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Reaction of β-Iminoalcohols with Sulfur Dioxide. Synthesis of (±)-(2-Hydroxyalkylamino)phenyl(isopropyl)-methanesulfonic Acids

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Abstract—Reactions of 2-(*N*-isopropylidene)amino-2-methylpropanol, 2-(*N*-benzylidene)-, and 2-(*N*-isopropylidene)aminoethanols with sulfur dioxide in aqueous ethanol medium produce (±)-(2-hydroxyalkylamino)-phenyl(isopropyl)methanesulfonic acids. Structure of (±)-(2-hydroxyethylamino)phenylmethanesulfonic acid was determined by X-ray diffraction method.

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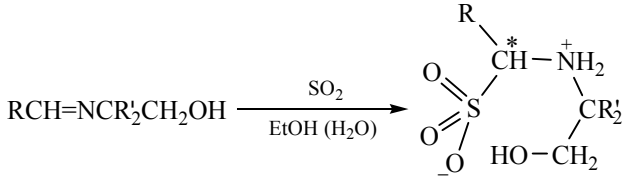
α-Aminomethanesulfonic acids are known already over 100 years [1]. Being structural analogues of aminocarboxylic acids, in some cases they display sufficiently high biological activity. Aminomethanesulfonic acids and their salts exhibit antimitotic [2–4], cytostatic and antitumor activities [5], bactericidal and chlamydiostatic actions [6]. Some β-hydroxyalkyl-α-aminomethanesulfonic acids and their salts can be used as bactericides, insecticides, and germicides. Some copper and mercury β-hydroxyalkyl-α-aminomethanesulfonates show antiparasitic activity [7].

Procedures for syntheses of α-aminometanesulfonic acids and their salts were described. Sodium α-aminomethanesulfonates were synthesized by the reaction of azomethines with sodium bisulfate in water [2, 8, 9], by treating of a mixture of aldehyde and aromatic amine with sulfur dioxide in a diluted solution of sodium hydroxide [2, 3] or with sodium bisulfate directly in water [10], or by reaction of the initial amine and sodium α-oxymethansulfonate in aqueous medium [2, 4, 5, 8]. Amine salts of α-aminomethanesulfonic acids were obtained by hydrolysis of aminomethanesulfonamides forming on treating benzalmethyl(phenyl)amines with sulfur dioxide in the presence of alkylamine [6, 11, 12] or by treating of mixture of 1 mol of aromatic aldehyde and 2 mol of aniline with sulfur dioxide in the alcohol medium [13].

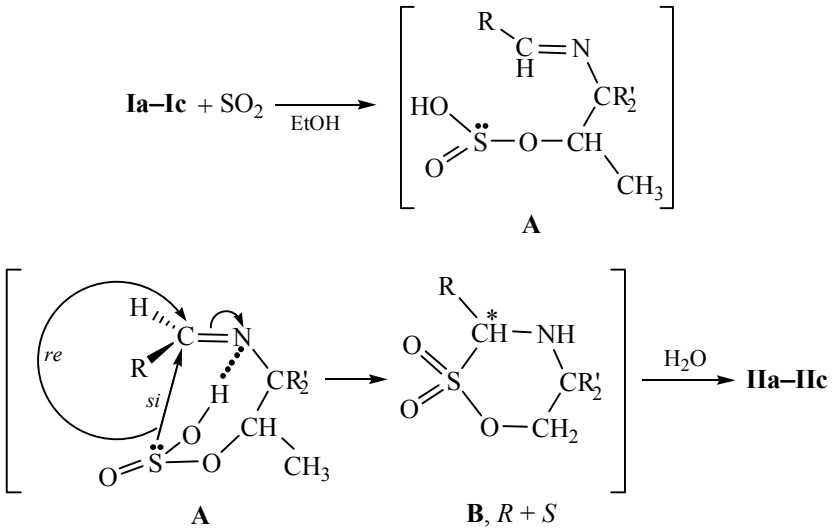
Sodium β-hydroxyalkyl-α-aminomethanesulfonates were prepared by the reaction of α-oxymethanesulfonate with aminoalcohols [7, 14] or by oxazole ring opening in 2,3,5,6-tetrahydro-10bH-oxazolo[2,3-a]isoquinoline under the action of sodium bisulfate [15]. Achiral 2-hydroxyethyl-α-aminomethanesulfonic acid is one of examples of free acid of this series. It was obtained by the action of sulfur dioxide on the condensation product of formaldehyde and monoethanolamine [16].

Until the present time the free β-hydroxyethyl-α-aminomethanesulfonic acids having a chiral center were not described. In this work we describe the method of synthesis of (±)-(2-hydroxyalkylamino) phenyl(isopropyl)methanesulfonic acids (**IIa–IIc)** by reaction of iminoalcohols **Ia–Ic** with sulfur dioxide in rectified ethanol medium. 2-(*N*-Benzylidene)aminoethanol (**Ia)**, 2-(*N*-isopropylidene)aminoethanol (**Ib**) and 2-(*N*-isopropylidene)amino-2-methylpropanol (**Ic**) were chosen as the starting materials. This process may be represented by the following scheme:

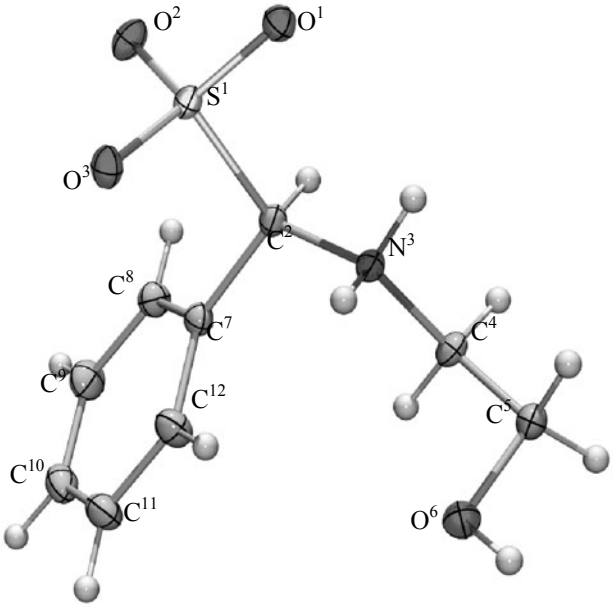


Ia–Ic **IIa–IIc**

R = Ph, R' = H (**a**); R = *i*-Pr, R' = H (**b**), Me (**c**).



Initially, the adduct **A,** acidic alkylsulfite, forms through sulfur dioxide insertion into the bond O-H [17]. Further the racemic adduct **B** forms as a result of hydrogen bond N···H formation and *re*- and *si*-attack of the sulfur atom on the electron-deficient azomethine carbon atom followed by the ring closure. The latter transforms into the racemic β-hydroxyethyl-α-aminomethanesulfonic acid **IIa**–**IIc** under the action of water contained in the rectified ethanol.



Molecular structure of (±)-(2-hydroxyethylamino)-phenylmethanesulfonic acid (**IIa**). The selected bond lengths, Å: S^1–O^2 1.4497(6); S^1–O^3 1.4534(6); S^1–O^1 1.4647(6); S^1-C^2 1.8207(7); C^2–N^3 1.4927(10); C^2–C^7 1.5034(11); N^3–C^4 1.5040(10); C^4–C^5 1.5041(12); C^5–O^6 1.4212(11).

Structure of (±)-(2-hydroxyethylamino)phenylmethanesulfonic acid **IIa** was determined by X-ray diffraction analysis (Fig. 1).

The ^{1}H NMR spectra of α-aminomethanesulfonic acids **IIa–IIc** contain characteristic signals originating from methine group protons bonded to the anion SO_3^- at 5.5 (singlet, **IIa**), 4.16 ($^3J_{HH}$ 5.14 Hz) and 4.18 ppm ($^3J_{HH}$ 5.14 Hz) (doublets, **IIb** and **IIc**). The signals of protons of diastereotopic methyl groups of isopropyl radical of α-aminoisopropylmethanesulfonates **IIb** and **IIc** appear in the spectrum as two doublets at δ 1.02 and 1.05 ppm ($^3J_{HH}$ 6.97 Hz) and 1.00 and 1.16 ppm ($^3J_{HH}$ 6.97 Hz) respectively.

In the mass spectrum (electron impact) of **IIa** and **IIb** the peaks belonging to the molecular ions ($M^{+\cdot}$) of molecule with the structure **IIa** and **IIb** are absent that is probably connected with the branched structure of **IIa** and **IIb** which essentially destabilizes peak of ion $M^{+\cdot}$. The first stage of the molecule **IIa** and **IIb** fragmentation at electron impact is due to C–S bond cleavage with the charge localizing on the nitrogen-containing fragment. This process is accompanied with migration of one hydrogen atom to the neutral fragment. This results in appearance of the ion peaks *m/z* 150 and 116 in the spectrum of **IIa** and **IIb** respectively. Evidently the presence of other fragment ions with the low *m/z* values in the mass-spectra of **IIa** and **IIb** is caused by the consecutive fragmentation of the mentioned above ions at electron impact. The

assumed composition of ions is given in the experimental part.

EXPERIMENTAL

The IR spectra were recorded on a Vector-22 IR-Fourier spectrometer (Bruker) in the range of 400–4000 cm^{-1} (KBr, pellets). The ^1H NMR spectra were registered on an Avance-600 spectrometer (600 MHz), as internal reference served the residual protons of D_2O, $CDCl_3$, CD_3OD. The mass spectra (electron impact) were obtained on a TRACE MS Finnigan MAT device (70 eV) at 200°C. The system of direct admission into the ions source was used. The ampule-evaporator was heated from 35 to 150°C at a rate 35°C/min. The processing of mass spectral data was made using Xcalibur program.

The initial 2-(*N*-benzylidene)- and 2-(*N*-isopropylidene)aminoethanols **Ia** and **Ib** were prepared by known procedures from 1,2-aminoethanol and benzaldehyde [18] and isobutyric aldehyde [19] respectively.

2-(*N*-Isopropylidene)amine-2-methylpropanol (Ic)/2-isopropyl-4,4-dimethyloxazolidine (Ic'). To a solution of 5.9 g of 2-methyl-2-amino-1-propanol in 10 ml of anhydrous diethyl ether was added a solution of 4.8 g of isobutyric aldehyde in 10 ml of anhydrous diethyl ether under stirring at 15–20°C. After 2 h 2 g of sodium chloride was added to this mixture. Then the mixture was decanted and concentrated in a water-jet pump vacuum. The residue was distilled. Yield 8.1 g (85.4%), colorless liquid, bp 68–70°C (15 mm Hg), n_D^{20} 1.4300. ^1H NMR spectrum (the ratio **Ic**:**Ic'** = 1:35) (600 MHz, CD_3OD), δ, ppm: **Ic,** 1.09 d [6H, $(CH_3)_2CH$, $^3J_{HH}$ 7.0 Hz], 1.15 s [6H, $(CH_3)_2C$], 2.41–2.50 m [1H, $(CH_3)_2CH$], 3.41 s (2H, CH_2), 7.53 d (1H, =CH, $^3J_{HH}$ 6.6 Hz); **Ic'**, 0.99 d and 1.01 d [3H + 3H, $(CH_3)_2CH$, $^3J_{HH}$ 6.8 Hz], 1.20 s and 1.29 s [3H + 3H, $(CH_3)_2C$], 1.72–1.81 m [1H, $(CH_3)_2CH$], 3.35 d and 3.53 d (H + H, CH^aH^b, $^2J_{HH}$ 7.3 Hz), 4.24 d (1H, NCHO, $^3J_{HH}$ 6.2 Hz).

(±)-(2-Hydroxyethylamino)phenylmethanesulfonic acid (IIa). Throug a solution of 2.98 g 2-(*N*-benzylidene)aminoethanol **Ia** in 15 ml of ethanol sulfur dioxide was bubbled at 15–20°C to pH 4–5. The reaction mixture was kept overnight. At the next day the precipitate was filtered off. Yield 4.2 g (90.9%), white fine-crystalline powder, mp 86–87°C (methanol). ^1H NMR spectrum (600 MHz, D_2O), δ, ppm: 3.12 t (2H, CH_2N, $^3J_{HH}$ 5.5 Hz), 3.80 t (2H, CH_2O, $^3J_{HH}$ 5.5 Hz), 5.5 s (1H, CH), 7.43–7.45 m (3H) and 7.54–7.57 m (2H) (C_6H_5). Mass spectrum, *m/z* (%): 151 (2.1) 150(19.4) $[C_9H_{12}NO]^+$,[1] 149 (26.7) $[C_9H_{11}NO]^+$, 121 (17.4) $[C_8H_{11}N]^+$, 107 (2.2) $[C_7H_9N]^+$, 106 (19.9) $[C_7H_8N]^+$, 105 (34.5) $[C_7H_7N]^+$, 92 (40.0) $[C_7H_8]^+$, 91(100.0) $[C_7H_7]^+$, 77(47.4) $[C_6H_5]^+$, 51 (42.0) $[C_4H_3]^+$, 64(47.0) $[SO_2]^+$, 45 (14.1) $[C_2H_5O]^+$, 44 (6.9) $[C_2H_6N]^+$. Found, %: C 46.06; H 5.07; N 6.16; S 13.59. $C_9H_{13}NO_4S$. Calculated, %: C 46.75; H 5.63; N 6.06; S 13.85.

(±)-(2-Hydroxyethylamino)isopropylmethanesulfonic acid (IIb) was prepared similarly from 4.6 g of 2-(*N*-isopropylidene)aminoethanol **Ib**. Yield 7.1 g (90.1%), mp 98–100°C. ^1H NMR spectrum (600 MHz, D_2O), δ, ppm: 1.02 d and 1.05 d [3H + 3H, $(CH_3)_2CH$, $^3J_{HH}$ 7.0 Hz], 2.12–2.21 m [1H, $CH(CH_3)_2$], 3.13 t (2H, CH_2N, $^3J_{HH}$ 5.5 Hz), 3.80 t (2H, CH_2O, $^3J_{HH}$ 5.5 Hz], 4.21 d (1H, $CHSO_3$, $^3J_{HH}$ 5.2). Mass spectrum, *m/z* (%): 117 (0.5) 116 (4.1) $[C_6H_{14}NO]^+$,[1] 85 (11.1) $[C_5H_{11}N]^+$, 84 (70.7) $[C_5H_{10}N]^+$, 73 (11.5) $[C_4H_{11}N]^+$, 72 (100.0) $[C_4H_{10}N]^+$, 64 (56.1) $[SO_2]^+$, 45 (75.8) $[C_2H_5O]^+$, 44(54.8) $[C_2H_6N]^+$. Found, %: C 36.36; H 7.47; N 6.91; S 16.04. $C_6H_{15}NO_4S$. Calculated, %: C 36.55; H 7.61; N 7.11; S 16.24.

(±)-(2-Hydroxy-1,1-dimethylethylamino)isopropylmethanesulfonic acid (IIc) was prepared similarly from 2.86 g of 2-(*N*-isopropylidene)amino-2-methylpropanol **Ic**. Yield 3.9 g (86.7%), mp 87–89°C. ^1H NMR spectrum (600 MHz, D_2O), δ, ppm: 1.00 d and 1.04 d [2×3H, $(CH_3)_2CH$, $^3J_{HH}$ 7.0], 1.29 s [6H, $C(CH_3)_2$], 2.11–2.19 m [1H, $CH(CH_3)_2$], 3.53 s (2H, CH_2), 4.18 d (H, SCHN, $^3J_{HH}$ 5.2 Hz). Found, %: C 42.53; H 8.32; N 6.08; S 14.11. $C_8H_{19}NO_4S$. Calculated, %: C 42.67; H 8.44; N 6.22; S 14.22.

X-Ray structural analysis of compound **IIa** was performed on an automatic diffractometer Bruker AXS Kappa APEX II CCD (λMoK_α, graphite monochromator, θ ≤ 33.2°) at –120°C using APEX2 (APEX2 v2008. 6-1, Bruker AXS) [20] and SAINT (Bruker, 2004) programs [21].Crystals are monoclinic: $C_9H_{13}NO_4S$, space group $P2_1/n$, the cell parameters at –120°C are as follows: *a* 11.5262(3) Å, *b* 5.6582(2) Å, *c* 16.2319(5) Å, β 105.464(1)°, *V* 1020.28(5) $Å^3$, *Z* 4, d_{calc} 1.506 g cm^{-3}. Intensities of 30682 reflections were measured, from which 3908 were independent (R_{int} = 0.020). Empirical accounting for extinction was done using SADABS version 2.10 (Sheldrick, Bruker AXS

[1] The peaks are given for ions containing the most abundant isotopes.

Inc., 2002) program [22]. Structure was solved by the direct method using SHELXS-97 program [23] and refined using SHELXL-97 program [24]. The final values of divergence factors were R 0.029, R_w 0.081 for 3908 independent reflections with $F^2 \geq 2\sigma$. Atomic coordinates and their thermal parameters are deposited in the Cambridge Data-base of X-ray Structural Data, no. CCDC 735633.

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