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Study of Preparation and Properties of Imidazolium Betaines

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To investigate the posibility for the preparation of 1,3-dicarboxyalkyl(benz)imidazolium betaines a number of monosubstituted 1-carboxyalkyl(benz)imidazoles has been prepared (I—X) and their basic *p*Ka value determined. The betaines (XI—XIV) can be prepared only from the imidazole derivatives which had basic (N^3) *p*Ka values above 3—4 *p*Ka units. 1-Substituted benzimidazoles decomposed under reaction conditions employed for quaternization, yielding N,N'-dicarboxyalkyl *o*-phenylenediamines. Dimethylformamide when used as the solvent under highly basic reaction conditions reacted with halogen carboxylic acids giving rise to the formation of betaines of dimethyl-dicarboxyalkyl amines (XV, XVI) and hydrochlorides of dimethyl-carboxyalkyl amines (XVII, XVIII), respectively.

The reaction course of 1,3-disubstitution is briefly discussed, as well as some chemical and physical properties of the betaines are described.

INTRODUCTION

Preparation of imidazolium betaines has been attempted because no systematic studies of this group of compounds could be found in the literature. The only example concerns[1] the preparation of a histidine derivative possessing a betaine structure. It was found[2] that diphosphoimidazoles (DPI) also have betaine structures and a resonance stabilized symmetrical structure of the imidazolium cation has been proposed.[3] However, some further interesting chemical and physical properties, as well as the potential biological activity prompted the authors to investigate more thoroughly this group of imidazolium derivatives.

Preparation of Imidazolium Betaines and Characteristics of N^1,N^3-Substitution in the Imidazole Ring

The betaine compounds listed in Table II may be prepared from unsubstituted imidazoles, or from intermediate 1-carboxyalkyl derivatives (Table I).

For the preparation of symmetrical betaines XI—XIV the most convenient route appears to be isolation of 1-substituted products followed by quaternization (in KOH/ethylcellosolve solution) employing the second mole of ω-halogen carboxylic acid.

A mixture of N^1-substituted and N^1,N^3-disubstituted products was obtained only starting from the unsubstituted imidazoles and ω-halogen carboxylic

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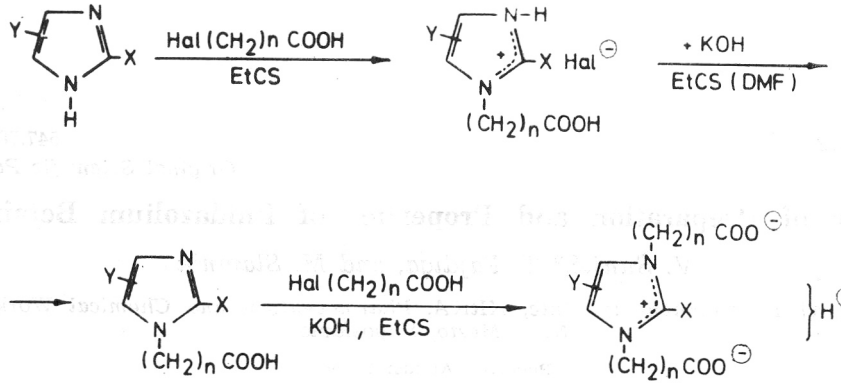
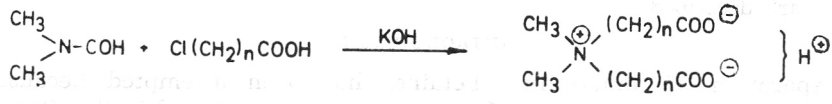


acid in the molar ratio 1 : 2 or more. In attempted quaternization of some benzimidazoles only N^1-monosubstituted products VI—IX could be isolated. Benzimidazolium betaines were unstable species which decompose giving rise to the formation of N,N'-dicarboxyalkyl phenylenediamines XXIII and XXIV. This is the usual reaction path of quaternary benzimidazoles in strongly basic media.[4]

As the most convenient medium for quaternization the solution of potassium hydroxide in ethylcellosolve has been found. Although DMF is mentioned in the literature[7] as a particularly appropriate solvent for quaternization of heterocyclic compounds we have noticed that it reacted with ω-halogen carboxylic acid.



XV n = 1

XVI n = 2

Above 130° C this reaction yielded betaines XV and XVI in about 60—70% yield. However by lowering the molar ratio of potassium hydroxide ammonium salts XVII and XVIII could be isolated.

$(CH_3)_2 \cdot {}^{+}NH(CH_2)_n \cdot COOH/Cl^-$

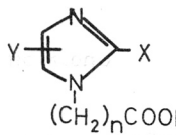
XVII n = 1

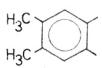
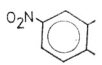
XVIII n = 2

Because of the observed reactivity of DMF for subsequent studies ethylcellosolve, was used as the most convenient solvent. The basic *p*Ka values of compounds I—X have been measured (Table I) in order to obtain a qualitative relation between the basicity of N^3 atom and the reactivity in the quaternization reaction. From the data presented in Tables I and II it can be concluded that stable imidazolium betaines with ω-halogen carboxylic acids can be obtained if the basic *p*Ka value of the reaction site is greater than 3—4 *p*Ka units. This finding is in accordance with the fact that imidazole derivatives with strong electron-withdrawing substituents in the ring, *i. e.*

TABLE I

1-Carboxyalkyl-(benz)imidazoles

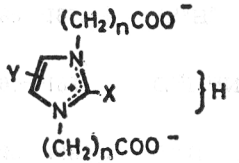


Compd.	n	X	Y	yield %	Recrystn. solvent[a]	M. p. °C	Formula	pKa_2^b	Calc'd			Found		
									C	H	N	C	H	N
I	2	H	H	46.5	A	153—154	$C_6H_8N_2O_2$	7.2	51.41	5.75	19.99	51.24	5.49	20.06
II	2	CH_3	H	49.8	A	123—124	$C_7H_{10}N_2O_2$	8.2	54.53	6.54	18.17	54.76	6.69	18.26
III	2	CH_3	4-Br	74.6	A	199—201	$C_7H_9N_2O_2Br$	4.4	36.07	3.89	12.02	35.94	4.01	11.82
IV	2	CH_3	4,5-Br	82.7	B	224—226	$C_7H_8N_2O_2Br_2$	2.9	26.95	2.58	8.98	27.07	2.89	8.82
V	2	CH_3	4-NO_2	c				1.1						
VI	2	H		70.2	C	147—148	$C_{10}H_{10}N_2O_2$	3.6	63.15	5.31	14.73	63.46	5.45	14.78
VII	2	H		56.4	C	190—192	$C_{12}H_{14}N_2O_2$	3.7	66.04	6.46	12.84	65.90	6.57	12.58
VIII	2	H		6.2	B	189—191	$C_{10}H_9N_3O_4$	3.1	51.07	3.86	17.87	50.78	4.47	18.03
IX	2	CH_3		58.2	C	171—173	$C_{11}H_{12}N_2O_2$	3.9	64.68	5.93	13.72	64.60	5.85	13.49
X	1	CH_3	H			245—247		7.18[d]						

a.) A = cyclohexan/EtOH, B = ethylcelosolve/H_2O, C = EtOH. b.) Protonation of the ring N^3 atom. c.) Described in ref. 5. d.) Measured in ref. 6.

TABLE II

Imidazolium Betaines



Compd.	n	X	Y	yield %	Recrystn. solvent[a]	M. p. °C	Formula	pKa$_1$[b]	Calc'd			Found		
									C	H	N	C	H	N
XI	2	H	H	54	A	205—207	$C_9H_{12}N_2O_4$	4.4	50.94	5.70	13.20	50.84	5.77	13.27
XII	2	CH_3	H	58	A	212—214	$C_{10}H_{114}N_2O_4$	4.3	53.08	6.24	12.39	52.76	5.96	12.68
XIII	2	CH_3	4 (5)-Br	22	A	148—150	$C_{10}H_{13}N_2O_4Br$	4.4	39.36	4.30	9.18	39.44	4.67	8.98
XIV	1	CH_3	H		A	314—315	$C_8H_{10}N_2O_4$	3.9	48.48	5.09	14.14	48.55	5.10	14.32

a.) A = DMSO/EtOH 3 : 1. b.) Ionization of the carboxylic group

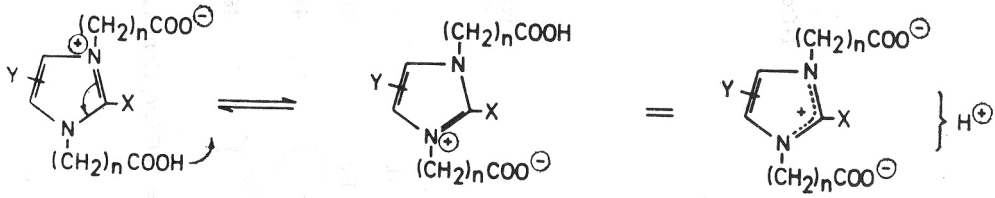
with low basicity of the N^3 atom, can be easily 1-substituted. Namely, 1-substitution of the neutral imidazole ring is an S_N2' reaction[5] where the intermediate addition to N^3 atom preceeds the elimination of the proton at position 1. Hence, the more basic N^3 is the more stable is the quaternary compound so that the reaction stops at this point. Evidence of this is presented in Table III where some products of addition on N^1 of (benz)imidazoles are listed. (Benz)imidazole derivatives of this type are best described as resonance hybrids between structures *A* and *B*.

A. B.

An earlier statement[8] that substitution of imidazoles at position 1 is promoted at higher temperatures at the expense of quaternization as the more exothermic reaction can hardly be accepted. From the previous considerations it is obvious that these two reactions are consecutive rather than paralel. In strongly basic medium the imidazolium anion is present and substitution preceeds quaternization. In this case, however, it is impossible to ascribe the reaction site to any of the two nitrogen atoms because of the symmetrical distribution of the negative charge, recently confirmed by HMO-calculations.[9]

Some Physical and Chemical Properties of Imidazolium Betaines

Betaines XI—XIV are 1,3-disubstituted derivatives of imidazole. The positive charge is distributed on both nitrogen atoms by resonance. The electron delocalisation in the ring is accompanied by prototropy between the two carboxylic groups as shown in the following Scheme.



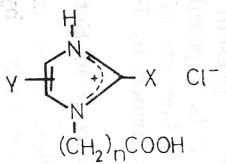
A. B. C.

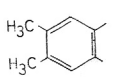
Very strong hydrogen bonding in all betainic compounds has been supported by the infrared spectra.[10] A series of bands caused by hydrogen bonding overlaped all other characteristic frequences in the region 6.2—13μ (~770—1500 cm^{-1}).

The imidazolium cation shows in the UV-region (see Table IV) a B-band which is slightly bathochromically shifted in relation to the uncharged imidazole chromophore.[12,6,11] This is a common feature in the UV-spectra of quaternized nitrogen heterocyclyc compounds,[12] (see Table IV).

TABLE III

1-Carboxyalkyl-(benz)imidazolium-chlorides



Compd.	n	X	Y	yield %	Recrystn. solvent[a]	M. p. °C	Formula	Calc'd %			Found %		
								C	H	N	C	H	N
XIX	1	CH_3	H	52.2	A	293—295	$C_6H_9N_2O_2Cl$	40.80	5.14	15.87	41.25	5.48	16.16
XX	2	H	Br	38.5	B	196—197	$C_7H_{10}N_2O_2BrCl$	31.22	4.72	10.41	31.57	3.85	10.24
XXI	2	H		41.5	C	208—210 dec.	$C_{10}H_{11}N_2O_2Cl$	53.19	4.88	12.37	53.28	5.16	12.06
XXII	2	H		46	C	182—184	$C_{12}H_{15}N_2O_2Cl$	56.58	5.95	10.88	56.69	6.24	10.53

a.) A = EtOH/H_2O (3 : 1), B = EtOH/cyclohexane (2 : 1), C = THF/DMF (4 : 1).

TABLE IV

Characteristic Constants of Some 1-Carboxyalkyl Imidazoles and Related Symmetrical Betaines

Compd.	pKa[a]		UV-VIS λ_{max}; $\varepsilon \times 10^{-3}$	NMR[b] N-$(CH_2)_n$ (integr.)	Compd.	pKa[a]		UV-VIS λ_{max}; $\varepsilon \times 10^{-3}$	NMR[b] N-$(CH_2)_n$ (integr.)
	pKa_1	pKa_2				pKa_1	pKa_2		
I	3.5	7.2	209; 4.23	t. 4.35 (2); t. 2.74 (2)	XI	4.4	—	213; 4.26	t. 4.48 (4); t. 2.92 (4)
II	3.1	8.2	209; 4.88	t. 4.33 (2); t. 2.79 (2)	XII	4.3	—	213; 4.69	t. 4.51 (4); t. 2.90 (4)
III	3.15	4.4	219; 5.82	t. 4.28 (2); t. 2.71 (2)	XIII	4.4	—	227; 5.67	t. 4.46 (4); t. 2.75 (4)
X	2.82	7.18	210; 4.12	s 4.42 (2)	XIV	2.9	—	216; 4.40	s 4.57 (4)

a.) All pKa_1 values belong to an acidic function and pKa_2 values to the basic function (N^3) atom, b.) s-singlet; t-triplet; integr.-number of protons according to integrated area of the peaks.

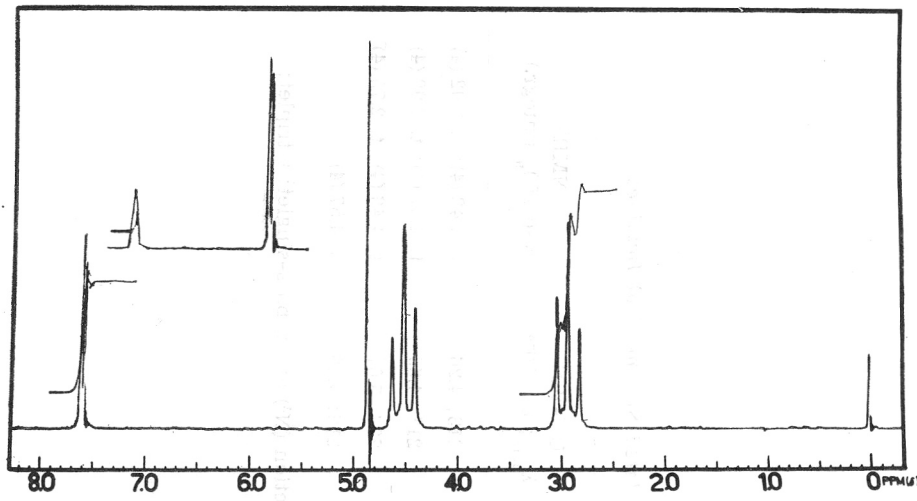
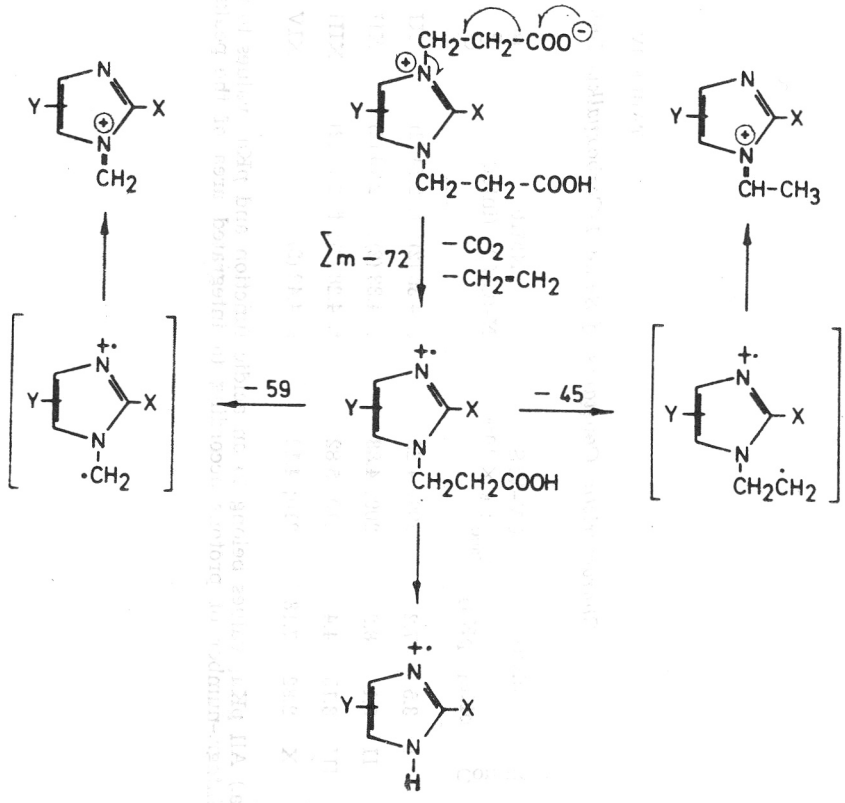


Fig. 1. Nmr spectrum of the compound XI.



NMR spectra furnish further support for the symmetrical structure of betaines (see C). Perfect superposition of the peaks of methylenic protons in the side chains is regularly observed and is exemplified in the spectrum of compound I (Fig. 1). Long-range coupling between the protons in the imidazolium cation of the compound XI ($J_{2,4} = J_{2,5} = 1.9$ cps) is somewhat stronger than in the imidazole itself[13] ($J_{2,4} = J_{2,5} = 1.4$ cps).

Mass spectra offer information which is complementary to that derived from other methods. The fragmentation pattern is presented above, and the spectrum of compound XII in Fig. 2.

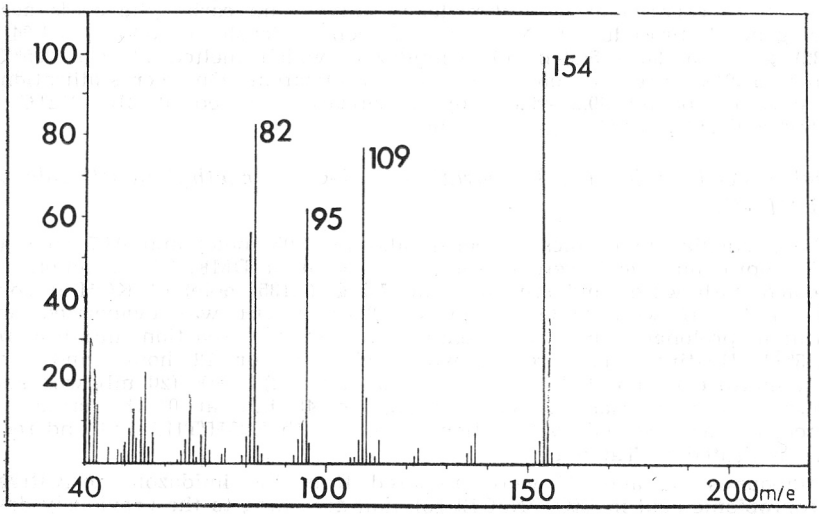


Fig. 2. Mass spectrum of the compound XII.

It is noteworthy that the imidazolium cation possesses appreciable stability, although the loss of aromaticity is reflected in a very low molecular ion peak which is observable only in the low voltage spectra. Further fragmentation of N^1-substituted imidazolium ion corresponds to the principal fragmentation pattern of N^1-substituted imidazoles,[14] *i. e.* a high abundance of the peaks which correspond to the formation of N^1-methylene imidazolium cation and aziridine radical ion could be observed.

EXPERIMENTAL

NMR spectra were obtained on a Varian 60 A Spectrometer. Samples were prepared as 5—10% salutions in D_2O and recorded with DSS (2,2-dimethyl--2-silapenthane-5-sulfonic acid) as internal standard. All UV spectra were recorded on a Perkin-Elmer M 127 Spectrophotometer. Solvents and concentrations were used as indicated in the text. IR spectra were taken on a Perkin-Elmer M-137 Spectrophotometer. Mass spectra were recorded on AEI MS 9 Mass spectrophotometer at 70eV and 150° C source temperature.

pKa Values were measured potentiometrically or spectrophotometrically. In cases where solubility of the substance was sufficient a potentiometric method was prefered. All the potentiometric measurements were performed on the Radiometer pHM 22 apparatus using glass and calomel electrodes. The apparatus was standardized on phthalate (pH = 4.00) and phosphate (pH = 6.86) buffers. The titration flask was specially designed and equipped with a connection for bubbling pure nitrogen through the solution during measurement. For spectrophotometric measurements

Hitachi-Perkin Elmer UV-VIS Spectrophotometer M 139 was used. Other experimental details were described earlier.[5] Melting points were determined on a Böetius-Mikroheiztisch apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory, Department of Organic Chemistry, University of Ljubljana, Ljubljana, Yugoslavia. All compounds confirmed to their IR spectra.

Starting Materials

2-Methyl-4(5)-bromoimidazole (a) and 2-methyl-4,5-dibromoimidazole (b) were obtained according to the procedure described by Pyman.[15] However, the pure compound (b) has m. p. 167—168° C (lit.[15] m. p. 161—162° C). Benzimidazoles were prepared from corresponding *o*-phenylenediamines and carboxylic acids according to the general procedure.[16] Nitration of benzimidazole (HNO_3, $\gamma = 1.64/H_2SO_4$, $\gamma = 1.82$) gave 85—90% 5(6)-nitrobenzimidazole which melted at 200—205° C, and was 97.5—99.0% pure as determined by diazotization. On recrystallization from water pure compound 99.2—99.8% by diazotization melted at 210—212° C (lit.[17,18] m. p. 204° and 205°, resp.), $\lambda_{max} = 299$ mμ.

General Procedure for the Preparation of 1-Carboxyethyl benz(imidazoles) I, II and VI—IX

The particular imidazoles or benzimidazole (0.05 mole) and 0.07 mole (7.6 g.) of β-chloropropionic acid were dissolved in 80 ml of DMF. The reaction mixture was cooled with water and stirred while 7.5 g. (0.135 mole) of KOH dissolved in 60 ml. of MeOH were added dropwise. Then MeOH was evaporized and the evaporation prolonged until the temperature in the reaction mixture reached 140—145° C. Heating under reflux was prolonged for 12 hours and then the reaction mixture evaporated to dryness (0.3 mm. Hg). THF (20 ml) was added to the viscous residual mass. After standing for 48 hrs, at 0° the crude product separated. It was collected by filtration, washed with EtOH/THF 1 : 1 and recrystallized as indicated in Table I.

Compounds III and IV were prepared from the imidazole derivatives and β-chloropropionic acid in EtOH/NaOEt solution according to the previously described procedure.[19]

General Procedure for the Preparation of 1,3-Dicarboxyethyl-Imidazolium Betaines XI—XIII

1-Carboxyethyl-imidazoles I, II or III (0.05 mole), and 0.05 mole (5.4 g.) of β-chloropropionic acid were dissolved in 120 ml of ethylcellosolve and a solution of 15 g. (0.27 mole) KOH in 120 ml. ethylcellosolve was added, dropwise, under stirring at room temperature. The reaction mixture was refluxed for 6 hrs. The solvent was evaporated (0.3 mm. Hg) and the residual hygroscopic mass neutralized with a dry solution of HCl in MeOH. Inorganic salt was filtered off, filtrate evaporated and the residue crystallized by adding 10 ml. of THF/EtOH (1 : 1) and chilling on ice. After recrystallization (solvents listed in Table II) pure products separated very sluggishly so that prolonged cooling was frequently required to obtain the yields given in Table II.

Compound XIV was prepared from X (0.05 mole) and 0.12 mole of chloroacetic acid which were dissolved in 150 ml. ethylcellosolve. To this solution 0.205 mole (11.55 g.) of KOH dissolved in 80 ml. of MeOH was added, dropwise, during 2 hrs. The reaction mixture was stirred and heated on a steambath for 12 hrs, then the inorganic precipitate filtered off and the filtrate evaporated. The residue was crystallized by adding *n*-BuOH and chilling on ice.

Preparation of Compounds XV—XVIII

To prepare compounds XV and XVI 0.416 mole (23.4 g.) of KOH and 0.1 mole of β-chloropropionic or chloroacetic acid were dissolved in 150 ml. of DMF and heated on reflux for 24 hrs. Then the pH was adjusted to 3—3.5 (HCl in MeOH), inorganic salt filtered off and the solvents evaporated *in vacuo*. The oily residue

was crystallized by adding 5 ml. THF and cooling overnight. Further recrystallizations of these compounds caused substantial loss of the material because it crystallized very sluggishly from any solvent mixture employed. The most convenient solvent was found to be EtOH/DMSO (5 : 1).

Compd. XV. M. p. 239—241° C (dec.) (lit. m. p. for hydrochloride 207—208° dec.[20]). NMR: s (6H) 3.18; s (4H) 3.76

Anal. $C_6H_{11}NO_4$ (161.16) calc'd.: C 44.72; H 6.88; N 8.69%
found: C 44.66; H 6.61; N 8.72%

Compd. XVI. M. p. 152—154° C. NMR: s (6H) 3.12; t (4H) 2.79; t (4H) 3.65.

Anal. $C_8H_{15}NO_4$ (189.21) calc'd.: C 50.78; H 7.99; N 7.40%
found: C 50.59; H 7.74; N 7.58%

To prepare compounds XVII and XVIII the same procedure was performed but only 0.165 mole (9.3 g.) of KOH was employed. After the reaction was over the *p*H was adjusted to 1—1.5 (HCl in MeOH).

Compd. XVII. M. p. 190—192° C (lit. m. p. 187—189° C[21]).
NMR: s (6H) 3.09; s (2H) 3.72.

Anal. $C_4H_{10}NO_2Cl$ (127.59) calc'd.: C 47.08; H 7.91; N 10.98%
found: C 46.89; H 7.80; N 10.69%

Compd. XVIII. M. p. 191—193° C. NMR: s (6H); t (2H) 2.73; t (2H) 3.60.

Anal. $C_5H_{12}NO_2Cl$ (153.62) calc'd.: C 39.09; H 7.87; N 9.12%
found: C 38.96; H 7.36; N 9.04%

General Procedure for the Preparation of Compounds XIX—XXII

2-Methylimidazole, 4(5)-bromoimidazole, benzimidazole or 5,6-dimethylbenzimidazole (0.05 mole), chloroacetic or β-chloropropionic acid (0.05 mole) and NaOAc (0.05 mole) in 150 ml. of ethylcellosolve were stirred and heated on a steambath for 24 hrs. Then undissolved reagents were filtered off, the filtrate was evaporated *in vacuo* and the residue was crystallized on ice by adding 5—6 ml. of the solvent mixtures as given in Table III.

N,N'-Dicarboxyethyl-1,2-diaminobenzene (XXIII)

Compound VI (0.95 g.; 5 mmols) and β-chloropropionic acid (0.54 g;. 5 mmols were dissolved in 10 ml ethylcellosolve and a solution of 0.85 g. (15 mmols) of KOH in 10 ml. of ethylcellosolve were added dropwise, and thereafter heated on an oil-bath at 110° C and stirred for 2 hrs. The reaction mixture was dilluted with 200 ml. water and extracted with 4 × 100 ml. ether. The water solution was neutralized to pH 6.5 with acetic acid and extracted with ethylacetate (3 × 100 ml.). Evaporation of the dried organic phase gave further 0.2—0.3 g. of tarry substance from which 0.1—0.15 g. of unreacted VI could be recovered after recrystallization from ether/EtOH (2 : 1). The remaining water solution was acidified with 5% hydrochloric acid to pH 3—3.5 and extracted once more with ethylacetate (3 × 100 ml). The residue obtained on evaporation of the organic phase, was dissolved in 2 ml. of acetic acid and purified by chromatography on a short column of silicagel (20 g.) using benzene/ethylacetate (3 : 2) as eluent. On evaporation of the main fraction there remained 0.4—0.45 g. of yellow-brownish crystalls of XXIII — m. p. 96—102°, which were further crystallized from ethylacetate/ethanol (3 : 1). The pure substance melted at 104—106°;

Anal. $C_{12}H_{16}N_2O_4$ (252.1) calc'd.: C 57.19; H 6.38; N 11.12%
found: C 56.96; H 6.17; N 11.39%

The same compound (XXIII) was obtained from IX, using the same procedure as described for VI. From 1.02 g. (5 milimols) of IX only 0.15 g. chromatographically purified XXIII could be obtained. Mixed melting point of two samples exhibited no depresion and their infrared spectra were identical (3440, 2890 broad, 1595, 1570, 1510, 1405, 1395, 1280, 1270, 875, 740 $cm.^{-1}$ only strong bands are cited).

N,N'-Dicarboxyethyl-4-nitro-1,2-diaminobenzene (XXIV)

Compound VIII (1.68 g.; 5 milimoles) and 0.54 g. (5 milimoles of β-chloropropionic acid were dissolved in 15 ml. of ethylcellosolve and then solution of 0.85 g. (15 milimoles) of KOH in 10 ml. of ethylcellosolve was added. The reaction mixture was stirred and heated on an oil-bath at 110° C for 3 hrs. Then 300 ml. of water was added and resulting basic water solution extracted with ether (4 × 100 ml.). The ethereal extracts were discarded, and the aqueous solution was repeatedly extracted, firstly at *p*H 6.5 (adjusted with HAc) with 3 × 100 ml. of ethylacetate and after acidification to pH 3—3.5 (5% HCl) once again with 3 × 100 ml. of ethylacetate. The extract at *p*H 6.5 gave after evaporation brownish, partially crystallizing residue from which upon addition of ether/ethanol (9 : 1) mixture, 0.4—0.6 g. of unchanged VIII could be isolated The extract at pH 3—3.5 was evaporated and the residue chromatographed on the column of silicagel (30 g.) using benzene/ether/ethylacetate (1 : 1 : 8) as the eluent. Evaporation of the main fraction gave 0.25—0.3 g. yellow-brownish crystals, which when moist soon darkened if exposed to the air. After recrystallization from ethylacetate the pure compound decomposed above 160—165° C. IR spectrum: 2920 broad, 2600 broad, 1610, 1590, 1560, 1540, 1440, 1375, 1330, 1105, 810, 745, 735 cm.$^{-1}$).

Anal. $C_{12}H_{15}N_3O_6$ (297.12) calc'd.: C 48.51; H 5.09; N 14.14%
found: C 48.14; H 4.84; N 14.43%

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IZVOD

Studij preparacije i svojstava imidazolium betaina

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Da bismo ispitali mogućnost priprave 1,3-dikarboksialkil (benz)imidazolijevih betaina, pripravili smo niz monosupstituiranih 1-karboksialkil benzimidazola (I—X) i odredili njihovu bazičnu *p*Ka vrijednost. Betaine (XI—XIV) je bilo moguće pripraviti samo iz derivata imidazola čija je bazična (N^3) *p*Ka vrijednost bila iznad cca 3—4 *p*Ka jedinice. 1-Supstituirani benzimidazoli raspadali su se u primijenjenim reakcionim uvjetima kvarternizacije, dajući N,N'-dikarboksialkil-*o*-fenilendiamine XXIII i XXIV. Zapaženo je da dimetilformamid u jako baznom mediju reagira s halogen karbonskim kiselinama, dajući betaine dimetildikarboksialkilamina (XV, XVI), ili hidroklorida dimetil-karboksialkilamina (XVII, XVIII).

Tok reakcija 1,3-disupstitucije je ukratko diskutiran, kao i neka zanimljivija kemijska i fizikalna svojstva opisanih betaina.

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