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Studies on anti-amoebic compounds. Part V. Synthesis of dichloromethanesulphonamides

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Summary — Synthesis of a variety of dichloromethanesulphonamides, including a close structural analogue of a well-known drug, namely diloxanide furoate, and their anti-amoebic activities are reported.

anti-amoebic compounds / diloxanide furoate / dichloroacetamides / dichloromethanesulphonamides

Introduction

Amoebiasis, an infection by the pathogenic amoeba, *Entamoeba histolytica,* is an endemic disease in developing countries, where poverty and poor sanitation encourage its incidence and perpetuation. The premier class of compounds used in the treatment of amoebiasis, namely nitroimidazoles, are very effective in eliminating tissue-invading amoeba, but their effectiveness in luminal amoebiasis has not been proven. Even though the benefits of nitroimidazole therapy far outweigh the side effects of the drug, the potential mutagenicity of the nitroimidazoles and their ineffectiveness in non-invasive amoebiasis are strong reasons for continuing the search for new amoebicides. Therefore, we have pursued our efforts in this domain [1].

Diloxanide furoate **1** has been used in combined therapy for amoebiasis, **1** being particularly effective against lumen-dwelling amoeba (fig 1). Quinfamide **2** a cyclised analogue of **1,** which is twice as effective as **1,** is also primarily a luminally active agent [2, 3]. Both compounds contain a dichloroacetyl group and we thought that the dichloromethanesulphonyl group, $-SO_2-CHCl_2$, which closely resembles the pharmacophore dichloroacetyl, $-CO-CHCl_2$, present in **1** and **2**, would be an isosteric pharmacophore worth investigating, especially when attached to diverse molecular skeletons. Surprisingly, very little is known about the synthesis of dichloromethanesulphonyl compounds and, evidently, much less about their biological activities. Three types of dichloromethanesulphonamides, namely **I, II** and **III** (**I**, diloxanide analogues, **6–8**; **II**, Mannich bases, **9–14**; and **III**, miscellaneous, **15–21**) were prepared according to schemes 1, 2 and 3.

We were motivated to synthesize these compounds because there is an acute need for a single drug with minimal side effects and which is effective at tissue and luminal sites [4] but no such candidate drug seems to have reached any advanced stage of development.

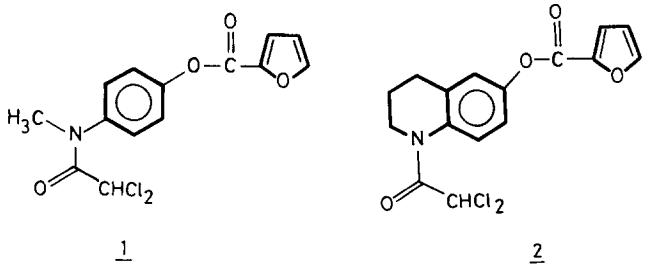

Fig 1. Structure of compounds **1** and **2**.

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Chemistry

Dichloromethanesulphonyl chloride was synthesised according to a procedure described in the literature [5] with minor modifications.

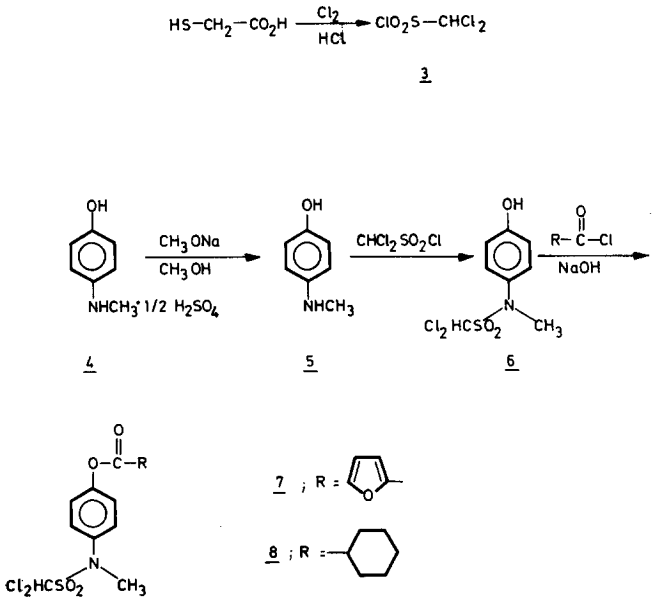
A dichloromethanesulphonyl structural analogue **7,** which closely resembles **1,** was synthesised according to scheme 1. Analogously, the cyclohexanoyl ester of **6** also was synthesised.

Since Mannich bases of phenolic compounds exhibit anti-amoebic activity [6, 7], Mannich bases of **6,** namely **9–12,** were synthesised by condensing **6** with formaldehyde in the presence of a secondary amine (scheme 2). The sulphur atom present in compound **12** was oxidised to the corresponding sulphoxide **13.** A salicylamide derivative **14** was also synthesised starting from **6,** after condensation of **6** with phenylisocyanate using zinc chloride as the catalyst.

A variety of dichloromethanesulphonamides **15–21** were synthesised by reacting dichloromethanesulphonyl chloride and the corresponding secondary amine (scheme 3). In many cases, the relatively high acidity of the proton in $CHCl_2SO_2Cl$ caused problems by generating HCl in the presence of the amine thus producing amine hydrochlorides as by-products.

The pyridazine analogues **19** and **20** were synthesised essentially according to the same procedure that we developed [8] for phenolic compounds.

It would be interesting to see whether the dichloroketene analogue $CCl_2{=}SO_2$ could be generated from dichloromethanesulphonyl chloride, even though some of our attempts were futile.



Scheme 1.

In the ^{1}H-NMR spectra of these dichloromethanesulphonamides, the methine proton in $-SO_2-CHCl_2$ group, appeared in the range δ 6.30–6.80, which is about the same as for the proton in the $-CO-CHCl_2$ group (table I). The IR spectral frequencies characteristic of this dichloromethanesulphonyl group fall in 3 regions around 1160, 1360 and 1460 cm^{-1}.

Pharmacology

The dichloromethanesulphonamides synthesised in this study were tested for their efficacy at eradicating natural *E muris* infection in rats. The details of this model are described elsewhere [9]. Briefly, the drugs were homogenously suspended in 0.2% carboxymethylcellulose in water and administered to Wistar rats of either sex weighing 100–200 g and harbouring an *E muris* infection of the rate and intensity as previously described [9]. Procedures for drugging, examination and the criteria for activity were essentially the same as those of Slighter *et al* [2]. Using a hypodermic syringe and a blunt-mantled needle, 2 daily doses were given orally 8 h apart for 3 consecutive days. On the day following the last administration, animals were killed and their caeca examined for *E muris* trophozoites as described in [9]. The lowest dose which completely eradicated the *E muris* infection, based upon the examination of 3 different sites of the caecum, was considered the minimum curative dose. For initial screening, a starting dose of 10 mg/kg bid x 3 d was adopted.

Results and discussion

Of all the compounds tested, only one compound, namely **7**, exhibited 100% curative activity at a dose of 10 mg/kg, bid x 3 d. At lower doses, **7** was not 100% curative. This should be compared with the activity of diloxanide furoate **1** with its minimum curative dose of 1.6 mg/kg, bid x 3 d.

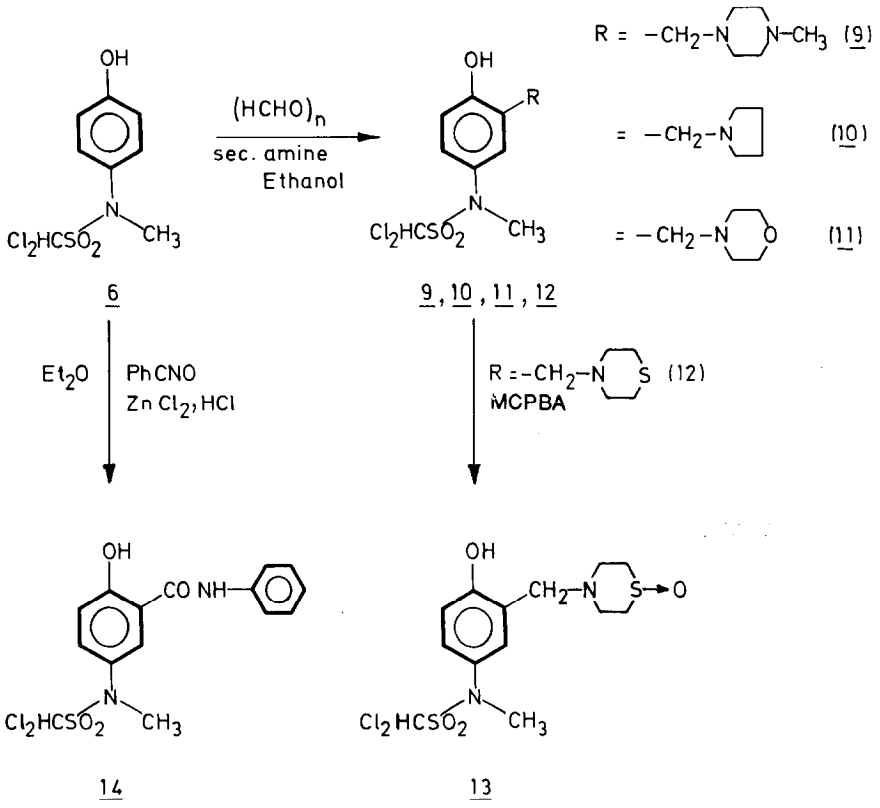
Hence, even though the $CHCl_2-SO_2-$ group bears a strong resemblance to the $-CHCl_2-CO-$ group (compare **1** and **7**), the present results indicate a high specificity of the dichloroacetamido group in the anti-amoebic compounds. In addition, differences in the absorption behaviour of **1** and **7** may also play a critical role in determining their activity.

None of the other compounds exhibited 100% curative activity at the initial dose level.

Experimental protocols

Preparation of dichloromethanesulphonyl chloride

Chlorine gas was passed as a slow stream through a solution of thioglycolic acid (46 g, 0.5 mol) in concentrated HCl for 2 d, and the temperature was kept below 10°C. Upon cooling, an



Scheme 2.

Table I. Spectral and analytical data for some dichloromethanesulphonamides.

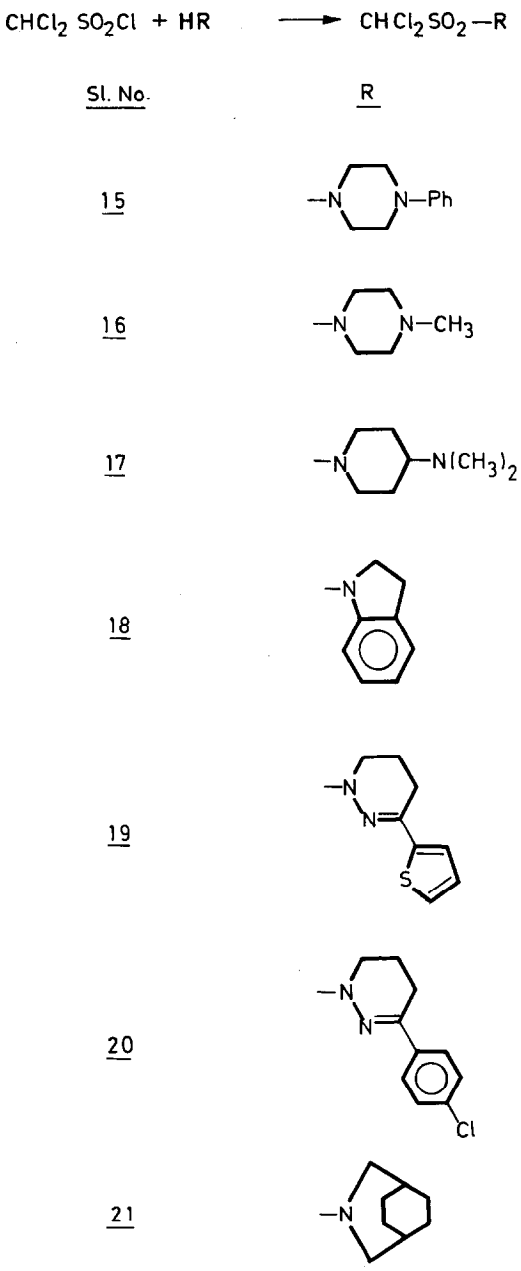
No	*mp (°C)*	*Solvent for recrystallization*	*Molecular formula*		*^{1}H-NMR data (δ values)*
18	60	Ethylacetate–hexane	$C_9H_9Cl_2NO_2S$	(C, H)	3.16(T, 2H, J = 8 Hz, 3-CH_2); 4.25 (t, 2H, J = 8 Hz, 2–CH_2); 6.33(s, 1H, –CHl_2); 6.84–7.54(m, 4H, aromatic)
19	138	Benzene–pet ether	$C_9H_{10}Cl_2N_2O_2S_2$	(C, H)	2.15(pentet, 2H, J = 6 Hz, 3-CH_2); 2.75(t,2H, J = 6 Hz, 4-CH_2); 3.91(t, 2H, J = 6 Hz, 2-CH_2); 6.77(s, 1H, –CHCl_2); 7.00–7.68(m, 3H, aromatic)
20	130	Benzene–pet ether	$C_{11}H_{11}Cl_3N_2O_2S$	(C, H)	2.10(pentet, 2H, J = 6 Hz, 3-CH$_2$); 2.64(t, 2H, J = 6 Hz, 4-CH_2); 3.85(t, 2H, J = 6 Hz, 2-CH_2); 6.60(s, 1H, – CHCl_2); 7.26(d, 1H, J = 8 Hz, aromatic); 7.65(d, 1H, J = 8 Hz, aromatic)
21	128	Chloroform–hexane	$C_9H_{15}Cl_2NO_2S$	(C, H)	1.40–2.20(br m, 10H); 3.66(d, 4H, J = 4 Hz, N–CH_2); 6.28(s, 1H, –CHCl_2)

oily layer separated. This was taken up in chloroform and washed several times with ice-cold water. It was then dried over anhydrous sodium sulphate. Solvent chloroform was removed on a rotary evaporator and the residue was distilled under vacuum; bp: 70°C (8 mm); yield: 35 g (19%); ^{1}H-NMR ($CDCl_3$ solvent): δ 6.64.

Synthesis of N-Methyl-N-dichloromethanesulphonyl-p-hydroxybenzene ***6***

To a cooled suspension of metol **4** in methanol, solid sodium methoxide was added and stirred for 2 h at 0°C. The solution was then filtered and the filtrate was concentrated to yield a brown-coloured solid.

Dichloromethanesulphonyl chloride **3** in CH_2Cl_2 was cooled to –10 to –20°C in the reaction flask. To this, the liberated amine **5**, the brown-coloured solid described above was added dropwise as a solution in CH_2Cl_2 with stirring. The reaction was continued overnight with stirring. Excess CH_2Cl_2 was added to the reaction mixture which was washed successively with dilute HCl, $NaHCO_3$ solution and water. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4. Removal of the solvent yielded a gummy solid which was crystallised from ether–hexane, mp: 136°C; Anal $C_8H_9Cl_2NO_3S$ (C, H).



Scheme 3.

*Synthesis of furoyl and cyclohexanoyl esters of **6** (**7** and **8**)*
To the sodium salt of **5** (prepared by adding sodium hydroxide in solution to **5**), an equivalent amount of furoyl chloride or cyclohexanoyl chloride was added with stirring. After 2 h, ice-cold water was added to the reaction mixture and stirred. The solid separated was then filtered, washed with water and recrystallised from ether–hexane. For **7**: mp: 89–100°C; yield 55%; Anal $C_{13}H_{11}Cl_2NO_5S$ (C, H). For **8**: mp: 95°C; yield: 20%; Anal $C_{15}H_{19}Cl_2NO_4S$ (C, H).

*Synthesis of Mannich bases of **6** (**9**, **10**, **11** and **12**)*
Representative procedure: paraformaldehyde and morpholine were taken up in alcohol and the reaction mixture was refluxed until a clear solution was obtained. To this, an equimolar amount of **6** in alcohol was added and refluxing was continued for 48 h. The solvent was then removed, the residue was treated with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water until it was free of base and dried over anhydrous $Na_{197}SO_4$. The residue was chromotographed over silica gel using $CHCl_3$ as the eluent. The appropriate fractions were combined and the crude product was crystallised from chloroform (table III).

*Synthesis of sulphoxide **13***
To one equivalent of a solution of **12** in CH_2Cl_2, *meta*-chloroperbenzoic acid (1.2 eq) was added and the reaction mixture was stirred overnight. KF was added and stirred for 1 h. The resulting solution was filtered and the filtrate was concentrated to obtain a solid which was recrystallised from ethyl acetate/ether (1:1) mp: 165°C; yield: 80%; Anal $C_{13}H_{18}Cl_2N_2O_4S_2$ (C, H).

*Synthesis of **14***
To a solution of **6** in ether, an equivalent amount of $ZnCl_2$ and PhNCO were added and cooled to 0° C. HCl gas was passed

Table II. Activity data against *E muris* infection in Wistar rats.

Compound	*Dose (mg/kg, bid x 3 d)*[a]
1	1.6
2	0.8
7	10.0

[a]Please see text for further details.

Table III. Yield and physical data for Mannich bases **9–12**.

Compd	*Yield (%)*	*mp (°C)*	*Analysis*	
9	30	130	$C_{14}H_{21}Cl_2N_3O_3S$	(C, H)
10	29	90	$C_{13}H_{18}Cl_2N_2O_3S$	(C, H)
11	30	138	$C_{13}H_{18}Cl_2N_2O_4S$	(C, H)
12	65	125	$C_{13}H_{18}Cl_2N_2O_3S_2$	(C, H)

through this solution for 2 h. The reaction mixture was then stirred at 0°C for further period of 3 h and at room temperature overnight. Removal of the solvent yielded a mixture of starting material **6** and product **14.** The product was then recrystallised from ether, mp: 185°C; yield: 30%; Anal $C_{15}H_{14}C1_2N_2O_4S$ (C, H).

*Synthesis of **15–21***
To a solution of dichloromethanesulphonyl chloride (1 eq) in chloroform, the appropriate amine in chloroform was added under cooling (dry ice–acetone). The stirring was continued overnight. The reaction mixture was neutralised with sodium bicarbonate. The chloroform layer was dried and the solvent removed. The residue was crystallised from an appropriate solvent (table IV).

Table IV. Yield and physical data for dichloromethanesulphonamides **15–17**.

Compd	*Yield (%)*	*mp (°C)*	*Analysis*	
15	40 (Hexane)	92	$C_{11}H_{14}C1_2N_2O_2S$	(C, H)
16	21 (Hexane)	126	$C_6H_{12}C1_2N_2O_2S$	(C, H)
17	20 (Hexane–ethylacetate	243	$C_8H_{16}C1_2N_2O_2S$	(C, H)

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