New Thiazolo[5,4-*d*]pyrimidines with Molluscicidal Properties

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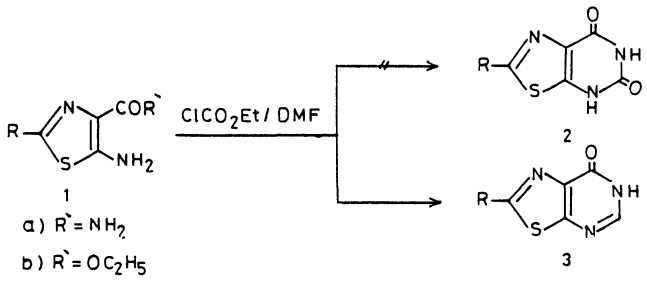
Synopsis. Ethyl chloroformate/DMF mixture is used as a reagent for the facile ring closure of 5-amino-2-(ethylthio)-thiazole-4-carboxamide (**1a**) to afford an excellent yield of 2-ethylthiothiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (**3**). The action of phosphoryl chloride on the latter product gave its 7-chloro derivative (**4**). The corresponding 7-(dicyanomethyl) (**5a**), 7-[cyano(ethoxycarbonyl)methyl] (**5b**), and 7-(substituted amino)derivatives (**6a—j**) are synthesized from reactions of malononitrile, ethyl cyanoacetate, and primary amines, respectively, with compound **4**. Most of the obtained products have been screened for activity against the intermediate host of schistosomiasis, *B. alexandrina* snails.

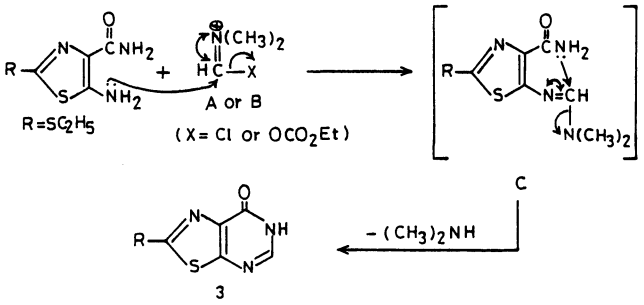
In connection with a program for preparing new purine and purine analogue derivatives with potentially useful biological properties,[1-3] the present paper reports the synthesis of some new thiazolo[5,4-*d*]pyrimidines and their molluscicidal effect.

Thus, when 5-amino-2-(ethylthio)thiazole-4-carboxamide (**1a**) was allowed to react with ethyl chloroformate/*N*,*N*-dimethylformamide (2 : 1), 2-(ethylthio)thiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (**3**) was obtained in an excellent yield instead of the expected dione **2**. Compound **3** was found to be identical (mp and mixed mp) with the product obtained from the reaction of **1a** with triethyl orthoformate or from either **1a** or **1b** with formamide (2 h, 190 °C). Moreover, the ^{1}H NMR spectrum of **3** included a sharp signal at δ=8.24 representing H-5 of the thiazolopyrimidine nucleus,[4] and the mass spectrum of it observed M^+ 213 (100%). Such observations accord with structure **3** and exclude structure **2**.



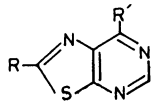
A possible mechanism consistent with this result is shown in Scheme 1. It involves the formation of intermediate **A** or **B** in the reaction medium, either of which can attack (or be attacked by) the 5-amino nitrogen of the thiazole system **1a** to give the intermediate **C** which in turn can eliminate dimethylamine leaving a formate residue for incorporating as C5 of the thiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (**3**). The reaction under investigation, presumably, proceeds via intermediate formation of a Vilsmeier-Haack reagent.[5]

The present work employs product of type **3** for the synthesis of new 7-substituted 2-(ethylthio)thiazolo[5,4-*d*]pyrimidines required for biological screening as antischistosomal agents. Accordingly, 7-chloro-2-



Scheme 1.

(ethylthio)thiazolo[5,4-*d*]pyrimidine (**4**) was prepared by the action of phosphoryl chloride on **3**. The chloro substituent of product **4** was easily replaced by the dicyanomethanide or the cyano(ethoxycarbonyl)methanide anion: reaction with malononitrile or ethyl cyanoacetate in DMSO and in presence of alkali gave the dinitrile **5a** and the nitrile ester **5b**,respectively. Treatment of **4** with primary amines in the presence of triethylamine likewise gave the corresponding 7-(substituted amino)-2-(ethylthio)thiazolo[5,4-*d*]pyrimidines (**6a—j**) in good yield.



4, **5**, and **6**

R=SC_2H_5 for all cases.
4; R'=Cl.
5; R'=a) $CH(CN)_2$, and b) $CH(CN)CO_2Et$.
6; R'=a) $NHCH_3$, b) NHC_2H_5, c) $NHCH(CH_3)_2$,
d) $NHCH_2C_6H_5$,
e) NHC_6H_5, f) $NHC_6H_4CH_3$-*p*,
g) $NHC_6H_4OCH_3$-*p*,
h) NHC_6H_4Cl-*p*, i) NH-thiazolyl,
j) NH-CH_2-furyl.

Molluscicidal Activity. Snails: *Biomphalaria alexandrina*, the snail intermediate host of schistosomiasis, are used in this study. They are collected from

Table 1. Molluscicidal Activity of the Synthesized Products

Compound	% of mortality of adult snails/ppm			
	12.5	25	50	100 ppm
4	100	100	100	100
5a	0	50	100	100
5b	0	40	100	100
6a	15	25	100	100
6c	0	0	40	100
6e	30	70	100	100
6g	20	60	100	100
6i	0	25	100	100
6j	50	100	100	100

Table 2. Characterization of 7-(Substituted amino)-2-(ethylthio)thiazolo[5,4-*d*]pyrimidines (**6a—j**)

Compound	Mp/°C (solvent)	Yield %	Formula (Mol. wt.)	Analysis (%) Calcd (Found) C	H	N
6a	147—148 (ethanol)	79	$C_8H_{10}N_4S_2$ (226)	42.50 (42.50)	4.40 (4.10)	24.80 (24.40)
6b	79—81 (methanol)	67	$C_9H_{12}N_4S_2$ (240)	45.00 (44.60)	5.00 (5.20)	23.30 (23.30)
6c	89—91 (aqueous ethanol)	83	$C_{10}H_{14}N_4S_2$ (254)	47.20 (47.40)	5.50 (6.00)	22.00 (21.90)
6d	90—92 (methanol)	64	$C_{14}H_{14}N_4S_2$ (302)	55.60 (55.70)	4.60 (4.80)	18.50 (18.20)
6e	80—82 (aqueous ethanol)	72	$C_{13}H_{12}N_4S_2$ (288)	54.20 (54.50)	4.20 (4.40)	19.40 (19.60)
6f	103—105 (ethanol)	87	$C_{14}H_{14}N_4S_2$ (302)	55.60 (55.30)	4.60 (4.90)	18.50 (18.30)
6g	73—75 (ethanol)	76	$C_{14}H_{14}N_4OS_2$ (318)	52.80 (52.50)	4.40 (4.40)	17.60 (17.30)
6h	112—114 (ethanol)	75	$C_{13}H_{11}N_4ClS_2$ (322.5)	48.40 (48.40)	3.40 (3.70)	17.40 (17.60)
6i	89—90 (methanol)	82	$C_{10}H_9N_5S_3$ (295)	40.70 (40.50)	3.00 (3.10)	23.70 (23.80)
6j	85—87 (ethanol)	69	$C_{12}H_{12}N_4OS_2$ (292)	49.30 (49.60)	4.10 (4.10)	19.20 (19.30)

irrigation canals that were not already treated with molluscicides.

Exposure and recovery periods are 24 h each. Standard procedures are followed throughout this study.[6,7] Control experiments for each case are carried out. These experiments showed mortality of 0%. The results are recorded in Table 1.

From Table 1 the following comments are pointed out:

1. Most of the tested compounds showed a 100% snails mortality at 100 as well as at 50 ppm dilution.

2. For compounds **4**, **5a**, **6e**, and **6j** a 50—100% snails mortality is attained at 25 ppm dilution.

3. Compounds **4** and **6j** reached, comparatively to the others, the highly active status at 12.5 ppm.

Moreover, the activity showed by products **4** and **6j** is found to be stable >12.5 ppm to pH changes "4—10", temperature changes "10—30 °C", sun radiations, and high mud concentration media (up to 10000 ppm mud).

So, incorporating a chloro or furfurylamino residue on C7 of the thiazolo[5,4-*d*]pyrimidine ring system bearing ethylthio moiety on position 2 is recommended for obtaining antischistosomal agents with a stable activity against *B. alexandrina* snails.

Experimental

Melting points are uncorrected.

2-(Ethylthio)thiazolo[5,4-*d*]pyrimidin-7(6*H*)-one (3). A) A mixture of **1a** (2 g) (prepared from 5-amino-2-mercaptothiazole-4-carboxamide[8] and ethyl iodide) and ethyl chloroformate (5 ml) in *N,N*-dimethylformamide (7 ml) was left overnight at 25 °C. The reaction mixture was then diluted with water and the obtained solid was filtered off, washed with water, dried and crystallized from ethanol to give **3** (2 g, 95%), mp 184—6 °C.

B) When the same reaction was repeated under reflux for 5—10 min, **3** (77%) was obtained.

C) A solution of **1a** (2 g) in formamide (15 ml) was heated in an oil bath (180—190 °C) for 1 h. The solid which separated on cooling, was filtered off, washed with water, dried and crystallized from ethanol to give **3** (68%), undepressed on admixture with the product above.

D) When **1b** (2 g) was allowed to react in formamide as described above, **3** (65%) was obtained. (Found: C, 39.8; H, 2.9; N, 19.7%. Calcd for $C_7H_7N_3OS_2$: C, 39.4 ; H, 3.3; N, 19.7%. IR (KBr), ν/cm^{-1}; 3300—2600 (NH and SC_2H_5), 1715 (CO-NH). UV (ethanol) λ_{max}/nm ($\varepsilon\times10^{-3}$); 325 (7.55), 311 (10.90), 270 (7.07), 223 (14.15), 214 (15.33). ^{1}H NMR (DMSO-d_6), δ=1.4 (s, t, 3H, CH_3), 3.38 (s, q, 2H, CH_2), 8.25 (s, s, 1H, C-5), 12.4 (b, s, 1H, NH). MS: *m/z* 213 (100%).

7-Chloro-2-(ethylthio)thiazolo[5,4-*d*]pyrimidine (4). A mixture of **3** (5 g) and phosphoryl chloride (30 ml) was heated in an oil bath at 120—25 °C for 1.5 h. After cooling, the reaction mixture was poured onto crushed ice. The solid was filtered off, washed with water several times, dried, then crystallized from ethanol to give **4** (4 g, 73.6%) mp 73—5 °C. Found: C, 36.1; H, 2.9; N, 17.8%. Calcd for $C_7H_6N_3S_2Cl$: C, 36.3; H, 2.6; N, 18.1%. UV (ethanol) λ_{max}/nm ($\varepsilon\times10^{-3}$); 300 (18.10), 295(18.63), 241(9.76), 229(13.54), 208—202(10.35). ^{1}H NMR ($CDCl_3$) δ=1.5 (s, t, CH_3), 3.4 (s, q, 2H, CH_2), 8.63 (s, s, 1H, C-5).

α-[2-(Ethylthio)thiazolo[5,4-*d*]pyrimidin-2-yl]malononitrile (5a). A mixture of **4** (2.3 g), malononitrile (0.73 g), and potassium hydroxide (0.5 g in 2 ml water) in dimethyl sulfoxide (15 ml) is heated on a steam-bath for 1 h. After cooling, the reaction mixture was diluted with water and then treated with cold dilute acetic acid solution. The solid was filtered off, washed with water, dried, then crystallized from ethanol to give **5a** (1.9 g, 73%) mp 258—60 °C. Found: C, 46.1; H, 2.8; N,26.4%. Calcd for $C_{10}H_7N_5S_2$: C, 46.0; H, 2.7; N, 26.8%. IR (KBr) ν/cm^{-1}, 2220, 2200 (CN). UV (ethanol) λ_{max}/nm ($\varepsilon\times10^{-3}$), 343 (24.34), 261(17.11), 231(14.54), 201 (13.72). ^{1}H NMR (DMSO-d_6) δ=1.45 (s, t, 3H, CH_3), 3.17 (s, q, 2H, CH_2), 8.3 (s, s, 1H, C-5). MS *m/z* 261(100%).

Ethyl α-Cyano-α-[2-(ethylthio)thiazolo[5,4-*d*]pyrimidin-2-yl]acetate (5b). To a solution of **4** (2.34 g) in dimethyl sulfoxide (15 ml) it was added ethyl cyanoacetate (1.24 g) and potassium hydroxide (0.5 g in 2 ml water) and the solution was heated on a steam-bath for 1 h. After cooling, the reaction mixture was treated with cold dilute acetic acid to give a solid which was filtered off, washed with water, dried, then crystallized from 1-butanol to give **5b** (2.1 g, 67.5%), mp

Table 3. Spectral Properties of 7-(Substituted amino)-2-(ethylthio)thiazolo-[5,4-*d*]pyrimidines (**6a—j**)

Compound	IR (KBr) ν/cm^{-1} NH	UV (ethanol) (λ_{max}/nm ($\varepsilon\times10^{-3}$))	^{1}H NMR ($CDCl_3$) (δ values from TMS)	MS *m/z* (% intensity)
6a	3350	312 (10.66); 287 (13.18); 282 (12.30); 246 (16.97); 213 (14.71) and 207 (13.84)	1.5 (s, t, 3H, CH_3); 3—3.4 (s, m, 5H, CH_2, NCH_3); 6.1 (b, 1H, NH) and 8.43 (s, s, 1H, C-5).	226 (100)
6b	3460—3100	307 (10.04); 287 (15.82); 279 (15.82); 247 (17.84); 213 (13.72); 205(13.55).	1.15—1.17(s, m, 6H, $2CH_3$); 3.8—3.9 (s, m, 4H, $2CH_2$); 5.9(b, 1H, NH); 8.33 (s, s, 1H, C-5).	
6c	3400—3100	312.5 (11.10); 288 (14.80); 285 (14.09); 247 (18.13); 213 (14.57), 206 (14.24).	1.2—1.7 (s, m, 9H, $3CH_3$); 3.35 (s, q, 2H, CH_2; 4.6 (s, m, 1H, CH); 5.8 (b, 1H, NH); 8.46 (s, s, 1H, C-5).	
6d	3440—3130	311 (11.34); 289 (15.98); 284 (15.29); 248 (14.39); 205 (22.04).	1.4 (s, t, 3H, CH_3); 3.25 (s, q, 2H, CH_2); 4.8 (s, d, 2H, CH_2 of benzyl); 6.3 (b, 1H, NH); 7.4—8.0 (s, m, 5H, C_6H_5); 8.5(s, s, 1H, C-5).	
6e	3420—3100	310 (25.01); 265 (16.55); 214 (21.23); 204 (24.44).	1.45 (s, t, 3H, CH_3); 3.30 (s, q, 2H, CH_2); 7.30—8.0 (s, m, 6H, NH, C_6H_5); 85 (s, s, 1H, C-5).	
6f	3420—3240	309 (25.00); 263 (16.44); 214 (21.06); 204 (24.44).	1.45 (s, t, 3H, CH_3); 2.3 (s, s, 3H, CH_3); 3.3 (s, q, 2H, CH_2); 7.30—8.0(s, m, 5H, NH, C_6H_4); 8.5 (s, s, 1H, C-5).	
6g	3500—3050	309 (22.13); 267 (16.53); 214 (19.71); 204 (23.83).	1.45 (s, t, 3H, CH_3); 3.35 (s, q, 2H, CH_2); 3.80 (s, s, 3H, OCH_3); 7.30—7.90 (s, 5H, NH, C_6H_5); 8.47 (s, s, 1H, C-5).	318 (100)
6h	3400—3220	311 (22.02); 270 (16.34); 213 (19.60); 204 (23.55).	1.51 (s, t, 3H, CH_3); 3.40 (s, q, 2H, OH_2); 7.2—8.0 (s, m, 5H, NH, C_6H_4); 8.6 (s, s, 1H, C-5).	
6i	3440—3220	293 (23.02); 241 (11.86); 229 (17.06); 207 (12.68); 201 (12.98).	1.53 (s, t, 3H, CH_3); 3.50 (s, q, 2H, CH_2); 5.25 (b, 1H, NH); 6.45—7.02 (s, 2d, 2H, CH=CH); 8.8 (s, s, 1H, C-5).	
6j	3440—3140	308 (11.48); 287 (15.43); 280 (14.33); 246 (19.20); 214 (21.14).	143 (s, t, 3H, CH_3); 3.30 (s, q, 2H, CH_2); 4.90 (s, d, N, CH_2); 6.3—7.4 (s, m, 4H, NH, furyl); 8.45 (s, s, 1H, C-5).	

189—91 °C. Found: C, 46.6; H, 3.8; N, 17.9%. Calcd for $C_{12}H_{12}N_4O_2S_2$: C, 46.7; H, 3.9; N, 18.2%. IR(KBr) ν/cm^{-1}: 2210 (CN), 1650 (CO). UV (ethanol) λ_{max}/nm ($\varepsilon\times10^{-3}$), 348 (31.08), 263 (17.61), 229 (21.04), 202 (15.65). ^{1}H NMR (DMSO-d_6) δ=1.4 (s, m, 6H, $2CH_3$), 3.5 (s, q, 2H, CH_2), 4.3 (s, q, 2H, CH_2), 8.47 (s, s, 1H, C-5). MS *m/z* 308(100%).

7-(Substituted amino)-2-(ethylthio)thiazolo[5,4-*d*]pyrimidines (6). General Method: To a mixture of **4** (0.01 mol) and the desired primary amine (0.01 mol) in absolute ethanol (20 ml) it was added triethylamine (few drops), and the mixture was heated under reflux for 1 h. The solution was then concentrated and left to cool. The solid obtained was identified and characterized (cf. Tables 2 and 3).

References

1) Kh. A. M. El-Bayouki, E. N. Flemming, and B. P. Erik, *Synthesis*, **1985**, 104.

2) J. Frank, J. Anker, Kh. A. M. El-Bayouki, and B. P. Erik, *Chem. Scri.*, **26**, 337 (1986).

3) B. P. Erik, K. E. Andersen, Kh. A. El-Bayouki, and E. N. Flemming, Eur. Patent. Appl., EP 155,911; *Chem. Abstr.*, **104**, 186245c (1986).

4) M. Benedek-Vamos and R. Promei, *Tetrahedron Lett.*, **1969**, 1011; K. E. Andersen, M. Hammad, B. P. Erik, *Liebigs Ann. Chem.*, **1986**, 1255.

5) K. Ikawa, F. Takami, Y. Fukui, and K. Tokuyama, *Tetrahedron Lett.*, **1969**, 3279.

6) World Health Organization. Expert Committee on Bilharziasis. Control methods of molluscicides and other means of snails distruction. *Wld. Hlth. Org.*, **65**, 33—38 (1953).

7) World Health Org. Molluscicides Screening and evaluation, *Bull. Wld. Hlth. Org.*, **33**, 567—81 (1956).

8) A. H. Cook, I. Heilbron, and E. Smith, *J. Chem. Soc.*, **1949**, 1440.