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The Chemistry of 1,1-Dithiolates

2.* Thieno-1,2,3-triazines by Diazotation of 3-Aminothiophene-2- and 4-carboxamides

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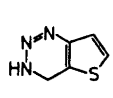
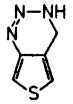
A series of thieno[3,2-e]-3,4-dihydro-1,2,3-triazin-4-ones (V) and thieno[3,4-e]-3,4-dihydro-1,2,3-triazin-4-ones (VI) were prepared by diazotation of 3-aminothiophene-2-carboxamides (III) and 4-aminothiophene-3-carboxamides (IV), respectively, both obtained by cyclization of 2-cyanoethylene-1,1-dithiolates with α-halogenocarbonyl compounds. Characteristic differences between the two systems were found in the position of the long-wavelength UV absorption maximum and the acidity of the triazine ring proton. The latter property was reflected in the ^{1}H NMR signal from this proton.

As a part of the study of the use of ethylene-1,1-dithiolates as precursors for various heterocyclic systems [1] this paper deals with the preparation of some derivatives of the two new ring systems, thieno[3,2-e]-3,4-dihydro-1,2,3-triazine (I) and thieno[3,4-e]-3,4-dihydro-1,2,3-triazine (II). The 1,2,3-triazin-4-one system, fused to aromatic rings, is generally obtained by the diazotation of *o*-aminoarenecarboxamides as first reported by Weddige and Finger.[2] This



I



II

synthesis has also been applied successfully to heteroaromatic aminocarboxamides, *e.g.* in the thiazole [3] and pyrazole [4] series. We have now found that its application to a series of both 3-aminothiophene-2-carboxamides

* For previous paper in this series: see Ref. 1.

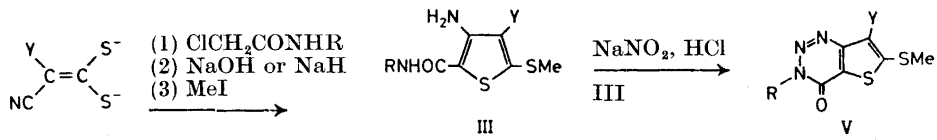
Table 1. Analytical data for thienotriazines (V and VI).

Compound	Formula	Yield (%)	M.p. (°C)	Analyses (% C, H, N)
Va	$C_9H_9N_3O_3S_2$	65	170[a]	Found: 39.92; 3.33; 15.24 Calc.: 39.84; 3.34; 15.49
Vb	$C_7H_4N_4OS_2$	57	190[a]	Found: 37.32; 1.83; 25.10 Calc.: 37.49; 1.80; 24.99
Vc	$C_8H_6N_4OS_2$	80	179 – 180	Found: 40.29; 2.55; 23.42 Calc.: 40.32; 2.53; 23.51
Vd	$C_8H_8N_4O_2S_2$	66	225[a]	Found: 37.42; 3.26; 21.93 Calc.: 37.49; 3.14; 21.86
Ve	$C_8H_8N_4O_2S_2$	78	302 – 305	Found: 37.42; 3.18; 21.90 Calc.: 37.49; 3.14; 21.86
VIa	$C_9H_9N_3O_3S_2$	81	210[a]	Found: 39.95; 3.46; 15.34 Calc.: 39.84; 3.34; 15.49
VIb	$C_8H_7N_3O_2S_2$	74	220[a]	Found: 39.58; 2.97; 17.39 Calc.: 39.82; 2.92; 17.41
VIc	$C_{13}H_9N_3O_2S_2$	80	220[a]	Found: 51.41; 3.05; 13.64 Calc.: 51.47; 2.99; 13.85
VId	$C_8H_8N_4O_2S_2$	28	300 – 303	Found: 37.41; 3.20; 21.68 Calc.: 37.49; 3.14; 21.86
VIe	$C_8H_8N_4O_2S_2$	2	260[a]	Found: 37.38; 3.08; 21.82 Calc.: 37.49; 3.14; 21.86
VIf	$C_9H_9N_3O_3S_2$	48	228 – 229	Found: 39.85; 3.39; 15.39 Calc.: 39.84; 3.34; 15.49

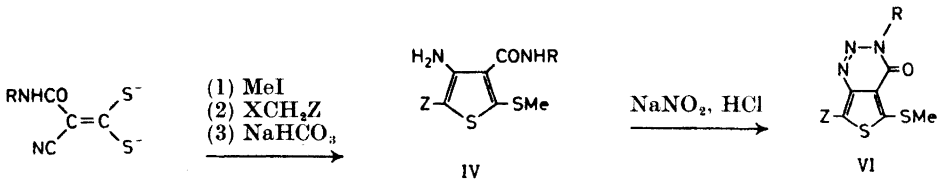
[a] Approximate decomposition point; ± 3°C, determined on a Kofler Heizbank as the lowest temperature at which the substance underwent sudden decomposition.

(IIIa-e) and 4-aminothiophene-3-carboxamides (IVa-f) resulted in cyclization to give, respectively, Va-e and VIa-f (Table 1).

The aminothiophenecarboxamides were prepared from 2-cyanoethylene-1,1-dithiolates by alkylation with an α-halogenocarbonyl compound followed by base-induced cyclization.[5,6] A 2-carboxamide group was introduced by alkylation with chloroacetamide, a 3-carboxamide group by the use of 2-carbamoyl-2-cyanoethylene-1,1-dithiolate as starting material. The reaction sequences leading to V and VI are outlined below.



III and V	a	b	c	d	e
Y	CO_2Et	CN	CN	CONHMe	$CONH_2$
R	H	H	Me	N	Me



IV and VI[a]	a	b	c	d	e	f
Z	CO_2Et	COMe	COPh	$CONH_2$	CONHMe	CO_2Me
R	H	H	H	Me	H	Me

[a] IVd=IIId and IVe=IIIe.

In agreement with recent reports on the benzo-1,2,3-triazine system,[7–12] we assign the lactam structures, V and VI, to the diazotation products. For Vc, the assignment is unambiguous since this compound was prepared from the *N*-methylamide, IIIc. The fact that the electronic spectra of compounds Va, b, d, and e are very similar to that of Vc (Table 2) indicates that the same conjugated system is present in all of the compounds V and thus supports the structural assignment. In the same way, compounds VI could be correlated to VIf which structure likewise is defined by its synthesis.

A comparison of compounds V and VI revealed two properties which remained almost constant inside each series but varied from one series to the

Table 2. Spectroscopic data for the thienotriazines, V and VI.

Compound	Substituents		^{1}H NMR[a] (ring N*H*)	UV/VIS[b] (λ_{max}(nm), log ε)
Va	Y=CO_2Et	R=H	15.2–15.5	306, 3.96
Vb	Y=CN	R=H	15.0–15.4	303, –[c]
Vc	Y=CN	R=Me	–	308, –[c]
Vd	Y=CONHMe	R=H	15.3–15.8	309, –[c]
Ve	Y=$CONH_2$	R=Me	–	310, –[c]
VIa	Z=CO_2Et	R=H	14.63	383, 3.98
VIb	Z=COMe	R=H	14.57	394, 3.99
VIc	Z=COPh	R=H	14.65	399, 4.07
VId	Z=$CONH_2$	R=Me	–	396, 3.85
VIe	Z=CONHMe	R=H	14.47	392, 3.83
VIf	Z=CO_2Me	R=Me	–	385, 3.94

[a] Recorded on a Varian A 60 A instrument (DMSO-d_6; 40°C); chemical shifts are given in ppm relative to TMS as internal standard.

[b] Recorded on a Unicam SP 1800 spectrophotometer (dioxan solution). Additional maxima at 284±10 and 245±10 nm were observed for both series.

[c] Occurs as a shoulder on the 284 nm band.

other and which therefore can be used to differentiate between V and VI: (1) The long wavelength absorption maximum in the electronic spectra is found inside a narrow range around 305 nm for (V), but around 390 nm for VI (Table 2). Accordingly, (V) are colourless compounds whereas VI are intensely yellow. Even more characteristic of VI is a strong yellow fluorescence which make them observable at a very low concentration. (2) Both V and VI are acidic compounds when the triazine ring contains an *NH*-group (R=H) but V are stronger acids than VI. The p*K*a-value for Va, determined as the point of half neutralization in 50 % aqueous ethanol, is 6.6; that of the isomer VIa is 8.4. The difference in acidity is reflected in the ^{1}H NMR spectra of V and VI. The ring-*NH* signal of the more acidic V is found *ca.* 0.8 ppm downfield from that of the less acidic VI (Table 2).

The diazotation of the two 3-aminothiophene-2,4-dicarboxamides, IIId and IIIe, was investigated in order to obtain an estimate of the relative rates of cyclization to the 2- and 4-substituent, respectively. Starting materials with one *N*-substituted amide group were used since the reaction products could then be separated by extraction with base of the acidic product (Vd and VIe, respectively) from the non-acidic one (VId and Ve, respectively). At the same time the identities of the products were established by the separation procedure.

The results (64 % of Vd and 22 % of VId from IIId; 78 % of Ve and *ca.* 2 % of VIe from IIIe) indicate that cyclization to the 2-substituent is preferred and, further, that it is facilitated by *N*-methylation of the donor amide group.

EXPERIMENTAL

Dithiolates. Pure disodium salts were used as starting materials; disodium 2,2-dicyanoethylene-1,1-dithiolate trihydrate and disodium 2-cyano-2-ethoxycarbonylethylene-1,1-dithiolate pentahydrate were prepared by the Söderbäck procedure [13,6] and disodium 2-carbamoyl-2-cyanoethylene-1,1-dithiolate trihydrate [14] and 2-cyano-2-(*N*-methylcarbamoyl)ethylene-1,1-dithiolate pentahydrate (Found: C 19.49; H 4.33; N 8.84. Calc. for $C_5H_{14}N_2O_8S_2Na_2$: C 19.48; H 4.55; N 9.09) by a modification of this procedure.[15]

3-Aminothiophene-2-carboxamides (III) and 4-aminothiophene-3-carboxamides (IV). Satisfactory elemental analyses, IR- and ^{1}H NMR-spectra were obtained for all compounds described. Typical examples are:

Ethyl 4-amino-5-carbamoyl-2-(methylthio)thiophene-3-carboxylate (IIIa). Chloroacetamide (5 mmol) followed by methyl iodide (5 mmol) were added to the 2-cyano-2-ethoxycarbonylethylene-1,1-dithiolate (5 mmol) in dimethyl formamide (5 ml). The mixture was stirred for 5 min after the addition of each halide and then diluted with water (100 ml) and heated to 70°C. Potassium carbonate (5 mmol) was added to induce the cyclization and the solution was left to cool. The product was filtered from the cold solution and recrystallized from 1-propanol to give IIIa. Yield 560 mg, 42 %; m.p. 189–192°C. (Found: C 41.50; H 4.67; N 11.02. Calc. for $C_9H_{12}N_2O_3S_2$: C 41.53; H 4.61; N 10.78.)

5-Acetyl-4-amino-2-(methylthio)thiophene-3-carboxamide (IVb). Methyl iodide (5 mmol), followed by chloroacetone (5 mmol), was added to the 2-carbamoyl-2-cyanoethylene-1,1-dithiolate (5 mmol) in DMF (5 ml). Water (30 ml) was added and insoluble material was filtered off, dried and recrystallized from ethanol to give IVb. Yield 605 mg, 53 %; m.p. 180–181°C. (Found: C 41.63; H 4.34; N 12.18. Calc. for $C_8H_{12}N_2O_2S_2$: C 41.74; H 4.35; N 12.17.)

Compound IIId (=IVd, yield 65 %, m.p. 240–242°C) was prepared in the same way as IIIa. In the preparation of IIIb (yield 78 %, m.p. 233–235°C) 1 ml 2 M sodium hydroxide, and in those of IIIc (71 %, m.p. 153–155°C) and IIIe (=IVe, 66 %, m.p. 238–240°C) sodium hydride (5 mmol), was added before the methyl iodide. Compound

IVc (59 %, m.p. 186 – 188°C) was prepared in the same manner as IVb; in the preparations of IVa (64 %, m.p. 183 – 185°C) and IVf (58 %, m.p. 147 – 149°C) sodium hydrogencarbonate was added to induce the cyclization.

Thienotriazines (V and VI). The aminothiophenecarboxamide (1.0 mmol) was dissolved or suspended in conc. hydrochloric acid (20 ml). Sodium nitrite (*ca.* 1.1 ml 1 M aqueous solution) was added at −10°, and the mixture was stirred for 10 min. Then ice (*ca.* 100 g) was added and the solution was left for 2 h when the product was filtered off and washed with water. The thienotriazines were recrystallized from ethanol, except for those containing an amide group for which dioxan-water was used. Analytical data for the pure compounds are given in Table 1. *Separation of Vd and VId:* The crude product from 1 mmol of IIId was dissolved in DMF (at *ca.* 60°) and 0.5 ml 2 M NaOH was added, followed by 100 ml of water. The nonacidic VId was filtered from the cooled mixture and the acidic Vd was precipitated from the filtrate with hydrochloric acid. The same method was used to separate VIe from Ve.

REFERENCES

1. Henriksen, L. and Autrup, H. *Acta Chem. Scand.* **24** (1970) 2629.
2. Weddige, A. and Finger, J. *J. prakt. Chem.* **35** (1887) 262.
3. Wiedel, H. and Niemilowicz, L. *Monatsh.* **16** (1895) 746.
4. Justoni, R. and Fusco, R. *Gazz. Chim. Ital.* **68** (1938) 59.
5. Compper, R., Kutter, E. and Töpfl, W. *Ann.* **659** (1962) 90.
6. Jensen, K. A. and Henriksen, L. *Acta Chem. Scand.* **22** (1968) 1107.
7. Wagner, G. and Gentzsch, H. *Pharmazie* **23** (1968) 628.
8. Gibson, M. S. and Murray, A. W. *J. Org. Chem.* **27** (1962) 4083.
9. Sieper, H. *Chem. Ber* **100** (1967) 1646.
10. Herlinger, H. *Angew. Chem.* **76** (1964) 437.
11. Smalley, R. K. and Suschitzky, H. *Tetrahedron Letters* **1966** 3465.
12. Jacini, G. *Gazz. Chim. Ital.* **77** (1947) 308.
13. Söderbäck, E. *Acta Chem. Scand.* **17** (1962) 362.
14. Söderbäck, E. *Acta Chem. Scand.* **24** (1970) 228.
15. Henriksen, L. and Baltzer, B. *To be published.*

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