CCA-642

547.794.3.07
Original Scientific Paper

Thiadiazoles. III*. Some 5-Substituted Derivatives of 2-Amino-1,3,4-Thiadiazoles and Some Mesoionic 1,3,4-Thiadiazoles

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Received January 29, 1970

New derivatives of 1,3,4-thiadiazoles with potential phytohormonic (compds. I—V) and antibacterial (compds. VI—IX) activity have been prepared. Mesoionic structure of the compounds VI—IX is indicated by their IR and UV spectra.

Continuing work on the synthesis of mercaptothiadiazoles, compounds with potential phytohormonic activity[1,2], some new 5-substituted derivatives of 2-amino-1,3,4-thiadiazoles have been prepared (compounds I—V, Table I). Potassium salts of 2-amino-5-mercapto-1,3,4-thiadiazole (X), have served as starting materials for I and II. Acid hydrolysis of I gave rise for III, and hydrogen peroxide oxydation of X led to IV and, after neutralization, to the diethylammonium salt V.

The IR spectra of the compounds I—V showed three significant bands, in the region 1430—1440 cm^{-1}, 1330—1350 cm^{-1}, and 1170 ± 90 cm^{-1}, respectively, characterizing the thiadiazolic ring[3]. Additionaly, compound II showed characteristic bands at 1709 cm^{-1} (ester-carbonyl), 3311 cm^{-1}, 3226 cm^{-1} (primary amine), and 1680 cm^{-1}, 1538 cm^{-1} (amide I and II band, respectively). Compound IV showed two characteristic bands between 2650—2950 cm^{-1} for the sulphonic acid, along with some other characteristic bands at 1050 cm^{-1}, and 1200—1300 cm^{-1}. A broad band with a maximum at 2445 cm^{-1} characterized ammonium group in the compound V in connection with other characteristic bands at 1210—1235 cm^{-1}, and 1020 cm^{-1}.

Ultraviolet spectra of the compounds I—V in 95% ethanol exhibited absorption maxima at 260—290 nm, with corresponding ε values in the range of 4800—9000.

New mesoionic 1,3,4-thiadiazoles[4] VI—IX (Table II) have been prepared following the procedure described by Kier *et al.*[5,6] because of interesting biological properties of this group of compounds[5].

The preparations of these compounds, analogs of sydnones[7,8], started from the corresponding acid chlorides and potassium phenyldithiocarbazinate according to the reaction scheme:

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* The paper cited under 2. should be refered to as part II of this series.

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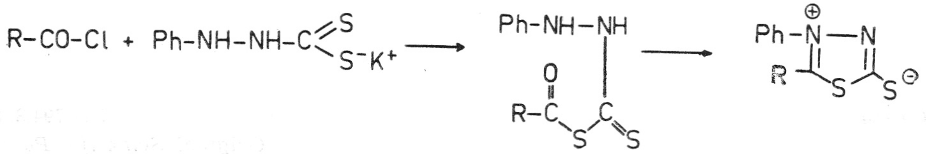


Infrared absorption bands of the compounds VI—IX at 1500—1508 cm^{-1} and 1445—1465 cm^{-1} can be assigned[9] to $>N-\underset{|}{C}=S$, and $-N=\underset{|}{C}-S-$ group, respectively. Other very strong absorption bands had been repeatedly found in the range 1315—1350 cm^{-1} and 1030—1050 cm^{-1}, respectively. Several authors[6,10] made a frequency assignment of 1395—1338 cm^{-1} for the C=S linkage. Other investigators, however[11,12,13], assigned the band of strong intensity in the region 1200—1050 cm^{-1} to the C=S grouping, and the band in the 1350—1300 cm^{-1} region to CN vibration.

The ultraviolet spectra of the compounds VI—IX exhibited characteristic features as described by Stewart and Kier[6].

EXPERIMENTAL

All melting points are determined on Boëtius Mikroheiztisch and are uncorrected. Infrared spectra were run on a Unicam SP 200 and Perkin Elmer M-137 apparatus, the ultraviolet spectra were obtained on a Zeiss PMQ II spectrophotometer.

2-Amino-5-mercaptoehylacetate-1,3,4-thiadiazole (I)

To the solution of 3.7 g. of KOH in 66. ml. of EtOH 6.6 g. (0.049 mole) of 2-amino-5-mercaptan-1,3,4-thiadiazole were added. After the dissolution was complete 6.2 g. (0.05 mole) of ethylchloroacetate were added and the solution heated under reflux for 2 hrs. The deposited potassium chloride was then filtered off, the filtrate evaporated to dryness, and the residue recrystallized from EtOH. 8.3 g. (74.6%) of I was obtained, m. p. 96—98° C. IR spectrum (KBr); ν_{NH_2} 3311 and 3226 cm^{-1}, ν_{CO} 1709 cm^{-1}, $\nu_{C=N}$ 1608 cm^{-1}; ν_{CS} 1443 cm^{-1}. UV spectrum λ_{max}^{EtOH} 287 nm (ε 7700).

2-Acetylamino-5-mercaptoethylacetate-1,3,4-thiadiazole (II)

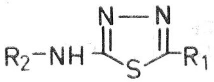
2-Acetyl derivative of X 8.74 g. (0.05 mole) was dissolved in ethanolic KOH as described for I. After the complete dissolution, 6.2 g. (0.05 mole) of ethylchloroacetate were added and the reaction mixture refluxed for 2 hrs. The inorganic precipitate was filtered off and the crude product, obtained after evaporation of the solvent, was recrystallized from EtOH. Yield 7.5 g. (58.6%) m. p. 168—169° C. IR Spectrum (KBr); ν_{NH} 3125 cm^{-1}; ν_{CO} 1739 cm^{-1}; ν_{CONH} 1680 cm^{-1} and 1538 cm^{-1}; ν_{CN} 1600 cm^{-1}; ν_{CS} 1439 cm^{-1}. UV spectrum; λ_{max}^{EtOH} 281 nm (ε 8100).

2-Amino-5-mercaptoacetic acid-1,3,4-thiadiazole (III)

Compound I, 9.0 g. (0.041 mole) was heated in 90 ml of 10% HCl for 0.5 hr at 70—80° C (steambath). Thereafter, the reaction mixture was neutralized with 10% NH_4OH to *p*H 4.5. On standing, white needle-shaped crystals were deposited, which were succtioned off and dried. The yield on the recrystallized product (EtOH was 4.7 g. (57.5%), m. p. 230° C. IR spectrum (KBr); ν_{NH_2} 3335 and 3205 cm^{-1}; ν_{COOH} 3000—2500 cm^{-1} (broad); ν_{CO} 1620 cm^{-1}; $\nu_{C=N}$ 1615 cm^{-1}; ν_{CS} 1410 cm^{-1}. UV spectrum; λ_{max}^{EtOH} 282 nm (ε 7800).

TABLE I

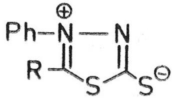
5-Substituted Derivatives of 2-Amino-1,3,4-thiadiazole

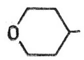
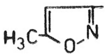
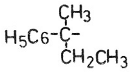
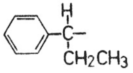


Compound	R_1	R_2	Formula	M. w.	M. p. °C	Calc'd			Found		
						% C	% H	% N	% C	% H	% N
I	SCH_2COOEt	H	$C_6H_9N_3O_2S_2$	219.28	96—98	32.87	4.13	19.16	32.95	3.89	18.78
II	SCH_2COOEt	CH_3CO	$C_8H_{11}N_3O_3S_2$	261.28	168—9	36.77	4.24	16.08	36.46	4.11	15.97
III	SCH_2COOH	H	$C_4H_5N_3O_2S_2$	191.23	230	25.14	2.64	21.98	25.42	2.50	21.80
IV	SO_3H	H	$C_2H_3N_3O_3S_2$	181.00	> 300 decomp.	13.25	1.88	23.20	13.05	1.73	23.07
V	$SO_3^{-+}NH_2(Et)_2$	H	$C_6H_{14}N_4O_3S_2$	254.10	161	28.35	5.51	22.04	28.33	5.61	22.01

TABLE II

Mesoionic Derivatives of 1,3,4-Thiadiazoles



Comp.		Formula	Yield	M. w.	M. p. °C	Absorption maximum in UV spectrum		Calc'd			Found		
						λ_{max}	ε	% C	% H	% N	% C	% H	N %
						nm							
VI		$C_{13}H_{14}N_2OS_2$	17.8	278.63	199—200	262 364	11200 3400	56.08	5.07	10.06	55.87	4.93	10.03
VII		$C_{12}H_9N_3OS_2$	21.5	275.21	225	273 427	11800 2700	52.34	3.30	15.26	52.18	3.23	15.54
VIII	 $H_5C_6-C(CH_3)(CH_2CH_3)-$	$C_{18}H_{18}N_2S_2$	9.5	326.43	223—4	269 368	12200 4200	66.20	5.56	8.58	66.46	5.60	8.29
IX		$C_{17}H_{16}N_2S_2$	12.5	312.33	175—6	263 368	11900 3700	65.34	5.16	8.97	65.74	5.51	9.04

2-Amino-5-sulphonic acid-1,3,4-thiadiazole (IV)

2-Amino-5-mercaptan-1,3,4-thiadiazole 2.6 g. (0.02 mole) and 7 ml. of 30% H_2O_2 were placed in an Erlenmeyer flask and 25 ml. of water were added. The reaction mixture was heated under reflux and stirred (magnetic stirrer) until all was dissolved. The solution was then cooled, evaporated to dryness and the residue recrystallized from water. The yield was 2.2 g. (60.7%); the substance decomposed above 300° C. IR spectrum (KBr); ν_{NH_2} 3380 and 3280 cm^{-1}; ν_{SO_2OH} 2950—2650 cm^{-1} (broad two bands); ν_{SO_3H} 1300—1200 cm^{-1} and 1050 cm^{-1}, $\nu_{C=N}$ 1625 cm^{-1}; ν_{CS} 1430 cm^{-1}. UV spectrum; λ_{max}^{EtOH} 272 nm (ε 4800).

2-Amino-5-diethylammonium sulphonate-1,3,4-thiadiazole (V)

Compound IV 1.0 g. (0.0055 mole) was dissolved in 4 ml. of water under gentle heating (steambath) and then diethylamine was gradually added until the solution was alkaline (0.64 g, 0.0064 mole). Thereafter 15 ml. of EtOH were added and the resultant mixture evaporated to dryness. This procedure was repeated until no water could be indicated in the destilate. The residue was dissolved in the minimum amount of EtOH and then an equal quantity of ether was added. On standing, a white needle-shaped substance crystallized; yield 1.1 g. (78.4%), m. p. 160—161° C. IR spectrum (KBr); ν_{NH_2} 3300 and 3075 cm^{-1}; $\nu_{NH_4^+}$ 2445 cm^{-1}; ν_{SO_3H} 1210—1235 cm^{-1} and 1020 cm^{-1} $\nu_{C=N}$ 1590 cm^{-1}; ν_{CS} 1440 cm^{-1}. UV spectrum λ_{max}^{EtOH} 268 nm (ε 6900).

General Procedure for the Preparation of Mesoionic Derivatives of 1,3,4-thiadiazole VI—IX (Table II)

To the solution of 8.0 g. (0.044 mole) potassiumphenyldithiocarbazinate (prepared as described in ref. 6) in 500 ml. of toluene heated to 50°C, 0.05 mole of the corresponding acid chloride was added (dropwise, during 5 min) dissolved in 10 ml. of toluene. (All the acid chlorides have been prepared using $SOCl_2$ as chlorinating agent and prolonged heating under reflux — 12 to 24 hrs —, and subsequent evaporation of the excess of $SOCl_2$ with benzene). The reaction mixture was stirred overnight at room temperature during which time the reaction product separated. The crude product was filtered off and recrystallized from abs. EtOH. Yields and mps. of the recrystallized products are listed in Table II.

Acknowledgement. The authors are indebted to Dr. V. Šunjić for helpful discussion, and Mrs. M. Galonja of Department of Chemistry for microanalyses.

REFERENCES

1. K. Dostal, S. Stavrić, and D. Kolbach, *Acta Pharm. Jug.* **9** (1959) 81.
2. K. Dostal and D. Kolbach, *ibid.* **11** (1961) 15.
3. D. Postescu, C. Daicovicin, and U. Binder, *Rev. Roum. Chim.* **13** (1968) 961.
4. M. Busch, *Ber.* **28** (1895) 2635.
5. L. B. Kier, M. C. Dodd, and D. Sapko, *Nature* **204** (1964) 697.
6. G. T. Stewart and L. B. Kier, *J. Pharm. Sci.* **54** (1965) 731.
7. A. Schoenberg, *J. Chem. Soc.* **1938** 824.
8. W. Baker and W. D. Ollis, *Quart. Rev.* **11** (1957) 15.
9. G. D. Thorn, *Can. J. Chem.* **38** (1960) 1439.
10. E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.* **36** (1958) 801.
11. E. Spinner, *J. Org. Chem.* **23** (1958) 2037.
12. R. Mecke, R. Mecke, and A. Lüttringhaus, *Chem. Ber.* **90** (1957) 975.
13. R. Mecke, Jr. and R. Mecke, Sr., *Chem. Ber.* **89** (1956) 343.

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Tiadiazoli III*. Neki 5-supstituirani derivati 2-amino-1,3,4-tiadiazola i mezoionski 1,3,4-tiadiazoli

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Pripravljeni su novi derivati 1,3,4-tiadiazola s potencijalnim fitohormonskim (spojevi I—V) i antibakterijskim (spojevi VI—IX) djelovanjem. Mezoionska struktura spojeva VI—IX u skladu je s njihovim IR i UV spektrima.

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Primljeno 29. siječnja 1970.