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Note

Chemical Constitution and Anthelmintic Activity—VI. Some Diphenylamines and Mono- and Dicyclic Analogues of Phenothiazine

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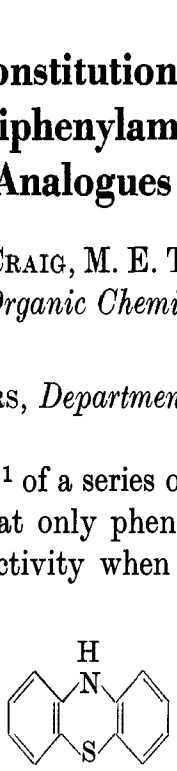
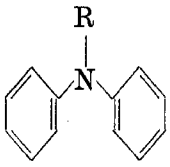
Examination[1] of a series of tricyclic analogues of phenothiazine (I) revealed that only phenothiazine and phenoxazine possessed anthelmintic activity when tested against mixed infestations of



(I)



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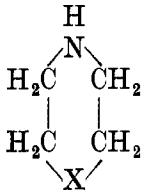

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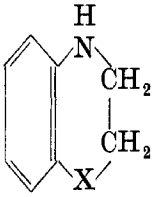

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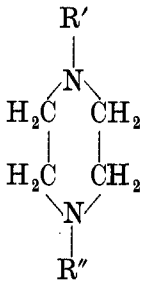

(V)

Syphacia obvelata and *Aspiculuris tetraptera* in mice. It was of interest to investigate (*a*) diphenylamines (II), and (*b*) mono- and dicyclic analogues (III) and (IV) of phenothiazine to examine the minimal structural requirements for anthelmintic activity.

Materials and Methods

The synthesis of the new compounds used in this work has been described.[2,3] All samples were of analytical purity.

The method of biological assay and the assessment of results is as previously described.[4]

Results

Diphenylamine (II) has been reported[1, 5] to possess only slight anthelmintic activity. Twenty-seven diphenylamines were examined, and the results are shown in Table I.

Table I. Anthelmintic activity of substituted diphenylamines at 2 g/kg

Laboratory reference no.	Diphenylamine derivative	Anthelmintic activity
3	Diphenylamine	0
49	4-Methyl-	±
40	4-Amino-	0[a]
42	4-Nitro-	±
56	4-Methoxy-	0
57	4-Triphenylmethyl-	0
60	4-Chloro-	+
47	2-Carboxy-	0
48	2-Nitro-	0
39	2,3-Benzo-	±
41	3,4-Benzo-	±
76	2,4-Dinitro-	0
44	4,4′-Dimethyl-	+
65	4,4′-Dimethoxy-	±
58	4,4′-Bis(triphenylmethyl)-	0
45	3,4,3′,4′-Dibenzo-	0
61	2,3,2′,3′-Dibenzo-	0
74	4,4′-Dichloro-	+
77	2,4,2′,4′-Tetrabromo-	0
53	*N*-Nitroso-	0
51	*N*-Formyl-	±
50	*N*-Acetyl-	0
55	*N*-Methyl-	±
54	*N*-Methyl-4,4′-dimethyl-	0[b]
59	*N*-Acetyl-4,4′-dimethyl-	±
66	*N*-Formyl-4,4′-dimethyl-	0
72	*N*-Benzoyl-	0

[a] Toxic at 2 g/kg and 1 g/kg; tested at 0·5 g/kg.
[b] Toxic at 2 g/kg and 1 g/kg.

These substances do not form stable semiquinones and presumably act by a totally different mechanism from that of the phenothiazines.[4, 6] Although several of the compounds (Nos. 44, 60 and 74) had appreciable activity, their increased toxicity to the host did not warrant further investigation. No clear correlation of structure and activity emerges in this series.

Dicyclic analogues of phenothiazine comprised 1,2,3,4-tetrahydroquinoxaline (IV; X = NH), 3,4-dihydrobenzoxazine (IV, X = O), and 2,3-dihydrobenzo-1,4-thiazine (IV; X = S). All were toxic to the host at 2 g/kg and were not investigated further.

Table II. Anthelmintic activity of substituted piperazines at 2 g/kg

Laboratory reference no.	Derivative of piperazine	Anthelmintic activity
86	Piperazine	++
100	1-Methyl-	±
91	1,4-Dimethyl-	0
95	1-Carbethoxy-	0[a]
97	1-Benzyl-	—[b]
98	1,4-Dibenzyl-	—[b]
109	1-(β-Hydroxyethyl)-	±
108	1,4-Di(β-hydroxyethyl)-	0
111	1-(β-Methoxyethyl)-	0
107	1,4-Di(β-methoxyethyl)-	0

[a] Toxic at 2 g/kg; tested at 0·1 g/kg.
[b] Toxic at 2 g/kg.

Monocyclic analogues included neutral salts of morpholine (III; X = O), piperidine (III; X = CH_2), tetrahydro-1,4-thiazine (III; X = S) and piperazine (III; X = NH). Of this group, only the last displayed anthelmintic activity, in agreement with the results of Brown, Chan and Hussey.[7] A total of ten substituted piperazines (V) were therefore tested as neutral salts, by the method previously described; the results are summarized in Table II.

All disubstituted piperazines were inactive, and of the monosubstituted derivatives, only the 1-methyl and the 1-(β-hydroxyethyl) compounds (Nos. 100 and 109) showed activity, although

appreciably less than that of piperazine itself. Brown, Chan and Hussey[7] reported, from an examination of 32 substituted piperazines, that none exceeded the activity of the parent substance, and Harfenist[8] described the preparation of 100 piperazine monoquaternary salts and their activity[9] against *Syphacia obvelata* in mice, given orally. A maximum in the therapeutic index was found to occur at about the 1-methyl-1-tridecyl- or -tetradecylpiperazinium halides, in which the therapeutic index approached, but did not exceed, that of piperazine itself.[7] When the alkyl substituent was larger than this, inconsistent results were obtained.

It was not possible to make any deductions concerning the relation of structure to therapeutic index, and attempts to correlate either the surface tensions or the oil–water partition coefficients of these cationic substances with their anthelmintic actions proved unsuccessful.[9] It has been shown[10] that piperazine causes paralysis of *Ascaris lumbricoides* by blocking the response of the neuromuscular junction to acetylcholine, and this may account for the therapeutic effectiveness of piperazine against *Ascaris*.

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