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Synthesis of 4-Substituted Aroyloxymethylcarbonyl-3-Methyl-Substituted Phenyl-6-Imino-4,7-Dihydro-1,3-Thiazino (5,4–d) Pyrazolones as Antihistaminic Agents†

S.M. KUDARI* and A.S. SAJJANSHETTY
Department of Chemistry
Gulbarga University, Gulbarga–585 106, India

Reaction of substituted aroyloxy acid hydrazide (1a–c) with ethylacetate gave the corresponding 4-substituted aroyloxymethylcarbonyl-3-methyl-Δ^2-pyrazolin-5-one (2a–c) in good yields. Condensation of (2a–c) with different aryl aldehydes under Knoevenagal conditions furnished 4-substituted aroyloxymethyl carbonyl-4-arylideno-3-methyl-5-pyrazolone (3a–e). These on refluxing with thiourea and potassium hydroxide gave 4-substituted aroyloxymethyl carbonyl-3-methyl-substituted phenyl-6-imino-4,7-dihydro-1,3-thiazino-(5,4-d)-pyrazolone (4a–e). Few 5-pyrazolones were screened for antihistaminic activity against ileum portion of an adult guinea pig.

INTRODUCTION

5-Pyrazolones are known to possess antiinflammatory[1,2], antipyretic[3], antifungal[4], antidiabetic[5], analgesic[6], vasodilating, respiration stimulating[7] and hypotensive[8] properties. Several reports have appeared in the literature which highlight their chemistry and use[9]. In continuation of our research programme on bis-heterocyclic compounds, we report some 4-substituted aroyloxy-methylcarbonyl-3-methyl-4-substituted phenyl-6-imino-4,7-dihydro-1,3-thiazino-(5,4-d) pyrazolones and these compounds have been tested for antihistaminic activity. They have show histamine-like activity instead of antihistaminic activity.

Aroyloxymethylcarbonyl-3-methyl-Δ^2-pyrazolin-5-one (2a) exhibited absorption peaks at 1700 and 1610 cm^{-1} due to ν(C=O) and ν(C=N) respectively in its IR spectrum. The condensation of pyrazolin-5-one with aryl aldehydes in the presence of glacial acetic acid and fused sodium acetate gave the corresponding 5-pyrazolones. The PMR spectrum of 3a exhibited two sharp singlets at 2.8 δ and 3.2 δ accounting for methylene protons. The aromatic cluster was observed at 7.1 to 8.2 δ representing integral values for ten aromatic protons. On treatment with thiourea and potassium hydroxide, 3a gave 4-substituted aroyloxymethylcarbonyl-3-methyl-4-substituted phenyl-6-imino-4,7-dihydro-1,3-thiazino-(5,4-d)-pyrazolone (4a). The structure of 4a is supported by its PMR and mass spectral data. The PMR spectrum of 4a showed NH protons of thiazino moiety at 9.8 δ and the aromatic protons observed at 7.3–8 δ. The mass spectrum of 4a showed molecular ion M^+ peak at m/e 378 (21%) which corresponds to the molecular

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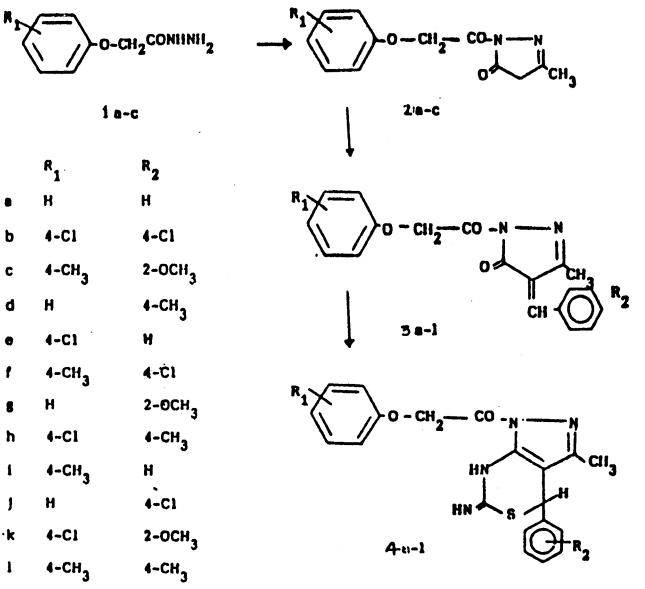
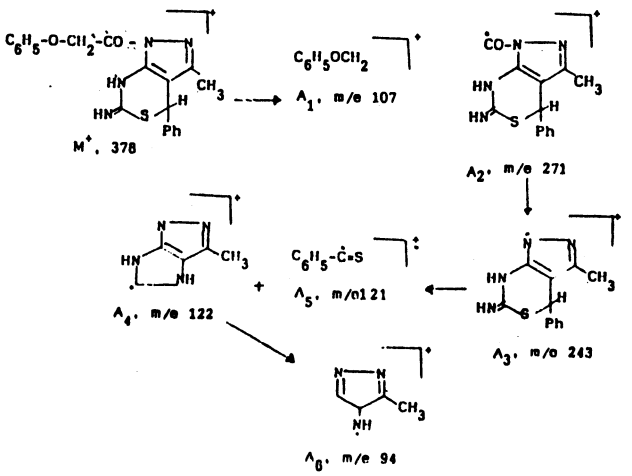
Scheme-1



	R_1	R_2
a	H	H
b	4-Cl	4-Cl
c	4-CH_3	2-OCH_3
d	H	4-CH_3
e	4-Cl	H
f	4-CH_3	4-Cl
g	H	2-OCH_3
h	4-Cl	4-CH_3
i	4-CH_3	H
j	H	4-Cl
k	4-Cl	2-OCH_3
l	4-CH_3	4-CH_3

Scheme-2



weight of 4a. This moleculaar ion undergoes elimination of $C_6H_5OCH_2^+$ ion (m/e = 107, 100%) and gives peak at m/e 271 ($A_2 = M^+$-107, 66.2%). Further the molecular ion A_2 Losses CO and gave peak at m/e 243 ($A_3 = A_2$: CO, 27%) in the mass spectrum. The molecular fragment ion A_3 has also undergone bond cleavage to give peak at m/e 122 (22%) correspond to A_4 and m/e 121 (11.8%) corresponding to A_5. Further fragmentation has resulted by favourable expulsion of HCN and a proton from A_4 molecular ion to give peak at m/e 94 ($A_6 = A_4$—HCN, H^+, 67%). All these spectral evidences confirm the formation of compound 4a (Scheme-2).

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer-297 spectrophotometer, while PMR were recorded on a GSX-4-NMR spectrometer using TMS as internal standard and mass spectra was recorded on Finigan MAT 8230 GC-MS mass spectrometer. Structures of compounds were established on the basis of IR, PMR, mass spectral data. All compounds showed satisfactorily elemental and analytical results (Table-1).

4-Substituted aroyloxymethylcarbonyl hydrazide (1a–c)

The 4-substituted aroyloxyacetic acids prepared according to the literature methods[10-12], were esterified to give aroyloxyacetates in good yield. Esters on condensation[13] with hydrazinehydrate (80%) in abs. alcohol gave the corresponding aroyloxymethyl carbonyl hydrazide (1a–c).

4-Substituted aroyloxymethylcarbonyl-3-methyl-Δ^2-pyrazolin-5-ones (2a–c)

4-Substituted aroyloxymethylcarbonylhdrazide (2a–c) (0.01 mol) was condensed with ethylacetoacetate (1.3 mL, 0.01 mol) by gentle heating on low flame for 2 h. The reaction mixture was cooled to room temperature when crystalline solid was obtained. The resulting solid was filtered and crystallised from aqueous ethanol.

4-Substituted aroyloxymethylcarbonyl-4-arylideno-3-methyl-5-pyrazolone (3a–l)

A mixture of arylaldehyde (0.005 mol) and 4-substituted aroyloxymethylcarbonyl-3-methyl-Δ^2-pyrazolin-5-one (0.005 mL) in ethanol (20 mL) was refluxed in the presence of acetic acid (few drops) for 6 h. The reaction mixture was then cooled to room temperature and the poured on to crushed ice. The resulting solid was filtered, washed with filtered cold ethanol (2 mL) and crystallised from aqueous ethanol.

4-Substituted aroyloxymethylcarbonyl-3-methyl-4-substituted phenyl-6-imino-4,7-dihydro-1,3-thiazino-(4,5-d)-pyrazolone (4a–l)

A mixture of (3a–l), thiourea (0.001 mol) and potassium hydroxide (0.002 mol) was refluxed in methanol for 3 h. On cooling it was acidified with dilute

TABLE-1
CHARACTERIZATION DATA OF THE COMPOUNDS SYNTHESISED

Compound	Substituents		m.p. (°C)	Yield (%)	Nature (solvent)	Molecular formula	% Analysis C, H and N, Found (Calcd.)		
	R_1	R_2					C	H	N
3a	H	H	197	52	Yellow granules (Aq. ethanol)	$C_{19}H_{16}N_2O_3$	71.15 (71.25)	4.81 (5.00)	8.62 (8.75)
3b	4-Cl	4-Cl	221	50	Orange crystals (Aq. ethanol)	$C_{19}H_{17}N_2O_3Cl_2$	58.50 (58.61)	4.25 (4.37)	7.00 (7.19)
3c	4-CH_3	2-OCH_3	202	60	Red needles (Aq. ethanol)	$C_{21}H_{19}N_2O_4$	69.50 (69.42)	5.31 (5.23)	7.82 (7.71)
3d	H	4-CH_3	198	62	Orange needles (Ethanol)	$C_{20}H_{19}N_2O_4$	71.62 (71.85)	5.23 (5.38)	8.50 (8.38)
3e	4-Cl	H	213	61	Light brown crystals (Ethanol)	$C_{19}H_{15}N_2O_3Cl$	64.40 (64.31)	4.21 (4.23)	7.90 (7.89)
3f	4-CH_3	4-Cl	207	55	Brown needles (Ethanol)	$C_{20}H_{16}N_2O_3Cl$	65.42 (65.39)	4.37 (4.35)	7.50 (7.62)
3g	H	2-OCH_3	196	63	Orange crystals (Ethanol)	$C_{20}H_{19}N_2O_4$	68.25 (68.37)	5.32 (5.41)	8.00 (7.97)
3h	4-Cl	4-CH_3	201	66	Yellow needles (Ethanol)	$C_{20}H_{19}N_2O_4$	68.25 (68.37)	5.32 (5.41)	8.00 (7.97)
3i	4-CH_3	H	186	60	Pale yellow crystals (Aq. ethanol)	$C_{20}H_{19}N_2O_3$	71.50 (71.64)	5.50 (5.67)	8.50 (8.35)
3j	H	4-Cl	199	59	Orange needles (Aq. ethanol)	$C_{19}H_{15}N_2O_3Cl$	64.20 (64.31)	4.25 (4.23)	8.00 (7.90)
3k	4-Cl	2-OCH_3	213	58	Reddish needles (Ethanol)	$C_{20}H_{17}N_2O_4Cl$	62.50 (62.47)	4.50 (4.42)	7.41 (7.28)
3l	4-CH_3	4-CH_3	206	62	Orange granules (Ethanol)	$C_{21}H_{19}N_2O_3$	72.52 (71.62)	5.52 (5.47)	8.00 (8.06)

Compound	Substituents		m.p. (°C)	Yield (%)	Nature (solvent)	Molecular formula	% Analysis C, H and N, Found (Calcd.)		
	R_1	R_2					C	H	N
4a	H	H	213	50	Yellow crystals (Rectified spirit)	$C_{20}H_{19}N_4O_2S$	63.21 (63.32)	5.00 (5.01)	14.60 (14.77)
4b	4-Cl	4-Cl	231	55	Yelow needles (Ethanol)	$C_{20}H_{18}N_4O_2SCl_2$	53.10 (53.20)	4.42 (4.43)	12.30 (12.41)
4c	4-CH_3	2-OCH_3	198	52	Orange plates (Ethanol)	$C_{22}H_{22}N_4O_3S$	62.50 (62.55)	5.00 (5.20)	13.00 (12.27)
4d	H	4-CH_3	204	60	Yellow silky needles (Ethanol)	$C_{21}H_{21}N_4O_2S$	64.00 (64.12)	5.21 (5.32)	14.20 (14.24)
4e	4-Cl	H	209	52	Light brown needles (Ethanol)	$C_{20}H_{18}N_4O_2ClS$	58.10 (58.00)	4.40 (4.35)	13.54 (13.54)
4f	4-CH_3	4-Cl	215	54	Brown crystals (Ethanol)	$C_{21}H_{19}N_4O_2ClS$	59.10 (59.00)	4.50 (4.45)	13.00 (13.13)
4g	H	2-OCH_3	189	50	Orange plates (Ethanol)	$C_{21}H_{22}N_4O_3S$	61.50 (61.46)	5.40 (5.36)	13.70 (13.65)
4h	4-Cl	4-CH_3	201	56	Orange granules (Ethanol)	$C_{21}H_{20}N_4O_2ClS$	59.00 (58.94)	4.70 (4.67)	13.10 (13.00)
4i	4-CH_3	H	196	60	Light yellow crystals (Ethanol)	$C_{21}H_{22}N_4O_2S$	64.00 (63.95)	5.61 (5.58)	14.00 (14.21)
4j	H	4-Cl	216	56	Yellow needles (Ethanol)	$C_{20}H_{18}N_4O_2ClS$	58.08 (58.00)	4.45 (4.35)	13.50 (13.54)
4k	4-Cl	2-OCH_3	202	54	Orange plates (Rectified spirit)	$C_{21}H_{30}N_4O_3ClS$	55.60 (55.56)	6.60 (6.61)	12.20 (12.34)
4l	4-CH_3	4-CH_3	199	62	Yellow crystals (Rectified spirit)	$C_{22}H_{22}N_4O_2S$	65.0 (65.0)	5.50 (5.41)	13.87 (13.80)

hydrochloric acid. The solid obtained was filtered washed with water and crystallised from ethanol to get 4a–l.

Antihistaminic activity

The overnight tested guinea pig weighing 400–600 g was selected. The drugs used were histamine and selected samples of 3b, 3f, 3h, 3k, 4b, 4f, 4h and 4k. The stock solution of histamine at a concentration of 1 mg/mL was prepared and selected compounds were made into suspension using 1% Tween-80 at a conc. of 40 mg/mL. The tyrode physiological solution was also prepared for guinea pig ileum preparation.

One piece of the ileum (2–3 cm long) was selected and the top and bottom ends with lumen openings were tied by a thread.It was mounted in organ bath containing tyrode solution at 32–35°C with oxygen supply. After 30 min, the responses due to histamine and due to histamine samples at various concentrations were recorded on the smoked drum. The results were recorded in Table-2.

RESULTS AND DISCUSSION

The samples of compounds 3b, 3f, 3h, 3k, 4b, 4f, 4h and 4k have shown histaminic-like activity instead of antihistaminic activity. The 4b sample has got 44% of antihistaminic activity at a concentration of 4 mg in 50 mL organ bath.

TABLE-2

Volume of histamine/test solutions added in mL	Peak height in mm	Histaminic activity in %
0.2 std	14	30.43
0.4 std	22	47.82
0.5 std	46	100.00
Sample of 3b + 0.5 std	58	126.00
Sample of 3f + 0.5 std	60	130.00
Sample of 3h + 0.5 std	49	106.50
Sample of 3k + 0.5 std	39	84.78
Sample of 4b + 0.5 std	27	56.00
Sample of 4f + 0.5 std	59	128.26
Sample of 4h + 0. 5 std	61	132.60
Sample of 4k + 0.5 std	48	104.34

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