SYNTHESIS AND CNS ACTIVITY OF N, N-DIALKYLAMINO-ETHYL-(5′-SUBSTITUTED 1′, 3′, 4′-THIADIAZOLYL-2′-SUBSTITUTED-AMINO)-DITHIOCARBAMATES AND THEIR METHIODIDES

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SOME new sodium-(5-substituted-1, 3, 4-thiadiazolyl-2-substituted amino) dithiocarbamates (I) were synthesised by the reaction of carbon disulphide with the corresponding 5-substituted amino-1, 3, 4-thiadiazoles in NaOH. The reaction of (I) with N, N-dialkylamino ethyl chloride gave N, N-dialkyl amino ethyl-(5′-substituted-1′, 3′, 4′-thiadiazolyl-2′-substituted amino)-dithiocarbamates (II). The dialkyl amino ethyl group was quaternised under mild conditions to get the corresponding methiodides (III). The composition of these compounds has been confirmed by elemental percentage analyses. The compounds are CNS excitants. Anti-tremorine and analgesic properties were also tested in these compounds, but these were negative.

Anti-cholingergics are usually recommended in the diseases of extrapyramidal system of brain. According to Marxer and Schier[1], anticholinergics were among the first antiparkinsonian agents. Ahmed and Marshall[2] and Das and Ganguli[3] have found a correlation between anticholinergic activity and antitremorine effect of anticholinergic drugs. Quaternary ammonium salts have shown varieties of reactions on CNS. Acetyl-choline, a quaternary ammonium compound, plays a complex role in neurotransmission. According to Burn and Rand[4], Burn and Gibbens[5], and Douglas[6], acetyl-choline may act as an intermediate in the release of dopaminergic transmitters from adrenergic terminals. The dopaminergic transmitters are inhibitory in their effect on CNS. Many anticholinergics are structurally related to acetyl-choline and have been found inhibiting various spasms and convulsions[7,8]. Some quaternary ammonium salts have also been reported to antagonise the parkinsonian features[9,10].

A change in acyl group of choline esters often changes their effect[11]. The introduction of aryl rings in the ester part of acetyl-choline, changes it to an anticholinergic agent. Kuznetov and Golikov[12] have described that sulphur containing 'thienyl' group increases the anticholinergic activity. Further, 2-substituted-amino-5-alkyl-1, 3, 4-thiadiazoles have been reported as anticholinergics[13], antiparkinsonian[14], anticonvulsant[15] and catecholamine potentiating[13] compounds. A few dithiocarbamates have been found to be active in minimising some parkinsonian features[16].

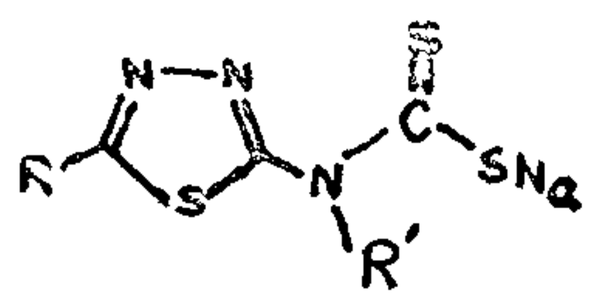
All these observations prompted the authors to synthesise new esters (III) of choline analogs, and to study their effects on CNS and parkinsonism, an extrapyramidal disorder.

2-Methylamino-5-alkyl-1, 3, 4-thiadiazoles were, synthesised by the method of Pulver[17]. 2-Methtyl-amino-5-phenyl-1, 3, 4-thiadiazole was synthesised by the method of De and Roy[18]. 2-Arylamino-5-methyl-mercapto-1, 3, 4-thiadiazoles were synthesised by the method of Busch and Biehler[19].

5-Substituted-1, 3, 4-thiadiazolyl-2-substituted amino, sodium dithiocarbamates (I) were prepared by shaking, for 50 hrs., the corresponding thiadi zole (0·02 mole) with CS_2 (0·04 mole) in 10% aqueous solution of NaOH (50 ml). The unreacted thiadiazole was filtered off and the orange coloured filtrate was distilled at 60° C as to eliminate unreacted CS_2. The solution was concentrated till orange crystals started appearing. The solution was kept at 5° C overnight and the crystals of 5-substituted-1, 3, 4-thiadiazolyl-2-substituted amino, sodium dithiocarbamates were collected. Table I describes their relevant data.

TABLE I

*5-Substituted-1, 3, 4-thiadiazolyl-2-substituted amino dithio sodium carbamates****



(I)

1. R = –H; R′ = CH_3 (>280, 0·86, 62)*.
2. R = –CH_3; R′ = –CH_3 (>280, 0·85, 60).
3. R = –C_2H_5; R′ = –CH_3 (>280, 0·87, 40).
4. R = –*n* . C_3H_7; R′ = –CH_3 (>280, 0·82, 45).
5. R = –*n* . C_4H_9 ; R′ = –CH_3 (>280, 0·92, 45).
6. R = –C_6H_5; R′ = –CH_3 (>280, 0·95, 32).
7. R = –SCH_3; R′ = –C_6H_5 (>280, 0·83, 55).
8. R = –SCH_3; R′ = *o* . CH_3–C_6H_4– (>280, 0·83, 55).
9. R = –SCH_3; R′ = *m* . CH_3–C_6H_4– (>280, 0·77, 48).
10. R = –SCH_3; R′ = *p* . CH_3–C_6H_4– (>280, 0·85, 50).

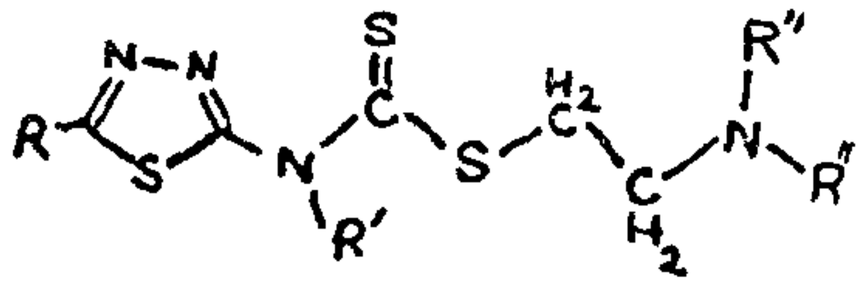
* Figures in brackets indicate m.p (° C), R_f value (100% methanol) and yield (%). The m.p. were taken in open capillaries and are uncorrected.

** All the compounds gave correct data for C, H, N and S elemental % analysis.

N, N-Dialkylaminoethyl-(5′-substituted-1′, 3′, 4′-thiadiazolyl-2′-substituted amino-dithiocarbamates (II)

TABLE II

*N, N-Dialkylaminoethyl, (5'-substituted-1', 3', 4'-thiadiazolyl-2'-substituted amino) dithiocarbamates***



(II)

11.	R = –H;	R′ = $-CH_3$;	R″ = $-CH_3$	(192, 0·45, 67)*.
12.	R = $-CH_3$;	R′ = $-CH_3$;	R″ = $-CH_3$	(200, 0·47, 60).
13.	R = $-C_2H_5$;	R′ = $-CH_3$;	R″ = $-CH_3$	(151, 0·50, 52).
14.	R = $-n \cdot C_3H_7$;	R′ = $-CH_3$;	R″ = $-CH_3$	(135–37, 0·55, 62).
15.	R = $-n \cdot C_4H_9$;	R′ = $-CH_3$;	R″ = $-CH_3$	(149, 0·52, 48).
16.	R = $-C_6H_5$;	R′ = $-CH_3$;	R″ = $-CH_3$	(161–62, 0·58, 58).
17.	R = $-SCH_3$;	R′ = $-C_6H_5$;	R″ = $-CH_3$	(132–33, 0·50, 65).
18.	R = $-SCH_3$;	R′ = $o \cdot CH_3-C_6H_4-$;	R″ = $-CH_3$	(139–40, 0·45, 50).
19.	R = $-SCH_3$;	R′ = $m \cdot CH_3-C_6H_4-$;	R″ = $-CH_3$	(149, 0·49, 68).
20.	R = $-SCH_3$;	R′ = $p \cdot CH_3-C_6H_4-$;	R″ = $-CH_3$	(156, 0·37, 55).
21.	R = $-C_6H_5$;	R′ = $-CH_3$;	R″ = $-C_2H_5$	(198, 0·42, 45).
22.	R = $-SCH_3$;	R′ = $-C_6H_5$;	R″ = $-C_2H_5$	(152, 0·35, 62).
23.	R = $-SCH_3$;	R′ = $o \cdot CH_3-C_6H_4-$;	R″ = $-C_2H_5$	(138–39, 0·44, 60).
24.	R = $-SCH_3$;	R′ = $m \cdot CH_3-C_6H_4-$;	R″ = $-C_2H_5$	(147, 0·43, 33).
25.	R = $-SCH_3$;	R′ = $p \cdot CH_3-C_6H_4-$;	R″ = $-C_2H_5$	(134, 0·37, 40)

* Figures in brackets indicate m.p. (° C), R_f values (Benzene/ethyl acetate; 90%: 10%) and yield. The m.p. were taken in open capillaries and are uncorrected.

** All the compounds gave correct data for C, H, N and S elemental % analysis.

were synthesised by refluxing the corresponding 5-substituted-1, 3, 4-thiadiazolyl-2-substituted amino, sodium dithiocarbamates (0·02 mole) with N, N-dialkyl amino ethyl chloride[20] in dry acetone on a steam bath for 3–4 hrs. The reaction mixture was cooled and filtered to eliminate NaCl formed. The filtrate was distilled off and the syrupy liquid, so obtained, was taken in ether. The ethereal layer was washed thrice with 5% NaOH and dried over anhydrous $MgSO_4$. The ether was distilled off and the residue was recrystallised from dry benzene. Various dithiocarbamates (II) synthesised in this way are listed in Table II.

Methiodides (III) of N, N-dialkylaminoethyl- (5'-substituted -1, 3', 4'-thiadiazolyl-2'substituted amino) dithiocarbamates were synthesised by refluxing, for 1 hr., the corresponding dithiocarbamate (II) (0·02 mole) and methyl iodide (0·03 mole) in dry methanol (20 ml). The reaction mixture was cooled in ice chest and the solid was filtered and recrystallised from methanol. The relevant data of methiodides are given in Table III.

Pharmacology.—Five final compounds (III) were screened for CNS activity and toxicity test.

For toxicity test, the compounds were administered intraperitoneally to albino mice of either sex in different doses and the approximate lethal doses in 50% of animals (ALD_{50}) were determined by the method of Weil[21]. ALD_{50} of the compounds are noted in Table III.

The compounds were also tested for anti-tremorine and analgesic activities at 1/5th of the ALD_{50}. No significant activity was found.

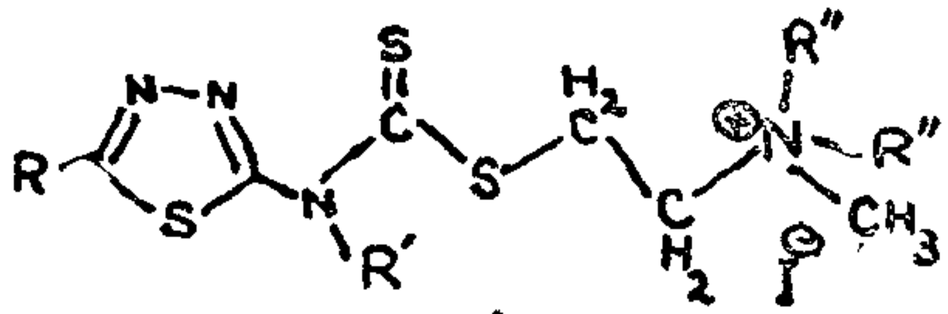
In gross CNS observations, the compounds were excitant. They induced writhing, and straub-tail (erection of tail) phenomena. Compounds No. 27, 36 and 38 induced tremor at the dose of 1000 mg/kg (intraperitoneally). Spontaneous motor activity and reactivity were increased at all doses, in mice treated with these compounds.

ACKNOWLEDGEMENT

Thanks are due to Dr. B. N. Dhawan, Professor and Head of Pharmacology Department, CDRI, Lucknow, for the pharmacological testing. The authors are also grateful to CSIR, New Delhi, for the award of the J.R.F. to one of them (R. K. S.).

TABLE III

*Methiodides of N, N-dialkylaminoethyl, (5′-substituted-1′, 3′, 4′-thiadiazolyl-2′-substituted amino)-dithiocarbamates***



(III)

26.	R = –H;	R′ = –CH_3;	R″ = –CH_3	(275, 0·07, ***)*.
27.	R = –CH_3;	R′ = –CH_3;	R″ = –CH_3	(272, 0·10, >1000).
28.	R = –C_2H_5;	R′ = –CH_3;	R″ = –CH_3	(>280, 0·16, ***)*.
29.	R = –*n* . C_3H_7;	R′ = –CH_3;	R″ = –CH_3	(245, 0·30, ***).
30.	R = –*n* . C_4H_9;	R′ = –CH_3;	R″ = –CH_3	(269, 0·12, ***).
31.	R = –C_6H_5;	R′ = –CH_3;	R″ = –CH_3	(>280, 0·14, ***).
32.	R = –SCH_3;	R′ = –C_6H_5;	R″ = –CH_3	(215, 0·15, 215).
33.	R = –SCH_3;	R′ = –*o* . CH_3–C_6H_4–;	R″ = –CH_3	(>280, 0·16, 38·3).
34.	R = –SCH_3;	R′ = *m* . CH_3–C_6H_4–;	R″ = –CH_3	(253, 0·21, ***).
35.	R = –SCH_3;	R′ = *p* . CH_3–C_6H_4–;	R″ = –CH_3	(259, 0·22, ***).
36.	R = –C_6H_5;	R′ = –CH_3;	R″ = –C_2H_5	(270, 0·10, 1000).
37.	R = –SCH_3;	R′ = –C_6H_5;	R″ = –C_2H_5	(>280, 0·11, ***).
38.	R = –SCH_3;	R′ = *o* . CH_3–C_6H_4–;	R″ = –C_2H_5	(255, 0·14, 1000).
39.	R = –SCH_3;	R′ = *m* . CH_3–C_6H_4–;	R″ = –C_2H_5	(>280, 0·14, ***).
40.	R = –SCH_3;	R′ = *p* . CH_3–C_6H_4–;	R″ = –C_2H_5	(>280, 0·17, ***).

* Figures in brackets indicate m.p. (°C), R_f values (Benzene/methanol; 90%: 10%), and ALD_{50} (mg./kg.). m.p. were taken in open capillaries and are uncorrected. Yield ranged between 70–80%.

** All the compounds gave correct data for C, H, N and S elemental % analysis.

*** ALD_{50} of these compounds not done.

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