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Tri-(2-hydroxyethyl)-ammonium-acetic Acid Betaine

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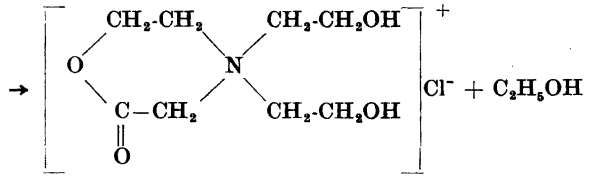
The synthesis from triethanolamine and ethyl chloroacetate of tri-(2-hydroxyethyl)-ammonium-acetic acid betaine (II) and its intermediate 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (I) is described. The hydrochloride of (II) was unstable. The infrared spectra of both compounds, and of related N,N-di-(2-hydroxyethyl)-amino-acetic acid are presented.

As far as the author was able to ascertain tri-(2-hydroxyethyl)-ammonium acetic acid betaine (II) has not been previously reported in chemical literature. One known, and well authenticated [1-5] similar compound is di-(2-hydroxyethyl)-amino-acetic acid, known both in its open, acid form and as a lactone. This compound is crystalline and soluble only in water and hot 80 % methanol; quaternization of it would therefore present serious difficulties.

Direct quaternization was first attempted, using triethanolamine and ethyl chloroacetate but the results were somewhat surprising. The expected ethyl ester of tri-(2-hydroxyethyl)-ammonium-acetic acid betaine chloride was not obtained, but a lactone, 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (I), and ethyl alcohol were formed instead.

$$(HOCH_2CH_2)_3N + Cl\text{-}CH_2CO\text{-}OC_2H_5 \rightarrow [(HO\text{-}CH_2CH_2)_3N^+\text{-}CH_2\text{-}CO\text{-}OC_2H_5]Cl^- \rightarrow$$



$$\rightarrow \quad Cl^- + C_2H_5OH$$

(I)

Even when the reaction was carried out in the absence of any solvent, ethyl alcohol appeared after some time as an easily identifiable product.

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2-Oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (m.p. 123—124° decomp.) is very easily soluble in water. The pH of the aqueous solution drops gradually, reaching a constant value about 40 min after dissolution. After crystallization from water the new compound had a m.p. of 177—178°C. One would expect that hydrolysis of the lactone ring in aqueous medium had taken place, with a resultant increase in acidity and an increase of the melting point, but elementary analysis and infrared spectra showed unequivocally that only triethanolamine hydrochloride was formed.

Since the lactone (I) was insoluble in all the common organic solvents, it was recrystallized by dissolving it in the least possible amount of water and very quickly precipitating with ethanol or acetone. In this way structure (I) could be preserved.

The formation of triethanolamine hydrochloride cannot be readily explained. It occurs not only by the action of water on lactone (I), but also under certain conditions during the synthesis of (I). The lactone is obtained by the very slow, dropwise addition of ethyl chloroacetate to triethanolamine or its solution in absolute alcohol. When the addition of ethyl chloroacetate is somewhat faster, or when triethanolamine is dropped into the ester, triethanolamine hydrochloride is obtained in yields of up to 97 %, calculated on triethanolamine. This strange result was obtained even with reagent grade chemicals.

For the conversion of 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (I) to betaine, (I) was added in very small portions at long time intervals to an aqueous suspension of silver oxide.

$$(C_8H_{16}O_4NCl) + AgOH \rightarrow (HO\text{-}CH_2CH_2)_3N^+\text{-}CH_2COO^- + AgCl$$

(I) (II)

After separation and purification by crystallization, product (II) melted at 179—180 °C with decomp. This m.p. is rather low in comparison with the m.p. 293—294 °C [6] of betaine $(CH_3)_3N^+\text{-}CH_2\text{-}COO^-$. The compound (II) is soluble in water and insoluble in all common organic solvents.

DISCUSSION

The proposed structures (I) and (II) are based on analyses (see Experimental part), infrared spectra and chemical evidence.

The spectrum of 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (Fig. 1 A) has all the characteristic bands of morpholine and N-methylmorpholine.[7] The quaternary nitrogen structure of 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride is further supported by a very strong band at 1750 cm^{-1} which is also present in the spectra of betaine hydrobromide and 2-pyridone-α-bromoacrylic adduct.[8-9] The band is shifted to 1615—1630 cm^{-1} in the spectrum of betaine, hydrobromide-free 2-pyridone-α-bromoacrylic adduct and also tri-(2-hydroxyethyl)-ammonium-acetic acid betaine (II) (Fig. 1 B). A very weak but sharp band in the region of 2100 cm^{-1} (2090 cm^{-1}) in the spectra of both (I) and (II) confirms the presence of positively charged quaternary nitrogen.[9] The aim, indeed, was to obtain such a group.

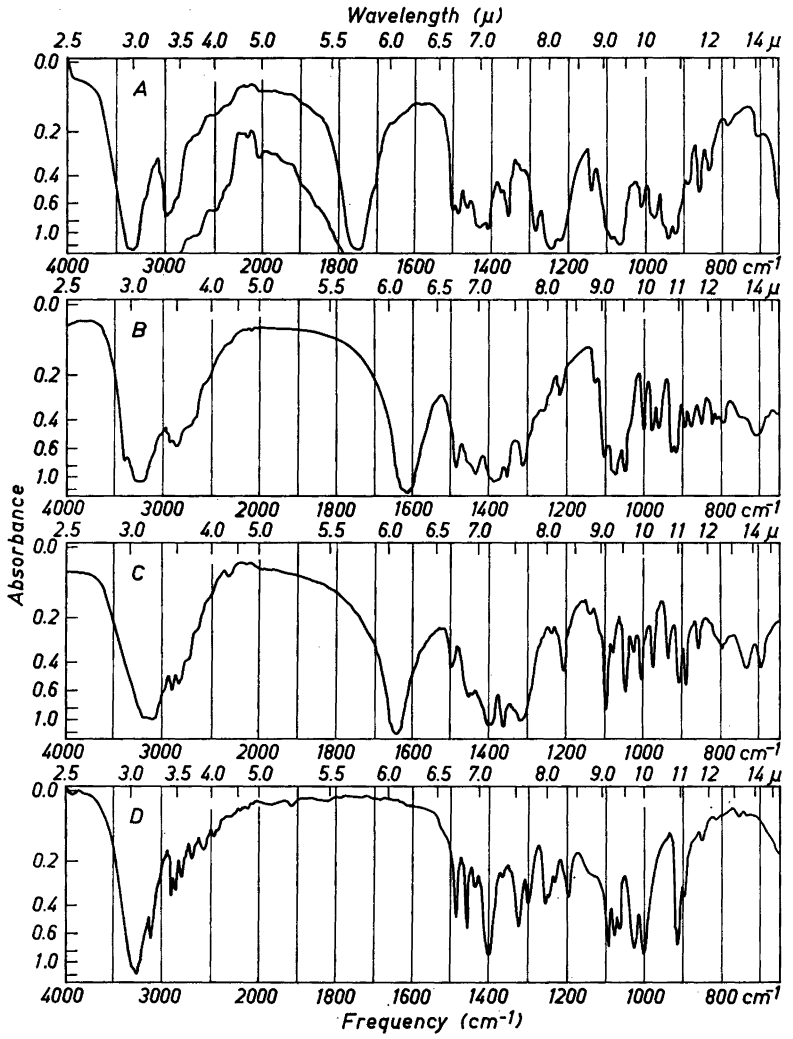

Fig. 1. Infrared spectra: A. 2-Oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride. B. Tri-(2-hydroxyethyl)-ammonium-acetic acid betaine. C. N,N-Di-(2-hydroxyethyl)-aminoacetic acid. D. Triethanolamine hydrochloride.

2-Oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride, when crystallized from water, gave the spectrum shown in Fig. 1 D. This is identical with the spectrum of triethanolamine hydrochloride obtained by reacting pure triethanolamine with hydrochloric acid and there can be no doubt as to the result of the hydrolysis of compound (I).

It may be worth adding that N,N-di-(2-hydroxyethyl)-amino acetic acid, obtained by the method of Khromov and Remizov,[3] has a strong band in the region of 1640 cm^{-1} (carboxylic group), like betaines (Fig. 1 C). On the other hand, N-carboxymethyl-morpholone-2, prepared according to Ziemlak *et al.*,[10] has the carboxylic group band in the region of 1720 cm^{-1}, like betaine hydrochlorides.*

After consideration of the behaviour of the compounds described above, it is concluded that the hydrochloride of the open betaine form exists but is not stable. This conclusion is supported by the relatively slow decrease in pH of aqueous solutions of the cyclic form (I) and more significantly by the transformation in aqueous solution of 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (I) to the open form of true betaine tri-2-(hydroxyethyl)-ammonium acetic acid betaine (II). The compound $[(HO\text{-}CH_2\text{-}CH_2)_3\text{-}N\text{-}CH_2COOH]^+ Cl^-$ should be capable of existing as an unstable reaction intermediate.

It must be stressed that this instability is not a result of the acidity of the reaction medium. The betaine structure is preserved in the presence of silver hydroxide (silver oxide suspension), in an alkaline medium. Dissolution of compound (I) in an aqueous solution of sodium hydroxide (both of the stoichiometric strength necessary to neutralize the carboxyl gruop and in 10—50 % excess of NaOH) gave results similar to those obtained on dissolution of the compound in distilled water. Such a behaviour of the proposed structure may be due to the influence of hydroxy groups. The analogous hydrochloride of common betaine does not exist as a stable compound.[11] It is difficult to explain the extreme sensitivity of the course of the reaction to the rate at which the reagents are contacted, or the sensitivity to the concentration of ethyl chloroacetate in the reaction medium.

Carrying out the reaction at various temperatures, or using materials of different degree of purity, had no observable effect on the reaction products.

The final result was the same whether the reaction was carried out in absolute ethanol, or in the absence of solvent. Strict exclusion of water vapour from the reaction vessel also had no influence on the course of the reaction. It seems that some kind of rearrangement must be responsible for the unexpected result of this reaction. When the reaction was carried out using monochloroacetic acid or sodium chloroacetate instead of ethyl chloroacetate, the product was invariably triethanolamine hydrochloride.

EXPERIMENTAL

2-Oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride. Reaction between triethanolamine and ethylchloroacetate was carried out in a glass flask fitted with stirrer, reflux condenser, thermometer, and dropping funnel. (In some cases a calcium chloride tube was also attached.) The flask was heated either in a water bath or with an electric heating mantle. Ethyl chloroacetate was dropped into triethanolamine and vigorously agitated in the flask at 90 °C. An equimolar amount of ester was added continuously over a period of 4 h. Reflux of ethyl alcohol appeared 30—35 min after the first addition of ethyl chloroacetate. Product crystals which were suspended in the reaction mixture began to

* KBr pellets were used in obtaining all IR spectra.

form about 1½ h from the start of the reaction. After the final addition of ester, heating and stirring were continued for a further 1 to 1½ h whereupon the number of crystals in the flask further increased. The reaction mixture was then cooled to room temperature and filtered; the crystals were washed thoroughly with absolute alcohol and ether. The filtrate was evaporated on an evaporating dish to yield more crystals. The reaction was carried out in flasks of three different sizes, 25, 500, and 2500 ml; similar results were obtained in all cases.

The yields varied between 84 % and 95.5 % of crude product (the first crystallization yielding 60—70 %), and depended on the purity of the chemicals used. Some reactions were carried out in absolute alcohol, which made the agitation easier. Towards the end of the reaction, the amount of crystalline product was greater and the stirring was hindered, especially when bigger apparatus was used. Crude product was obtained in a relatively pure state, as indicated by a melting point of about 122 °C (decomp.) The final melting point, after 5—7 crystallizations, was 123—124 °C (decomp.).

Recrystallization was carried out by dissolving the product in the smallest possible amount of water (about 100 g of product in in 100—150 ml of distilled water) and immediately precipitating with ethanol or acetone. After filtration the product was washed thoroughly with alcohol and ether, and dried under vacuum at room temperature. (Found: C 42.41; H 7.20; O 28.18; N 6.19: Cl 15.86. Calc. for $C_8H_{16}O_4NCl$: C 42.58; H 7.15; O 28.36; N 6.21; Cl 15.71).

After crystallization of 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride from water, analysis gave: C 38.99; H 8.56; O 26.08; N 7.46; Cl 18.84, corresponding to the formula for triethanolamine hydrochloride, $C_6H_{16}O_3NCl$: calc. C 38.81; H 8.68; O 25.89; N 7.55; Cl 19.10.

Tri-(2-hydroxyethyl)-ammonium-acetic acid betaine. 2-Oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride (I) was introduced in very small portions (when the total amount to be added was 56.5 g, portions of 0.5 g each were added every 10 min) into an aqueous suspension of silver oxide heated on a water bath and vigorously stirred. When the addition was completed, heating and stirring were continued for a further 1 or 1½ h. Silver chloride formed was filtered off and washed thoroughly with distilled water.

The filtrate was evaporated on a water bath at about 50 °C and left to crystallize. The crude product formed platelets and had a m.p. of 174 °C (decomp.). After 5—7 recrystallizations from distilled water, followed by washing with ethanol and ether, it melted at 179—180 °C (decomp.). Recrystallization could be aided by precipitation with alcohol or acetone, to give the same results as above. Yields were 66 and 74 % of theory, calculated on 2-oxo-4,4-di-(2-hydroxyethyl)-morpholinium chloride. (Found: C 46.65; H 8.00; O 38.48; N 6.87. Calc. for $C_8H_{17}O_5N$: C 46.37; H 8.27; O 38.61; N 6.76).

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