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SYNTHESIS OF CONDENSED THIAZOLO-[3,2-*a*]PYRIMIDINE SYSTEMS

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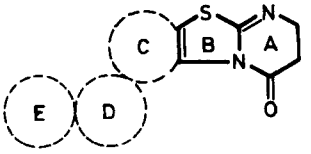
Syntheses of condensed tri-, tetra- and pentacyclic thiazolo[3,2-*a*]pyrimidine systems are described.

Key words: Thiazolo[3,2-*a*]pyrimidines.

CONTENTS

1. INTRODUCTION AND NOMENCLATURE

The bulk of the literature dealing with the chemistry of condensed thiazolopyrimidines has forced us to restrict this review to only those methods which describe the synthesis of thiazolo[3,2-*a*]pyrimidine systems represented by the general formula **I** given below.



Formula - I

The C, D and E rings in **I** represent arene, hetarene, cycloalkene, etc. The systematic nomenclature of these condensed heterocyclic ring systems is based on the following names:

(1) thiazolo[3,2-*a*]pyrimidine
(2) pyrimido[2,1-*b*]thiazole
(3) pyrimido[2,3-*b*]thiazole

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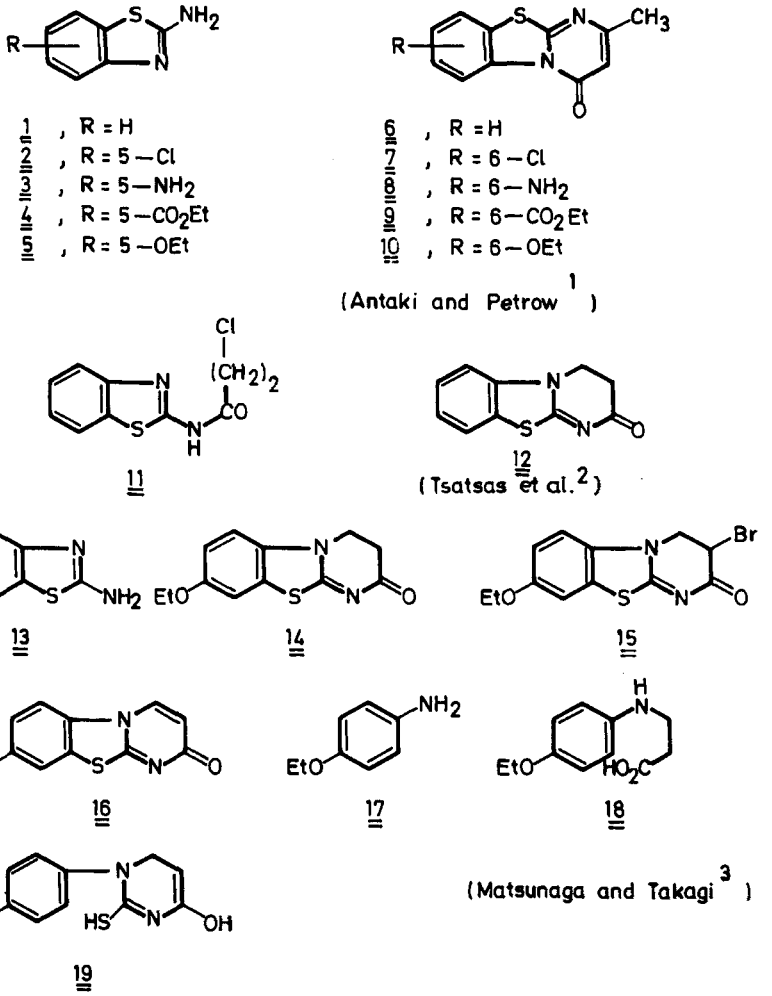
Though a large number of publications have appeared on the chemistry of thiazolopyrimidines during the last three decades it is quite surprising to note that no review of this subject has appeared so far. The present review on the synthesis of condensed thiazolo[3,2-*a*]pyrimidines is for the sake of convenience divided into three sections mainly based on the number of rings [C, D and E — *vide* **I**] (arene, hetarene or cycloalkene attached to the thiazole moiety).

2. SYNTHESES OF TRICYCLIC THIAZOLO[3,2-*a*]PYRIMIDINES

Antaki and Petrow[1] reported the first synthesis of a tricyclic thiazolopyrimidinone, *i.e.* 2-methyl-4-oxo-benzothiazolo[3,2-*a*]pyrimidine **6** (Scheme 1), by condensing 2-amino-benzothiazole **1** with ethyl β-aminocrotonate. A similar procedure was adopted to



Scheme 1.

obtain the variously substituted thiazolo[3,2-*a*]pyrimidin-4-ones **7–10** (Scheme 1) starting with the appropriately substituted 2-aminobenzothiazoles **2–5.**

Tsatas *et al.*[2] have reported the synthesis of tricyclic thiazolopyrimidinone derivative **12** (Scheme 1) by condensation of 2-aminobenzothiazole **1** with β-chloropropionyl chloride under alkaline conditions. The anticipated thiazolopyrimidine derivative **12** was, however, obtained in low yield (18–20%), while the major product isolated was found to be the acylated derivative, 2-(β-chloropropionylamino)benzothiazole **11** as shown in Scheme 1.

Syntheses of pyrimido[2,3-*b*]benzothiazoles have been achieved[3] starting with 2-amino-6-ethoxybenzothiazole **13** as detailed below.

Condensation of **13** with β-bromopropionic acid gave the corresponding thiazolopyrimidine derivative **14** (Scheme 1).

The same authors[3] also reported an alternative procedure for the synthesis of the same heterocycle viz., 3,4-dihydro-8-ethoxy-2*H*-pyrimido[2,1-*b*]benzothiazol-2-one **14** (Scheme 1) as discussed below.

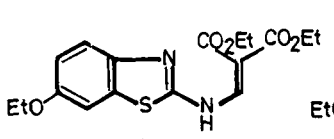
p-Phenetidine **17** was treated with ethyl β-bromopropionate in the presence of a catalytic amount of *t*-butylcatechol in ethanol to afford ethyl β-ethoxyphenylaminopropionate **18**. Thus, the ethyl propionate derivative **18** was condensed with ammonium thiocyanate to give 1,6-dihydro-1-(4-ethoxyphenyl)-4-hydroxy-2-mercaptopyrimidine **19**, which on treatment with bromine gave the expected tricyclic heterocycle **14**.

Conversion of **14** into the new heterocyclic system **16** (Scheme 1) was achieved in two steps. Treatment of **14** with *N*-bromosuccinimide in chlorobenzene afforded the expected bromo derivative **15** which on dehydrobromination catalysed by lithium chloride in dry DMF gave the expected heterocycle, 7-ethoxy-2-oxo-2*H*-benzothiazolo[3,2-*a*]pyrimidine **16**.

The synthesis of the tricyclic thiazolopyrimidinone **22** was achieved by the same authors[3] in a slightly modified way as outlined below. 6-Ethoxy-2-aminobenzothiazole **13** (Scheme 1) on condensation with diethyl 8-ethoxy-2-benzothiazolylaminomethylenemalonate **20**, which on strong heating to 200 °C gave the cyclized product viz., ethyl 4-oxo-8-ethoxy-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxylate **21**. The tricyclic heterocycle **21** on hydrolysis and decarboxylation gave the expected 8-ethoxy-4*H*-pyrimido[2,1-*b*]benzothiazole-4-one **22** (Scheme 2).

Nair and George[4] have also reported the synthesis of various thiazolopyrimidinone derivatives **25a–u** (Scheme 2) by adopting the same methodology as that reported by Matsunaga and Takagi.[3] Condensation of variously substituted 2-aminobenzothiazoles **23a–u** with diethyl (ethoxymethylene)malonate yielded the corresponding malonate ester derivatives **24a–u**, which upon reflux with acetic anhydride gave the expected tricyclic thiazolopyrimidine derivatives **25a–u** (*vide* Table 1 for details). Similarly, 3-cyano-4-imino-4*H*-pyrimido[2,1-*b*]benzothiazole **27** (Scheme 2) was also synthesized by these authors.[4]

Nair and George[5] also reported an alternative method for the synthesis of the tricyclic thiazolopyrimidines **29a–d** (Scheme 2). Thus, phenyl isothiocyanate was treated with diethyl aminomethylenemalonate and cyclized with acetic anhydride to give 5-ethoxycarbonyl-2-mercapto-6-oxo-1-phenyl-1,6-dihydropyrimidine **28**. Bromination of **28** as stated above, followed by alkali mediated cyclization gave the thiazolopyrimidinones **29a–d** (Scheme 2) (*vide* Table 2).



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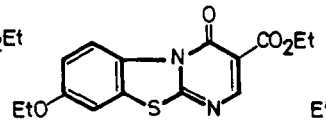

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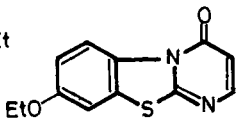

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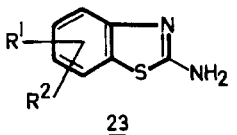
(Matsunaga and Takagi [3])



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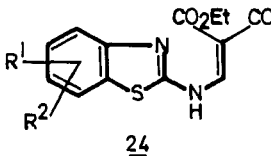

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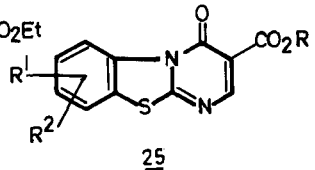

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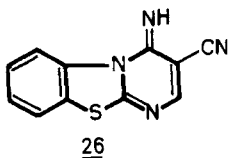
Table 1

Entry	R	R^1	R^2	Entry	R	R^1	R^2
a	Et	6-(4-Cl C_6H_4O)	H	m	Et	7-NO_2	8-EtO
b	H	H	H	n	Et	6-Cl	H
c	H	7-NO_2	H	o	Et	7-Me	8-Me
d	Et	H	H	p	Et	H	8-NO_2
e	Et	7-NO_2	H	q	Et	6-Ph	H
f	Et	7-NH_2	H	r	Et	7-(4-AcNH$C_6H_4SO_2$NH)	H
g	H	7-NH_2	H	s	Et	7-(4-AcNH$C_6H_4SO_2$NH)	H
h	H	H	8-Me	t	Et	7-(3-ClC_6H_4NHCONH)	H
i	H	7-NO_2	8-Me	u	Et	7-(4-FC_6H_4CH=N)	H
j	Et	H	8-Me				
k	Et	H	8-MeO				
l	Et	H	8-EtO				



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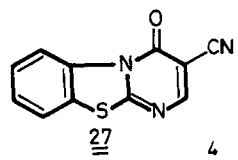
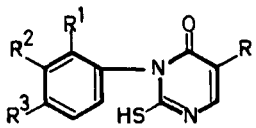


27

(Nair and George [4])



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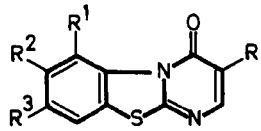

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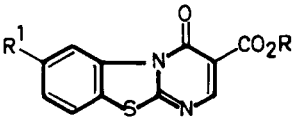
Scheme 2.

Table 2

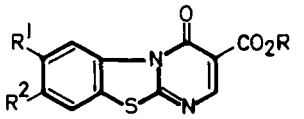
Entry	R	R^1	R^2	R^3
a	CO_2Et	H	H, p-$O_2NC_6H_4SO_2NH$	H
b	CO_2H	Cl	Me, p-F $C_6H_4CH=N$	Me
c	$CONHNH_2$	Ph	NO_2, m-Cl $C_6H_4NHCONH$	OEt
d	CN	p-ClC_6H_4	NH_2, p-O_2N $C_6H_4SO_2NH$	OMe

(Nair and George[5])



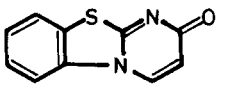
25d (R=CO_2Et, R^1=H)

(CIBA Ltd.[6])



25

(Alaimo[7])



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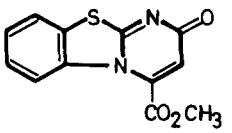

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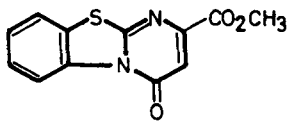

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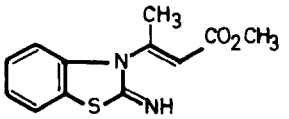

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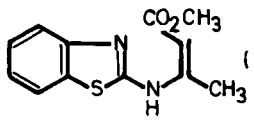


(Reimlinger et al.[8])

34

Scheme 2 (continued).

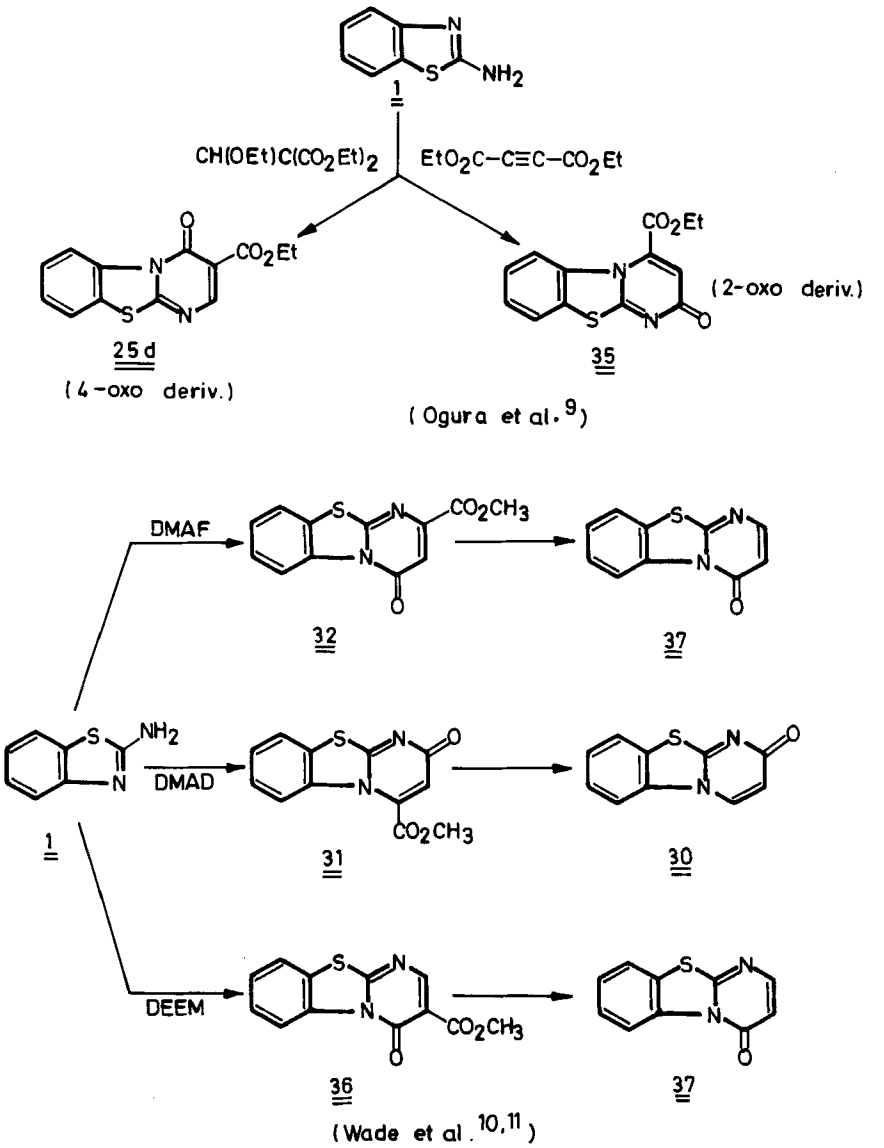
Authors[5] from the CIBA-Geigy Research Centre (Switzerland) also reported the synthesis of a pyrimidobenzothiazolinone **25d** similar to that reported by Nair and George.[4]

Alaimo[7] has reported the synthesis of 8-substituted 4-oxo-3-(4*H*-pyrimido[2,1-*b*]benzothiazole)carboxylic acids and esters **25** (Scheme 2) by condensation of 2-aminobenzothiazoles with diethyl ethoxymethylenemalonate.

Reimlinger *et al.*[8] reported the synthesis of various thiazolopyrimidinones (**30, 31** and **32**) (Scheme 2) from 2-aminobenzothiazole **1**. Condensation of **1** with methyl propionate in THF gave 2-oxo-2*H*-pyrimido[2,1-*b*]benzothiazole **30** in 14% yield. Similarly, condensation of **1** with dimethyl acetylenedicarboxylate in THF gave a mixture of products, which were separated and characterized in the indicated yields *i.e.* methyl 2-oxo-2*H*-

pyrimido[2,1-*b*]benzothiazol-4-carboxylate **31** (4%), methyl 4-oxo-4*H*-pyrimido[2,1-*b*] benzothiazole-2-carboxylate **32** (2%) and 0.5% of **33** and **34** (Scheme 2).

Ogura *et al.*[9] reported the synthesis of 4-ethoxycarbonyl-2*H*-benzothiazoto[3,2-*a*]pyrimidin-2-one **35** (Scheme 3) by condensation of 2-aminobenzothiazole with diethyl acetylenedicarboxylate (DEAD) and performed a comparative study of the product structure with that obtained by condensation of benzothiazole with diethyl (ethoxymethylene)malonate. In the former reaction, the 2-oxo compound **35** was obtained, while the 4-oxo derivative **25d** (Scheme 3) was the product in the latter condensation.



Scheme 3.

Wade *et al.*[10,11] studied extensively the synthesis as well as the NMR behaviour of 4-oxo-pyrimido[2,1-*b*]benzothiazoles **37** (Scheme 3). Condensation of 2-aminobenzothiazole with dimethyl 2-aminofumarate (DMAF) gave methyl 4-oxopyrimido[2,1-*b*]benzothiazole-2-carboxylate **32**. The ester **32** was hydrolyzed and decarboxylated to **37**, which was identical with a compound obtained by hydrolysis and decarboxylation of the ester **36**, obtained from 2-aminobenzothiazole and diethyl ethoxymethylenemalonate (DEEM). The decarboxylated derivatives **36** are different from **30** obtained by hydrolysis and decarboxylation of the dimethyl acetylenedicarboxylate (DMAD) derived esters **31**.

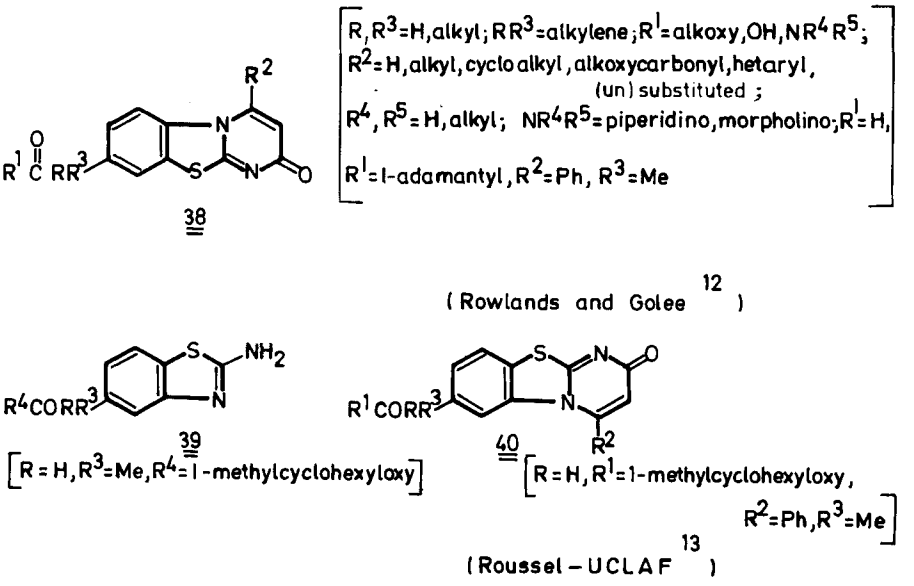
Rowlands and Gole[12] have synthesized the thiazolopyrimidinone derivative **38** (Scheme 4) by heating 2-amino-6-benzothiazole acetate and ethyl β-phenylpropionate at 200 °C.

A new method for the construction of the pyrimido[2,1-*b*]benzothiazole ring system **40** (Scheme 4) has been reported[13] involving the cyclocondensation of the benzothiazol-2-amine derivatives **39** with acetylenic esters ($R^2C{\equiv}CCO_2R^5$) (R^5 = alkyl), followed by transesterification with alcohols in the presence of palladium.

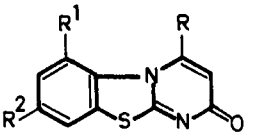
Syntheses of the substituted 7*H*-benzothiazolo[3,2-*a*]pyrimidin-7-ones **41a,b** (Scheme 4) were also achieved by Evans[14] by cycloaddition of 2-aminobenzothiazole to the appropriate propiolic esters as mentioned above.

Dash *et al.*[15] have described the synthesis of the thiazolopyrimidines **42** (Scheme 4) by condensation of 2-aminobenzothiazole with ethyl acetoacetate, followed by aminoethylation.

Al-Jallo and Muniem[16] in 1978 reported the synthesis of 4-phenyl-2-oxo-2*H*-pyrimido[2,1-*b*]benzothiazole **43** (Scheme 4) by condensation of 2-aminobenzothiazole with ethyl β-phenylpropiolate.



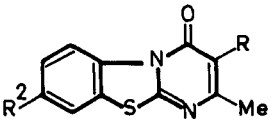
Scheme 4.



41 a,b

[a , R=R^1=R^2=H
b , R=Me, R^1=H , R^2=OMe]

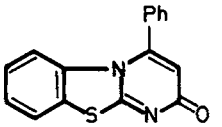
(Evans [14])



42

[R^1= piperidinomethyl, morpholinomethyl
R^2= H, Cl , Me]

(Dash et al. [15])



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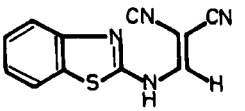
(Al-Jallo and Muniem [16])



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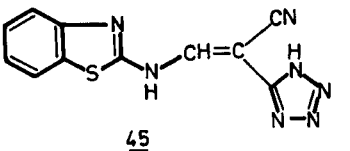

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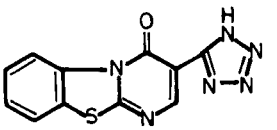
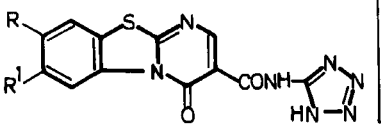


46

(Covington et al [17])



47

[R = H, Me, Et, C_3H_7, OMe, OEt, F, Cl, CF_3, OH, NO_2, NH_2, MeS
R^1 = H, Me, Et, C_3H_7, OMe, OEt, OH, Cl, F, MeS
RR^1 = OCH_2O , OCH_2CH_2O]

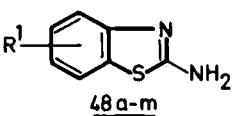
(Bindra and Kadin [18,19])

Scheme 4 (continued).

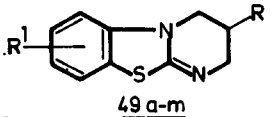
Covington *et al.*[17] have described the successful synthesis of a new type of benzothiazolopyrimidinones **46** (Scheme 4). This route involves the condensation of 2-aminobenzothiazole with ethoxymethylenemalononitriles in the presence of a catalytic amount of sodium in ethanol and reflux of the resulting mixture to give the benzothiazole **44**. Heating of **44** with sodium azide and ammonium chloride in DMF gave the tetrazole derivative **45**, which on cyclization with 48% hydrobromic acid containing trifluoroacetic acid gave the pyrimidobenzothiazolone **46** (Scheme 4).

Bindra and Kadin[18,19] also achieved the synthesis of the tetrazolylpyrimidobenzothiazolecarboxamides **47** (Scheme 4) by treating pyrimidobenzothiazolecarboxylic acids with 5-aminotetrazole.

Singh and Bahl[20] reported the synthesis of the substituted pyrimido[2,1-*b*]benzothiazoles **49a–m** as depicted in Scheme 5. Equimolar quantities of an alcoholic solution of



48a-m

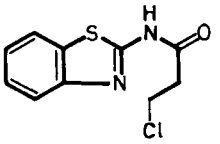


49a-m

Table 3

Entry	R	R^1	Entry	R	R^1
a	8-Me	H	g	7-Me	H
b	8-Cl	H	h	H	OH
c	8-EtO	H	i	8-Me	OH
d	8-MeO	H	j	8-Cl	OH
e	6-Me	H	k	8-MeO	OH
f	6-Cl	H	l	8-EtO	OH
			m	6-Me	OH

(Singh and Bahl[20])



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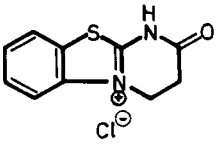

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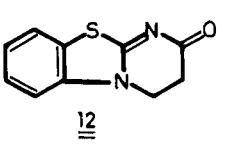
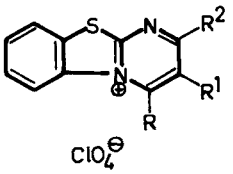


12

(Weinhardt and Neumeyer[21])



51a-d

Table 4

Entry	R	R^1	R^2
a	Et	H	Me
b	$EtOCH_2$	H	Me
c	Ph	H	Me
d	Ph	Me	Me

(Shul'ga and Chuiguk[22])

Scheme 5.

a 2-aminobenzothiazole **48a–m** and 1,3-dibromopropane or 1,3-dibromo-2-propanol were refluxed to yield the corresponding hydrobromides. The free base was generated by treatment with sodium carbonate. It is remarkable that the rate of the condensation of **48a–m** with dibromopropane is faster than that with dibromopropanol. No explanation was given by these authors[20] for the observed difference in the behaviour of these two substrates (*vide* Table 3).

Weinhardt and Neumeyer[21] found that 1,2,3,4-tetrahydro-2-oxopyrimido[2,1-*b*]benzothiol-5-ium chloride **50** (Scheme 5) could be readily obtained by the fusion of its precursor, *viz.* 2-(β-chloropropionylamino)benzothiazole **11** (Scheme 1) at 190 °C. Treatment of the quaternary halide **50** with anhydrous diethylamine resulted in the formation of the halogen-free heterocycle **12** (Scheme 5) which has also been reported earlier by Tsatsas *et al.*[2] as a minor product in the condensation of 2-aminobenzothiazole with β-chloropropionyl chloride under alkaline conditions (*vide* Scheme 1).

Shul'ga and Chuiguk[22] have described the synthesis of the thiazolo[3,2-*a*]pyrimidinium perchlorates **51a–d** (Scheme 5) starting with substituted 1,3-diketones such as $RCOCH_2COCH_3$ (R = Et, $EtOCH_2$, Ph) or with monoketones such as $C_6H_5CH_2CH(Me)\ COCH_3$ in perchloric acid (Scheme 5) (*vide* Table 4). Similarly, the tricyclic thiazolo[3,2-*a*]pyrimidinium perchlorate **52** (Scheme 6) was prepared by the same authors[23] by the condensation of 2-aminobenzothiazolium perchlorate with 1,3-diethoxypropane as shown in Scheme 6.

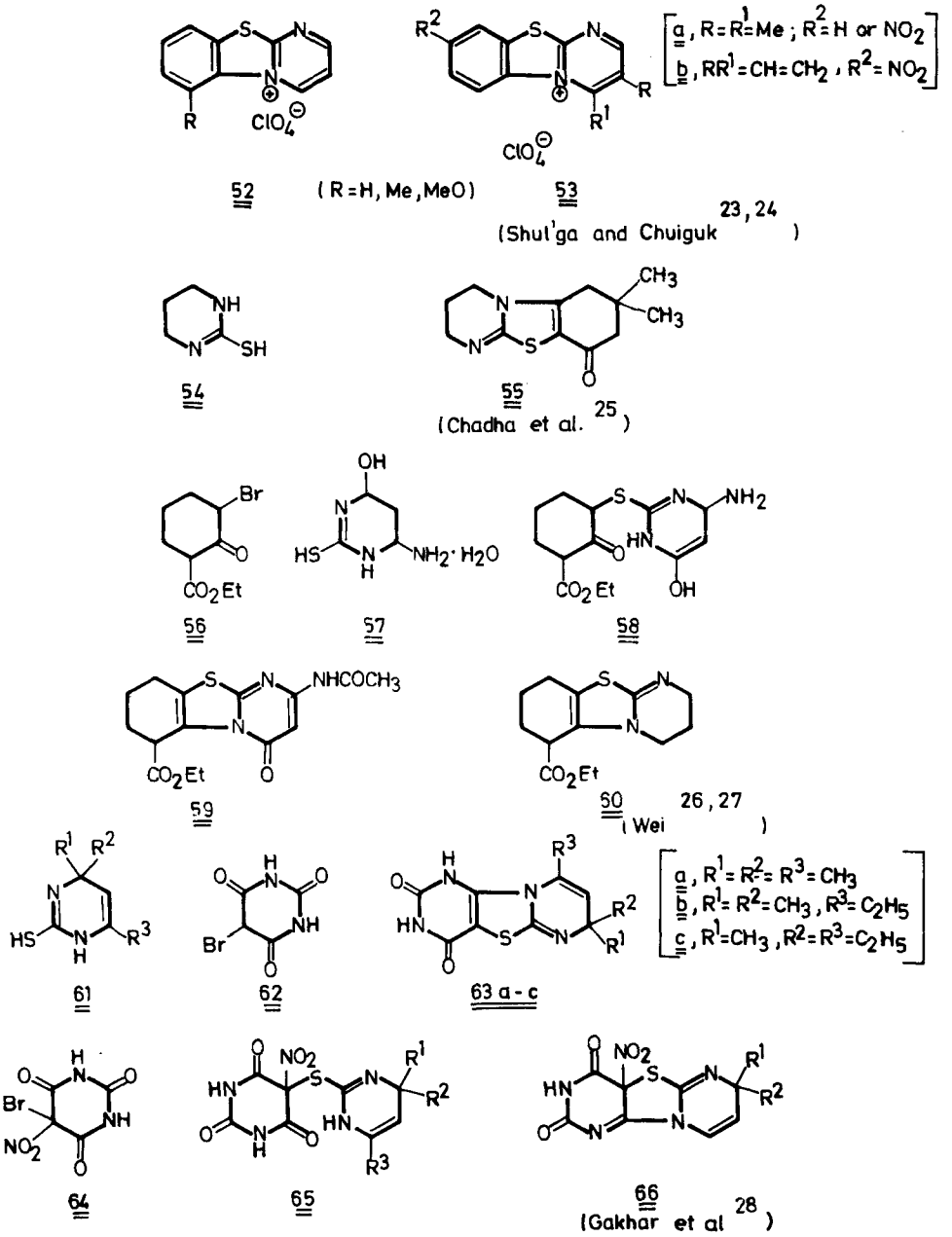
Shul'ga and Chuiguk[24] also reported the perchlorates of the benzothiazolopyrimidines **53** (Scheme 6) by treatment of 2-aminobenzothiazole with β-chlorovinyl aldehydes (ClCR=CR'CHO).

Chadha *et al.*,[25] in 1971, reported the synthesis of 4*H*-7,7-dimethyl-2,3,6,7-tetrahydropyrimido[2,1-*b*]benzothiazol-9(8*H*)-one **55** (Scheme 6) from 2-mercapto-3,4,5,6-tetrahydropyrimidine **54**. Condensation of **54** with dimedone in the presence of iodine and subsequent basification with potassium carbonate of the resulting hydroiodide gave the desired thiazolo[3,2-*a*]pyrimidine **55** (Scheme 6).

Wei,[26] in 1972, achieved the synthesis of the thiazolo[3,2-*a*]pyrimidinone **59** (Scheme 6) starting with cyclohexanonecarboxylic acid esters. Condensation of 6-bromo-2-carboethoxycyclohexanone **56** with 4-amino-6-hydroxy-2-mercaptopyrimidine monohydrate **57** yielded 4-amino-2-[(3-carbethoxy-2-oxocyclohexyl)thio]-6-hydroxypyrimidine **58** as the key intermediate. Compound **58** upon reflux with acetic anhydride gave the expected thiazolo[3,2-*a*]pyrimidinone **59** (Scheme 6). The synthesis of a new class of heterocycles such as 5-carbethoxy-2,3,4,5,6,7,8-heptahydropyrimido[2,1-*b*]benzothiazole **60** has also been described.[27] Treatment of 6-bromo-2-carbethoxycyclohexanone **56** with 2-mercapto-3,4,5,6-tetrahydropyrimidine **54** (*vide* Scheme 6) in acetic acid gave directly **60**.

The synthesis of the thiazolo[3,2-*a*:4,5-*d'*]dipyrimidines **63a–c** (Scheme 6) has also been achieved[28] as detailed below.

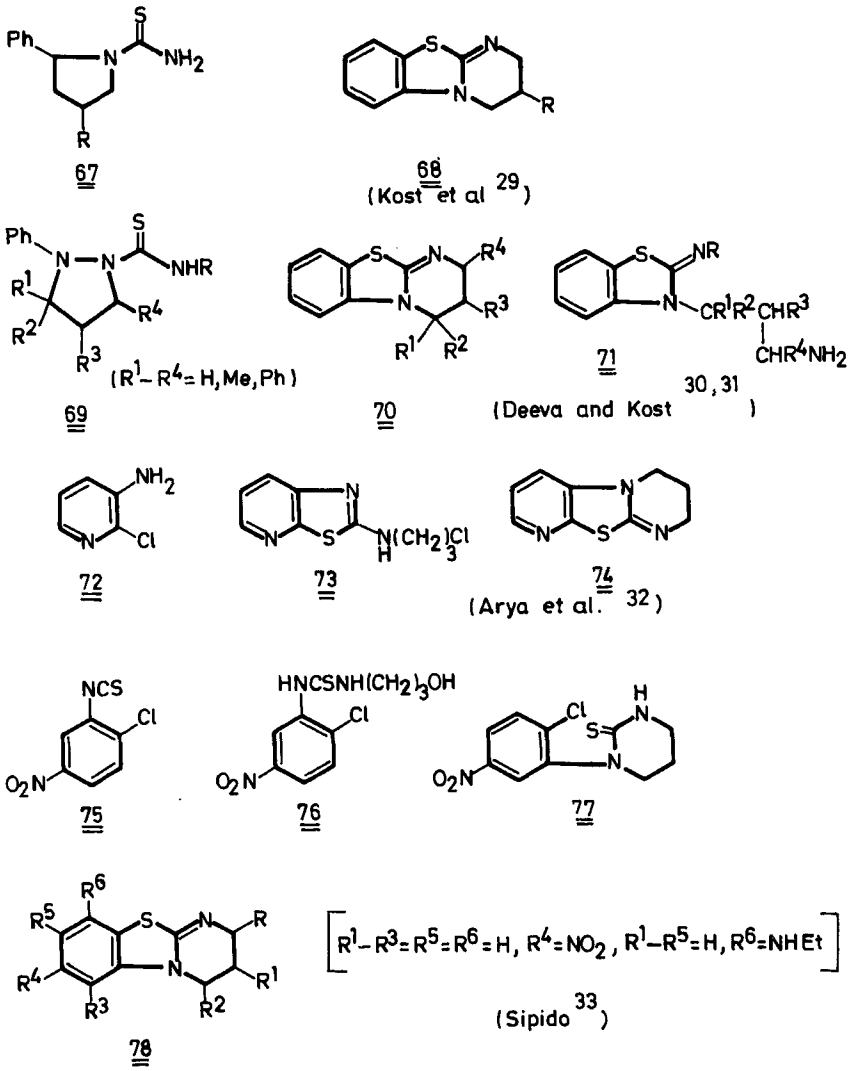
Condensation of 2-mercapto-4,4,6-trialkyl-1*H*,4*H*-pyrimidine **61** with 5-bromobarbituric acid **62** gave the 7,7,9-trialkyl-7*H*-thiazolo[3,2-*a*:4,5-*d'*]dipyrimidine-2,4(1*H*,3*H*)diones **63a–c**. A similar condensation of **61** with 5-bromo-5-nitrobarbituric acid **64** resulted in the formation of intermediates **65**, which, upon cyclization with PPA, gave the 7,7,9-trialkyl-4a-nitro-7*H*-thiazolo[3,2-*a*:4,5-*d'*]dipyrimidine-2,4(3*H*,4a*H*)-diones **66** (Scheme 6).



Scheme 6.

Kost *et al.*[29] achieved the synthesis of 2,3,4,5-tetrahydropyrimido[2,1-*b*]benzothiazole **68** (Scheme 7) by cyclization of the pyrazolidine **67** with hydrochloric acid in a sealed tube at 130 °C.

Deeva and Kost[30,31] reported the synthesis of the thiazolopyrimidines **70** (Scheme 7) in 65–70% yield. Cyclization of the cyclic thiosemicarbazides **69** with hydrochloric acid



Scheme 7.

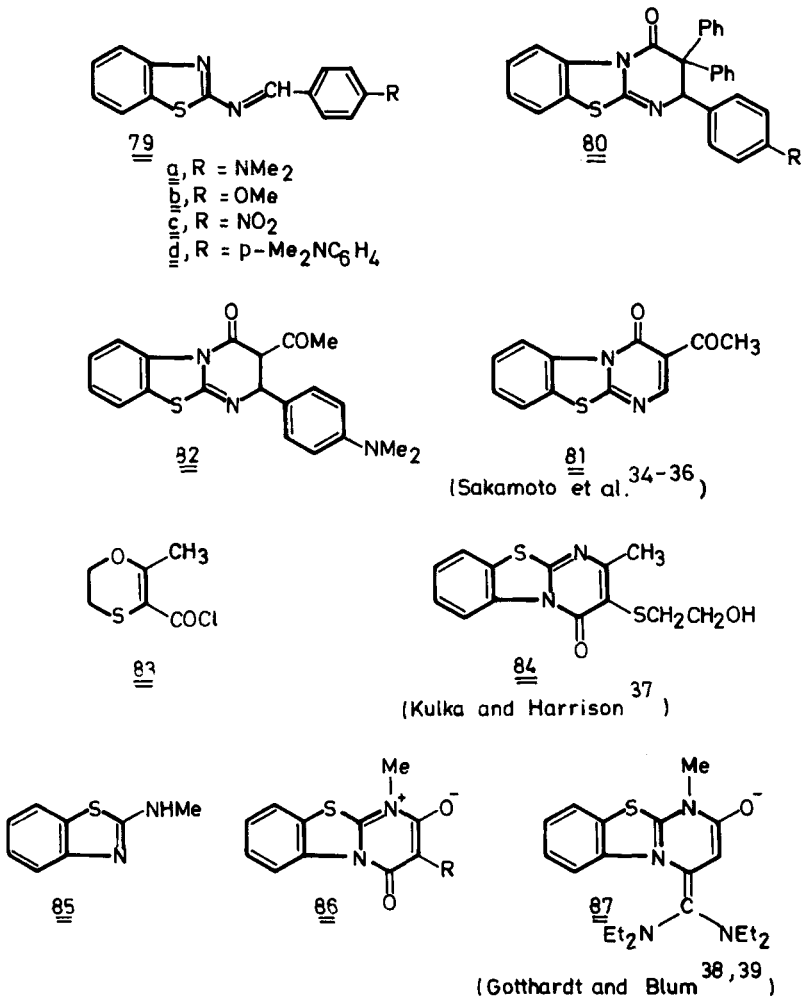
in ethanol gave the expected thiazolopyrimidines **70** and the uncyclized products **71** in equal amounts.

Arya *et al.*[32] have described the synthesis of 1*H*-2,3-dihydropyrimido[2,3-*b*]thiazolo-[5,4-*b*]pyridine **74** (Scheme 7) in 50% yield by treatment of 3-chloropropyl isothiocyanate with 3-amino-2-chloropyridine **72** to yield 2-(3-chloro-1-propylamino)thiazolo[5,4-*b*]pyrimidine **73**. Thermal cyclization of **73** in anhydrous DMF furnished **74**.

The synthesis of 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole **78** (Scheme 7) has also been reported.[33] Thus, 2-chloro-5-nitroaniline was treated with thiophosgene to give the isothiocyanato derivative **75**, which was treated with 1,3-propanolamine to afford the thiourea **76** which was cyclized in two steps to the thiazolopyrimidine **78** via the intermediate **77**.

Sakamoto *et al.*[34] in 1974, developed an elegant method for the synthesis of the thiazolopyrimidinones **80** in a [4 + 2] cycloaddition. They employed a 1,3-diaza-1,3-diene system as the diene component and diketenes as the dienophile component. This constitutes an excellent example for dipolar addition reactions leading to the formation of the desired heterocycles. The mode of addition of the diketenes to 1,3-diazadiene was thoroughly studied by these authors.[34]

In order to establish a structure-reactivity relationship for 1,3-diaza-1,3-butadiene systems, Sakamoto and coworkers[35,36] carried out several reactions of conjugated C=N compounds with diketenes. The formamidines **79** (Scheme 8) reacted with diketenes (acyl ketenes) in benzene to furnish **81**, probably via 1,4-dipolar cycloaddition with elimination of Me_2NH. Similarly, **79a** gave the 4*H*-pyrimido[2,1-*b*]benzothiazole **82**. These authors[35,36] believe that in such cycloaddition reactions (with ketenes) only the 4-oxopyrimidinone derivatives are formed.



Scheme 8.

Kulka and Harrison[37] reported the synthesis of 3-[(2-hydroxyethyl)thio]-2-methyl-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one **84** (Scheme 8) by ring opening of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carbonyl chloride **83** with 2-aminobenzothiazole in the presence of triethylamine in toluene.

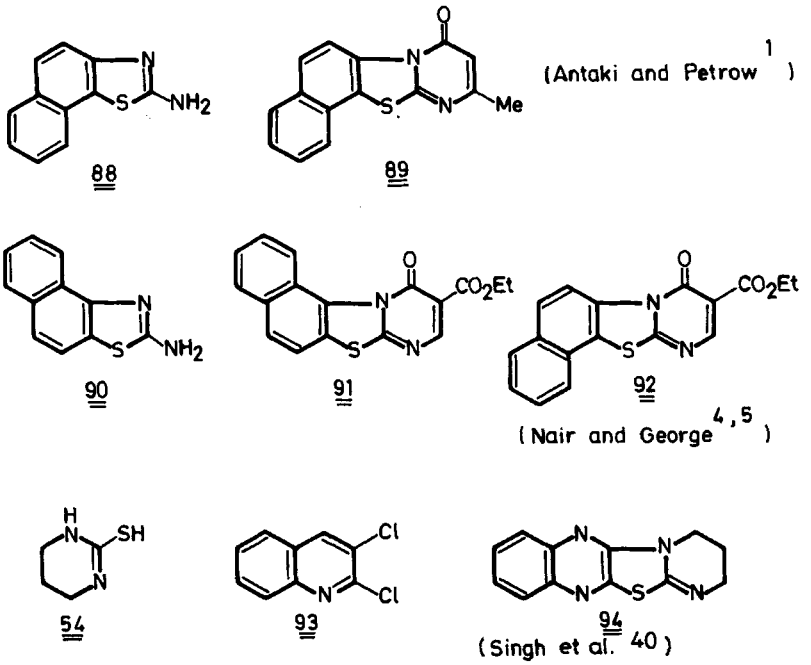
The synthesis of 4-oxo-4*H*-benzothiazolo[3,2-*a*]pyrimidin-1-ium-2-olates **86** (Scheme 8) has recently been described.[38,39] Cyclocondensation of 2-(methylamino)benzothiazole **85** with malonates such $RCH(CO_2C_6H_2Cl_3\text{-}2,4,6)_2$ gave a heterocyclic intermediate **86** which on reaction with $R^1C{=}CR^2$ (R^1 = R^2 = Et_2N) afforded the benzothiazolo-pyrimidinium **87** (as *cis* and *trans* isomers).

3. SYNTHESIS OF TETRACYCLIC THIAZOLO[3,2-*a*]PYRIMIDINES

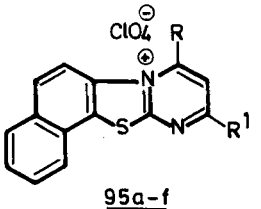
In this section, methods for the synthesis of condensed thiazolopyrimidines are discussed. Invariably, the C and D rings of **I** represent arene, naphthalene, cycloalkene, *etc.*

Antaki and Petrow[1] first reported the synthesis of the tetracyclic thizaolopyrimidinone **89** (Scheme 9). Condensation of 2-aminonaphtho[2′,1′:4,5]thiazole **88** with ethyl *β*-aminocrotonate leads to 2-methyl-4*H*-naphtho[2′,1′:4,5]thiazolo[3,2-*a*]pyrimidin-4-one **89**.

Nair and George[4,5] reported 10-carbethoxy-11-oxo-11*H*-naphtho[1′,2′:4,5]thiazolo-[3,2-*a*]pyrimidine **91** (Scheme 9) and 9-carbethoxy-8-oxo-8*H*-naphtho[2′,1′:4,5]thiazolo[3,2-*a*]-pyrimidine **92** (Scheme 9) by condensation of the corresponding tricyclic 2-aminothiazoles (**88** and **90**) with diethyl ethoxymethylenemalonate.



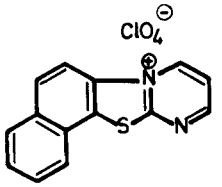
Scheme 9.



95a–f

Table 5

Entry	R	R^1	Entry	R	R^1
a	H	Me	d	Me	Et
b	Me	H	e	Me	CH_2OEt
c	Ph	Me	f	CH_2OEt	Me



96

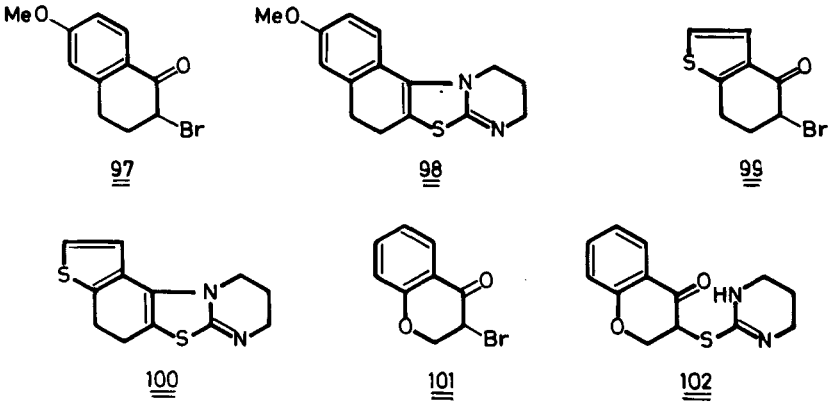
(Shul'ga and Chuiguk[22,41])

Scheme 9 (continued).

The synthesis of 3,4-dihydro-2*H*-pyrimido[2′,1′:2,3]thiazolo[4,5-*b*]quinoxaline **94** was achieved by Singh *et al.*[40] and involved the condensation of 2-mercapto-3,4,5,6-tetrahydropyrimidine **54** with 2,3-dichloroquinoxaline **93** in ethanol via hydrochlorides which on basification gave rise to the expected heterocycles **94** (Scheme 9).

Shul'ga and Chuiguk[41] reported the synthesis of the perchlorates of pyrimido[2,1-*b*]naphtho[2,1-*d*]thiazoles **95a–f** (Scheme 9) by condensation of 2-aminonaphtho[2,1-*d*]thiazole **88** with methyl β-chlorovinyl ketone, benzoylacetone, propionylacetone or ethoxyacetylacetone in ethanol and perchloric acid (*vide* Table 5). Alternatively, the synthesis of naphtho[2,1-*d*]thiazolo[3,2-*a*]pyrimidinium perchlorate **96** (Scheme 9) was achieved by treatment of 2-aminonaphtho[2,1-*d*]thiazolium perchlorate with 1,1,3,3-tetraethoxypropane in alcohol.

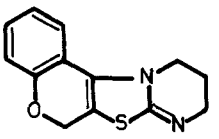
Arya and Ghate[42] reported the synthesis of various tetracyclic thiazolopyrimidine derivatives (**98, 100, 103** and **106**) (Scheme 10) starting with the corresponding α-bromoketones and 2-mercapto-3,4,5,6-tetrahydropyrimidine **54**.



97 98 99

100 101 102

Scheme 10.



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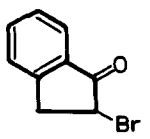
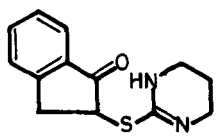


104



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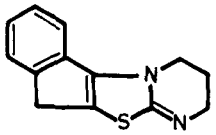
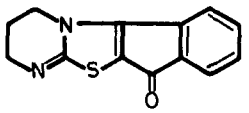


106

(Arya and Ghate[42])



107

(Chadha et al.[25])

Scheme 10 (continued).

8-Methoxy-2,3,4,5,10,11-hexahydronaphtho[1,2-*d*]thiazolo[3,2-*a*]pyrimidine **98** and 2,3,4,5,9,10-hexahydrothianaphthaleno[4,5-*d*]thiazolo[3,2-*a*]pyrimidine **100** have been synthesized directly by condensation of the corresponding α-bromoketones **97** and **99** with 2-mercapto-3,4,5,6-tetrahydropyrimidine **54** in ethanol. Similarly, 11*H*-2,3,4,5-tetrahydrochromeno[4,3-*d*]thiazolo[3,2-*a*]pyrimidine **106** was synthesized via the intermediates **102** and **105**, respectively, by adoption of this synthetic strategy.

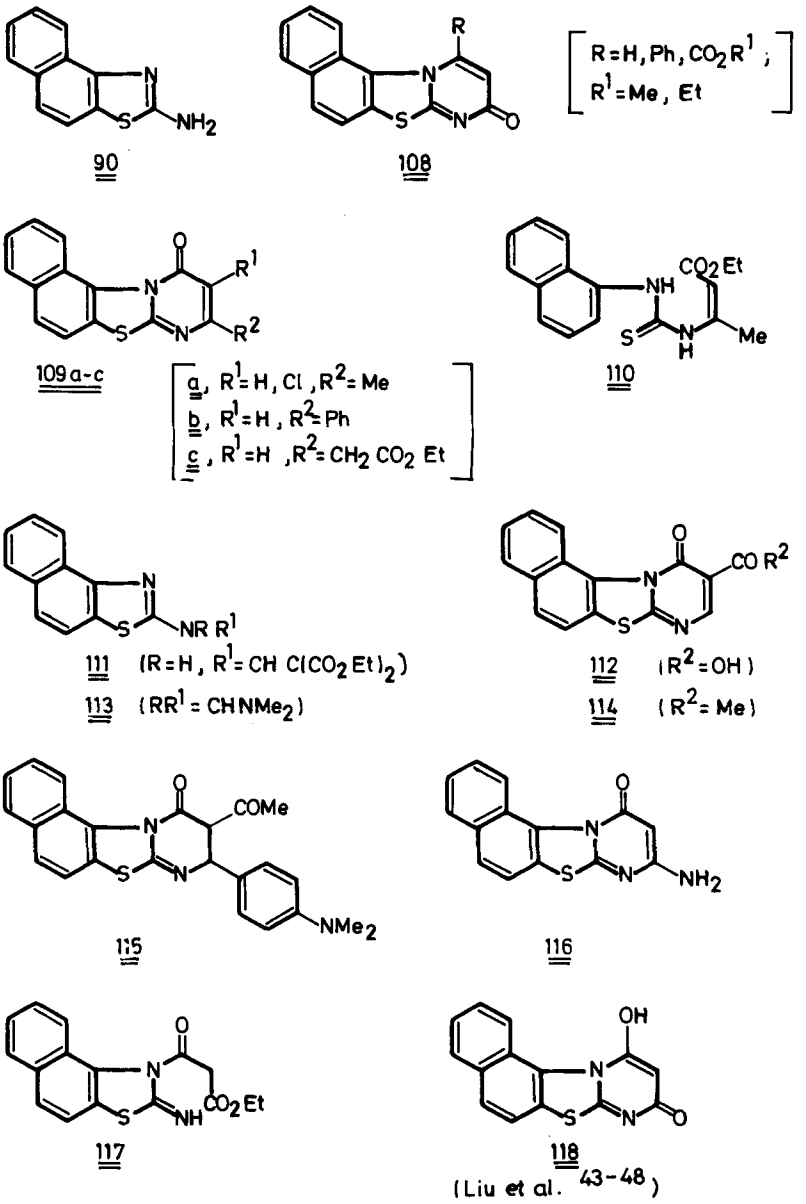
Chadha *et al.*[25] reported the synthesis of 2,3,4,5-tetrahydroindeno[1,2-*d*]thiazolo[3,2-*a*]pyrimidin-10(H)-one **107** (Scheme 10) by condensation of 2-mercapto-3,4,5,6-tetrahydropyrimidine **54** with indan-1,3-dione in the presence of iodine and subsequent basification of the resulting iodide with K_2CO_3.

Liu *et al.*[43] achieved the synthesis of 2-oxonaphtho[1,2-*d*]thiazolo[3,2-*a*]pyrimidine **108** (Scheme 11) by treatment of 2-aminonaphtho[1,2-*d*]thiazole **90** with acetylenic carboxlic acid esters [$R\text{-}C{\equiv}CCO_2R^1$].

Liu *et al.*[44] also synthesized the 4-oxonaphtho[1,2-*d*]thiazolo[3,2-*a*]pyrimidines **109a–c** (Scheme 11) by two different routes. (i) Cyclocondensation of 2-aminoaphtho[1,2-*d*]thiazole **90** with β-keto esters such as ($R^2COCHR^1CO_2Et$) to afford the thiazolopyrimidinones **102a–c** in 40–50% yield, (ii) condensation of 1-naphthyl isothiocyanate with ethyl β-aminocrotonate [$H_2N\text{-}C(Me){=}CHCO_2Et$] gave the intermediate **110**. Cyclization of **110** with bromine yielded the naphthothiazole **111**, which on heating to 150 °C gave the desired tetracyclic thiazolopyrimidinone **109a** in 72% yield.

The synthesis of the 4*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*a*]pyrimidin-4-ones[45] **112** and **114** (Scheme 11) has been realised as detailed below.

Condensation of 2-aminonaphtho[1,2-*d*]thiazole **90** with diethyl ethoxymethylenemalonate gave an intermediate **111** which was cyclized thermally to afford the 3-sub-



Scheme 11.

stituted thiazolopyrimidinone **112**. Similarly, condensation of **113** with $(EtO)_2CHNMe_2$ furnished **114** which on condensation with diketene (acylketene) gave **115** (Scheme 11).

Liu *et al.*[46] reported the synthesis of 3-acetyl-2,3-dihydro-2-[4-(dimethylamino)-phenyl]-4*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*a*]pyrimidin-4-one **115** (Scheme 11). The condensation of **90** with *p*-(*N*,*N*-dimethylamino)benzaldehyde gave the azomethane derivative, which on reaction with diketene (acylketene) in refluxing xylene yielded **115**.

The synthesis of 2-amino-4*H*-oxo-naphtho[1′,2′:4,5]thiazolo[3,2-*a*]pyrimidine **116** (Scheme 11) was recently reported[47] by condensation of naphtho[1,2-*b*]thiazol-2-amine **90** with ethyl cyanoacetate.

Liu and Shih,[48] in 1985, achieved the synthesis of 4-hydroxy-2*H*-naphtho[1′,2′:4,5]-thiazolo[3,2-*a*]pyrimidin-2-one **118** (Scheme 11). Treatment of **90** with diethyl malonate furnished 3-(ethoxymalonyl)-2-iminonaphtho[1,2-*d*]thiazole **117**, which underwent thermal cyclization to give the naphthothiazolopyrimidinone **118**.

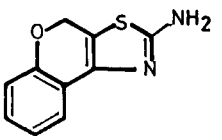
Ramada *et al.*,[49] in 1986, achieved the synthesis of 9-methyl-6*H*,11*H*-[1]benzopyrano-[4′,3′:4,5]thiazolo[3,2-*a*]pyrimidin-11-one **120** (Scheme 7) by condensation of 2-amino-4*H*-[1]benzopyrano[4,3-*d*]thiazole[50] **119** with ethyl acetoacetate.

Similarly, the synthesis of the tetracyclic thiazolopyrimidinone derivative 9-methyl-6*H*,11*H*-[1]benzothiopyrano[4′,3′:4,5]thiazolo[3,2-*a*]pyrimidin-11-one **122** (Scheme 12) was described by the same authors[51] by condensation of 2-amino-4*H*-[1]benzothiopyrano[4,3-*d*]-thiazole[50] **121** with ethyl acetoacetate in the presence of a catalytic amount of *p*-toluenesulfonic acid.

Ramesh *et al.*[52] reported the synthesis of 5,5,8-trimethyl-4*H*,5*H*-1,2,3-benzothiadiazolo[7′,6′:4,5]thiazolo[3,2-*a*]pyrimidin-10-one **126** (Scheme 12). Dimedone, upon treatment with *p*-toluenesulfonylhydrazine, afforded the corresponding monotosyl hydrazone **123**, which was treated with excess thionyl chloride to give 6,6-dichloro-5,5-dimethyl-4,5,6,7-tetrahydro-7-oxo-1,2,3-benzothiadiazole1,1-dioxide **124** in 50% yield. This dichloro keto derivative was converted into the desired 2-aminothiazole derivative, 7-amino-5,5-dimethyl-4*H*,5*H*-1,2,3-benzothiadiazolo[7,6-*d*]thiazole **125**, by condensation with thiourea. Condensation of **125** with ethyl acetoacetate in the presence of *p*-toluenesulfonic acid furnished **126** in 40% yield.

4. SYNTHESIS OF PENTACYCLIC THIAZOLO[3,2-*a*]PYRIMIDINES

Ramadas *et al.*[49,51] obtained the pentacyclic thiazolopyrimidone 9-methyl-6*H*,11*H*-naphtho[2″,1″:5′,6′]thiopyrano[4′,3′:4,5]thiazolo[3,2-*a*]pyrimidin-11-one **128** (Scheme 12) by condensation of the corresponding tetracyclic 2-aminothiazole derivative **127** with ethyl acetoacetate in the presence of excess *p*-toluenesulfonic acid.



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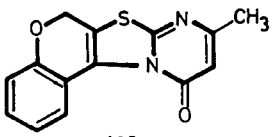
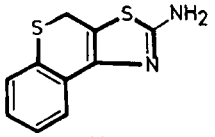


120



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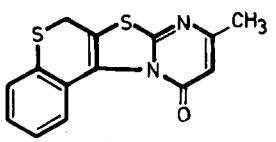
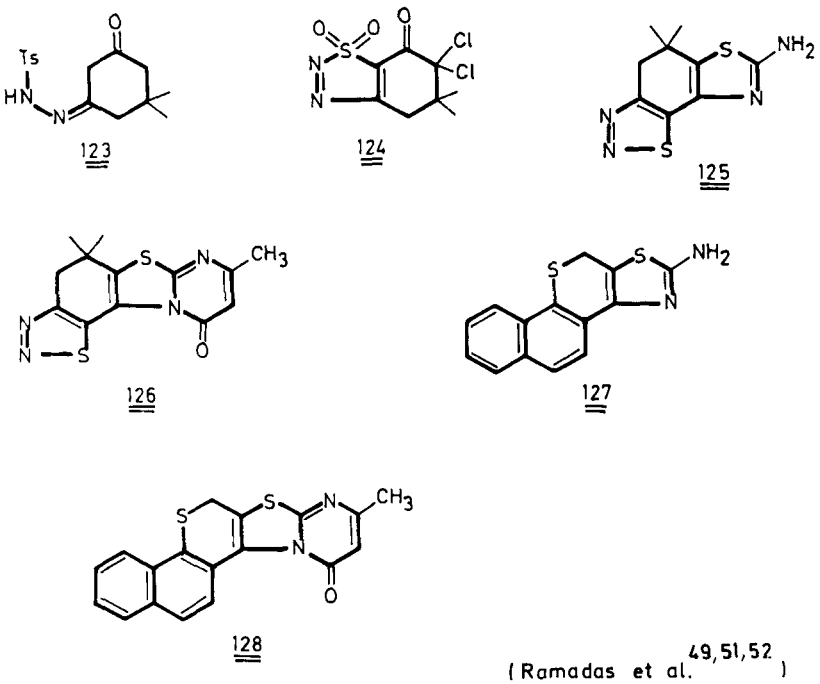


122

Scheme 12.



(Ramadas et al.[49,51,52])

Scheme 2 (continued).

5. BIOLOGICAL ACTIVITY

Thiazolo[3,2-*a*]pyrimidines are well known to display interesting biological properties such as antiinflammatory, antiallergic, antibacterial and antitumour. In 1972, Wei[26] claimed that 6,7,8,9-tetrahydropyrimido[2,1-*b*]benzothiazole-6-carboxylic acid **59** (Scheme 6) [Section 2] exhibits antiinflammatory activity.

Dash *et al.*[15] have described the synthesis of the thiazolopyrimidinones **42** (Scheme 4) [Section 2] and found that these heterocycles cause 71.5–78.0% inhibition of curculria at the 500 ppm level and also exhibited antitumour activity in mice (10–400 mg/kg). In 1982, Liu *et al.*[44] described the synthesis of the tetracyclic thiazolo[3,2-*a*]pyrimidinones **109a–c** (Scheme 9) [Section 3] and tested them in rats for antihypertensive effect and on the isolated ileum of the guinea pig for anticholineric and antihistaminic activities.

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