Tattersfield and Gimingham, Ann. Appl. Biol., 14, 217.(1927).
7 Hixon and Johns, J. Am. Chem. Soc., 49, 1786 (1927).

CHEMICAL STUDIES

PYRROLE. Pyrrole is a constituent of coal tar and is also present in bone oil. The separation and purification from either of these sources is difficult and if chemically pure pyrrole is desired, synthetic methods of preparation are preferable. Of the several known syntheses of pyrrole the only one worthy of mention is the convenient pyrogenic synthesis from dry ammonium mucate which was first discovered by Schwanert[8].

Bell and Lapper[9] found that the synthesis could also be accomplished by using ammonium saccharate instead of its optical isomer, ammonium mucate. In these studies it was found that the synthesis from ammonium saccharate is much more troublesome as the neutral ammonium salt is very soluble in water and practically impossible to obtain crystalline. When a distillation of the viscous residue remaining upon evaporating its solution was attempted the undecomposed material largely came over into the receiver as a result of foaming. Reduced pressure only increased this effect.

Goldschmidt[10] was able to increase the yield in the distillation of ammonium mucate to forty or fifty percent of

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8 Schwanert, Ann., 116, 287 (1860).
9 Bell and Lapper, Ber., 10, 1861 (1877).
10 Goldschmidt, Z. Chem., 280 (1867); Khotinsky, Ber., 42, 2506 (1909).

the theoretical by the use of glycerine as a solvent in the distillation. The function of the glycerine is probably in offering a means of even distribution of heat throughout the mixture. Goldschmidt's method is slow and troublesome and when the relative prices of mucic acid and glycerine are considered, is not as suitable for the laboratory synthesis as the direct heating of the dry salt.

Although the exact mechanism of this pyrogenic reaction is not known, it was thought that heating under pressure in an atmosphere of ammonia would increase the yield of pyrrole. Accordingly 50 g. of the dry salt was heated in a bomb to 240° for three hours under approximately 140 lb. pressure of ammonia. The material was carbonized but no pyrrole could be isolated. Evidently if the pyrrole was formed, it decomposed at the temperature used.

The most convenient method of synthesis was the following: 500 g. of mucic acid was converted to the neutral ammonium salt with excess ammonia, then filtered and the moist residue subjected to dry distillation in an iron retort. The pyrrole was extracted from the distillate with ether, the ether evaporated off and the residue distilled. Fifty cc. of a fraction boiling at 125-130° was obtained. The yield was 32% of the theoretical.

PYRROLE DERIVATIVES. Two general methods of synthesis are to be recommended for the synthesis of N-substituted pyrrole derivatives. One is the method of Bell and Lapper[9] which is identical with the pyrrole synthesis from mucic acid except that a primary amine is used instead of ammonia. The other depends upon the reaction of RX with potassiumpyrrole. Of the two the first is a more convenient synthesis.

By the pyrogenic synthesis the comparative yields of the pyrroles prepared are the following:

Pyrrole	32%
N-phenylpyrrole	25%
N-methylpyrrole	22%
N-butylpyrrole	14%

Distillation under reduced pressure raised the yield of butylpyrrole from 14% to 26%. A like distillation was not carried out with the other derivatives.

N-METHYLPYRROLE. The method of preparation was essentially that of Bell and Lapper with a few minor changes. To 390 g. mucic acid suspended in enough water to make a thin paste, 250 g. of a 33% solution of methylamine was added. After stirring well the mixture was cooled in ice and filtered by / means of suction. The moist precipitate was then placed in an iron retort and heated till decomposition was

complete. The distillate was extracted with ether, dried over potassium hydroxide, then fractionated. A yield of 33 g. boiling at 110-112° was obtained. 35 g. N-methyl-pyrrole-α-carboxy-methylamide remained as a by product. This compound was first reported by Bell and Lapper.

N-NORMAL-BUTYLPYRROLE. The method of preparation was that of Reichstein[11] except that mucic acid was used instead of saccharic. To 86 g. of mucic acid in enough water to make a thin paste, 60 g. butylamine was added. Upon cooling, the reaction mixture solidified. It was transferred to a 500 cc. Claisen flask and subjected to distillation under reduced pressure (35 mm.). The distillate contained 35 g. of an oil which was extracted with ether, dried and fractionated; 13.5 g. of oil distilled at a temperature of 165-180°. The yield was 26% of the theoretical. On a following run, using 200 g. mucic acid, the same procedure was used except that the distillation was carried out at atmospheric pressure. 17 g. crude N-butylpyrrole was obtained in this case or a yield of 14% of the theoretical. 13 g. of the crude product was refractionated and 11 g. of oil distilling at a temperature of 166-168° collected. It was a colorless oil with a very sharp disagreeable odor.

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11 Reichstein, Helv. chim. acta., 10, 387 (1927).

N-BUTYLPYRROLE-α-CARBOXY-BUTYLAMIDE.+ The high boiling residue from the above original distillation (21.5 g.) was subjected to distillation under reduced pressure (165-170° at 10-12 mm.). The colorless distillate solidified. It melted at 57° and crystallized in needles from an alcohol-water mixture.

An attempt to hydrolyze the substituted acid amide by refluxing over strong caustic was unsuccessful as was also an attempt using alcoholic potash at 130°. The compound was finally hydrolyzed by heating ten grams of the amide for ten hours, at 200° in an alcoholic solution containing 8 g. of potassium hydroxide in 40 cc. of 95% alcohol. After being heated, most of the alcohol was distilled off and water added to the residue. Fractionation of this mixture by solubility in ether, acid solution and basic solution yielded about one gram unchanged amide, N-butylamine and an acid fraction. The oily acid fraction which was N-butylpyrrole-α-carboxylic acid was finally characterized by conversion to the acid amide. It was soluble in all organic solvents and insoluble in water. The Ca, Ba and Ag salts were too soluble to crystallize. 6 g. of the free

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+ Reichstein reported a compound which corresponded to the above, as N-butylpyrrole-α-isobutylamide. No doubt it is a typographical error since normal butylamine was used in the synthesis of his compound.

acid was subjected to distillation under 6 mm. pressure. From the distillate 3 g. of an alkali insoluble oil was obtained that distilled at 165-168° and had all the characteristics of N-butylpyrrole. 2 g. of the original acid was present in the distillate. Evidently carbon dioxide splits off quite readily from this acid.

N-BUTYLPYRROLE-α-CARBOXY-ACID AMIDE. To one cc. of the free acid, an excess of thionyl chloride was added. After heating, as much of the excess thionyl chloride was evaporated as possible using reduced pressure and heating on the water bath. The residue was dropped into cold concentrated ammonia and the resulting oily mass extracted with ether. The ether extract was evaporated to dryness and the residue crystallized from hot water. The yield is low. M. P. 108°.

Anal. Calcd. for $C_9H_{19}N_2O$: C, 64.9: H, 8.99.

Found: C, 64.98, 65.00: H, 8.52, 8.88.

N-PHENYLPYRROLE. The method of preparation was essentially that of Feist[12]. 200 g. of mucic acid was added with constant stirring, to an excess of aniline heated to a temperature just below boiling. This mixture was then placed in an iron retort and heated till no more liquid came

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12 Feist, Ber., 35, 1655 (1902).

over. The distillate was extracted with ether and the aniline removed by washing with a dilute solution of hydrochloric acid. After evaporating off the ether, the residue was distilled under reduced pressure; the yield was 25% of the theoretical. N-phenylpyrrole colors slightly on standing. It crystallized from 95% alcohol in lustrous leaves, melted at 60-61° and boiled at 234° as reported in the literature.

α-SUBSTITUTED PYRROLINES. In the past a general method of synthesis for α-substituted pyrrolines has not been known. Cloke[13] described a rearrangement of γ-chloropropylketimines to pyrroline derivatives and proposed this as a convenient synthesis of α-substituted pyrrolines. His work was devoted chiefly to a study of the mechanism of the reaction. The yields of pyrroline compounds formed were particularly disappointing for the preparation of the aliphatic substituted pyrrolines. With a view to increasing the yields, a study of his reaction was undertaken.

If we accept the mechanism given by Cloke for the formation of the α-substituted pyrrolines as indicated by either or both of the following equations --

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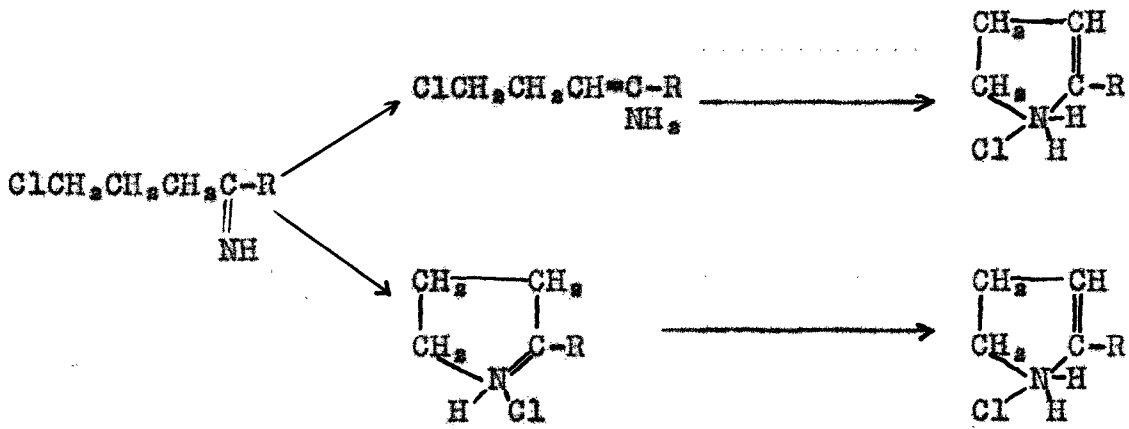
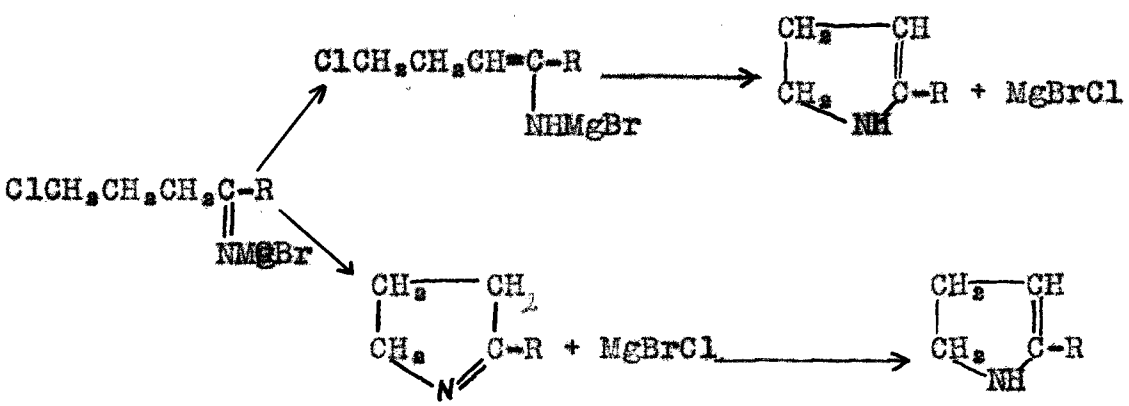
13 Cloke, J. Am. Chem. Soc., 51, 1174 (1929).



then it would seem that ring closure could be effected by raising the temperature of the reaction mixture containing the addition product of the γ-chlorobutyronitrile with the Grignard reagent without going through the steps of forming the ketimine itself. The reaction would then go according to either or both of the following equations --



Accordingly an experiment was performed in which the ether was removed by distillation from the phenylmagnesiumbromide-nitrile addition product, and dry xylene added,

keeping the volume constant. When the temperature approached that of boiling xylene, the mixture suddenly reacted to give a viscous semicrystalline material which was probably a mixture of MgBrCl and α-phenylpyrroline-N-magnesiumbromide, the latter compound being formed by reaction of the α-substituted pyrroline with the excess phenylmagnesiumbromide. This method of ring closure gives much better yields than are obtained by passing through the ketimines since there is partial hydrolysis of the ketimine to the corresponding ketone. The procedure is also shorter as the pyrroline can easily be removed from the mixture by either steam distillation or extraction with ether according to solubility in water. The yields of α-phenyl, α-ethyl and α-benzylpyrroline are respectively 55, 46 and 13% of the theoretical. The order of reactivity of the Grignard reagents from which they are derived is the reverse of this.

α-PHENYLPYRROLINE. A solution of phenylmagnesiumbromide was prepared which contained 150 cc. of anhydrous ether, 8.6 g. of magnesium and 56 g. of bromobenzene. To this 15 g. of γ-chlorobutyronitrile in an equal volume of ether was added. The Grignard addition product precipitated when most of the nitrile had been added. The mixture was refluxed for two hours. The reflux condenser was then reversed and the ether allowed to distil off, the volume being

maintained constant by addition of xylene dried over sodium. When the ether had practically all distilled over, the mixture suddenly reacted to give a solid semi-crystalline mass. The mixture was then treated with a solution of ammonium chloride and the xylene layer removed. The aqueous layer was extracted once with ether and the ether extract added to the xylene solution. The α-phenylpyrrolidine was extracted from the organic solvents with a small volume of hydrochloric acid, the hydrochloric acid layer washed once with ether to remove xylene and heated to remove the ether. It was then treated with excess strong caustic solution, the oily layer dried over solid potassium hydroxide and distilled; 11 g. distilled at 120-130° under 18 mm. The yield was 55% of the theoretical. Several grams of a high boiling residue were left. The picrate melted at 158° as was reported by Gabriel and Coleman[14].

α-ETHYLPYRROLINE. A Grignard reagent was prepared from 8.6 g. magnesium, 38 g. ethylbromide and 150 cc. anhydrous ether. To this was added 15 g. γ-chlorobutyronitrile in an equal volume of ether. The mixture was refluxed for two hours, then the ether removed by distillation, anhydrous xylene being added to replace it as a solvent.

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14 Gabriel and Coleman, Ber., 41, 517 (1908).

After the mixture had reacted it was treated with 50 cc. water and the xylene decanted. The residue was treated with caustic solution and steam distilled. After adding 15 cc. concentrated hydrochloric acid to the distillate, it was shaken in a separatory funnel with the xylene layer. The acid layer was washed once with ether and concentrated to a volume of approximately 50 cc. It was then treated with strong caustic, the oily layer drawn off and dried over solid potassium hydroxide. The oil, amounting to 11 cc., was distilled; 6.5 g. of distillate came over under a temperature of 140°. The yield was 46% of the theoretical. It gave a picrate which melted at 87° when crystallized from absolute alcohol. The gold chloride could be crystallized from water strongly acidified with hydrochloric acid and melted at 122°. A sample for analysis was dried in a vacuum dessicator at room temperature. α-Ethylpyrroline was first prepared by Dennstedt[15] but the only derivative reported was the chloroplatinate.

Anal. Calcd. for $C_6H_{11}NHAuCl_4$: Au, 45.21.

Found: Au, 45.21, 45.30.

A sample of the free oil with a constant boiling point was obtained by recrystallizing the picrate and regener-

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15 Dennstedt, Ger. 137,086, C., 1902, I, 338.

ating. 12 g. of distillate and 25 g. of picric acid were added to 300 cc. of absolute alcohol. The alcohol was heated to effect solution and slowly cooled to the temperature of ice water; 24 g. of crystalline picrate, melting at 85-86° was filtered off. The whole was treated with 50 cc. water containing 15 cc. concentrated hydrochloric acid, heated to boiling, cooled, then filtered and the picric acid washed with a small volume of water. The filtrate was then treated with strong caustic, the oil separating dried over solid potassium hydroxide and distilled. It distilled entirely at 125-126° and weighed 5.5 g. It was a colorless oil with a foul musty odor and did not color on standing. It is interesting to note that Hielscher[16] was not able to distil pure α-methylpyrroline or α-methyl-N-methylpyrroline without decomposition. There was no sign of decomposition during the distillation of pure α-ethylpyrroline.

In the literature it is reported[17] that α-methylpyrroline and compounds of like structure exist in water solution in a state of equilibrium, a molecule of α-substituted pyrroline reacting with one of water to form γ-aminopropyl-substituted ketones. Pure α-ethylpyrroline, dissolved in a small volume of water, did not react with either phenylhydrazine

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16 Hielscher, Ber., 31, 277 (1898).
17 Lipp and Widnmann, Ann., 409, 80 (1915).

or phenylsemicarbazide in the cold. However, when warmed in a small volume of water for one hour on the water bath, equivalent quantities of α-ethylpyrroline and phenylsemicarbazide hydrochloride formed a white solid which was insoluble in water and alcohol and melted at 244°.

α-BENZYLPYRROLINE. A Grignard reagent was prepared from 8.6 g. of magnesium, 45 g. of benzylchloride and 220 cc. of anhydrous ether. 15 g. of γ-chlorobutyronitrile was slowly added and the mixture refluxed for two hours. The ether was then removed by distillation and replaced as a solvent by xylene. As was the case with the other two derivatives prepared, there was no sudden separation of solid material. When all the ether had volatilized, the mixture was heated for one-half hour and the α-benzylpyrroline recovered in the same manner as was α-phenylpyrroline. 3 g. of distillate boiling at 126-128° under 15 mm. pressure was obtained. The yield was 13% of the theoretical. It was a colorless oil which rapidly colored in air and was soluble in all organic solvents but insoluble in water. A picrate crystallized from an alcohol-water mixture strongly acidified with hydrochloric acid, melted with decomposition at 125°. A sample was dried in a vacuum dessicator at room temperature and immediately analyzed as it showed some signs of decomposition.

Anal. Calcd. for $C_{11}H_{13}NHAuCl_4$: Au, 39.50.

Found: Au, 39.45, 39.43.

Calcd. for $C_{11}Hl_2N$: C, 82.8: H, 8.23.

Found: C, 82.7: H, 8.61.

A reference to this compound could not be found in the literature.

PYRROLIDINE. The methods reported in the literature[18] for the preparation of pyrrolidine are all difficult and tedious. During the progress of the studies reported below, Anderson and McElvain[19] published their work on the catalytic reduction of pyrrole. In their work they used specially purified pyrrole, glacial acetic acid, a large quantity of platinum oxide platinum black catalyst and shook the mixture continuously for four to five days.

The catalytic reduction is much more convenient with the platinum oxide platinum black catalyst if absolute alcohol containing a slight excess over an equivalent of hydrogen chloride, is used as a solvent. With the latter solvent 0.2 g. of catalyst can be used for three successive reduc-

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18 Ciamacian and Magnaghi, Ber., 18, 2079 (1885).
Ladenburg, ibid., 19, 780 (1886), 20, 2215 (1887).
Wohl, Schafer and Theile, ibid., 38, 4157 (1906).
Gabriel, ibid., 42, 1254 (1912).
Keil, ibid., 59, 2816 (1926).
Putochin, ibid., 55, 2742 (1922).
Willstatter and Hatt, ibid., 45, 1477 (1912).
Willstatter and Waldschmidt, ibid., 54, 125 (1921)
Hess, ibid., 46, 3113 (1913).

19 Anderson and McElvain, J. Am. Chem. Soc., 51, 887 (1929).

tions of 10 cc. portions of pyrrole. The reduction was complete in six hours and the yield was 80% of the theoretical.

Pyrrole, obtained from Kahlbaum, although carefully distilled, had a different odor from the synthetic and probably was prepared from bone oil; this product could not be reduced by the above method. Commercial synthetic samples reduced equally as well as that freshly prepared from ammonium mucate. Pyrrole not freshly prepared and colorless reduced slowly if at all. The pyrrole was dried over anhydrous calcium chloride or solid potassium hydroxide before the final distillation.

The platinum oxide platinum black catalyst was prepared according to the method of Adams and Shriner[20]. The shaking machine was a modification of that ordinarily used in that the connections and tubing were all metal with a rubber gasket for the bottle. The reduction was started with a pressure of approximately 90 lb.

To 100 cc. of absolute alcohol, 0.2 g. of catalyst, 10 cc. of pyrrole, and a slight excess over an equivalent of concentrated hydrochloric acid (6 cc.) were added. The pyrrole reduced the catalyst at once; previous reduction

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20 Adams and Shriner, J. Am. Chem. Soc., 45, 2171 (1923).

of the catalyst before addition of pyrrole did not increase the rate of reduction. Absolute alcohol containing a calculated amount of dry hydrogen chloride did not increase the rate of reduction, although there is less pyrrole red formed. When 95% alcohol was used, the reduction was slower and there was considerable pyrrole red formed. The reduction was completed in about six hours. The catalyst was allowed to settle and the reduction products decanted. To the catalyst fresh portions of alcohol, acid and pyrrole were added. A third reduction could also be run on the same catalyst without seriously impairing the efficiency. No occasion was had to run more than three reductions on the same catalyst but there appeared to be no tendency for it to become poisoned if good pyrrole was used. After decantation, the alcohol was removed by evaporation under reduced pressure, the unreduced pyrrole was extracted with ether, solid potassium hydroxide was added to the solution of the salt until an oil separated and the oil finally dried over solid potassium hydroxide. It distilled at 86-88°, small residues of a high boiling fraction were left behind. Derivatives showed the constant boiling fraction to be pyrrolidine.

N-SUBSTITUTED PYRROLIDINES. Three general methods can be recommended for the synthesis of N-substituted pyrroli-

dine derivatives although several others are known. They are the following:

1. Reaction of RX with pyrrolidine.

2. Reduction of N-substituted pyrroles.

3. Condensation of tetramethylene halides with primary amines.

The first method cannot be used for the preparation of N-arylpyrrolidines. Piperidine when heated in a sealed tube with bromobenzene to 250-260°, gives a small yield of N-phenylpiperidine[21]. The analagous synthesis fails with pyrrolidine although reaction takes place at 220°. Apparently ring cleavage takes place under these conditions since a very stable amine was isolated with too high a ratio between hydrogen and carbon to permit of its containing a benzene nucleus.

Contrary to the literature[22] the first method is not satisfactory for the preparation of most N-alkyl pyrrolidine derivatives, as the yields are low due to the formation of quaternary derivatives instead of tertiary. The yields are influenced somewhat by the solvent.

Catalytic reduction of N-substituted pyrroles using Adams and Shriner catalyst and alcohol acidified with

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21 Lellman and Geller, Ber., 21, 2279 (1888).
22 Schlinck, Ber., 32, 952 (1899).
Ciamacian and Magnaghi, ibid., 18, 2079 (1885).

hydrochloric acid, as a solvent renders the second method of preparation of N-substituted pyrrolidines very satisfactory if the alkyl radical is saturated. However with the aryl or unsaturated alkyl N-substituted pyrroles, the double bond is reduced as well as the pyrrole ring. N-phenylpyrrole was reduced quantitatively to N-cyclohexylpyrrolidine. The fact that the intermediate products could not be isolated pure indicated simultaneous reduction of the two rings. The N-substituted pyrroles are in general more easily reduced than pyrrole, probably due to the fact that they are more stable toward polymerization by acid and do not thereby ruin the catalyst as easily.

J. P. Wibaut[23] and DeJong and Wibaut[24] were successful in catalytically reducing a number of substituted pyrroles using glacial acetic acid as a solvent. However their reduction required larger amounts of catalyst and shaking for a longer period of time.

Chemical reduction of pyrroles to pyrrolidines is difficult although it has been accomplished[25].

The third method is the only suitable method of the three for the preparation of aryl N-substituted pyrrolidines. However, it is not perfectly general. The condensa-

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23 J. P. Wibaut, Rec. trav. chim., 44, 1101 (1925).
24 DeJong and Wibaut, ibid., 49, 237 (1930).
25 Ciamacian and Magnaghi, Ber., 18, 2079 (1885).
Ciamacian and Zanetti, ibid., 22, 659 (1889).

tion will not take place with compounds of the type of ortho-toluidine, as is shown by the fact that the analogous condensation will not take place with pentamethylene bromide[26]. Steric hindrance has been offered as the reason for this behavior as the condensation will take place with para-toluidine.

N-METHYLPYRROLIDINE. The N-methylpyrrole was redistilled before reduction. To 10 cc. of N-methylpyrrole in 100 cc. of absolute alcohol, 0.2 g. Adams and Shriner catalyst and an equivalent of hydrochloric acid was added. With pyrrole the catalyst was immediately reduced but not with N-methylpyrrole. Evidently the N-substituted derivative is more stable toward oxidation than pyrrole. In three hours, practically the theoretical volume of hydrogen had been absorbed. The catalyst was filtered off and the alcohol removed by distillation. The residue was washed with ether and treated with solid potassium hydroxide till an oil separated. The oil was dried over solid potassium hydroxide and distilled almost entirely at 76-78°. A picrate crystallized from alcohol melted at 220° as reported by Wibaut. N-methylpyrrolidine has a stifling odor and a very high vapor pressure at room temperature. Its vapor pressure is 99 mm. at 25°. This may account for the emphasis in the

26 Scholtz and Wassermann, Ber., 40, 857 (1907).

literature placed on its physiological properties.

N-n-BUTYLPYRROLIDINE. To 100 cc. of absolute alcohol, 0.2 g. of catalyst, 10 cc. of butylpyrrole and 7 cc. of concentrated hydrochloric acid were added. Because of the temperature at which butylpyrrole distils, there might have been some danger of rearrangement, but if that had been the case the catalyst at this point would have been reduced since α- and β-substituted pyrroles are very susceptable to oxidation. The catalyst, however, remained in its original state till placed in the shaker. In five hours 1.35 moles of hydrogen were absorbed which is 88% of the theoretical. The N-butylpyrrolidine was recovered and dried in the same way as N-methylpyrrolidine. A yield was obtained of 7 g. colorless oil distilling at a temperature of 152-153°. It is slightly soluble in water and has an odor similar to pyrrolidine. A patent covering the synthesis of this compound by ring closure of dibutylamine has been issued to E. C. Britton[27]. A picrate crystallized in leaflets from 95% alcohol and showed a constant melting point of 124°.

An attempt was made to prepare a chloroplatinate by addition of a solution of chloroplatinic acid to the hydrochloride of the free base but the salt appeared to be

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27 U. S. 1,607,605 Nov. 23, 1917.

too soluble to crystallize. A chloroaurate was prepared by this method using chloroauric acid. It was very soluble in alcohol but crystallized in yellow leaflets from hot water. It melted without decomposition at 78°.

Anal. Calcd. for $C_8H_{17}NHAuCl_4$: Au, 42.13

Found: 42.14, 42.08.

N-CYCLOHEXYLPYRROLIDINE. As N-phenylpyrrole colors slightly on standing, it was recrystallized from 95% alcohol immediately before reduction. A 10 g. sample was dissolved in 100 cc. of absolute alcohol, a slight excess over one equivalent of concentrated hydrochloric acid and 0.2 g. of catalyst were added. The reduction was rapid and was complete in two and one-half hours, five moles of hydrogen having been absorbed. The reaction mixture was colorless and on recovery in the same way as with pyrrolidine, a constant boiling oil (209-211°) was obtained. The yield was quantitative. It did not react with phenylisothiocyanate. It gave a picrate which on repeated crystallization from alcohol melted at 163-164°. The hydrochloride was hygroscopic and not suitable for a melting point determination.

If the reduction was stopped when two moles of hydrogen were absorbed, 6 cc. of an oil that did not show a constant boiling point (206-247°) was obtained. It was probably a mixture of N-phenyl and N-cyclohexylpyrrolidine.

Separation by chemical means failed and all attempts at fractional crystallization of picrates gave only the cyclohexyl derivative.

The identity of the cyclohexylpyrrolidine was proven by a different synthesis as follows: Six cc. of pyrrolidine and an excess of cyclohexylbromide were refluxed for two hours. Two layers were present, showing that a reaction had taken place. The base when recovered in the usual way and dried over solid potassium hydroxide gave a small amount of a high boiling fraction. A picrate of this, crystallized from alcohol, melted at 163°. Mixed melting points proved its identity with that from the reduction product of N-phenylpyrrole.

N-BENZYLPYRROLIDINE. This compound was first prepared by Schlinck[22]. He reported a nearly quantitative yield which could not be duplicated by the same method. To 5 cc. of pyrrolidine, one-half equivalent of benzyl chloride was added (a full equivalent gave a lower yield of N-benzylpyrrolidine than a half). The mixture was warmed for two hours on a water bath. Dilute hydrochloric acid was added and the unreacted halide removed by washing with ether. Upon addition of caustic solution, an oil separated; when solid potassium hydroxide was added, a third layer appeared. The top layer was drawn off and identified as N-benzylpyrrolidine.

It amounted to 4 g. or a yield of 40% of the theoretical. Its picrate melted at 128° as reported by Schlinck.

The second layer which was the larger, was viscous, insoluble in ether, very soluble in water, and required a concentrated solution of potassium hydroxide to make it separate. It could not be prepared in a form suitable for analysis but its properties are what would be expected of dibenzylpyrrolidinium hydroxide.

N-PHENYLPYRROLIDINE. To 8 g. of tetramethylene chloride prepared from pyrrolidine according to the directions of Braun and Beschke[28], two equivalents of freshly distilled aniline were added and the mixture kept at 100° for four hours. On cooling, the mixture became solid with crystals. A dilute solution of hydrochloric acid was added and the unreacted tetramethylene halide removed by extraction with ether. The free base was liberated by strong caustic and the two layers separated. The excess aniline was removed from the oily layer with benzene sulfonyl chloride in dilute alkali. The tertiary amine fraction was extracted with ether and precipitated with dry hydrogen chloride. The free base was then recovered and dried with potassium hydroxide. It had a slight red color and did not react with acetyl chloride. When it was subjected to distillation at atmospheric

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28 Braun and Beschke, Ber., 39, 4119 (1906).

pressure the boiling point did not remain constant, and a colorless oil distilled over that reacted vigorously with acetyl chloride. Evidently the pyrrolidine ring must partially rupture during distillation. The base showed a constant boiling point when distilled under reduced pressure (2-3 mm.) and did not react with acetyl chloride. It formed a chloroplatinate that crystallized from alcohol acidified with hydrochloric acid, in yellow needles and melted with decomposition at 174-175°, varying slightly with the rate of heating.

Anal. Calcd. for $(C_{10}H_{13}N)_2H_2PtCl_6$: Pt 27.7.

Found: Pt 27.6, 27.7.

A crystalline picrate could not be obtained. On addition of an ether solution of oxalic acid to an ether solution of the base, a white precipitate formed that could be recrystallized from a mixture of acetone and petrolic ether: M.P. 156°. The only oxalate that corresponds to the analysis is the tetroxalate with one-half molecule of water of crystallization.

Anal. Calcd. for $C_{10}H_{13}N(COOH)_4$ 1/2 H_2O: C, 49.9, H, 5.36.

Found: C, 50.00, 50.10. H, 5.46, 5.52.

In attempting to prepare N-phenylpyrrolidine, several other methods were tried without success.

Le Seuer[29] has prepared the compound N-phenyl-α,α'-dicarboxy-pyrrolidine. This compound evolves carbon dioxide when subjected to dry distillation under reduced pressure. Small amounts of N-phenylpyrrolidine are produced but the method cannot be recommended for purposes of preparation.

DRY DISTILLATION OF α,α'-DICARBOXY-N-PHENYLPYRROLIDINE. This compound could best be prepared by the method of LeSeuer. On dry distillation of α,α'-dicarboxy-N-phenylpyrrolidine under reduced pressure, an oil with a slight red color distilled over. It gave an oxalate that corresponded with that of N-phenylpyrrolidine reported above. Mixed melting points showed the oxalates to be identical.

REACTION OF PYRROLIDINE WITH BROMOBENZENE. Ten cc. of pyrrolidine was heated with an equivalent of bromobenzene in a sealed tube at 220° for six hours. Experiment had shown this to be the minimum temperature at which reaction takes place. Two layers had separated in the tube and on recovery and distillation 6 cc. of a very stable oil (B. P. 250-256°) was obtained. It reacted vigorously with acetyl chloride but a crystalline derivative could not be isolated. It gave a non-hygroscopic hydrochloride when dry hydrogen chloride was passed through its ether solution. This was

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29 Le Seuer, J. Chem. Soc., 95, 273 (1909).

recrystallized from absolute alcohol and analyzed.

Anal. Found: C, 52.8, 53.1: H, 10.02, 10.05:
Cl, 26.43, 26.46.

The ratio of carbon to hydrogen is too high for this compound to contain a benzene ring. When shaken with water the free base formed leaf like crystals that melted slightly above room temperature. It also gave a picrate with a melting point of 155°.

N-PARA-TOLYLPYRROLIDINE. To 5 g. of tetramethylene chloride (boiling point 154-164°), 12.6 g. of para-toluidine was added. Upon heating on a steam bath for ten hours, it formed a solid mass of crystals that entirely dissolved in dilute hydrochloric acid. The acid solution was washed with ether, made strongly alkaline and the oily layer run through a primary-secondary-tertiary amine separation with benzenesulfonylchloride. A yield of 4.5 g. of a tertiary amine was obtained. It was dried over solid potassium hydroxide and distilled at a constant temperature of 120° under 8 mm. pressure. It crystallized in leaflets from an alcohol-water mixture and showed a constant melting point of 42.5°. It had a rather pleasant odor.

A chloroplatinate was prepared in the usual way but it could only be recrystallized from water containing considerable hydrochloric acid as reduction took place in

water alone. It showed a decomposition point of 175°. For analysis the material was recrystallized and dried at room temperature in a vacuum dessicator.

α-SUBSTITUTED PYRROLIDINES. Four general methods can be given for the preparation of α-substituted pyrrolidines although several more are possible. They are the following:

1. Reduction of α-substituted pyrroles.

2. Reduction of α-substituted pyrrolines.

3. Condensation of 1,4-dihalogen-1-substituted butanes with ammonia, primary amines or unsubstituted amides.

4. Ring closure of 1-amino-1-substituted-4-halogen butanes.

The first method would be very suitable if a satisfactory method of reduction was available, as the α-substituted pyrroles can easily be obtained. In this laboratory the only derivative on which catalytic reduction was attempted was a mixture of α- and β-methylpyrroles. The attempt was unsuccessful. It is doubtful if any of the α- or β-substituted derivatives could be reduced using alcohol acidified with hydrochloric acid as a solvent. Substitution on the carbon renders pyrroles more susceptible to acid and polymerization takes place before reduction or at least far enough to ruin the catalyst. DeJong and Wibaut[24] were

successful in reducing α-substituted pyrroles to pyrrolidines catalytically using glacial acetic acid as a solvent although Anderson and McElvain[19] were unsuccessful ~~using~~ with the same solvent. If the substituting group contained a benzene ring it was reduced to cyclohexyl.

α-substituted pyrrolines can be reduced both chemically and catalytically to pyrrolidines. If it is desired to prepare an α-substituted pyrrolidine with a benzene ring, chemical reduction must be used as catalytic reduction using alcohol acidified with hydrochloric acid as a solvent will also reduce the benzene ring.

The third method of synthesis of α-substituted pyrrolidines is perfectly general although synthesis of the 1,4-dihalogen butanes is difficult[30].

The fourth method is similar to the third. In the synthesis of α-substituted pyrrolines by the method of Cloke, γ-chloro-substituted ketimine acetates are formed but are in solution and are difficult to isolate due to their instability. It was thought that perhaps they could be reduced to the corresponding amine either by chemical reduction by adding magnesium to the acid solution or catalytically in glacial acetic acid solution using platinum oxide platinum

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30 Muller and Wacks, Monats., 53 & 54, 420 (1929).

black catalyst. Both methods of reduction were successful in an attempt to synthesize α-phenylpyrrolidine, the latter gave a more pure product. The yield, however, was not as high as with the synthesis going through α-phenylpyrroline. Hence no attempt was made to extend the method of preparation to α-alkylpyrrolidines.

α-PHENYLPYRROLIDINE. The compound was obtained by chemical reduction of α-phenylpyrroline according to the directions of Gabriel and Coleman[14]. LaForge[4] was unable to obtain α-phenylpyrrolidine by this method but synthesized the compound in another way.

Five g. of α-phenylpyrroline was added to 37 cc. of concentrated hydrochloric acid and 27 g. of granulated tin in an Erlenmeyer flask. As soon as the reaction had somewhat subsided, it was placed on the steam bath for two hours. The solution was decanted and the residual tin washed with water. The washings were added to the acid solution. The solution was then made strongly alkaline and steam distilled. To the distillate, 10 cc. of concentrated hydrochloric acid was added and the solution evaporated to a syrup. A small amount of water and strong caustic was then added. The oily layer was dried over solid potassium hydroxide and distilled; 4.5 g. base distilled at 120° under 20 mm. pressure. A picrate crystallized from alcohol melted

at 148° as previously reported. A chloroaurate melted at 108-109°.

METHYLATION OF α-PHENYLPYRROLIDINE. In attempting to prepare α-phenyl-N-methylpyrrolidine by methylation of α-phenyl-pyrrolidine according to the directions of LaForge[4], it was found that large quantities of the quaternary derivative were formed and purification by the Hinsburg secondary-tertiary amine separation gave a few drops only of a tertiary amine when 5 g. of starting material were used. A picrate prepared from the tertiary amine melted at 196°. This tertiary amine in ether solution reacted with benzoyl chloride which indicated ring rupture in analogy to nicotine. Purification of α-phenyl-N-methylpyrrolidine is for this reason difficult and analysis is not sufficiently sensitive to show the absence of large amounts of α-phenylpyrrolidine in the α-phenyl-N-methylpyrrolidine fraction.

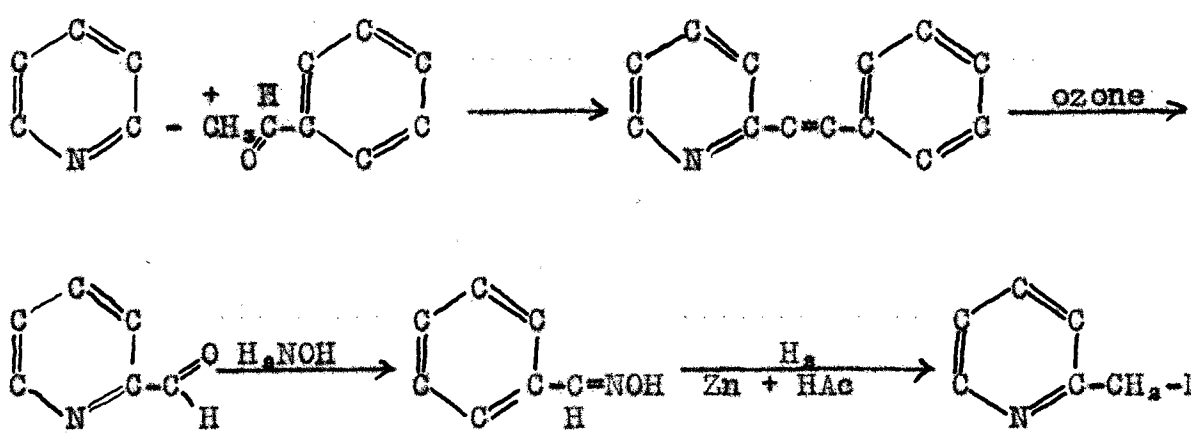
REDUCTION OF PHENYL-γ-CHLOROPROPYLKETIMINE. The phenyl magnesiumbromide addition product of γ-chlorobutyronitrile was prepared as in the synthesis of α-phenylpyrroline the same quantities being used throughout. Glacial acetic acid was then slowly added till all the Grignard reagent was destroyed, the ether decanted and the residue dissolved in as little glacial acetic acid as possible. After adding 0.3 g. of platinum oxide platinum black catalyst, the solution

was shaken in an atmosphere of hydrogen. In two hours reduction was complete and the catalyst was filtered off. Most of the acetic acid was removed by distillation using a water bath and reduced pressure. The residue was then made strongly alkaline and steam distilled. Recovery of the base by making the distillate strongly acid with hydrochlorid acid, evaporating to a small volume, treating with excess strong caustic and drying over solid potassium hydroxide gave 5 g. of base boiling at 120° under 20 mm. pressure. A picrate melted at 148° as reported by Gabriel and Coleman for α-phenylpyrrolidine and a mixed melting point confirmed its identity. It is interesting to note that in this case the benzene ring was not reduced.

α-ETHYLPYRROLIDINE. This compound was first prepared by Muller and Wacks[29]. It was prepared in this investigation by catalytic reduction using Adams and Shriner catalyst and absolute alcohol acidified with hydrochloric acid as a solvent. To 100 cc. of absolute alcohol, 0.2 g. of catalyst, 6 g. of α-ethylpyrroline boiling at 125-126°, and a slight excess over an equivalent of hydrochloric acid was added. In five hours reduction was complete, the theoretical amount of hydrogen having been absorbed. The base was recovered as was pyrrolidine and dried over solid potassium hydroxide. It distilled at a constant temperature

of 122° and gave a picrate melting at 85° as reported by Muller and Wacks.

α-PICOLYLAMINE. A review of the literature showed that this compound had not heretofore been prepared. All methods by which its synthesis was contemplated promised too many side reactions as a result of the reactivity of the pyridine nucleus except the method finally adopted which is long and tedious. The steps are shown in the following reaction:



Lenart[31] has made a study of α- and β-pyridyl aldehydes and had carried the above synthesis to that point. The procedure given here differs only slightly from his.

α-stilbazole was prepared according to directions of Lenart using 75 g. α-picoline, 110 g. freshly distilled benzaldehyde and 37 g. anhydrous zinc chloride. Upon

31 Lenart, Ann., 409, 95 (1915).

distillation of the crude stilbazole 95 g. came over at a temperature of 185-190° under 14 mm. pressure, or a yield of 67% of the theoretical. The product was almost colorless.

For the ozonization ~~of~~ a commercial ozone machine was used. Oxygen, dried by bubbling through sulfuric acid, was ozonized by passing through the ozonizer at the rate of approximately 60 liters per hour and bubbled through the solution of 30 g. stilbazole and 300 cc. concentrated hydrochloric acid in an Erlenmeyer flask. The duration of ozonization was 7-8 hours.

The separation and recovery of the aldehyde was carried out according to Lenarts directions except that the aldehyde was not recovered as such. After potassium carbonate had been added to make the aldehyde separate, an excess of hydroxylamine hydrochloride (4 g.) was added and the flask warmed slightly. In one-half hour the solution was cooled and the oxime filtered off and dried. In order to remove the inorganic salts, the crude product was treated with 30-40 cc. of benzene, the mixture heated to the boiling point of the solvent and the benzene layer decanted. Upon cooling in ice, 3.3 g. oxime was filtered off. From the reaction products some undecomposed stilbazole was recovered. The yield is 33% of the theoretical. The oxime

melted on repeated crystallizations at 113° as reported by Lenart. It is quite soluble in warm water and can readily be crystallized from this solvent.

For the reduction of α-pyridylmethanaldoxime 5 g. dissolved in 75 cc. of 95% alcohol was treated over a period of several hours with small portions alternately of glacial acetic acid and zinc dust until 40 g. of acid and 40 g. of zinc had been added. The flask was allowed to stand 24 hours, the zinc and zinc acetate were filtered off, and washed with fresh alcohol. The alcoholic solution was then evaporated to a thick syrup using a water bath and reduced pressure. Water was then added and the evaporation repeated, after which more water was added and a third evaporation carried out in order to remove as much of the acetic acid as was possible. The residue was saturated with potassium hydroxide and the oil coming to the surface drawn off. The caustic solution was subjected to steam distillation to recover the base retained by the viscous solution, and the base was then recovered from the distillate as above, after adding hydrochloric acid. The combined fractions were dried over solid potassium hydroxide and distilled; 3 g. of oil distilled at a constant temperature of 91° under 15 mm. pressure.

The picrate precipitated from ether solution was light yellow in color. On the first crystallization from

alcohol it melted with decomposition at 156°. On the second crystallization the compound crystallizing out was an orange color and began to darken at 156°, finally melting at 190°. It was unsuitable as a derivative.

The amine formed an oxalate from ether solution that could readily be crystallized from alcohol and melted at 167°.

The base formed a chloroaurate that crystallized nicely from water acidified with hydrochloric acid. Upon taking a melting point it began to darken at 170° and melted with decomposition at 204°. A sample for analysis was dried in a vacuum dessicator at room temperature.

Anal. Calcd. for $C_6H_8N_2HAuCl_4$: Au, 43.9.

Calcd. for $C_6H_8N_2(HAuCl_4)_2$: Au, 49.8.

Calcd. for $C_6H_8N_2AuCl_4HCl$: Au, 40.7.

Found: Au, 40.3, 40.1, 41.2.

The separate analyses did not agree very well among themselves but indicated a mixed hydrochloride-chloroaurate.

As the analysis of the chloroaurate was unsatisfactory for identification, a chloroplatinate was prepared. It behaved in solubility like the chloroaurate and was prepared in the same way.

Anal. Calcd. for $C_6H_8N_2H_2PtCl_6$: Pt, 37.7.

Found: Pt, 37.7, 37.7.

α-picolylamine was a colorless oil that had only a faint odor and remained colorless for several days but immediately gave a bright red color when a piece of solid potassium hydroxide was added to it. It was soluble in water in all proportions.

β-PICOLYLAMINE. A review of the literature showed that this compound had not heretofore been prepared. Its synthesis was open to the same difficulties as the synthesis of its α- isomer and the yields throughout were lower. The method of synthesis was essentially the same, benzoylmetanicotine, prepared from nicotine according to the directions of Pinner[32], being used as a starting point. Thirty g. of benzoylmetanicotine were dissolved in 300 cc. of 15% hydrochloric acid for ozonization and the synthesis from this point carried out exactly as that of the α- isomer. When concentrated acid was used as a solvent for the ozonization, the yield was lower.

β-pyridylmethanaldoxime was much less soluble in benzene than was its α- isomer. It crystallized in needles from this solvent and could also be crystallized from water. On repeated crystallizations it melted at 148°. Lenart prepared the β-pyridyl aldehyde but did not report the oxime.

The reduction of β-pyridylmethanaldoxime was carried out identically as for the α- isomer. From three 5 g. runs

32 Pinner, Ber., 27, 1057 (1894).

a total of 6 g. base distilling at a constant temperature of 112° under 18 mm. pressure was obtained.

A chloroplatinate when recrystallized from water acidified with hydrochloric acid, did not melt at a temperature as high as 320° although it darkened slightly. Enough for analysis was dried in a vacuum dessicator at room temperature.

Anal. Calcd. for $C_6H_8N_2H_2PtCl_6$: Pt, 37.70.

Found: 37.75, 37.70.

A picrate was not very soluble in alcohol but crystallized nicely in leaves. It melted sharply at 211° on repeated recrystallization.

β-picolylamine was a colorless oil with but a faint odor. It was soluble in water in all proportions and formed a solid carbonate when a drop was allowed to stand in the atmosphere. Unlike its α- isomer it did not become colored when potassium hydroxide was added to it.

MEASUREMENT OF DISSOCIATION CONSTANTS

INTRODUCTION

In reviewing the various methods given in the literature for the determination of dissociation constants, it was evident that the most accurate method was that described by Carothers, Bickford and Hurwitz[33]. By this method the dissociation constant was calculated from the hydrolysis constant which is equal to the hydrogen ion concentration when the base is half neutralized. The hydrogen ion concentration can be best determined throughout a series of compounds, which will give at partial neutralization solutions varying from basic to acidic, by a hydrogen electrode.

In attempting to measure the dissociation constants of N-phenylpyrrolidine and N-p-tolylpyrrolidine it was found impossible to use the method of half neutralization. Both compounds are very weakly basic and very insoluble in water. It was impossible to get them in solution by any amount of acid less than an equivalent. In these cases, after adding an exact equivalent of hydrochloric acid to the free base,

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33 Carothers, Bickford and Hurwitz, J. Am. Chem. Soc., 49, 2908 (1927).

the solution was diluted to a known volume and the pH measured. If the weight of base added and the volume is known, the total concentration of base existing as free base and as salt could be calculated. From these data the dissociation constant was calculated as follows: If the equilibrium expression for the hydrolysis of the neutral salt is written we obtain

$$B^+Cl^- + H_2O \rightleftharpoons BOH + H^+Cl^- \qquad \text{or}$$

$$\frac{(C_{BOH})(C_{H^+})(C_{Cl^-})}{(C_{B^+})(C_{Cl^-})(C_{H_2O})} = K_{hyd} = \frac{K_{H_2O}}{K_B}$$

The concentration of chloride ion is constant, that of water essentially one and the concentration of hydrogen ion obtained by measurement. From the hydrolysis equation the concentration of free base is the same as that of hydrogen ion and of unhydrolyzed base equal to the total concentration of base minus the hydrogen ion concentration. The above expression is then

$$\frac{(C_{H^+})^2}{(C_{Base}-C_{H^+})} = K_{hyd} = \frac{K_{H_2O}}{K_B}$$

EXPERIMENTAL

For measurement of dissociation constants it was necessary to obtain the compounds in a high state of purity. No steps were taken to specially purify pyrrolidine, α-ethylpyrrolidine, α-phenylpyrrolidine, α-picolylamine and β-picolylamine other than that already reported in their synthesis. They were all prepared by one step synthesis from pure compounds. The tertiary amines, N-phenylpiperidine, N-cyclohexyl, N-benzyl, N-methyl, N-butyl, N-phenyl and N-p-tolylpyrrolidine were all run through a Hinsberg primary-secondary-tertiary amine separation. α-ethyl-pyrroline was especially purified as described under its preparation. Nicotine was purified by crystallization of its hydrochloride from absolute alcohol-acetone as described by Harlan and Hixon[34]. From the hydrochloride the free base was regenerated. All compounds measured showed an absolutely constant boiling point.

Small ampules were filled by distillation of from 5 to 15 cc. of the purified compound as described by Ware[35].

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34 Harlan and Hixon, J. Am. Chem. Soc., 52, 3385 (1930).
35 Ware, The Electron Sharing Ability of Organic Radicals-Orthochlorobenzyl Radical, Ph. D. thesis, Iowa State College. Unpublished M. S.

The first compound measured was pyrrolidine. It was found necessary in order to remove all traces of water from the base, to add small strips of metallic sodium to it in the distillation flask and after allowing it to stand in contact with the sodium for several hours, to distil directly into the receiver. Solid potassium hydroxide failed to remove as much as two percent of water from the base. This method of drying was used in all the other derivatives measured.

In the case of the pyridine derivatives, sodium polymerized the material quite badly, and they were not allowed to stand in contact with it long. However the material which distilled over showed a high degree of purity. In the case of α-picolylamine, the distillate was slightly colored. A second distillation was run in which the material was dried over solid potassium hydroxide only and distilled perfectly colorless. Electrometric titration showed both runs to be equally pure.

Before distilling, in order to ascertain if the system was air tight, it was evacuated with an oil pump. The air in the system was dried by passing through concentrated sulfuric acid. After distillation the ampules were sealed as quickly as possible. To prepare for sealing the bulb of each ampule was emersed in warm water and then in

cold. The expansion and contraction removed the free base from the mouth of the ampule and allowed it to be sealed easily. After being sealed, each bulb was washed first in alcohol and then in ether. Each fraction was tested for purity by titrating against 0.0655 normal hydrochloric acid standardized against sodium carbonate using sodium alizarin sulfonate as indicator. If the purity fell below 99.7% the compound was rejected.

Very weakly basic compounds such as N-phenylpyrrolidine which are also very insoluble in water will not give a satisfactory end point in titration. No check could be made on the purity of these compounds except that they showed a very constant boiling point. A color change sharp enough for a satisfactory analysis of nicotine, α-picolylamine and β-picolylamine could not be obtained. This behavior is peculiar as aniline, a weaker base and less soluble, will give a sharp end point. The purity of these three compounds was proven by electrometric titration.

Before the hydrogen ion concentration of a solution was determined the hydrogen electrode was always checked by measurement of the pH of a 0.05 normal standard potassium acid phthalate buffer solution. The value of the solution was always checked by duplicate electrodes against both 0.1 normal potassium chloride and saturated potassium

chloride calomel half cells. The temperature was maintained constant by use of an air bath with a variation of not more than plus or minus 0.2° or a water bath with the same variation.

TABLE I

DISSOCIATION CONSTANTS OF A FEW NITROGEN HETEROCYCLICS

Compound	E.M.F. against Sat. Calomel	Purity Mol. Wt. Theory	found	Acid Added	Dissociation Constant
Pyrrolidine	.9009	71.1	71.3	1/2 equiv.	1.3×10^{-3}
N-Cyclohexyl-Pyrrolidine	.8787	153.19	153	1/2 equiv.	5.0×10^{-4}
N-Benzyl-Pyrrolidine	.8070	161.12	161.7	1/2 equiv.	3.2×10^{-3}
N-Methyl-Pyrrolidine	.8474	85.1	85.4	1/2 equiv.	1.5×10^{-4}
N-n-Butyl-Pyrrolidine	.8581	127.1	127.1	1/2 equiv.	2.3×10^{-4}
N-Phenyl-Pyrrolidine	.4490	--	--	1 equiv.	2×10^{-10}
N-p-tolyl-Pyrrolidine	.4772	--	--	1 equiv.	5×10^{-10}
α-Ethyl Pyrrolidine	.8630	99.1	99	1/2 equiv.	2.7×10^{-4}
α-Phenyl-Pyrrolidine	.8143	147.1	147.3	1/2 equiv.	4×10^{-3}
β-Pyridyl-α-N-Methyl Pyrrolidine	.7157	162.2	162	1/2 equiv.	9×10^{-7}
β-Picolylamine	.7220	108.1	108	1/2 equiv.	1.1×10^{-4}
α-Picolylamine	.7165	108.1	108	1/2 equiv.	1×10^{-4}
α-Ethylpyrroline	.6850	97.1	96.8	1/2 equiv.	2.7×10^{-7}
N-Phenyl piperidine	.4762	--	--	1 equiv.	1×10^{-8}

DISCUSSION OF RESULTS

The data are shown in Table I. The method for measuring dissociation constants leaves much to be desired yet it is the most accurate method in use at present. In measuring the pH of some of the solutions the E.M.F. soon reached a maximum and then showed a gradual drop indicating electrode poisoning. However, the results could easily be duplicated on another solution of the same base and the electrode showed the correct value when placed in the standard phthalate buffer solution immediately after use. The solutions in general did not accurately follow Ostwald's dilution law for those that were one-half neutralized showed some change in K_b when measured at different dilutions.

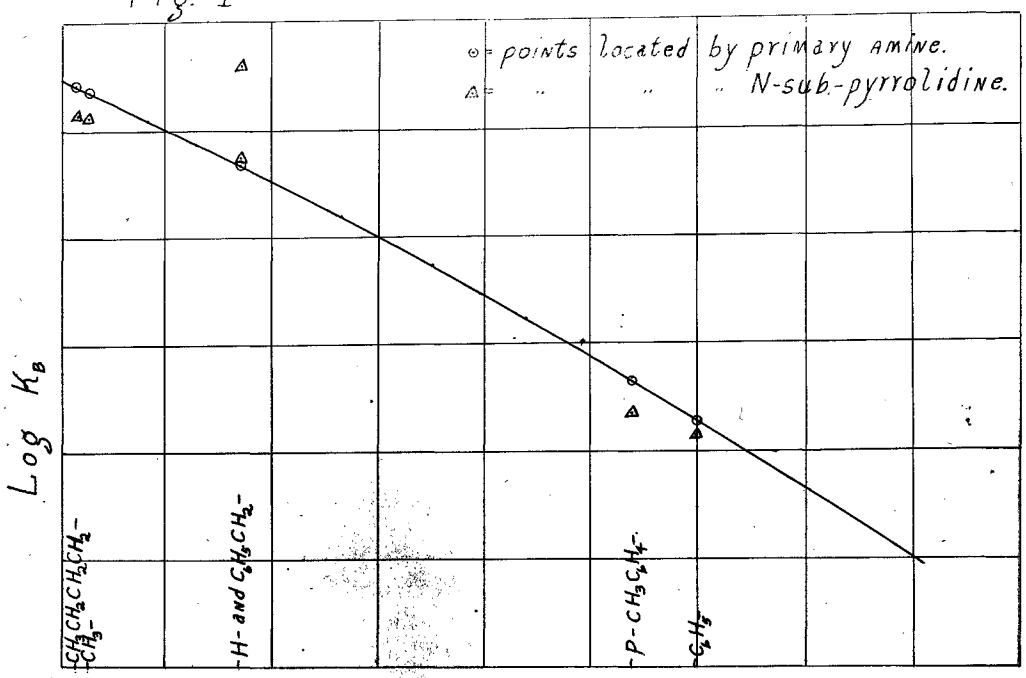
The accuracy of Carother's method of determining dissociation constants depends to a large extent on the fact that at partial neutralization the free base acts as a buffer and small errors in the amount of acid added are negligible. When it was necessary to completely neutralize the base in order to get it into solution it is evident that the accuracy is much less since by the method of calculation the error made in measuring the hydrogen ion concentration is squared.

In the first paper of the series by Hixon and Johns[36]

36 Hixon and Johns, J. Am. Chem. Soc., 49, 1786 (1927).

the available data in the literature were collected and a mathematical relationship pointed out between the dissociation constants and between the free energies of ionization of the five series R(NH_2), R(COOH), R(CH_2COOH), R(CH_2CH_2COOH), and R(OH). In Fig. 1 the data are presented graphically to show that the same relationship holds for the N-substituted pyrrolidine series R(C_4H_8N). The values of electron sharing ability plotted on the abscissa are obtained from the literature as described by Hixon and Johns. The only poor agreement between the values for the radicals given in the literature and those obtained by the pyrrolidine series is that of the radical paratolyl which is not significant when the accuracy of the value given for the dissociation constant of N-p-tolylpyrrolidine is considered. It is a compound very insoluble in water and weakly basic. Hence it was necessary to completely neutralize the base and to use a larger volume of water in order to get it in solution. It had been predicted that the value of the electron sharing ability of hydrogen as shown by pyrrolidine would not be the same as that shown by the primary amine series since in the acid series formic acid shows a dissociation constant not to be expected from the primary amines. This variation in hydrogen can best be attributed to its small size and mass. In organic chemistry the first member of a homologous series

Fig. I



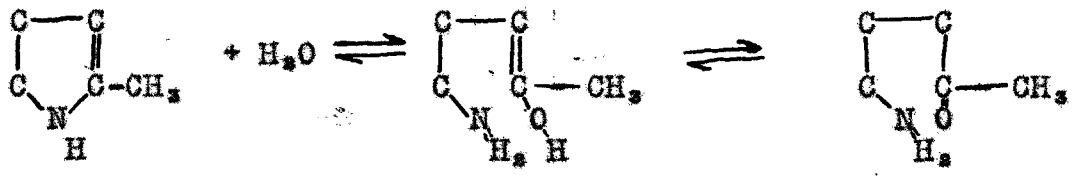
Electron Sharing Ability

is ordinarily considered abnormal.

On the graph an examination will show that there are values lacking between the value for p-tolyl and benzyl or dissociation constants between approximately 5×10^{-5} and 5×10^{-8}. The primary amine curve can be practically superimposed on this curve and a survey of the literature shows that there are few dissociation constants which will have a value in this range. The scarcity of data may indicate that amines of this type are difficult to synthesize due to instability. It is known that the terpene amines are unstable and upon distillation split out ammonia. From their structure it may be predicted that they would have a dissociation constant falling in this range. Glucose amine, an unstable amine, has a dissociation constant of 10^{-5}. Nicotine, having a dissociation constant of 9×10^{-7}, is a very reactive compound and difficult to synthesize. If such a range exists for each series of compounds whether it be an unstable range or not, it will fall when plotted as the pyrrolidine series was plotted, in approximately the same place with slight deviations either to the right or to the left.

The chemistry of the tetrahydropyridines and pyrrolines is interesting in the light of a postulated unstable range as we substitute increasingly negative groups on the nitrogen. The only compound of these series of which a

dissociation constant is measured is α-ethylpyrroline. It has a value 2.7×10^{-7} and is quite a reactive compound. On a basis of comparison of structure it would be predicted that other derivatives of pyrroline as well as the tetrahydropyridines would have a dissociation constant in this range. According to Lipp and Widnmann[17] α-methylpyrroline is not stable as such in aqueous solution but exists in the following equilibrium -

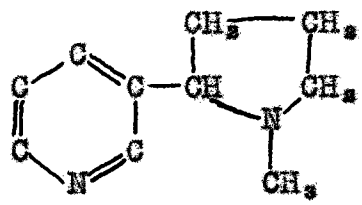


Substitution on the nitrogen increased the tendency to react with water, a negative group having more influence than a less negative. An analogous equilibrium was found with the tetrahydropyridines. It is evident that with these compounds there is not enough affinity in the nitrogen atom to make the ring stable.

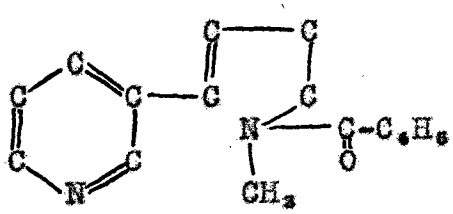
The evidence at present is not sufficient to say conclusively that there is an unstable range since the observations are entirely qualitative in nature. It should also be emphasized that the only measure of affinity recognized must be on the basis of free energy. It is impossible to obtain such a measure where an irreversible reaction is

concerned. However, if such an unstable range does exist, a few cases of so called steric hindrance could be explained simply on lack of affinity. Pentamethylene chloride will condense smoothly with aniline to form N-phenylpiperidine ($K = 10^{-8}$) but if we substitute the more positive radical orthotolyl for phenyl the condensation will not take place. On the basis of the electron sharing ability of the radical orthotolyl it would be predicted that the dissociation constant of N-o-tolylpiperidine would be approximately 10^{-7}.

The chemistry of nicotine may be considered more in detail. It has the following structural formula:



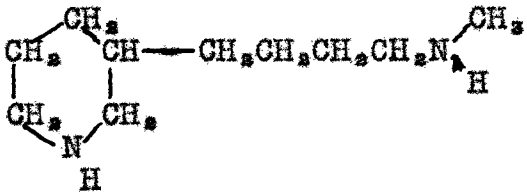
It reacts with benzoyl chloride vigorously at room temperature to form benzoylmetanicotine[31], which is:



An analogous reaction takes place with benzenesulfonyl chloride yet this reagent is used extensively in organic chemistry to separate tertiary amines from secondary

amines assuming that tertiary amines will either not react or form only unstable addition products.

Catalytic reduction of nicotine hydrochlorides at room temperature yields 72% of octahydrometanicotine which is:



These two reactions show that the most reactive point in the nicotine molecule is the carbon-nitrogen bond in the pyrrolidine ring in which the carbon atom is substituted and is a tertiary carbon atom.

If the dissociation constant of nicotine which is 9×10^{-7} and the dissociation constant of α-phenylpyrrolidine, 4×10^{-8}, are considered, it is evident that the β-pyridyl radical is much more negative than the phenyl. An objection to this statement may be raised that the two are not strictly comparable since nicotine has a methyl group on the nitrogen, yet methylation of pyrrolidine, which has much less mass than α-phenylpyrrolidine changes the dissociation constant only from 1.3×10^{-3} to 1.5×10^{-4}. An approximation of the change in dissociation constant caused by methylation of β-pyridyl-α-pyrrolidine can be made by comparison of the value of benzylamine (2.35×10^{-5})[+] and

benzylmethylamine (3.8×10^{-8}).+

Nitrogen is ordinarily considered to be positive in an organical radical and on this basis it has been predicted[37] that the pyridyl radical would be more positive than the phenyl. However, it has also been pointed out that the pyridine ring is very negative[38].

A comparison of the dissociation constants shown in Table II will support the latter conclusion.

TABLE II

Ethylamine	$CH_3CH_2NH_2$	5×10^{-4}
2-phenylethylamine	$C_6H_5CH_2CH_2NH_2$	6.78×10^{-5} ++
Benzylamine	$C_6H_5CH_2NH_2$	2.3×10^{-5} ++
Orthochlorobenzylamine	$O\text{-}ClC_6H_4CH_2NH_2$	6×10^{-6} ++
β-picolylamine	$\beta\text{-}C_5H_4NCH_2NH_2$	1.1×10^{-6}
α-picolylamine	$\alpha\text{-}C_5H_4NCH_2NH_2$	1×10^{-6}

+ Obtained from the literature.
37 Rath, Ber., 57, 840 (1924).
38 Marckwald, Ber., 26, 2887 (1893).
++ Values obtained from literature.

If we plot a curve for the RCH_2NH_2 series against the electron sharing ability of the radicals as determined by the RNH_2 series, we obtain a curve which can be extrapolated to give an approximate value for the electron sharing ability of the pyridyl radical as shown in Fig. 2. The slope of the curve when an intervening CH_2 group is inserted is not as great as the primary amine curve due to the intervening $-CH_2-$ group and hence the sensitivity of the determination of electron sharing ability is much less. However if an attempt were made to locate a pyridyl radical on the primary amine curve by measurement of the dissociation constant of pyridylamine, the constant for the substituting nitrogen would be so near that for the value of the pyridine nitrogen that the result would be inconclusive[39]. The curve does show conclusively that the pyridyl radical is roughly as much more negative than the phenyl as the phenyl is more negative than the methyl.

The substitutents on a carbon atom attached to a negative radical are generally considered to be more reactive. The reactivity of benzyl chloride, bromide etc., is explained on this basis. In the case of nicotine,

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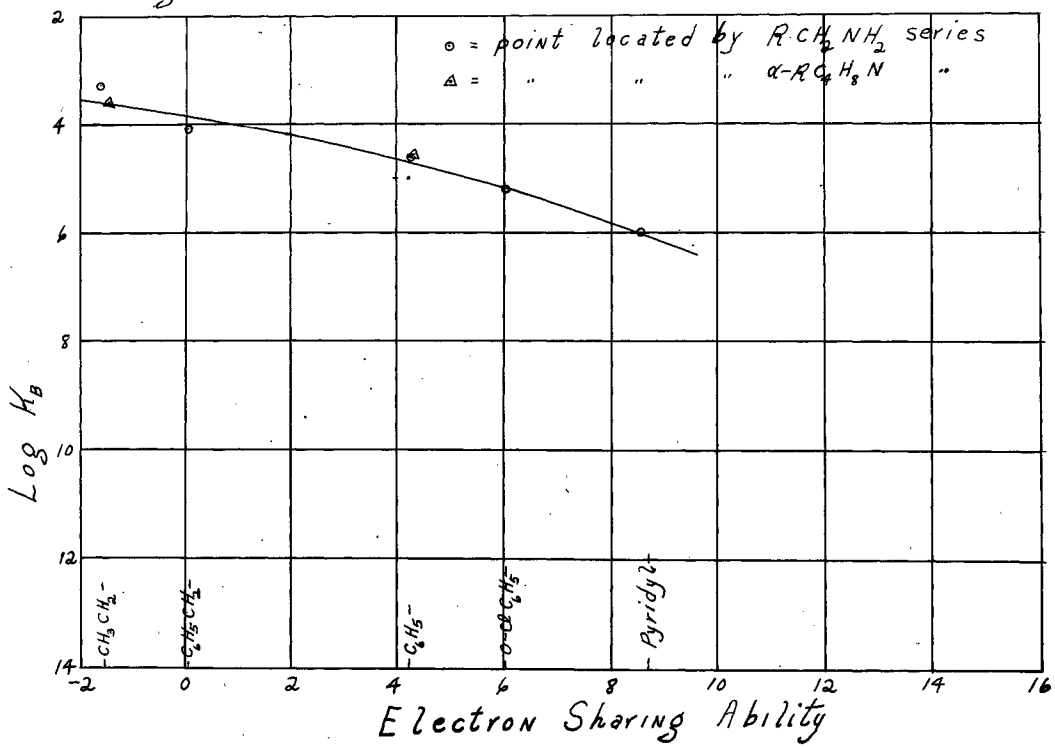
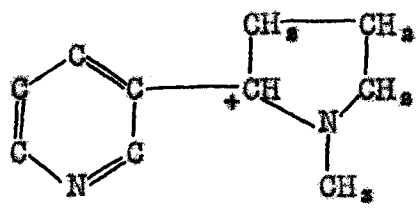
39 Wibaut and LaBastide, Verslag. Akad. Wetenschappen Amsterdam, XXX No 6. (1927).

Fig. II


⊙ = point located by $R.CH_2NH_2$ series
△ = " " " α-RC_4H_8N "
Log K_B
2
4
6
8
10
12
14
-2
0
2
4
6
8
10
12
14
16
CH_3CH_2-
$C_6H_5CH_2$-
C_6H_5-
o-$CH_3C_6H_5$-
-Pyridyl
Electron Sharing Ability



the carbon atom starred has a very negative group, the ρ-pyridyl group, attached to it, an aliphatic group having some degree of negativity, and an amine grouping. It is to be expected that its substituents would be very reactive. This explains the unusual chemical reactivity of nicotine and the ease of rupture of the carbon-nitrogen linkage.

Moreover an amine grouping is not positive in comparison to unsubstituted radicals. If the relative dissociation constants of hydrazine, 2×10^{-6}+, ammonia 2×10^{-5}+ and ethylenediamine, 8.5×10^{-4}+, are considered, it is evident that the direct attachment of an NH_2 grouping lowers the basicity. In pyrrole if the methylene groups are replaced by -N= groupings the acidity is increased. Tetrazine is acidic enough to turn litmus red.

From the information that the pyridine radical is extremely negative, some further interesting pyridine chemistry can be explained. If we consider the dissociation

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+ Values obtained from Landolt Bornstein tables.

constant of the compound $CH_3C{\equiv}CCOOH$, we can place a rough value on the electron sharing ability of the acetylenic radical, $HC{\equiv}C-$. It falls in the same range as the pyridyl radical. Pyridine on the basis of its structural formula, contains no active hydrogen, yet its reaction with metallic sodium has long been known[40]. Undoubtedly acetylene owes its ability to react with metals to the very negative properties of the $HC{\equiv}C-$ radical and it is likewise probable that pyridine forms the isomeric dipyridyls through removal of sodium by oxygen from the compound pyridylsodium. The fact that there is reduction to the compound neonicotine[41] during the formation of the dipyridyls indicates liberation of hydrogen.

If pyridine chemistry is considered from this standpoint it is not extraordinary that pyridine forms peculiar complexes with many metallic compounds and reacts with the Grignard reagent although many of its reactions can be explained on the basis of complex ammonium compounds.

From dissociation constants of the two α-substituted pyrrolidines, α-ethyl and α-phenyl, which are also plotted in Fig. 2 it is evident that the slope of the curve for α-substituted pyrrolidines is identical with that for the RCH_2NH_2

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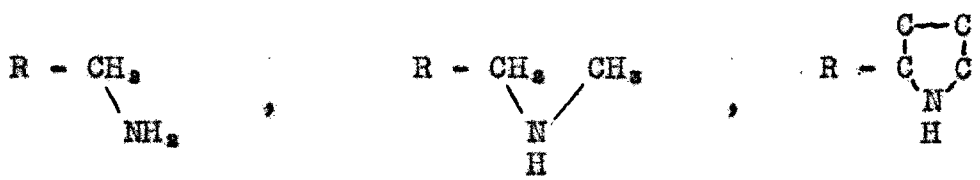
40 C. R. Smith, J. Am. Chem. Soc., 46, 414 (1929).
41 C. R. Smith, J. Am. Chem. Soc., 53, 277 (1931).

series. It is not surprising when the similar structures



are considered although neither the effect of ring formation nor substitution on the nitrogen in RCH_2NH_2 to make a secondary amine, has been shown.

ELECTROMETRIC TITRATION OF NICOTINE, α-PICOLYLAMINE AND β-PICOLYLAMINE

In the titration of these compounds using sodium alizarin sulfonate as indicator in proving the purity of the bases before determining dissociation constants, a sharp color change could not be obtained at the neutralization point. In the hope that some light would be thrown on the reason for this and also as a check on the purity of the samples, electrometric titrations of the three bases were carried out. The titration curves are shown in Fig. 3. Pyridine was titrated also in order that its curve might be compared with that of nicotine.

In carrying out these titrations, an ampule prepared as described under the determination of dissociation constants, was broken under water in the titration beaker. The purity of all the compounds checked the theoretical within the experimental error if the base was considered monobasic.

The curves of nicotine, α-picolylamine and β-picolylamine are similar in type and are plainly the curves of monoacidic bases. They give absolutely no indication of a second break where a weak break should be expected for the pyridine nitrogen. It is evident when a comparison is made with the pyridine titration curve that the basicity of the pyridine nitrogen is lowered by the substitution.

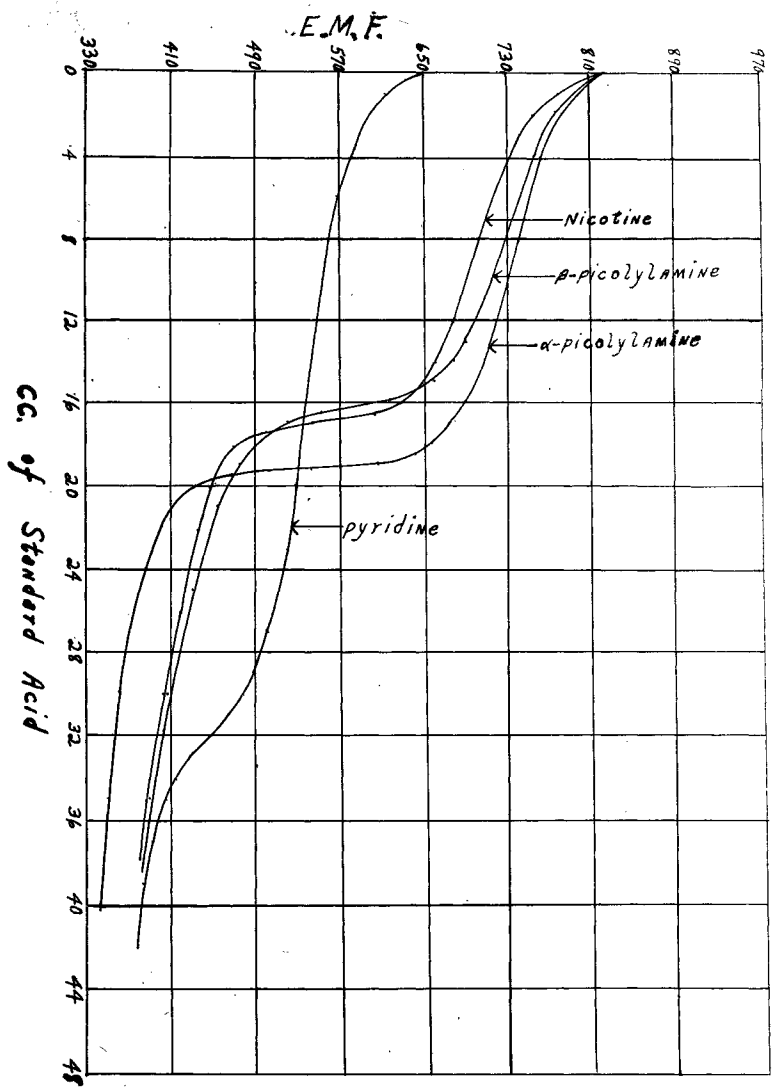

E.M.F.
330
410
490
570
650
730
810
890
970
0
4
8
12
16
20
24
28
32
36
40
44
48
Nicotine
β-picolylamine
α-picolylamine
pyridine
cc. of Standard Acid

Fig II

MEASUREMENT OF INSECTICIDAL ACTION

INTRODUCTION

Two methods have in the past been employed in the testing of insecticides in solution. One depends upon dipping the insect for a certain length of time in varying concentrations[42] and the other upon spraying varying amounts of the solution upon each insect[5]. The latter method may also be used with emulsions.

While the above methods give a relative measure yet results are difficult to duplicate by either method and they are not sufficiently sensitive to accurately show small differences in toxicities.

Most of the compounds for which a relative measure is desired have considerable vapor pressure at room temperature. This suggested testing them as a fumigant. It was thought that uniformity of dosing through control of temperature, concentration, time etc. could be more accurately obtained by working with gases. This fact apparently was upheld by experiment.

For the test animal the insect, Tribolium confusum Duval, was chosen. It is a very hardy beetle of convenient

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42 Shepard and Richardson, Unpublished M.S.

size, is comparatively long lived and does not require very close attention to rear. It does not have pulvilli, which makes it impossible for the insect to climb out of a glass beaker or bottle, and although it has quite well developed wings, seldom attempts to fly.

EXPERIMENTAL

Fig. 4 is a drawing of the apparatus used for toxicity determinations. A. and D. are flowmeters[43] accurately calibrated. Since one flowmeter has only a limited range it was necessary to calibrate enough flowmeters to measure rates of flow varying all the way from 100 cc. per hour to 200 liters per hour. B. and E. are flasks or bottles of approximately three liter capacity which are empty but act as an air cushion eliminating the fluctuations in the flowmeter reading due to bubbling.

The bases being tested are quite strong bases and will absorb carbon dioxide from the atmosphere. They are also hygroscopic and will absorb water. Hence in order to get a constant vapor pressure it is necessary to remove carbon dioxide and water from the gas which bubbles through

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43 Craig and Richardson, J. Econ. Entmol., 23, 988-991(1930).

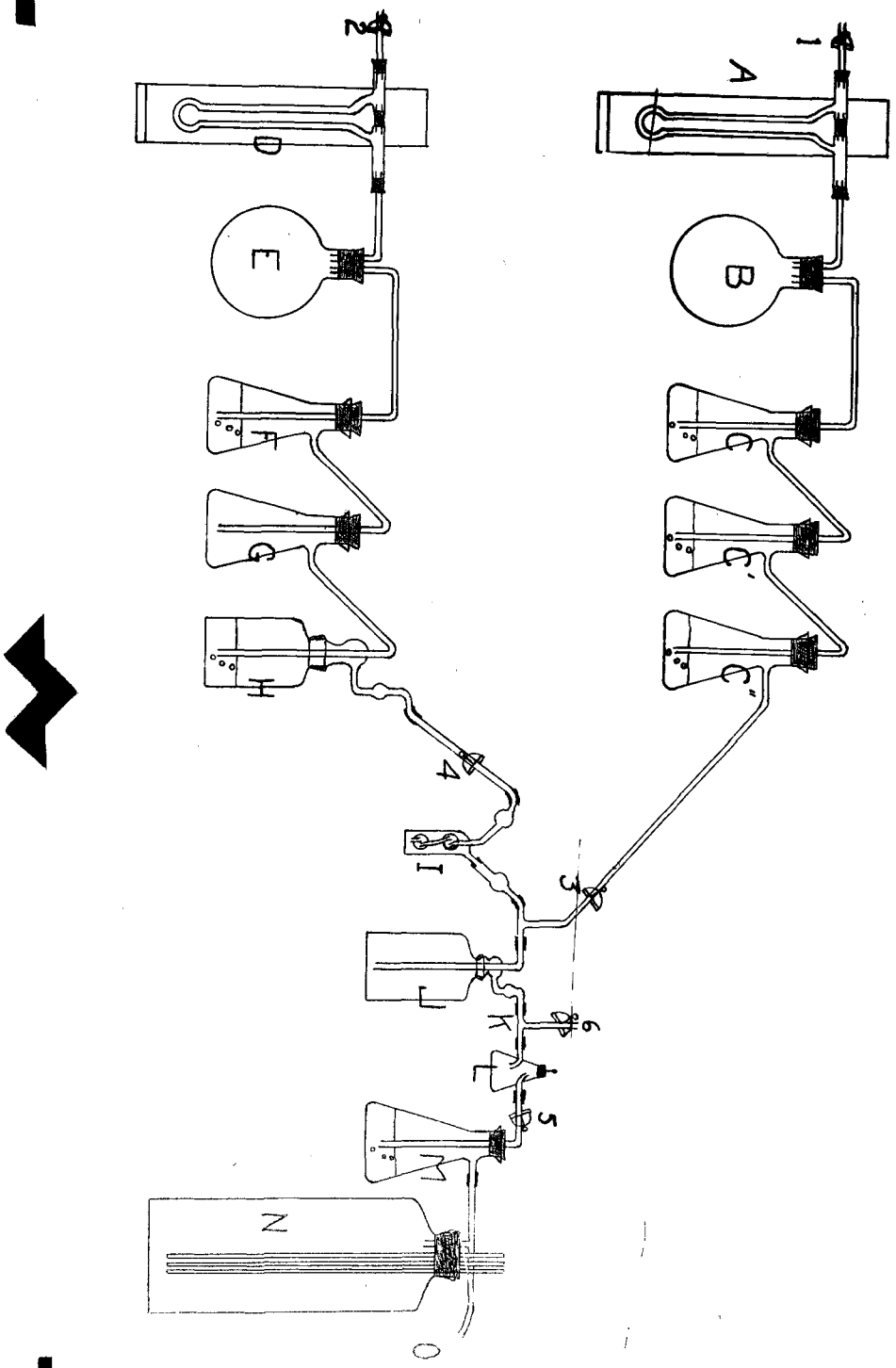

Fig IV

the absorption bottle. F, G and H serve this purpose. F contains strong sodium hydroxide, G is an empty catch bottle to prevent explosions if the system should suck back and H is a ground glass gas absorption bottle containing concentrated sulfuric acid. I is a three compartment potash absorption bottle containing the pure base. In the calcium chloride tube on the side of the absorption bottle is placed glass wool to prevent spray from being carried over.

The various flasks were connected with rubber tubing except from the absorption bottle I to the flask L. Rubber will absorb large amounts of the bases, hence it was necessary that the gas containing the compound did not come in contact with the rubber connections. The joints from I to L were fitted glass to glass as tightly as possible and the pieces of rubber tubing covering the joints dipped in molten paraffin before being placed over the joints. It would be better if these joints were ground glass. However an analysis of the gas going through L checked quite closely the amount lost by the saturating bulb I, when nicotine was used as the test compound. The vapor was analyzed by allowing the gas to bubble through hydrochloric acid and analyzing the resulting solution by the silicotungstic acid method.

As the gas from I is dry and free from carbon dioxide it is necessary to insert the line coming from flowmeter A

which carries air of a known relative humidity in order that the insects will be exposed to an atmosphere not anhydrous but of a constant humidity. The filter flasks C, C' and C" contain sulfuric acid of the correct concentration[44] to make the gas in M have a relative humidity of sixty per-cent.

J is an empty ground glass stoppered gas absorption bottle which acts as a mixer for the gases coming from the two sources. K is a glass T and L is a ground glass stoppered Erlenmeyer of 125 cc. capacity with an inlet and an outlet glass tube sealed into it. It is the chamber in which the insects are exposed. M is a filter flask containing hydrochloric acid to catch the base after it has served its purpose. O leads to an ordinary water pump. Since over long periods of time the water pressure changes and thus alters the rate of gas which would go through the system, it was necessary to insert a device for automatically regulating the pressure. The bottle N acts in this capacity. It is a bottle approximately forty cm. in height and is filled with water. It is fitted with a rubber stopper through which passes one arm of a glass T reaching only barely through the stopper and three glass tubes of three cm. diameter. The glass tubes reach to the bottom of the bottle and are open

44 R. E. Wilson, Ind. Eng. Chem., 13, 327 (1921).

at the top. As long as there is sufficient suction at O to cause bubbles to pass from the lower ends of the glass tubes the pressure throughout the system will be practically constant. If only one glass tube is used, the rate at which bubbles pass will have more effect on the pressure in the system.

The rate and movement of gases through the system are regulated by means of Hoffman clamps which are numbered in the figure. In order to ascertain if the system is air tight before starting an experiment, the clamps one and two are closed and the water pump turned on. If after a few minutes when the system should come to equilibrium, no bubbles appear in N the system is tight.

For each compound the vapor pressure or the weight of base per liter of gas passed through must be determined. This is easily done by accurately weighing the absorption bulb I, allowing a known volume of gas to pass through and weighing again. The value obtained should be checked by repeating the experiment when the rate of flow is different. With this type of absorption bulb a rate of flow exceeding six liters per hour cannot be accurately used.

To obtain the sample of insects for an experiment, the culture flask of cracked wheat containing the insects was shaken. The insects would come to the surface and climb

in large numbers on a piece of blotting paper. They could easily be brushed from the blotter into a beaker with a camels hair brush. This method of obtaining a sample gives a random sample of varying ages. A hundred insects gives a convenient sized sample and was used throughout the experiments performed.

When the concentration of base desired in L was obtained by varying the relative rates of flow through A and D, the clamps were all closed as quickly as possible. The insects were dropped through a glass funnel into L and the glass stopper replaced. The clamps except 6 were then opened and the time noted. After the correct time of exposure clamp 4 was closed to prevent sucking back and clamp 6 opened which allowed a fresh current of air to immediately flow through L. The insects were placed in a small bottle containing a little cracked wheat and covered with cheese cloth. The bottles were kept at a temperature of 30° for several days and the dead counted. Each day a control was run. A control sample received the same treatment except that the insects were not exposed to the gas.

Throughout the experiments the time of exposure to the gas was held constant and the concentration of gas varied. The arbitrary time of 2 hours 38 minutes was selected because the first compound tested, pyridine, at a maximum

concentration gave a fifty percent kill when the insects were exposed for that time.

For each compound tested enough runs were made, usually from eight to twelve, to plot a curve showing the variation of percent kill with concentration, the curve reaching from the unaffected range to the range where one hundred percent were killed. From these data the fifty percent kill point was calculated using the statistical method of evaluating biological data given by Snedecor and Wallace[45]. As the fifty percent kill point is the most valuable point statistically[46] for comparative purposes, relative toxicities of the compounds listed are based on it.

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45 Correlation and Machine Calculation, Official Publication, Iowa State College, Vol. 23, No. 35, 47 P., (1925).

46 J. W. Trevan, Proc. Roy. Soc. (London) 101 B, 483-514 (1927).

RESULTS

Compound	Conc. in g. per liter giving 50% kill in 2 hr. 38 min.	Dissociation Constant
Pyridine	.0346	10^{-10}
N-methyl Pyrrolidine	.0095	1.5×10^{-4}
N-n-butyl-Pyrrolidine	.0017	2.3×10^{-4}
Pyrrolidine	.00109	1.3×10^{-3}
N-phenyl-Pyrrolidine	greater than .000408	2×10^{-10}
α-phenyl-Pyrrolidine	.000245+	4×10^{-5}
Nicotine	.0000306	9×10^{-7}

+ This result is not on the basis of 50% kill but is approximately correct. At maximum concentration obtainable a 25% kill was effected in the time allowed. For all the compounds tested the change in the concentration from 25% to 50% was very slight.

DISCUSSION OF RESULTS

While the method used to determine relative toxicity is slow and tedious yet considering the uniformity of dosage for each insect it should permit quite accurate duplications by other experimenters. If a strain of insects of equal resistance is used the large number of test animals should promote accuracy, at least eight hundred insects being used to test each compound. The chief limitation of the method is that it can only be used for compounds that show considerable vapor pressure or high toxicity.

In any study of toxicity there are three variables to take into consideration namely, concentration, percent kill and time of exposure. In this study the percent kill was held constant at fifty percent through the series as this has been shown to be the most valuable point statistically for comparative purposes in evaluating biological data and with the exception of the first compound, pyridine, the time of exposure was held constant, the relative toxicities being made to depend solely on relative concentrations. While it is permissible to hold the percent kill constant at fifty percent for reasons stated, yet it may not be entirely permissible to hold the time of exposure constant since a slightly different relative toxicity might be obtained for

another time of exposure[47]. The question involves rates of penetration, respiration, etc. There are no data at hand on the question but it seems probable that the same relative toxicity would be obtained as a gas when the time of exposure is not too small.

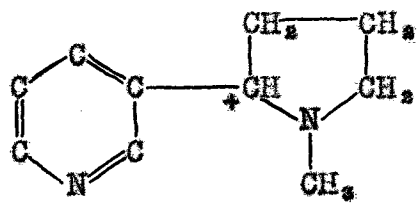
The number of compounds tested is not sufficiently great to make any far reaching statements in regard to the relation of structure and insect toxicity. However, it does suggest a very profitable field in which further research should be done. It is with this idea in mind that the following speculations are made.

Very little is known concerning the basic nature of the cause of high physiological action. Nicotine and related compounds are thought to act as poisons through paralysis of the nervous system. Yet the basic nature of the nerve stimulus itself is not known. As the field is one concerning which so little is known the most that we can hope to do at present is to point out a correlation of effect with some chemical property or combination of properties.

If the nerve stimulus is chemical in nature it might be profitable to look for some point of unusual chemical reactivity in the nicotine molecule. On page 60 of the chemical studies it was pointed out that the most reactive

47 J.B.Allison, Iowa State College J. Sci., Vol. 2, No. 4, 243-252 (1928).

point in the nicotine molecule was the C-N linkage starred in the structural formula,



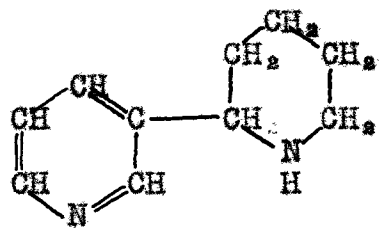
and the explanation for this high reactivity given that the ρ-pyridyl radical is very negative and is able to require a large amount of the affinity of the carbon atom adjoining it which makes the C-N bond weak and very reactive. In the case of hexaphenylethane[48] the same condition in a somewhat higher degree made it possible to isolate the free radical triphenylmethyl. In this compound both carbon atoms are attached to three negative radicals and therefore have very little affinity for each other. Compounds producing free radicals easily have been reported to be very reactive physiologically[49].

The high chemical reactivity of nicotine would make it very easily oxidized or it would have a very low oxidation potential. This is upheld by the fact that pure nicotine rapidly becomes colored and absorbs oxygen when exposed to the atmosphere at room temperature.

Recently Smith, Richardson and Shepard[50] synthesized

48 Gomberg, Ber. 33, 3150 (1900).
49 Nef, J. Am. Chem. Soc., 26, 1549 (1904).
50 Smith, Richardson and Shepard, J. Econ. Entomol., 23, 863 (1930).

neonicotine which is β-pyridyl-α-piperidine and found it to have a toxicity approximately equalling that of nicotine. A close examination of its structural formula,



shows that it should have the same reactive carbon-nitrogen linkage caused chiefly by the β-pyridyl radical.

These authors found α-pyridyl-α-piperidine to be of a much lower order of toxicity. This fact is particularly disturbing, if we wish to correlate chemical reactivity with toxicity, in view of the fact that the dissociation constants of α-picolylamine and β-picolylamine are so close together. Neonicotine should have approximately the same reactivity as α-pyridyl-α-piperidine from a comparison of the negativities of the radicals. However, catalysis has much to do with chemical reactivity and concerning this we have no information.

The toxicity of α-phenylpyrrolidine is lower than that of nicotine and it is to be expected that its chemical reactivity would also be lower since the phenyl radical is less negative than the pyridyl. Its toxicity is greater than the other pyrrolidine derivatives and its chemical reactivity should be greater. It shows some polymerization when heated

with metallic sodium as does nicotine but the other pyrrolidine derivatives do not.

It has been suggested that there might be a correlation between dissociation constants and toxicity[3]. This study shows that if such is the case there is a maxima as we go from the stronger bases to the weaker. It is more probable that toxicity is related to the dissociation constants only as the dissociation constants are related to chemical reactivity. The relation between the dissociation constants and chemical reactivity was pointed out on page 60 of the chemical studies. However, it is significant that the two most toxic compounds, nicotine and α-phenylpyrrolidine fall in the postulated unstable range.

If neonicotine is considered with the series of compounds tested a series of compounds of increasing toxicity approaching and equalling nicotine has been synthesized. This shows that the high toxicity of nicotine is not a property of the nicotine molecule alone or its peculiar molecular makeup but can be duplicated in other compounds.

It is entirely possible that the degree of reactivity has a narrow range, the more reactive compound never reaching the vital centers as such and hence being of low order of toxicity.