g. (0.25 mole) of silver cyanide in 125 ml. of refluxing anhydrous ether. After refluxing for three hours, the silver salts were removed by filtration, the ether was distilled off, and the residue was fractionated under reduced pressure. The yield was 8.4 g. (38%) of a colorless liquid, b.p.$_{22}$ 81.5°,[3] n_D^{20} 1.4425, d_4^{20} 1.0128.

Anal.[4] Calc'd for C_6H_9NO: C, 64.86; H, 8.11; N, 12.61; MR, 29.01. Found: C, 65.03; H, 8.32; N, 12.40; MR, 29.02.

Tetrahydropyran-2-carboxylic acid. 2-Cyanotetrahydropyran (6.1 g.; 0.055 mole) was refluxed for five hours with 5.0 g. (0.12 mole) of sodium hydroxide in 45 ml. of water. The solution was acidified with 15 ml. of 6 *N* sulfuric acid, extracted with several 35-ml. portions of ether, and the ether solution was dried over sodium sulfate. After removal of the ether, the residue was fractionated under reduced pressure to yield 4.8 g. (67%) of a clear viscous liquid, b.p.$_{24}$ 144–147°, n_D^{20} 1.4661, d_4^{20} 1.161.

Anal. Calc'd for $C_6H_{10}O_3$: C, 55.38; H, 7.75; MR, 30.75; Neut. equiv. 130.1. Found: C, 55.30; H, 7.85; MR, 31.01; Neut. equiv. 130.2.

An approximate ionization constant is 1.3×10^{-4} at 25° based upon the Beckman *p*H values of 0.1 to 0.2 *M* solutions of the acid.

2-Benzoyltetrahydropyran. 2-Cyanotetrahydropyran (6.1 g.; 0.055 mole) in 40 ml. of dry ether was added dropwise with stirring to a 0.1 mole solution of phenylmagnesium bromide in 75 ml. of ether. After standing for eight hours, the mixture was poured over 75 g. of crushed ice and 10 ml. of concentrated sulfuric acid. The ether layer was separated, the water layer extracted with three 20-ml. portions of ether, and the combined ether solutions were dried over sodium sulfate. Removal of the ether, followed by fractionation of the residue under reduced pressure yielded 7.0 g. (67%) of a very slightly yellow, viscous liquid, b.p.$_{26}$ 170–171°, n_D^{20} 1.5445, d_4^{20} 1.102.

Anal.[4] Calc'd for $C_{12}H_{14}O_2$: C, 75.79; H, 7.33; MR, 53.36. Found: C, 75.59; H, 7.47; MR, 54.51.

The *2,4-dinitrophenylhydrazone* of the 2-benzoyltetrahydropyran melted at 171–173°.

Anal.[4] Calc'd for $C_{18}H_{18}O_5N_4$: N, 15.14. Found: N, 14.90.

2-Aminomethyltetrahydropyran. A modified procedure of Amundsen and Nelson[5] was employed. Lithium aluminum hydride (7.6 g., 0.2 mole) was crushed under dry ether and then was refluxed with stirring in 400 ml. of dry ether for two hours. After cooling to 0°, 22.2 g. (0.2 mole) of 2-cyanotetrahydropyran in 40 ml. of dry ether was added dropwise over a period of 0.5 hour. The reaction was allowed to continue for an additional 0.5 hour, when 8 ml. of water was added, followed by 6 ml. of 6 *N* sodium hydroxide and then 28 ml. of water. The ether layer was decanted through a fluted filter and the residual salts were refluxed for ten minutes with two successive 100-ml. portions of ether. The combined ether decantates were dried with sodium sulfate. The ether was removed and the residue was fractionated under reduced pressure to yield 15.3 g. (66%) of a colorless, partly water-soluble liquid having a strong ammonia odor, b.p.$_{21}$ 64–66°, n_D^{20} 1.4598, d_4^{20} 0.9635.

Anal.[4] Calc'd for $C_6H_{13}NO$: C, 62.61; H, 11.30; N, 12.17; MR, 32.65. Found: C, 62.24; H, 11.40; N, 12.27; MR, 32.68.

N-(2-Tetrahydropyranylmethyl)-4-aminobenzenesulfonamide. *p*-Acetamidobenzenesulfonyl chloride (31.6 g., 0.13 mole) was added cautiously to a solution of 15.0 g. (0.13 mole) of 2-aminoethyltetrahydropyran in 20.8 g. (0.26 mole) of anhydrous pyridine. The reaction mixture was heated for 45 minutes at 100° and then was poured into 130 ml. of water acidified with hydrochloric acid. The solidified product was crushed with a stirring rod, filtered, and washed with 25 ml. of ice-water. The yield was 30.0 g., m.p. 131.5–133.5°, after recrystallization from water. The crude product was refluxed with 200 ml. of 2 *N* sodium hydroxide for one hour, filtered, and the filtrate was neutralized with concentrated hydrochloric acid. An oily substance, which solidified upon standing and cooling, was separated and recrystallized from 1600 ml. of hot water. The product, separating in fine white flakes, weighed 16.2 g. (46%), m.p. 95–97°.

Anal.[4] Calc'd for $C_{12}H_{18}N_2O_3S$: C, 53.32; H, 6.71; S, 11.87. Found: C, 52.50; H, 6.74; S, 11.91.

Trimethyl(2-tetrahydropyranylmethyl)ammonium iodide. A mixture of 1.2 g. (0.01 mole) of 2-aminoethyltetrahydropyran and 2.3 g. (0.04 mole) of potassium hydroxide in 25 ml. of ethyl alcohol was treated gradually with 14.0 g. (0.1 mole) of methyl iodide to maintain a gentle refluxing of the alcohol. After heating for 0.5 hour, the mixture was cooled, filtered, and the solids were washed with 20–25 ml. of warm ethyl alcohol. The filtrate was evaporated to expel unused methyl iodide and was cooled in ice and salt. The crude product was recrystallized from ethyl alcohol to yield 1.2 g. (40%) of granular, white crystals, m.p. 188–190°.

Anal. Calc'd for $C_9H_{20}INO$: I, 44.52. Found: I, 44.83, 44.76.

Replacing 2-aminomethyltetrahydropyran with aminomethyl-1,4-dioxane[1] yielded trimethyl(dioxanylmethyl)ammonium iodide (51%), m.p. 214–215°.

Anal. Calc'd for $C_8H_{18}INO_2$: I, 44.22. Found: I, 44.20.

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(3) Reported b.p. 80° (12 mm.). Office of the Publications Board, PB 823, Office of Technical Services, U. S. Dept. of Commerce, Washington, D. C.

(4) Analysis by Micro-Tech Laboratories, Skokie, Ill.

(5) Amundsen and Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

Partial Hydrogenation of Benzhydrylpyridines[1]

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In an attempt to evaluate differences in the pharmacological action of identically substituted pyridines and piperidines, we have reduced the 4-amyl and the 4-methyl substituted 1-(diphenylmethyl)pyridines to the corresponding piperidine moieties.

EXPERIMENTAL

(All melting points uncorrected. Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.)

1-(Diphenylmethyl)-4-amylpiperidine hydrobromide (I). 1-(Diphenylmethyl)-4-amylpyridinium bromide[2] (50 g., 0.126 mole) was dissolved in 180 ml. of aqueous 66% ethanol and hydrogenated in the presence of 1.0 g. Adams' platinum oxide catalyst ("Parr" hydrogenation apparatus, max. pressure 50 lbs./inch^2). Hydrogen absorption ceased after 15–18 hours. The platinum oxide was filtered off and the solvents were removed under reduced pressure (max. pot temp. 50°). The residue was dissolved in anhydrous benzene and crystallization was induced by adding anhydrous

(1) This investigation is supported by grants from the Geschickter Foundation for Medical Research and the U. S. Public Health Service.

(2) Courtesy Bristol Laboratories, Syracuse, New York.

ethyl ether to the solution. The white crystalline material (28 g., 55% yield) was recrystallized from an ethanol-ethyl acetate solvent system. The compound melted at 217.0–217.8°.

Anal. Calc'd for $C_{23}H_{32}BrN$: C, 68.64; H, 8.02; Br, 19.86; N, 3.48. Found: C, 68.45; H, 7.91; Br, 19.5; N, 3.42.

1-(Diphenylmethyl)-4-methylpiperidine hydrobromide (II). 1-(Diphenylmethyl)-4-methylpyridinium bromide[2] (25 g., 0.0735 mole) was dissolved in 500 ml. of aqueous 49% ethanol and hydrogenated, in two portions, as described in the preparation of I. The reaction mixtures were combined, the platinum oxide was filtered off, and the solvents were removed under reduced pressure (max. pot temp. 50°). The crystalline residue was recrystallized from ethanol, yielding a total of 8.6 g. (33.8% yield) of product. The product was further purified by recrystallization from the ethanol-ethyl acetate solvent system. The crystalline material sintered at 160° and melted at 218.6–219.5°. The compound was dried at 130°/0.1 mm. for 1–2 hours immediately preceding analysis.[3]

Anal. Calc'd for $C_{19}H_{24}BrN$: C, 65.90; H, 6.99; Br, 23.08; N, 4.05. Found: C, 65.87; H, 7.00; Br, 22.8; N, 3.99.

The pharmacological evaluation of these compounds is in progress.

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(3) The analytical laboratory reported sublimation during this operation.

Reaction Between Acrolein and Ethyl β-Aminocrotonate

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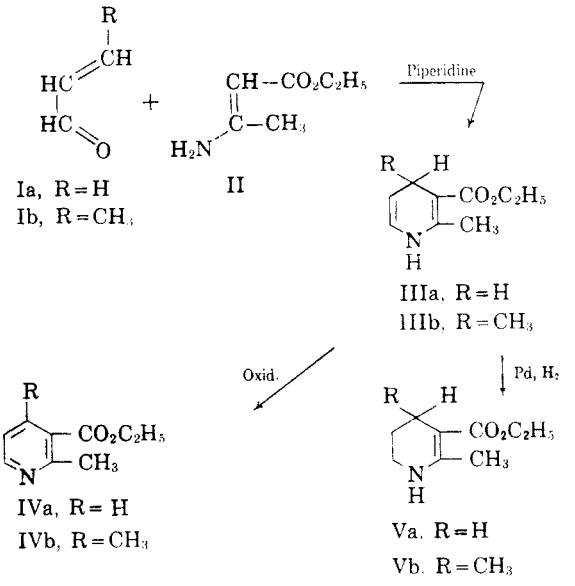
Reaction of acrolein (I) with ethyl β-aminocrotonate (II) in ethanol with piperidine as catalyst leads to the formation of 57% of ethyl 2-methyl-1,4-dihydronicotinate (IIIa), 15% of ethyl 2-methylnicotinate (IVa),[1] and 28% of a material assumed from ultraviolet absorption data to be a mixture of IIIa and an ethyl 2-methyltetrahydronicotinate.

The product IIIa, obtained crystalline by distillation of the crude reaction mixture, showed an infrared absorption maximum at 3500 cm.$^{-1}$, indicating the presence of the >NH function. Ultraviolet absorption maxima were observed at 220 and at 375 mμ, similar to those observed by Bohlmann and Bohlmann[2] for the 1,4-dihydro compounds obtained by lithium aluminum hydride reduction of ethyl dinicotinate and ethyl 2-methyldinicotinate. Reduction of IIIa over palladium affords ethyl 2-methyl-1,4,5,6-tetrahydronicotinate (Va).[3] Compound IIIa gives a positive reaction with silver nitrate, and is easily attacked by oxidizing agents. It is converted to IVa by such reagents as nitrous and nitric acids, picric acid, and air. Repeated recrystallization of the picrate of IIIa from ether gives the picrate of IVa. Distillation of IIIa in a vacuum leads to partial conversion of this substance to IVa, suggesting that IVa was formed from IIIa during vacuum distillation of the crude reaction product of Ia with II.

Reaction of crotonaldehyde (Ib) with II gave IIIb as the only isolated reaction product in 75% yield. Compound IIIb showed an ultraviolet absorption spectrum similar to that of IIIa. Although IIIb is less reactive toward oxidation than is IIIa, oxidation with nitric acid gives ethyl 2,4-dimethylnicotinate (IVb).

On shaking IIIa or IIIb with a palladium catalyst in methanol at room temperature, a disproportionation occurs leading to the formation of mixtures of IVa and Va or IVb and Vb respectively.



Ia, R = H
Ib, R = CH_3

II

IIIa, R = H
IIIb, R = CH_3

IVa, R = H
IVb, R = CH_3

Va, R = H
Vb, R = CH_3

EXPERIMENTAL[4]

Condensation of acrolein with ethyl β-aminocrotonate. Acrolein, 31 g. (0.55 mole), was added during a period of two hours to a stirred solution of 65 g. (0.5 mole) of ethyl β-aminocrotonate and 2 g. of piperidine in 250 ml. of anhydrous ethanol at 40–50°. After addition was complete, the solution was heated to reflux for 3 hours, during which time the color changed from yellow to brown. The ethanol was removed by distillation, and the residue was distilled under reduced pressure to give: (1) 7.5 g. of oil, b.p. 100–120° (5 mm.); (2) 27.6 g. of crystalline material, b.p. 125–127° (5 mm.); and (3) 13.6 g. of oil, b.p. 130–140° (5 mm.).

Fraction (1) showed λ_{max}^{EtOH} 220 mμ (ε = 7.55) and 268 mμ (ε = 3.47) and gave a *picrate*, needles, m.p. 146°, which did not depress the m.p. of a known sample of ethyl 2-methylnicotinate picrate.

Anal. Calc'd for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58; N, 14.21. Found: C, 45.74; H, 3.34; N, 14.01.

Fraction (2) showed m.p. 50–60°; recrystallization from

(1) P. Baumgarten and A. Dornow, *Ber.*, **72**, 564 (1939); A. Dornow and H. Bormann, *Ber.*, **82**, 216 (1949); E. Ochiai and Y. Ito, *Ber.*, **74**, 1111 (1941).

(2) F. Bohlmann and M. Bohlmann, *Ber.*, **85**, 1419 (1953).

(3) N. F. Albertson, *J. Am. Chem. Soc.*, **74**, 3816 (1952).

(4) Melting and boiling points are uncorrected.