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RESEARCHES ON IMIDAZOLES.
XVIII. 1-Alkyl (1,2-dialkyl)4-chloroimidazoles*

P. M. Kochergin

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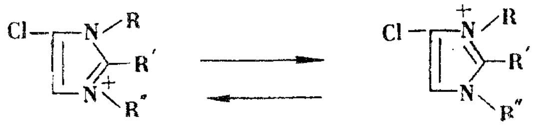
With a view to preparing 1-alkyl(1,2-dialkyl)-4-chloroimidazoles, a more detailed a study has been made of the pyrolysis of a number of 1,3-dialkyl(1,2,3-trialkyl)-5-chloroimidazole iodides. Decomposition of quaternary salts with identical groups at positions 1 and 3 in the imidazole ring leads to formation of two isomers, 1-alkyl-(1,2-dialkyl)-4-chloro- and 1-alkyl(1,2-dialkyl)-5-chloroimidazoles. Decomposition of salts with different groups at positions 1 and 3, results in formation of a mixture of four N-substituted 4-chloro- and 5-chloroimidazoles (two pairs of isomers).

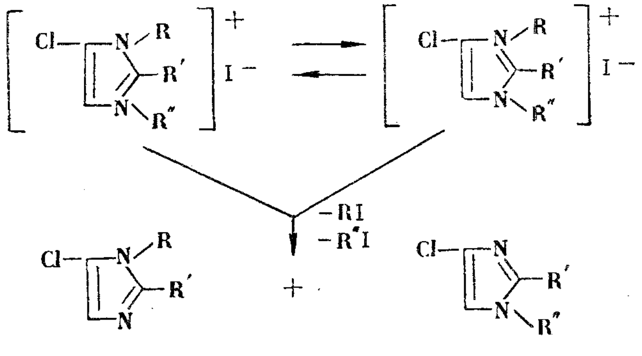
It is known that N, N'-dialkyloxamides and PCl_5 give, by Wallach's method, 1-alkyl(1,2-dialkyl)-5-chloroimidazoles [1-3]. Sarasin and Wegmann [4,5] heated alkhalogenides of 1-methyl-5-chloro- and 1-ethyl-2-methyl-5-chloroimidazoles, and obtained some 1-alkyl-4-chloro- and 1-alkyl-2-methyl-4-chloroimidazoles, initially wrongly assigned the structure of N-substituted 5-chloroimidazoles [4]. Those authors did not give details of the method of preparation, and degradation of the quaternary salts of the 5-chloroimidazoles. Side reaction products were not investigated, and no yields were given for the compounds prepared. So from the available information it is difficult to assess the preparative value of this unusual reaction for converting 5-chloroimidazoles into 4-chloroimidazoles inaccessible by direct synthesis.

With a view to preparing 1-alkyl(1,2-dialkyl)-4-chloroimidazoles, a more detailed study has now been made of the pyrolysis of a number of alkhalogenides of 1-methyl(1,2-dialkyl)-5-chloroimidazoles. The latter was obtained in good yields (60-92%) by reacting 1-methyl(1,2-dialkyl)-5-chloroimidazoles [3] with alkyl halides in organic solvents. With the lower alkyl halides, reaction proceeds best of all in boiling acetone. In a number of cases the quaternary salts formed were pyrolyzed without being isolated.

1,3-Dialkyl (1,2,3-trialkyl)-4(5)-chloroimidazolinium halides can be prepared from both 1-alkyl(1,2-dialkyl)-5-chloroimidazoles and 1-alkyl(1,2-dialkyl)-4-chloroimidazoles. For example, the action of methyl iodide on 1-methyl-5-chloroimidazole (VIII) or 1-methyl-4-chloroimidazole (VII), or a mixture of both of them gives one and the same compound, 1,3-dimethyl-4(5) chloroimidazolinium iodide (I). Compound VIII and ethyl iodide, or 1-ethyl-4-chloroimidazole (XIV) and methyl iodide, give 1-methyl-3-ethyl-5-chloroimidazolinium iodide; (II) [4]. This property of 1,3-dialkyl(1,2,3-trialkyl) chloroimidazolinium iodides, and of quaternary salts of other imidazole derivatives [2, 6-8] is evidently due to the positive charge of the imidazolinium cation not being stationary on any one nitrogen atom, but readily moving from one to another.



It was assumed, on this view of the structure of alkhalogenides of 1-alkyl(1,2-dialkyl)-5-chloroimidazoles, that thermal decomposition of the salts will lead to formation of 1-alkyl (1,2-dialkyl)-4-chloroimidazoles, as was previously thought [4,5], and 1-alkyl-(1,2-dialkyl)-5-chloroimidazoles. Then if R = R", two isomers must be formed.



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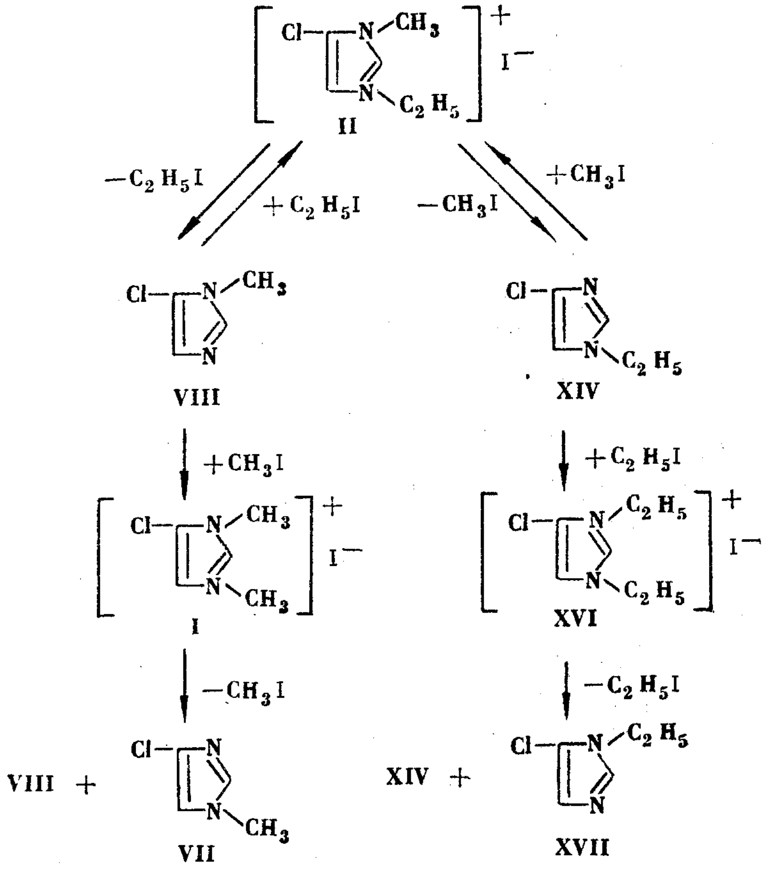
* For Part XVII see [9].

Experiments carried out supported this view. When quaternary salts I and V were heated, the 5-chloroimidazoles VIII and X were isolated along with the N-substituted 4-chloroimidazoles VII and IX. They are also found when preparing the 4-chloroimidazoles XI, XII, and XIII.

Pyrolysis of 1,3-dialkyl(1,2,3-trialkyl)-4(5)-chloroimidazole iodides could theoretically give equal amounts of 5-chloro- and 4-chloroimidazoles. Actually, the higher-boiling 4-chloro isomer is the predominant degradation product (yield 46-61%, yield of 5-chloroimidazoles does not exceed 15%, part of the quaternary salts completely resinifying). Boiling point differences make it possible to separate mixtures of these isomers comparatively readily, by fractional distillation under vacuum, and thus to obtain 1-alkyl(1, 2)-4-chloroimidazoles hitherto inaccessible by other methods.

Decomposition of 1,3-dialkyl-5-chloroimidazolinium iodides with the groups at positions 1 and 3 different, e.g., 1-methyl-3-ethyl-5-chloroimidazolinium iodide (II) is more complex. There not only methyl iodide splits out [4], but also ethyl iodide. However, reaction does not terminate at the stage of formation of a mixture of 1-methyl-5-chloro- and 1-ethyl-4-chloroimidazole (VIII and XIV), but is accompanied by a secondary reaction, quaternization of compounds VIII and XIV. The result is that a mixture of quaternary salts II, I, and XVI pyrolyzes to the quaternary compounds VIII, XIV, VII (converted to crystalline 1-methyl-4-chloro-5-nitroimidazole [1] without being isolated in a pure state) and 1-ethyl-5-chloro-imidazole (XVII, not isolated as the individual compound).

For the reasons given this method of preparing 1-alkyl(1,2-dialkyl)-4-chloroimidazoles is of limited application



Experimental

1,3-Dimethyl-4(5)chloroimidazolinium iodide (I). a) 105.3 g 1-methyl-5-chloroimidazole [3] was added over 1-1.5 hr, to a solution of 152 g methyl iodide in 300 ml dry acetone at 30-35°, the mixture refluxed for 6-8 hr left overnight, the precipitate filtered off, washed with acetone (100 ml), and dried to give 210-215 g (91-92%) of pale brown crystals mp 170-174° (the literature [4] gives 174-175°). Using benzene (6-8 hr) or ether (140 hr at 18-20°), the yield of salt I mp 170.5-172.5° was 82.6% and 88% respectively.

b) A mixture of 0.5 g compound VII, 0.62 g methyl iodide, and 20 ml ether was left for 7 days at 18-20°, the precipitate filtered off and dried. Yield 0.52 g (46.5%) compound mp 171-172.5°, undepressed mixed mp with a specimen of salt I prepared by method (a) above.

c) 25.1 g of mixed compounds VII and VIII, obtained when purifying VII (see below), 65 ml acetone, and 33 g methyl iodide were refluxed together and the product worked up as described in (a) above, to give 51.2 g (92%) compound I, mp 172-174°.

1-Methyl-3-ethyl-5-chloroimidazolinium iodide (II). Prepared similarly to compound I, from 90 g 1-methyl-5-chloroimidazole and 132.5 g ethyl iodide in 180 ml acetone. Yield 175 g (83.5%) mp 154-155° (the literature gives [4] mp 156-157°). When the reaction was run in ether (100 hr at 18-22°) there was a 75.5% yield of compound II, mp 156.5-157°.

1-Methyl-3-ethyl-4-chloroimidazolinium iodide (III). Prepared in the way described above, from 2.25 g compound VII and 3.3 g ethyl iodide in 5 ml acetone. Yield 3.53 g (68%), mp 197-198°. Colorless prisms mp 201-201.5° (from alcohol), readily soluble in water. Mixed mp with salt II 134-140°. Found: C 26.19; H 10.47; N 10.47; I 45.73%. Calculated for $C_6H_{10}ClIN_2$: C 26.42; H 3.70; N 10.28; I 46.57%.

1-Methyl-3-butyl-5-chloroimidazolinium bromide (IV). Prepared from 81.6 g 1-methyl-5-chloroimidazole, 105.6 g butyl bromide, and 100 ml methanol (7 hr refluxing). Colorless long prisms, mp 53.55° (from acetone-ethyl acetate), readily soluble in water and lower alcohols; hygroscopic in air. Found: C 37.29; H 5.51; N 10.74%. Calculated for $C_8H_{14}ClBrN_2$: C 37.89; H 5.56; N 11.05%.

1,3-Diethyl-2-methyl-4(5)-chloroimidazolinium iodide (V). A mixture of 24.4 g 1-ethyl-2-methyl-5-chloroimidazole [3], 30 g ethyl iodide, and 75 ml dry acetone was refluxed for 11 hr, and left overnight, the precipitate filtered off, and washed with acetone. Yield 37.08 g material mp 140-141° (according to the literature [5] mp 142-143°). Evaporation of the mother liquor to dryness, and recrystallization of the residue from 15 ml acetone gave a further 5.2 g compound V, mp 140-141°, total yield 42.8 g (82.9%).

1,3-Dipropyl-2-ethyl-4(5)-chloroimidazolinium iodide (VI). A solution of 50.5 g 1-propyl-2-ethyl-5-chloroimidazole [3], 56 g propyl iodide, and 100 ml dry toluene was refluxed for 4-6 hr, left overnight, the precipitate filtered off, washed with ether, dissolved in 20 ml dry acetone, and poured into ether (150 ml). This latter operation was repeated once more, to give 60.5 g (60%) colorless crystals mp 89.5-90.5°, readily soluble in water, lower alcohols, acetone, and methylene chloride, insoluble in ether, carbon tetrachloride, benzene, and toluene. Found: C 38.57; H 5.61; N 8.01; I 36.99%. Calculated for $C_{11}H_{20}ClIN_2$: C 38.55; H 5.88; N 8.18; I 37.04%.

1-Methyl-4-chloroimidazole (VII). 235.4 g quaternary salt I was carefully heated for 1-1.5 hr at 175-230° under a water pump vacuum, the distillate being collected in a receiver. 108.3 g dark brown liquid 84° (55 mm) – 105° (37 mm), $n_D^{17.5}$ 1.5309 was obtained. The material obtained was dissolved in 250 ml dichloroethane, this solution shaken with 50 ml water, the layer separated, and worked up separately. The aqueous solution was evaporated to dryness, the crystalline precipitate washed with 25 ml acetone, and dried. 13.6 g starting salt I were obtained, mp 172-174°. The acetone mother liquor was added to the dichloroethane solution, and the solvent distilled off under reduced pressure. 95.5 g dark brown liquid was obtained, n_D 1.5121, and this was fractionated under reduced pressure, using a rod and disc column (25 cm), to give fraction 1) bp 119-120° (51-54 mm), 9.9 g, n_D^{17} 1.5120, which was almost pure 1-methyl-5-chloroimidazole (VIII). Picrate – yellow crystals mp 166-167° (from alcohol), mixed mp with an authentic specimen (mp 167-168°) [3] undepressed; fraction 2) bp 121-154° (44-45 mm) 6.9 g n_D^{17} 1.5139 – a mixture of compounds VII and VIII; fraction 3) bp 155-157° (44 mm), 59.1 g, $n_D^{17.5}$ 1.5112, basically compound VII. Redistillation of fraction 3 gave: fraction 1) bp 133-137° (22.5 mm), 1.6 g n_D^{18} 1.5110 – a mixture of compounds VII and VIII; fraction 2) bp 138-140° (22.5 mm), 50.2 g, n_D^{18} 1.5125 – pure compound VII. Colorless liquid, bp 138-140° (22.5 mm), 156-157° (44 mm) (the literature [4] gives bp 250-252°), n_D^{20} 1.5115, d_{20}^{20} 1.2520. Darkened on standing, miscible in all proportions with water and organic solvents. Picrate – yellow crystals (from alcohol) mp 165-166° (the literature gives [4] mp 166-167°). Mixed mp with picrate of VIII (mp 167-168°) 133-136°. Nitrate – colorless prisms (from alcohol) mp 129-130° (with foaming). Mixed mp with nitrate of VIII (mp 144-145°) [3] 105-106°. Found: C 26.59; H 3.35; N 23.12; Cl 19.85%. Calculated for $C_4H_5ClN_2 \cdot HNO_3$: C 26.75; H 3.37; N 23.40; Cl 19.74%.

1-Ethyl-2-methyl-4-chloroimidazole (IX). 42.3 g salt V were heated as described in the preparation of compound VII. A distillate bp 114-160° (40-75 mm) was dissolved in 100 ml chloroform, the solution washed with water, dried over magnesium sulfate, and the solvent distilled off, to give 15.68 g dark brown liquid which was then fractionated, using a rod and disc column (25 cm), into the following fractions: 1) bp 114-119° (27 mm), 1.03 g, $n_D^{19.5}$ 1.5000, mainly 1-ethyl-2-methyl-5-chloroimidazole (X). Picrate – yellow crystals mp 154-155° (from alcohol). Mixed mp with an authentic specimen of the picrate (mp 154-155°) [3] undepressed; 2) bp 120-156° (27 mm), 2.65 g, $n_D^{19.5}$ 1.5021 – mixture of compounds IX and X; 3) bp 157-158° (27 mm) (literature [5] 263-265°), 7.05 g, n_D^{20} 1.5030 – pure compound X. Colorless liquid, darkening on standing, soluble in water and organic solvents. Picrate – yellow crystals (from alcohol) mp 155-156° (literature [5] mp 154-155°). Mixed mp with picrate of compound (mp 154-155°), prepared from fraction 1, 129-130°.

1-Propyl-2-ethyl-4-chloroimidazole (XI). 60 g salt VI was heated in a vacuum as described previously, to give 22.86 g material bp 120-130° (10 mm), which was twice distilled in a vacuum, using a column (25 cm), the high boiling cut being collected. 15 g (49.5%) pure compound XI was isolated, bp 122-123° (6 mm), n_D^{20} 1.4968, d_{20}^{20} 1.0699, forming a colorless liquid which darkened on standing, soluble in organic solvents, slightly soluble in water. Found: C 55.91; H 7.50; N 16.24; Cl 20.63%. Calculated for $C_8H_{13}ClN_2$: C 55.67; H 7.59; N 16.29; Cl 20.53%.

Picrate — yellow crystals mp 135-136° (from alcohol). Mixed mp with 1-propyl-2-ethyl-5-chloroimidazole picrate (mp 156-157°) [3], 118-119°. Found: N 17.36%. Calculated for $C_8H_{13}ClN_2 \cdot C_6H_3N_3O_7$: N 17.43%.

1-Butyl-2-propyl-4-chloroimidazole (XII).* A mixture of 40.5 g 1-butyl-2-propyl-5-chloroimidazole [3], 29.6 g butyl iodide, and 50 ml dry xylene was refluxed for 6 hr, left overnight, the solvent distilled off under reduced pressure, the residue transferred to a Claisen flask (with column), and decomposed by heating in a vacuum. 45.23 g material was obtained bp 150-159° (10-13 mm), n_D^{23} 1.4982, and that was fractionated as described for the previous experiment, to give 24.8 g (61%) compound XII bp 149-150° (7-8 mm), n_D^{20} 1.4920, d_{20}^{20} 1.0410, a colorless liquid which darkened on storage, soluble in organic solvents, almost insoluble in water. Found: C 60.09; H 8.45; N 13.63; Cl 17.55%. Calculated for $C_{10}H_{17}ClN_2$: C 59.87; H 8.54; N 13.96; Cl 17.67%.

Picrate — yellow prisms mp 120-121° (from alcohol). Mixed mp with 1-butyl-2-propyl-5-chloroimidazole picrate (mp 96-97° [3]) 85-95°. Found: C 44.54; H 4.68; N 16.36; Cl 8.29%. Calculated for $C_{10}H_{17}ClN_2 \cdot C_6H_3N_3O_7$: C 44.71; H 4.69; N 16.29; Cl 8.25%.

1-Isoamyl-2-isobutyl-4-chloroimidazole (XIII). A mixture of 59.1 g 1-isoamyl-2-isobutyl-5-chloroimidazole [3], 56.3 g isoamyl iodide, and 100 ml toluene was refluxed for 5 hr 30 min, the toluene distilled off under reduced pressure, and the liquid residue pyrolyzed in a vacuum. Fractionation of the resultant mixture of halogenated imidazoles led to isolation of 20 g (33.6%) compound XIII bp 165-167° (9.5 mm), n_D^{20} 1.4860, d_{20}^{20} 1.0028, a colorless liquid, which darkened on standing, was soluble in most organic solvents, but insoluble in water. Found: C 63.11; H 8.98; Cl 15.98; N 12.64%. Calculated for $C_{12}H_{21}ClN_2$: C 63.00; H 9.25; Cl 15.50; N 12.25%.

Picrate — yellow crystals mp 90-90.5° (from aqueous ethanol). Mixed mp with 1-isoamyl-2-isobutyl-5-chloroimidazole picrate (mp 97.5-98° [3]) 85-88°. Found: N 15.41%. Calculated for $C_{12}H_{21}ClN_2 \cdot C_6H_3N_3O_7$: N 15.36%.

Pyrolysis of 1-methyl-3-ethyl-5-chloroimidazole iodide (II). 58 g salt II was placed in a Wurtz flask, 100 ml capacity (with collar extension) fitted with a capillary (3-4 cm) going to the bottom of the flask. A slow current of nitrogen was passed through the capillary, and the material was quickly heated with a free flame. After the alkyl halides had distilled off, the distillate was collected in a receiver. Three runs of this kind gave 65.8 g dark brown liquid n_D^{19}, which was vacuum-distilled, to give the following fractions: 1) 102-127° (14 mm), 9.51 g, n_D^{20} 1.5067; 2) 128-137° (14 mm), 35.86 g, n_D^{20} 1.5068; 3) 137° (14 mm) — 167° (75 mm), 4.98 g, n_D^{20} 1.5178.

Investigation of fraction 1. To demonstrate the presence of 1-methyl-5-chloroimidazole (VIII), the entire fraction was distilled using a rod and disc column (25 cm), a small first fraction bp 105-106° (31 mm), $n_D^{16.5}$ 1.5082 being collected, picrate mp 142-149°, recrystallized from water mp 164-165°. Mixed mp with pure 1-methyl-5-chloroimidazole picrate (mp 167-168° [3]) undepressed. Mixed mp with 1-methyl-4-chloroimidazole (VII) picrate (mp 165-166°) 136-141°.

Investigation of fraction 2. The entire fraction was vacuum-distilled, using a rod and disc column (25 cm) a narrow middle cut bp 132-134° (14 mm), 22.81 g, $n_D^{21.5}$ 1.5150 being taken, consisting mainly of 1-ethyl-4-chloroimidazole (XIV), picrate mp 145-146° (from alcohol, then from water; the literature [4] gives 146-147°). Mixed mps with picrates of compounds VII and VIII 139-144° and 129-140° respectively. Found: C 36.46; H 2.86; N 19.48; Cl 9.91%. Calculated for $C_5H_7ClN_2$. $C_6H_3N_3O_7$: C 36.73; H 2.80; N 19.47; Cl 9.86%. Methiodide (obtained by heating base XIV with methyl iodide in acetone) — colorless crystals mp 144-148°. Mixed mp with pure salt II undepressed. To show the presence of 1-methyl-4-chloroimidazole (VII), 20.5 g fraction 2 was added to a mixture of 62 ml concentrated sulfuric acid and 8.7 ml 98% nitric acid, and the mixture stirred and heated for 1 hr at 100°. After cooling it was poured into 600 ml water, the oily product extracted with chloroform, the extract washed with water, and dried over sodium sulfate. After distilling off the solvent there was obtained 24.5 g nitrochloroimidazole which was vacuum-distilled to give the following fractions: 1) bp 134-137° (0.45-0.62 mm), 1.98 g, $n_D^{16.5}$ 1.5731; 2) 137° 0.6 mm) — 142° (1.25 mm), 15.37 g, $n_D^{16.5}$ 1.5744; 3) bp 143° (0.8 mm), 4.7 g. On cooling the last fraction partly crystallized, the crystals were filtered off, washed with carbon tetrachloride, and dried, to give 0.86 g 1-methyl-4-chloro-5-nitroimidazole (XV) mp 78.5 79°. Undepressed mixed mp with an authentic specimen of that compound (mp 78-79° [1]).

Investigation of fraction 3. The entire fraction was vacuum-distilled, and a narrow last cut taken bp 149-150° (33 mm), n_D^{17} 1.7079; picrate mp 141-142°, recrystallized from alcohol, then from water, mp 145-146°. Undepressed mixed mp with the picrate of compound XIV (mp 145-146°) prepared from fraction 2). Part of the fraction was nitrated in the way described above. After distilling off the solvent, the mixtrue of nitrochloroimidazoles partly crystallized, the crystals were filtered off, and washed with petrol ether, mp 78.5-79° (from alcohol). Mixed mp with compound XV undepressed.

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* Compounds VI, XI, and XII were obtained in work with I. S. Shmidt.

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Ordzhonikidze All-Union Chemical-Pharmaceutical
Scientific Research Institute, Moscow