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Synthesis, Characterization and Biological studies of some 3,5-diaryl-tetrahydro- N-ethoxycarbonyl-1,4-thiazine-1,1-dioxide

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ABSTRACT

A series of some new 3, 5-diaryl-tetrahydro-N-ethoxycarbonyl-1, 4-thiazine-1, 1-dioxides has been synthesized from their respective thiazine compounds. The structural assignments are based on their elemental and spectral data. All the synthesized compounds were preliminarily screened for their in vitro antimicrobial activity against Gram positive organisms (Bacillus subtilis, Staphylococcus aureus) and Gram negative organisms (Escherichia coli and Klebsiella pneumonia) and antifungal activity for Aspergillus niger and Aspergillus fumigatus by disc diffusion method. Among the tested compounds, ***2c*** *showed the most potent antibacterial and antifungal activities.*

Keywords: 1,4-thiazine, N-ethoxycarbonyl thiazine, antibacterial and antifungal activity, acute toxicity studies.

INTRODUCTION

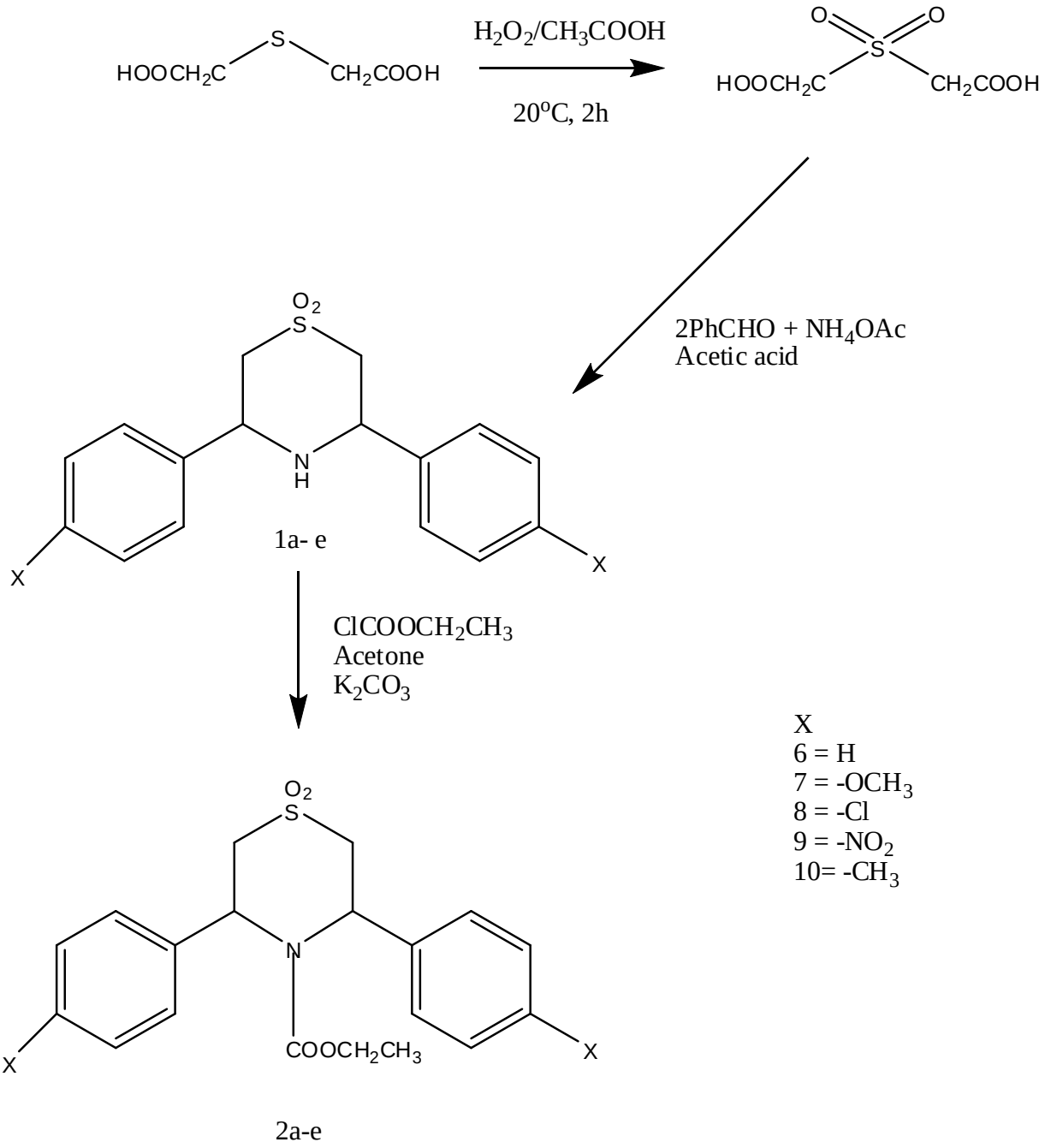
The incorporation of heteroatoms within a carbon framework often leads to new type of molecules, which are sometimes biologically important. Heterocyclic compounds having nitrogen and sulphur have potential pharmacological properties [1-5]. One such class of compounds are 1,4-thiazine-1,1-dioxides which possess two important pharmacophores, -NH and $-SO_2$. A large number of 1, 4-thiazine compounds have been synthesized and screened for their biological studies [6-8]. Preliminary assay of these compounds have shown antimicrobial activities [9-11]. In view of the above importance we have synthesized some 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides and preliminarily screened for their biological activities.

MATERIALS AND METHODS

Baliah and Rangarajan [12] synthesized 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides by the condensation of sulphonyldiacetic acid with aryl aldehydes and ammonia. The 3,5-diaryl tetrahydro-1,4-thiazine and its N-methyl derivatives were synthesized [13].

A series of 3, 5-diaryl-tetrahydro-N-ethoxycarbonyl-1, 4-thiazine-1, 1-dioxide (**2**) was synthesized. The above compounds **2a-e** have been synthesized by the reaction of ethyl chloroformate was added to a

solution of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide in the presence of dry acetone **(Scheme I)**. 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide has been synthesized by the chemoselective cyclization between aromatic aldehyde with sulphonyl diacetic acid and ammonium acetate in the presence of glacial acetic acid. The analytical data, IR, ^{1}H and ^{13}C NMR data are given.



Scheme - 1

All the melting points were noted in open capillaries and are uncorrected. IR absorption spectra were recorded on a Perkin-Elmer spectrophotometer using KBr pellet and ^{1}HNMR spectra on a Bruker AMXC-

500 FT NMR spectrometer (500 MHz) using $CDCl_3$ using TMS as an as internal standard. Purity of the compounds were routinely checked by TLC using silica gel coated aluminium plates (Merck).

General Method for the preparation of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide (1a-e) : All the parent 3, 5-diaryl tetrahydro-1,4-thiazine-1,1-dioxides (**1a-e**) were prepared according to the procedure of Baliah and Rangarajan[12] by the condensation of sulphonyldiacetic acid with araldehydes and ammonium acetate. Benzaldehyde (1.06 g, 0.02 mole), sulphonyldiacetate (0.02 mol) and ammonium acetate (0.01 mol) were condensed in the presence of glacial acetic acid (25 ml).

General method for the preparation of 3,5-diaryl-N-ethoxycarbonyl-tetrahydro-1,4-thiazine-1, 1-dioxide (2a): A solution containing 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide **2a** (3.87 g, 0.01 mole), ethyl chloroformate (0.01 mole) in dry acetone (40 ml). To this mixture anhydrous potassium carbonate (3 g) was added and the reaction mixture was refluxed for 12 h. Acetone was removed in vacuum and the residue crystallized from ethanol.

RESULTS AND DISCUSSION

The IR spectrum of a representative example **2a** is discussed below. The characteristic infra red absorptions around 1340-1240 and 1165-1120 cm^{-1} which are assigned to asymmetric and symmetric stretching vibrations of sulphonyl group present. The bands at 710-700 and 1040-1015 cm^{-1} show the presence of C-S and S-O bonds. Aromatic C-H band displays a medium band at 3000-3100cm^{-1}. A weak band at 1620-1510 cm^{-1} is safely assigned to the C=C band of the aromatic ring. It is well known that C=O group has characteristic absorption between 2000-1600cm^{-1}. The C=O absorption has been observed in the range of 1750-1700cm^{-1}. The observed C=O and SO_2 stretching vibrational bands are supporting evidence for the formation of compounds.

The ^1H NMR spectrum of a representative example **2a** is discussed below. The benzyl and methine protons (C-2 and C-6 and C-3 and C-5) of the thiazine shows distinct doublet at 3.21-3.10 and a triplet at 4.40ppm. The aromatic protons are showed their peaks at 7.00-7.50ppm at multiplet. The N-COCH_3 shows a multiplet at 4.10ppm and the methyl group at 1.30ppm as triplet.

The ^{13}C NMR spectrum is also in agreement with the structure, showing the expected number of signals. The aromatic carbons appear in the range of 120-144ppm and ipso carbons at 138-144ppm. The signals of C-3 and C-5 and C-2 and C-6 appear in the range of 55-60 ppm. The carbonyl carbon of CO appears in the range of 150-180ppm. The COCH_2CH_3 shows signals at 60-65ppm and the methyl group at 10-15ppm. All the other thiazines also give similar spectroscopic features.The structures of all these new products were elucidated on the basis of their elemental analysis, IR, ^1H NMR and ^{13}C NMR data (table 1 and 2). The antimicrobial activities of compounds 2a-e are given in table 3**.**

TABLE I Physical data of 3,5-diaryl-tetrahydro-N-ethoxycarbonyl-1,4-thiazine-1,1-dioxide (**2**)

Compound	m.p. (^oC)	Yield (%)	Molecular formula	Calc. (found) (%)		
				C	H	N
2a	214	58	$C_{19}H_{21}NO_4S$	63.49 (63.42	5.89 5.68	3.90 3.60)
2b	216	52	$C_{21}H_{25}NO_6S$	60.13 (60.02	6.01 5.94	3.34 3.12)

2c	215	54	$C_{19}H_{19}NO_4SCl_2$	53.28 4.47 3.20 (53.12 4.12 3.04)
2d	216	52	$C_{19}H_{19}N_3O_8S$	50.78 4.26 9.35 (50.68 4.12 9.02)
2e	217	56	$C_{21}H_{25}NO_4S$	65.09 6.56 3.61 (64.92 6.42 3.42)

Antimicrobial activity : The compounds 2a-e were evaluated *in vitro* for antibacterial activity against *E. Coli, K. pnemoniae, S. aureus, B. subtilis* and for antifungal activity against *Aspergillus niger* and *Aspergillus fumigatus* using acetone as solvent as 25 µg concentration by disc method. After 24 hr of incubation at 37°C the zone of inhibition were measured in mm. The activity was compared with the known antibiotics, viz., Norfloxacin, Griseofulvin at the same concentration, which is represented in table1.

To test for antibacterial activity, plates containing Nutrient Agar were seeded with different organisms at a concentration of 2-3 x 10^{-7} colony forming units (CFU) using a sterile swab. The filter paper discs containing the synthesized compounds were placed at different positions with the help of fine-pointed forceps. The plates were incubated at 37°C for 24 hours and the zone of inhibition was measured. The antifungal activity of the synthesized compounds 2a-e was also tested. The subculture and the viable count were carried out by the same procedure as for the antibacterial studies. The temperature maintained at 28±1°C and the results were noted after 72-96 hours. The concentration of the test compounds were as described previously and the solvent and Griesoflavin (standard drug) were used for the antifungal studies. Of the compounds tested, 2c (chloro substituted) inhibit the growth of tested bacteria and fungi at a minimum concentration of 25 µg ml^{-1}. The rest of the compounds show inhibition at higher concentration ranging from 50 to 200 µg $ml^{-1}$and 2a, 2e do not have inhibition even at 200µg ml^{-1}. 2b and 2d showed moderate activity when compared to the standard Norfloxacin and Griseofulvin.
All the melting points were noted in open capillaries and are uncorrected. IR absorption spectra were recorded on a Perkin-Elmer spectrophotometer using KBr pellet and ^{1}HNMR spectra on a Bruker AMXC-500 FT NMR spectrometer (500 MHz) using $CDCl_3$ using TMS as an as internal standard. Purity of the compounds were routinely checked by TLC using silica gel coated aluminium plates (Merck).

TABLE 2. ^{1}H and ^{13}C NMR data of 3,5-diaryl-tetrahydro-N-ethoxycarbonyl-1,4-thiazine-1,1-dioxide (2)

Compound	^{1}H NMR ($CDCl_3$)/TMS, δ (ppm)	^{13}C NMR ($CDCl_3$)/TMS, δ (ppm)
2a	3.10-3.21 (m, 2H) (C-2, C-5) 4.41 (t, 4H) (C3, C5) 1.20 (t, 3H, CH_3) 4.12 (s, 2H, CH_2), 7.21-7.45 (m, 10H) Aromatic	13.01 (CH_3), 58.77 (C2, C6) 59.03 (C3, C5), 62.22 (CH_2) 128.13-134.28 (Aromatic) 138.17 (ipso) 158.07(C=O)
2b	3.08-3.21 (m, 2H) (C-2, C-5) 3.82 (s, 6H, OCH_3) 4.42 (t, 4H) (C3, C5) 6.78 (d, 7.21-7.45 (m, 8H) Aromatic 1.12 (t, 3H, CH_3), 4.12 (s, 2H, CH_2)	55.24(-OCH_3), 58.29 (C2,C 6), 59.40 (C3, C5), 115.36-138.84 (Aromatic) 157.13 (ipso) 159.75(C=O), 61.76 (CH_2), 12.68 (CH_3)
2c	3.10-3.21 (m, 2H) (C-2, C-5) 4.42 (t, 4H) (C3, C5), 6.8 (d, 7.21-7.52 (m, 8H) Aromatic 1.24 (t, 3H, CH_3), 4.12 (s, 2H CH_2),	58.88 (C2, C6) 59.47 (C3,C5) 126.01-137.50 (Aromatic) 137.50 (ipso) 157.23(C=O) 13.03 (CH_3), 62.02 (CH_2)
2d	3.11-3.22 (m, 2H) (C-2, C-5) 4.42 (t, 4H) (C3, C5), 7.21-7.52 (m, 8H) Aromatic	58.12 (C2, C6) 59.52 (C3, C5) 126.05-129.75 (Aromatic)

	1.21 (t, 3H, CH_3), 4.12 (s, 2H, CH_2)	140.34 (ipso) 157.90(C=O) 13.84 (CH_3), 62.26 (CH_2)
2e	1.12 (s, 3H, CH_3), 3.10-3.21 (m, 2H) (C-2, C-5) 4.42 (t, 4H) (C3, C5), 7.11-7.52 (m, 8H) Aromatic 1.12 (t, 6H, CH_3) , 2.32 (s, 6H, CH_3), 4.12 (t, 2H, CH_2)	13.01 (CH_3), 58.76 (C2, C6), 59.02 (C3, C5), 61.83 (CH_2) 126.31-138.75 (Aromatic) 142.62 (ipso) 168.74(C=O) 21.30 (CH_3).

General Method for the preparation of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide (1a-e) : All the parent 3, 5-diaryl tetrahydro-1,4-thiazine-1,1-dioxides (**1a-e**) were prepared according to the procedure of Baliah and Rangarajan[12] by the condensation of sulphonyldiacetic acid with araldehydes and ammonium acetate. Benzaldehyde (1.06 g, 0.02 mol), sulphonyldiacetate (0.02 mol) and ammonium acetate (0.01 mol) were condensed in the presence of glacial acetic acid (25 ml).

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APPLICATIONS

In this the synthesis forms the major part followed by the preliminary screening of antimicrobial studies. Further studies are undergoing.

CONCLUSIONS

In the present study we synthesize some novel N- substituted thiazine compounds and they are preliminarily screened for their antimicrobial activities. The chloro substituted thiazine compounds show significant biological activities.

Table 3. Antibacterial activities of compounds 2a-e ***(Diameter of the zone of inhibition in mm)***

Compound No.	*Gram positive*		Gram negative		Fungi	
	A	**B**	**C**	**D**	**E**	**F**
2a	7	7	7	6	7	6
2b	9	10	10	11	10	9
2c	15	14	15	14	16	15
2d	12	13	14	12	14	14
2e	7	6	7	7	6	7
Norfloxacin	24	23	24	26	-	-
Griseofulvin	-	-	-	-	23	24
Acetone	**-**	**-**	**-**	**-**	**-**	**-**

A – Streptococci; B – Bacillus subtilis; C – Klebsiella pneumoniae; D – Escherichia coli; E – Aspergillus flavus, F – Aspergillus fumigatus.
Reference compound: Norfloxacin and Griseofulvin.
Inactive < 8 mm; Moderate - 8-12 mm; Active > 12 mm

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