Relative Efficacies :

The molarities just sufficient to suppress the maxima are the in order : Al(III)<Sr(II), Ba(II)< <Ca(II)<Na(I). Thus relative efficacies of these cations obey the valency rule. This confirms the results of previous workers[1-3]. At any comparative situation the order of αn_a values signifies the extent to which the addition of these cations push the electrode reaction towards the irreversibility from the position in the absence of these cations. In the present study this push towards irreversibility at the point of just suppression is in the order : Al(III)<Sr(II)<Ba(II), Ca(II)<Na(I). Thus Al(III) eliminates the maximum with minimum influence on the kinetics of the electron transfer followed by Sr(II), Ba(II), Ca(II) and Na(I) in order.

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References

1. J. Heyrovsky, *Chem. Listy*, 1942, **36**, 267.
2. S. Lal and S. N. Srivastava, *Indian J. Appl. Chem.* 1969, **32**, 287.
3. S. Lal and S. N. Srivastava, *Indian J. Chem*, 1969, **7**, 80.
4. J. Koutecky, *Chem. Listy*, 1953, **47**, 323 ; *Coll. Czech. Chem. Commun.*, 1953, **18**, 597 ; J. Koutecky and J. Cizek, *Coll. Czech. Chem. Commun.*, 1956, **21**, 836.
5. J. E. Strassner and P. Delahay, *J. Amer. Chem. Soc.*, 1952, **74**, 6232.
6. S. K. Jha, S. Jha and S. N. Srivastava, *Z. Naturforsch*, 1975, **30b**, 859.
7. P. Delahay, '*New Instrumental Methods in Electrochemistry*'. (Interscience, New York), 1954, 33.
8. M. Singh, Gita Ram and S. K. Jha, *Indian J. Chem.*, 1977, **15A**, 406.

Synthesis of N-Aryloxy (or thio)acetyl/ acetamido Pyrazoles and Pyrroles

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A series of N^1-aryloxy (or thio)acetyl-3, 5-dimethylpyrazoles and N-aryloxy (or thio)acetamido-2, 5-dimethylpyrroles have been prepared to study their hypoglycemic and CNS activities. A slight reduction of blood sugar was observed when six of these compounds were screened on rats at an oral dose of 250 mg/kg body weight. Some of these compounds were found CNS stimulant, relatively non-toxic, induced writhing and piloerections in albino mice.

Several N-substituted 3, 5-dimethylpyrazoles[1,2,3] and pyrroles[4] have recently been known to display significant hypoglycemic activity. Some compounds having N-acyl[5] and N-aryloxyacetyl[6] moieties have also evinced substantial hypoglycemic efficacy. It seemed, therefore, of interest to synthesise the title compounds, bearing aryloxy (or thio)acetyl moiety. Visualising the CNS activity in some pyrazole[7] and pyrrole[8] derivatives, it was considered worthwhile to screen some of these compounds also for their CNS activity.

An aryloxy (or thio)acetyl hydrazine was stirred with acetyl acetone in D.M.F. in the presence of HCl to furnish the desired pyrazoles. The same hydrazine was also refluxed with acetonylacetone in the presence of ethanol and glacial acetic acid to give N-substituted pyrroles.

Experimental

Melting points were recorded in sulphuric acid bath in open capillary tubes and are uncorrected. Infra-red spectra were determined on Perkin-Elmer 137 Spectrophotometer in KBr.

Aryloxy (or thio) acetyl hydrazines were prepared by known procedures[9,10,11].

N^1-Aryloxy (or thio)acetyl-3, 5-dimethylpyrazoles(I) :

Acetylacetone (.005 mole) and aryloxy (or thio)-acetyl hydrazine (.005 mole) were added to a mixture of D.M.F. (25 ml) and 2*N*.HCl (25 ml). The reaction mixture was stirred for 10 mts below 20° and then for about 45 mts at the room temperature. The solid separated was filtered, dried and recrystallised from ethanol. Melting points and relevant data of the prepared compounds are given in Table 1.

The structure of the compounds(I) was confirmed by the presence of I.R. spectral bands at 1740-1760 cm^{-1} (C=O of tert. amide having N in pyrazole ring[2]), 2900 cm^{-1} (CH-str.), 1600 cm^{-1} (C=N−) and absence of −NH− str. bands at 3000-3300 cm^{-1}.

N-Aryloxy (or thio)acetamido-2, 5-dimethylpyrroles(II) :

A mixture of acetonyl acetone (.003 mole) and aryloxy (or thio)acetylhydrazine (.002 mole) was refluxed in 50 ml of ethanol in the presence of few drops of glacial acetic acid for 6 hr. The crystalline solid obtained on cooling was filtered, dried and recrystallised from ethanol. The compounds thus prepared are recorded in Table 2.

The I.R. spectra of compounds(II) show bands at 3200-3260 cm^{-1} (–NH—str.), 2900-3000 cm^{-1} (CH-str.) and 1640-1680 cm^{-1} (C=O of sec-amide).

Pharmacology :

Compounds recorded in Table 3 were examined for their hypoglycemic and CNS activities as well as toxicity test in the Department of Pharmacology, C.D.R.I., Lucknow.

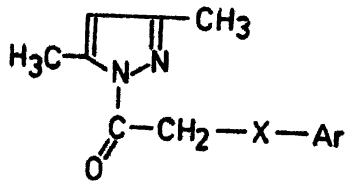
Hypoglycemic Activity :

Albino rats weighing between 200 and 250 gms were kept on fast for 10 hrs (water was allowed ad lib). Fasting blood samples were drawn from the tail vein and their glucose contents were estimated by *Nelson-somogyi method.* The compounds under test were administered to rats at a dose of 250 mg/kg body weight. Blood samples were again taken at intervals of 1, 2 and 4 hr and their glucose contents were estimated. Results are summarised in Table 3.

CNS activity :

For toxicity test, the compounds No. 1,4,16,17,18 (Tables 1 and 2) were administered intraperitoneally to albino mice of either sex in different doses and an approximate lethal dose in 50% of animals tested (ALD_{50}) was determined by conventional method[12]. ALD_{50} of the above compounds was quite high,

TABLE 1—N^1-ARYLOXY (OR THIO)ACETYL-3,5-DIMETHYL-PYRAZOLES*

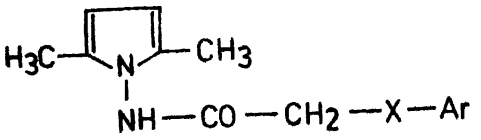


I

Compound No.	Ar	X	Molecular formula	M.P.°C
1.	4-$CH_3C_6H_4$	O	$C_{14}H_{16}N_2O_2$	155
2.	2-$CH_3C_6H_4$	O	$C_{14}H_{16}N_2O_2$	145
3.	4-ClC_6H_4	O	$C_{13}H_{13}N_2O_2Cl$	178
4.	2,4-$(Cl)_2C_6H_3$	O	$C_{13}H_{12}N_2O_2Cl_2$	142
5.	4-$NO_2C_6H_4$	O	$C_{13}H_{13}N_3O_4$	175
6.	4-$CH_3CONHC_6H_4$	O	$C_{15}H_{17}N_3O_3$	205
7.	α-$C_{10}H_7$	O	$C_{17}H_{16}N_2O_2$	134
8.	β-$C_{10}H_7$	O	$C_{17}H_{16}N_2O_2$	158
9.	4-ClC_6H_4	S	$C_{13}H_{13}N_2OSCl$	112

* Analyses for nitrogen were found within ±0.4% of theoretical values and yields varied between 60 to 70%.

TABLE 2—N-ARYLOXY (OR THIO)ACETAMIDO-2,5-DIMETHYLPYRROLES+



II

Compound No,	Ar	X	Molecular formula	M.P.°C
10.	4-$CH_3C_6H_4$	O	$C_{15}H_{18}N_2O_2$	164
11.	2-$CH_3C_6H_4$	O	$C_{15}H_{18}N_2O_2$	145
12.	4-ClC_6H_4	O	$C_{14}H_{15}N_2O_2Cl$	215
13.	2,4-$(Cl)_2C_6H_3$	O	$C_{14}H_{14}N_2O_2Cl_2$	173
14.	4-$NO_2C_6H_4$	O	$C_{14}H_{15}N_3O_4$	183
15.	4-$CH_3CONHC_6H_4$	O	$C_{16}H_{19}N_3O_3$	225
16.	α-$C_{10}H_7$	O	$C_{18}H_{18}N_2O_2$	145
17.	β-$C_{10}H_7$	O	$C_{18}H_{18}N_2O_2$	169
18.	4-ClC_6H_4	S	$C_{14}H_{15}N_2OSCl$	162

+ Analysed satisfactorily for nitrogen and the yields ranged between 55 to 62%.

TABLE 3—PHARMACOLOGICAL SCREENING DATA

Compound No.	ALD_{50} mg/kg wt of mice	Gross CNS observation at the dose of 464 mg/kg				Gross CNS observation at the dose of 1/5th of ALD_{50}				Blood sugar lowering		
		SMA	React	writh	Pilo	SMA	React	writh	Hypoth °C	Dose mg/kg	In vivo test route of administration	Response %
1.	>1000	↑	↑	(+)	(+)	↑	↑	(+)	(–)	–	–	–
4.	1000	↑	↑	(+)	(–)	(–)	(–)	(+)	1.6	–	–	–
16.	681	↑	↑	(+)	(+)	↑	↑	(+)	1.0	–	–	–
17.	825	↑	↑	(+)	(+)	↑	↑	(+)	(–)	250	oral	9
18.	1000	↑	↑	(+)	(–)	(–)	(–)	(+)	0.4	–	–	–
2.	–	–	–	–	–	–	–	–	–	250	oral	6
5.	–	–	–	–	–	–	–	–	–	,,	,,	6
8.	–	–	–	–	–	–	–	–	–	,,	,,	16
10.	–	–	–	–	–	–	–	–	–	,,	,,	9
11.	–	–	–	–	–	–	–	–	–	,,	,,	0

↑ =Increased ; (+)=Present ; (–)=Not effected ; SMA=Spontaneous motor activity ; React=Reactivity ; Writh=Writhing ; Pilo=Piloerection ; Hypoth=Hypothermia ; – =not done.

which showed their relative non-toxicity. These compounds, when tested for their antielectroshock seizure protection and anorexigenic activities at 1/5th of the ALD_{50}, were found inactive. They, however, affected the animals in their gross CNS behaviour. In general, all of them induced stimulations on CNS (SMA and reactivity increased) and writhing. Hypothermia ranged between 0.4 to 1.6°. Results are discussed in Table 3.

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References

1. W. Milton, U. S. 3, 291640, Dec, 27 (1966); *Chem. Abs.*, 1967, **66**, 85786.
2. G. Zenaida and B. Cornelia, *Rev. Med.*, 1971, **17** (3-4), 415 (Rom); *Chem. Abs.*, 1972, **76**, 15366.
3. T. Irikura, (Kyorin, Pharmaceutical Co. Ltd.) *Belg.* 829, 785; *Chem. Abs.*, 1977, **86**, 89810.
4. B. Lotti and O. Vezzosi, *Formaco. Ed. Sci.* 1972, **24**(4), 317 (Ital); *Chem. Abs.*, 1972, **77**, 48127.
5. Z. Budesinsky, A. Emr., V. Musil, Z. Perina and E. Zikmund, *Ceskoslov. Farm.*, 1960, **9**, 179-82; *Chem. Abs.*, 1961, **55**, 10495.
6. *Fr. Pat.* M. 6416 (to Laboratories Anphar) 2 Dec. 1968; *Chem. Abs.*, 1971, **74**, 100413.
7. S. Shoji and O. Sachio, *J. Med. Chem.*, 1977, **20**, 80.
8. R. C. John, N. M. Doris and W. Stewart; *J. Med. Chem.*, 1971, **14**, 646.
9. Janicchung-Chinchao and P. T. Peter, *Rec. Trav. Chim.*, 1949, **68**, 506; *Chem. Abs.*, 1950, **44**, 1044.
10. L. Conti, *Bull. Sci. Fac. Chim. Ind. Bolonga*, 1964, **22**(1), 13-15, *Chem. Abs.*, 1964, **61**, 4253.
11. M. Nasir, Ph.D. Thesis, Lucknow University 1977, p. 124.
12. C. S. Weil, *Biometrics*, 1952, **8**, 249.

Piperazine-1,4-bis-Salts of 2-mercapto, 3,6,8-trisubstituted-quinazolin-4(3H)-ones as Anti-inflammatory Agents

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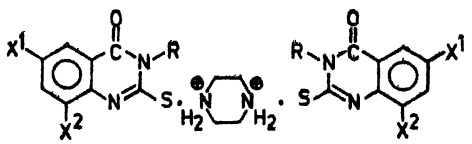
1,4-SUBSTITUTED-PIPERAZINE compounds have been reported[1] to possess potent anti-inflammatory activity. Further, a potent anti-inflammation in some quinazolinones is well established[2]. 'Thiol' group containing compounds have, further, been found to possess enhanced anti-inflammatory activity[3]. These observations led us to prepare piperazine-1,4-bis-salts of 2-mercapto, 3,6,8-trisubstituted-quinazolin-4(3H)-ones as anti-inflammatory agents.

Experimental

Aryl(Alkyl)-isothiocyanates[4], *5-Bromo-anthranilic acid and 3,5-dibromo-anthranilic Acid*[5]; *5-Iodoanthranilic acid*[6] *and 3,5-Dichloro-anthranilic acid*[7] were prepared by the conventional methods. *2-Mercapto-3-aryl(alkyl)-6,8-disubstituted-quinazolinones* have been synthesised by the procedure given by Dave *et al*[8].

Piperazine-1,4, bis-salts of 2-mercapto-3,6,8-trisubstituted-quinazolin-4(3H)-one were prepared by the method earlier reported by us[9]. The absence of a peak at 2550-2600 cm^{-1} indicates for the utilization of SH group in final step, forming salt with piperazine. A peak at 1500 cm^{-1} also confirms the formation of aforesaid amine salts. See Table-1 for relevant data of these piperazine 1,4-bis salts of the corresponding 2-mercapto-quinazolinones.

Table 1—Piperazine-1,4-bis-salts of 2-mercapto-3,6,8-trisubstituted quinazolin-4(3H)-ones



Compound Nos.	R	m.p.°C	ALD_{50} (mg/kg.wt. of mice)	Percentage protection
		$X^1=X_2=H$		
1.	$-C_6H_{11}$	292-293	316	8.4%
2.	$-C_6H_5$	266-68		
3.	$p.CH_3.C_6H_4-$	242-244		
4.	$p.OCH_3.C_6H_4-$	235-236	1000	33.7%
		$X^1=X^2=Br$		
5.	$-C_6H_{11}$	290-292	100	34.2%
6.	$-C_6H_5$	>300		
7.	$p.CH_3.C_6H_4-$	>300		
8.	$p.OCH_3.C_6H_4-$	298-300		
		$X^1=X^2=Cl$		
9.	$-C_6H_{11}$	198-200	464	30.4%
10.	$p.CH_3.C_6H_4-$	267-68		
		$X^1=H$; $X^2=Br$		
11.	$-C_6H_{11}$	245-46		
12.	$-C_6H_5$	285-86		
13.	$p.CH_3.C_6H_4-$	295-96		
14.	$p.OCH_3.C_6H_4-$	>300	>1000	28.4%
		$X^1=H$, $X^2=I$		
15.	$-C_6H_{11}$	298-99	262	43.6%
16.	$-C_6H_5$	252-53		
17.	$p.CH_3.C_6H_4$	>300		
18.	$p.OCH_3.C_6H_4-$	>300		

The m.p are uncorrected. Analyses for N, C, H and S gave percentage error- ±0.5% of the theoretical values.