ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 4, pp. 633–635. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © I.A. Tokareva, I.A. Dorofeev, L.V. Klyba, L.G. Shagun, M.G. Voronkov, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 4, pp. 646–648.

SHORT COMMUNICATIONS

Reaction of 2-Sulfanylbenzoic Acid with 3,3-Dibromobutane-2-thione as a Route to Benzoxathiepine Derivatives

I. A. Tokareva, I. A. Dorofeev, L. V. Klyba, L. G. Shagun, and M. G. Voronkov

Favorskii Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia
e-mail: shag@irioch.irk.ru

Received July 16, 2008

DOI: 10.1134/S1070428009040319

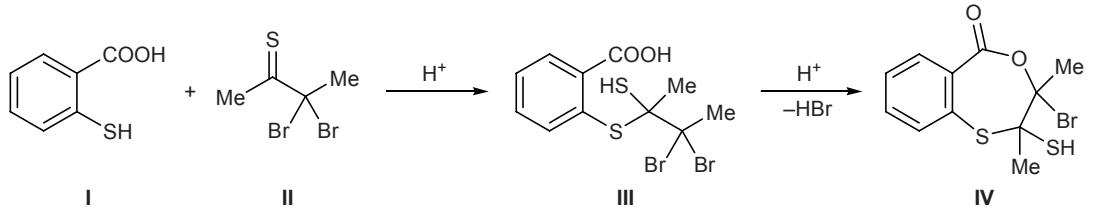
Benzoxathiepine derivatives exhibit strong and specific biological activity [1]. Up to now, two general procedures for their synthesis were reported, starting from cinnamic acid and 2-sulfanylphenol or from 2-sulfanylbenzoic acid and phenyloxirane [2]. Both these procedures include a number of steps. The results of our systematic studies in the field of synthesis and properties of α-haloalkanethiones [3] prompted us to examine the possibility of using 3,3-dibromobutane-2-thione [4] as starting compound in a novel synthesis of benzoxathiepine derivatives. We thus succeeded in obtaining previously unknown benzoxathiepine derivatives having reactive sulfanyl group and bromine atom in one preparative step.

The reaction of 2-sulfanylbenzoic acid (**I**) with 3,3-dibromobutane-2-thione (**II**) in a solution of hydrogen chloride in diethyl ether at –40°C afforded 3-bromo-2,3-dimethyl-2-sulfanyl-2,3-dihydro-5*H*-4,1-benzoxathiepin-5-one (**IV**) in 70% yield (Scheme 1). The mass spectrum of the reaction mixture contained a peak with *m*/*z* 400 which was assigned to the molecular ion of intermediate **III**. Presumably, the heterocyclization process begins with addition of the SH group in acid **I** at the thiocarbonyl group of **II**, and the subsequent intramolecular condensation of intermediate adduct **III** leads to benzoxathiepine **IV** via elimination of hydrogen bromide.

The structure of 3-bromo-2,3-dimethyl-2-sulfanyl-2,3-dihydro-5*H*-4,1-benzoxathiepin-5-one (**IV**) was proved by ^{1}H and ^{13}C NMR, IR, and mass spectra. In the ^{1}H and ^{13}C NMR spectra of **IV**, signals from the SH proton (δ 2.06 ppm) and carbonyl carbon atom (δ_C 167.48 ppm) are displaced upfield relative the corresponding signals of initial acid **I** (δ 3.31 ppm, δ_C 169.82 ppm). The S–H stretching vibration band in the IR spectrum of **IV** (2563 cm^{-1}) appears at higher frequencies as compared to acid **I** (2517 cm^{-1}).

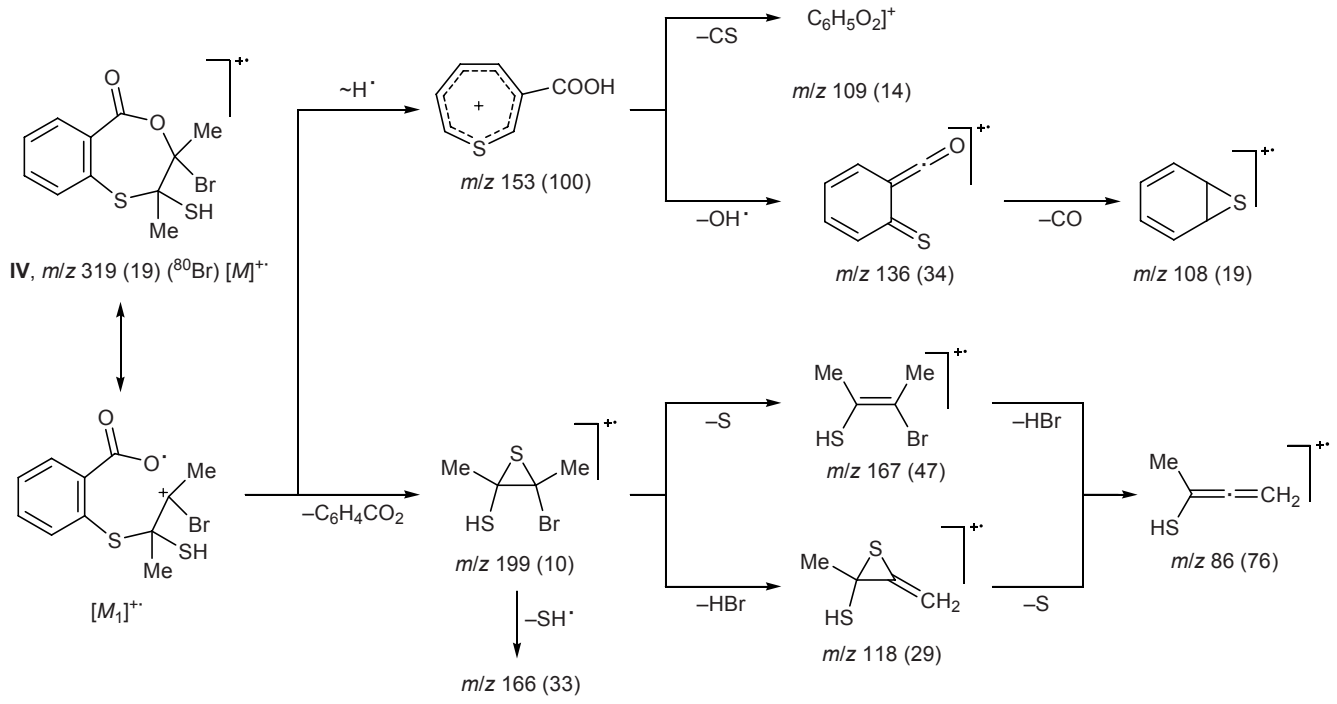
The mass spectrum of compound **IV** contained the molecular ion peak $[M]^{+\cdot}$ with a fairly high intensity, *m*/*z* 319 (I_{rel} 19%, ^{80}Br). The main fragment ions originate from cleavage of the C^3–O bond and both C–S bonds. Most probably, the molecular ion undergoes isomerization into structure $[M_1]^{+\cdot}$ with separated cationic and radical centers [5] (Scheme 2). The main fragmentation pathway is determined by the position of the radical center; it involves cleavage of the C^2–S bond, which is accompanied by migration of hydrogen atom to give ion with *m*/*z* 153 as the most abundant ion in the spectrum. Its stability is rationalized by formation of thiatropylium structure typical of benzene

Scheme 1.



I **II** **III** **IV**

Scheme 2.



derivatives [6]. The subsequent decomposition via elimination of C=S fragment or hydroxyl radical leads to ions with *m*/*z* 109 and 136, respectively. The structure of the latter was proved by analysis of metastable ions in the fragmentation of 3-phenyl-4,1-benzoxathiepin-5-one [1].

The second pathway of fragmentation of $[M_1]^{+\cdot}$ may be regarded as charge-controlled. It involves cleavage of the C^1–S bond so that the positive charge and unpaired electron are localized on the sulfur-containing fragment, in keeping with the data of [7]. Odd-electron 3-bromo-2,3-dimethyl-2-thiiranethiol radical cation thus formed, *m*/*z* 199 (10%), decomposes via successive elimination of HBr and sulfur atom or vice versa to give 2-methyl-3-methylidene-2-thiiranethiol (*m*/*z* 118, I_{rel} 29%), 1-methylpropa-1,2-diene-1-thiol (*m*/*z* 86, 76%), and 3-bromobut-2-ene-2-thiol radical cations (*m*/*z* 167, 47%). Thus the fragmentation pattern of benzoxathiepine **IV** under electron impact corresponds to decomposition of the open-chain molecular ion structure $[M_1]^{+\cdot}$ and follows general relations typical of sulfides [6].

3-Bromo-2,3-dimethyl-2-sulfanyl-2,3-dihydro-5*H*-4,1-benzoxathiepin-5-one (IV). A solution of 1 g (0.4 mmol) of compound **II** in 10 ml of anhydrous diethyl ether saturated with hydrogen chloride was cooled to –70°C, and a solution of 0.6 g (0.4 mmol) of 2-sulfanylbenzoic acid (**I**) in 20 ml of anhydrous diethyl ether, cooled to –50°C, was added. The mixture was allowed to warm up to –20°C and was left to stand for 7 days at that temperature until initial thione **II** disappeared completely. The mixture was allowed to warm up to room temperature and washed with water until neutral reaction, the organic phase was separated, dried over calcium chloride, and evaporated under reduced pressure, and the residue was recrystallized from methanol. Yield 0.9 g (70%), colorless crystals, mp 142–143°C. IR spectrum, ν, cm^{-1}: 2563 (S–H), 1664 (C=O), 739 (C–S), 652 (C–Br). ^{1}H NMR spectrum, δ, ppm: 2.063 s (3H, CH_3), 2.18 s (3H, CH_3), 2.06 s (SH), 7.32–7.97 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 22.17 (CH_3), 27.11 (CH_3), 49.81 and 59.00 (C^2, C^3), 125.80–140.31 (C_{arom}), 167.48 (C=O). Mass spectrum: *m*/*z* 319 $[M]^+$. Found, %: C 41.55; H 3.45; Br 25.52; S 20.46. $C_{11}H_{11}BrO_2S_2$. Calculated, %: C 41.38; H 3.45; Br 25.08; S 20.06.

The IR spectra were recorded in KBr on a Bruker IFS-25 instrument. The ^{1}H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker DPX-400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The mass spectrum (electron impact, 70 eV) of compound **IV** was obtained on a Shimadzu GCMS-QP5050A instrument (quadrupole mass analyzer, a.m.u. range 34–650; direct sample admission into the ion source; ion source temperature 200°C,

direct inlet probe temperature 180°C). The purity of the product was checked by TLC on Silufol UV-254 plates using chloroform as eluent.

REFERENCES

1. Gelebe, A.C. and Kaye, P.T., *J. Chem. Res., Synop*., 1999, p. 584.
2. Gelebe, A.C. and Kaye, P.T., *Synth. Commun*., 1996, vol. 26, p. 4459.
3. Voronkov, M.G., Shagun, L.G., and Shagun, V.A., *Russ. J. Org. Chem*., 2003, vol. 39, p. 905.
4. Dorofeev, I.A., Shagun, L.G., Mikhailova, I.A., Shagun, V.A., and Voronkov, M.G., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1732.
5. Takhistov, V.V. and Ponomarev, D.A., *Organicheskaya mass-spektrometriya* (Organic Mass Spectrometry), St. Petersburg: VVM, 2005.
6. Johnstone, R.A.W., *Mass Spectrometry for Organic Chemists*, Cambridge: Cambridge Univ., 1972; Vul'fson, N.S., Zaikin, V.G., and Mikaya, A.I., *Mass-spektrometriya organicheskikh soedinenii* (Mass Spectrometry of Organic Compounds), Moscow: Khimiya, 1986; Zaikin, V.G., Varlamov, A.V., Mikaya, A.I., and Prostakov, N.S., *Osnovy mass-spektrometrii organicheskikh soedinenii* (Foundations of Mass Spectrometry of Organic Compounds), Moscow: MAIK Nauka/Interperiodika, 2001.
7. Stevenson, D.P., *Discuss. Faraday Soc*., 1951, vol. 10, p. 35; Audier, H.E., *Org. Mass Spectrom*., 1969, vol. 2, p. 283.