

## Chemistry of Pyrazolines. Part VI. Synthesis of Some New Pyrazolines

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**Summary:** Substituted 2-pyrazolines have been prepared by the reaction of chalcones with hydrazines in different media, benzenesulfonyl hydrazide and acyl-hydrazines. The pyrazolines are converted to benzoyl, benzyl derivatives, Mannich bases and to 4-bromopyrazoles. Chalcone dibromide is converted to isoxazole.

### Introduction

Previous reports [1-3] dealing with the synthesis and pharmacological screening of pyrazolines revealed that some of these compounds exhibited a local anesthetic activity. This paper deals with the preparation of a new series of pyrazolines. The synthesis of 2-pyrazoline derivatives II-XII are outlined in Scheme 1.

Reaction of Ia-c with hydrazine hydrate, phenylhydrazine and benzenesulfonyl hydrazide in ethanol gave the corresponding pyrazolines IIa-c, IIIa-c and IVa-c, respectively.

The 1-acetyl, 1-formyl, 1-propionyl and 1-butyryl derivatives V, VIa-c, VIIa,b and VIIIa,b respectively were prepared from the crude pyrazoline II through the action of acetic, formic, propionic and butyric acids respectively. Alternatively, the 1-acyl compounds V-VIII were obtained directly from the chalcone I and hydrazine hydrate in appropriate acid, as solvent.

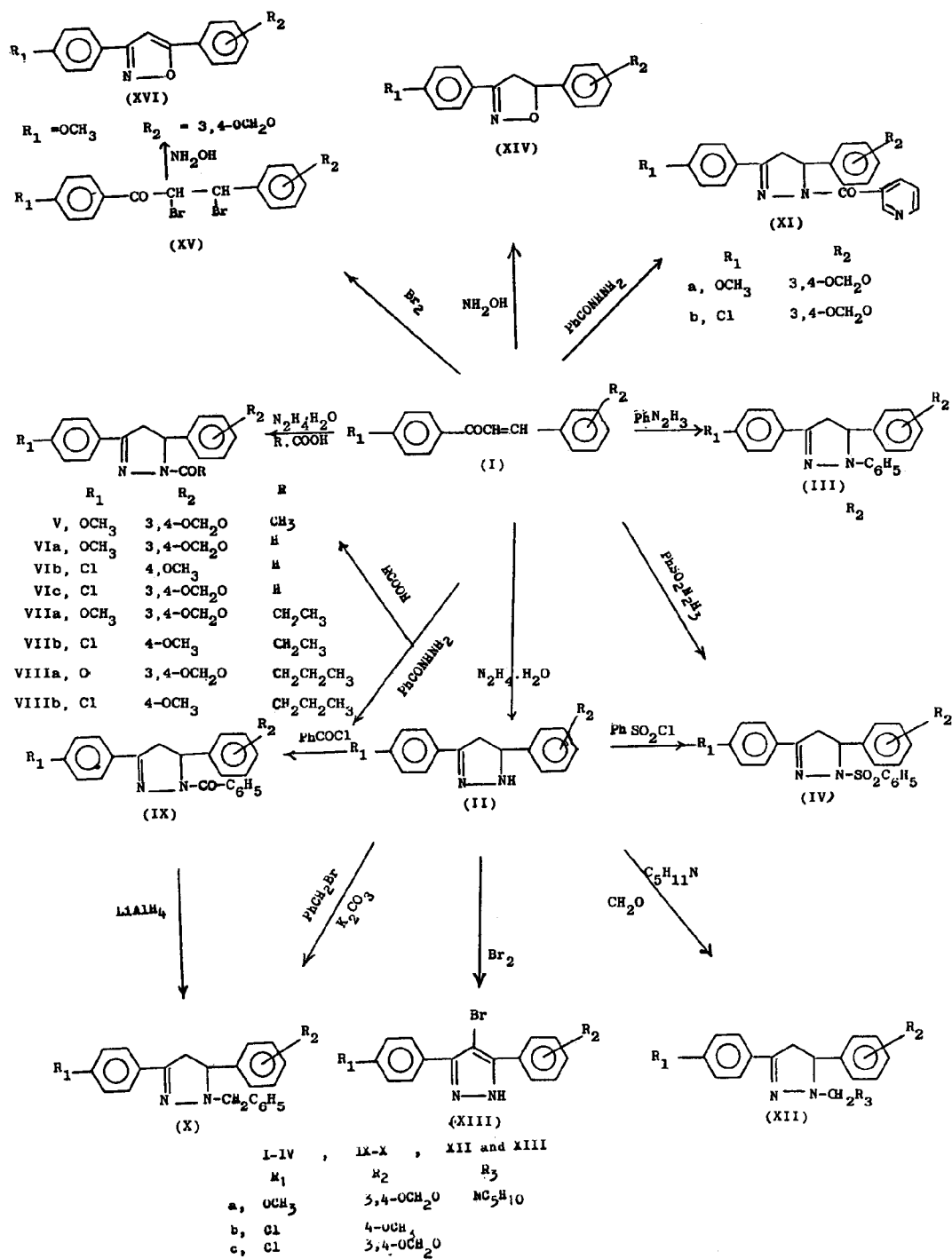
The  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) spectrum of V showed signals at 7.5-6.5 (7H, m,  $\text{Ar}_2\text{H}$ ), 5.74 (2H, s,  $\text{OCH}_2\text{O}$ ), 5.17 (1H, q, C5-Pyrazoline), 3.62 (3H, s,  $\text{OCH}_3$ ), 2.92 (1H, d, C4-pyrazoline), 2.62 (1H, d, C4-pyrazoline), 2.10 (3H, s,  $\text{COCH}_3$ ).

The reaction of the crude parent 2-pyrazolines II with benzenesulfonyl chloride in pyridine afforded an alternative preparation of the 1-benzenesulfonyl

pyrazolines IV, above, whereas with benzoyl chloride the 1-benzoyl derivatives IXa-c were obtained. The latter compounds were reduced with lithium Aluminium hydride to the 1-benzyl derivatives Xa-b; this is in accordance with our previous results [4]. The 1-benzyl derivatives were also obtained by N-alkylation of crude IIa,b with benzyl bromide in acetone in the presence of potassium carbonate. Significantly, chalcones Ia-c react with benzoylhydrazine in refluxing butanol to give pyrazolines IXa-c which were identified by direct comparison with authentic samples (mp, mixed mp and IR). Similarly, the reaction of chalcones Ia-c with nicotinoylhydrazine afforded the pyrazolines XIa-b. The reaction is analogous to that involving acetylenic ketones and acylhydrazines giving pyrazoles [5].

Treatment of methanolic solution of pyrazolines IIa-b with secondary amine, namely piperidine and aqueous formaldehyde yielded N-Mannich bases XIIa-b. Attempted  $\alpha$ -bromination of the parent pyrazolines II with bromine in chloroform solution gave the corresponding 4-bromopyrazoles XIIIa-b presumably via dibromination followed by elimination of hydrogen bromide through the nucleophilic action of the N-1 lone pair of electrons. This is in accordance with the results obtained by D'yakonov [6].

When the chalcone Ia was condensed with hydroxylamine hydrochloride in pyridine, the isoxazoline derivative XIV was obtained.



(Scheme 1)

Table 1: Characterisation of the new Compounds

Compound	M.P. °C	Yields % M.Wt.	M.Formula M.Wt	Analysis % (Found/ Calc.)		
				C	H	N
IIIa	130	85	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> 372	73.80 74.19	5.50 5.38	7.60 7.53
IIIb	155	83	C <sub>22</sub> H <sub>19</sub> ClN <sub>2</sub> O 362.5	72.90 72.83	5.40 5.24	7.80 7.72
IIIc	200	87	C <sub>22</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub> 376.5	69.90 70.12	4.60 5.24	7.70 7.72
IVa	190	89	C <sub>23</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> S 436	63.10 63.30	4.50 4.59	6.50 6.42
IVb	170	87	C <sub>22</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub> S 426.5	62.10 61.90	4.60 4.45	6.80 6.57
IVc	205	90	C <sub>22</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub> S 440.5	59.70 59.93	4.00 3.86	6.30 6.36
V	140	65	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> 338	67.40 67.46	5.30 5.33	8.50 8.28
VIa	142	79	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> 324	67.80 66.67	5.10 4.94	8.80 8.64
VIb	158	76	C <sub>17</sub> H <sub>15</sub> Cl N <sub>2</sub> O <sub>2</sub> 314.5	65.10 64.86	4.80 4.77	9.10 8.90
VIc	105	80	C <sub>17</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> 328.5	62.30 62.10	4.10 3.96	8.50 8.52
VIIa	125	69	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> 352	67.90 68.18	5.70 5.68	8.20 7.95
VIIb	130	72	C <sub>19</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub> 342.5	66.50 66.57	5.80 5.55	7.90 8.18
VIIIa	105	68	C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> 366	69.10 68.85	5.80 6.01	7.60 7.65
VIIIb	120	65	C <sub>20</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>2</sub> 356.5	67.50 67.32	6.10 5.89	7.90 7.85
IXa	105	67	C <sub>24</sub> H <sub>20</sub> N <sub>2</sub> O 352	71.80 72.00	5.10 5.00	6.80 7.00
IXb	125	60	C <sub>23</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub> 390.5	70.70 70.68	4.70 4.87	7.30 7.17

Continued Table 1:

Compound	M.P. °C	Yields % M.Wt.	M.Formula	Analysis % (Found/ Calc.)		
				C	H	N
IXc	130	80	C <sub>23</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub> 404.5	68.20	4.40	7.10
				68.23	4.20	6.92
Xa	115	83	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> 370	74.80	5.80	4.40
				74.61	5.70	7.25
Xb	98	81	C <sub>23</sub> H <sub>21</sub> ClN <sub>2</sub> O 376.5	73.40	5.60	7.70
				73.31	5.58	7.44
XIa	170	85	C <sub>23</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub> 385	68.60	4.70	10.50
				68.83	4.74	10.47
XIb	120	92	C <sub>22</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>3</sub> 405.5	64.90	4.10	10.30
				65.10	3.95	10.36
XIIa	85	48	C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>3</sub> 393	70.40	7.10	10.70
				70.23	6.87	10.69
XIIb	70	50	C <sub>22</sub> H <sub>26</sub> ClN <sub>3</sub> O 383.5	68.70	6.90	11.10
				68.84	6.78	10.95
XIIIa	180	90	C <sub>17</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>3</sub> 373	54.70	3.40	7.70
				54.69	3.49	7.51
XIIIb	230	88	C <sub>16</sub> H <sub>12</sub> BrClN <sub>2</sub> O 363.5	52.70	3.10	7.70
				52.82	3.30	7.70
XIV	165	70	C <sub>17</sub> H <sub>15</sub> NO <sub>4</sub> 297	68.90	4.90	4.80
				68.69	5.05	4.71
XVI	158	73	C <sub>17</sub> H <sub>13</sub> NO <sub>4</sub> 295	68.90	4.50	4.90
				69.15	4.41	4.75

As a point of interest, the chalcone dibromide XV was condensed with hydroxylamine hydrochloride in boiling acetic acid, where the isoxazole derivative XVI was obtained.

#### Experimental

Melting points are uncorrected, I.R. spectra were measured on a Beckmann IR-20 infrared Spectrophotometer in KBr. The <sup>1</sup>H-NMR spectrum of compound V on a Varian S-60 T instrument using

TMS as an internal standard. All the compounds were crystallized from ethanol except for IIIc, IVa, IVb, IXb(benzene), IXa (Pet.ether) and Xa (acetic acid).

#### Preparation of pyrazolines IIa-c, IIIa-c, IVa-c, IXa-c and XIa-b

To a solution of chalcone I (0.01 mol) in ethanol and/or butanol (20 ml), hydrazine hydrate, phenylhydrazine, benzenesulfonyl hydrazide, benzoyl

hydrazine or nicotinoyl hydrazine (0.01 mol) was added. The reaction mixture was refluxed for 5 hrs. and then cooled to give solid IIa-c, IIIa-c, IVa-c, IXa-c or XIa-b respectively. The IR spectra of IIIa-c, IVa-c, IXa-c and XIa-b showed bands at 1625-1580  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{N}$ ), those of IXa-c, and XIa-b showed bands at 1660-1635  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{O}$ ) and those of IVa-c showed bands at 1355-1335  $\text{cm}^{-1}$  ( $\nu\text{SO}_2$ ).

*Preparation of pyrazolines V, VIa-c, VIIa-b and VIIIa-b*

To a solution of chalcone I (0.01 mol) in acetic, formic, propionic or butyric acid (20 ml), hydrazine hydrate (0.01 mol) was added and the reaction mixture refluxed for 5 hrs. Cooling and evaporation of the solvent afforded solid V, VIa-c, VIIa-b or VIIIa-b. The IR spectra of V, VIa-c, VIIa-b and VIIIa-b showed bands at 1605-1585  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{N}$ ) and 1650-1635  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{O}$ ).

*Preparation of 1-ac-2-pyrazolines V, VIa-c, VIIa-b and VIIIa-b*

A solution of II in acetic, formic, propionic or butyric acid (20 ml) was refluxed for 5 hrs. Cooling and evaporation of the solvent gave V, VIa-c, VIIa-b or VIIIa-b as solids. The IR spectra of V, VIa-c, VIIa-b and VIIIa-b showed bands at 1640-1650  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{O}$ ) and at 1580-1605  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{N}$ ).

*Preparation of IVa-c and IXa-c*

A solution of II (0.01 mol) in pyridine (10 ml) was treated with benzenesulfonyl or benzoyl chloride (0.01 mol) and the reaction mixture heated on a water-bath for 2 hrs., cooled and poured into dil. HCl to give solid IVa-c or IXa-c.

*Preparation of Xa-b*

A mixture of IXa or IXb (0.01 mol) and lithium aluminum hydride (0.1 mol) in dry ether (20 ml) was refluxed for 5 hrs. and filtered while hot. Evaporation of the solvent gave Xa or Xb as solids. The IR spectra showed bands between 1605-1600  $\text{cm}^{-1}$  due to ( $\nu\text{C}=\text{N}$ ).

*Preparation of Xa and Xb*

To a solution of IIa or IIb (0.01 mol) in acetone (20 ml) containing anhyd. potassium carbonate (1 g.), benzyl bromide (0.01 mol) was added and the reaction mixture refluxed for 10 hrs. Filtration of the hot reaction mixture followed by evaporation of the solvent yielded Xa or Xb.

*Preparation of the Mannich bases XIIa or XIIb*

To a suspension of the pyrazolines IIa or IIb (0.01 mol) and piperidine (0.02 ml) in methanol (20 ml), aqueous formaldehyde (35%, 2.5 ml) was added. The reaction mixture was heated on a water-bath for 5 hrs., kept overnight at room temperature and then diluted with water. The resulting solid product was crystallized to afford the N-Mannich bases XIIa or XIIb. The IR spectra showed bands at 1610-1600  $\text{cm}^{-1}$  due to ( $\nu\text{C}=\text{N}$ ).

*Preparation of XIIIa-b*

A solution of pyrazoline IIa or IIb (0.01 mol) in chloroform (20 ml) was treated with a solution of bromine (0.03 mol) in chloroform (20 ml). The product obtained was crystallized to give XIIIa or XIIIb. The IR spectra showed bands at 1610-1600  $\text{cm}^{-1}$  ( $\nu\text{C}=\text{N}$ ) and 3420-3380  $\text{cm}^{-1}$  ( $\nu\text{NH}$ ).

*Preparation of XIV*

A mixture of each of Ia (2 g), hydroxylamine hydrochloride (1 g) and pyridine (20 ml) was heated on a water-bath for 5 hrs., cooled and poured into dil. HCl to give XIV. The IR spectra showed bands at 1610  $\text{cm}^{-1}$  due to ( $\nu\text{C}=\text{N}$ ).

*Preparation of XVI*

A mixture of XV (2 g), hydroxylamine hydrochloride (1 g) and acetic acid (20 ml) was refluxed for 5 hrs. The product that separated on cooling was crystallized to give XVI. The IR spectra showed bands at 1600  $\text{cm}^{-1}$  due to ( $\nu\text{C}=\text{N}$ ).

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