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SYNTHESIS OF SOME NEW PYRAZOLINES FROM 4-AMINO-4-METHOXYBENZALACETOPHENONE AS DYESTUFFS INTERMEDIATES

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New aminopyrazoline derivatives (II-V) has been obtained by the reaction of new benzalacetophenone derivatives (Ia, b) with hydrazine hydrate and their derivatives. Further reactions were carried out on pyrazolines (VI-XI). The structural determination of the prepared compounds has been confirmed using elemental analysis, chemical reactions and spectral data.

Key words. P-aminoacetophenone, Pyrazoline derivatives, Pyrazole derivatives.

Introduction

It has been reported that pyrazolines and pyrazoles show a broad spectrum biological activity.Thus, pyrazolines have been used as anthelmentics and anaesthetics [1-4]. Meanwhile, certain pyrazole derivatives are used as systemic insecticides and others have a stimulating actions on plants [5-8].

The pyrazolines and pyrazoles containing an active methylene group are used as coupler for synthesis of some dyestuffs [9]. The object of this work, is to synthesise of some new aminopyrazolines as intermediates for preparation of some new dyestuffs.

Experimental

Melting points were taken on Griffin melting point apparatus and are uncorrected. Infrared spectra of solid samples were run as KBr discs on a Shimadzu model 440 spectrometer. ^{1}HNMR spectra were measured in DMSO-d6 using Fx 90Q fourier Transform ^{1}NMR. Analytical data were performed in Microanalytical Center at Cairo University, Cairo, Egypt.

4-amino-4'-methoxybenzalacetophenone (Ia) and 4-acetamido-4'-methoxybenzalacetophenone (Ib). P-methoxybenzaldehyde (0.01mol) was added to a cold mixture of 4-aminoacetophenone and 4-acetamidoacetophenone (0.01 mole) and sodium hydroxide (0.03 mol) in water (10ml) and ethanol (6 ml). The reaction mixture was stirred for 3 hrs at room temp. The product was obtained and recrystallized from the ethanol to give (Ia) and IB) respectively; (Table 1).

IR (Ia) showed bands at ν 3500, 3460 (NH_2), ν 1680 (C=O), ν 2970 (aliphatic CH) and ν 1620 cm^{-1} (CH=CH). ^{1}HNMR of (Ia; DMSO-d_6) showed signals at δ 3.2 [3H, s, OCH_3], δ 4.9 [2H, br, NH_2 cancelled with D_2O], δ 6.7 [2H, d, CH=CH] and δ 7.2-8.2 ppm [8H, m, Arh's].

Reaction of Chalcones (Ia, b) with Hydrazines. (a) In ethanol: Formation of Pyrazolines (II-V). To a solution of chalcone (Ia and Ib; 0.01 mol) in ethanol (20 ml), hydrazine hydrate, phenylhydrazine, benzenesulphonyl- . hydrazine, p-toluenesulphonylhydrazine and 5-acetamido-5-toluene-2-sulphonyl hydrazine (0.2 mol) was added and the reaction mixture was refl used for 5 hrs. The separated solid was recrystallized from a suitable solvent to give (IIa, b-v). IR spectrum of (II-V) shows the absence of C=O and the presence of ν C=N group at 1630 cm^{-1} due to the formation of pyrazoline ring; (Table 1).

*(b) In acids: Formation of Pyrazolines (VIIa-g).*Formic, acetic, propionic, butyric, isobutyric, valeric and hexanoic acid (20 ml) and hydazine hydrate (0.01 mol) were added to a solution of chalcone (Ib; 0.01 mol) and the reaction mixture was refluxed for 5 hrs. The product (VIa-g) was obtained by cooling and recrystallized from suitable solvent.

Compounds (VIIa-g) were obtained by refluxing (VIa-g) with hydrochloric acid (30ml) in ethanol (20 ml) for half an hour. After the neutralization, the product was obtained and recrystallized fom a suitable solvent; (Table 1).

IR spectrum of (VIIa) is taken as an example in agreement with the proposed structure. It shows the bands at ν3450, 3410 (NH_2), ν 1715 (C=O), ν 1630 cm^{-1} (C=N) and absence of the stretching frequency of the -NH group. ^{1}HNMR of (VIIa; DMSO-d_6); δ 2.7 [3H,s,-OCH_3], δ 3.4 [2H,s,CH_2], δ 4.5 [H, t, CH], 5.8 [2H, br,-NH_2 canceled with D_2O], δ 7.2-8.2 [8H, m, ArH's] and δ 9.1 ppm [H, s, -CHO]. ^{1}HNMR of (VIIb; DMSO-d_6): δ2.4 [3H,s,-OCH_3], δ3.2 [2H, s, CH_2], δ 4.4 [H, t, CH], δ 5.2 [3H, s, -CH_3], 6.1 [2H, br, NH_2] cancelled with D_2O], and δ 7.2-8.2ppm [8H, m, ArH's].

Formation of 1-acyl-2-pyrazolines (VIIa-g). A solution of (IIb; 0.01 mol) in formic, acetic propionic, butyric isobutyric, valeric and hexanoic acid (20 ml) was refluxed for 5 hrs and poured into cold water. The product was refluxed with hydrochloric acid in ethanol and neutralizd by alkali. The products were recrystallized from a suitable sol-

vent to give (VIIa-g) which were found to be identical (m.m.p.) with those obtained above.

Action of Sulphonyl chlorides and acid chlorides on Pyrazoline (IIb). A solution of (IIb; 0.01 mol) in pyridine (10 ml) was treated with benzensulphonyl chloride, p-toluenesulphonyl chloride, p-toluidine-2-sulphonyl chloride, acetyl chloride, benzoyl chloride, and cinnamoyl chloride (0.01 mol) and the reaction mixture was heated in a water-bath for 2 hrs, cooled and poured into dilute hydrochloric acid. The products (IVa-c) and (VIb, h-j) were obtained and recrystallized from suitable solvent; (Table 1).

Compounds (Va-c) and (VIIh-j) were obtained by refluxing (IVa-) for (VIb, h-j) with hydrochloric acid (30 ml) in ethanol (20 ml) for half an hour. After neutrilization, the product was obtained and recrystallized from a suitable solvent which were found to be identical (m.m.p.) with those obtained above; (Table 1).

Reduction of (VIIa,b & h) with Lithium Aluminum hydride: Formation of (VIIIa-c). A solution of (VIIa,b & h; 0.01 mol) and lithium aluminium hydride (0.01 mol) in dry ether (20 ml) was refluxed for 5 hrs and filtered while hot.The solid product obtained after evaporation of the solvent was crystallized from a suitable solvent to give (VIIIa-c); (Table 1).

IR of (VIIIa-c) shows the absence of C=O, this indicate that the reduction was proceed. ^{1}HNMR of (VIIIb; DMSO-d_6); δ 2.5 [3H,s,-OCH_3], δ 3.1 [2H, s,H_2], δ 3.5 [H,t,CH], δ 4.2 [3H,t,-CH_3], δ 5.4 [2H,q,CH_2], δ 6.2 [2H,br, NH_2; canceled with D_2O] and δ 7.2-8.4 ppm [8H,mArH's].

Methylation, Ethylation and Benzoylation of Pyrazoline (II) Formation of (VIIIa-c). To a solution of (IIb; 0.01 mole) in acetone (20 ml) cantaining anhydrous potassium carbonate (1 gm), methyl iodide, ethyl iodide and benzyl bromide (0.01 mol) was added and the reaction mixture was refluxed for 48 hrs. The solid product obtained after filtration of the reaction mixture while hot and evaporation of the solvent was crystallized from ethanol and hydrolysis by refluxing in hydrochloric acid (30 ml) in ethanol (20 ml) for half an hour to give (VIIIa-c), which showed nod epression in mixed melting point determination with that prepared above; (Table 1).

Reaction of (IIb) with isothiocyanate and isocyanate derivatives. Formation of (Xa-e). To a solution of pyrazoline (IIb; 0.01 mol) in THF (20 ml), methyl isothiocyanate, phenyl isothiocyanate, benzoyl isothiochyanate, methyl isocyanate and phenyl isocynate (0.01 mol) and few drops of triethylamine were added. The mixture was stirred at room temperature for 4 hrs. The solid product (IXa-e) which separated out, was compounds (Xa-e) were obtained by refluxing with hydrochloric acid (30 ml) in ethanol (20 ml) for half an hour. After the neutration, the product was obtained and recrystallized from a suitable solvent; (Table 1).

TABLE 1. PHYSICAL DATA OF COMPOUNDS (I-X).

No.of compd	Solvent* of ryst	m.p °C	Yield %	Molecular formula	Elemental analysis Calculated/Found (%C)	(%H)	(%N)
Ia	A	136	89	$C_{16}H_{15}NO_2$	75.89	5.93	5.53
					75.90	5.90	5.60
Ib	B	160	92	$C_{18}H_{17}NO_3$	73.22	5.76	4.75
					73.00	5.80	5.00
IIa	A	198	87	$C_{18}H_{17}N_3O$	71.91	6.37	15.73
					72.00	6.00	15.90
IIb	B	220	89	$C_{18}H_{19}N_3O_2$	69.90	6.15	13.59
					79.10	6.00	13.60
III	A	211	83	$C_{22}H_{21}N_3O$	76.97	6.12	12.24
					76.70	6.10	12.20
IVa	B	168	65	$C_{24}H_{23}N_3O_4S$	64.14	5.12	9.35
					64.00	5.10	9.40
IVb	B	190	71	$C_{25}H_{25}N_3O_4S$	64.79	5.40	9.07
					64.80	5.30	9.10
IVc	B	210	72	$C_{27}H_{28}N_4O_5S$	62.31	5.38	10.77
					62.80	5.50	11.00
Va	A	148	60	$C_{22}H_{21}N_3O_3S$	64.86	5.16	10.32
					65.00	5.20	10.20
Vb	A	160	66	$C_{23}H_{23}N_3O_3S$	65.56	5.46	9.98
					65.60	5.50	10.00
Vc	A	170	68	$C_{23}H_{24}N_3O_3S$	63.30	5.50	12.84
					63.20	5.40	12.90
VIa	B	127	75	$C_{19}H_{19}N_3O_3$	67.66	5.64	12.46
					67.70	5.70	12.50
VIb	B	130	77	$C_{20}H_{21}N_3O_3$	68.38	5.98	11.97
					68.40	5.90	12.00
VIc	B	119	80	$C_{21}H_{24}N_3O_3$	68.85	6.56	11.48
					69.00	6.60	11.40
VId	B	120	78	$C_{22}H_{25}N_3O_3$	69.66	6.60	11.08
					69.70	6.70	11.10
VIe	B	126	75	$C_{22}H_{25}N_3O_3$	69.66	6.60	11.08
					69.70	6.50	11.20
VIf	B	131	71	$C_{23}H_{27}N_3O_3$	70.23	6.87	10.69
					70.30	6.90	10.90
VIg	B	133	69	$C_{24}H_{29}N_3O_3$	70.76	7.13	10.32
					70.80	7.10	10.50
VIh	B	205	60	$C_{25}H_{23}N_3O_3$	72.64	5.57	10.17
					73.00	5.60	10.30
VIi	B	234	67	$C_{25}H_{22}N_4O_5$	65.50	4.80	12.23
					65.40	4.70	12.30
VIj	B	210	67	$C_{27}H_{25}N_3O_3$	73.80	5.69	9.57
					73.90	5.80	10.10
VIIa	A	109	73	$C_{17}H_{17}N_3O_2$	69.15	5.76	14.24
					69.20	5.70	14.30
VIIb	A	121	76	$C_{18}H_{19}N_3O_2$	69.90	6.15	13.59
					70.00	6.20	13.60
VIIc	A	115	80	$C_{19}H_{22}N_3O_2$	70.37	6.79	12.96
					70.20	6.80	12.90
VIId	A	117	76	$C_{20}H_{23}N_3O_2$	71.22	6.82	12.46
					71.20	6.80	12.50
VIIe	A	124	73	$C_{20}H_{23}N_3O_2$	71.22	6.82	12.46
					71.20	6.90	12.50
VIIf	A	123	72	$C_{21}H_{25}N_3O_2$	71.79	7.12	11.97
					72.00	7.10	11.90

(Contd.....)

(Table 1 Contd .....)

VIIg	A	120	67	$C_{22}H_{27}N_3O_2$	72.33	7.40	11.51
					72.30	7.30	11.50
VIIh	A	179	58	$C_{23}H_{21}N_3O_2$	74.39	5.66	11.32
					74.40	5.60	11.30
VIIi	A	224	63	$C_{23}H_{20}N_4O_4$	66.35	4.81	13.46
					66.40	4.80	13.30
VIIj	A	204	64	$C_{25}H_{23}N_3O_2$	75.57	5.79	10.58
					75.60	5.90	11.10
VIIIa	A	175	56	$C_{17}H_{19}N_3O$	72.60	6.76	14.95
					72.70	6.80	15.00
VIIIb	A	190	58	$C_{18}H_{21}N_3O$	73.22	7.12	14.24
					73.30	7.20	14.30
VIIIc	A	201	60	$C_{23}H_{23}N_3O$	77.31	6.44	11.76
					77.40	6.50	11.80
IXa	B	197	74	$C_{20}H_{22}N_4O_2S$	62.83	5.76	14.66
					62.90	5.70	14.70
IXb	B	218	86	$C_{25}H_{24}N_4O_2S$	67.57	5.49	12.61
					67.70	5.60	13.50
IXc	B	190	72	$C_{26}H_{24}N_4O_3S$	66.10	5.08	11.86
					66.20	5.00	12.00
IXd	B	230	68	$C_{20}H_{22}N_4O_3$	65.57	6.01	15.30
					65.60	6.00	15.20
IXe	B	202	66	$C_{25}H_{24}N_4O_3$	70.09	5.61	13.08
					70.10	5.50	13.20
Xa	C	177	64	$C_{18}H_{20}N_4OS$	63.53	5.88	16.47
					63.30	5.90	16.30
Xb	C	180	66	$C_{23}H_{22}N_4OS$	68.66	5.47	13.93
					68.70	5.50	14.00
Xc	C	160	62	$C_{24}H_{22}N_4O_2S$	66.97	5.12	13.02
					67.00	5.00	13.00
Xd	C	169	58	$C_{18}H_{20}N_4O_2$	66.67	6.17	17.28
					67.00	6.20	16.90
Xe	C	182	56	$C_{23}H_{22}N_4O_2$	71.50	5.70	14.51
					71.60	5.60	14.60
XI	A	207	88	$C_{16}H_{14}BrN_3O$	55.83	4.07	12.21
					55.80	4.10	12.00

*Solvent of crystalization: A=Ethanol, B=Acetic acid, C=Methanol.

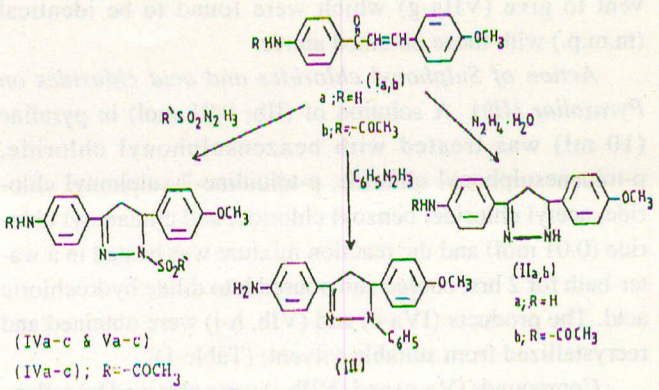
IR spectrum of (Xe) showed the bands at ν 1610 cm^{-1} (C=N), ν 1690 cm^{-1} (C=O) and ν 3400 cm^{-1} (-NH).

4-Bromopyrazoles (XI). A solution of pyrazoline (IIa) (0.01 mol) in chloroform (20 ml) was treated with a solution of bromine (0.3 mol) in chloroform (20 ml). The product obtained was crystallized from ethanol to give (XI); (Table 1).

Results and Discussions

4-amino-4'methoxybenzalacetophenone (Ia) reacted with hydrazine hydrate, phenylhydrazine, benazenesulphonyl hydrazine, p-toluenesulphonyl hydrazine and 2-acetamido-5-toluene-2-sulphonyl hydrazine in boiling ethanol with the formation of corresponding pyrazolines (II-V).

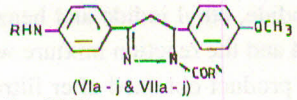
The structural identification of compounds (II), (III), and (V) have been confirmed from the IR data due to the absence of the stretching mode of C=O in (II, III & V) compared to the one observed at 1715 cm^{-1} in compound (I). Also, the



structure of the previous compounds were supported by the observed bands at 1690-1640 cm^{-1} for ν C=N).

The compounds (Va-c) were also prepared from (IIb) in two steps involving initial interaction of (IIb) with benzene sulphonyl chloride, p-toluenesulphonyl chloride and p-toluidine-2-sulphonyl chloride in pyridine to give (IVa-c), followed by hydrolysis to produce (Va-c).

The condensation of the chalcone (Ia) with hdrazine hydrate was carried out in boiling formic, acetic, propionic, butyric, isobutryric, valeric and hexanoic acid to form the corresponding 1-formyl-, 1-acetyl-, 1-propionyl-, 1-butyryl-, 1-isobutyryl-, 1-pentyl- and 1-hexyl-pyrazolines (VIIa-g). The latter compounds (VIIa-g) were also produced by heating the pyrazoline (IIb) with formic, acetic, propionic, butyric, isobutyric, valeric and bexanoic acid followed by hydrolysis.

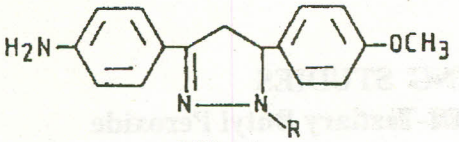


(VIa-g); R = -$COCH_3$
a ; R' = H
b ; R' = -CH_3
c ; R' = -CH_2CH_3
d ; R' = -$CH_2CH_2CH_3$
e ; R' = -$CH(CH_3)_2$

(VIIa-j); R = H
f ; R' = -$CH_2(CH_2)_2CH_3$
g ; R' = -$CH_2(CH_2)_3CH_3$
h ; R' = C_6H_5 -
i ; R' = 4-$NO_2C_6H_4$ -
j ; R' = $C_6H_5CH{=}CH$ -

From the ^{1}HMNR spectroscopic data, the structure of compound (VIIa) has been approved unquestionably from the disappearance of the doublet band observed at δ 6.7 (CH=CH) in compound (Ia) compared to that in compound (VIIa) and by the observed singlet of the CH_2 group at δ 3.4 and triplet at 4.5 for CH as well as the singlet observed at δ 9.1 for -CHO group.

Additionally the structure of pyrazolines (VII) was confirmed using independent synthesis of (VII) from (IIb) with acyl chloride followed by hydrolysis. Also, different pyrazoline derivatives (VIIh-j) were obtained by interaction of (IIb) with benzoyl chloride, p-nitrobenzoyl chloride and cinnamoyl chlorie in pyridine followed by hydrolysis.



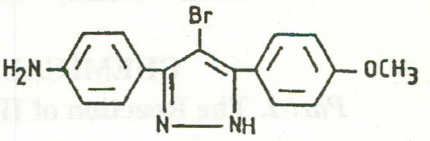
(VIIIa-c)

a ; R = $-CH_3$
b ; R = $-CH_2CH_3$
c ; R = $-CH_2C_6H_5$

Pyrazoline derivatives (VIIIa-c) were obtained via the reduction of (VIIa-b) and (VIh) with lithium aluminium hydride in ether. The structure of (VIIIa-c) has been supported by the absence of υ C=O band in the IR spectra of compounds (VIIIa-c) compared with the one observed at 1715 cm-1 for (VII). ^{1}HNMR spectrum for (VIIIb) shows the appearance of new band at δ 5.4 [q, 2H, CH_2] compared with (VIIb).

Also, the structure of (VIIIa-c) was established by the interation of methyl iodide, ethyl iodide and benzyl bromide with (IIb) in acetone aand potassium carbonate, followed hydrolysis afforded (VIIIa-c) with identical (m.m.p.) to those obtained by the reduction of (VIIa, b) and (VIIh) with lithium aluminium hydride.

The interaction (IIb) with methyl isothiocyanate, phenyisothiocyanate, benzoyl isothiocyanate, methyl isocyanate and phenyl isocyanate afforded (IXa-e) which on hydrolysis gave (Xa-e).



(XI)

Compound (IIa) was treated with excess bromine in chloroform to give the corresponding (XI) in order to investigate the activity of methylene group in pyrazoline.

References

1. S. Rich and J. G. Horsfall, Phytophatology, **42,** 457 (1952).
2. N. V. Valyashko and I. T. Depeshko, J. Gen. USSR, **23,** 355, (1953), C.A.49, 4629h (1955).
3. E. Herrman and I. Gabliks, cancer Chemotherapy Rept., **14,** 85 (1961).
4. R. Laliberte, D. Campbell, and f. Bruderlein, Can. J. Pharma. Sci., **2,** 37 (1967), C. A. 67, 9805g (1967).
5. G. H. Sayed, Indian J Chemisty, **19B,** 364 (1980).
6. F. M. Asaad, Egypt. J. Chem., **25,** (3), 293 (1982).
7. D. Bhaskar Reddy, K. Radha Krishna Murthyy, T. Seeshamma, B. Senaiah and A. Padmaja, Sulfur Letters, **12,** 73 (1990).
8. H. E. Thompson, C. P. Swanson and A. G. Norman, Botam. Gaz., **107,** 476 (1946).
9. *Colour Index,* Vol 4&7, third edition (The Society of Dyes and Colourists, 1992), Vol.487, 3rd ed.