GENERALITY AND SCOPE OF THE SYNTHESIS OF 2-ARYLPYRROLO[3,4-*b*]QUINOXALINE-1,3-DIONES FROM 2,3-DICHLORO-*N*-ARYLMALEIMIDES. II

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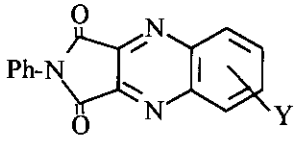
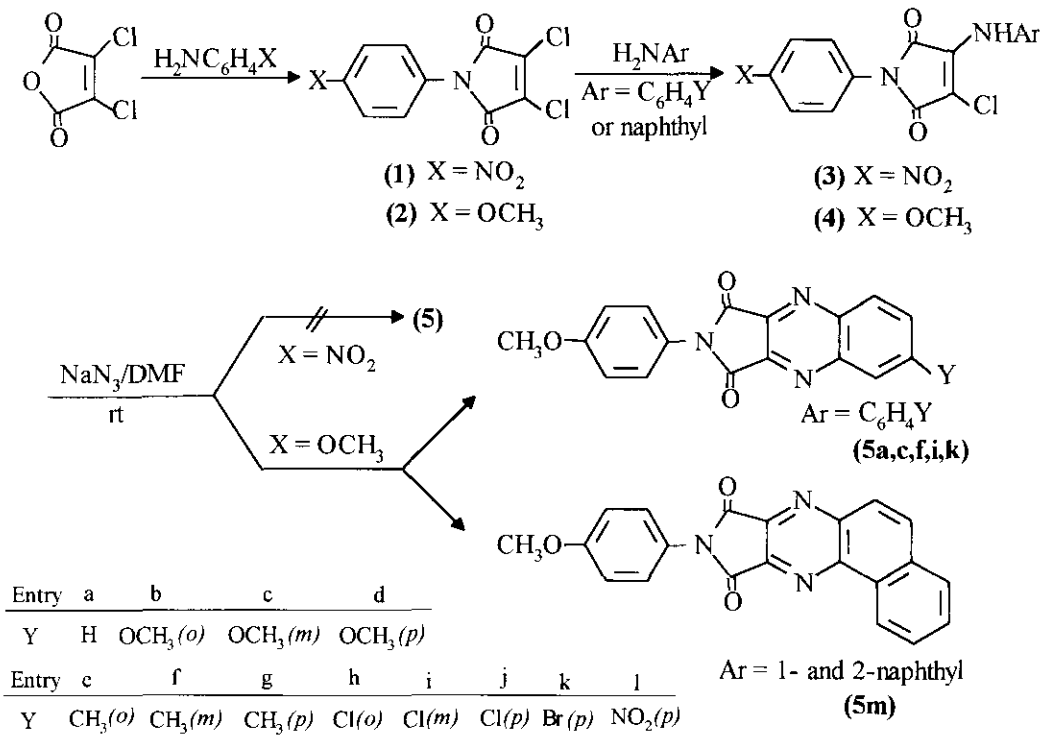
Abstract- Nucleophilic substitution of 2,3-dichloro-*N*-arylmaleimides **(1)** and **(2)** with a series of arylamines gives 2-arylamino-3-chloro-*N*-arylmaleimides **(3)** and **(4)**, respectively. When **4** is treated with sodium azide at room temperature, it cyclizes to the 2-(*p*-methoxyphenyl)pyrrolo[3,4-*b*]quinoxaline-1,3-diones **(5)**. Under the same conditions, the 2-(*p*-nitrophenyl) analogue **(3)** fails to cyclize. Ring closure is also subject to the steric and electronic effects of substituents in the nucleophile.

With a view to preparing heterocycles of the type below which, on hydrolysis of the imide link, can lead to a wide variety of quinoxaline derivatives, the synthetic potential of nucleophilic substitution reactions of 2,3-dichloro-*N*-phenylmaleimide was explored in Part I.[1]



With mono- and bi-functional arylamines as nucleophiles the products, 2-substituted or 2,3-disubstituted *N*-phenylmaleimides, depended on the nucleophile and the solvent. Only specific 2-arylamino-3-chloro-*N*-phenylmaleimides, when treated with NaN_3/DMF at room temperature, cyclized to 2-phenylpyrrolo- [3,4-*b*]quinoxaline-1,3-diones.[1] This study now describes the influence of substituents in the maleimide and in the nucleophile on ring closure and hence assesses the generality and scope of this cyclization reaction. In the present work, the 2,3-dichloro-*N*-arylmaleimides were prepared[2] by refluxing 2,3-dichloromaleic anhydride with the substituted aniline to give **1** (X = NO_2) and **2** (X = OCH_3) (Scheme 1). Because of the weak nucleophilicity of the *p*-nitroaniline compared to *p*-anisidine, **1** was formed at a slower rate and in lower yield relative to **2**.

Scheme 1



Refluxing **1** and **2** with the appropriate arylamine[1] gave the 2-arylamino-3-chloro-*N*-arylmaleimides **(3)** and **(4)**, respectively. This conjugate addition-elimination reaction was influenced by the electronic nature of X in the maleimide and the nature and location of Y in the nucleophile. The effect of X was reflected in the formation of **3** in shorter reaction times and at lower reaction temperatures relative to **4** (Table 1). For example, while *p*-nitroaniline with **1** gave **3l** after 5 h, 24 h of reflux with **2** failed to yield **4l**. 2,3-Dichloro-*N*-phenylmaleimide (X = H) also failed to react with *p*-nitroaniline.[1] This suggests that an electron withdrawing group in the *N*-aryl moiety of the maleimide facilitates displacement of the chlorine atom, particularly with a weak nucleophile like *p*-nitroaniline.

Substituent Y in the nucleophile also influenced the formation of **3** and **4**. *p*-Substituted nucleophiles with both **1** and **2** gave the highest yields in the shortest reaction times and at lower temperatures as compared to the corresponding *o*-substituted nucleophiles which showed the reverse, or failed to react altogether as with *o*-bromoaniline (Table 1). The electronic nature of Y similarly influenced reaction of **1** and **2** with the nucleophile. For example, reacting **1** with various *p*-substituted nucleophiles showed that the yield was the lowest and the reaction time the longest for **3l** (Y = NO_2) as compared to **3d**, **3g**, **3j** and **3k** where Y was an electron releasing group.

Table 1. Physical data for compounds **(3,4** and **5)**

Compd ($X=NO_2$)	Time	Yield (%)	Compd ($X=OCH_3$)	Time	Yield (%)	Compd ($X=OCH_3$)	Time	Yield (%)
3a	-	-	**4a**	30 min	91	**5a**	13 h	63
3b	25 min	68	**4b**	50 min	68	**5b**	-	-
3c	20 min	90	**4c**	40 min	75	**5c**	3 d	47
3d	15 min	95	**4d**	20 min	98	**5c**	24 h	73
3e	60 min	60	**4e**	90 min	71	**5e**	-	-
3f	20 min	87	**4f**	54 min	83	**5f**	4 d	61
3g	5 min	92	**4g**	30 min	95	**5f**	24 h	70
3h	2.5 h	63	**4h**	4 h	62	**5h**	-	-
3i	1.5 h	83	**4i**	2 h	82	**5i**	3 d	45
3j	15 min	91	**4j**	30 min	90	**5i**	12 h	63
3k	20 min	95	**4k**	40 min	95	**5k**	4 d	30
3l	5 h	31	**4l**	> 24 h	-	**5l**	-	-
3m	15 min	93	**4m**	45 min	49	**5m**	12 h	63
3n	-	-	**4n**	20 min	84	**5m**	7 d	55

Compounds **(3)**, although formed more readily than **4**, failed to cyclize to the title compounds and are therefor only identified by their molecular ions (EXPERIMENTAL). Compounds **(4)** were fully characterized by elemental analysis (Table 2) and spectral data (Table 3). IR spectra revealed NH absorption bands in the range 3285-3370 cm^{-1} and two C=O absorptions at about 1710-1736 and 1659-1685 cm^{-1} assigned to the $\overset{O}{\overset{\|}{C}}$-CCl and $\overset{O}{\overset{\|}{C}}$-CNH stretching modes, respectively. In the ^1H NMR spectra the exchangeable NH appeared as a broad singlet in the range δ 9.8-10.1 while in the maleimide fragment the aromatic protons (f, g) appeared as AA' BB' at δ 7.0 and 7.3 (*J* 9.0 Hz) and the sharp singlet at δ 3.8 (3H) characterized the methoxy group. Protons in the arylamine moiety (a-e) reflected the substituent in Ar (Table 3).

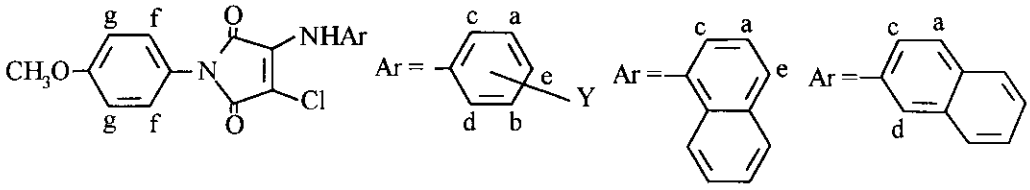
Treatment of compounds **(4)** with sodium azide at room temperature transformed them into the corresponding pyrroloquinoxalines **(5)**. Cyclization was clearly subject to strong substituent effects since the NO_2 group in the maleimide moiety inhibited ring closure in compounds **(3)** while in compounds **(4)**, *o*-substituents in the arylamine moiety (**4b**, **4e** and **4h)** inhibited cyclization in confirmation of previous findings.[1] *m*-Substituted compounds (**4c**, **4f** and **4i**) gave quinoxalines **(5c**, **5f** and **5i)** in lower yields and longer reaction times as compared to their *p*-substituted isomers (**4d**, **4g**, and **4j**) which gave the same

quinoxalines **(5c, 5f** and **5i)** (Table 1). The 1- and 2-naphthylamines **(4m** and **4n)** also cyclized to the same quinoxaline **(5m)** confirming previous findings.[1]

Table 2. Charcterization data for compounds **(4)** and **(5)**

Compd	mp	$[M]^{+\cdot}$ [a]	Calcd/ Found (%)			Compd	mp	Calcd/ Found (%)		
	(°C)	*m/z*	C	H	N		(°C)	C	H	N
4a	164-165	328	62.10	3.98	8.52	**5a**	245	66.88	3.63	13.76
		(100)	62.32	4.10	8.45		(decomp)	66.88	3.86	13.90
4b	146-147	358	60.26	4.21	7.80	-	-	-	-	-
		(100)	60.38	4.30	7.64					
4c	131-132	358	60.26	4.21	7.80	**5c**	262	64.47	3.90	12.53
		(100)	59.98	4.36	7.61		(decomp)	64.33	3.92	12.54
4d	182-183	358	60.26	4.21	7.80	**5c**		64.47	3.90	12.53
		(100)	60.39	4.21	7.66			64.63	3.92	12.54
4e	162-163	342	63.07	4.41	8.17	-	-	-	-	-
		(100)	63.00	4.35	8.07					
4f	126-127	342	63.07	4.41	8.17	**5f**	240	67.70	4.10	13.16
		(100)	63.02	4.45	8.09		(decomp)	67.80	4.09	13.16
4g	189-190	342	63.07	4.41	8.17	**5f**		67.70	4.10	13.16
		(60)	62.87	4.36	7.99			67.58	4.03	13.16
4h	145-146	362	56.22	3.32	7.71	-	-	-	-	-
		(100)	56.37	3.26	7.59					
4i	162-163	362	56.22	3.32	7.71	**5i**	220	60.10	2.96	12.36
		(100)	56.01	3.39	7.65		(decomp)	59.96	3.04	12.16
4j	184-185	362	56.22	3.32	7.71	**5i**		60.10	2.96	12.36
		(100)	56.06	3.41	7.70			59.97	3.06	12.21
4k	190-191	408	50.09	2.96	6.87	**5k**	250	53.15	2.62	10.94
		(100)	50.20	2.91	6.78		(decomp)	53.24	2.71	10.91
4m	185-186	378	66.58	3.99	7.39	**5m**	265	70.98	3.68	11.82
		(75)	66.47	4.10	7.34		(decomp)	71.10	3.60	11.72
4n	171-172	378	66.58	3.99	7.39	**5m**		70.98	3.68	11.82
		(100)	66.41	4.19	7.46			71.08	3.66	11.70

[a] % relative intensities given in parentheses



(4a-k) **(4m)** **(4n)**

Table 3. Chemical shifts (δ-values) for compounds **(4)**

Compd	a	b	c	d
4d	6.9 (d, 2H) (*J* 9.0 Hz)		7.2 (d, 2H) (*J* 9.0 Hz)	
4g	7.1 (d, 2H) (*J* 8.9 Hz)		7.2 (d, 2H) (*J* 8.9 Hz)	
4j	7.4 (d, 2H) (*J* 8.7 Hz)		7.2 (d, 2H) (*J* 8.7 Hz)	
4k	7.5 (d, 2H) (*J* 8.7 Hz)		7.1 (d, 2H) (*J* 8.7 Hz)	

Compd	a	b	c	e
4b	7.3 (m, 1H)	7.1 (dd, 1H) (*J* 8.0 Hz) (*J* 2.1 Hz)	7.2 (dd, 1H) (*J* 7.9 Hz) (*J* 1.8 Hz)	6.9 (m, 1H)
4e	←	7.2 (m, 4H)	→	
4h	7.33 (m, 1H)	7.5 (dd, 1H) (*J* 8.0 Hz) (*J* 2.1 Hz)	7.2 (dd, 1H) (*J* 9.0 Hz) (*J* 2.7 Hz)	7.0 (m, 1H)

Compd	a	e	c	d
4c	6.8 (m,2H)		7.3 (d, 1H) (*J* 8.0 Hz)	7.0 (s, 1H)
4f	7.0 (m,2H)		7.2 (d, 1H) (*J* 7.8 Hz)	7.0 (s, 1H)
4i	7.1 (m,2H)		7.2 (d, 1H) (*J* 8.0 Hz)	7.5 (s, 1H)

Compd	a	b	e	c	d
4a	7.2 (m, 3H)			7.4 (m, 2H)	
4m	7.6 (m, 3H)*	*	8.0 (m, 1H)	7.4 (d, 1H) (*J* 6.7 Hz)	*
4n	7.5 (m, 2H)*	*	*	7.4 (dd, 1H) (*J* 8.7 Hz) (*J*2.2 Hz)	7.7 (d, 1H) (*J* 2.2 Hz)

* These form the second aromatic ring of naphthalene whose protons appear at δ 7.6 (m, 2H + Ha), 7.9 (d, 1H) (*J* 8.2) and 8.05 (m, 1H) in **(4m)** and at δ 7.5 (m, 1H + Ha) and 7.9 (m, 3H) in **(4n)**.

The structures of the title compounds **(5)** were supported by elemental analysis (Table 2) and spectral data (Tables 4 and 5). The IR absorption band assigned to the NH group in **4** disappeared in **5**, and the two C=O absorptions now appeared as one unresolved broad band in the range 1727-1738 cm^{-1}. All UV spectra exhibited similar absorption patterns with three principal bands in the ranges 238-246, 271-302 and 359-405 nm typical of the quinoxaline nucleus.[3]

In the ^1H NMR spectra, the methoxy protons in the arylmaleimide moiety appeared as a singlet at about δ 3.9 (3H) and the aromatic protons Ha and Hb appeared as AA' BB' at around δ 7.1 and 7.4 (J 9.0 Hz). The multiplicity patterns in the quinoxaline nucleus supported the structure of a 6-substituted quinoxaline (Table 4). H-5 appeared as a broad singlet or a doublet ($J_{5\text{-}7}$ 1.8-2.7 Hz) in the range δ 7.8-8.8 except for **5m** where C5 was part of the naphthalene nucleus and **5a** where H5/8 formed part of the aromatic multiplet at δ 8.5.[4] The doublet ($J_{7\text{-}8}$ 8.6-9.2 Hz) which appeared in the range δ 8.3-8.5 was assigned to H8. H7 showed up as a doublet of doublets ($J_{7\text{-}8}$ 8.6-9.2 and $J_{5\text{-}7}$ 1.8-2.7 Hz) resonating between δ 7.7 and 8.2 except for **5m** where it was shifted downfield to δ 9.3 (m) and **5a** where with H6 it formed part of the upfield multiplet at δ 8.2.

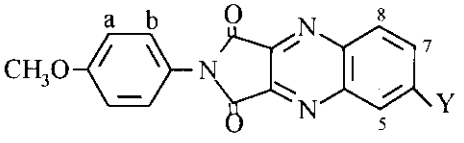


Table 4. Chemical shifts (δ-values) for compounds **(5)**

Compd	H-5	H-8	H-7	Y	$J_{7\text{-}8}$ (Hz)	$J_{5\text{-}7}$ (Hz)
5a	8.45 (m, 2H)		8.15 (m, 2H)		-	-
5c	7.8 (d)	8.3 (d)	7.7 (dd)	4.1 (s, 3H)	9.2	2.7
5f	8.2 (br s)	8.3 (d)	8.0 (dd)	2.7 (s, 3H)	8.6	1.8
5i	8.6 (d)	8.5 (d)	8.2 (dd)	-	9.0	2.4
5k	8.8 (d)	8.4 (d)	8.2 (dd)	-	9.0	2.1
5m	*	8.5 (d)	9.3 (m)	*	9.1	-

* The second aromatic ring of naphthalene appeared as two multiplets at δ 8.0 (2H) and 8.3 (2H).

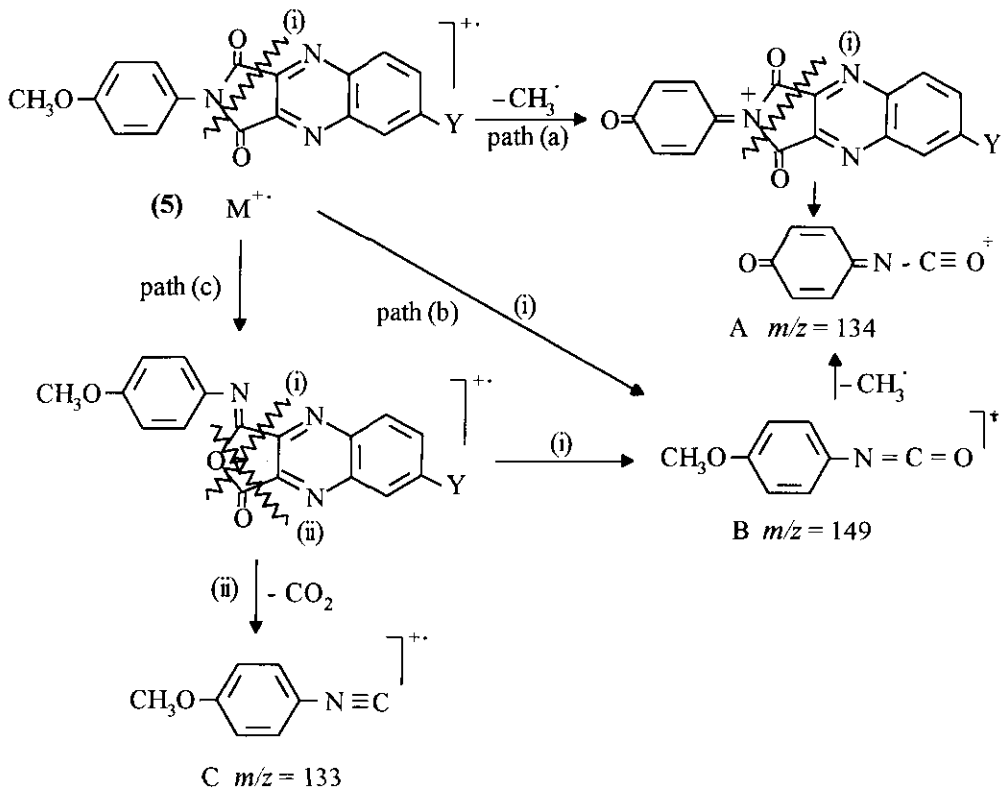
MS data (Table 5) showed intense peaks corresponding to the correct molecular ions in addition to other prominent fragment ions. These fragment ions $[A]^+$-$[C]^+$ are produced by bond cleavages as postulated in Scheme 2. Since direct loss of a hydrogen from $[A]^+$ (m/z = 134) to give $[C]^+$ (m/z = 133) cannot satisfactorily be explained, a different pathway leading to $[C]^+$ is suggested. An initial rearrangement of the parent molecular ion (path (c)), loss of CO_2, followed by bond cleavage will give the isocyanate ion $[C]^+$. Similar rearrangements have been reported in the phthalimide system.[5,6] The elemental composition of ions

$[A]^+$ and $[C]^+$ were confirmed by HRMS. As expected, additional minor peaks arising from loss of CO and HCN were also observed in the MS of compounds **(5)**.

Table 5. Mass spectral data for compounds **(5)** (*m/z* values, relative intensities in parentheses)

Compd	$[M]^{+\cdot}$ *m/z*	$[A]^+$ 134	$[B]^+$ 149	$[C]^+$ 133
5a	305 (100)	(68)	(32)	(70)
5c	335 (100)	(68)	(45)	(90)
5f	319 (92)	(79)	(43)	(100)
5i	339 (60)	(90)	(36)	(100)
5k	383 (100)	(96)	(50)	(90)
5m	355 (80)	(82)	(40)	(100)

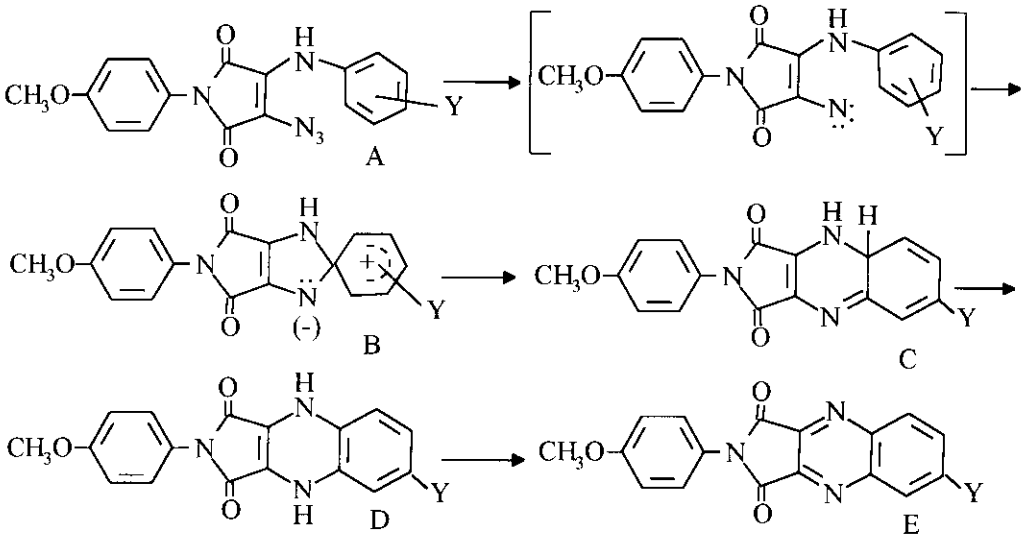
Scheme 2



Compounds **(5)** were obtained in optimum yields at room temperature, while heating the reaction mixture to 90-100°C led to their reduction to the 2-arylamino-3-amino-*N*-(*p*-aryl)maleimides as observed previously,[1] and in agreement with results in analogous six-membered ring systems.[7]

A mechanism proposed by both Messer *et al.*[8] and Cadogan *et al.*[9] and shown for compounds **(5)** is presented in Scheme 3. A nitrene-induced reaction, proceeding *via* a five-membered spirodienyl intermediate [B], rearranges to the six-membered ring [C] followed by a prototropic shift to give first 4,9-dihydroquinoxaline [D] then quinoxaline [E]. The isomeric *m*- and *p*-substituted spirodienyl cations can give rise to the same 6-substituted quinoxalines, as observed experimentally, depending on which nitrogen atom becomes attached to C2 of the arylamine ring. The failure of *o*-substituted isomers (**4b**, **4e**, and **4h**) to give **5** can be explained on the basis of steric inhibition to formation of the spirodienyl cation and subsequent rearrangement to an adjacent ortho position to give [C]. This mechanism can also explain the failure of compounds **(3)** to cyclize as a result of destabilization of the spirodienyl cation by the NO_2 group.

Scheme 3



Since ring closure was optimized at room temperature, it could suggest a concerted decomposition of the azide with loss of nitrogen and cyclization to **5**, while at the higher temperature a nonconcerted decompositon of the azide would allow a "free" nitrene to be reduced to the amine derivative.[10] The fact that the 2-naphthylamine isomer **(4n)**, which had a choice of attack at the α- or β-position, gave the same benzoquinoxaline **(5m)** as the 1-isomer **(4m)** supports the many cited examples[1,9,11,12] that ring closure occurs preferentially at the reactive α-position.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr pellets) were recorded on a Nicolet Fourier Transform spectrophotometer. UV spectra ($CHCl_3$) were recorded on a Beckman DU-7 spectrophotometer. ^1H NMR spectra were measured on a Bruker WM-300 spectrometer using DMSO-d_6 as solvent and DMSO

as an internal standard. A Finnigan MAT 731 mass spectrometer at 70 eV. was used to obtain electron-impact (EI) MS. Microanalyses were performed by M. H. W Laboratories, Arizona, U.S.A.

2,3-Dichloro-N-(p-nitrophenyl)maleimide **(1)**[2] : mp 186-187 °C (lit.,[13] mp 187-188 °C), yield 52%. MS (*m/z*) : 286 ($M^{+\cdot}$, 100%). ^{1}H NMR δ : 7.7 (2H, d, *J* 9.1 Hz) and 8.4 (2H, d, *J* 9.1 Hz).

2,3-Dichloro-N-(p-methoxyphenyl)maleimide **(2)**[2] : mp 205-206°C (lit.,[2] mp 206-207 °C), yield 63%. MS (*m/z*): 271 ($M^{+\cdot}$, 100%). ^{1}H NMR δ : 7.0 (2H,d, *J* 8.9 Hz) and 7.3 (2H,d, *J* 8.9 Hz), 3.8 (3H, s).

2-Arylamino-3-chloro-N-(p-nitrophenyl)maleimides **(3b-m)**[1]

Refluxing 2,3-dichloro-*N*-(*p*-nitrophenyl)maleimide **(1)** with the various arylamines in absolute ethanol gave compounds **(3)** which were charaterized by their melting points and mass spectra.

3b : mp 168-169 °C. MS for $C_{17}H_{12}N_3O_5Cl$: *m/z* 373 ($M^{+\cdot}$, 100%).

3c : mp 200-201 °C. MS for $C_{17}H_{12}N_3O_5Cl$: *m/z* 373 ($M^{+\cdot}$, 100%).

3d : mp 203-205 °C. MS for $C_{17}H_{12}N_3O_5Cl$: *m/z* 373 ($M^{+\cdot}$, 100%).

3e : mp 175-176 °C. MS for $C_{17}H_{12}N_3O_4Cl$: *m/z* 357 ($M^{+\cdot}$, 100%).

3f : mp 125-126 °C. MS for $C_{17}H_{12}N_3O_4Cl$: *m/z* 357 ($M^{+\cdot}$, 100%).

3g : mp 221(decomp). MS for $C_{17}H_{12}N_3O_4Cl$: *m/z* 357 ($M^{+\cdot}$, 100%).

3h : mp 205-206 °C. MS for $C_{16}H_9N_3O_4Cl_2$: *m/z* 377 ($M^{+\cdot}$, 60%).

3i : mp 176-177 °C. MS for $C_{16}H_9N_3O_4Cl_2$: *m/z* 377 ($M^{+\cdot}$, 100%).

3j : mp 210-211 °C. MS for $C_{16}H_9N_3O_4Cl_2$: *m/z* 377 ($M^{+\cdot}$, 100%).

3k : mp 211-212 °C. MS for $C_{16}H_9N_3O_4BrCl$: *m/z* 423 ($M^{+\cdot}$, 100%).

3l : mp 247(decomp). MS for $C_{16}H_9N_4O_6Cl$: *m/z* 388 ($M^{+\cdot}$, 100%).

3m : mp 198-199 °C. MS for $C_{20}H_{12}N_3O_4Cl$: *m/z* 393 ($M^{+\cdot}$, 100%).

2-Arylamino-3-chloro-N-(p-methoxyphenyl)maleimides **(4)**[1]

2-(p-Methoxyphenyl)pyrrolo[3,4-b]quinoxaline-1,3-diones **(5)**[1]**:** Different solvents (CH_3CN, THF, Me_2SO) and reaction temperatures were attempted in a bid to improve yields, but the optimum conditions for compounds **(5)** were found to be room temperature with DMF as solvent.

In HRMS the exact MS was measured by matching technique with C_3F_5 (*m/z* = 130.992) as reference ion. The exact mass (*m/z* = 134.0246) for $[A]^+$ corresponded to that calculated (*m/z* = 134.0242) and (*m/z* = 133.0520) observed for $[C]^+$ compared to that calculated (*m/z* = 133.0528).

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REFERENCES

1. Part I : L. Hanaineh-Abdelnour, S. Bayyuk, and R. Theodori, accepted by Tetrahedron.
2. E. L. Martin, C. L. Dickinson, and H. R. Ronald, *J. Org. Chem.*, 1961, **26**, 2032.
3. A. E. A. Porter, in *Comprehensive Heterocycl. Chem.*, Vol. **3**, ed. by A. R Katritzky, C. W. Rees, C. W. Bird, and G. W. H. Cheeseman, Pergamon Press, Oxford, 1984, p. 157.
4. P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, 1965, **18**, 707.
5. a) R. A. W. Johnstone, B. J. Millard, and D. S. Millington, *Chem. Commun.*, **1966**, 600.
   b) J. L. Cotter and R. A. Dine-Hart, *Ibid.*, **1966**, 809.
6. A. F. Janzen and E. A. Kramer, *Can. J. Chem.*, 1971, **49**, 1011.
7. E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 2298 and refs therein.
8. H. Messer and D. Farge, *Bull, Soc. Chim. Fr.*, **1968**, 2832 and **1969**, 4395
9. a) J. I. G. Cadogan, S. Kulik, and M. J. Todd, *J. Chem. Soc., Chem. Commun.*., 1968, **13**, 736.
   b) J. I. G. Cadogan, *Acc. Chem. Res.*, 1972, **5**, 303.
10. V. P. Semenov, A. N. Studenikov, and A. A. Potekhim, *Chem. Heterocycl. Comp.*, 1978, **14**, 233.
11. J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, 1963, **28,** 520.
12. R. N.Carde and G. Jones, *J. Chem. Soc., Perkin Trans. I*, **1974**, 2066.
13. T. M. Velikokhat'ko, V. V. Simonov, and A. F. Anishchenko, in *Synthesis of Dichloromaleic Acid Derivatives*, ed. by S. R. Rafikov, Akad. Nauk SSSR, Bashkir. Fil : Ufa, USSR, 1977, p. 26, (*Chem. Abstr.*, 1980, **93**, 46305b).

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