Experimental

The samples of compounds used in the experiments reported here were prepared as described by Turner and Scholz[9] and had the melting points and properties recorded by them.

Ultraviolet spectrophotometric measurements were made with solutions of the compounds studied, in 95% ethanol. The instrument used was a Beckman Quartz Spectrophotometer, made by the National Technical Laboratories.

Infrared spectrophotometric measurements were made with crystals of the compound, mulled in mineral oil. The mineral oil suspension was held between two sodium chloride plates. A stream of dry nitrogen was allowed to sweep through the carriage holding the salt plates, so that the absorption spectrum of air (due to water and carbon dioxide, chiefly) was greatly diminished. Small absorption bands due to water remained in the spectrophotometric tracings in the region below 1600 cm.$^{-1}$. The instrument used was a Perkin–Elmer Infrared Spectrometer, Model 12A, equipped with a Brown automatically recording potentiometer, and with an adjustable attenuator to oppose and counterbalance the irregularities of emission of infrared radiation from the source (Globar).

The infrared curves are tracings of photographs of the original recording obtained from the spectrometer. The spectra in all cases were determined in the region 650 to 4000 cm.$^{-1}$ but only pertinent regions are shown in the figure. Values of bands given in the discussion were taken from the original recording and are accurate to about ± 5 cm.$^{-1}$ in the region near 1700 cm.$^{-1}$. The per cent. of absorption is only approximate.

Acknowledgment.—The author takes pleasure in expressing his appreciation to Professor Charles P. Smyth of Princeton University, who kindly read and criticized this paper before it was submitted for publication. The author wishes to acknowledge his debt to Professor du Vigneaud for his interest and encouragement in this work. The author also wishes to express his thanks to Dr. Julian R. Rachele for many helpful consultations in relation to the infrared determinations; and to Dr. Caesar R. Scholz of Ciba Pharmaceutical Products, Inc., for samples of imidazole derivatives.

(9) Turner and Scholz, THIS JOURNAL, **71**, 2801 (1949).

Summary

The general properties of imidazoles are discussed, taking into consideration resonance and tautomerism. Comparisons with similar open-chain and ring systems are made.

The structure of imidazole-4-aldehyde is discussed in detail in the light of ultraviolet and infrared spectrophotometric data. These data reveal that, contrary to the postulate of Hubball and Pyman,[2] the aldehyde does not exist as an enol. Its peculiar properties must be explained on the basis of its aldehyde structure.

In connection with the structure theory of the aldehyde related compounds such as the oxime, the corresponding alcohol, and the corresponding acid are discussed.

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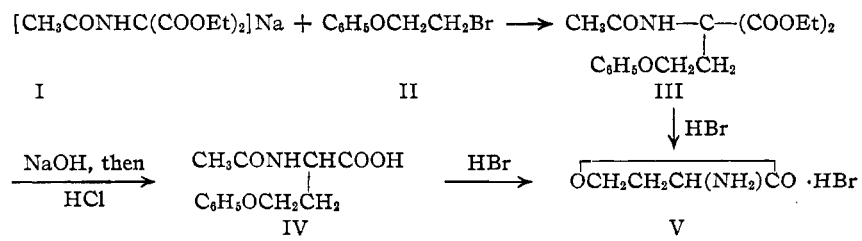
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Studies of Imidazole Compounds. III. Synthesis of 4-(2-Chloroethyl)-imidazole

BY ROBERT A. TURNER

In a previous paper of this series[1,2] the synthesis of certain derivatives of 4-methyl-imidazole was described. These derivatives were made from 4-chloromethyl-imidazole, and in order to prepare related derivatives of 4-ethyl-imidazole, 4-(2-chloroethyl)-imidazole was required.

4-(2-Chloroethyl)-imidazole hydrochloride IX has been synthesized in small amounts by Garforth and Pyman[3] through a long series of reaction steps. For our purpose a more practicable and reliable synthesis was needed. In order to achieve this a requisite intermediate was α-amino-γ-butyrolactone hydrobromide V, of which a preparation was recently described.[4] However, this preparation depends on the availability of γ-butyrolactone, and an alternate synthesis of V was devised according to the scheme



Ethyl acetylaminomalonate I and phenoxyethyl bromide II were condensed to the ester III. The latter was not isolated, but was saponified directly to the sodium salt of the corresponding dicarboxylic acid. In aqueous solutions this acid spontaneously released carbon dioxide, and when decarboxylation was complete, the α-acetylamino-γ-phenoxybutyric acid IV was isolated by continuous extraction with chloroform. Conversion of IV into V was performed through long boiling in 48% hydrobromic acid. It was also found

(1) Turner, Huebner and Scholz, THIS JOURNAL, **71**, 2801 (1949).

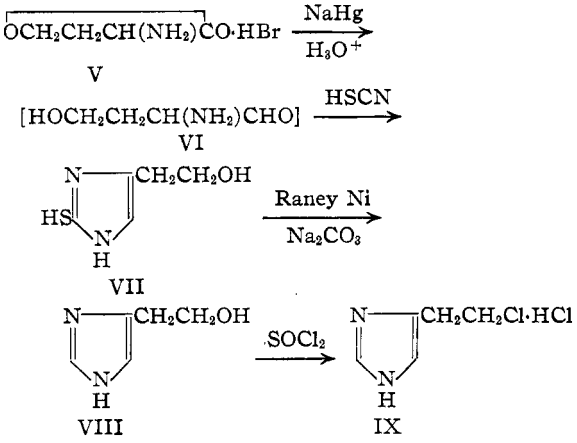
(2) For the second paper of this series, see Turner, *ibid.*, **71**, 3472 (1949).

(3) Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

(4) Livak, Britton, Vander Weele and Murray, THIS JOURNAL, **67**, 2219 (1945).

that the malonic ester derivative III could be hydrolyzed directly into V by means of hydrobromic acid; however, the procedure involving separation of the intermediate IV gave a purer product.

The synthesis of the hydrochloride IX from the lactone V was performed according to the following scheme



The Neuberg–Fischer reduction[5] of V has been reported,[3] but the method was found to be unreliable. We have devised a procedure for the Neuberg–Fischer reduction which gives a consistently good yield of the thiol VII (VI was not isolated). It was found that the success of the reduction depended on careful control of several variables, chief among which were the temperature and *p*H. An acidic reaction mixture was necessary in order to prevent the reduction of the amino-aldehyde VI to the corresponding alcohol, as well as the self-condensation of VI to a dihydropyrazine.

Treatment of the acidic solution of VI with ammonium thiocyanate yielded VII, which was isolated in crystalline form. Since VII bears a primary alcohol group, we sought a method of desulfurization differing from the usual[6] addition of a 2-thiolimidazole to boiling 10% nitric acid, and it was found that the desulfurization of VII could be performed smoothly by the action of Raney nickel catalyst suspended in sodium carbonate solution.[7] Attempts to crystallize VIII, either as the base or as the hydrochloride failed.[8] This did not prove to be a serious mischance as the sirupy hydrochloride of VIII was smoothly converted by means of thionyl chloride into 4-(β-chloroethyl)-imidazole IX, which crystallized readily.

Experimental

Condensation of Diethyl Acetylaminomalonate with Phenoxyethyl Bromide.—In a flask equipped with stirrer, dropping funnel, and reflux condenser, was prepared a solution of sodium ethoxide from 10.3 g. of sodium and 250 ml. of anhydrous ethanol. To this solution were added in turn 105 g. of diethyl acetylaminomalonate,[9] 200 ml. of anhydrous ethanol, a solution of 103 g. of phenoxyethyl bromide[10] in 200 ml. of anhydrous ethanol, and 2 g. of potassium iodide. When the reaction mixture had been stirred under reflux for forty-eight hours, the solvent was distilled. A solution of 120 g. of sodium hydroxide in 500 ml. of water was added, and after warming for a time to remove a little ethanol which remained, the mixture was boiled under reflux for two hours, cooled, and made just acid to congo paper with about 250 ml. of concentrated hydrochloric acid. During the acidification the solution seethed as carbon dioxide was evolved, and it was extracted continuously with chloroform for five hours. Following evaporation of the chloroform *in vacuo* a brown sirup remained which was dissolved in a mixture of 250 ml. of benzene and 200 ml. of methanol. The solution was concentrated until crystallization commenced in the hot. After having stood in the cold the crystals were filtered. The filtrate was concentrated to obtain another crop; total yield of **α-acetylamino-γ-phenoxybutyric acid (IV)**, 68 g. (64%); m. p. 131.5–132°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.33; H, 6.27; N, 5.74.

Concentration of the aqueous layer after the extraction with chloroform gave a crystallizate which was a mixture of sodium chloride and **α-amino-γ-phenoxybutyric acid.** Recrystallization from water gave 5.30 g. (6.1%) of this acid; m. p. 229°; reported,[11] 233°. After admixture with an authentic specimen of the acid the melting point was not depressed. In preliminary experiments on a small scale IV was isolated as an oil which later crystallized; m. p. 116–120°. After two recrystallizations the melting point was 122.5–123°, unchanged by further recrystallization.

Anal. Found: C, 60.71; H, 6.32; N, 5.72.

After a few experiments in which IV was isolated as a substance of m. p. 122.5° a preparation was performed which yielded IV as a substance of m. p. 131.5–132°. Subsequent to the appearance of this higher-melting, dimorphic modification the other form was never obtained.

α-Amino-γ-phenoxybutyric Acid from IV.—To 2.68 g. of IV was added 17 cc. of concentrated hydrochloric acid and 11 cc. of water. The mixture was heated for fifteen hours on the steam-bath and then distilled *in vacuo* to dryness. The residue was dissolved in 30 cc. of water and again taken to dryness. Solution of the residue in a little water, neutralization with lithium hydroxide solution, and acidification with dilute hydrochloric acid gave a precipitate of the product; yield, approximately quantitative; m. p. 231° (decomposition); after recrystallization, 233° (decomposition).

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.65; H, 6.67; N, 6.95.

α-Amino-γ-butyrolactone Hydrobromide. (V).—A solution of 6.85 g. of IV in 25 g. of 48% hydrobromic acid was boiled under reflux in a stream of nitrogen for four and one-half hours. Then 20 ml. of hydrobromic acid was added, and 20 ml. of solution was distilled (to remove phenol). After two hours more under reflux the solution was distilled *in vacuo* to dryness. The semi-crystalline mass was digested with anhydrous ethanol until the sirup dissolved, then left in the cold, and finally filtered. By reworking the mother liquor a total of 2.70 g. (61%) of the lactone hydrobromide was obtained; m. p. 224–226° (dec.). Five grams of the oily malonic ester III was boiled eight hours with 50 g. of 48% hydrobromic acid. Isolation as described above gave 1.20 g. of lactone; m. p. 227° (decomposition); after recrystallization the melting point was somewhat lower, 224–226°.

(5) *Cf.* Neuberg, *Ber.*, **41**, 956 (1908); Fischer, *ibid.*, 1019 (1908).

(6) *Cf.* Gabriel and Pinkus, *ibid.*, **26**, 2199 (1893); Gabriel and Posner, *ibid.*, **27**, 1037 (1894).

(7) *Cf.* Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943).

(8) The base has been reported to crystallize after several months (ref. 2). Since the preparation of this paper it has been noticed that a sample of VIII has crystallized after having stood for approximately two years.

(9) Prepared by the procedure of Snyder and Smith, THIS JOURNAL, **66**, 351 (1944).

(10) Prepared according to "Organic Syntheses," Coll. Vol. I, p. 436 (1941).

(11) Fischer and Blumenthal, *Ber.*, **40**, 108 (1907).

Anal. Calcd. for $C_4H_8O_2NBr$: C, 26.39; H, 4.43; N, 7.70; Br, 43.91. Found: C, 26.54; H, 4.34; N, 7.96; Br, 44.45.

α-Amino-γ-butyrolactone Hydrobromide (V) from γ-Butyrolactone.—γ-Butyrolactone was brominated to α-bromo-γ-butyrolactone by the method of Livak, *et al.*[4] Amination of the bromolactone was performed essentially by their procedure, but the isolation of α- and amino-γ-butyrolactone hydrobromide V was greatly facilitated with the use of anhydrous propanol. The mixture of crystalline hydrobromide and brown sirup which was first obtained was partially dried at 100° and 20 mm. and then treated with hot, anhydrous propanol until the sirup dissolved. The first crop of the crystalline hydrobromide, which formed in the cold, was filtered; treatment of the mother liquor in the manner just described gave a second crop; total yield, 64%; m. p. 212–220°.

The lactone hydrobromide was recrystallized by solution in 95% ethanol, addition of an equal volume of benzene, and distillation of ethanol–benzene–water azeotrope through a column. The cooled solution yielded colorless crystals; m. p. 228–231° (dec.), with emollescence at 221°; recovery, 90%.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.70; Br, 43.91. Found: N, 7.89; Br, 44.32.

2-Thiol-4-(2-hydroxyethyl)-imidazole (VII).—To a three-necked, 250 ml. flask, equipped with stirrer, dropping funnel and thermometer, and set in a dry ice-cellosolve-bath, were added 18.2 g. (0.10 mole) of α-amino-γ-butyrolactone hydrobromide V and 50 ml. of water. When the lactone had dissolved, 50 ml. of alcohol was poured in, and as soon as the temperature had fallen below −20°, simultaneous addition of 230 g. of 3% sodium amalgam and of 60 ml. of 5 *N* hydrochloric acid from the dropping funnel was begun. The amalgam was added in seven portions at intervals of six minutes, and the acid was allowed to flow in at such a rate that the reaction mixture was maintained just acid to congo paper. After the last portion of amalgam had been introduced the mixture was stirred and kept acid for ten minutes longer. During the whole reaction period the temperature was regulated to the range −16 to −20°.

Following decantation of the supernatant solution and washing of the mercury with 50 ml. of water, the combined solution and washing were filtered, treated with 16.2 g. of ammonium thiocyanate, and, after one-half hour, distilled *in vacuo* to dryness. The yellow, semi-crystalline residue was extracted four times with 50-ml. portions of warm ethanol, and the united extracts were treated with 30 ml. of water and concentrated *in vacuo* until crystallization commenced. After refrigeration overnight the product was filtered; yield, 12.5–14.6 g. (87–100%); m. p. 176° (incomplete). This crude material contained sodium and ammonium halides; after three recrystallizations from water a pure sample was obtained; m. p. 191–192°. After two recrystallizations the melting point was 188–190°; yield, 60–71%. Material of this purity was employed in desulfurization.

Anal. Calcd. for $C_5H_8OSN_2$: C, 41.64; H, 5.59; S, 22.20; N, 19.43. Found: C, 41.67; H, 5.28; S, 21.87; N, 19.32.

4-(2-Chloroethyl)-imidazole Hydrochloride IX. Desulfurization of 2-Thiol-4-(2-hydroxyethyl)-imidazole VII.—A solution of 21.6 g. of VII (m. p. 188° or higher) in 300 ml. of water, containing 23 ml. of saturated aqueous sodium carbonate solution, was distilled to remove traces of ammonia and then added to a suspension of 80 g. of Raney nickel catalyst[12] in 50 cc. of alcohol. The mixture was then stirred and heated under reflux for five and one-half hours.

The nickel was filtered, returned to the flask with 50 ml. of water and stirred and heated for one-half hour. After repetition of the extraction the combined filtrates were acidified with 40 ml. of concentrated hydrochloric acid, and distilled to dryness *in vacuo*. The residue of **4-(2-hydroxyethyl)-imidazole hydrochloride** and inorganic salts was treated with 80 cc. of anhydrous propanol and warmed until the sirup dissolved. After filtration of the salts the solvent was distilled *in vacuo*. The hydrochloride remained as 18.4 g. (83%) of yellow sirup.[13]

The hydrochloride was mixed with 23 ml. of purified thionyl chloride until solution was effected. The mixture was warmed under gentle reflux for one-half hour with exclusion of moisture, treated with an equal volume of benzene, and distilled to dryness *in vacuo*. On cooling, the residue formed a mass of sticky crystals; m. p. 106–110°. Recrystallization from anhydrous propanol–ethyl acetate gave 16.5 g. (79% based on 4-(β-hydroxyethyl)-imidazole hydrochloride) of light yellow platelets; m. p. 118–121, raised to 124° by another recrystallization.

Anal. Calcd. for $C_5H_8N_2Cl_2$: C, 35.95; H, 4.83; Cl, 42.45. Found: C, 35.60; H, 5.02; Cl, 42.03.

Acknowledgment.—We wish to acknowledge the capable assistance of Mrs. Kathryn Oney in these experiments. We are grateful to the Cliffs Dow Chemical Co. for a sample of γ-butyrolactone.

Summary

4-(2-Chloroethyl)-imidazole has been synthesized through this series of steps: α-amino-γ-butyrolactone was reduced to α-amino-γ-hydroxybutyraldehyde, which was converted to 2-thiol-4-(2-hydroxyethyl)-imidazole with ammonium thiocyanate; desulfurization of the thiol led to 4-(2-hydroxyethyl)-imidazole; the latter was converted to 4-(2-chloroethyl)-imidazole hydrochloride with thionyl chloride.

A new synthesis of α-amino-γ-butyrolactone, starting from diethyl acetylaminomalonate has been described.

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(12) Prepared according to Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(13) Attempts to prepare crystalline salts were unsuccessful, with the exception of the picrate, which was more soluble in water than picric acid and could not be isolated in pure form.