[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALTBIE CHEMICAL CO.]

β-(2- and 4-Pyridylalkyl)-amines[1]

BY L. A. WALTER, WILLIAM H. HUNT AND RUSSEL J. FOSBINDER

Certain β-(2- and 4-pyridylethyl and propyl) amines have been synthesized for the purpose of investigating their pharmacological properties. Some of the 2-pyridyl compounds were first prepared and described by Loffler.[2,3] A second method, illustrated below, also was used for the preparation of the β-(2- and 4-pyridylethyl)-amines and their quaternary methochloride hydrochlorides.

$$PyCH_3 \longrightarrow PyCH_2CHOHCCl_3 \longrightarrow$$
$$PyCH{=}CHCOOH \longrightarrow PyCH_2CH_2CONH_2 \longrightarrow$$
$$PyCH_2CH_2NHCOOCH_3 \longrightarrow$$
$$\downarrow$$
$$PyCH_2CH_2NH_2$$
$$PyCH_2CH_2NHCOOCH_3 \xrightarrow[CH_3I]{} PyCH_2CH_2NH_2 \cdot HCl$$
$$CH_2Cl$$

Pharmacological Results

The pyridyl alkylamines described in this paper were originally investigated with the object of ascetaining whether or not they would exhibit sympathomimetic activity. Hartung,[4] in an excellent review on epinephrin and related compounds, concluded that: "The aromatic portion of the molecule need not necessarily be a phenyl or substituted phenyl group. Various naphthalene and heterocyclic derivatives also possess pressor activity."

All of the compounds investigated, with the exception of β-(4-pyridyl)-ethylamine hydrochloride and the N-methochlorides, produced a moderate or marked fall in blood pressure following intravenous administration to anesthetized cats, while in rabbits a rise in blood pressure was always observed. In the case of β-(4-pyridyl)-ethylamine hydrochloride, a definite but transitory rise in blood pressure was observed with a typical "epinephrin reversal" noted following the injection of ergotamine tartrate.

These unexpected results led us to investigate the action of the compounds on isolated strips of smooth muscle such as guinea pig and rabbit uterus and intestine, using the familiar method of Magnus.

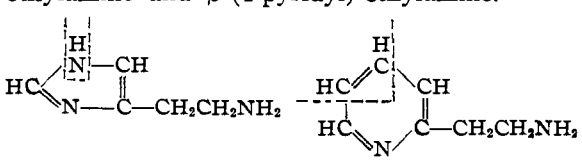
Table I shows the concentrations of the various active agents in gammas per cc. which, in contact with the tissues, produced near-maximal contraction of the muscle. With the exception of β-(2-pyridyl)-ethyldiethylamine the activity of these derivatives approached that of histamine phosphate. All of the β-(2-pyridyl)-alkylamines and histamine phosphate exerted a stimulative effect on rabbit uterus and intestine; this tissue was far less sensitive as doses of the compounds 40 to 100-fold those used in the guinea pig work were required to produce sub-maximal contractions. All of the compounds were found to be less toxic than histamine on intravenous injection in the rabbit.

TABLE I

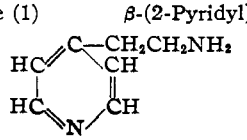
CONCENTRATIONS OF THE AMINES PRODUCING NEAR-MAXIMAL CONTRACTIONS IN GUINEA PIG UTERUS AND INTESTINE

Compound	Guinea pig uterus, gammas per cc.	Guinea pig intestine, gammas per cc.
β-(2-Pyridyl)-ethyldiethyl-amine hydrochloride	80	6
β-(2-Pyridyl)-ethylmethyl-amine hydrochloride	1	2–3
1-(2-Pyridyl)-2-methylamino-propane hydrochloride	1	1
β-(2-Pyridyl)-ethylamine hydrochloride	4	1
Histamine phosphate	0.2	0.2

The pharmacological findings, which are to be described in detail elsewhere, reveal that β-(2-pyridyl)-alkylamines exhibit a physiological action similar to histamine, while the action of β-(4-pyridyl)-ethylamine resembles epinephrin. This interesting and striking relationship may be explained, we believe, by a comparison of the structural formulas of histamine, β-(2-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine.



Histamine (1) β-(2-Pyridyl)-ethylamine (2)



β-(4-Pyridyl)-ethylamine (3)

(1) Presented before the Division of Medicinal Chemistry at the Detroit meeting of the American Chemical Society, September, 1940.
(2) Loffler, *Ber.*, **37**, 161 (1904).
(3) Loffler and Kirschner, *ibid.*, **38**, 3330 (1905).
(4) Hartung, *Chem. Rev.*, **9**, 389 (1931).

An obvious similarity in structure exists between (1) and (2) while (3) resembles an aromatic alkylamine and would be expected to have epinephrin-like activity.

Experimental

β-(2-Pyridylethyl)-methylamine.[2]—This compound was purified by crystallization of the dihydrochloride from absolute alcohol. The salt was not hygroscopic when pure; m. p. 148–149°.

Anal. Calcd. for $C_8H_{14}N_2Cl_2$: Cl, 33.90. Found: Cl, 34.03.

β-(2-Pyridylethyl)-diethylamine.[2]—This compound was also purified by crystallization of its dihydrochloride; m. p. 171–172°.

Anal. Calcd. for $C_{11}H_{20}N_2Cl_2$: Cl, 28.22. Found: Cl, 28.42.

1-(2-Pyridyl)-2-propanol.—Only 4–6% yields are obtained by heating 2-picoline with acetaldehyde.[3,5]

To a well-stirred suspension of 6.9 g. of lithium filings in 500 cc. of dry ether under an atmosphere of nitrogen was slowly added 79 g. of bromobenzene. This mixture was stirred overnight, 46 g. of 2-picoline was added and after stirring for one hour at room temperature a dark red solution of picolyl-lithium resulted. The flask was immersed in an ice–salt mixture and acetaldehyde slowly distilled into the flask until the red color disappeared. After fifteen minutes 100 cc. of water was slowly added followed by 100 cc. of concentrated hydrochloric acid. When all the solid had dissolved the aqueous layer was separated and poured with stirring into a solution of 200 g. of sodium carbonate decahydrate in 100 cc. of water. The lithium carbonate was filtered off and washed well with chloroform. The filtrate was extracted with chloroform and the combined fractions distilled to give 40 g. of product; b. p. 110–111° (10 mm.).

1-(2-Pyridyl)-2-methylaminopropane.—This compound was obtained in 75% yield from 1-(2-pyridyl)-2-bromopropane[3] and excess absolute alcoholic methylamine at 100°. The product distilled at 72° (2 mm.) and was extremely hygroscopic.

Anal.[6] Calcd. for $C_9H_{14}N_2$: N, 18.65. Found: N, 18.71.

This amine was purified by crystallization of its dihydrochloride, m. p. 158–158.5°.

Anal. Calcd. for $C_9H_{16}N_2Cl_2$: Cl, 31.78. Found: Cl, 32.03.

β-(2-Pyridyl)-propionamide.—β-(2-Pyridyl)-acrylic acid[7] was hydrogenated in aqueous alkali with Raney nickel and hydrogen at 40-lb. pressure. After removal of the catalyst the solution was acidified with hydrochloric acid, evaporated to dryness and the acid esterified in the usual manner with methanol and hydrogen chloride. The methyl ester, b. p. 102–103° (2 mm.), was treated with five volumes of aqueous ammonia saturated at 0°, and kept in an icebox for several days. The amide was filtered off and the filtrate evaporated to a small volume *in vacuo* to give an additional small quantity; m. p. 129–130°; yield from the ester 95%.

Anal.[6] Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.71. Found: C, 64.34; H, 6.71.

This amide was also prepared by refluxing β-(2-pyridyl)-ethyl bromide with sodium cyanide in 80% alcohol for seven hours to give a 65% yield of β-(2-pyridyl)-propionitrile, b. p. 85–87° (1 mm.). Twenty-three grams of this nitrile, 2.3 g. of potassium hydroxide, 150 cc. of water, and 100 g. of 30% hydrogen peroxide were vigorously stirred, carefully warmed to 40° and kept at that temperature by immersion in an ice-bath until the temperature dropped to 30° without external cooling. The solution was treated with 4 cc. of concentrated hydrochloric acid and evaporated to a volume of 100 cc. in a vacuum. On cooling overnight 17.5 g. of crystals melting sharply at 76–77° separated. When crystallized from hexone the material melted at 129–130° and gave no melting point depression when mixed with a sample prepared by the other method.

β-(2-Pyridyl)-ethylamine-methylurethan.—Fifteen grams of the above amide was added to a cold solution of 4.6 g. of sodium in 150 cc. of absolute methanol. The mixture was stirred and kept below 0° while 16 g. of dry bromine was added drop by drop. When all the amide had dissolved the solution was refluxed one hour, the alcohol distilled and the residue treated with 75 cc. of water. The urethan was extracted with ethyl acetate and crystallized from ether–petroleum ether. The yield was 15 g.; m. p. 53–54°.

Anal.[6] Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71. Found: C, 59.81; H, 6.48.

β-(2-Pyridyl)-ethylamine Dihydrochloride.—The above urethan was hydrolyzed with hydrochloric acid, evaporated to dryness and crystallized from alcohol; m. p. 185–186°.

Anal. Calcd. for $C_7H_{12}N_2Cl_2$: Cl, 36.33. Found: Cl, 36.48.

β-(2-Pyridyl)-ethylamine-methylurethan Methiodide.—A solution of the urethan and excess methyl iodide in ether was kept at room temperature for several weeks. The reaction proceeded very slowly. The semi-solid precipitate was separated by decantation and crystallized from butanol to give bright yellow crystals; m. p. 110–111°.

Anal. Calcd. for $C_{10}H_{15}O_2N_2I$: I, 39.38. Found: I, 38.87.

β-(2-Pyridyl)-ethylamine-methochloride Hydrochloride.—The above methiodide was dissolved in water and shaken with an excess of freshly precipitated silver chloride until the filtrate no longer gave a test for iodide ion. An equal volume of hydrochloric acid was added and the mixture refluxed and evaporated to dryness. The product was crystallized from alcohol and melted at 191–193°.

Anal. Calcd. for $C_8H_{14}N_2Cl_2$: Cl, 33.91. Found: Cl, 34.05.

β-(4-Pyridyl)-propionamide.—β-(4-Pyridyl)-acrylic acid[8] (the intermediate 1,1,1-trichloro-3-(4-pyridyl)-2-propanol was obtained in much better yields (35%) by treating chloral with three times its weight of pyridine base fraction b. p. 142–144° as described, and removing the excess at 10 mm. on a water-bath before working up the

(5) Meisenheimer and Mahler, *Ann.*, **462**, 301 (1928).
(6) Analyses by Arlington Laboratories, Chagrin Falls, Ohio.
(7) Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939).
(8) Alberts and Bachman, *ibid.*, **57**, 1285 (1935).

mixture) was converted to the amide as described for the 2-pyridyl analog. The intermediate methyl ester distilled at 95° (2 mm.). The amide, m. p. 166–167°, was crystallized from alcohol.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 63.98; H, 6.71. Found: C, 63.99; H, 6.90.

The following compounds were prepared as described for the 2-pyridyl analogs.

β-(4-Pyridyl)-ethylamine-methylurethan Hydrochloride.—The urethan could not be obtained crystalline and decomposed on attempted distillation. The crude material was converted to the hydrochloride with dry hydrogen chloride in ethyl acetate and crystallized from methanol–ether, m. p. 132–133°.

Anal. Calcd. for $C_9H_{13}O_2N_2Cl$: Cl, 16.36. Found: Cl, 16.46.

β-(4-Pyridyl)-ethylamine Dihydrochloride.—M. p. 222°.

Anal. Calcd. for $C_7H_{12}N_2Cl_2$: Cl, 36.33. Found: Cl, 36.43.

β-(4-Pyridyl)-ethylamine-methylurethan Methiodide.—M. p. 121–122°.

Anal. Calcd. for $C_{10}H_{15}O_2N_2I$: I, 39.38. Found: I, 39.04.

β-(4-Pyridyl)-ethylamine-methochloride Hydrochloride.—M. p. 186–187°.

Anal. Calcd. for $C_8H_{14}N_2Cl_2$. Cl, 33.91. Found: Cl, 34.05.

Summary

The preparation as well as the chemical and pharmacological properties of some β-(2-, and 4-pyridylethyl and propyl)-amines have been described.

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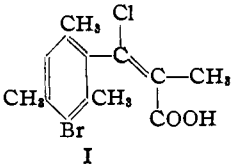
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

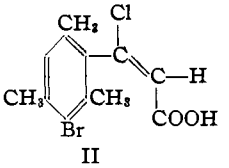
Restricted Rotation in Aryl Olefins. III. Preparation and Resolution of β-Chloro-β-(2-methyl-1-naphthyl)-acrylic Acids[1]

BY ROGER ADAMS AND L. O. BINDER[2]

Among the aryl olefins with restricted rotation between the benzene ring and an acrylic acid residue reported in previous articles[1,3] in this series are compounds I and II.



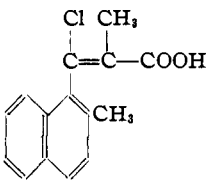
I



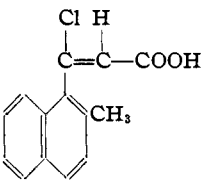
II

Both of these molecules were resolved readily. Compound I did not racemize in boiling *n*-butanol; compound II under similar conditions had a half-life of about two hundred minutes. Although no direct chemical proof was offered for the relative placement of the side-chain methyl and carboxyl groups in I or the hydrogen and carboxyl groups in II, by indirect deductions the structures assigned them appear to be the more likely.

A series of analogous derivatives of this type has been under investigation in order to compare the effects of various groups on the restricted rotation. The corresponding naphthalene compounds have now been synthesized and their structures are shown in formulas III and IV.



III



IV

Compounds III and IV are assumed to have the same geometric configuration as compounds I and II since they were formed from the appropriate ketones by exactly the same process used for the benzene derivatives.

Evidence deduced from previous work in this field would lead to the conclusion that the two methyls adjacent to the acrylic acid side-chain in I and II and the methyl and the aromatic grouping —CH= adjacent to the side-chain in III and IV represent the bulk of the hindrance contributed by the aromatic part of the molecules. A direct comparison of the steric effect of the methyl and —CH= groups is thus possible. Although many substituted binaphthyls and biphenyls have been prepared and resolved, none has been synthesized which allows a direct comparison of these groups just mentioned.

Compound III had a half-life in boiling *n*-butanol of seventy hours in contrast to compound I which did not racemize at all in boiling *n*-butanol. Compound IV had a half-life of about seventy

(1) For previous paper see Adams, Anderson and Miller, THIS JOURNAL, **63**, 1589 (1941).

(2) An abstract of a thesis submitted in partial fulfillment for the degree of Doctor of Philosophy in Chemistry.

(3) Adams and Miller, THIS JOURNAL, **62**, 53 (1940).