Preparation of Tetrahydro-1 : 4-*thiazine* 1 : 1-*Dioxides.*

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Sulphonyldiacetic acid and its ethyl and methyl esters, when condensed with aromatic aldehydes and ammonia or aliphatic primary amines, give substituted tetrahydro-1 : 4-thiazine 1 : 1-dioxides.

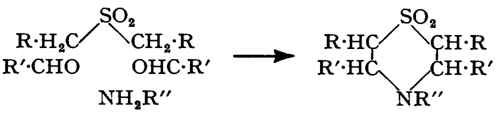
By analogy with the well-known condensation of acetonedicarboxylic esters or ketones with aromatic aldehydes and ammonia or certain aliphatic amines to give 4-piperidones, it might be expected that sulphones might yield tetrahydro-1 : 4-thiazine 1 : 1-dioxides (I). Failure of sulphones to condense thus was reported by Balasubramanian and Baliah (*J.*, in the press), it being probable that the α-hydrogen atoms are not sufficiently labile. However, diethyl sulphonyldiacetate, in which the methylene groups are activated by ethoxycarbonyl as well as by sulphonyl groups, condensed with a variety of aldehydes and ammonia or amines, giving excellent yields of the thiazine derivatives listed in Table 1.

Table 1. *Substituted tetrahydro*-1 : 4-*thiazine* 1 : 1-*dioxides* (I; R = CO_2Et).

R′	R″	Yield (%)	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Ph	H	83	184—185°	$C_{22}H_{25}O_6NS$	61·2	5·8	61·2	5·8
p-MeO·C_6H_4	H	57	171—173	$C_{24}H_{29}O_8NS$	58·3	5·6	58·6	5·9
o-MeO·C_6H_4	H	73	140—141	$C_{24}H_{29}O_8NS$	58·5	5·7	58·6	5·9
3 : 4-CH_2O_2:C_6H_3	H	67	216—218	$C_{24}H_{25}O_{10}NS$	55·4	4·7	55·5	4·9
3 : 4-MeO(OH)C_6H_3 [a]	H	46	185—187	$C_{24}H_{29}O_{10}NS$	55·0	5·3	55·0	5·6
p-Cl·C_6H_4	H	95	209—210	$C_{22}H_{23}O_6NCl_2S$	52·6	4·9	52·8	4·6
o-Cl·C_6H_4	H	63	143—145	$C_{22}H_{23}O_6NCl_2S$	52·5	4·9	52·8	4·6
m-O_2N·C_6H_4	H	87	183—184	$C_{22}H_{23}O_{10}N_3S$	50·6	4·3	50·7	4·4
o-O_2N·C_6H_4 [b]	H	73	198—199	$C_{22}H_{23}O_{10}N_3S$	50·6	4·5	50·7	4·4
p-Me·C_6H_4	H	65	169—171	$C_{24}H_{29}O_6NS$	62·9	6·4	62·7	6·4
2-Thienyl	H	54	158—159	$C_{18}H_{21}O_6NS_3$	48·4	4·8	48·7	4·8
3 : 4-$(MeO)_2C_6H_3$	H	46	160—162	$C_{26}H_{33}O_{10}NS$	56·6	6·2	56·6	6·0
Ph	Me	76	205—207	$C_{23}H_{27}O_6NS$	61·8	5·7	62·0	6·1
Ph	Et	73	199—201	$C_{24}H_{29}O_6NS$	63·1	6·3	62·7	6·4
Ph	Allyl	51	165—167	$C_{25}H_{29}O_6NS$	63·5	6·1	63·7	6·2
Ph	Bu^n	34	141—142	$C_{26}H_{33}O_6NS$	64·3	6·8	64·1	6·8
Ph	*n*-C_8H_{17}	35	120—121	$C_{30}H_{41}O_6NS$	66·0	7·4	66·3	7·6
Ph	C_6H_5·CH_2	58	159—161	$C_{29}H_{31}O_6NS$	66·9	5·8	66·8	6·0

[a] Rhombic crystals from dioxan–water. [b] Pale yellow needles from acetone–ethanol.

In ether or benzene these compounds form hydrochlorides which in water regenerate the bases and cannot be recrystallised.

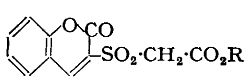


(I)

Only aliphatic amines undergo the condensation; the yields decrease with the higher homologues.

Only aromatic aldehydes undergo this condensation, *p*-chlorobenzaldehyde being the most reactive of those tried. No condensation occurred with *m*-hydroxy-, *p*-hydroxy-, or 2 : 4-dinitro-benzaldehyde. Salicylaldehyde gave a monocoumarin derivative (II; R = Et), and cinnamaldehyde gave only the unsaturated sulphone (III) (Backer, *Rec. Trav. chim.*, 1953, **72**, 119). Of aliphatic aldehydes investigated, only formaldehyde reacted and that gave only an unidentified product.

(II)



$[C_6H_5\cdot CH{:}CH\cdot CH{:}C(CO_2Et)-]_2SO_2$ (III)

Dimethyl sulphonyldiacetate reacted as well as the ethyl ester, and the compounds prepared from it are given in Table 2. Salicylaldehyde gave 3 : 3′-dicoumarinylsulphone (IV) as well as the monocoumarin (II; R = Me).

TABLE 2. *Substituted tetrahydro*-1 : 4-*thiazine* 1 : 1-*dioxides* (I; R = CO_2Me).

R′	R″	Yield (%)	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Ph	H	62	219—221°	$C_{20}H_{21}O_6NS$	59·8	5·0	59·6	5·2
3 : 4-$CH_2O_2{:}C_6H_3$ [a] ...	H	82	225—226	$C_{22}H_{21}O_{10}NS$	53·6	4·3	53·8	4·3
3 : 4-MeO(OH)C_6H_3 [b]	H	40	204—206	$C_{22}H_{25}O_{10}NS$	53·5	5·3	53·3	5·2
m-$O_2N{\cdot}C_6H_4$ [c]	H	83	205—207	$C_{20}H_{19}O_{10}N_3S$	48·7	4·0	48·7	3·9
o-$O_2N{\cdot}C_6H_4$ [c]	H	54	210—211	$C_{20}H_{19}O_{10}N_3S$	48·8	3·8	48·7	3·9
p-$Me{\cdot}C_6H_4$	H	39	203—205	$C_{22}H_{25}O_6NS$	61·2	5·8	61·2	5·8
2-Thienyl	H	77	177—178	$C_{16}H_{17}O_6NS_3$	46·7	4·0	46·3	4·1
p-$Cl{\cdot}C_6H_4$	H	91	220—221	$C_{20}H_{19}O_6NCl_2S$	51·1	4·4	50·9	4·1
o-$Cl{\cdot}C_6H_4$	H	73	174—176	$C_{20}H_{19}O_6NCl_2S$	50·7	4·2	50·9	4·1
3 : 4-$(MeO)_2C_6H_3$ ...	H	64	173—174	$C_{24}H_{29}O_{10}NS$	54·8	5·3	55·1	5·6
Ph [d]	Allyl	54	163—164	$C_{23}H_{25}O_6NS$	62·0	5·7	62·3	5·7
m-$O_2N{\cdot}C_6H_4$ [c]	Et	32	239—241	$C_{22}H_{23}O_{10}N_3S$	51·0	4·8	50·7	4·4

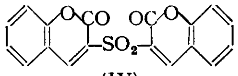
[a] Needles from acetone–ethanol. [b] Needles from dioxan–water. [c] Pale yellow needles from acetone–ethanol. [d] Softens at 129°.

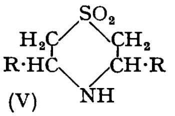
TABLE 3. 3 : 5-*Diaryltetrahydro*-1 : 4-*thiazine* 1 : 1-*dioxides* (V).

R	Yield (%)	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
Ph	34	205—206°	$C_{16}H_{17}O_2NS$	67·2	5·9	66·9	6·0
p-$MeO{\cdot}C_6H_4$	40	210—212	$C_{18}H_{21}O_4NS$	62·0	5·8	62·2	6·1
p-$Me{\cdot}C_6H_4$	30	168—170	$C_{18}H_{21}O_2NS$	69·0	6·8	68·6	6·7
p-$Cl{\cdot}C_6H_4$	52	194—195	$C_{16}H_{15}O_2NCl_2S$	54·0	4·4	53·9	4·2
m-$O_2N{\cdot}C_6H_4$ [a]	42	240—242	$C_{16}H_{15}O_6N_3S$	51·2	4·3	50·9	4·0
3 : 4-$CH_2O_2{:}C_6H_3$	25	237—240	$C_{18}H_{17}O_6NS$	57·6	5·0	57·6	4·6

[a] Plates from acetone–ethanol. The hydrochlorides of the last two compounds did not crystallise. The *hydrochlorides* of the first four compounds had m. p. (all with decomp.) 275—278° (Found : Cl, 11·0. Reqd. : Cl, 11·0%), 268—270° (Found : Cl, 9·2. Reqd. : Cl, 9·2%), 245—247° (Found : Cl, 9·9. Reqd. : Cl, 10·1%), and 267—270° (Found : Cl, 9·2. Reqd. : Cl, 9·0%), respectively.

Unlike the esters, sulphonyldiacetic acid did not undergo this condensation in ethanol, but with several aldehydes and ammonium acetate in glacial acetic acid it gave, with decarboxylation, products of type (V) (for details see Table 3). These compounds form hydrochlorides which are stable in water and can be recrystallised from ethanol or ethanol–ether. Sulphonyldiacetic acid with *m*-nitrobenzaldehehyde and ammonium acetate gives 2 : 2′-di-(*m*-nitrophenyl)divinyl sulphone (VI) in addition to the expected thiazine 1 : 1-dioxide.


(IV)


(V)

$(m\text{-}NO_2{\cdot}C_6H_4{\cdot}CH{:}CH\text{–})_2SO_2$
(VI)

EXPERIMENTAL

Diethyl Sulphonyldiacetate.—Sulphonyldiacetic acid (20 g.) (Alden and Houston, *J. Amer. Chem. Soc.*, 1934, **56**, 413) in absolute ethanol (100 c.c.) was saturated with dry hydrogen chloride. The excess of ethanol was removed by distillation and the residual solution was poured into water (150 c.c.). The separated liquid was taken up in ether and dried ($CaCl_2$); the solvent was removed and the residue distilled, giving the ester (24 g., 92%), b. p. 185—187°/10 mm. (cf. Backer, *loc. cit.*).

Dimethyl sulphonyldiacetate, similarly prepared in 96% yield, formed plates, m. p. 115—116° (from water) (Found : C, 34·6; H, 4·7. $C_6H_{10}O_6S$ requires C, 34·3; H, 4·8%).

Preparation of Substituted Tetrahydro-1 : 4-*thiazine* 1 : 1-*Dioxides from Sulphonyldiacetic Esters*.—The ester (0·01 mole), the aldehyde (0·02 mole), and ammonium acetate or the amine (0·01 mole) were refluxed in ethanol (20 c.c.) for 10—15 min. and then set aside overnight. The *compound* that separated was recrystallised from ethanol (see Tables 1 and 2).

Preparation of Substituted Tetrahydro-1 : 4-*thiazine* 1 : 1-*Dioxides from Sulphonyldiacetic*

Acid.—Sulphonyldiacetic acid (0·02 mole), the aldehyde (0·04 mole), and ammonium acetate (0·02 mole) were refluxed for 15—20 min. in glacial acetic acid (15 c.c.). After the evolution of carbon dioxide had subsided, the mixture was cooled and extracted with ether (30 c.c.). Dry hydrogen chloride was then passed through the ether solution which was set aside for a day. The *hydrochloride* that separated was recrystallised from ethanol or ethanol–ether. The *base* was liberated by dissolving the hydrochloride in ethanol, adding aqueous ammonia, and diluting with water (see Table 3).

Diethyl αα′*-Dicinnamylidenesulphonyldiacetate* [*Di-*(1*-ethoxycarbonyl-*4*-phenylbuta-*1 : 3*-dienyl*) *Sulphone*].—To an ethanolic solution of diethyl sulphonyldiacetate (2 g.), freshly distilled cinnamaldehyde (2·05 g.) and ammonium acetate (0·65 g.) were added and the mixture was refluxed for 10 min. Overnight, diethyl αα′-dicinnamylidenesulphonyldiacetate (2·5 g.) separated. Recrystallisation from ethanol gave yellow plates, m. p. 140—141° (Found : C, 67·0; H, 5·4; S, 7·1. Calc. for $C_{26}H_{26}O_6S$: C, 66·9; H, 5·6; S, 6·9%). Backer (*loc. cit.*) gives m. p. 134—136°.

*Ethyl Coumarin-*3*-sulphonylacetate.*—Diethyl sulphonyldiacetate (3 g.), salicylaldehyde (3·08 g.), and ammonium acetate (0·97 g.) gave this *compound* (2 g.) as plates, m. p. 195—196° (from ethanol) (Found : C, 53·0; H, 4·2; S, 10·75. $C_{13}H_{12}O_6S$ requires C, 52·7; H, 4·10; S, 10·8%).

*Di-*3*-coumarinyl Sulphone.*—Dimethyl sulphonyldiacetate (2·1 g.), salicylaldehyde (2·44 g.), and ammonium acetate (0·77 g.) were refluxed in 95% ethanol (20 c.c.) for 15 min. and left aside. Gradually, *di-*3*-coumarinyl sulphone* (2·3 g.) separated as pale yellow needles, m. p. 322—324° (decomp.) (from dioxan) (Found : C, 60·9; H, 3·0; S, 9·1. $C_{18}H_{10}O_6S$ requires C, 61·0; H, 2·8; S, 9·0%).

*Methyl Coumarin-*3*-sulphonylacetate.*—Evaporation of the solvent from the mother-liquor of the above preparation and removal of the unchanged salicylaldehyde from the residue with sodium carbonate solution gave *methyl coumarin-*3*-sulphonylacetate* (0·5 g.). It crystallised as shining plates (from ethanol), m. p. 214—216° (Found : C, 51·3; H, 3·8. $C_{12}H_{10}O_6S$ requires C, 51·05; H, 3·6%).

2 : 2′*-Di-*m*-nitrophenyldivinyl Sulphone.*—Sulphonyldiacetic acid (2 g.), *m*-nitrobenzaldehyde (3·32 g.), and ammonium acetate (0·9 g.) were refluxed in glacial acetic acid (3 c.c.) for 30 min. After cooling, the product was shaken with ether (30 c.c.), and the ether-insoluble material was dissolved in acetone and precipitated by water. The unsaturated *sulphone* (1 g.) was obtained as light-yellow needles, m. p. 179—180° (from acetone–ethanol) (Found : C, 53·8; H, 3·7. $C_{16}H_{12}O_6N_2S$ requires C, 53·3; H, 3·4%).

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