The Reactivity of the A-CH=N-NR-CX-B System. 1,3,4-Oxadiazoles and 2,3,4,5-Tetrahydro-1,2,4-triazin-3-ones Through the 1-5 and 1-6 Cyclization Reactions of α-Thienylglyoxal Monosemicarbazones

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The factors influencing the reactivity of α-thienylglyoxal monosemicarbazones when treated with cyclizing reagents (bromine/sodium acetate and hydrobromic acid in acetic acid) were investigated. Depending on the experimental conditions, on the position of the substituent on the semicarbazide residue, and on the cyclizing agent, the substrates **1a-e** give the semicarbazone bromides **2a-b**, **5**, the 1,3,4-oxadiazoles **3a-c**, the 1,2,4-triazine **11** and the 2,3,4,5-tetrahydro-1,2,4-triazine-3-ones **6**, **8** and **9**. Compound **6** by thermolysis undergoes ring contraction in the Δ^2-1,3,4-oxadiazoline **12**, while treatment with base involves the conversion of **6** into 1,2,4-triazol-5-one **13**. Ir, nmr and mass spectra support the reported structures.

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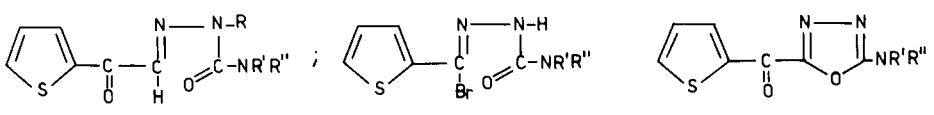
Continuing our studies on the reactivity of the A-CH=N-NR-CX-B system (1), we have examined the behaviour of monosemicarbazone derivatives of α-thienylglyoxal **1a-e** to the action of reactants (bromine-sodium acetate in acetic acid, hydrobromic acid-acetic acid) which promote cyclization. Our studies were aimed at elucidating how the course of the reaction is influenced by the following factors: (i) Acidity of the reaction medium, (ii) substituents R, R′, R″ at the semicarbazide residue, and (iii) the change of A from previously examined groups (2) to the thenoyl group. The carbonyl function of the latter, in fact, being neighbouring to a methine proton =CH-, can be envisaged to compete in cyclization reactions giving rise to 1-5 as well as to 1-6 ring closure; furthermore, one might envisage that the thenoyl group, owing to the marked aromatic character of the thiophene ring, can itself undergo competitive reaction with the same reactant which promotes cyclization (*e.g.* with bromine).

The action of the bromine-sodium acetate mixture on the substrates **1a-e** produces different reactions depending upon the substitution on the semicarbazide residue and on the experimental conditions. At room temperature, the substrates **1a** and **1b** give the semicarbazone bromides **2a** and **2b**, intermediates in the 1,3,4-oxadiazole cyclization (3). The triethylamine action in fact, changes them quantitatively in the 1,3,4-oxadiazoles **3a** and **3b**, respectively. Performing the reaction at 120°, **1a** and **1b** give **3a** and **3b** directly. In the case of **1c**, we could not isolate the intermediate **2c**: also at room temperature we did obtain the 1,3,4-oxadiazole **3c**. On the other hand, compound **1d** was recovered unchanged. From the compound **1e** we obtained the semicarbazone **4** brominated in the thiophene ring, the dibrominated semicarbazone **5**, and a dibrominated compound $C_9H_9Br_2N_3O_2S$ to which, from the chemical and spectroscopic data, we assign the structure of 2,4-dimethyl-5-hydroxy-5-(5-bromo-2-thienyl)-6-bromo-2,3,4,5-tetrahydro-1,2,4-triazin-3-one **6**. The product is soluble in aqueous sodium hydroxide and precipitates unchanged after acidification. The ir spectrum of **6** exhibits bands at 3185 cm^{-1} (OH) and 1631 cm^{-1} (C=O); in the starting compound **1e** two carbonyl bands can be seen at 1681 and 1645 cm^{-1}. The mass spectrum of **6** shows characteristic patterns for the proposed structure, *e.g.*: 381 $(M)^+$, 364 $(M\text{-}OH)^+$, 220 $(M\text{-}BrC_4H_2S)^+$, 189 $(BrC_4H_2SCO)^+$ (see Experimental). The nmr spectrum, besides the 5-substituted thiophene ring protons signals [just as in **4** and **5**, deduced from the $J_{3,4}$ values

SCHEME I



1a-e ; 2a-b ; 3a-c

a : R = R′ = R″ = H
b : R = R′ = H ; R″ = CH_3
c : R = H ; R′ = R″ = CH_3
d : R = CH_3 ; R′ = R″ = H
e : R = R′ = CH_3 ; R″ = H

a : R′ = R″ = H
b : R′ = H ; R″ = CH_3
c : R′ = R″ = CH_3

Table I

Physical Data

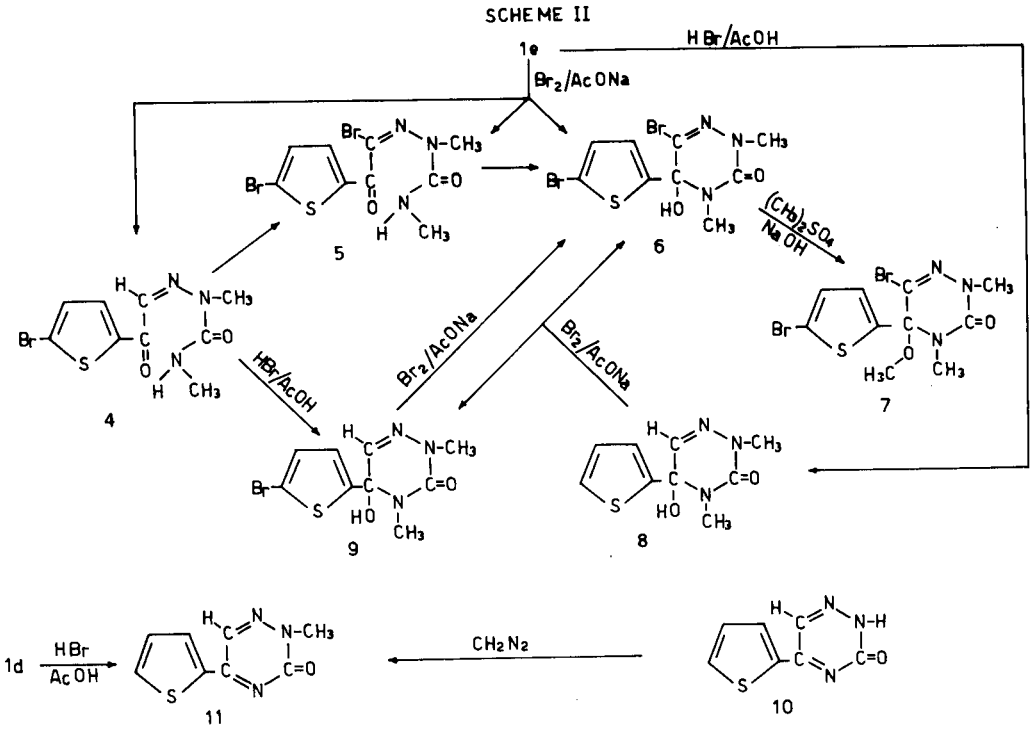
Compound	M.p. °C (solvent)	Formula	*Anal.*	C (%)	H (%)	N (%)	Br (%)
1a	222-224 (ethanol) (a)	$C_7H_7N_3O_2S$	Calcd.	42.64	3.58	21.32	
			Found	42.60	3.38	21.14	
1b	177-178 (ethyl acetate)	$C_8H_9N_3O_2S$	Calcd.	45.50	4.30	19.90	
			Found	45.35	4.40	19.88	
1c	194-195 (ethanol)	$C_9H_{11}N_3O_2S$	Calcd.	48.00	4.92	18.66	
			Found	47.84	5.02	18.60	
1d	170-172 (ethanol)	$C_8H_9N_3O_2S$	Calcd.	45.50	4.30	19.90	
			Found	45.60	4.28	20.10	
1e	131-132 (benzene-ligroin)	$C_9H_{11}N_3O_2S$	Calcd.	48.00	4.92	18.66	
			Found	47.86	4.90	18.55	
2a	189-191 (methanol)	$C_7H_6BrN_3O_2S$	Calcd.	30.45	2.19	15.22	28.94
			Found	30.64	1.98	15.34	29.02
2b	146-147 (benzene)	$C_8H_8BrN_3O_2S$	Calcd.	33.11	2.78	14.48	27.54
			Found	32.94	2.81	14.50	27.44
3a	232-233 (acetic acid)	$C_7H_5N_3O_2S$	Calcd.	43.08	2.58	21.54	
			Found	42.94	2.50	21.64	
3b	203 (acetic acid)	$C_8H_7N_3O_2S$	Calcd.	45.94	3.37	20.09	
			Found	46.02	3.48	19.85	
3c	135 (carbon tetrachloride)	$C_9H_9N_3O_2S$	Calcd.	48.43	4.06	18.83	
			Found	48.60	3.99	19.02	
4	167-168 (ethanol)	$C_9H_{10}BrN_3O_2S$	Calcd.	35.54	3.31	13.82	26.27
			Found	35.38	3.40	14.01	26.45
5	110-111 (ligroin)	$C_9H_9Br_2N_3O_2S$	Calcd.	28.22	2.37	10.97	41.72
			Found	27.98	2.50	11.10	41.55
6	181-182 (acetonitrile)	$C_9H_9Br_2N_3O_2S$	Calcd.	28.22	2.37	10.97	41.72
			Found	28.01	2.15	11.08	41.82
7	oil	$C_{10}H_{11}Br_2N_3O_2S$	Calcd.	30.24	2.79	10.58	40.25
			Found	30.11	2.85	10.61	40.08
8·HBr	215 (acetic acid)	$C_9H_{11}N_3O_2S$·HBr	Calcd.	35.30	3.95	13.73	26.10
			Found	35.50	4.02	13.80	25.92
8	138-139 (water)	$C_9H_{11}N_3O_2S$	Calcd.	48.00	4.92	18.66	
			Found	47.94	5.15	18.60	
9	138-139 (benzene ligroin)	$C_9H_{10}BrN_3O_2S$	Calcd.	35.54	3.31	13.82	26.27
			Found	35.65	3.12	14.02	26.30
10	293-295 (b) (ethanol-acetic acid)	$C_7H_5N_3OS$	Calcd.	46.93	2.81	23.46	
			Found	47.05	2.75	23.50	
11	240-241 (methanol)	$C_8H_7N_3OS$	Calcd.	49.74	3.65	21.76	
			Found	49.91	3.64	21.80	
12·HBr	259-261 (water)	$C_9H_8BrN_3O_2S$·HBr	Calcd.	28.22	2.37	10.97	41.72
			Found	28.10	2.46	11.15	41.58
12	165-166 (ethanol)	$C_9H_8BrN_3O_2S$	Calcd.	35.78	2.67	13.91	26.45
			Found	35.67	2.70	13.82	26.29

(a) Reference 9 reports m.p. 222° dec. (b) Reference 4 reports m.p. 273-275° dec.

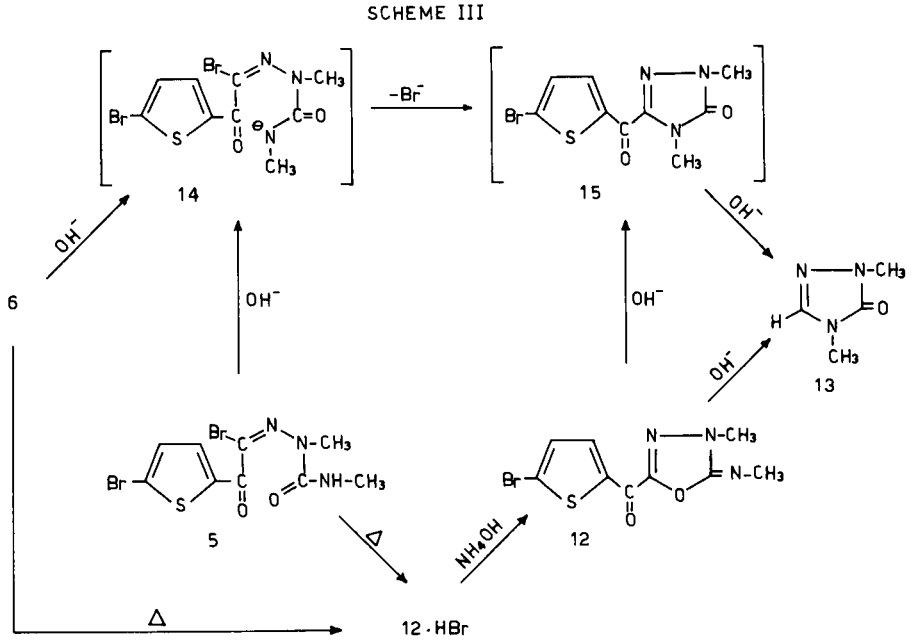
(see Table II)], exhibits two singlets at 2.76 and 3.32 δ for the two methyls N-CH_3 and a singlet at 8.15 δ (exchangeable with deuterium oxide) for the OH proton. In **1e**, beside the thiophene proton signals, can be seen a singlet for the methine =CH- proton, a singlet for the N-CH_3 protons, and signals for the $NHCH_3$ system (see Table II). The methylation of **6** by dimethyl sulfate in aqueous sodium hydroxide gives the corresponding *O*-methyl derivative **7**.

The formation of the triazine **6** can be explained with the sequence of reactions reported in Scheme II. The detection in the reaction mixture of compounds **4** and **5** (rather than **8** and **9**) led us to consider them as intermediates in the cyclization reaction. This would proceed

SCHEME II



SCHEME III



through an intramolecular nucleophilic attack of the methylamide nitrogen atom of the halogenide **5** on the carbonyl carbon atom. In agreement with this, by allowing the halogenide **5** to stand for a long time, or by treating substrates **1e** or **4** with bromine-sodium acetate with stirring for many days, we obtained only the triazine **6**.

The spontaneous cyclization of **5** to **6** led us to consider the possibility of other 1-6 cyclization reactions of the same type. In this connection we tested the behaviour of the substrates **1a-e** and **4** towards an hydrobromic acid-acetic acid mixture. We have observed that compounds **1a**, **1b**, and **1c** undergo hydrolysis to unidentified products only. At the same time, compound **1d**, as expected (4), gave the 1,2,4-triazine cyclization to **11**, which has also been obtained by methylation of **10**.

The substrate **1e** gives a product melting at 138-139° having the same elemental composition of the starting product. It is soluble in aqueous sodium hydroxide and

Table II

Spectrophotometric Data

Compound	Ir (cm^{-1}) NH, NH_2	Ir (cm^{-1}) C=O	Nmr Solvent	Chemical Shift, ppm δ
1a	3401, 3175-3077	1709, 1621	DMSO-d_6	6.65 (s, 2H, NH_2), 7.24 (q, 1H, H_4, J = 5.1 Hz, J = 3.9 Hz), 7.65 (s, 1H, CH), 8.07 (q, 1H, H_5, J = 5.1 Hz, J = 1.1 Hz), 8.19 (q, 1H, H_3, J = 3.9 Hz, J = 1.1 Hz), 11.75 (br. s, 1H, NH)
1b	3401	1686, 1623	Deuteriochloroform	2.95 (d, 3H, $NHCH_3$, J = 4.8 Hz), 6.17 (br. s, 1H, $NHCH_3$), 7.11 (q, 1H, H_4, J = 5.4 Hz, J = 4.1 Hz), 7.64 (s, 1H, CH), 7.72 (q, 1H, H_5, J = 5.4 Hz, J = 1.1 Hz), 8.04 (q, 1H, H_3, J = 4.1 Hz, J = 1.1 Hz), 10.72 (br. s, 1H, NH)
1c	3205	1669, 1631	DMSO-d_6	2.95 [s, 6H, $N(CH_3)_2$], 7.25 (q, 1H, H_4, J = 5.1 Hz, J = 3.9 Hz), 7.92 (s, 1H, CH), 8.05 (q, 1H, H_5, J = 5.1 Hz, J = 1.1 Hz), 8.39 (q, 1H, H_3, J = 3.9 Hz, J = 1.1 Hz), 11.17 (s, 1H, NH)
1d	3425, 3205	1701, 1623	DMSO-d_6	3.31 (s, 3H, NCH_3), 6.92 (br. s, 2H, NH_2), 7.27 (q, 1H, H_4, J = 5.4 Hz, J = 4.1 Hz), 7.47 (s, 1H, CH), 8.02 (q, 1H, H_3, J = 4.1 Hz, J = 1.1 Hz), 8.18 (q, 1H, H_5, J = 5.4 Hz, J = 1.1 Hz)
1e	3356	1681, 1645	Deuteriochloroform	2.97 (d, 3H, $NHCH_3$, J = 4.8 Hz), 3.36 (s, 3H, NCH_3), 6.58 (br. s, 1H, $NHCH_3$), 7.14 (q, 1H, H_4, J = 5.3 Hz, J = 3.7 Hz), 7.24 (s, 1H, CH), 7.70 (q, 1H, H_5, J = 5.3 Hz, J = 1.3 Hz), 8.03 (q, 1H, H_3, J = 3.7 Hz, J = 1.3 Hz)
2a	3448, 3155-3086	1748, 1642	DMSO-d_6	6.95 (br. s, 2H, NH_2), 7.26 (q, 1H, H_4, J = 5.3 Hz, J = 3.9 Hz), 8.13 (q, 1H, H_5, J = 5.3 Hz, J = 1.1 Hz), 8.41 (q, 1H, H_3, J = 3.9 Hz, J = 1.1 Hz), 10.55 (s, 1H, NH)
2b	3413, 3145	1681, 1653	Deuteriochloroform	2.97 (d, 3H, $NHCH_3$, J = 4.8 Hz), 6.75 (br. s, 1H, $NHCH_3$), 7.12 (q, 1H, H_4, J = 4.9 Hz, J = 3.9 Hz), 7.75 (q, 1H, H_5, J = 4.9 Hz, J = 1.2 Hz), 8.08 (q, 1H, H_3, J = 3.9 Hz, J = 1.2 Hz), 8.70 (s, 1H, NH)
3a	3322, 3125	1664	DMSO-d_6	7.33 (q, 1H, H_4, J = 5.0 Hz, J = 3.9 Hz), 8.04 (s, 2H, NH_2), 8.22 (q, 1H, H_5, J = 5.0 Hz, J = 1.1 Hz), 8.52 (q, 1H, H_3, J = 3.9 Hz, J = 1.1 Hz)
3b	3268	1618	DMSO-d_6	2.98 (d, 3H, $NHCH_3$, J = 4.6 Hz), 7.34 (q, 1H, H_4, J = 5.1 Hz, J = 3.9 Hz), 8.25 (q, 1H, H_5, J = 5.1 Hz, J = 1.1 Hz), 8.39 (br. s, 1H, $NHCH_3$), 8.50 (q, 1H, H_3, J = 3.9 Hz, J = 1.1 Hz)
3c		1626	DMSO-d_6	3.13 [s, 6H, $N(CH_3)_2$], 7.30 (q, 1H, H_4, J = 5.1 Hz, J = 4.1 Hz), 8.17 (q, 1H, H_5, J = 5.1 Hz, J = 1.1 Hz), 8.45 (q, 1H, H_3, J = 4.1 Hz, J = 1.1 Hz)
4	3333	1686, 1626	Deuteriochloroform	2.98 (d, 3H, $NHCH_3$, J = 4.8 Hz), 3.36 (s, 3H, NCH_3), 6.62 (br. s, 1H, $NHCH_3$), 7.16 (d, 1H, H_4 or H_3, J = 4.8 Hz), 7.19 (s, 1H, CH), 7.77 (d, 1H, H_3 or H_4, J = 4.8 Hz)
5	3378	1715, 1656	Deuteriochloroform	2.95 (d, 3H, $NHCH_3$, J = 4.8 Hz), 3.85 (s, 3H, NCH_3), 6.10 (br. s, 1H, $NHCH_3$), 7.20 (d, 1H, H_4, J = 4.0 Hz), 7.75 (d, 1H, H_3, J = 4.0 Hz)
6	3185 (OH)	1631	DMSO-d_6	2.76, 3.32 (2s, 6H, 2 x NCH_3), 6.90 (d, 1H, H_4 or H_3, J = 4.3 Hz), 7.12 (d, 1H, H_3 or H_4, J = 4.3 Hz), 8.15 (s, 1H, OH)
7		1675	Deuteriochloroform	2.87, 3.32 (2s, 6H, 2 x NCH_3), 3.50 (s, 3H, OCH_3), 6.80 (d, 1H, H_3 or H_4, J = 3.8 Hz), 7.02 (d, 1H, H_4 or H_3, J = 3.8 Hz)
8·HBr		1718	DMSO-d_6	2.72, 3.20 (2s, 6H, 2 x NCH_3), 6.67 (s, 3H, CH, OH, HBr), 6.92-7.65 (m, 3H, H_3, H_4, H_5)
8	3175 (OH)	1639	Deuteriochloroform	2.95, 3.42 (2s, 6H, 2 x NCH_3), 5.85 (s, 1H, OH), 6.72 (s, 1H, CH), 6.98-7.45 (m, 3H, H_3, H_4, H_5)
9	3175 (OH)	1645	Deuteriochloroform	2.89, 3.37 (2s, 6H, 2 x NCH_3), 5.84 (s, 1H, OH), 6.60 (s, 1H, CH), 6.72 (d, 1H, H_4 or H_3, J = 4.1 Hz), 6.95 (d, 1H, H_3 or H_4, J = 4.1 Hz)
10	3125	1672	DMSO-d_6	7.32 (q, 1H, H_4, J = 5.3 Hz, J = 4.1 Hz), 8.14 (q, 1H, H_5, J = 5.3 Hz, J = 1.1 Hz), 8.36 (q, 1H, H_3, J = 4.1 Hz, J = 1.1 Hz), 8.76 (s, 1H, CH), 13.14 (br. s, 1H, NH)

Table II (Continued)

Compound	Ir (cm^{-1}) NH, NH_2	Ir (cm^{-1}) C=O	Nmr Solvent	Chemical Shift, ppm δ
11		1656	DMSO-d_6	3.68 (s, 3H, NCH_3), 7.38 (q, 1H, H_4, J = 5.3 Hz, J = 4.1 Hz), 8.13 (q, 1H, H_5, J = 5.3 Hz, J = 1.2 Hz), 8.35 (q, 1H, H_3, J = 4.1 Hz, J = 1.2 Hz), 8.79 (s, 1H, CH)
12·HBr		1658; (a)	DMSO-d_6	3.13, 3.80 (2s, 6H, 2 x NCH_3), 7.58 (d, 1H, H_4, J = 4.5 Hz), 8.20 (d, 1H, H_3, J = 4.5 Hz)
12		1618; (b)	Deuteriochloroform	3.12, 3.52 (2s, 6H, 2 x NCH_3), 7.15 (d, 1H, H_4, J = 4.5 Hz), 8.07 (d, 1H, H_3, J = 4.5 Hz)

(a) 1718 (C=N). (b) 1721 (C=N) (5).

precipitates unchanged after acidification. Ir and nmr data allow us to assign structure **8** to this compound, which originated from a nucleophilic attack of the methylamide nitrogen atom to the carbonyl carbon atom under acidic catalysis. The same intramolecular 1-6 cyclization takes place on the semicarbazone derivative **4**, when treated with hydrobromic acid-acetic acid mixture, yielding **9**. The behaviour of compounds **8** and **9** towards the bromination reaction with bromine-sodium acetate, is reported in Scheme II.

The triazine **6** undergoes some interesting nuclear changes. By heating **6** in the absence of solvent, we obtained the oxadiazoline **12**-hydrobromide, which after neutralization with dilute aqueous ammonium hydroxide gives the free base **12**. In this thermal-induced transformation it is possible to reason that the triazine **6** changes into the semicarbazone halogenide, which, under the particular reaction conditions (melting without solvent) cyclizes to Δ^2-1,3,4-oxadiazoline, involving the oxygen atom as the nucleophile (see Scheme III). In agreement with this idea, we have found that the semicarbazone halogenide **5**, by the same treatment, gives **12**. The ir spectrum of **12** shows a strong band in the 1700 cm^{-1} region, characteristic for an imino-1,3,4-oxadiazoline structure (5), and the mass spectrum shows a fragmentation pattern similar to those that we have observed for other imino-1,3,4-oxadiazoline derivatives (6,7). Treatment of **12** with aqueous sodium hydroxide produces the 1,2,4-triazol-5-one **13**, together with 5-bromothenoic acid. The fact that we obtained **13** could be explained by assuming an initial base-induced transformation of the oxadiazoline **12** into **15** (8), followed by a cleavage of the thenoyl group. Of course the reaction sequence could also be the inverted one.

We have also found that the triazine **6**, by heating with aqueous sodium hydroxide, gives a base-induced transformation into the 1,2,4-triazol-5-one **13** directly. In this transformation, the anion **14** derived from the cleavage of the N_4-C_5 bond of **6**, produces the triazole cyclization to **15** through the nucleophilic attack of the nitrogen atom on the bromo-substituted methyne carbon. From **15** then, by alkaline cleavage of the thenoyl group (this detachment could happen before the triazole cyclization) gives **13** together with 5-bromothenoic acid. The same triazole cyclization takes place from the bromosemicarbazone **5**, when treated with aqueous sodium hydroxide at room temperature, yielding **13**.

EXPERIMENTAL

Melting points were determined using a Kofler hotplate and are uncorrected. Ir spectra (nujol mull) were recorded on a Perkin-Elmer Infracord 137 instrument. Nmr spectra (60 MHz) were obtained using a Jeol C-60 H spectrometer with TMS as the internal standard. Mass spectra were recorded on the Jeol-JMS-01S-Z instrument (m/e values for ^{79}Br). Semicarbazide was of Fluka AG.; thienylglyoxal was prepared following reference (9); 2-methyl-, 4-methyl-, 2,4-dimethyl-, and 4,4-dimethyl-semicarbazide were obtained following reference (10). Analytical, physical, and spectroscopic data of all compounds are reported in Tables I and II.

General Procedure for Preparation of the Semicarbazones **1a-e**.

To a stirred solution of thienylglyoxal (0.06 mole) in ethanol-water 1:1 (50 ml.) and acetic acid (1 ml.), there was added dropwise a solution of the appropriate semicarbazide (0.06 mole in 50 ml. of water). In the case of **1a** semicarbazide hydrochloride and sodium acetate (0.06 mole) was used. The monosemicarbazone was filtered and crystallized from the suitable solvent (yields 70-85%).

Reaction of **1a-e** with Bromine-Sodium Acetate. General Procedure.

To a solution or suspension of the semicarbazone **1a-e** (0.01227 mole) in acetic acid (17.5 ml.) at room temperature, anhydrous sodium acetate (4 g.) was added and then, dropwise and with stirring, 6.6 ml. of a cooled solution of bromine in acetic acid (prepared from 5.5 ml. of bromine in 50 ml. of acetic acid) was added. The reaction mixture was stirred for 1 hour (2 hours in the case of **1e**) and then diluted with water. After standing 12 hours the crude material was collected and washed with water. From **1a**, **1b**, and **1c**, after crystallization of the crude material from the suitable solvent we obtained **2a** (90%), **2b** (79%), and **3c** (71%), respectively. Compound **1d** was recovered unchanged.

Compounds **4**, **5**, and **6**.

The crude material (4.14 g.) obtained as above from **1e** was treated with benzene and filtered. The insoluble fraction was treated with aqueous sodium hydroxide (5%) and filtered again.

The alkali insoluble material, after crystallization, gave the semicarbazone **4** (0.35 g.). Acidification of the alkaline solution with aqueous hydrochloric acid gave the triazine **6** (2.9 g.); ms: m/e (relative intensity) 381 (9, M^+), 364 (5), 302 (42), 245 (5), 223 (33), 220 (29), 202 (13), 197 (28), 189 (62), 162 (16), 140 (100), 138 (6), 111 (12), 95 (9), 82 (32), 69 (9). The initial benzene solution, after evaporation, gave a residue which was chromatographed on a dry column of silica-gel, deactivated with 15% of water. Elution with cyclohexane-ethyl acetate (2:1) gave the semicarbazone bromide **5** (0.15 g.). Compound **5**, if allowed to stand alone, changes into **6**.

Use of the general procedure for bromination described above with a time-reaction of a week, gave good yield of the triazine **6** only, working up the semicarbazone **1e** or the semicarbazone **4**, independently.

Cyclization of Semicarbazone Bromides **2a** and **2b**.

To a hot solution or suspension of the semicarbazone bromides (**2a** or **2b**) (0.01 mole) in ethanol (50 ml.), triethylamine (2.8 ml.) was added and the mixture was refluxed for 10 minutes. Dilution with water (100 ml.) gave a solid which was filtered. Crystallization from the proper solvent gave the 1,3,4-oxadiazole derivatives **3a** (87%) and **3b** (95%).

Compound **3a** and **3b** were also obtained directly from **1a** and **1b** by action of the bromine-sodium acetate mixture in acetic acid at 120°.

Methylation of **6**.

A mixture of **6** (1.9 g.), aqueous 10% sodium hydroxide (10 ml.) and dimethylsulfate (2 ml.) was stirred at room temperature and allowed to stand for several days. After dilution with water, the mixture was extracted with chloroform which was washed with aqueous 5% sodium hydroxide, dried and evaporated. Purification of the residue gave **7** (1.8 g.).

Reaction of **1a-e** and **4** with Hydrobromic Acid in Acetic Acid.

To a solution or suspension of the semicarbazone (0.005 mole) in acetic acid (7.5 ml.), hydrobromic acid (48%) (0.5 ml.) was added and the mixture was refluxed for 30 minutes. Compounds **1a**, **1b**, and **1c** gave decomposition products only. Compound **1d** (1.05 g.) after dilution with water, gave **11** (0.45 g.). Compound **1e** (1.12 g.), after cooling of the reaction mixture, gave **8**-HBr (1.2 g.). This latter, in water, after neutralization with aqueous ammonium hydroxide, gave the free base **8**. Compound **4** (1.52 g.), after cooling, dilution with water and neutralization with aqueous ammonium hydroxide, gave **9** (0.9 g.).

Methylation of **10**.

To a suspension of **10** (4) (0.5 g.) in methanol-water (10:1) mixture (22 ml.), an excess of ethereal diazomethane was added, allowing to stand for 24 hours. Removal of the solvent and crystallization of the residue gave **11**.

Reaction of **8** and **9** with Bromine and Sodium Acetate.

To a solution of **8** or **9** (0.00614 mole) in acetic acid (9 ml.), anhydrous sodium acetate (2 or 5 g., respectively) was added and then, dropwise and with stirring, a cooled solution of bromine in acetic acid (prepared as above) (3.3 or 7.5 ml., respectively). The reaction mixture was stirred for an half hour, diluted with water and the solid filtered off. In the case of **8**, the crude material was chromatographed on a dry column of silica-gel (cyclohexane-ethyl acetate 3:2 as eluent), yielding **6** (0.38 g.) and **9** (0.33 g.). In the case of **9**, crystallization of the crude material gave **6**.

Thermal Transformation of **5** and **6**.

A sample of **5** or **6** (1 g.) was carefully heated in an oil bath at 115° (for **5**) or 185° (for **6**), keeping there for one minute. After cooling, the solid was crystallized from hot water to yield the hydrobromide of **12** in 85% and 35% yield, respectively. Neutralization of a water solution of the hydrobromide with diluted (1:1) aqueous ammonium hydroxide gave the oxadiazoline **12**; ms: m/e (relative intensity) 301 (52, M^+), 189 (46), 161 (7), 117 (9), 112 (100), 82 (38), 81 (10), 70 (75), 69 (42), 42 (18).

Reaction of **5**, **6**, and **12** with Bases.

Compound **5**, or **6**, or **12** (0.005 mole) was dissolved in 10% aqueous sodium hydroxide (15 ml.), at room temperature in the case of **5**, and by refluxing 30 minutes in the case of **6** and **12**. The alkaline solution was extracted with chloroform. The dried extracts, after evaporation, gave the triazolone **13** (11) in 75, 85, and 37% yield, respectively. Acidification of the alkaline solution gave the 5-bromothenoic acid.

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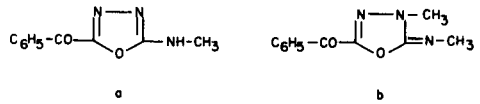
(7) Moreover, by comparing the uv spectra of **3a-c** and **12**, we notice the typical trend on passing from an aminooxadiazole to an iminooxadiazoline structure (5). The same trend we observe for others aminooxaidazoles/iminooxadiazolines, *e.g.* for **a** and **b** (6):



a b

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