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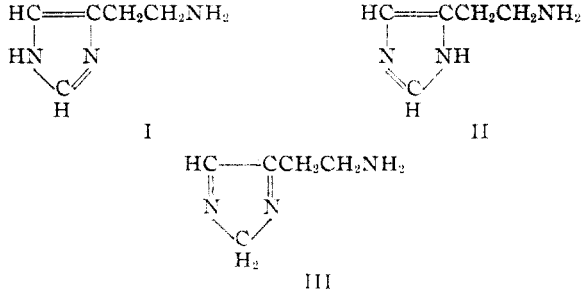
The Relation between Structure and Histamine-Like Activity

BY CARL NIEMANN AND JOHN T. HAYS

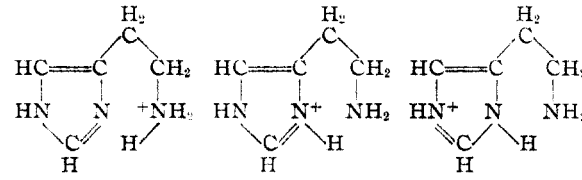
Recently Walter, Hunt and Fosbinder[1] reported that the physiological action of β-(2-pyridyl)-ethylamine is similar to that of histamine and that the action of β-(4-pyridyl)-ethylamine resembles that of epinephrine. This striking difference in the pharmacological behavior of the above two isomeric β-pyridylethylamines led us to inquire as to the physiological properties of the third and remaining isomeric β-pyridylethylamine, *i. e.*, β-(3-pyridyl)-ethylamine in the hope that information about the latter compound would lead to a more general understanding of the relation between structure and histamine-like activity.

dl-β-(3-Pyridyl)-alanine[2] was decarboxylated using the method of Abderhalden and Gebelein[3] to give β-(3-pyridyl)-ethylamine. A comparative study of the physiological properties of the three isomeric β-pyridylethylamines was undertaken by Dr. G. A. Alles of this Institute and it has been found that β-(3-pyridyl)-ethylamine resembles β-(4-pyridyl)-ethylamine in its pharmacological properties and does not show any notable histamine-like activity, which characterizes the pharmacological action of β-(2-pyridyl)-ethylamine.[4] For histamine we may write the three tautomeric structures I, II and III. However, it is clear from



I II III

a consideration of the possible resonance forms of each tautomer[5] and from the bond energies[6,7] that at equilibrium we need consider only structures I and II. Under physiological conditions tautomers I and II will add a proton and exist in the form of cations. If we ignore interaction between the side-chain and the nucleus, we must assign equal weight to each cation, but if we assume that side chain–nucleus interaction does take place through the medium of an intramolecular hydrogen bond, it follows that the cation has the structure (IV, V, VI). This ion with respect to



IV V VI

bond distances and chelation is more nearly related to tautomer I than to tautomer II. A similar chelation is to be expected in the cation of β-(2-pyridyl)-ethylamine. Thus it appears that the characteristic pharmacological properties of histamine are associated with structures that have their origin in tautomer I and we may look upon this tautomer as containing the obligatory structural requirements requisite for histamine-like activity.

The similarity of the physiological action of histamine and β-(2-pyridyl)-ethylamine led Walter, Hunt and Fosbinder[1] to conclude that the molecular fragment —CH=N—C($CH_2CH_2NH_2$)=CH—, which they consider as being present in both histamine (tautomer I) and β-(2-pyridyl)-ethylamine, is primarily responsible for the histamine-like activity of these compounds. Taking advantage of the studies of Hill and Branch[5] and of Schomaker and Pauling,[8] we can give greater precision to the above conclusion of Walter, Hunt and Fosbinder[1] by defining the obligatory structural fragment requisite for histamine-like activity as —CH—*a*—N—*b*—C($CH_2CH_2NH_2$)—*c*—CH— where $a = 1.36 \pm 0.01$ Å., $b = 1.38 \pm 0.02$ Å., and $c = 1.40 \pm 0.01$ Å., and when chelation between the nitrogen atoms occurs in the cation.

A comparison of the structures that can be written for β-(3-pyridyl)-ethylamine and for

(1) L. A. Walter, W. H. Hunt and R. J. Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

(2) C. Niemann, R. N. Lewis and J. T. Hays, *ibid.*, **64**, 1678 (1942).

(3) E. Abderhalden and F. Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926).

(4) The authors wish to express their indebtedness to Dr. Alles for this information.

(5) T. H. Hill and G. E. K. Branch, *Science*, **91**, 145 (1940).

(6) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940.

(7) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, New York, N. Y., 1941.

(8) V. Schomaker and L. Pauling, THIS JOURNAL, **61**, 1769 (1939).

tautomer II reveals that each of these substances contains the molecular fragment —CH—*a*—N—*b*—CH—*c*—C($CH_2CH_2NH_2$)—. As β-(3-pyridyl)-ethylamine is devoid of any histamine-like activity, we conclude, on the basis of the preceding argument, that tautomer II is likewise devoid of any histamine-like activity. This conclusion is in accord with and supports the previous contention that tautomer I is the structure responsible for the histamine-like activity of histamine and that the principle obligatory structural requirement for histamine-like activity is the molecular fragment —CH—*a*—N—*b*—C($CH_2CH_2NH_2$)—*c*—CH—.

Experimental[9]

β-(3-Pyridyl)-ethylamine Dihydrochloride.—A mixture of 1 g. of *dl*-β-(3-pyridyl)-alanine[2] and 20 g. of diphenylamine was heated to 245–250° and maintained at that temperature for two hours.[3] The reaction mixture was digested with 40 ml. of 3 *N* hydrochloric acid and the digest allowed to cool to 25° with vigorous stirring. The diphenylamine was removed by extraction with ether, an excess of aqueous sodium hydroxide added to the aqueous phase and the latter extracted with ether. The ethereal solution was dried over sodium sulfate and then acidified with dry hydrogen chloride. The amine dihydrochloride separated as an oil, which was collected and crystallized from 20–25 ml. of hot absolute ethanol. This product (0.4 g.) was recrystallized from a mixture of absolute ethanol and ether to give β-(3-pyridyl)-ethylamine dihydrochloride, m. p. 195–205° with decomposition.

(9) Microanalyses by Dr. G. Oppenheimer and G. A. Swinehart.

Anal. Calcd. for $C_7H_{12}N_2Cl_2$ (195.1): C, 43.1; H, 6.2; N, 14.4; Cl, 36.4. Found: C, 43.3; H, 6.3; N, 14.4; Cl, 36.4.

Preliminary Pharmacological Report.[10]—In the cat both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine are pressor in minimally active and higher doses, being about one-fifth to one-tenth as active as β-phenylethylamine. In the rabbit the pressor responses are not great with minimally active doses and with higher doses an initial depressor effect may be noted that is, however, unlike that of histamine, and is shown in similar degree by both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine. In sufficient concentration both β-(3-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine decrease movement and tone of isolated rabbit jejunum preparations. This resembles the activity of more than minimally active concentrations of β-phenylethylamine, and is the reverse of the effect of histamine. No stimulant effect in concentrations up to 10^{-3} molar was noted upon isolated guinea-pig ileum preparations though this same concentration of β-phenylethylamine causes some increase in tone and concentrations of but 10^{-6} molar histamine are very active upon such preparations.

Summary

β-(3-Pyridyl)-ethylamine has been prepared and it has been found that this amine, in common with β-(4-pyridyl)-ethylamine and in contrast to β-(2-pyridyl)-ethylamine, has pressor activity. The relation between structure and histamine-like activity is discussed.

(10) The authors are indebted to Dr. G. A. Alles for this report and to Dr. L. A. Walter for samples of β-(2-pyridyl)-ethylamine and β-(4-pyridyl)-ethylamine.

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The Addition of Hydrogen Fluoride to the Triple Bond[1]

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We have recently demonstrated[2] that olefins will add hydrogen fluoride, even in the complete absence of catalysts, to give good yields of alkyl fluorides. Likewise the cyclopropane ring is opened by hydrogen fluoride to give *n*-propyl fluoride. The chemical literature contains no reference to a similar addition of hydrogen fluoride to the triple bond. In view of the ease of addition to the double bond, a similar behavior was expected of the *triple bond*. This proved to be the case and we found that unsaturates of this type readily *add hydrogen fluoride* in the *absence of catalysts*, according to the equations

$$R—C\equiv C—R' + HF \longrightarrow R—CF=CH—R' \quad (1)$$
$$R—CF=CH—R' + HF \longrightarrow R—CF_2—CH_2—R' \quad (2)$$

giving *difluorinated hydrocarbons* of the type

$$R—CF_2—CH_2—R'$$

Previous to our investigation only the two simplest[3] members of this series were known, namely, 1,1-difluoroethane[4] and 2,2-difluoropropane.[5] Subsequently A. L. Henne, in his well known studies of aliphatic fluorine compounds, has extended the reaction of antimony or mercuric

(1) Presented before the Organic Section of the American Chemical Society at its Baltimore meeting, April, 1939 (see Abstracts, Section M., p. 27).

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(2) A. V. Grosse and C. B. Linn, *J. Org. Chem.*, **3**, 26 (1938).

(3) For CH_2F_2, see A. L. Henne, THIS JOURNAL, **59**, 1400 (1937).

(4) A. L. Henne and M. W. Renoll, *ibid.*, **58**, 889 (1936).

(5) A. L. Henne and M. W. Renoll, *ibid.*, **59**, 2434 (1937).