# ISOTHIOCYANATES WITH ANTHELMINTIC ACTIVITY*

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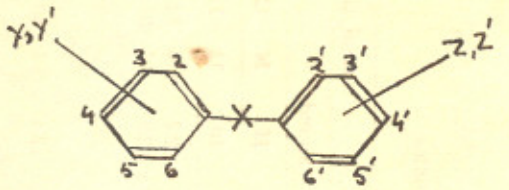
A series of di-(substituted phenyl)- sulphides, disulphides, sulphoxides, sulphones, ethers, methanes, ketones and ethylenes carrying an isothiocyanate moiety in one or both of the phenyl rings have been synthesized and screened for their anthelmintic activities. Diphenylsulphide-4, 4′ diisothiocyanate and diphenylsulphone-4, 4′diisothiocyanate were found to possess strong cestocidal activity.

Among the more important compounds claimed as effective cestocidal agents are dichlorophen and its esters,[1] chlorinated diphenylsulphones,[2] *N*-(2′-chloro-4′ nitro)-5-chloro salicylanilide (Yomesan)[3], halogenated thioureas,[4] *p*-phenylene diisothiocyanate,[5] 2, 4, 6-tribromo-3-acetamidophenol,[6] N, N-dimethyloctadecylamine hydrochloride[7] and isoxazoles.[8] Some of these compounds find application in veterinary medicine, but even today the drug of choice for the chemotherapy of cestode infections appears to be quinacrine.[9] Though more effective in *Taenia saginata* and *Diphyllobothrium latum* infections than the old remedy namely extracts of male fern (Aspidium oleoresin), quinacrine is less effective against *Hymenolepis nana* and in *Taenia solium* infection; there is a potential danger of producing cysticercosis when quinacrine is administered.[10] Because of the lack of a safe and effective drug against *Taenia solium* and *Hymenolepis nana*, and because of the need for a drug with less side-effects than quinacrine, the search for a cestocide continues.

The efforts in this Institute to develop an effective cestocide, having a greater margin of safety and less side-effects than the existing drugs, led us to synthesize and test a series of isothiocyanates. This work is based on the reported powerful anthelmintic action of aryl isothiocyanates particularly *p*-phenylene diisothiocyanate[5] on one hand and of di-(substituted phenyl) - methanes,[1, 11, 12] ethers,[11] sulphides[13, 14] sulphoxides[15] and sulphones on the other. It was considered of interest to synthesize and test compounds of the general formula (A) which incorporate both these features. The




(A)

synthesis of these compounds and their anthelmintic activity when tested against *H. nana* in rats[16] are presented in this paper.

These isothiocyanates were prepared by the reaction of thiophosgene in chloroform or benzene solution with an aqueous solution of the hydrochlorides of the corresponding amines. Those amines which were not commercially available were generally made by the catalytic reduction of the corresponding nitro compounds, prepared by known methods, except for 4-nitro-4′-aminodiphenylsulphone which was obtained by the acid hydrolysis of 4-nitro-4′-acetamidodiphenylsulphone.

The sulphide (1) and sulphone (4) (Table 1) were found to be the most active. Introduction of two sulphur atoms as in compound (2) or oxidation of the sulphide to sulphoxide in compound (3) lead to loss of activity. An extra substituent on one of the benzene rings of diphenylsulphone-4, 4′-diisothiocyanate as in compound (5) or replacement of one of the isothiocyanate moieties by an acetamide group (7) or a nitro group (6) also reduced the activity. Replacing the central sulphur atom by an oxygen (8) lowered the activity, but shifting the isothiocyanate moieties to the 2, 2′-positions in diphenylether (9) restored the

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TABLE 1

*Analytical data and anthelmintic activity of isothiocyanates*

| Sl. no. | X | Y | Y′ | Z | Z′ | Molecular formula | m.p. °C | Analysis | | | | | | MED.* mg/kg. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Found | | | Required | | | |
| | | | | | | | | C | H | N | C | H | N | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
| 1. | -S- | 4-NCS | -H | 4′-NCS | -H | $C_{14}H_8N_2S_3$ | 65 | 55.5 | 2.7 | 9.8 | 56.0 | 2.7 | 9.8 | 50 |
| 2. | -S-S- | 4-NCS | -H | 4′-NCS | -H | $C_{14}H_8N_2S_4$ | 63 | 50.3 | 2.9 | 8.8 | 50.6 | 2.4 | 8.4 | i |
| 3. | -SO- | 4-NCS | -H | 4′-NCS | -H | $C_{14}H_8N_2OS_3$ | 139 (Lit. 30, 138-40) | | | | | | | i |
| 4. | $-SO_2-$ | 4-NCS | -H | 4′-NCS | -H | $C_{14}H_8N_2O_2S_3$ | 180 (Lit. 31, 170-72) | 50.6 | 2.4 | 8.4 | 50.6 | 2.8 | 8.5 | 50 |
| 5. | $-SO_2-$ | 4-NCS | $2-OCH_3$ | 4′-NCS | -H | $C_{15}H_{10}N_2O_3S_3$ | 129 | 50.0 | 3.4 | 7.4 | 49.5 | 3.4 | 7.7 | 250 |
| 6. | $-SO_2-$ | 4-NCS | -H | $4′-NO_2$ | -H | $C_{13}H_8N_2O_4S_2$ | 145 | 48.6 | 2.9 | 8.2 | 48.6 | 2.5 | 8.7 | 250 |
| 7. | $-SO_2-$ | 4-NCS | -H | 4′-NHCO $CH_3$ | -H | $C_{15}H_{12}N_2O_3S_2$ | 176 | 54.9 | 4.2 | 8.1 | 54.2 | 3.6 | 8.4 | 250 |
| 8. | -O- | 4-NCS | -H | 4′-NCS | -H | $C_{14}H_8N_2OS_2$ | 60 | 59.2 | 3.2 | 9.5 | 59.1 | 2.8 | 9.8 | 250 |
| 9. | -O- | 2-NCS | -H | 2′-NCS | -H | $C_{14}H_8N_2OS_2.\frac{1}{2}H_2O$ | 55-57 | 57.2 | 3.0 | 9.7 | 57.3 | 3.1 | 9.6 | 100 |
| 10. | $-CH_2-$ | 4-NCS | -H | 4′-NCS | -H | $C_{15}H_{10}N_2S_2$ | 142 (Lit. 32, 143-144) | | | | | | | i |
| 11. | $-CH_2-$ | 4-NCS | $2-CH_3$ | 4′-NCS | $2′-CH_3$ | $C_{17}H_{14}N_2S_2$ | 129 | 65.3 | 4.2 | 9.1 | 65.8 | 4.5 | 9.0 | 250 |
| 12. | $-CH_2-$ | 4-NCS | $3-CH_3$ | 4′-NCS | $3′-CH_3$ | $C_{17}H_{14}N_2S_2$ | 95 | 66.2 | 4.8 | 8.7 | 65.8 | 4.5 | 9.0 | i |
| 13. | -CO- | 4-NCS | -H | 4′-NCS | -H | $C_{15}H_8N_2OS_2$ | 130 | 60.4 | 3.1 | 9.6 | 60.8 | 2.7 | 9.5 | 100 |
| 14. | -CO- | 4-NCS | $3-CH_3$ | 4′-NCS | $3′-CH_3$ | $C_{17}H_{12}N_2OS_2$ | 130 | 63.0 | 3.7 | 8.6 | 62.8 | 3.6 | 8.5 | i |
| 15. | -CH=CH- | 4-NCS | -H | 4′-NCS | -H | $C_{16}H_{10}N_2S_3$ | 132 | 65.5 | 3.9 | 8.9 | 65.3 | 3.4 | 9.5 | 250 |
| 16. | $-CH_2-CH_2-$ | 4-NCS | -H | 4′-NCS | -H | $C_{16}H_{12}N_2S_2$ | 130 | 64.9 | 4.5 | 9.9 | 64.9 | 4.1 | 9.5 | i |

* Minimum effective dose for 90% clearance of *Hymenolepis nana* in infected rats.

i: Ineffective at 250.

activity, though not to the level of the sulphone (4). When X was a methylene group (10), the resulting compound was inactive, but introduction of methyl groups in the 2, 2′-positions (11) rendered the compound active. However, shifting the methyl groups to the 3, 3′-positions (12) caused loss of activity. Oxidation of methylene to a ketonic function made the compound quite active (13), but introduction of extra methyl groups in the 3, 3′-positions gave inactive compound (14). When X was -CH=CH- an active compound (15) was obtained but saturation of the double bond (16) again caused loss of activity.

The sulphone (4) was chosen for further testing because of its high oral chemotherapeutic index which was about 250 in mice. Though it showed little activity *in vitro* it is remarkably active *in vivo;* a dose of 5 mg./kg. sufficed to clear mice infected with *H. nana* of all the parasites. Clinical trials on naturally infected dogs also showed encouraging results.[16] Further work on the synthesis and biological screening of related compounds is in progress.

## EXPERIMENTAL

All melting points are uncorrected.

*Preparation of amines:* 4, 4′-Diaminodiphenylsulphone used was the commercially available drug and 4, 4′-diaminodiphenylmethane was B.D.H. quality.

2-Methoxy - 4, 4′ - diaminodiphenylsulphone was the sample prepared by Vyas *et al.*[17] 2,2′-Dimethyl-4, 4′-diaminodiphenylmethane and the corresponding 3, 3′-dimethyl derivatives were prepared according to Wagner,[18] 4, 4′-diaminodiphenylsulphoxide by the method of Buu-Hoi *et al.*,[19] 4, 4′ diaminobenzophenone by the method of River *et al.*,[20] and 4, 4′-diamino-3, 3′-dimethylbenzophenone according to Barker *et al.*[21]

*4 - Nitro-4′-aminodiphenylsulphone*: 4-Nitro-4′-acetaminodiphenylsulphone[22] (10 g.) was refluxed for one hour with conc. hydrochloric acid (20 ml.). The reaction mixture was cooled and carefully basified with aqueous sodium hydroxide (10%). The solid which precipitated was filtered and crystallized from ethanol-water, yield 8.5 g., m.p. 169-70° (lit.[23] m.p. 167-9°).

*4 - Amino - 4′ - acetaminodiphenylsulphone:* 4 - Nitro - 4′ - acetaminodiphenylsulphone[22] (5 g.) suspended in ethanol (50 ml.) was shaken with Raney nickel (1 g.) and hydrogen at 35 lb./sq in. pressure in a Parr Hydrogenator. The catalyst was removed by filtration and solvent removed from the filtrate under reduced pressure. The residue crystallized from ethanol, yield 4.5 g., m.p. 240° (lit.[24] m.p. 242-3°). The same method was employed for the preparation of the diamines from 4, 4′-dinitrodiphenylsulphide,[25] 4, 4′-dinitrodiphenyldisulphide,[26] 4, 4′-dinitrodiphenylether,[27] 2, 2′-dinitrodiphenylether[27], 4, 4′-dinitrostilbene[28] and 4, 4′-dinitrodibenzyl.[29]

*Preparation of isothiocyanates:* The preparation of various isothiocyanates listed in Table 1 is illustrated by the preparation of diphenylsulphide 4, 4′-di*iso*thiocyanate.

*Diphenylsulphide 4, 4′-diisothiocyanate:* To a mechanically stirred solution of 4, 4′-diaminodiphenylsulphide (5 g.) in 4*N* hydrochloric acid (50 ml.), thiophosgene (4.3 ml., 2.2 mole) in chloroform (25 ml.) was added and mechanical agitation was continued until the reaction was complete, as judged by the disappearance of the orange colour of chloroform layer and the absence of smell of thiophosgene in the reaction mixture. The organic layer was separated, washed with water and dried ($Na_2SO_4$). Removal of solvent and crystallization of the residue from aqueous acetone gave diphenylsulphide 4, 4′-di*iso*thiocyanate (4 g.).

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