STUDIES IN VILSMEIER–HAACK REACTION: REACTION OF 3-METHYL-1-PHENYL-4-ARYLIDENE-5-PYRAZOLONE

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The 3-methyl group in *Ia, b* has been found to undergo diformylation by Vilsmeier reagent to give the aminoacrolein derivatives (*IIa, b*). Treatment of *IIa, b* with different reagents affords the related 1-phenyl-4-arylidene-5-pyrazolone derivatives with different heterocyclic systems in the 3-position. The Vilsmeier reaction on pyrazolopyrazole (*XIII*) have been utilized to prove chemically that new heterocyclic systems are formed only at the 3-position and no addition on the carbon–carbon double bond in the conjugated system O=C—C=C—(B) takes place.

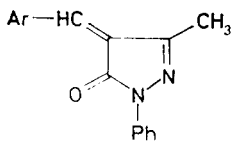
The Vilsmeier reaction on 3-methyl-1-phenyl-5-pyrazolone was early reported[1]. The only product separated is 5-chloro-4-formyl-3-methyl-1-phenylpyrazole in a very poor yield. The reaction was reexamined[2] and a new product, derivative of amino-acrolein, was separated. In view of the current interest in the pharmacological activity of pyrazolones as germicides[3], antifungal[4] and antibacterial agents[5], it was intented to prepare a wide variety of heterocyclic compounds containing a pyrazolone moiety for studying their utility as pharmacological agents. Thus, the present paper describes the application of the Vilsmeier reaction to 3-methyl-1-phenyl-4--arylidene-5-pyrazolones (*Ia, b*). The reaction was performed under usual conditions[6] and the expected aminoacrolein derivatives (*IIa, b*) were obtained in good yields.

The structures of *IIa, b* were established by elemental analysis, ^{1}H NMR and IR spectra and by their ready conversions with hot alkali (evolution of dimethylamine) to the corresponding malonaldehydes (*IIIa, b*), which give a pale brown coloration with ferric chloride. The ^{1}H NMR spectrum of *IIa* in $CDCl_3$ showed signals at δ 2·9 s, 6 H ($N(CH_3)_2$, (ref.[2])), δ 8·6 s, 1 H (acrolein —CHO (ref.[2])) and at δ 8·23–7·01 m, 12 H (10 Ar—H, 1 H acrolein methin and 1 H —CH=). The IR spectra showed two carbonyl peaks, one at 1 680 cm^{-1} (acrolein —CHO, vinylogous amide[2]) and the other at 1 620–1 625 cm^{-1} pyrazolone carbonyl[7].

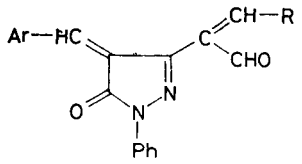
It must be pointed out that chlorination of the 5-oxo positions in *IIa, b* was not affected by the action of phosphorous oxychloride under the experimental conditions.

The aminoacroleins (*IIa, b*) reacted in ethanol with hydroxylamine, hydrazine and phenylhydrazine to yield the corresponding heterocyclic derivatives *IVa, b,*

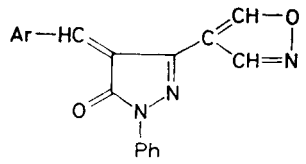
Va, *b* and *VIa*, *b*, respectively in the 3-position. The structures of these compounds were confirmed by their correct elemental analysis. the IR spectra showed the absence of the carbonyl bands related to the —CHO groups and the presence of the pyrazolone carbonyl at 1 620–1 625 cm^{-1}. The characteristic chemical confirmation of isoxazoles (*IVa*, *b*) was carried out. Thus, treatment of *IVa*, *b* with alkali gave the cyanoaldehydes (*VIIa*, *b*) as shown by its solubility in alkali and the characteristic strong absorption at 2 239 cm^{-1} (C≡N group) in their IR spectra.



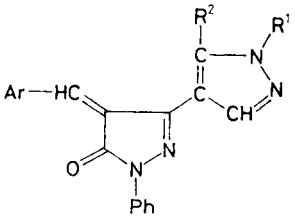
Ia, Ar = C_6H_5
Ib, Ar = p-C_6H_4—Cl



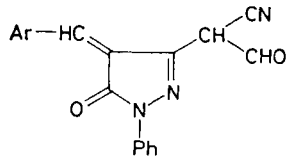
IIa, *b*, R = $N(CH_3)_2$
IIIa, *b*, R = OH



IVa, *b*



Va, *b*, $R^1 = R^2 = H$
VIa, *b*, $R^2 = H$; $R^1 = Ph$
VIIIa, *b*, $R^1 = H$; $R^2 = NH_2$
IXa, *b*, $R^2 = NH_2$; $R^1 = Ph$



VIIa, *b*

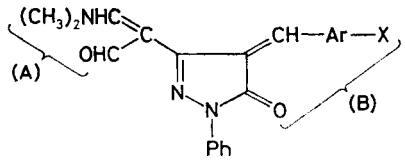
Reaction of *VIIa*, *b* with hydrazine and phenylhydrazine in acetic acid gave the respective aminopyrazoles (*VIIIa*, *b* and *IXa*, *b*), as shown by their ready solubility in dilute hydrochloric acid and by their elemental analysis. The IR spectra of these compounds were also in agreement with the structures indicating the presence of a sharp NH_2 band at 3 450 cm^{-1} in addition to the pyrazolone carbonyl absorption.

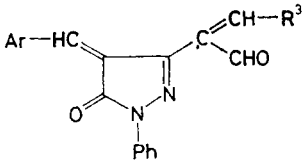
The aminoacroleins (*IIa*, *b*) were also reacted with different secondary heterocyclic amines, namely piperazine, morpholine and piperidine giving the expected aminomethylenes (*Xa*, *b*, *XIa*, *b* and *XIIa*, *b*), respectively. The structures of these products were confirmed by their elemental analysis, ^{1}H NMR and IR spectra. The ^{1}H NMR spectrum of *IIIa* in $CDCl_3$ showed signals at δ 3·55 and 3·10 due to the piperidine ring (—N—CH_2— (ref.[8])) besides signals due to the aromatic protons and other protons. The IR spectra of these compounds were also in agreement with their structures, indicating the presence of the pyrazolone carbonyl absorption at

1 615–1 610 cm^{-1}, at 1 680–1 670 cm^{-1} (acrolein —CHO) and a sharp absorptions at 3 190 cm^{-1} (NH group) for compounds *Xa*, *b*.

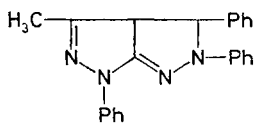
From the foregoing reactions on *IIa*, *b* it must be concluded that the aminoacrolein centre (A) is much more reactive with all the reagents used throughout this work than the carbon–carbon bond in the conjugated system O=C—C=C—(B). The chemical confirmation of this conclusion should be discussed latter on.

Vilsmeier reaction has been extended to substituted 3-methyl-pyrazolopyrazole (*XIII*) with an intention to make sure that neither the addition nor the cyclization reactions do take place on the centre O=C—C=C—(B) of compounds *IIa*,*b*.

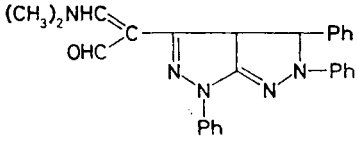




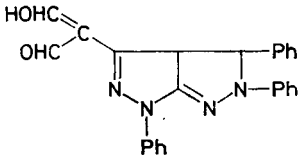
Xa,b, R^3= piperazino
XIa,b, R^3= morpholino
XIIa,b, R^3= piperidino



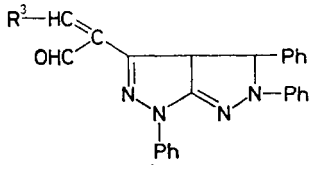
XIII



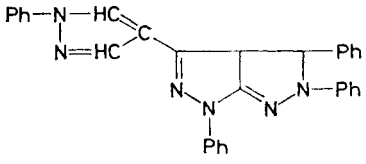
XIV



XV



XVI, R^3= piperidino



XVII

Thus, reaction of *XIII* with Vilsmeier reagent under the usual condition gave the expected aminoacrolein (*XIV*) in a poor yield. The structure of *XIV* was established by elemental analysis, ^{1}H NMR and IR spectra and by its ready conversion with hot alkali to the corresponding malonaldehyde (*XV*). The ^{1}H NMR spectrum of *XV* in $CDCl_3$ showed signals at δ 2·7 ($N(CH_3)_2$ (ref.[2])), δ 8·9 (acrolein —CHO (ref.[2])) besides signals δ 8·7 – 7·1 m, 15 H (Ar—H, 1 H acrolein methin —CH=N— and 1 H, 4-CH—). The IR spectrum was also in agreement with the structure indicating the presence of one carbonyl band at 1 690 cm^{-1} (acrolein —CHO, vinylogous amide[2])

Reaction of compound *XIV* in ethanol with phenylhydrazine and/or piperidine gives products *XVI* and *XVII*. The structure of these products were confirmed by their correct elemental analyses and IR spectra which are in agreement with their structures. The IR spectra, elemental analyses and melting points of these compounds are completely different in comparison with compounds *VIa* and *XIIa* prepared from the reaction of *IIa* with the same reagents. Our previously made conclusion indicated that no addition reaction takes place on the centre (B) during the reaction of *IIa, b* with the reagents used in this work.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Perkin–Elmer 599B spectrophotometer using the KBr disc technique. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz instrument.

Substituted 3-*methyl*-1-*phenyl*-4-*arylidene*-5-*pyrazolones* (Ia, b) were prepared as reported previously[7].

3-(α-*Dimethylaminomethylene*-α-*formylmethyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolones* (IIa, b): To dimethylformamide (5 ml) cooled to 0°C phosphorous oxychloride was added (1·8 ml, 0·04 mol) and the mixture left to stand for 15 min. To this was added with stirring the pyrazolone *Ia, b* (2g) dissolved in dimethylformamide (10 ml) The reaction mixture was heated at 70–80°C for 6 h, the cooled reaction mixture was poured into ice-cold water and treated with $NaHCO_3$ to pH 9. The orange solid (*IIa, b*) that separated out was filtered, washed with cold water and crystallized from benzene. The physical and analytical data are given in Table I.

3-(α-*Hydroxymethylene*-α-*formylmethyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolone* (IIIa, b): The acrolein derivative *IIa, b* (1g) taken in 5% aq. sodium hydroxide (10 ml) was heated (smell of dimethylamine) at 80°C till a clear solution was obtained (30 min). It was then cooled, filtered and acidified. The solid (*IIIa, b*) that separated was filtered, washed and crystallized from aq. ethanol. The data are presented in Table I.

3-(4-*Isoxazolyl or Pyrazolyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolones* (IVa, b, Va, b and VIa, b): To a solution of acrolein derivative (*IIa, b*) in ethanol (20 ml) was added an equimolar quantity of hydroxylamine hydrochloride, hydrazine hydrate or phenylhydrazine, respectively. The reaction mixture was refluxed for 2 h, cooled, concentrated and added on the crushed ice. The precipitated coloured solid was filtered, washed thoroughly with water and crystallized from aq. ethanol. The physical and chemical data are quoted in Table I.

TABLE I

Physico-chemical characteristics of compounds *IIa, b — XIIa, b*

Compound	M.p. °C	Formula (M.w.)	Calculated/Found			
			%C	%H	%N	%Cl
IIa	106—107	$C_{21}H_{19}N_3O_2$	73·04	5·50	12·17	—
		(345·4)	73·32	5·66	12·77	—
IIb	94—95	$C_{21}H_{18}ClN_3O_2$	66·40	4·74	11·06	9·35
		(379·9)	66·56	5·02	11·23	9·41
IIIa	128—129	$C_{19}H_{14}N_2O_3$	71·69	4·40	8·80	—
		(318·3)	71·52	4·52	9·01	—
IIIb	180—192	$C_{19}H_{13}ClN_2O_3$	64·68	3·68	7·94	10·07
		(352·7)	64·59	3·30	8·00	10·23
IVa	115—116	$C_{19}H_{13}N_3O_2$	72·38	4·12	13·33	—
		(315·3)	72·51	4·32	13·09	—
IVb	168—169	$C_{19}H_{12}ClN_3O_2$	65·23	3·43	12·05	10·15
		(349·8)	65·42	3·80	12·23	10·42
Va	82—83	$C_{19}H_{14}N_4O$	72·61	4·45	17·83	—
		(314·3)	72·70	4·63	18·09	—
Vb	118—120	$C_{19}H_{13}ClN_4O$	65·42	3·73	16·06	10·18
		(348·8)	65·56	4·01	16·42	10·53
VIa	97—98	$C_{25}H_{18}N_4O$	76·92	4·61	14·35	—
		(390·5)	77·00	4·55	14·53	—
VIb	89—90	$C_{25}H_{17}ClN_4O$	70·77	4·00	13·19	8·36
		(425·0)	70·77	4·05	13·09	8·55
VIIa	130—131	$C_{19}H_{13}N_3O_2$	72·38	4·12	13·33	—
		(315·3)	72·44	4·34	13·15	—
VIIb	151—152	$C_{19}H_{12}ClN_3O_2$	65·23	3·43	12·05	10·15
		(349·8)	65·56	3·61	11·98	10·25
VIIIa	195—196	$C_{19}H_{15}N_5O$	69·30	4·55	21·27	—
		(329·3)	69·56	4·77	21·52	—
VIIIb	210—211	$C_{19}H_{14}ClN_5O$	62·72	3·85	19·25	9·76
		(363·8)	62·30	4·00	19·52	10·06
IXa	185—186	$C_{25}H_{20}N_5O$	73·89	4·92	17·24	—
		(406·4)	74·00	5·03	17·39	—
IXb	180—182	$C_{25}H_{19}ClN_5O$	68·10	4·31	15·89	8·05
		(440·9)	68·09	4·40	16·09	8·51
Xa	120—122	$C_{23}H_{22}N_4O_2$	71·50	5·69	14·50	—
		(386·4)	71·84	5·70	14·67	—

TABLE I
(*Continued*)

Compound	M.p. °C	Formula (M.w.)	Calculated/Found			
			%C	%H	%N	%Cl
Xb	132–133	$C_{23}H_{21}ClN_4O_2$	65·63	4·99	13·31	8·44
		(420·9)	65·92	5·03	13·54	8·67
XIa	128–130	$C_{23}H_{21}N_3O_3$	71·31	5·42	10·85	—
		(387·4)	71·34	5·62	11·15	—
XIb	137–138	$C_{23}H_{20}ClN_3O_3$	65·48	4·74	9·96	8·42
XIIa	155–157	$C_{24}H_{23}N_3O_2$	74·80	5·97	10·90	—
		(385·4)	74·53	6·01	11·02	—
XIIb	142–143	$C_{24}H_{22}ClN_3O_2$	68·65	5·24	10·01	78·46
		(419·9)	68·43	4·99	9·99	8·65

3-(α-*Formyl*-α-*cyanomethyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolone* (VIIa, b): The isoxazole *IVa, b* (1g) taken in 5% aq. sodium hydroxide was heated till a clear solution was obtained (40 min). It was then cooled and acidified with hydrochloric acid. A white solid *VIIa, b* separated out was filtered, washed thoroughly with water and crystallized from aq. ethanol. The physical data are listed in Table I.

3-(5-*Amino*-4-*pyrazolyl* and 1-*phenyl*-5-*amino*-4-*pyrazolyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolone* (VIIIa, b and IXa, b): A mixture of *VIIa, b* (1g) and hydrazine hydrate (80%, 0·4 ml) or phenylhydrazine (0·3 ml) taken in acetic acid (20 ml) was heated under reflux for 2 h. The reaction mixture was concentrated, cooled and added onto crushed ice. The aminopyrazoles *VIIIa, b* and *IXa, b* obtained as pale yellow solid were filtered, washed with water and crystallized from aq. ethanol. The data are presented in Table I.

Condensation of IIa, b *with secondary amines*: *Preparation of* 3-(α-*piperazino or morpholino and piperidinomethylene*-α-*formyl*-*methyl*)-1-*phenyl*-4-*arylidene*-5-*pyrazolones* (Xa, b, XIa, b *and* XIIa, b): To the acrolein derivative *IIa, b* (1g) taken in ethanol (20 ml) was added equimolar quantity of the amine and the mixture gently heated on a water bath. The solution was evaporated to dryness and tne resulting residue crystallized from benzene to afford the following products *Xa, b, XIa, b* and *XIIa, b*, respectively. The data are listed in Table I.

Substituted 3-*methyl*-1-4-5-*triphenyltetrahydropyrazolo*[3,4-*c*]-*pyrazole* (XIII): This compound is prepared by a described method[7].

Substituted 3-(α-*dimethylaminomethylene*-α-*formylmethyl*)-1,4,5-*triphenyltetrahydropyrazolo*-[3, 4-*c*]*pyrazole* (XIV): This compound was prepared by the same procedure as for *II* as yellow needles. Yield 0·3 g (27·3%), m.p. 83–84°C (ethanol). For $C_{27}H_{25}N_5O$ (435·5) calculated: 74·48%C, 5·74%H, 16·09%N; found: 74·71%C, 5·80%H, 15·99%N.

Substituted 3-(α-*hydroxymethylene*-α-*formylmethyl*)-1,4,5-*triphenyltetrahydropyrazolo*[3,4-*c*]-*pyrazole* (XV): This compound was prepared similarly as *III* as a yellow powder. Yield 1·2 g (63·15%), m.p. 133–135°C (alcohol). For $C_{25}H_{20}N_4O_2$ (409·3) calculated: 73·52%C, 4·90%H, 13·92%N; found: 73·82%C, 5·05%H, 14·01%N.

Substituted 3-(α-*piperidylmethylene*-α-*formylmethyl*)-1,4,5-*triphenyltetrahydropyrazolo*[3,4-*c*]*pyrazole* (XVI): This compound was prepared similarly as *XII* as pale yellow crystals. Yield 1·9 g (82·6%), m.p. 152—154°C (dioxan). For $C_{30}H_{29}N_5O$ (475·6) calculated: 75·78%C, 6·10%H, 14·73%N; found: 75·51%C, 6·00%H, 14·32%N.

Substituted 3-(1-*phenyl*-4-*pyrazolyl*)-1,4,5-*triphenyltetrahydropyrazolo*[3,4-*c*]*pyrazole* (XVII): This compound was prepared similarly as *VI* as redish needles. Yield 1·5 g (75%), m.p. 140—142°C (alcohol). For $C_{31}H_{24}N_6$ (480·5) calculated: 77·50%C, 5·00%H, 17·50%N; found: 77·72%C, 4·98%H, 17·83%N.

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