Synthesis of some new β-Aroyl- α-[4(1,3-disubstituted-2-pyrazolin-5-one)] propionic Acids and 4-pyrazolinonyl-pyridazinones and the study of their antibacterial Activities

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Summary: β-Aroylacrylic acids(I) react with 1,3-disubstituted-2-pyrazolin-5-ones in dry benzene to give β-aroyl- α-[4(1,3-disubstituted-2-pyrazolin-5-one)] propionic acids(II). Esterification of IId with diazomethane gives the corresponding methyl ester (III). Reactions of II with hydrazine hydrate and phenylhydrazine afford the corresponding 4-pyrazolinonyl-pyridazinones (V and VI). Dehydration of II yield the butenolides (VII), which undergo ring opening reaction with amines to give the β-substituted α aroylpropionic acid N-alkylamides(VIII). Reactions of 4-pyrazolinonyl-pyridazinones (V) with anisaldehyde, ethyl bromoacetate, diethylsulfate, Grignard reagents have also been described. The in vitro antibacterial screening reveals substantial activities against Gram-positive and Gram-negative bacteria for compounds IIc and IId; while compounds IIa, IIb and Vb are inactive.

Introduction

The object of the present work has been to prepare new series of pyridazinones through the nucleophilic addition of 1,3-disubstituted-2-pyrazoline-5-ones to β-aroylacrylic acids, followed by cyclization of the adducts to the corresponding 4-pyrazolinonyl-pyridazinones and to screen the antibacterial activities of the resulting adducts and the 4-pyrazolinonyl-pyridazinones.

The reaction of p-bromo-(Ia), and 3,4-dichloro-(Ib)- β-benzoylacrylic acids with 3-methyl-I-phenyl-2-pyrazolin-5-one and 1,3-diphenyl-2-pyrazolin-5-one in dry benzene gave β-aroyl- α-[4(1,3-disubstituted-2-pyrazolin-5-one)] -propionic acids (IIa-d). Structure of the acids (IIa-d) was derived from their IR spectra* which showed ν C=O (acid) at 1750-1735, νC=O at 1690-1685 and ν C=N at 1600-1590. The PMR (DMSO-d_6) spectrum of IIa showed singals at δ 7.8 - 6.7 (9H,m,ArH), δ 4.7-4.08 (4H,m,CH_2.CH + COCH), δ 3.3 (3H,s,CH_3).

Esterification of IId with diazomethane in ether at O° yielded the corresponding methyl ester (III). The infrared spectrum of III showed ν C=O (ester) at 1730, ν C=O at 1690 and ν C=N at 1600. When methyl 3,4-dichloro- β-benzoylacrylate (IV) was allowed to react with 1,3-diphenyl-2-pyrazolin-5-one, it gave III, identical (m.p. and m.m.p.) with that prepared above.

The acids (IIa-d) on reaction with hydrazine hydrate and phenylhydrazine yielded the corresponding 6-aryl-4-pyrazoninoyl-2,3,4,5-tetrahydropyridazin-3-ones(Va-c) and 2,6-diaryl-4-pyrazoninoyl-2,3,4,5-tetrahydropyridazin-3-ones (VIa-d). The IR spectra of Va-c and VIa-d showed ν C=O at

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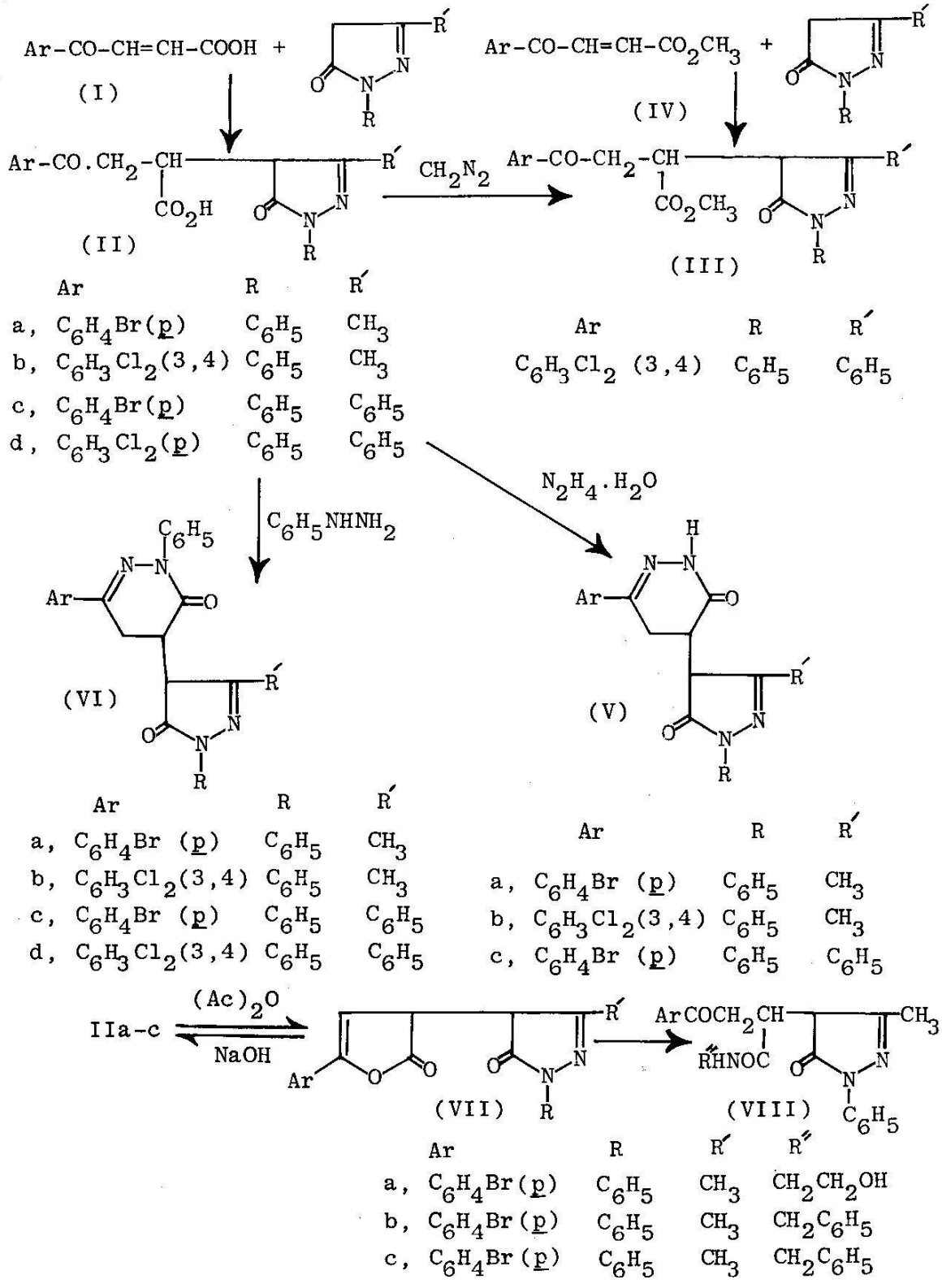
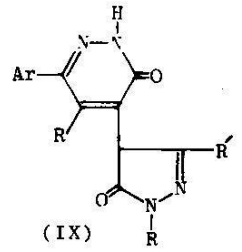
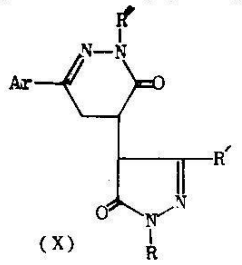
* IR ν_{max} here and elsewhere in the paper in cm^{-1}.


Ar-CO-CH=CH-COOH +
(I)
Ar-CO-CH=CH-CO2CH3 +
(IV)
Ar-CO.CH2-CH
CO2H
(II)
CH2N2
Ar-CO-CH2-CH
CO2CH3
(III)
Ar R R´
a, C6H4Br(p) C6H5 CH3
b, C6H3Cl2(3,4) C6H5 CH3
c, C6H4Br(p) C6H5 C6H5
d, C6H3Cl2(p) C6H5 C6H5
Ar R R´
C6H3Cl2 (3,4) C6H5 C6H5
N2H4.H2O
C6H5NHNH2
(VI)
(V)
Ar R R´
a, C6H4Br (p) C6H5 CH3
b, C6H3Cl2(3,4) C6H5 CH3
c, C6H4Br (p) C6H5 C6H5
d, C6H3Cl2(3,4) C6H5 C6H5
Ar R R´
a, C6H4Br (p) C6H5 CH3
b, C6H3Cl2(3,4) C6H5 CH3
c, C6H4Br (p) C6H5 C6H5
(Ac)2O
IIa-c
NaOH
(VII)
ArCOCH2CH
RHNOC
CH3
(VIII)
C6H5
Ar R R´ R´´
a, C6H4Br(p) C6H5 CH3 CH2CH2OH
b, C6H4Br(p) C6H5 CH3 CH2C6H5
c, C6H4Br(p) C6H5 CH3 CH2C6H5



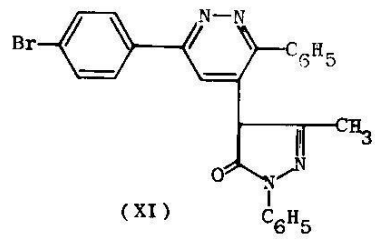
(IX)

	Ar	R	R′	R″
a,	C_6H_4Br (p)	C_6H_5	CH_3	$CH_2C_6H_4OCH_3$ (p)
b,	C_6H_4Br (p)	C_6H_5	C_6H_5	$CH_2C_6H_4OCH_3$ (p)



(X)

	Ar	R	R′	R″
a,	C_6H_4Br (p)	C_6H_5	CH_3	C_2H_5
b,	C_6H_4Br (p)	C_6H_5	C_6H_5	C_2H_5
c,	C_6H_4Br (p)	C_6H_5	CH_3	$CH_2CO_2C_2H_5$
d,	$C_6H_4Cl_2$(3,4)	C_6H_5	CH_3	$CH_2CO_2C_2H_5$
e,	C_6H_4Br (p)	C_6H_5	C_6H_5	$CH_2CO_2C_2H_5$



(XI)

1685-1655, ν C=N at 1605-1595, in addition to νNH at 3070-3060 for compounds Va-c.

The acids (IIa-c) easily dehydrated by boiling acetic anhydride or heated at their melting points, yielded [4(1,3-disubstituted-2-pyrazoline-5-one)] - γ -aryl- $\Delta^{\beta,\gamma}$ -butenolides (VIIa-c). The structure of VII was established from the following findings:-

1.The IR spectra of VII showed strong absorption at 1775-1765 characteristic of five membered lactones and the bands for C=O at 1655-1630 and C=N at 1600.

2. They readily hydrolysed by hot alkali giving the corresponding acids IIa-c[1].

3. Compounds VIIa and VIIc reacted with ethanolamine and benzylamine in boiling ethanol to give the corresponding α-substituted-β-aroylpropionic acid N-alkylamides VIIIa-c.

Condensation of Va and Vc with anisaldehyde in the presence of ethanolic KOH took place at 5-position to give 4,5,6-trisubstituted-2,3-dihydropyridazin-3-ones (IXa and b). Its infrared -spectra showed ν C=O at 1660-1655 and νC=N at 1600. This is in accordance with our previous results [2].

Alkylation of Va-c with diethylsulfate and ethyl bromoacetate gave the N-alkylated products (Xa-e). The infrared spectra of X showed ν C=O at 1670-1650 and ν C=N at 1600-1590, in addition to a strong band at 1760-1740 characteristic of the C=O of ester, for compounds Xc-e.

Reaction of Va with phenylmagnesium bromide gave the 3,4,6-trisubstituted pyridazine XI. The reaction involved addition to the carbonyl group followed by elimination of a molecule of water and two hydrogen atoms to give XI [3]. Its IR spectrum νC=O pyrazolone at 1650 and νC=N at 1600. The PMR (pyridine-d_5) spectrum of XI showed signals at δ 8.6-6.9 (14H,m,ArH), δ 5.1 (1H,s,pyrazolone proton), δ 4.4(1H,s, pyridazine proton), δ 3,4(3H,s,CH_3). The mass spectrum of XI showed the parent peak at m/z 482 (24.3%) (calculated for the isotope ^{79} Br).

Screening for antibacterial activity:

It was stated [4] previously that 2-diethylaminoethyl- β-(4-octyl-

benzoyl)-acrylates possess bacteriostatic and bactericidal properties. It was reported [5] also, that β-benzoyl-acrylates prevented the growth of staphylococcus aureus at aqueous dilutions of 1:256,000. Both the ethyl and methyl esters of β-acetylacrylic acid were bacteriostatic at 1:14,000, whereas the acid itself was not bacteriostatic at 1:4000 and a concentration of 1:2000 was required to prevent growth of staphylococcus aureus.

In the present investigation, the prepared compounds IIa-d and Vb were tested for in vitro antibacterial activity using the method described by Heatley [6]. The medium for screening was composed of (g 11000 ml): "Lab-lemco" Beef extract, 1.0; yeast extract (Oxoid L 20), 2.0; peptone (Oxoid L 37), 5.0; sodium chloride, 2.0 and agar 15.0 (pH 7.0).

Cylinders of known volume (0.1 ml) are placed on the solid medium seeded with a Gram positive and Gram negative test organism. A known constant volume (0.05 ml) of the compounds IIa-d and Vb, soluble in SDS introduced into each cylinder and allowed to diffuse through the agar at room temperature for one hour and finally incubated at 37°C for about 18-20 hours. Clear circular zones of inhibition of the test organisms were formed around the holes containing compounds IIa and IId.

It is suggested that compounds IIc and IId possess substantial activities against Gram positive and Gram negative bacteria as shown in table 1.

Table-1: In vitro Antibacterical Activities of some of the Prepared Compounds.

Compound	B.S. PCI219	Staph.aureus smith	Staph.aureus 209	E.Coli	Salmonella Typhi T-58	Pseudomonas pyogenes
IIa	-	-	-	-	-	-
IIb	-	-	-	-	-	-
IIc	+++	+++	+++	++	+++	++
IId	++	++	+++	++	++	+
Vb	-	-	-	-	-	-

= The width of the zone of inhibition indicates the potency of antibacterial activity.
(-) no antibacterial activity
(+) mild activity with the diameter of the zone equal to 1 cm
(++) moderate activity with the diameter of the zone equal to 1.8 cm
(+++) marked activity with the diameter of the zone equal to 2.5 cm.

Experimental

All melting points are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer and PMR spectra on Varian VN 1009 (S-60T) instrument using TMS as internal standard.

Reaction of Ia,Ib and IV with pyrazolinones: Formation of IIa-d and III.

To a solution of Ia, Ib or IV (0.01 mol) in dry benzene (20 ml), 3-methyl-I-phenyl-2pyrazolin-5-one or 1,3-diphenyl-2pyrazolin-5-one (0.01 mol) was added and the reaction mixture refluxed for 10 hrs. The solid that separatd on cooling was crystallised from a suitable solvent to give IIa-d and III respectively (Table 1).

Esterification of IId: Formation of III.

A solution of 1 g of the acid IId in ether (ca 50 ml) was treated with ethereal diazomethane solution[7]. The reaction mixture was kept at O° for 48 hours. The reaction products were washed with cold light petrol (b.p. 40-60°) several times and crystallized from a suitable solvent to give III.

Reaction of IIa-d with hydrazines: Formation of Va-c and VIa-d.

To a solution of the acid IIa-d (0.01 mol) in ethanol (20 ml), hydrazine hydrate or phenylhydrazine (0.01 mol) was added and the reaction mixture refluxed for 5 hours. The solid that separated on cooling was crystallized from a suitable solvent to give Va-c and VIa-d, respectively.

Dehydration of the acids IIa-c: Formation of the butenolide VIIa-c.

Method A: A solution of the acid IIa-c (0.01 mol) in acetic anhydride (20 ml) was refluxed for 4 hours. The solid obtained after concentration and cooling was crystallized from a suitable solvent to give the butenolide VIIa-c, respectively.

Method B: The acid IIa-c (0.01 mol) was heated at the melting point for half an hour and the solid was crystallized from a suitable solvent to give the butenolide VIIa-c, respectively.

Hydrolysis of the butenolide VII: Formation of the acid IIa-c.

A solution of VIIa-c (1 g) in ethanol (10 ml) was treated with sodium hydroxide (1 g in 5 ml water) and then under reflux for 2 hours. The solid solution was acidified with dilute hydrochloric acid and the solid separated was crystallized from a suitable solvent to give the corresponding acid IIa-c, respectively.

Reaction of VII with amines: Formation of VIII.

To a solution of VIIa or VIIc (0.02 mol) in ethanol (20 ml) ethanolamine or benzylamine (0.01 mol) was added and the reaction mixture refluxed for 6 hours. The solid that separated on cooling was crystallized from a suitable solvent to give VIIIa-c, respectively.

Condensation of anisaldehyde with V: Formation of IX.

A warm solution of Va or Vc (0.01 mol) in ethanol (20 ml) was treated with an ethanolic KOH solution (25 ml; 4%) and anisaldehyde (0.01 mol) added portionwise with continuous shaking. The reaction mixture was refluxed for 2 hours, cooled, poured into cold water and the solid obtained crystallized from a suitable solvent to give IXa and IXb, respectively.

Reaction of Va-c with diethyl sulfate or ethyl bromoacetate:Formation of Xa-e.

A mixture of Va-c (0.01 mol), anhydrous potassium carbonate (0.03 mol), diethyl sulfate or ethyl bromo-

bromobenzene and 0.03 atoms of magnesium) was added to a solution of Va (0.01 mol) in dry ether. The solution obtained was refluxed for 4 hours in a boiling water bath and left overnight. The reaction mixture was then hydrolyzed with saturated solution of ammonium chloride, extracted with ether, and the solvent removed to give a solid product which was crystallized from a suitable solvent to give XI.

Acknowledgement

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Table-2: Physical Data of Various Compounds Prepared

Compd[+] -	M.P. °C	Yield (%)	Compd[+] -	M.P. °C	Yield (%)
IIa	230	97[a]	VIIb	228	58[a]
IIb	217	95[a]	VIIc	259	54[c]
IIc	166	88[a]	VIIIa	180	69[b]
IId	154	93[a]	VIIIb	215	64[a]
III	139	82[b]	VIIIc	172	66[d]
Va	237	89[a]	IXa	241	52[a]
Vb	241	85[a]	IXb	300	59[a]
Vc	229	87[a]	Xa	74	72[e]
VIa	167	78[a]	Xb	71	68[e]
VIb	181	74[a]	Xc	169	74[a]
VIc	169	70[a]	Xd	125	63[e]
VId	186	73[a]	Xe	171	69[a]
VIIa	224	62[a]	XI	130	45[a]

[+] All compounds gave satisfactory elemental analysis. Compounds were recrystallized (a) ethanol, (b) benzene, (c) acetic acid (d) carbon tetrachloride (e) light petroleum (100-120°)

acetate (0.03 mol) and dry acetone (50 ml) was refluxed for 20 hours. After removing the excess solvent the products were crystallized from the proper solvent to give compounds Xa-e, respectively.

Action of Grignard reagents on Va: Formation of XI.

The solution of phenylmagnesium bromide (prepared from 0.03 mol of

Physical Data of Various Compounds Prepared

Compound	Mol.Formula	Found %			Required %		
		C	H	N	C	H	N
IIa	$C_{20}H_{17}BrN_2N_2O_4$	55.5	3.9	6.3	55.94	3.96	6.53
IIb	$C_{20}H_{16}Cl_2N_2O_4$	57.6	4.1	6.8	57.28	3.82	6.68
IIc	$C_{25}H_{19}BrN_2O_4$	60.9	3.9	5.5	61.10	3.87	5.70
IId	$C_{25}H_{18}Cl_2N_2O_4$	62.6	3.8	5.8	62.37	3.74	5.82
III	$C_{26}H_{20}Cl_2N_2O_4$	62.8	4.2	5.3	63.03	4.04	5.66
Va	$C_{20}H_{17}BrN_4O_2$	56.6	3.8	13.4	56.47	4.00	13.18
Vb	$C_{20}H_{16}Cl_2N_4O_2$	58.1	3.7	13.5	57.83	3.86	13.49
Vc	$C_{25}H_{19}BrN_4O_2$	61.3	4.2	11.7	61.60	3.90	11.50
VIa	$C_{26}H_{21}BrN_4O_2$	62.4	3.9	11.3	62.28	4.19	11.18
VIb	$C_{26}H_{20}Cl_2N_4O_2$	63.6	4.2	11.7	63.54	4.07	11.41
VIc	$C_{31}H_{23}BrN_4O_2$	65.8	4.3	10.2	66.07	4.09	9.95
VId	$C_{31}H_{22}Cl_2N_4O_2$	67.5	4.3	10.2	67.27	3.98	10.13
VIIa	$C_{20}H_{15}BrN_2O_3$	58.1	3.9	6.7	58.39	3.65	6.81
VIIb	$C_{20}H_{14}Cl_2N_2O_3$	60.0	3.3	7.1	59.85	3.49	6.98
VIIc	$C_{25}H_{17}BrN_2O_3$	63.6	3.4	6.1	63.42	3.59	5.92
VIIIa	$C_{22}H_{22}BrN_3O_4$	55.8	4.3	9.1	55.93	4.66	8.90
VIIIb	$C_{27}H_{24}BrN_30_3$	62.6	4.4	7.9	62.55	4.63	8.11
VIIIc	$C_{32}H_{26}BrN_3O_3$	66.3	4.6	6.9	66.21	4.48	7.24
IXa	$C_{28}H_{23}BrN_4O_3$	62.0	4.3	10.5	61.88	4.24	10.31
IXb	$C_{33}H_{25}BrN_4O_3$	65.6	3.9	9.4	65.45	4.13	9.26
Xa	$C_{22}H_{21}BrN_4O_2$	58.4	4.3	12.5	58.28	4.64	12.36
Xb	$C_{27}H_{23}BrN_4O_2$	63.2	4.7	11.1	62.91	4.47	10.87
Xc	$C_{24}H_{23}BrN_4O_4$	56.3	4.6	11.2	56.36	4.5	10.96
Xd	$C_{24}H_{22}Cl_2N_4O_4$	57.3	4.5	11.4	57.49	4.39	11.18
Xe	$C_{29}H_{25}BrN_4O_4$	60.9	4.2	9.9	60.73	4.36	9.77
XI	$C_{26}H_{19}BrN_4O$	64.7	4.2	11.8	64.60	3.93	11.59