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Derivatives of 7H-5, 6-Dihydro-6-oxo-s-triazolo-(3, 4-b)-1, 3, 4-thiadiazine

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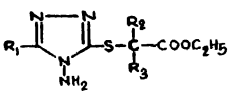
In the course of our work on heterocyclic systems, we wanted to investigate the pharmacological potentialities of the sparsely-studied heterocyclic system, *s*-triazolo-(3,4-b)-1,3,4-thiadiazine[1,2].

4-Amino-3-mercapto-1,2,4-triazole derivatives required for this work were all prepared by reported methods[3,4]. The 3-mercapto-1,2,4-triazole derivatives were condensed with ethyl chloroacetate, ethyl-2-chlorophenylacetate and ethyl-2-chloro-2-phenylpropionate to obtain the 3-carbethoxymethylmercapto-1,2,4-triazole derivatives listed in Table 1. The condensation of 3-mercapto-1,2,4-triazoles with ethyl chloroacetate and ethyl 2-chlorophenylacetate proceeded smoothly in refluxing ethanol in presence of anhydrous potassium carbonate. The condensation of 3-mercapto-1,2,4-triazoles with ethyl 2-chloro-2-phenylpropionate had, however, to be carried out in refluxing ethanol in presence of one equivalent of sodium ethoxide.

TABLE 1

Analytical data of derivatives of 4-*amino*-3-*carbethoxymethylmercapto*-1,2,4-*triazole*



No.	R_1	R_2	R_3	m.p. °C	Nitrogen % Found	Nitrogen % Required
1	2-Chlorophenyl	H	H	99–100	17.92	17.92
2	4-Chlorophenyl	H	H	180	17.85	17.92
3	3-Methylphenyl	H	H	112–13	18.93	19.18
4	4-Methylphenyl	H	H	169–70	18.89	19.18
5	4-Pyridyl	H	H	182–83	25.26	25.09
6	Phenyl	C_6H_5	H	130–31	15.64	15.81
7	4-Chlorophenyl	C_6H_5	H	177–78	14.11	14.42
8	3-Methylphenyl	C_6H_5	H	146–47	15.37	15.22
9	4-Methylphenyl	C_6H_5	H	169–70	15.33	15.22
10	Phenyl	C_6H_5	CH_3	139–40	15.52	15.22
11	4-Chlorophenyl	C_6H_5	CH_3	142–43	13.74	13.92
12	4-Methylphenyl	C_6H_5	CH_3	135–36	14.34	14.66

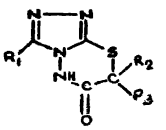
All melting points are uncorrected.

The cyclisation of 3-carbethoxymethyl-mercapto-1,2,4-triazole derivatives to the corresponding derivatives of 7H-5,6-dihydro-6-oxo-*s*-triazolo-(3,4-b)-1,3,4-thiadiazine (Table 2) could be easily accomplished by refluxing the former in absolute ethanol containing sodium ethoxide.

The compounds (Tables 1 & 2) were screened for hypnotic, anticonvulsant, analgesic and anti-inflammatory properties by standard methods[5], using methaqualone, phenobarbital and dilantin sodium, aspirin and butazolidine respectively as standards. Except for 4-amino-3-carbethoxybenzylmercapto-5-*m*-tolyl-1,2,4-triazole (Tables 1–8) which showed at 200 mg/kg level analgesic properties equivalent to those of aspirin, none of the compounds showed any significant pharmacological activities.

TABLE 2

Analytical data of 7H-5,6-dihydro-6-oxo-s-triazolo-(3,4-b)-1,3.4-thiadiazine derivatives



No.	R_1	R_2	R_3	m.p. °C	Nitrogen % Found	Nitrogen % Required
1	2-Chlorophenyl	H	H	232–34	20.85	21.01
2	4-Chlorophenyl	H	H	236–37	20.96	21.01
3	3-Methylphenyl	H	H	205–07	22.63	22.77
4	4-Methylphenyl	H	H	234–35	22.87	22.77
5	4-Pyridyl	H	H	272–73	30.32	30.04
6	Phenyl	C_6H_5	H	215–17	18.36	18.18
7	2-Chlorophenyl	C_6H_5	H	260–61	16.50	16.35
8	4-Chlorophenyl	C_6H_5	H	222–24	16.60	16.35
9	3-Methylphenyl	C_6H_5	H	106–08	17.60	17.39
10	4-Methylphenyl	C_6H_5	H	206–08	17.33	17.39
11	Phenyl	C_6H_5	CH_3	203–05	17.59	17.39
12	2-Chlorophenyl	C_6H_5	CH_3	110–12	16.10	15.71
13	4-Chlorophenyl	C_6H_5	CH_3	256–57	15.48	15.71
14	3-Methylphenyl	C_6H_5	CH_3	251–53	16.34	16.65
15	4-Methylphenyl	C_6H_5	CH_3	243–44	16.60	16.65

All melting points are uncorrected.

EXPERIMENTAL

4-Amino-3-carbethoxymethylmercapto-5-o-chlorophenyl-1,2,4-triazole (*Table* 1-1) : 4-Amino-3-mercapto-5-*o*-chlorophenyl-1,2,4-triazole (4·5 g; 0·02 mole) and anhydrous potassium carbonate (1·39 g; 0·01 mole) were refluxed and stirred for 30 min. in absolute ethanol (50 ml).

Ethyl chloroacetate (2·2 ml; 0·02 mole) was then added dropwise to the reaction mixture over 10 mins. The reaction mixture was then stirred and refluxed for 3 hrs. Alcohol was then distilled off *in vacuo*. The solid residue was washed with water and then crystallised from benzene-hexane to obtain the title product in 75% yield.

4-*Amino*-3-(2′-*carbethoxy*-2′-*methyl*)-*benzylmercapto*-5-*phenyl*-1,2,4-*triazole* (*Table* 1–10). 4-Amino-3-mercapto-5-phenyl-1,2,4-triazole (3·85 g; 0·02 mole) was refluxed for 30 min. in absolute ethanol (80 ml) containing 0·02 mole of sodium ethoxide. Ethyl 2-chloro-2-phenyl-propionate (4·25 g; 0·02 mole) in absolute ethanol (20 ml) was added to the reaction mixture over 10 min. and refluxed for 3 hrs. more. Alcohol was distilled off *in vacuo*; the solid residue was washed with water and crystallised from benzene-hexane to obtain the title product in 50% yield.

3-o-*Chlorophenyl*-7*H*-5,6-*dihydro*-6-*oxo*-s-*triazole*-(3,4-*b*)-1,3,4-*thiadiazine* (*Table* 2–1) 4-Amino-3-carbethoxymethylmercapto-5-*o*-chlorophenyl-1,2,4-triazole (6·25 g; 0·02 mole) was refluxed in absolute ethanol (200 ml) containing sodium ethoxide (0·04 mole) for 3 hrs. The solvent was distilled from the reaction mixture; the residue was taken in water (40 ml), filtered and acidified. The solid obtained was crystallised from benzene-hexane to obtain the title product in 60% yield.

The rest of the compounds in Tables 1 and 2 were similarly prepared.

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REFERENCES

1. G. P. Sokolov and S. Hillers, *Khim. Geterotsikl. Soedin.*, 1967, **3**, 556; *Chem. Abs.*, 1968, **68**, 105174^{s}.
2. G. Westphal and P. Henklein, *Z. Chem.*, 1969, **9**, 111; *Chem. Abs.*, 1969, **70**, 96771^{w}.
3. E. Hoggarth, *J. Chem. Soc.*, 1952, 4811.
4. M. Kanaoka, *J. Pharm. Soc.*, (Japan), 1956, **76**, 1133.
5. S. Somasekhara, V. S. Dighe, G. F. Shah and S. V. Gokhale, *Indian J. Pharm.*, 1971, **33**, 24,