Bromine-induced Cyclization of 1-Acyl-3-(3-thienyl)-2-thioureas to 2-Acylaminothieno[3,2-*d*]thiazoles

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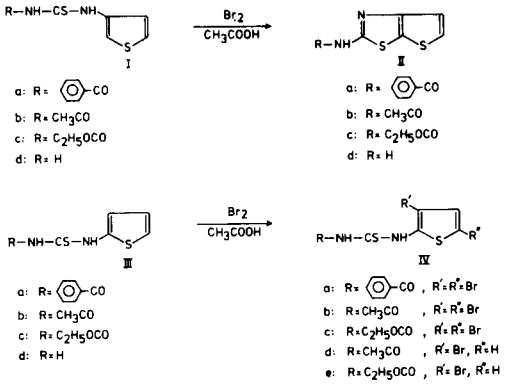
Received July 8, 1977

Three different 1-acyl-3-(3-thienyl)-2-thioureas were cyclized to 2-acylaminothieno[3,2-*d*]-thiazoles with bromine in acetic acid whereas the corresponding 2-thienylthiourea derivatives were brominated under the same reaction conditions. The parent thieno[3,2-*d*]thiazole was prepared by acid hydrolysis and deamination of 2-benzoylaminothieno[3,2-*d*]thiazole. This new heterocyclic compound was nitrated and brominated in the 5-position.

J. Heterocyclic Chem., 15, 81 (1978)

A recent study of the formation of thiazolopyridine derivatives from various pyridylthioureas (1) prompted us to communicate results concerning intramolecular cyclization of 1-acyl-3-(3-thienyl)-2-thioureas (I) to 2-acylaminothieno[3,2-*d*]thiazoles (II). When a solution of Ia in dimethyl sulfoxide was left in the open air for several weeks a minor contaminant with a molecular weight of 260 (mass spectrum) appeared. This compound, IIa, was also formed in low yield when Ia was treated with polyphosphoric acid at 70-80°. It has long been known that arylthioureas can react to give condensed thiazoles in the presence of oxidation agents such as bromine, sulfuryl chloride, thionyl chloride and sulfur monochloride (2). Heterocyclic thioureas have also been studied, pyrazolylthioureas afford pyrazolothiazole derivatives in good yields on treatment with bromine in acetic acid or chloroform (3).

This investigation shows that the substituted 3-thienylthioureas (Ia-c) are readily converted to the expected thieno[3,2-*d*]thiazoles (IIa-c) in fair to good yields using bromine in acetic acid as dehydrogenative agent. Compound Id however gave a very low yield of IId. The main reaction product in this case was probably, in analogy with previous results (4) 3,5-di-(3-thienylamino)-1,2,4-thiadiazole (mass spectrum of the crude reaction mixture gave base peak m/e = 280, M^+). Compounds IIa-c are



stable, high melting, crystalline substances, and this method constitutes a facile route to simple thieno[3,2-*d*]-thiazoles, which hitherto have only occurred seldom in the literature (5,6). Acetic acid seems to be the solvent of choice in these reactions since the products precipitate in very pure state from the reaction mixture either on standing or on dilution with water. Preliminary attempts using dichloromethane or chloroform gave lower yields of impure products. Trimethyl phosphate, recently claimed to be a superior reaction medium for some electrophilic substitution reactions in acid sensitive substrates (7), offered no special advantage in the synthesis of IIc, containing the acid-labile ethoxycarbonylamino group. Iodine in this solvent gave only the starting material while chlorine in trimethyl phosphate gave a mixture of IIc and a chloro-substituted product (mass spectrum of the crude mixture gave m/e = 252 and m/e = 254, M^+ ratio 3:1).

In the 2-thienylthioureas (IIIa-c) however, in striking contrast to the 3-thienyl isomers, the same reaction conditions gave only the bromo substitution derivatives IV, and not the expected thieno[2,3-*d*]thiazoles. One equivalent of bromine gave the monobromo analogues and two equivalents gave the dibromo compounds. The structure of the monobromo-2-thienylthioureas (IVd-e) in which the substitution occurred in the 3-position, is supported by the large coupling between the remaining thiophene protons. Thus $J_{4,5}$ is 5.8 Hz and 5.9 Hz for IVd and IVe respectively, compared to 6.0 Hz for 3-acetylamino-2-bromothiophene. All other substitution patterns should have given smaller coupling constants (8). No other monobromothienylthioureas were detected on examining the ^1H nmr spectra of the crude reaction mixtures. Generally, thiophene derivatives with electron donating groups in the 2-position give mixtures of 3- and 5-substituted products on reaction with electrophiles; usually the 5-isomer predominates. Thus the second bromo substituent is likely to enter the 5-position to give the 3,5-dibromo-2-thienylthioureas (IVa-c).

The mechanism of halogen-induced coupling of thione groups to aromatic (4) and heterocyclic compounds (1) has been considered, and an electrophilic sulfenyl halide intermediate has been suggested (9,10). Although the 2-position is considered to be more reactive than the 3-position in electrophilic substitution reactions, the reason for the large difference in reactivity between I and III remains somewhat obscure. A similar difference in reactivity between α- and β-positions in thiophene deriva-

Table 1

Properties of Thienylthioureas

Compound No.	Formula	Molecular weight (mass spectrum)	Recrystallization solvent (a)	Yield % (b)	R_f-value	M.p. °C	Elemental Analyses *Calcd.* Found		
Ia	$C_{12}H_{10}N_2OS_2$	262	Ethanol-acetone 2:1	61	0.67	201-202	C 54.9 C 54.9	H 3.8 H 3.8	N 10.7 N 10.7
Ib	$C_7H_8N_2OS_2$	200	Ethanol	57	0.56	166-167 (d)	C 42.0 C 42.1	H 4.0 H 4.0	N 14.0 N 13.9
Ic	$C_8H_{10}N_2O_2S_2$	230	Ethanol	70	0.62	119-120 (d)	C 41.7 C 41.7	H 4.4 H 4.4	N 12.2 N 12.1
Id	$C_5H_6N_2S_2$	158	Ethanol-water 1:1	74 (c)	0.31	190-191 (e)	C 37.9 C 38.0	H 3.8 H 3.8	N 17.7 N 17.4
IIIa	$C_{12}H_{10}N_2OS_2$	262	Benzene	22	0.66	216-217	C 54.9 C 55.6	H 3.8 H 4.0	N 10.7 N 10.6
IIIb	$C_7H_8N_2OS_2$	200	Ethanol-acetone 5:1	37	0.56	195-196	C 42.0 C 42.0	H 4.0 H 4.1	N 14.0 N 13.9
IIIc	$C_8H_{10}N_2O_2S_2$	230	Ethanol	38	0.61	151-152	C 41.7 C 41.8	H 4.4 H 4.4	N 12.2 N 12.1
IIId	$C_5H_6N_2S_2$	158	Ethanol-water 1:1	58 (c)	0.34	184-185 (f)	C 37.9 C 38.0	H 3.8 H 3.8	N 17.7 N 17.8

(a) Decolourizing carbon. (b) Recrystallized product calculated from nitrothiophene. (c) Yield on hydrolysis from benzoyl derivative. (d) ^1H nmr revealed trace amounts of 2-isomer. (e) lit. (33) m.p. 192-193°. (f) lit. (33) m.p. 186-186.5°.

Table 2

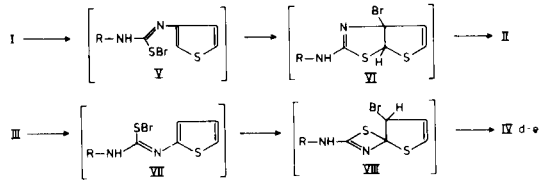
Properties of Bromothienylthioureas

Compound No.	Formula	Molecular weight (mass spectrum)	Yield % (a)	Recrystallization solvent (b)	R_f-value	M.p. °C	Elemental analyses *Calcd.* *Found*		
IVa	$C_{12}H_8Br_2N_2OS_2$	420	78	Hexane:dichloro-ethane 1:1	0.70	203-304 dec.	C 34.3 C 34.8	H 1.9 H 2.3	N 6.7 N 6.3
IVb	$C_7H_6Br_2N_2OS_2$	358	77	Ethanol	0.62	>200 dec.	C 23.5 C 23.7	H 1.7 H 1.7	N 7.8 N 7.9
IVc	$C_8H_8Br_2N_2O_2S_2$	388	62	Ethanol	0.68	193-194 dec.	C 24.8 C 24.9	H 2.1 H 2.2	N 7.2 N 7.3
IVd	$C_7H_7BrN_2OS_2$	279	75	Ethanol, hexane:dichloro-ethane 1:1 (c)	0.59 (d)	~185 dec.	C 30.1 C 29.8	H 2.5 H 2.6	N 10.0 N 9.7
IVe	$C_8H_9BrN_2O_2S_2$	309	84	Ethanol, hexane-dichloro-ethane 1:1 (c)	0.64 (d)	~160 dec.	C 31.1 C 30.5	H 2.9 H 2.9	N 9.1 N 8.8

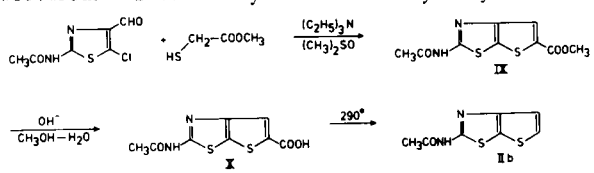
(a) Crude product. (b) Decolourizing carbon. (c) Fractional crystallization. (d) Tlc showed minor contamination of dibromo compound.

tives has previously been found in certain electrophilic cyclizations (11). The CS-group is a strong nucleophile (12) and a previous report (5) claims that, on heating with phosphorus pentasulfide, 3-acetylamino-2-bromothiophene can be converted to 2-methylthieno[3,2-*d*]thiazole, presumably via the intermediate 2-bromo-3-thioacetylaminothiophene. The latter then undergoes intramolecular nucleophilic attack to give the end product. The compounds IVa-c however can be recrystallized from boiling ethanol, and are recovered unchanged even after heating in quinoline or dimethylformamide (prolonged heating gave tarry mixtures). Treatment of IIIb with thionyl chloride gave a complex mixture. Synthetic routes for preparing 2-bromo analogue of Ic failed. Thus *N*-bromosuccinimide in dichloromethane converted Ic to a mixture of IIc and the starting material. Attempts to obtain the intermediate 3-amino-2-bromothiophene by hydrolysis of the acetyl derivative (13) only afforded resinous gums.

Electrophilic agents are known to add to the 2,3-bond in benzothiophene derivatives (14) and, in analogy with these findings, the sulfenyl bromide V would add to the 2,3-bond to give VI which, after elimination of hydrogen bromide, gives II. Similarly, treatment of compounds III with bromine could give VII which cyclizes to VIII. Similar four-membered intermediates have been proposed for some electrophilic cyclizations among pyrrole derivatives (15). The strained structure VIII would, after intramolecular elimination of an SH-group, give IVd-e. However, none of the suggested intermediates V-VIII have been detected in the reaction mixtures.



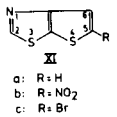
The structure of IIb has been further established by independent synthesis: condensation of 2-acetylamino-5-chloro-4-thiazolecarboxaldehyde with methyl thioglycollate in the presence of triethylamine with dimethyl sulfoxide as solvent afforded IX in fair yield. Other solvents used in similar condensation reactions, such as pyridine or alkaline ethanol-water mixtures (16), gave only negligible yields of IX and the starting material was recovered. This methyl ester was hydrolyzed to the



corresponding acid X in aqueous sodium hydroxide-methanol. Decarboxylation was effected by heating the acid briefly to 290°. The usual copper oxide-quinoline procedure (17) destroyed the substrate. The product thus obtained was identical in all respects with IIb.

The acylamino group in IIa-c is very resistent to hydrolysis. Compounds IIa and IIc are recovered unchanged after 2 hours reflux in 10% aqueous sodium hydroxide, whereas Ia-c and IIIa-c are easily cleaved in this medium. Attempted hydrolysis in hydrochloric acid caused extensive destruction of the heterocyclic ring system in full agreement with an earlier study of the corresponding 2-acylaminothieno[2,3-*d*]thiazole derivatives (18). Successful hydrolysis of IIa however was accomplished in 30% sulfuric acid-ethanol to give IId in fair but somewhat varying yield.

Amine IId smoothly deaminated to XIa in sodium nitrite-hypophosphorous acid, in analogy with the method reported for 5-aminotetrazole (19). The parent thieno[3,2-*d*]thiazole is a faintly coloured, high boiling viscous liquid with a quinoline-like odour. Its low resolution 70eV mass spectrum exhibits many features in common with that of thieno[2,3-*b*]thiophene (20). (See Experimental for some probable fragmentations). The ^{1}H nmr spectrum of XIa consists of an AB-quartet (C_5-H and C_6-H) further split by a long range coupling to C_2-H. The measured coupling constants ($J_{5,6}$ = 5.35 Hz, $J_{2,5}$ = 1.10 Hz and $J_{2,6}$ = ~ 0) are of similar magnitude to those reported for the comparable couplings in various thieno[2,3-*b*]thiophenes (21).



Nitration of XIa with cupric nitrate-acetic anhydride (22) and bromination with *N*-bromosuccinimide or pyridine perbromide in dichloromethane afforded the 5-substituted derivatives. The ^{1}H nmr spectra of XIb and XIc show only two singlets with no visible coupling, indicating substitution at C_5. In some cases, however, the expected long range couplings among substituted thiophene derivatives have not been detected (23), and therefore the absence of coupling is not conclusive evidence for the structure of XIb,c. Fortunately further support for the proposed structure was obtained from the ^{13}C nmr spectra of XIa-c.

It has been shown that the $J_{C_\alpha\text{-}H_\alpha}$- and $J_{C_\beta\text{-}H_\beta}$-values for a number of substituted thiophenes fall into two distinct groups with no overlap (184 Hz $< J_{C_\alpha\text{-}H_\alpha} <$ 199 Hz and 168 Hz $< J_{C_\beta\text{-}H_\beta} <$ 177 Hz) (24). The measured coupling constants in XIa were 216 Hz (C_2-H_2), 189 Hz (C_5-H_5) and 172 Hz (C_6-H_6). The two latter values fit well into the "α"- and "β-group", respectively. In XIb the remaining coupling constants were 219 Hz (C_2-H_2) and 181 Hz (C_6-H_6). The corresponding values for XIc were 216 Hz and 177 Hz. Furthermore, $J_{C_6\text{-}H_6}$ = 174 Hz in IX, the structure of which has been ascertained by

independent synthesis. (In the thieno[3,2-*d*]thiazoles all direct C-H coupling constants seem to increase with about 4 Hz in comparison with the values given for similarly substituted thiophene derivatives). The assignments of the signals in the spectra of XIa-c were made tentatively by comparison with ^{13}C nmr parameters reported for thiophenes (24) and benzothiazoles (25).

No other substitution product could be detected on examining the ^{1}H nmr spectra of the crude reaction mixtures, but glc analyses were not made. Both the bromo and the nitro derivative are, in contrast to the monobromothienothiophenes (26), stable, crystalline compounds which could be stored for months at ambient temperature without significant deterioration. A methanolic solution of XIb gradually became discoloured when exposed to sunlight at room temperature. A solution of the same compound in dimethyl sulfoxide darkened considerably when held at 50-60° for one day.

EXPERIMENTAL

All melting points are uncorrected. Tlc analyses and preparative chromatography were performed on Merck's precoated uv-sensitive silica gel plates. All solvents used were analytical grade or redistilled, and the R_f values given in text refer to toluene-acetonitrile 1:1, freshly prepared mixture (chamber saturation). All compounds described were chromatographically pure unless otherwise stated. The ^{1}H nmr spectra were recorded on a JEOL FX 60 and ^{13}C nmr spectra on a JEOL FX 100 (shifts in ppm relative TMS). An LKB 9000 gc-mass spectrometer was employed for determination of the low resolution 70 eV mass spectra using the direct inlet system. The more important peaks are given in the text (the relative abundances as percent of the base peak in parentheses, p+1 and p+2 peaks are not included) and some probable fragmentations are indicated.

2-Aminothiophene.

2-Nitrothiophene (27) was reduced with tin and hydrochloric acid (28), and the resulting double salt was washed with hydrochloric acid, ethanol and ether to remove the more soluble 3-isomer double salt which was present in trace amounts. The dried salt was added in small portions with ice-cooling and rapid stirring (nitrogen) to a large excess of 2*M* sodium hydroxide. The liberated amine was extracted with methylene chloride three times (10 ml. each per gram of double salt). The combined extracts were dried (magnesium sulfate) and used as such immediately.

3-Aminothiophene.

3-Nitrothiophene (29) was reduced in analogy with the 2-isomer and the resulting double salt was collected after cooling of the reaction mixture overnight. Rinsing did not improve the purity of the salt but caused severe losses. Liberation of the amine was effected as described for the 2-isomer.

1-Acyl-3-thienyl-2-thioureas (Ia-c, IIIa-c).

A solution of the crude aminothiophene (~ 10% in dichloromethane) was cautiously added to a 10% solution of the appropriate *N*-acylisothiocyanate (30) in dichloromethane (20% excess calculated from the starting nitrothiophene assuming 100% yield in the reduction). The reaction mixture was refluxed briefly and concentrated to a small volume and diluted with petroleum ether. The precipitate was collected, washed with petroleum ether to remove excess isothiocyanate and recrystallized from a suitable solvent with addition of decolourizing carbon. Compounds Ia and IIIa were hydrolysed in aqueous sodium hydroxide to Id and IIId according to a previously described procedure (31). The properties of Ia-d and IIIa-d are compiled in Table 1.

2-Benzoylaminothieno[3,2-*d*]thiazole (IIa).

Compound Ia (2.62 g., 10 mmoles) in acetic acid (100 ml.) was treated dropwise with stirring with bromine (1.60 g., 10 mmoles) in acetic acid (10 ml.) during 15 minutes. After 2 hours at 20° the white precipitate was collected and washed with acetic acid and ether. One recrystallization from ethanol (50 ml./g. of decolourizing carbon) gave 2.53 g. (97%) of straw-coloured crystals; R_f = 0.54, m.p. 218-218.5°; ms m/e: 260 (23%; $[M^{\bullet}]^{+}$), 105 (100%; $[C_6H_5CO]^{+}$), 77 (46%; $[C_6H_5]^{+}$), 74 (5%), 59 (11%), 51 (12%), 45 (12%).

Anal. Calcd. for $C_{12}H_8N_2OS_2$: C, 55.4; H, 3.1; N, 10.8. Found: C, 55.5; H, 3.0; N, 10.7.

2-Acetylaminothieno[3,2-*d*]thiazole (IIb).

To Ib (200 mg., 1.0 mmole) in acetic acid (3 ml.) was added bromine (160 mg., 1.0 mmole) in acetic acid (1 ml.) at 40° with rapid stirring. The reaction mixture was set aside for 10 minutes and then diluted with water (5 ml.). The solid was collected, washed with a small volume of cold aqueous ethanol, and the moist residue was recrystallized from ethanol-water 1:1 (10 ml., decolourizing carbon), yield 120 mg. (61%) of white, flat lustrous needles; R_f = 0.35, m.p. 214.5-215.5°; ^{1}H nmr (DMSO-d_6): δ = 2.18 (s, 3H, CH_3CO), δ = 7.33 (d, 1H, C_6-H), δ = 7.63 (d, 1H, C_5-H, $J_{5,6}$ = 5.13 Hz), δ = 12.24 (s broad, 1H, N*H*); ms m/e: 198 (33%; $[M^{\bullet}]^{+}$), 156 (100%; $[M\text{-}CH_2CO]^{+}$), 129 (17%; $[M\text{-}CH_2CO\text{-}HCN]^{+}$), 114 (2%), 113 (4%), 84 (4%), 70 (6%), 69 (11%), 53 (12%), 43 (50%); $[CH_3CO]^{+}$).

Anal. Calcd. for $C_7H_6N_2OS_2$: C, 42.4; H, 3.1; N, 14.1. Found: C, 42.5; H, 3.1; N, 14.1.

2-Ethoxycarbonylaminothieno[3,2-*d*]thiazole (IIc).

A. In Acetic Acid.

A solution of bromine (1.43 g., 8.9 mmoles) in acetic acid (3 ml.) was added dropwise with stirring at 50° to a slurry of Ic (2.03 g., 8.8 mmoles) in acetic acid (12 ml.). After 15 minutes, the mixture solidified and water (15 ml.) was added and the precipitated grayish solid was filtered, rinsed with water and a small volume of cold ethanol. Recrystallization from ethanol (100 ml./g., decolourizing carbon) gave 1.32 g. (66%) of fine white needles; R_f = 0,50, m.p. ~215° dec.; ^{1}H nmr (DMSO-d_6): δ = 1.27 (t, 3H, CH_3CH_2O), δ = 4.23 (q, 2H, CH_3CH_2O), δ = 7.28 (d, 1H, C_6-H), δ = 7.59 (d, 1H, C_5-H $J_{5,6}$ = 5.37 Hz), δ = 11.86 (s broad, 1H, N*H*); ms m/e: 228 (67%; $[M]^{+}$), 183 (5%; $[M\text{-}C_2H_5O]^{+}$), 182 (17%; $[M\text{-}C_2H_5OH]^{+}$), 169 (19%; $[M\text{-}HSCN]^{+}$), 156 (100%; $[M\text{-}C_2H_4CO_2]^{+}$), 155 (50%; $[M\text{-}C_2H_5OCO]^{+}$), 142 (3%), 129 (22%; $[M\text{-}C_2H_4OCO\text{-}HCN]^{+}$), 113 (13%), 96 (4%), 84 (9%), 70 (10%), 69 (23%), 53 (15%), 45 (17%).

Anal. Calcd. for $C_8H_8N_2O_2S_2$: C, 42.1; H, 3.5; N, 12.3. Found: C, 41.8; H, 3.6; N, 12.2.

B. In Trimethyl Phosphate.

Compound Ic (460 mg., 2.0 mmoles) in trimethyl phosphate (5 ml.) was treated with bromine (320 mg., 2.0 mmoles) in the same solvent (2 ml.) at room temperature with stirring. The reaction mixture became olive-green and a solid appeared. After standing in a cool place for one day, the precipitate was collected and washed with a few milliliters of trimethyl phosphate followed by cold ether. The yield of the crude product was 320 mg. (70%).

One recrystallization from ethanol (~25 ml.) gave 290 mg. of the pure product identical with the substance obtained in acetic acid (tlc, mass spectrum).

Attempted Cyclization of 2-Thienylthioureas (IIIa-c).

A. One Equivalent Bromine. The Monobromothienylthioureas (IVd-e).

Compounds IIIb and c, respectively, (0.01 mole) in acetic acid, enough to give a clear solution at 40° (30-50 ml.), was treated with bromine (1.60 g., 0.01 mole) in acetic acid (10 ml.) with rapid stirring at 40°. The dark reaction mixture was left for 1 hour and diluted with water (40 ml.). A solid separated gradually and after 2 hours the mixture was filtered and gray residue was repeatedly washed with a large volume of water and dried. Fractional crystallization from various solvents (Table 2) did not remove trace amounts of contaminating dibromo derivative completely.

B. Two Equivalents of Bromine. The Dibromothienylthioureas (IVa-c).

Compound IIIa-c (0.01 mole) was treated with bromine (3.20 g., 0.02 mole) as above at 60-70°. After 1 hour stirring, the precipitate was collected, washed with acetic acid and dried. The compounds IIIa-c were easily purified by recrystallization. The properties of the bromine-substituted 2-thienylthioureas IVa-e are summarized in Table 2.

Methyl 2-Acetylaminothieno[3,2-*d*]thiazole-5-carboxylate (IX).

A mixture of 2-acetylamino-5-chloro-4-thiazolecarboxaldehyde (32) (1.02 g., 5.0 mmoles) and methyl thioglycollate (1.5 g., 14 mmoles, 3 times excess) in dry dimethyl sulfoxide (5 ml.) was treated with triethylamine (2 ml.) with rapid stirring at ambient temperature. After the addition of the amine, the temperature was raised to 140° for 30 minutes and the initially yellow solution darkened. The cooled mixture was then diluted with water (100 ml.), and the precipitate was filtered off and rinsed with water, methanol and ether and dried. The residual powder weighed 650 mg. (51%). Recrystallization from 1,2-dichloroethane (100 ml., decolourizing carbon) gave short white needles; R_f = 0.43, m.p. 273-275°; ^{1}H nmr (DMSO-d_6): δ = 2.20 (s, 3H, CH_3CO), δ = 3.85 (s, 3H, $COOCH_3$), δ = 7.97 (s, 1H, C_6-H), δ = 12.40 (s broad, 1H, N*H*); ^{13}C nmr (DMSO-d_6, 90°): δ = 21.93 (CH_3CO), δ = 51.63 (CH_3O), δ = 123.04 (C_6), δ = 132.30, 133.83, 153.13, 161.15, 161.42, 168.65, $J_{C_6\text{-}H_6}$ = 174 Hz; ms m/e: 256 (28%; $[M^\cdot]^+$), 225 (5%; $[M\text{-}CH_3O]^+$), 214 (100%; $[M\text{-}CH_2CO]^+$), 213 (4%), 199 (1%), 183 (36%; $[M\text{-}CH_2CO\text{-}CH_3O]^+$), 156 (3%), 155 (5%), 154 (3%), 128 (1%), 127 (1%), 113 (7%), 85 (5%), 84 (3%), 83 (6%), 81 (3%), 70 (5%), 69 (11%), 53 (4%), 43 (64%; $[CH_3CO]^+$).

Anal. Calcd. for $C_9H_8N_2O_3S_2$: C, 42.2; H, 3.1; N, 10.9. Found: C, 42.2; H, 3.2; N, 10.9.

2-Acetylaminothieno[3,2-*d*]thiazole-5-carboxylic Acid (X).

A mixture of IX (210 mg., 0.82 mmoles), aqueous sodium hydroxide (5 ml., 2*M*) and methanol (5 ml.) was refluxed gently for 10 minutes. The clear solution was concentrated to 5 ml., diluted with water (5 ml.) and boiled for another 10 minutes. After cooling in ice, the yellow-brown reaction mixture was cautiously acidified with dilute hydrochloric acid and the solid acid was collected, washed with water and dried. The yield of crude product was 150 mg. (75%). In contrast to the methyl ester, the acid was unstable and could not be purified by crystallization or chromatography; R_f = 0, R_f (toluene-ethyl formate-formic acid, 5:4:1) = 0.33 m.p. ~290° dec.; ^{1}H nmr (DMSO-d_6): δ = 2.19 (s, 3H, CH_3CO), δ = 7.89 (s, 1H, C_6-H), δ = ~12.4 (s broad, ~2H, N*H* + COO*H*); ms m/e: 242 (25%; $[M^\cdot]^+$), 200 (98%; $[M\text{-}CH_2CO]^+$), 173 (6%; $[M\text{-}CH_2CO\text{-}HCN]^+$), 156 (7%; $[M\text{-}CH_2CO\text{-}CO_2]^+$), 97 (15%), 76 (17%), 69 (15%), 45 (18%), 44 (49%), 43 (100%; $[CH_3CO]^+$).

Anal. Calcd. for $C_8H_6N_2O_3S_2$: C, 39.7; H, 2.5; N, 11.6. Found: C, 39.2; H, 2.6; N, 11.5.

2-Acetylaminothieno[3,2-*d*]thiazole (IIb).

Crude X (8.0 mg., 0.033 mmole) in narrow glass tubes was immersed in a melting point apparatus pre-heated to 290°. On heating, the solid was observed to shrink and became dark and there was evolution of gas. After 1 minute the tubes were cooled and the contents were extracted with acetone. The dark extract was filtered, evaporated to dryness, and the tarry residue was subjected to repeated preparative tlc. The spot with R_f = 0.4 was eluted with acetone to give 1.5 mg. (23%) of a slightly coloured solid which was identical in all respects (^{1}H nmr, ir, ms and R_f-value) with IIb.

2-Aminothieno[3,2-*d*]thiazole (IId).

A mixture of crude IIa (6.7 g., 26 mmoles) 30% aqueous sulfuric acid (300 ml.) and ethanol (100 ml.) was refluxed with stirring. After 3 hours, the greenish suspension was concentrated to 300 ml. and refluxing was continued for 2 hours. (Further concentration of the reaction mixture raises the temperature and decreases the yield significantly). The mixture was chilled, diluted with water (250 ml.) and unchanged IIa (1.8 g., 7 mmoles) was recovered by filtration. The green solution was extracted with ether (3 x 100 ml. extract discarded), and the aqueous layer was made strongly alkaline with 40% aqueous sodium hydroxide while cooled below 40°. Extraction with ether (3 x 200 ml.) gave an almost colourless extract which was dried (magnesium sulfate) and evaporated to give 1.8 g. (61% calcd. on consumed IIa) of a yellow solid. One recrystallization from hexane-carbon tetrachloride 1:1 (150 ml., decolourizing carbon) gave the pure amine as white, shiny crystals, R_f = 0.25, m.p. 107.0-107.5°; ^{1}H nmr (d_6-acetone): δ = 6.61 (s broad, 2H, NH_2), δ = 7.07 (d, 1H, C_6-H), δ = 7.35 (d, 1H, C_5-H, $J_{5,6}$ = 5.22 Hz); ms m/e: 156 (100%; $[M]^+$), 129 (32%); $[M\text{-}HCN]^+$), 114 (6%; $[M\text{-}NH_2CN]^+$), 102 (2%), 97 (2%), 96 (3%), 88 (4%), 85 (2%), 84 (2%), 81 (2%), 80 (3%), 78 (4%), 76 (3%), 71 (4%), 70 (13%), 69 (32%), 53 (35%), 45 (12%).

Anal. Calcd. for $C_5H_4N_2S_2$: C, 38.4; H, 2.6; N, 17.9. Found: C, 38.3; H, 2.7; N, 17.9.

Thieno[3,2-*d*]thiazole (XIa).

A chilled solution of IId (0.62 g., 4.0 mmoles) in 25% aqueous hypophosphorous acid (10 ml.) was cautiously treated with sodium nitrite (0.35 g., 5.0 mmoles) in water (2 ml.). The dark mixture was stirred at room temperature for 1 hour, made alkaline with 2*M* sodium hydroxide, and extracted with ether (3 x 50 ml.). The dark red extract was dried (magnesium sulfate) and evaporated under reduced pressure to give a reddish, oily residue with a smell reminiscent of quinoline. Column chromatography on silica gel (dichloromethane-acetone 30:1) gave a yellow oil (0.44 g., 78%). Distillation through a short column (bath temperature 65-75°/1 mm Hg) yielded an almost colourless volatile liquid Rf = 0.52; glc (SE 30, 7.5% on Chromosorb W 120° carrier gas nitrogen) showed a single peak; ^{1}H nmr (d_6-acetone): δ = 7.52 (d, 1H, C_6-H), δ = 7.72 (q, 1H, C_5-H), δ = 9.11 (d, 1H, C_2-H), $J_{5,6}$ = 5.35 Hz, $J_{2,5}$ = 1.10 Hz; ^{13}C nmr (d_6-acetone): δ = 119.19 (C_6), δ = 130.57 (C_5), δ = 130.67 (quaternary carbon at S), δ = 157.00 (C_2), δ = 162.46 (quaternary carbon at N), $J_{C_6\text{-}H_6}$ = 172 Hz, $J_{C_5\text{-}H_5}$ = 189 Hz, $J_{C_2\text{-}H_2}$ = 216 Hz, $J_{C_6\text{-}H_5}$ = 3.7 Hz,

$J_{C_5\text{-}H_6}$ = 7.3 Hz; uv (methanol): λ max nm (log ε), 226 (4.20), 249 sh (3.47; ir (liq. pl.): 3103, 3080, 1493, 1434, 1419, 1409, 1362, 1220, 1121, 1080, 1009, 846, 791, 729, 661 cm^{-1}; ms (glc, SE 30, 120°, carrier gas helium): m/e: 141 (100%; $[M^{\cdot}]^+$), 114 (23%; $[M\text{-}HCN]^+$), 97 (13%; $[M\text{-}CS]^+$), 96 (4%; $[M\text{-}CHS]^+$), 88 (6%), 82 (3%), 81 (3%), 76 (3%; $[CS_2^{\cdot}]^+$), 71 (15%), 70 (18%), 69 (44%), 65 (2%; $[M\text{-}CS_2]^+$), 64 (2%), 58 (2%), 57 (3%), 56 (4%), 45 (19%), 44 (5%), 38 (6%), 37 (5%).

Anal. Calcd. for $C_5H_3NS_2$: C, 42.5; H, 2.1; N, 9.9. Found: C, 42.1; H, 2.2; N, 10.0. M^+ (peak matching) = 140.973±0.002. Calcd. for $C_5H_3NS_2$: M^+ = 140.971.

5-Nitrothieno[3,2-*d*]thiazole (XIb).

Crude XIa (310 mg., 2.2 mmoles) in acetic anhydride (4 ml.) was chilled to +5° and a solution of cupric nitrate trihydrate (290 mg., 1.1 mmoles) in acetic anhydride (4 ml.) was added dropwise with stirring during 15 minutes. The reaction was allowed to continue for 2 hours at 25° and the brown slurry was quenched in ice-water (100 ml.) and neutralized with solid sodium bicarbonate (20 g.). Shaking the mixture with dichloromethane (3 x 50 ml.) gave a bright yellow extract. Drying (magnesium sulfate) and evaporating to dryness gave an orange solid residue (210 mg. 51%), essentially pure on tlc. Recrystallization from acetone (15 ml. decolourizing carbon) gave yellow needles R_f = 0.56, m.p. ~200° dec.; ^1H nmr (d_6-acetone): δ = 8.51 (s, 1H, C_6-H), δ = 9.34 (s, 1H, C_2-H), ^{13}C nmr (DMSO-d_6, 50°): δ = 121.09 (C_6), δ = 160.74 (C_2) $J_{C_6\text{-}H_6}$ = 181 Hz, $J_{C_2\text{-}H_2}$ = 219 Hz; uv (methanol): λ max nm (log ε), 238 (4.03), 310 sh (3.76), 339 (3.82), 458 (3.53); ms m/e: 186 (64%; $[M^{\cdot}]^+$), 170 (3%; $[M\text{-}O]^+$), 156 (19%; $[M\text{-}NO]^+$), 140 (5%; $[M\text{-}NO_2]^+$), 128 (9%; $[M\text{-}NO\text{-}CO]^+$), 113 (22%; $[M\text{-}NO_2\text{-}HCN]^+$), 112 (4%), 101 (4%), 96 (3%), 94 (3%), 88 (2%), 85 (2%), 83 (2%), 76 (4%), 69 (100%), 68 (8%), 57 (4%), 56 (5%), 52 (3%), 45 (15%), 37 (6%).

Anal. Calcd. for $C_5H_2N_2O_2S_2$: C, 32.2; H, 1.1; N, 15.0. Found: C, 32.3; H, 1.1; N, 14.9.

5-Bromothieno[3,2-*d*]thiazole (XIc).

A.

A stirred solution of XIa (110 mg., 0.78 mmole) in dichloromethane (2 ml.) was treated with solid *N*-bromosuccinimide (150 mg., 0.84 mmole) at room temperature. After 1 hour the mixture was kept in a cool place overnight. The dark slurry was chromatographed through a short silica gel column with ether as eluant and the crude non-polar fraction was further purified with tlc (petroleum ether: ether 1:1) to give 80 mg. (47%) of pure product. Recrystallization from hexane (1 ml. of decolourizing carbon) gave white needles, R_f = 0.60, m.p. 122-123°; ^1H nmr (d_6-acetone): δ = 7.66 (s, 1H, C_6-H), δ = 9.17 (s, 1H, C_2-H); ^{13}C nmr (d_6-acetone, 50°): δ = 115.63 (C_5), δ = 123.09 (C_6), δ = 130.74 (quaternary carbon at S), δ = 157.11 (C_2), δ = 160.95 (quaternary carbon at N), $J_{C_6\text{-}H_6}$ = 177 Hz, $J_{C_2\text{-}H_2}$ = 216 Hz; uv (methanol): λ max nm (log ε), 232 (4.38), 255 sh (3.67); ms m/e: [[221 (100%)/219 (93%); $[M^{\cdot}]^+$]], [[194 (8%)/192 (8%); $[M\text{-}HCN]^+$]], 140 (46%; $[M\text{-}Br]^+$), 113 (61%; $[M\text{-}Br\text{-}HCN]^+$), 112 (7%), 96 (8%), 88 (5%), 81 (7%), 76 (5%), 69 (71%), 68 (12%).

Anal. Calcd. for $C_5H_2BrNS_2$: C, 27.3; H, 0.9; N, 6.4. Found: C, 27.1; H, 0.8; N, 6.3.

B.

To a stirred solution of XIa (17.2 mg., 0.12 mmoles) in dichloromethane 0.5 ml. was added freshly prepared pyridine perbromide (35 mg., 0.15 mmole) in one portion. After stirring one night at room temperature, the brown-yellow solution was purified as above to give 18.0 mg. (67%) of a light yellow solid. The ^1H nmr spectrum was identical with that of XIc as prepared above.

Acknowledgements.

The author is indebted to Dr. Ulf Obenius for assistance in recording the nmr spectra and wishes to thank Professor G. Bendz for many helpful and stimulating discussions. This work was facilitated by a scholarship from The Committee for Bengt Lundquist Memorial Fund and by grants from the Faculty of Mathematics and Natural Sciences, University of Uppsala. Support from the Swedish Natural Science Research Council (G. Bendz) is gratefully acknowledged.

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