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SYNTHESES OF 2,2'-DIIMIDAZOLE

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New methods of preparation of 2,2'-diimidazole have been developed, by the reaction of ammonia with 1,1-dibromoacetaldehyde (20% yield) or with glyoxal sulfate (40%), and by the cyclization of 1,2-dihydroxyethylenediamine dihydrochloride in the presence of sodium acetate (yield 60%).

2,2'-Diimidazole (I) was synthesized long ago, but there are no satisfactory methods for its preparation. Its chemistry has received little attention, although its derivatives include compounds with useful biological properties [1, 2]. One method of preparation is from 2,2,2-trichlorolactic acid and aqueous ammonia [3], and another is based on the reaction of glyoxal with ammonia [4] or ammonium salts [5]. Common disadvantages of these methods are the low yields obtained (no greater than 25%) and the formation of highly contaminated (I), which can be purified only by sublimation. A method of synthesis developed recently [6] involving the aromatization of 2,2'-di-(2-imidazoline), although it gives high yields of (I), is complicated even for preparative use.

Despite the apparent diversity of the first three methods [3-5], they are in our view united in the ability of the starting materials to produce during the reaction intermediates which are structurally analogous and have similar properties, namely alkylamines containing a halogen or hydroxy group in the α-position. We therefore addressed ourselves to reactions in which such compounds are possible intermediates. Such reactions include the condensation of ammonia with 1,1-dibromoacetaldehyde and glyoxal sulfate. It was in fact found that 1,1-dibromoacetaldehyde reacts with aqueous ammonia on prolonged heating at a temperature not exceeding 60°C to give (I). However, this reaction is attended the same deficiencies as are inherent in the reaction of glyoxal with ammonia, namely similar yields of crude diimidazole, and the difficulty of its purification. When the reaction was carried out at temperatures above 60°C, a mixture of resinous materials was obtained which contained no (I). The best yields (up to 40%) were obtained by reacting glyoxal sulfate with aqueous ammonia at 60-80°C.

(See scheme on following page.)

In these syntheses of (I), intermediates of similar chemical structure and properties are undoubtedly present, one of which could be 1,2-dihydroxyethylenediamine (II). The latter compound is quite stable as its hydrochloride [7], but has not been obtained in the free state. It appears that in neutral or basic media, as with the simplest geminal aminoalcohols [8], (II) decomposes to glyoxal and ammonia, which may give (I), as described in [4]. In

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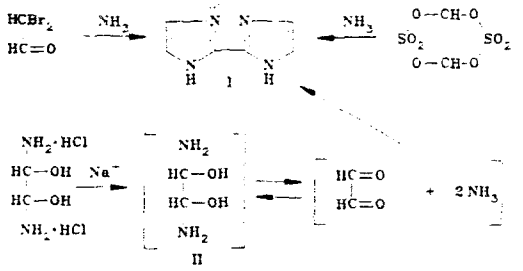

fact, when (II) dihydrochloride was heated with sodium acetate, the required product was obtained in 59-60% yields.

In this reaction, the sodium acetate can be replaced by ammonium acetate or organic bases, and in particular imidazole, the yields of (I), remaining essentially unchanged.

A method has thus been developed for the synthesis of 2,2'-diimidazole, by heating an aqueous solution of 1,2-dihydroxyethylenediamine dihydrochloride with sodium acetate.

EXPERIMENTAL

IR spectra were obtained on a UR-20 spectrophotometer in KBr disks. Assignment of absorption bands was carried out using the data given in [9].

2,2'-Diimidazole. A. To 140 ml of 25% aqueous ammonia was added portionwise at 40°C 60.6 g (300 mmole) of dibromoacetaldehyde [10]. The mixture was stirred for 7 h at 40°C, then for 3 h at 60°C, and cooled to 20°C. The solid was filtered off, washed with water and acetone, and dried. Yield 3.4 g (30%). This was dissolved in 3-5% hydrochloric acid, boiled with activated charcoal, cooled, and the filtrate treated with 100 ml of 25% aqueous ammonia to precipitate 2,2'-diimidazole as a colorless, infusible powder, which sublimed at temperatures above 300°C. Yield 2.7-2.8 g (20-21%). IR spectrum: 1415, 1445, 1550 cm^{-1} (skeletal vibrations of the imidazole rings). Found, %: C 54.0, H 4.6, N 41.3. $C_6H_6N_4$. Calculated, %: C 53.7, H 4.5, N 41.8.

B. To 900 ml of 25% aqueous ammonia was added in portions with stirring at 20°C 654 g (3.0 mole) of glyoxal sulfate and 1 liter of aqueous ammonia of the same concentration. The temperature thereupon rose to 60°C. Both reactants were added at such a rate that the addition of each was completed at the same time, and the temperature of the reaction mixture stayed within the range 60-80°C. The mixture was then cooled, and the solid filtered off, washed with water, dried, and dissolved with heating in 1 liter of glacial acetic acid. The solution was filtered, and 39 g (21.5 ml) of concentrated sulfuric acid (d = 1.84) added dropwise at 20°C. The 2,2'-diimidazole sulfate which separated was filtered off, and the solid washed on the filter with ether, and dried. Yield 73 g (85%), mp 220-238°C. This material was recrystallized from acetone–water (4:1) to give 60 g (70%) of product, mp 244-245°C (decomp.). IR spectrum: doublet 1575, 1590, 1470; doublet 1420, 1435 (skeletal vibrations of the imidazole rings); 1000, 1120 (SO_4^{2-}); 795, 1660, 3470 cm^{-1} (NH_2^+). Found, %: C 31.2, H 3.5, N 24.1. $C_6H_6N_4 \cdot H_2SO_4$. Calculated, %: C 31.0, H 3.4, N 24.1. The sulfate was converted into the base by treatment with 25% aqueous ammonia. In its physicochemical properties, the compound corresponded to a sample obtained by method A. The yield was 39-41 g (29-30%).

C. A solution of 21.6 g (264 mmole) of sodium acetate and 11 g (66 mmole) of 1,2-dihydroxyethylenediamine dihydrochloride [7] in 60 ml of water was heated for 2 h at 90°C. The mixture was cooled, and the solid which separated was filtered off, washed with water and acetone, and air-dried. Yield 1.8 g (60.4%). The product corresponded in its physicochemical properties with those obtained by methods A and B.

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TAUTOMERISM OF 1-METHYL-5-AMINO-2,3-DIHYDRO-1,2,4-TRIAZOLIUM–1-ALKYLIDENE (OR ARYLIDENE)-2-METHYLAMINOGUANIDINIUM IODIDE

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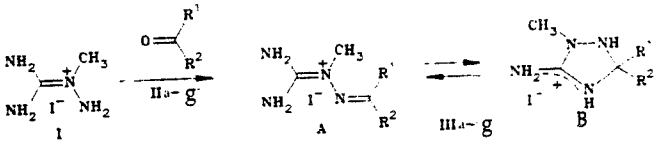
^{1}H and ^{13}C NMR spectroscopy has been used to examine the structures of the products of the condensation of aldehydes and ketones with 1-methyl-1-aminoguanidinium iodide, which in some instances in solution are involved in a ring–chain tautomeric equilibrium between 1-methyl-5-amino-2,3-dihydro-1,2,4-triazolium iodide and 1-alkylidene(or arylidene)-2-methylaminoguanidinium iodide.

It is known that the introduction of substituents into the 2-position of semi- and thiosemicarbazones [1, 2] and of 1-alkylidene(and arylidene)amidrazones [3], and to an even greater extent the protonation of these compounds, facilitate their cyclization to 1,2,4-triazolines and 1,3,4-thiadiazolines, respectively. In this connection salts of 2-alkylguanylhydrazones have not been studied, the only compounds of this type having been reported being the nitrate [4], chloride and sulfate [4, 5], picrate [4], and iodide [6] of benzylidene-1-methyl-1-aminoguanidine, these having been used to identify 1-methyl-1-aminoguanidine. However, no information is available on the fine structure of these compounds.

We here present information on the structures of 2-methylguanylhydrazonium salts obtained by condensing 1-methyl-1-aminoguanidinium iodide (I) with aldehydes and ketones (IIa-g).



II, III a–e R^1=H, f,g R^1=CH_3; e,f R^2=CH_3, b R^2=C_6H_5, c R^2=4-$CH_3OC_6H_4$; d R^2=4-$O_2NC_6H_4$; e R^2=C_6H_5CH=CH; g R^2=C_2H_5

The guanylhydrazonium iodides (IIIa-g) are obtained in near-quantitative yields following prolonged standing of the reactants at 20°C, but with p-nitrobenzaldehyde (IId) prolonged boiling of the reaction mixture was necessary. With branched-chain ketones (pinacoline, acetophenone), however, condensation failed to take place.

In assigning structures of the compounds (III), which may exist in solution either in the straight-chain (A) or the cyclic (B) forms or a mixture of the two, we made use of previously developed structural criteria [3]. In the PMR spectra, the signals for the R^1 and R^2 substituents in the cyclic form B should occur at higher field than in the linear tautomer A, and when R^1 = R^2, these substituents are equivalent. In the ^{13}C NMR spectra of the cyclic form B a signal for the sp^3-hybridized atom $C_{(3)}$ should occur, resonating in the range 70-80 ppm [3], whereas in the linear form A the C=N signal should lie at much lower field.

From the results obtained (Tables 1 and 2), it may be concluded that: the arylidene compounds (IIIb-d) exist in solution in DMSO and DMF as the linear tautomers, irrespective of the nature of the para-substituent, together with the cinnamaldehyde derivative (IIIe),

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