Notes

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Den-itsu Shiho, Noboru Takahayashi, Rikuko Honda, and Reiko Morikawa: Synthesis of 6-Substituted 3-Sulfanylamido-5-methylpyridazines

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It is known that 3-sulfanylamido-6-methoxypyridazine has excellent chemotherapeutic activity. Several compounds of its analogous series have already been investigated.[1~3]

6-Substituted 3-sulfanylamido-5-methylpyridazines were prepared by a method similar to that used by Clark.[2] 3-Sulfanylamido-5-methyl-6-chloropyridazine (I) was obtained from 3-amino-5-methyl-6-chloropyridazine by the action of one mole of N-acetylsulfanilyl chloride and by subsequent treatment with sodium hydroxide. 3-Sulfanylamido-5-methyl--6-alkoxypyridazines were prepared by using (I) as an intermediate which was reacted with sodium alkoxides. The alcohols taken up in the present work were methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and benzyl alcohols. 3-Sulfanylamido-5-methyl-6-hydroxypyridazine was obtained as an unexpected product in the reaction of (I) with sodium methoxide. These products are summarized in Table I.

TABLE I. 6-Substituted 3-Sulfanylamido-5-methylpyridazines

No.	6-Substituent	Formula	Crystal form**	m.p. (°C)	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
(II)	HO	$C_{11}H_{12}O_3N_4S$	colorless leaflets	242	47.13	4.32	46.81	4.76
(III)	CH_3O	$C_{12}H_{14}O_3N_4S$	pale Y prisms	182	48.96	4.79	48.64	4.66
(IV)	C_2H_5O	$C_{13}H_{16}O_3N_4S$	white leaflets	174	50.64	5.23	50.84	5.33
(V)	*n*-C_3H_7O	$C_{14}H_{18}O_3N_4S$	pale Y needles	155.5	52.16	5.62	52.29	5.78
(VI)	*iso*-C_3H_7O	$C_{14}H_{18}O_3N_4S$	pale Y needles	205	52.16	5.62	51.96	5.77
(VII)	*n*-C_4H_9O	$C_{15}H_{20}O_3N_4S$	pale Y prisms	145	53.55	6.00	53.61	6.13
(VIII)	*iso*-C_4H_9O	$C_{15}H_{20}O_3N_4S$	colorless leaflets	174.5	53.55	6.00	53.38	6.07
(IX)	*sec*-C_4H_9O	$C_{15}H_{20}O_3N_4S$	pale Y needles	184.5	53.55	6.00	53.60	6.02
(X)	$C_6H_5CH_2O$	$C_{18}H_{18}O_3N_4S$	pale Y needles	217	58.38	4.90	58.14	4.92

** Y: yellow

The chemotherapeutic activities of these compounds are now being tested.

Attempt to condense 3-amino-4-methyl-4-chloropyridazine with N-acetylsulfanilyl chloride under the same condition as in the case of 3-amino-5-methyl-6-chloropyridazine was unsuccessful.

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Experimental

3-Sulfanylamido-5-methyl-6-chloropyridazine (I)—To 7.2 g. of 3-amino-5-methyl-6-chloropyridazine suspended in 25 cc. of dehyd. pyridine, 11.5 g. of N-acetylsulfanilyl chloride was added and the resulting yellow solution was warmed on a water bath at 55~60° for 1 hr. Then 100 cc. of 2*N* NaOH was added and allowed to stand at 55~60° for 30 mins. After dilution with water, the reaction mix-

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1) W. G. Overend, L. F. Wiggins: J. Chem. Soc., **239**, 545(1947).
2) American Cyanamid Co.: U. S. Pat. 2,712,012 (June 28, 1955).
3) R. F. Homer, H. Gregory, L. F. Wiggins: J. Chem. Soc., **1948**, 2191; J. Druey, Kd. Meier, K. Eichenberger: Helv. Chim. Acta, **37**, 121(1954); C. Grundmann; Ber., **81**, 1(1948).

ture was evaporated, the residue was chilled, and acidified with conc. HCl. The yellow precipitate was collected and recrystallized twice from EtOH; m.p. 223°. *Anal.* Calcd. for $C_{11}H_{11}O_2N_4ClS$: C, 44.52; H, 3.71. Found: C, 44.23; H, 3.98.

3-Sulfanylamido-5-methyl-6-methoxypridazine (III) and 3-Sulfanylamido-5-methyl-6-hydroxypridazine (II)—To a MeOH solution of MeONa (0.12 g. of Na dissolved in 15 cc. of MeOH), 0.6 g. of (I) was added and the mixture was heated in a sealed tube at 130~140° for 8 hrs. After cool, the reaction mixture was filtered, acidified with 10% AcOH under ice-cooling, and evaporated to dryness. The residue was dissolved in 5% NaOH, chilled, and acidified with 10% AcOH. The crude product was collected and recrystallized from MeOH to give 3-sulfanylamido-5-methyl-6-methoxypridazine, m.p. 182°.

In the above-mentioned reaction, 3-sulfanylamido-5-methyl-6-hydroxypridazine was obtained as colorless leaflets, m.p. 242°, when the temperature was at 40~60° during acidification.

3-Sulfanylamido-5-methyl-6-alkoxypyridazines (IV~X)—To an alcoholic solution of sodium alkoxides (0.01 mole of Na dissolved in 10~15 cc. of the alcohol) 1.16 g. of (I) was added and the reaction mixture was heated in a sealed tube at 130~150° for 8~13 hrs. After cool, the mixture was filtered, acidified with 10% AcOH, and evaporated to dryness. The residue was dissolved in 5% NaOH, chilled, and acidified with 10% AcOH. The crude product was collected and, recrystallized from EtOH or water-EtOH (see Table I).

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Noboru Takahayashi and Rikuko Honda: Synthesis of Pyridazine Derivatives. IX.[1] On the Oxidation Products of Sulfur-containing Compounds of Pyridazine. (3).[2]

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In one of the previous papers[2] of this series, one of the present authors (N.T.) reported the oxidation of 3-chloro-6-alkylthiopyridazine (I). It was at first assumed that the oxidation product obtained from (I) with peracetic acid might be its N-oxide.

A more extensive studies, especially on the oxidation products of 3-chloro-6-methylthio-, -6-ethylthio-, and -6-isopropylthio-pyridazines revealed that they are 6-alkylsulfonyl-3-pyridazinols (II) and it was further clarified that 3-methoxy-6-alkylthio- and 3-phenoxy-6-alkylthio-pyridazines also produced corresponding (II) with peracetic acid.

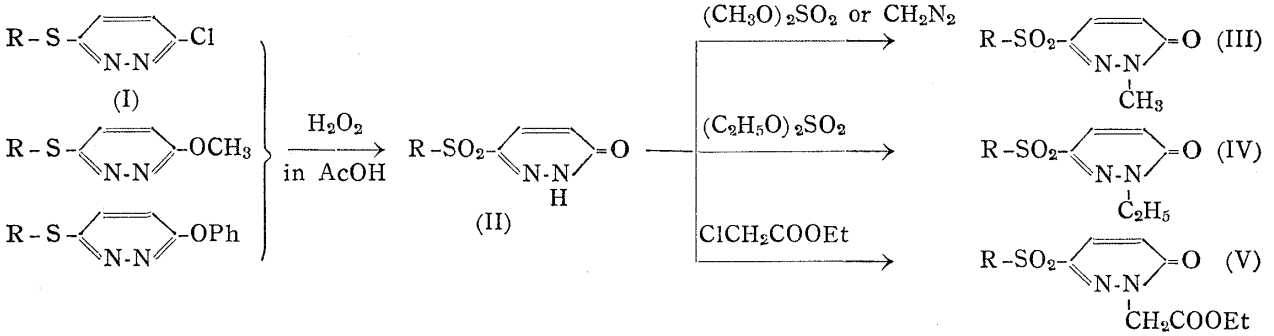

Chart 1. R=(a) CH_3, (b) C_2H_5, (c) *iso*-C_3H_7

Infrared absorption spectra of (IIa) and (IIb) support the formula (II), namely, as listed in Table I, they exhibit absorptions of C=O, N-H, and S-O.

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1) Part VIII: This Bulletin, **5**, 229 (1957).

2) Part IV: Yakugaku Zasshi, **75**, 1245 (1955); Part VI: *Ibid.*, **76**, 1293 (1956).