Chemistry of Heterocyclic Compounds, Vol. 34, No. 4, 1998

SYNTHESIS OF BETAINES FROM 1,4-DIAZA[2.2.2]BICYCLOOCTANE

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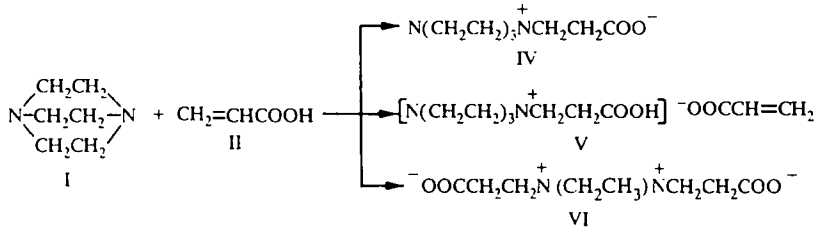
Betaine formation occurs on reacting 1,4-diaza[2.2.2]bicyclooctane with acrylic acid, 2-acrylamido-2-methylpropanesulfonic acid, and 4-acrylamido-4-methyltetrahydrothiophene-1,1-dioxide-3-sulfonic acid. Various products such as monobetaines, their salts, or dibetaines may be obtained in the reaction with acrylic acid depending on the solvent and the reactant ratio. With an excess of diamine reaction occurs more rapidly with sulfonic acids, but with a deficiency of diamine reaction occurs more rapidly with the carboxylic acid.

One of the more convenient means of obtaining betaines is the nucleophilic addition reaction of tertiary amines to the C=C bond of α,β-unsaturated acids [1, 2]. According to [3], 1,4-diaza[2.2.2]bicyclooctane (I) forms a monobetaine in 55-80% yield on reaction with acrylic (II) or ethene sulfonic acids, i.e., only one amino group of the diamine (I) is involved in the reaction. The aim of the present work was to study the special features of the synthesis of betaines from diamine (I) and three acids of the acrylic series, viz., acid (II), 2-acrylamido-2-methylpropanesulfonic acid (IIIa), and 4-acrylamido-4-methyltetrahydrothiophene-1,1-dioxide-3-sulfonic acid (IIIb).

It turned out that on using compound (II) betaine products of various composition were obtained depending on the solvent chosen. These products were the monobetaine (IV), the monobetaine acrylate (V), and the dibetaine (VI).



The monobetaine (IV) was precipitated as a solid on mixing the reactants in DMF, the monobetaine salt (V) was precipitated from ethyl acetate solution, and from isopropyl alcohol the solid formed was a mixture of (IV) and (VI) (at a ratio of 4:1). Spectral data showed that salt formation in (V) occurs as a result of protonation of the carboxylate group of the betaine and not of the free tertiary amino group. This is indicated by the presence in the IR spectrum of a signal typical of tertiary amines (1050 cm^{-1}) [there is a similar signal in the spectrum of the initial diamine (I)], and also by the absence of a band for a protonated tertiary amino group (2250-2700 cm^{-1}) [4].

The reason for obtaining products of different composition on changing the solvent is linked with the different solubility of the compounds formed in the various solvents and with the presence of a nucleophilic reaction center in the monobetaine. The same phenomena are observed, according to [3], on reacting a series of aliphatic and heterocyclic tertiary amines with acid (II). It is known that all betaines (including those synthesized in the present study) are readily soluble in water, have a limited solubility in alcohols, and are insoluble in the majority of other organic solvents. Consequently the partial formation of the dibetaine (VI) in isopropyl alcohol may be explained by the somewhat better solubility of the monobetaine in it compared with DMF or ethyl acetate. This enables the second nitrogen atom to be involved in the reaction before separation of the monobetaine as a precipitate, since the nucleophilic reactivity of this tertiary nitrogen atom in monobetaine (IV) is reduced due

Dzerzhinsk Branch, Novgorod State Medical University, Dzerzhinsk 606007, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 547-550, April, 1998. Original article submitted October 10, 1997.

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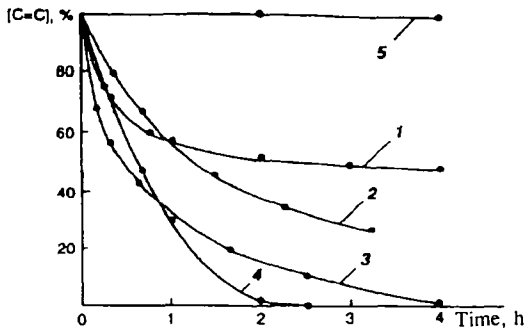
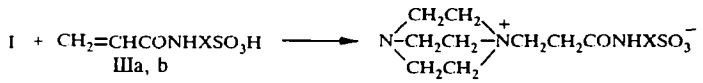
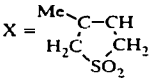


Fig. 1. Change of C=C bond concentration in aqueous solutions of: 1-3) (I)-(II), 4) (I)-(IIIa), 5) $(C_2H_5)_3N$-(IIIa). Amine concentration, M: 1) 0.50; 2, 4, 5) 0.75; 3) 1.50. Acid concentration, M: 2, 4, 5) 0.50; 1, 3) 1.00. Temperature, °C: 1-4) 25; 5) 50.

to the presence of the strongly accepting substituent in the β position. The second stage of betaine formation occurs far more slowly than the first and the formation of dibetaine is prevented when the monobetaine is rapidly precipitated. Consequently the possibility of obtaining dibetaine is realized more readily on carrying out the process in water since here the monobetaine and its salt remain in solution. In reality the monobetaine (V) is obtained on mixing equimolar amounts of diamine (I) and acid (II) in water. At concentrations of acid and amine of 3.0 M and 1.5 M respectively about 50% of the C=C bonds have disappeared after 15 min (at 20°C), after which their decrease slows sharply. After 15 days these bonds are 98% consumed which indicated the close to quantitative formation of betaine (VI). This compound was obtained in 93% yield as the dihydrate after removal of the water. The rapid abrupt disappearance of approximately half the C=C bonds of acid (II) was also observed on using a twofold excess of acid (see Fig. 1, curve 1).

Another special feature of the reaction in water is the reduction of the equilibrium conversion on increasing the temperature. For the same reactant concentrations (3.0 and 1.5 M) and temperature (80°C) equilibrium was achieved at a decrease of 65% C=C bonds. Monobetaines (VIIa) and (VIIb) were also obtained on replacing acid (II) by acrylamide sulfonic acids (IIIa) and (IIIb).



III, VII a X = CMe_2CH_2, b X = 

These reactions almost do not proceed in organic solvents but in aqueous medium they occur rapidly with an excess of amine (curve 4) and very slowly with an excess of acid. Consequently only monobetaines were obtained as reaction products on using acids (IIIa) and (IIIb) in water (see Experimental). The reaction of diamine (I) with acid (IIIa) was effected somewhat more rapidly than with acid (II) (see curves 2 and 4). As regards the pair (I)-(IIIb), at amine concentration 0.75 M, acid concentration 0.5 M, and temperature 25°C, the consumption of C=C bonds was 85% directly after mixing the reactants and 96% after 3 min.

There are therefore several important differences when obtaining carboxyl and sulfo betaines from diamine (I) and acid-containing acrylic monomers. Firstly, the formation of sulfobetaines is strongly inhibited with a deficiency of diamine in relation to sulfonic acid. This is linked with the far stronger acid properties of the sulfonic acids, since the pK_a of acids (II) and (IIIa) at 25°C are 4.26 [5] and 1.0 [6] respectively. As a result a larger proportion of the diamine is bound as a salt on mixing with an excess of sulfonic acid than in a mixture with acid (II). The protonated nitrogen atom then loses its nucleophilic properties completely and the reactivity of the second unprotonated amino group is sharply reduced. Secondly, betaines of various structures are not obtained for the sulfobetaines, unlike the carboxybetaines, and finally, under identical conditions [an excess of diamine (I)] the rate of reaction with acrylic acid is less than is probably explained by electronic effects. For any acid

the main portion of the acidic groups are in the salt form under these conditions. However, although the carboxylate anion does not activate the C=C bond for participation in nucleophilic addition, the substituted amide groups of compounds (IIIa) and (IIIb) retain an acceptor influence on these bonds even when a sulfonate anion remote from the acryloyl fragment is present. The concentration of activated C=C bonds in the (I)-(IIIa) and (I)-(IIIb) systems is therefore far greater than in the (I)-(II) system.

In conclusion we note that the fairly ready formation of all the betaines described above becomes possible primarily due to the molecular structure of diamine (I). In this diamine all three ethylene substituents are rigidly bound by the terminal nitrogen atoms. Consequently the steric obstacles towards nucleophilic attack with participation of nitrogen are small. In the triethylamine molecule practically the same alkyl substituents are not part of a ring and strongly hinder addition to α,β-unsaturated acids. As a result triethylamine adds to acid (IIIa) by only 1.5% overall after 4 h under more forcing conditions than when diamine (I) reacts quantitatively after 2 h (Fig. 1, curves 4 and 5).

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrometer in KBr disks, and the PMR spectra on Tesla BS 487 (80 MHz) and Gemini 300 instruments. The content of C=C bonds was determined by bromide-bromate titration. Acid (IIIb) was synthesized by the procedure in [7].

3-(1,4-Diaza[2.2.2]bicyclo-1-octylium)propionate (IV). Acid (II) (1.44 g, 0.02 mole) was added to a solution of diamine (I) (1.12 g, 0.01 mole) and hydroquinone (0.007 g) in DMF (11.8 ml). Crystals began to form in the solution after 20-30 min. The solid was separated after 1 h, washed with ether, and dried at 30°C (2 mm Hg). A hygroscopic product (1.47 g, 80%) was obtained, from which C=C bonds and acid groups were absent, mp 165°C. PMR spectrum (D_2O): 3.44-3.89 (12H, m, N^+CH_2, NCH_2); 3.14 ppm (2H, t, CH_2COO^-). Found, %: N 15.01. $C_9H_{16}N_2O_2$. Calculated, %: N 15.22.

3-(1,4-Diaza[2.2.2]bicyclo-1-octylium)propionic Acid Acrylate (V). Acid (II) (2.88 g, 0.04 mole) was added to a solution of diamine (I) (2.24 g, 0.02 mole) and hydroquinone (0.014 g) in ethyl acetate (15 ml). A solid separated from the solution after several minutes. A hygroscopic product (4.22 g, 82%) was obtained after washing with ether and drying at 30°C (2 mm Hg). PMR spectrum (CD_3OD): 2.68 (2H, t, CH_2COO^-); 5.55-6.43 (3H, m, $CH_2=CH$); 2.95-3.63 ppm (12H, m, N^+CH_2, NCH_2). IR spectrum: 1660 (C=C), 1590 (COO^-), 1460 (CH_2), 1370 (COO^-), 1050 cm^{-1} (R_3N). Found: C=C bond content 3.74 meq/g, acid group content 4.10 meq/g, % N 10.89. $C_{12}H_{20}N_2O_4$. Calculated: C=C bond content 3.91 meq/g, acid group content 3.91 meq/g, % N 10.94.

3,3'-(1,4-Diaza[2.2.2]bicyclo-1,4-octylenium)bispropionate (VI). An aqueous solution (25 g) containing 1.5 M diamine (I) and 3.0 M acid (II) was stored at 20°C for 15 days. The solution was then evaporated using an air stream. After removing the solvent the residue was washed with ether, and dried at 30°C (2 mm Hg). A nonhygroscopic product (11.0 g, 93%) was obtained from which C=C bonds and acid groups were absent, mp 120°C. PMR spectrum (CD_3OD): 2.57 (4H, t, CH_2COO^-); 3.23 ppm (12H, t, N^+CH_2). Found, %: C 50.02; H 8.36; N 9.91. $C_{12}H_{20}N_2O_4 \cdot 2H_2O$). Calculated, %: C 49.32; H 8.22; N 9.59.

Mixture of 3-(1,4-Diaza[2.2.2]bicyclo-1-octylium)propionate (IV) and 3,3'-(1,4-Diaza[2.2.2]bicyclo-1,4-octylenium)bispropionate (VI). Diamine (I) (1.12 g, 0.01 mole), acid (II) (1.44 g, 0.02 mole), and hydroquinone (0.007 g) were dissolved in isopropyl alcohol (6 ml). A solid began to precipitate after stirring for 5-10 min. This was separated after 1 day, washed with ether, and dried at 30°C (2 mm Hg). A hygroscopic product (1.41 g) was obtained containing no C=C bonds or acid groups, mp 155-160°C. PMR spectrum (CD_3OD): 2.51 (2.4H, m, CH_2COO^-); 3.04-3.48 ppm (14.4H, m, N^+CH_2, NCH_2). Found, %: C 56.31; H 8.57; N 14.08. $C_9H_{16}N_2O_2$ (80 wt. %) + $C_{12}H_{20}N_2O_4$ (20 wt. %). Calculated, %: C 56.92; H 8.33; N 14.35.

2-{3-(1,4-Diaza[2.2.2]bicyclo-1-octylium)propionamido}-2-methylpropanesulfonate (VIIa). Acid (IIIa) (1.85 g, 0.0091 mole) was added to a solution of diamine (I) (1.53 g, 0.0137 mole) in water (3 ml) and the mixture was stored for 1 day at room temperature. The solution was then evaporated in a stream of air, the residue was washed with acetone, and dried in vacuum (2 mm Hg) at 20°C. A product (2.76 g, 81.7%) was obtained containing no C=C bonds or free acid groups. PMR spectrum (D_2O): 1.50 (6H, s, CH_3); 2.80 (2H, t, CH_2CON); 3.24-3.61 ppm (16H, m, CH_2N^+, CH_2N, $CH_2SO_3^-$). IR spectrum (characteristic signals): 1663 (C=O), 1560 (NH), 1040 and 119 cm^{-1} (RSO_3^-). Found, %: N 13.36. $C_{13}H_{25}N_3O_4S$. Calculated, %: N 13.16.

4-{3-(1,4-Diaza[2.2.2]bicyclo-1-octylium)propionamido}-4-methyltetrahydrothiophene-1,1-dioxide-3-sulfonate (VIIb). Acid (IIIb) (1.42 g, 0.005 mole) was added to a solution of diamine (I) (0.84 g, 0.0075 mole) in water (7 ml) and the mixture maintained at 25°C for 10-15 min. The solution was evaporated, the residue was washed with acetone, and dried in vacuum (2 mm Hg) at 20°C. A product (1.88 g, 83%) was obtained having no C=C bonds or free acidic groups. PMR spectrum (D_2O): 1.57 (3H, s, CH_3C); 2.70 (2H, t, CH_2CON); 3.05-3.26 (6H, m, $NCH_2CH_2N^+$); 3.38-3.73 (6H, N^+CH_2CCON, $CH_2SO_2CH_2$); 3.95-4.02 ppm (1H, d, $CH_2SO_3^-$).

REFERENCES

1. US Patent 4012437; Ref. Zh. Khim., 22S329 (1977).
2. E. N. Zil'berman, V. N. Salov, V. L. Krasnov, and S. Yu. Atopshev, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., **29**, 22 (1986).
3. A. Le Berre and A. Delacroix, Bull. Soc. Chim. Fr., **7-8**, 2404 (1973).
4. A. Gordon and R. Ford, Chemist's Companion [Russian translation], Khimiya, Moscow (1976).
5. M. Chiary, C. Ettori, and P. Righetti, J. Chromatog., **559**, 119 (1991).
6. O. A. Kazantsev, K. V. Shirshin, S. M. Danov, and S. A. Kazakov, Abstracts of First Scientific Technical Conference "Farberovsk Readings 96," Yaroslavl (1996), p. 70.