THE REACTION OF 2-IMINOBENZIMIDAZOLINE DERIVATIVES WITH CHLOROSULFURIC ACID

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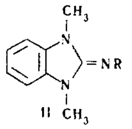
The reaction of 2-imino-1,3-dimethylbenzimidazoline and its N-substituted derivatives with chlorosulfuric acid is examined. It is shown that the reaction leads to the formation of the sulfonic acid in those cases where the hydrogen of the NH group is unsubstituted, or where the substituent possesses an electron-donor character. Sulfonyl chlorides are obtained only when the exocyclic nitrogen atom bears an electrophilic radical, which reduces the basicity of the guanidine moiety.

In order to synthesize a series of 2-iminobenzimidazolinesulfonyl chlorides, we reacted 2-imino-1,3-dimethylbenzimidazoline (IIa) and its N-substituted derivatives (IIb–h) [1] with chlorosulfuric acid.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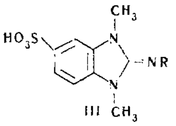
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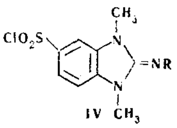

IV

II a R=H
b $R=CH_3$
c $R=CH_3(CH_2)_4$
d $R=CH_3CO$
e $R=C_6H_5CO$
f $R=C_6H_5SO_2$
g $R=p\text{-}O_2NC_6H_4CO$
h R= picryl

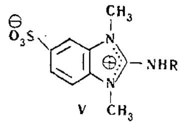
III a R=H
b $R=CH_3$
c $R=CH_3(CH_2)_4$
d $R=p\text{-}O_2NC_6H_4CO$*
e R=picryl*

IV a R=H(hydrochloride)
b $R=p\text{-}O_2NC_6H_4CO$
c R=picryl

Reaction of IIa with an excess of I yielded a compound containing only ionic chlorine, which was liable to sodium carbonate in aqueous solution, and which did not afford the expected sulfonamide on treatment with ammonia. It was, therefore, not the expected sulfonyl chloride, but the hydrochloride of IIIa. Under the experimental conditions, IId lost the acetyl group and was converted into IIIa and its hydrochloride. Formation of the sulfonic acid was also observed in the reaction of I with IIb and IIc. The location of the sulfonic acid group in these compounds was established by alkali fusion to give 5-hydroxy-1,3-dimethylbenzimidazolone (V) [2] after prior hydrolytic removal of the NH (or NR) group—if this is not done, an oily product of unknown structure is obtained.

The reaction of I with IIe and IIf gives a compound which contains ionic chlorine, reacts with ammonia to give a sulfonamide, and in boiling water is converted to IIIa. This compound must obviously be 2-imino-1,3-dimethylbenzimidazoline-5-sulfonyl chloride hydrochloride (IVa). Reaction of I with IIg and IIh likewise affords the sulfonyl chlorides (IVb) and (IVc) (the sulfonyl chloride group obviously occupies the 5-position in this case also). It follows that the presence of an electrophilic substituent in the NH group of II results in the formation of the sulfonyl chloride in this type of compound (the cleavage of the benzoyl and benzene-sulfonyl groups apparently occurs immediately after this reaction).

It is known that the first stage of the chlorosulfonation reaction is the formation of the sulfonic acid, which is converted in the presence of an excess of I into the sulfonyl chloride. The first stage occurs with all the imines II (obviously, the chlorosulfuric acid salt of the imine enters into reaction). The ability to undergo the second stage of the reaction under investigation is apparently determined by the fine structure of the benzimidazolinesulfonic acid first formed, and this in turn is dependent on the nature of the substituent in the NH group. Infrared spectroscopy shows that the sulfonic acids IIIa and IIIb, which are not converted into the sulfonyl chlorides under the conditions of the reaction (nor can they be converted by treatment with phosphorus pentachloride), possess the betaine structure (VI), the IR spectra showing strong bands at 1040 and 1190 cm^{-1} characteristic of the SO_3^- group, and an absence of a band at 1340 cm^{-1} characteristic of the SO_3H group [3,4].


V

R = H, alkyl

The formation of these acids during the chlorosulfonation reaction is followed by their rearrangement to the betaine structure, which is dependent on the high basicity of the guanidine grouping. It may be assumed that the ionization of the sulfonic acid group, and its interaction with the positively charged imidazole ring hinders the conversion to the sulfonyl chloride.

The spectrum of IIIe has no bands at 1040 and 1190 cm^{-1}, but has a strong band at 1343 cm^{-1}. This acid does not, therefore, exist in the betaine form, since the formation of the latter is hindered by the substantial reduction in the basicity of the guanidine grouping by the picryl substituent. The conversion of the sulfonic acid to the sulfonyl chloride is therefore not hindered, and the reaction of I with IIh (and also with IIe–g) gives the sulfonyl chloride. In agreement with this hypothesis, chlorosulfonation of 1,3-dimethylbenzimidazolone, in which the benzimidazoline ring is devoid of basic properties, gives 1,3-dimethylbenzimidazolone-5-sulfonyl chloride (VII) in 87% yield.

EXPERIMENTAL

The reaction of benzimidazoline derivatives with chlorosulfuric acid. In a three-necked flask, fitted with a stirrer and a reflux air

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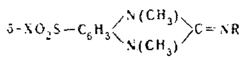
*Obtained by hydrolysis of the corresponding sulfonyl chloride.



$$5\text{-}XO_2S\text{-}C_6H_3\begin{matrix}\diagup N(CH_3)\diagdown \\ \diagdown N(CH_3)\diagup\end{matrix}C{=}NR$$

Compound	R	X	Mp °C	Molecular formula	Found, %			Calculated, %:		
					C	H	S	C	H	S
IIIa	H	OH	—	$C_9H_{11}N_3O_3S$	44.65	4.60	13.47	44.80	4.60	13.29
IX	H	NH_2	319—20	$C_9H_{12}N_4O_2S$	44.91	5.17	13.2	44.99	5.04	13.35
IIIb	CH_3	OH	—	$C_{10}H_{13}N_3O_3S \cdot H_2O$	44.00	5.34	11.80	43.93	5.53	11.73
IIIc	$CH_3(CH_2)_4$	OH	—	$C_{14}H_{21}N_3O_3S$	53.65	7.02	10.10	53.99	6.80	10.29
IIIe	2,4,6-$(O_2N)_3C_6H_2$	OH	291—93	$C_{15}H_{12}N_6O_9S$	39.87	2.77	7.16	39.84	2.67	7.09
IIId	*n*-$O_2NC_6H_4CO$	OH	347 (разл.)	$C_{16}H_{14}N_4O_6S$	49.35	3.85	7.94	49.22	3.61	8.21
X	То же	NH_2	219—20	$C_{16}H_{15}N_5O_5S$	49.12	4.12	8.62	49.35	3.88	8.23

Notes: 1) Compound IX was crystallized from ethanol, X from acetic acid, and the remaining compounds from water; 2) compounds IIIa–c decompose at about 400° C; 3) Found for IX, %: N 23.30, calculated, %: N 23.32; Found for X, %: N 18.27, calculated, %: N 17.99.

condenser provided with a calcium chloride tube, were placed 4 ml (0.06 mole) of freshly-distilled I, and 0.01 mole of the benzimidazoline derivative was added with stirring at such a rate that it dissolved completely (20–45 min). If the mixture began to warm up, the flask was cooled in cold water. The reaction was brought to completion by stirring the mixture until evolution of hydrogen chloride ceased (0.5–2 hr) at 55–60° C (for IIa, b, d, h and VIII), at 65–70° C (for IIc, e), at 85–90° C (for IIf), and at 75–80° C (for IIg). The reaction mixture was poured on to finely-crushed ice (20–30 g), the beaker being cooled in an ice-salt mixture. The resulting precipitate (A) was filtered from the solution (B), washed with ice-water and dried in a desiccator over $CaCl_2$.

2-Imino-1,3-dimethylbenzimidazoline-5-sulfonic acid hydrochloride (IIIa,HCl). This was obtained from I and IIa as a precipitate in 90% yield. It was soluble in warm water, but insoluble in acetone, benzene, chloroform, nitrobenzene and other solvents (a sample was therefore prepared for analysis by washing it with various solvents). Decomposed at about 400° C. Found, %: N 15.21; Cl 13.02. Calculated for $C_9H_{11}N_3O_3S$, %: N 15.12; Cl 12.76. The compound was also prepared by the reaction of I with IId in 29–34% yields. The filtrate B was boiled for a few minutes and kept overnight to give a precipitate of IIIa (see table), which was filtered off and dried at 120° C. Yield 50–65%.

2-Imino-1,3-dimethylbenzimidazoline-5-sulfonyl chloride hydrochloride (IVa). Obtained by chlorosulfonation of IIf in 85% yield. Small colorless prisms (from glacial acetic acid), decomposing at about 380° C. Found, %: N 13.98, 14.37. Calculated for $C_9H_{10}ClN_3O_2S \cdot HCl$, %: N 14.19. From the filtrate B (an emulsion), benzenesulfonyl chloride was isolated by extraction with benzene, in 62% yield.

IVa was also obtained by the reaction of I with IIe. The gummy precipitate was separated from the solution B, stirred with 20 ml of acetone, and the residue separated, washed with acetone and dried in the vacuum desiccator. Yield 61%. The solution B on standing deposited IIIa (16%), and the acetone filtrate afforded a yield of 53% of benzoic acid.

2-p-Nitrobenzoylimino-1,3-dimethylbenzimidazoline-5-sulfonyl chloride (IVb). Precipitate A was stirred with 20 ml of acetone. The insoluble residue of IVb was separated, washed with acetone and dried in the vacuum desiccator. Yield 65%. Pale yellow powder, decomposing at about 300° C, insoluble in aqueous sodium carbonate, chloroform, nitrobenzene, xylene, and other solvents. Purified for analysis by washing with various solvents. Found, %: N 13.50, 13.63. Calculated for $C_{16}H_{13}ClN_4O_5S$, %: N 13.71.

2-Picrylimino-1,3-dimethylbenzimidazoline-5-sulfonyl chloride (IVb). Yellow crystalline product, mp 304° C (decomp.), insoluble in aqueous sodium carbonate and in the usual solvents (purified for analysis by washing with various solvents), yield 96%. Found, %: N 17.72, 18.19%. Calculated for $C_{15}H_{11}ClN_6O_8S$, %: N 17.85.

1,3-Dimethylbenzimidazolone-5-sulfonyl chloride (VII). Colorless needles (from benzene-light petroleum), mp 180° C. Found, %: N 10.93, 11.02. Calculated for $C_9H_9ClN_2O_3S$, %: N 10.75.

Various benzimidazoline-5-sulfonic acids (see table). IIIb and IIIc were prepared by reaction of I with the sulfate of IIb (the free base is extremely hygroscopic) and with IIc in yields of 68 and 71%, respectively. The solution B (no precipitate A separated) was neutralized with solid sodium carbonate to pH 2. The precipitate of mineral salts was separated, and the filtrate on standing gave a precipitate of the sulfonic acid. This was filtered off, washed with ice water and dried at 120° C. The sulfonic acids IIId and IIIe were obtained by treatment of the sulfonyl chlorides IVb and IVc with a small amount of boiling water. In contrast to the sulfonyl chlorides, they are soluble in aqueous sodium carbonate. Compound IIIe, which is pale yellow in color, gives an orange solution.

1,3-Dimethylbenzimidazoline-5-sulfonic acid (VIII). Compound IX was hydrolyzed by evaporating to dryness the aqueous solution, and the residue recrystallized from glacial acetic acid. Mp 256–257° C. Found, %: C 44.82; H 3.88; S 13.05. Calculated for $C_9H_{10}N_2O_4S$, %: C 44.62; H 4.16; S 13.23.

2-Methylimino-1,3-dimethylbenzimidazoline sulfate. To a solution of 1.66 g (5 mM) of 2-methylamino-1,3-dimethylbenzimidazolium benzenesulfonate [1] in 10 ml of ethanol was added 0.4 ml (7.5 mM) of sulfuric acid (d 1.84). The precipitate was filtered off, and washed with ethanol and ether to yield 0.94 g (80%) of fine, colorless needles (from ethanol), mp 237–238° C. Found, %: N 15.46; S 11.61. Calculated for $C_{10}H_{13}N_3 \cdot H_2SO_4$, %: N 15.37; S 11.73.

Various benzimidazoline-5-sulfonamides (IX, X). These were prepared by boiling the appropriate sulfonyl chlorides with an excess of conc. aqueous ammonia for 5–10 min. Compound IX was readily soluble in water, and was isolated by evaporating the solution to dryness.

1,3-Dimethylbenzimidazoline-5-sulfonamide. Colorless needles, mp 277° C (from aqueous ethanol). Found, %: C 44.63; H 4.87; S 13.24. Calculated for $C_9H_{11}N_3O_3S$, %: C 44.80; H 4.60; S 13.29.

Alkaline fusion of 2-imino-1,3-dimethylbenzimidazoline-5-sulfonic acid. A solution of 1.2 g (5 mM) of IIIa and 0.85 g (15 mM) of KOH in 10 ml of water was boiled under reflux for 7 hr, until the evolution of ammonia had ceased. The solution was evaporated, and the residue introduced during 1 hr to a fused mixture of 4 g of NaOH and 2 g KOH in a brass vessel at 290° C, the mixture being stirred with a steel stirrer. The temperature was then raised during 30 min to 310° C, and stirred for 1 hr. The melt was cooled and dissolved in 50 ml of water, and the warm solution neutralized with dil (1 : 2) H_2SO_4 to pH 7. After filtration to remove impurities, the filtrate was acidified with conc HCl to pH 1, and the V recrystallized from ethanol to yield 0.42 g (43%), mp 212° C (literature [2], 212° C). Compounds IIIb and VIII were similarly converted into V.

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