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Note

Zwitterion Structure in Some 1-Carboxymethylimidazoles and Their Analgetic Activity*

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The ratio (R) of zwitterions to neutral molecule was determined for the derivatives of 1-carboxymethylimidazole. 1-Carboxymethylimidazole (I) and its 2-methyl derivate (III) were found to be entirely in the form of zwitterion. Of the two 1-carboxymethyl-2-methyl-nitroimidazoles (V and VII) the 4-nitroisomer (V) possesses no zwitterionic structure, but the 5-nitroisomer (VII) was found to be about 65% in the zwitterionic form. The results obtained are discussed in view of the significant analgetic and sedative effect observed with the compounds having a zwitterionic structure.

4-(5)-Carboxymethylimidazole, or imidazole acetic acid (IMA) exhibits pronounced pharmacological activities[1–3]. Recently, its analgetic and sedative activity was interpreted as a consequence of the fact that its molecular structure contains the carboxylic group bonded by an intramolecular hydrogen bond to the N^3 atom in the ring[4]. Following the mentioned postulation it could be proposed that derivatives of 1-carboxymethylimidazole have a neutral chelated form.

However, knowing the high basicity of the imidazole ring (*p*Ka = 6.95; 6.89[5]) and its inductive acid strengthening (electron-attracting) effect on the α-carboxylic group we have assumed that the zwitterion structure in the solution of IMA could be of greater importance than the unionized, chelated form. This assumption is based on an earlier observation[6] that the imidazole-4(5)-carboxylic acid is about 98% in a zwitterionic form (R = 57).

One of the preliminary tests for the qualitative assessment of the structure of the zwitterion in aromatic amino-carboxylic acids[7] and pyridine carboxylic acids[8] is the hypsochromic shift of the K-band in the UV spectrum of carboxylic group on addition of alkali. However, UV spectra of the compounds I, II, V and VII remained unchanged at various *p*H's. This is probably caused by an insulation effect of the CH_2 group, which hinders conjugative interaction. Only a weak ($\varepsilon \cong 60$) R-band of a carboxylic group at 204—210 nm has been observed, which was regularly superimposed by a B-band of the imidazole ring[9]. The K-band of the nitroimidazole chromophore at 300—320 nm[10] remained unchanged.

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Therefore, we have measured *p*Ka values and estimated the ratio (R) of zwitterions to neutral molecule for the compounds I, III, V, and VII (Table I). The R values were calculated according to Ebert's equation[7,11]; R = antilog ($pK_{OMe} - pK_z$) — 1, where pK_{OMe} is pK_a of the corresponding methyl ester, and pK_z is the lower pK_a of the zwitterion.

TABLE I

pKa and R values of some derivatives of 1-carboxymethylimidazole[a]

No.	Compound	pK'_a	pK''_a	pK'''_a	R	Analgetic activity[b]
I	1-Carboxymethylimidazole	2.66	6.64		28.089	++
II	1-Carbomethoxymethylimidazole			7.12		
III	1-Carboxymethyl-2-methylimidazole	2.82	7.18		121.278	++
IV	1-Carbomethoxymethyl-2-methylimidazole			7.90		
V	1-Carboxymethyl-2-methyl-4-nitroimidazole	0.20		1.94		—
VI	1-Carbomethoxymethyl-2-methyl-4-nitromidazole		0.44			
VII	1-Carboxymethyl-2-methyl-5-nitroimidazole	2.06	2.40		1.9	±
VIII	1-Carbomethoxymethyl-2-methyl-5-nitroimidazole			2.52		

[a] The values pK'_a, pK''_a etc., are given, by convention (ref. 7), in order of increasing pK_a.
[b] Measured by the hot plate method (ref. 12) at doses 30—50 mg/kg. Data in reference to codeine phosphate as a standard; + means effect prolonging response time of animal 50% above that of standard; ± 10% above that of standard; —, no observable effect.

The compounds I and III are to a high degree in the zwitterionic form, and accordingly we assume that the carboxylic group in IMA could not be chelated as it was previously stated[4]. The assignment of the *p*Ka to a given basic or acidic group in the compounds V and VII have been performed according to the data[10] obtained earlier for the pK_a values of a basic group in the 1-substituted nitroimidazoles. It can be concluded that the compound V is not a zwitterion but an amphoteric substance because *p*Ka value of its carboxylic group is numerically higher than that of the basic group[7].

Compound VII proved to be *ca.* 65% in the zwitterionic form.

Our pharmacological tests revealed that derivatives of 1-carboxymethylimidazole possesses high pharmacological activity (analgetic, hypnotic and muscular-relaxant). Compounds I and II exhibited pronounced analgetic activity, and the same activity has been observed with compound VII. Compound V, which has no zwitterionic structure, proved to be analgetically inactive. These qualitative data suggest that there could be some correlation between zwitterionic structure and analgetic activity of these compounds.

EXPERIMENTAL

All melting points are determined on Boetius-Mikroheiztisch apparatus, F. Küstner/Dresden and are uncorrected. UV spectra were run on the Perkin-Elmer UV 129 Spectrophotometer. Potentiometric titrations were performed at 25 °C in 0.025 *M* water solutions deaerated with nitrogen before and during titration. Compounds VI

and VIII were titrated in 0.01 *M* solutions because of their lower solubility. The equivalency point was determined from the slope of the titration curve. *p*H measurements were performed using glass and standard calomel (SCE) electrodes. Potassium biphthalate buffer (*p*H = 4.00) and borate buffer (*p*H = 9.18) were used as standards.

Compounds V and VII were prepared according to the procedure previously described[13]. Compounds I and VIII were prepared following the methods mentioned in ref. 14 and 15, respectively.

Analgetic activity was evaluated by the standard hot plate method used also in our previous work[16].

1-Carbomethoxymethylimidazole (II)

3.15 g. (0.025 mole) of the compound I were dissolved in 25 ml. of methanol saturated with dry HCl. The solution was heated on the steam bath for 2 hrs., cooled and neutralized with methanolic NaOH to *p*H 6. The solvent was evaporated *in vacuo,* the residue dissolved in 30 ml. of water and extracted with EtAc(3×30 ml). The combined extracts were dried (Na_2SO_4) and the solvent evaporated *in vacuo.* The oily residue was fractionated at 0.1 mmHg yielding 2.8 g. of (II) b. p. 126—132° C/0.1 mmHg.

Picrate was prepared, and recrystallized from methanol — m. p. 148—149 °C.

Anal. $C_{18}H_9N_5O_9$ (321.23) calc'd.: C 41.13; H 2.83; N 22.80%
found: C 40.96; H 2.70; N 21.67%

1-Carboxymethyl-2-methylimidazole (III)

Compound III was prepared from 8.2 g. (0.1 mole) of 2-methylimidazole and 18.3 g. (0.15 mole) of ethyl α-chloroacetate in 28 g. (35 ml) of *iso*-butanol. The reaction mixture was refluxed for 4 hours, and after evaporation of the solvent the residue was hydrolized with 30 ml. of 4 *N* NaOH on a steam bath. Acidification afforded 9. 1 g. (64%) of crude III m. p. 314—320 °C. On recrystallization from water the substance melted at 322—324 °C with decomposition.

Anal. $C_6H_8N_2O_2$ (140.13) calc'd.: C 51.43; H 5.76; N 20.00%
found: C 51.14; H 5.56; N 19.79%

1-Carbomethoxymethyl-2-methylimidazole (IV)

According to the procedure described for II, from 3.5 g. (0.025 mole) of 1-carboxymethyl-2-methylimidazole, 2.35 g. (60.8%) of IV was obtained. The crude product was purified by fractionation; an oily substance was obtained, b. p. 134—140°C/0.08—0.1 mmHg.

Anal. $C_7H_{10}N_2O_2$ (154.17) calc'd.: C 54.53; H 6.54; N 18.17%
found: C 54.45; H 6.87; N 18.08%

1-Carbomethoxymethyl-2-methyl-4-nitroimidazole (VI)

This ester was prepared from compound V[13] in the same way as described for compound II. After evaporation of the solvent the residue was slurried in water and the crude VI was filtered off, m. p. 138—141 °C (yield 72%). On recrystallization from water the substance, m. p. 141—142 °C was obtained.

Anal. $C_7H_9N_3O_4$ (199.17) calc'd.: C 42.21; H 4.56; N 21.10%
found: C 41.97; H 4.32; N 21.33%

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IZVOD

Struktura dipolnog iona u nekim 1-karboksimetilimidazolima i njihova analgetska aktivnost

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Na osnovi mjerenja pK_a određen je omjer (R) dipolnog iona prema neutralnoj molekuli za četiri derivata 1-karboksimetilimidazola. Nađeno je da su 1-karboksimetilimidazol (I) i njegov 2-metil derivat (III) pretežno u obliku dipolnog iona. Od dva izomerna 1-karboksimetil-2-metil-4 i 5-nitroimidazola (V) i (VII) spoj V se ne nalazi u obliku dipolnog iona dok je spoj VII *cca* 65% u tom obliku. Dobiveni rezultati su diskutirani u odnosu na ranije zapaženo analgetsko i sedativno djelovanje spojeva iz ove grupe.

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