

CONCERNING CERTAIN PYRIDINE HOMOLOGS

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Ladenburg has synthesized certain of the simpler alkaloids from pyridine homologs, for example coniine¹ from 2-methylpyridine. Moreover, pyridine or its homologs are found among the decomposition products of many of the important alkaloids, hence it is believed that other alkaloids can be built up from these simple bases if the proper methods are employed. For instance, nortropine is an intermediate between pyridine and tropine. It can be converted into 2-ethylpyridine, or into tropine, by proper treatment. Attempts² have been made to convert 2-ethylpyridine into nortropine. The authors consider 2:6-dimethylpyridine a better starting material than the ethyl isomer for this synthesis. Linking two methyl-groups, after halogenation, to produce the desired seven-membered ring should be easier than linking the ethyl-group at the proper place on the pyridine nucleus.

Residues from the commercial rectification of pyridine were used as a source of 2:6-dimethylpyridine. The method for separation and purification outlined by Heap, Jones and Speakman³ was followed. Fractional distillation of the dry bases brings about partial separation of the homologs. The fraction boiling at $137^{\circ} \pm 2^{\circ}\text{C}$. is composed largely of the 2:6-dimethylpyridine and a smaller quantity of 3-methylpyridine. The approximate proportions of these two bases are reversed in the fraction boiling at $143^{\circ} \pm 2^{\circ}\text{C}$. The 3-methylpyridine was removed as the double zinc chloride salt. The non-crystallizable mother liquid was then converted into the double mercuric chloride salt for separation of the 2:6-dimethylpyridine. The proportions of reagents recommended by Heap, Jones and Speakman for the production of these double salts failed to give us well formed salts. In order to overcome this difficulty, the proportions of the reagents were varied; this caused a change in the composition of the resulting salts, however, their physical constants showed that pure products had been obtained.

Bromination of the methyl-group of the pure base, 3-methylpyridine, was carried out. Monobrom-3-picoly hydrobromide dibromide was obtained by the use of an excess of bromine upon a solution of the base in carbon tetrachloride, maintained at the boiling temperature and exposed to sunlight.

The great difficulty of purification of the bases and of the brominated product lead to the attempt at chlorination of the fractions obtained by distillation without further purifying them. We sought thereby to eliminate one of the lengthy separation procedures in preparing pure halogenated pyridyl compounds. The chlorinating agent was nascent chlorine produced by the action of hydrogen chloride on potassium chlorate, both in the aqueous and in the anhydrous condition. A crystalline substance, having the formula $\text{C}_5\text{H}_5\text{Cl}_3$ was produced in about constant amounts with either chlorination mixture. The dry chlorination mixture yielded resinous trichloropyridines, one of which was isolated in the hydrated form.

¹Ladenburg, Ber. 14, 2409 (1881); 17, 1676 (1884); 18, 1587 (1885); 19, 439, 2578 (1886); 22, 1403, 2583 (1889); 26, 854 (1893); 27, 3062 (1894); 28, 163, 1991 (1895).

²Ladenburg and Adams, Ber. 24, 1671 (1890).

³Heap, Jones and Speakman, J. Am. C. S. 43, 1876, 1936 (1921).

Sell and Dootson⁴ have studied the action of phosphorous pentachloride upon pyridine and of dry chlorine upon fused pyridine hydrochloride. From these reaction mixtures, they isolated the highly chlorinated derivatives of pyridine, the pentachloride, all of the tetrachlorides and three of the trichlorides. A tar remained, which they presumed contained lower chlorinated derivatives. We have not been able to separate from the resinous mixture any substance containing more than three chlorine atoms per molecule. The trichloropyridine isolated from this reaction mixture appears to have very weak basic properties, or none at all, for it forms neither double salts nor an hydrochloride.

Apparatus. The mixture of the dry bases was fractionated by means of a ten-section Young and Thomas still head. One portion of the bases was fractionated through the Young and Thomas still head connected in series with two Dufton type columns as used by Wilke and Shaw⁵. The apparatus was put together with cork stoppers. The pyridine disintegrated the stoppers, even when wrapped with tin-foil, rather rapidly. The three column still gave good fractionation but the leakage was great. Therefore, most of the bases were distilled four times through the single still head rather than once through the triple column head. The receivers were protected from the moisture of the air by means of a calcium chloride tube.

The pure bases were dried at the boiling temperature over solid caustic soda in a flask sealed to a condenser tube, the upper end of which carried a calcium chloride tube.

A three neck, 500 cc. pyrex flask constituted the reaction vessel for the chlorination experiments with dry materials. This flask was equipped with an inlet tube of wide bore for bringing in the hydrogen chloride, a stirrer bearing a mercury seal and a reflux condenser.

Experimental. *3-Methylpyridine Zinc Chloride Hydrochloride.* A cooled mixture of 1 mole of zinc chloride, 1 mole of hydrochloric acid and 2 moles of water was added slowly, with cooling, to 2 moles (methylpyridine) of each of the pyridine fractions boiling at $137^{\circ}\pm 2^{\circ}\text{C}$. and $143^{\circ}\pm 2^{\circ}\text{C}$. respectively. The resulting mixture was cooled with ice until the crystallization was complete. The viscous mass was filtered with suction, whereby most of the non-crystalline zinc chloride double salts were removed. Recrystallization of the residue four times from alcohol gave a white crystalline substance having a constant melting point of 175° . Analysis: 0.5008g.Sbst.: 27.75 cc.N/10HCl—0.4555g.Sbst.: 0.0829g. Zn. (electrolytic), 0.5125g.Sbst.: 42.24 cc. N/10 AgNO₃, (C₆H₇N)₂. ZnCl₂.HCl.Calc. Base 51.88, Zn 18.13, Cl 29.71. Found Base 51.37, Zn18.1, Cl 29.3.

The base was liberated with excess sodium hydroxide, extracted with ether, the extract dried and the ether removed. The base so obtained distilled completely between 143.6°C . and 143.8°C . (all of mercury column immersed in vapor), barometer 747 mm. Analysis: 0.3005g.Sbst.: 0.8521g.CO₂, 0.2121g.H₂O C₆H₇N. Calc. C 77.4, H 7.5. Found C 77.6, H 7.9.

The picrate melted at 149°C ., the auric chloride salt at 179°C ., the platinum chloride salt at 224°C ., the mercuric chloride salt at 145°C ., the carboxylic acid at 230°C .

2,6-Dimethylpyridine Mercuric Chloride Tetrahydrate. The viscous filtrate obtained from the preparation of the 3-methylpyridine zinc chloride was made

⁴Sell and Dootson, J. C. S. Trans. 73,432 (1898); 75,979 (1899); 87,799 (1905).

alkaline and steam distilled. This distillate was acidified with hydrochloric acid and concentrated. Hot aqueous mercuric chloride solution was added to the concentrated distillate until precipitation was complete. Recrystallization of the product from fifth normal hydrochloric acid gave blade-like crystals. To free the dimethylpyridine salt from the accompanying methylpyridine salt, the hot concentrated acid solution was cooled slowly to near room temperature. When needles began to appear, the blade-like crystals were quickly filtered free of the mother liquid. Repeating this operation a few times produced a salt of constant composition melting at 178°C. Analysis: 0.5531g.Sbst.: 7.5 cc. N/10HCl. —0.5047g.Sbst.: 0.0.2961g, HgS.—0.5071g.Sbst.: 0.5047g. AgCl. (CH₃)₂. C₅H₃N.HCl.2HgCl₂.4H₂O. Calc. Base 14.2, Hg 52.8, Cl 23.5. Found Base 14.7, Hg 50.6, Cl 24.6.

The base obtained from this salt boiled at 138° ± 0.5°C. at 745 mm. Analysis: 0.3012g.Sbst.: 0.8651g. CO₂, 0.2217g. H₂O. C₇H₅N. Calc. C 78.5, H 8.4. Found C 78.4, H 8.2.

The platinum chloride salt melted at 209°C.

Monobrom-3-picoly Hydrobromide Dibromide. 10g. of 3-methylpyridine in 100 cc. of carbon tetrachloride and a small crystal of iodine were placed in a 250 cc. transparent silica flash fitted with a reflux condenser. The apparatus was set up outside of the window to permit conducting the bromination in direct sunlight. To the boiling solution, 27 g. of bromine dissolved in 40 g. of carbon tetrachloride were added dropwise over a period of about two hours, and the mixture refluxed for an hour after the addition of the bromine was completed. The brominated product separated as a heavy brown oil. The free bromine was extracted with several portions of carbon tetrachloride. Large brown crystals were obtained from the oil when dissolved in a mixture of equal volumes of alcohol and ethyl acetate. After decolorization and recrystallization, pale yellow thick prisms were obtained, melting at 200°C. The picrate melted at 207°C. The crystals lost their pale yellow color when exposed to the air for a few days, becoming covered with a white film. Heating to 110° causes slow volatilization. Analysis: 0.1250g.Sbst.: 0.0797g. CO₂, 0.0237g. H₂O—0.1054g.Sbst.: 5.04 cc. N/10 Na₂S₂O₃—0.1995g.Sbst.: 0.3592g.AgBr.BrCH₂.C₅H₅N.HBr.Br₂. Calc. C 17.35, H 1.93, Br (perbromide) 38.7, Br(total) 77.4. Found C 17.35, H 2.12, Br(perbromide) 38.3, Br(total) 76.7.

Chlorination with Aqueous Hydrogen Chloride and Potassium Chlorate. One mole of pyridine (fraction distilling below 130°) was mixed with 4.5 moles of concentrated hydrochloric acid. To this was added one third mole of a hot saturated solution of potassium chlorate. Chlorine was evolved, the solution turned yellow and a precipitate formed. The amount of material separating bore a constant ratio to the quantity of base used in the reaction. This substance, when filtered off and recrystallized from alcohol, separated as slender needles, melting at 217°. Melting points had to be taken quickly before the material sublimed to the cold portion of the tube. The analytical data approximated the formula C₅H₅Cl₃.1.5H₂O. 0.1527g.Sbst.: 0.2340g. CO₂, 0.0385g. H₂O—0.1846g.Sbst.: 0.3281g. AgCl. C₅H₅Cl₃.1.5H₂O. Calc. C 40.6, H 3.4, Cl 45.2. Found C 41.8, H 2.8, Cl 44.4.

This compound gives neither a precipitate with alcoholic silver nitrate, nor a blue color with starch-potassium iodide solution, nor a double salt with platinum chloride. These tests show that it is not basic. This substance has been

formed either by chlorination of a hydrocarbon or by the condensation of non-nitrogenous remnants from the cleavage of the pyridine nucleus.

After removal of the precipitate, the acid mixture was distilled under reduced pressure. Chlorine, water and hydrochloric acid were removed before any of the pyridine derivatives started to volatilize. The separated potassium chloride was filtered off when it caused excessive bumping. The hydrochlorides of the pyridine bases distilled between 130° and 138° at 10 mm. Fractions were taken at each degree. When sodium hydroxide solution was added to these solid distillates, a brown solution resulted. Dehydrated magnesium sulfate, although slower in removing the water, was used to dry the ether extract of the base rather than the usual solid sodium hydroxide, since the caustic soon became covered with a brown resin. The brown gum or resin which remains after distilling off the ether and the pyridine from the dried ethereal extract, chars, with evolution of hydrogen chloride, when strongly heated, but does not volatilize. Since no method for preparing a crystalline product from this brown resin could be found, it was not analysed.

The results show that only small quantities of chlorinated substances are obtained by the action of aqueous hydrogen chloride-potassium chlorate mixture upon pyridine.

Chlorination with Dry Hydrogen Chloride and Potassium Chlorate.

Difficulties are to be anticipated in the use of this chlorinating mixture, since the chlorine dioxide, produced by the action of hydrogen chloride upon potassium chlorate, is a powerful oxidizing agent, which reacts explosively with many substances. Although pyridine is very resistant to oxidation, its hydrochloride will char if the temperature of the reaction mixture reaches 140°C.

To execute this method of chlorination, the base and the chlorate were placed in a flask equipped with a condenser, a stirrer and an inlet tube for hydrogen chloride. Keeping the reaction mixture below 75°C., slow introduction of hydrogen chloride and efficient stirring are essential to the smooth procedure of the reaction. The potassium chlorate does not enter the reaction until most of the base has been changed to the hydrochloride. Solid hydrochlorides collecting on the sides of the flask permit local overheating, which starts a violent reaction with the evolution of hydrogen chloride and the formation of a tar. This type of decomposition usually results when the temperature of the reaction mixture is kept above 75°C. after the potassium chlorate begins to react. The fact that pyridine hydrochloride has a low melting point and, when fused, dissolves the hydrochlorides of the higher homologs to some extent, permitted the use of fractions boiling below 130°C., while higher boiling fractions gave a reaction mass which could not be kept broken up. The end of the reaction was marked by the evolution of free chlorine, which was evidently due to the action of the water formed in the reaction inhibiting the union of chlorine and pyridine while not affecting the action of hydrogen chloride on the chlorate. If only 0.05 mole of water was added to the reaction mixture, chlorine was freely evolved after the hydrochloride was formed and the amount of the chlorinated product was greatly decreased.

One mole of pyridine and one third mole of potassium chlorate were treated with 2.2 moles (10% excess) of dry hydrogen chloride. Such a ratio of reagents will produce the hydrochloride and slightly more chlorine than will enter into reaction with the base. The resulting product was a pasty mass. The potassium

chloride could be removed quantitatively by filtering and washing the residue with absolute alcohol.

Pouring the resulting filtrate into a large amount of water produces a yellow flocculent precipitate. The aqueous solution (to be designated as portion A), obtained by removal of the material insoluble in water (portion B) contains the hydrochloride of the base and a chlorinated derivative similar to, if not the same as, the chlorinated derivative which separated as a brown tar when the base was distilled in the experiments with the aqueous chlorinating mixture.

Portion B was resinous, dissolving readily in alcohol and acetone, slightly in ether and ethyl acetate, scarcely at all in water, benzol and carbon disulfide. A solution of the resin B in alcohol or in acetone deposited crystals in about the same amount, having the same melting point and composition as those obtained from the aqueous chlorinating mixture. No other crystalline substance was separated. Steam or direct distillation caused decomposition without separating any volatile substance. Reducing the pressure did not change these results.

A mixture of trichloropyridines was obtained by the purification or decomposition produced by repeatedly dissolving the resin B in alcohol and pouring the solution into water. The substance during this treatment became lighter in color and lost its power to liberate iodine from potassium iodide. When dried over phosphorous pentoxide under vacuum, the material had a light tan color, subsequent drying at 110°C. caused only a slight darkening, while if the moist precipitate was placed in an oven at 110°C. considerable blackening occurred and some hydrochloric acid was liberated. The material dried at 110°C. discolors at 170°C. and melts with frothing at 177°C. A small amount of a platinic chloride salt separates as flattened pale yellow diamond shaped crystals, melting at 258°C., whenever the alcoholic solution is evaporated almost to dryness.

Dissolving the resin in hot concentrated nitric acid liberated quantities of nitrogen peroxide and gave a yellow solution, which, when poured into water, yielded a yellow precipitate. When freed from nitric acid by reprecipitating the alcoholic solution with water and dried, a clear brittle resin was obtained melting at 90° C. with much frothing. Drying at 110°C. to determine water of hydration was impossible, since hydrogen chloride was freely evolved. Analysis: 0.2985g. Sbst.: 0.3104g. CO₂, 0.0507g. H₂O—0.2971g. Sbst.: 0.5598g. AgCl.—0.4198g. Sbst.: 23.5 ccm. N (27°/745 mm.) C₅H₂NCl₃.1.5 H₂O. Calc. C 28.6, H 2.4, N 6.7, Cl 51.0. Found C 28.4, H 1.9, N 6.0, Cl 51.0.

This trichloropyridine does not form salts with platinic chloride or with mercuric chloride; it gives no precipitate with silver nitrate. The arrangement of the chlorine atoms is such, therefore, that the basic properties of the nitrogen atom are neutralized. Treatment with alcoholic ammonia in a sealed tube at 180°C. caused a change in the composition of the resin but crystallizable products could not be isolated from the resulting reaction mixture. The investigation is to be continued.

