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Synthesis and Anti-Inflammatory and Analgesic Activities of 2,4-Di-n-butyl-3,5-diarylimino-1,2,4-thiadiazolidines

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Abstract □ Ten 1,2,4-thiadiazolidines were synthesized and screened for their anti-inflammatory and analgesic activities. Butyl isothiocyanate was used as a starting material. Several compounds showed significant anti-inflammatory and analgesic activities. The unsubstituted and *o*-methyl, *p*-acetoxy and *o*-chloro substituted compounds were found to be more potent anti-inflammatory and analgesic agents than the other compounds.

Keywords □ *Anti-inflammatory, analgesic activity, thiadiazolidine.*

Heterocyclic compounds having thiadiazole moieties exhibit a wide spectrum of biological activities which include anti-convulsants and β-blocking activities[1], anti-inflammatory and analgesic activities[2] and diuretic activities[3].

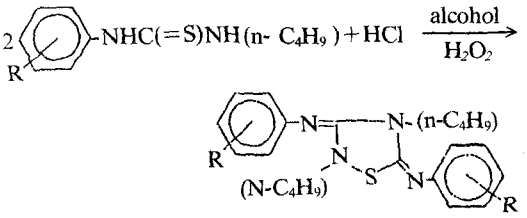
Since the 1,2,4-thiadiazoles had been little investigated for their biological properties it was thought pertinent to synthesize several 1,2,4-thiadiazolidines and screen them for their anti-inflammatory and analgesic activities. The selection of the butyl group was made because of its high lipoidal character. Compounds were synthesized by the oxidation of 1-n-butyl-3-aryl-thioureas with hydrogen peroxide in acidic medium. Vide Scheme 1 and 2.

EXPERIMENTAL METHODS

Materials

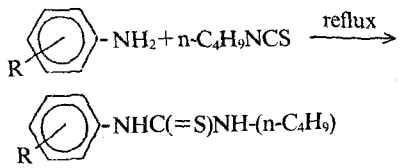
The amines were procured from BDH, India and solvents from Glindia and G.S. Fine Chemicals, India. Butyl isothiocyanate was prepared by methods described in the literature[4]. The required 1,3-dialkyl thioureas were prepared by the interaction of butyl isothiocyanate and aryl amines[5].

Melting points were determined in capillaries on Buchi melting point apparatus and were uncorrected. IR Spectra were measured on a Perkin-Elmer 720 spectrophotometer.



where, R=H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 4-Br, 3-OCH_3 and 4-CO · CH_3

Scheme 1. Preparation of 1,2,4-thiadiazolidines. (Christophersen, 1975)



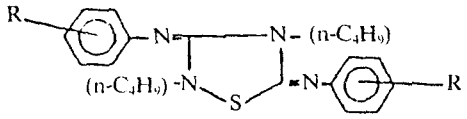
where, R=H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 4-Br, 3-OCH_3 and 4-CO · CH_3

Scheme 2. Preparation of N-alkyl-N'-arylthiourea.

Preparation of 2,4-di-n-butyl-3,5-di(4-chlorophenyl-imino)-1,2,4-thiadiazolidine[6]

The solution of 1-n-butyl,3-(4-chlorophenyl)-thiourea (0.05 mol) in 150 m*l* of ethanol containing conc. hydrochloric acid (0.15 mol) was oxidized by hydrogen peroxide (0.1 mol). The solution was then cool-

Table I. 1,2,4-thiodiazolidines



Compd. No.	R	Mol. formula	m.p. (°C)	Yield (%)	Partition coeff. at pH 7.4	λ Max
1.	H	$C_{22}H_{28}N_4S$	98	48	1.41	280
2.	o-Cl	$C_{22}H_{26}N_4SCl_2$	125	60	3.20	265
3.	m-Cl	$C_{22}H_{26}N_4SCl_2$	97	40	3.32	283
4.	p-Cl	$C_{22}H_{26}N_4SCl_2$	138	70	3.40	302
5.	p-Br	$C_{22}H_{26}N_4SBr_2$	186	64	3.68	295
6.	m-OCH_3	$C_{24}H_{32}N_4O_2S$	95	46	1.60	300
7.	p-$COCH_3$	$C_{26}H_{32}N_4O_2S$	106	76	4.20	305
8.	o-CH_3	$C_{24}H_{32}N_4S$	130	40	1.94	290
9.	m-CH_3	$C_{24}H_{32}N_4S$	146	45	1.80	285
10.	p-CH_3	$C_{24}H_{32}N_4S$	154	65	1.95	302

Table II. Anti-inflammatory activities of 1,2,4-thiadiazolidines

Compounds No.	Edema inhibition after 1 hour (%)	"t" value
1.	74.14	7.50**
2.	65.52	6.02**
3.	53.25	4.38*
4.	22.48	1.96
5.	38.66	3.37*
6.	32.92	2.95
7.	69.62	6.08**
8.	79.52	7.68**
9.	31.45	2.93
10.	23.25	1.92
Naproxen	87.14	9.28***

No. of animals: 4, dose: 10 mg/kg, body weight, *p< 0.05, **p<0.01, ***p<0.001.

Table III. Analgesic activities of 1,2,4-thiadiazolidines

Compounds No.	Latent period of tail flick response (sec.) Control (± S.E.)	Treated (± S.E.)	"t" value
1.	3.44 (± 0.07)	5.29 (± 0.69)	3.84**
2.	4.56 (± 0.21)	5.48 (± 0.51)	3.02**
3.	4.52 (± 0.39)	5.12 (± 0.25)	2.79*
4.	3.94 (± 0.16)	4.76 (± 0.78)	1.29
5.	4.40 (± 0.45)	5.24 (± 0.85)	0.91
6.	3.92 (± 0.13)	4.27 (± 0.46)	1.54
7.	4.00 (± 0.52)	5.38 (± 0.35)	3.51**
8.	4.42 (± 0.42)	5.14 (± 0.28)	2.82*
9.	3.06 (± 0.52)	3.92 (± 0.65)	1.50
10.	4.26 (± 0.43)	5.58 (± 0.54)	2.77*
Aspirin	3.48 (± 0.36)	5.18 (± 0.38)	6.20***

No. of animals: 5, dose: 10 mg/kg, body weight, *p<0.05, **p<0.01, ***p<0.001.

ed and washed with carbon disulphide and distilled water to remove the precipitated sulphur. The aqueous acidic extract was basified with ammonia solution to give the product, which was crystallized from ethanol, (yield: 70%). Other compounds were prepared in a similar manner given above (physical data: Table I).

Biological evaluation

a) Anti-inflammatory activity: The anti-inflammatory activity was studied by Carrageenin-induced edema in the paw of albino rats of either sex on a plethysmograph[7,8]. Solutions of compounds in propylene glycol were administered in rats at a dose of 10 mg/kg (*i.p.*). The edema was induced in the left paw of rats by injecting Carrageenin solution and the percentage of edema inhibition was observed after one hour. Results were compared with the standard drug Naproxen. The statistical analysis was

done by Dunnetts *"t"* test[9-11] (Table II).

b) Analgesic activity: The synthesized compounds were screened for their analgesic activity by rat hot wire technique[12,13], with a cut off time of 30 seconds in albino rats of either sex. Solutions of compounds in propylene glycol were administered in rats at a dose of 10 mg/kg (*i.p.*). and the tail flick response was observed after one hour. Results were compared with the standard drug Aspirin. Statistical analysis was done by Students *"t"* test. (Table III).

RESULTS AND DISCUSSION

a) Anti-inflammatory activity: The decrease in paw volume (percent inhibition) was observed after 1 hr. Compounds with the *o*-methyl substitution showed the highest percent of edema inhibition. Unsubstituted, *o*-chloro and *p*-acetoxy substituted compounds also gave highly significant results. Compounds with *m*-chloro and *p*-bromo substitutions showed significant anti-inflammatory activities. Percent edema inhibition of the compounds was found between 20-80%.

b) Analgesic activity: The latent periods of tail flick response of rats were observed after 1 hour of drug administration. The unsubstituted as well as the *o*-chloro and *p*-acetoxy substituted compounds showed highly significant analgesic activities. Compounds with *m*-chloro, *o*-methyl and *p*-methyl substitution also showed significant activities.

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