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Studies on Imidazole Compounds. I. 4-Methylimidazole and Related Compounds

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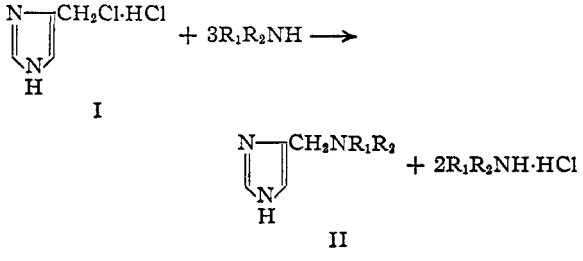
In connection with a program now in progress in these laboratories we have prepared substances resembling histamine in structure, for the purpose of obtaining competitive inhibitors of histamine. It was also desirable to find analogs having only one of the pharmacological properties of histamine without displaying its whole complex of actions.[1]

This paper describes the chemistry of 4-methylimidazole derivatives, especially 4-aminomethyl- and 4-(substituted aminomethyl)-imidazoles. The starting material was 4-(hydroxymethyl)-imidazole, which by treatment with thionyl chloride in benzene was converted to 4-(chloromethyl)-imidazole hydrochloride (I). The covalently bound chlorine atom in this derivative is very reactive, as evidenced by the following facts: (i) I is rapidly hydrolyzed in aqueous solution at room temperature to 4-(hydroxymethyl)-imidazole; (ii) its reaction with amines is strongly exothermic; (iii) it readily undergoes hydrogenolysis to 4-methylimidazole.

It has been reported[2] that 4-(aminomethyl)-imidazole can be prepared from the chloride I and ammonia, but we were unable to obtain it in pure form. 4-(Aminomethyl)-imidazole was synthesized by hydrogenation of the oxime of imidazole-4-aldehyde, the latter being obtained in good yields from 4-(hydroxymethyl)-imidazole by oxidation.

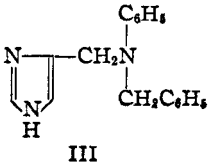
The 4-(disubstituted aminomethyl)-imidazoles were easily prepared by treating I with an excess of a secondary amine in anhydrous ethanol. The tertiary amines (II) could not be isolated as the bases since they were usually non-crystalline. Even the corresponding dihydrochlorides were sometimes difficult to crystallize and were strongly hygroscopic.



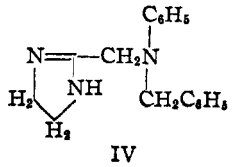
I

II

4-(Benzylphenylaminomethyl)-imidazole (III), is of interest because it is a position isomer of the imidazole corresponding to the antihistaminic, 2-(benzylphenylaminomethyl) - imidazoline (IV). The amine III possesses about one-half the antihistaminic action of IV.



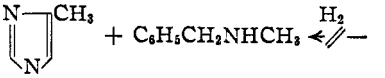
III



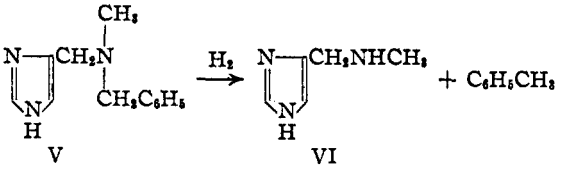
IV

4-(Monosubstituted aminomethyl)-imidazoles could not be prepared in a pure state by the same method used for the tertiary amines, since only intractable mixtures resulted. Therefore, we resorted to debenzylation of the appropriate tertiary amine. For example, 4-(methylaminomethyl)-imidazole (VI) was prepared by hydrogenolysis of 4-(benzylmethylaminomethyl)-imidazole (V).

It is of interest to note that under the ordinary hydrogenolysis conditions only the benzyl group was split off and not the 4-methylene-imidazole group which can be considered a benzyl-type radical; the reaction products were 4-(methylaminomethyl)-imidazole (VI) and toluene. In this connection we found that 4-(dimethylaminomethyl)-imidazole failed to undergo hydrogenolysis. It



VII



V VI

may be mentioned further that 4-(hydroxymethyl)-imidazole was not reduced to 4-methylimidazole (VII), whereas under the same conditions benzyl alcohol afforded toluene. The cleavage of only one benzyl group during the hydrogenolysis of 4-(dibenzylaminomethyl)-imidazole was in accord with similar cases reported in the literature.[3]

An effort was made to prepare ethers by treating the 4-chloromethyl-imidazole hydrochloride (I) with sodium alkoxides, but only resinous substances resulted. Presumably, the highly active chloroamine liberated from its hydrochloride (I) by the alkoxide rapidly self-condensed. In the sulfur series, however, reaction with sodium benzylmercaptide yielded 4-(benzylmercaptomethyl)-imidazole.

Some of the 4-(substituted aminomethyl)-imidazoles showed a weak antihistaminic action on the guinea pig ileum, while others imitated his-

(1) Since the completion of this work, the preparation of several of the compounds included in this study has been reported by another laboratory: R. J. Turner, THIS JOURNAL, 70, 3523 (1948).

(2) Pyman, *J. Chem. Soc.*, 99, 2175 (1911).

(3) Birkofer, *Ber.*, 75, 429 (1942); *cf.* also Baltzly and Buck, THIS JOURNAL, 65, 1984 (1943).

tamine. These results will be reported by our colleagues of the Division of Macrobiology.

Experimental[4,5]

4-(Hydroxymethyl)-imidazole.—The hydrochloride of this compound was prepared according to Totter and Darby.[6] The free base was obtained in the following manner. A solution of 22 g. of the hydrochloride in water was treated with 25 ml. of saturated aqueous sodium carbonate solution. Distillation of the resulting solution to dryness *in vacuo* left a residue, which was twice extracted with 30 ml. of anhydrous ethanol and filtered. Thirty ml. of benzene was added and the solution concentrated to 10 ml. It was then cooled in a Dry Ice-bath, and induced to crystallize with scratching.[7] After several days in the cold, the large, somewhat yellow prisms were filtered; m. p. 91°. From the mother liquor a second crop of the same m. p. was obtained. The total yield was 13.6 g. (85%); recorded melting points, 91°[8a] and 93°.[8b]

4-(Chloromethyl)-imidazole Hydrochloride. (I).—To a suspension of 69.0 g. (0.51 mole) of 4-(hydroxymethyl)-imidazole hydrochloride in 50 ml. of benzene, protected from moisture, and vigorously stirred, was slowly added a solution of 50 ml. (0.69 mole) of thionyl chloride in 100 ml. of benzene. The mixture was refluxed for two hours. After having stood overnight it was filtered, washed with benzene and stored *in vacuo;* it weighed 78 g. (99%). After recrystallization from 70 ml. of anhydrous ethanol, 60 g. (77%) of somewhat yellow crystals was obtained; m. p. 138–141°; reported, 144°.[9] The filtrate, on concentration, gave 8.5 g. of somewhat less pure product.

When pure, the compound is very slightly hygroscopic. It is hydrolyzed rapidly even at room temperature. When a sample of *ca.* 0.1 g. was dissolved in 50 ml. of water and titrated (mercuric nitrate) at 24.5°, these values for ionic chloride were obtained: after eight minutes, 43.0%; after fifteen minutes, 46.6%. Calcd. for $C_4H_5N_2Cl\cdot HCl$: ionic chloride, 23.2%; total chloride, 46.4%.

4-(Dimethylaminomethyl)-imidazole Dihydrochloride.—To 100 ml. of anhydrous ethanol cooled to 0° was added 52 g. of dimethylamine cooled to −50°. A solution of 15.0 g. of I in 60 ml. of anhydrous ethanol was added with stirring during forty-five minutes. The mixture was then allowed to stand at room temperature for two days. The solvent was distilled and the residue was dissolved in a little water, treated with 25 ml. of saturated aqueous sodium carbonate solution, and evaporated *in vacuo* to dryness. Extraction four times with 25 ml. of anhydrous ethanol, combination of the extracts, and evaporation of the solvent *in vacuo* gave a brown sirup which failed to crystallize. When digested briefly with 2 molar equivalents of dry ethanolic hydrogen chloride, crystallization commenced at once. The cooled mixture was filtered; 16.4 g. (84%) of almost pure material was obtained; m. p. 196–202°, which, when recrystallized twice from 95% ethanol, gave colorless prisms; m. p. 197–197.5°. The hygroscopic dihydrochloride was slightly soluble in anhydrous ethanol.

Anal. Calcd. for $C_6H_{13}N_3Cl_2$: C, 36.38; H, 6.61; N, 21.21; Cl, 35.80. Found: C, 36.43; H, 6.70; N, 21.55; Cl, 36.38.

4-(Diethylaminomethyl)-imidazole Dihydrochloride (Typical Procedure).—To a solution of 20 g. of diethylamine in 100 ml. of anhydrous ethanol, boiling under reflux, was added during one hour, 7.00 g. of I in 30 ml. of anhydrous ethanol. After two hours under reflux, 25 ml. of saturated aqueous sodium carbonate solution was stirred into the hot solution, the crude base isolated, and the hydrochloride prepared as described for 4-(dimethylaminomethyl)-imidazole; yield 7.1 g. (69%) of crystals of indefinite melting point. Following recrystallization from anhydrous ethanol 5.24 g. of the dihydrochloride was obtained; m. p. 192–193°, unchanged by further crystallization.

Anal. Calcd. for $C_8H_{17}N_3Cl_2$: N, 18.58; Cl, 31.36. Found: N, 18.44; Cl, 31.20.

By the above typical procedure the following compounds were prepared:

4-(1-Piperidylmethyl)-imidazole Dihydrochloride.—Recrystallized from ether–ethanol; yield, 69%; m. p. 223–225°.

Anal. Calcd. for $C_9H_{17}N_3Cl_2$: C, 45.33; H, 7.22. Found: C, 45.48; H, 6.95.

4-(Benzylmethylaminomethyl)-imidazole (V) Dihydrochloride.—Recrystallized from ethanol–ethyl acetate; yield 67%, m. p. 229–230°.

Anal. Calcd. for $C_{12}H_{17}N_3Cl_2$: N, 15.33; Cl, 25.86. Found: N, 15.20; Cl, 25.80.

4-(Benzylethylaminomethyl)-imidazole Dihydrochloride.—Recrystallized from anhydrous ethanol; yield, 90%; m. p. 208–209°.

Anal. Calcd. for $C_{13}H_{19}N_3Cl_2$: C, 54.17; H, 6.64; N, 14.58. Found: C, 53.91; H, 6.35; N, 14.38.

4-(Dibenzylaminomethyl)-imidazole.—To a boiling solution of 30 g. of dibenzylamine in 150 ml. of anhydrous ethanol, was added a solution of 4.60 g. of I during one-half hour and the mixture refluxed for seven hours. After removal of the solvent *in vacuo*, addition of 150 ml. of water and 20 ml. of saturated aqueous sodium carbonate solution, the cooled mixture was extracted twice with ether to separate excess dibenzylamine. The aqueous phase was evaporated *in vacuo* to dryness and the residue extracted thoroughly with anhydrous ethanol. Following distillation *in vacuo* of the combined alcohol extracts, a pink, crystalline mass remained which again was taken up in anhydrous ethanol, filtered (to free it of traces of inorganic salts), and brought to dryness. The crystalline residue weighed 7.0 g. (84%); m. p. 140–144°. After two recrystallizations from 50% aqueous ethanol the substance was obtained as platelets; m. p. 148.5–149.5°.

Anal. Calcd. for $C_{18}H_{19}N_3$: C, 77.94; H, 6.90; N, 15.15. Found: C, 77.91; H, 6.96; N, 15.53.

4-(Benzylphenylaminomethyl)-imidazole (III).—Eighteen grams of benzylaniline in 100 ml. of anhydrous ethanol was allowed to react in the usual way with 5 g. of I. After twelve hours of reflux, an excess of sodium carbonate was added and the crude base isolated as described above. The oil was extracted ten times with 100 ml. of boiling petroleum ether (b. p. 30–60°), which removed much of the excess benzylaniline. The residue was adsorbed from a benzene solution on 100 g. of alumina (Alorco), was washed exhaustively with 5% methanol in benzene, and 6 g. of brown oil was eluted with ethanol. The material partially crystallized on standing, and after two recrystallizations from ethanol, 1.5 g. of III was obtained, m. p. 147–148°.

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.50; H, 6.53. Found: C, 77.60; H, 6.79.

4-(Methylaminomethyl)-imidazole (VI) Dihydrochloride.—4-(Benzylmethylaminomethyl)-imidazole (3.30 g.) in 40 ml. of anhydrous methanol containing 5 ml. of alcoholic hydrogen chloride solution (8 *N*) was hydrogenated at atmospheric pressure over 1.00 g. of 5% palladium-charcoal catalyst (American Platinum Works). Approximately one molar equivalent of hydrogen was absorbed during ninety minutes. The filtered solution was distilled to dryness *in vacuo* and the residue on recrystallization from anhydrous ethanol yielded a very hygroscopic dihydrochloride (75%), m. p. 198–199.5°.

Anal. Calcd. for $C_5H_{11}N_3Cl_2$: C, 32.62; H, 6.02; N, 22.83. Found: C, 32.42; H, 6.10; N, 22.83.

(4) All melting points are uncorrected.

(5) The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J. We are grateful to Mrs. Kathryn Oney for assistance in the experimental work.

(6) "Organic Syntheses," **XXIV**, 64 (1944).

(7) Subsequent batches were seeded.

(8) (a) Pyman, *J. Chem. Soc.*, **99**, 673 (1911); (b) Darby, Lewis and Totter, THIS JOURNAL, **64**, 464 (1942).

(9) Pyman, *ibid.*, **99**, 675 (1911).

4-(Ethylaminomethyl)-imidazole Dihydrochloride.—Hydrogenation of 4-(benzylethylaminomethyl)-imidazole in the manner described for the homologous methyl compound yielded the hygroscopic dihydrochloride (81%), which after two crystallizations from anhydrous ethanol–ethyl acetate melted at 169–170.5°.

Anal. Calcd. for $C_6H_{13}N_3Cl_2$: C, 36.36; H, 6.61; N, 21.21; Cl, 35.80. Found: C, 36.14; H, 6.74; N, 20.80; Cl, 35.48.

4-(Benzylaminomethyl)-imidazole Dihydrochloride. Hydrogenation of 4-(dibenzylaminomethyl)-imidazole, in the manner described above, produced the *dihydrochloride* in 70% yield as colorless crystals; m. p. 195–200°. Two recrystallizations from anhydrous methanol raised the melting point to 200.5–201°.

Anal. Calcd. for $C_{11}H_{15}N_3Cl_2$: C, 50.78; H, 5.81; N, 16.15; Cl, 27.26. Found: C, 51.19; H, 5.72; N, 15.86; Cl, 27.31.

4-(Benzylmercaptomethyl)-imidazole Hydrochloride.—To a stirred, refluxing solution of 11.4 g. of benzylmercaptan in 70 ml. of 1.30 *N* sodium methoxide in methanol and 100 ml. of dry ethanol was added a solution of 7.0 g. of I in ethanol. After refluxing for four hours, the mixture was acidified with ethanolic hydrogen chloride. After filtration of the precipitated sodium chloride and evaporation of the solvent *in vacuo*, the residue was suspended in water and extracted several times with ether to remove the excess benzylmercaptan. The aqueous phase was added to a boiling solution of 13 g. of picric acid in water and the picrate recrystallized twice from water; m. p. 145–146°.

Anal. Calcd. for $C_{11}H_{12}N_2S \cdot C_6H_3N_3O_7$: S, 7.32. Found: S, 7.13.

The picrate was suspended in an excess of hydrochloric acid and the picric acid removed with ether. The aqueous solution was concentrated to a sirup and the hydrochloride was recrystallized from ethanol–ether, m. p. 125–128°.

Anal. Calcd. for $C_{11}H_{13}N_2SCl$: C, 54.45; H, 5.40. Found: C, 54.51; H, 5.28.

Oxidation of 4-(Hydroxymethyl)-imidazole.—The oxidation was performed essentially by the method of Pyman.[10] From 19.6 g. of 4-(hydroxymethyl)-imidazole was obtained 9.50 g. (49%) of *imidazole-4-aldehyde*, m. p. 165–169°, as straw-colored crystals. Recrystallization from aqueous methanol or water gave an almost white product of m. p. 173–174°.

When yellow or brown material was obtained it was purified by chromatography of a dry acetone solution on alumina. The aldehyde was eluted with a 25% (by volume) mixture of anhydrous ethanol in acetone (equal in volume to the acetone solution) and formed after concentration to a small volume colorless crystals of m. p. 173–174.5° (with some decomposition); reported,[11] 173°; recovery 75–80%.

Anal. Calcd. for $C_4H_4ON_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.21; H, 4.50; N, 29.16.

Attempts to prepare the aldehyde from 4-(chloromethyl)-imidazole hydrochloride and hexamethylenetetramine in anhydrous ethanol gave an addition compound, but the aldehyde could not be prepared from it.[12]

After removal of the aldehyde from the sodium carbonate solution the filtrate was acidified with concentrated hydrochloric acid and left in the cold. Next day 4.80 g. (21%) of *imidazole-4-carboxylic acid*, of m. p. 270° dec., was filtered. Recrystallization from 80 ml. of water yielded 3.50 g.; m. p. 280.5° dec.; reported,[9] 281°.

Anal. Calcd. for $C_4H_4O_2N_2$: C, 42.86; H, 3.60; N, 25.00. Found: C, 42.63; H, 3.71; N, 25.17.

4-(Aminomethyl)-imidazole Dihydrochloride.—A solution of 1.11 g. (0.01 mole) of imidazole-4-aldehyde oxime[13] in 80 ml. of methanol containing 0.05 mole of dry hydrogen chloride was hydrogenated at atmospheric pressure over 5% palladium–charcoal. The theoretical quantity of hydrogen was absorbed in eighty minutes. After evaporation of the filtered solution to dryness the residue was recrystallized from methanol–water (9:1) to give 1.24 g. of amine hydrochloride; m. p. 239–242°. An analytically pure sample was obtained after two recrystallizations from ethanol containing just sufficient water to effect solution while hot: m. p. 246–247° with a slight emollescence at 105°; reported m. p. 236°[14a] and 244°.[14b]

Anal. Calcd. for $C_4H_9N_3Cl_2$: C, 28.25; H, 5.34; N, 24.71; Cl, 41.70. Found: C, 28.17; H, 5.46; N, 24.49; Cl, 42.34.

4-Methylimidazole Picrate.—A solution of 3.06 g. of 4-chloromethylimidazole hydrochloride (I) in 40 ml. of anhydrous ethanol was hydrogenated in the presence of 1.00 g. of 5% palladium–charcoal.[11] The theoretical quantity of hydrogen was absorbed during one hundred minutes. To the filtered reaction mixture was added an equal volume of benzene, and the brown residue remaining after distillation of the solvent could not be induced to crystallize. The residue was dissolved in a little water and added to a hot solution of 5.5 g. of picric acid in 130 cc. of water. The picrate obtained on cooling was recrystallized twice from ethanol; 3.80 g. of m. p. 162–163.5; reported 160–162°.[15]

Anal. Calcd. for $C_{10}H_9O_7N_5$: C, 38.59; H, 2.92; N, 22.51. Found: C, 38.67; H, 3.08; N, 22.34.

Summary

The synthesis of a series of 4-(disubstituted aminomethyl)-imidazoles by the alkylation of secondary amines with 4-(chloromethyl)-imidazole hydrochloride has been described. Reaction of the latter with sodium benzylmercaptide yielded 4-(benzylmercaptomethyl)-imidazole. 4-(Monosubstituted aminomethyl)-imidazoles were prepared by hydrogenolysis of the appropriate N-benzyl derivatives.

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(10) Pyman, *J. Chem. Soc.*, **109**, 191 (1916).

(11) Pyman, *ibid.*, **101**, 542 (1912).

(12) *Cf.* Sommelet, *Compt. rend.*, **157**, 852 (1913).

(13) Hubball and Pyman, *J. Chem. Soc.*, 25 (1928).

(14) (a) Windaus and Opitz, *Ber.*, **44**, 1722 (1911); (b) Pyman, *J. Chem. Soc.*, **99**, 2175 (1911).

(15) Pyman, *ibid.*, **99**, 680 (1911).