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

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The titled compounds have been synthesized by the oxidative cyclization of N-ethyl-N'-aryl-thioureas and screened for their anti-inflammatory and analgesic activities. Some of the compounds exhibit significant activities.

Key words: Thiadiazolidines, Anti-inflammatory, Analgesic

INTRODUCTION

Thiadiazoles are reported to have diverse range of biological activities including anti-inflammatory and analgesic activities (Puglisi *et al.*, 1989; Pandeya *et al.*, 1988). It was, therefore, considered 1,2,4-thiadiazole derivatives and screen them for anti-inflammatory and analgesic activities. The present paper, thus, reports the synthesis of eleven 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines by the oxidative cyclization of N-ethyl-N'-arylthioureas as shown in Scheme 1 and the profile of their anti-inflammatory and analgesic activities.

EXPERIMENTAL METHODS

Materials

Amines are BDH, India products. Ethyl isothiocyanate and thioureas were prepared according to reported methods (Deuins *et al.*, 1948; Schroeder, 1955).

Melding points were determined on Büchi melting point apparatus and uncorrected. UV and IR spectra were recorded on Cary-14 and Perkin-Elmer-823 spectrophotometers, respectively. NMR spectra were recorded on Jeol Fx 90 spectrometer in $CDCl_3$ using TMS as an internal standard. Partition coefficient was determined by the reported method (Chandra *et al.*, 1980).

Synthesis of 2,4-diethyl-3,5-di(4'-methoxyophenyl) imino-1,2,4-thiadiazolidines (Christophersen *et al.*, 1975)

To a stirred solution of N-ethyl-N'-(4'methoxyphenyl) thiourea (10.5 g, 0.05 M) and Conc. HCl (36%, 12.9 ml, 0.15 M) in ethanol (50 ml) was added slowly aquous solution of sodium nitrite (6.9 gm, 0.1 M in 25 ml of water). The precipitated sulphur was filtered and the filtrate was added dropwise to ammonia solution poured in ice. The precipitate was washed with distilled water and recrystallised from ethanol to give **IIc**. The other compounds **IIa**, **IIb**, **IId-k** were prepared by same method. The physical data are given in Table I.

(a) Anti-inflammatory Activity: It was studied by carrgeenin induced edema in the paw of albino rats of either sex on a plethylsmograph (Winter *et al.*, 1962; Haris *et al.*, 1962). The propylene glycol solution of compounds 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 1% carrageenin solution and the percentage of edema inhibition was observed after three hours. Ibuprofen was used as a standard drug for comparison. The statistical analysis was done by two way annova and student 't' test (Sandford, 1984; Youden *et al.*, 1967) (Table II).

(b) Analgesic Activity: The compounds were tested for their analgesic activities by rat hot wire technique with a cut-off time of 30 seconds in albino rats of either sex (Davis *et al.*, 1946). The tail-flick response was observed after one hour of administering the propylene glycol soulution of compounds at 10 mg/kg does level. Comparisons were made using aspirin and pentazocine as standard drugs. The statistical analysis was done as in previous cases (Sandford, 1984; Youden *et al.*, 1967).

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Table I. Physical data of 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines

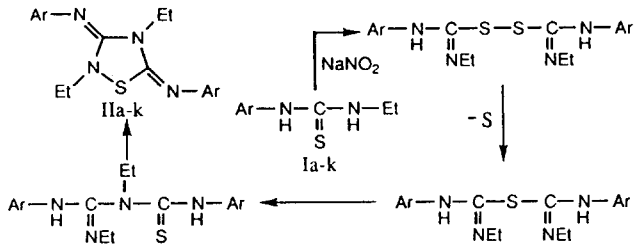
Compound No.	Ar	Mol. formula[+]	M.P. (°C)	Yield (%)	Partition coefficient
IIa	C_6H_5	$C_{18}H_{20}N_4S$	82-84	58.2	5.89
IIb	4'-$CH_3 \cdot C_6H_4$	$C_{20}H_{24}N_4S$	129-130	51.6	2.62
IIc	4'-$CH_3O \cdot C_6H_4$	$C_{20}H_{24}N_4O_2S$	109-110	44.6	5.02
IId	4'-$C_2H_5O \cdot C_6H_4$	$C_{22}H_{28}N_4O_2S$	106-109	51.2	2.72
IIe	4'-$CH_3CO \cdot C_6H_4$	$C_{22}H_{24}N_4O_2S$	117-119	30.3	3.89
IIf	4'-$Cl \cdot C_6H_4$	$C_{18}H_{18}N_4SCl_2$	138-139	52.4	4.76
IIg	4'-$Br \cdot C_6H_4$	$C_{18}H_{18}N_4SBr_2$	148-150	46.5	2.64
IIh	3'-$CH_3 \cdot C_6H_4$	$C_{20}H_{24}N_4S$	132-133	40.5	2.12
IIi	3'-$CH_3O \cdot C_6H_4$	$C_{20}H_{24}N_4O_2S$	121-123	40.3	2.42
IIj	3'-$Cl \cdot C_6H_4$	$C_{18}H_{18}N_4SCl_2$	136-138	36.7	3.04
IIk	2'-$CH_3O \cdot C_6H_4$	$C_{20}H_{24}N_4O_2S$	107-109	39.2	2.10

[+] The elemental analyses were found in the range of ± 0.3

Table II. Anti-inflammatory and analgesic activities of 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines

Compound No.	Edema inhibition (%) after 3 hours mean (± S.E.)	Latent period of tail flick response (sec.) after 1 hours Control (± S.E.)	Treated (± S.E.)
IIa	38.73(± 1.77)**	4.06(± 0.14)	6.66(± 0.39)**
IIb	30.58(± 1.60)*	4.06(± 0.18)	5.92(± 0.10)*
IIc	41.42(± 1.55)**	4.26(± 0.30)	6.72(± 0.34)**
IId	5.30(± 1.92)	4.12(± 0.22)	4.60(± 0.23)
IIe	40.35(± 2.06)**	4.30(± 0.26)	6.66(± 0.22)**
IIf	30.90(± 2.59)**	4.10(± 0.14)	6.40(± 0.29)**
IIg	6.19(± 2.66)	4.00(± 0.26)	4.52(± 0.24)
IIh	4.26(± 1.67)	4.30(± 0.26)	4.48(± 0.25)
IIi	35.19(± 1.67)**	4.20(± 0.10)	5.50(± 0.22)*
IIj	22.67(± 1.58)*	4.08(± 0.14)	5.16(± 0.21)
IIk	11.46(± 1.59)	4.02(± 0.17)	4.62(± 0.12)
Ibuprofen	59.19(± 2.36)***		
Aspirin		4.34(± 0.20)	6.70(± 0.22)**
Pentazocine		4.32(± 0.20)	12.00(± 0.14)***

Number of animals=10; Dose=10 mg/kg, i.p.; *p<0.05, **p<0.01, ***p<0.001



Scheme 1.

RESULTS AND DISCUSSION

The oxidative cyclization of thiourea leads to desired compounds which have been characterised on the basis of satisfactory elemental analyses and spectral data. The UV spectra of all the compounds showed λ_{max} at 285± 5 nm. The IR spectra exhibtied characteristic bands of imino bond at 1610± 5 cm^{-1}. The proton NMR spectra displayed the aromatic protons in the range of δ 6.80-7.33 ppm. The methyl and methylene protons of ethyl group were observed as triplet at δ 1.15 ppm. (J=7 Hz) and quartet at δ 3.65 ppm. (J=7 Hz), respectively.

Biology

(a) Anti-inflammatory Activity: The results listed in Table II indicate that compound **IIc** having *p*-anisyl group is the most potent compound with 41.42% edema inhibition which is highly significant. The compound **IIh** with *p*-tolyl group is the least potent with 4.26% inhibition. Among others, compounds **IIa**, **IIe**, **IIf** and **IIi** are also having highly significant activities. There does not appear any correlationship between the activity and electron withdrawing or releasing nature of substituents. However, among particular substituents the orientation of group seems to play important role as in the case of **IIc**, **IIi** and **IIk** having 4'-, 3'-and 2'-methoxy group, respetively on phenyl

ring the 4'-methoxy is the most active followed by 3'- and 2'-methoxy substituted. The partition coefficient seems to be related with the activity. The compounds having high partition coefficient are having high activity.

(b) Analgesic Activity: As analgesic also, compound **IIc** is the most potent in the series showing activity almost parallel to aspirin. It is followed by **IIa** with unsubstituted phenyl ring, **IIe** with acetyl group and **IIf** with 4'-chloro substituted phenyl ring. Statistically, these three compounds from same class but they are different according to the magnitude of their activities. Other compounds are almost inactive. A perusal of analgesic activity reported earlier in thiadiazolidine derivatives with methyl group at 2,4-position indicate that the present series of compounds with unsubstituted phenyl ring and with 4'-methoxyphenyl ring are more active.

CONCLUSIONS

1. It can be inferred from this study that the compound with *p*-anisyl substituent is the most potent and can be further investigated with different alkyl and aryl substituents at 2',4'-positions to get a better insight into the biological activity of such compounds.
2. The other important conclusion is about the effect of orientation of group that is among particular groups *p*-substituted ring is having highest activity.
3. The compounds with high partition coefficient are having higher activity and vice-versa.

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