THE USE OF 4-HYDROXYMETHYL-1-PHENYL-2-PYRAZOLIN-5-ONE IN THE SYNTHESIS OF NEW HETEROCYCLES OF PHARMACEUTICAL INTEREST

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Condensation of the title compound **1** with malononitrile, ethyl cyanoacetate , cyanoacetophenone, acetophenone, 1,3-diphenylacetone, ethyl acetoacetate and/or diethyl malonate resulted in the formation of derivatives **2a-c, 6a,b** and **8a,b.** The reaction of **2a** with hydrazine hydrate gave the diaminopyrazole **4**. On the other hand condensation of **6a,b** with hydrazine hydrate gave the 1,2-diazepinones **7a,b.** Reaction of **1** with o-phenylenediamine afforded the 1,5-benzodiazepine **11.** Treatment of **1** with $POCl_3$ afforded the 4-chloromethyl derivative **12** which underwent condensation with o-phenylenediamine to give **11.** Reaction of **12** with aromatic amines and hydrazines gave derivatives **13a,b** and **15a,b**. The structures of the unknown ring systems have ben confirmed by analytical and spectral methods.

Introduction

In view of the well known importance[1-8] of 2-pyrazolin-5-ones as versatile intermadiates for the synthesis of different types of heterocyclic moieties, which may be substituted, condensed or fused to other systems, 4-hydroxymethyl-1-phenyl-3-methyl-2-pyrazolin-5-one (**1**) represent an adaptable starting material for the preparation of some new heterocycles of pharmaceurical interest.

Discussion

Malononitrile reacts with (**1**) in ethanol-piperidine to give the corresponding 4-(2,2-dicyanoethyl) derivative (**2a**) rather than the pyranopyrazole derivative (**3**). Formulation of (**2a**) was based on elemental analysis, IR and ^{1}H-NMR spectra. The IR spectrum shows absorption bands at 2220, 1710 and 1600 cm^{-1} attributed to CN group and the pyrazoline moiety. The ^{1}H-NMR spectrum displyed signals at 2.2 (s, 3H, CH_3), 2.5 (m, 1H, CO-CH-CH_2-), 3.1 (m, 2H, -CH_2-) and 6.9-7.8 (m, 5H, ArH). A search of the literature showed that phenylmalononitrile reacted with hydrazine hydrate to give the diaminopyrazole[9]. An aatempts to obtain the corresponding diaminopyrazole (**4**) from (**2**) and hydrazine hydrate as inferred from the absorption due to CN. The mass spectrum of (**4**) gave an M^+ at 284 fitted exactly with the obtained molecular weight.

It seemed of interest to react (**1**) with ethyl cyanoacetate and/or -cyanoacetophenone. Thus, compound (1) was treated with ethyl cyanoacetate and/or -cyanoacetophenone to give derivatives (**2b,c**) rather than the pyranopyrazole derivative (**3**). Structures (**2b,c**) were confirmed by their correct elemental analyses, IR and ^{1}H-NMR spectra. The IR spectrum of **2b** showed absorption bands at 1600

(C=N), 1700 (CO pyrazolone) 1640 (CO ester) and 2225 cm^{-1} (C=N). The ^{1}H-NMR spectrum of (**2b**) displayed signals at 1.3 (t, 3H, CH_3 ester), 1.6 (s, 1H, CH-COOEt), 2.1 (s, 3H, CH_3 pyrazolone), 2.8 (m, 1H, -CH-CH_2), 3.2 (m, 2H, -CH-CH_2), 4.1 (q, 2H, CH_2 ester) and 7-7.8 (m, 5H, ArH). The IR and ^{1}H-NMR spectra of 2c were in agreement with the proposed structure (cf experimental).

In connection with the above successful reactions, it was the intention to examine the reaction of (**1**) with acetophenone, 1,3-diphenyl acetone, ethyl acetoacetate, and/or diethyl malonate to give derivatives (**6a**), (**6b**), (**8a**) and (**8b**) rather than (**5**), (**9**), and (**10**) on the basis of their correct analytical and spectral data. The IR spectrum of (**6a**) shows two absorption bands at 1690 and 1710 cm^{-1} characteristic for the two carbonyl groups, while the ^{1}H-NMR spectrum displayed signals at 1.6 (s, 3H, CH_3), 2.15 (m, 2H, CH_2CO), 2.9 (m, 1H, -CH-CH_2), 3.3 (m, 2H, CH_2-CH_2-CO) and 7-8.1 (m, 10H, ArH). The mass spectrum of (**6a**) gave a M^++1 at 307. In the IR spectrum of compound (**6b**) a broad band extended from 1680 to 1720 cm^{-1} has been noticed. Further confirmation for structures (**6a**) and (**6b**) was gained upon treatment with hydrazine hydrate in ethanol to give the corresponding diazepines (**7a**) and (7b). Their structures were in accordance with the analytical and spectral data (see experimental). Similar behaviour has been reported[10]. Structure (**8a,b**) finds support from their correct analytical and spectral data (cf experimental)

As a further extension to the preparation of the diazepinones (**7a**) and (**7b**) it was the intention to react (**1**) with o-phenylenediamine to obtain the benzodiazepine (**11**) as inferred from the absence of the absorption due to CO and the presence of one NH group in its IR spectrum. In the mass spectrum of (**11**) no molecular ion was observed, but the fragment m/z 273 corresponding to $C_{17}H_{13}N_4$ was obviously formed by loss of a proton from the parent ion.

Treatment of (**1**) with phosphorous oxychloride afforded the 4-chloromethyl-2-pyrazolin-5-one (**12**). The IR spectrum lacked the band of the OH group and showed the absorption due to the (C=O pyrazolone) at 1700 cm^{-1} cofirming structure (**12**). Compound (**12**) gave a peak at m/z 174 (base peak) corresponding to $C_{10}H_{10}N_2O$, which was obviously formed due to a loss of CHCl from the parent ion.

When compound (**12**) was treated with hydrazine hydrate or phenylhydrazine we obtained only derivatives (**13a,b**) rather than (**14**). The structure of these compounds is based on the correct elemental analyses and the IR spectra which showed absorption bands at 1705-1710 (C=O pyrazolone) and 1595-1600 cm^{-1} due to (C=N). Our interest, in the reactivity of compound (**12**), was focuassed on the reaction with primary amines. Thus, equimolar amounts of (**12**) and primary aromatic amines, namely p-toluidine and p-anisidine were fused to give the arylaminomethyl derivatives (**15a,b**). The structure (**15**) was established for the reaction products on the basis of their spectra which showed absorption bands at 1650-1670 and 1595-1600 cm^{-1}. It was the intention to react (**12**) with o-phenylenediamine in dry acetone and anhydrous potassium carbonate to obtain the benzodiazepine derivative (**11**) in a good yield. The structure of compound (**11**) was based on the IR spectrum which lacked the absorption due to C=O and the identity of the product with that obtained from (**1**) and o-phenylenediamine (m.p. and mixed m.p.).

Experimental

Melting points (uncorrected) were determined on Fisher-Jones electric melting point appratus. Microanalysis of C and H were detrnined at the Microanalytical lab., Faculty of Science (Mansoura and Cairo Universities). IR spectra in KBr or nujol were recorded on a Pye Unicam SP 1000 and 2000 and Beckman IR spectrophotometers. ^{1}H-NMR spectra were determined on Varian XL 100 and Brucker 400 MHz in $CDCl_3$ or DMSO solvents. Mass spectra were measured using AET MS-9 mass spectrophotometer at 70 ev.

Condensation of 1 with active nitriles and active methylene compounents: Formation of (2a-c) and (6a,b): General Procedure:

To a solution of (1) (0.001 mol) and malononitrile, ethyl cyanoacetate, -cyanoacetophenone, acetophenone and 1,3-diphenylacetone (0.002 mol) in (100 ml) EtOH, few drops of piperidine was added. The reaction mixture was refluxed for 6h. The solid products that separated were filtered off and crystallized from EtOH to give compounds (**2a-c**) and (**6a,b**) (Table 1).

Condensation of (2a) with hydrazine hydrate: Formation of 4:

To a mixture of (**2a**) (3.52 g., 0.001 mol) and (1 ml., 0.002 mol) hydrazine hydrate in (30 ml) EtOH few drops of conc. HCl was added and the reaction mixture was refluxed for 5h. The solid product that separated was filtered off, dried and crystallized from EtOH to give compound (**4**) (Table 1).

Condensation of (6a,b) with hydrazine hydrate: Formation of (7a,b):

A mixture of (**6a,b**) (0.01 mol) and hydrazine hydrate (0.02 mol) in EtOH (50 ml) was refluxed for 6h. The solid products that separated were filtered off, dried and recrystallized from pet.ether (60-80°) (7a), EtOH (**7b**), (Table 1).

Condensation of (1) with ethyl acetoacetate and/or diethyl malonate: Formation of (8a,b):

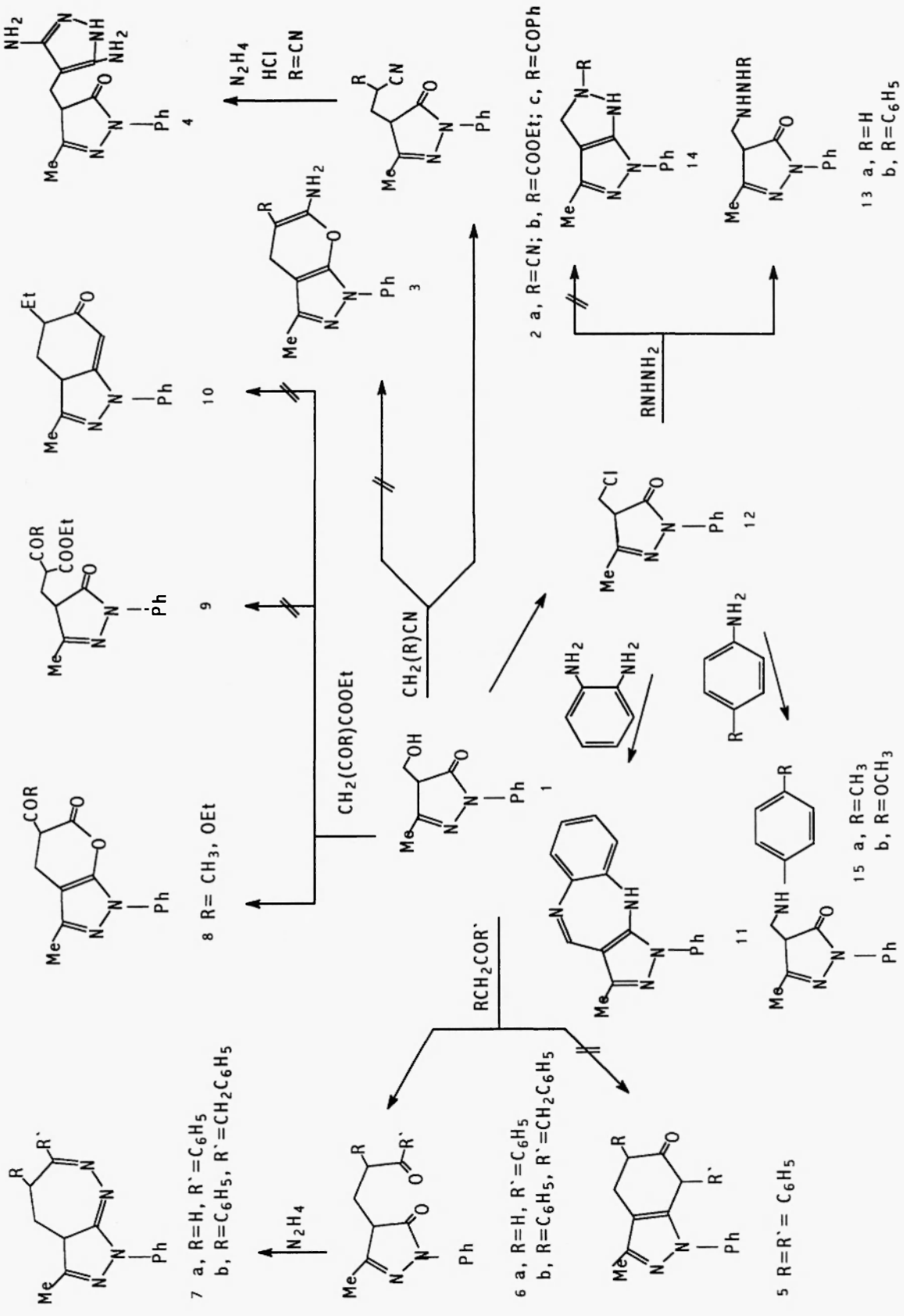
To a mixture of (1) (0.02 mol), ethyl acetoacetate and/or diethyl malonate (0.02 mol), conc. H_2SO_4 (20 ml) was added. The temperature was kept between 0-5°C for 3h and left for two days at room temperature. The reaction mixture was poured into ice-bath. The solid products that separated were filtered off washed with water and sodium bicarbonate solution, dried and crystallized from EtOH to give compounds (8a,b) (Table1).

Condensation of (1) with o-phenylenediamine: Formation of (11):

An equimolar ratio of (1) (0.01 mol) and o-phenylenediamine in EtOH (50 ml) and piperidine (4 drops) were refluxed for 6h. The separated product was filtered and crystallized from EtOH to give compound (**11**) (Table 1).

Reaction of (1) with phosphorous oxychloride: Formation of (12):

A mixture of (1) (0.05 mol) and $POCl_3$ (0.05 mol) was heated on a water-bath for 8-10 h. The reaction mixture was poured into ice-water dropwise with stirring. The solid product that separated was filtered off, washed with water till the filterate became neutral, crystallized from dil. EtOH to give white crystals of (**12**) (Table 1).


CH2(COR)COOEt
CH2(R)CN
RCH2COR'
RNHNH2
N2H4
HCl
R=CN
8 R= CH3, OEt
2 a, R=CN; b, R=COOEt; c, R=COPh
7 a, R=H, R'=C6H5
b, R=C6H5, R'=CH2C6H5
6 a, R=H, R'=C6H5
b, R=C6H5, R'=CH2C6H5
5 R=R'= C6H5
15 a, R=CH3
b, R=OCH3
13 a, R=H
b, R=C6H5

Tabic 1: Characterization Data Of Compounds 2a-c, 4, 6a,b, 8a,b, 11, 12, 13a,b, and 15a,b.

Comp. Ound	Yield (%)	M.P. (°C)	Colour	Mol.Formula (Mol. Wt)	Analysis Calcd C	H	N	Found C	H	N
2a^{+}	92	>290	Deep-brown	$C_{14}H_{12}N_4O$ (252.27)	66.65	4.7	33.21	66.4	4.9	22.3
2b^{+}	77	127	" "	$C_{16}H_{17}N_3O_3$ (299.32)	64.19	5.73	14.03	63.9	5.8	14.3
2c	63	144	Red	$C_{20}H_{17}N_3O_2$ (331.36)	72.48	5.17	12.68	72.6	5.4	12.4
4*	97	188	Brown	$C_{14}H_{16}N_6O$ (284.32)	59.13	5.67	29.56	59.5	5.4	29.7
6a^{+}*	90	133	Deep-red	$C_{19}H_{19}N_2O_2$ (306.35)	74.48	5.92	9.14	74.6	5.8	9.3
6b	76	100	Brown	$C_{26}H_{24}N_2O_2$ (396.47)	78.76	6.10	7.07	78.9	6.3	6.9
7a	83	96	Red	$C_{19}H_{18}N_4$ (302.36)	74.47	6.00	18.53	75.6	5.9	18.4
7b^{+}	82	138	Brown	$C_{26}H_{24}N_4$ (392.48)	79.56	6.16	14.27	79.7	4.2	14.1
8a	89	219	White	$C_{15}H_{14}N_2O_3$ (270.28)	66.65	5.22	10.36	66.7	5.2	10.4
8b	87	230	Yellow	$C_{16}H_{16}N_2O_4$ (300.31)	63.98	5.37	9.33	63.8	5.2	9.1
11^{+}*	69	230	Red	$C_{17}H_{14}N_4$ (274.31)	74.43	5.14	20.42	74.7	5.3	20.6
12*	90	195-7	White	$C_{11}H_{11}N_2OCl$ (222.67)	59.32	4.98	12.58	59.4	4.8	12.7

+ ^{1}H-NMR (,ppm): **2a** (DMSO), 2.2, 3.5, 3.1, 6.9-7.8; **2b**, ($CDCl_3$), 1.3, 1.6, 2.1, 2.8, 3.2, 4.1, 7-7.8 (J=7Hz, 7,14 Hz); **6a** ($CDCl_3$), 1.6, 2.15, 2.9, 3.3, 7-8.1; **7b** (DMSO) 2.3, 2.5, 3.1, 6.7-7.7; **11** (DMSO) 2.3, 5.6, 7.7-7.9, 10.2.

* MS, m/z: **4**, M^+ 284; **6a**, (M^++1) 307, 273, 223 (100), 205, 161, 102; **11**, (M^+-1) 273, 186, 174, 132, 91, 77 (100); **12**, (M^+-CHCl), 174 (100), 145, 132, 119, 91, 77.

Condensation of (12) with hydrazine hydrate and/or phenylhydrazine: Formation of (13a,b):

To a well stirred solution of (12) (0.01 mol) and hydrazine hydrate or phenylhydrazine (0.02 mol) in EtOH (50 ml), $CHCl_3$ (3-4 drops) was added. After stirring for 3-4 h , the solution left to stand at room temperature for 72 h diluted with water. The solid products that separated were filtered off and crystallized from EtOH and /or pet.ether (60-80°C) to give compounds (13a,b) (Table 1).

Reaction of (12) with p-toluidine and/or p-anisidine: Formation of (15a,b):

A mixture of compound (12) (0.01 mol) and p-toluidine or p-anisidine (0.01 mol) was fused at 120-140°C for 3-4 h. The solid mass obtained was crystallized from EtOH to give compounds (15a,b) (Table 1).

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