BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 1890—1891 (1973)

The Synthesis of Some 2*H*-Pyrazino[2,3-*e*][1,2,4]thiadiazine 1,1-dioxides

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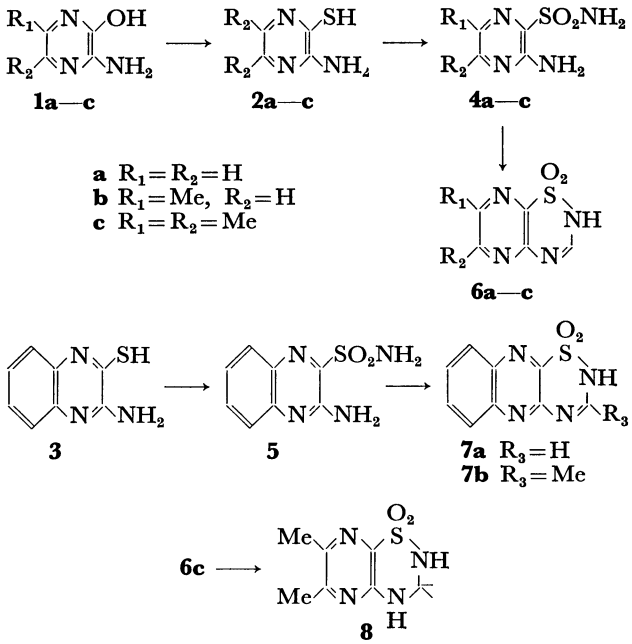
(Received September 29, 1972)

Some benzothiadiazine derivatives are nowadays used as potential diuretics. The object of this research is to synthesize the corresponding pyrazinothiadiazine derivatives,[1] analogues of benzothiadiazine diuretics. The ring system of pyrazinothiadiazine has not hitherto been reported. This paper deals with the synthesis of some compounds of the new heterocycles.

For the synthesis of aminopyrazine-3-sulfonamides, the conventional method applied to the synthesis of benzenesulfonamides starting from sulfonyl chloride is not adequate, as pyrazines have little tendency to react with electrophilic reagents. Aminopyrazine-3-thiols (**2**) were first converted into aminopyrazine-3-sulfonamides (**4**) *via* aminopyrazine-3-sulfenamides by a method similar to that described by Korman.[2] The sulfonamides thus obtained were condensed with ethyl orthoformate to give 2*H*-pyrazino[2,3-*e*][1,2,4]thiadiazine 1,1-dioxides (**6**).

Similarly 2*H*-quinoxalino[2,3-*e*][1,2,4]thiadiazine 1,1-dioxide (**7a**) and its 3-methyl derivative (**7b**) were synthesized from 2-aminoquinoxaline-3-thiol (**3**) as a starting material.

6,7-Dimethyl-2*H*-pyrazino[2,3-*e*][1,2,4]thiadiazine



Scheme 1.

Table 1.

No	Mp °C[a]	% Yield[b]	Solv[c]	UV[d] nm (ε)		
2b	219 dec	62.3	EtOH	236 (4000)	278 (4300)	387 (6300)
2c	231 dec	61.1	EtOH	228 (4600)	275 (2800)	392 (4500)
4a	216 dec	32.8	H_2O	240 (10700)	335 (4800)	
4b	217 dec	32.1	H_2O	242 (12100)	345 (4900)	
4c	222 dec	33.1	H_2O	246 (12800)	340 (7300)	
5	224—225	42.4	H_2O	248 (23300)	301 (3200)	379 (5800)
6a	256 dec	56.6	EtOH	233 (3800)	256 (3500)	300 (6600)
6b	291 dec	52.3	EtOH	233 (4000)	267 (4600)	317 (6700)
6c	>275	59.1	EtOH	231 (4300)	276 (4100)	315 (8700)
7a	>256	60.4	DMF	246 (22700)	277 (13900)	363 (8400)
7b	>300	48.3	DMF	246 (28700)	273 (15600)	362 (9600)
8	214—215	57.7	EtOH	251 (9900)	348 (7000)	

a) All the melting points were corrected.
b) Calculated after recrystallization except for **5**.
c) Recrystallization solvent.
d) Solvent, 95% EtOH.

1) The effect of pyrazinothiadiazine 1,1-dioxides on tyrosine hydroxylase was tested preliminarily; none of them exhibited either an inhibitory or accelerating effect on the enzyme.

2) J. Korman, *J. Org. Chem.*, **23**, 1768 (1958).

Table 2. Analytical data

No	Formula	Calcd %				Found %			
		C	H	N	S	C	H	N	S
2b	$C_5H_7N_3S$	42.55	5.00	29.78	22.67	42.93	5.03	29.81	22.70
2c	$C_6H_9N_3S$	46.44	5.85	27.08	20.62	46.74	5.89	26.94	21.01
4a	$C_4H_6O_2N_4S$	27.58	3.47	32.17	18.41	27.47	3.21	32.49	18.77
4b	$C_5H_8O_2N_4S$	31.91	4.28	29.77	17.04	32.05	4.27	30.04	17.01
4c	$C_6H_{10}O_2N_4S$	35.63	4.98	27.70	15.84	35.55	4.89	27.91	15.74
5	$C_8H_8O_2N_4S$	42.85	3.59	24.99	14.30	42.68	3.36	24.88	14.52
6a	$C_5H_4O_2N_4S$	32.61	2.19	30.42	17.41	32.85	2.08	30.61	17.52
6b	$C_6H_6O_2N_4S$	36.36	3.05	28.27	16.18	36.50	2.89	28.37	16.08
6c	$C_7H_8O_2N_4S$	39.62	3.84	26.40	15.08	39.69	3.64	26.47	15.10
7a	$C_9H_6O_2N_4S$	46.15	2.58	23.92	13.69	46.33	2.42	24.20	13.81
7b	$C_{10}H_8O_2N_4S$	48.38	3.25	22.57	12.92	48.52	3.11	22.48	12.59
8	$C_7H_{10}O_2N_4S$	39.24	4.70	26.15	14.97	39.23	4.61	26.43	15.24

1,1-dioxide (**6c**) was converted into the corresponding 3,4-dihydro-compound (**8**) by reduction with sodium borohydride.

Experimental

Aminopyrazine-3-thiols (2). A mixture of aminopyrazinol[3] (**1**) (10 mmol) and phosphorus pentasulfide (1.5 g) in β-picoline (30—50 ml) was refluxed for 1.5 hr. After chilling, the solvent was evaporated *in vacuo*, and the residue was dissolved in 1 M sodium hydroxide (30—50 ml). The solution was filtered and adjusted to pH 3 with concd hydrochloric acid. After the mixture was chilled overnight, the product was collected.

Aminopyrazine-3-sulfonamides (4). Concd ammonia (15 ml) was added to aminopyrazinethiol[4] (**2**) (5 mmol) in 1.5 M sodium hydroxide (5 ml). Into the solution was then poured 10% sodium hypochlorite (3.7 ml) with stirring at 5 °C. The precipitate was collected and washed well with ice water to remove ammonia. The moist product was suspended in water (30 ml) and 5% aqueous potassium permanganate solution (15 ml) was added with vigorous stirring at room temperature. The solution was filtered, neutralized with concd hydrochloric acid and concentrated to dryness *in vacuo*. The residue was crystallized from water.

2-Aminoquinoxaline-3-sulfonamide (5). Aminoquinoxalinethiol[5] (**3**) was treated as in the synthesis of **4**. The filtered solution was concentrated to a half volume and adjusted to pH 3 with concd hydrochloric acid. After the mixture had been put to stand for 1 hr, the product was collected by filtration. The product is fairly unstable against alkaline media and boiling water. For the analysis, a small portion was recrystallized from a large amount of water (85 °C).

2H-Pyrazino[2,3-e][1,2,4]thiadiazine 1,1-Dioxides (6). A mixture of aminopyrazinesulfonamide (**4**) (5 mmol) and ethyl orthoformate (7.5 ml) was heated at 130 °C for 6 hr. After the mixture had been chilled well, the product was collected and washed with ethanol.

2H-Quinoxalino[2,3-e][1,2,4]thiadiazine 1,1-Dioxide (7a). Aminoquinoxalinesulfonamide (**5**) was treated at 110 °C for 4 hr as in the synthesis of **6**.

3-Methyl-2H-quinoxalino[2,3-e][1,2,4]thiadiazine 1,1-Dioxide (7b). A mixture of aminoquinoxalinesulfonamide (**5**) (667 mg) and ethyl orthoacetate (9 ml) was heated at 100 °C for 3 hr. After the mixture had been chilled, the product was collected and washed with ethanol.

3,4-Dihydro-6,7-dimethyl-2H-pyrazino[2,3-e][1,2,4]pyrazinothiadiazine 1,1-Dioxide (8). To sodium borohydride (47.5 mg) in water (2.25 ml) was added dimethylpyrazinothiadiazine 1,1-dioxide (**6c**) (212 mg) over a period of 30 min at room temperature. After the mixture had been put to stand for 6 hr, the product was collected.

The authors wish to express their thanks to Professors T. Nagatsu and H. Kuzuya, Aichigakuin University, for testing the enzyme.

3) F. L. Muehlmann and A. R. Day, *J. Amer. Chem. Soc.*, **78**, 242 (1956).

4) F. Chillemi and G. Palamidessi, *Farmaco. Ed. Sci.*, **18**, 566 (1963).

5) H. Saikachi and S. Tagami, *Chem. Pharm. Bull.* (Tokyo) **9**, 941 (1961).