A mechanism was proposed not only for this condensation reaction but also for all similar condensation reactions between compounds containing the ethylenic linkage and phenols in the presence of sulfuric acid.

Further work, as to the condensation possibilities of unsaturated hydrocarbons, mono- and di-olefins, alcohols, (esters, ethers), aldehydes (acetals) and ketones, acids, nitriles, amines and halides with mono- and polyhydroxy phenols is being carried out.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

NEONICOTINE AND ISOMERIC PYRIDYLPIPERIDINES[1]

BY C. R. SMITH

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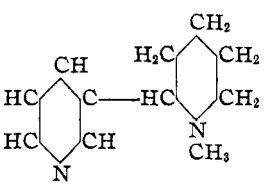
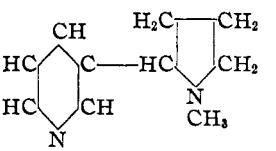
In a previous publication[2] on the interaction of sodium, pyridine and oxygen, the principal products isolated by the procedure outlined were γ,γ-, α,α-, β,γ- and β,β-dipyridyls. Later work has shown that, in addition to these compounds, there are formed water-insoluble bases boiling between 200 and 270°, richer in hydrogen than the dipyridyls, and a water-soluble base of especial interest which has been isolated and identified as β-pyridyl-α-piperidine. This compound has been called "neonicotine" because of its resemblance to nicotine in chemical structure and its toxicity to aphids and other soft-bodied insects.[3]

Neonicotine, $C_{10}H_{14}N_2$, resembles nicotine in structure more than does any of the other isomeric pyridylpiperidines. It is the only one of the pyridylpiperidines that has yet been prepared which shows any marked toxicity to insects.

A comparison of the formulas of neonicotine and nicotine reveals the similarity in structure. The N-methylneonicotine is shown in Formula I for comparison with nicotine (II)



Methylneonicotine I



Nicotine II

[1] Presented as a part of the Insecticide Symposium before the Division of Agricultural and Food Chemistry at the 79th Meeting of the American Chemical Society, Atlanta, Georgia, April 7 to 11, 1930.

[2] C. R. Smith, THIS JOURNAL, **46**, 414 (1924).

[3] Toxicity results are to be reported elsewhere in a joint publication with Dr. C. H. Richardson and H. H. Shepard.

Pictet and Rotschky[4] reported the alkaloids nicotelline, nicoteine and nicotimine, in addition to nicotine, as being present in the tobacco plant. They suggested that nicotelline, $C_{10}H_8N_2$, was possibly an unknown dipyridyl. This must be incorrect since all the dipyridyls are now known, and the properties of nicotelline do not agree with any of them. Nicotimine, $C_{10}H_{14}N_2$ was described as an oil boiling at 250–255°, forming a picrate which crystallizes in thick prisms melting at 163°. It was suggested that nicotimine might be β-pyridyl-α-piperidine, which is the constitution ascribed by the author to neonicotine. Neonicotine boils at 280–282°, forms a picrate which melts at 213° (corr.) and crystallizes from water in prismatic needles. The two substances are evidently different.

There are nine possible pyridylpiperidines. The γ,γ-derivative, called isonicotine, was first prepared by Weidel and Russo.[5] The β,β-derivative, nicotidine, was prepared by Skraup and Vortmann.[6]

To these are now added the α,α, one β,γ and the two α,β-derivatives (one of which is neonicotine) prepared in this study.

Attempts to synthesize neonicotine directly from α,β-dipyridyl have usually resulted in the production of α-pyridyl-β-piperidine or isoneonicotine. It is plausible to assume that neonicotine is formed in the sodium, pyridine and oxygen reaction by some secondary reduction of α,β-dipyridyl, in spite of the fact that the author has been unable actually to separate and identify that dipyridyl. But this failure might well be ascribed to its complete reduction or the difficulties encountered in its detection. Also, attempts to increase the yield of neonicotine by the preliminary addition of α,β-dipyridyl to the sodium reaction have not as yet succeeded.

Weidel and Russo, using a different sodium–pyridine reaction, reported the presence of isonicotine. There is no indication according to the author's method of any pyridylpiperidine other than neonicotine being formed. If present, certain of these, including isonicotine, would undoubtedly appear in the neonicotine fraction as separated by the methods used.

Neonicotine has been shown to be a reduced α,β-dipyridyl because reduction with hydrogen using platinum as catalyst leads to α,β-dipiperidyl. Tin and hydrochloric acid reduction of α,β-dipyridyl leads to the formation of isoneonicotine, which is shown to be α-pyridyl-β-piperidine because it readily forms picolinic acid on oxidation with alkaline permanganate. Neonicotine would be expected to oxidize to nicotinic acid but seems to be oxidized to an intermediate product which resists complete oxidation to the acid. This oxidation will be still further studied. All the pyridylpiperidines that have been prepared except isonicotine are liquids which fume in air more readily than the dipyridyls. When warmed their odor

[4] Pictet and Rotschky, *Ber.*, **34**, 696 (1901).

[5] Weidel and Russo, *Monatsh.*, **3**, 851 (1882).

[6] Skraup and Vortmann, *ibid.*, **4**, 597 (1883).

is usually suffocating, suggesting nicotine to a certain extent. The freshly distilled oil on standing develops a sperm-like odor. Isonicotine, however, has a pleasant odor (resembling commercial opium according to Weidel and Russo). The hydrochlorides of the pyridylpiperidines are hygroscopic and are soluble in alcohol, whereas those of the dipyridyls and dipiperidyls are insoluble. The bases themselves are soluble in water in all proportions and are not extracted by ether unless strongly alkaline. When completely dried all are soluble in ether. α-Pyridyl-α-piperidine is the most soluble in ether; neonicotine is the most difficult to extract from alkaline media.

The pyridylpiperidines undergo some decomposition on distillation at atmospheric pressure, whereas the dipyridyls and dipiperidyls are unaffected. The picrates of the pyridylpiperidines crystallize well from hot water and melt with little or no decomposition, thus differing from the dipiperidyls, which usually decompose before the melting point is reached (α,β-dipiperidyl is excepted). Their nitroso derivatives all appear to be non-crystalline except nitroso-isonicotine, and are of little use in identification but may be used in freeing the pyridylpiperidines from the dipyridyls. This separation can also be effected satisfactorily by the absolute alcohol–hydrochloric acid method as used for neonicotine.

The tin reduction method of preparing the pyridylpiperidines is not satisfactory except in the case of isonicotine. Experiments that have been made with sodium reduction show that in all probability reduction to dipiperidyl is never complete but that some hexahydro product is formed along with considerable unaltered dipyridyl and tar. New methods of reduction are being tried in the hope of obtaining better yields and purer products with less manipulation.

Experimental

Isolation of Neonicotine.—Twenty-five grams of sodium, cut in thin slices, was treated with 700 cc. of dry pyridine (b. p. 115°) at room temperature for twenty-four hours or longer until the sodium had completely reacted, forming sodium dipyridine. The mixture was then digested for ten hours at 115°, cooled, and oxidized with dry oxygen at 90° until the black color had completely changed to brown with no lumps remaining. Twenty-five cubic centimeters of water and 400 cc. of ether were then added to the mixture, which was maintained at a temperature below the boiling point of ether. After standing, the sodium hydroxide tarry liquor slowly settled out, permitting decantation of the pyridine–ether layer. Fresh quantities of ether were added to the residue until it was essentially free of pyridine and soluble oils. After the pyridine and ether were removed by distillation from an oil-bath, the oil residue was distilled in a vacuum until a slight decomposition and darkening of the distillate was apparent. The dipyridyl mixture containing the neonicotine was next treated with an excess of hydrochloric acid and evaporated with 95% alcohol to separate γ,γ-dipyridyl dihydrochloride. After the dihydrochloride was filtered off, fresh additions of 95% alcohol were made and evaporation repeated until nearly all the γ,γ-dipyridyl had been removed. The alcohol was next removed from the filtrate by evaporation, and the bases were freed by caustic soda. Most of the oily layer was removed mechanically and the

remainder extracted with ether. The combined oil and ether extractions were dried with solid caustic and distilled in a vacuum, the water, pyridine and alcohol in the first part of the distillation being rejected. The distilled oil was dissolved in ether, and the water-soluble dipyridyls and neonicotine were washed out with several small portions of water. The ether contained principally α,α-dipyridyl and the oils boiling below 270° contained a little β,γ-dipyridyl, and some unidentified oils boiling above 305°.

The water-soluble oils and neonicotine were evaporated with a slight excess of hydrochloric acid to low volume, freed by caustic soda, and dried in ethereal solution. The ether was removed and the oils were distilled *in vacuo*. In order to remove the water-soluble dipyridyl, principally the β,γ, the distillate was dissolved in absolute alcohol and then absolute alcohol saturated with dry hydrochloric acid gas was added to precipitate the dipyridyls. In all about 300 cc. of alcohol was required, and complete precipitation was insured by passing hydrochloric acid gas through the mixture. The filtrate was evaporated until the alcohol was removed and the impure neonicotine was then liberated with caustic soda.

The neonicotine was extracted with ether only when completely dried with lumps of caustic soda or potash. The ether was removed and the residue containing neonicotine distilled first in vacuum to remove traces of water, pyridine, etc., and then under atmospheric pressure, being collected between 275 and 285°. In order further to purify the neonicotine it was necessary to form the picrate first in alcohol solution and to recrystallize it from water. The neonicotine picrate formed prismatic needles melting at 213° (corr.). The base obtained from the picrate after careful drying boiled at 280–281° at 775 mm. pressure.

Neonicotine picrate is very insoluble in 95% alcohol, but digestion with several portions of boiling alcohol probably dissolves contaminating dipyridyl picrates from the impure picrate, causing it to become hard instead of oily. Water is excellent for recrystallizing the neonicotine picrate as well as all the other picrates of the pyridylpiperidines.

The first impure preparations of neonicotine that were prepared analyzed low in hydrogen, but as the methods of separation were improved the hydrogen content reached 7.9 to 8.8%. Considerable difficulty was encountered in low carbon determinations but this was overcome by using platinum asbestos catalyst and burning slowly in oxygen.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.07; H, 8.64; N, 17.33. Found: C, 73.69; 74.21; H, 8.30, 7.94; N (Dumas), 17.7.

Reduction of Neonicotine.—Neonicotine was hydrogenated in dilute hydrochloric acid solution, with the Adams–Vorhees platinum catalyst. The theoretical for 6H is 3.7%; the absorption found ranged between 3.9 and 4.0%. The filtered solution was concentrated, the base liberated and extracted with alcohol–ether mixture, and a weighed portion of the purified base was titrated with standard acid. The results agreed closely with the titration of dipiperidyl.

Neonicotine obtained from the picrate was reduced with hydrogen and the boiling point of the dipiperidyl was found to be 269–270°, the same as α,β-dipiperidyl. The nitroso derivative of the dipiperidyl melted at 88°. The melting point was unchanged when the substance was mixed with pure dinitroso-α,β-dipiperidyl (m. p. 88°). The dipiperidyl picrate melted at 225° and was unchanged by admixture of α,β-dipiperidyl picrate. Neonicotine is thus shown to be a hexahydro-α,β-dipyridyl. It might be either β-pyridyl-α-piperidine or α-pyridyl-β-piperidine.

α,β-Dipyridyl.—The preparation of α,β-dipyridyl followed the procedure previously described[7] except that it has been very much simplified by the elimination of the

[7] C. R. Smith, THIS JOURNAL, **52**, 397 (1930).

lead acetate precipitation which was followed by hydrogen sulfide to remove the lead. In the improved method the solution of the potassium dicarboxylate of the α,β-dipyridyl, after filtration of the manganese dioxide, is evaporated to low volume and acidulated with hydrochloric acid until congo-red paper is just turned blue. This assures the proper hydrogen-ion concentration to precipitate quantitatively the dicarboxylic acid. If too much acid is used, alkali may be added, followed carefully by acid until the indicator just changes color. The precipitated acid can be obtained very pure by dissolving in boiling water, decolorizing with carbon and evaporating to low volume.

Reduction of α,β-Dipyridyl.—When α,β-dipyridyl was reduced with tin and hydrochloric acid, it was found that only a part was reduced to the hexahydro compound. In the reduction experiments four to five parts of tin were used to one of dipyridyl in a large excess of hydrochloric acid. After removal of the hydrochloric acid by evaporation on the steam-bath, the addition of water always disclosed an insoluble portion of double chloride of tin and unreduced α,β-dipyridyl. These precipitates can be filtered off and reduced with additional quantities of tin and acid although the author preferred to reject all insoluble fractions formed at first or during subsequent removal of the tin with hydrogen sulfide. The α,β-dipyridyl was often recovered from the insoluble precipitates by adding alkali and extracting with ether and used for later reductions. When free from tin the hydrochloric acid solution turned wine-red on evaporation. The addition of caustic potash produced an orange-red color and liberated the base, which was extracted with ether containing alcohol. The extract was evaporated and the residue distilled under reduced pressure. The distillate was dissolved in ether, and the reduced product was washed out with a small quantity of water. The reduced product was recovered by adding alkali and extracting with ether–alcohol, followed by evaporation of the solvent and distillation. The product thus obtained should be either neonicotine or isoneonicotine. Results show that the product obtained by the tin reduction of α,β-dipyridyl is probably isoneonicotine and is α-pyridyl-β-piperidine.

Isoneonicotine picrate melted at 217–218° (corr.); neonicotine picrate melted at 212–213°. A mixture of the two melted at 200°. When isoneonicotine was oxidized with potassium permanganate, the only acid produced was picolinic acid. Neonicotine was at first readily oxidized by permanganate but then seemed to resist further oxidation so that the expected nicotinic acid was not found. The permanganate oxidation of neonicotine and its alkyl derivatives will be studied further.

Isoneonicotine boils at 282° (760 mm.) with partial decomposition. Its odor is similar to that of neonicotine.

α,α-Pyridyl-piperidyl.—α,α-Dipyridyl was reduced with tin and hydrochloric acid, four parts of tin to one of dipyridyl. Heat was applied toward the end of the reaction to dissolve the tin completely. Considerable insoluble double chloride of tin and unreduced dipyridyl was formed and removed by filtration. Filtration was also used to eliminate it when it was formed during the removal of the hydrochloric acid by evaporation and of the tin with hydrogen sulfide. When free from tin, the acid solution of the α,α-pyridylpiperidine turns green on evaporation. Addition of alkali turns the solution purple and liberates the base, which was extracted by ether. The base, after removal of the ether, was distilled under reduced pressure. It still contains some α,α-dipyridyl and other contaminating oil, which can be removed by petroleum ether extraction of the aqueous solution. The free base finally obtained has a sperm-like odor similar to neonicotine. It boiled at 265–266° (756 mm.).

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.07; H, 8.64. Found: C, 73.97; H, 8.71.

α,α-Pipyridylpiperidine forms a picrate melting at 187°, crystallizing from water in small prisms. The nitroso derivative was formed as an insoluble oil. After extraction by ether and evaporation of the solvent it remained an oil and was not further studied.

Isonicotine (**γ-Pyridyl-γ-piperidine**).—Isonicotine was first prepared by Weidel and Russo. The author prepared several lots of 30 g. each by hydrochloric acid reduction of γ,γ-dipyridyl, rejecting all insoluble double chlorides formed during the isolation of the base. The reduction of γ,γ-dipyridyl by this method appears to be more readily effected than the reduction of any of the other dipyridyls tried.

Isonicotine was obtained as a pleasant smelling substance quite different in odor from the other pyridylpiperidines studied, which have more of a sperm- and nicotine-like odor. It distilled water white in a partial vacuum, solidifying to a hard mass of crystals melting at about 80° as described by Weidel and Russo. After several distillations in a partial vacuum to remove all water, isonicotine begins to boil at 292° under atmospheric pressure. The thermometer slowly rises during the distillation because of polymerization, and a residue is left in the flask. Evidently 292° is the proper boiling point (Weidel and Russo gave it as far above 260°). Isonicotine forms a picrate, crystallizing from water in prismatic needles which melt at 215–218° with evolution of gas.

When treated in concentrated solutions with sodium nitrite and dilute hydrochloric acid, the nitroso derivative separated as an oil, which was extracted with ether. The evaporation of the ether leaves the nitroso derivative, which crystallizes. After recrystallization from dilute alcohol it was found to melt at 112°.

The methylation of isonicotine by means of dimethyl sulfate, methyl iodide or potassium methyl sulfate always resulted in complete failure. The first two reagents caused the formation of nothing but tar even when the reaction was very carefully moderated. The potassium methyl sulfate did not react at all.

Nicotidine.[8]—The reduction of β,β-dipyridyl with tin and hydrochloric acid was found to be very incomplete. More than 80% of the dipyridyl was recovered as the hydrochloride after the removal of the tin and the addition of absolute alcohol. β,β-Dipyridyl seems to resist reduction more than any of the other dipyridyls tried (α,γ not available).

The reduction of β,β-dipyridyl with sodium and absolute alcohol was also tried. Eight grams of dipyridyl dissolved in 300 cc. of absolute alcohol was reduced with 15 g. of sodium. Examination of the reduced base showed considerable unaltered dipyridyl along with nicotidine. Treatment with absolute alcohol and hydrochloric acid was used to remove dipyridyl and dipiperidyl. The nicotidine distilled at 284–285° and is a viscous oil with an odor similar to that of neonicotine. The product was not pure, as shown by the character of the picrate first formed. Several recrystallizations were required to obtain a product melting at about 206°.

β-Pyridyl-γ-piperidine.—β,γ-Dipyridyl seems to be more readily reduced than α,α-, β,β- or α,β-dipyridyl but less readily than γ,γ-dipyridyl. The usual insoluble double salt did not appear until the acid was evaporated to low volume and the residue diluted with water. The combined insoluble precipitates contained about 30% of the original dipyridyl. The reduced oil fraction was shown still to be impure by the appearance and melting point of the picrate obtained after precipitation in alcoholic solution and recrystallization from water. The picrate consisted largely of leaflets mixed with needles and melted around 233° after darkening around 210°. The product was finally purified through the nitroso derivative, which separated as an oil and was extracted with ether. After decomposition with concentrated hydrochloric acid, liberation of the base with alkali, and distillation under reduced pressure, the resulting oil formed a picrate in long fern-like needles. The recrystallized product melted with slight darkening at 240° and appeared to be a uniform product.

The reduction product of this dipyridyl proved to be β-pyridyl-γ-piperidine because it gave only nicotine acid on oxidation with potassium permanganate.

[8] Skraup and Vortmann, *Monatsh.*, **4**, 597 (1883).

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.07; H, 8.64. Found: C, 73.87, 74.20; H, 8.67, 8.82.

Summary

1. Neonicotine (β-pyridyl-α-piperidine) was separated from the products obtained in the author's sodium–pyridine–oxygen reaction. Nicotimine, isolated by Pictet and Rotschky from the nicotine alkaloids and tentatively identified by them as the same product, is probably different.

2. The reduction of γ,γ-, β,γ-, α,α- and β,β-dipyridyls by tin and hydrochloric acid results in varying yields of the corresponding pyridylpiperidines. The ease of reduction is probably greatest with γ,γ, diminishing in the order given, β,β being the least easily reduced.

3. Attempted synthesis of neonicotine from α,β-dipyridyl usually resulted in isoneonicotine but further study is to be made to accomplish this end successfully.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE α,α'-DIMETHYLSUBERIC AND α,α'-DIBROMO-α,α'-DIMETHYLSUBERIC ACIDS

BY CATHERINE CASSELS STEELE[1]

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Satisfactory methods for the preparation of tetramethylene bromide (1,4-dibromobutane) have not been available until recent years, with the result that, although several α,α'-dialkyl substituted adipic[2] and pimelic[3] acids have been synthesized, the corresponding derivatives of suberic acid (1,6-hexane-dicarboxylic acid) are unknown. Perkin[4] used a crude mixture of tetra- and pentamethylene bromides on the sodium salt of malonic ester, but obtained from the action of the tetramethylene bromide only the closed chain compound, ethyl 1,1-pentamethylene-dicarboxylate. In the preparation of the dialkyl acids, one molecular proportion of the bromide was condensed with one of the sodium salt of malonic ester to give two products; one was the ester of a closed chain acid[5] and the other the ester of a straight chain tetracarboxylic acid.[6] The latter results from the action of one mole of bromide on two moles of malonic ester.

[1] Commonwealth Fund Fellow.

[2] Lean, *J. Chem. Soc.*, **65**, 1004 (1894).

[3] Perkin and Prentice, *ibid.*, **59**, 829 (1891).

[4] Perkin and Haworth, *ibid.*, **65**, 88 (1894).

[5] Ethyl trimethylene-dicarboxylate, Perkin, *ibid.*, **47**, 807 (1885); ethyl tetramethylene-dicarboxylate, Perkin, *ibid.*, **51**, 2 (1887).

[6] Ethyl butane-tetracarboxylate, Perkin, *ibid.*, **51**, 19 (1887); ethyl pentane-tetracarboxylate, Perkin, *ibid.*, **51**, 241 (1887); Curtius, *J. prakt. Chem.*, [2] **94**, 340 (1916).