minutes, after which the catalyst was neutralized by agitation with 72 g. of 10% alcoholic sodium hydroxide solution. The reaction product was distilled under vacuum to recover the unreacted diethyl butyral and the products, 1,1,3-triethoxyhexane and 1,1,3,5-tetraethoxyoctane, which were obtained in yields of 72 and 16%, respectively, based on vinyl ethyl ether.

(c) **1,1,3-Triethoxy-2-ethylbutane.**—Three hundred grams (3 moles) of 1-butenyl ethyl ether was added dropwise to 1063 g. (9 moles) of diethyl acetal containing 1 cc. of an ethyl ether solution of boron trifluoride etherate (35% boron trifluoride). The mixture was stirred constantly during the addition of the ether and the temperature was maintained between 45 and 48° with slight cooling of the reaction flask. The addition of the ether was complete in fifteen minutes, although the reaction continued for another fifteen minutes. The catalyst was neutralized by agitation with 5 g. of anhydrous, powdered sodium carbonate for a period of three hours. Distillation of the reaction product gave 1,1,3-triethoxy-2-ethylbutane in 48% yield, based on 1-butenyl ethyl ether.

Hydrolysis and De-alkanolation

(a) **2,4-Hexadienal and 5-Methoxy-2-hexenal.**—One mole (206.2 g.) of 1,1,3,5-tetramethoxyhexane was distilled with 220 g. of 5.0% aqueous sulfuric acid solution. Methanol was removed as fast as formed until the vapor temperature could no longer be maintained at 65°. The removal of methanol (110 g.) required three and one-half hours. Distillation was stopped and the kettle residue was cooled to room temperature. This product consisted of a lower layer containing 5.75% sulfuric acid and 6.0% of aldehyde (as 5-methoxy-2-hexenal), and an upper layer containing essentially 2,4-hexadienal and 5-methoxy-2-hexenal. The upper layer was distilled under vacuum in the presence of 0.5 g. of sodium acetate. The yields of 2,4-hexadienal and 5-methoxy-2-hexenal were 47 and 38%, respectively. Physical properties of 2,4-hexadienal: b. p. 43° (5 mm.); d^{20}_{20} 0.898; $n^{20}_{\rm D}$ 1.5384. Physical properties of 5-methoxy-2-hexenal: b. p. (approx.) 58° (5 mm.); d^{20}_{20} 0.931; $n^{20}_{\rm D}$ 1.4615; *MR*, observed 36.1; calcd. 35.8.

(b) **2-Hexenal and 2-Ethyl-2-butenal.**—1,1,3-Triethoxyhexane, 327 g. (1.5 moles), was distilled with 375 cc. of 2% aqueous hydrochloric acid solution. After refluxing this mixture ten minutes the vapor temperature dropped to 77.5° and an ethanol fraction was removed. After five hours the removal of ethanol was essentially complete, water was added to the kettle and crude 2-hexenal (94% purity) was recovered as the upper layer of the 2-hexenal–water steam distillate. The yield of 2-hexenal was 94%. Physical properties of 2-hexenal: b. p. 50–51° (20 mm.); d^{20}_{20} 0.845; $n^{20}_{\rm D}$ 1.4464. 1-Hexanol was prepared from the aldehyde by hydrogenation; 3,5-dinitrobenzoate, m. p. 58°.

Using the same procedure, 2-ethyl-2-butenal was prepared in 95% yield from 1,1,3-triethoxy-2-ethylbutane. Physical properties of 2-ethyl-2-butenal: b. p. 58° (50 mm.); d^{20}_{20} 0.858; $n^{20}_{\rm D}$ 1.4478. 2-Ethyl-1-butanol was prepared from the aldehyde by hydrogenation; 3,5-dinitrobenzoate, m. p. 50°.

Acknowledgment.—The authors wish to acknowledge the helpful suggestions made by other members of the Process Development Laboratory and Research Laboratory of this Corporation and also the assistance of Dr. Samuel F. Clark who was formerly associated with this project.

Summary

1. The reaction of acetaldehyde acetals and vinyl ethers was extended to include acetals of other aldehydes and α,β-unsaturated ethers of alcohols other than vinyl alcohol.

2. The manner in which acetals and α,β-unsaturated ethers react was shown to be in disagreement with that suggested by Mueller-Cunradi and Pieroh.

3. The utility of the acetal–α,β-unsaturated ether reaction is discussed.

SOUTH CHARLESTON, W. VA. RECEIVED MAY 12, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

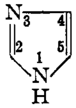
Studies of Imidazole Compounds. II. The Structure of Certain Simple Imidazole Derivatives

BY ROBERT A. TURNER

Although the structures of several aromatic nuclei have been discussed extensively in the chemical literature, the structure of the imidazole nucleus has been given scant attention. In this paper we discuss the structure of imidazoles, as revealed by the spectrophotometric data of certain simple derivatives.

Discussion

Imidazole (I) possesses an aromatic sextet (II) and thus satisfies one of the known requirements for aromatic character.

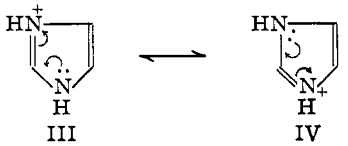


I

II

The nitrogen atom in position 3 has an electron pair, not included in the sextet, and which may be donated to a proton. Imidazole is a basic substance which readily forms salts with acids. Since the two unshared electrons of the nitrogen atom in position 1 are needed to form the sextet, they may not be donated to a proton, and consequently imidazole is a monoacid base.[1]

When the imidazole nucleus has acquired a proton, the charged molecule has the resonance forms III and IV.



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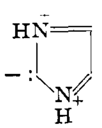
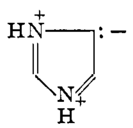
[1] The structure of pyrrole is, by contrast, enlightening in this connection. It loses its aromatic stability in the presence of hydrogen ions because the sextet is destroyed when the two unshared electrons of the nitrogen atom are donated. Not only is pyrrole a weak base, but it is unstable in the presence of acids.

This resonance is the same as that of an amidine salt and is very similar to that of an imido ester salt. Like amidine salts, imidazole salts are uncolored. The resonance of salts of amidines and of imido esters contributes stability to these substances, but this resonance does not extend through a sufficiently long conjugated system, nor are the resonating forms sufficiently polarized so that the salts are colored.

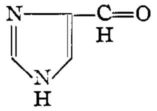
If the electrons of the carbon-to-carbon double bond of III could enter into the resonance between the nitrogen atoms, the resonance of an imidazole salt would not be that of an amidine salt but would be of a more complex kind. However, if the electrons of the carbon-to-carbon double bond do enter into the resonance, structures such as would

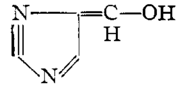

V


VI

contribute to the total structure of imidazole. These structures would not have much significance, for well substantiated reasons.

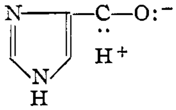
Imidazole-4-aldehyde is a colorless, crystalline substance, of molecular weight 96.09 and m. p. 174°. It is not easily oxidized, contrary to the expected behavior of aldehydes. On the basis of

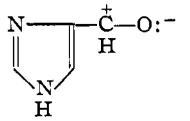

VII

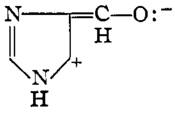

VIII

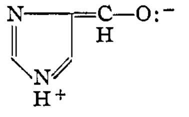
properties such as these, and others, *e. g.*, the extreme reluctance with which the aldehyde enters into most condensation reactions, Hubball and Pyman[2] postulated that the aldehyde existed chiefly in the enol form VIII rather than in the aldehyde form VII.[3] However, this proposition is simply that VII and VIII are in equilibrium, with the equilibrium shifted so that the enol form VIII preponderates greatly over the aldehyde. It seems unlikely that such a state would effectuate the masking of aldehyde properties in the absence of steric factors, for special steric conditions must usually exist in order to quench the lability which is known to attend the equilibrium between an aldehyde and its enol. In view of this and the evidence to be discussed below we believe the explanation of Hubball and Pyman[2] to be untenable.

Besides the usual structure VII for imidazole-4-aldehyde there are others for which evidence exists if we accept certain premises of modern structure theory. The variable amount of ionic character in the C–H bond makes IX a contributory structure. The strongly electronegative oxygen atom causes the C–O bonding to have considerable ionic character so that X is also a contributory structure. Related to X are structures such as XI and XII. Of these we regard XII as having special significance and contributing to a greater degree to the total structure of imidazole-4-aldehyde than any of the corresponding structures for benzaldehyde contribute to its total structure, because of the stability of quadrivalent, positively charged nitrogen.


IX


X

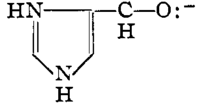

XI


XII

The structures X, XI and XII are very probably those responsible for the absorption of imidazole-4-aldehyde in the ultraviolet region (Fig. 1). Since imidazole does not absorb light in either the visible or near ultraviolet region, this absorption of imidazole-4-aldehyde is attributable only to the (conjugated) aldehyde group.[4]

An interesting phenomenon appears when acid is added to imidazole-4-aldehyde: the absorption peak at 256 mμ is obliterated. The change occurs immediately, for it does not matter whether the aldehyde is dissolved in acid before its spectrum is measured, or whether a drop is added just prior to the determination of absorption at 256 mμ. We explain the phenomenon as follows.

Addition of a proton to VII causes its stabilization in forms corresponding to III and IV. Either of the nuclear nitrogen atoms has a charge of +1. Thus electrons would be drawn toward the nucleus, and forms corresponding to X, XI and XII would be very improbable. For example, XIII,


XIII

the structure which corresponds to X after the addition of a proton, is very unlikely. We say, then, that the addition of a proton to imidazole-4-aldehyde reduces the contribution of forms such as X, XI and XII to a negligible amount. Since only these forms absorb in the ultraviolet region, absorption *in that region* is eliminated.

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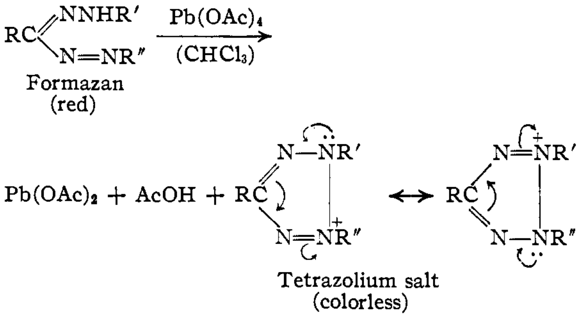
[2] Hubball and Pyman, *J. Chem. Soc.*, 21 (1928).

[3] Imidazole-4-aldehyde forms a cyanohydrin, a phenylhydrazone, an anil, an oxime, a sodium bisulfite addition compound and a semicarbazone; it condenses with pyruvic acid and β-naphthylamine to form 2-(imidazol-4-yl)-benzo-f-quinoline-4-carboxylic acid. It does not undergo the Cannizzaro reaction, or the Perkin reaction; it gives a negative Schiff test; it does not form an acetal; and it is not oxidized either by air or by ammoniacal silver nitrate.

[4] 4-Hydroxymethylimidazole, the alcohol corresponding to imidazole-4-aldehyde, has no absorption peak in the ultraviolet region.

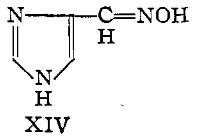
In this connection it is interesting to compare the structure and absorption characteristics of a formazan with those of the tetrazolium salt formed from the formazan by oxidation.[5] It is to be noted that the tautomerism which is present in the formazan is not present in the tetrazolium salt, which exhibits resonance. Imidazole-4-aldehyde has, like the formazan, a tautomerism in which a hydrogen atom migrates from one nitrogen atom to another; in acid solution imidazole-4-aldehyde is no longer tautomeric but possesses a resonance very similar to that of the tetrazolium salt. A formazan has large absorption peaks in the regions 290 and 420 mμ. Tetrazolium salts have a single, broad peak near 300 mμ, the peak at the longer wave length having been eliminated. Thus the analogy between imidazole-4-aldehyde and a formazan, on one hand, and between imidazole-4-aldehyde hydrochloride and a tetrazolium salt, on the other, is accountable in structure theory and is further supported by the absorption spectra of the several compounds.



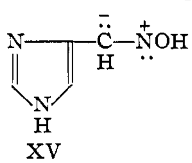
Formazan (red)

Tetrazolium salt (colorless)

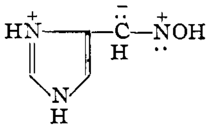
The absorption of imidazole-4-aldehyde oxime (Fig. 2) in alcohol solution, and in alcohol solution containing hydrochloric acid, parallels that of the aldehyde. The oxime absorbs strongly, with a peak at 249 mμ; in the presence of hydrochloric acid the peak is shifted to 240 mμ. Thus the effect found to occur in the aldehyde also occurs in the oxime, but to a lesser extent. We account for this as follows. The oxime XIV has a contribution to its structure of the form XV. Data from dipole moment determinations support this view.[6] Structures with a positive nitrogen contribute to the total structure, whereas in the analogous oxygen compound the related form with positive oxygen is unimportant. Furthermore, we may expect that addition of a proton to XV to yield XVI would not depress the absorption at all, but rather augment it, inasmuch as the positive charge in the nucleus would mobilize the electron pair which shifts when XV is formed from XIV.



XIV



XV



XVI

We now turn to the evidence derived from infrared spectrometry which bears upon the structure of imidazole-4-aldehyde and related compounds. Generally, aldehydes exhibit a peak, which may be quite broad, in the region 1640 to 1690 cm.$^{-1}$. Aldehydes which are conjugated with a double bond, whether it is part of a chain or in an aromatic ring, have peaks which are shifted toward shorter wave lengths; the peaks of these aldehydes are near 1700 cm.$^{-1}$ and are large. The infrared spectrum of imidazole-4-aldehyde is shown in Fig. 3. It will be noticed that the peak which extends from 1654 to 1696 cm.$^{-1}$ is typical of an aromatic aldehyde. While the spectrometric evidence for the aldehyde group is satisfactory, there is no certain evidence of an alcohol group. We consider that this evidence, which shows that imidazole-4-aldehyde exists as the aldehyde, or that at least a large fraction of it so exists, negates the postulate of Hubball and Pyman[2] that imidazole-4-aldehyde exists chiefly in the enol form VIII.

The comparison of the spectrum of imidazole-4-aldehyde with the spectrum of 4-hydroxymethyl-imidazole (Fig. 4) reveals two easily discernible features. First, the broad band from 1654 to 1696 cm.$^{-1}$, present in the spectrum of the aldehyde, is absent from the spectrum of the alcohol. Second, the spectrum of the alcohol in the region 3000 to 3500 cm.$^{-1}$ (the region of vibrations of hydroxyl groups) shows more absorption than does the spectrum of the aldehyde, Comparison of the spectrum of the aldehyde with those of several blank determinations of mineral oil in the region near 2900 cm.$^{-1}$ has shown that the absorption of the aldehyde is almost identical with the absorption of mineral oil in that region.

If the aldehyde existed in the enol form VIII, either wholly or partly, it would exhibit some absorption in the region 3100 to 3500 cm.$^{-1}$. Thus the evidence from infrared spectrometry shows that the aldehyde is not enolated.[7]

The infrared spectrum of the aldehyde oxime (Fig. 5) now becomes of interest. From what has been stated in the foregoing discussion it might be expected that the oxime would have a peak at

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(5) Kuhn and Jerchel, *Ber.*, **74**, 941 (1941).

(6) Hurdis and Smyth, THIS JOURNAL, **65**, 89 (1943), have adduced evidence from dipole moment measurements which strongly indicates a structure with positive nitrogen to be contributory in the case of certain nitriles. It is reasonable to expect the same structure in an oxime, which is a hydrated nitrile.

(7) It may be remarked that both the data from Raman spectra and from polarographic reduction indicate that pyrrole-2-aldehyde exists as the aldehyde and not as the enol, and is slightly more difficult to reduce than benzaldehyde. *Cf.* Bonino and Scaramelli, *Ricerca sci.*, **6**, II, 111-112 (1935); *C. A.*, **30**, 8208 (1936).

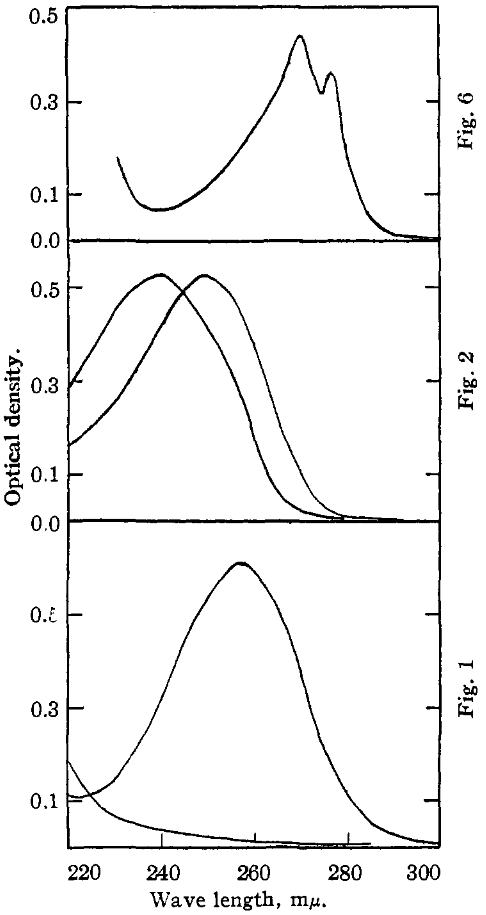


Fig. 1.—Ultraviolet absorption spectra of imidazole-4-aldehyde: upper curve, 0.0050 mg. per ml. in 95% ethanol; peak at 256.5 mμ with ε equal to 11,700. Lower curve, 0.0050 mg. per ml. in 96% ethanol which was 0.040 N in hydrochloric acid.

Fig. 2.—Ultraviolet absorption spectra of imidazole-4-aldehyde oxime: right curve, 0.0050 mg. per ml. in 95% ethanol; peak at 249 mμ with ε equal to 11,600. Left curve, 0.0050 mg. per ml. in 95% ethanol which was 0.040 N in hydrochloric acid; peak at 240 mμ with ε equal to 11,710.

Fig. 6.—Ultraviolet absorption spectrum of imidazole-4-carboxylic acid: 0.050 mg. per ml. in 95% ethanol; peaks at 270.5 mμ, with ε equal to 980, and at 277 mμ with ε equal to 810.

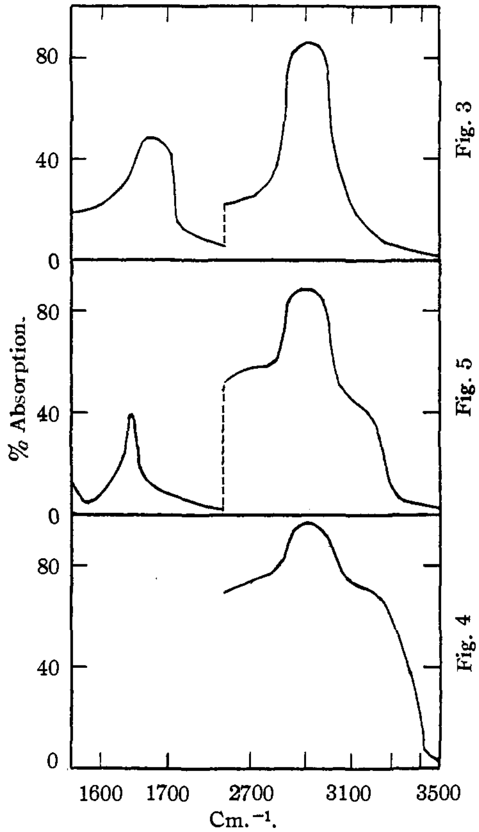


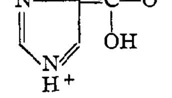
Fig. 3.—Infrared absorption spectrum of imidazole-4-aldehyde: regions 1570 to 1800 cm.$^{-1}$ (left curve) and 2650 to 3350 cm.$^{-1}$ (right curve).

Fig. 4.—Infrared absorption spectrum of 4-hydroxymethyl-imidazole: region 2400 to 3600 cm.$^{-1}$.

Fig. 5.—Infrared absorption spectrum of imidazole-4-aldehyde oxime regions 1570 to 1800 cm.$^{-1}$ (left curve) and 2650 to 3350 (right curve).

the usual place for absorption due to the group C-N of an oxime (1650 cm.$^{-1}$), and also that the spectrum of the oxime would exhibit absorption in the high frequency region on account of the O-H group. The spectrum shows how well these expectations are fulfilled. There is a peak at 1653 cm.$^{-1}$, and there is considerable absorption in the high-frequency region.

Imidazole-4-carboxylic acid presents an absorption spectrum in the ultraviolet (Fig. 6) which has two peaks: at 270.5 mμ, ε = 980; and at 277 mμ, ε = 810. Because the values of these peaks are so much lower than the value for imidazole-4-aldehyde, the electronic transitions to which they are attributable are much less probable. However, there is no certainty that the transitions for both compounds are the same, or even similar. The two peaks must be the result of interaction between the carboxyl group and the imidazole ring since neither moiety alone absorbs radiation in this region. We postulate the structure XVII, corresponding to XII for imidazole-4-aldehyde,



XVII

as the one to which the absorption at 277 mμ is due.[8]

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[8] The peak at 270.5 mμ is such a peak, both with respect to position and to intensity, as would be expected for an aromatic acid. Benzoic acid, for example, exhibits a peak at 270 mμ with ε = 800; *cf.* Kumler and Strait, THIS JOURNAL, 65, 2352 (1943).

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.

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.

NEW YORK 21, N. Y. RECEIVED FEBRUARY 25, 1949

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

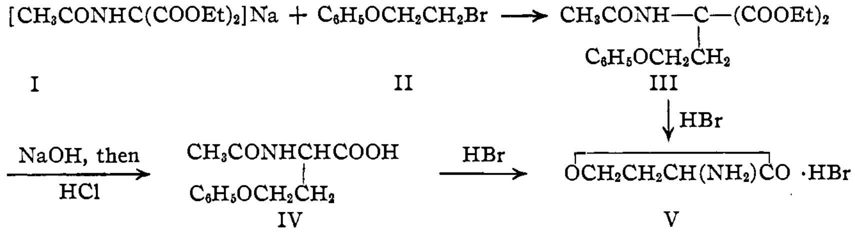
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

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



$$\underset{\text{I}}{[CH_3CONHC(COOEt)_2]Na} + \underset{\text{II}}{C_6H_5OCH_2CH_2Br} \longrightarrow \underset{\text{III}}{CH_3CONH\text{—}\underset{C_6H_5OCH_2CH_2}{\underset{|}{C}}\text{—}(COOEt)_2} \xrightarrow{HBr}$$

$$\xrightarrow[HCl]{NaOH,\ then} \underset{\text{IV}}{\underset{C_6H_5OCH_2CH_2}{CH_3CONH\underset{|}{C}HCOOH}} \xrightarrow{HBr} \underset{\text{V}}{\overline{OCH_2CH_2CH(NH_2)CO} \cdot HBr}$$

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

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[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).