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

Sami S. Ghabrial* and Hussein H. Moharram

National Organisation for Drug Control and Research, P.O. Box 29, Cairo, A.R. Egypt

Suzan I. Aziz

Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt

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

The considerable biological activities of pyrazole derivatives as antipyretic[1-3], active CNS regulants[4-6], bacteriostatic, bacteriocidal and fungicidal[7-9] agents stimulated our interest for the synthesis of several new derivatives of this ring system. In previous work from this laboratory[10] we have recently reported a new procedure for the synthesis of pyrrolidinopyrazolidine and pyrrolinopyrazole derivatives. 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 derivatives 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 different arylhydrazones as 4-electron three atomic centers in dipolar cycloaddition reactions. Thus, it has been found that the phenylhydrazone derivatives 1a-d reacted 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

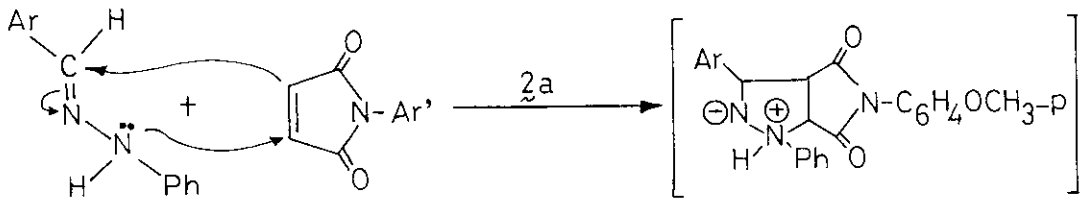
were assigned the pyrrolidino[3,4-d]pyrazolidine-2,6-dione structure, while compounds 4a-d were assigned the pyrrolidino[3,4-d]-Δ^2-pyrazoline-2,6-dione structure based on elemental analyses and spectroscopic data. Thus, the IR spectra of 3a-d revealed absorption bands at 1790-1720 and 1710-1690 cm^{-1} 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).

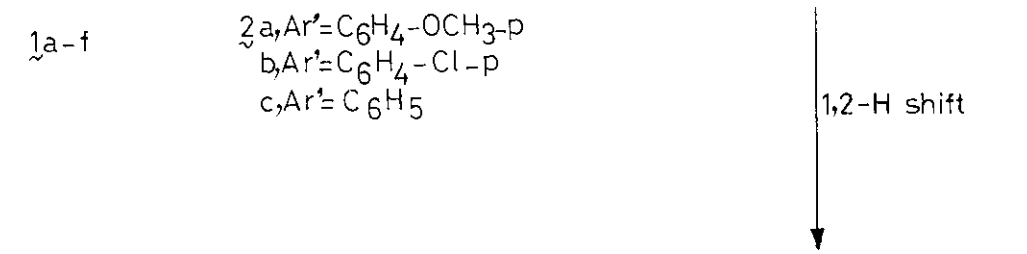
In contrast to the behaviour of 2a toward 1a-f, the N-arylmaleimides 2b,c reacted with the arylhydrazone derivatives 1a-f in a molar ratio of 1:1 to afford the pyrrolidino[3,4-d]pyrazolidine-2,6-dione derivatives 6a-f and 7a-f respectively.

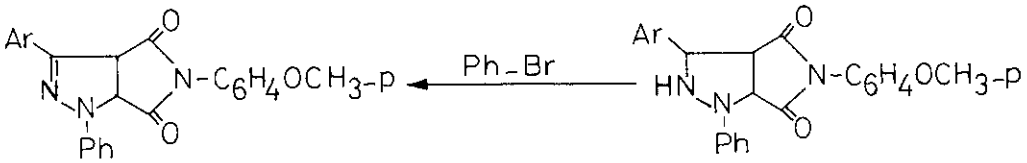
All the synthesised compounds gave also correct molecular ions in the mass spectra. Several new, otherwise difficult to obtain, pyrrolidino[3,4-d]pyrazolidine-2,6-



1a-f

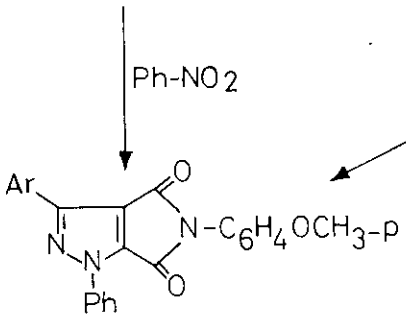
2a, Ar' = C_6H_4-OCH_3-p
b, Ar' = C_6H_4-Cl-p
c, Ar' = C_6H_5





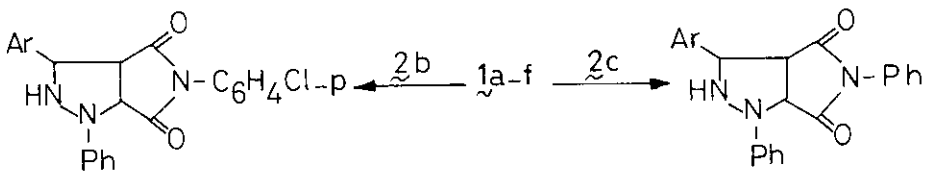
4a-d

3a-f



5a-f

For 1 and 3-7:
a, Ar = $C_7H_5O_2$ (piperonyl)
b, Ar = C_6H_3-$(OCH_3)_2$-2,4
c, Ar = C_6H_3-$(OCH_3)_2$-3,4
d, Ar = C_6H_2-$(OCH_3)_3$-3,4,5
e, Ar = C_6H_4-OH-p
f, Ar = C_6H_3-(OCH_3)(OH)-3,4



6a-f

7a-f

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. ^{1}H 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
3a	235-6	45	$C_{25}H_{21}O_5N_3$	67.72(67.90)	4.74(4.82)	9.48 (9.50)	-
3b	229-30	50	$C_{26}H_{25}O_5N_3$	67.97(68.10)	5.44(5.52)	9.15 (9.22)	-
3c	237-8	35	$C_{26}H_{25}O_5N_3$	67.97(67.85)	5.44(5.50)	9.15 (9.20)	-
3d	226	25	$C_{27}H_{27}O_6N_3$	66.25(66.35)	5.52(5.45)	8.85 (8.72)	-
3e	267	75	$C_{24}H_{21}O_4N_3$	69.39(69.44)	5.06(5.20)	10.12(10.18)	-
3f	224	70	$C_{25}H_{23}O_5N_3$	67.41(67.53)	5.16(5.22)	9.43 (9.54)	-
4a	210-11	40	$C_{25}H_{19}O_5N_3$	68.02(68.21)	4.30(4.42)	9.52 (9.55)	-
4b	206	25	$C_{26}H_{23}O_5N_3$	68.27(68.42)	5.03(5.12)	9.19 (9.26)	-
4c	219	35	$C_{26}H_{23}O_5N_3$	68.27(68.34)	5.03(5.24)	9.19 (9.32)	-
4d	209	25	$C_{27}H_{25}O_6N_3$	66.52(66.66)	5.13(5.20)	8.62 (8.75)	-
5a	253-5	95	$C_{25}H_{17}O_5N_3$	68.33(68.44)	3.87(4.00)	9.56 (9.62)	-
5b	278-9	90	$C_{26}H_{21}O_5N_3$	68.57(68.72)	4.61(4.80)	9.23 (9.40)	-
5c	271	93	$C_{26}H_{21}C_5N_3$	68.57(68.67)	4.61(4.75)	9.23 (9.36)	-
5d	280-1	90	$C_{27}H_{23}O_6N_3$	66.80(66.92)	4.74(4.85)	8.65 (8.78)	-
5e	262	95	$C_{24}H_{17}O_4N_3$	70.07(70.20)	4.13(4.25)	10.21(10.35)	-
5f	257	92	$C_{25}H_{19}O_5N_3$	68.02(68.25)	4.30(4.45)	9.52 (9.36)	-
6a	225	75	$C_{24}H_{18}O_4N_3Cl$	64.35(64.45)	4.02(4.15)	9.38 (9.55)	7.93(8.10)
6b	240	70	$C_{25}H_{22}O_4N_3Cl$	64.72(64.88)	4.74(4.82)	9.06 (9.15)	7.66(7.80)
6c	200	70	$C_{25}H_{22}O_4N_3Cl$	64.72(64.75)	4.74(4.90)	9.06 (0.10)	7.66(7.70)
6d	226	65	$C_{26}H_{24}O_5N_3Cl$	63.22(63.35)	4.86(5.00)	8.51 (8.62)	7.19(7.25)
6e	240	75	$C_{23}H_{18}O_3N_3Cl$	65.79(65.86)	4.29(4.40)	10.01(10.20)	8.46(8.55)
6f	219	70	$C_{24}H_{20}O_4N_3Cl$	64.07(64.20)	4.45(4.52)	9.34 (9.45)	7.89(8.00)
7a	205	65	$C_{24}H_{19}O_4N_3$	69.73(69.85)	4.60(4.72)	10.16(10.24)	-
7b	263-4	80	$C_{25}H_{23}O_4N_3$	69.93(70.12)	5.36(5.44)	9.79 (9.90)	-
7c	216	70	$C_{25}H_{23}O_4N_3$	69.93(70.10)	5.36(5.50)	9.79 (9.82)	-
7d	229	60	$C_{26}H_{25}O_5N_3$	67.97(68.13)	5.44(5.60)	9.15 (9.22)	-
7e	265-6	75	$C_{23}H_{19}O_3N_3$	71.68(71.76)	4.93(5.10)	10.90(10.98)	-
7f	237-8	68	$C_{24}H_{21}O_4N_3$	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.

ACKNOWLEDGEMENT

Thanks are due to Prof. Dr. Sadek E. Abdou, Department of Chemistry, Faculty of Science, Cairo University for his valuable discussions.

REFERENCES

1. W. E. Kirkpatrick, T. Okake, I. W. Hillyard, R. K. Robins, A. T. Dren and T. Novinson, J. Med. Chem., 20, 386 (1977).
2. H. Ochi, T. Miyasaka, K. Kanada and K. Arakawa, Bull. Chem. Soc. Japan, 49, 1980 (1979).
3. S. M. Hecht, D. Werner, D. D. Traficante, M. Sundaralinga, P. Prusiner and T. Sakurai, J. Org. Chem., 40, 1815 (1975).
4. T. Nouinson, R. Hanson, M. K. Dimmitt, L. N. Simon, R. K. Robins and D. E. O'Brien, J. Med. Chem., 17, 645 (1974).
5. H. A. DeWald, S. Lobbestael and D. E. Butler, J. Med. Chem., 20, 1562 (1977).
6. F. Hawking, "Experimental Chemotherapy", 1, Academic Press, New York, 1963, p. 197.
7. R. J. W. Cremlyn, Internat. Pest. Control, 13, 12 (1971).
8. H. Dorn, K. L. P. Hilgetag and G. Hilgetag, Ber., 95, 1372 (1962).
9. S. Rich, "Fungicidal Chemistry" in "Plant Pathology", Eds., J. G. Horsfall and A. Diamond, Vol. 2, Academic Press, New York, 1960, p. 588.
10. S. S. Ghabrial, M. M. H. Arief and S. E. Abdou, Arch. Pharm., 1984, in press.
11. G. W. Raiziss, L. W. Clemence and M. Freifelder, J. Amer. Chem. Soc., 63, 2739 (1941).
12. R. Cremlyn, "Pesticides, Preparation and Mode of Action", John Wiley and Sons, Inc., New York, 1978.
13. Y. A. Ibrahim, S. E. Abdou and S. Selim, Heterocycles, 19, 819 (1982).

Received, 7th January, 1985