Pyridazino[4,5-*e*][1,2,4]thiadiazine 1,1-Dioxides

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Compared to the abundance of publications over the past decade in the field of 1,2,4-benzothiadiazine 1,1-dioxides, attempts to combine the 1,2,4-benzothiadiazine 1,1-dioxide ring system with other heterocycles received little attention. (1)

4,5-Dichloro-2-methyl-3(2*H*)-pyridazinone (I) (2) was a convenient starting material for both isomeric title compounds, IV and VII.

It is well known that reaction of 4,5-dichloro-2-substituted-3(2*H*)-pyridazinones of type I, with nucleophiles, either replaces both halogens (3) or the 5-position halogen only (3b,4), depending on conditions.

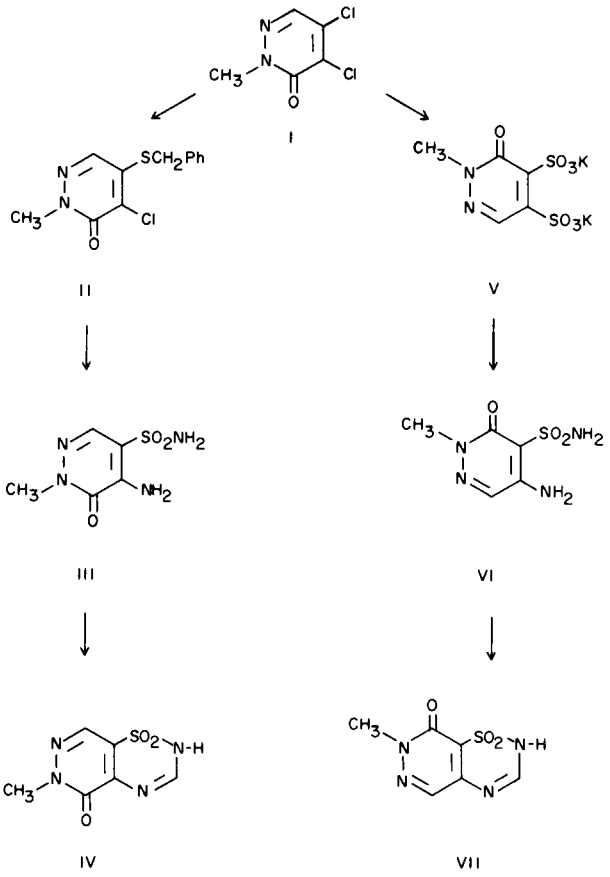
The dichloropyridazinone (I) was converted to the 5-(benzylthio)-4-chloro-3(2*H*)-pyridazinone (II) in 37% yield, which on oxidative chlorination and subsequent amination gave the 5-amino-4-sulfonamide (III). Ring closure to IV was accomplished in good yield with triethyl orthoformate.

For the preparation of the isomer (VIII), again the dichloropyridazinone (I) served as starting material. Reaction with potassium sulfite gave in excellent yield the disulfonic acid as potassium salt (V). Surprisingly, this disulfonic acid (V) was quite labile. On attempted conversion to the sulfonyl chloride with thionyl chloride and dimethylformamide it converted back to I in good yield.

On the other hand, a mixture of phosphorus pentachloride and phosphorus oxychloride converted V to a sulfonyl chloride which after amination gave an aminopyridazinonesulfonamide isomeric to III, namely VI. Its ring lcosure with triethyl orthoformate gave VII, distinctly different from its isomer (IV).

Biological Results.

Both pyridazino[4,5-*e*][1,2,4]thiadiazine 1,1-dioxides (IV and VII) were tested for diuretic activity by the method which has been described previously (5). They were void of diuretic activity at 2, 20 and 100 mg/kg/rat.



EXPERIMENTAL (6)

5-(Benzylthio)-4-chloro-2-methyl-3(2*H*)-pyridazinone (II).

To a refluxing solution of benzyl isothiuronium chloride, prepared from 76 g. (1 mole) of thiourea and 126.6 g. (1 mole) of benzyl chloride in 1000 ml. of absolute ethanol was added 179 g. of I and dropwise with stirring a solution of 128 g. of 87% potassium hydroxide in 1000 ml. of absolute ethanol. The suspension was kept at reflux temperature for 3 hours. After cooling, the inorganic material was removed by filtration, the filtrate was freed

of solvent under reduced pressure at steam-bath temperature and the residue was taken up in ether and washed with water. The yellow oil obtained after evaporation of ether crystallized readily from 2-propanol, to give 99.5 g. (37%) of white crystalline solid, m.p. 112-113°.

Anal. Calcd. for $C_{12}H_{11}ClN_2OS$: C, 54.00; H, 4.16; N, 10.51. Found: C, 53.81; H, 4.45; N, 10.36.

5-Amino-1,6-dihydro-1-methyl-6-oxo-4-pyridazinesulfonamide (III).

A solution of 86.3 g. (0.323 mole) of II in 200 ml. of acetic acid and 11.6 ml. (0.646 mole) of water was saturated with chlorine at 15°. After standing for 0.5 hour the excess chlorine was removed by introducing a stream of air. The yellow solution was poured into ice and water, the sulfonyl chloride was taken up in ~200 ml. of chloroform and without delay added to an excess of liquid ammonia. The residue after evaporation of ammonia and chloroform was washed with ether and recrystallized from water to give 28.5 g. of crude product. Recrystallization from 95% ethanol gave 25.1 g. (38%) of white crystalline solid, m.p. 222-223°.

Anal. Calcd. for $C_5H_8N_4O_3S$: C, 29.40; H, 3.95; N, 27.44. Found: C, 29.80; H, 3.97; N, 27.83.

6-Methyl-2*H*-pyridazino[4,5-*e*][1,2,4]thiadiazin-5(6*H*)-one 1,1-dioxide (IV).

A mixture of 18 g. of III and 100 ml. of triethyl orthoformate was distilled under a column for 2.5 hours. The suspension was allowed to cool, the product was collected by filtration, 18 g., m.p. >300°. Recrystallization from ethanol gave 12.5 g. (66%) of white platelets, m.p. 335-340° dec.; uv max (methanol) 320 (ϵ, 7,550) and 240 mμ (ϵ, 6,050).

Anal. Calcd. for $C_6H_6N_4O_3S$: C, 33.64; H, 2.82; N, 26.16. Found: C, 33.83; H, 3.09; N, 26.51.

2,3-Dihydro-2-methyl-3-oxo-4,5-pyridazinedisulfonic Acid Dipotassium Salt. (V).

A mixture of 316 g. (2 moles) of potassium sulfite in 750 ml. of water, 179 g. (1 mole) of I and 300 ml. of 2-propanol was heated at reflux temperature for 3 hours. Most of the 2-propanol was evaporated and the remaining solution was allowed to crystallize. The product was collected by filtration, washed with about 250 ml. of cold water, dried at 80° to give a white crystalline solid, 297.5 g. (86%), m.p. 365-370° dec.

Anal. Calcd. for $C_5H_4N_2O_7S_2K_2$: C, 17.33; H, 1.16; N, 8.09. Found: C, 16.98; H, 1.33; N, 7.73.

Conversion of V to I.

A suspension of 107 g. of V in 200 ml. of thionyl chloride and 20 ml. of dimethylformamide was heated at reflux temperature for 3 hours. The solid was filtered and the filtrate was evaporated under reduced pressure to give a yellow oil which solidified spontaneously, 43 g. (78%), m.p. 87-89°. A recrystallized sample, m.p. 90-91°, was identical in every respect with I.

5-Amino-2,3-dihydro-2-methyl-3-oxo-4-pyridazinesulfonamide (VI).

A suspension of 50 g. (0.145 mole) of V and 84 g. (0.4 mole) of phosphorus pentachloride in 100 ml. of phosphorus oxychloride was stirred at reflux temperature for 5 hours. After cooling the inorganic solid was filtered, and the filtrate was evaporated under reduced pressure at steam-bath temperature to give 26.2 g. of solid sulfonyl chloride. This was added gradually to about 200 ml. of liquid ammonia. The residual solid after evaporation was slurried in water, to give 6.5 g. (22%) of product, m.p. 255-260°. One recrystallization from ethanol raised the melting point to 267-269°. A mixed m.p. with III was depressed to 208-213°.

Anal. Calcd. for $C_5H_8N_4O_3S$: C, 29.40; H, 3.94; N, 27.44. Found: C, 29.67; H, 4.11; N, 27.27.

7-Methyl-2*H*-pyridazino[4,5-*e*][1,2,4]thiadiazin-8(7*H*)-one 1,1-dioxide (VIII).

A mixture of 1,2 g. of VI was boiled in 20 ml. of triethyl orthoformate for 3 hours. The suspension was allowed to cool and the product was collected by filtration to give 1.1 g. (95%), ~400° dec. Recrystallization from ethanol gave white platelets slowly decomposing above 400°, on fast heating at 425-430°; uv max (methanol) 292 (ϵ, 6,000) and 227 mμ (ϵ, 10,150).

Anal. Calcd. for $C_6H_6N_4O_3S$: C, 33.64; H, 2.82; N, 26.16. Found: C, 33.83; H, 2.94; N, 26.28.

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(6) Melting points were determined on a Thomas-Hoover capillary melting point apparatus with a calibrated thermometer.

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