SYNTHESIS AND REACTIONS OF 1-ACETYL-3H-3(3\-METHYL-5\-OXO-1\-PHENYLPYRAZOLIDINE)-2H-INDOL-2-ONE

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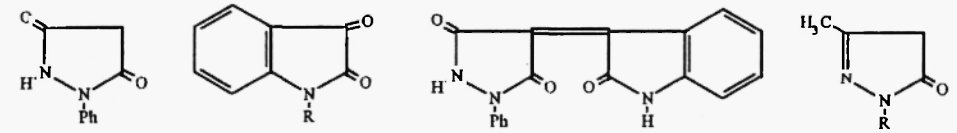
Abstract : 1-Acetyl-3H-3(3\-methyl-5\oxo-1\-phenylpyra-zolidine)-2H-indol-2-one **VII** is synthesized and its reactions with amines, hydrazines, and active methylenes were studied.

In a previous paper[(1)] we prepared 1,3-dihydro-3-(3\,5\-dioxo-2H-1\-phenylpyrazolidine)-2-indol-2-one **III** by condensing of 2H-1-phenylpyrazolidine-3,5-dione **I** with isatin **IIa**. Owing to the great importance of both pyrazolone[(2)] and isatin[(3)] in medical field and industerial uses, this paper deals with syntheses of novel heterocylic compounds contain both moities in one molecule. Thus treating of 3-methyl-1-phenyl-2-pyrazolin-5-one **IVb** with N-acetylisatin **IIb** gave the addition product **V**. The latter compound when stirred with N-bromosuccinimide (NBS) in chloroform we obtained a mixture composed of four products. These products can be separated by fractional crystallization to give the products **VI** - **IX**. The structure of the products **VI** - **IX** could be identified by elemental as well as spectral analyses.

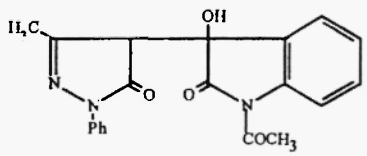


I

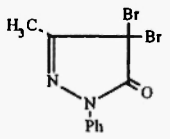
II a) R = H
b) R = $COCH_3$

III

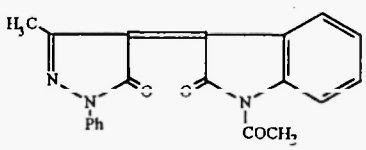
IV a) R = H
b) R = Ph



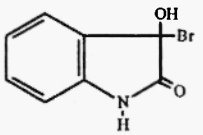
V



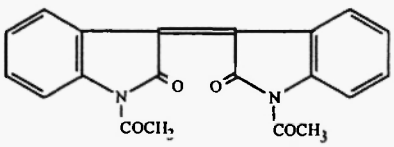
VI



VII



VIII

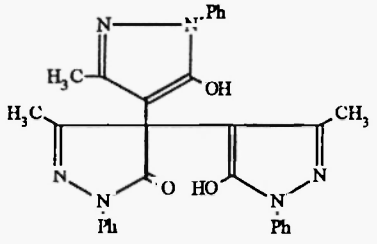


IX

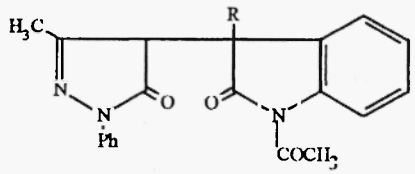
1-Acetyl-3H-3(3\-methyl-5\-oxo-1\-phenylpyrazolidine)-2H-indol-2-one **VII** was subjected to some reactions using amines, hydrazines, and active methylenes. Thus stirring of **VII** with aniline in ethanol, we obtained the trione **X**, whose structure was identified by spectral, elemental analysis as well

as m.m.p. with an authentic sample[4], while treating of **VII** with benzylamine under the same reaction coudition leads to the addition product **XIa.** The structure of **XIa** was confirmed on the basis of the presence of absorption bands at γ 3100 and 1700 cm^{-1} in the IR spectrum corresponding to NH and CO respectively. Treating of **VII** with N,N-diethylaniline we obtained **XIb**, whose structure based on spectral and elemental analysis. Using o-phenylenediamine with **VII**, the spiroproduct **XII** was formed. The structure of **XII** was established by spectral, elemental analysis as well as m.m.p. with an authentic sample[5].

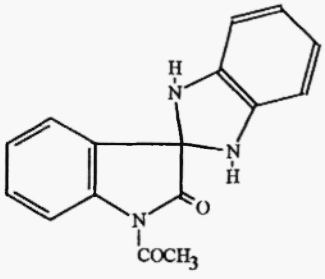
When hydrazine hydrate was added to **VII** at room temperature it afforded **XIc**, based on the presence of absorption bands at γ 3400, 3200 cm^{-1} and at γ 3100 cm^{-1} in the IR spectrum, corresponding to NH_2 and NH respectively. Using phenyhydrazine with **VII** under the same reaction condition, 4,4\-bis(3-methyl-1-phenyl-2-pyrazolin-5-one) **XIII** was obtained. The structure of **XIII** was confirmed by elemental, spectral analysis as well as m.m.p. with an authentic sample[4].



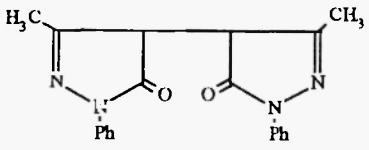
X



XI a) R = NH CH_2Ph
b) R = p. $C_6H_4N(C_2H_5)_2$
c) R = $NHNH_2$



XII

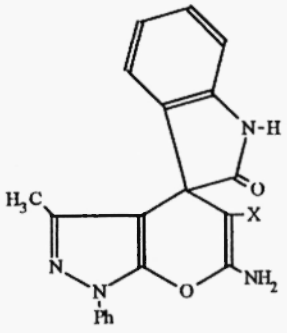


XIII

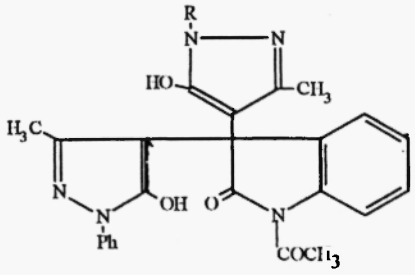
Compound **VII** was reacted with active methylene compounds namely malononitrile, ethyl cyanoacetate and 3-methyl-2-pyrazolin-5-ones using ethanol as a solvent.

Malononitrile and / or ethyl cyanoacetate reacts with **VII** to give the spiro products **IVXa,b** through addition followed by cyclization. The structures of **IVXa,b** were confirmed on the basis of the presence of absorption bands at γ 3500, 3450 cm^{-1} and at γ 2220 cm^{-1} corresponding to NH_2 and CN for **IVXa** and absorption bands at γ 3400, 3200 cm^{-1} and at γ 1740 cm^{-1} for NH_2 and CO (ester) for **IVXb**. On the other hand ^{1}H-NMR and mass spectra for **IVXa,b** were in agreement with the suggested structures.

Using 3-methyl-2-pyrazolin-5-oue derivatives **IVa,b** we obtained the addition products **XVa,b**. The structure of **XVa,b** were confirmed by spectral and elemental analyses.



IXV a) X = CN
b) X = CO_2Et



XV a) R = H
b) R = Ph

Experimental

All melting points are uncorrected. Infrared spectra were recorded with a Shimadzo 408 spectrometer using KBr discs. ^{1}H-NMR spectra were measured with a Varian XL-100 spectrometer, Chemical Shifts are reported in ppm. Initial standard was TMS (δ scale). Mass spectra were obtained by mass spectrum unit at Cairo University. Microanalyses were carried out at microanalysis unit at Assiut University.

1-Acetyl-3-hydroxy-3-[4\H-3\-methyl-5\-oxo-1\-phenylpyra-zolidine]-2H-indol-2-one V

A mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one **IVb** (3.48 g; 0.02 mol) and N-acetylisatin **IIb** (3.78 g; 0.02 mol) in 150 ml of absolute ethanol was refluxed for 5h. The colourless precipitated product formed was collected, and washed several times with hot ethanol to give white powder.

Reaction of 1-acetyl-3-hydroxy-3-[4\H-3\-methyl-5\-oxo-1\-phenylpyrazolidine]2H-indol-2-one V with N-bromosucc-inimide

N-Bromosuccinimide (0.53 g; 0.003 mol) in 30 ml of chloroform was added to a solution of **V** (1.09 g; 0.003 mol) in 50 ml of chloroform during stirring in an ice bath. Stirring was continued for 30 min. and then the solvent was removed under reduced pressure. The residue formed showed 4 spots on TLC. The products could be separated by fractional crystallization as follows : the solid was trituated with petroleum ether (40-60) and from its solution a yellowish compound was obtained, m.p. 80 °C. It was identified as 4,4-dibromo-3-methyl-1-phenyl-2-pyrazolin-5-one **VI**[7]. The residue was trituated with petroleum ether (60-80) and from its solution a black precipitate is formed. It was collected to give **VII**. The petroleum ether insoluble residue portion was further trituated with ethanol, where colourless crystals were separated from the ethanol solution. It was collected and identified as 3-bromo-3-hydroxy-2-oxindole **VIII**. The ethanol insoluble portion was further recrystallized from methanol to give **IX**.

Reaction of 1-acetyl-3H-3(3\-methyl-5\oxo-1\-phenylpyra-zolidine)-2II-indol-2-one VII with amines and hydrazines

Amine and / or hydrazine namely aniline, benzylamine, N,N-diethylaniline, o-phenylenediamine and / or hydrazine hydrate, phenyl hydrazine](0.001 mol) in absolute ethanol (20 ml) was added to a stirred solution of VII (0.001 mol) in 30 ml of absolute ethanol. Stirring was continued for 1/2 - 2 h. The precipitated product was collected and crystallized from the proper solvent (cf. table).

Reaction of 1-acetyl-3H-3(3\-methyl-5\oxo-1\-phenylpyra-zolidine)-2H-indol-2-one VII with active methylenes

An equimolar amount of VII and active methylene [malononitrile, ethyl cyanoacetate, and / or pyrazolone] (0.001 mol) in 50 ml of absolute ethanol was refluxed for 2-3 h. After cooling the precipitated product was collected and crystallized from the proper solvent (cf. table).

References

(1) M.F. Aly, A.H. Atta, M. I. Younes, I.M. Abou Zeid, S.A. Metwally, Bull. of Assiut, in press

(2) M.I. Younes, S.A. Metwally, A.H. Atta, Synthesis 704 (1990)

(3) M.I. Younes, H.H. Abbas, S.A. Metwally, Arch. Pharm. (weinheim) 320, 1191 (1987)

(4) M.F. Aly, M.I. Younes, A.H. Atta, S.A.M. Metwally, J. Chem. Research(s), under publication

(5) F.D. Popp, J. Heterocyclic Chem. 9, 1399 (1972)

(6) A. Alam, J.A. Ballantine, J. Chem. Soc. 255 (1968)

(7) M.F. El-Zohry, M.I. Younes, S.A. Metwally, Synthesis 972 (1984)

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Table : Physical data of prepared compounds.

Product	Yield %	m.p. °C solvent of crystallization	Molaecular formula	M.S. m/z (%)	IR γ(cm^{-1})	^{1}H-NMR (solvent)	Calcd. / found C	H	N
V	65	240	$C_{20}H_{17}N_3O_4$ (363.4)	-	3450 (OH), 1770, 1715 (CO)	1.9 s, 3H, CH_3), 2.2 s 1H OH), 2.7(s 3H $COCH_3$), 7.2-7.5 m, 9H Ar-H) 8.3(s 1H, OH) (TFA).	66.11 66.49	4.68 4.78	11.57 11.71
VI	9	80 pet. ether (40-60)	$C_{10}H_8N_2OBr_2$ (332)	332 (7.7)	-	2.35(s, 3H, CH_3), 7.1-7.7(m, 5H, Ar-H) ($CDCl_3$).	-	-	-
VII	40	180 pet. ether (60-80)	$C_{20}H_{15}N_3O_3$ (345.4)	345 (58.2)	1750, 1715, 1690 (CO)	2.6(s, 3H, CH_3), 2.7(s, 3H, $COCH_3$), 7.1-8.35(m, 9H, Ar-H) ($CDCl_3$).	69..56 69.01	4.34 4.44	12.16 12.29
VIII	30	196 ethanol	$C_8H_7NO_2Br$ (227)		3500 (OH), 3250 (NH), 1750, 1715 (CO)	2.6(s, 1H, OH), 6.6-7.5(m,4H, Ar-H), 10.7(s, 1H, OH) ($CDCl_3$).	42.32 42.51	2.22 2.31	6.17 6.10
IX	12	207 methanol	$C_{20}H_{16}N_2O_4$ (348.4)	348 (35.2)	3400(enolic OH), 1720, 1620 (CO)	2.2(s, 6H, 2 $COCH_3$), 6.9-7.9(m, 10H, 8 Ar-H + 2OH) (DMSO).	68.96 69.21	4.63 4.52	8.04 8.31
X	85	200 ethanol	$C_{30}H_{26}N_6O_3$ (518.6)	518 (86.4)	3450 (OH), 1720 (CO)	2.2(s, 9H, $3CH_3$), 7.0-7.8(m, 15H, Ar-H) (DMSO).	69.48 69.61	5.05 5.21	16.21 15.98
XIa	53	156 ethanol	$C_{27}H_{24}N_4O_3$ (452.5)		3100 (NH), 1720 (CO)	1.4(s, 1H, NH), 2.05(s, 3H, CH_3), 2.5(s, 3H, CH_3), 4.4(s, 2H, CH_2), 7.1-7.9(m, 15H, Ar-H) ($CDCl_3$).	71.67 71.43	5.35 5.42	12.38 12.17
XIb	53	198-200 ethanol	$C_{30}H_{30}N_4O_3$ (494.6)		1760, 1710 (CO)	0.9-1.2(t, 6H, 2 CH_3), 1.75(s, 3H, CH_3), 2.5(s, 3H, $COCH_3$), 3.1-3.4(q, 4H, 2 CH_2), 6.6-8.15(m, 14H, Ar-H) (DMSO).	72.85 72.62	6.11 6.21	11.33 11.19

Table : cont.

Product	Yield %	m.p. °C solvent of crystallization	Molaecular formula	M.S. m/z (%)	IR γ(cm^{-1})	^{1}H-NMR (solvent)	Calcd. / found C	H	N
XI	52	162-164 pet. ether(60-80)	$C_{20}H_{19}N_5O_3$ (377.4)		3400 3200 (NH_2), 3100 (NH), 1750 (CO)	2.05(s 3H CH_3), 2.8(s, 3H $COCH_3$), 7.2-8.25(m, 10H, 9 Ar H + 1 enolic OH) (TFA)	63.65 63.71	5.07 5.19	18.56 18.62
XII	91	291-292 ethanol	$C_{16}H_{13}N_3O_2$ (279.3)		3200 (NH), 1680,(CO)		68.82 68.70	4.66 5.04	15.04 15.12
XIII	81	320 ethanol	$C_{20}H_{18}N_2O_2$ (346.4)			2.5(s, 6H, 2 CH_3), 7.2-7.75(m, 12H, 10 Ar-H + 2 enolic CH) (DMSO).	69.36 68.97	5.20 5.28	16.18 16.23
IXVa	79	235 pet. ether (60-80)	$C_{21}H_{15}N_5O_2$ (369.4)	369 (11.5)	3500, 3450 (NH_2), 2220 (CN), 1710, 1660 (CO).	1.9(s, 3H CH_3), 6.8-7.8(m, 11H, 9 Ar-H + NH_2), 10.7 (s, 1H, NH) (DMSO).	68.28 68.41	4.09 4.31	18.96 19.13
IXVb	72	210-212 pet. ether(60-80)	$C_{23}H_{20}N_4O_4$ (416.4)	416 (1.8)	3400, 3200 (NH_2), (NH), 1700, 1640 (CO).	0.6-0.9(t, 3H, CH_3), 1.65(s, 3H, CH_3), 3.6-3.9(q 2H, CH_2), 6.8-7.9(m, 9H, Ar-H), 8.2(s, 2H NH_2), 10.35(s, 1H, NH) (DMSO).	66.34 66.51	4.84 4.79	13.45 13.61
XVa	71	242-243 ethanol	$C_{24}H_{23}N_5O_4$ (443.5)		3400 (OH), 1750, 1720, 1630 (CO).	1.95(s, 3H, CH_3), 2.1(s, 3H, CH_3), 2.65(s, 3H, $COCH_3$), 7.2-7.6(m, 9H Ar-H), 8.1(s, 1H, OH), 8.2(s, 1H, OH) (DMSO).	65.01 64.91	4.74 4.87	15.80 15.49
XVb	63	182-183 ethanol	$C_{30}H_{25}N_5O_4$ (519.6)		3500 (OH), 1760, 1715 (CO)	2.05(s, 6H, 2 CH_3), 2.65(s, 3H, $COCH_3$), 7.15-7.7(m, 14H Ar-H) 8.1(s, 1H, OH) 8.2(s, 1H, OH) (DMSO).	69.35 69.46	4.85 4.62	13.48 13.35