SYNTHESIS OF SOME NEW BENZOTHIADIAZINE-1,1-DIOXIDES OF ANTIMICROBIAL ACTIVITY DERIVED FROM METHYLACETANILIDES

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ABSTRACT

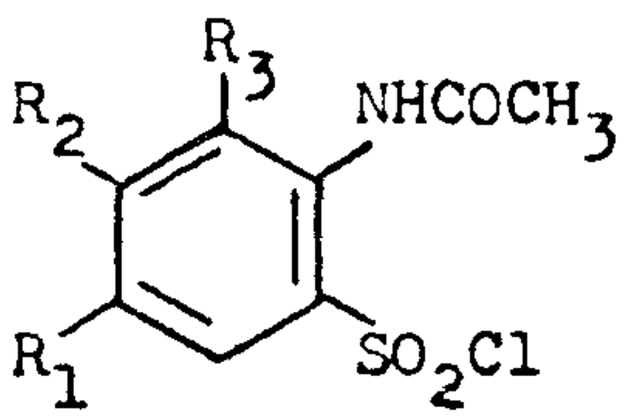
The preparation of different types of benzothiadiazine-1,1-dioxides is described. The structures of some of the prepared products are discussed in the light of their IR and NMR spectra. The biological activity of some of the compounds tested is described.

INTRODUCTION

RECENTLY, 1,2,4-benzothiadiazine-1,1-dioxides and their derivatives have assumed increasing importance being diuretics[1-3], and hypotensive agents and exhibiting anti-microbial properties[4]. It was thought that incorporation of the acylamino groups into the disulphonamides and benzothiadiazine-1,1-dioxides might modify their biological activity.

RESULTS AND DISCUSSION

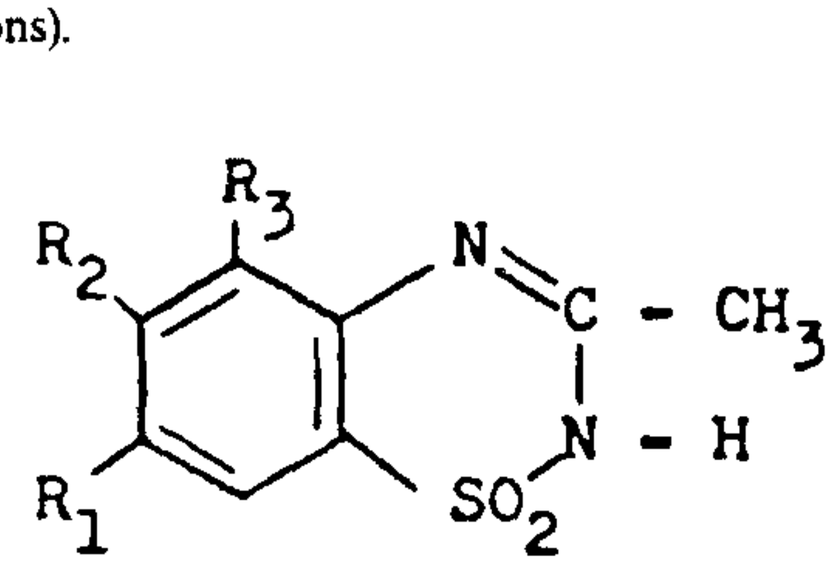
In the present work, we have found that direct chlorosulphonation of *o*-, *m*- and *p*-methylacetanilides gave the corresponding disulphonyl chlorides (Ia–c); the addition of sodium chloride ensured maximum dichlorosulphonation[5]. The structure of I is confirmed by its analytical data and its IR spectrum[6] which showed ν_{NH} at 3410 cm^{-1} as a broad band, $\nu_{C=O}$ at 1640 cm^{-1} and ν_{SO_2} at 620 cm^{-1}.



(I)

Ia; $R_1 = SO_2Cl$; $R_2 = H$; $R_3 = CH_3$
b; $R_1 = SO_2Cl$; $R_2 = CH_3$; $R_3 = H$
c; $R_1 = CH_3$; $R_2 = H$; $R_3 = SO_2Cl$

Amination of the disulphonyl chlorides (Ia–c) gave the corresponding 3-methyl-1,2,4-benzothiadiazine-1,1-dioxide derivatives of the type (II), which were identical with the products obtained by reaction of *o*-, *m*- and *p*-toluidine disulphonamides[4, 5, 7] with acetic acid (m.p. and m.m.p.). The structure of II was consistent with its elemental analysis and IR spectrum ($\nu C=N$ at 1640 cm^{-1} and νSO_2NH_2 at 3320 cm^{-1}). The ^1H NMR spectrum (DMSO) of IIa showed the following signals at: $\delta = 2.6$ and 2.9 p.p.m. (for the two CH_3 groups), $\delta = 6.4$ p.p.m. (2H, t (broad), NH_2 group) and $\delta = 6.9$ and 8.3 p.p.m. (2H, S, aromatic protons).

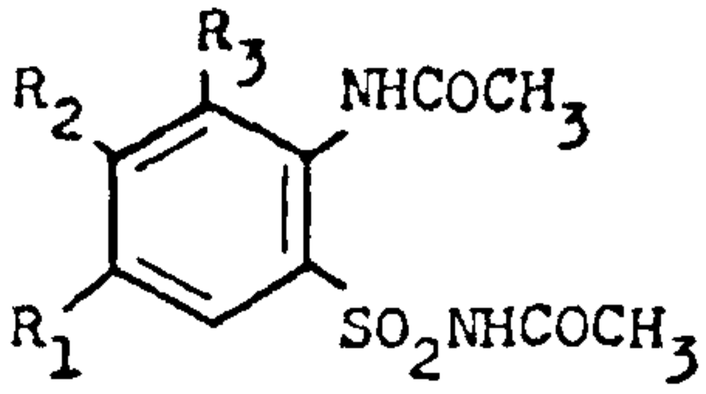


(II)

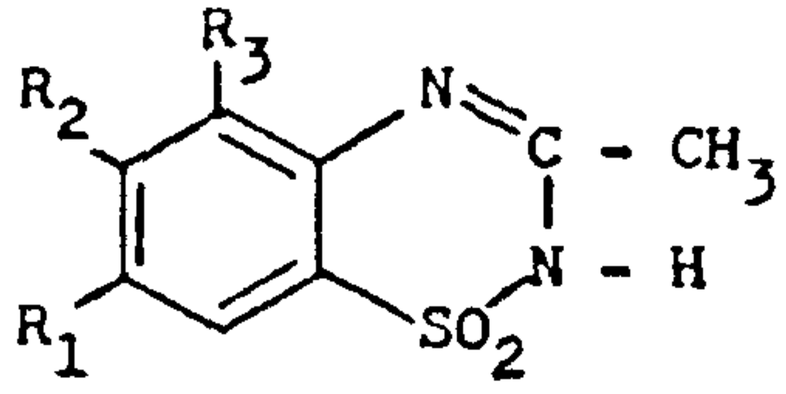
IIa; $R_1 = SO_2NH_2$; $R_2 = H$; $R_3 = CH_3$
b; $R_1 = SO_2NH_2$; $R_2 = CH_3$; $R_3 = H$
c; $R_1 = CH_3$; $R_2 = H$; $R_3 = SO_2NH_2$

Acylation of *o*-, *m*- and *p*-toluidine disulphonamides with excess acetic anhydride resulted in acylation of both the sulfamyl groups as well as the amino group to give the triacetylamino derivatives (IIIa–c). Acylation of the amino group was substantiated by a negative colour test for diazotizable amine and UV spectroscopy.

Heating of the triacyl derivatives (III) separately at



(III)



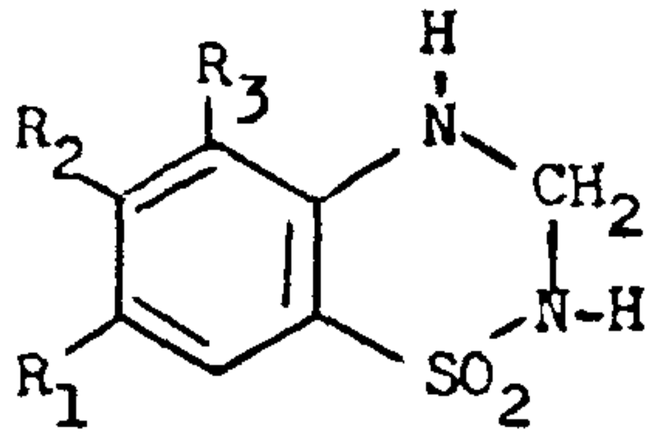
(IV)

III, IVa; $R_1 = SO_2NHCOCH_3$; $R_2 = H$; $R_3 = CH_3$
b; $R_1 = SO_2NHCOCH_3$; $R_2 = CH_3$; $R_3 = H$
c; $R_1 = CH_3$; $R_2 = H$; $R_3 = SO_2NHCOCH_3$

their melting points effected their cyclisation and gave the corresponding acylamino-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide derivatives (IVa–c). The structure of the latter was based on elemental analysis and IR spectra which showed ν_{SO_2NH} at 3200, 3340 cm^{-1} as a broad band and $\nu_{C=O}$ at 1630 cm^{-1}.

Hydrolysis of acylamino-3-methyl-1;2,4-benzothiadiazine-1,1-dioxides (IVa–c) with dilute sulphuric acid gave products which were exactly identical with compounds (II) (m.p. and mixture m.p. and IR spectra). Also, acetylation of the compounds of type II with acetic anhydride or acetyl chloride yielded compounds of type IV (m.m.p.).

Ring closure of *o*-; *m*- and *p*-toluidine disulphonamides with formaldehyde in acidic medium gave another type of 1,2,4-benzothiadiazine-1,1-dioxide derivatives (V), whose structure was established by elemental analysis and IR spectra which showed ν_{NH} at 3300, 3380 cm^{-1} as a broad band.



(V)

Va; $R_1 = SO_2NH_2$; $R_2 = H$; $R_3 = CH_3$
b; $R_1 = SO_2NH_2$; $R_2 = CH_3$; $R_3 = H$
c; $R_1 = CH_3$; $R_2 = H$; $R_3 = SO_2NH_2$

Biological activity

Some of the synthesised antibacterial acylamino benzothiadiazine derivatives were tested for activity against micro-organisms including gram-positive and gram-negative strains of *Bacillus subtilis*, *B. mycoides*, *B. cereus*. *E. coli* and *Salmonella typhosa*. One filamentous strain of *Penicillium chrysogenum* (tangus) was used to detect antifungal activity. The sensitivity of micro-organism to the test compound was determined by the filter paper disk method[8]. The results obtained indicated that for *Penicillium chrysogenum*, compounds (IIIb) and (IIIc) showed the maximum activity (+ + + +) whereas compounds (IVa, b, c) showed fairly good activity (+ +). In other types of bacteria, compounds (IIb) and (IVb) showed fairly good activity (+ +) while other compounds were less active (+) or inactive.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Pye-Unicam SP 1200 spectrophotometer.

Chlorosulphonation of o-, m- and p-methylacetanilides

Methylacetanilide (0.1 mol) was added drop-wise, with stirring, to ice-cold chlorosulphonic acid (140 ml) while sodium chloride (excess) was added portion-wise over a period of 2 hr. The mixture was heated gradually in an oil bath at 150° for 4 hr. The mixture was cooled in ice and the contents collected, washed, dried and recrystallised from the proper solvent to give the corresponding methylacetanilide disulphonyl chlorides (Ia–c) in 60–75% yield (table 1).

Table 1 *Methylacetanilide disulphonyl chlorides (I a–c) and triacetyl derivatives (III a–c)*

Compound No.	Cryst. solvent	M.P. (°C)
I a	C	162
I b	A/W	145
I c	B	161
III a	E	280
III b	A	176
III c	A	275

C = chloroform, A = acetic acid, W = water, B = benzene, E = ethyl alcohol.

Sulphamido dimethyl-1,2,4-*benzothiadiazene*-1,1-*dioxides* (*IIa–c*)

(a) A mixture of methylacetanilide disulphonyl chloride (Ia–c; 0.01 mol) and ammonia solution (excess) was heated under reflux for 1 hr. The precipitated solid was collected and recrystallised from the proper solvent to give compounds (II a–c) in 56 to 63% yield (table 2).

Table 2 *Benzothiadiazine*-1, 1-*dioxide derivatives (II a–c, IV a–c and V a–c).*

Compound No.	Cryst. solvent	M.P. (°C)
II a	A	256
II b	A	264
II c	A	277
IV a	E	280
IV b	E	267
IV c	E	280
V a	E/W	230
V b	E/W	253
V c	E/W	245

A = acetic acid, E = ethyl alcohol, W = water.

(b) A mixture of toluidine disulphonamides (0.001 mol) and glacial acetic acid (excess) was heated under reflux for 5–6 hr. The precipitated solid after cooling was collected and recrystallised from the proper solvent to give the compounds (II a–c) which were obtained by the above procedure.

Triacetyl derivatives (*III a–c*)

A mixture of methylacetanilide disulphonamide (0.01 mol) and acetic anhydride (excess) was heated under reflux for 2 hr. The solid obtained, after concentration, was collected and recrystallised from a suitable solvent to give the triacetyl derivatives (III a–c) in 50 to 62% yield (table 1).

Benzothiadiazine-1,1-*dioxide derivatives* (*IV a–c*)

The methylacetanilide diacetylsulphonamide (0.01 mol) was pyrrolyzed for 2 hr in an oil bath at 280°. The resulting product was recrystallized from the proper solvent to give compounds (IV a–c) in 50 to 60% yield (table 2).

Cyclisation of o-, m- and p-toluidinedisulphonamides with formaldehyde

The toluidinedisulphonamide (0.05 mol) was dissolved in ethanol (25 ml) containing few drops of HCl and formaldehyde (0.05 mol) was added. The mixture was warmed over water bath for 2–3 hr. The solid obtained was recrystallised from the proper solvent to give the cyclic compounds (V a–c) in 50–60% yields (table 2).

Hydrolysis of N-acetylsulphamido-dimethyl-1,2,4-*benzothiadiazine*-1,1-*dioxides*

N-acetylsulphamido-dimethyl-1,2,4-benzothiadiazine-1,1-dioxide (IV a–c); 0.01 mol) and dilute sulphuric acid (100 ml) were heated under reflux for 24 hr. After cooling, the solid obtained was crystallised from the proper solvent to give the corresponding sulphamido compounds (II a–c) (m.p. and m.m.p.).

All new compounds gave satisfactory C, H and N analysis.

16 August 1983; Revised 7 November 1983

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