Chemistry and CNS activity of 1-(4-methyl-coumarin-7yl)-oxyacetyl-3-methyl-4-(substituted phenyl hydrazono/azo)-pyrazolin-5-ones

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Summary: Twelve title compounds (IVa-l) were synthesised by two different methods. The first method involved the reaction of 4-methyl-7-coumarin-oxyacetyl hydrazine (I) and corresponding, ethyl-2 3-dioxo butyrat -2-aryl hydrazones (II), while the second method involved the diazo-coupling of 1-(4-methyl-coumarin-7yl)-oxyacetyl-3-methyl-pyrazolin-5-one (III) with different substituted phenyl diazonium chlorides. The structures of 1-(4-methyl-coumarin-7yl)-oxyacetyl-3-methyl-4-(substituted phenyl hydrazono/azo)-pyrazolin-5-ones (IVa-l) have been assigned on the basis of IR and PMR spectroscopy. The obtained data indicate that these compounds exist in hydrazone form instead of tautomeric keto-azo or enol-azo forms. The compounds are relatively non-toxic except one and are CNS stimulants.

It is of worth to point out that the structure of 1,3-disubstituted-4-arylazo-pyrazolin-5-one has been controversial. On the basis of spectroscopic studies, various workers proposed that 1,3-disubstituted-4-arylazo-pyrazolin-5-one exists in three different forms i.e. IV^{1}_{A}, IV^{2}_{C} and IV^{3-6}_{B}. Recently, aryl hydrazono structure (IV_{B}) for the 1,3-disubstituted-4-arylazo-pyrazolin-5-one was favoured by two groups of workers[7,8]. The investigations of another group of workers[9] concluded that the compounds of this nature exist as hydrazone-form (IVB) in solid state and as azo-form (IVA) in aqueous buffer media.

On the other hand, chromones have recently been introduced into the field of Central Nervous System (CNS) as CNS depressants[10] and anticonvulsants[11]. The CNS depressant 12 and neurotropic[13] properties of some coumarin analogs have also been reported. Pyrazolinone derivatives have also been known as CNS active analgesics 14 and depressants[15].

Therefore, the aforesaid findings prompted us to investigate the actual structures and CNS activity of some newer 1,3-disbustituted-4-aryl hydrazono/azo-pyrazolin-5-ones. This paper reports the results of investigations aiming to establish the structures of title compounds, prepared by two different routes (Chart-I) and their effect on the CNS.

To synthesise new pyrazolinone derivatives, 4-methyl-7-coumarin-oxyacetyl hydrazine (I) was selected as the starting material. The first route involves the cyclisation of the (I) to respective N^{1}-substituted-3-methyl-pyrazolin-5-one (III) with ethyl-acetoacetate. In the subsequent step the 1-(4-methyl-coumarin-7-yl)-oxyacetyl-3-methyl-pyrazolin-5-one (III) was coupled with corresponding aryl diazonium chlorides to give (IV) in good yields. In the second route, the diazo-coupling of aryl diazonium chlorides with ethylacetoacetate, in alcoholic sodium acetate buffer, resulted in the formation of different 2,3-dioxo butyrate-2-aryl hydrazones (II), which on the reaction with the coumarin hydrazide (I) in ethanol containing gl.AcOH, resulted in the formation of (IV). The compounds prepared by the aforesaid two methods had same melting points without any depression in mixed melting point technique and imparted superimposable spectrographs. Hence the two compounds were the same. It is noteworthy that the compounds synthesised by the second route exist in 'hydrazone' form (IVB) because the intermediates (II), used in their preparation, already existed as hydrazono tautomer (more stable due to chelation[16]) rather than, as azo form.

In the light of above studies, it was expected that the keto-azo product (IVA), initially formed by diazo-

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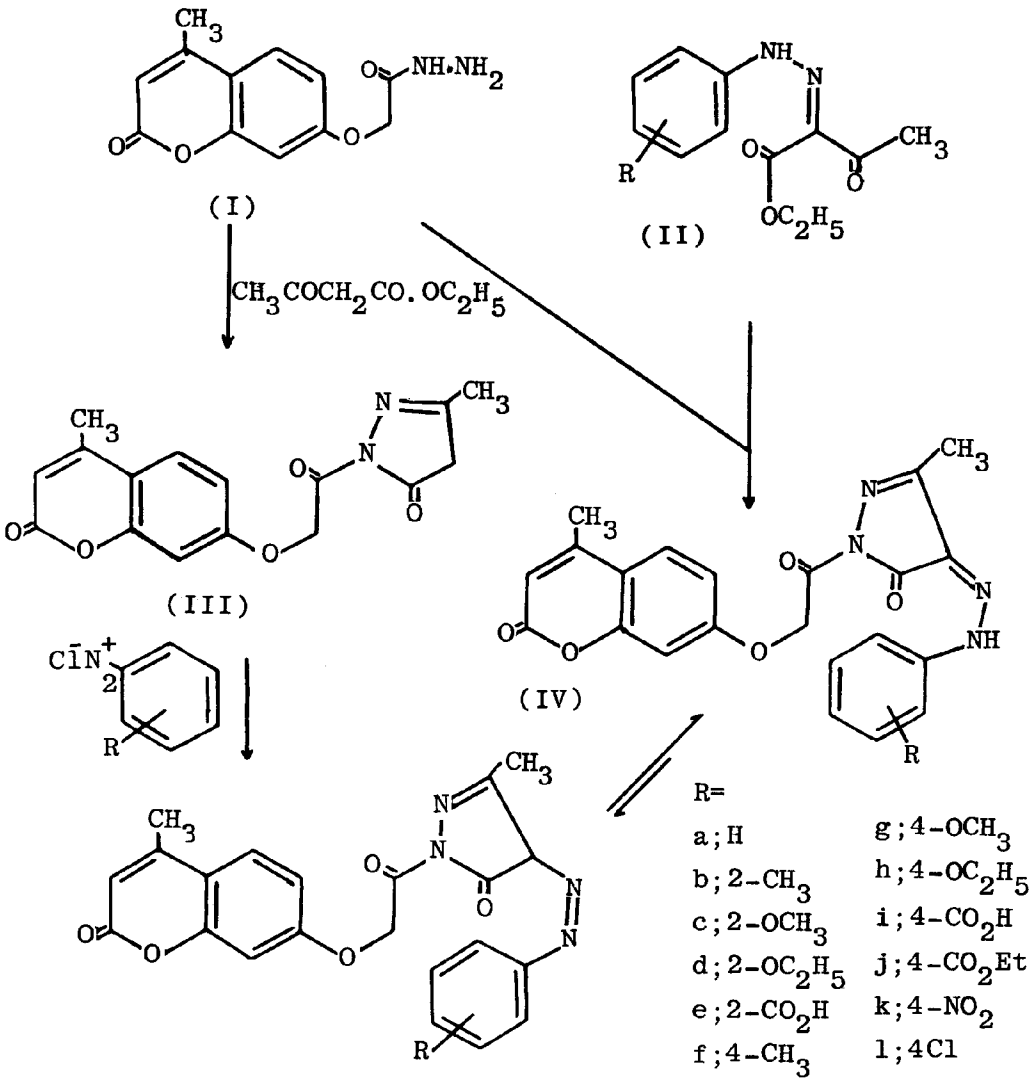
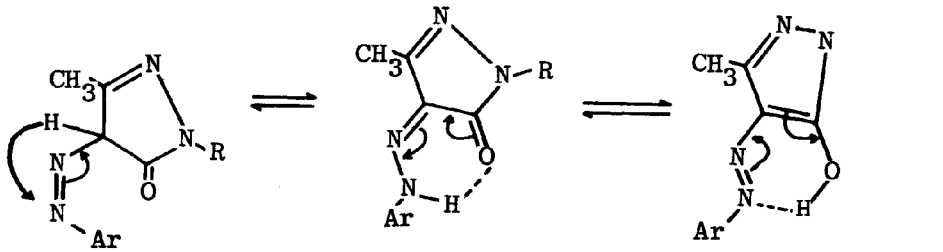


Chart I

coupling, would undergo a tautomeric proton shift, transforming the azoform into hydrazone form (IVB). This transformation to hydrazone form is presumably due to the existance of a strong chelation of hydrazone hydrogen with carbonyl oxygen, as the bond energy of the hydrazone N-H bond is slightly more than the C-H bond energy of the azo form[17]. The enol-azo form (IVc) may also be expected, which could get tautomerised from hydrazone form by a proton shift (Chart-II), but the spectral data support the assignment of chelated hydrazone structure to the final compounds.

The IR spectra of the final products (IV) showed sharp bands at 1670, 1620 and 1540 assignable to C=0 cyclic C=N and C=C-NH-N= groups, respectively. The band for N-H was observed in the range of 3300-3100 for different compounds. The absence of conspicuous bands at 3500 and 1580, showed the absence of OH (expected in enol-azo form) and N=N groups. The PMR spectra of the compounds showed a singlet due to N-H proton at 14.3 (D_2O exchangeable). This down field position of N-H proton is in evidence of chelation with the carbonyl group.



Keto-Azo form (IVA) | Keto-azo form (IVB) | enol-azo form (IVC)

Chart II

Pharmacological activities

All the compounds (IVa-l) were screened for their action on the CNS of albino mice and for toxicity test.

For toxicity test, the compounds were administered, at the doses of 464 and 1000 mg/kg weight of mice, intra-peritoneally as gum acacia suspension and the approximate lethal doses in 50% of the animals tested (ALD_{50}), were determined by the method of Weil[18]. The compounds are relatively non-toxic except one compound (IVf), the ALD_{50} values are noted in Table 1.

For their actions on the CNS, the compounds were administered to albino mice at 1/5th of ALD_{50} and their behavioural changes in spontaneous motor activity and reactivity to sound and touch, were noted. To substantiate these observations on the SMA and reactivity, mobility counts were taken in the actophotometer, equipped with photocells. The effect of the compounds on the body temperature was also noted (Table 1). At higher doses (464 & 1000 mg/kg) and also at 1/5th of ALD_{50} all the compounds were found to be CNS stimulant.

Experimental

M-ps were determined in open capillaries using A.R. H_2SO_4 bath and are uncorrected. IR spectra in KBr phase, were recorded on a Perkin–Elmer 157 spectrophotometer (λ max in cm^{-1}). The PMR spectra were recorded in $CDCl_3$ on a Varian A60D instrument using TMS as internal standard (chemical shift in 8, ppm.). The purity of compounds was checked by TLC using plates coated (0.25 mm) with silica gel-G and the solvent system: benzene-methanol, 100:5.

4-Methyl-7-coumarin-oxyacetyl hydrazine (I) was prepared following the method of Husain & Shukla[19].

Ethyl-2,3-dioxobutyrat -2-substituted phenyl hydrazones (IIa-l)- These were prepared according to the previously reported procedure (ref.8), by the diazo-coupling of ethlacetoacetate with aryl diazonium chlorides in alcoholic sodium acetate buffer. The azo products formed, get tautomerised into hydrazone form, which is more stable due to chelation (ref.16).

1-(4-Methyl-coumarin-7yl)-oxyacetyl-3-methyl-pyrazolin-5-one (III)- An equimolar (0.05 mole) mixture of 4-methyl-7-coumarinyl oxyacetyl hydrazine and ethylacetoacetate in ethanol (70 ml) was refluxed on steam bath for 6 hrs. Nearly 30 ml of ethanol was then distilled off, the reaction mixture was cooled to room temperature and left for 12 hours. The solid separated was filtered, washed well with hot water and finally recrystallised from ethanol, m.p. 157°C, yield 96%;

IR: 3050, 2900 (C-H, aromatic and aliphatic), 1720 (cyclic ester), 1680 (amidic C=0), 1620 (C=N), 1510, 1420 and 1150;

PMR: 7.3-8.0 (complex multiplet, 4H, aromatic), 4.45 (s, 2H, O-CH_2-CO), 4.3 (s, 2H, CH_2 cyclic), 2.2 (s, 3H, Me of coumarin), 1.4 (s, 3H, Me of pyrazolinone) (Found C, 60.96; H, 4.19; N, 8.90; $C_{16}H_{14}N_2O_5$ requires C, 61.14; H, 4.45; N, 8.91%.

1- (4-Methyl-coumarin-7yl) oxyacetyl-3-methyl-4-(substituted phenyl hydrazono)-pyrazolin-5-ones (IVa-1) (Table2).

Method-1 : Firstly the diazonium salt solution was

Table 1.

Physical data of 1-(4-methyl-coumarin-7-yl)-oxyacetyl-3-methyl-4-(substituted phenyl hydrazono)-pyrazolin-5-ones (IV)

Compd.	R	m.p.* °C	Yield (%)	Mol. formula	Colour of compound	N (%)+ Found	Calcd.
IVa	H	196(197)	60(62)	$C_{22}H_{18}O_5N_4$	Light brown	13.49	13.39
IVb	2-CH_3	224(224)	69)65)	$C_{23}H_{20}O_5N_4$	Golden yellow	13.06	12.96
IVc	2-OCH_3	229(229)	70(66)	$C_{23}H_{20}O_6N_4$	Orange	12.31	12.50
IVd	2-OC_2H_5	226(225-26)	65(63)	$C_{24}H_{22}O_6N_4$	"	11.99	12.12
IVe	2-COOH	243(243)	75(80)	$C_{23}H_{18}O_7N_4$	Golden yellow	12.42	12.12
IVf	4-CH_3	130(129-30)	55(65)	$C_{23}H_{20}O_5N_4$	"	12.81	12.96
IVg	4-OCH_3	133-34(133)	60(69)	$C_{23}H_{20}O_6N_4$	Dark Orange	12.79	12.50
IVh	4-OC_2H_5	175(176)	65(62)	$C_{24}H_{22}O_6N_4$	Orange	12.16	12.12
IVi	4-COOH	27069(65)	70(70)	$C_{23}H_{18}O_7N_4$	Golden yellow	12.35	12.12
IVj	4-$COOC_2H_5$	264(264)	75(70)	$C_{25}H_{22}O_7N_4$	Yellow	11.36	11.43
IVk	4-NO_2	242d(242d)	78(80)	$C_{22}H_{17}O_7N_5$	Leaf brown	14.92	15.12
IVl	4-Cl	146(145-46)	65(69)	$C_{22}H_{17}O_5N_4Cl$	"	12.44	12.37

The values indicated in brackets stand for results obtained from the compounds prepared by method-2.

*Compounds were recrystallised from dioxane.

+All the compounds gave satisfactory C & H analyses.

prepared by dissolving aromatic amine (0.0025 mole) in dil HCl (2.5 ml) [1:1 of HCl & water] and adding $NaNO_2$ (0.0025 mole) gradually to ice cooled (0-5°C) solution of amine hydrochloride, prepared.

This diazonium salt solution was then added dropwise into the chilled, well stirred mixture of sodium acetate (1.5 gm) and III (0.0025 mole) in ethanol (20 ml). After the addition of all the diazonium salt solution, the flask was kept at room temperature for two hours.

Thereafter, the whole mixture was poured into ice water (150 ml). The product was separated out as a coloured solid. It was filtered after keeping 2 hours, washed well with cold water and recystallised from dioxane. IVf (R= 4-CO_2 Et)-

IR: 3200,3050, 2900 (N-H & C-H), 1760, 1730, 1670 C=O of ester, acetyl and cycloamidic, respectively), 1620 (C=N), 1540 (C=C- NH-N=), 1420 & 1150; PMR: 14.3 (s, 1H, N-H), 7.2-8.0 (complex multiplet, 8H,Ar-H), 4.45 (s, 2H, o-CH_2), 4.3 [q(J=9Hz) 2H, CH_2 of $CO_2CH_2CH_3$], 2.2 (s, 3H, Me of coumarin), 1.4 (s, 3H, Me of pyrazolinone), 1.3 [t(J=9Hz) 3H, Me of $CO_2CH_2CH_3$].

Method-2: An equimolar (0.0025 mole) mixture, of 4-methyl-7-coumarinyl-oxyacetyl hydrazine (I) and ethyl-2-,3-dioxo-butyrat -2-susbtituted phenyl hydrazone (II) in ethanol (30 ml), was refluxed on a steam bath for 2 hrs, followed by the addition of glacial AcOH (5 ml) and again refluxed for 3 hrs. The product was precipitated out on concentrating the reaction mixture. It was cooled, filtered, washed with cold water and dried well in air. Finally it was recrystallised from dioxane. IVa (R=H) - IR: 3300, 3100, 2920 (N-H & C-H), 1780, 1720, 1660 (C=0), 1620 (C=N), 1540 (C=C-NH-N=), 1430 & 1180; PMR: 14.2 (s, 1H, NH), 7.3 - 8.1 (complex multiplet, 9H, Ar-H), 4.45 (s, 2H,

Table 2.

Gross CNS observations of the compounds described in Table-1, at 1/5the of ALD_{50}

S.No.	Gross CNS activities				ALD_{50} mg/kg (i.p.)
	SMA and Reactivity	Writhing	Change in body temperature (^{o}C)	Other effects	
IVa	↑	(+)	↑ 0.9	(-)	825
IVb	↑	(+)	↑ 0.6	Resp.↑	>1000
IVc	↑	(+)	(-)	"	>1000
IVd	↑	(-)	↓ 1.2	"	>1000
IVe	↑	(+)	↓ 0.3	"	>1000
IVf	↑	(+)	↑ 0.4	(-)	383383
IVg	↑	(-)	(-)	Resp.↑, Ataxia	>1000
IVh	↑	(-)	↓ 0.4	Resp.↑	>1000
IVi	↑	(-)	↓ 1.0	(-)	825
IVj	↑	(-)	↑ 0.2	Piloerection	>1000
IVk	↑	(+)	↑0.4	(-)	>1000
IVl	↑	(+)	(-)	Resp.↑	>1000

↑=Increased; ↓ = Decreased; (+) = Present; (-) Not effected; Resp. = Respiration; SMA = Spontaneous Motor Activity.

CH_2), 2.2 (s, 3H, Me of coumarin), 1.4 (s, 3H, Me of pyrazolinone).

It is important to note that the compounds, prepared by two different methods were run on the same paper for IR spectroscopy, gave the superimposable peaks in all the regions. The compounds, obtained from different procedures have got the same melting point, without any lowering in mixed melting point (Table 1).

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