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Synthesis of 1-Aryl-2-mercapto-4-aryl-1,6-dihydro-1,3,5-triazine-6-thione and their Latentiation Products as Antithyroidal Agent

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Two new 1-aryl-2-benzylmercapto-4-aryl-1,6-dihydro-1,3,5-triazine-6-thiones have been synthesized by known methods (Goerdeler *et al.*, 1967). These triazines on treatment with thiourea as dealkylating agent, in acidic medium afforded the corresponding 1-aryl-2-mercapto-4-aryl-1,6-dihydro-1,3,5-triazine-6-thione whch on further reaction with different α, β-unsaturated carbonyl compounds and aryl-cyanamide hydrochloride afforded the related adducts. Some of these compounds show appreciable antithyroidal activity.

Key words : Triazing thione, Mercaptotriazine, Aryl-cyanamide hydrochloride, α,β-unsaturated carbonyl compounds, Antithyroidal activity.

INTRODUCTION

Mercapto compounds or thiols have proved their worth as potential antithyroid agents (Astwood *et al.*, 1945; Nichlolas, 1988). This is by virtue of their easy oxidation by iodine or other oxidants to the corresponding disulfide. On account of the mechanism involving redox potential, simple thiols cannot penetrate the reaction site of thyroid gland. Contrary to this, heterocyclic mercaptans that can be isomerised (Havbottle *et al.*, 1984) to the thione form, sail freely inside the reaction site, and there they revert back to thiol form and consume the excess iodine present there in. Thus this group of heterocycles proves to be superior to surgical thyroidectomy in the treatment of hyperthyroidism, whereby excess of thyroxine hormone is produced. These interesting observations prompted us to synthesize and examine some mercapto triazines and their latentiation (Field *et al.*, 1973) products i.e. synthesis of some typical derivatives of highly potent compounds, which could incorporate structural modifications of known anti-thyroid drugs in such a way so as to reduce their toxicity and improve their activity (Mevigh *et al.*, 1971). This may provide a favourably influencing absorption, transport, distribution, localization, metabolism as well as stability (Gupta *et al.*, 1982). In light of the above observation it was thought worthwhile to latentiate mercaptotriazines with different α,β-unsaturated carbonyl compounds and arylcyanamide hydrochloride.

It was presumed that the adduct, thus, formed would exhibit improved activity and that at a biologically appropriate site, reverse conjugate addition might form the original thiol.

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MATERIALS AND METHODS

Materials

Thiouracil, Succinic acid, Malic acid (Sigma Chemicals, USA), Aniline, Thiourea, Ammonium thioxyanate, 4-Chlorobenzoic acid cinnamaldehyde (Ranbaxy), 4-Nitrobenzoic acid (Fluka).

Pharmacological Screening

Male Holtzman rats (100-125 gm) were maintained on low Iodide diet for 3 days. Then divided into groups consisting of four rats. The animals in each group received injection (i.p.) of 1 ml of either a blank (0.9% NaCl) thiouracil, or one of the test compounds. 1 hour after the injection of ^{131}I the animals were sacrificed and the thyroid were removed. The whole lobes were placed in a ground glass homogenizing tubes and counted in nuclear chicago well scintillation counter to determine total thyroid uptake. The whole lobes were then homogenized in 1 ml of 0.5 M barbital buffer pH 8.6* containing 10×10^{-5} thiouracil, 1 ml of cold 20% trichloroacetic acid

(TCA) was added and the homogentate was centrifuged. The precipetate was washed twice with 1 ml of cold 10% TCA. The original supernatant and the two washed were combined and the radioactivity was determined. ^{131}I in this fraction indicated the concentration of inorganic ^{131}I or TCA soluble ^{131}I. The washed precipitate was counted in the homogenizing tube. The radioactivity in this fraction indicated the $PB^{131}I$ or TCA precipitable ^{131}I. The counts were all corrected for counting efficiency and are expressed as disintegeration per min.

All compounds were dissoloved saline for injection thiouracil was dissolved with heating to 50°C. All compounds were assayed at concentration equimolar to 0.5 mg of thiouracil (.39 mole) and the biological effect was noted.

RESULTS AND DISCUSSION

1-Aryl-2-benzylmercapto-4-aryl,1,6-dithydro-1,3,5-triazine-6-thione(1) (Scheme 1) was synthesized by known method (Goerdeler *et al.*, 1971, 1972).

Dealkylation of 1-aryl-2-benzylmercapto-4-(-4-aryl)-1, 6,-dihydro-1,3,5-triazine-6-thione afforded the corresponding 2-mercaptotriazine (2) (Scheme 2). Instead of using pyridine, triethylamine and hydrogensulfide combination we employed thiourea in acidic medium as dealkylating agent, which led to improved yield of mercaptotriazine and eliminate tedious process of product separation. In this process equimolar mixture of triazine (1), thiourea and conc. hydrochloric acid in ethanol was refluxed for 2.5 hour and product isolated by pouring the reaction mixture on crushed ice. The desired mercapto-triazine was separated out as insoluble product, while S-benzylisothiouronium chloride, as side product being water soluble was removed along with filtrate. IR in the nujol showed a characteristic peak at 3370, 1250 cm^{-1} indicating the presence of -NH- and C=S group. But the same taken in chloroform medium exhibited a weak peak at 2600 cm^{-1} characterizing the presence of -SH group.

Furthermore, NMR ($CDCl_3$) spectrum revealed the presence of a single peak at S 2.45 supported by non aromatic proton of -SH group in addition to the other aromatic protons at S 7.56-8.26.

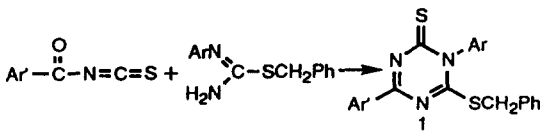
It was inferred that triazine existed in mercapto form in polar solvents and thione form in non polar solvents. Its existence in mercapto form was further confirmed by the following observations. (a) Mercaptotriazine(2) formed a complex with heavy metal salt e.g. $CuCl_2$, $HgCl_2$ in ethanol, involving depotonation of -SH group.

Magnetic moment 1.78 very close to that showing the presence of one unpaired electron. UV at 12360 cm^{-1} shoving d-d transition and octahedral configuration. IR of ligand showed following characteristic peaks: 2600 (SH), 1635 (C=N) and 1080 (C=S) cm^{-1}. IR of the complx showed following variations: broad peak at 3500 (OH), 1620 (C=N), 1080 (C=S) cm^{-1}, SH peak was eliminated. These data confirmed that free nitorgen involved in (C=N) bond of the ring S of (C=S) bond were the coordination sites and SH also took part in coodination by deprotonation. Peak at 3580 cm^{-1} indicates the presence of H_2O molecule.

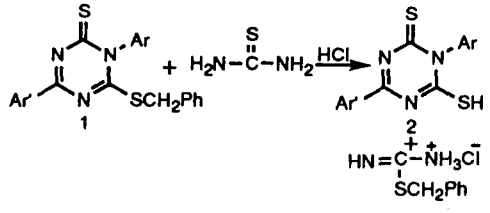
(b) With 2,4 dintrochlorobenezene in presence of sodium acetate, mercaptotriazine(2) formed corresponding sulfide. Presence of mercapto group in (2) was further confirmed by oxidation of (2) with Br_2/ $CHCl_3$ into corresponding disulfide.

Disappearance of SH peak in IR spectra and appearance of peak at 460 (S-S)cm^{-1} confirmed formation of disulfide.

Latentiation of 2-mercaptotriazine (2) with diferent



Scheme 1.



Scheme 2.

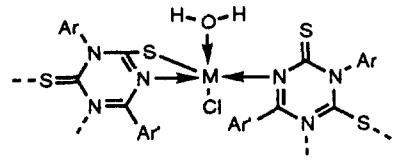
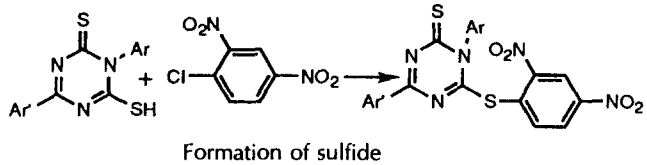
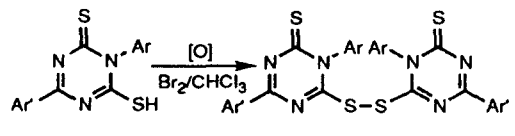


Fig. 1. Complex of 2a with Cu.

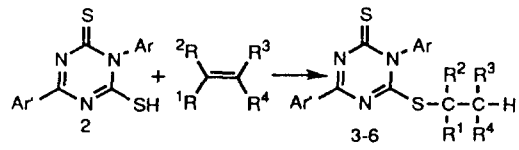


Formation of sulfide

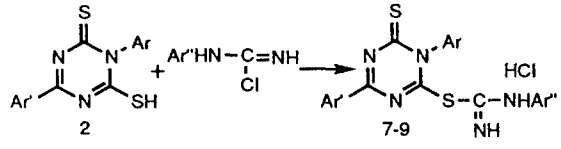


Formation of disulfide

Fig. 2.



Scheme 3.



Scheme 4.

α,β-unsaturated carbonyl compounds via maleic acid, acrylic acid, cinnamic acid and cinnamaldehyde (Scheme 3), was achieved by refluxing them in ethyl acetate. The IR spectra (nujol) showed strong absorption band at 1690-1710, 1615-1645 and 1070-1120 cm^{-1} region indicate the presence of (C=0), (C=N) and (C=S) group respectively and confirmed the adduct (3) formation.

N-aryl-s-(1aryl-4aryl-6-thioxo-1-6,dihydro-1,3,4-triazin-2-yl) isothiouronium chloride (7) was synthesized by treating (2) with various cyanamide hydrochlorides (amidino chloride) (Sheme 4).

All these compounds were well defined white crystalline solids. Purification was achieved by their repeated washing with dry acetone and benzene. The IR spectra showed 1520 (thioureidolinkage), 3400 (NH), 1635 (C=N) cm^{-1}. Further more conversion of acetone soluble (2) into actenone insoluble (7) also confirmed the formation of the adduct.

Pharmacological screening results of the compounds 3a to 6b and 7a to 9b are summarized in the table V and VI. It is obvious from the result that componds 3a, 3b, 4b, 5b, 6b and 7b, 8b, 9b have appreciable antithyroid activity and it may be concluded that presence of chloro grouping in molecule led to better antithyroidal activity in comparison to the nitro group.

Analysis

All melting points are uncorrected. IR spectra were measured on Perkin Elmer, model 720 spectrometer. ^1H spectra were recorded on JEOL FX 90 Q Fourier Transform spectrometer using Me_4Si as an internal standard. MS were performed on Simadzu GCMS-QP 1000A spectrometer. UV were recorded on CARY-2390 spectrophotometer (UV-VIS-NIR).

Preparation

2-Mercapto-1-(4-chlorophenyl)-4-(4-nitrophenyl)-1,6-dihydro-1,3,5-triazine-6-thione (2a) (Scheme 2).

1 was prepared by known methods (Scheme 1). A solution of 1a (4 mmol) was mixed with alcoholic solution of thiourea (4 mmol) and then conc. hydrochloric acid was added to it. The reaction mixture was refluxed for 2.5 hrs. It was cooled and then poured in crushed ice, yellow compound separated. Which was thoroughly washed with water. Recrystallization from ethanol gave the mercapto compound 2a.

Yield 66%. m.p.150°C. IR (KBr): 2600 (SH), 1630 (C=N), 1080 (C=S)cm^{-1}. ^1H NMR (DMSO-d_6) δ=7.3-8.2 (m, 8 H), 2.57 (S, 1 H). UV absorption at 326 nm. MS : M^+ (376.5). Found C, 47.86; H, 2.32; N, 14.80%. Calculated for $C_{15}H_9ClN_4O_2S_2$ C, 47.81; H, 2.39; N, 14.87%.

2b was synthesized by the similar method as discussed for synthesis of 2a (Table II).

Table I.

	Ar	Ar'	Yield%	m.p.°C
1a.	4-ClC_6H_4	4-$NO_2C_6H_4$	78	185
1b.	4-ClC_6H_4	4-ClC_6H_4	84	174

C, H, N analyses were within ±0.1-0.5%.

Table II.

	Ar	Ar'	Yield%	m.p.°C
2a.	4-ClC_6H_4	4-$NO_2C_6H_4$	66	150
2b.	4-ClC_6H_4	4-ClC_6H_4	58	242

C, H, N analyses were within ±0.1-0.5%

Complex of 2a with Cu

2a (5 mmole) was dissolved in alcohol and alcholic solution of $CuCl_2$. $2H_2O$ (5mmole) was added to it with stirring. Reaction mixture was refluxed for 4 hrs, cooled and then filtered. Black residue was washed with excess of water and acetone to remove the trace of reactants present. The black residue thus obtained did not melt, but decomposed at higher temperature and insoluble in most of organic solvents. So it was thought to be polymeric in nature. Ratio of ligand and $CuCl_2$ $2H_2O$ (1 : 1) magnetic moment: 1.78, UV: V_1 12360, V_2 15360 and V_3 19500 cm^{-1} (d-d transition and octahedral configuration). IR: 3580 (OH), 1620 (C=N), 1080 (C=S)cm^{-1}. Found Cu, 12.76; Cl, 14.39; N, 11.57% Calculated for $C_{15}H_9N_4S_2O_2Cl$. CuCl. H_2O (Single Unit) Cu,12.75; Cl, 14.57; N, 11.36%.

Bis-1[1-(4-chlorophenyl)2-mercapto-4-(4-nitrophenyl)-1,6-dihydro-6-thioxo-1,3,5-triazin-2-yl] disulfide

2a (10 mmol) was dissolved in chloroform and very dilute solution of bromine in chloroform was added to it drop by drop till a slight turbidity appeared. Reaction mixture was left for an hour, disulfide separated, which was filtered and washed with ammonical alcohol and recrystallized with alcohol.

Yield 62%. m.p. 198°C: IR(KBr): 1625 (C=N).

1100(C=S), 460(S-S)cm^{-1}. Found C, 47.89; H, 2.14; N, 14.90; S, 17.04% Calculated for $C_{30}H_{16}Cl_2N_8O_4S_4$ C, 47.94; H, 2.13; N, 14.91; S, 17.04%.

S-[1-(4-Chlorophenyl)-4-(4-nitrophenyl)-6-htioxo-1,6-dihydro-1,3,5-triazine-2-Yl]-mercatosuccinic Acid(3a) (Scheme 3)

A solution of 2a (10 mmol) and maleic acid (15 m. mol) in 100 ml of ethyl acetate, was refluxed for 4 hrs and then cooled overnight. Some fumaric acid separated which was filtered, and the filtrate was concentrated. A paste, thus obtained was washed with benzene and petroleum ether. Recrystallization from ethanol gave the adduct 3a.

Yield 77%. m.p. 155°C: IR(KBr): 3350 (-COOH), 1710 (C=0), 1630 (C=N), 1130 (C=S)cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=10.1-10.4 (m, 2 H), 7.1-7.8 (m, 8 H), 2. 1-2.4 (m, 3 H). UV absorption at 304 nm. MS:M$^+$ (192. 5) Found C, 46.16; H.2.59; N,11.29% Calculated for $C_{19}H_{13}ClN_4O_6S_2$, C, 46.29; H, 2.63; N,11.37%. (Similarly 3b was synthesised (Table III)).

S-[1-(4-chlorophenyl)-4-(4-nitrophenyl)-6-thioxo-1,6-dihydro-1,3,5-triaxin-2-yl]-mercapto propionic acid (4a) (Scheme 3).

A solution of 2a and acrylic acid (10 m.mol) in 100 ml of ethyl acetate was refluxed for 4 hours and then cooled overnight. The solvent was evacuated under vacuo. The residue was then washed with petroleum ether and then with benzene. crystallization from ethanol gave the adduct 4a.

Yield 68%. m.p. 169°C: IR(KBr): 3380 (-COOCH), 1700 (C=0), 1640(C=N), 1150(C=S)cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=10.2-10.5 (s, 1 H), 7.3-8.2 (m, 8 H), 2. 2-2.5 (m, 4 H). UV absorption at 300 nm. MS : M$^+$ (448.5). Found C, 47.98; H 2.82; N12.31% Calculated for $C_{12}H_{13}ClN_4O_4S_2$, C, 48.16; H 2.89; N 12. 48%. (Similarly 4b was synthesized (Table III)).

S-[1-(4-cholorophenyl)-4-(4-nitrophenyl)-6-thioxo 1,6-dihydro-1,3,5-triazine-2-yl]-mercapto-3-phenyl-propionic acid (5a). (Scheme 3)

A solution of 2a (10 mmol) and cinnamic acid (10 m. mol) in 100 ml of ethyl acetate was refluxed for 4 hours, and then cooled overnight. Solvent was evacuated under vacuo. The residue was washed with petroleum ether and then with benzene. Recrystallization fom ethanol gave the product 5a.

Yield 66%. m.p. 172°C. IR(KBr): 3340 (COOH); 1710 (C=0), 1650(C=N), 1140 (C=S)cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=10.2-10.6 (s, 1 H), 7.5-8.3 (m, 13 H), 2. 2-2.6 (m, 3 H). UV absorption at 308nm. MS : M$^+$ (524.5). Found C, 54.98; H, 3.19; N, 10.52% Calculated for $C_{24}H_{17}ClN_4O_4S_2$ C, 45.90; H, 3.24; N 10. 67%. (Similarly 5b was synthesized (Table III)).

S-[1-(4-Chlorophenyl)-4-(4-nitrophenyl)-6-thioxo-1,6,-dihydro-1,3,5-triazin-2yl]-mercato-3-phenyl propion-aldehyde (6a). (Schem 3)

A solution of 2a (10 mmol) and cinnamaldehyde (10 mmol) in 100 ml of ethyl acetate was refluxed for 4 hrs and cooled overnight, solvent was evacuated under vacuo. The residue was then washed with petroleum ether and then with benzene. Recrystalli-

Table III.

S.No.	Ar	Ar'	R^1	R^2	R^3	R^4	Yield%	m.p.°C
3a.	4-ClC_6H_4	4-$NO_2C_6H_4$	COOH	H	COOH	H	77	155
3b.	4-ClC_6H_4	4-ClC_6H_4	COOH	H	COOH	H	61	175
4a.	4-ClC_6H_4	4-$NO_2C_6H_4$	H	H	H	COOH	68	169
4b.	4-ClC_6H_4	4-ClC_6H_4	H	H	H	COOH	69	198
5a.	4-ClC_6H_4	4-$NO_2C_6H_4$	C_6H_5	H	H	COOH	66	172
5b.	4-ClC_6H_4	4-ClC_6H_4	C_6H_5	H	H	COOH	69	187
6a.	4-ClC_6H_4	4-$NO_2C_6H_4$	C_6H_5	H	H	CHO	62	195
6b.	4-ClC_6H_4	4-ClC_6H_4	C_6H_5	H	H	CHO	68	178

C,H,N analyses were within ±0.1-0.5%

Table IV.

S.No.	Ar	Ar'	Ar''	Yield%	m.p.°C
7a.	4-ClC_6H_4	4-$NO_2C_6H_4$	C_6H_5	68	230
7b.	4-ClC_6H_4	4-ClC_6H_4	C_6H_5	66	210
8a.	4-ClC_6H_4	4-$NO_2C_6H_4$	4-$OCH_3C_6H_4$	71	177
8b.	4-ClC_6H_4	4-ClC_6H_4	4-$OCH_3C_6H_4$	77	249
9a.	4-ClC_6H_4	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	69	183
9b.	4-ClC_6H_4	4-ClC_6H_4	4-$CH_3C_6H_4$	66	199

C,H,N analyses were within ±0.1-0.5%

Table V. Pharmacological screening results of addition product of mercaptotriazine and α,β-unsaturated carbonyl compounds.

Compound No.	Thyroid radio activity dpm±Std error		Inorgainc ^{131}I	Approx estimated activity in rats (Thiouracil=1.00)
	^{131}I uptake	^{131}I PB		
Control	112345±42	98378±36	7936±12	-
Thiouracil	42976±18	35421±16	5448±09	1.00
3a.	47843±13	40737±17	5432±19	0.89
4a.	44376±18	37964±10	6007±14	0.96
5a.	46408±12	40097±20	5313±14	0.92
6a.	49647±32	43305±29	5991±05	0.86
3b.	35623±35	26426±15	7215±11	1.20
4b.	30189±27	24575±13	5641±11	1.42
5b.	38793±24	31647±21	6728±07	1.10
6b.	36376±13	29648±03	6542±16	1.18

Table VI. Pharmacoloical screening results of N-aryl-S-[1-(4-chlorophenyl)-4-aryl-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-isothiouroniumhydrochloride

Compound No.	Thyroid radio activity dpm±Std error		Inorgainc ^{131}I	Approx estimated activity in rats (Thiouracil=1.00)
	^{131}I uptake	^{131}I PB		
Control	8470±50	7183±42	1221±23	-
Thiouracil	4460±62	3813±30	611±18	1.00
7a.	5931±19	4387±34	848±14	0.75
8a.	5193±14	4391±18	792±08	0.85
9a.	5018±23	4168±13	731±12	0.88
7b.	4317±57	4132±17	831±13	1.03
8b.	4384±29	4071±21	764±18	1.01
9b.	4278±14	3951±41	695±14	1.04

zation from ethanol gave the adduct 4a.

Yield 62%. m.p. 195°C. IR(KBr): 1710 (C=0), 1650 (C=N), 1150 (C=S)cm^{-1}. ^1H NMR (DMSO-d_6) δ=9.2-9. 6 (s, 1 H), 7.5-8.2 (m, 13 H), 2.2-2.6 (m, 3 H). UV absorption at 318nm. MS : M^+ (508.5). Found C, 56.56; H, 3.33; N, 10.91% Calculated for $C_{24}H_{17}ClN_4O_3S_2$ C, 56.63; H, 3.34; N 11.01%. (Similarly 6b was synthesized (Table III)).

N-phenyl-S[1-(4-cholorophenyl)-4-(4-nitrophenyl)-6-thioxo-1,6-dihydro-1,3,5-triazine-2-yl]-isothiouronium-chloride (Scheme 4)

A solution of 2a(10 mmol) in acetone was mixed with cold solution of phenylcyanamide hydrochloride (10 mmol) in acetone with stirring. after an hour granular white isothiouronium salt separated, which was washed by acetone to remove unreacted cyanamide hydrochloride to afford 7a.

Yield 68%. m.p. 230°C: IR(KBr): 1650 (C=N), 1150(C=S)cm^{-1}. ^1H NMR (DMSO-d_6) δ=8.9-8.6 (2d, 2 H), 6.9-7.6(m, 13 H). Found C, 49.92; H, 2.97; N, 15. 83% Calculated for $C_{22}H_{16}Cl_2N_6O_2S_2$ C, 49.71; H, 3. 01; N 15.81%.

Similarly other compounds of the series were synthesized by above procedure (7b-9b) (Table IV).

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