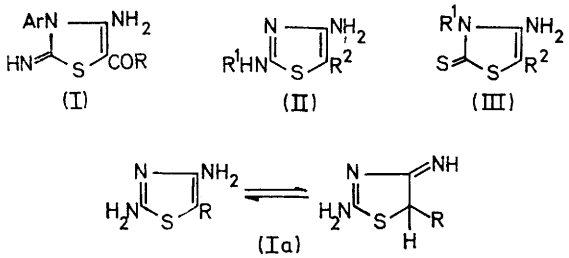
Studies on Bisthiazolo[3,2-*a*:4′,5′-*d*]pyrimidine Derivatives. Part II.[1]

By **Amrik Singh, Harjit Singh,* C. K. Dewan, and K. S. Narang,** Department of Chemistry, Panjab University, Chandigarh-14, India

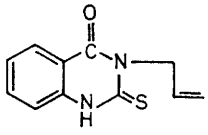
Ethyl 4-allylthioureido-3-aryl-2-imino-4-thiazoline-5-carboxylates (V), obtained by condensation of ethyl 4-amino-3-aryl-2-imino-4-thiazoline-5-carboxylates (I) with allyl isothiocyanate, were converted into 9*H*-3-aryl-6,7-dihydro-6-methylbisthiazolo[3,2-*a*:4′,5′-*d*]pyrimidine-2(3*H*),9-diones (IX) when heated in polyphosphoric acid. Treatment of compounds (V) with bromine, followed by dehydrobromination, gave ethyl 3-aryl-4-(5-bromomethylthiazolidin-2-ylideneamino)-2-imino-4-thiazoline-5-carboxylates (XI), which were cyclised to 9*H*-3-aryl-6-bromomethyl-6,7-dihydrobisthiazolo[3,2-*a*:4′,5′-*d*]pyrimidine-2(3*H*),9-diones (XII).

4-Aminothiazoles are unstable to acid and to base [2-5] and their weakly basic nature made Davies [5] conclude that they are devoid of amino-character. These factors are probably responsible for the fact that these compounds have not been extensively investigated. We have reported the preparation of ethyl 4-amino-3-aryl-2-imino-4-thiazoline-5-carboxylates (I; R = OEt),[1] in which we hoped that the presence of the ethoxycarbonyl group, by extended conjugation and/or hydrogen bonding would inculcate stability. A 4-ethoxycarbonyl group has also been found to enhance the stability of 5-aminothiazoles.[6] The instability of the 4-amino-compounds was thought by Davies [5] and Land [4] to be due to the existence of the tautomeric 4-imino-structure (Ia); however these thiazolines (I; R = OEt) and their 4-substituted amino-derivatives have been shown to exist entirely as the 4-amino-tautomers by their n.m.r. spectra,† and were found to be stable, especially towards acids. More recently the preparation of similar 4-aminothiazoles (II) [7] and 4-aminothiazolines (III) [8] has been reported (R^2 = CO_2R, COR, $CONH_2$, or CN).

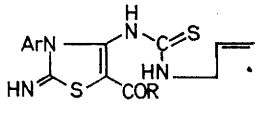


In addition to imparting stability, this relationship of amino and ethoxycarbonyl groups turns these thiazolines into suitable intermediates for developing new heterocyclic systems; we report here the synthesis of bisthiazolo[3,2-*a*:4′,5′-*d*]pyrimidine derivatives.

In contrast to the condensation of anthranilic acids or esters with allyl isothiocyanate, which gives the corresponding 3-allyl-2-thioxo-quinazolin-4-ones [9] (IV) by instantaneous cyclisation of the intermediate thiourea derivatives, condensation of (I; R = OEt) with allyl isothiocyanate furnished only the ethyl 4-allylthioureido-3-aryl-2-imino-4-thiazoline-5-carboxylates (V) (Table). The n.m.r. spectrum of (V; Ar = *o*-tolyl, R = OEt) showed the presence of the ethoxycarbonyl group and the i.r. spectra of all the products (V) (Table) exhibited two sharp peaks at 3200—3350 cm.$^{-1}$ and ester carbonyl absorption at 1665—1670 cm.$^{-1}$.



(IV)



(V)

The failure of (V; R = OEt) to undergo intramolecular cyclisation to the pyrimidone is analogous with our report [1] of the condensation of (I; R = OEt) with α-thiocyanato-ketones, and Cook's observation [10] that ethyl 5-aminothiazole-4-carboxylate (VI) on condensation with various isothiocyanates gave the corresponding thioureas (VII). The latter underwent cyclisation to (VIII) only after treatment with alkali. However our attempts at cyclisation of (V; R = OEt) with sodium hydroxide under similar conditions have so far proved unsuccessful. Cyclisation was finally achieved by heating in polyphosphoric acid. These reactions were attended by hydrolysis of the 2-imino-group with concomitant formation of the thiazolidine ring to furnish 9*H*-3-aryl-6,7-dihydro-6-methylbisthiazolo[3,2-*a*:4′,5′-*d*]-pyrimidine-2(3*H*),9-diones (IX) (Table). The i.r. spectra of (IX) showed no secondary NH absorptions, and a carbonyl band at 1710—1720 cm.$^{-1}$.‡ These data and

† Our earlier observation on this tautomerism [1] is further supported by the n.m.r. spectrum of (XI). Spectra of other similar compounds (unpublished) agree with these results.

‡ Hall and Tauren [11] have reported absorption at *ca.* 1700 cm.$^{-1}$ for fused 2-thiazolidones. We have found that for other similar compounds containing the 2-thiazolidone system, the carbonyl absorption appeared at this high frequency; the pyrimidone absorption is hidden under this peak, and is resolved as a lower frequency dent at *ca.* 1690 cm.$^{-1}$ in a few cases.[1,12]

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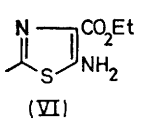
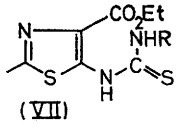
[12] A. Singh, unpublished results.

Compound (R = OEt)	M.p.	Formula	Found (%)	Required (%)
(V; Ar = *p*-MeC_6H_4)	164—165° [a]	$C_{17}H_{20}N_4O_2S_2$	N, 15·1	14·9
			C, 53·9	54·25
			H, 5·4	5·3
(V; Ar = Ph [b]	149—151 [a]	$C_{16}H_{18}N_4O_2S_2$	N, 15·8	15·45
			C, 53·2	53·3
			H, 4·6	4·95
(V; Ar = *p*-ClC_6H_4) [c]	175—176 [a]	$C_{16}H_{17}ClN_4O_2S_2$	N, 14·45	14·15
			C, 48·9	48·5
			H, 4·7	4·3
(V; Ar = *p*-MeO·C_6H_4)	170—171 [a]	$C_{17}H_{20}N_4O_3S_2$	N, 14·15	14·3
(V; Ar = *o*-MeC_6H_4)	162—163 [a]	$C_{17}H_{20}N_4O_2S_2$	N, 15·15	14·9
(V; Ar = *m*-ClC_6H_4)	163—165 [a]	$C_{16}H_{17}ClN_4O_2S_2$	N, 14·3	14·15
(V; Ar = *o*-ClC_6H_4) [d]	165—167 [a]	$C_{16}H_{17}ClN_4O_2S_2$	N, 14·1	14·15
(V; Ar = *m*-MeC_6H_4)	161—162 [a]	$C_{17}H_{20}N_4O_2S_2$	N, 14·8	14·9
(IX; Ar = Ph) [e]	231—233 [a]	$C_{14}H_{11}N_3O_2S_2$	N, 13·2	13·25
(IX; Ar = *o*-MeC_6H_4)	185—187 [f]	$C_{15}H_{13}N_3O_2S_2$	N, 12·35	12·7
			C, 54·5	54·4
			H, 3·75	3·9
(IX; Ar = *p*-MeC_6H_4)	228—229 [f]	$C_{15}H_{13}N_3O_2S_2$	N, 12·45	12·7
(IX; Ar = *m*-MeC_6H_4)	210—211 [f]	$C_{15}H_{13}N_3O_2S_2$	N, 12·5	12·7
(IX; Ar = *o*-ClC_6H_4) [g]	187—188 [f]	$C_{14}H_{10}ClN_3O_2S_2$	N, 12·1	11·95
			C, 48·1	47·75
			H, 2·65	2·85
(IX; Ar = *m*-ClC_6H_4)	197—199 [f]	$C_{14}H_{10}ClN_3O_2S_2$	N, 12·35	11·95
(IX; Ar = *p*-MeO·C_6H_4)	229—230	$C_{15}H_{13}N_3O_3S_2$	N, 12·35	12·1
(XI; Ar = Ph)	201—202 [h]	$C_{16}H_{17}BrN_4O_2S_2$	N, 12·95	12·7
(XI; Ar = *p*-MeC_6H_4)	186—188 [h]	$C_{17}H_{19}BrN_4O_2S_2$	N, 12·95	12·7
(XI; Ar = *p*-ClC_6H_4)	180—182 [h]	$C_{16}H_{16}BrClN_4O_2S_2$	N, 11·9	11·8
			C, 40·55	40·4
			H, 3·75	3·35
(XI; Ar = *o*-ClC_6H_4)	210—211 [h]	$C_{16}H_{16}BrClN_4O_2S_2$	N, 12·1	11·8
(XI; Ar = *o*-MeC_6H_4)	195—197 [h]	$C_{17}H_{19}BrN_4O_2S_2$	N, 12·75	12·3
			C, 44·7	44·85
			H, 4·3	4·15

[a] From ethanol. [b] $\nu_{max.}$ 3300 and 3420 (NH), and 1670 (CO) $cm.^{-1}$. [c] $\nu_{max.}$ 3330 and 3400 (NH), and 1670 (CO) $cm.^{-1}$. [d] ν_{max} 3345 and 3460 (NH), and 1665 (CO) $cm.^{-1}$. [e] $\nu_{max.}$ 1720 $cm.^{-1}$ (CO). [f] From ethanol–dioxan. [g] $\nu_{max.}$ 1715 $cm.^{-1}$. [h] From dioxan.

the absence of ethoxy- and vinylic proton peaks in the n.m.r. spectra are consistent with the assigned structure.


(VI)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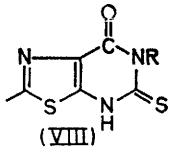
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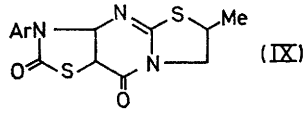
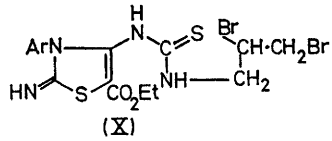

(IX)

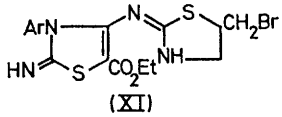
Compound (IX; Ar = Ph) was also prepared by heating (V; R = NH_2) in polyphosphoric acid. The amide (V; R = NH_2) was obtained by condensation of allyl isothiocyanate with 4-amino-2-imino-3-phenyl-4-thiazoline-5-carboxamide (I; R = NH_2, Ar = Ph), which was prepared from phenyl thiourea and bromocyanoacetamide.

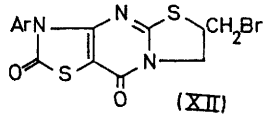
The reluctance to form the pyrimidone ring is probably due to weakening of the electrophilicity of the ethoxycarbonyl carbon atom through electron release from the sulphur atom. A strong acid evidently helps the cyclisations by protonation of the carbonyl group with simultaneous production of a secondary carbonium ion in the allylic chain.

Bromination of (V) was carried out in acetic acid solution. Dibromo-derivatives (X) were susceptible to cyclodehydrobromination, and could not be purified. However treatment of the crude products with ethanolic sodium hydroxide (1 equiv.) or boiling water gave ethyl 3-aryl-4-(5-bromomethylthiazolidin-2-ylideneamino)-2-imino-4-thiazoline-5-carboxylates (XI) (Table). The presence of an ethoxy-group and of two secondary amino-groups which exchange with deuterium oxide is evident from the n.m.r. spectrum of (XI; Ar = *o*-tolyl).

Compounds (XI; Ar = *o*-chlorophenyl or *o*-tolyl),


(X)


(XI)


(XII)

when heated in polyphosphoric acid underwent cyclisation accompanied by hydrolysis of the 2-imino-group to give 9*H*-3-aryl-6-bromomethyl-6,7-dihydrobisthiazolo-[3,2-*a*:4′,5′-*d*]pyrimidine-2(3*H*),9-diones (XII), which exhibited i.r. absorption bands at 1710—1715 $cm.^{-1}$. The absence of signals for an ethoxy-group and for exchangeable protons in the n.m.r. spectrum of (XII; Ar = *o*-tolyl) corroborates the assigned structure.

EXPERIMENTAL

M.p.s were determined for samples in capillaries. I.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 grating spectrophotometer. Elemental analyses were performed by B. N. Anand and L. K. Khullar of this department; n.m.r. spectra were determined with a Varian A-60 instrument. For t.l.c., plates coated with silica gel G were eluted with chloroform; spots were developed with iodine.

Ethyl 4-Allylthioureido-2-imino-3-phenyl-4-thiazolin-5-carboxylate (V; R = OEt).—(*a*) A solution of ethyl 4-amino-2-imino-3-phenylthiazolin-5-carboxylate (I) (0·01 mole) and allyl isothiocyanate (0·01 mole) in ethanol was refluxed for 6 hr., then cooled. The product separated as a yellow crystalline solid, m.p. 146—149° (from ethanol) (2·53 g., 70%).

(*b*) Alternatively, a mixture of the reagents was heated at 110—115° for 15 min. By washing the cooled product with ethanol a sufficiently pure crystalline material, m.p. 145—148° (3·26 g., 90%), was obtained. The products obtained in (*a*) and (*b*) were identical (R_F values and mixed m.p.).

The latter procedure was followed for synthesising the other derivatives (V; R = OEt) (Table). The n.m.r. spectrum of (V; Ar = *o*-tolyl, R = OEt) showed signals at δ ($CDCl_3$) 1·25 (3H, t, *J* 7 Hz), 3·6 (2H, q, *J* 7 Hz), 2·03 (3H, s), 3·3—5·7 (m, 10H including the 2H quartet at δ 3·6), and 7·2—7·45 (4H, m).

9H-3-*Aryl*-6,7-*dihydro*-6-*methylbisthiazolo*[3,2-a:4′,5′-d]-*pyrimidine*-2(3H),9-*diones* (IX) (Table): *General Procedure*. —The thiazoline (V; R = OEt) (0·0055 mole) was heated in freshly prepared polyphosphoric acid (4 g.) on an oil-bath at 120—130° for 4 hr., or at 160—170° for 15 min. The mixture was then cooled, diluted with water (40 ml.), and neutralised with ammonia solution. The product was extracted with chloroform. The solvent was removed from the dried (Na_2SO_4) extract and the product was crystallised from ethanol (80%). The n.m.r., spectrum of (IX; Ar = *p*-chlorophenyl) showed signals at δ ($CF_3{\cdot}CO_2H$) 1·67 (3H, d, *J* 7 Hz), 3·84 (1H, m), 4·53 (2H, s), and 7·1—7·7 (4H, m).

4-Amino-2-imino-3-phenyl-4-thiazoline-5-carboxamide (I; R = NH_2).—Bromocyanoacetamide (0·033 mole) in ethanol (20 ml.) was added to phenyl(thiourea) (0·04 mole) in ethanol (15 ml.). An exothermic reaction took place immediately. The mixture was refluxed for 2 hr. and diluted with water. The cloudy solution was filtered and neutralised with dilute ammonia solution. The *product* which separated was collected under suction and crystallised from ethanol–dioxan; m.p. 146—148°, yield 60% (Found: C, 50·9; H, 4·2; N, 23·6. $C_{10}H_{10}N_4SO$ requires C, 51·3; H, 4·2; N, 23·6%).

Alternatively bromocyanoacetamide (0·033 mole) in acetone (25 ml.) was added to phenyl(thiourea) (0·04 mole) in acetone (20 ml.) and the mixture was refluxed for 2 hr. It was then cooled and the hydrobromide isolated was basified with dilute ammonia solution, furnishing a relatively pure product (70%).

4-Allylthioureido-2-imino-3-phenyl-4-thiazoline-5-carboxamide (V; R = NH_2).—A mixture of allyl isothiocyanate (0·01 mole) and (I; Ar = Ph, R = NH_2) (0·01 mole) was heated at 110—115° for 10 min., then triturated with ethanol. The product gave brown *needles* (90%), m.p. 217° (from dioxan) (Found: N, 20·9; $C_{14}H_{15}N_5SO$ requires N, 21·0%).

9H-6,7-Dihydro-6-methyl-3-phenylbisthiazolo[3,2-a:4′,5′-d]-*pyrimidine*-2(3H),9-*dione* (IX; Ar = Ph).—The thiazoline (V; Ar = Ph, R = NH_2) was cyclised by heating in polyphosphoric acid at 160—170° for 15 min. as mentioned earlier. The product was identical with that obtained from (V; R = OEt, Ar = Ph) (i.r., t.l.c., and mixed m.p.).

Ethyl 3-Aryl-4-(2,3-dibromopropylthioureido)-2-imino-4-thiazoline-5-carboxylates (X): *General Procedure*.—Bromine (1·25 ml., 0·005 mole) in acetic acid was added slowly with shaking to a solution of the appropriate 4-allylthioureido-4-thiazoline (0·005 mole) in acetic acid (100 ml.). The mixture was set aside overnight and then diluted with anhydrous ether (500 ml.). Attempted crystallisation of the product which separated gave material melting over a wide range (70%).

Ethyl 3-Aryl-4-(5-bromomethylthiazolidin-2-ylideneamino-2-imino-4-thiazoline-5-carboxylates (XI): *General Procedure*. —(*a*) Ethanolic sodium hydroxide (2%, 7·6 ml.) was added to a solution of the dibromopropylthioureido-4-thiazoline (X) (0·0038 mole) in ethanol (5 ml.). The product which separated was recrystallised from dioxan (80%).

(*b*) Alternatively, (X) was boiled in water (10 ml.) for 5 min., cooled, and basified with dilute ammonia solution. The product which separated was identical with that from (*a*). The n.m.r. spectrum of (XI; Ar = *o*-tolyl) show signals at δ ($CDCl_3$) 1·38 (3H, t, *J* 7 Hz), 4·32 (2H, q, *J* 7 Hz), 2·15 (3H, s), 7·3—7·5 (4H, m), 5·6 (2H, s, exchangeable), and 3·4—4·6 (7H, m, including quartet at δ 4·32).

9H-6-*Bromomethyl*-6,7-*dihydro*-3-*o*-*tolylbisthiazolo*-[3,2-a:4′,5′-d]*pyrimidine*-2(3H),9-*dione* (XII; Ar = *o*-tolyl). A solution of (XI; Ar = *o*-tolyl) (0·0023 mole) in freshly prepared polyphosphoric acid (4 g.) was heated at 160—170° for 15 min. It was then cooled, diluted with water (30 ml.), and neutralised with ammonia solution. The product was extracted with chloroform. The solvent was removed from the dried (Na_2SO_4) extract. The *residue*, crystallised from ethanol, had m.p. 180—181° (yield 80%) (Found: C, 45·5; H, 3·2; N, 10·75. $C_{15}H_{12}N_3O_2S_2$ requires C, 45·7; H, 3·45; N, 10·65%), δ ($CDCl_3$) 2·18 (3H, s), 7·3—7·45 (4H, m), and 3·35—4·45 (5H, m), $\nu_{max.}$ 1710, 1600, 1540, 1480, 1440, 1370, and 1300 $cm.^{-1}$.

Similarly (XI; Ar = *o*-chlorophenyl) on cyclisation with polyphosphoric acid furnished the 3-*o*-*chlorophenyl derivative* (XII; Ar = *o*-chlorophenyl), m.p. 146—147° (Found: N, 10·3. $C_{14}H_9BrClN_3O_2S_2$ requires N, 10·15%), $\nu_{max.}$ 1715, 1600, 1570, 1480, 1450, 1370, and 1330 $cm.^{-1}$.

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