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SYNTHESIS OF SUBSTITUTED 5-AMINOTHIENO[2,3-*d*]PYRIMIDINES

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The corresponding N,N-dimethyl-N'-(thieno[2,3-d]pyrimidin-5-yl)formamidines and 5-acylaminothieno[2,3-d]pyrimidines have been synthesized by the reaction of ethyl 5-amino-2-substituted thieno[2,3-d]pyrimidine-6-carboxylates with (a) either the dimethylacetal of dimethylformamide or chloroacetyl chloride or (b) ethoxycarbonylacetyl chloride or acetic anhydride. Heating ethyl 5-amino-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate with allyl isothiocyanate in pyridine gave 3-allyl-2-allylthio-7-methylthiothieno[2,3-d:4,5-d']pyrimidin-4(3H)-one.

Some derivatives of thieno[2,3-*d*]pyrimidine possess herbicidal, insecticidal, fungicidal and regulatory functions with respect to seed germination [1, 2]. In a continuation of studies of a series of thieno[2,3-*d*]-pyrimidines and similar heterocycles [3-6] this paper is concerned with the synthesis of compounds for biological testing by the interaction of ethyl 5-amino-2-substituted thieno[2,3-*d*]pyrimidine-6-carboxylates with some C-electrophiles. The C-electrophiles chosen were the dimethylacetal of dimethylformamide, chloroacetyl chloride, ethoxycarbonylacetyl chloride, acetic anhydride, allyl- and phenyl isothiocyanates.

The starting materials Ia and Ib were obtained from the corresponding 4-chloropyrimidine-5-carbonitriles and ethyl thioglycolate in the presence of sodium ethoxide [3, 4], while ethyl 5-amino-2-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylate (Ic) was obtained by boiling compound Ib with an excess of piperidine for 30 min.

Boiling the thienopyrimidines Ia-Ic with a twofold excess of the dimethylacetal of DMF in benzene gave the corresponding N,N-dimethyl-N'-(thieno[2,3-*d*]pyrimidin-5-yl)formamidines IIa-IIc in about 70% yield. The IR spectra of these compounds do not contain amino group absorptions but the 6-carbonyl absorptions occur at 1680-1700 cm^{-1} which is shifted 16-28 cm^{-1} to shorter wavelength in comparison to the corresponding starting compounds Ia and Ib [3, 4] and Ic. All the expected signals are observed in ^1H NMR spectra of the formamidines IIa to IIc. The protons of the dimethylamino and azomethine groups resonate at 3.09-3.16 and 7.757-7.96 ppm respectively which, according to [7], indicates that these formamidines exist as the *E* isomers.

Boiling compounds Ib and Ic with chloroacetyl chloride or ethoxycarbonylacetyl chloride in benzene for 4 h gave only the monoacylamino derivatives IIIb and c and IVb and c, whereas acetylation of Ic with acetic anhydride gave ethyl 5-diacetylamino-2-piperidinothieno[2,3-*d*]pyrimidin-6-carboxylate (Vc).

Esters of aryl and thiophenecarboxylic acids with an (ethoxycarbonylacetylamino) group in the *ortho* position are known to cyclize to form a pyridine ring under the influence of sodium ethoxide [8, 9]. However compounds IVb and IVc underwent solvolysis at the amide bond when treated with sodium ethoxide in ethanol at room temperature to give the starting compounds Ib and Ic and not VIb and VIc.

Esters of *ortho*-aminothiophenecarboxylic acids usually react with isothiocyanates by addition of the isothiocyanate to the amino group with subsequent cyclocondensation of the thioureide intermediate with the ester group to give 3-substituted 2-mercaptothienopyrimidin-4-ones [10, 11]. We have studied the reaction of ethyl 5-amino-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (Ia) with phenyl and allyl isothiocyanates. Compound Ia was found to be a weak nucleophile with respect to these reagents. We were unable to obtain any product from the reaction of Ia with phenyl isothiocyanate: in all cases the starting material Ia was recovered quantitatively after prolonged heating of the reactants in such solvents as ethanol, pyridine and dimethylformamide. Boiling compound Ia with allyl isothiocyanate in pyridine for 22 h gave 3-allyl-2-allylthio-7-methylthio-

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TABLE 1. Characteristics of Compounds Ic, IIa-c, IVb and c, Vc and VIIa

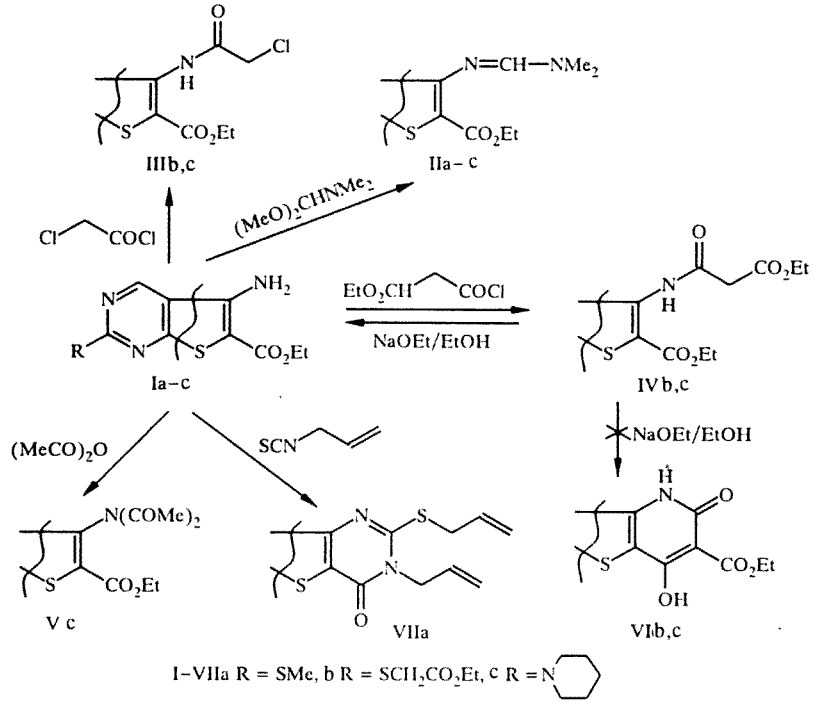
Compound	M.p., °C (solvent)	IR spectrum, cm^{-1}	^1H NMR spectrum*, δ, ppm	Yield, %
Ic	185,5...186,5 (2-PrOH)	3424, 3320 (NH, NH_2), 1664 (CO)	1,06 (3H, t, CH_3), 1,45 (6H, br.s, $3CH_2$), 3,54 (4H, br.s, $2NCH_2$), 4,08 (2H, q, OCH_2), 8,51 (1H, s, CH)	70
IIa	107...108 (benzene)	1700 (CO), 1616 (N=CH)	1,33 (3H, t, CH_3), 2,61 (3H, s, SCH_3), 3,11 (6H, s, $2NCH_3$), 4,27 (2H, q, OCH_2), 7,79 (1H, s, N=CH), 8,86 (1H, s, CH)	70
IIb	93...94 (hexane-EtOH)	1736 (CO), 1688 (CO), 1624 (N=CH)	1,23 (3H, t, CH_3), 1,29 (3H, t, CH_3), 3,13 (6H, s, $2NCH_3$), 4,01 (2H, s, SCH_2), 4,08 (2H, q, OCH_2), 4,25 (2H, q, OCH_2), 7,96 (1H, s, N=CH), 8,86 (1H, s, CH)	68
IIc	134...135 (EtOH)	1680 (CO), 1624 (N=CH)	1,31 (3H, t, CH_3), 1,64 (6H, br.s, $3CH_2$), 3,09 (6H, s, $2NCH_3$), 3,85 (4H, br.s, $2NCH_2$), 4,23 (2H, q, OCH_2), 7,75 (1H, s, N=CH), 8,65 (1H, s, CH)	69
IIIb	149...150 (2-PrOH)	3304 (NH), 1736 (CO), 1704 (CO), 1684 (CO)	1,28 (3H, t, CH_3), 1,42 (3H, t, CH_3), 4,01 (2H, s, SCH_2), 4,17 (2H, q, OCH_2), 4,29 (2H, s, CH_2Cl), 4,43 (2H, q, OCH_2), 9,37 (1H, s, CH), 11,0 (1H, br.s, NH)	70
IIIc	214...216 (2-PrOH)	3256 (NH), 1696 (CO), 1680 (CO)	1,10 (3H, t, CH_3), 1,46 (6H, br.s, $3CH_2$), 3,56 (4H, br.s, $2NCH_2$), 4,05 (2H, s, CH_2Cl), 4,18 (2H, q, OCH_2), 9,09 (1H, s, CH)	74
IVb	148,5...149,5 (2-PrOH)	3272 (NH), 1740 (CO), 1712 (CO), 1668 (CO)	1,31 (9H, m, $3CH_3$), 3,6 (2H, s, SCH_2), 4,0 (2H, s, $COCH_2CO$), 4,25 (6H, m, OCH_2), 9,25 (1H, s, CH), 10,84 (1H, br. s, NH)	
IVc	175...176 (2-PrOH)	3288 (NH), 1752 (CO), 1696 (CO), 1672 (CO)	1,31 (3H, t, CH_3), 1,37 (3H, t, CH_3), 1,65 (6H, br.s, $3CH_2$), 3,6 (2H, s, $COCH_2CO$), 3,9 (4H, br.s, $2NCH_2$), 4,3 (4H, m, OCH_2), 9,15 (1H, s, CH), 10,9 (1H, br.s, NH)	87
Vc	147...149 (2-PrOH)	1710 (CO), 1704 (CO), 1672 (CO)	1,3 (3H, t, CH_3), 1,64 (6H, br.s, $3CH_2$), 2,32 (6H, s, $2COCH_3$), 3,85 (4H, br.s, $2NCH_2$), 4,31 (4H, q, OCH_2), 8,69 (1H, s, CH)	66
VIIa	161...163 (EtOH)	1684 (CO)	2,47 (3H, s, SCH_2), 3,62 (2H, d, SCH_2), 4,55 (2H, d, NCH_2), 4,67...5,15 (4H, m, $2CH_2$), 5,25...5,8 (2H, m, CH), 9,0 (1H, s, CH)	50

*^1H NMR spectra of compounds IIa, IIc, IIIb, IVb and IVc were obtained in $CDCl_3$, IIb in $(CD_3)_2CO$, IIIc in CF_3COOD and VIIa in CF_3COOH.

TABLE 2. Elemental Analyses of the Compounds Synthesized

Compound	Molecular formula	(Found, %)/ (Calculated, %)		
		C	H	N
Ic	$C_{14}H_{18}N_4O_2S$	54,99 54,88	6,14 5,92	18,06 18,29
IIa	$C_{13}H_{16}N_4O_2S_2$	48,39 48,13	5,06 4,97	17,11 17,27
IIb	$C_{16}H_{20}N_4O_4S_2$	48,55 48,47	5,17 5,08	13,85 14,13
IIc	$C_{17}H_{23}N_5O_2S$	56,12 56,49	6,29 6,41	19,53 19,38
IIIb	$C_{15}H_{16}N_3ClO_5S_2$	43,04 43,11	3,83 3,86	9,98 10,06
IIIc	$C_{16}H_{19}N_4ClO_3S$	49,91 50,19	5,12 5,0	14,5 14,63
IVb	$C_{18}H_{21}N_3O_7S_2$	47,6 47,46	5,07 4,65	9,18 9,23
IVc	$C_{19}H_{24}N_4O_5S$	54,69 54,27	5,98 5,75	13,63 13,33
Vc	$C_{18}H_{22}N_4O_4S$	55,51 55,37	5,24 5,68	14,42 14,35
VIIa	$C_{15}H_{14}N_4OS_3$	49,45 49,7	3,53 3,89	15,48 15,46

thieno[2,3-*d*:4,5-*d'*]dipyrimidin-4(3H)-one (VIIa), i.e, allylation of the mercapto group accompanied formation of the pyrimidine ring. The best yield of the thienodipyrimidine VIIa was obtained by using a threefold excess of allyl isothio-cyanate although compound VIIa was formed when equimolar amounts of the reagents were used. A carbonyl absorption band was observed at 1684 cm^{-1} in the IR spectrum of VIIa. Its ^1H NMR spectrum showed no signals corresponding to an ester group but there were two sets of allyl signals with the proton signals of the SCH_2 and NCH_2 groups at 3.62 and 4.55 ppm respectively. The molecular ion peak with *m/z* 362 in the mass spectrum corresponds to the molecular mass of compound VIIa.



A preliminary investigation of pesticidal activity showed that compounds IIa-c, IIIb and IVb and IVc possess fungicidal activity. For example, compound IVb is active against *Septoria nodorum* (30%), *Rhizoctonia solani* (10%), *Botrytis cinerea* (40%), *Pythium altinum* (40%), *Fusarium nivale* (15%), *Sclerotinia minor* (15%), *Colletotrichum gossypii* (10%), *Erisyphe cichoracearum* (80%).

EXPERIMENTAL

IR spectra were recorded in Nujol with a Specord M-80. ^1H NMR spectra were recorded with a Tesla BS-567 A (80 MHz) with HMDS internal standard. Mass spectra were obtained with Kratos MS-50 machine (70 eV) with direct input of the samples into the ion source. Progress of the reactions and purity of the products were monitored by TLC on DC-Alufolien Aluminiumoxid 150 F 254 neutral (type T) plates.

Elemental analyses for C, H and N are compared to the calculated values for compounds Ic, IIa-c, IIIb and IIIc, IVb and IVc, Vc, and VIIa are given in Table 2.

Ethyl 5-Amino-2-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylate (Ic). A mixture of compound Ib (6.8 g, 20 mmole) and piperidine (8.5 g, 100 mmole) was boiled for 30 min. The reaction mixture was cooled to room temperature and poured into cold water (50 ml). The precipitate was filtered off, washed with water and recrystallized to give Ic (Table 1).

N,N-dimethyl-N'-(2-substituted 6-ethoxycarbonylthieno[2,3-*d*]pyrimidin-5-yl)formamidines (IIa-c). A mixture of compound Ia, Ib or Ic (3 mmole), the dimethylacetal of DMF (0.476 g, 4 mmole) and absolute benzene (5 ml) was boiled for 3-6.5 h. The solvent was removed under reduced pressure to dryness and the residue was recrystallized to give compounds IIa-c (Table 1).

Ethyl 2-Substituted 5-(Chloroacetylamino)thieno[2,3-*d*]pyrimidine-6-carboxylates (IIIb and IIIc). A mixture of compound Ib or Ic (3 mmole), chloroacetyl chloride (1.47 g, 13 mmole) and absolute benzene (30 ml) was boiled for 4 h. The

reaction mixture was cooled to room temperature, the precipitate was filtered off, washed with benzene and recrystallized to give compounds IIIb and IIIc (Table 1).

Ethyl 2-Substituted 5-(ethoxycarbonylacetylamino)thieno[2,3-*d*]pyrimidine-6-carboxylates (IVb and IVc) were synthesized similarly except that the ratio of ethoxycarbonylacetyl chloride to starting material (Ib or Ic) was 2:1 (Table 1).

Ethyl 5-Diacetylamino-2-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylate (Vc). A mixture of compound Ic (0.3 g, 0.97 mmole) and acetic anhydride (2.7 g, 26.5 mmole) was boiled for 2.5 h. The mixture was cooled to room temperature, the precipitate filtered off and recrystallized to give Vc (Table 1).

3-Allyl-2-allylthio-7-methylthiothieno[2,3-*d*:4,5-*d'*]dipyrimidin-4(3H)-one (VIIa). A mixture of compound Ia (1.5 g, 5.6 mmole), pyridine (20 ml) and allyl isothiocyanate (1.67 g, 16.8 mmole) was boiled for 22 h. Water was then added to the hot solution until a precipitate appeared and the mixture was cooled to 5°C. The precipitate was filtered off, washed with ethanol and recrystallized to give compound VIIa (Table 1). Mass spectrum, m/z (%): 362 M^+ (63), 347 (100), 329 (30), 321 (63), 315 (13), 307 (37), 289 (96), 266 (70), 262 (22).

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