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4- NITROSO -1- PHENYL -3- METHYL -2- PYRAZOLIN -5- ONE IN THE SYNTHESIS OF: SOME NEW 4- SUBSTITUTED HETEOCYCLES OF PHARMACEUTICAL INTEREST

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Condensation of 4- nitrosopyrazolone (1) with active methylene components namely, malononitrile, acetophenone, ω-cyano-acetophenone and / or 1,3- diphenylacetone gave compounds (2a-c) and (4). Treatment of (2a, 2b) with hydrazine hydrate gave the aminopyrazoles (3a, 3b). Reaction of (1) with some hydrazines afforded derivatives (5, 6, 7a, 7b).

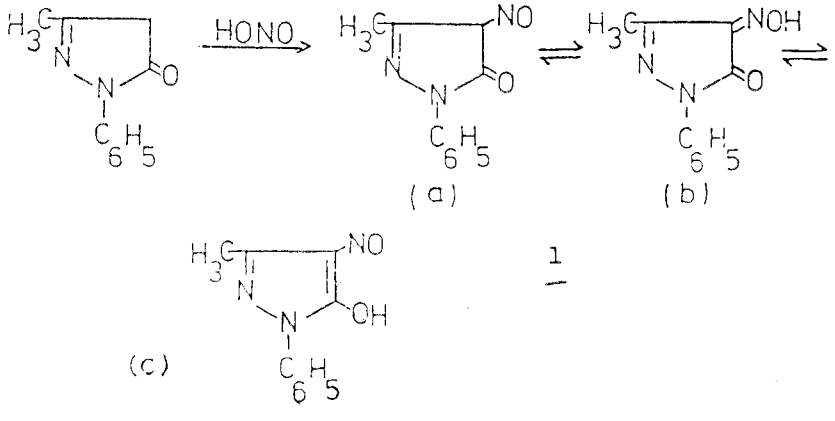
While the condensation of (1) with hydrazine hydrate gave the bispyrazolone (8). The structures of the ring systems have been confirmed by their IR, ^{1}H-NMR and mass spectral data.

INTRODUCTION

Nitroso compounds are reactive compounds and thus enter into different types of reactions[1].

Nitroso compounds are potentially versatile synthetic intermediates and some research has focussed on exploring the synthetic potentialities of 4- nitroso -1- phenyl -3- methyl -2- pyrazolin -5- one 1[2,3] with these studies.

On the other hand, 4- nitroso -1- phenyl -3- methyl -2- pyrazolin -5- one 1 can exist in tautomeric forms (a-c) and the formation of the reaction products depends on the reaction conditions.



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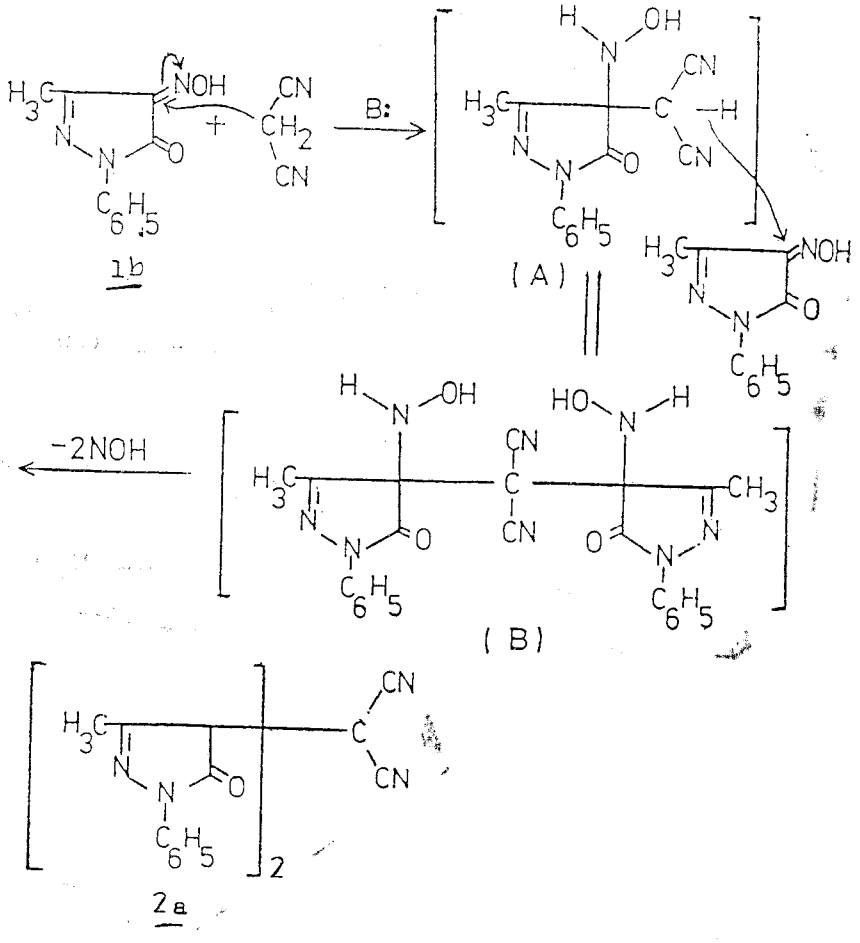
DISCUSSION

Treatment of (1b) with malononitrile in ethanol containing few drops of piperidine lead to the formation of the bis -pyrazolone 2a in a good yield.

The reaction involves addition of malononitrile to the 4- nitroso -1- phenyl -3- methyl -2- pyrazolin -5- one (1b) as a nucleophile leading to the intermediate (A), which underwent addition of second molecule of (1b) to give the intermediate (B). The intermediate (B) undergoes elimination of 2 NOH group to yield the bis -pyrazolone (2a). Analytical data confirm the structure of (2a). Its IR spectrum shows characteristic bands corresponding to (C ≡ N, C = O and C = N) groups. The ^1H — NMR spectrum is consistent with the structure.

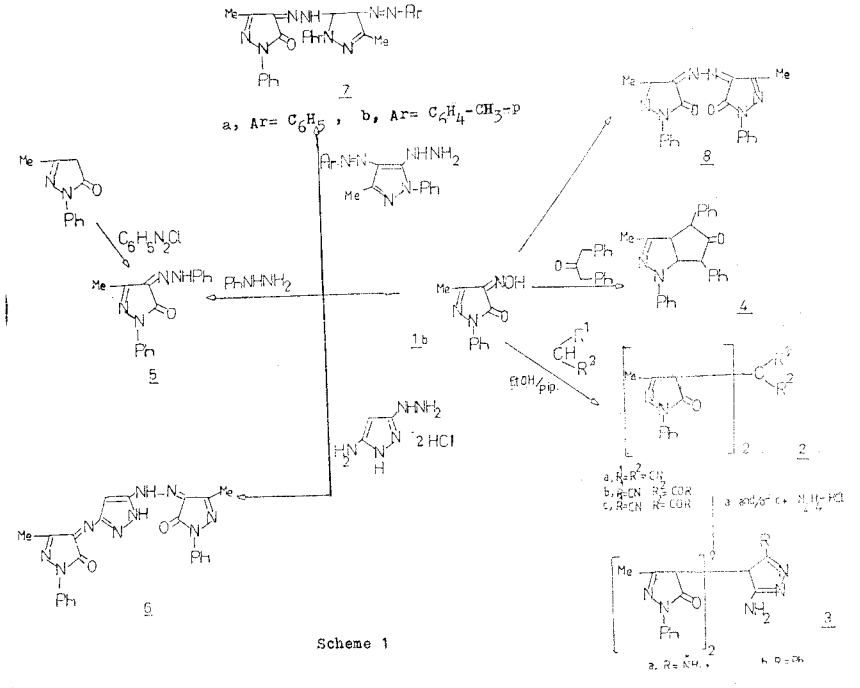
The formation of (2a) finds support from the mass spectrum, which gave a peak at m / z 410 corresponding to $C_{23}H_{18}N_6O_2$ (M^+).



3- Arylimino -2- indolinones undergo an addition elimination reaction with 2- hydrazinobenzothiazoles to yield the respective 3- (2- benzothiazolyhydrazono) -2- indolinone[4]. This was in agreement with our suggestions.

In connection with the above successful reaction it was the intention to examine the reaction of (2a) with hydrazine hydrate and hydrochloric acid as a further confirmation for its structure.

Thus, treatment of 2a with hydrazine hydrate in presence of hydrochloric acid gave the diaminopyrazole derivative (3a). The formation of (3a) finds support from the IR (no absorptions due to C ≡ N) and ^1H — NMR (cf, experimental). The mass spectrum gave a peak at m/z 414 corresponding to $C_{23}H_{22}N_6O_2$, which was obviously formed due to a loss of N_2 from the parent ion (c.f. Scheme 1).

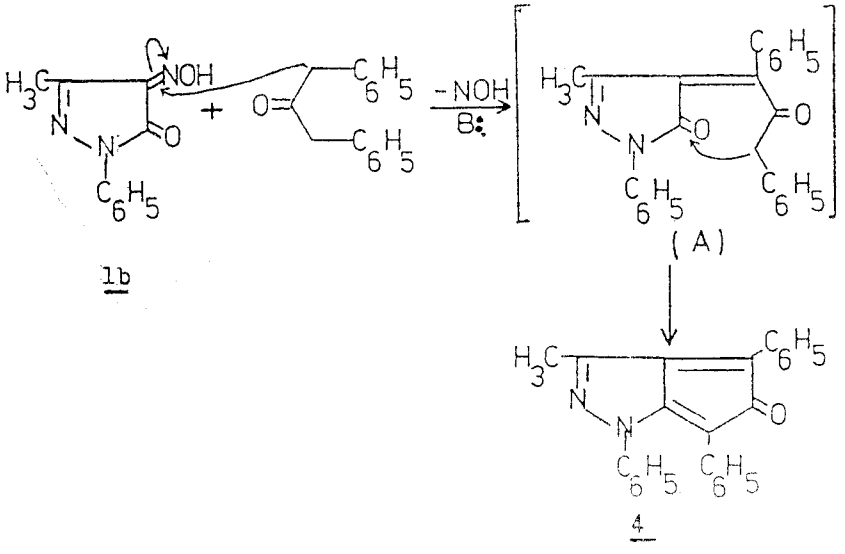


Scheme 1

In one instance with a view to providing additional evidence for the reaction of (1b) with active methylene components, it was treated with 1,3- diphenylacetone in ethanol-piperidine to furnish the pyrazolo-pen-

tanone derivative (4). Beside the correct analytical data, compound 4 exhibit in its IR spectrum characteristic bands at 1700 and 1630 cm^{-1} corresponding to (CO and C = N) groups.

The formation of 4 is believed to proceed as follows:



1b

4

In the presence of a base such as piperidine, intramolecular cyclization takes place directly and the reaction between (1b) and 1,3-diphenylacetone is postulated to proceed as follows: the NOH in (1b) was replaced by the 1,3- diphenylacetone and the intermediate (A) formed was converted to (4) upon loss of a molecule of water.

The formation of (4) finds support from the mass spectrum, which gave a peak at m / z 362 corresponding to $C_{25}H_{18}N_2O$ (M^+).

As a further extension to the reaction of (1b) with active methylene components, it was reacted with acetophenone to give the bis-pyrazolone 2b in a good yield (c.f. Scheme 1).

The formation of (2b) seems to proceed similar to (2a). The IR spectrum showed absorption bands at 1700, 1670 and 1595 cm^{-1} characteristic for (CO-Ph. CO of pyrazolone and C = N) groups respectively. The ^1H — NMR spectrum displayed signals at σ 1.7,1.8 (2s. 6H, 2C H_3), 2.4. 2.5, (2s. 2H, 2—CHCO-N-), 3.4 (s. 1H, PhCO — CH) and 7.2—7.9 (m, 15 H, ArH).

In connection with the above successful reaction, it was the intention to react (1b) with ω — cyanoacetophenone using piperidine as a catalyst. Thus, (1b) was treated with ω — cyanoacetophenone to give the bispyrazolone (2c) in a good yield (c.f. Scheme 1).

The IR spectrum of (2c) clearly showed the absorption band at 2200 cm^{-1}, attributable for C ≡ N. The ^1H — NMR spectrum displayed signals at δ 1.5 and 1.7 (2s, 6H, 2 CH_3), 2.4, and 2.5 (2s, 2H, 2 — CHCO —N—) and 7.3 — 7.9 (m, 15 H, ArH).

3— Oxaoalkanenitriles are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates since the keto and the cyano functions of these compounds are suitably situated to enable reactions with common bidentate reagents to form a variety of heterocyclic compounds. In addition the diverse biological activities reported for many of these compounds have also drawn the attention of biochemists[5–7].

In the light of the above findings, we treated the bis-pyrazolone (2c) with hydrazine hydrate to give the tripyrazole derivative (3b) in a good yield.

The structure assigned to the product (3b) is based on: the correct elemental analysis and the IR spectrum which showed no absorption due to — CO -Ph and C ≡ N groups and instead peaks at 3250 and 3400 cm^{-1} (NH_2).

Phenylhydrazine has two basic nitrogen atoms in the molecule, and its reaction with (1b) is of interest. When a mixture of (1b) and phenylhydrazine was heated in ethanol, 4- phenylhydrazono -1- phenyl -3- methyl -2- pyrazolin -5- one (5)[8] was obtained in a good yield.

The same compound was also obtained when phenyldiazonium chloride was allowed to couple with 1 -phenyl -3- methyl -2- pyrazolin -5- one. This compound was determined to be (5)[8] on the basis of its analytical, spectral data and (m.p., mixed m.p.).

As a further extension of studies on the reaction of (1b) with similar reagents, reaction with 5- hydrazino -pyrazole dihydrochloride was investigated.

Taking into account the above procedure for the condensation of hydrazines with nitroso-compounds (ethanol-piperidine), compound (1b) was allowed to react with 3-amino-hydrazinopyrazole dihydrochlo-

ıide in a molar ratio (2:1) to afford the bis-pyrazolone derivative (6), as inferred from its correct analytical and spectral data (cf. experimental).

Similarly, it seemed of interest to react 4- arylazo -1- phenyl -3- methyl -5- hydrazinopyrazole with (1b) to give (7a, 7b) on the basis of their correct analytical and spectral data (cf. experimental).

In the light of the above interesting reaction, hydrazine hydrate was used to react with (1b). Thus, condensation of two equivalent of (1b) with one equivalent of hydrazine hydrate gave a single product which was formulated as (8) as inferred from the absence of NH absorption in its IR spectrum (cf. experimental).

EXPERIMENTAL

Melting points (uncorrected) were determined on Fisher-Jones electric melting point apparatus. Microanalysis of C and H was determined at the Microanalytical lab., Faculty of Ssience (Mansoura and Cairo Universities). IR spectra in KBr or nujol were recorded on a Pye Unicam SP 1000 and 2000 and Beckman IR spectrophotometers. ^1H — NMR spectra were determined on Varian XL 100 and Brucker 400 MHz in $CDCI_3$ or DMSO solvents. Mass spectra were measured using AET MS — 9 mass spectrophotometer at 70 ev.

Condensation of (1) with malononitrile, acetophenone, ω — cyanoacetophenone and / or 1,3 — diphenylacetone: Formation of (2a-c) and (4):

To a mixture of (1) (0.02 mole) and malonitrile, acetophenone, ω— cyanoacetophenone, and / or 1,3- diphenylacetone (0.01 mole) in ethanol (30 ml) was added few drops of piperidine. The reaction mixture was refluxed for 6 hrs, left to stand at room temperature over night. The solid products that separated were filtered off, dried and crystallized from ethanol to give comounds (2a-c) and (4) (Table 1 and 2).

Reaction of (2a), with hydrazine hydrate: Formation of (3a, b):

A solution of (2a) and / or (2c) (0.01 mole) in ethanol (30 ml) was treated with hydrazine hydrate (0.02 mole) and conc. HCI (8 ml in case of (2a) and (4 drops of piperidine in case of (2c)).

The reaction mixture was refluxed for 4–6 hrs. Dilution with water gave (3a), while (3b) was precipetated. The solid products that separated were filtered off, dried and crystallized from ethanol (3a) and acetic acid (3b.) Condensation of (1) with phenylhydrazine: Formation of (5):

Table 1. Characterization data of compounds 2a-c, 3a,b, 4, 6, 7a, b, and 8.

Comp. no.	Yield (%)	M.P. (C)	Colour	M.F. (M. Wt)	Calcd. Analysis			Found		
					C	H	N	C	H	N
2a	93	175	deep-brown	$C_{23}H_{18}N_6O_2$ (410.42)	67.7	4.41	20.47	67.8	4.3	20.3
2b	91	165	yellow	$C_{28}H_{24}N_4O_3$ (464.5)	72.36	5.2	12.06	72.4	5.3	11.9
2c	86	122	brown	$C_{29}H_{23}N_5O_3$ (489.51)	71.15	4.73	13.4	71.3	4.5	13.3
3a	63	203	deep-brown	$C_{23}H_{22}N_8O_2$ (442.48)	62.28	5.01	25.27	62.3	5.1	25.4
3b	89	–290	red	$C_{29}H_{25}N_7O_2$ (503.56)	69.16	5.0	19.47	58.9	4.9	19.6
4	77	178	red	$C_{25}H_{18}N_2O$ (362.41)	82.84	5.0	7.73	82.7	4.9	7.6
6	76	205	brown	$C_{23}H_{21}N_9O_2Cl_2$ (526.37)	52.47	4.02	23.95	52.7	3.8	34.9
7a	58	140	brownish-yellow	$C_{26}H_{22}N_8O$ (462.5)	67.51	4.79	24.22	67.8	4.5	24.4
7b	61	100	brown	$C_{27}H_{24}N_8O$ (476.52)	68.04	5.07	23.51	67.8	4.8	23.7
8	56	–290	brown	$C_{20}H_{16}O_6N_2$ (372.38)	64.5	4.33	22.57	64.7	4.2	22.7

A mixture of (1) (0.01 mole) and phenylhydrazine (0.01 mole) in ethanol (50 ml) was refluxed for 5 hrs. The solid product that separated was filtered off and crystallized from ethanol to give red crystals of (5), m.p. 135° (reported 135°)[8].

Condensation of (1) with 3- amino -5- hydrazinopyrazole dihydrochloride: Formation of 6:

A mixture of (1) (0.02 mole) and 3- amino -5- hydrazinopyrazole dihydrochloride (0.01 mole) in abs. methanol was refluxed for 18 hrs. The reaction mixture was left to stand for 24 hrs, at room temperature, filtered and crystallized from ethanol to give compounds (6) (Table 1 and 2).

Condensation of (1) with 4- arylazo -1- phenyl -3- methyl -5- hydrazinopyrazole: Formation of (7a,b):

Table 2. IR, ^{1}H-NMR and Mass Spectral data for Compounds (2a-c, 3a,b, 4, 4, 7a, b and 8)

Comp-no.	IR (cm^{-1})	^{1}H-NMR δ(ppm)	Mass Spectra
2a	1640, 1750, 2200	1.48, 1.62, 1.86, 1.95 7.2-7.8	410 [M^+] 381, 344, 315, 236, 203 (100), 174, 119
2b	1595, 1670, 1700	1.7, 1.8, 2.4, 2.5, 3.4, 7.2,-7.9	—
2c	1595, 1690, 2200	1.5, 1.7,2.4,2.5,7.3-7.9	—
3a	1610, 1690	—	415 (M^+–N_2), 341 (100), 327, 264, 222, 185
3b	1600, 1670, 3250, 3400	—	—
4	1630, 1700	—	362 [M]$^+$, 347, 203 (100), 158, 145
6	1595,1620,1670,3350,3450	—	—
7a	1595, 1670, 3100	2.3, 2.4, 7.1,-7.9, 10.5	—
7b	1600, 1700, 3100	—	—
8	1600, 1670	2.4, 2.5, 7.0-7.8	—

A mixture of (1) (0.01 mole) and 4- (phenyl or p- tolylazo) -1- phenyl-3- methyl -5- hydrazino-pyrazole (0.01 mole) in ethanol (50 ml) was refluxed for 6 hrs. The solid products that separated were filtered off, and crystallized from acetic acid to give compounds (7a,b). (Table 1 and 2). Condensation of (1) with hydrazine hydrate: Formation of (8):

A mixture of (1) (0.02 mole) and hydrazine hydrate (0.01 mole) in ethanol (50 ml) was refluxed for 5 hrs. The solid product that separated was filtered off, and crystallized from ethanol to give compound (8). (Table 1 and 2).

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