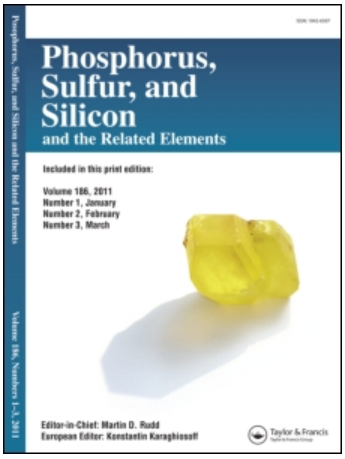

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REACTIONS WITH SULFOLENES II.[1] "CRISS-CROSS" ADDITION OF ALDAZINES: SYNTHESIS OF SEVERAL NEW ANNELATED PYRAZOLO[1,2-a]PYRAZOLE DERIVATIVES

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New annelated pyrazolo[1,2-a]pyrazole derivatives were synthesised via the reaction of aryl aldazines with sulfolene and treatment of the resultant products with different reagents. Structures were established using elemental analysis and spectral data.

Key words: Aldazines; sulfolene; criss-cross cycloaddition; pyrazoles; bis-thiazolopyrazoles.

INTRODUCTION

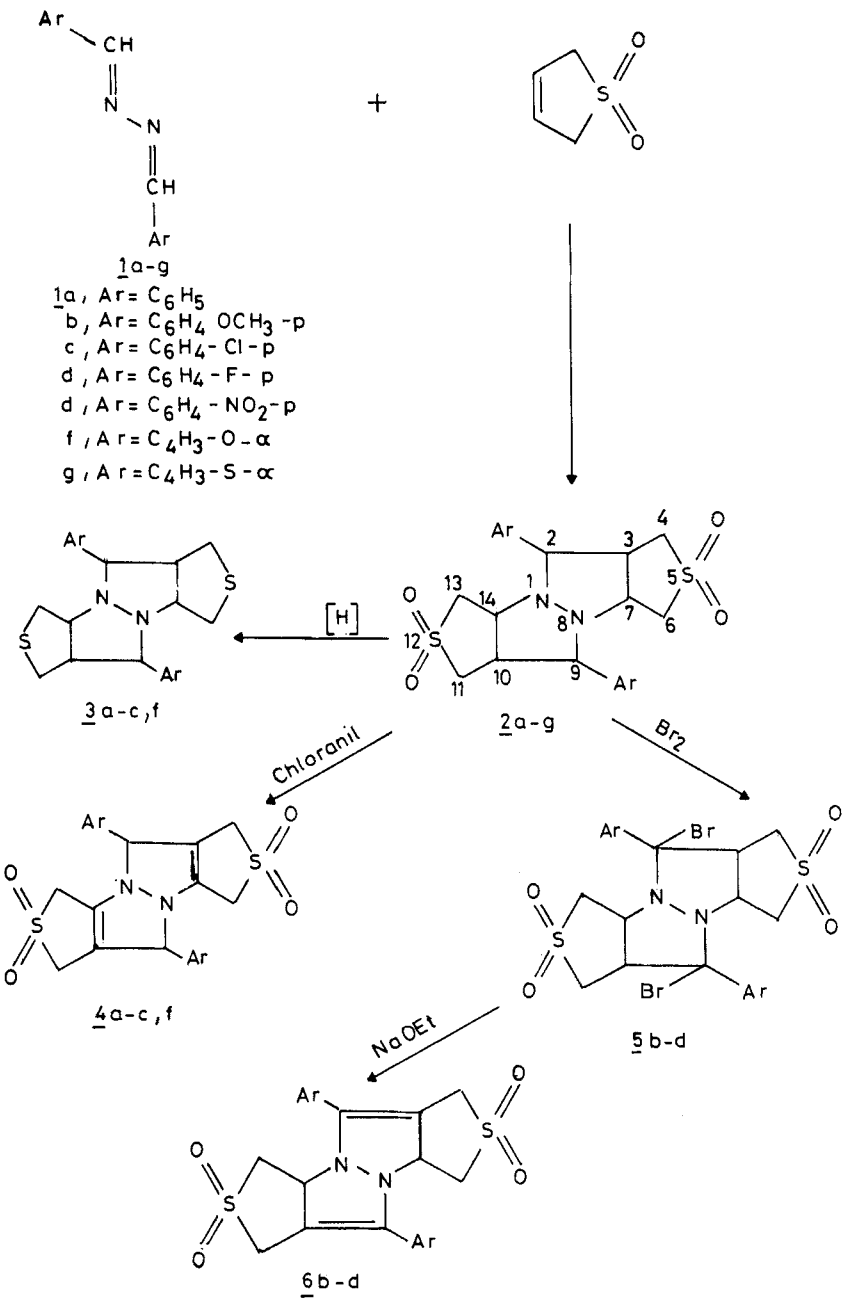
Pyrazole and its derivatives are known to exhibit diverse biological activities.[2–6] They exhibit antilieprotic,[7,8] bactericidal, insecticidal[9] and antitubercular[10] activities. Sulfones also are reported to possess several activities and are also used as antileprotic,[8,11] bactericidal,[12] insecticidal[12] and antitubercular[10] agents.

The incorporation of the two moieties in the same compound will certainly add to the overall activities of the compound. Therefore it was decided to synthesize several derivatives, containing both of the two moieties, required for a medicinal chemistry program. The 1,3-2,4-dipolar "Criss-Cross" cycloaddition reaction of some aldazines and sulfolene seems to be the sole route for the synthesis of these derivatives (Scheme I).

RESULTS AND DISCUSSION

It was found that benzaldehydeazine (**1a**) reacted with 2,5-dihydrothiophene-1-dioxide (3-sulfolene) to yield a product resulting from the addition of one molecule of **1a** to **2** molecules of sulfolene. The reaction product could be formulated as 2,9-diphenyl-5,12-dithia-1,8-diazatetracyclo[6.6.0.0,^{3,7}0^{10,14}] tetradecane **2a** based on correct elemental analysis and spectral data. The IR spectrum of **2a** showed bands corresponding to the presence of the $-SO_2$ group at 1350 cm^{-1}. The signals of thiophene dioxide-CH_2 and pyrazole H-3, H-4 and H-5 were detected in the ^{1}H-NMR spectrum of **2a** in their proper positions (Table I).

In the same manner, the aldazines **1b–g** were reacted with sulfolene to yield the corresponding tetradecane derivatives (**2b–g**) in good yields. Structures of **2b–g** were established on the basis of elemental analysis and spectral data.



SCHEME I

Compounds **2a–c,f** could be reduced using LAH to effect the removal of the oxygen atoms on sulfur to yield the corresponding bis-thieno[3,4-c]-pyrazole derivatives **3a–c,f** respectively. The IR spectra of **3a–c,f** were found completely free of the bands due to the SO_2 group.

TABLE I
^{1}H-NMR spectral data

Comp.	^{1}H-NMR (DMSO-d_6 ; δ ppm
2a	1.6[d,4H,H(4);H(11)]; 1.8[d,4H,H(6),H(13)]; 2.1[td,2H,H(7); H(14)]; 2.3[m,2H,H(3);H(10)]; 2.7[d,2H,H(2); H(9)] and 7.1-7.8 (m,10H,ArH's).
2b	1.5[d,4H,H(4); H(11)]; 1.7[d,4H,H(6); H(13); 2.1[td,2H,H(7); H(14)]; 2.4[m,2H,H(3); H(10)]; 2.6[d,2H,H(2); H(9)] and 7.0-7.6 (m,8H,ArH's).
3b	1.2[d,4H,H(4); H(11)]; 1.4[d,4H,H(6); H(13)]; 2.0[td,2H,H(7); H(14)]; 2.2[m,2H,H(3);H(10)]; 2.8[d,2H,H(2); H(9)]; 3.7(s,6H, two OCH_3) and 7.2-8.0(m,8H,ArH's).
4a	1.6[d,4H,H(4); H(11)]; 1.7(d,4H,H(6); H(13)]; 4.1[s,2H,H(2); H(9)] and 6.9-7.7(m,10H,ArH's).
4b	1.6[d,4H,H(4); H(11)]; 1.8[d,4H,H(6); H(13)]; 3.8(s,6H,two OCH_3); 4.0 [s,2H,H(2); H(9)] and 7.0-7.7 (m,8H,ArH's).
5b	1.6[d,4H,H(4); H(11)]; 1.8[d,4H,H(6); H(13)]; 2.0[td,2H, H(7); H(14)]; 2.4[m,2H,H(3); H(10)]; 3.8(s,6H,two OCH_3) and 7.1-7.7 (m,8H,ArH's).
6b	1.6[d,4H,H(4); H(11)]; 1.7[d,4H,H(6); H(13)]; 2.3[t,2H,H(7); H(14)]; 3.7(s,6H,two OCH_3) and 7.1-7.7 (m,8H,ArH's).
6f	1.5(d,4H,H(4); H(11)]; 1.7[d,4H,H(6); H(13)]; 2.4[t,2H,H(7); H(14)] and 6.8-7.6(m,6H,furyl H's).
6g	1.5(d,4H,H(4); H(11)]; 1.6[d,4H,H(6); H(13)]; 2.6[t,2H,H(7); H(14)] and 6.9-7.7(m,6H, thienyl H's).

Compounds **2a–c,f** could also be dehydrogenated by the action of chloranil to give the corresponding 2,9-diaryl-5,12-dithiadioxide-1,8-diazatetracyclo-[6.6.0.0.^{3,7}0^{10,14}]-tetradeca-$\Delta^{3(7)}$, $\Delta^{10(14)}$-diene derivatives **4a–c**. The ^{1}H-NMR spectra of **4a–c,f** were found free of the signals due to the pyrazole H-3 and H-4 thus proving the dehydrogenation reaction.

The isomeric tetradeca-2,9-diene derivatives were synthesised via an indirect route. Compounds **2b–d** could be brominated using bromine in glacial acetic acid to yield the corresponding 2,9-dibromotetradecane derivatives **5b–d**. Structures of **5b–d** were established on the basis of elemental analysis and spectral data.

The action of sodium ethoxide on **5b–d** resulted in a dehydrobromination reaction and led to the formation of the isomeric tetradeca-2,9-diene derivatives **6b–d**.

Structures of **6b–d** were again based on elemental and spectral data studies.

TABLE II
Characteristic data of compounds **2–6**

Comp.	M.P.	Yield	Mol. Formula	Analysis %, Calcd./Found				
				C	H	N	S	Halogen
2a	271	86	$C_{22}H_{24}N_2O_4S_2$	59.45 59.5	5.40 5.3	6.30 6.4	14.41 14.3	-- --
2b	278	85	$C_{24}H_{28}N_2O_6S_2$	57.14 57.2	5.55 5.6	5.55 5.4	12.69 12.5	-- --
2c	224	82	$C_{22}H_{22}N_2O_4S_2Cl_2$	51.46 51.5	4.22 4.1	5.45 5.5	12.47 12.5	13.64 13.7
2d	210	84	$C_{22}H_{22}N_2O_4S_2F_2$	55.0 55.1	4.58 4.6	5.83 5.7	13.33 13.4	7.91 8.0
2e	277	90	$C_{22}H_{22}N_4O_8S_2$	49.43 49.5	4.11 4.0	10.48 10.6	11.48 11.8	-- --
2f	280	89	$C_{18}H_{20}N_2O_6S_2$	50.94 50.8	4.71 4.8	6.6 6.5	15.09 15.2	-- --
2g	285	90	$C_{18}H_{20}N_2O_4S_4$	47.36 47.2	4.32 4.2	6.14 6.0	22.07 22.1	-- --
3a	230	70	$C_{22}H_{24}N_2S_2$	69.47 69.40	6.31 6.2	7.36 7.4	16.84 16.7	-- --
3b	240	75	$C_{24}H_{22}N_2S_2O_2$	66.36 66.4	5.06 5.2	6.4 6.5	14.7 14.8	-- --
3c	210	60	$C_{22}H_{22}N_2S_2Cl_2$	58.92 58.8	4.91 4.8	6.25 6.3	14.54 14.6	15.62 15.5
3f	220	62	$C_{18}H_{20}N_2S_2O_2$	60.0 60.1	5.5 5.4	7.7 7.8	17.7 17.0	-- --
4a	298	80	$C_{22}H_{20}N_2S_2O_4$	60.0 60.1	4.54 4.4	6.36 6.4	14.54 14.4	-- --
4b	299	82	$C_{24}H_{24}N_2S_2O_6$	57.60 57.5	4.80 4.7	5.60 5.5	12.8 12.7	-- --
4c	300	85	$C_{22}H_{18}N_2S_2O_4Cl_2$	51.26 51.4	3.53 3.5	5.5 5.6	12.57 12.6	13.75 13.7
4f	305	89	$C_{18}H_{16}N_2S_2O_6$	51.42 51.3	3.80 3.8	6.66 6.5	15.23 15.1	-- --
5b	291	65	$C_{24}H_{26}N_2S_2O_6Br_2$	43.5 43.4	3.92 3.8	4.22 4.1	9.66 9.5	24.16 24.0
5c	296	60	$C_{22}H_{20}N_2S_2O_4Cl_4Br_2$	39.4 39.3	2.98 3.0	4.17 4.0	9.55 9.4	10.44 10.30
5d	298	60	$C_{22}H_{20}N_2S_2O_4F_2Br_2$	41.37 41.3	3.13 3.1	4.38 4.4	10.03 10.0	5.95 5.8
6d	210	75	$C_{24}H_{24}N_2S_2O_6$	57.60 57.5	4.80 4.7	5.60 5.5	12.80 12.9	-- --
6c	218	70	$C_{22}H_{18}N_2S_2Cl_2$	51.86 51.7	3.53 3.4	5.50 5.4	12.57 12.5	13.75 13.6
6d	220	70	$C_{22}H_{12}N_2S_2O_4F_2$	55.46 55.4	3.78 3.6	5.88 5.7	13.94 13.3	7.98 7.8

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr discs) were measured on a Pye Unicam SP-1100 Spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM 390 90 MHz and Gemnai-200 MHz Spectrometers in DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are

TABLE III
IR spectral data

Compound	
2a - g	2980- (aliphatic CH and CH_2) and 1350,1150 (SO_2).
3a - c,f 5b - d	2960 (aliphatic CH and CH_2).
4a - c,f 6b - d	2980 (aliphatic CH and CH_2); 1610-1630 (C=C) and 1360,1140 (SO_2).

expressed as δ ppm units. Microanalyses were performed at the Microanalytical Center of Cairo University. Compounds **1a–g** were prepared following literature procedures.

General procedure for the reaction of **1a–g** *with sulfolene.* A solution of each of **1a–g** (0.01 mole) in toluene (20 ml) was treated with sulfolene (0.02 mole) and the reaction mixture was heated under reflux for 4 hours. The excess solvent was removed under reduced pressure. The precipitate formed was filtered and crystallised from ethanol to give **2a–g** (Tables II and III).

General procedure for the reduction of **2.** A solution of **2a–c,f** (0.01 mole) in dry ether (50 ml) was treated with lithium aluminium hydride (LAH, 0.1 mole) in portions and the reaction mixture was heated on the water-bath for 1 hour then left overnight. The reaction mixture was then decomposed using dilute sulfuric acid. The obtained solid was filtered, washed with water and crystallised from ethanol to give **3a–c**, (Tables II and III).

General procedure for the dehydrogenation of **2.** A solution of **2a–c,f** (0.1 mole) in xylene (30 ml) was heated with excess of chloranil under reflux for 48 hours. Removal of the solvent left a solid product which was washed with sodium hydroxide solution then with water and crystallised from ethanol to yield **4a–c,f** (Tables II and III).

General procedure for the bromination of **2.** A solution of each of **2b–d** in glacial acetic acid (20 ml) was treated with bromine (0.02 mole) in the same solvent (5 ml) at room temperature. The reaction mixture was poured into ice-water. The solid formed was filtered and crystallised from ethanol to give **5b–d** (Tables II and III).

General procedure for the dehydrobromination of **5.** A solution of each of **5b–d** (0.01 mole) in absolute ethanol (20 ml) was treated with a solution of sodium ethoxide (0.01 mole, prepared with equivalent amounts of sodium metal and ethanol). After refluxing for 5 hours the reaction mixture was poured into ice-water. The solid formed was filtered, washed with water, then crystallised from ethanol to give **6b–d** (Tables II and III).

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