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SYNTHESIS OF NEWER SULPHONAMIDES

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ABSTRACT

The synthesis of some new sulphonamides is described. Treatment of m-acetamidophenyl acetate (1a) or m-methylacetanilide (1b) with four moles of chlorosulphonic acid afford the corresponding sulphonylchlorides (2 a and 2 b), respectively. These acid chlorides react with certain amines yielding the expected sulphonamides (3a-h), which on hydrolysis with 2N NaOH gave the corresponding amino-derivatives (4a-h) . Hydrolysis of the acid chlorides (2a and 2b) afforded the corresponding sulphonic acids (5a and 5b).

INTRODUCTION

Sulphonamide derivatives are famous for their bacteriostatic activity and have been widely used under the name of sulpha-drugs as bacteriostatic agents (1,2). The present investigation deals with the synthesis of certain sulphanilamide derivatives in order to produce a series of compounds with expected bactericidal activity.

The compounds (2 a) and 2 b) were prepared via chlorosulphonation of m-acetamidophenyl acetate (1a) or m-methylacetanilide (1b) with chlorosulphonic acid at 50 °C.

When (2a) and (2b) were allowed to react with different amino-compounds, the corresponding sulphonamides (3 a-h) were obtained. On the other hand, (4 a-h) were prepared by hydrolysing (3 a-h) with boiling 2N NaOH.

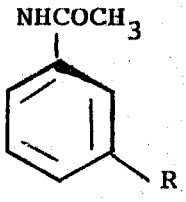
The starting acetamido-compounds (1a) and (1b) have been prepared via acetylation of m-aminophenol and m-toluidine with acetic anhydride at 0°C in presence of NaOH. 6-Sulphonamido-1,3-aminophenol derivatives (3 a-d) were prepared by chlorosulphonation of m-acetamidophenyl acetate with four moles chlorosulphonic acid. The produced sulphonylchloride (2a) was treated with 25 % ammonium hydroxide solution to give rise to 6-sulphonamido-3-acetamido-1-phenyl acetate (3a). Reaction of (2a) with the primary amines, guanidine, 2-aminopyridine and 2-aminopyrimidine yielded the N-substituted sulphonamides (3 b-d), respectively. The reaction was carried out at room temperature using equimolecular amounts of the reactants. The HCl gas evolved during the reaction was traped with triethylamine or pyridine. Hydrolysis of (3 a-d) with 2N HCl yielded the corresponding -2-hydroxy-4-aminobenzenesulphonamide derivatives (4 a-d), respectively.

3-Methyl-4-aminobenzenesulphonamide derivatives (4 e-h) were prepared similarly through chlorosulphonation of m-cetamidotoluene, followed by condensation with ammonia, guanidine, 2-aminopyridine and 2-aminopyrimidine yielded (3 e-h). Hydrolysis of (3 e-h) with 2N NaOH yielded the 3-methyl-4-aminobenzenesulphonamides (4 e-h).

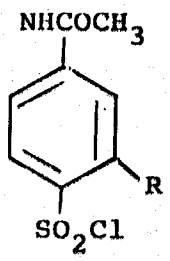
The sulphonic acids (5a and 5b) were prepared through hydrolysis of the corresponding acid chlorides (2a and 2b).

Synthesis of newer sulphonamides.

The structure of the sulphonamides (3 a-h) and (4 a-h) is based on i) analytical data and ii) infrared spectra which show νSO_2-N at 1300 cm^{-1}[3] and 1140 cm^{-1} and, beside i.r. spectra of (4 a-h) which show two bands at 3500 and 3300 cm^{-1} characteristic for NH_2 group[4].

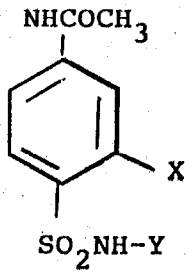


(1)



(2)

1,2	R
a	$OCOCH_3$
b	CH_3



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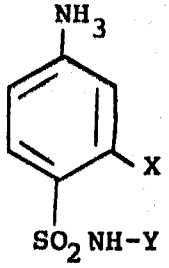
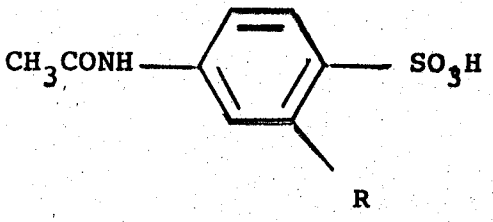


(4)

3	X	Y
a	$OCOCH_3$	H
b	$OCOCH_3$	guanyl
c	$OCOCH_3$	2-pyridyl
d	$OCOCH_3$	2-pyrimidyl
e	CH_3	H
f	CH_3	guanyl
g	CH_3	2-pyridyl
h	CH_3	2-pyrimidyl

4	X	Y
a	OH	H
b	OH	guanyl
c	OH	2-pyridyl
d	OH	2-pyrimidyl
e	CH_3	H
f	CH_3	guanyl
g	CH_3	2-pyridyl
h	CH_3	2-pyrimidyl



(5)

5	R
a	$OCOCH_3$
b	CH_3

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer-297 Infrared Spectrophotometer. Elemental analysis was performed by

the Microanalytical Unit of the National Research Center, Cairo.

Synthesis of the acetamido compounds (1a and 1b):

To a suspension of the amino-compound (0.1 mole) in 25 % NaOH solution (50 ml), 200 gm of crushed ice were added to the cold solution, 20.4 gm (0.2 mole) of acetic anhydride were added under thorough stirring. The resulting precipitate was filtered off, washed with water and crystallized from methanol to give the product as colourless crystals of melting points undepressed when admixed with authentic samples prepared by boiling the amino-compound with acetic anhydride.

Synthesis of (2a and 2b):

To 46.6 gm (0.4 mole) chlorosulphonic acid, (0.1 mole) of (1a) or (1b) was added in small portions with stirring. When the addition has been completed, the reaction mixture was heated gradually on a water-bath at 50°C. The temperature waskept at 50°C for 3 hours, to complete the reaction. The reaction mixture was left to cool and the oily mixture was poured in a thin stream with stirring into 200 gm of crushed ice and the mixture was stirred for several minutes. The product was filtered off, washed with cold water, dried, and crystallized from acetone to give (2a) or (2b) as colourless crystals (cf. Table 1).

Synthesis of (3a and 3e):

A suspension of (2a) or (2b) (5 gm) in 25 % NH_4OH (20 ml) was stirred for 30 minutes. After cooling, the mixture was neutralized by 2N HCl (pH = 6) when (3a) or

(3e) was separated out. The product was filtered off , washed with cold water dried and crystallized from water to give (3a) or (3e) as colourless crystals (cf. Table 1).

General procedure for synthesis of N-substituted Sulphonamids (3b-d , 3f-h):

0.01 mole of the amino-compound, guanidine, 2-aminopyridine or 2-aminopyrimidine was dissolved in (20 ml) of dry ether. To the solution (0.01 mole) of triethylamine were added while stirring. The reaction mixture was kept overnight at the room temperature. The ether was distilled off, and 20 ml of H_2O was added with stirring to the residue. The separated product (3a-d , 3f-h) was filtered off, washed with water dried and crystallized from ethanol (cf. Table 1).

General procedure for the synthesis of N-substituted (4 a-h):

A suspension of (3 a-h) (2 gm) in 2N NaOH (10 ml) was boiled under reflux for 2 hours. After cooling, the solution was neutralized with 2N HCl till PH = 6,were (4 a-h) were separated out. The product was filtered off, washed with water, dried and crystallized from water (cf. Table 2).

Synthesis of the Sulphonic acid (5a):

A suspension of 2 gm of (2a) and (20 ml) of water were kept overnight. The separated product (5a) was filtered off, washed with water, dried and crystallized

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Table (1):

No.	Formula	M.P.°C	Analysis Calcd/found C	H	N
2a	$C_{10}H_{10}ClNO_5S$	220	41.17	3.43	4.80
			41.08	3.21	4.70
2b	$C_9H_{10}ClNO_3S$	207	43.64	4.04	5.65
			43.52	4.01	5.62
3a	$C_{10}H_{12}O_2N_2O_5S$	280	44.12	4.41	10.29
			44.12	4.39	10.30
3b	$C_{11}H_{14}N_4O_5S$	270	42.04	4.46	17.83
			42.14	4.25	17.63
3c	$C_{15}H_{15}N_3O_5S$	262	51.58	4.30	12.03
			51.02	4.30	12.12
3d	$C_{14}H_{14}N_4O_5S$	285	48.00	4.00	16.00
			47.89	4.19	15.79
3e	$C_9H_{12}N_2O_3S$	242	47.37	5.26	12.28
			47.01	5.10	12.10
3f	$C_{10}H_{14}N_4O_3S$	266	44.44	5.19	20.74
			44.40	5.01	20.24
3g	$C_{14}H_{15}N_3O_3S$	281	55.08	4.92	13.77
			54.81	5.08	13.42
3h	$C_{13}H_{14}N_4O_3S$	293	50.98	4.58	18.30
			51.21	4.41	18.24

Table (2):

No.	Formula	M.P.°C	Analysis	Calcd/found	
			C	H	N
4a	$C_6H_8N_2O_3S$	261	38.30	4.26	14.89
			38.35	4.06	14.61
4b	$C_7H_{10}N_4O_3S$	200	36.52	4.35	24.35
			36.24	4.21	24.25
4c	$C_{11}H_{11}N_3O_3S$	240	49.81	4.14	15.85
			50.01	4.15	15.62
4d	$C_{10}H_{10}N_4O_3S$	261	45.11	3.76	21.05
			45.21	3.96	21.25
4e	$C_7H_{10}N_2O_2S$	253	45.16	5.38	15.05
			45.14	5.29	14.08
4f	$C_8H_{12}N_4O_2S$	242	42.11	5.26	24.56
			42.0	5.10	24.72
4g	$C_{12}H_{13}N_3O_2S$	260	54.75	4.94	15.97
			54.21	4.61	16.01
4h	$C_{11}H_{12}N_4O_2S$	274	50.00	4.55	21.21
			50.20	4.25	21.21

from water to give (5a) as colourless crystals m.p. 325°C Analysis for $C_{10}H_{11}N\,O_6S$ calcd. C 43.95 % , H 4.03 % and N 5.15 % , found C 43.18 % , H 4.65 % and N 5.13 %.

Preparation of the Sulphonic acid (5b):

This compound was prepared by hydrolysis of (2b) in a similar manner as described in (5a) , m.p. = 310°C Analysis for $C_9H_{11}NO_4S$ calcd. N 6.11 % and found N 6.0 %.

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