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Note

Synthesis and antiallergy activity of 2-aryl-5-aroylmethylimidazo [1,2-*a*]quinoxalin-4-one

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Quinoxaline-2,3-diones **1** have been alkylated with phenacyl bromides **2** using K_2CO_3, acetone and PTC to give 1,4-bis(aroylmethyl)quinoxaline-2,3-diones **3,4** which when refluxed in acetic acid containing ammonium acetate yield the imidazo 1,2-*a*quinoxalines **5,6**. Antiallergy activity of these compounds is discussed.

Keywords: Triazoles, 1,5-diaryl-bis-imidazoquinoxaline, passive cutaneous anaphylaxis (PCA)

Synthesis of fused tricyclic triazoles have yielded compounds with marked diuretic activity[1,2], muscle relaxant[3,4] and anti-inflammatory activity[5]. Certain ditriazolo quinoxaline-diones[6] and triazoloquinoxaline-diones[7] have been reported to possess anti-allergy property. The synthesis and anti-allergy activity of 1-substituted [1,2,4]-triazolo [4,3-*a*] quinoxalin-4-one has been reported[8]. In an effort towards getting better anti-allergy agents, it was of interest to investigate the effect of imidazole fusion to quinoxaline on the activity. Herein is reported the synthesis and anti-allergy activity of 1-aryl-5-aroyl methyl, imidazo [1,2-*a*] quinoxalin-4-ones **5** and **6**.

Results and Discussion

Quinoxaline-2,3-diones **1** were alkylated with phenacyl bromides **2** in refluxing acetone containing K_2CO_3 and PTC to give 1,4-bis aroyl methyl-quinoxalin-2,3-dione **3** and **4**. Various **3** and **4** were refluxed in large excess of NH_4OAc in acetic acid with the intention of synthesizing 1,5-diaryl-bis-imidazo (1,2-*a*, 2′,1′-*c*) quinoxaline **7** (**Scheme I**).

IR, ^{1}H NMR and elemental analyses indicated the formation of 1-aryl-5-aroylmethylimidazo(1,2-*a*)-quinoxalines **5,6**. Mass spectral fragmentation data also confirmed the formation of **5** and **6**. The base peak is formed by the loss of aroyl cation from M^+.

Anti-allergy activity was carried out according to the procedure described earlier[9]. Out of all the compounds, **4a** showed moderate anti-allergy activity in passive cutaneous anaphylaxis (P.C.A.) test in rats, exhibiting inhibition of 33% at a dose of 20 mg/kg peros (P.O.) All the other compounds did not show any significant activity (**Table I**).

Experimental Section

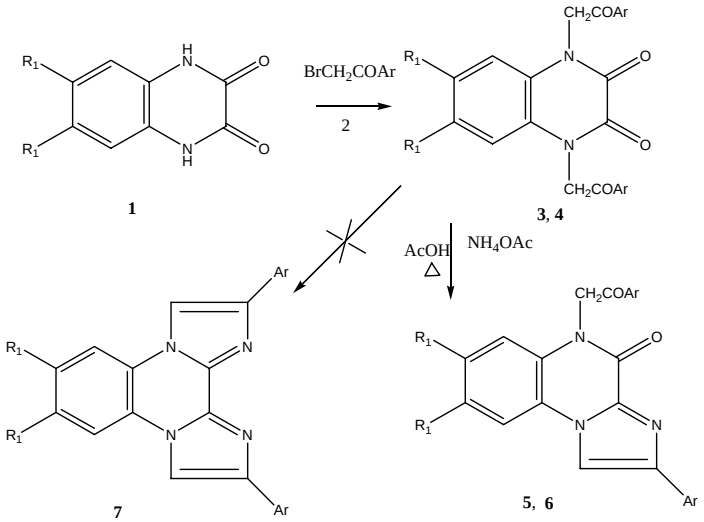
Melting points were determined in open capillaries on Mettler F.P. 90 apparatus and are uncorrected. IR spectra (Nujol, cm^{-1}) were recorded on a Perkin-Elmer 577 grating spectrometer. ^{1}H NMR spectra (δ, ppm) were recorded on a Varian A-90 (EM-390) instrument using TMS as internal standard.

The following experimental procedures are illustrative of the general methods used.

6,7-Dinitro-1,4-bis(4-methoxyphenylcarbonylmethyl)quinoxaline 2,3-dione, 4b

A mixture of 6,7-dinitroquinoxaline-2,3-dione (**1b**, 2.52 g 0.01 mole), K_2CO_3 (3.45 g, 0.025 mole), Bu_4NBr (0.16 g, 0.0005 mole) and 18-C_6 (0.07 g, 0.00025 mole) in acetone (50 mL) was refluxed under stirring. An acetone solution of 4-methoxyphenacyl bromide (**2h**, 4.81 g, 0.021 mole) was added dropwise to the reaction mixture. After the addition the reaction mass was refluxed with stirring for 2 hr. Subsequently the solvent was distilled off under reduced pressure. The crude product was purified by recrystallization from dichloroethane containing 10% methanol to give pure **4b**, 4.11 g (75%). m.p. 281-82°C; IR(Nujol): 3080, 1720, 1710, 1670, 1600, 1380, 1320, 1275, 1250, 1170 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.87 (s, 6H, 2 × OCH_3), 5.88 (s, 4H, 2 × CH_2CO-), 7.09 and 8.07 (A_2B_2 q, J = 9 Hz, 8H, 2 × 4-MeO-C_6H_4-CO-); MS: *m/z* 548$(M)^+$. Anal. Found: C, 56.75; H, 3.53; N, 10.46. $C_{26}H_{20}N_4O_{10}$ requires C, 56.93; H, 3.65; N, 10.22%.

The following compounds were similarly prepared (Yield %, m.p.); **3a**,79%, 265-66°C, M^+398; **3b**, 94%, 285-86°C, M^+458; **3c**, 84%, 289-90°C, M^+555.8; **3d**, 76%, 300°C, M^+467; **3e**, 82%, 287-88°C, M^+434; **4a**, 80%, 260-62°C, M^+488; **4b**, 75, 281-83°C, M^+548; **4c**, 93%, 291-93°C, M^+645.8; **4d**, 85%, 296-97°C,



2-6	Ar
a	C_6H_5
b	4 - $MeOC_6H_4$
c	4 - BrC_6H_4
d	4 - ClC_6H_4
e	4 - FC_6H_4

1a, **3**, **5** : R_1 = H

1b, **4**, **6**: R_1 = NO_2

Scheme I

Table I — Physical characterization data and antiallergy screening results for compounds **5a-e** and **6a-e**

Compd	R_1[a]	Ar	Yield (%)	m.p. °C	Mol. formula	N %[b]		Antiallergy activity[c]%
						Found	Calcd	
5a	H	C_6H_5	96	276-77	$C_{24}H_{17}N_3O$	11.08	11.46	33.33
5b	H	4-CH_3O-C_6H_4	73	290-91	$C_{26}H_{21}N_3O_4$	9.57	9.58	N.A.
5c	H	4-Br-C_6H_4	75	300	$C_{24}H_{15}Br_2N_3O_2$	7.82	7.54	″
5d	H	4-Cl-C_6H_4	94	300	$C_{24}H_{15}Cl_2N_3O_2$	9.37	9.00	″
5e	H	4-F-C_6H_4	72	290-92	$C_{24}H_{15}F_2N_3O_2$	10.12	10.33	″
6a	NO_2	C_6H_5	94	298-99	$C_{24}H_{15}N_5O_6$	14.92	15.17	″
6b	NO_2	4-CH_3O-C_6H_4	95	300	$C_{26}H_{19}N_5O_3$	13.23	12.90	″
6c	NO_2	4-Br-C_6H_4	81	300	$C_{24}H_{13}Br_2N_5O_6$	11.16	11.32	″
6d	NO_2	4-Cl-C_6H_4	93	300	$C_{24}H_{13}Cl_2N_5O_6$	13.01	13.41	″
6e	NO_2	4-F-C_6H_4	78	300	$C_{24}H_{13}F_2N_5O_6$	13.96	13.78	″

N.A: Not active

[a] Compounds **5a** and **5b** were recrystallized from dichloroethane-methanol; **5c**, **6a**, **6c-e** from *N*,*N*-dimethyl acetamide and **5d** and **5e** from aqueous DMF.

[b] Satisfactory C,H analyses were obtained for all the compounds.

[c] All the compounds were tested by oral route at the 20 mg/kg. dose.

M^+557; **4e**, 77, 259-60°C, M^+524; Compounds **3a**, **3e** and **4b** were purified by recrystallization from dichloroethane-methanol. **3b-d** and **4c-e** were purified by recrystallization from N,N-dimethylacetamide while compound **4a** from dichloroethane-hexane.

7,8-Dinitro-2(4-methoxyphenyl)-5(4-methoxyhphenylcarbonylmethyl) imidazo [1,2-*a*] quinoxalin-4-one, 6b

A mixture of **4b** (2.74 g, 0.005 mole) and NH_4OAc (1.56 g, 0.02 mole) in acetic acid (10 mL) was refluxed with stirring for 10 hr. Acetic acid was then distilled off under reduced pressure. The residue was stirred with water (10 mL) and the mass was neutralized with 25% aqueous ammonia. The stirring was continued for 10 min. The solid was filtered, washed with water and pressed dry. The crude compound was purified by recrystallization from *N*,*N*-dimethylacetamide to give **6b**, 2.51 g, 95%; IR(Nujol): 3150, 3060, 1690, 1670, 1610, 1600, 1380, 1340, 1265, 1240, 1170 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.82 (s, 6H, 2 × OCH_3), 3.92 (s, 2H, CH_2); 7.1 and 7.96 (A_2B_2 q, *J*=9Hz, 4H, 4′-MeO-C_6H_4), 7.21 and 8.19 (A_2B_2 q, *J*=9Hz, 4H, 4′′-MeO-C_6H_4-CO-), 8.53 (s, 1H, C_6-H), 9.21 (s, 1H, C_1-H) and 9.33 (s, 1H, C_9-H); MS: *m/z* 529 M^+. Anal. Found: C, 58.88; H, 3.71; N, 12.90. $C_{26}H_{19}N_5O_8$ requires C, 58.98; H, 3.59; N, 13.23%.

Compounds **5a-e**, **6a** and **6c-e** were similarly prepared.

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