SYNTHESIS OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE AND PURINES

VI.* 5(4)-AMINOIMIDAZOLE-4(5)-SULFONAMIDE DERIVATIVES

V. I. Ofitserov, Z. S. Mokrushin,
Z. V. Pushkareva, and N. V. Nikiforova

UDC 547.784.1'785'87.07

4(5)-Sulfonyl chlorides, which were converted to the corresponding sulfamoyl derivatives, were obtained from the amide and ethyl ester of 4(5)-mercaptoimidazole-5(4)-carboxylic acid by oxidative chlorination. The azide of 4(5)-sulfamoylimidazole-5(4)carboxylic acid was synthesized through 4(5)-sulfamoylimidazole-5(4)-carboxylhydrazide, and its conversion in various media to 5(4)-aminoimidazole-4(5)-sulfonamide derivatives and to 3,4-dihydro-3-oxoimidazo[4,5-e]-1,2,4-thiadiazine 1,1-dioxide was studied.

The synthesis of 5(4)-aminoimidazole-4(5)-sulfonamide (I) and its acyl derivatives, which are analogs of the biosynthetic precursor of purines 5(4)-aminoimidazole-4(5)-carboxamide (AICA), has been the goal of a number of studies [2-4]; however, all attempts to obtain these imidazolesulfonamides have given negative results. The present communication is devoted to the study of a new method for the synthesis of the previously inaccessible derivatives of I.

We synthesized the corresponding sulfonyl chlorides (IIIa, b) by oxidative chlorination of the ester and amide (IIa, b) [5] of 4(5)-mercaptoimidazole-5(4)-carboxylic acid; the IR spectra of IIIa, b contain intense bands of symmetrical and asymmetrical stretching vibrations of the SO_2 group at 1172, 1368, and 1179, 1367 cm^{-1}, respectively. Ethyl 4(5)-sulfamoylimidazole-5(4)-carboxylate (IVa) and 4(5)-sulfamoylimidazole-5(4)-carboxamide (IVb) were obtained by reaction of IIIa, b with ammonia. Sulfonamide IVa was converted to 4(5)-sulfamoylimidazole-5(4)-carboxylic acid hydrazide (V) by refluxing with hydrazine hydrate; we were also able to synthesize V from IVd by transamination of the carboxamide group with hydrazine. Reaction of carboxyhydrazide V with nitrous acid gave the azide (VI) of 4(5)-sulfamoylimidazole-5(4)-carboxylic acid, the IR spectrum of which contains an intense band of an N_3 group of 2176 cm^{-1}. We used azide VI as the key compound for the synthesis of labeled analogs of AICA via the Curtius reaction.

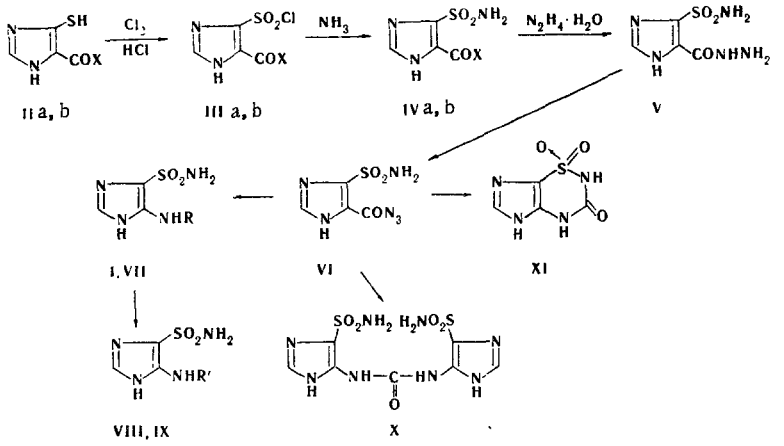
Thus, when VI was refluxed in absolute ethanol, it was converted to 5(4)-ethoxycarbonylamidoimidazole-4(5)-sulfonamide (VII), which was converted to the corresponding 5(4)-(3-methylureido)- and 5(4)-(4-semicarbazido)imidazole-4(5)-sulfonamides (VIII, IX) by reaction with methylamine and hydrazine hydrate. Decomposition of azide VI in water or in aqueous dioxane and toluene leads to the formation of symmetrical urea derivative 5,5'(4,4')-ureylenebis[imidazole-4(5)-sulfonamide] (X). We were unable to isolate the corresponding isocyanate derivative of imidazole by refluxing VI in anhydrous solvents (dioxane, toluene, and nitromethane), and the final product in all cases was 3,4-dihydro-3-oxoimidazo[4, 5-e]-1,2,4-thiadiazine 1,1-dioxide (XI). The IR spectrum of the latter contains bands of stretching vibrations of a CO group at 1682 cm^{-1} and of an NH group at 3090, 3140, and 3360 cm^{-1}; the band of vibrations of the N=C=O group at 2240-2275 cm^{-1} is absent. (See equation following page).

Attempts to effect the hydrolysis of VII, X, and XI under various conditions by means of HCl, NaOH, and $Ba(OH)_2$ in order to synthesize unsubstituted amine I were unsuccessful, and only destruction of the starting

*See [1] for communication V.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1119-1122, August, 1976. Original article submitted September 22, 1975.

This material is protected by copyright registered in the name of Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for $7.50.



II-IV a X = OC_2H_5; b X = NH_2; I R = H; VII R = $COOC_2H_5$; VIII R′ = $CONHCH_3$; IX R′ = $CONHNH_2$

compounds was observed. As seen from Table 1, the frequency of the symmetrical vibrations of the SO_2 group is found at 1152-1170 cm^{-1} in the IR spectra of synthesized sulfonamides IV-XI. The range of the frequency of the asymmetrical vibrations is 1310-1325 cm^{-1}, but the corresponding vibrations appear 50 cm^{-1} higher in the spectrum of cyclic sulfonamide XI.

EXPERIMENTAL

The IR spectra of potassium bromide pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Perkin-Elmer 402 spectrophotometer. Chromatography was carried out on Silufol UV-254 in butanol-acetic acid-water (4:1:1) R_f and propanol-0.2 N NH_4OH (R'_f) systems. The physical constants, yields, and results of analysis of the compounds are presented in Table 1.

4(5)-Chlorosulfonylimidazole-5(4)-carboxylic Acid Ethyl Ester and Amide (IIIa, b). Chlorine was bubbled with stirring at −2° through a suspension of 27.0 mmole of mercaptoimidazole IIa or IIb in 33 ml of 1 N HCl, and the precipitated sulfonyl chloride was removed by filtration, washed with water and ethanol, and dried over P_2O_5.

4(5)-Sulfamoylimidazole-5(4)-carboxylic Acid Ethyl Ester and Amide (IVa, b). An 8.05-mmole sample of sulfonyl chloride IIIa or IIIb was added to with stirring at 0° to 10 ml of concentrated NH_4OH, and the mixture was vacuum evaporated to dryness. Water (5 ml) was added to the residue, and the mixture was acidified to pH 3 with concentrated HCl. The precipitate was removed by filtration and crystallized from water.

4(5)-Sulfamoylimidazole-5(4)-carboxylic Acid Hydrazide (V). A) A solution of 0.32 g (1.46 mmole) of IVa in 5 ml of hydrazine hydrate was refluxed for 3 h, after which it was vacuum evaporated to dryness. The residue was dissolved in 4 ml of water, and the solution was acidified to pH 4 with concentrated HCl and cooled. The resulting precipitate was removed by filtration to give 0.24 g (80.1%) of V.

B) A 3.1-g (14.9 mmole) sample of IVb was refluxed in 25 ml of hydrazine hydrate for 4 h, and hydrazide V was isolated as in method A. The yield was 2.8 g (88.9%).

4(5)-Sulfamoylimidazole-5(4)-carboxylic Acid Azide (VI). A solution of 0.22 g (3.19 mmole) of sodium nitrite in 3 ml of water was added gradually with stirring at −3° to a solution of 0.6 g (2.92 mmole) of V in 6 ml of 1 N HCl, and the mixture was allowed to stand for 15 min. The precipitate was removed by filtration and washed with water, alcohol, and ether to give 0.55 g of VI.

5(4)-Ethoxycarbonylamidoimidazole-4(5)-sulfonamide (VII). A 1.5-g (6.95 mmole) sample of VI was refluxed in 60 ml of absolute ethanol for 3 h, after which the mixture was vacuum evaporated to dryness, and the residue was crystallized from water to give 1.17 g of VII.

5(4)-(3-Methylureido)imidazole-4(5)-sulfonamide (VIII). A solution of 0.45 g (1.95 mmole) of VI in 45 ml of ethanol saturated at 0° with methylamine was heated in a sealed tube to 145° and maintained at this temperature for 5 min. It was then cooled and vacuum evaporated to dryness. The residue was crystallized from water acidified to pH 4. The yield was 0.26 g.

5(4)-(4-Semicarbozido)imidazole-4(5)-sulfonamide (IX). A 0.2-g (0.86 mmole) sample of VI was heated in 5 ml of hydrazine hydrate on a boiling-water bath for 1.5 h, after which it was vacuum evaporated to dry-

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	R_f	R'_f	Empirical formula	Found, %				Calculated, %				UV spectrum*		IR spectrum, cm^{-1}			Yield, %
					C	H	N	S	C	H	N	S	λ_{max}, nm	lg ε	$\nu^{s}SO_2$	$\nu^{as}SO_2$	νCO	
IIIa	155—156	0,64	—	$C_6H_7ClN_2O_4S$	30,4	3,1	12,0	13,4	30,2	2,9	11,8	13,4	224, 253	3,75; 3,92	1172	1367	1712	70
IIIb	154	0,25	—	$C_4H_4ClN_3O_3S$	22,7	2,1	20,4	15,1	22,9	1,9	20,1	15,3	237, 250	3,77; 3,77	1179	1368	1670	68
IVa	220—221	0,83	0,82	$C_6H_9N_3O_4S$	33,0	4,3	19,2	14,4	32,9	4,1	19,2	14,6	211, 243	3,89; 3,97	1164	1325	1694	83
IVb	260—262	0,58	0,62	$C_4H_6N_4O_3S \cdot H_2O$	23,2	3,8	27,2	15,4	23,1	3,8	27,0	15,4	206, 244	3,87; 3,96	1168	1325	1655	78
V	237—238	0,48	0,46	$C_4H_7N_5O_3S$	23,4	3,5	34,5	15,5	23,4	3,4	34,2	15,6	248	4,00	1155	1320	1668	89
VI	151†	0,62	0,65	$C_4H_4N_6O_3S$	22,3	2,1	38,8	14,7	22,2	1,9	38,9	14,8	274	4,16	1170	1325	1680	87
VII	175—176	0,65	0,76	$C_6H_{10}N_4O_4S$	30,9	4,1	23,7	13,7	30,8	4,3	23,9	13,7	230	4,12	1167	1325	1737	72
VIII	210—211	0,47	0,69	$C_5H_9N_5O_3S$	27,2	4,1	32,0	14,6	27,4	4,1	31,9	14,6	235	4,23	1160	1310	1730	59
IX	214—215	0,60	0,47	$C_4H_8N_6O_3S$	21,5	3,5	38,2	14,2	21,8	3,6	38,2	14,5	236	4,18	1152	1312	1677	53
X	192—193	0,39	0,54	$C_7H_{10}N_8O_5S_2$	23,9	3,1	31,8	18,0	24,4	2,9	32,0	18,3	234	4,19	1160	1312	1683	64
XI	260	0,30	0,52	$C_4H_4N_4O_3S$	25,5	2,3	29,9	17,0	25,5	2,1	29,8	17,0	227	4,17	1167	1375	1682	68

*The UV spectra of IIa, b were obtained from methanol solutions, and the UV spectra of III-XI were obtained from aqueous solutions.

†Decomposes explosively.

ness. The residue was dissolved in 3 ml of water, and the solution was acidified to pH 5 with concentrated HCl and cooled. The precipitate was removed by filtration and crystallized from water. The yield was 0.1 g.

5,5'(4,4')-Ureylenebis[imidazole-4(5) sulfonamide] (X). A 0.21-g (0.97 mmole) sample of VI was refluxed in 10 ml of 80% dioxane or water for 10 min, after which the mixture was vacuum evaporated to dryness, and the residue was crystallized from water. The yield was 0.11 g.

3,4-Dihydro-3-oxoimidazo[4, 5-e]-1,2,4-thiadiazine 1,1-Dioxide (XI). A 1-g (4.63 mmole) sample of VI was added in portions to 10 ml of refluxing pyridine, and the mixture was allowed to stand for 5 min. It was then cooled and treated with 10 ml of ethanol, and the resulting precipitate was removed by filtration and crystallized from water acidified to pH 4. The yield was 0.7 g.

LITERATURE CITED

1. V. S. Mokrushin, V. I. Ofitserov, T. V. Rapakova, A. G. Tsaur, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 4, 556 (1976).
2. L. L. Bennett and H. T. Baker, J. Am. Chem. Soc., 79, 2188 (1957).
3. M. H. Fisher, W. H. Nickolson, and R. S. Stuart, Can. J. Chem., 31, 501 (1961).
4. V. S. Mokrushin, V. I. Nifontov, Z. V. Pushkareva, and V. I. Ofitserov, Khim. Geterotsikl. Soedin., No. 10, 1421 (1971).
5. V. I. Ofitserov, V. I. Nifontov, V. S. Mokrushin, Z. V. Pushkareva, and E. A. Shtokareva, Inventor's Certificate No. 437,764 (1972); Byul. Izobr., No. 28, 53 (1974).

1,4-DIAZABICYCLO[2.2.2]OCTANES

III*. SYNTHESIS AND PROPERTIES OF 1,4-DIAZABICYCLO[2.2.2] OCTANE-2-CARBOXYLIC ACID BIS(METHYLBROMIDE)

L. B. Mrachkovskaya, K. F. Turchin, and L. N. Yakhontov

UDC 547.895'861.3.8.07:542.944

1,4-Diazabicyclo[2.2.2]octane-2-carboxylic acid bis(methylbromide), which is readily converted with splitting out of hydrogen bromide to the corresponding quaternary betaine, was synthesized.

1,4-Diazabicyclo[2.2.2]octane-2-carboxylic acid derivatives are of interest in connection with the pharmacological activity of the corresponding deaza analogs – quinuclidine-2-carboxylic acid derivatives and primarily diokhin (diethylaminoethyl quinuclidine-2-carboxylate dimethiodide). Moreover, 1,4-diazabicyclo[2.2.2]-octane-2-carboxylic acid and its derivatives are unknown, and attempts to obtain them have been unsuccessful: intramolecular fragmentation occurs during the synthesis through 4-(β,β-diethoxycarbonylethyl)piperazines [2, 3], 1,1,4,4-tetramethylpiperazinium bromide is formed in reactions of 1,4-dimethylpiperazine with methyl α,β-dibromopropionate or α,β-dibromopropionitrile [4], and monothiooxalic acid bis(N-methylpiperazide) is obtained in the synthesis from 3-(N-methylpiperazinyl)propionic acid through its α-bromo derivative.

Our experiments on the condensation of piperazine with diethyl acetylenedicarboxylate also gave negative results. Instead of the bicyclic derivative we obtained a mixture of products, from which we isolated 1-(α,β-diethoxycarbonylethylene)piperazine (I) and 1,4-bis(α,β-diethoxycarbonylethylene)piperazine (II).

* See [1] for communication II.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1123-1126, August, 1976. Original article submitted September 19, 1975.

This material is protected by copyright registered in the name of Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for $7.50.