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Reactions with Maleimides VII[1]: Synthesis of Several New Pyrazolonyl-pyrrolidino[3,4-d]pyrazoline and Pyrazolonyl-pyrrolo [3,4-d]pyrazole Derivatives

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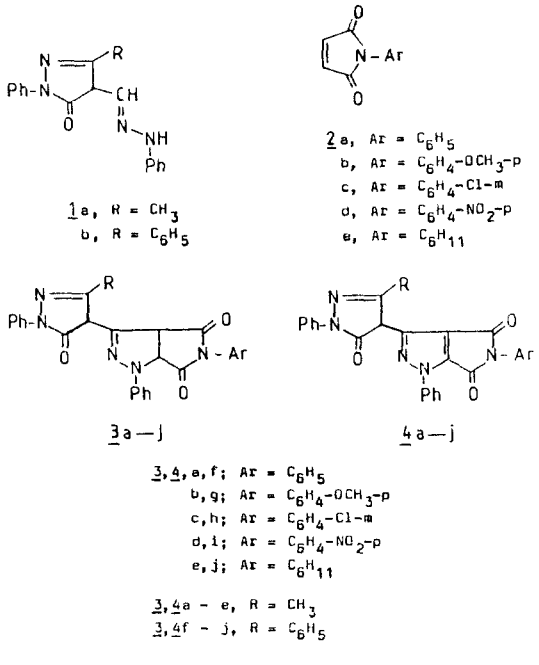
Abstract□Several new pyrazolonyl-pyrrolidino[3,4-d]pyrazolidines and pyrazolonyl-pyrrolo[3,4-d]pyrazoles were synthesised via the reaction of N-arylmaleimides with the phenylhydrazones of 3-methyl-4-formyl-2-pyrazoline-5-one and 1-phenyl-3-methyl-4-formyl-pyrazolin-5-one and treating of the resulting adducts with chloranil. Structures were based on elemental analyses and spectral data.

Keywords□N-Arylmaleimide, pyrazoline phenylhydrazone, cycloaddition, pyrazolonyl-pyrrolidino[3,4-d]pyrazoline, pyrazolonyl pyrrolo[3,4-d]pyrazole derivatives.

In the last few years we have been interested in the synthesis of heterocyclic derivatives of expected biological activity utilizing N-aryl-maleimides[2-6]. In this connections, it is remarkable to report that these reactions resulted in the synthesis of several new heterocycles containing the substituted phenyl-, furyl, thienyl and pyridyl moieties could be obtained. As a continuation of this effort, we report, here, on the use of the hydrazones of 1-phenyl-3-methyl-4-formyl-2-pyrazolin-5-one (**1a**) and 1,3-diphenyl-4-formyl-2-pyrazolin-5-one (**1b**) in the dipolar cycloaddition reacitons with the objective of introduction of the pyrazolonyl moiety which will certainly adds to the biological activity of the derivatives. Pyrazoles and their annelated derivatives are used as antipyretic[7], and antimicrobial[8] agents. The reactions of **1a** and **1b** with a variety of N-arylmaleimides (**2a-e**) constitute a new example of the use of hydrazones and thiosemicarbazones of certain aldehydes as four-electron three atomic center in dipolor cycloaddition reactions first reported[2] from this laboratory.



Thus, it has been found that **1a** reacted with N-phenylmaleimide (**2a**) in toluene or bromobenzene or fusion of the reactions in an oil-bath at 160-180°C to afford a product of molecular formula $C_{27}H_{21}N_5O_3$. This formula corresponds to the addition of one molecule of **1a** to one molecule of **2a** followed by the loss of two hydrogens. The reaction products could, however, be assigned the 3-(pyrazolino-4'-yl)-pyrrolidino[3,4-d]pyrazolin structure (**3a**) based on correct elemental analysis and spectal data. The IR (cm^{-1}) spectrum of **3a** showed the absorption bands related to the presence of NH (3250), saturated CH (2980), CO-NR-CO (1790, 1690) and CO (1770).

The ^{1}H-NMR (δ ppm) spectrum of **3a** revealed signals at 1.65 (s, 3H, CH_3); 4.8 (s, 1H, pyrazolone H-4); 5.3 (s, 1H, pyrazoline H-4); 5.6 (d, 1H, pyrazoline H-5) and 7.1-8.2 (m, 15H, ArH's) (cf. Experimen-

tal Part).

In a similar manner, **1a** reacted with the N-arylmaleimides (**2b-e**) under the same experimental conditions to afford the 3-(pyrazolino-4'-yl)-pyrrolidino [3,4-d]pyrazoline derivatives (**3b-e**) respectively in good yields. The structure of **3b-e** was, in turn, established on the basis of correct elemental analysis and spectral data studies which were in good agreement of the asigned structures (Tables I and II).

Similarly, compound **1b** reacted with the N-arylmaleimides (**2a-e**) to yield the corresponding pyrrolidino[3,4-d]pyrazoline derivatives (**3f-j**) respectively.

The IR spectra of **3f-j** showed the bands related to the presence of the (CO-NR-CO) grouping at 1780-1720 and 1710-1690 cm^{-1} in addition to those of the saturated CH (2980) and the CO (1680).

The ^{1}H-NMR spectrum of **3f**, as a typical example of the series, revealed signals (δ ppm) at 4.9 (s, 1H, pyrazolone H-4); 5.2 (d, 1H, pyrazoline H-4); 5.4 (d, 1H, pyrazoline H-5) and 7.1-8.3 (m, 20H, ArH's) (Tables I and II).

The structure of **3a-j** was further confirmed via

Table I.

Comp.	mp. (°C)	Yield (%)	Colour	Mol. formula	% Analysis Calcd./Found			
					C	H	N	Cl
3a	113	80	Yellow	$C_{27}H_{21}N_5O_3$	69.9	4.5	15.1	
					70.0	4.6	15.3	
3b	130	85	Brown	$C_{28}H_{24}N_5O_4$	68.0	4.8	14.1	
					68.2	4.9	13.9	
3c	125	90	White	$C_{27}H_{21}ClN_5O_3$	64.9	4.2	14.0	7.1
					65.1	4.1	13.9	7.3
3d	172	92	Brown	$C_{27}H_{21}N_6O_5$	63.6	4.1	16.5	
					63.4	4.3	16.3	
3e	126	86	White	$C_{27}H_{28}N_3$	68.9	5.9	14.8	
					68.7	5.7	15.0	
3f	96	87	Yellow	$C_{32}H_{23}N_5O_3$	73.1	4.3	13.3	
					72.9	4.1	13.5	
3g	162	90	White	$C_{33}H_{26}N_5O_4$	71.2	4.6	12.5	
					71.4	4.5	12.3	
3h	131	90	White	$C_{32}H_{23}ClN_5O_3$	68.5	4.1	12.4	6.3
					68.7	4.3	12.2	6.4
3i	133	93	Brown	$C_{32}H_{23}N_6O_5$	67.2	4.0	14.7	
					67.4	4.1	14.9	
3j	98	85	Yellow	$C_{32}H_{30}N_5O_3$	72.1	5.6	13.1	
					72.3	5.5	13.3	
4a	190	82	Yellow	$C_{27}H_{19}N_5O_3$	70.2	4.1	15.2	
					70.4	3.9	15.3	
4b	195	87	Yellow	$C_{28}H_{22}N_5O_4$	68.3	4.5	14.2	
					68.5	4.4	14.4	
4c	185	88	Yellow	$C_{27}H_{19}ClN_5O_3$	65.2	3.8	14.1	7.2
					65.1	3.7	14.3	7.4
4d	225	90	Yellow	$C_{27}H_{19}N_6O_5$	63.9	3.7	16.6	
					64.0	3.9	16.4	
4e	170	80	Yellow	$C_{27}H_{26}N_5O_3$	69.2	5.5	15.0	
					69.0	5.7	15.1	
4f	160	83	Yellow	$C_{32}H_{21}N_5O_3$	73.4	4.0	13.4	
					73.6	4.1	13.6	
4g	210	80	Yellow	$C_{33}H_{24}N_5O_4$	71.5	4.3	12.6	
					71.3	4.1	12.8	
4h	188	80	Yellow	$C_{32}H_{21}ClN_5$	68.9	3.7	12.5	6.4
					69.1	3.8	12.7	6.5
4i	188	90	Yellow	$C_{32}H_{21}N_6O_5$	67.5	3.6	14.8	
					67.6	3.8	15.0	
4j	158	78	Yellow	$C_{32}H_{28}N_5O_3$	72.4	5.3	13.2	
					72.2	5.5	13.3	

Table II.

Comp.	^{1}H-NMR (δ ppm)
3a	1.65 (s, 3H, CH_3); 4.8 (s, 1H, pyrazolone H-4); 5.3 (d, 1H, pyrazoline H-4); 5.6 (d, 1H, pyrazoline H-5) and 7.1-8.2 (m, 15H, ArH's).
3c	1.7 (s, 3H, CH_3); 4.8 (s, 1H, pyrazolone H-4); 5.2 (d, 1H, pyrazoline H-4); 5.4 (d, 1H, pyrazoline H-5) and 7.0-8.1 (m, 14H, ArH's).
3d	1.6 (s, 3H, CH_3); 4.9 (s, 1H, pyrazolone H-4); 5.2 (d, 1H, pyrazoline H-4); 5.4 (d, 1H, pyrazoline H-5) and 6.8-7.9 (m, 14H, ArH's).
3b	1.6 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 4.8 (s, 1H, pyrazolone H-4); 5.1 (d, 1H, pyrazoline H-4); 5.3 (d, 1H, pyrazoline H-5) and 7.0-8.2 (m, 14H, ArH's).
3f	4.9 (s, 1H, pyrazolone H-4); 5.2 (d, 1H, pyrazolone H-4); 5.4 (d, 1H, pyrazoline H-5) and 7.1-8.3 (m, 20H, ArH's).
3g	3.7 (s, 3H, OCH_3); 4.6 (s, 1H, pyrazolone H-4); 5.0 (d, 1H, pyrazoline H-4); 5.2 (d, 1H, pyrazoline H-5) and 7.0-8.4 (m, 19H, ArH's).
3h	4.8 (s, 1H, pyrazolone H-4); 5.2 (d, 1H, pyrazoline H-4); 5.5 (d, 1H, pyrazoline H-5) and 7.0-8.1 (m, 19H, ArH's).
3i	4.7 (s, 1H, pyrazolone H-4); 5.1 (d, 1H, pyrazoline H-4); 5.3 (d, 1H, pyrazoline H-5) and 7.3-8.2 (m, 19H, ArH's).
4a	1.6 (s, 3H, CH_3);4.6 (s, 1H, pyrazolone H-4) and 7.1-8.2 (m, 15H, ArH's).
4b	1.6 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 4.8 (s, 1H, pyrazoline H-4) and 7.0-8.2 (m, 15H, ArH's).
4f	4.7 (s, 1H, pyrazolone H-4); 7.1-8.3 (m, 20H, ArH's).
4g	3.8 (s, 3H, OCH_3); 4.6 (s, 1H, pyrazolone H-4); 7.2-8.3 (m, 19H, ArH's).

conversion of **3a-j** into the corresponding pyrazole derivatives. Thus, **3a-j** were treated with chloranil in xylene to affect dehydrogenation with the formation of the corresponding 3-(pyrazolidinon-4'-yl)-pyrrolo[3,4-d]pyrazole-2,6-dione derivatives **4a-j** respectively whose structures were based on correct elemental analyses and spectral data studies (cf. Experimental Part). It was observed that the bands related to the presence of saturated CH groups were entirely absent in the IR spectra of **4a-j** indicating dehydrogenation of the pyrrolidine moiety.

Moreover, the ^{1}H-NMR spectra of **4a-j** did not reveal any signals which might be attributed to the presence of pyrazoline H-4 or pyrazoline H-5 protons thus establishing further the dehydrogenation reaction (Tables I and II).

EXPERIMENTAL

All melting points are uncorrected. IR in KBr discs were recorded on a Pye Unicam SP 1100 spectrometer. ^{1}H-NMR spectra were obtained in DMSO-d_6 on a Varian EM-360-60 spectrometer with TMS as an internal reference. Elemental analyses were carried out by the Microanalytical Centre, Cairo University.

Reaction of 1a,b with 2a-e

A solution of **1a,b** (0.01 mol) and 0.01 mol of the appropriate **2a-e** in 25 m*l* toluene or bromobenzene was heated under reflux for 4 h, then evaporated in vacuum. The solid thus obtained was collected and crystallized from ethanol to give **3a-j** (Table I).

Dehydrogenation of the adducts 3a-j

A mixture of coloranil (0.005 mol) and the appropriate **3a-j** (0.005 mol) in 40 m*l* xylene was refluxed for 48 h. The reaction mixture was washed with a solution of 0.1 N sodium hydroxide (3 × 50 m*l*), dried and evaporated under reduced pressure. The solid collected was crystallized from acetic acid to give **4a-j** (Table I).

LITERATURE CITED

1. Part VI: Ghabrial, S.S. and Abdou, S.E.: *Sulfur Letter,* **7**, 127 (1988).

2. Ghabrial, S.S., Arief, M.M.H. and Abdou, S.E.: *Arch. Pharm.* (*Weinheim*), **318,** 999 (1985).
3. Ghabrial, S.S., Moharram, H.N. and Aziz, S.I.: *Heterocycles,* **23,** 1161 (1985).
4. Ghabrial, S.S. and Abdou, S.E.: *Sulfur Letters,* **5,** 87 (1986).
5. Ghabrial, S.S. and Abdelhamid, A.O.: *Arch. Pharm.* (*Weinheim*), **320,** 1281 (1987).
6. Abdelhamid, A.O. and Ghabrial, S.S.: *Sulfur Letters,* **7,** 19 (1987).
7. Goodman, L.S. and Gilman, A.: The Pharmacological Basis of Therapeutics,Six Edition (1980), M. Milian Publishing Co. Inc., New York.