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SYNTHESIS OF SOME NEW ANTIMICROBIAL 2-PYRAZOLIN-5-ONES OF PHARMACEUTICAL INTEREST

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This study was undertaken in an attempt to evaluate the reactivity of α-[3-methyl-1-phenyl-5-oxo-2- pyrazolin-4-(nitromethyl)-methyl] cresotaldehyde 4 as a key intermediate in the synthesis of different heterocyclic derivatives (**5-11**) with a view of evaluating antibacterial and antifungal activities of the products. Most of these products gave positive results.

Key words: Antibacterial and antifungal activities, 3-Coumarin derivatives, Synthesis.

Introduction

The high antipyretic and analgesic activities of pyrazolinones [1] continues to stimulate the preparation of structurally related compounds and derivatives. The introduction of alkyl substituent at the desired position of heterocycles is important because heterocycles are often key intermediates in the synthesis of pharmaceutical drugs.

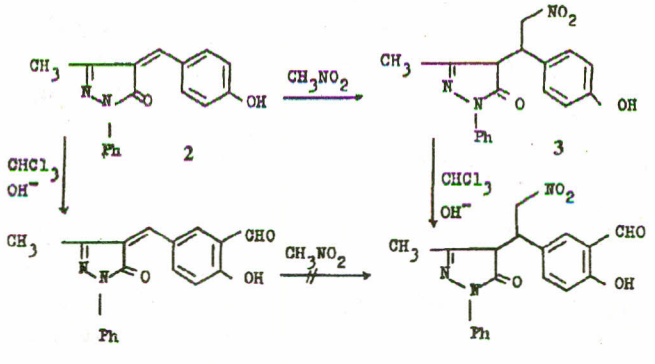
Results and Discussion

We have been interested in α-[3-methyl-1-phenyl-5-oxo-2-pyrazolin-4- (ylidine)]-2,5-cresotaldehyde 1 skeleton because this is one of the skeleton of certain analgesic and antipyretic drugs [2,3]. In the course of our attempt to utilize **1** [4] in organic synthesis we found that the introduction of nitromethane at the exocyclic double bond via Michael addition inhibit the activity of the double bond in order to react the salicylaldehyde moiety with active nitriles, active methcylene components and some aminoazoles. Thus Michael addition of nitromethane to4-(*p*-hydroxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one 2 [4] resulted in the formation of 3. The Riemer - Tiemann reaction of **3** gave our key intermediate **4**. In its mass spectrum the molecular ion was observed at 367, fitted exactly with the obtained molecular weight. Knoevenagel reaction of **4** with malononitrile, ethyl cyanoacetate and/or cyanoacetamide gives 6-[3-methyl-1-phenyl-5-oxo-2-pyrazolin-4(nitromethyl) methyl] coumarin-3-nitrile **5**, 6-[3-methyl-1-phenyl-5-oxo-2-pyrazolin-4-(nitromethyl) methyl]-3-carbethoxy coumarin **6** and 6-[3-methyl-1-phenyl-5- oxo-2-pyrazolin-4-(nitromethyl) methyl] coumarin-3-carboxamide **7** respectively. The IR are in accordance with the proposed structures **5**, **6** and **7** and revealed the presence of absorption bands at 2203 (C=N), 1708 (CO ester), and 3203, 3300 ($CONH_2$) scheme 1. Moreover, compound **6** can also be obtained from condensation of **4** with diethylmalonate (m.p. and mixed m.p.).

As a further extension of the above studies, reactions with ethyl acetoacetate was investigated. Thus reaction of **4** with ethyl acetoacetate gave 6-[3-methyl-1-phenyl-5-oxo-2-pyrazolin-4-(nitromethyl) methyl] 3- acetyl coumarin **8**. In addition to the correct analytical data the structure of **8** is confirmed by spectral data (see experimental).

As a point of interest and due to the fact that the presence of heterocyclic system containing two hetero atom fused to an aromaic ring generally possess the biological activity, **4** was reacted with 3-amino- 1,2,4-triazole, 3-amino-1-phenyl-2-pyrazolin-5-one and 2- aminobenzimidazole in methanolic potassium methoxide to give 7-[3-methyl- 1-phenyl-5-oxo-2-pyrazolin-4-(nitromethyl) methyl] (1,2,4) triazolo [4,3,a] quinazoline **9**, 7[3-methyl-1-phenyl-5-oxo-2-pyrazolin-4-(nitromethyl)methyl-1]-1-oxo-1H-pyrazolo [3,4e] isoquinoline **10** and benzimidazolo [1,2-a] quinazoline **11** respectively. (Scheme 2).

Compounds **9**,**11** were identical in all respects with the products; obtained from direct condensation of **4** with 3-amino-1,2,4-triazole and 2- aminobenzimidazole in dry ethanol. IR spectra revealed the absence of OH absorption band. In the mass spectrum of **9**, the molecular ion was



Scheme I.

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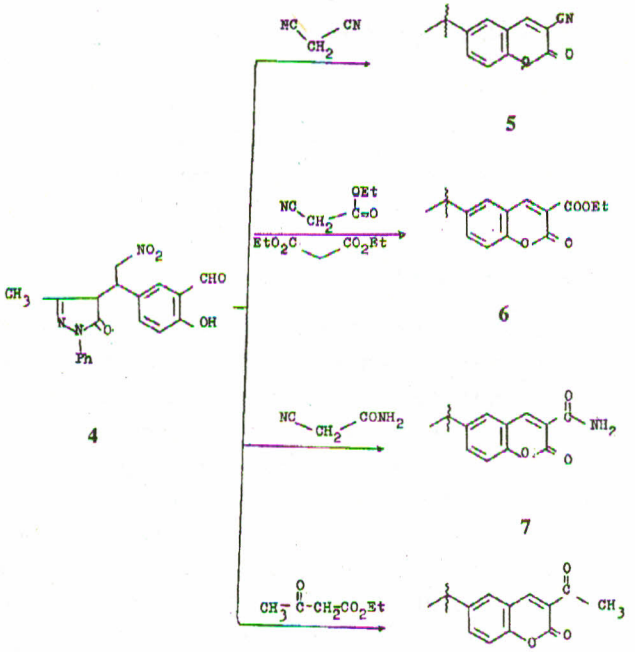
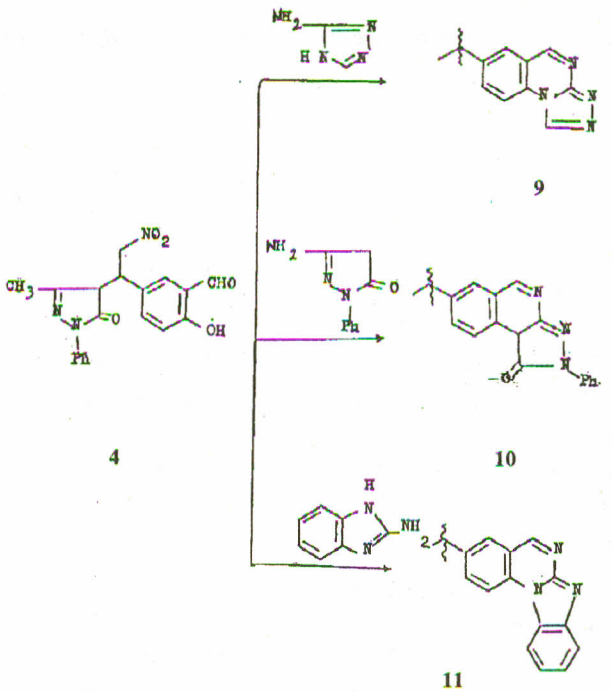
observed at 415, fitted exactly with the obtained molecular weight.

Experimental

Chemistry. All m.p.'s are uncorrected. Elemental analysis was performed in the microanalytical unit, Cairo University. IR spectra (in cm^{-1}) were recorded by means of pressed KBr on a Perkin - Elmer 883 Infrared Spectrophotometer. Mass spectra were obtained on Varian Mat 711 instrument using direct inlet system at 70 ev.



Scheme 2.



Scheme 3.

TABLE 1. CHARACTERIZATION DATA OF COMPOUNDS [4-11].

Compd. No.	Yield (%)	M.P. (°C)	Colour	Solvent	Formula (M.Wt.)	Analysis Found C	Analysis Calcd. H	IR(cm^{-1})
4.	68	205	Brown	aq EtOH	$C_{19}H_{17}O_5N_3$ (367.34)	61.9 (62.12	4.0 4.7)	3450 (OH), 1710 (CO) 1697 (Co pyrazolone) 1610 (C=N), 1500 (NO_2)
5.	63	280	Dark brown	aq EtOH	$C_{22}H_{16}O_5N_4$ (416.38)	62.9 (63.4	4.1 3.9)	2203 (conjugated C≡N), 1720 (α,β unsaturated Lactone,1697 (CO pyrazolone),1620 (C=N),1600 (C=C).
6.	37.2	220-5	Brown	aq EtOH	$C_{24}H_{21}O_7N_3$ (463.43)	62.7 (62.2	4.8 4.6)	1710 (CO Lactone), 1697 (CO pyrazolone), 1620 (C=N), 1600 (C=C).
7.	56.6	>300	Brown	EtOH	$C_{22}H_{18}O_6N_4$ (434.39)	61.1 (60.8	5.0 4.2)	3203, 3300 (NH) 1708 (CO α, β unsaturated Lactone) 1697 (CO pyrazolone), 1612 (C=N), 1600 (C=C).
8.	48.8	285	Brown	aqEtOH	$C_{25}H_{23}O_6N_3$ (461.45)	65.1 (65.07	5.0 5.02)	1713 (CO, β-diketone), 1665 (CO pyrazolone), 1620 (C=N), 1600 (C=C), 1500 (NO_2).
9.	44.6	240	Brown	EtOH	$C_{21}H_{17}O_3N_7$ (415.407)	61.0 (60.71	4.6 4.13)	1703 (CO pyrazolone), 1630 (C=N).
10.	44.7	>300	Brown	aq EtOH	$C_{28}H_{22}O_4N_6$ (506.51)	66.7 (66.4	5.2 4.4)	1703, 1697 (CO pyrazolone), 1600 (C=N), 1500 (NO_2).
11.	74.07	275	Brown	Acetic	$C_{26}H_{20}O_3N_6$ (464.47)	66.8 (67.2	5.2 4.34)	1705 (CO pyrazolone), 1660 (C=N), 1605 (C=C), 1500 (NO_2).

Condensation of **4** *with active nitriles and active methylene components, formation of (5-8). General procedures.* A mixture of **4** (0.01 mole); active nitriles namely malononitrile, ethyl cyanoacetate and cyanoacetamide; active methylene components namely diethyl malonate and ethyl acetoacetate (0.01 mole) each one respectively; glacial acetic acid (2.5 ml) and ammonium acetate (1.5 g) in dry benzene (20 ml) was stirred and heated to reflux with continuous removal of water for 20 hrs. The excess of solvent was evaporated in vacuo and the obtained products were filetered off, washed with water and recrystallized from the proper solvent (Table 1).

Condensation of **4** *with aminoazoles, Formation of* (**9 - 11**). *General procedures.* In 50 ml of methanolic potassium methoxide (prepared from (0.01 mole K metal and 50 ml dry methanol) containing (0.01 mole) **4** was added (0.01 mole) of 3-amino-1,2,4-triazole; 1-phenyl-3-amino-2-pyrazolin-5-one and 2-aminobenzimidazole, each one respectively. The reaction mixture was refluxed for 6 - 8 hrs, cooled, diluted with ice-cold water and acidified with dilute acetic acid (Ph = 4).

The solid products that separated were crystallized from the appropriate solvent. (Table 1).

Antimicrobial activity. The antimicrobial activity of the newly synthesized compounds were tested. Thus the compounds were screened for their antibacterial activity against *Staph. albus, Staph. aureaus* and *E. coli* at different concentration using agar pour plate method [5] and the results were represented as MIC (CF Table 2). The antifungal activity was tested to determine MIC against *Saccharomyces cervisiae* using turbidimetric method [6] and the results were tabulated in Table 2.

TABLE 2. *IN VITRO* BIOLOGICAL ACTION OF COMPOUNDS (5 -11) ON BACTERIA AND FUNGI.

Compd. No.	MIC *Staph. albus*	MIC *Staph. aureaus*	MIC *E. coli*	Yeast
5	100	100	-ve	-ve
6	-ve	-ve	-ve	-ve
7	-ve	100	50	-ve
8	-ve	100	50	-ve
9	-ve	100	100	-ve
10	50	100	100	-ve
11	100	-ve	50	-ve

References

1. J.M. Sala, Chim. Ther., **2**, 272 (1967); Chem. Abstr., **68**, 95751m (1968).
2. L.A. Mitscher and D. Lednicer, T*he Organic Chemistry of Drug Synthesis* (John Wily and Sons, New York, 1977).
3. M.A. Metwally, A.A. Fada, H.M. Hassan and E. Afsah, Org. Prep. Proc. Inter., **17** (3), 198 (1985).
4. E. Afsah, F.A. Amer and M. Sofan, Z. Naturforsch, **35b**, 1313 (1980).
5. F.S. Stewart and Berwick, *Bacteriology, Virology and Immunity for Students of Medicine* (1979), 10th ed., pp. 68.
6. V.A.H. Goweulock, M. Bell, *Practical Chemical Biochemistry* (1980), Vol. 1, 5th ed., pp. 179.