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

Amine Exchange Reactions of 1-Methylgramine

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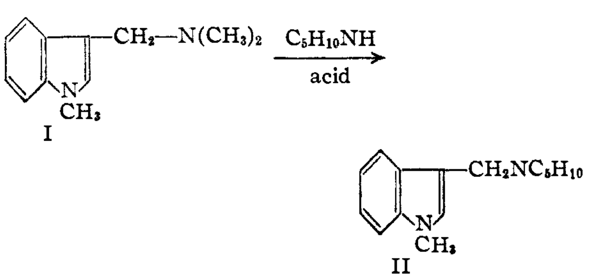
While a number of examples of amine exchange reactions of quaternary ammonium salts of the benzyl type are recorded in the literature,[2] analogous reactions of tertiary amines have been reported only for Mannich bases[2d,3] which are capable of reacting by amine elimination followed by amine addition to the activated double bond.[4a]

Since 1-methylgramine (I), a Mannich base which cannot react by amine elimination, acts as an alkylating agent,[4b] it is of interest to determine whether this compound is also capable of undergoing amine exchange reactions. The free amine (I) proved to be unreactive in this sense; 90% of the 1-methylgramine was recovered after twenty-four hours of refluxing with piperidine in hexanol solution. Since there had been some evidence that the carbon alkylations by this amine are acid-catalyzed, the experiment was repeated with 1-methylgramine hydrochloride; amine exchange took place and 3-piperidinomethyl-1-methylindole (II) was isolated in 60% yield. Thus the amine exchange reaction of I is subject to acid catalysis and apparently proceeds by a substitution mechanism. The amine exchange of gramine with piperidine[3b] may or may not proceed by the same mechanism; if it does, the acid catalyst is presumably the hydrogen atom attached to the indole nitrogen.

In order to test whether acidic substances of other types are as effective catalysts for the amine exchange as the proton, the reaction between I and piperidine was carried out in the presence of boron trifluoride. In this case also, amine exchange took place. Thus a proton is not a specific catalyst for reactions of this type.

The structure of the product (II) was confirmed by direct synthesis from 1-methylindole, formaldehyde, and piperidine in the presence of acetic acid, and by synthesis through an amine exchange reaction of 1-methylgramine methiodide with piperidine.



Experimental[5,6]

1-Methylgramine Hydrochloride.—To 5 g. of 1-methylgramine[4a] (I) in 25 ml. of absolute ethanol was added a solution of 5 ml. of concentrated hydrochloric acid in 25 ml. of absolute ethanol. The hydrochloride crystallized after a few seconds. After the suspension had been allowed to cool in the icebox, the white crystals were collected and washed twice with absolute ethanol and three times with absolute ether; wt. 5.3 g. (89%) m. p. 198–199° (dec.). Recrystallization from 95% ethanol did not change the melting point.

Anal. Calcd. for $C_{12}H_{17}N_2Cl$: C, 64.13; H, 7.63. Found: C, 64.29; H, 7.78.

3-Piperidinomethyl-1-methylindole (II). From 1-Methylindole.—A solution of 1 ml. of piperidine in 2 ml. of glacial acetic acid was cooled to 5°, and 0.8 ml. of 40% aqueous formaldehyde was added. The resulting mixture was cooled to 5° and added in one lot to 1.22 ml. (1.31 g.) of 1-methylindole. The reaction mixture was swirled gently until it became homogeneous. During this process a spontaneous rise of temperature was noted. The solution was allowed to stand at room temperature for eighteen hours; it was then added to 20 ml. of 10% aqueous sodium hydroxide, and the oil which separated was extracted with ether. The ether solution was exhaustively extracted with 1 *N* hydrochloric acid, the acid extract was made alkaline with 10% aqueous sodium hydroxide, and the oil which separated was extracted with ether. The ether solution was washed twice with water, dried over sodium sulfate, and distilled. The oily residue was distilled *in vacuo* at 0.06 mm., the distillate being collected at a bath temperature of 120–155°. 3-Piperidinomethyl-1-methylindole (II) was obtained as an almost colorless oil, $n^{20}D$ 1.5820; yield 1.6 g. (70%).

The picrate was prepared in ethanol (in which it is only slightly soluble, even at the boiling point); it melted at 166.5–167.5° (dec.). Two recrystallizations from 95% ethanol yielded yellow platelets of melting point 174.5–176° (dec.).

Anal. Calcd. for $C_{21}H_{23}N_5O_7$: C, 55.13; H, 5.07. Found: C, 55.06; H, 5.25.

The methiodide, obtained by adding an excess of methyl iodide to a solution of the base in absolute ethanol and then adding ether to hasten crystallization, melted at 148–149° (dec.) after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{16}H_{23}N_2I$: C, 51.90; H, 6.26. Found: C, 51.82; H, 6.47.

From 1-Methylgramine Methiodide.—A mixture of 3.3 g. (0.01 mole) of methylgramine methiodide[4a] and 16.5 ml. of piperidine was refluxed for three hours. There was a vigorous evolution of trimethylamine, and the suspension became homogeneous after one and one-half hours. Crystals separated when the solution was cooled. Ether was added, the suspension was filtered, and the crystals were washed with ether. Since an aqueous solution of the crystals did not become cloudy on the addition of alkali, they presumably consisted of piperidine hydriodide. The ether–piperidine filtrate was concentrated on the steam-bath, first at atmospheric pressure and then *in vacuo*. Water was added to the residue, which was then extracted

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(2) (a) Scholtz, *Ber.*, **24**, 2402 (1891); *ibid.*, **31**, 414, 1700 (1898); (b) von Braun, *et al.*, *Ann.*, **445**, 247 (1925); *Ber.*, **59**, 1786, 2330 (1926); (c) Hultquist, *et al.*, THIS JOURNAL, **70**, 23 (1948).

(3) (a) Duden, Bock and Reid, *Ber.*, **38**, 2046 (1905); (b) Howe, Zambito, Snyder and Tishler, THIS JOURNAL, **67**, 38 (1945); (c) Snyder and Brewster, *ibid.*, **70**, 4230 (1948).

(4) (a) Snyder and Eliel, *ibid.*, **70**, 1703 (1948); (b) "Carbon Alkylations with 1-Methylgramine and its Methiodide," *ibid.*, in press.

(5) All melting points are corrected.

(6) Microanalyses by Miss Emily Davis, Mrs. Jane Wood and Mr. Howard Clark.

with ether. The ether extract was washed with water, dried over sodium sulfate, and distilled. The residue was dried for a short time *in vacuo* at 150°; it weighed 2.03 g. (89%). Distillation at 0.06 mm. (air-bath 130–160°) yielded a nearly colorless liquid of $n^{20}\text{D}$ 1.5809. The picrate melted at 171–172.5° (dec.); recrystallization from ethanol raised the melting point to 175–175.5° (dec.), and the mixed melting point with material obtained from methylindole was the same. The methiodide melted at 146–147.5° (dec.) and gave no depression of the melting point when mixed with the analytical sample obtained as described above.

From 1-Methylgramine Hydrochloride.—A mixture of 2.25 g. (0.01 mole) of methylgramine hydrochloride, 4.25 g. (0.05 mole) of piperidine, and 25 ml. of *n*-hexanol was refluxed for twenty-four hours. On cooling, the solution deposited crystals. Ether was added and the suspension was extracted several times, first with 3 *N* and then with 1 *N* hydrochloric acid. The combined acid extract was made alkaline with 40% aqueous sodium hydroxide and extracted with ether. The ether layer was dried and distilled. The residue was distilled at 0.08 mm. (air-bath 130–175°) to yield a nearly colorless oil of $n^{20}\text{D}$ 1.5798; yield 1.38 g. (60.5%). The picrate melted at 168.5–170.5° (dec.); one recrystallization raised the melting point to 174.5–175.5° (dec.). The mixed melting point with samples obtained as described above was the same. The methiodide, after recrystallization from absolute ethanol, melted at 147–149 (dec.) and showed no depression in melting point when mixed with samples obtained by the methods described above.

Attempted Reaction of 1-Methylgramine with Piperidine.—This reaction was carried out under exactly the same conditions as described for the hydrochloride, except that 1.9 g. (0.01 mole) of methylgramine was employed instead of the methylgramine hydrochloride. The reaction mixture was worked up as described above. The oil obtained after distillation of the solvents distilled at a bath temperature of 90–115° (0.1 mm.) and had $n^{20}\text{D}$ 1.5740. It weighed 1.7 g. The picrate, without recrystallization, melted at 144.5–145.5°; the mixed melting point with 1-methylgramine picrate was 145–146°. Hence the product was practically pure 1-methylgramine, recovered in 90% yield.

Methylgramine was also recovered when refluxed with ten times its weight of piperidine for twenty-four hours.

Reaction of 1-Methylgramine with Piperidine in the Presence of Boron Trifluoride.—This reaction was carried out in the same way as the experiment just described, except that 2 g. (0.014 mole) of boron trifluoride etherate was added before the beginning of the reflux period. The product, isolated as previously described, distilled at an air-bath temperature of 150–180° at 0.1 mm. and had $n^{20}\text{D}$ 1.5802. The picrate melted at 171–173° (dec.); recrystallization from 95% ethanol-acetone raised the melting point to 175–176.5° (dec.), and the mixed melting point with samples of the picrate obtained by other routes was 175–176.5° (dec.). Hence the product was II and amine exchange had taken place. The yield was about the same as in the reaction of the hydrochloride of I with piperidine.

Summary

1-Methylgramine hydrochloride undergoes an amine exchange reaction with piperidine in refluxing hexanol, whereas 1-methylgramine does not react under the same conditions. Boron trifluoride, an acid in the Lewis sense, also catalyzes the amine exchange.

3-Piperidinomethyl-1-methylindole, the product of the amine exchange reaction, was also obtained from 1-methylindole, aqueous formaldehyde and piperidine in the presence of glacial acetic acid, and from 1-methylgramine methiodide and piperidine at the reflux temperature.

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Herculin, A Pungent Insecticidal Constituent of Southern Prickly Ash Bark[1]

BY MARTIN JACOBSON

Various species of the genus *Zanthoxylum* (family *Rutaceae*) have been reported to be insecticidal. Manson[2] found a hot water extract of *Z. hamiltonianum* roots to be an effective mosquito larvicide, and concluded that the active material was a saponin. An acetone extract of "prickly ash" berries (*Zanthoxylum sp.*) was found to be effective against mosquito larvae.[3] Extracts of the dried bark of northern prickly ash, *Z. americanum* Mill., were reported to be repellent to the Japanese beetle,[4] but the ground bark was ineffective against southern armyworms, melonworms and bean leaf rollers, while petroleum ether extracts of both the bark and wood of this species showed neither toxicity to house flies nor synergism with the pyrethrins.[5] The pericarp of a species of *Zanthoxylum*, known as "hua chiao" in China, is used in that country as an anthelminthic and anesthetic.[6] The powdered leaves of southern prickly ash, *Z. clava-herculis*, were repellent to cotton caterpillars.[7] Acetone extracts of the bark of this species are reported to be toxic to mosquito larvae, but non-toxic to aphids[8] and cyclamen mites.[9]

Zanthoxylum clava-herculis L. (*Z. carolinianum* Lam., *Fagara caroliniana* Engler), commonly called southern prickly ash, Hercules' club, or toothache tree, is indigenous to the southern United States. The bark is used medicinally as an irritant and stomachic, and is available commercially. Chewing of various parts of the plant, especially the bark, gives a persistent burning, para-

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[1] Report of a study made under the Research and Marketing Act of 1946.

[2] D. Manson, *J. Malaria Inst. India*, **2**, 85 (1939).

[3] A. Hartzell and F. Wilcoxon, *Contrib. Boyce Thompson Inst.*, **12** [2], 127 (1941).

[4] F. W. Metzger and D. H. Grant, U. S. Dept. Agr. Tech. Bul. 299, 1932.

[5] Unpublished reports of this Bureau.

[6] C. W. Wang, Y. Y. Lu and T. H. Chen, *J. Pharm. Soc. China*, **2**, 13 (1944); *C. A.*, **39**, 4717 (1945).

[7] C. V. Riley, *U. S. Ent. Comm. Rept.*, **4**, 185 (1885).

[8] A. Hartzell, *Contrib. Boyce Thompson Inst.*, **13** [5], 243 (1944).

[9] L. D. Goodhue and F. F. Smith, *J. Econ. Ent.*, **37**, 214 (1944).