Synthesis of 4(Pyrazol-3-yl)[1,2,4]triazolo[4,3-*a*]quinoxalines and Tetrazolo Analog [1]

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The transformation of 2-chloro-3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl]quinoxaline **3** to 1-aryl-4-[5-(hydroxymethyl-1-phenylpyrazol-3-yl][1,2,4]triazolo[4,3-*a*]quinoxalines **4a-c** has been achieved upon treatment with aroylhydrazines in boiling butanol. Compounds **4a-c** were smoothly acetylated by acetic anhydride to give their acetyl derivatives **5a-c** in good yield. 4-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]-1-methyl[1,2,4]triazolo[4,3-*a*]quinoxaline was prepared by ring closure of 2-hydrazino-3-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl]quinoxaline **6** by the action of acetic anhydride. The reaction of **6** with acetylacetone afforded 3-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl]-2-(3,5-dimethylpyrazol-1-yl)quinoxaline **8**. In addition, the reaction of **3** with sodium azide in boiling *N,N*-dimethylformamide yielded the fused tetrazolo[1,5-*a*]quinoxaline **9**.

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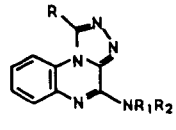
In the course of a program directed to synthesis of quinoxalines annelated with various five and six membered heterocycles [2-6], derivatives of [1,2,4]-triazolo[4,3-*a*] quinoxaline became an object of interest. Quinoxalines as well as pyrazoles exhibit useful pharmacological properties [7-13] such as antipyretic, analgesic, anti-inflammatory and anti-ucler agents. A search of the literature revealed that a series of 4-amino[1,2,4]triazolo[4,3-*a*]quinoxalines **1** are among the most potent and A_1 or A_2 selective nonxanthine adenosine antagonists known [14], which prompted our interest in the synthesis of their 4-(pyrazol-3-yl) analog.



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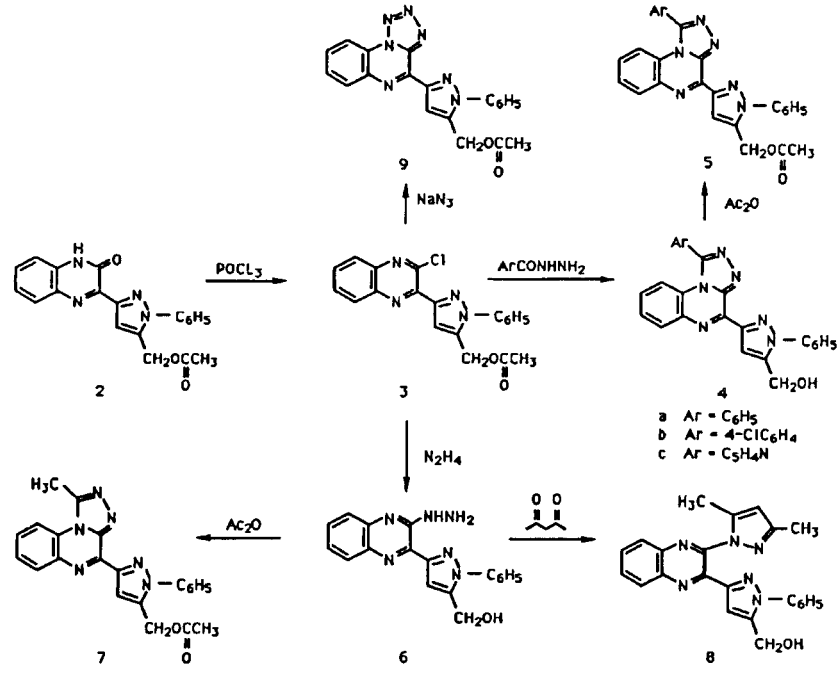
The 4-(pyrazol-3-yl)[1,2,4]triazolo[4,3-*a*]quinoxaline derivatives were prepared as shown in the Scheme below. The 3-[5-(acetoxymethyl)-1-phenylpyrazol-3-yl]quinoxalin-2(1*H*)-one, **2** [15] was transformed with phosphorus oxychloride to **3** as previously described [16]. Reaction of **3** with excess aroylhydrazines (Ar = C_6H_5, 4-ClC_6H_4,



Table

1-Aryl-4-[5-(hydroxymethyl)-1-phenylpyrazol-3-yl] [1,2,4]triazolo[4,3-*a*]quinoxalines **4a-c** and 4-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]-1-aryl[1,2,4]triazolo[4,3-*a*]quinoxalines **5a-c**

No	Yield (%)	Ar	MP (°C)	Molecular Formula	Analysis (%) Calcd./Found			IR (KBr) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz) 250 MHz	MS (70 eV) m/z (%)
					C	H	N			
4a	82	C_6H_5	235-236	$C_{25}H_{18}N_6O$	71.75 71.52	4.34 4.61	20.09 19.89	3237	4.67 (d, J = 5.04, 2H, CH_2O), 5.75 (t, J = 5.04, 1H, OH), 7.40-8.16 (m, 15H arom)	418 (M^+, 100), 417 (49) 401 (11), 317 (22), 105 (15), 103 (12), 77 (50)
4b	56	4-ClC_6H_4	256-258	$C_{25}H_{17}ClN_6O$	66.30 66.49	3.78 3.68	18.56 18.71	3375	4.66 (d, J = 5.12, 2H, CH_2O), 5.71 (t, J = 5.12, 1H, OH), 7.43, 7.51-7.91, 8.15 (d, m, d, 14H arom)	454 (M^+ + 2 ,36), 452 (M^+, 100), 453 (43), 451 (51), 317 (17), 157 (4), 155 (12), 141 (5), 139 (17), 77 (39)
4c	75	C_5H_4N	237-238	$C_{23}H_{17}N_7O$	67.80 67.81	4.21 4.23	24.07 23.87	3498	4.66 (br s, 2H, CH_2O), 5.72 (br t, 1H,OH), 7.44-8.14, 8.29 (m, s, 14H arom)	419 (M^+, 100), 418 (70), 390 (13), 90 (10), 77 (35)
5a	91	C_6H_5	204-205	$C_{27}H_{20}N_6O_2$	70.42 70.65	4.38 4.50	18.25 18.45	1745	2.11 (s, 3H, CH_3CO), 5.23 (s, 2H, CH_2O), 7.27-7.78, 8.18, 829 (m, s, d, 15H arom)	460 (M^+, 27) 418 (30), 417 (99), 359 (16), 103 (11), 77 (18)
5b	91	4-ClC_6H_4	235-237	$C_{27}H_{19}ClN_6O_2$	65.52 65.72	3.87 3.91	16.98 17.02	1737	2.05 (s, 3H, CH_3CO), 5.28 (s, 2H, CH_2O), 7.42, 7.54-7.93, 8.14 (d, m, d, 14H arom)	
5c	93	C_5H_4N	262-263	$C_{25}H_{19}N_7O_2$	66.80 66.72	4.26 4.45	21.82 21.98	1742	2.11 (s, 3H, CH_3CO), 5.23 (s, 2H, CH_2O), 7.28, 7.43-7.77, 8.14, 8.33, 8.95 (s, m, s, d, d, 14H arom)	

C_5H_4N) in boiling *n*-butanol resulted in the formation of the corresponding compounds **4a-c** in good yield. The structure of the products was established from their spectral characteristics which indicated that in addition to heterocyclization, deacetylation had taken place. Heating **4a-c** in acetic anhydride led to the formation of their acetyl derivatives **5a-c**.

For the preparation of the 1-methyl analog, **7**, compound **3** was treated with hydrazine to form **6** which on treatment with boiling acetic anhydride afforded **7**. On the other hand, treatment of **6** with acetylacetone yielded compound **8**. The structural assignment of **8** was confirmed by ^{13}C-nmr analysis.

Compound **3** was converted to tetrazolo[1,5-*a*]pyridazine **9** by the reaction of the former with sodium azide in *N,N*-dimethylformamide. The structure of **9** was supported by infrared spectroscopy.

Currently, the products isolated herein are being screened for biological activity.

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are reported uncorrected. Analytical tlc was performed using ascending technique with EM silica gel 60 F_{254} precoated on plastic sheets. The ir spectra were obtained on Unicam SP 1025 spectrometer, and were calibrated against the 1601 cm^{-1} band of polystyrene. The nmr spectra were recorded on Bruker AC-250 or Nicolet NT 300 MHz spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Apparent coupling constants (J) are given in Hertz (Hz). A Hewlett-Packard 5995 Gas Chromatograph/Mass Spectrometer was used to record eims data at 70 eV. Elemental analyses were preformed in the Chemistry Department, Faculty of Science, Alexandria, and/or Ain-Shames Universities, Egypt.

1-Aryl-4-(hydroxymethyl)-1-phenylpyrazol-3-yl][1,2,4]triazolo-[4,3-*a*]quinoxaline (**4**).

General Procedure.

A solution of **3** (2.6 mmoles) and the desired aroylhydrazine (5.9 mmoles) in butanol (20 ml) was heated under reflux for 8 hours. The reaction mixture was concentrated and the desired product that separated out was filtered off and recrystallized from ethanol or purified by flash column chromatography on silica gel using ethyl acetate as an eluent (Table).

4-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]-1-aryl[1,2,4]triazolo[4,3-*a*]quinoxaline (**5**).

General Procedure.

A solution of **4** (0.72 mmole) in acetic anhydride (5 ml) was heated under reflux for 1 hour. The mixture was then cooled and poured onto crushed ice. The product was filtered off, washed with water, dried, and recystallized from ethanol (Table).

2-Hydrazino-3-[5-hydroxymethyl)-1-phenylpyrazol-3-yl]quinoxaline (**6**).

A suspension of **3** (0.3 g, 0.79 mmole) in hydrazine hydrate (1 ml) was heated under reflux for 1 hour. The resulting product was filtered, washed with ethanol, and dried to yield 0.25 g (95%), mp 224-226°; ir (potassium bromide): 3311, 3213, 3138 cm^{-1}; ^1H-nmr (300 MHz, DMSO-d_6): δ 4.62 (d, J = 5.52 Hz, 2 H, CH_2O), 4.77 (br s, 2H, NH_2), 5.70 (t, J = 5.52 Hz, 1H, OH), 7.35-7.90 (m, 10H, arom), 9.44 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_6O$: C, 65.04; H, 4.85; N, 25.29. Found: C, 65.24; H, 4.91; N, 25.32.

4-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]-1-methyl[1,2,4]triazolo[4,3-*a*]quinoxaline (**7**).

A solution of **6** (0.3 g, 0.90 mmole) in acetic anhydride (5 ml) was refluxed for 1 hour. The mixture was allowed to cool to room temperature and was then poured onto crushed ice. The product was collected by filtration, washed with water and dried to yield 0.3 g (83%) mp 214-215°; ir (potassium bromide): 1745 (COO) cm^{-1}; ^1H-nmr (250 MHz, DMSO-d_6): δ 2.10 (s, 3H, CH_3CO), 3.23 (s, 3H, CH_3), 5.20 (s, 2H, CH_2O), 7.48-7.65, 8.11, 8.21, 8.30 (m, s, m, m, 10H arom).

Anal. Calcd. for $C_{22}H_{18}N_6O_2$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.11; H, 4.39; N, 20.86.

3-[5-(Hydroxymethyl)-1-phenylpyrazol-3-yl]-2-(3,5-dimethylpyrazol-1-yl)quinoxaline (**8**).

A solution of **6** (0.5 g, 1.5 mmoles) in acetylacetone (5 ml) was refluxed for 1 hour. The mixture was allowed to cool to room temperature and the precipitate was filtered and crystallized from methanol-benzene to yield 0.54 g (91%), mp 173-174°; ir (potassium bromide): 3245 (OH) cm^{-1}; ^1H-nmr (300 MHz, DMSO-d_6): δ 2.09, 2.31 (2 s, 6H, 2 CH_3), 3.19 (bs, 1H, OH), 4.53 (bs, 2H, CH_2O), 6.04, 6.18 (2s, 2H, proton at 4-positions of the pyrazolyl rings), 7.33-8.29 (5 m, 9H arom); ^{13}C-nrmr (75.5 MHz, deuteriochloroform): δ 11.4, 13.5, 55.1, 106.9, 108.5, 124.1, 127.8, 127.9, 128.9, 129.1, 129.3, 130.6, 131.1, 139.3, 140.2, 141.7, 142.2, 143.7, 144.2, 144.8, 147.5, 150.0.

Anal. Calcd. for $C_{23}H_{20}N_6O$: C, 69.68; H, 5.09; N, 21.20. Found: C, 69.53; H, 4.98; N, 21.37.

4-[5-(Acetoxymethyl)-1-phenylpyrazol-3-yl]tetrazolo[1,5-*a*]-quinoxaline (**9**).

A solution of **3** (0.5 g, 1.32 mmoles) and sodium azide (0.18 g, 2.76 mmoles) in *N,N*-dimethylformamide (20 ml) was heated under reflux for 8 hours. The solution was then cooled and poured into water. The precipitate was filtered and recystallized from chloroform-ethanol to obtain **9**, (yield 0.42 g (83%) mp 185°; ir (potassium bromide): 1738 cm^{-1}; ^1H-nmr (250 MHz, DMSO-d_6): δ 2.05 (s, 3H, CH_3CO), 5.28 (s, 2H, CH_2O), 7.59-8.63 (m, 10H arom); ms: m/z 385 (M^+,2), 358 (23); 357 (49), 315 (55), 314 (100), 286 (24), 77 (24).

Anal. Calcd. for $C_{20}H_{15}N_7O_2$: C, 62.33; H, 3.92; N, 25.44. Found: C, 62.11; H, 3.74; N, 25.18.

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