β-Ketoalkylthioacrylic acid derivatives as precursors of thiophenes, thiazolines, and thienopyrimidines[1]

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Nous avons poursuivi l'étude de la réaction de certains sels sodés de dérivés de l'acide amino-3-cyano-2-thioacrylique avec des dérivés halogénés. L'action de méthylcétones α-halogénées a permis d'obtenir dans certaines conditions soit des dérivés d'acide acyl-5-diamino-2,4-thiophène-3-carboxylique soit des dérivés d'acide thiazoline-$\Delta^{2\alpha}$-acétique. L'acétylation de certains thiophènes a conduit à la formation de thiènopyrimidines.

Reactions of sodium salts of substituted 3-amino-2-cyano-3-thioacrylic esters and amides with α-halomethylketones were studied. Conditions were found which led to the synthesis of either 5-acyl-2,4-diaminothiophene-3-carboxylic esters and amides or thiazoline-$\Delta^{2\alpha}$-acetic esters and amides. Some thiophene-3-carboxamides were also transformed into thienopyrimidines upon acetylation.

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Introduction

Some thioamides with a carbonyl group in β position (i.e. **13**) exist mainly as enols **12** and form sodium salts **3** which may be reacted further to produce substituted heterocycles by mechanisms involving additions, eliminations or displacements. The first example of this type of reaction goes as far back as 1908 (1), but it is only since 1965 that these β-thioamides **13** were used as starting materials versatile enough to yield heterocycles as diverse as 3,4-diarylthiazole-2-acetic esters (2), benzothiazoline-2-acetic esters (3, 5), 5-amino-3-hydroxythiophenedicarboxylic esters (6), 3-amino-5-hydroxypyrazoles (7, 8), 3-amino-5-hydroxypyrazole-4-carboxylic acid derivatives (6), 3-anilino-5-hydroxyisoxazoles (8, 9), 3-aminoisothiazoles (10), and tetrahydrobenzothiazoline-2-acetic esters (4).

The presence of a nitrile group in some of these β-thioamides **13** allows an easy synthesis of the hitherto unreported 5-acyl-2,4-diaminothiophene-3-carboxylic acid derivatives **8**, herein described as thiophene-3-carboxylic esters and amides. This paper will elaborate on the use of those β-thioamides **13** and will show how they yielded selectively derivatives of thiophene-3-carboxylic esters and amides **8** or derivatives of thiazoline-2-acetic esters and amides **11**. We will also show how some of these thiophene-3-carboxamides **8** have been transformed into fused thienopyrimidines **15**.

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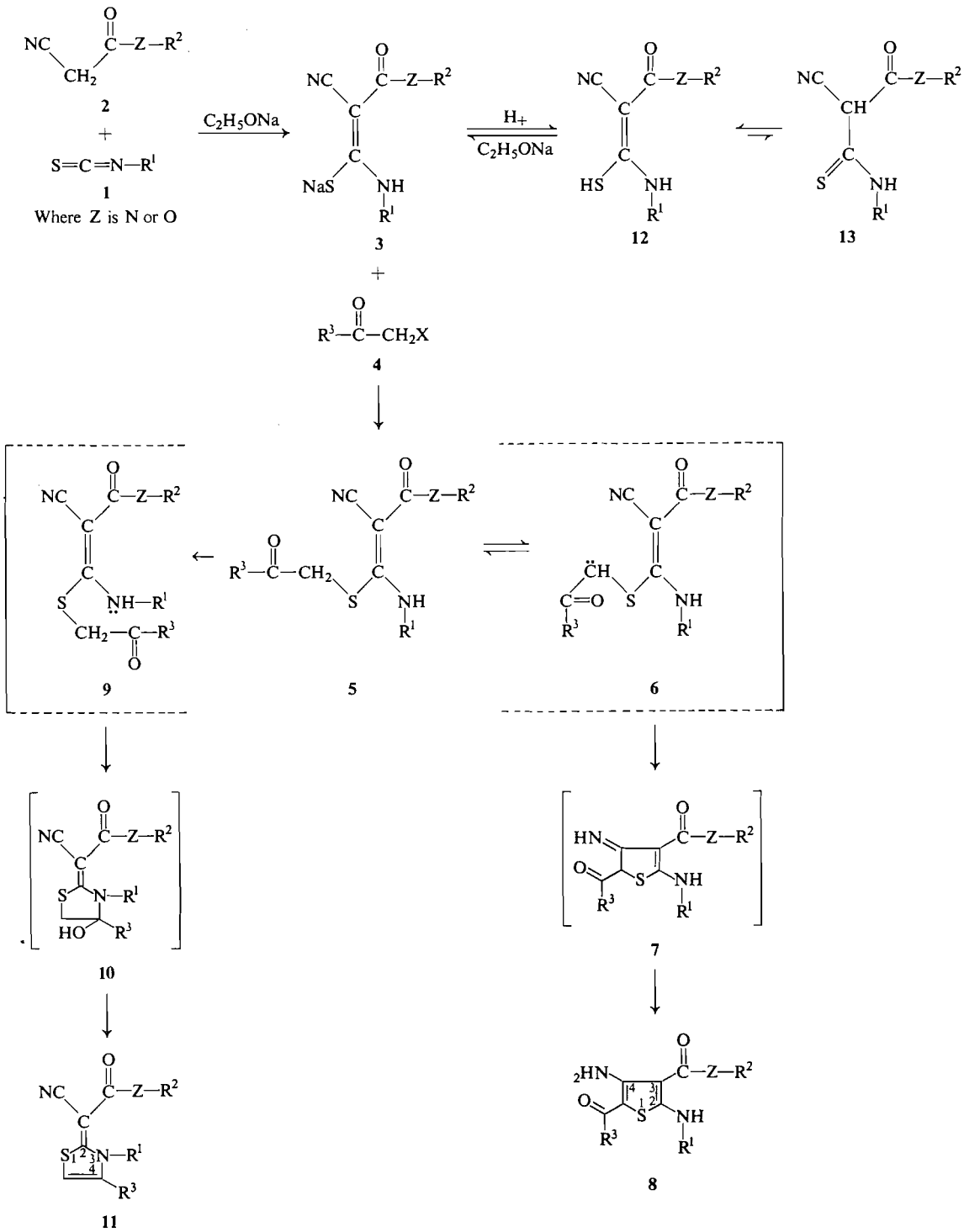
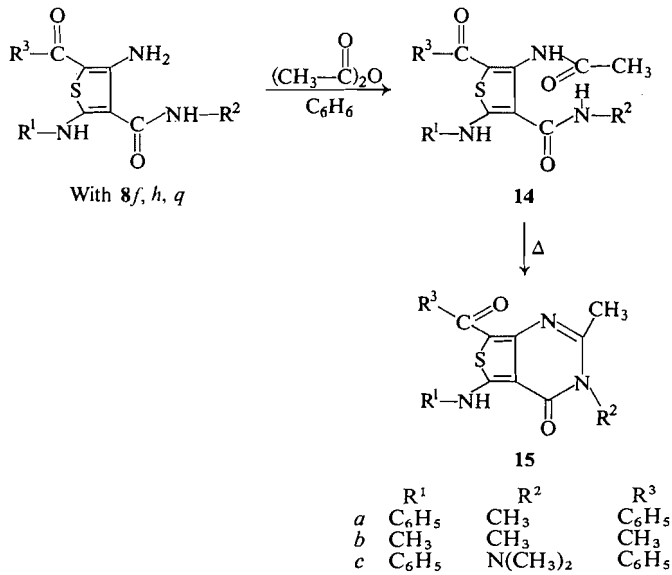
Synthesis

The sodium salts **3** of the enol form of β-thioamides **13**, herein described as sodium salts of 3-substituted amino-2-cyano-3-thioacrylic esters and amides **3** have provided versatile starting materials for this synthesis. They were obtained "in situ" by reaction of isothiocyanates **1** to derivatives of cyanoacetic acid (**2** where Z is O or N) (see Scheme 1). Originally described (1, 11) as an addition of cyanoacetic ethyl ester (**2** where ZR^2 is OC_2H_5) to an aryl isothiocyanate this reaction has been extended to include alkyl isothiocyanates such as methyl (4), allyl, *tert*-butyl, cyclohexyl, and benzyl isothiocyanates. We have also used cyanoacetamides in addition to the cyanoacetic ethyl ester. Accordingly we were able to prepare as starting materials a variety of sodium salts of 3-arylamino and 3-alkylamino-2-cyano-3-thio-acrylic esters as well as amides (**3** where ZR^2 is OC_2H_5, $NH{-}CH_3$, NHC_6H_5, $NH{-}N\langle\rangle$, $NHN(CH_3)_2$).

The sodium salts **3** were reacted "in situ" with halocompounds. This addition of α-halomethylketones was carried out at temperatures ranging from 0 °C to the boiling point of ethanol. In most cases, the use of either low or high temperature resulted in a selective preparation of thiophene-3-carboxylic esters or amides **8** or of thiazoline-2-acetic esters, **11**, respectively. For example, the reaction of an α-halomethylarylketone (**4** where R^3 is aryl) with the sodium salt of a 3-arylamino-2-cyano-3-thioacrylic ester (**3** where ZR^2 is OC_2H_5 and R^1 is aryl) in *boiling* ethanol resulted in the formation of a 3-arylthiazoline-2-acetic



SCHEME 1
Synthesis of thiophenes and thiazolines



SCHEME 2

ester, **11**, as published earlier (2). When the same reaction was effected in the same solvent in the *cold*, a 5-acyl-4-amino-2-arylamino-thiophene-3-carboxylic ester **8***a*, was the only product isolated.

We have applied this modification of a known reaction (2) to a variety of new 3-amino-2-cyano-3-thioacrylamides (**3** where Z is N) and observed similarly the formation of 12 substituted thiophene-3-carboxamides (Table 1, **8***e*, *g*–*q* where Z is N), in yields ranging from 30 to 80%. This procedure has allowed the use of 3-arylamino as well as 3-alkylamino-2-cyano-3-thioacrylamides and has worked nicely with the 3 α-halomethyl-*aryl*ketones investigated (**4** where R^3 is phenyl, *p*-chlorophenyl, and biphenylyl).

Difficulties were encountered when an α-halomethyl*alkyl*ketone (**4** where R^3 is alkyl) such as chloroacetone was used. Reaction with a sodium salt of a 3-arylamino-2-cyano-3-thioacrylamide (**3** where R^1 is aryl) was found to give the expected 5-acetyl-2-arylamino-4-aminothiophene-3-carboxamide, **8***o*, while the same reaction with a 3-alkylamino-2-cyano-3-thioacrylamide (**3** where R^1 is alkyl) yielded a 3-alkylthiazoline-2-acetamide, **11**. This difficulty was overcome by changing the reaction conditions, by adding chloroacetone slowly at a higher temperature. A 5-acetyl-4-amino-2-methylaminothiophene-3-carboxamide, **8***f*, was obtained.

The above showed that certain combinations of substituents R^1 and R^3 have a pronounced influence on the course of the reaction. In addition, the ZR^2 group was also quite important. As mentioned above, amides yielded easily thiophene-3-carboxamides but the esters of 3-thioacrylic acid **3** were more sensitive to substituent influences. For example, when R^1 and R^3 were phenyls, reaction in the cold gave the expected thiophene-3-carboxylic ester **8***a*, in good yield. When R^1 was a large aliphatic group such as *tert*-butyl, cyclohexyl, or even benzyl, the addition of chloropropanone (R^3 is CH_3) had to be done slowly in warm ethanol, to result in the preparation of thiophene-3-carboxylic esters, **8***b*, *c*, *d*, and the yields were poor. When R^1 was a small alkyl group such as a methyl or an ethyl the slow addition of chloropropanone (R^3 is CH_3) in warm ethanol yielded thiazoline-2-acetic esters, **11**. We were unable to isolate the corresponding thiophene-3-carboxylic esters, **8**.

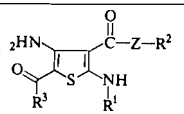
We also observed the reaction of 2,4-diaminothiophene-3-carboxamides (**8** where Z = N) with acetic anhydride to yield a monoacetamide, **14**, the primary amine being the only one to react. Heating a solution of a thiophene-3-carboxamide in benzene containing some pyridine for 1 h to reflux has not acylated the secondary amine in position 2, no difference being seen between arylamine and alkylamine. A prolonged heating period has rather effected ring closure between amides in positions 3 and 4 to generate thieno-[3,4-*d*]pyrimidines, **15**, described in Scheme 2.

TABLE 1

Derivatives of 5-acyl-2-alkylamino-4-aminothiophene carboxylic acid*

8	R^1	ZR^2	R^3	Method	Solvent of crystallization	Yield**	Melting point (°C)	Anal. Found (Calcd.) (%) C	H	N	S	Formula
a	C_6H_5	OC_2H_5	C_6H_5	*a*	Acetone†	60	138–139	65.51 (65.56)	5.24 (4.95)	7.89 (7.65)	8.80 (8.73)	$C_{20}H_{18}N_2O_3S$
b	CH_2—C_6H_5	OC_2H_5	CH_3	*b*	Acetone, toluene	20	130	60.30 (60.37)	5.80 (5.70)	8.62 (8.80)	9.84 (10.02)	$C_{16}H_{18}N_2O_3S$
c	$C(CH_3)_3$	OC_2H_5	CH_3	*b*	Acetone,‡ methyl-cyclohexane	40	88–90	54.75 (54.92)	7.04 (7.09)	9.97 (9.85)	11.37 (11.25)	$C_{13}H_{20}N_2O_3S$
d	C_6H_{11}	OC_2H_5	CH_3	*b*	Acetone§ + hexane, methylcyclohexane	40	80–82	57.79 (58.05)	7.00 (7.15)	8.93 (9.03)	10.48 (10.31)	$C_{15}H_{22}N_2O_3S$
e	CH_3	NH—CH_3	C_6H_5	*a*	Acetonitrile‖	40	220–222 d	58.53 (58.12)	5.27 (5.23)	14.25 (14.53)	11.27 (11.06)	$C_{14}H_{15}N_3O_2S$
f	CH_3	NH—CH_3	CH_3	*b*	Acetonitrile	30	221–223 d	47.76 (47.57)	5.85 (5.77)	18.30 (18.49)	14.16 (14.07)	$C_9H_{13}N_3O_2S$
g	C_3H_5¶	NH—CH_3	C_6H_5	*a*	Propanol	30	127–128 d	61.25 (60.94)	5.63 (5.43)	13.08 (13.33)	10.02 (10.15)	$C_{16}H_{17}N_3O_2S$
h	C_6H_5	NH—CH_3	C_6H_5	*a*	Isopropanol	75	207–209 d	64.95 (64.95)	4.89 (4.88)	11.91 (11.96)	9.35 (9.11)	$C_{19}H_{17}N_3O_2S$
i	C_6H_5	NH—CH_3	*p*-C_6H_4Cl	*a*	Acetonitrile	30	233–235 d	59.17 (59.13)	4.31 (4.17)	10.70 (10.88)	8.26 (8.31)	$C_{19}H_{16}ClN_3O_2S$
j	C_6H_5	NH—CH_3	C_6H_4–C_6H_5	*a*	Ethoxyethanol	60	251–253 d	70.33 (70.24)	4.87 (4.95)	9.84 (9.83)	7.69 (7.48)	$C_{25}H_{21}N_3O_2S$
k	*m*-$C_6N_4NO_2$	NH—CH_3	C_6H_5	*a*	Ethoxyethanol	45	259–260 d	57.85 (57.57)	4.30 (4.07)	13.94 (14.14)	8.25 (8.07)	$C_{19}H_{16}N_4O_4S$
l	C_6H_5	NH—C_6H_5	C_6H_5	*a*	Methoxyethanol	70	228–230 d	69.63 (69.72)	4.61 (4.63)	10.40 (10.61)	7.83 (7.74)	$C_{24}H_{19}N_3O_2S$
m	C_6H_5	NH—C_6H_5	C_6H_4–C_6H_5	*a*	Methoxyethanol	70	256–258 d	73.41 (73.60)	4.60 (4.74)	8.48 (8.58)	6.48 (6.53)	$C_{30}H_{23}N_3O_2S$
n	*m*-$C_6H_4NO_2$	NH—C_6H_5	C_6H_5	*a*	Ethoxyethanol	60	213–215 d	63.11 (62.88)	4.25 (3.96)	12.46 (12.22)	6.98 (6.98)	$C_{24}H_{18}N_4O_4S$
o	C_6H_5	NH—C_6H_5	CH_3	*a*	Acetonitrile	30	223–225 d	64.73 (64.95)	4.73 (4.88)	11.92 (11.96)	9.20 (9.11)	$C_{19}H_{17}N_3O_2S$
p	C_6H_5	NH—N⟨⟩	C_6H_5	*a*	Methoxyethanol	80	243–245 d	65.66 (65.70)	5.93 (5.75)	13.42 (13.33)	7.65 (7.61)	$C_{23}H_{24}N_4O_2S$
q	C_6H_5	NH—$N(CH_3)_2$	C_6H_5	*a*	Acetonitrile	60	232–234 d	63.51 (63.15)	5.50 (5.30)	14.70 (14.73)	8.47 (8.41)	$C_{20}H_{20}N_4O_2S$

*The compound has the following general structure:



8

†Chromatographed on Merck silica gel with 2% ethyl acetate in benzene.
‡Chromatographed on alumina of activity I with 20% ethyl acetate in benzene.
§After chromatography on alumina activity I with 10% ethyl acetate in benzene.
‖This substance crystallized partly from the reaction mixture.
¶Allyl.
**In most cases, as obtained after a single assay, calculated from quantity of cyanoacetamide used.

This has afforded an easy synthesis of a new group of substituted thieno-pyrimidines.

Discussion

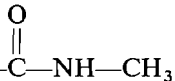
The reaction which led to derivatives of thiophene-3-carboxylic acids, **8**, or of thiazoline-2-acetic acids, **11**, could be explained as shown in Scheme 1. Reaction of a sodium salt of a 3-amino-2-cyano-3-thioacrylic ester or amide **3** with a α-halomethylketone resulted in a hypothetical 3-(β-ketomethylthio)-3-amino-2-cyanoacrylic ester or amide **5**. This unstable substance **5** having a methylene adjacent to a carbonyl and a sulfur could have formed a carbanion **6** in the presence of unreacted sodium salt **3**. This could have added to the nitrile to form a 4-iminothiophene-3-carboxylic ester or amide[2] **7** that stabilized itself by rearranging into a 4-aminothiophene-3-carboxylic ester or amide **8**. Obviously a key step in this reaction would have been the formation of a carbanion, **6**, originating by interaction of a 3-(β-ketomethylthio) acrylic acid derivative, **5**, and some unreacted sodium salt **3**, indicating that some kind of equilibrium must exist between **3**, **5**, and **6**. Ring closure of the carbanion **6** to a 4-iminothiophene-3-carboxamide regenerated the sodium salt **3** and the reaction proceeded further as long as some sodium salt was present. This reaction mechanism is supported by the fact that thiophenes were obtained only when the reaction conditions favored such an equilibrium, namely when the reaction was carried out in the cold as in "method *a*", or when the addition of the α-halomethylketone to a warm solution was effected slowly as in "method *b*".

The dehydrative cyclization route (sequences **5** to **9** to **10** and **11**) ensued if the reaction was carried out under conditions enhancing the formation of the 3-(β-ketomethylthio) acrylic acid derivatives, namely when the haloketone was added at once in warm ethanol. The simultaneous presence in the molecule of a nucleophile and of an available carbonyl should lead to addition products. 4-Hydroxythiazolidine-2-acetic esters, **10**,[3] were indeed formed which, on loss of water, yielded thiazoline-2-acetic esters, **11**. This addition was also influenced by the bulkiness of the groups R^1 on the nitrogen; a small alkyl or an aryl giving a faster addition than large alkyl groups such as *tert*-butyl or cyclohexyl.

We previously assigned the *cis* configuration to the sodium salt of 3-amino-2-cyano-3-thioacrylic acid, esters and amides **3** and their *S*-alkyl derivatives **5** (4). This choice was based mainly on infrared (i.r.), and ultraviolet (u.v.) data. The easy addition of the carbanion **6** to the adjacent nitrile provides an additional argument for the *cis* configuration. The reverse configuration would have made this addition impossible, the nitrile being too far from the active methylene. We isolated, in many cases, the free thio compound **12**. Theoretically **12** could have been transformed via **13** into the *trans* isomer to give a mixture of isomers. This was not the case and addition of C_2H_5ONa regenerated the same sodium salt **3**. This can be explained by the increased stability due to hydrogen bonding

between —NH— and —C—.

All i.r. and u.v. data of thiophene-3-carboxylic esters and amides **8** are summarized in Table 2. The u.v. maxima were more influenced by R^1 than by R^3. Carbonyls of esters at 1655 ± 5 cm^{-1} in $CHCl_3$ and of amides at 1625 ± 15 cm^{-1} in Nujol were normal for this type of compound (5). In some cases, more than one crystalline structure were detected in Nujol. Similarity of isomers was then proven by comparison of u.v. and nuclear magnetic resonance (n.m.r.) data. All n.m.r. spectra were recorded and found to agree with the proposed structure. The absence of any proton on the thiophene ring has given n.m.r. spectra showing the substituents only, rendering their description unnecessary. However, they have consistently shown a broad NH_2 and a sharp NH, plus an additional NH for amides. In one case, namely for **8***h*, a mass spectrum of a thiophene-3-carboxamide was recorded. As expected, the correct molecular ion was detected together with a strong peak at 294 resulting from the loss of



The presence in the i.r. of a strong conjugated nitrile at 2190 cm^{-1} ± 10 for thiazoline-2-acetic esters, **11**, made it possible to differentiate **11** from thiophene **8** or to detect **11** in mixtures. The i.r., u.v., and n.m.r. data for thiazoline-2-acetic esters, **11**, and thienopyrimidines, **15**, are included in the Experimental.

[2]The stability of those iminothiophenes is influenced to a great extent by the substituents on the ring. Examples of stable 4-iminothiophene-3-carboxamides will be given in another paper.

[3]Stable 4-hydroxythiazoline-2-acetic esters were described in a previous paper (4).

TABLE 2

The u.v. and i.r. of 5-acyl-2-alkylamino-4-aminothiophene-3-carboxylic acids

				Ultraviolet			Infrared					
								ν (cm^{-1})				
8	R^1	ZR^2	R^3	λ_{max} (ε) (mμ)	λ_{max} (ε) (mμ)	λ_{max} (ε) (mμ)	Solvent	NH	C=O	O ‖ C	C=C strong	
a	C_6H_5	OC_2H_5	C_6H_5	262 (15 500)	297 (20 500)	369 (23 900)	$CHCl_3$	3490, 3460, 3360, 3280	1660	1580	1550	
b	$CH_2—C_6H_5$	OC_2H_5	CH_3	258 (17 600)	277 (26 100)	340 (22 100)	$CHCl_3$	3490, 3390, 3300	1655	1580	1550	
c	$C(CH_3)_3$	OC_2H_5	CH_3	260 (22 500)	278 (26 600)	345 (23 700)	$CHCl_3$	3490, 3370, 3255, 3200	1650	1580	1545	
d	C_6H_{11}	OC_2H_5	CH_3	260 (19 200)	277 (27 400)	343 (25 400)	$CHCl_3$	3490, 3380, 3295	1655	1575	1545	
e	CH_3	NH—CH_3	C_6H_5	254 (16 040)	285 (12 210)	357 (23 700)	Mull	3420, 3300, 3260	1625	1595	1570	
f	CH_3	NH—CH_3	CH_3	253 (6 500)	278 (6 740)	347 (10 900)	Mull	3410, 3320, 3275	1635	1598	1550	
g	C_3H_5	NH—CH_3	C_6H_5	253 (17 250)	285 (13 250)	350 (25 200)	Mull	3410, 3270	1618	1580	1540	
h	C_6H_5	NH—CH_3	C_6H_5	258 (15 700)	308 (18 500)	375 (27 800)	Mull	3400, 3330, 3300	1610	1590	1550	
i	C_6H_5	NH—CH_3	*p*-C_6H_4Cl	260 (18 000)	305 (17 250)	376 (26 200)	Mull	3400, 3320	1616	1585 1570	1550	
j	C_6H_5	NH—CH_3	$C_6H_4—C_6H_5$	272 (27 500)	300 (21 250)	380 (27 600)	Mull	3400, 3300	1615	1580 1560	1550	
k	*m*-$C_6H_4NO_2$	NH—CH_3	C_6H_5	Insoluble			Mull	3435, 3350, 3280	1640	1585 1565	1550	
l	C_6H_5	NH—C_6H_5	C_6H_5	Insoluble			Mull	3400, 3300	1620	1580	1550	
m	C_6H_5	NH—C_6H_5	$C_6H_4—C_6H_5$	Insoluble			Mull	3390, 3280	1620	1580 1565	1550	
n	*m*-$C_6H_4NO_2$	NH—C_6H_5	C_6H_5	282 (24 800)	305 (23 500)	378 (24 000)	Mull	3420, 3340, 3275	1638	1590	1550	
o	C_6H_5	NH—C_6H_5	CH_3		300 (25 100)	360 (21 500)	Mull	3430, 3300, 3265	1640	1590	1550	
p	C_6H_5	NH—N⟨ ⟩	C_6H_5	258 (16 650)	307 (18 750)	375 (29 100)	Mull*	3425, 3310, 3225	1620	1585	1565	
q	C_6H_5	NH—$N(CH_3)_2$	C_6H_5	258 (16 500)	305 (18 500)	375 (29 500)	Mull	3435, 3325		1585	1565	

*Two crystalline structures were found—the other one has shown C=O at 1580.

Experimental

The melting points were determined with a Reichert melting point apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin–Elmer model 225 spectrometer as a solution in $CHCl_3$ or as dispersion in Nujol. All u.v. spectra were obtained on a Perkin–Elmer 350 spectrophotometer in ethanol solution. The n.m.r. spectra were obtained with a Varian A-60-A apparatus and were recorded in deuterated chloroform, trifluoroacetic acid, or dimethylsulfoxide by Mrs. J. Jachner. Exchanges with D_2O were performed to detect NH and NH_2. Microanalyses were performed in our laboratories by Mr. W. Turnbull.

Preparation of Substituted Cyanoacetamides 2

2a, N-Methylcyanoacetamide (2 where ZR^2 is $NHCH_3$)

To 24 g of ethyl cyanoacetate in 50 ml of ethanol, 30 ml of 30% CH_3NH_2 in water were added. The solution was kept at 50° for 3 h and the solvents were evaporated to leave a residue which was crystallized twice from isopropanol to give the title compound in 30% yield. It melted at 98–99° (lit. (12*a*) m.p. 101°).

2b, Cyanoacetanilide (2 where ZR^2 is $NH—C_6H_5$)

A solution of 45 g of aniline in 37 g of ethyl cyanoacetate was kept at 150–160° for 6 h. It was left at room temperature overnight and the crystals were filtered off and washed with some ethanol. The solid (30 g) crystallized from acetone on addition of water. It melted at 199–200° (lit. (12*b*) m.p. 199–200°).

2c, N-(1-Piperidinyl)cyanoacetamide

(2 where ZR^2 is NH—N⬡)

A mixture of 0.2 mole of ethyl cyanoacetate and of *N*-aminopiperidine was left at room temperature for 4 days. A solid resulted that was filtered off and crystallized from isopropanol. It was obtained in 65% yield and melted at 131–132°.

Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.48; H, 7.88; N, 25.25.

2d, Cyanoacetic Acid, N,N-Dimethylhydrazide (2 where ZR^2 is $NH—N(CH_3)_2$)

Prepared as described by E. G. Howard in ref. (13).

Sodium Salts of Substituted 3-Amino-2-cyano-3-thioacrylic Esters and Amides, 3

3a, Sodium Salt of 3-Anilino-2-cyano-3-thioacrylic Acid, Ethyl Ester

To a cold solution of sodium ethoxide (0.05 mole of sodium in 50 ml of ethanol), 0.05 mole of cyanoacetic acid ethyl ester was added. The solution was cooled and 0.05 mole of phenyl isothiocyanate was added. It was left on ice for 3 min and at room temperature for 1 h. The yellow solution was used as such.

3b, Sodium Salt of 2-Cyano-3-methylamino-3-thioacrylic Acid, Ethyl Ester

Prepared as for **3***a* using methyl isothiocyanate instead of phenyl isothiocyanate and refluxing for 1 h.

3c, Sodium Salt of 2-Cyano-3-ethylamino-3-thioacrylic Acid, Ethyl Ester

Prepared as for **3***b* but using ethyl isothiocyanate.

3d, Sodium Salt of 3-Allylamino-2-cyano-3-thioacrylic Acid, Ethyl Ester

Prepared as for **3***a* but using allyl isothiocyanate and refluxing for 30 min.

3e, Sodium Salt of 2-Cyano-3-methylamino-3-thioacrylic Acid, Methyl Ester

To a cold solution of sodium methoxide (0.05 mole of sodium in 75 ml of dry methanol) cyanoacetic acid, methyl ester was added. The solution was cooled and 0.05 mole of methyl isothiocyanate was added. The solution was heated under reflux for 1 h.

3f, Sodium Salt of 3-Benzylamino-2-cyano-3-thioacrylic Ethyl Ester

A solution of this salt in ethanol was obtained by the same procedure as described for **3***a* but using benzyl isothiocyanate instead of phenyl isothiocyanate.

3g, Sodium Salt of 3-tert-Butylamino-2-cyano-3-thioacrylic Acid, Ethyl Ester

Prepared as **3***a* using *tert*-butyl isothiocyanate instead of phenyl isothiocyanate. The solution was heated for 90 min to complete the reaction.

3h, Sodium Salt of 3-Cyclohexylamino-2-cyano-3-thioacrylic Ethyl Ester

Prepared as **3***a* using cyclohexyl isothiocyanate. The solution was heated for 60 min.

3i, Sodium Salt of 2-Cyano-3-methylamino-N-methyl-3-thioacrylamide

To a solution of sodium ethoxide (0.05 mole) in 150 ml of dry ethanol, 0.05 mole of *N*-methylcyanoacetamide, **2***a*, followed after 2 min by 0.05 mole of methyl isothiocyanate were added. The mixture was heated on a steam-bath for 2 h, some solid was filtered off, and the solution was used as such.

3j, Sodium Salt of 3-Allylamino-2-cyano-N-methyl-3-thioacrylamide

It was prepared as **3***i* using allyl isothiocyanate.

3k, Sodium Salt of 3-Anilino-2-cyano-N-methyl-3-thioacrylamide

It was prepared as **3***i* using phenyl isothiocyanate.

3l, Sodium Salt of 2-Cyano-N-methyl-3-m-nitroanilino-3-thioacrylamide

It was prepared as **3***i* using *m*-nitrophenyl isothiocyanate

3m, Sodium Salt of 3-Anilino-2-cyano-3-thioacrylanilide

It was prepared as **3***i* using cyanoacrylanilide **2***b* as starting material and replacing methyl isothiocyanate by phenyl isothiocyanate.

3n, Sodium Salt of 2-Cyano-3-m-nitroanilino-3-thioacrylanilide

It was prepared as **3***i* using *m*-nitrophenyl isothiocyanate.

3o, Sodium Salt of 3-Anilino-2-cyano-N-piperidino-3-thioacrylamide

It was prepared as **3***i* using *N*-(1-piperidinyl)cyanoacetamide **2***c* as starting material and replacing methyl isothiocyanate by phenyl isothiocyanate.

3p, Sodium Salt of 3-Anilino-2-cyano-3-thioacrylic Acid, N,N-Dimethyl Hydrazide

It was prepared as **3***i* using cyanoacetic acid, *N,N*-dimethyl hydrazide **2***d* as starting material and replacing methyl isothiocyanate by phenyl isothiocyanate.

Preparation of 5-Acyl-2,4-diaminothiophene-3-carboxylic Esters and Amides

They are described in Table 1. Two methods were used to prepare them. All the thiophenes were yellow solids.

Method a for **8***a, e, g–q*

The solution in ethanol of a convenient sodium salt of a substituted 3-amino-2-cyano-3-thioacrylic ester or amide (0.05 mole) prepared as described above was cooled to 5°. A solution in ethanol of an equivalent of an α-chloromethylketone such as chloropropanone, 2-chloroacetophenone, or an α-bromomethylketone such as 4′-phenyl-2-bromoacetophenone was added to it slowly with stirring and keeping the temperature between 5–10°. The solution was left at 10° for 2 h. In some cases, as for **8***j, l, m,* and *p*, the thiophene crystallized out of the reaction mixture. It was then filtered off and recrystallized twice from the solvent given in Table 1. If no yellow solid appeared, the ethanol was evaporated under vacuum and the residue was dissolved in $CHCl_3$ and washed. Evaporation of the $CHCl_3$ left a residue that was crystallized from the given solvent as for **8***e, g, h, i, k, n, o, q* or chromatographed as for **8***a*.

Method b for **8***b, c, d, f*

In most cases the addition of 0.05 mole of chloroacetone was effected slowly on a warm solution in ethanol of 0.05 mole of an appropriate sodium salt of a 3-amino-2-cyano-3-thioacrylic ester **3***f–h*; or amine **3***i*. The mixture was heated for 1 h. The solvent was then evaporated, the residue was taken into $CHCl_3$ and washed. The residue after evaporation was crystallized as shown for **8***b* and *f* or chromatographed and crystallized as for **8***c* and *d*.

Preparation of α-*Cyanothiazoline-*$\Delta^{2\alpha}$*-acetic Acid, Ethyl Ester,* **11**

11a*,* α-*Cyano-3,4-dimethylthiazoline-*$\Delta^{2\alpha}$*-acetic Acid, Ethyl Ester*

Chloropropanone 0.06 mole was added slowly to a warm solution in ethanol of 0.05 mole of the sodium salt of 2-cyano-3-methylamino-3-thioacrylic acid, ethyl ester **3***b*. The mixture was refluxed for 2 h and the solvent evaporated. The residue was dissolved in $CHCl_3$, washed with diluted HCl and with water. Evaporation left an oil that was crystallized from isopropanol and from ethyl acetate. This substance was obtained as a white solid (75%) melting at 176°; ν_{max} ($CHCl_3$) CN 2195, C=O 1650 cm^{-1}. In n.m.r. ($CDCl_3$) H_5 was at 388 Hz, u.v. ν_{max} 335 (ε 19 500).

Anal. Calcd. for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.39; N, 12.50; S, 14.27. Found: C, 53.50; H, 5.39; N, 12.76; S, 14.03.

11b*,* α-*Cyano-3-ethyl-4-methylthiazoline-*$\Delta^{2\alpha}$*-acetic Acid, Ethyl Ester*

This substance was prepared as described for **11***a* using the sodium salt of 2-cyano-3-ethylamino-3-thioacrylic acid ethyl ester **3***c* as starting material. It was crystallized from isopropanol and was obtained as a white solid (65%) melting at 112°; ν_{max} ($CHCl_3$) CN 2190, C=O 1650 cm^{-1}. In n.m.r. ($CDCl_3$) H_5 was a singlet at 385 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.45; H, 5.92; N, 11.76; S, 13.43. Found: C, 55.35; H, 6.18; N, 12.01; S, 13.46.

11c*, 3-Allyl-*α-*cyano-4-methylthiazoline-*$\Delta^{2\alpha}$*-acetic Acid, Ethyl Ester*

This substance was prepared as described for **11***a* using as starting material the sodium salt of 3-allylamino-2-cyano-3-thioacrylic acid ethyl ester **3***d*. Hexane was added to a concentrated solution of it in $CHCl_3$. The white solid obtained (40%) was crystallized from isopropanol and from ethyl acetate. It melted at 99°; ν_{max} ($CHCl_3$) CN 2200, C=O 1652 cm^{-1}. In n.m.r. ($CDCl_3$) H_5 was a singlet at 389.

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.29; H, 5.64; N, 11.20; S, 12.79. Found: C, 57.66; H, 5.89; N, 11.37; S, 12.65.

11d*,* α-*Cyano-3,4-dimethylthiazoline-*$\Delta^{2\alpha}$*-acetic Acid, Methyl Ester*

This substance was prepared as described for **11***a* using as starting material the sodium salt 2-cyano-3-methylamino-3-thioacrylic acid methyl ester **3***e*. Evaporation of the methanol left a dark solid which was filtered out, washed with isopropanol, and crystallized from acetonitrile. This methyl ester was much less soluble than the ethyl ester **11***a*. It was obtained in 55% yield as a white solid melting at 222–224°; ν_{max} (Nujol) CN 2195, C=O 1645 cm^{-1}. In n.m.r. (TFA) H_5 was at 420 Hz, u.v. ν_{max} at 333 (ε 22 600).

Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.80; N, 13.33; S, 15.22. Found: C, 51.40; H, 4.84; N, 13.52; S, 15.30.

11e*,* α-*Cyano-N,3,4-trimethylthiazoline-*$\Delta^{2\alpha}$*-acetamide*

To a cold solution (5°) of the sodium salt of 2-cyano-3-methylamino-*N*-methyl-3-thioacrylamide, **3***i* (0.05 mole), 0.055 mole of chloropropanone was added slowly with constant stirring while keeping the temperature at 5°. After 1 h the ethanol was evaporated, the residue was dissolved in $CHCl_3$, and washed with diluted HCl and with water. Evaporation of the solvent left a solid that was washed with hexane and crystallized from CH_3CN or 2-heptanone. The pale yellow solid obtained in 35% yield melted at 257–259°; ν_{max} (Nujol) NH 3380, CN 2160, C=O 1610 cm^{-1}; n.m.r. (TFA) has shown H_5 to be at 445 Hz; u.v.$_{max}$ at 336 (ε 41 800).

Anal. Calcd. for $C_9H_{11}N_3OS$: C, 51.67; H, 5.30; N, 20.09; S, 15.29. Found: C, 51.70; H, 5.33; N, 20.38; S, 15.44.

14*, 4-Acetamido-2-anilino-5-benzoyl-N-methylthiophene-2-carboxamide*

To 0.017 mole of 4-amino-2-anilino-*N*-methyl-5-benzoylthiophene-3-carboxamide, **8***h*, in 100 ml of benzene, 0.10 mole of acetic anhydride and 15 drops of pyridine were added. The mixture was refluxed for 1 h. On cooling, a yellow solid precipitated. It was filtered off, washed with isopropanol, and crystallized from acetonitrile. The yellow solid (55%) melted at 182–184°: ν_{max} (Nujol) NH 3330, C=O 1690 and 1620 cm^{-1}; u.v. ν_{max} at 290 (ε 12 810).

Anal. Calcd. for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; S, 8.13. Found: C, 64.39; H, 4.99; N, 10.60; S, 8.04.

15a*, 5-Anilino-7-benzoyl-2,3-dimethylthieno[3,4-d]-pyrimidin-4(3H)-one*

To 0.04 mole of 4-amino-2-anilino-*N*-methyl-5-benzoylthiophene-3-carboxamide, **8***h*, in 150 ml of benzene, 0.24 mole of acetic anhydride and 5 drops of pyridine were added. The mixture was kept under reflux overnight. On cooling a solid precipitated out. It was filtered off, washed with isopropanol, and crystallized from methoxyethanol. The yellow solid (55%) melted at 232–234°; ν_{max} (Nujol)

NH 3170, C=O 1655 and 1590 cm^{-1}; in u.v. maxima at 247 (ε 13 900), 288 (ε 22 600) and 420 (ε 23 600).

Anal. Calcd. for $C_{21}H_{17}N_3O_2S$: C, 67.19; H, 4.57; N, 11.20; S, 8.52. Found: C, 67.38; H, 4.67; N, 11.58; S, 8.40.

15b, 7-Acetyl-2,3-dimethyl-5-methylaminothieno[3,4-d]-pyrimidin-4(3H)-one

To 0.09 mole of 5-acetyl-4-amino-*N*-methyl-2-methyl-aminothiophene-3-carboxamide, **8***f*, in 300 ml of benzene, 0.4 mole of acetic anhydride and 8 drops of pyridine were added. The solution was kept under reflux overnight. On cooling a solid was obtained. It was filtered off, washed with isopropanol, and crystallized from methoxyethanol. The yellow solid obtained (75%) melted at 276–278°; ν_{max} (Nujol) NH 3300, C=O 1650 and 1605 cm^{-1}; in u.v. maxima at 282 (ε 27 700), 321 (ε 6460) and 380 (ε 19 250).

Anal. Calcd. for $C_{11}H_{13}N_3O_2S$: C, 52.58; H, 5.22; N, 16.73; S, 12.73. Found: C, 52.67; H, 5.37; N, 16.44; S, 12.76.

15c, 5-Anilino-7-benzoyl-3-dimethylamino-2-methylthieno[3,4-d]pyrimidin-4(3H)-one

To 0.033 mole of 4-amino-2-anilino-5-benzoylthiophene-3-carboxylic acid, *N,N*-dimethyl hydrazide, **8***q*, in 250 ml of benzene, 0.165 mole of acetic anhydride and 7 drops of pyridine were added. The mixture was refluxed overnight, cooled, and the solid formed was filtered off. It was washed with isopropanol and crystallized from 2-methoxyethanol. This yellow solid (90%) melted at 223–224°; ν_{max} (Nujol) NH 3220, C=O 1650 and 1580 cm^{-1}; in u.v. maxima at 248 (ε 16 100) and 286 (ε 24 300).

Anal. Calcd. for $C_{22}H_{20}N_4O_2S$: C, 65.33; H, 4.99; N, 3.86; S, 7.91. Found: C, 65.46; H, 5.27; N, 4.04; S, 8.04.

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