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A Convenient Synthesis of Thiazolopyrimidines, Thiazolodipyrimidines and Heterocyclo-thiazolopyrimidines

Sherif M. Sherif, Mohamed M. Youssef, Khaled M. Mobarak and Abdel-Samei M. Abdel-Fattah*

Chemistry Department, Faculty of Science, University of Cairo, Giza, A.R.Egypt

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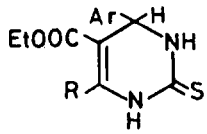
Abstract: Ethyl 4-aryl-6-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **1** reacted with bromomalononitrile (**2**) to give ethyl 3-amino-5-aryl-2-cyano-7-substituted-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **3**. The latter compounds reacted with formic acid, hydroxylamine hydrochloride and with formamide to give 9H-3,4-dihydrothiazolo[3,2-a:4,5-b]dipyrimidine-8-carboxylates **5**, 1H,8H-pyrazolo[3,4-d]thiazolo[3,2-a]pyrimidine-7-carboxylates **8** and 2,7-diaminothiazolo[4,5-d]pyrimidine (**7**), respectively. Compounds **1b,e** reacted with chloroacetyl chloride to yield ethyl 5-aryl-3-oxo-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **9a,b** which coupled with arenediazonium chlorides to give the corresponding 2-arylhydrazone derivatives **10a,b**. Compound **9a** adds ∝-cyanocinnamonitriles **12a-c** to yield ethyl 2-amino-4-aryl-3-cyano-9-(4-methoxyphenyl)-7-methyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylates **13a-c**. Refluxing **1b-d** with phenacyl bromide produced ethyl 5-aryl-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **14a-c**.

Thiazolopyrimidines have been of recent interest due to their ability to inhibit the enzyme 3',5'-cyclic AMP phosphodiesterase and found to have theophylline-like activity.[1] Additionally, such a ring system has antimicrobial[2] and antiinflammatory[3] properties, useful as insecticides[4] and reported to be active against virulent Lewis lung tumor in mice.[5] Prompted by the aforesaid biological and medicinal activities, and in connection with our synthetic programme aimed at the synthesis of several polyfunctionally substituted thiazolopyrimdines[6,7] of expected biological activity, samples of differently substituted thiazolopyrimidines and heterocyclothiazolopyrimidines were required. The reaction of the precursor ethyl 4-aryl-6-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **1a-e** with some bifunctional reagents seems to be a facile convenient route for the synthesis of such samples.

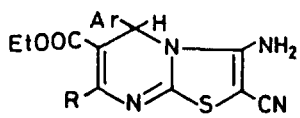
The precursor pyrimidine derivatives **1a-e** were prepared by the acid-catalysed condensation of a ternary mixture of aromatic aldehyde, the proper ester and thiourea in ethanol, commonly known as Biginelli reaction.[8,9] Both elemental and spectral data of **1b-e** are consistent with the assigned structure (cf. Experimental).



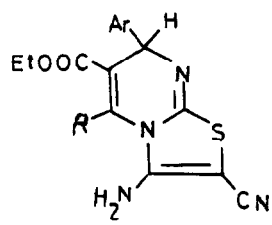
1	R	Ar
a	CH_3	C_6H_5
b	CH_3	C_6H_4-OCH_3-p
c	CH_3	C_6H_4-Cl-p
d	CH_3	C_6H_4-$N(CH_3)_2$-p
e	C_6H_5	C_6H_5

When a solution of each of **1a-c,e** in ethanol containing potassium hydroxide was treated with bromomalononitrile (**2**), a single product, in each case, was isolated in high yield (88-91%). The IR spectra of such products displayed absorption bands characteristic for the NH_2, CN and the ester CO functions. Theoretically, such products may be formulated as the 5H-thiazolo[3,2-a]pyrimidine structure **3** or the isomeric 7H-thiazolo[3,2-a]pyrimidine structure **4**. Structure **3** for the reaction products was tentatively preferred over **4** based on comparison of the ^{1}H-NMR spectral data for both compounds **1** and **3**. Thus, ^{1}H-NMR spectrum of **3b** showed, in addition to the ethyl ester, the methoxy, the aromatic and the NH_2 proton signals, a singlet signal (3H) at $\delta = 2.30$ ppm assigned for the CH_3 protons and a singlet signal (1H) at $\delta = 6.31$ ppm assigned for the pyrimidine H-5 in **3b**. The appearance of the CH_3 protons signal at the same position as that for the CH_3 protons in the pyrimidine **1b**, and also the down field shift of the pyrimidine H-5 in **3b** compared to the pyrimidine H-4 in **1b**, which appeared at $\delta = 5.12$ ppm, indicates that the moeity around C-5 in **3b** differs from that around C-4 in **1b**. Also, the moiety around C-7 in **3b** is, to some extent, similar to that around C-6 in **1b**. Consequently, we have assigned structure **3** for the reaction products. Had we had structure **4** for such products, δ values for the methyl groups in **4b** and **1b** would be different, and δ values for H-7 in **4b** and H-4 in **1b** would be equal.

$BrCH(CN)_2$
(2)



3	R	Ar
a	CH_3	C_6H_5
b	CH_3	C_6H_4-OCH_3-p
c	CH_3	C_6H_4-Cl-p
d	C_6H_5	C_6H_5



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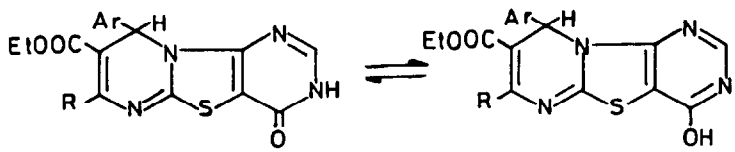
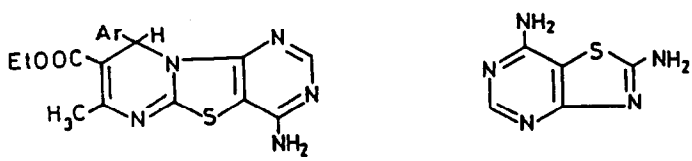
Compounds **3**, as typical enaminonitriles, reacted with formic acid, on heating several hours, to yield ethyl 9-aryl-4-oxo-7-substituted-9H-3,4-dihydrothiazolo[3,2,-a:4,5-b]dipyrimidine-8-carboxylates **5a-d.** Assignment of structure **5** was confirmed on the basis of its correct values in elemental analyses as well as compatible spectral data (cf. Experimental).

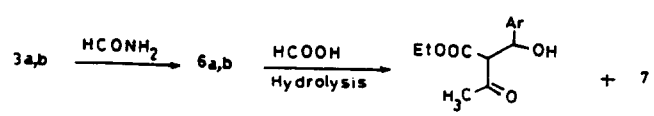


5	R	Ar
a	CH_3	C_6H_5
b	CH_3	C_6H_4-OCH_3-p
c	CH_3	C_6H_4-Cl-p
d	C_6H_5	C_6H_5

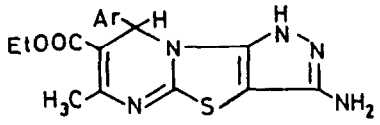
When each of **3a,b** was heated under reflux with formamide in the presence of formic acid and dimethylformamide to obtain the expected thiazolo[3,2-a : 4,5-b]dipyrimidine derivatives **6**,[6] only one and the same product was obtained. The obtained product was proved to be 2,7-diaminothiazolo[4,5-d]pyrimidine (**7**). The identity of **7** was established on the basis of analytical and spectral data. Thus, its mass spectrum revealed a molecular formula $C_5H_5N_5S$ ($M^+/z = 168$). Its ^{1}H-NMR spectrum revealed the absence of any signals characteristic for the aromatic protons or the ethyl ester function. It only showed a singlet signal (1H) at $\delta = 3.34$ ppm for the NH_2 group (D_2O-exchangeable), singlet signal (2H) at $\delta = 8.07$ ppm for the NH_2 group (D_2O-exchangeable) together with a singlet signal (1H) at $\delta = 10.4$ ppm characteristic for the pyrimidine H-5. Formation of **7** is assumed to proceed via intermediacy of **6a,b** which then undergo hydrolytic cleavage, under the reaction conditions, to yield **7**.



6a,b **7**

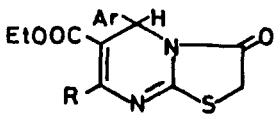


When **3b,c** were heated with hydroxylamine hydrochloride, in acetic acid in the presence of anhydrous sodium acetate, the corresponding ethyl 3-amino-8-aryl-6-methyl-1H,8H-pyrazolo[3,4-d]thiazolo[3,2-a]pyrimidine-7-carboxylates **8a,b** were formed.

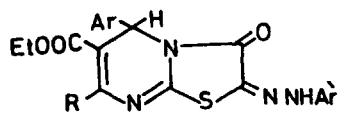


8	R	Ar
a	CH_3	C_6H_4-OCH_3-p
b	CH_3	C_6H_4-Cl-p

When a solution of each of **1b,e** in dry dioxane was treated with an equimolar amount of chloroacetyl chloride, the corresponding ethyl 5-aryl-3-oxo-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **9a,b** were isolated in good yields. As expected, compounds **9a,b** coupled with arenediazonium chlorides in ethanol in the presence of sodium acetate (pH = 8) to afford the corresponding ethyl 5-aryl-2,3-dioxo-2-arylhydrazono-7-substituted-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate derivatives **10a-d**.

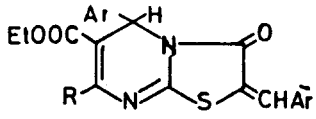


9	R	Ar
a	CH_3	C_6H_4-OCH_3-p
b	C_6H_5	C_6H_5



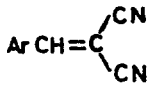
10	R	Ar	Ar`
a	CH_3	C_6H_4-OCH_3-p	C_6H_5
b	CH_3	C_6H_4-OCH_3-p	C_6H_4-Cl-p
c	CH_3	C_6H_4-OCH_3-p	C_6H_4-CH_3-p
d	C_6H_5	C_6H_5	C_6H_4-Cl-p

Heating under reflux a mixture of **1b-e**, chloroacetic acid, an appropriate aromatic aldehyde, anhydrous sodium acetate, acetic anhydride and acetic acid afforded the corresponding ethyl 5-aryl-2-arylmethylene-3-oxo-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **11a-e**, in almost quantitative yields. Assignment of structure **11** is established via its alternative synthesis. Thus, compound **9a** condensed with anisaldehyde in ethanol in the presence of catalytic amount of piperidine to afford a single product which is identical in all respects with **11a** (m.p., mixed m.p. and IR spectrum).



11	R	Ar	Ar`
a	CH_3	C_6H_4-OCH_3-p	C_6H_4-OCH_3-p
b	CH_3	C_6H_4-OCH_3-p	C_6H_4-Cl-p
c	CH_3	C_6H_4-Cl-p	C_6H_4-$N(CH_3)_2$p
d	CH_3	C_6H_4-$N(CH_3)_2$p	C_6H_4-$N(CH_3)_2$p
e	C_6H_5	C_6H_5	C_6H_4-Cl-p

Compound **9a** adds α-cyanocinnamonitriles **12a-c** in refluxing pyridine to furnish the corresponding ethyl 2-amino-4-aryl-3-cyano-9-(4-methoxyphenyl)-7-methyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylates **13a-c.** Alternatively the reaction of malononitrile with **11a** in refluxing ethanol in the presence of a catalytic amount of piperidine furnished a single product identical in all respects with **13b** (m.p, mixed m.p. and IR spectrum).



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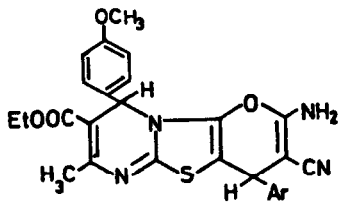
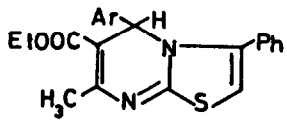


13	Ar
a	C_6H_5
b	C_6H_4-OCH_3-p
c	C_6H_4-Cl-p

Long heating under reflux of **1b-d** with phenacyl bromide in absolute ethanol produced ethyl 5-aryl-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates **14a-c** as their hydrobromide salts.



14	Ar
a	C_6H_4-OCH_3-p
b	C_6H_4-Cl-p
c	C_6H_4-$N(CH_3)_2$-p

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian ^{1}H-Gemini 200 MHz spectrometer and chemical shifts are expressed in δ (ppm) units using TMS as internal reference. Ms spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 eV. Microanalytical data were obtained from the Microanalytical Data Center at Cairo University.

Ethyl 4-aryl-6-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates 1a-e. A ternary mixture of each of the appropriate ester (0.1 mol), thiourea (0.12 mol) and the appropriate aromatic aldehyde (0.1 mol) in ethanol (30 ml) containing a catalytic amount of concentrated hydrochloric acid (10 drops) was refluxed for 3 h. The reaction mixture was then allowed to stand at room temperature overnight, whereby the solid precipitate so formed was collected by filtration, washed with ethanol and crystallized from ethanol.

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a) : yield 76%, m.p. 207°C , Lit. m.p. 207-208°C[10].

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimi-dine-5-carboxylate (1b) : yield 75%, m.p. 150°C. - IR : $\bar{\nu}$= 3318, 3173 (NH), 1672 (CO).- ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.10 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.00 (q, 2H, CH_2), 5.12 (s, 1H, pyrimidine H-4), 6.90 (d, 2H, aromatic protons), 7.12 (d, 2H, aromatic protons), 9.61 (s, 1H, NH, exchangeable), 10.35 (s, 1H, NH, exchangeable). Found C 58.9 H 5.8 N 9.0 S 10.5. Calcd. for $C_{15}H_{18}N_2O_3S$ (306.4) C 58.80 H 5.90 N 9.14 S 10.46.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimi-dine-5-carboxylate (1c) : yield 65%, m.p. 187°C. -IR : $\bar{\nu}$= 3331, 3177 (NH), 1678 (CO). Found C 54.3 H 4.9 Cl 11.2 N 9.2 S 10.2 Calcd. for $C_{14}H_{15}ClN_2O_2S$ (310.8) C 54.10 H 4.86 Cl 11.42 N 9.03 S 10.34.

Ethyl 4-[4-(N,N-dimethylamino)phenyl]-6-methyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (1d) : yield 60%, m.p. 198°C. - IR : $\bar{\nu}$= 3328, 3176 (NH), 1668 (CO). Found C 60.2 H 6.5 N 13.3 S 10.1 Calcd. for $C_{16}H_{21}N_3O_2S$ (319.4) C 60.16 H 6.62 N 13.15 S 10.03.

Ethyl 4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1e) : yield 70%, m.p. 192°C. -IR : $\bar{\nu}$= 3319, 3157 (NH), 1683 (CO).-^{1}H-NMR(DMSO-d_6) : δ = 0.78(t, 3H, CH_3), 3.78 (q, 2H, CH_2), 5.30 (s, 1H, pyrimidine H-4), 7.41 (m, 10H, aromatic protons), 9.81 (s, 1H, NH, exchangeable), 10.35 (s, 1H, NH, exchangeable). Found C 67.5 H 5.4 N 8.3 S 9.6. Calcd. for $C_{19}H_{18}N_2O_2S$ (338.4) C 67.43 H 5.36 N 8.27 S 9.47.

Ethyl 6-amino-5-aryl-2-cyano-7-substituted-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates 3a-d. To a warm ethanolic potassium hydroxide solution [prepared by dissolving KOH (0.01 mol) in ethanol (50 ml)] of each of **1a-c,e** (0.01 mol), bromomalononitrile (**2**) (0.01 mol) was added portionwise with stirring. The reaction mixture was then left overnight at room temperature, where by the solid product so precipitated upon dilution with water was filtered off and crystallized from dilute dimethylformamide.

Ethyl 3-amino-2-cyano-7-methyl-5-phenyl-5H-thiazolo[3,2-a]pyrimidine-5-carboxylate (3a) : yield 90%, m.p. 247°C.-IR : $\bar{\nu}$= 3381, 3241 (NH), 2989 (CH), 2191 (CN), 1712 (CO). Found C 59.9 H 4.6 N 16.3 S 9.3. Calcd. for $C_{17}H_{16}N_4O_2S$ (340.4) C 59.98 H 4.70 N 16.40 S 9.43.

Ethyl 3-amino-2-cyano-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-5-carboxylate (3b) : yield 92%, m.p. 227°C.-IR : $\bar{\nu}$ = 3405, 3302 (NH), 2997 (CH), 2189 (CN), 1712 (CO).-^{1}H-NMR (DMSO-d_6) : δ = 1.22 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.08 (q, 2H, CH_2), 6.31 (s, 1H, pyrimidine H-4), 6.92 (d, 2H, aromatic protons), 7.32 (d, 2H, aromatic protons), 7.71 (s, 2H, NH_2, exchangeable). Found C 58.4 H 4.9 N 15.0 S 8.4. Calcd. for $C_{18}H_{18}N_4O_3S$ (370.4) C 58.36 H 4.89 N 15.12 S 8.60.

Ethyl 3-amino-5-(4-chlorophenyl)-2-cyano-7-methyl-5H-thiazolo[3,2-a]pyrimidine-5-carboxylate (3c) : yield 88%, m.p. 230°C.-IR : $\bar{\nu}$= 3382, 3297 (NH), 2989 (CH), 2192 (CN), 1715 (CO). Found C 54.6 H 4.2 Cl 9.3 N 14.8 S 8.3. Calcd. for $C_{17}H_{15}ClN_4O_2S$ (374.8) C 54.47 H 4.03 Cl 9.46 N 14.90 S 8.55.

Ethyl 3-amino-2-cyano-4,7-diphenyl-5H-thiazolo[3,2-a]pyrimidine-5-carboxylate (3d) : yield 91%, m.p. 205°C.-IR : $\bar{\nu}$= 3335, 3212 (NH), 2986 (CH), 2197 (CN), 1700 (CO). Found C 65.8 H 4.7 N 14.0 S 8.0. Calcd. for $C_{22}H_{18}N_4O_2S$ (402.5) C 65.65 H 4.50 N 13.92 S 7.96.

Ethyl 9-aryl-4-oxo-7-substituted-9H-3,4-dihydrothiazolo[3,2-a : 4,5-b]dipyrimidine-8-carboxylates 5a-d. Each of 3a-d (1.0 g) was heated under reflux in formic acid (85%, 10 ml) for 10 h. The solid product so formed on cooling at room temperature was filtered off and crystallized from the proper solvent.

Ethyl 9-phenyl-4-oxo-7-methyl-9H-3,4-dihydrothiazolo[3,2-a:4,5-b]di-pyrimidine-8-carboxylate (5a) : yield 57%, m.p. 212°C (DMF). -IR : $\bar{\nu}$= 3333 (NH), 1670 (CO). Found C 58.7 H 4.4 N 15.1 S 8.6. Calcd. for $C_{18}H_{16}N_4O_3S$ (368.4) C 58.68 H 4.37 N 15.20 S 8.70.

Ethyl 9-(4-methoxyphenyl)-7-methyl-4-oxo-9H-3,4-dihydrothiazolo[3,2-a:4,5-b]dipyrimidine-8-carboxylate (5b) : yield 63%, m.p. 154°C (EtOH).-IR : $\bar{\nu}$= 3320 (NH), 1673 (CO). ^{1}H-NMR (DMSO-d_6) : δ = 1.28 (t, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.02 (q, 2H, CH_2), 5.14 (s, 1H, pyrimidine H-9), 6.91 (d, 2H, aromatic protons), 7.18 (d, 2H, aromatic protons), 9.66 (s, 1H, NH, exchangeable), 10.32 (s, 1H, pyrimidine H-2). Found C 57.3 H 4.5 N 14.0 S 8.0. Calcd. for $C_{19}H_{18}N_4O_4S$ (398.4) C 57.27 H 4.55 N14.06 S 8.04.

Ethyl 9-(4-chlorophenyl)-7-methyl-4-oxo-9H-3,4-dihydrothiazolo[3,2-a:4,5-b]dipyrimidine-8-carboxylate (5c) : yield 59%, m.p. 302°C (DMF).-IR : $\bar{\nu}$= 3320 (NH), 1676 (CO). Found C 53.6 H 3.8 Cl 8.7 N 13.8 S 8.0. Calcd. for $C_{18}H_{15}ClN_4O_3S$ (402.9) C 53.66 H 3.75 Cl 8.80 N 13.90 S 7.96.

Ethyl 7,9-diphenyl-4-oxo-9H-3,4-dihydrothiazolo[3,2-a:4,5-b]dipyrimi-dine-8-carboxylate (5d) : yield 60%, m.p. 193°C (EtOH).-IR : $\bar{\nu}$= 3318 (NH), 1685 (CO). Found C 64.3 H 4.0 N 13.2 S 7.6. Calcd. for $C_{23}H_{17}N_4O_3S$ (429.5) C 64.32 H 3.99 N 13.04 S 7.46.

2,7-Diaminothiazolo[4,5-d]pyrimidine (7) Each of **3a,b** (1 g) was heated under reflux with a ternary mixture of formic acid (5 ml), formamide (5 ml) and dimethylformamide (5 ml) for 10 h. The reaction mixture was then allowed to stand at room temperature overnight, whereby the solid product so precipitated was filtered off and crystallized from dilute dimethylformamide to give only one and the same product, m.p. 430°C. Ms (M^+/e) = 168.-IR : $\bar{\nu}$= 3080 (NH_2 & NH).-^{1}H-NMR (DMSO-d_6) : δ = 3.34 (s, br, 2H, NH_2, exchangeable), 8.07 (s, br, 2H, NH_2 exchangeable), 10.40 (s, br, 1H, pyrimidine H-5). Found C 35.8 H 3.1 N 41.7 S 19.2. Calcd. for $C_5H_5N_5S$ (167.2) C 35.92 H 3.01 N 41.88 S 19.17.

Ethyl 3-amino-8-aryl-6-methyl-1H,8H-pyrazolo[3,4-d]thiazolo[3,2-a]pyri-midine-7-carboxylates 8a,b. A mixture of each of **3b,c** (0.01 mol), hydroxylamine hydrochloride (0.012 mol) and sodium acetate (2 g) in acetic acid (20 ml) was refluxed for 5h. The reaction mixture was then poured onto cold water, whereby the solid precipitated so formed, in each case, was filtered off and crystallized from ethanol.

Ethyl 3-amino-8-(4-methoxyphenyl)-6-methyl-1H,8H-pyrazolo[3,4-d]thia-zolo[3,2-a]pyrimidine-7-carboxylate (8a) : yield 60%, m.p. 200°C. IR : $\bar{\nu}$= 3171 (NH), 2938 (CH), 1686 (CO). Found C 56.2 H 4.9 N 18.2 S 8.5 Calcd. for $C_{18}H_{19}N_5O_3S$ (385.4) : C 56.09 H 4.96 N 18.7 S 8.32.

Ethyl 3-amino-8-(4-chlorophenyl)-6-methyl-1H,8H-pyrazolo[3,4-d]thia-zolo[3,2-a]pyrimidine-7-carboxylate (8b) : yield 58%, m.p. 184°C. IR : $\bar{\nu}$ = 3180 (NH_2 & NH), 2950 (CH), 1692 (CO). Found C 52.2 H 4.2 Cl 9.2 N 17.8 S 8.1 Calcd. for $C_{17}H_{16}ClN_5O_2S$ (389.9) : C 52.37 H 4.13 Cl 9.09 N 17.96 S 8.22.

Ethyl 5-aryl-3-oxo-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimi-dine-6-carboxylates 9a,b. To a solution of each of **1b,e** (0.01 mol) in dry dioxane (30 ml), chloroacetyl chloride (0.01 mol) was added at room temperature. The precipitate that was suddenly formed, in each case, filtered off and crystallized from ethanol.

Ethyl 5-(4-methoxyphenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (9a) : yield 93%, m.p. 233°C.-IR : $\bar{\nu}$ = 3010 (CH), 1771 and 1717 (2 CO).-^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.14 (t, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.06 (q, 2H, CH_2), 4.20 (s, 2H, CH_2), 5.88 (s, 1H, pyrimidine H-4), 6.22 (br, s, 1H, NH, exchangeable), 6.93 (d, 2H, aromatic protons), 7.20 (d, 2H, aromatic protons). Found C 53.4 H 5.0 Cl 9.3 N 7.5 S 8.2 Calcd. for $C_{17}H_{19}ClN_2O_4S$ (382.9) C 53.33 H 5.00 Cl 9.26 N 7.32 S 8.37.

Ethyl 5,7-diphenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (9b) : yield 90%, m.p 125°C.-IR : 3040 (CH), 1744, 1704 (2 CO). Found C 59.0 H 5.3 N 8.2 S 9.3 Calcd. for $C_{17}H_{18}N_2O_4S$ (346.4) C 58.94 H 5.24 N 8.08 S 9.25.

Ethyl 5-aryl-2,3-dioxo-2-arylhydrazono-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates 10a-d .To a cold solution of each of compounds **9a,b** (0.01 mol) in ethanol (80 ml), containing sodium acetate (3 g), the appropriate arenediazonium chloride (0.01 mol) [prepared by adding concentrated hydrochloric acid (3 ml) to the appropriate aromatic amine (0.01 mol) at 0-5°C and treating the resulting hydrochloride solution with a cold solution of sodium nitrite (0.01 mol) in water (5 ml)] was added dropwise with constant stirring at 0-5°C. The coupling mixture was stirred at room temperature for 2 h and then

diluted with water (30 ml) where by the resultant crude product thus precipitated in each case, was filtered off, washed with water and crystallized from the proper solvent.

Ethyl 2,3-dioxo-2-phenylhydrazono-5-(4-methoxyphenyl)-7-methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (10a) : yield 70%, m.p 126°C (EtOH),-IR : $\bar{\nu}$ = 3178 (NH), 2969 (CH), 1720 and 1690 (2 CO). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.22 (t, 3H, CH_3); 2.31 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3); 4.18 (q, 2H, CH_2); 6.23 (s, 1H, pyrimidine H-4); 6.54 (d, 2H, aromatic protons), 6.83 (d, 2H, aromatic protons), 7.15 (d, 2H, aromatic protons), 7.28 (m, 3H, aromatic protons), 9.24 (s, 1H, NH, exchangeable). Found C 61.5 H 5.0 N 12.2 S 6.9 Calcd. for $C_{23}H_{22}N_4O_4S$ (450.5) C 61.32 H 4.92 N 12.43 S 7.12.

Ethyl 2,3-dioxo-2-(4-chlorophenyl)-5-(4-methoxyphenyl)-7-methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (10b) : yield 68% m.p. 151°C (EtOH),-IR : $\bar{\nu}$= 3239 (NH), 2982 (CH), 1719, 1696 (2 CO). Found C 56.8 H 4.5 Cl 7.2 N 11.7 S 6.5 Calcd. for $C_{23}H_{21}ClN_4O_4S$ (485.0) C 56.96 H 4.36 Cl 7.31 N 11.55 S 6.61.

Ethyl 5-(4-methoxyphenyl)-7-methyl-2,3-dioxo-2-(4-methylphenyl-hydrazono)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (10c) : yield 72%, m.p 196°C (EtOH).-IR : $\bar{\nu}$ = 3246 (NH), 2953 (CH), 1722, 1695 (2 CO). Found C 62.1 H 5.3 N 12.1 S 6.8 Calcd. for $C_{24}H_{24}N_4O_4S$ (464.5) C 62.05 H 5.20 N 12.06 S 6.90.

Ethyl 2,3-dioxo-2-(4-chlorophenylhydrazono)-5,7-diphenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (10d) : yield 78%, m.p. 240°C (AcOH). -IR : $\bar{\nu}$ = 3230 (NH), 2934 (CH), 1728, 1714 (2 CO). -^{1}H-NMR (DMSO-d_6) : δ (ppm) = 0.82 (t, 3H, CH_3), 3.82 (q, 2H, CH_2), 6.18 (s, 1H, pyrimidine H-4), 7.42 (m, 14H, aromatic protons), 11.04 (s, 1H, NH, exchangeable). Found : C 62.7 H 4.2 Cl 6.9 N 11.0 S 6.4. Calcd. for $C_{27}H_{21}ClN_4O_3S$ (517.0) C 62.73 H 4.09 Cl 6.86 N 10.84 S 6.22.

Ethyl 5-aryl-2-arylmethylene-3-oxo-7-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates 11a-e.

Method (A) : A mixture of each of **1b-e,** (0.01 mol), chloroacetic acid (0.012 mol), the appropriate aldehyde (0.01 mol), anhydrous sodium acetate (2 g) in glacial acetic acid (30 ml) and acetic anhydride (15 ml) was refluxed for 3 h. The reaction mixture was then poured onto water, whereby the solid precipitate so formed was filtered off, and crystallized from the proper solvent.

Method (B) : A mixture of **9a** (0.005 mol), p-anisaldehyde (0.005 mol) in ethanol (30 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 3 h. The reaction mixture was then poured onto cold water, whereby the solid product so formed was filtered off and crystallized from acetic acid to give compound identical in all respects (m.p, mixed m.p. and IR spectrum) with **11a** prepared according to method (A).

Ethyl 5-(4-methoxyphenyl)-2-(4-methoxyphenylmethylene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (11a) : yield 89%, m.p. 153°C (AcOH).-IR : $\bar{\nu}$ = 1715, 1659 (2 CO). ^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.15 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.75 (s, 3H,

OCH_3), 3.87 (s, 3H, OCH_3), 4.08 (q, 2H, CH_2), 6.05 (s, 1H, pyrimidine H-4), 6.72 (s, 1H, ylidene CH), 6.92 (d, 2H, aromatic protons), 7.15 (d, 2H, aromatic protons), 7.25 (d, 2H, aromatic protons), 7.70 (d, 2H, aromatic protons). Found C 64.5 H 5.0 N 6.1 S 7.1 Calcd. for $C_{25}H_{24}N_2O_5S$ (464.5) C 64.64 H 5.20 N 6.03 S 6.90.

Ethyl 2-(4-chlorophenylmethylene)-5-(4-methoxyphenyl)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (11b) : yield 87% m.p. 147°C (EtOH). - IR : $\bar{\nu}$= 1710, 1690 (2 CO). Found C 61.3 H 4.6 Cl 7.4 N 5.8 S 6.7 Calcd. for $C_{24}H_{21}ClN_2O_4S$ (468.9) C 61.47 H 4.51 Cl 7.56 N 5.97 S 6.80.

Ethyl 5-(4-chlorophenyl)-2-[4-(N,N-dimethylamino)phenylmethylene]-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (11c) : yield 82%, m.p. 225°C (AcOH). - IR : $\bar{\nu}$= 1720, 1690 (2 CO). Found C 62.3 H 5.2 Cl 7.5 N 8.6 S 6.5 Calcd. for $C_{25}H_{24}ClN_3O_3S$ (482.0) C 62.29 H 5.02 Cl 7.35 N 8.70 S 6.60.

Ethyl 5-[4-(N,N-dimethylamino)phenyl]-2-[4-(N,N-dimethylamino)phenyl-methylene]-7-methyl-3-oxo-5H-thiazolo[3,2,a]pyrimidine-6-carboxylate (11d) : yield 89%, m.p. 183°C (AcOH).-IR : $\bar{\nu}$= 1720, 1705 (2 CO). Found : C 66.0 H 6.0 N 11.4 S 6.4. Calcd. for $C_{27}H_{30}N_4O_3S$ (490.6) C 66.09 H 6.16 N 11.42 S 6.53.

Ethyl 2-(4-chlorophenylmethylene)-5,7-diphenyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-7-carboxylate (11e) : yield 87%, m.p. 164°C (AcOH).-IR : $\bar{\nu}$= 1728, 1720 (2 CO). Found : C 67.0 H 4.4 Cl 7.1 N 5.6 S 6.3. Calcd. for $C_{28}H_{21}ClN_2O_3S$ (501.0) C 67.13 H 4.22 Cl 7.07 N 5.59 S 6.40.

Ethyl 2-amino-4-aryl-3-cyano-9-(4-methoxyphenyl)-7-methyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylates 13a-c :

Method (A) : A mixture of **8a** (0.01 mol) and each of **12a-c** (0.01 mol) was refluxed in pyridine (25 ml) for 12 h. The reaction mixture was then poured onto cold water, neutralized with hydrochloric acid, whereby the solid precipitated so formed, in each case, was filtered off and crystallized from the proper solvent.

Method (B) : A solution of **11a** (0.01 mol) and malononitrile (0.01 mol) was refluxed in ethanol (30 ml) in the presence of a catalytic amount of piperidine (3 drops) for 3 h. The reaction mixture was then poured onto water, neutralized with hydrochloric acid, whereby the solid product so formed was filtered off and neutralized from ethanol to give a compound (60% yield) identical in all respects (m.p. mixed m.p. and IR spectrum) with **13b** obtained by method (A).

Ethyl 2-amino-3-cyano-9-(4-methoxyphenyl)-7-methyl-4-phenyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylate (13a) : yield 65%, m.p. 147°C (MeOH).-IR : $\bar{\nu}$ =3212, 3103 (NH), 2220 (CN), 1720 (CO). Found C 64.8 H 4.7 N 11.0 S 6.5. Calcd. for $C_{27}H_{24}N_4O_4S$ (499.6) C 64.92 H 4.82 N11.21 S 6.42.

Ethyl 2-amino-3-cyano-4,9-[di-(4-methoxyphenyl)]-7-methyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylate (13b) : yield 68%, m.p. 135°C (EtOH). IR : $\bar{\nu}$= 3220,

3150 (NH), 2230 (CN), 1715 (CO). Found C 63.3 H 4.9 N 10.4 S 6.2. Calcd. for $C_{28}H_{26}N_4O_5S$ (530.6) C 63.38 H 4.94 N 10.56 S 6.04.

Ethyl 2-amino-4-(4-chlorophenyl)-3-cyano-9-(4-methoxyphenyl)-7-methyl-4H,9H-pyrano[2,3-d]thiazolo[3,2-a]pyrimidine-8-carboxylate (13c) : yield 63%, m.p. 142°C (EtOH).-IR : $\bar{\nu}$= 3225, 3153 (NH), 2204 (CN), 1714 (CO).-^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.16(t, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.35 (s, 2H, NH_2, exchangeable), 3.72 (s, 3H, OCH_3), 4.07 (q, 2H, CH_2), 6.00 (s, 1H, pyrimidine H-4), 6.92 (d, 2H, aromatic protons), 7.26 (d, 2H, aromatic protons), 7.64 (s, 4H, aromatic protons), 7.82 (s, 1H, pyran H-4). Found : C 60.8 H 4.3 Cl 6.8 N 10.2 S 6.2. Calcd. for $C_{27}H_{23}ClN_4O_4S$ (535.0) C 60.60 H 4.30 Cl 6.63 N 10.47 S 5.99.

Ethyl 5-aryl-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxy-late hydrobromides 14a-c . A solution of each of **1b-d** (0.01 mol) and phenacyl bromide (0.01 mol) in absolute ethanol (50 ml) was heated under reflux for 10 h. The solid precipitated so formed, in each case on long standing at room temperature was filtered off and crystallized from the proper solvent.

Ethyl 5-(4-methoxyphenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimi-dine-6-carboxylate hydrobromide (14a) : yield 70%, m.p. 194°C (EtOH).-IR : $\bar{\nu}$= 2914 (CH), 1712 (CO).-^{1}H-NMR (DMSO-d_6) : δ (ppm) = 1.13 (t, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.09 (q, 2H, CH_2), 5.56 (s, 1H, pyrimidine H-4), 6.43-7.04 (m, 6H, thiazole H-5+aromatic protons), 7.28 (d, 2H, aromatic protons), 7.58 (d, 2H, aromatic protons). Found C 56.6 H 4.4 Br 16.2 N 5.8 S 6.7. Calcd. for $C_{23}H_{22}BrN_2O_3S$ (486.5) C 56.84 H 4.56 Br 16.43 N 5.76 S 6.59.

Ethyl 5-(4-chlorophenyl)-7-methyl-3-phenyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate hydrobromide (14b) : yield 68%, m.p. 173°C (MeOH).IR : $\bar{\nu}$= 2930 (CH), 1720 (CO). Found C 53.6 H 4.0 Br 16.3 Cl 7.4 N 5.5 S 6.4 Calcd. for $C_{22}H_{20}BrClN_2O_2S$ (491.8) C 53.72 H 4.10 Br 16.24 Cl 7.21 N 5.69 S 6.52.

Ethyl 5-[4-(N,N-dimethylamino)phenyl]-7-methyl-3-phenyl-5H-thiazolo-[3,2-a]pyrimidine-6-carboxylate hydrobromide (14c) : yield 65%, m.p. 159°C (MeOH). IR : $\bar{\nu}$ = 2925 (CH), 1712 (CO). Found : C 57.7 H 5.1 Br 15.8 N 8.5 S 6.2 Calcd. for $C_{24}H_{26}BrN_2O_2S$ (500.5) C 57.59 H 5.24 Br 15.97 N 8.39 S 6.40.

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