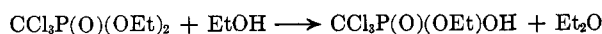


whether the ester was a possible intermediate in the formation of triethyl phosphate and chloroform from triethyl phosphite, carbon tetrachloride, and ethanol.⁵ The ester was recovered unchanged after being boiled in ethanol for 4 hr.⁵

In the present work it is shown that a reaction *does* take place on prolonged boiling, though not in the sense indicated above. Prolonged boiling of a solution of diethyl trichloromethylphosphonate in ethanol produced a low-boiling material identified as **diethyl ether**. The residue, which was strongly acidic, was identified as **ethyl hydrogen trichloromethylphosphonate**. The reaction therefore took the following path.



The ester behaved in this reaction as an alkylating agent, as in the reaction with amines. The mildness of the reaction, however, was remarkable because such alkylations usually require a catalyst and temperatures of the order of 200°.⁶

No alkylation was observed when diethyl ethylphosphonate or diethyl acetylphosphonate was refluxed with ethanol for the same length of time. The strong $-I$ inductive effect of the trichloromethyl group appears to be necessary.

The alkylation of phenol by diethyl trichloromethylphosphonate produced an 85% yield of phenetole in 4.5 hr. at 150°.

Experimental

Reaction with Ethanol.—A solution of 25.6 g. (0.1 mole) of diethyl trichloromethylphosphonate⁷ in 100 ml. of anhydrous ethanol was heated at total reflux in a small distillation assembly which included a K-head and a 3-in. column packed with glass helices. The vapor temperature dropped over an 8-hr. period from 79.5 to 54°, while the liquid temperature remained constant at 80°. A test for chloroform with pyridine and 5 *N* sodium hydroxide⁸ was negative. The low-boiling material was then drawn off from time to time as required to keep the vapor temperature above 78°, and fresh ethanol was added to the boiling solution as required to maintain the original volume. The distillation was stopped after 26 hr. when it was evident that no more low-boiling material was being formed. The distillate (200 ml.) was redistilled, giving 2.0 g., b.p. 36°, n_D^{25} 1.34, and 2.5 g., b.p. 43–74°, n_D^{25} 1.3580. Both fractions contained diethyl ether, identified by its odor and infrared spectrum.

The undistilled portion of the reaction proper was stripped of solvent under vacuum, leaving 26.6 g. of strongly acidic residue, n_D^{25} 1.4631. Titration with 0.1 *N* sodium hydroxide gave a curve with inflections at 32.0 and 33.9 ml./g., corresponding to 0.080 mole of ethyl hydrogen trichloromethylphosphonate and 0.005 mole of trichloromethylphosphonic acid. Together they accounted for 72.3% of the residue, the remainder being neutral, presumably ethanol. A portion of the product was dissolved in benzene and treated dropwise with aniline, giving the known aniline salt of ethyl hydrogen trichloromethylphosphonate, m.p. 186.5° dec. (cor.) after recrystallization from ethanol.

Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{Cl}_3\text{NO}_3\text{P}$: N, 4.37. Found: N, 4.35.

The literature^{3,4} gives melting points ranging from 174° dec. to 198° dec. for this salt.

Neither diethyl ethylphosphonate nor diethyl acetylphosphonate showed any evidence of reaction with ethanol under these conditions, save for a small increase in acidity. The refractive indices of the recovered esters were unchanged.

(5) P. C. Crofts and I. M. Downie, *J. Chem. Soc.*, 2559 (1963).

(6) Y. Runavot, P. Schneebeli, D. Chabrier, and R. Ramain, *Compt. rend.*, **253**, 1573 (1961).

(7) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **69**, 1002 (1947).

(8) F. Feigl, "Spot Tests in Organic Analysis," 5th Ed., Elsevier Publishing Co., Amsterdam, 1956, p. 313.

Reaction with Phenol.—A solution of 51.2 g. (0.2 mole) of diethyl trichloromethylphosphonate and 18.8 g. (0.2 mole) of phenol was heated at 150° for 4.5 hr. and then distilled, giving 20.7 g. (85%) of a fraction, b.p. 68–70° (18 mm.), n_D^{25} 1.5056, identified by its infrared spectrum as phenetole.

The Dehydrative Dimerization of 2- and 4-Methyl-5-imidazolecarboxylic Acids

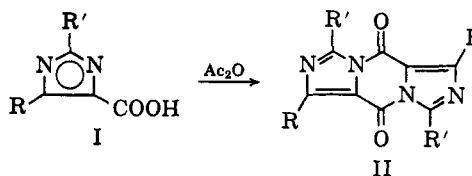
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In connection with our imidazole studies we have had occasion to treat a number of imidazolecarboxylic acids with acetic anhydride.

4-Methyl-5-imidazolecarboxylic acid (Ia), upon refluxing in acetic anhydride, deposited on cooling a crystalline product, m.p. 238–239°. Infrared examination revealed the absence of carboxylic acid absorption and the appearance of a carbonyl band at 1690 cm^{-1} . Loss of a molecule of water was indicated from analytical results, with titration data furnishing a molecular weight of ca. 215. The material reacted readily with aniline, giving 4-methyl-5-imidazolecarboxanilide. These data led us to believe that the compound in question was, in fact, a dehydrated dimer of Ia, corresponding to structure IIa.



a, R = CH₃; R' = H
b, R = H; R' = CH₃

Structures of this type are not entirely unknown. For example the action of thionyl chloride on 2-benzimidazolecarboxylic acid has been reported to yield dibenzimidazo[1,2-*a*:1',2'-*d*]tetrahydropyrazine-6,13-dione.¹ Likewise thionyl chloride is known to effect a comparable dehydrative dimerization of 4,5-diphenyl-2-imidazolecarboxylic acid.² Pyman,³ however, failed to get any reaction between 4-imidazolecarboxylic acid and thionyl chloride, an observation which was subsequently confirmed by Weidenhagen.⁴ Our own observations, as seen in the light of the cited literature reports, led us to investigate the effect of thionyl chloride on Ia. Upon refluxing a suspension of these reagents, only 4-methyl-5-imidazolecarboxylic acid hydrochloride was obtained. However, addition of DMF to the reaction mixture initiated an exothermic reaction, leading not to the formation of IIa, but giving instead the acid chloride hydrochloride, identified by transformation to the carboxanilide.

(1) R. A. Copeland and A. R. Day, *J. Am. Chem. Soc.*, **65**, 1072 (1943).

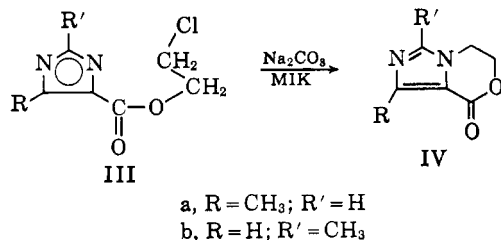
(2) R. Gompper, E. Hoyer, and H. Herlinger, *Ber.*, **92**, 550 (1959).

(3) F. L. Pyman, *J. Chem. Soc.*, 109 (1916).

(4) R. Weidenhagen and H. Wegner, *Ber.*, **70**, 2309 (1937).

2-Methyl-4-imidazolecarboxylic acid⁵ (Ib) was also treated with acetic anhydride, furnishing dimer IIB in 90% yield. The preparation of the latter, initially impeded by the laborious route into Ib, was subsequently simplified by the observation that 2-methyl-4,5-imidazolecarboxylic acid, when treated with acetic anhydride, afforded IIB directly in 54% yield.

Of interest is the fact that both IIa and b reacted smoothly with ethylene chlorhydrin to give β -chloro esters IIIa and b. Treatment of the latter with sodium carbonate in methyl isobutyl ketone (MIK) brought about cyclization to lactones IVa and b.



Experimental^{6,7}

4,9-Dimethyl-5H,10H-diimidazo[1,5-a:1',5'-d]pyrazine (IIa).—A stirred mixture of 20 g. (0.158 mole) of 4-methyl-5-imidazolecarboxylic acid^{8,9} and 120 ml. of acetic anhydride was brought to reflux in an apparatus equipped with a distillation take-off. After ca. 60 ml. of distillate, b.p. 124–139°, had been collected (this required about 1 hr.), the reaction mixture was cooled. Filtration afforded 15 g. (89% yield) of product, m.p. 230–232°. An analytical sample, m.p. 238–239°, was prepared from DMF-ether.

Anal. Calcd. for C₁₀H₈N₄O₂: C, 55.55; H, 3.73. Found: C, 55.50; H, 3.72.

2,7-Dimethyl-5H,10H-diimidazo[1,5-a:1',5'-d]pyrazine (IIb). **Method A.**—Treatment of 76.0 g. (0.60 mole) of 2-methyl-4-imidazolecarboxylic acid⁵ with 800 ml. of acetic anhydride, in the fashion described above, furnished 59 g. (90% yield) of dimer IIB, m.p. 269–270°. Recrystallization from dioxane gave yellow leaflets, m.p. 274–275°.

Anal. Calcd. for C₁₀H₈N₄O₂: C, 55.55; H, 3.73. Found: C, 55.31; H, 4.03.

Method B.—Dry 2-methyl-4,5-imidazole dicarboxylic acid⁵ (200 g., 1.18 moles) was suspended in 3 l. of acetic anhydride and the mixture was refluxed for 72 hr. Upon completion, 2.5 l. of solvent was removed at atmospheric pressure. Cooling of the residue yielded 69 g. (54%) of product, m.p. 274–275°, which was identical with the material prepared by method A.

4-Methyl-5-imidazolecarboxanilide.—To a suspension of 4.32 g. (0.02 mole) of freshly prepared IIa in 15 ml. of DMF was added 5 g. (0.054 mole) of aniline. The mixture was briefly warmed to 100° and was then poured onto ice-water. The anilide, 3.8 g., crystallized immediately and was recrystallized from alcohol, m.p. 259–260°.

Anal. Calcd. for C₁₁H₁₁N₃O: C, 65.65; H, 5.51; N, 20.88. Found: C, 65.57; H, 5.46; N, 20.84.

4-Methyl-5-imidazolecarboxylic Acid Chloride, Hydrochloride.—To a suspension of 10 g. (0.079 mole) of Ia in 100 ml. of benzene containing 1 ml. of DMF was added 20 ml. of thionyl chloride. An exothermic reaction ensued, giving a pasty suspension. The mixture was refluxed for 0.5 hr., and the product was isolated by filtration, to give, upon washing and drying, 10.3 g. of acid chloride hydrochloride. The material was not further purified, m.p. 221–223°. Reaction of this material with an excess of aniline gave the **carboxanilide**, m.p. 259–260°, identical with the material obtained from IIa.

(5) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 217 (1919).

(6) Melting points were recorded on a Fisher-Johns block and are uncorrected.

(7) We are indebted to Messrs. F. Sels and W. Verkest for microanalytical data.

(8) H. Böhme and H. Schneider, *Ber.*, **91**, 988 (1959); O. Gerngross, *ibid.*, **45**, 909 (1912).

(9) W. Hubball and F. L. Pyman, *J. Chem. Soc.*, 21 (1928).

4-Methyl-5-imidazolecarboxylic Acid, 2-Chloroethyl Ester (IIIa).—To 228 g. of ethylene chlorhydrin, previously saturated with hydrogen chloride, was added 57 g. (0.264 mole) of IIa. The mixture was refluxed 2 hr., after which sufficient dry ether was added to the cooled solution to precipitate the product **hydrochloride salt**. The filtered material was dissolved in water, brought to pH 8 by addition of solid sodium bicarbonate, and filtered to give 76 g. of ester, m.p. 155–156°, yield 77%. An analytical sample from aqueous alcohol melted at 159–160°.

Anal. Calcd. for C₇H₉ClN₂O₂: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.35; H, 4.73; N, 14.68.

2-Methyl-4-imidazolecarboxylic Acid, 2-Chloroethyl Ester (IIIb).—The reaction of 2.36 g. (0.11 mole) of IIB with 15 ml. of ethylene chlorhydrin saturated with hydrogen chloride, according to the method described above, yielded 2.0 g. (49%) of product, m.p. 145–146° (dioxane-isopropyl ether).

Anal. Calcd. for C₇H₉ClN₂O₂: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.64; H, 4.91; N, 14.86.

8-Methyl-3,4-dihydro-1-oxo-1H-imidazo[5,1-c](1,4)oxazine (IVa).—A suspension of 76 g. (0.40 mole) of IIIa, 1500 ml. of methyl isobutyl ketone, 127 g. of anhydrous sodium carbonate, and 1 g. of potassium iodide was refluxed in an apparatus equipped with a water trap for 2 days. The solids were then removed by filtration, whereupon the filtrate was taken down *in vacuo*. Recrystallization of the residue from isopropyl alcohol gave 18.6 g. of product, m.p. 173–174°, yield 31%. The hydrochloride salt, m.p. 224–225°, was submitted for analysis.

Anal. Calcd. for C₇H₈N₂O₂·HCl: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.46; H, 4.89; N, 14.63.

6-Methyl-3,4-dihydro-1-oxo-1H-imidazo[5,1-c](1,4)oxazine (IVb).—This compound, m.p. 175–176° (dioxane-isopropyl ether), was prepared in a fashion analogous to the method offered for IVa. The yield was 38%.

Anal. Calcd. for C₇H₈N₂O₂: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.21; H, 5.10; N, 18.75.

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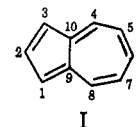
Structure vs. Reactivity in Azulene Carboxylic Acids and Esters

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From simple and also from more sophisticated molecular orbital calculations¹ successful predictions have been made concerning the dipole moment of the azulene nucleus and the relative electron densities on the various carbon atoms. The 1- and 3-positions of azulene (I) are



predicted to have a fairly substantial net negative charge, the 4-, 6-, and 8-positions a net positive charge; with the other positions being approximately neutral. Like other aromatic compounds, azulene undergoes electrophilic and nucleophilic substitution reactions. As predicted from a consideration of charge densities

(1) (a) R. D. Brown, *Trans. Faraday Soc.*, **44**, 984 (1948); (b) A. Julg, *Compt. rend.*, **239**, 1498 (1954).