molecular weight becomes high the addition of another carbon atom does not produce such marked changes in the melting point.

TABLE I

Compound, mercaptan	M. p., °C.		Half time drop of curve, °C.
Nonyl	− 20.1		0.0
Octyl	− 49.2		.0
Heptyl	− 43.4		.0
Hexyl	− 81.03		.0
Amyl	− 75.7		.0
Butyl	−115.9		.03
Propyl	−113.3	−115.5[a]	.19
Ethyl	−147.3		1.04
Methyl	−123.1	−121.0[a]	0.19

[a] Values from literature "I. C. T."

Since we know accurately the melting points of the normal mercaptans we have a method to test

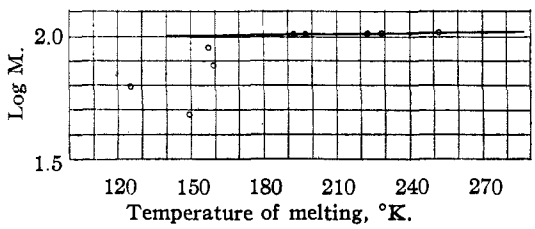


Fig. 3.—Normal mercaptans, Austin method.

the accuracy of the Austin method.[2] A plot of log M against the temperature of melting is given in Fig. 3, where we see that when the logarithm of the molecular weight is two or more the points do lie on a straight line. In Fig. 2 we notice that nonyl mercaptan deviates from the simple linear function, indicating that if we were to plot more members the simple addition rule would break down. Figure 3 shows that Austin's method breaks down completely for the lower members of the series. This indicates that the method applies when the molecular weight is above 100 and that the lower members of the chain series obey the linear addition method.

In Fig. 2 the even membered line has been extended to obtain a value for the melting temperature of methane, which is equivalent to removing two carbon atoms or one sulfur atom. The value obtained is 91°K. while the value given in the literature ("I. C. T") is 89°K.

The author wishes to express his appreciation to Dr. D. H. Andrews, who has given valuable advice in this investigation. Thanks are also due Drs. Reid and Ellis for supplying the compounds.

Summary

1. A modification of the melting point apparatus of Andrews and co-workers is given.

2. The melting temperatures of a series of normal mercaptans are reported.

3. The relation of the melting temperature to the number of carbon atoms in the chain is discussed.

BALTIMORE, MARYLAND RECEIVED JANUARY 15, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Synthesis of Alpha-Nicotine and Alpha-Nornicotine

BY LYMAN C. CRAIG[1]

The results of a previous paper indicate[2] that toxicity in the alpha substituted N-methylpyrrolidine series increases as the negativity of the alpha substituting radical increases. Nicotine may be considered a member of the series and is more toxic than the synthetic preparations. However, the beta pyridyl radical is far more negative than the other alpha substituting radicals in the series. The alpha pyridyl radical has been shown to be of a like order of negativity as the beta[3] and the alpha pyrrole radical somewhat less negative but yet more negative than any of the radicals in the series prepared above. In view of this it seemed interesting to prepare and study the physiological properties of α-(α-pyridyl)-N-methylpyrrolidine (α-nicotine) and α-(α-pyrrole)-N-methylpyrrolidine. This paper reports the synthesis of the former compound and some intermediates in the synthesis of the latter. The literature contains two accounts[4] in which a proposed synthesis of α-nicotine was partially completed.[5]

For the preparation of these compounds the

(1) National Research Fellow.

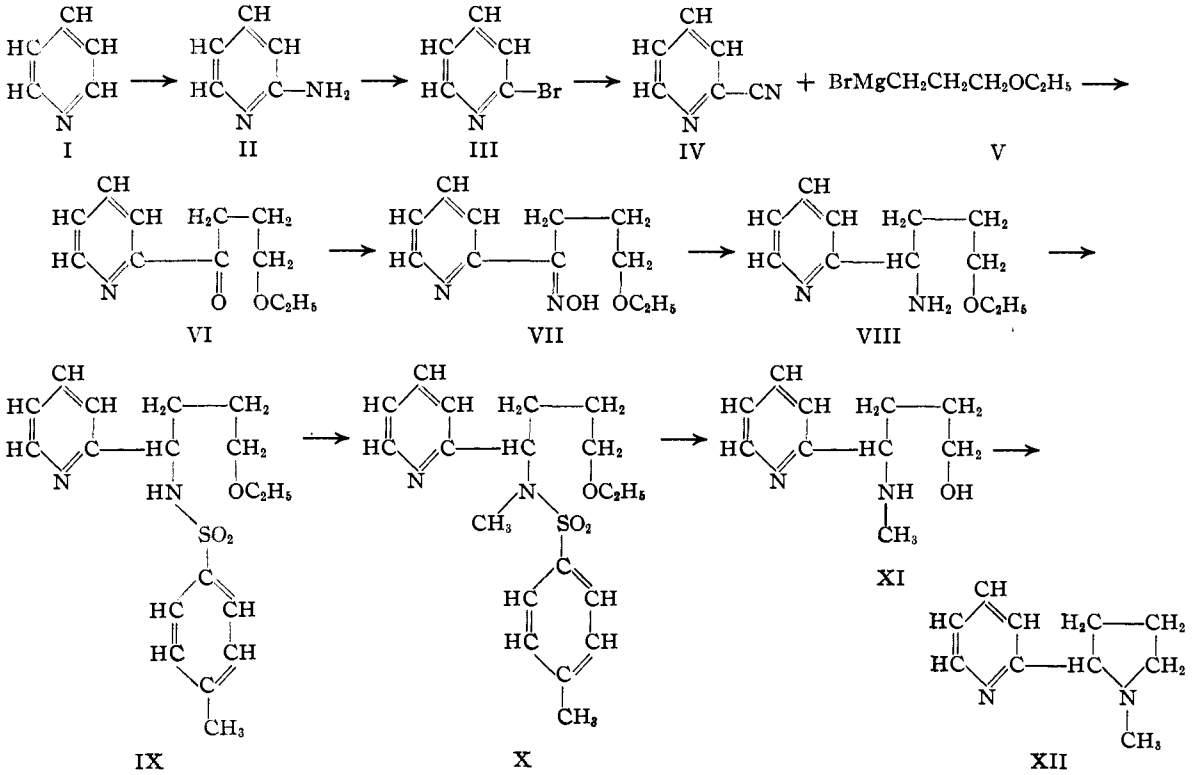
(2) Craig, THIS JOURNAL, **55**, 2543 (1933).

(3) Craig and Hixon, *ibid.*, **53**, 4367 (1931).

(4) Wibaut and Dingemanse, *Rec. Trav. Chim.*, **42**, 1033 (1923); Tschitschibabin and Bylinkin, *Ber.*, **56**, 1745 (1923).

(5) Shortly after the completion of the experimental work reported in this paper Wibaut and Oosterhuis, *Rec. Trav. Chim.*, **52**, 941 (1933), reported the synthesis of α-nicotine although according to their analytical data a final pure product was not isolated. Their method of synthesis is entirely different from the one reported here.

general method of synthesis reported[2] cannot be used since it requires a preparation of the Grignard reagent of the radical desired and while the pyrrole radical forms a Grignard reagent the reagent is not sufficiently reactive to react with α-N-methylpyrrolidone. The following synthesis is suitable for the preparation of alpha-nicotine and allowed the preparation of the compound in this Laboratory.

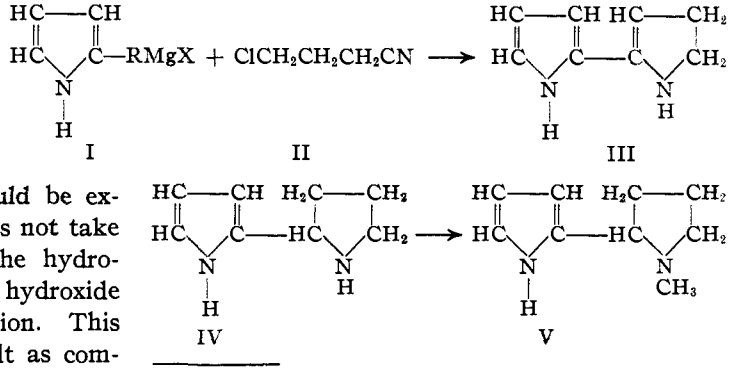


Although the above synthesis is quite long, entailing eleven separate and distinct synthetic steps, none of the steps require elaborate synthetic procedure and each gives a rather good yield, the lowest being 53% of the theoretical; 200 g. of pyridine will yield approximately 25 g. of α-nicotine.

The elimination of water from compound XI to form XII offered considerable difficulty. Compound XI is unstable and cannot be isolated. The spontaneous elimination of water would be expected. However, this apparently does not take place. Treatment of a solution of the hydrobromide of XI with strong potassium hydroxide solution results in complete tar formation. This was a surprising and unexpected result as compound XII was later found to be perfectly stable to potassium hydroxide. Water was finally withdrawn from compound XI by means of potassium carbonate in the presence of ethyl ether.

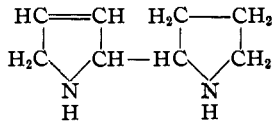
α-Nornicotine was prepared from compound VIII by splitting the ether linkage with hydrobromic acid and subsequent elimination of water from the resulting amino alcohol. Elimination of a molecule of water was accompanied by the same difficulty as in the above synthesis.

It is doubtful whether the above synthesis could be modified to allow the preparation of α-(α-pyrrole)-N-methylpyrrolidine because of the susceptibility of the pyrrole ring to strong acid. A more probable method of synthesis is the following.[6]



(6) Craig, Bulbrook and Hixon, THIS JOURNAL, **53**, 1831 (1931).

Compound III was prepared without exceptional difficulty but attempts to reduce it to IV with zinc and alcoholic hydrochloric acid gave a smooth reduction to a base having the empirical formula $C_8H_{14}N_2$, which is most probably α-pyrroline-α-pyrrolidine. The base so obtained is a very stable compound as compared to the 4,5-dihydropyrroles[7] and therefore probably has the formula



The pharmacological and also the insecticidal properties of the above compounds are being studied and will be reported in separate publications in the pharmacological and entomological literature.

Experimental

α-Pyridyl-α-ethoxypropyl Ketone.—A Grignard reagent prepared from 64 g. of γ-ethoxypropyl bromide,[8] 12 g. of magnesium and 320 cc. of anhydrous ether is allowed to drop slowly into a solution of 40 g. of picolinic acid nitrile[9] in 300 cc. of ether, which is being stirred vigorously with a mechanical stirrer. After standing overnight the addition product is hydrolyzed with 70 cc. of concentrated hydrochloric acid in an equal volume of water. Excess ammonium hydroxide is then added to the mixture. The ether layer is fractionated; 5 g. of unreacted nitrile and 40 g. of compound boiling at 124–127° (5 mm.) are obtained. Upon redistillation practically the entirety of the second fraction passes at 125° (5 mm.). The yield is 54% of the theoretical as based on the bromide used or 62% on the nitrile.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.3; H, 7.82. Found: C, 68.3; H, 7.82.

α-Pyridyl-α-methoxypropyl ketone is a colorless odorless oil which is slightly soluble in water and soluble in organic solvents. It forms an oxime and phenylhydrazone but both derivatives are oils. The compound has not heretofore been reported in the literature.

1-(α-Pyridyl)-1-amino-3-ethoxypropane.—A solution of 410 cc. of 90% alcohol, 29 g. of hydroxylamine hydrochloride and 40 g. of α-pyridyl α-ethoxypropyl ketone is refluxed overnight. The alcohol is then distilled off on the steam-bath and 50 cc. of water added to the residue. Potassium carbonate is then added until all the oxime is separated and the oxime extracted with a small volume of ether. The ether is evaporated on the steam-bath. The oily oxime could not be made to crystallize. It is an undistillable oil and as it does not lend itself readily to purification an analysis was not made.

The oily oxime is dissolved in 460 cc. of 95% alcohol and 242 g. of zinc dust and 242 cc. of glacial acetic acid added alternately in small portions over a period of two to three hours. During the reduction the temperature of the mixture is not allowed to rise above 50°. The mixture is allowed to stand overnight, then cooled to 0°. The excess zinc and zinc acetate are filtered off and washed with a small volume of cold alcohol. The alcoholic filtrates are evaporated to a thick sirup on the steam-bath using reduced pressure (20 mm.); 50 cc. of water is added to the sirup and solid potassium hydroxide until the oily base readily separates from the zinc hydroxide mixture. The oily layer is removed and dried over solid potassium hydroxide. Upon fractionation 33 g. distil at 132–135° (5 mm.). The yield is 84% of the theoretical. Upon refractionation all but a small amount passes at 133° (5 mm.).

Anal. Calcd. for $C_{11}H_{18}ON_2$: C, 67.8; H, 9.37. Found: C, 67.5; H, 9.2.

1-(α-Pyridyl)-1-amino-4-ethoxybutane is a colorless odorless oil that is soluble in water and in organic solvents in all proportions. Neither a picrate nor an oxalate could be made to crystallize. The phenyl thiourea could not be made to crystallize. A report of the compound could not be found in the literature.

α-Nornicotine.—A solution of 33 g. of 1-(α-pyridyl)-1-amino-4-ethoxybutane and 210 g. of 45% hydrobromic acid is placed in a flask which has an air condenser approximately 61 cm. long attached. The top of the air condenser is bent downward into a water condenser. The solution is heated by means of an oil-bath at a temperature just barely insufficient to cause the hydrobromic acid to distil over the air condenser (140–150°). Heating is continued until the theoretical weight of ethyl bromide has distilled over.

The solution is evaporated to a thick sirup on the water-bath using reduced pressure (20 mm.) and the basic oil liberated with a slight excess of ammonium hydroxide while the mixture is immersed in ice water; 100 cc. of ether is added and sufficient anhydrous potassium carbonate to remove the aqueous layer. The solid layer is extracted repeatedly with ether. Fractionation of the ether extracts gives 11.5 g. of material passing at 120° (12 mm.). The yield is 45% of the theoretical.

Anal. Calcd. for $C_9H_{12}N_2$: C, 73.0; H, 8.16. Found: C, 73.25; H, 8.36.

α-Nornicotine is a rather pleasant smelling oil that is soluble in water and in organic solvents in all proportions. It forms a picrate that melts at 166° when recrystallized from alcohol. The base reacts vigorously with phenyl isothiocyanate but a crystalline product could not be isolated.

1-(α-Pyridyl)-1-(*p*-toluenesulfonyl-amino)-4-ethoxybutane.—A mixture of 25 g. of sodium hydroxide, 300 cc. of water, 33 g. of 1-(α-pyridyl)-1-amino-4-ethoxybutane and 40 g. of *p*-toluenesulfonyl chloride is well shaken and finally heated to dissolve the excess chloride. The sulfonamide is then precipitated by a stream of carbon dioxide. It is filtered off, washed with water and dried. It weighs 45 g.; 12 g. more of the amide can be obtained from the filtrate by treating with a fresh portion of *p*-toluenesulfonyl chloride.

Anal. Calcd. for $C_{18}H_{24}N_2O_3S$: C, 62.2; H, 6.95. Found: C, 62.45; H, 7.03.

(7) Craig, THIS JOURNAL, **55**, 295 (1933).

(8) Noyes, *Am. Chem. J.*, **19**, 766 (1897).

(9) The synthesis of this compound is to be reported in connection with another study and will appear in the near future.

The sulfonamide is a white crystalline solid that is soluble in ethyl alcohol but insoluble in water. It shows a constant melting point of 96° when recrystallized from a mixture of alcohol and water.

α-Nicotine.—1-(α-Pyridyl)-1-(*p*-toluenesulfonyl-amino)-4-ethoxybutane can be methylated in the cold with methyl sulfate but the reaction is not quantitative. After numerous trials the following procedure was found to give a sharp separation of the methylated from the unmethylated derivative.

Thirty-seven grams of the amide is dissolved in a solution of 12 g. of sodium hydroxide in 120 cc. of water. After cooling to 0°, 13 g. of dimethyl sulfate is added and the mixture shaken vigorously for ten minutes, after which it is allowed to stand for one-half hour with occasional shaking. The mixture is repeatedly extracted with petroleum ether until the oily layer has disappeared. The petroleum ether is distilled off on the steam-bath; 13 g. of oily residue remains which cannot be made to crystallize. Twelve grams of unmethylated amide can be recovered from the alkaline solution. As the methylated product is an undistillable oil that is difficult to purify an analysis was not made.

Thirty-nine grams of the methylated residue described above is dissolved in 300 cc. of 46% hydrobromic acid and placed in the flask described under the synthesis of α-nornicotine. The procedure from this point on is identical with that of α-nornicotine, both the *p*-toluenesulfonyl group and the ethoxy group being split off by the hydrobromic acid; 11.5 g. of oil is obtained which boils at 122° (25 mm.). The yield is 66% of the theoretical.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.0; H, 8.69. Found: C, 74.2; H, 6.78.

α-Nicotine is a colorless oil with a faint odor resembling nicotine but less sharp. It is soluble in water and organic solvents in all proportions. It forms a picrate that upon repeated recrystallization from alcohol melts at 169°. It does not react with phenyl isothiocyanate.

α-Pyrrole-α-pyrroline.—A pyrrole Grignard reagent is prepared from 22 g. of pyrrole, 20 g. of ethyl bromide, 9 g. of magnesium and 300 cc. of ether; 30 g. of α-chlorobutyronitrile is added slowly to the Grignard reagent and the mixture refluxed for four hours. It is then hydrolyzed with ice and ammonium chloride and the mixture extracted with ether. Fractionation of the ether extract yields 13.5 g. of pyrrole, 15.5 g. of γ-chlorobutyronitrile and 9.5 g. of an oil boiling at 144–145° (5 mm.).

Anal. Calcd. for $C_8H_{10}N_2$: N, 20.9. Found: N, 20.9.

The yield is 45% of the theoretical as based on the nitrile used or 56% as based on the pyrrole used. The compound is a colorless oil that is odorless and insoluble in water but soluble in organic solvents. It is soluble in strong acid. It does not form a well-defined picrate or oxalate. The compound has not heretofore been reported.

α-Pyrroline-α-pyrrolidine.—A solution of 9.5 g. of α-pyrrole-α-pyrroline in 50 cc. of 95% alcohol is constantly stirred while 43 cc. of hydrochloric acid in 120 cc. of alcohol is added dropwise and a slight excess of zinc dust added from time to time in small portions. The flask is kept below room temperature during the reduction. Concentrated potassium hydroxide is then added until the mixture is slightly alkaline and the solid precipitate filtered off. The alcoholic filtrate is made acid with acetic acid and the alcohol distilled off on the steam-bath under reduced pressure. The residue is washed well with ether. It is then treated with potassium hydroxide until two layers separate. The oily layer is dried with solid potassium hydroxide and distilled; 4.5 g. of oil distil at 135–140° (12 mm.).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.5; H, 10.2. Found: C, 69.3; H, 10.2.

α-Pyrroline-α-pyrrolidine is a colorless oil that is soluble in water and in organic solvents. It titrates as a monoacidic base. It forms a phenylthiourea that melts at 151° when recrystallized from alcohol. A picrate recrystallized from water melts at 141°.

Several experiments were made to effect the reduction of α-pyrrole-α-pyrroline to α-pyrrole-α-pyrrolidine by a catalytic method using the Adams and Shriner platinum oxide platinum black catalyst. The theoretical volume of hydrogen was absorbed when either acetic acid or alcohol to which an equivalent of hydrochloric acid had been added, was used as a solvent but the reduction product in all cases, although colorless in the hydrogen atmosphere, decomposed rapidly to a tarry material as soon as air was admitted to the reaction chamber. This decomposition took place even when the acid of the solution was neutralized before air was admitted. Since it appeared that α-pyrrole-α-pyrrolidine was unstable to the atmosphere the synthesis was abandoned.

Summary

The synthesis of α-nicotine and α-nornicotine is described.

Some intermediates in the synthesis of α-(α-pyrrole)-N-methylpyrrolidine are reported.

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