NEW COMPOUNDS

Synthesis of 1-Aryl-2-mercapto-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones and Their Addition Products with α,β-Unsaturated Compounds, Cyanamides, and Diarylcarbodiimides

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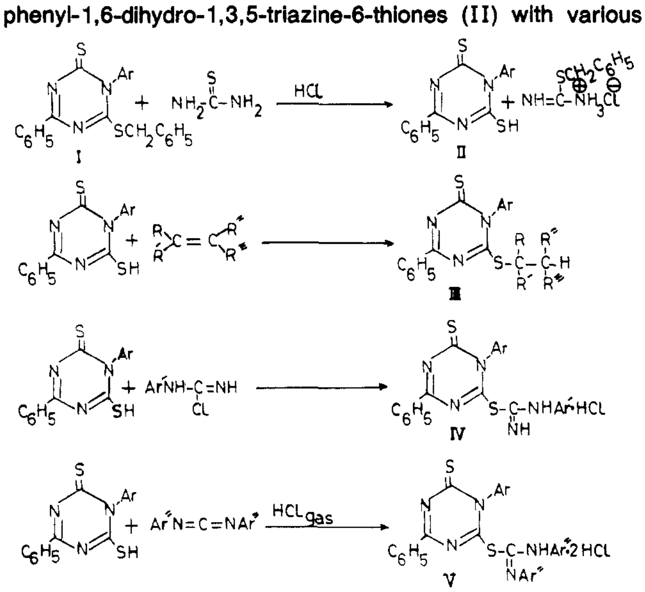
Different 1-aryl-2-mercapto-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones have been synthesized for the first time by dealkylating 1-aryl-2-(benzylmercapto)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones with thiourea and HCl. These mercaptotriazines when treated with α,β-unsaturated carbonyl compounds, arylcyanamides, and diarylcarbodiimides gave corresponding addition products.

With the intention of synthesizing compounds which would modify antithyroid thiols so as to reduce their toxicity and improve their activity (*1-3*), addition of 1-aryl-2-mercapto-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones (II) with various



α,β-unsaturated carbonyl compounds, arylcyanamides, and diarylcarbodiimides was taken up. This type of addition may favorably influence adsorption, transport, distribution, localization, and toxicity as well as stability (*4*, *5*).

Mercaptotriazine II was obtained by dealkylating (*6*) 1-aryl-2-(benzylmercapto)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thione (I) by refluxing it with thiourea and concentrated HCl in ethanol. The precursor was obtained by known methods (*7-9*).

Mercaptotriazine II, when refluxed with α,β-unsaturated carbonyl compounds in ethyl acetate, afforded addition products (III). A cold solution of II in acetone when mixed with a solution of arylcyanamide hydrochloride (*10*) in acetone gave crystalline *N*-aryl-*S*-(1-aryl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium hydrochloride (IV). When solutions of II and diarylcarbodiimide (*11*, *12*) in acetone were mixed and HCl gas was passed through them under cold conditions, crystals of *N*,*N'*-diaryl-*S*-(1-aryl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium dihydrochloride (V) were separated in quite good yield.

Table I. 1-Aryl-2-(benzylmercapto)-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones[a]

Ar	mp, °C	yield, %
C_6H_5	186	70
o-$CH_3C_6H_4$	178	65
p-$CH_3C_6H_4$	195	62
m-ClC_6H_4	161	55
p-ClC_6H_4	215	60

[a] All of these compounds gave elemental analyses within ±0.30 of calculated values.

Table II. 1-Aryl-2-mercapto-4-phenyl-1,6-dihydro-1,3,5-triazine-6-thiones[a]

Ar	mp, °C	yield, %
C_6H_5	212	60
o-$CH_3C_6H_4$	268	62.5
p-$CH_3C_6H_4$	126	55
m-ClC_6H_4	231	55
p-ClC_6H_4	262	60

[a] All of these compounds gave elemental analyses within ±0.30 of calculated values.

Experimental Section

All the melting points are determined with a Kofler hot stage apparatus and are uncorrected.

2-(Benzylmercapto)-1,4-diphenyl-1,6-dihydro-1,3,5-triazine-6-thione (I). This class of compounds are synthesized by known methods (*7-9*), and the details are listed in Table I.

1,4-Diphenyl-2-mercapto-1,6-dihydro-1,3,5-triazine-6-thione (II). A solution of I (3.87 g, 10 mmol), thiourea (0.76, 10 mmol), and concentrated hydrochloric acid (0.35 mL, 10 mmol) was refluxed with 50 mL of absolute alcohol for a period of 2.5 h, cooled, and poured into an excess of water. The separated light yellow compound was washed with excess of water and cold alcohol to remove excess of thiourea and then crystallized with alcohol to give II: yield 1.77 g (60%); mp 212 °C; IR ($CHCl_3$) 1080 (C=S), 1635 (C=N), 1170 (N-C(=S)-N) cm^{-1}; NMR (CD_3COCD_3) δ 1.57 (s, 1 H, SH), 7.46-7.90 (m, 10 H, Ar-H). The compound is soluble in dilute NaOH, its oxidation with Br_2/CCl_4 affords disulfide, and it gives salts with $HgCl_2$ and $CuCl_2$, etc. Similarly other mercaptotriazines were synthesized (Table II).

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Table III. Addition Products of II and α,β-Unsaturated Carbonyl Compounds[a,b]

Ar	R	R′	R″	R″	mp, °C	yield, %
C_6H_5	H	COOH	H	COOH	223	60
C_6H_5	H	H	H	CHO	234	50
o-$CH_3C_6H_4$	H	COOH	H	COOH	268	55
o-$CH_3C_6H_4$	H	C_6H_5	H	COC_6H_5	235	65
o-$CH_3C_6H_4$	H	H	H	COOH	284	70
o-$CH_3C_6H_4$	H	C_6H_5	H	$COOC_2H_5$	272	70
o-$CH_3C_6H_4$	H	C_6H_5	H	COOH	269	65
p-ClC_6H_4	H	H	H	CHO	289	60
p-ClC_6H_4	H	COOH	H	COOH	277	55
p-ClC_6H_4	H	C_6H_5	H	COC_6H_5	284	75

[a] All of these compounds gave elemental analyses within ±0.30 of calculated values. [b] Compounds were submitted for biological testing.

Table IV. N-Aryl-S-(1-aryl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium Hydrochlorides[a,b]

Ar	Ar′	mp, °C	yield, %
C_6H_5	C_6H_5	254	70
C_6H_5	m-ClC_6H_4	234	72
C_6H_5	p-ClC_6H_4	159	60
C_6H_5	o-$CH_3OC_6H_4$	205	64
C_6H_5	m-$CH_3OC_6H_4$	305	65
C_6H_5	p-$CH_3OC_6H_4$	182	55
p-ClC_6H_4	C_6H_5	247	60
p-ClC_6H_4	m-ClC_6H_4	312	75
p-ClC_6H_4	p-ClC_6H_4	176	68
p-ClC_6H_4	o-$CH_3OC_6H_4$	131	60
p-ClC_6H_4	m-$CH_3OC_6H_4$	319	65
p-ClC_6H_4	p-$CH_3OC_6H_4$	151	55

[a] All of these compounds gave elemental analyses within ±0.30 of calculated values. [b] These compounds were submitted for biological testing.

S-(1,4-Diphenyl-1,6-dihydro-6-thioxo-1,3,5-triazinyl)-mercaptosuccinic Acid (III). A solution of II (2.97 g, 10 mmol) and maleic acid (1.74 g, 15 mmol) in 100 mL of ethyl acetate was refluxed for 4 h and then cooled overnight. Some fumaric acid was separated which was filtered and the filtrate was concentrated. A paste thus obtained was washed with benzene, ether, and petroleum ether and then crystallized from alcohol to get III: yield 2.5 g (60%); mp 223 °C; IR (Nujol) 3405 (COOH), 1700 (C=O), 1610 (C=N), 1080 (C=S) cm^{-1}; NMR ($CDCl_3$) δ 1.96–2.21 (m, 3 H, $CHCH_2$), 7.3–7.8 (m, 10 H, ArH), 9.17–9.45 (m, 2 H, COOH).

Similarly, addition products with other α,β-unsaturated compounds were prepared (Table III).

N-Phenyl-S-(1,4-diphenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium Hydrochloride (IV). A solution of II (1.5 g, 5 mmol) in acetone (10 mL) was cooled in a freezing mixture and to this a solution of phenylcyanamide hydrochloride (*10*) (0.77 g, 5 mmol) in acetone (5 mL) was added drop by drop with constant stirring. After 1 h crystalline product was formed which was washed with acetone and ether to remove the unreacted fraction: yield 1.45 g (70%); mp 254 °C; IR (Nujol) 1520 (N=C—S), 1625 (C=N), 1020 (C=S), 3400 (NH) cm^{-1}. By adopting the same procedure, we obtained other compounds of this series (Table IV).

N,N′-Diphenyl-S-(1,4-diphenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium Dihydrochloride (V). A solution of diphenylcarbodiimide (1.98 g, 10 mmol) (*11*, *12*) in acetone (10 mL) was added drop by drop to a well-cooled solution of II (2.9 g, 10 mmol) in acetone (15 mL) with constant stirring and then HCl gas was passed through it. After 0.5 h V was separated and was washed with acetone and ether to remove the unreacted fraction: yield 3.8 g (65%); mp 227 °C. By adopting the same procedure, we obtained other compounds of this series (Table V).

Table V. N,N'-Diaryl-S-(1-aryl-4-phenyl-6-thioxo-1,6-dihydro-1,3,5-triazinyl)isothiouronium Dihydrochlorides[a,b]

Ar	Ar″	mp, °C	yield, %
C_6H_5	C_6H_5	227	65
o-$CH_3C_6H_4$	C_6H_5	263	62
p-$CH_3C_6H_4$	C_6H_5	268	60
p-ClC_6H_4	C_6H_5	288	70
C_6H_5	o-$CH_3C_6H_4$	220	60
o-$CH_3C_6H_4$	o-$CH_3C_6H_4$	259	65
p-$CH_3C_6H_4$	o-$CH_3C_6H_4$	186	60
C_6H_5	o-$CH_3OC_6H_4$	282	70
o-$CH_3C_6H_4$	o-$CH_3OC_6H_4$	265	65
p-$CH_3C_6H_4$	o-$CH_3OC_6H_4$	199	62

[a] All these compounds gave elemental analyses within ±0.30 of calculated values. [b] These compounds were submitted for biological testing.

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Registry No. **10**, 60129-88-6; I (Ar = C_6H_5), 39543-11-8; I (Ar = o-$CH_3C_6H_4$), 85442-31-5; I (Ar = p-$CH_3C_6H_4$), 85442-32-6; I (Ar = m-ClC_6H_4), 85442-33-7; I (Ar = p-ClC_6H_4), 15998-34-2; II (Ar = C_6H_5), 85442-34-8; II (Ar = o-$CH_3C_6H_4$), 85442-35-9; II (Ar = p-$CH_3C_6H_4$), 85442-36-0; II (Ar = m-ClC_6H_4), 85442-37-1; II (Ar = p-ClC_6H_4), 85442-38-2; III (Ar = C_6H_5; R, R″ = H; R′, R‴ = COOH), 85442-39-3; III (Ar = C_6H_5; R, R′, R″ = H; R‴ = CHO), 85442-40-6; III (Ar = o-$CH_3C_6H_4$; R, R″ = H; R′, R‴ = COOH), 85452-90-0; III (Ar = o-$CH_3C_6H_4$; R, R″ = H; R′ = C_6H_5; R‴ = COC_6H_5), 85442-41-7; III (Ar = o-$CH_3C_6H_4$; R, R′, R″ = H; R‴ = COOH), 85442-42-8; III (Ar = o-$CH_3C_6H_4$; R, R″ = H; R′ = C_6H_5; R‴ = $COOC_2H_5$), 85442-43-9; III (Ar = o-$CH_3C_6H_4$; R, R″ = H; R′ = C_6H_5; R‴ = COOH), 85442-44-0; III (Ar = p-ClC_6H_4; R, R′, R″ = H; R‴ = CHO), 85442-45-1; III (Ar = p-ClC_6H_4; R, R″ = H; R′, R‴ = COOH), 85442-46-2; III (Ar = p-ClC_6H_4; R, R″ = H; R′ = C_6H_5; R‴ = COC_6H_5), 85442-47-3; IV (Ar, Ar′ = C_6H_5), 85442-48-4; IV (Ar = C_6H_5, Ar′ = m-ClC_6H_4), 85442-49-5; IV (Ar = C_6H_5, Ar′ = p-ClC_6H_4), 85442-50-8; IV (Ar = C_6H_5, Ar′ = o-$CH_3OC_6H_4$), 85442-51-9; IV (Ar = C_6H_5, Ar′ = m-$CH_3OC_6H_4$), 85442-52-0; IV (Ar = C_6H_5, Ar′ = p-$CH_3OC_6H_4$), 85442-53-1; IV (Ar = p-ClC_6H_4, Ar′ = C_6H_5), 85442-54-2; IV (Ar = p-ClC_6H_4, Ar′ = m-ClC_6H_4), 85442-55-3; IV (Ar, Ar′ = p-ClC_6H_4), 85442-56-4; IV (Ar = p-ClC_6H_4, Ar′ = o-$CH_3OC_6H_4$), 85442-57-5; IV (Ar = p-ClC_6H_4, Ar′ = m-$CH_3OC_6H_4$), 85442-58-6; IV (Ar = p-ClC_6H_4, Ar′ = p-$CH_3OC_6H_4$), 85442-59-7; V (Ar, Ar″ = C_6H_5), 85442-60-0; V (Ar = o-$CH_3C_6H_4$, Ar″ = C_6H_5), 85442-61-1; V (Ar = p-$CH_3C_6H_4$, Ar″ = C_6H_5), 85442-62-2; V (Ar = p-ClC_6H_4, Ar″ = C_6H_5), 85442-63-3; V (Ar = C_6H_5, Ar″ = o-$CH_3C_6H_4$), 85442-64-4; V (Ar, Ar″ = o-$CH_3C_6H_4$), 85442-65-5; V (Ar = p-$CH_3C_6H_4$, Ar″ = o-$CH_3C_6H_4$), 85442-66-6; V (Ar = C_6H_5, Ar″ = o-$CH_3OC_6H_4$), 85442-67-7; V (Ar = o-$CH_3C_6H_4$, Ar″ = o-$CH_3OC_6H_4$), 85442-68-8; V (Ar = p-$CH_3C_6H_4$, Ar″ = o-$CH_3OC_6H_4$), 85442-69-9; maleic acid, 110-16-7; diphenylcarbodiimide, 622-16-2.

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