THE ANTIWORM ACTIVITY OF SOME NATURAL AND SYNTHETIC COMPOUNDS. III

THE ACTIVITY OF AROMATIC ISOTHIOCYANATES OF THE R-C_6H_4-X-C_6H_4NCS TYPE ON *TURBATRIX ACETI*

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Data are presented on the antiworm activity against *Turbatrix aceti* of 66 isothiocyanates derived from stilbene, azobenzene, arylalkylsulphides, diarylsulphides, arylalkylsulphones, diarylsulphones, as well as 4-terphenyl isothiocyanates, 4-phenoxyphenyl, diphenylmethane, and diphenylamine derivatives of isothiocyanates. A noteworthy activity against *T. aceti* has been found for 4-substituted phenoxyphenylisothiocyanates, 4-methylsulphidphenylisothiocyanates, 4-methylsulphonephenylisothiocyanates, and 4-benzylsulphidphenylisothiocyanate.

In previous papers we characterized the activity of phenylisothiocyanates[1], diphenyl-, benzhydryl-, and aryl-alkylisothiocyanates[2] on *Turbatrix aceti*. In this communication we deal with the antiworm activity of isothiocyanates of the general formula R-C_6H_4-X-C_6H_4, where X= -N=N-, -CH=CH-, -NH-, -CH_2-, -O-, -C_6H_4-; they present isothiocyanates derived from stilbene, azobenzene, diphenylamine, diphenylmethane, phenoxyphenyl, and diphenyl. Besides these derivatives, other groups studied include R-X-C_6H_4-NCS, where X=S or SO_2, and R is an aryl or alkyl radical. Our previous data on the noteworthy activity of diphenylisothiocyanates against *T. aceti* and other data[2] on the antihelminthic activity of these isothiocyanates inspired us to focus our attention on the afore-mentioned compounds. Furthermore, some isothiocyanate derivatives of stilbene and azobenzene are interesting because they represent analogues of known carcinogens, possessing meanwhile biological properties differing from them[3]. Our interest in isothiocyanate derivatives of arylsulphides and arylsulphones follows from the fact that 4,4'-diisothiocyanate diphenylsulphone, has low toxicity and shows noteworthy cesticidal activity[19]. In addition, the sulphur derivatives included in the present work, representing phenylisothiocyanate derivatives, exhibit antifungal and antibacterial activity[10].

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Experimental Procedure

Compounds studied:

Tables 1~5 show the structural formulae of the isothiocyanates studied and references describing their preparation and their physico-chemical properties. All the compounds under study were prepared in our laboratories; most of them are new compounds.

Materials and methods:

For testing antiworm activity a strain of *Turbatrix aceti* was used as described previously[2].

Results and Discussion

In Tables 1~5 are presented the antiworm activities of the isothiocyanates studied against *Turbatrix aceti*. They are characterized by the values of ED_{100}, *i.e.* the minimal inhibitory concentration, causing irreversible arrest of motility, expressed in μg/ml and in mole/liter. In order to facilitate the comparison of activities, the activity of each compound is expressed relative to that of phenylisothiocyanate.

Table 1 summarizes the data on the antiworm activity of stilbene isothiocyanates and substituted stilbenes. Except the fundamental 4-stilbeneisothiocyanate, these compounds are ineffective against *T. aceti*. Likewise ineffective is the group of isothiocyanates derived from azobenzene with the exception of azobenzene-4-isothiocyanate with halogen in position -4'-, exhibiting minimal activity (Table 2). Extremely low water solubility is characteristic of the afore-mentioned group of compounds. Some of these compounds exhibit conspicuous effects on animal cells such as EHRLICH ascites carcinoma cells, in which they cause inhibition of glycolysis in low concentrations[3].

Table 3 presents the isothiocyanates derived from diphenylamine, diphenylmethane, 4-phenoxyphenyl-, and 4-terphenyl-. With the exception of diphenylamine-4-isothiocyanate, 4-phenoxyphenylisothiocyanate and its 4'-substituted analogues, these compounds fail to exhibit any activity at all or their activity is weak.

Of all sulphur derivatives of isothiocyanates studied (Tables 4 and 5), a pronounced activity against *T. aceti* was found only for the group of (4-isothiocyanatophenyl)-

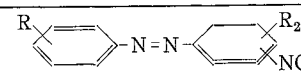
Table 1. Activity of stilbene isothiocyanates against *Turbatrix aceti*.

SCN-C6H4-CH=CH-C6H4-R	R=	Mol. wt.	Reference	ED_{100}		RE*
				μg/ml	mole/liter $\cdot 10^{-5}$	
2-NCS	H-	237.31	4	>100	>42	<0.12
3-NCS	H-	237.31	4	>100	>42	<0.12
4-NCS	H-	237.31	3	25	11	0.46
4-NCS	NCS-	294.39	3	>100	>34	<0.15
4-NCS	CH_3-	251.34	3	>100	>40	<0.13
4-NCS	CH_3-O-	267.39	3	>100	>37	<0.14
4-NCS	$(CH_3)_2$=N-	280.38	3	>100	>36	<0.14
4-NCS	NO_2-	296.23	3	>100	>34	<0.15
4-NCS	Cl-	271.76	3	>100	>37	<0.14
4-NCS	Br-	316.22	3	>100	>32	<0.16

* Relative effectivity compared with that of phenylisothiocyanate (molar concentration) ED_{100} for phenylisothiocyanate: $5.01 \cdot 10^{-5}$ mole/liter.

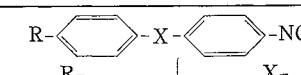
alkylsulphides and (4-isothiocyanatophenyl)-alkylsulphones where the methyl group constitutes the aliphatic radical. It is surprising that such isothiocyanates with an aliphatic radical longer than the methyl group, or with an ethyl group, are practically ineffective against *T. aceti*. Likewise ineffective are the isothiocyanate derivatives of

Table 2. Activity of azobenzeneisothiocyanate analogues against *Turbatrix aceti*.

			Mol. wt.	Reference	ED_{100}		RE*
					μg/ml	mole/liter $\cdot 10^{-5}$	
R_1=	R_2=	-NCS					
H-	H-	4-	240.30	7	100	42	0.12
4-CH_3-	H-	4-	253.32	8	>100	>39	<0.13
4-NCS-	H-	4-	296.39	8	>100	>34	<0.15
4-NO_2-	H-	4-	296.30	8	>100	>34	<0.15
4-$(CH_3)_2$=N-	H-	4-	282.36	5	>100	>35	<0.14
4-CH_3-O-	H-	4-	269.32	8	>100	>37	<0.14
4-Cl-	H-	4-	275.74	8	50	18	0.28
4-Br-	H-	4-	319.21	8	50	17	0.29
2-CH_3-	3-CH_3-	4-	267.34	8	>100	>37	<0.14
4-$(CH_3)_2$=N-	2-CH_3-	4-	296.39	5	>100	>34	<0.15
4-$(CH_3)_2$=N-	3-CH_3-	4-	296.39	5	>100	>34	<0.15
4-$(CH_3)_2$=N-	6-CH_3-	3-	296.39	5	>100	>34	<0.15
4-$(CH_3)_2$=N-	4-CH_3-	3-	296.39	5	>100	>34	<0.15
4-$(CH_3)_2$=N-	H-	3-	282.36	5	>100	>36	<0.14
4-$(CH_3)_2$=N-	3-CH_3-	2-	296.39	6	>100	>34	<0.15

* See footnote of Table 1.

Table 3. Activity of isothiocyanate derivatives of 4-terphenyl, 4-phenoxyphenyl, diphenylamine and diphenylmethane against *Turbatrix aceti*.

		Mol. wt.	Reference	ED_{100}		RE*
				μg/ml	mole/liter $\cdot 10^{-5}$	
R-	X-					
H-	-NH-	226.29	16	6.5	2.9	1.7
NO_2-	-NH-	271.29	16	> 50	>18	<0.28
H-	-CH_2-	225.30	16	> 50	>22	<0.23
CH_3-	-CH_2-	239.33	16	> 50	>21	<0.24
$(CH_3)_2$=N-	-CH_2-	268.37	16	> 50	>19	<0.26
NO_2-	-CH_2-	270.30	16	> 50	>19	<0.26
CH_3-CO-NH-	-CH_2-	283.36	16	> 50	>18	<0.28
SCN-	-CH_2-	282.38	16	> 50	>18	<0.28
H-	-O-	227.28	18	14	6.2	0.81
CH_3-	-O-	241.30	16	14	5.8	0.86
SCN-	-O-	284.35	16	16	5.6	0.89
Cl-	-O-	261.72	16	10	3.8	1.3
Br-	-O-	306.18	16	12	3.9	1.3
H-	-C_6H_4-	287.37	17	>100	>35	<0.14
Br-	-C_6H_4-	366.28	17	>100	>27	<0.19
NO_2	-C_6H_4-	332.37	17	>100	>30	<0.17

* See footnote of Table 1.

Table 4. Activity of arylsulphide and alkylsulphide analogues of phenylisothiocyanate against *Turbatrix aceti*.

R-S-C$_6$H$_4$-NCS R=	Mol. wt.	Reference	ED_{100}		RE*
			μg/ml	mole/liter $\cdot 10^{-5}$	
CH_3	181.28	11	0.2	0.11	46
CH_3-CH_2-	197.80	11	>100	>51	<0.10
CH_3-$(CH_2)_8$-	293.48	12	>100	>34	<0.15
CH_3-$(CH_2)_{11}$-	335.56	12	>100	>30	<0.17
C$_6$H$_5$-	167.26	13	>100	>60	<0.08
Br-C$_6$H$_4$-	322.25	14	>100	>31	<0.16
Cl-C$_6$H$_4$-	277.79	14	>100	>36	<0.14
CH_3-C$_6$H$_4$-	257.37	14	>100	>39	<0.13
NO_2-C$_6$H$_4$-	288.34	14	>100	>35	<0.15
$(CH_3)_2$-N-C$_6$H$_4$-	286.41	14	>100	>35	<0.15
SCN-C$_6$H$_4$-	310.42	13	>100	>32	<0.16

* See footnote of Table 1.

Table 5. Activity of alkylsulphone and arylsulphone analogues of phenylisothiocyanate against *Turbatrix aceti*.

R-SO_2-C$_6$H$_4$-NCS R=	Mol. wt.	Reference	ED_{100}		RE*
			μg/ml	mole/liter $\cdot 10^{-5}$	
CH_3	213.28	11	0.2	0.094	53
CH_3-CH_2-	227.30	11	100	>44	<0.11
$(CH_3)_2$CH-	241.33	11	100	>41	<0.12
$CH_3(CH_2)_6$-	373.52	11	>100	>27	<0.19
$CH_3(CH_2)_8$-	401.58	12	>100	>25	<0.20
$CH_3(CH_2)_{11}$-	443.65	12	>100	>23	<0.22
C$_6$H$_5$-CH_2-	289.37	15	>100	>35	<0.14
C$_6$H$_5$-	259.34	13	>100	>39	<0.13
Cl-C$_6$H$_4$-	309.79	14	>100	>32	<0.16
Br-C$_6$H$_4$-	353.25	14	>100	>28	<0.18
CH_3-C$_6$H$_4$-	289.37	14	>100	>35	<0.14
NO_2-C$_6$H$_4$-	314.34	14	>100	>32	<0.16
$(CH_3)_2$N-C$_6$H$_4$-	318.41	14	>100	>31	<0.16
SCN-C$_6$H$_4$-	236.22	13	>100	>42	<0.12

* See footnote of Table 1.

diphenylsulphone and diphenylsulphide, including 4,4'-diisothiocyanate diphenylsulphone whose cesticidal efficacity against *Hymenolepis nana* has been confirmed also in experiments *in vivo*.

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