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Synthesis of new 1,3,5-thiadiazine and 1,3,5-triazine derivatives and their antimicrobial activity

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Abstract. Interaction of ethyl chloroformate with γ-N-substituted trithioallophanic acids has been found to yield the corresponding 6-oxo-5-aryl-2,4-dithio-hexahydro-1,3,5-thiadiazines. These on reaction with amines yield 1,3,5-triazines. γ-N-substituted β-oxo-dithio-allophanic acid with ethyl chloroformate similarly yields 4,6-dioxo-5-aryl-2-thio-1,3,5-thiadiazine. Antimicrobial activity of thiadiazines has been reported.

Keywords. 1,3,5-Thiadiazines; trithioallophanic acids; ethyl chloroformate; 1,3,5-triazines.

1. Introduction

In continuation of our work on trithioallophanic acids (Chande 1969, 1970; Chande and Dravid 1981), we now report the synthesis of new 1,3,5-thiadiazines and 1,3,5-triazines by reaction of ethyl chloroformate with γ-N-substituted trithioallophanic acids (Damle 1976, 1979). Since a large number of organic compounds containing nitrogen or sulphur or both are known to possess antimicrobial activity, the compounds reported in this communication have been tested for their activity.

2. Experimental

2.1 *Reaction of trithioallophanic acid (1) with pyridine*

γ-N-Chlorophenyl trithioallophanic acid (5 g) was suspended in 25 ml benzene and to this pyridine (5 ml) was added. The acid first dissolved and the solution became yellow. On shaking the contents, a yellow solid immediately separated out (6 g). This was first filtered, then washed with ether and dried in vacuum m.p. 92°C. It could not be crystallized as it decomposed. Hence it was probably the pyridinium salt of trithioallophanic acid (1, R = *m*-chlorophenyl). By a similar method the pyridinium salts of γ-N-*p*-chlorophenyl, γ-N-phenyl, γ-N-*p*-tolyl, γ-N-*o*-tolyl, γ-N-*o*-chlorophenyl trithioallophanic acids and γ-N-phenyl-β-oxo-dithioallophanic acid were prepared.

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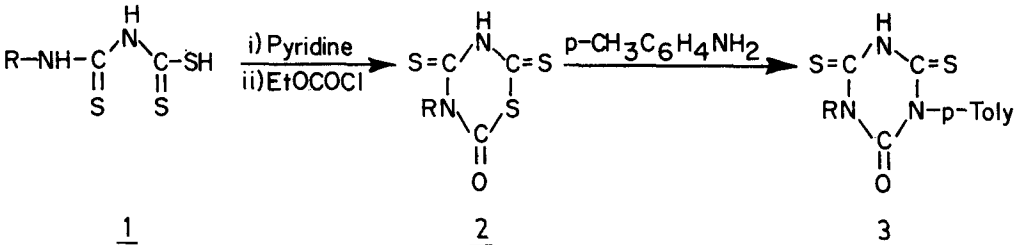
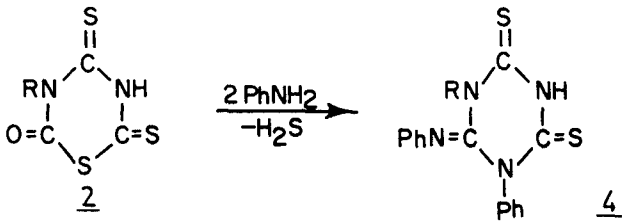
2.2 *Interaction of ethyl chloroformate with pyridinium salt of γ-N-m-chlorophenyl trithioallophanic acid (1, R = m-chlorophenyl)*

Five grams of the pyridinium salt of 1 (R = *m*-chlorophenyl) were suspended in benzene (30 ml) and to this ethyl chloroformate (5 ml) was added in the cold. A vigorous exothermic reaction set in during which the strong characteristic smell of S-carbethoxy compound was perceptible. After 5 min the benzene solution was filtered from the precipitated pyridine hydrochloride. On evaporating the benzene, shining light yellow needles were obtained (5 g). The product was washed repeatedly with petroleum ether (60–80°C) and dried. It was then crystallized from rectified spirit, m.p. 144°C. Elemental analysis found C, 37·38; H, 1·76; N, 9·5; S, 33·1%. $C_9H_5N_2S_3OCl$ requires C, 37·43; H, 1·73; N, 9·70; S, 33·27%. On heating, the compound decomposed to give *m*-chlorophenyl isothiocyanate, carbon oxysulphide and thiocyanic acid, which were detected by the usual methods. It could not be benzylated as it decomposed during benzylation to give benzyl thiocyanate. Its IR spectrum in nujol showed the following main bands (in cm^{-1}): 3000 (NH), 1700 (C=O), 1580 (NH), 1240 (C=S), 680 (–C–S–C–). The compound was identified as 6-oxo-5-*m*-chlorophenyl-2,4-dithio-hexahydro-1,3,5-thiadiazine (2). Thiadiazines prepared from other trithioallophanic acids are listed in table 1.





where R = phenyl, *o*-chlorophenyl, *m*-chlorophenyl, *p*-chlorophenyl, *o*-tolyl, *p*-tolyl.

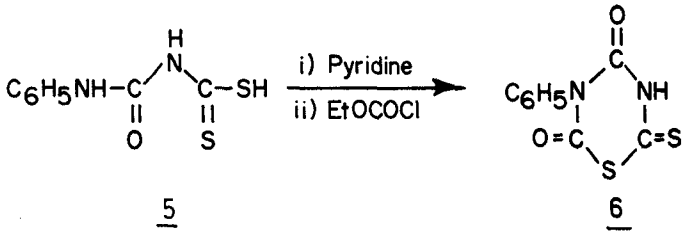


Table 1. Properties of thiadiazines prepared from trithioallophanic acids.

γ-aryl trithio-allophanic acid (1) Aryl =	Thiadiazine (3) Formula	m.p. (°C)	Yield (%)	Analysis		Molecular weight (cryoscopically), benzene as solvent	
				Found (%)	Cacld. (%)	Found	Cacld.
Phenyl	$C_9H_6N_2S_3O$	161	94	C 42·46 H 2·31 N 10·9 S 37·5	C 42·51 H 2·36 N 11·02 S 37·79	253·4	254·0
o-Chlorophenyl	$C_9H_5N_2S_3OCl$	184	98	C 37·18 H 1·85 N 9·6 S 33·2	C 37·43 H 1·73 N 9·705 S 33·27	289·0	288·5
m-Chlorophenyl	$C_9H_5N_2S_3OCl$	144	98	C 37·38 H 1·76 N 9·5 S 33·1	C 37·43 H 1·73 N 9·705 S 33·27	286·0	288·5
p-Chlorophenyl	$C_9H_5N_2S_3OCl$	146	98	C 37·01 H 1·77 N 9·6 S 33·1	C 37·43 H 1·73 N 9·705 S 33·27	288·0	288·5
o-Totyl	$C_{10}H_8N_2S_3O$	136	81	C 44·65 H 2·91 N 10·32 S 35·65	C 44·77 H 2·98 N 10·44 S 35·82	269·2	268·0
p-Totyl	$C_{10}H_8N_2S_3O$	170	83	C 44·71 H 2·87 N 10·2 S 35·55	C 44·77 H 2·98 N 10·44 S 35·82	268·5	268·0

In all the experiments γ-aryl trithioallophanic acid (5 gm), pyridine (5 ml), ethyl chloroformate (5 ml) and benzene (30 ml) were used.

2.3 *Reaction of 2 (R = m-chlorophenyl) with aniline*

Two grams of compound (2) (R = *m*-chlorophenyl) were dissolved in 25 ml chloroform and to this aniline (2 ml) was added. After about 20 min a colourless product separated out (2·2 g). Hydrogen sulphide was evolved during the reaction. The compound was filtered and washed with petroleum ether (60–80°C). It was crystallized from rectified spirit, m.p. 163°C. Analysis found C, 59·42; H, 3·21; N, 13·29; S, 16·0%. $C_{21}H_{15}N_4S_2Cl$ requires C, 59·64; H, 3·55; N, 13·25; S, 15·14%. The IR spectrum in nujol showed the following main bands: 1600 (–C(=N)–), 1550 (*s*-triazine), 1200 (cyclic NH–C(=S)–), 760 (*iso* form of *s*-triazine). The compound did not desulphurize on heating with alkali plumbite solution although it could be S-alkylated (ethyl derivatives, m.p. 197°C). It was identified as 6-phenylimino-5-*m*-chlorophenyl-2,4-dithio-1-phenyl-hexahydro-1,3,5-triazine (4, R = *m*-chlorophenyl).

2.4 *Reaction of 2 (R = m-chlorophenyl) with p-toluidine*

Two grams of compound 2 (R = *m*-chlorophenyl) were dissolved in chloroform (30 ml) and to this *p*-toluidine (2 g) was added. A solid separated out after about 30 min. It was filtered (2 g), crystallized from alcohol, m.p. 160–162°C. The IR spectrum showed the following bands: 1680 (–C=O) (cyclic), 1535 (*s*-triazine), 1210 (NH–C(=S)), 760 (*iso* form of *s*-triazine). The compound gave *m*-chlorophenyl isothiocyanate on heating. Analysis found C, 52·98; H, 3·38; N, 11·1; S, 17·76%. $C_{16}H_{12}N_3S_2OCl$ requires C; 53·11; H, 3·31; N, 11·61; S, 17·70%. This compound also did not desulphurize. It was identified as 6-oxo-5-*m*-chlorophenyl-2,4-dithio-1-*p*-tolyl-hexahydro-1,3,5-triazine (3, R = *m*-chlorophenyl).

Reaction of 2 (R = *p*-chlorophenyl) with *p*-toluidine yielded 6-oxo-5-*p*-chlorophenyl-2,4-dithio-1-*p*-tolyl-hexahydro-1,3,5-triazine, m.p. 180°C (R = *p*-chlorophenyl). Its IR spectrum is similar to that of 3 (R = *m*-chlorophenyl).

2.5 *Reaction of γ-N-phenyl-β-oxo-dithioallophanic acid (5) with ethyl chloroformate*

Compound 5 (2·1 g) was suspended in benzene (25 ml) and to this pyridine (2 ml) and ethyl chloroformate (2 ml) were added. The vigorous exothermic reaction was followed by liberation of the intense smell of S-carbethoxy compound. Upon evaporation of benzene white needles were formed. Crystallized from alcohol, m.p. 258°C. On analysis found N, 11·7; S, 26·1%. $C_9H_6N_2S_2O_2$ requires N, 11·76; S, 26·89%. The compound was identified as 4,6-dioxo-5-phenyl-2-thio-hexahydro-1,3,5-thiadiazine (6).

3. Results and discussion

On carrying out the reaction of ethyl chloroformate with trithioallophanic acids in benzene the latter decomposed. However, by using the pyridinium salts of the trithioallophanic acids the reaction was found to be smooth. For example, γ-N-*p*-chlorophenyl trithioallophanic acid (1, R = *p*-chlorophenyl) on reaction with pyridine in benzene yielded the pyridinium salt, which on reaction with ethyl chloroformate gave a silky shining light yellow product with molecular composition $C_9H_5N_2S_3OCl$, m.p. 146°C. This product, on pyrolytic decomposition, gave *p*-chlorophenyl isothiocyanate, carbonyl sulphide and thiocyanic acid. Benzylation of it was unsuccessful as it readily decomposed yielding benzyl thiocyanate. Thus, it had only one replaceable proton in the form of the –NH–C(=S)– group. The IR spectrum in nujol showed the presence of carbonyl group (1700*s* cm^{-1}), –C–S–C– linkage (600 cm^{-1}) and >C=S group (1240 cm^{-1}) (Colthup *et al* 1964; Scheinmann 1970). On keeping, the compound slowly decomposed. It was identified as 6-oxo-5-*p*-chlorophenyl-2,4-dithio-hexahydro-1,3,5-thiadiazine (2, R = *p*-chlorophenyl). By following a similar procedure different thiadiazines were synthesized (see §5)

The thiadiazine 2 can be looked upon as cyclic thio-anhydride (O–C(=S)–C(=S)) which can be used as an acylating agent. On reaction with *p*-toluidine in chloroform, 2 yielded 6-oxo-5-*p*-chlorophenyl-2,4-dithio-1-*p*-tolyl-hexahydro-1,3,5-triazine (3, R = *p*-chlorophenyl). Hydrogen sulphide was found to have been eliminated.

Reaction of 2 with aniline in chloroform, however, followed a different course. The product, obtained in quantitative yield, did not show the presence of a carbonyl band in its IR spectrum. Instead it had an extracyclic >C=NR group (1580 cm^{-1}). On the basis of its IR spectrum and elemental/chemical analysis, it was identified as 6-phenylimino-5-*p*-chlorophenyl-2,4-dithio-1-phenyl-hexahydro-1,3,5-triazine (4). The different course followed in the reaction of 2 with *p*-toluidine may probably be due to the greater bulk of the tolyl group.

In another experiment γ-N-phenyl-β-oxo-dithioallophanic acid (5) was treated with pyridine and ethyl chloroformate. A vigorous exothermic reaction was followed by liberation of the intense smell of S-carbethoxy group. The white silky compound formed, m.p. 258°C, was identified as 4,6-dioxo-5-phenyl-2-thio-hexahydro-1,3,5-thiadiazine (6).

4. Antimicrobial activity

For studying the bactericidal and fungicidal activities, 6-oxo-5-aryl-2,4-dithio-hexahydro-1,3,5-thiadiazine (2, R = *m*-chlorophenyl and *p*-chlorophenyl) were tested against the bacterium *Bacillus subtilis*, and the fungi *Helminthosporium sativum*, *Alternaria tenuis* and *Curvularia lunata*. The experiment was performed by the paper disc method (Thornberry 1950). Four different concentrations, viz., 10 mg/100 ml, 20 mg/100 ml, 30 mg/100 ml and 50 mg/100 ml were prepared in DMF. The bactericidal property was found to be highest at 50 mg/100 ml concentration while optimum fungicidal activity was observed at 30 mg/100 ml. The compounds, in general, have good antimicrobial activity.

5. Conclusion

The reaction of trithioallophanic acids and dithioallophanic acid with ethyl chloroformate is found to be a general one. The thiadiazines thus prepared appear to have considerable antimicrobial activity.

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