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Note

Synthesis of biologically active 4-amino-6-arylmethyl-3-mercapto-1, 2, 4-triazin-5(4*H*)-ones and their Schiff bases

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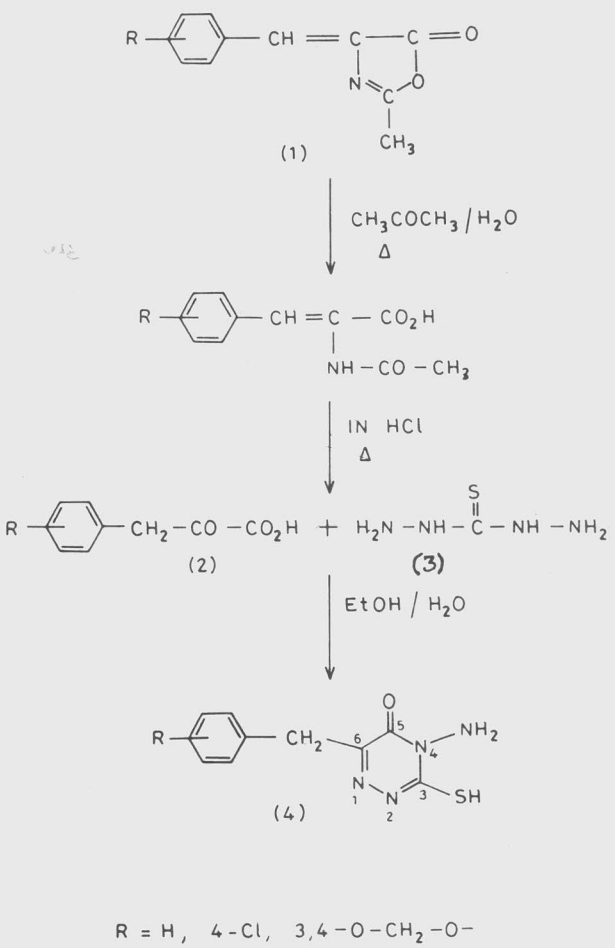
Three arylpyruvic acids **2** are condensed with thiocarbohydrazide **3** in aqueous ethanol to yield 4-amino-6-arylmethyl-3-mercapto-1, 2, 4-triazin-5(4*H*)-ones **4**. In a modified method these title compounds **4** have also been prepared by direct condensation of the intermediate azalactones **1** with thiocarbohydrazide **3**. Compounds **4** on condensation with substituted benzaldehydes afford corresponding Schiff bases. Some of them are screened for their antifungal activities.

Several triazinones and their condensation products find important applications in medicinal and agricultural fields[1]. The synthesis of triazinones have already been reported in the literature[2-6]. Syntheses of aza-uracils and their thio and thioalkyl derivatives having anti-diuretic and neuro-depressant activities were reported by Timar *et al.*[7]. Some of the *s*-alkylated mercaptotriazinones exhibited herbicidal activities. Among them 4-amino-3-methylthio-6-*t*-butyl-1, 2, 4-triazin-5(4*H*)-one is being used as a commercial herbicide for the control of weeds in potato crops[8]. 4-Amino-3-mercapto-1, 2, 4-triazin-5(4*H*)-ones were used for the synthesis of several N-bridged heterocycles[9,10].

Prompted by these observations it was contemplated to synthesize a new series of 4-amino-6-arylmethyl-3-mercapto-1, 2, 4-triazin-5-(4*H*)-ones **4** by the condensation of arylpyruvic acids **2** with thiocarbohydrazide **3** in ethanol (Scheme I, Table I). The results of these experiments along with the antifungal activities of some compounds are reported in this paper. Triazinones **4** were also prepared by a modified synthetic procedure by direct condensation of azalactones **1** with thiocarbohydrazide **3** in aqueous ethanol or aqueous dioxane depending upon the solubility of azalactones used.The parent compounds were thus obtained in a single step without the isolation of arylpyruvic acids.



Scheme I

Table I—Physical data of compounds **4a-c**

Compd	R	m.p. °C	yield (%)	Mol. formula
4a	H	195-98	78	$C_{10}H_{10}N_4OS$
4b	4-Chloro-	215-18	80	$C_{10}H_9N_4ClOS$
4c	3,4-methyl-enedioxy-	220-23	69	$C_{11}H_{10}N_4O_3S$

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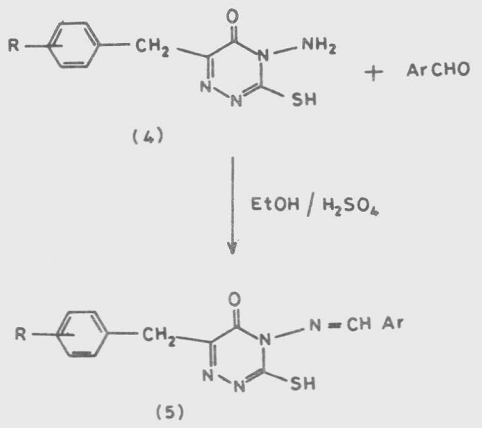
The substituted triazinones **4** were then condensed with aromatic aldehydes in ethanol in the presence of conc. H_2SO_4 to yield 4-arylidineamino-6-arylmethyl-3-mercapto-1, 2, 4-triazin-5(4*H*)-ones **5** (Scheme II, Table II). The parent triazinones **4** and their Schiff bases **5** were characterized by elemental analyses and spectral (IR, ^{1}H NMR and mass) data.

^{1}H NMR spectrum of benzyltriazinone **4a** showed a sharp singlet at δ 6.48 integrating for 2 protons which is characteristic of N-NH_2 group. The phenyl protons resonated as a singlet at δ 7.28 integrating for 5 protons, while -SH protons resonated as a singlet at δ 13.87. The signal for methylene protons of benzyl moiety was seen as a singlet at δ 3.91.

The mass spectra of benzyltriazinone **4a** and *p*-chlorobenzyltriazinone **4b** were in conformity with the structures assigned. Mass spectrum of **4a** showed a molecular ion peak at m/z 234, consistent with the molecular formula $C_{10}H_{10}N_4OS$. The mass spectrum of **4b** showed a molecular ion peak at m/z 268 and M+2 peak at m/z 270 corresponding to its molecular formula $C_{10}H_9N_4ClOS$. The IR spectrum of **4a** showed an absorption band due to carbonyl stretching at 1640 cm^{-1}. The asymmetric and symmetric frequencies of $-NH_2$ group manifested as absorption bands at 3250 and 3160 cm^{-1}, respectively.



R = H 4-Cl 3,4-O-CH_2-O-

Ar = Methylphenyl, methoxyphenyl, 4-chlorophenyl, 3 4-methylenedioxyphenyl, o-hydroxyphenyl 2-Bromo-3,4-methylenedioxyphenyl, 5-Bromo-2-hydroxyphenyl

Scheme II

^{1}H NMR spectrum of **5b** showed a singlet at δ 3.85 corresponding to methylene protons of benzyl group. The methoxy protons resonated as a singlet at δ 3.9. The signals of aromatic protons of the benzyl and anisyl moieties appeared as multiplets at δ 7-8 and the signal due to -N=CH proton was

Table II—Physical data of compounds **5a-p**

Compd	R	Ar	m.p. °C	Yield (%)	Mol. formula
5a	H	4-methylphenyl	188	65	$C_{18}H_{16}N_4OS$
5b	H	4-methoxyphenyl	196	65	$C_{18}H_{16}N_4O_2S$
5c	H	3,4-methylenedioxyphenyl	200	66	$C_{18}H_{14}N_4O_3S$
5d	H	2-bromo-3,4-methylenedioxyphenyl	210	84	$C_{18}H_{13}BrN_4O_3S$
5e	H	4-chlorophenyl	184	65	$C_{17}H_{13}N_4ClOS$
5f	H	2-hydroxyphenyl	200	77.5	$C_{17}H_{14}N_4O_2S$
5g	H	5-bromo-2-hydoxyphenyl	260	80	$C_{17}H_{13}BrN_4O_2S$
5h	4-chloro	4-methylphenyl	208	70	$C_{18}H_{15}N_4ClOS$
5i	4-chloro	4-methoxyphenyl	204	69	$C_{18}H_{15}N_4ClO_2S$
5j	4-chloro	3,4-methylenedioxyphenyl	215	68	$C_{18}H_{13}N_4ClO_3S$
5k	4-chloro	2-bromo-3,4-methylene-dioxyphenyl	175	67	$C_{18}H_{12}BrClN_4O_3S$
5l	4-chloro	4-chlorophenyl	192	67	$C_{17}H_{12}Cl_2N_4O_5$
5m	4-chloro	2-hydroxyphenyl	158	72	$C_{17}H_{13}ClN_4O_2S$
5n	3,4-methylenedioxy	4-methylphenyl	212	55	$C_{19}H_{16}N_4O_3S$
5o	3,4-methylenedioxy	4-methoxyphenyl	207	56	$C_{19}H_{16}N_4O_4S$
5p	3,4-methylenedioxy	3,4-methylenedioxyphenyl	202	57	$C_{19}H_{14}N_4O_5S$

seen as a singlet at δ 8.6 while -SH proton resonated as a singlet at δ 13.75. The mass spectrum of Schiff base **5b** showed a molecular ion peak at m/z 352 consistent with its molecular formula $C_{18}H_{16}N_4O_2S$. The IR spectrum of **5b** showed no absorption bands corresponding to the –NH stretching frequencies of parent triazinone. However, a sharp absorption band was seen at 1580 cm^{-1} corresponding to C=N linkage. The carbonyl stretching frequency was observed at 1650 cm^{-1}.

Antifungal activity

Some of the triazinones and their Schiff bases were tested for antifungal activity against *Candida albicans* and *Paccilomyces variotti* by filter disc method. Hamycin was used as standard drug. Among the compounds tested **5e** (R=H, Ar=4-chlorophenyl) possessed the highest degree of antifungal activity against *C. albicans* (Table III). Compound **5c** (R=H, Ar=3,4-methylenedioxyphenyl) was found to be the most active compound against *P. variotti* (Table III).

Table III—Antifungal activities of triazinones **4** and their Schiff bases **5**

Compd	MIC in μg/mL [zone of inhibition in nm] Antifungal activity	
	C. albicans	*P. variotti*
4a	—	—
4b	—	—
4c	—	—
5a	7.5 (10)	10 (10)
5b	7.5 (10)	12.5 (10)
5c	10 (12.5)	7.5 (10)
5e	5 (10)	10 (12)
5h	10 (12)	—
5j	—	—
5o	—	—
5p	—	—
Hamycin	0.01 (12.5)	0.25 (14.5)

Experimental Section

Melting points were determined by capillary method and are uncorrected. IR spectra (nujol mull) were recorded on a Perkin-Elmer infrared spectrophotometer; ^{1}H NMR spectra in DMSO-d_6 on a JEOL GS×400 spectrometer; and mass spectra on a VG-micromass Mass spectrometer. Azalactones **1**, arylpyruvic acids **2** and thiocarbohydrazide **3** were prepared by the literature methods[11].

Preparation of 4-amino-6-arylmethyl-3-mercapto-1, 2, 4-triaizin-5(4*H*)-ones (4a-c). General procedure.

Method-A. To a solution of thiocarbohydrazide **3** (1.06 g, 0.01 mole) in warm water (30 mL) was added dropwise a solution of arylpyruvic acid **2** (0.01 mole) in ethanol with stirring. The reaction mixture was refluxed on a water-bath for 1 hr. The solid product thus separated was filtered and recrystallised from ethanol to give **4a-c**. Their physical data are given in Table I.

Method-B. A mixture of azalactone **1** (0.01 mole) and thiocarbohydrazide **3** (0.01 mole) was refluxed in aq. ethanol or aq. dioxane for 4 hr. The excess solvent was distilled off under reduced pressure. The product obtained after cooling was filtered and crystallised from ethanol to give triazinones **4a-c**.

Preparation of 4-arylideneamino-6-arylmethyl-3-mercapto-1, 2, 4-triazin-5(4*H*)-ones 5a-p. General procedure. To a solution of **4a-c** (0.01 mole) and substituted benzaldehyde (0.01 mole) in ethanol (20 mL) were added a few drops of conc. H_2SO_4 and the mixture was heated under reflux on a water-bath for 2-3 hr. The solid mass obtained on cooling was collected by filtration and crystallised from ethanol to yield Schiff bases **5a-p**. Their physical data are given in Table II.

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