

REACTIONS WITH MALEIMIDES: SYNTHESIS OF SEVERAL NEW FUSED PYR-
AZOLIDINES, Δ^2 -PYRAZOLINE AND PYRAZOLE DERIVATIVES

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Abstract - Several new pyrrolidinopyrazolidinedione, pyrrolid-
ino- Δ^2 -pyrazolidinedione and pyrrolopyrazoledione derivatives
were synthesised via the reaction of different arylhydrazones
with N-arylmaleimides. The structures of the synthesized het-
erocyclic derivatives were established on the basis of elemental
analyses and spectroscopic data studies.

The considerable biological activities of pyrazole derivatives as antipyretic¹⁻³,
active CNS regulants⁴⁻⁶, bacteriostatic, bacteriocidal and fungicidal⁷⁻⁹ agents
stimulated our interest for the synthesis of several new derivatives of this ring
system. In previous work from this laboratory¹⁰ we have recently reported a new
procedure for the synthesis of pyrrolidinopyrazolidine and pyrrolinopyrazole der-
ivatives. Owing to the great biological activities of the compounds containing the
(-CO-NH-CO-) and (-CO-NR-CO-) moieties, as very effective and persistent foliage
fungicides^{11,12}, certain samples of the saturated pyrrolidinopyrazolidine derivat-
ives were required for a medicinal chemistry programme. In conjunction with our
previous work^{10,13} we report, here, on the reaction of N-arylmaleimides with dif-
ferent arylhydrazones as 4-electron three atomic centers in dipolar cycloaddition
reactions. Thus, it has been found that the phenylhydrazone derivatives 1a-d re-
acted with N-p-methoxyphenylmaleimide (2a) in boiling toluene or by fusion of the
reactants to give the two reaction products 3 and 4 in each case. Compounds 3a-d

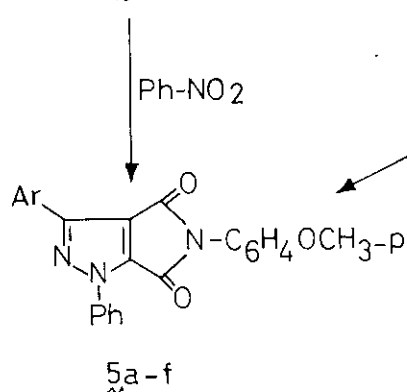
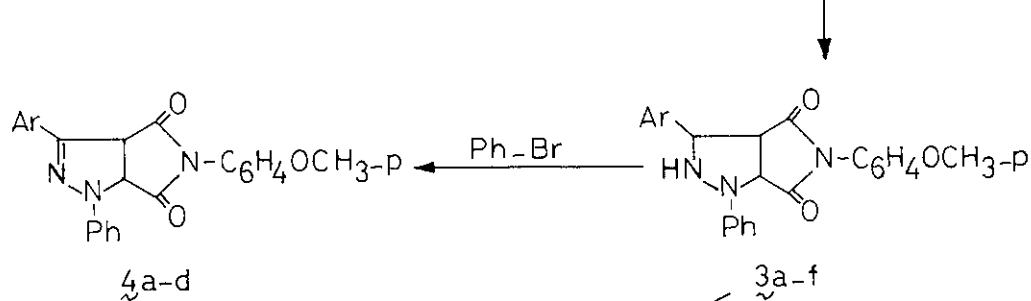
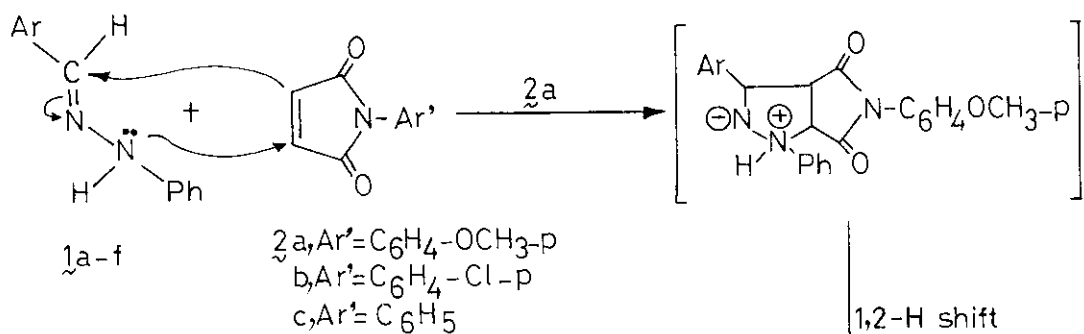
were assigned the pyrrolidino[3,4-d]pyrazolidine-2,6-dione structure, while compounds 4a-d were assigned the pyrrolidino[3,4-d]- Δ^2 -pyrazoline-2,6-dione structure based on elemental analyses and spectroscopic data. Thus, the IR spectra of 3a-d revealed absorption bands at 1790-1720 and 1710-1690 cm^{-1} attributed to the presence of the (-CO-NR-CO-) grouping besides the band related to the presence of the NH group at about 3200 cm^{-1} . The ^1H NMR spectra of both 3b and 4c, as typical examples of the series, revealed signals at (δ ppm) 2.38 (s, 3H, OCH_3); 3.4 (s, 3H, OCH_3); 3.8 (s, 3H, OCH_3); 7.25-7.95 (m, 12H, Ar'Hs); 8.5-8.7 (m, 3H, pyrazolidine H-3, H-4 and H-5) and 9.1 (s, br, 1H, NH). On the other hand, the IR spectra of 4a-d revealed only absorption peaks related to the presence of the (-CO-NR-CO-) grouping while the band attributed to the presence of the NH group was entirely absent. The ^1H NMR spectra of both 4b and 4c revealed signals at (δ ppm) 2.42 (s, 3H, OCH_3); 3.38 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 4.8 (d, 1H, pyrazoline H-4); 5.2 (d, 1H, pyrazoline H-5) and 6.5-7.7 (m, 12H, Ar'Hs).

An unequivocal support of the structure of 4a-d was achieved by their synthesis through another route by boiling the solution of compounds 3a-d in bromobenzene for 4 h (cf. experimental part). Moreover, both compounds 3a-d and 4a-d were converted into the same pyrrolino[3,4-d]pyrazole-2,6-dione derivatives 5a-d on boiling their solutions in nitrobenzene for 4 h.

In contrast to the behaviour of 1a-d toward 2a, the arylhydrazone derivatives 1e,f reacted with 2a, under the similar experimental conditions, to yield only the pyrrolidino[3,4-d]pyrazolidine-2,6-dione derivatives 3e,f respectively. The structure assigned for 3e,f was based on the same grounds as previously described for 3a-d. The ^1H NMR spectrum of 3e revealed signals at (δ ppm) 2.38 (s, 3H, OCH_3); 6.5-7.45 (m, 13H, Ar'Hs); 8.5-8.7 (m, 3H, pyrazolidine H-3, H-4 and H-5); 8.9 (s, br, 1H, NH) and 9.3 (s, 1H, OH). Moreover, compound 3e could be converted into the pyrrolinopyrazoledione derivative 5e on boiling its solution in nitrobenzene for 4 h. The ^1H NMR spectrum of 5e revealed signals at (δ ppm) 2.41 (s, 3H, OCH_3); 6.8-7.9 (m, 13H, Ar'Hs) and 9.8 (s, 1H, OH).

In contrast to the behaviour of 2a toward 1a-f, the N-arylmaleimides 2b,c reacted with the arylhydrazone derivatives 1a-f in a molar ratio of 1:1 to afford the pyrrolidino[3,4-d]pyrazolidine-2,6-dione derivatives 6a-f and 7a-f respectively.

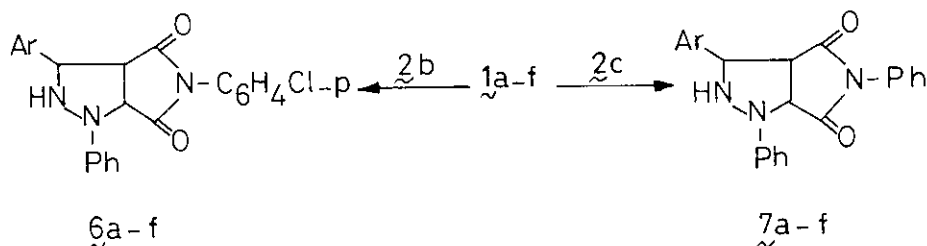
All the synthesised compounds gave also correct molecular ions in the mass spectra. Several new, otherwise difficult to obtain, pyrrolidino[3,4-d]pyrazolidine-2,6-



Ph-NO_2

For 1 and 3-7:

- a, Ar = $\text{C}_7\text{H}_5\text{O}_2$ (piperonyl)
- b, Ar = $\text{C}_6\text{H}_3-(\text{OCH}_3)_2$ -2,4
- c, Ar = $\text{C}_6\text{H}_3-(\text{OCH}_3)_2$ -3,4
- d, Ar = $\text{C}_6\text{H}_2-(\text{OCH}_3)_3$ -3,4,5
- e, Ar = $\text{C}_6\text{H}_4-\text{OH}-\text{p}$
- f, Ar = $\text{C}_6\text{H}_3-(\text{OCH}_3)(\text{OH})$ -3,4



dione, pyrrolidino[3,4-d]- Δ^2 -pyrazoline-2,6-dione and pyrrolino[3,4-d]pyrazole-2,6-dione derivatives with different functional substituents are now available for biological activity studies.

EXPERIMENTAL

Melting points are all uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1100 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-390 90 MHz and Varian XL-200 MHz spectrometers using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as ppm units. The microanalyses were performed by the microanalytical centre at Cairo University.

Reaction of 1a-f with 2a:

A solution of each of 1a-f (0.01 mol) and 2a (0.01 mol) in toluene (30 ml) was heated to boiling under reflux for 4 h, then the solvent was evaporated in vacuo. The remaining solid product was triturated with ethanol followed by crystallization from ethanol to give compounds 3a-f. Concentration and cooling of the mother-liquor gave compounds 4a-d (cf. Table 1).

The same compounds 3a-f and 4a-d could also be obtained in good yields by heating a solid mixture of each of 1a-f and 2a in an oil-bath for 90 min then proceeding as above (bath temperature, 160-180°C).

Conversion of 3a-d into 4a-d:

A solution of each of 3a-d (1 g) in bromobenzene (30 ml) was heated under reflux for 4 h followed by evaporation of the solvent in vacuo. The remaining solid product was triturated followed by crystallization from ethanol to give 4a-d.

Conversion of 3a-d and 4a-d into 5a-d:

A solution of each of 3a-d and 4a-d (1 g) in nitrobenzene (25 ml) was heated under reflux for 4 h. The solvent was evaporated in vacuo and the solid that separated was triturated, then crystallized from ethanol to give compounds 5a-d (cf. Table 1). Applying the same procedure compounds 3e,f could be converted into compounds 5e,f respectively (cf. Table 1).

Reaction of 1a-f with 2b,c:

A solution of each of 1a-f (0.01 mol) and each of 2b,c (0.01 mol) in toluene (30 ml) was heated under reflux for 4 h, then the solvent was evaporated in vacuo. The solid product thus formed was triturated from ethanol followed by crystallization

Table 1: Characterization data of compounds 3a-f, 4a-d, 5a-f, 6a-f and 7a-f

Comp.	M.p. (°C)	Yield (%)	Mol. Formula	% Analysis, Calcd. (Found)			
				C	H	N	Cl
<u>3a</u>	235-6	45	C ₂₅ H ₂₁ O ₅ N ₃	67.72(67.90)	4.74(4.82)	9.48 (9.50)	-
<u>3b</u>	229-30	50	C ₂₆ H ₂₅ O ₅ N ₃	67.97(68.10)	5.44(5.52)	9.15 (9.22)	-
<u>3c</u>	237-8	35	C ₂₆ H ₂₅ O ₅ N ₃	67.97(67.85)	5.44(5.50)	9.15 (9.20)	-
<u>3d</u>	226	25	C ₂₇ H ₂₇ O ₆ N ₃	66.25(66.35)	5.52(5.45)	8.85 (8.72)	-
<u>3e</u>	267	75	C ₂₄ H ₂₁ O ₄ N ₃	69.39(69.44)	5.06(5.20)	10.12(10.18)	-
<u>3f</u>	224	70	C ₂₅ H ₂₃ O ₅ N ₃	67.41(67.53)	5.16(5.22)	9.43 (9.54)	-
<u>4a</u>	210-11	40	C ₂₅ H ₁₉ O ₅ N ₃	68.02(68.21)	4.30(4.42)	9.52 (9.55)	-
<u>4b</u>	206	25	C ₂₆ H ₂₃ O ₅ N ₃	68.27(68.42)	5.03(5.12)	9.19 (9.26)	-
<u>4c</u>	219	35	C ₂₆ H ₂₃ O ₅ N ₃	68.27(68.34)	5.03(5.24)	9.19 (9.32)	-
<u>4d</u>	209	25	C ₂₇ H ₂₅ O ₆ N ₃	66.52(66.66)	5.13(5.20)	8.62 (8.75)	-
<u>5a</u>	253-5	95	C ₂₅ H ₁₇ O ₅ N ₃	68.33(68.44)	3.87(4.00)	9.56 (9.62)	-
<u>5b</u>	278-9	90	C ₂₆ H ₂₁ O ₅ N ₃	68.57(68.72)	4.61(4.80)	9.23 (9.40)	-
<u>5c</u>	271	93	C ₂₆ H ₂₁ O ₅ N ₃	68.57(68.67)	4.61(4.75)	9.23 (9.36)	-
<u>5d</u>	280-1	90	C ₂₇ H ₂₃ O ₆ N ₃	66.80(66.92)	4.74(4.85)	8.65 (8.78)	-
<u>5e</u>	262	95	C ₂₄ H ₁₇ O ₄ N ₃	70.07(70.20)	4.13(4.25)	10.21(10.35)	-
<u>5f</u>	257	92	C ₂₅ H ₁₉ O ₅ N ₃	68.02(68.25)	4.30(4.45)	9.52 (9.36)	-
<u>6a</u>	225	75	C ₂₄ H ₁₈ O ₄ N ₃ Cl	64.35(64.45)	4.02(4.15)	9.38 (9.55)	7.93(8.10)
<u>6b</u>	240	70	C ₂₅ H ₂₂ O ₄ N ₃ Cl	64.72(64.88)	4.74(4.82)	9.06 (9.15)	7.66(7.80)
<u>6c</u>	200	70	C ₂₅ H ₂₂ O ₄ N ₃ Cl	64.72(64.75)	4.74(4.90)	9.06 (9.10)	7.66(7.70)
<u>6d</u>	226	65	C ₂₆ H ₂₄ O ₅ N ₃ Cl	63.22(63.35)	4.86(5.00)	8.51 (8.62)	7.19(7.25)
<u>6e</u>	240	75	C ₂₃ H ₁₈ O ₃ N ₃ Cl	65.79(65.86)	4.29(4.40)	10.01(10.20)	8.46(8.55)
<u>6f</u>	219	70	C ₂₄ H ₂₀ O ₄ N ₃ Cl	64.07(64.20)	4.45(4.52)	9.34 (9.45)	7.89(8.00)
<u>7a</u>	205	65	C ₂₄ H ₁₉ O ₄ N ₃	69.73(69.85)	4.60(4.72)	10.16(10.24)	-
<u>7b</u>	263-4	80	C ₂₅ H ₂₃ O ₄ N ₃	69.93(70.12)	5.36(5.44)	9.79 (9.90)	-
<u>7c</u>	216	70	C ₂₅ H ₂₃ O ₄ N ₃	69.93(70.10)	5.36(5.50)	9.79 (9.82)	-
<u>7d</u>	229	60	C ₂₆ H ₂₅ O ₅ N ₃	67.97(68.13)	5.44(5.60)	9.15 (9.22)	-
<u>7e</u>	265-6	75	C ₂₃ H ₁₉ O ₃ N ₃	71.68(71.76)	4.93(5.10)	10.90(10.98)	-
<u>7f</u>	237-8	68	C ₂₄ H ₂₁ O ₄ N ₃	69.39(69.42)	5.06(5.14)	10.12(10.23)	-

* All compounds are colourless except 4a-d, pale yellow and 5a-f, light brown.

from ethanol to give compounds 6a-f and 7a-f respectively (cf. Table 1). The same compounds 6a-f and 7a-f could also be synthesised when a solid mixture of each of 1a-f and each of 2b,c was heated in an oil-bath at 160-180°C for 90 min then proceeding as above.

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