Novel Eight-Membered Heterocycles. Synthesis of Dithiazolo[4,5-*d*:5′,4′-*g*][1,3]diazocine Derivatives

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A number of derivatives of dithiazolo[4,5-*d*:5′,4′-*g*][1,3]diazocine have been prepared by the ring closure of the diaminodithiazole derivatives 7-8 or by replacement of the corresponding alkylthio-function of 9-10.

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Of late, the seven-membered nitrogen heterocycles have been the source of much interest among medicinal chemists because of the development of several major drug entities within this area. The discovery of the marked antidepressant property of some compounds derived from the diazocine ring fused to aromatic [1] or heteroaromatic [2] rings and as part of our continuing programme to develop novel heterocyclic systems of therapeutic benefit in the central nervous system area, we have investigated the syntheses of dithiazolo[4,5-*d*:5′,4′-*g*][1,3]diazocine derivatives [9-16].

Since potassium cyanimidodithiocarbonate **1** and its OMe-derivative **2** are commonly used intermediates for a wide variety of 2-alkylthio- or alkoxyl-4-aminothiazoles [3-4], we tried the usefulness of this reaction for the synthesis of the dithiazolo-compounds **9-10** as shown in Scheme 1.

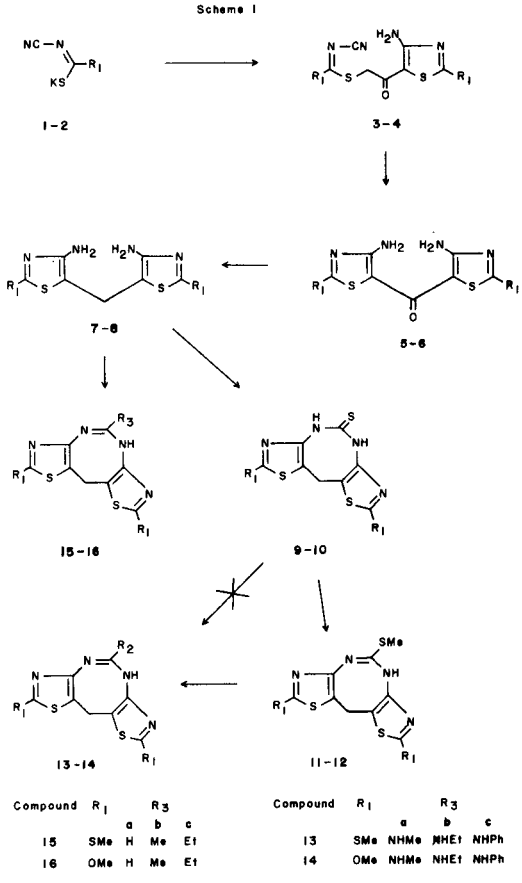
Reaction of **1-2** with α,α'-dichloro acetone afforded compounds **3-4**, which converted into the dithiazolyl keto-diamine **5-6** on heating [5], the latter of which underwent reduction with lithium aluminium hydride in tetrahydrofuran to afford the diamine intermediates **7-8** in good overall yields. Compounds **7-8** were converted into **9-10** by cyclisation with carbon disulphide in highly dilute solution and compounds **11-12** were produced in excellent yield by treatment of 5-thione derivatives **9-10** with methyl iodide in tetrahydrofuran.

We next showed that these alkylthio-compounds **11-12** could be converted into a range of 5-aminodithazolo[1,3]-diazocine derivatives **13-14**. The temperature at which the reaction commenced was clearly observable by evolution of mercaptan. Yields were generally between 50-90% of analytically pure sample. Compounds which contain the 5-substituent, **11-12** and **13-14**, should be capable of elaboration to give compounds of potential biological importance.

An attempt to prepare compounds **11-12** directly from the thione **9-10** by reaction with amines was unsuccessful.

The sequence shown in Scheme 1 was then extended to include the preparation of the 5-alkyl-substituted dithiazolo[1,3]diazocines **15-16**. The diamine compounds **7-8** readily gave the 5-alkyl compounds as major products on

Scheme I



Compound	R_1	R_3 a	b	c
15	SMe	H	Me	Et
16	OMe	H	Me	Et

Compound	R_1	R_3 a	b	c
13	SMe	NHMe	NHEt	NHPh
14	OMe	NHMe	NHEt	NHPh

treatment with triethyl orthoformate, triethyl orthoacetate and triethyl orthopropionate. The ir spectra of compounds **9-16** showed characteristic bands at cm^{-1} 3440, 3320, 3210 (NH), 1490 (C=O). The ^1H nmr spectra exhibit the NH protons at δ 10.20, SMe-substituent at 2.82, OMe-substituent at 3.64, CH_2-protons at 4.62, and other protons assignable to different substitutions at position 5 for the compounds **11-16**.

Of the condensed derivatives of diazocines that have been described, most of the compounds are dibenzo[1,3]-and [1,5]diazocines **7-8**, dipyrido[1,5]- and dipyrazolo[1,3]-diazocines **9-10** were synthesized, dithiazolo[1,3]diazocine has not been described and compounds **9-16** are members of a new heterocyclic system.

Table 1

Compounds	mp, C	% Yield	Formula	MW	Elemental Analysis Calcd. C	H	N	Found C	H	N
6	220-222	62	$C_9H_{10}N_4O_3S_2$	287.22	37.63	3.50	19.50	37.65	3.72	19.60
7	179-180	65	$C_9H_{12}N_4S_4$	304.47	35.50	3.97	18.41	35.52	4.00	18.40
8	184-185	62	$C_9H_{12}N_4O_2S_2$	272.34	39.69	4.44	20.57	39.66	4.58	20.90
9	241-243	72	$C_{10}H_{10}N_4S_5$	346.53	34.65	2.90	16.16	34.69	3.20	16.37
10	238-240	69	$C_{10}H_{10}N_4O_2S_3$	314.40	38.20	3.20	17.82	38.45	3.32	17.98
11	230-232	97	$C_{11}H_{13}IN_4S_5$	488.47	27.04	2.68	11.46	27.30	2.76	11.46
12	244-245	90	$C_{11}H_{13}N_5S_4$	456.34	28.95	2.87	12.27	28.99	3.00	12.35
13a	243-245	90	$C_{11}H_{13}N_5S_4$	343.51	38.46	3.81	20.38	38.58	3.84	20.39
13b	213-215	58	$C_{12}H_{15}N_5S_4$	357.54	40.31	4.22	19.58	40.30	4.35	19.56
13c	255-256	91	$C_{16}H_{15}N_5S_4$	405.58	47.38	3.72	17.26	47.39	3.76	17.34
14a	231-232	85	$C_{11}H_{13}N_5O_2S_2$	311.38	42.42	4.20	22.49	42.34	4.37	22.51
14b	189-192	41	$C_{12}H_{15}N_5O_2S_2$	325.41	44.29	4.64	21.52	44.28	4.50	21.70
14c	225-226	74	$C_{16}H_{15}N_5O_2S_2$	373.45	51.45	4.04	18.75	51.47	4.20	18.86
15a	240-242	43	$C_{10}H_{10}N_4S_4$	314.47	38.19	3.18	17.81	38.22	3.19	17.87
15b	248-249	50	$C_{11}H_{12}N_4S_4$	328.50	40.21	3.68	17.05	40.20	3.69	17.05
15c	208-210	38	$C_{12}H_{14}N_4S_4$	342.52	42.07	4.11	16.35	42.07	4.14	16.35
16a	222-223	41	$C_{10}H_{10}N_4O_2S_2$	282.34	42.54	3.75	19.84	42.55	3.78	19.86
16b	214-215	45	$C_{11}H_{12}N_4O_2S_2$	296.37	44.57	4.08	18.90	44.56	4.08	18.93
16c	205-206	25	$C_{12}H_{14}N_4O_2S_2$	310.39	46.43	4.54	18.05	46.47	4.55	18.06

EXPERIMENTAL

The structure of all compounds are supported by their ir (Perkin-Elmer 457) and ^{1}H nmr (JEOL C6 HL, tetramethylsilane) spectra. Molecular weights were obtained with an A. E. I. MS902 mass spectrometer. Melting points were taken on a Büchi capillary melting point apparatus and are uncorrected. Purity of compounds was established by tlc (on Merck silica gel $60F_{254}$) and by hplc (Varian 8 500 pump coupled to a Perkin-Elmer uv detector; Partisil C8 reversed-phase column). Elemental analysis were performed by Micro Tech. Laboratories. Results are within ±0.4% of theoretical values unless otherwise noted in Table 1. Reactions with moisture-sensitive reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents.

Potassium Cyanimidodithiocarbonate **1**.

Compound **1** was prepared according to the method of Wobig [5].

Potassium Cyanimidothiocarbonate **2**.

Compound **2** was prepared according to the method of Wieland [6].

Bis(4-amino-2-methoxy-5-thiazolyl)ketone **6**.

This was prepared by the method used for the methylthio-analogue 5 [5].

Bis(4-amino-5-thiazolyl)methane 7-8. Typical Procedure.

The diamines **5-6** (0.5 mole) were dissolved in anhydrous tetrahydrofuran (100 ml) and slowly added to a suspension of lithium aluminium hydride (0.55 mole) in anhydrous tetrahydrofuran (250 ml). The mixture was refluxed for 8 hours, then cooled, the excess of lithium aluminium hydride was destroyed by addition of 2:1 tetrahydrofuran/water, and the mixture filtered. Solvent was removed *in vacuo* to give a brown solid which purified by chromatography to afford the desired product which was recrystallized from methanol/water (Table 1).

Dithiazolo[4,5-*d*:5',4'-*g*][1,3]diazocine-5-thione **9-10**. Typical Procedure.

Compounds **7-8** (0.32 mole) were heated under reflux for 48 hours with a mixture of pyridine (300 ml), carbon disulphide (250 ml) and water (25 ml). The solvents were removed *in vacuo*, the solid residue was dissolved in acetone and acidified strongly with 20% hydrochloric acid to remove traces of pyridine, which forms a rather stable complex with the product. The mixture was diluted with a liter of water and chilled. The precipitate was collected and recrystallized twice from ethanol to give the desired product. Analytical data are listed in Table 1.

5-Methylthio-6*H*-dithiazolo[4,5-*d*:5',4'-*g*][1,3]diazocine Hydroiodide **11-12**.

The thione **9-10** (0.14 mole) was dissolved in tetrahydrofuran (260 ml) and stirred for 3 hours with methyl iodide (0.15 mole). After the mixture had been allowed to stand overnight, the solid was collected and air dried to give the required product. Analytically pure **11** or **12** was obtained by recrystallization from butanone/methanol and listed in Table 1.

Preparation of the 5-Amino Derivatives of 6*H*-Dithiazolo[4,5-*d*:5',4'-*g*]-[1,3]diazocine **13-14a-c**. Typical Procedure.

The methylthio derivative **11-12** (0.033 mole) was mixed well with the appropriate amine (0.039 mole) and heated strongly until the mixture melted (between 160-180°). The temperature was allowed to rise slowly to 200° where it was held for 30-60 minutes. The evolution of mercaptan was strong at 160°, but decreased after several minutes at 200°. The melt was cooled and stirred with an excess of 30% aqueous 2-propanol containing 5% sodium hydroxide. The gummy precipitate was collected and converted to the hydrochloride (recrystallized twice from methanol/2-propanol and once from 95% ethanol) to give the required compounds (see Table 1).

Preparation of the 5-Alkyl Derivatives of 6*H*-Dithiazolo[4,5-*d*:5',4'-*g*]-[1,3]diazocine **15-16a-c**. Typical Procedure.

A solution of the diamines **7-8** (0.37 mole) in triethyl orthoformate (70 ml) was heated for 24 hours. The mixture was cooled and the solid was collected and air dried to yield 6*H*-dithiazolo[4,5-*d*:5',4'-*g*][1,3]diazocine (R_3 = H). Analytically pure compound was obtained by recrystallization from ethyl acetate/hexane and listed in Table 1.

A similar procedure was employed to prepare **15-16b-c** using triethyl orthoacetate and triethyl orthopropionate respectively (see Table 1).

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