TABLE V

CONSTANTS OF ESTERS AND ACIDS

Compound	B. p., °C.	n_D^{20}	d_4^{20}	Found, % C	H
Diethyl dialkyl malonates (all alkyl groups normal)					
$C_3H_7C(CO_2C_2H_5)_2C_{14}H_{29}$	180–184 (0.2–1.0 mm.)	1.4459	0.9141	72.29	11.63
$C_5H_{11}C(CO_2C_2H_5)_2C_{12}H_{25}$	178–181 (0.2–1.0 mm.)	1.4460	.9112	72.30	11.58
$C_7H_{15}C(CO_2C_2H_5)_2C_{10}H_{21}$	182–186 (0.2–1.0 mm.)	1.4459	.9116	72.23	11.71
Calcd. for each isomer of $C_{24}H_{46}O_4$				72.29	11.64
Nonadecanoic Acids					
$C_3H_7CH(CO_2H)C_{14}H_{29}$	182–185 (0.5–1.5 mm.)	m. p. 35–37		76.56	12.81
$C_5H_{11}CH(CO_2H)C_{12}H_{25}$	184–188 (0.5–1.5 mm.)	1.4508	0.8752	76.47	12.85
$C_7H_{15}CH(CO_2H)C_{10}H_{21}$	180–184 (0.5–1.5 mm.)	m. p. 31.5–33.5		76.65	12.81
Calcd. for each isomer of $C_{19}H_{38}O_2$				76.43	12.84

Summary

A number of pentadecanoic, heptadecanoic and nonadecanoic acids have been prepared and tested bacteriologically toward *B. Leprae.* The C_{15} and the C_{17} acids are active but not to such a degree as the previously studied hexadecanoic acids. The C_{19} acids are very slightly bactericidal.

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

THE REDUCTION OF NICOTINE AND SOME DERIVATIVES OF HEXA- AND OCTAHYDRONICOTINES

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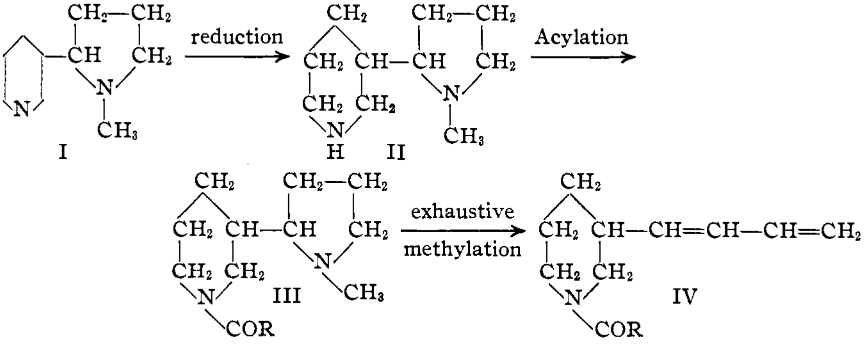
Nicotine (I) should be the cheapest basic product for the preparation of a piperidine ring with an unsaturated side chain in the beta position (IV), provided the following reactions proceed in the normal manner.



The reduction of nicotine by means of sodium and alcohol was first studied by Liebrecht,[1] who isolated a basic product which he called di-

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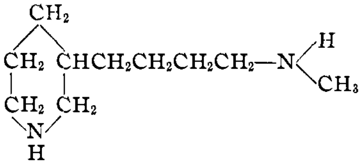
[1] Liebrecht, *Ber.*, **18**, 2969 (1885); **19**, 2587 (1886).

piperidyl. He prepared and analyzed a number of derivatives. A few years later Blau[2] made a more complete investigation of the reaction and showed that Liebrecht's base was not dipiperidyl, but was a mixture of two amines which he called hexahydronicotine (II) and octahydronicotine. The second compound is formed by the opening of the pyrrolidine ring in the reduction and presumably has the formula



Blau did not establish the relative amounts of these reduction products, but he did isolate both amines and prepare a number of derivatives. Pinner[3] has also studied the reduction of nicotine with sodium and alcohol and has reported the isolation of hexahydronicotine only.

In attempting to carry out the synthesis outlined above, nicotine has been reduced with sodium and alcohol and its hydrochloride has been reduced with hydrogen under pressure using the platinum-oxide platinum black catalyst of Adams and Shriner.[4] The relative amounts of hexahydronicotine and octahydronicotine obtained in these reductions were determined by benzoylating the mixed amines and separating the monobenzoyl derivative of the former from the dibenzoyl derivative of the latter by fractional distillation under reduced pressure. It was found that the sodium and alcohol reduction of nicotine produced approximately five parts of hexahydronicotine to one part of octahydronicotine. On the other hand, catalytic reduction of the hydrochloride produced about one part of hexahydronicotine to three parts of octahydronicotine.

The acetyl and benzoyl hexahydronicotines (III) were treated with methyl iodide and the quaternary ammonium iodides were easily obtained. However, distillation of the corresponding hydroxides gave unexpected results. The acetyl derivative lost methyl alcohol to give back the original acyl derivative of hexahydronicotine almost quantitatively. The benzoyl derivative gave very complex mixtures and the only product definitely identified was the original acyl derivative. Since neither reaction seemed to offer any promise as a method of obtaining the desired unsaturated piperidines, further work was discontinued.

It is interesting to note that reduction gave optically active hexahydronicotine derivatives, but optically inactive octahydronicotine derivatives.

[2] Blau, *Ber.*, **24**, 326 (1891); **26**, 628, 1029 (1893).

[3] Pinner, *ibid.*, **26**, 765 (1893).

[4] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923).

Experimental Part

Reduction of Nicotine with Sodium and Alcohol.—The procedure was essentially that used by Liebrecht,[1] Blau[2] and Pinner.[3] In one typical reduction the amounts used were 150 g. of nicotine, 2000 cc. of absolute alcohol and 130 g. of sodium. About 500 cc. of water was added. The alcohol was distilled and the residue was extracted with ether. Two such runs were combined and after distillation of the ether the residue was distilled under reduced pressure. There was thus obtained 98 g. of mixed bases boiling at 125–140° at 16 mm.; d_4^{20} 0.9800; n_D^{20} 1.5067.

Benzoylation of the Mixed Amines.—In a 500-cc. glass-stoppered bottle were placed 50 g. of the mixed amines and 120 g. of 10% aqueous sodium hydroxide solution. The mixture was cooled in an ice-bath and 50 g. of benzoyl chloride was added slowly with shaking. The shaking was continued until the odor of benzoyl chloride was no longer apparent. The mixed amides were then extracted with ether and the ether solution was dried and distilled. The amides were separated by fractional distillation under reduced pressure. There were thus obtained 48 g. of monobenzoylhexahydronicotine boiling at 195–198° at 0.8–1.0 mm.; d_4^{20} 1.072; n_D^{20} 1.5549; $[\alpha]_D^{20}$ $-11.39°$ (0.1903 g. in 25 cc. of absolute alcohol), and 8 g. of dibenzoyloctahydronicotine boiling at 280–300° at 1.5 mm.; d_4^{20} 1.106; n_D^{20} 1.5710. The dibenzoyl derivative was never obtained quite pure, as was shown by the wide boiling range and the nitrogen analysis. It was optically inactive.

Anal. (Dumas) Calcd. for $C_{17}H_{24}ON_2$: N, 10.29. Found: N, 10.38; 10.44. Calcd. for $C_{24}H_{30}O_2N_2$: N, 7.40. Found: N, 7.15.

Catalytic Reduction of Nicotine Hydrochloride.—Pure nicotine hydrochloride was prepared by dissolving 100 g. of nicotine in 400 cc. of dry ether and then passing in dry hydrogen chloride. The salt which precipitated was filtered off and recrystallized by dissolving in the minimum amount of hot absolute alcohol, adding anhydrous ether and cooling. This procedure gave 116 g. (80% of the theoretical amount) of nicotine hydrochloride melting at 163–165°.

The hydrochloride was reduced according to the general method of reducing pyridine derivatives recently described by Hamilton and Adams.[5] The individual runs were made with 0.2 of a mole of nicotine hydrochloride using 0.4 g. of catalyst. The reduction was run at 70°. The absorption of hydrogen seemed to be complete in about six hours. Altogether 160 g. of salt was reduced. After the reduction the solutions were combined, filtered and concentrated. The residue was treated with aqueous potassium hydroxide, the amine layer was extracted with ether and then dried over solid potassium hydroxide. On distillation there was obtained 86 g. of mixed bases boiling at 128–130° at 16 mm.; n_D^{20} 1.4858; d_4^{20} 0.9192.

The chloroplatinate of this material melted at 199–200°, which agrees with the m. p. recorded by Blau[2] for this derivative of octahydronicotine. Benzoylation of 50 g. of this base was carried out as described before. Fractionation of the mixed amides gave 11.5 g. of monobenzoylhexahydronicotine, b. p. 208–212° at 2 mm., and 39.5 g. of dibenzoyloctahydronicotine, b. p. 300–305° at 2 mm.

Acetylhexahydronicotine.—To 50 g. of a mixture of the bases from the sodium and alcohol reduction of nicotine was slowly added 30 g. of acetic anhydride. The mixture was kept cold and shaken while the two substances were reacting. The mixture was then distilled. Several portions were obtained. The two main fractions were collected at 140–150° (1 mm.) and 210–213° (1 mm.). These were analyzed and agreed with acetylhexahydronicotine and diacetyloctahydronicotine, respectively.

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[5] Hamilton and Adams, THIS JOURNAL, **50**, 2260 (1928).

Acetylhexahydronicotine had the following constants: d_4^{20} 1.034; n_D^{20} 1.5010; calcd. M_D 61.16; found, M_D 60.16; $[\alpha]_D^{20}$, −4.07° (0.2130 g. in 25 cc. of absolute alcohol).

Anal. (Dumas) Calcd. for $C_{12}H_{22}N_2O$: N, 13.32. Found: N, 13.51.

Diacetyloctahydronicotine had the following constants: d_4^{20} 1.041; n_D^{20} 1.5033; calcd. M_D, 72.32; found, M_D, 72.21. It was optically inactive.

Anal. (Dumas) Calcd. for $C_{14}H_{26}N_2O_2$: N, 11.01. Found: N, 10.96.

Methiodide of Benzoylhexahydronicotine.—To a solution of 113 g. of benzoylhexahydronicotine in 250 cc. of dry ether was added 65 g. of methyl iodide. Crystals began to form in a very short time. After twelve hours the precipitate was filtered and washed with dry ether. The salt was hygroscopic and was dried over phosphorus pentoxide in a vacuum desiccator. There was thus obtained 144 g. of salt which softened at about 85° and melted at 99–103° with decomposition.

Anal. (Volhard) Calcd. for $C_{18}H_{27}N_2OI$: I, 30.64. Found: I, 30.42, 30.56.

Methiodide of Acetylhexahydronicotine.—To 20 g. of acetylhexahydronicotine in dry ether was added an excess of methyl iodide. The derivative separated as an oily product which would not crystallize.

Distillation of Quaternary Ammonium Hydroxide from the Methiodide of Acetyl Hexahydronicotine.—Some of the oily methiodide was dissolved in water and the iodine content of this solution was determined. It was thus found that 14.3 g. of the methiodide was in solution. This solution was treated with an excess of silver oxide and shaken until the aqueous portion no longer gave a test for the iodide ion. The mixture was then filtered, the precipitate was washed with water several times and the filtrate and washings were evaporated, first under ordinary pressure and finally under reduced pressure until the water was removed. The residue was then heated and finally distilled at 1.1 mm. This gave 7 g. of product boiling at 142–148° at 1.1 mm.; d_4^{20} 1.017; n_D^{20} 1.4984. This material was very pure acetylhexahydronicotine.

Anal. (Dumas) Calcd. for $C_{12}H_{22}N_2O$: N, 13.32. Found: N, 13.55, 13.58.

Distillation of the Quaternary Ammonium Hydroxide from the Methiodide of Benzoylhexahydronicotine.—A solution of 154 g. of the methiodide in 300 cc. of water was treated with 41 g. of silver oxide. The mixture was treated as described for the corresponding acetyl derivative. Fractionation of the decomposition products gave several different substances. The main fraction boiled at 140–147° at 1.2 mm. Analysis of this material showed that it was not the expected exhaustive methylation product. A small portion (5 g.) boiling at 192–200° (1.2 mm.) was found to be benzoylhexahydronicotine.

Summary

1. Reduction of nicotine with sodium and alcohol produced a mixture of amines which contained about five parts of hexahydronicotine for one part of octahydronicotine.

2. Catalytic reduction of nicotine hydrochloride with hydrogen and a platinum-oxide platinum black catalyst gave a mixture of amines which contained about one part of hexahydronicotine to three parts of octahydronicotine.

3. Attempts to obtain piperidine derivatives with unsaturated side chains in the β-position by the exhaustive methylation of benzoyl and acetyl hexahydronicotines were unsuccessful.

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