INVESTIGATION OF THE INFLUENCE OF A SULFUR ATOM ON THE MOBILITY OF THE HYDROGEN ATOMS IN A METHYLENE GROUP OF SOME HETEROCYCLIC COMPOUNDS

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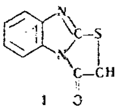
The action of dicyclohexylcarbodiimide on 2-benzimidazolylthioacetic, β-(2-benzimidazolylthio)propionic, β-(2-benzimidazolyl)propionic and 2-benzimidazolylacetic acids has given the anhydro derivatives of these acids. It has been shown that the hydrogen atoms in the methylene group of anhydro-2-benzimidazolylthioacetic acid have the highest mobility.

An investigation of the condensation of anhydro derivatives of 2-benzimidazyolylthioacetic acid (I) and β-(benzimidazolyltlhio)propionic acid (II) with aldehydes, ketones, and nitroso compounds has shown the high mobility of the hydrogen atoms in the methylene group of I; when the starting materials were heated in ethanol in the presence of piperidine, the corresponding benzylidene, isopropylidene, and azomethine derivatives were obtained in high yields [1]. The mobility of the hydrogen atoms in the methylene group of II proved to be insufficient for its condensation even with such active carbonyl compounds as aldehydes. The high mobility of the hydrogen atoms in the methylene group of I is associated with the mutal influence of the carbonyl group and the heteroatom of sulfur present immediately adjacent to the methylene group on the protonation of the hydrogen atoms of the latter. The hypothesis has been put forward that the low mobility of the hydrogen atoms in the methylene group of II is connected with a decrease in the inductive influence of the sulfur atom occupying the β position with respect to the methylene group under consideration.

The object of the present work was the synthesis of 2-benzimidazolylmethylthioacetic acid (III), β-(2-benzimidazolyl)propionic acid (IV), 4,5-dihydro-2-imidazolylthioacetic acid (V), and 5-nitro- and 5-acetylamino-2-benzimidazolylthioacetic acids (VI) and VII), the anhydridization of the latter, and the investigation of the mobility of the hydrogen atoms in the methylene groups of the anhydro derivatives obtained.

In the anhydridization of the acids III–VII, dicyclohexylcarbodiimide (DCHCD) was used as the water-eliminating agent. The reaction was carried out in pyridine solution at 5–10° C. The anhydro derivatives of the acids III and IV (compounds VIII and IX) were obtained with yields of 54.2 and 78.1%. The use of DCHCD for the anhydridization of 2-benzimidazolylthioacetic and β-(2-benzimidazolylthio)propionic acids permitted the anhydro derivatives of the latter (I and II) to be obtained with yields of 98 and 72%.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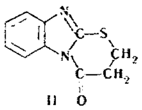
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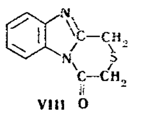
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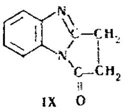
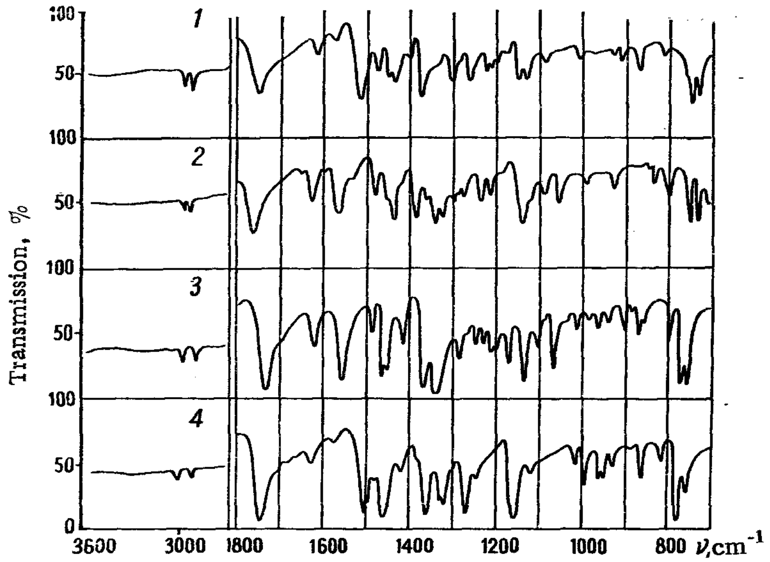

IX

The anhydro derivatives of the acids V, VI, and VII were obtained not only by the action of DCHCD on the latter but also by heating V, VI, and VII in acetic anhydride in the presence of pyridine [2].

An investigation of the mobility of the hydrogen atoms in the methylene groups of VIII and IX in condensation reaction of these compounds with p-[di(β-chloroethyl)amino]benzaldehyde (X) and p-nitrosodimethylamine (XI) has shown that VIII and IX do not take part in the above-mentioned reactions when the starting materials are heated in ethanol in the presence of piperidine. The benzylidene derivative VIII was obtained with a yield of 25% by heating VIII and X in glacial acetic acid. Compound IX does not take part in this reaction on being heated in glacial acetic acid.

The results obtained show that of the anhydro derivatives I, II, VIII, and IX investigated, benzimidazolo[2',1'-2,3]thiazolidin-4-one (I) possesses the most active hydrogen atoms in the methylene group. The low mobility of the hydrogen atoms in benzimidazolo[1',2'-1,2]pyrrolidin-5-one (IX), which is a structural analog of I, is apparently connected with the absence of a sulfur heteroatom in the latter. The high mobility of the hydrogen atoms in the methylene group of I as compared with VIII, in spite of the analogous α,α' position of the carbonyl group and the sulfur atom with respect to the methylene groups in both compounds is possibly connected with the interaction of the sulfur atom in compound I with the double bond C=N–, with the delocalization of the electrons of the latter on participation in the d orbital of the sulfur atom [3–5]. The possibility is not excluded of the positive influence on the mobility of the hydrogen atoms in the methylene group of I of the geometrical properties of the latter. as well.

It follows from a consideration of the IR spectra of I, II, VIII, and IX that the frequencies of the vibrations of the C=O group in compounds I and IX are 1748 and 1760 cm^{-1}, i. e., considerably higher than those for compounds II and VIII (1731 and 1728 cm^{-1}, respectively), which is apparently due to the greater strain of the five-membered rings than of the six-membered ones. The presence of a sulfur heteroatom in the β position with respect to the carbonyl group in the case of I and VIII leads to a lowering of the frequency of the vibrations of the CO group in the latter as compared with its value in the IR spectra of II and IX. The absence of a sulfur heteroatom from compound IX leads to a rise in the frequency of the vibrations of the CO group in the latter (1760 cm^{-1} in IX) in comparison with that in compound I (1748 cm^{-1}). The bands of the deformation vibrations of the methylene groups in the 1440–1445 and 760–780 cm^{-1} regions also have lower frequencies for the five-membered heterocycles (1440



IR spectra: 1) anhydro-2-benzimidazolythioacetic acid (I) ; 2) anhydro-β-(2-benzimidazolylthio) propionic acid(II) ; 3) anhydro-2-benzimidazolylmethylthioacetic acid (VIII); 4) anhydro-β-(2-benzimidazolyl)propionic acid (IX).

Anhydro Derivatives

Compound	Mp, ° C	Empirical formula	Found, %		Calculated, %		Yield, %
			C	H	C	H	
I	181	$C_9H_6N_2OS$	56.74	3.28	56.84	3.18	98.0
II	168	$C_{10}H_8N_2OS$	58.54	3.91	58.82	3.92	72.2
VIII	104	$C_{10}H_8N_2OS$	58.62	3.97	58.82	3.92	54.2
IX	142	$C_{10}H_8N_2O$	69.78	4.79	69.76	4.68	78.1

and 760 cm^{-1} for I, and 1441 and 765 cm^{-1} for IX) as compared with the six-membered rings (1446 and 767 cm^{-1} for VIII, and 1450 and 776 cm^{-1} for II). The α position of the sulfur atom with respect to the CH_2 group (compounds I and VIII) leads to a lowering of the frequencies of the deformation and stretching vibrations of the latter.

EXPERIMENTAL

2-Benzimidazolylmethylthioacetic acid (III) [6] was obtained by the reaction of mercaptoacetic acid with o-phenylenediamine and the subsequent condensation of the mercaptan obtained with chloroacetic acid. Mp 204° C.

4, 5-Dihydro-2-imidazolylthioacetic acid (V) was obtained by heating equimolecular amounts of ethylenethiourea, chloracetic acid, and anhydrous sodium acetate in ethanol for 2 hr. White crystalline powder. Mp 194.5–195° C (from ethanol). Found, %: C 37.37, 37.24; H 4.86, 5.02. Calculated for $C_5H_8N_2O_2S$, %: 37.50; H 5.00.

5-Nitro-2-benzimidazolylthioacetic acid (VI) was obtained by heating equimolecular amounts of 5-nitro-2-mercaptobenzimidazole and chloroacetic acid in 2 N sodium hydroxide. Lemon yellow crystalline powder. Mp 215–216° C (from methanol). Found, %: C 42.94, 42.60; H 2.75; 3.09. Calculated for $C_9H_7N_3O_4S$, %: C 42.68; H 2.76.

5-Acetylamino-2-benzimidazolylthioacetic acid (VII) was obtained from 5-acetylamino-2-mercaptobenzimidazole under conditions analogous to those for VI. Microcrystalline powder. Mp 261–262° C (after reprecipitation from ammoniacal solution with acetic acid). Found, %: C 49.64, 49.50; H 4.84, 4.95; S 11.79, 11.98. Calculated for $C_{11}H_{11}N_3O_3S$, %: C 49.81; H 4.15; S 12.07.

Synthesis of the anhydro derivatives I, II, VIII, and IX (table). A solution of 0.01 mole of dicyclohexylcarbodiimide in anhydrous pyridine or in a mixture of pyridine and dimethylformamide was added to a solution of 0.01 mole of one of the acids I–VII in the same solvent, and the mixture was left in the refrigerator at 5–10° C for 10–12 hr. The precipitate of dicyclohexylurea was filtered off, and the mother liquor was evaporated in vacuum at 30–35° C. The anhydro derivatives obtained were recrystallized from ethanol or from a mixture of ethanol and benzene.

In the reaction of DCHCD with V, VI, and VII, the latter were recovered unchanged. When the anhydridization of V, VI, and VII was carried out by heating in acetic anhydride containing pyridine according to [2], the acids VI and VII were recovered unchanged, while in the case of V resinification took place.

Condensation of the anhydroacid VIII with the aldehyde X.

a) A mixture of 1.02 g (0.005 mole) of VIII and 1.23 g (0.005 mole) of X in 10 ml of glacial acetic acid was boiled for 2 hr. The cooled reaction mixture was poured into an aqueous solution of sodium acetate and the precipitate was filtered off. Orange-yellow microcrystalline powder, mp 217–218° C (from acetone). Yield 0.54 g (25%). Found, %: C 58.12, 58.06; H 4.22, 4.08; S 7.66, 7.56%. Calculated for $C_{21}H_{19}Cl_2N_3OS$, %: C 58.33; H 4.39; S 7.40.

b) A mixture of 0.40 g (0.002 mole) of VIII and 0.49 g (0.002 mole) of X in 6 ml of ethanol containing five drops of pyridine was heated for 4 hr. After partial evaporation of the solvent and dilution of the residue with water, 0.3 g of X separated out (mp 87–88° C after two recrystallizations from aqueous ethanol).

The infrared spectra of I, II, VIII, and IX were recorded on a UR-10 spectrometer in the NaCl- and LiF-prism regions. For recording the spectra, a weighted sample of the substance was compressed in KBr to form a transparent tablet (in vacuum).

REFERENCES

1. I. I. Chizhevskaya, L. I. Gapanovich, and L. V. Poznyak, ZhOKh, 33, 945, 1963.

2. J. Pinnow and C. Sämann, Ber., 32, 2190, 1889.

3. Organic Sulphur Compounds, London, N.Y., Paris, 47, 1961.

4. D. W. Scott and J. P. McCullough, J. Am. Chem. Soc., 80, 3554, 1958.

5. J. A. Barltrop and K. T. Morgan, J. Chem. Soc., 3072, 1957.

6. B. P. Fedorov and R. M. Mamedov, Izv. AN SSSR, OKhN, 1629, 1962.

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