cause of the unusual speed of this reaction, it was thought possible that some product other than the expected 1-ethoxy-3-methyl-2-butene was formed. Only 1-ethoxy-3-methyl-2-butene was found as a product and in good yields. As yet no adequate hypothesis has been developed to explain the unusual reactivity of 1-chloro-3-methyl-2-butene compared to that of crotyl chloride and allyl chloride. These data, however, tend to substantiate a previous observation that the reactions between allylic chlorides and potassium iodide and sodium ethoxide go by different mechanisms.

The effect of replacing one of the methyl groups of 1-chloro-3-methyl-2-butene with a chlorine atom can be determined by comparing the relative reactivity of 1-chloro-3-methyl-2-butene (very fast) with that of 1,3-dichloro-2-butene at 50° (low boiling isomer 4.77, high boiling isomer 6.16). This comparison is possible because geometrical configuration is only a minor factor in determining reactivity in the reaction with sodium ethoxide. Apparently the replacing of one methyl group by a chlorine atom slows down the reaction very markedly. It is also apparent that the high rate of reaction is not associated with the lack of a hydrogen atom on the number 3 carbon. As with the potassium iodide reaction, there is no correlation between the electronegativity of the substituents on the number 3 carbon and the rate of reaction—both chlorine atoms and methyl groups when replacing hydrogen atoms activate the allylic chlorine toward sodium ethoxide.

The activating influence toward *cuprous chloride catalyzed hydrolysis* of methyl groups on the number 3 carbon has been shown by the fact that 1-chloro-3-methyl-2-butene is by far the most reactive of the allylic chlorides which have been studied.[8] This increased reactivity would be expected if the catalytic hydrolysis involves the formation of a complex between the cuprous ion and the carbon-to-carbon double bond of the allylic chloride.[9] The methyl groups would serve as an electron source for the double bond thus causing the double bond to become more neucleophilic and consequently more reactive toward cuprous ion.

Summary

The reactivity of 1-chloro-3-methyl-2-butene was determined with the following reagents: potassium iodide in acetone, sodium ethoxide in ethanol and cuprous chloride in hydrochloric acid.

Methyl groups on the number 3 carbon atom greatly increase the reactivity of the allylic chlorine toward all three of these reagents.

(8) Paper presented by Hatch, Brown and Bailey before the Southwest Regional Meeting of the American Chemical Society held at Shreveport, La., December 10 and 11, 1948.

(9) Andrews and Keefer, THIS JOURNAL, **70**, 3261 (1948).

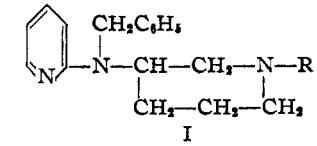
AUSTIN, TEXAS RECEIVED OCTOBER 5, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

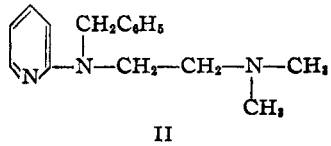
Syntheses of 3-Aminopiperidines

BY ROBERT H. REITSEMA AND JAMES H. HUNTER

A number of physiologically active compounds are known to have an ethylenediamine chain as a part of their structure. Since 3-aminopiperidines can be considered as cyclic ethylenediamines, it was of interest to investigate the effect of replacing the ethylenediamine unit with a 3-aminopiperidine group. Two potential histamine antagonists of type I have been synthesized as examples of such substitution in the antihistamine N,N-dimethyl-N′-benzyl-N′-(α-pyridyl)-ethylenediamine (II).[1]



I



II

(1) Huttrer, *et al.*, THIS JOURNAL, **68**, 1999 (1946).

The preparation of 3-alkylaminopiperidines was approached three ways. Reductive alkylation of amines with 1-alkyl-3-piperidones was the most successful procedure employed. In this manner 1-alkyl-3-benzylamino- and 1-alkyl-3-(β-dimethylaminoethylamino)-piperidines were obtained. The yields were comparable to those observed in the 4-aminopiperidine series.[2] The Hofmann rearrangement of 1-ethyl-nipecotamide gave the expected 1-ethyl-3-aminopiperidine, but the yield was low. The third synthesis involved selective alkylation of N-3-piperidyl-*p*-toluenesulfonamide. The preparation of N-3-pyridyl-*p*-toluenesulfonamide and its reduction to N-3-piperidyl-*p*-toluenesulfonamide was accomplished; however this approach was abandoned due to the slowness of the reduction. The more difficult selective alkylation of 3-aminopiperidine, prepared by reduction of 3-aminopyridine,[3,4] was not attempted.

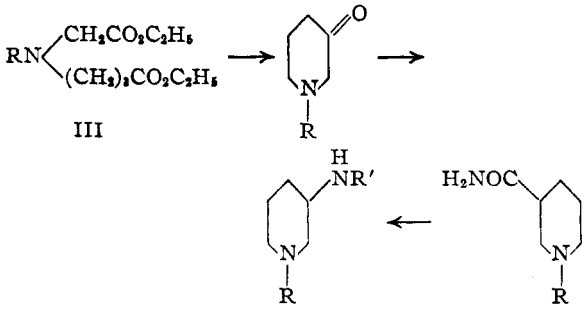
1-Methyl- and 1-ethyl-3-piperidone were prepared by the method of Prill and McElvain[5] from

(2) Reitsema and Hunter, *ibid.*, **70**, 4009 (1948).

(3) Tschitschibabin and Gertschuk, *Ber.*, **63B**, 1153 (1930).

(4) Nienburg, *ibid.*, **70B**, 635 (1937).

(5) Prill and McElvain, THIS JOURNAL, **55**, 1233 (1933).



III

alkylaminodicarboxylic esters (III). A simplification of this method, involving the cyclization of the cyano ester appeared unpromising in preliminary studies.

Treatment of 1-methyl- and 1-ethyl-3-benzylaminopiperidine with α-bromopyridine gave I (R = CH_3, C_2H_5). These compounds have been shown in preliminary assays[6] to possess some activity against histamine-induced spasms in the isolated intestinal strip. The order of activity, however, did not appear sufficiently high to warrant the preparation of additional members of this type.

Experimental[7]

Ethyl N-Ethyl-N-(γ-carbethoxymethylamino)-butyrate (III).—To 177.9 g. (1.355 moles) of ethyl N-ethylaminoacetate was added with cooling 132 g. (0.678 mole) of ethyl γ-bromobutyrate. After three days at room temperature 100.4 g. of the secondary amine hydrobromide was removed by filtration. Distillation of the filtrate and ethereal washings of the solid gave 109 g. (66%) of III, b. p. 161–163° (20 mm.); $n^{24}D$ 1.4392.

Anal. Calcd. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.50; H, 9.22; N, 5.85.

N-Ethyl-N-(γ-carbethoxymethylamino)-butyronitrile.—A solution of 101.5 g. (0.775 mole) of ethyl N-ethylaminoacetate and 40 g. (0.386 mole) of γ-chlorobutyronitrile gave no precipitate after standing overnight. After heating one and one-half hours on the steam-bath and cooling, 46.9 g. of solid secondary amine hydrochloride was obtained which was washed with ether. Distillation of the filtrate and washings gave 47.6 g. (62.2%) of the cyano ester, b. p. 156–159° (17 mm.); $n^{20}D$ 1.4453.

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.72; H, 9.15; N, 14.13. Found: C, 60.86; H, 8.93; N, 14.06.

1-Ethyl-3-piperidone Hydrochloride.—This was prepared in 97% yield from III by the procedure used for the preparation of 1-ethyl-4-piperidone.[8] The salt melted with decomposition at 172–173.5° after recrystallization from methanol–ether. The analysis indicated the presence of one mole of water of crystallization.

Anal. Calcd. for $C_7H_{13}NO\cdot HCl\cdot H_2O$: C, 46.28; H, 8.88; Cl, 19.52. Found: C, 45.98; H, 8.47; Cl, 19.6.

Nipecotamide.—Reduction of nicotinamide (48.8 g., 0.4 mole) with hydrogen at an initial pressure of 2000–3000 pounds in 100 cc. of absolute ethanol in the presence of 5 g. of W-2 Raney nickel gave 40.3 g. of product, b. p. 149–160° (0.3–0.5 mm.). The picrate, recrystallized from ethanol, melted at 193.5–194.5°.

Anal. Calcd. for $C_{12}H_{15}N_5O_8$: C, 40.34; H, 4.23; N, 19.60. Found: C, 40.45; H, 4.32; N, 19.62.

1-Ethyl Nipecotamide.—(a) Nicotinamide ethiodide was reduced according to the directions of Karrer and Stare[9] to give a very low yield of 1-ethylnipecotamide, m. p. 99–100°.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.31; H, 10.07; N, 18.16.

The picrate prepared in ethanol melted at 190–191°.

Anal. Calcd. for $C_{14}H_{19}N_5O_8$: C, 43.64; H, 4.86; N, 18.18. Found: C, 43.80; H, 4.72; N, 17.92.

(b) Pure 1-ethylnipecotamide was also obtained in 31% yield from the crude mixture from the reduction of nicotinamide by treatment with ethyl iodide and sodium hydroxide or potassium carbonate. The free base and the picrate were identical with the products obtained by method a.

1-Ethyl-3-aminopiperidine.—By treatment of the solution of the reduced nicotinamide with ethyl iodide a precipitate of crude 1-ethyl-nipecotamide appeared. To 24.1 g. (0.1 mole) of this product in 100 cc. of methanol containing 2.3 g. (0.1 mole) of sodium was added a solution of 4.6 g. (0.2 mole) of sodium in 150 cc. of methanol and then 17 g. of bromine. The mixture was warmed for ten minutes on a steam-bath. The cooled solution was acidified with concentrated hydrochloric acid, filtered from inorganic material and evaporated to dryness. The crude product was added to 35 g. of calcium oxide containing 15 cc. of water. The mixture was distilled. The distillate was treated with picric acid solution to give 2.8 g. of 1-ethyl-3-aminopiperidine dipicrate which melted at 231–232° (dec.) after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{22}N_8O_{14}$: C, 38.91; H, 3.78; N, 19.11. Found: C, 39.05; H, 3.68; N, 18.95.

1-Ethyl-3-benzylaminopiperidine. (a) **From 1-ethyl-3-piperidone.**—From 39 g. of crude 1-ethyl-3-piperidone hydrochloride was obtained 25.4 g. (0.2 mole) of the free base. The latter was mixed with 23.4 g. (0.2 mole) of benzylamine with cooling. After dilution with 100 cc. of methanol the solution was reduced at room temperature with hydrogen at 30–40 pounds pressure in the presence of 0.2 g. of platinum oxide. Distillation of the filtered solution gave 29.3 g. (67%) of 1-ethyl-3-benzylaminopiperidine, b. p. 128–137° (0.8 mm.). Redistillation gave 22.9 g. of amine, b. p. 118–120° (0.7 mm.); $n^{19.5}D$ 1.5273.

Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.20; H, 9.56; N, 12.98.

The dipicrate melted at 200–202° (dec.) after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{28}N_8O_{14}$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.06; H, 4.18; N, 16.34.

The *p*-nitrobenzamide hydrochloride, m. p. 235.5–236.5°, was recrystallized from methanol–ether.

Anal. Calcd. for $C_{21}H_{25}N_5O_3\cdot HCl$: C, 62.44; H, 6.49; N, 10.40. Found: C, 62.62; H, 6.48; N, 10.33.

(b) **From the Hofmann Hypobromite Reaction.**—To a cold solution of 15 g. (0.1 mole) of 1-ethylnipecotamide in 13 cc. of water was added 16 g. of bromine in 200 cc. of 10% sodium hydroxide during thirty minutes. The light yellow solution was heated in a steam-bath for forty-five minutes, cooled and 16.0 g. (0.15 mole) of benzaldehyde added. The mixture was shaken frequently during two hours. The organic product was extracted with ether and the ether removed by distillation after addition of 125 cc. of ethanol. The resulting solution was shaken under fifty pounds pressure of hydrogen in the presence of 0.1 g. of platinum oxide catalyst. Distillation after removal of catalyst gave 8.0 g. of benzyl alcohol, b. p. 93–94° (12 mm.), and 2.4 g. (12%) of 1-ethyl-3-benzylaminopiperidine, b. p. 162–164° (12 mm.). The dipicrate prepared from the latter fraction after recrystallization from ethanol melted at 202–203° (dec.) and did not depress the melting point of the compound prepared from the piperidone.

Anal. Calcd. for $C_{26}H_{28}N_8O_{14}$: N, 16.56. Found: N, 16.30.

(6) Grateful acknowledgment is made to Dr. Milton J. Vander Brook, of our Department of Pharmacology, for conducting these assays.

(7) Microanalyses by Mr. Harold Emerson and staff of these Laboratories.

(8) Fuson, Parham and Reed, THIS JOURNAL, **68**, 1239 (1946).

(9) Karrer and Stare, *Helv. Chim. Acta*, **20**, 418 (1937).

1-Methyl-3-benzylaminopiperidine.—From 22.6 g. (0.2 mole) of crude 1-methyl-3-piperidone and 23.4 g. (0.2 mole) of benzylamine after hydrogenation in 75 cc. of absolute ethanol in the presence of platinum oxide catalyst was obtained 27.0 g. (66%) of 1-methyl-3-benzylaminopiperidine, b. p. 112–117° (1 mm.); $n^{22.6}$D 1.5299. The dipicrate melted at 191–193°.

Anal. Calcd. for $C_{25}H_{26}N_8O_{14}$: C, 45.32; H, 3.96; N, 16.91. Found: C, 45.61; H, 4.22; N, 17.05.

1-Methyl-3-(β-dimethylaminoethylamino)-piperidine.—Reductive alkylation of β-dimethylaminoethylamine with 1-methyl-3-piperidone gave 61% of 1-methyl-3-(β-dimethylaminoethylamino)-piperidine, b. p. 121–130° (19–21 mm.). Redistillation gave a product which boiled at 120–123° (17 mm.); n^{24}D 1.4675.

Anal. Calcd. for $C_{10}H_{23}N_3$: C, 64.81; H, 12.51; N, 22.68. Found: C, 65.02; H, 12.01; N, 22.17.

The tripicrate melted at 216–217° (dec.).

Anal. Calcd. for $C_{28}H_{31}N_{12}O_{21}$: C, 38.54; H, 3.70; N, 19.26. Found: C, 38.62; H, 3.53; N, 18.81.

1-Ethyl-3-(N-benzyl-N-α-pyridylamino)-piperidine.—A mixture of 20.2 g. (0.0926 mole) of 1-ethyl-3-benzylaminopiperidine, 14.6 g. (0.0926 mole) of α-bromopyridine, 12.8 g. (0.0926 mole) of potassium carbonate and 0.2 g. of copper bronze was heated with stirring for forty-eight hours at 160–170°. After addition of 25 cc. of water and 100 cc. of ether the mixture was filtered, the layers were separated, and the aqueous layer was extracted with ether. Removal of solvent and distillation of the residue gave 11.1 g. of starting material, b. p. 109–120° (0.3–0.6 mm.), and 6.9 g. of an oil which boiled at 170° at 0.3 mm. Redistillation of the latter fraction gave a viscous light yellow tertiary amine, b. p. 155–160° (0.2 mm.). The dipicrate, m. p. 162–163° (dec.), was prepared in ethanol.

Anal. Calcd. for $C_{31}H_{31}N_9O_{14}$: C, 49.40; H, 4.15; N, 16.73. Found: C, 49.57; H, 4.7; N, 15.91.

The methyl analog, prepared by the procedure above, was obtained as a slightly impure oil[10] boiling at 163–164°. (0.1 mm.) after redistillation. The picrate and picrolonate were oils, and the hydrochloride deteriorated rapidly on standing.

N-3-Pyridyl-p-toluenesulfonamide.—A solution of 12.6 g. (0.134 mole) of 3-aminopyridine in 30 cc. of dry pyridine was treated with 25.6 g. (0.134 mole) of p-toluenesulfonyl chloride and warmed thirty minutes on a steam-bath. After removal of half of the pyridine by distillation under reduced pressure a white solid was precipitated by the addition of 50 cc. of water. This was purified by dissolving in 100 cc. of 5% sodium hydroxide, treating the solution with decolorizing charcoal and reprecipitating with sodium bicarbonate solution. The white N-3-pyridyl-p-toluenesulfonamide, m. p. 190.5–191.5°, weighed 28.8 g. (82%). The melting point was not raised by two crystallizations from xylene.

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28. Found: C, 58.31; H, 4.86; N, 11.52.

N-3-Piperidyl-p-toluenesulfonamide.—The reduction of 4.15 g. (0.017 mole) of N-3-pyridylamino-p-toluenesulfonamide was accomplished in 20 cc. of methanol containing 30 cc. of 6 *N* hydrochloric acid by the use of Adams platinum catalyst at room temperature. The uptake of hydrogen was very slow. After removal of the catalyst, the solution was evaporated to dryness, taken up in 20 cc. of water, and neutralized. Evaporation of the filtrate after removal of 3.1 g. of starting material which had precipitated, gave 0.6 g. (56% yield based on recovered N-3-pyridyl-p-toluenesulfonamide) of solid. Recrystallization from a large volume of petroleum ether (b. p. 90–110°) gave white N-3-piperidyl-p-toluenesulfonamide, m. p. 125–126°.

Anal. Calcd. for $C_{12}H_{18}N_2O_2S$: C, 55.66; H, 7.13; N, 11.02. Found: C, 56.06; H, 6.59; N, 10.93.

Reduction in glacial acetic acid with platinum oxide catalyst or with sodium and ethanol was less successful.

(10) *Anal.* Calcd. for $C_{11}H_{18}N_4$: C, 76.83; H, 8.26; N, 14.93. Found: C, 77.46; H, 8.07; N, 14.86.

Summary

1. Various syntheses of substituted 3-aminopiperidines have been investigated, of which reductive amination of 1-alkyl-3-piperidones was the most useful.

2. 1-Alkyl-3-amino-, 1-alkyl-3-benzylamino- and 1-alkyl-3-(β-dimethylaminoethylamino)-piperidines were prepared.

3. 1-Ethyl- and 1-methyl-3-(N-benzyl-N-α-pyridylamino)-piperidines were prepared by alkylation of the secondary amines.

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 20, 1948

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1] AND THE CORN INDUSTRIES RESEARCH FOUNDATION]

Isolation of 6-[α-D-Glucopyranosyl]-D-glucose (Isomaltose) from Enzymic Hydrolyzates of Starch[2]

BY EDNA M. MONTGOMERY,[3] F. B. WEAKLEY[3] AND G. E. HILBERT

Introduction

Starch is a polymer composed apparently of the repeating unit, maltose, and the cross linking unit, 6-[α-D-glucopyranosyl]-D-glucose (isomaltose). Amylose or the A fraction[4] of starch has been shown to consist almost entirely, if not completely, of maltose units arranged in a linear configuration. Amylopectin or the B fraction[4] of starch, on the other hand, is a branched molecule; it contains the anomalous or branching unit which serves to cross link chains composed of maltose units.[5] On the basis of studies dealing with the structure of the products resulting from the hy-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented at the 33rd Annual Meeting of Cereal Chemists at Cincinnati, Ohio, on May 25, 1948.

(3) Corn Industries Research Foundation Fellow at the Northern Regional Research Laboratory, Peoria, Illinois.

(4) T. J. Schoch, *J. Cereal Chem.*, **18**, 121 (1941); THIS JOURNAL, **64**, 2957 (1942).

(5) K. H. Meyer, *Naturwissenshaften*, **28**, 397, 564, 722 (1940); K. Freudenberg and H. Boeppel, *ibid.*, **28**, 264 (1940); W. N. Haworth, E. L. Hirst and F. A. Isherwood, *J. Chem. Soc.*, 577 (1937); E. L. Hirst and G. T. Young, *ibid.*, 1471 (1939); C. E. H. Bawn, E. L. Hirst, and G. T. Young, *Trans. Faraday Soc.*, **36**, 880 (1940); K. Myrbäck, B. Ortenblad, and K. Ahlborg, *Biochem. Z.*, **307**, 53 (1940); K. Myrbäck and K. Ahlborg, *ibid.*, **307**, 69 (1940); and K. Ahlborg and K. Myrbäck, *ibid.*, **308**, 187–195 (1941).