A Facile Synthesis of Novel Triazoloquinoxalinones and Triazinoquinoxalinones [1]

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A series of 1-aryl-*s*-triazolo[4,3-*a*]quinoxalin-4-ones, **3**, were synthesized *via* the pyrolysis of the corresponding hydrazones, **6**. Thus, the cyclodehydrogenation occurred by refluxing them in an inert solvent (*e.g.* ethylene glycol) to give the triazoloquinoxalin-4-ones in a satisfactory yield. Using DMSO as a solvent for the above transformation afforded as a minor by-product an *S*-ylid. In contrast to earlier findings, annelation of a six-membered ring was successful and achieved through the pyrolysis of the pyruvate hydrazones derived of the quinoxalin-4-ones at ~230° to give the *as*-triazino[4,3-*a*]quinoxalin-5-ones, **4**. The reaction of **5** with acetylacetone afforded 3-(3',5'-dimethylpyrazol-1-yl)-2(1*H*)-quinoxalinone, **10**. The structural assignments for the new compounds were based on their elemental analysis and spectroscopic data as well as an independent synthesis.

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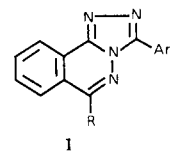
The search for antianxiety agents that are devoid of the side effects associated with the benzodiazepines (BZs) has led to the discovery of various non-BZ classes of compounds with high *in vitro* activity in the BZ binding assay. The discovery of the high BZ binding site affinity of several 3-aryl-*s*-triazolo[3,4-*a*]phthalazine [3-6], **1** and 2-arylpyrazolo[4,3-*c*]quinolin-3(5*H*)-ones, **2** [7] prompted us to synthesize a number of *s*-triazolo[4,3-*a*]quinoxalin-4-ones, **3** and *as*-triazino[4,3-*a*]quinoxalin-5-ones, **4** on the basis of the structural similarity with the active compounds.



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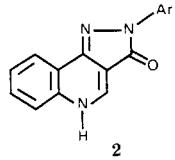

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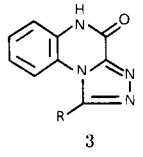

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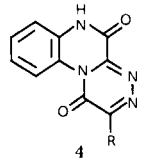

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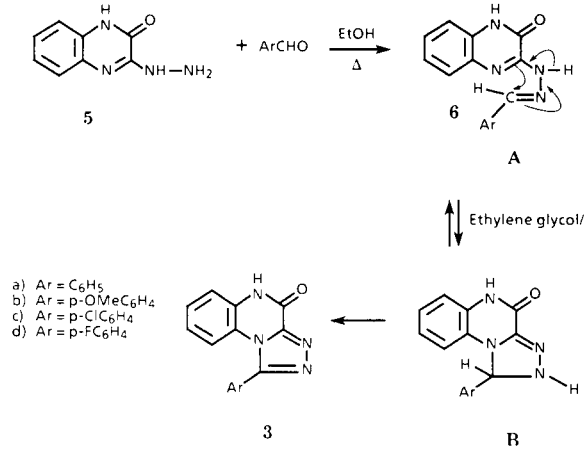
The synthesis of the skeleton frame of the novel compounds of type **3** was achieved *via* condensation of 3-hydrazino-2(1*H*)-quinoxalinone **5** with aldehydes to form the corresponding hydrazones **6** (Table I) followed by thermal annelation of the latter. Thus, refluxing the quinoxalyl hydrazones **6** in a high boiling inert solvent such as ethylene glycol [8] afforded colorless crystalline products whose elemental analyses were consistent with the *s*-triazoloquinoxalin-4-one structure, **3**.

The result of the reaction may be explained according to the mechanism illustrated in Scheme I. A ring-chain tautomerism [5] is proposed between the hydrazone form **A** and the dihydrotriazoloquinoxalin-4-one form **B**. The formation of the latter is being thermally initiated in this case. A facile dehydrogenation of **6B** will lead to formation of **3**.

Scheme I



5 6 A 3 B

In the case of **6d**, when dimethyl sulfoxide was used as a solvent instead of ethylene glycol for the above transformation, **3d** was formed along with about 6% of a by-product **7d** whose ^{1}H nmr spectrum in dimethyl sulfoxide-d_6 solution showed two singlets at δ 2.2 (3H) and 5.5 (2H) ppm which were assigned for a methyl and methylene group respectively adjacent to a sulfur atom. The aromatic protons gave rise to a multiplet at δ 7.0-7.95 ppm. Its mass spectrum showed the molecular ion at m/z 340 (M^+, RI = 1.8) and daughter fragments at m/z 77 (C_2H_5OS, 12.6) and 61 (C_2H_5S, 100). Based on the above spectroscopic data **7d** is tentatively assigned to be a sulfur ylid.

Table I

Physical Properties of Compounds **6a-6d** and **3a-3e**

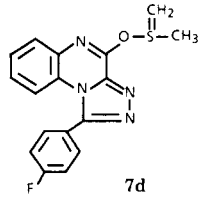
Compound no.	m.p. °C	Yield[a] %	IR cm^{-1}	Molecular formula	Analyses % C	H	N	^{1}H NMR (δ) ppm
6a	245-247	98	1680	$C_{15}H_{12}N_4O$	68.17 (68.10)	4.57 (4.40)	21.20 (20.80)	7.2-8.2 (m, 9H, ArH); 8.7 (s, 1H, CH=N); 11.3, 12.5 (2s, 2H, 2NH)
6b	240-244	99	1670	$C_{16}H_{14}N_4O_2$	65.30 (65.28)	4.79 (4.77)	19.04 (19.16)	3.8 (s, 3H, OCH_3); 6.9-8.2 (m, 8H, ArH); 8.5 (s, 1H, CH=N); 11.0, 12.6 (2s, 2H, 2NH)
6c	256-258	95	1672	$C_{15}H_{11}ClN_4O$	60.31 (60.42)	3.71 (3.69)	18.75 (18.70)	7.1 (s, 3H, ArH); 7.4, 7.7 (2d, 4H, ArH); 8.5 (s, 1H, CH=N); 11.2, 12.9 (2s, 2H, 2NH)
6d	285-287	99	1670	$C_{15}H_{11}FN_4O$	63.83 (63.87)	3.92 (3.89)	19.85 (19.72)	6.9-8.25 (m, 8H, ArH); 8.6 (s, 1H, CH=N); 10.5, 11.2, 11.6, 12.4 (bs, s, bs, s [~2:11:4:9], 2H, 2NH(OH))
3a	>300	60	1685	$C_{15}H_{10}N_4O$	68.70 (68.95)	3.84 (4.12)	21.36 (21.20)	7.0, 7.3, 7.7 (m, m, s, 9H, ArH); 12.1 (s, 1H, NH)
3b	>300	53	1670	$C_{16}H_{12}N_4O_2$	65.75 (65.74)	4.13 (4.35)	19.17 (19.18)	3.91 (s, 3H, OCH_3); 6.85-7.79 (m, 8H, ArH); 12.07 (s, 1H, NH)
3c	>300	70	1670	$C_{15}H_9ClN_4O$	60.72 (60.81)	3.05 (3.02)	18.88 (19.14)	7.09, 7.42 (2d, 4H, J=3.52, ArH); 7.76 (s, 4H, ArH); 12.08 (s, 1H, NH)
3d	>300	76	1680	$C_{15}H_9FN_4O$	64.29 (64.34)	3.23 (3.22)	19.99 (19.91)	6.95-7.9 (m, 3H, ArH); 12.05 (s, 1H, NH)
3e	>300	91	1695	$C_{10}H_8N_4O$	60.00 (60.18)	4.02 (4.20)	27.99 (28.00)	3.0 (s, 3H, CH_3); 7.4, 8.1 (s, d, 4H, ArH); 12.0 (s, 1H, NH)

[a]Obtained by method A

Table II

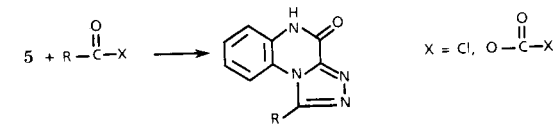
Physical Properties of Compounds **9** and **10**

Compound no.	m.p. °C	Yield %	IR cm^{-1}	Molecular formula	Analyses % C	H	N	^{1}H NMR (δ) ppm
8a	199-200	65	1680	$C_{20}H_{18}N_4O_4$	63.49 (63.10)	4.78 (4.60)	14.81 (14.90)	1.23 (t, 3H, CH_3); 4.3 (q, 2H, CH_2O); 4.4 (s, 2H, CH_2); 7.1-8.0 (m, 9H, ArH); 11.2, 13.3 (2s, 2H, 2NH)
8b	203-205	60	1670	$C_{21}H_{20}N_4O_5$	61.76 (61.49)	4.93 (5.10)	13.72 (13.50)	1.3 (t, 3H, CH_3); 3.9 (s, 3H, OCH_3); 4.3 (q, 2H, OCH_2); 4.4 (s, 2H, CH_2); 6.95, 7.33, 7.9, 8.0 (d, m, m, d, 8H, ArH); 11.7, 13.3 (2s, 2H, 2NH)
9a	>300	85	1715, 1680	$C_{18}H_{12}N_4O_3$	65.06 (64.75)	3.64 (3.90)	16.86 (16.78)	6.77 (s, 1H, = CH); 7.2, 7.5, 8.0, 8.8 (m, m, m, dd, 9H, ArH); 11.7, 13.8 (2s, 2H,2NH)
9b	>300	80	1712, 1680	$C_{19}H_{14}N_4O_4$	62.98 (63.14)	3.89 (3.92)	15.46 (15.48)	3.85 (s, 3H, OCH_3); 6.75 (s, 1H, = CH); 7.05, 7.25, 8.0, 8.8 (d, m, d, dd, 8H, ArH); 11.05, 13.5 (2s, 2H, 2NH)



7d

Compounds of type **3** could also be obtained *via* the reaction of **5** with aroyl (acyl) chlorides or anhydrides. Examples were the reaction of **5** with an excess of benzoyl chloride, *p*-chlorobenzoyl chloride, *p*-fluorobenzoyl chloride, or acetic anhydride which led to the formation of **3a**, **3c**, **3d** and **3e** respectively in good yields.



3a R = C_6H_5
3c R = p-ClC_6H_4
3d R = p-FC_6H_4
3e R = CH_3

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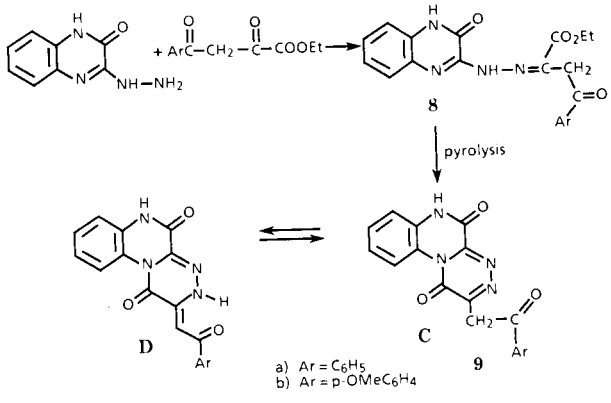
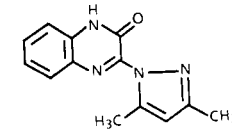
Reactions of **5** with ethyl aroyl pyruvates afforded the corresponding hydrazones **8a** and **8b** in high yields (Table II). Compounds **8a** and **8b** upon thermolysis at ~230° eliminated a molecule of ethanol to give the novel triazinoquinoxaline ring system **9**. The structure assignment of **9** was based on elemental analyses and spectroscopic data. However, this assignment does not agree with results by Shiho and Tagami, [9] who reported earlier that pyrolysis of pyruvic acid (3-phenylquinoxalin-1-yl)hydrazone failed to give the triazinoquinoxaline. These authors reported that they obtained instead, the triazoloquinoxaline ring system.

Type **9** compounds can occur in a number of tautomers, [6]; structures **C** and **D** might represent the most probable ones (Scheme II). Indeed, according to nmr evidence of **9a** and **9b** in dimethylsulfoxide-d_6 solution the predominant tautomer **D** was observed by showing a singlet at δ 6.77 or 6.75 ppm, respectively which is attributed to the vinylic proton of the side chain. Also, the appearance of two exchangeable peaks in the down field region of these spectra further corroborate the occurrence of tautomer **D** as the predominant one in the equilibrium. However, the position of the peaks of the ir spectra (Nujol) of the carbonyl groups of compounds **9a** and **9b** suggests that these compounds exist predominantly in the tautomeric form **C** in this state. Thus, the position of the equilibrium between **C** and **D** seems to be solvent dependent.

Scheme II



The reaction of **5** with 2,4-pentandione afforded 3-(3′,5′-dimethylpyrazol-1-yl)-2(1*H*)-quinoxalinone **10** as colorless crystals. In the ^1H nmr spectrum of **10** in deuteriochloroform, the signals for the protons of the methyl groups at C-3′ and C-5′ appeared at δ 2.34 (s) and 2.49 (s) respectively, and the signal for the proton at C-4′ showed up at δ 6.1 (s). The protons of the quinoxalinone ring cause a multiplet signals at δ 7.34-7.91 of four protons intensity (ArH) and exchangeable singlet at 12.56 (NH). The mass spectrum of **10** showed the molecular ion peak at m/z 240 (relative intensity 65%). Its mass spectrum was also characterized by the occurrence of only a few peaks with high relative intensity at m/z 198 (57%), 96 (100), 95 (55).



10

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Analytical tlc was performed using the ascending technique with EM silica gel 60 F_{254} precoated on plastic sheets. Column chromatography was performed using EM silica gel 60 (0.040-0.063 mm). The ^1H nmr spectra were obtained on an IBM NR-80 spectrometer, using tetramethylsilane as an internal standard. The ir spectra were obtained on a Perkin-Elmer model 599 spectrometer and were calibrated against the 1601 cm^{-1} band of poly(styrene). Elemental analyses were performed at Alexandria University, Faculty of Science Central Laboratory.

Typical Procedure for the Synthesis of Compounds **6a-6d**.

A mixture of **5** (0.01 mole) and the corresponding aldehyde (0.01 mole) in ethanol (20 ml) was refluxed for 5 hours. The precipitate which appeared on cooling was filtered off and dried. It was recrystallized from ethanol. Yields and physical properties are summarized in Table I.

Typical Procedures for the Synthesis Compounds **3a-3d**.

a) A solution of the corresponding hydrazone, **6** (1 g) in ethylene glycol (3 ml) was heated under reflux for 5-8 hours. The mixture was left to reach room temperature and then poured onto an ice-water mixture. The product was filtered off and dried. It was recrystallized from ethanol. Yields and physical properties are summarized in Table I.

b) A solution of **6d** in dimethylsulfoxide (2 ml) was refluxed for 8 hours. The mixture was poured onto an ice water mixture and the precipitate was filtered off, washed with water and dried. The products **3d** and **7d** were isolated by column chromatography using ethyl acetate as an eluent; **7d** had mp >300°; ms: m/e 340.0776 (Calcd. for $[C_{17}H_{13}FN_4OS]^+$, 340.07959).

c) A mixture of **5** (1 g) and slightly excess of the corresponding acid chloride was heated under reflux for 1 hour. The mixture was allowed to cool to room temperature then diluted with water and neutralized with sodium bicarbonate. The product was filtered off, washed with water, and dried.

1-Methyl-*s*-triazolo[4,3-*a*]quinoxalin-4-one (**3e**).

A solution of **5** (0.5 g, 0.0028 mole) in acetic anhydride (10 ml) was refluxed for 1 hour. The mixture was left to cool to room temperature and the precipitate was filtered off, washed with water and dried (yield = 91%).

General Procedure for the Synthesis of **8a** and **8b**.

A solution of an equimolar amount of **5** and the corresponding ethyl aroyl pyruvate in ethanol was refluxed for 1 hour. The material that separated was filtered off and recrystallized from ethanol. Yields and physical properties are summarized in Table II.

General Procedure for the Synthesis of **9a** and **9b**.

Type **8** hydrazone in a flask was immersed in an oil bath at ~230° for 30 minutes. After cooling, the residue was triturated with ethanol, filtered off and recrystallized from ethanol. Yields and physical properties are summarized in Table II.

3-(3',5'-Dimethylpyrazol-1-yl)-2(1*H*)-quinoxalinone **10**.

A solution of **5** (0.5 g, 0.0028 mole) in acetylacetone (5 ml) was refluxed for 1 hour. The mixture was left to cool to room temperature and the precipitate was filtered off and crystallized from methanol, yield 70%, mp 203°.

Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.47; H, 5.16; N, 23.16.

REFERENCES AND NOTES

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