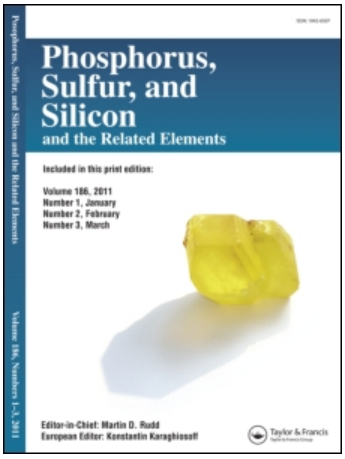

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SYNTHESIS AND REACTIONS OF SULFONYLMETHYLQUINOXALINES

Y. A. Ibrahim[a]; A. H. M. Elwahy[a]; A. A. Hashem[a]
[a] Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R., Egypt

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SYNTHESIS AND REACTIONS OF SULFONYLMETHYLQUINOXALINES

Y. A. IBRAHIM,* A. H. M. ELWAHY and A. A. HASHEM
Department of Chemistry, Faculty of Science, Cairo University, Giza, A. R., Egypt

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3-Sulfonylmethylquinoxalin-2(1H)-ones 2a,b were used for the synthesis of the 2-thioxo 3a,b and 2-hydrazino 8a,b derivatives. The alkyl-thio derivatives 4–7 were obtained from 3a,b. 8a,b were condensed or cyclocondensed with the appropriate reagents to give the hydrazones 9–11, triazolo[4,3-a]quinoxalines 13–16, tetrazolo[1,5-a]quinoxalines 17 and triazino[4,3-a]quinoxalines 12. The quinoxalino[2,1-b]quinazoline 20 was obtained from 4a and anthranilic acid.

Key words: Sulfones, quinoxalines, hydrazones, triazolo[4,3-a]quinoxalines, tetrazolo[1,5-a]quinoxalines, triazino[4,3-a]quinoxalines and quinoxalino[2,1-b]quinazoline.

INTRODUCTION

Many sulfonyl substituted five and six membered heterocyclic rings exhibit pronounced biological activities as pesticidal,[1] antiallergic,[2–5] anti-inflammatory,[5,6] antibacterial,[7,8] antihypertensive,[2,9–12] muscle relaxant, cardiovascular[12] and anticancer agents.[13,14]

RESULTS AND DISCUSSION

These facts prompted us to study the synthetic utility of 3-sulfonylmethylquinoxalin-2(1H)-ones 2a,b toward sulfonyl substituted condensed nitrogen heterocycles of expected biological activity. The starting compounds 2a,b were readily obtained by condensation of the appropriate ethyl sulfonylpyruvates 1a,b with *o*-phenylenediamine in dilute acetic acid. Thiation of 2a,b with Lawesson's reagent in boiling toluene gave the corresponding 2-thioxo derivatives 3a,b. Alkylation of the latters in basic medium with methyl iodide, ethyl iodide, ethyl bromoacetate and chloroacetic acid gave the corresponding 2-alkylthio derivatives 4a,b, 5a,b, 6a,b and 7a,b respectively.

Hydrazinolysis of 3a,b led to the formation of the corresponding 2-hydrazino derivatives 8a,b respectively. The latters were condensed with benzaldehyde and p-methoxy-benzaldehyde to give the corresponding hydrazones 9a,b, 10a,b. Condensation of 8a,b with phenylglyoxylic acid gave the corresponding hydrazones 11a,b. The latter underwent cyclization in acetic anhydride to give the corresponding [1,2,4]triazino[4,3-a]quinoxaline derivatives 12a,b.

Cyclocondensation of the 2-hydrazino derivatives 8a,b with formic acid, acetic anhydride and carbon disulfide (which act as 1,1-bielectrophiles) led to the for-

TABLE I

Analytical data of newly synthesized products

Compd No.	M.p. °C	Mol. Formula (Mol. Wt.)	Analysis Calcd./Found %C	%H	%N	%S
2a	248	$C_{10}H_{10}N_2O_3S$	50.41	4.23	11.75	13.45
		(238.26)	50.30	4.40	11.70	13.60
3a	204	$C_{10}H_{10}N_2O_2S_2$	47.22	3.96	11.01	25.21
		(254.33)	47.40	3.90	11.20	25.50
3b	215	$C_{15}H_{12}N_2O_2S_2$	56.94	3.82	8.85	20.26
		(316.40)	57.30	3.50	9.20	20.50
4a	145	$C_{11}H_{12}N_2O_2S_2$	49.23	4.50	10.44	23.89
		(268.35)	49.30	4.80	10.30	23.60
4b	170	$C_{16}H_{14}N_2O_2S_2$	58.16	4.27	8.48	19.41
		(330.42)	57.90	4.40	8.30	19.50
5a	118	$C_{12}H_{14}N_2O_2S_2$	51.04	4.99	9.92	22.71
		(282.38)	51.10	4.80	10.10	22.50
5b	163	$C_{17}H_{16}N_2O_2S_2$	59.28	4.68	8.13	18.62
		(344.45)	59.30	4.60	8.30	18.50
6a	165	$C_{14}H_{16}N_2O_4S_2$	49.40	4.74	8.23	18.84
		(340.42)	49.50	4.60	8.10	18.60
6b	110	$C_{19}H_{18}N_2O_4S_2$	56.70	4.51	6.96	15.93
		(402.49)	56.40	4.30	6.80	16.10
7a	141	$C_{12}H_{12}N_2O_4S_2$	46.14	3.87	8.97	20.53
		(312.37)	46.50	4.20	8.60	20.10
7b	110	$C_{17}H_{14}N_2O_4S_2$	54.53	3.77	7.48	17.13
		(374.44)	54.70	3.80	7.40	17.10
8a	180	$C_{10}H_{12}N_4O_2S$	47.61	4.79	22.21	12.71
		(252.29)	47.80	4.80	22.50	12.90
8b	202	$C_{15}H_{14}N_4O_2S$	57.31	4.49	17.82	10.20
		(314.37)	57.20	4.30	17.90	10.18
9a	210	$C_{17}H_{16}N_4O_2S$	59.98	4.73	16.46	9.42
		(340.41)	59.70	4.70	16.40	9.30
9b	240	$C_{22}H_{18}N_4O_2S$	65.65	4.50	13.92	7.97
		(402.48)	65.80	4.20	13.50	7.70
10a	238	$C_{18}H_{18}N_4O_3S$	58.36	4.89	15.12	8.65
		(370.43)	58.60	4.60	15.20	8.60
10b	270	$C_{23}H_{20}N_4O_3S$	63.87	4.66	12.95	7.41
		(432.50)	64.10	4.50	12.80	7.70
11a	147	$C_{18}H_{16}N_4O_4S$	56.24	4.19	14.57	8.34
		(384.41)	56.50	4.50	14.80	8.20

TABLE I (*Continued*)

Compd No.	M.p. °C	Mol. Formula (Mol. Wt.)	Analysis Calcd./Found %C	%H	%N	%S
11b	178	$C_{23}H_{18}N_4O_4S$	61.87	4.06	12.54	7.18
		(446.49)	61.60	4.10	12.40	7.40
12a	220	$C_{18}H_{14}N_4O_3S$	59.01	3.85	15.29	8.75
		(366.40)	58.80	3.90	15.50	8.60
12b	225	$C_{23}H_{16}N_4O_3S$	64.47	3.76	13.07	7.48
		(428.47)	64.10	3.80	13.30	7.20
13a	276	$C_{11}H_{10}N_4O_2S$	50.37	3.84	21.36	12.20
		(262.29)	50.10	3.70	21.50	12.00
13b	210	$C_{16}H_{12}N_4O_2S$	59.24	3.72	17.27	9.88
		(324.36)	59.50	3.90	17.10	9.80
14a	265	$C_{12}H_{12}N_4O_2S$	52.16	4.37	20.27	11.60
		(276.32)	51.90	4.40	20.00	11.90
14b	245	$C_{17}H_{14}N_4O_2S$	60.34	4.17	16.55	9.47
		(338.39)	60.40	4.20	16.20	9.60
16a	253	$C_{11}H_{10}N_4O_2S_2$	44.88	3.42	19.03	21.78
		(294.35)	44.60	3.10	18.80	21.70
16b	232	$C_{16}H_{12}N_4O_2S_2$	53.91	3.39	15.71	17.99
		(356.42)	54.10	3.50	15.50	18.30
17a	166	$C_{10}H_9N_5O_2S$	45.62	3.44	26.60	12.17
		(263.28)	45.60	3.20	26.30	12.30
17b	170	$C_{15}H_{11}N_5O_2S$	55.37	3.40	21.52	9.85
		(325.35)	55.50	3.10	21.60	9.60
19a	113	$C_{11}H_{12}N_2O_3S$	52.37	4.79	11.10	12.71
		(252.29)	52.60	4.90	11.00	12.90
19b	147	$C_{16}H_{14}N_2O_3S$	61.13	4.49	8.91	10.20
		(314.37)	61.00	4.60	8.80	10.40
20	195	$C_{17}H_{13}N_3O_3S$	60.16	3.86	12.38	9.45
		(339.38)	60.30	3.60	12.10	9.20

mation of the corresponding [1,2,4]triazolo[4,3-a]quinoxalines 13a,b, 14a,b, 15a,b. Spectral data showed that compounds 15a,b exist in the thioxo tautomers 16a–d. Thus, the IR (KBr) spectra showed no SH band around 2500 cm^{-1} but showed only bands at 1480, 1180 cm^{-1} due to C=S. The anisotropic effect of C=S causes a large deshielding effect on the aromatic H-9 proton which appears at $\delta \doteq 10.2$ ppm (d, $J = 8.1$). IR spectra showed NH band at 3300–3220 cm^{-1}. The action of nitrous acid on compounds 8a,b led to the formation of the corresponding tetrazolo[1,5-a]quinoxalines 17a,b.

TABLE II

Spectral data of newly synthesized products

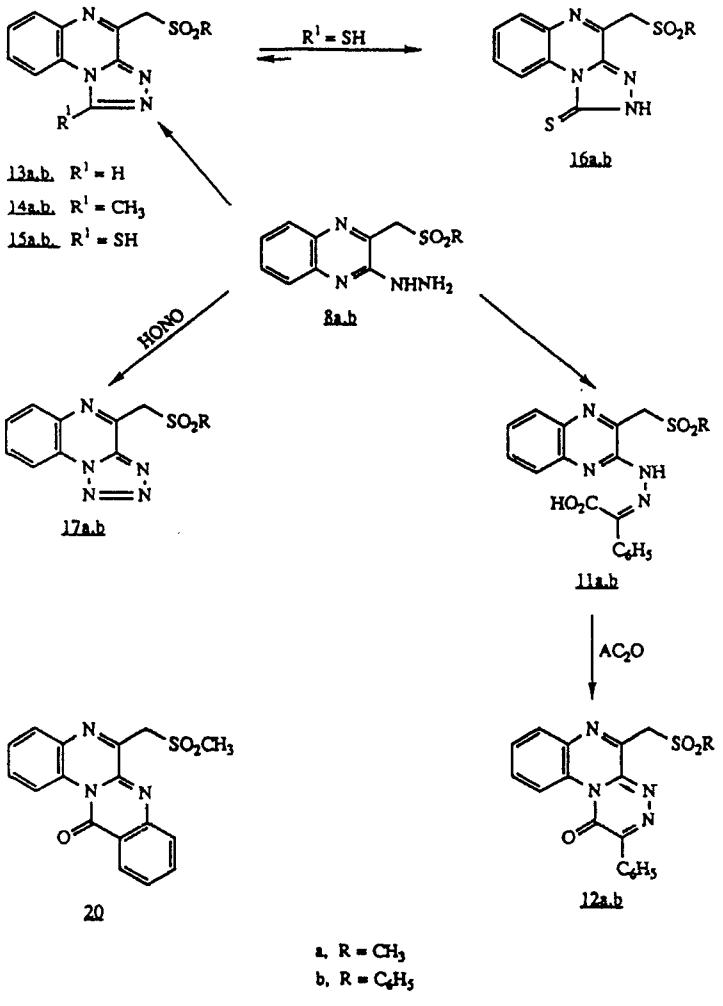
Compd. No.	IR (cm^{-1})	^{1}H-NMR (δ ppm) CH_2SO_2-R, Ar	other H's
2a	3340 1640 1300 1130		
3a	3162 1684 1302 1142		
3b		5.25 (s, 2H) 7.3-8.0 (m, 9H)	11.8 (br s, 1H)
4a		4.7 (s, 2H) 3.15 (s, 3H) 7.6-8.0 (m, 4H)	2.73 (s, 3H)
4b	1322 1150	4.85 (s, 2H) 7.45-7.95 (m, 9H)	2.65 (s, 3H)
6b	1739 1325 1148	4.7 (s, 2H) 7.45-7.9 (m, 9H)	1.3 (t, 3H) 4.2 (q, 2H) 4.82 (s, 2H)
8a	3411 3307 1312 1135		
8b	3438 3327 1309 1153		
12a	1700 1311 1143	5.25 (s, 2H) 3.25 (s, 3H) 7.55-9.55 (m, 9H)	
13b	1300 1125	5.35 (s, 2H) 7.6-8.48 (m, 9H)	10.15 (s, 1H)
14b	1350 1180	5.15 (s, 2H) 7.48-8.2 (m, 9H)	3.15 (s, 3H)
16b	3310 1330 1180	4.72 (s, 2H) 7.35-7.7 (m, 8H)	10.22 (d, 1H) 13.3 (s, 1H)
17b	1300 1120	5.25 (s, 2H) 7.52-8.65 (m, 9H)	
19b		4.85 (s, 2H) 7.4-7.9 (m, 9H)	3.85 (s, 3H)
20		5.3 (s, 2H) 7.15-8.1 (m, 7H)	9.15 (d, 1H) 3.3 (s, 3H)

NMR of 3b, 4a,b, 6b, 14b, 16b, 17b, 19b were measured in $CDCl_3$ and 12a, 13b, 20 were measured in DMSO-d_6.

^{13}C-NMR of 4a: 15.37 (SCH_3), 43.0 (SO_2CH_3), 61.12 (CH_2SO_2), 129.79, 130.7, 130.94, 133.03, 140.92, 144.24, 145.63, 158.84 (ArC's) ppm.

Attempts to cyclize the ethoxycarbonylmethylthioquinoxalines 6a,b to the corresponding thiopyrano[2,3-b]quinoxalines 18 in refluxing sodium methoxide solution gave the corresponding 2-methoxyquinoxalines 19a,b. Compound 19a was alternatively prepared by the action of sodium methoxide on 4a. The latter, also, underwent cyclocondensation with anthranilic acid to give the corresponding quinoxalino[2,1-b]quinazoline 20.

The previous results indicate the stability of the SO_2CH_2 under the reaction conditions used. All derivatives with carbonyl and thiocarbonyl group attached at the quinoxaline N-1 (compounds 12, 16, 20) display one aromatic proton signal (H-8 of quinoxaline system) with noticeable downfield shift due to the anisotropic effect of these groups.

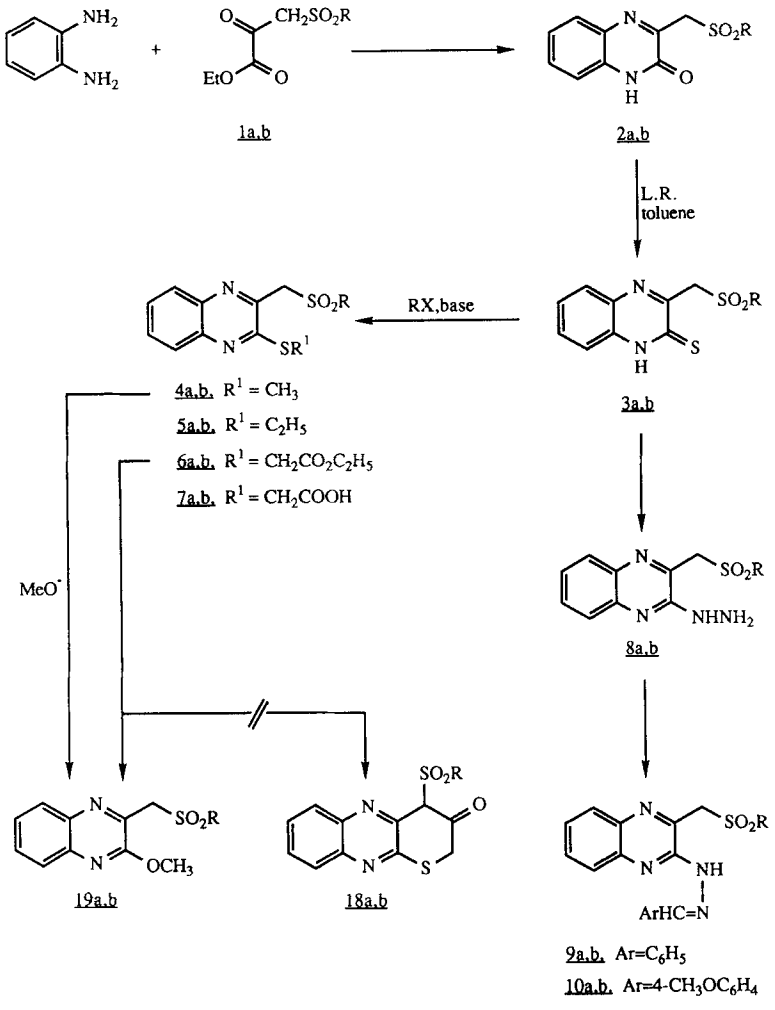


EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam SP-1200 spectrophotometer. NMR spectra were determined with a Varian GEMINI 200 (200 MHz ^{1}H-NMR, 50 MHz ^{13}C-NMR). All new compounds gave satisfactory elemental analyses (C, H, N) which were carried out at the Microanalytical Centre, Cairo University. Ethyl sulfonylpyruvates 1a,b[15] and 3-arylsulfonylmethylquinoxalin-2(1H)-ones 2b[16] were prepared as described.

3-Methylsulfonylmethylquinoxalin-2(1H)-one (2a): A solution of 1a (0.39 g, 2 mmol) in methanol (5 ml) was added slowly with stirring to a solution of *o*-phenylenediamine (0.22 g) in dilute acetic acid (20%, 10 ml). The reaction mixture was then heated under reflux for 15 min. After cooling the precipitate was collected and recrystallized from water to give brown needles of 2a.

3-Sulfonylmethylquinoxaline-2(1H)-thiones 3a,b: A mixture of each of 2a,b (10 mmol) and Lawesson's reagent (4 g) in dry toluene (20 ml) was heated under reflux for 3 h. After cooling the precipitate was collected and recrystallized from acetic acid (75%) as brown crystals of 3a,b respectively in 90–94% yields.



a, R = CH_3

b, R = C_6H_5

2-Alkylthio-3-sulfonylmethylquinoxalines 4–7: To a solution of each of 3a,b (2 mmol) in aqueous NaOH (10 ml, 1%) was added the appropriate alkyl halide (2.2 mmol) portionwise with stirring over a period of 1 h. The reaction mixture was then left overnight at room temperature. The solid precipitated was collected and crystallized from ethanol to give the corresponding 2-alkylthioquinoxalines 4–7.

2-Hydrazino-3-sulfonylmethylquinoxalines 8a,b: A mixture of each of 3a,b (10 mmol) and hydrazine hydrate (4 ml, 80%) in ethanol (20 ml) was heated under reflux for 3 h during which time H_2S evolved and brownish precipitate was formed. After cooling, the precipitate was collected and crystallized from ethanol to give yellow crystals of 8a,b in 78–82% yield.

Hydrazones 9a,b, 10a,b, 11a,b: A mixture of equimolecular amounts of each of 8a,b and the appropriate aldehyde or α-keto acid (10 mmol) in ethanol (20 ml) was heated under reflux for 15 min. After cooling the precipitate was collected and crystallized from ethanol to give yellow crystals of the corresponding hydrazones 9–11 in 75–85% yield.

[1,2,4]Triazino[4,3-a]quinoxalines 12a,b: A solution of each of 11a,b (10 mmol) in acetic anhydride (20 ml) was heated under reflux for 1/2 h and the solvent was then removed in vacuo. The remaining precipitate was triturated with ethanol and recrystallized from DMF to give yellow crystals of 12a,b in 75–80% yield.

[1,2,4]Triazolo[4,3-a]quinoxalines 13a,b: A mixture of each of 8a,b (10 mmol) and formic acid (1.5 ml, 85%) was heated under reflux for 5 h and then diluted with ice-cold water (10 ml). The precipitate was collected and crystallized from ethanol to give yellow crystals of 13a,b respectively in 70–75% yield.

1-Methyl-3-sulfonylmethyl[1,2,4]triazolo[4,3-a]quinoxalines 14a,b: A mixture of each of 8a,b (10 mmol) and acetic anhydride (20 ml) was heated under reflux for 1/2 h. After cooling the precipitate was collected and crystallized from ethanol to give colorless crystals of 14a,b respectively in 75–82%.

[1,2,4]Triazolo[4,3-a]quinoxaline-1(2H)-thiones 16a,b: A solution of each of 8a,b (10 mmol) and carbon disulfide (6 ml) in dry pyridine (20 ml) was heated under reflux for 5 h. After cooling the precipitate was collected and crystallized from acetic acid or ethanol to give yellow crystals of 16a,b respectively in 64–70% yield.

Tetrazolo[1,5-a]quinoxalines 17a,b: To a suspension of each of 8a,b (10 mmol) in aqueous HCl (15 ml, 6N) was added a solution of sodium nitrite (0.5 g) in H_2O (5 ml) dropwise with stirring at 0–10°C over a period of 10 min. The reaction mixture was further stirred for 1 h at room temperature and the solid formed was collected, washed with water and recrystallized from DMF/ethanol to give yellow crystals of 17a,b respectively in 74–79% yield.

2-Methoxyquinoxalines 19a,b: A solution of each of 4a, 6a,b (10 mmol) in sodium methoxide solution (prepared from 0.2 g of Na in 6 ml of dry methanol) was heated under reflux for 2 h. The solvent was then removed in vacuo and the residue was crystallized from dilute ethanol to give yellow crystals of the corresponding derivative 19a,b in 60–70% yield.

6-Methylsulfonylmethylquinoxalino[2,1-b]quinoxalin-12-one 20: An intimate mixture of 4a (0.3 g) and anthranilic acid (0.1 g) was heated at 180°C (oil bath) for 2 h. After cooling, the residue was triturated with ethanol and crystallized from acetic acid as pale yellow crystals of 20 in 60% yield.

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