

MICHAEL REACTION OF SOME CHALCONES WITH 1-PHENYL-3-METHYL-2-PYRAZOLIN-5-ONE

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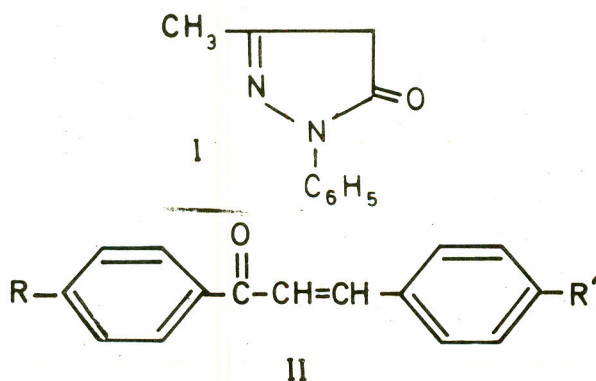
Abstract. 1-Phenyl-3-methyl-2-pyrazolin-5-one has been condensed with some chalcones to give the corresponding Michael adducts. The reaction of the Michael adducts with hydrazines, hydroxylamine, amines and Grignard reagents has been described.

It is known that the 4-position of 2-pyrazolin-5-ones is very reactive and undergoes the characteristic condensation reactions of active methylene group.^(1,4) The present work deals with the reactivity of 1-phenyl-3-methyl-2-pyrazolin-5-one, I towards some chalcones IIa-c at elevated temperature.

the carbonyl stretching frequency at 1680 cm^{-1} , CH_2 at 2900 cm^{-1} , and conjugated $\text{C}=\text{N}$ in the range 1625-1580 cm^{-1} .

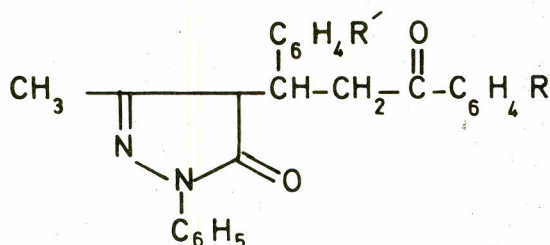
The NMR spectrum of IIIa showed bands centered at δ 2.3 (s, 3H, CH_3), δ 3.5 (d, 2H, $-\text{CO}-\text{CH}_2-$), δ 3.8 (d, 1H, $-\text{CH}-\text{CO}-$), δ 4.5 (q, 1H, $-\text{CH}-\text{C}_6\text{H}_5$) and δ 7.5 (m, 14H, Ar-H).

Reduction of IIIa-c by zinc dust and acetic acid gave the corresponding 4-[α (β -hydroxyphenethyl) benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one derivatives IVa-c. The IR spectra of IV showed a band at 3120 cm^{-1} attributable to the OH group.

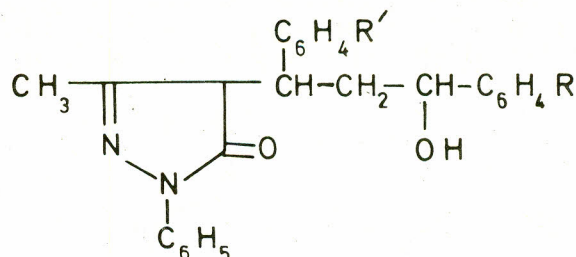


R	R'
a) = Cl	= H
b) = OCH_3	= H
c) = H	= $\text{N}(\text{CH}_3)_2$

On heating the pyrazolone I with chalcones IIa-c at 140-150°; gave pure Michael adducts 4-[α (phenacyl) benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one derivatives IIIa-c. The IR spectra of III showed



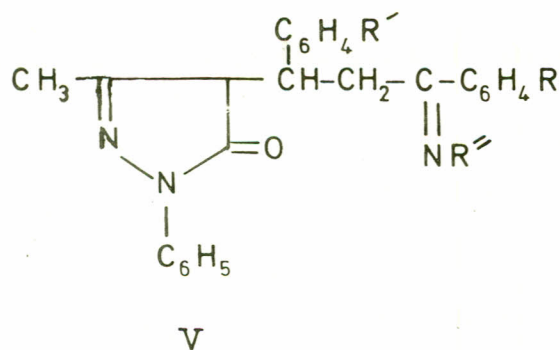
R	R'
a) = 4-Cl	= H
b) = 4- OCH_3	= H
c) = H	= 4-N-(CH_3) ₂



IV

R	R'
a) = 4-Cl	= H
b) = 4- OCH_3	= H
c) = H	= 4-N-(CH_3) ₂

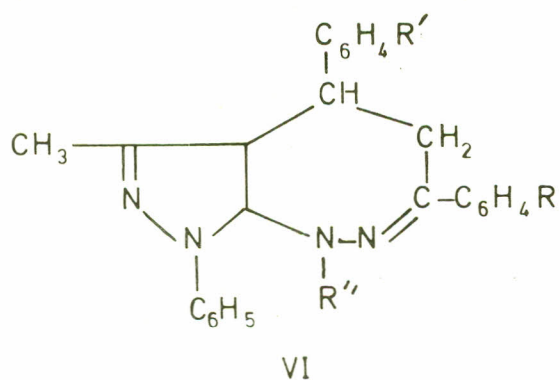
The Michael adducts IIIa-c reacted with hydrazines in boiling alcohol, and hydroxylamine hydrochloride in sodium acetate and acetic acid mixture to give the corresponding hydrazones and oximes V a-h. The IR spectra of Va-f showed a band attributed to the NH group in the range between 3430-3260 cm^{-1} , while the IR spectra of Vg and h showed band at 3420 cm^{-1} attributed to OH group.



R	R'	R''
(a) = 4-Cl	= H	= NH ₂
(b) = 4-OCH ₃	= H	= NH ₂
(c) = H	= 4-N(CH ₃) ₂	= NH ₂
(d) = 4-Cl	= H	= N-C ₆ H ₅
(e) = 4-OCH ₃	= H	= NHC ₆ H ₅
(f) = H	= 4-N(CH ₃) ₂	= NH ₆ CH ₅
(g) = 4-Cl	= H	= OH
(h) = H	= 4-N(CH ₃) ₂	= OH

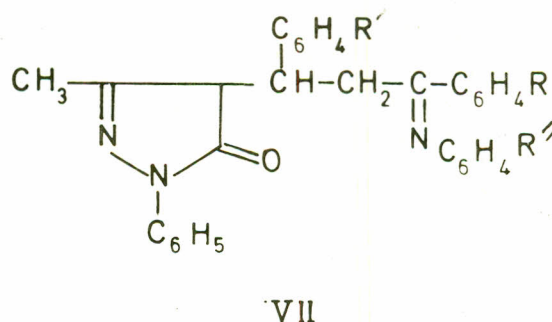
On the other hand the reaction of IIIa-c with hydrazines in boiling acetic acid gave the corresponding 1, 4, 5, 8-tetrahydro-3-methyl-1-phenyl-pyrazolo [3, 4-C] (1,2) diazepine derivatives VIa-f. The IR spectra of VIa-c showed band at 3430 cm⁻¹ attributed for NH group.

The NMR spectrum of VI_d showed band centered at δ 2.2 (s, 3H, CH₃), δ 3.6 (d, 2H, CH₂), δ 5.4 (t, 1H, CH) and δ 7.4 ppm. (m, 19H, Ar-H) :



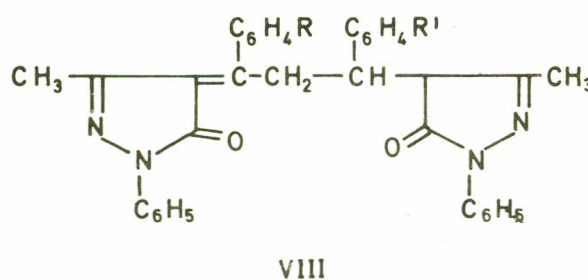
R	R'	R''
(a) = 4-Cl	= H	= H
(b) = 4-OCH ₃	= H	= H
(c) = H	= 4-N(CH ₃) ₂	= H
(d) = 4-Cl	= H	= C ₆ H ₅
(e) = 4-OCH ₃	= H	= C ₆ H ₅
(f) = H	= 4-N(CH ₃) ₂	= C ₆ H ₅

The Michael adducts III a-c were heated with primary aromatic amines namely *p*-toluidine and *p*-anisidine at 166°C and gave 4-[α -(N-benzimidoyl)-methyl] benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one derivatives VIIa-f. The IR spectra of VII showed no NH stretching frequency.



R	R'	R''
(a) = 4-Cl	= H	= 4-CH ₃
(b) = 4-OCH ₃	= H	= 4-CH ₃
(c) = H	= 4-N(CH ₃) ₂	= 4-CH ₃
(d) = 4-Cl	= H	= 4-OCH ₃
(e) = 4-OCH ₃	= H	= 4-OCH ₃
(f) = H	= 4-N(CH ₃) ₂	= 4-OCH ₃

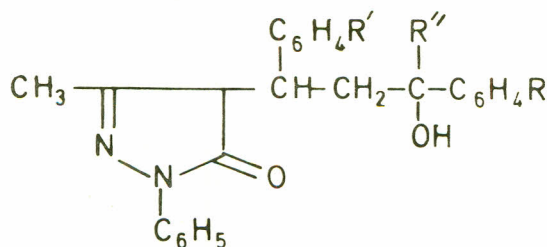
The Michael adducts IIIa and b were heated with the pyrazolone I at 160-170° to give 4, 4-(1, 3-diaryl-1-propanyl-3-pyridene) bis (3-methyl-1-phenyl-2-pyrazolin-5-one) VIII a and b. The IR spectra of VIII showed a strong band at 1680 cm⁻¹ attributed for carbonyl group of 5-pyrazolone, and at 1620 cm⁻¹ for C=N group.



R	R'
a) = 4-Cl	= H
b) = H	= 4-N(CH ₃) ₂

Treatment of IIIa-c with Grignard reagents yielded 4-[α -(β -hydroxyphenethyl) benzyl] 3-methyl-1-phenyl-2-pyrazolin-5-one derivatives IXa-j. The IR spectra of IX showed a strong band in the

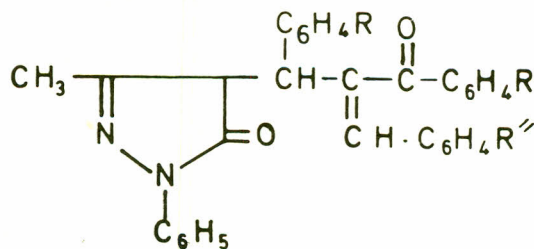
range between 3380 - 3420 cm^{-1} attributed for OH group of tertiary alcohols.



IX

R	R'	R''
(a) = 4-Cl	= H	= C ₂ H ₅
(b) = 4-Cl	= H	= C ₆ H ₅
(c) = 4-Cl	= H	= C ₆ H ₁₁
(d) = 4-Cl	= H	= 1-C ₁₀ H ₇
(e) = 4-OCH ₃	= H	= C ₂ H ₅
(f) = 4-OCH ₃	= H	= C ₆ H ₅
(g) = 4-OCH ₃	= H	= 1-C ₁₀ H ₇
(h) = H	= 4-N(CH ₃) ₂	= C ₂ H ₅
(i) = H	= 4-N(CH ₃) ₂	= C ₆ H ₅
(j) = H	= 4-N(CH ₃) ₂	= 1-C ₁₀ H ₇

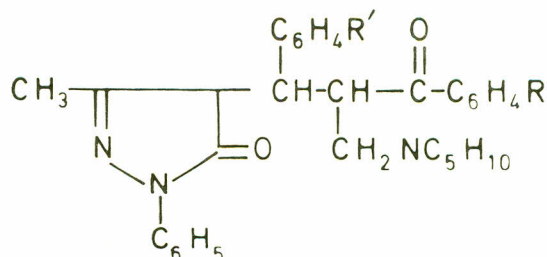
The Michael adducts IIIa-c contain an active methylene group which condensed with aromatic aldehydes in the presence of sodium ethoxide or piperidine to give 4-[β -(Aroyl)-*p*-substituted α -phenylcinnamyl]-3-methyl-1-phenyl-2-pyrazolin-5-ones Xa-h.



X

R	R'	R''
(a) 4-Cl	H	4-Cl
(b) 4-Cl	H	4-NO ₂
(c) 4-Cl	H	4-OCH ₃
(d) 4-OCH ₃	H	4-Cl
(e) 4-OCH ₃	H	4-NO ₂
(f) H	4-N(CH ₃) ₂	4-Cl
(g) H	4-N(CH ₃) ₂	4-NO ₂
(h) H	4-N(CH ₃) ₂	4-OCH ₃

As would be expected the Michael adducts III a and b undergo the Mannich reaction⁵ with formaldehyde and piperidine to give 4-[α -(piperidinomethyl)phenacyl benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one derivatives XI a and b. The IR spectra of XI showed a strong band at 1680 cm^{-1} attributed for C=O group and at 1600 - 1620 cm^{-1} for C=N



XI

R	R'
(a) 4-Cl	H
(b) 4-OCH ₃	H

Experimental

Melting points are not corrected. IR spectra were obtained using a Pye-unicam Sp 1200 spectrophotometer, using KBr disc technique. The NMR spectra determined by a Varian A 100 spectrophotometer using Cd Cl₂ as solvent.

Michael Reaction of 3-Methyl-1-Phenyl-2-Pyrazolin-5-One I with Chalcones IIa-c. Formation of IIIa-c. Method (A). A mixture of I (0.012 mole) and IIa-c (0.01 mole) was heated in an oil bath at 160°C for 3 hr. The reaction mixture was left to cool and the product formed was crystallized from ethanol to give colourless crystals (yield 85%). (cf Table 1).

Method (B). A solution of I (0.012 mole) and IIa-c (0.01 mole) in dry absolute ethanol (50 ml) was treated with sodium ethoxide (prepared from 0.75 g of sodium and 5 ml of absolute ethanol). The reaction mixture was refluxed for 6 hr, then concentrated and cooled. The solid product was filtered off and crystallized from ethanol to give colourless crystals (yield 70%) (cf Table 1).

Reduction of IIIa-c with Zinc/Acetic Acid. Formation of IV a-c. A mixture of IIIa-c (0.01 mole) and zinc dust (2.0 g) in glacial acetic acid (30 ml) was refluxed for 6 hr. The reaction mixture was filtered while hot and the filtrate was concentrated to give colourless crystals. The solid product was crystallized from a suitable solvent (yield 53%). (cf Table 2).

Reaction of Hydrazinehydrate and Phenylhydrazine with IIIa-c in Boiling Alcohol. Formation of the Hydrazones Va-f. A mixture of IIIa-c (0.01 mole), hydrazine hydrate/or phenylhydrazine (0.02 mole), and ethyl alcohol (15 ml) was refluxed for 8 hr. The solid separated after concentration and cooling was crystallized from ethanol to give yellow crystals (yield 60%) (cf. Table 3).

TABLE 1. 4-[α -(PHENACYL) BENZYL]-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONES.

Compound	M.p. °C	Formula	Analysis		
			C	calcd/found H	N
IIIa	184	C ₂₅ H ₂₁ ClN ₂ O ₂ (416.5)	72.1	5.1	6.7
			72.2	5.3	6.4
IIIb	135	C ₂₆ H ₂₄ N ₂ O ₃ (412)	75.7	5.8	6.8
			75.2	5.6	6.6
IIIc	164	C ₂₇ H ₂₇ N ₃ O ₂ (425)	76.2	6.4	9.9
			75.9	6.6	9.7

TABLE 2. 4-[α -(β -HYDROXYPHENETHYL) BENZYL]-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE DERIVATIVES IVA-C.

Compound	M. p. °C	Solvent of crystn.	Formula (mol. wt.)	Analysis %		
				C	calcd/found H	N
IVa	236	Ethanol	C ₂₅ H ₂₃ ClN ₂ O ₂ (418.5)	71.7	5.5	6.7
				71.6	5.3	6.5
IVb	235	Acetic acid	C ₂₆ H ₂₆ N ₂ O ₃ (414)	75.4	6.3	6.8
				74.9	6.4	6.7
IVc	214	Ethanol (dil.)	C ₂₇ H ₂₉ N ₃ O ₂ (427)	75.9	6.8	9.8
				75.6	6.7	9.4

TABLE 3. THE HYDROZONES AND OXIMES OF III a-c.

Com- pound	M.p. °C	Formula (mol. wt.)	Analysis %		
			C	calcd/found H	N
V a	181	C ₂₅ H ₂₃ ClN ₄ O (430.5)	69.7	5.3	13.0
			70.0	5.2	12.7
V b	184	C ₂₅ H ₂₆ N ₄ O ₂ (426)	73.2	6.1	13.1
			73.0	6.4	12.8
V c	189	C ₂₇ H ₂₉ N ₅ O (439)	73.8	6.6	15.9
			73.6	6.5	15.6
V d	192	C ₃₁ H ₂₇ ClN ₄ O (506.5)	73.4	5.3	11.1
			73.4	5.3	10.8
V e	193	C ₃₂ H ₃₀ N ₄ O ₂ (502)	75.5	6.0	11.2
			75.3	6.0	10.9
V f	182	C ₃₃ H ₃₃ N ₅ O (515)	76.9	6.4	13.6
			76.8	6.5	13.4
V g	239	C ₂₅ H ₂₂ ClN ₃ O ₂ (431.5)	69.5	5.1	9.7
			69.7	4.9	9.5
V h	over 300	C ₂₇ H ₂₈ N ₄ O (424)	76.4	6.6	13.2
			76.4	6.5	12.8

TABLE 4. 1,4,5,8-TETRAHYDRO-3-METHYL-1-PHENYL-PYRAZOLE (3,4-c) (1,2) DIAZEPINES VI a-f.

Compound	M.p. °C	Colour	Formula (mol. wt.)	Analysis %		
				C	calcd./found H	N
VI a	Over 300	Colourless	C ₂₅ H ₂₁ ClN ₄ (412.5)	72.7	5.1	13.6
				73.0	5.3	13.4
VI b	133	Colourless	C ₂₆ H ₂₃ N ₄ O (407)	76.7	5.7	13.8
				76.6	5.6	13.6
VI c	175	Yellow	C ₂₇ H ₂₇ N ₅ (421)	77.0	6.4	16.6
				76.8	6.3	16.3
VI d	146	Orange	C ₃₁ H ₂₅ ClN ₄ (488.5)	76.2	5.1	11.5
				76.3	4.9	11.1
VI e	145	Orange	C ₃₂ H ₂₈ N ₄ O (484)	79.3	5.8	11.6
				79.2	5.7	11.4
VI f	166	Yellow	C ₃₃ H ₃₁ N ₅ (497)	79.7	6.2	14.1
				79.6	6.1	13.8

TABLE 5. 4-[α -(N-BENZIMIDOYL) METHYL] BENZYL)-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE DERIVATIVES VIIa-f.

Compound	M.p. °C	Colour	Solvent of crystn.	Formula (mol. wt.)	Analysis		
					C	calcd./found H	N
VII a	279	Brown	B + P	C ₃₂ H ₂₈ ClN ₃ O (505.5)	76.0	5.5	8.3
					76.0	5.4	8.1
VII b	132	Brown	E	C ₃₃ H ₃₁ N ₃ O ₂ (501)	79.0	6.2	8.4
					78.8	6.1	8.1
VII c	209	Violet	E	C ₃₄ H ₃₄ N ₄ O (514)	79.4	6.6	10.9
					79.2	6.5	10.5
VII d	117	Brown	B + P	C ₃₂ H ₂₈ ClN ₃ O ₂ (521.5)	73.6	5.4	8.1
					73.6	5.3	7.7
VII e	109	Orange	E	C ₃₃ H ₃₁ N ₃ O ₃ (517)	76.6	6.0	8.1
					76.4	5.8	7.9
VII f	168	Violet	E	C ₃₄ H ₃₄ N ₄ O ₂ (530)	77.0	6.4	10.6
					76.8	6.2	10.3

E=ethanol, B=benzene ; P=light petrol (60-80).

TABLE 6. 4,4'-(1,3-DIARYL-1-PROPANYL-3-YLIDENE) BIS (3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE) VIIIa-b.

Compound	M.p. °C	Solvent of crystn.	Formula (mol. wt.)	Analysis %		
				C	calcd./found H	M
VIII a	Over 300	n-Butanol	C ₃₅ H ₂₉ ClN ₄ O ₂ (572.5)	73.4	5.1	9.8
				73.3	5.0	9.5
VIII b	82 (decomp)	light petrol (60-80)	C ₃₇ H ₃₅ N ₅ O ₂ (581)	76.4	6.0	12.0
				76.4	5.8	11.7

TABLE 7. 4-[α -(β -HYDROXYPHENETHYL) BENZYL]-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE DERIVATIVES IXa-j.

Compound	M.p. °C	Solvent of crystn.	Formula (mol. wt.)	Analysis		
				C	calcd./found H	N
IX a	64	H	C ₂₇ H ₂₇ ClN ₂ O ₂ (446.5)	72.6	6.0	6.3
				72.5	5.8	6.0
IX b	74	P	C ₃₁ H ₂₇ ClN ₂ O ₂ (494.5)	75.2	5.5	5.7
				74.9	5.6	5.4
IX c	99	H	C ₃₁ H ₃₃ ClN ₂ O ₂ (500.5)	74.3	6.6	5.6
				74.3	6.4	5.3
IX d	81	E	C ₃₅ H ₂₉ ClN ₂ O ₂ (544.5)	77.1	5.3	5.1
				77.0	5.2	4.8
IX e	over 300	But.	C ₂₈ H ₃₀ N ₂ O ₃ (442)	76.0	6.8	6.3
				75.7	6.6	6.1
IX f	131	E	C ₃₂ H ₃₀ N ₂ O ₃ (490)	78.4	6.1	5.7
				78.2	6.1	5.6
IX g	75	P	C ₃₆ H ₃₂ N ₂ O ₃ (540)	80.0	5.9	5.2
				80.1	5.7	5.0
IX h	161	P	C ₂₉ H ₃₃ N ₃ O ₂ (455)	76.5	7.3	9.2
				76.3	7.2	9.0
IX i	108	P	C ₃₃ H ₃₃ N ₃ O ₂ (503)	78.7	6.6	8.3
				78.6	6.5	8.0
IX j	74	E	C ₃₇ H ₃₅ N ₃ O ₂ (553)	80.3	6.3	7.6
				80.2	6.2	7.4

E=ethanol, But=n-butanol, H=n-hexane. P=light petrol (80-100)

Reaction of Hydroxylamine Hydrochloride with III a and b. Formation of Oximes Vg and h. A mixture of IIIa and b (0.01 mole) hydroxylamine hydrochloride (0.02 mole), sodium acetate (0.02 mole), and acetic acid (40 ml) was refluxed for 6 hr. The mixture was cooled and poured into ice-water. The solid product was filtered off and crystallized from benzene-light petrol mixture to give colourless crystals (yield 52%). (cf. Table 3).

Reaction of Hydrazinehydrate and Phenylhydrazine with IIIa-c in Boiling Acetic Acid. Formation of Diazepines VI a-f. A mixture of IIIa-c (0.01 mole) and hydrazinehydrate/or phenylhydrazine (0.02 mole) in acetic acid (30 ml) was refluxed for 8 hr. The mixture was cooled and poured into ice-water. The solid product was crystallized from ethanol (yield 55%). (cf. Table 4).

Reaction of IIIa-c with Primary Aromatic Amines. Formation of VIIa-f. A mixture of IIIa-c (0.01 mole) and amines (0.015 mole) namely *p*-toluidine and *p*-anisidine was fused at 160° for 4 hr. The mixture was poured into ice-cold dilute hydrochloric acid. The solid product was washed with water and then crystallized from the proper solvent (yield 75%). (cf. Table 5).

Reaction of IIIa and b with 3-Methyl-1-Phenyl-2-Pyrazoline-5-One I. Formation of VIIIa and b. A

mixture of III a-c (0.01 mole) and I (0.01 mole) was heated at 160° for 4 hr. The solid product separated after cooling was crystallized from the proper solvent as red crystals (yield 50%) (cf. Table 6).

Reaction of IIIa-c with Grignard Reagents. Formation of Tertiary Alcohols IXa-j. To a suspension of IIIa-c (0.01 mole) in dry benzene (50 ml) was added an ethereal solution of ethylmagnesium iodide, phenyl, cyclohexyl, and α -naphthylmagnesium bromide (0.06 mole). The reaction mixture was refluxed on a steam-bath for 4 hr, set aside overnight at room temperature, and then decomposed with a cold solution of hydrochloric acid (10%). The solid product obtained was crystallized from the proper solvent as reddish brown crystals (yield 45%) (cf. Table 7).

Reaction of IIIa-c with Aromatic Aldehydes. Formation of Xa-h. A mixture of IIIa-c (0.01 mole); aromatic aldehydes namely *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, or *p*-anisaldehyde (0.012 mole) and few drops of piperidine was refluxed for 9 hr. The solid product obtained after concentration and cooling was filtered off and crystallized from the proper solvent to give yellow crystals (yield 60%) (cf. Table 8).

Mannich Reaction of IIIa and b with Piperidine. Formation of XIa and b. A mixture of III a or b (0.01

TABLE 8. 4- β -(AROYL)-P-SUBSTITUTED- α -PHENYL CINNAMYL]-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONES Xa-h.

Com- pound	M.p. °C	Solvent of crystn.	Formula (mol. wt.)	Analysis %		
				C	calcd./found H	N
X a	over 300	E	C ₃₂ H ₂₄ Cl ₂ N ₂ O ₂ (539)	71.2 70.9	4.5 4.5	5.2 4.9
X b	142	B + P	C ₃₂ H ₂₄ ClN ₃ O ₄ (549.5)	69.9 69.7	4.4 4.2	7.6 7.4
X c	92	B + P	C ₃₃ H ₂₇ ClN ₂ O ₃ (534.5)	74.1 73.8	5.1 5.2	5.2 4.9
X d	218	E	C ₃₃ H ₂₇ ClN ₂ O ₃ (534.5)	74.1 73.9	5.1 5.0	5.2 5.0
X e	93	E	C ₃₃ H ₂₇ N ₃ O ₅ (545)	72.7 72.5	5.0 4.8	7.7 7.4
X f	181	T	C ₃₄ H ₃₀ ClN ₃ O ₂ (547.5)	74.5 74.3	5.5 5.4	7.7 7.4
X g	197	E	C ₃₁ H ₃₂ ClN ₃ O ₂ (513.5)	73.1 73.0	5.4 5.3	10.0 9.7
X h	Over 300	E	C ₃₂ H ₃₅ N ₃ O ₃ (509)	77.3 77.1	6.1 6.0	7.7 7.4

E=ethanol, B=benzene, T=toluene, P=light petrol (80-100)

TABLE 9. 4- α -[(PIPERIDINOMETHYL) PHENACYL] BENZYL]-3-METHYL-1-PHENYL-2-PYRAZOLIN-5-ONE DERIVATIVES XIa-b.

Com- pound	M.p. °C	Formula (mol. wt.)	Analysis %		
			C	calcd./found H	N
XI a	87	C ₃₁ H ₃₂ ClN ₃ O ₂ (513.5)	72.4 72.3	6.2 6.0	8.2 8.3
XI b	100	C ₃₂ H ₃₅ N ₃ O ₃ (509)	75.4 75.3	6.9 6.8	8.3 7.9

mole), paraformaldehyde (0.02 mole), and piperidine (0.012 mole) in 20% (w/v) hydrochloric acid was dissolved in 50 ml ethyl alcohol. The reaction mixture was heated under reflux for 6 hr and left to stand overnight, diluted with water. Dilute sodium hydroxide was added till the solution became alkaline, and the mixture was then extracted with ether. The alkaline solution was stirred with charcoal for one hr filtered, acidified with acetic acid. The solid was crystallized from ethanol to give yellow crystals (yield 70%). (cf. Table 9).

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