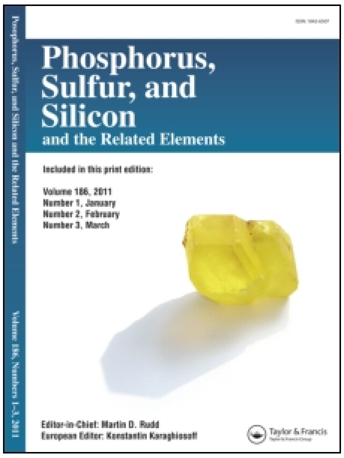

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CONDENSATION REACTION OF *BIS*(AROYLMETHYL) SULFIDES WITH AROMATIC ALDEHYDES AND AMMONIUM ACETATE

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Condensation reaction of *bis*(aroylmethyl) sulfides with aromatic aldehydes and ammonium acetate has been studied. The product obtained in each case is identified as 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazines by their analytical and spectral data. The stereochemistry of the products is also discussed. It is interesting to note that in most cases the only isomer isolable has the benzoyl group axially oriented.

Key words: Condensation; *bis*(aroylmethyl) sulfides; aromatic aldehydes; ammonium acetate; 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazines; stereochemistry.

INTRODUCTION

In our continued interest in the studies of the synthesis of heterocyclic compounds[1] containing two or more hetero atoms such as thiazines, oxathianes whose applications as sedatives, tranquilizers and other drug applications reported in the literature,[2] herein, we report the condensation reaction of *bis*(aroylmethyl) sulfides with aromatic aldehydes and ammonium acetate.

The reaction of active methylene function in ketone with aromatic aldehydes and ammonium acetate in the synthesis of a variety of heterocyclic compounds is well-known.[3] In the *bis*(aroylmethyl) sulfides used in this study, each methylene group is flanked between the carbonyl group and sulfur atom. From the literature, it is obvious that in *bis*(aroylmethyl) sulfides though the reaction of carbonyl group has been exploited in the synthesis of a variety of heterocyclic compounds[4] the reaction of active methylene has been little studied.[5] This is in contrast to its sulfone counterparts.[6] Hence, to study the reactions of *bis*(aroylmethyl) sulfides involving the —CH_2— function and to compare the behavior of these sulfides with the sulfone counterparts, we have carried out condensation reaction of *bis*(aroylmethyl) sulfides with different aromatic aldehydes and ammonium acetate and the results are presented here.

RESULTS AND DISCUSSION

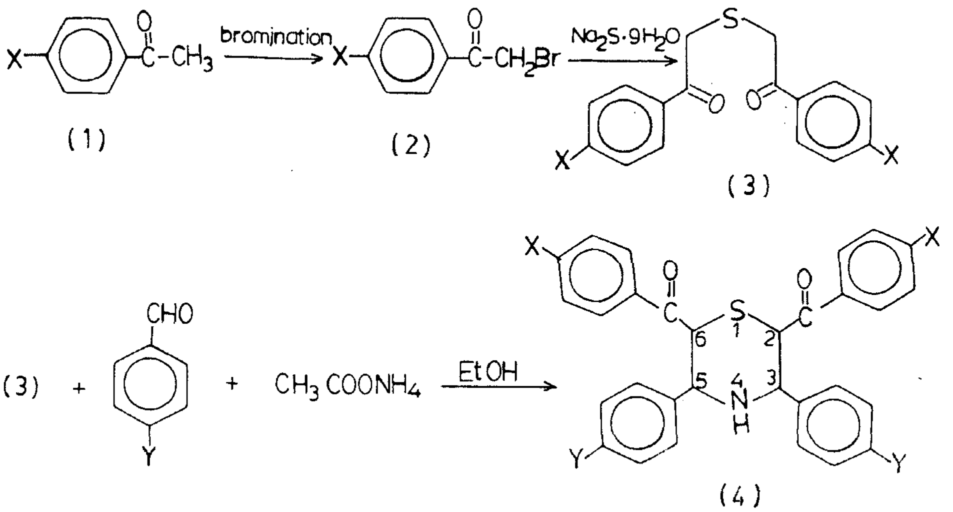
The condensation reaction of *bis*(aroylmethyl) sulfone with aromatic aldehydes and ammonium acetate under reflux produced 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxides as reported earlier.[6b] The *bis*(aroylmethyl) sulfides on condensing with aromatic aldehydes and ammonium acetate produced 2,6-diaroyl-3,5-

diaryltetrahydro-1,4-thiazine under mild experimental conditions as described in the typical procedure in moderate yield ranging from 42–50%.

If the mixture of *bis*(aroylmethyl) sulfide, aromatic aldehyde and ammonium acetate in ethanol is refluxed (as the procedure followed for sulfone counterparts), only an ether soluble red-resin resulted and no thiazine was obtained. On analysis by TLC—it was found to be a very complex mixture.

Bis(aroylmethyl) sulfide condensed with benzaldehyde, 4-chlorobenzaldehyde and 4-methylbenzaldehyde in the presence of ammonium acetate to give 2,6-dibenzoyl-3,5-diphenyltetrahydro-1,4-thiazine (4a), 2,6-dibenzoyl-3,5-di(4-chlorophenyl)tetrahydro-1, 4-thiazine (4b) and 2,6-dibenzoyl-3,5-di(4-methylphenyl)tetrahydro-1,4-thiazine (4c), respectively. *Bis*(4-methylbenzoylmethyl) sulfide condensed with 4-methylbenzaldehyde and ammonium acetate to produce 2,6-di(4-methylbenzoyl)-3,5-di(4-methylphenyl)tetrahydro-1,4-thiazine (4d). The reaction of *bis*(4-chlorobenzoylmethyl) sulfide with 4-methylbenzaldehyde and ammonium acetate gave 2,6-di(4-chlorobenzoyl)-3,5-di(4-methylphenyl)tetrahydro-1,4-thiazine (4e). (Scheme I.)

However, the reaction of *bis*(4-methoxybenzoylmethyl) sulfide with 4-methyl-



(4)	X	Y
a	H	H
b	H	Cl
c	H	CH_3
d	CH_3	CH_3
e	Cl	CH_3

SCHEME I

benzaldehyde and ammonium acetate yielded a resinous mass. The TLC analysis of this mass showed it to be a complex mixture of compounds. A similar result was obtained during the condensation of *bis*(2-naphthoylmethyl) sulfides with 4-methylbenzaldehyde and ammonium acetate. The reason for this behavior is not understood.

The condensation reaction attempted at room temperature with chloroform as co-solvent yielded pale yellow crystals after 24 hours which was identified in each case as 4 obtained by typical experimental procedure but in poor yield (~20%). The mother liquor on natural evaporation gave a red resinous product as described earlier.

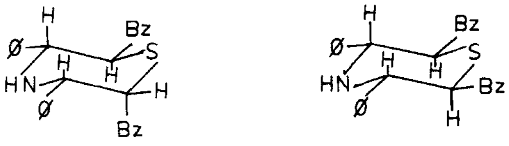
The physical data of these compounds are given in Table I. Their PMR spectral data are furnished in Table II. The structures of (4a–e) are assigned on the basis of their PMR spectra. The compounds (4a–e) exists as (i) except 4c which exists as (ii) as shown in Fig. 1. In the case of (4c), all the substituents are equatorially oriented. The compound (4c) exhibits two doublets for heterocyclic ring protons.

TABLE I
Physical data of compounds (4 a–e)

Compd.	Yield (%)	m.p °C	mol. formula	Found (%)		Calcd. (%)	
				C	H	C	H
4 a	48	188-90	$C_{30}H_{25}NO_2S$	77.65	5.30	77.75	5.39
4 b	45	190-1	$C_{30}H_{23}Cl_2NO_2S$	67.52	4.28	67.67	4.32
4 c	50	193-5	$C_{32}H_{29}NO_2S$	78.10	5.85	78.21	5.90
4 d	44	176-8	$C_{34}H_{33}NO_2S$	78.56	6.31	78.61	6.36
4 e	42	165-8	$C_{32}H_{27}Cl_2NO_2S$	68.48	4.75	68.58	4.82

TABLE II
PMR ($CDCl_3$) spectral data of compounds (4 a–e)

Compd.	Ar-H	C_2-H	C_6-H	C_3-H	C_5-H	-NH	Others
4 a	7.10-7.75	5.32	4.53	4.74	4.88	2.20	-
4 b	7.15-7.70	5.31	4.51	4.72	4.86	2.15	-
4 c	6.90-7.80	5.12		4.91		2.15	2.2 (CH_3)
4 d	7.00-7.70	5.32	4.52	4.73	4.88	2.2	2.2 (CH_3)
4 e	7.00-7.80	5.32	4.52	4.72	4.87	2.2	2.2 (CH_3)



(i) (ii)

FIGURE 1

By comparing the chemical shifts of its sulfone counterpart,[6b] the doublet at 5.15 (J = 10H) is assigned to proton at C_2 and C_6 and that at 4.90 (J = 10H) is assigned to protons at C_3 and C_5. Compounds (4a, b, d and e) exhibit four doublets each integrating to one proton, for the heterocyclic ring protons. The doublet at 5.32 may be ascribed to either C_2—H or C_6—H. The assignment is based on the following observations. The methylene protons of *bis*(benzoylmethyl) sulfone appears at 1.0 ppm downfield compared to the sulfide counterpart.[8] The ^{1}H NMR spectrum of 2,6-dibenzoyl-3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxide exhibited the C_2—H at about 6.4 ppm.[6b] On analogy with the ^{1}H NMR spectra of *bis*(benzoylmethyl) sulfone and the corresponding sulfide, the 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazines could be anticipated to exhibit C_2—H signal at about 5.4. In fact, the C_2—H signal appears at 5.32, which is closer to the anticipated value. The coupling constant 10 Hz for the C_2—H doublet indicates a diaxial coupling with its neighbor. Hence if the signal at 5.32 is arising due to C_2—H, then it follows that both the benzoyl group at C_2 and the phenyl group at C_3 are equatorially oriented. The C_3—H appears at 4.74 (J = 10 Hz). The doublet at 4.53 (J = 3 Hz) has been assigned to C_6—H based on comparison with the earlier work. In the ^{1}H NMR spectrum of 2e,6a-dibenzoyl-3e,5e-diaryltetrahydro-1,4-thiazine-1,1-dioxide, an upfield shift of about 0.65 ppm is noticed for the H at C_6 (benzoyl group axially oriented) compared to H at C_2 (benzoyl group equatorially oriented) attributed to lesser deshielding of the C_6—H by axial benzoyl group.[6b] The ^{1}H NMR spectrum of 2e,6a-dibenzoyl-3e,5e-diphenyltetrahydro-1,4-thiazine shows that C_6—H appears 0.79 ppm upfield compared to C_2—H, which is reasonably closer to 0.65 ppm observed in the ^{1}H NMR of sulfone counterparts. Hence C_6—H is equatorially oriented and C_5—H is axially oriented (δ = 4.88 ppm, J = 3 Hz). The unequal orientation of the carbonyl groups is further supported by two bands at 1660 cm^{-1} and 1648 cm^{-1} for carbonyl groups. Hence the conformation of 4a–e except for 4c may be represented as (i).

EXPERIMENTAL

Melting points reported were uncorrected. PMR spectra were recorded on an JEOL GSX-400 instrument with TMS as internal standard. The signal positions are indicated in δ scale. IR spectra were recorded on a Perkin-Elmer 577 instrument.

The *bis*(aroylmethyl) sulfides are readily obtained in high yields by the reaction of sodium sulfide nonahydrate with the corresponding α-bromoketones, which in turn are prepared in good yield by the bromination of the corresponding ketones by known methods.[7]

2,6-Diaroyl-3,5-diaryltetrahydro-1,4-thiazine (4a–e). A typical procedure: A mixture of *bis*(aroylmethyl) sulfide (0.01 mole), an aromatic aldehyde (0.02 mole) and ammonium acetate (0.01 mole) in ethanol (25 ml) was heated on a steam-bath until the reaction mixture became red-orange in color. On cooling, a red-orange mass was separated out which on washing with ether gave the 2,6-diaroyl-3,5-diaryltetrahydro-1,4-thiazine and it was recrystallized from the ethanol-chloroform mixture. The mother liquor on natural evaporation gave a red-orange resinous product which was found to be a very complex mixture by TLC.

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