

Oxidative Coupling of 2*H*-1,4-Thiazine Derivatives (1).

D. Sica, C. Santacroce and G. Prota

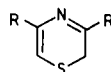
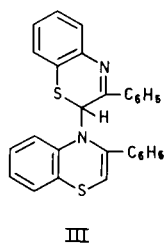
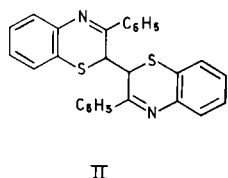
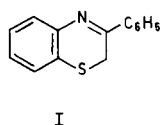
Istituto di Chimica Organica, Università di Napoli

When treated with oxidizing agents, 3,5-disubstituted 2*H*-1,4-thiazines undergo oxidative coupling at the 2-position yielding 2,2'-bithiazines. Under similar conditions 3-substituted 2*H*-1,4-benzothiazines behave similarly to give the corresponding 2,2'-dehydrodimers.

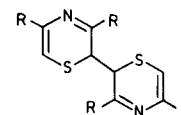
Evidence is presented that the oxidative coupling of all compounds examined proceeds preferentially to give the *meso*-isomers.

There are only a few examples in the literature on the oxidation behaviour of 2*H*-1,4-thiazine derivatives and these are all on the oxidative coupling of 3-phenyl-2*H*-1,4-benzothiazine (I). Fujii reported (2) that 2,2'-bi(3-phenyl-2*H*-1,4-benzothiazine) (II) was produced from I when treated with picric acid in ethanol solution. The structure of the oxidation product was later questioned by Bottex *et al.* (3) who presented evidence that aerial oxidation of a solution of I in organic solvents gave a dimeric product, the spectral properties of which were consistent with the unsymmetrical structure III rather than the symmetrical one (II). However, evidence in support of the symmetrical

crystalline yellow precipitate (Va) was obtained in 71% yield. Elemental analysis and mass spectrometry indicated the molecular formula  $C_{32}H_{24}N_2S_2$ , thus suggesting that under the reaction condition IVa underwent oxidative coupling. Apart from a complex series of signals at 7.1-8.15  $\delta$  attributable to 20 aromatic protons, the nmr spectrum of the product showed the presence of two equivalent protons having nearly the same chemical shift (6.13  $\delta$ ) of the 6-proton of IVa (6.44  $\delta$ ) and a signal at 4.48  $\delta$  which accounted for the two remaining protons. These data, combined with the uv spectrum (Table I) indicated 2,2'-bi(3,5-diphenyl-2*H*-1,4-thiazine) as the structure for compound Va.



IV a, R = C<sub>6</sub>H<sub>5</sub>  
IV b, R = p-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>



V a, R = C<sub>6</sub>H<sub>5</sub>  
V b, R = p-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>

structure was recently provided by Wilhelm and Schmidt (4) who have reported that during the distillation of I a dimeric product was obtained which was characterized as II on the basis of mass spectroscopy and nmr analysis.

Considering these observations, a more detailed investigation of the oxidative coupling of 2*H*-1,4-thiazine derivatives appeared to be desirable, since we have recently found that this reaction is probably involved in the biosynthesis of trichosiderins, a new group of natural pigments occurring in red hairs and feathers (5,6,7).

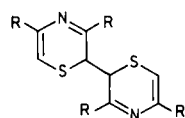
When a solution of 3,5-diphenyl-2*H*-1,4-thiazine (IVa) (8) in absolute ethanol was treated with picric acid, a

oxidative coupling of IVa could be also effected by using nitrobenzene as dehydrogenating agent. However in this case the oxidation proceeded smoothly and a 57% yield of the corresponding dehydrodimer was obtained only after prolonged heating (10 hours) at 140°. With a more powerful dehydrogenating agent, as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, the oxidation of IVa proceeded even at room temperature, but afforded a complex mixture of products among which only the desired dehydrodimer was isolated in 30% yield.

Likewise 3,5-bis(*p*-tolyl)-2*H*-1,4-thiazine (IVb) (8), when treated with the above mentioned dehydrogenating agents, underwent oxidative coupling at the 2-position yielding 2,2'-bi[3,5-bis(*p*-tolyl)-2*H*-1,4-thiazine] (Vb).

TABLE I

## 2,2'-Bi(3,5-diaryl-2H-1,4-thiazines)

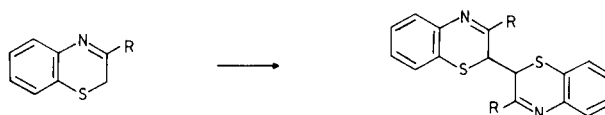


Compound	R	UV Data (a) m $\mu$ (log $\epsilon$ )	NMR Data (b)		MS Data m/e (relative intensity)
			Proton	$\delta$ -value	
Va	C <sub>6</sub> H <sub>5</sub>	272 (4.64)	2	4.48 (s)	500 (2.5)
		401 (3.87)	2	6.13 (s)	250 (100)
			20	7.1-8.15 (m)	
Vb	<i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	280 (4.67)	12	2.41 (s)	556 (2.4)
		401 (3.80)	2	4.43 (s)	278 (100)
			2	6.06 (s)	
			16	7.1-8.15 (m)	

(a) In 1,4-dioxane. (b) In deuteriochloroform.

TABLE II

## Oxidative Coupling of 2H-1,4-Benzothiazines

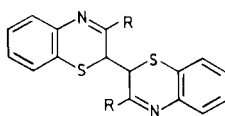


VI a-b

VII a-b

Compound	R	Solvent	Oxidizing Agent	Temp. (°C)	Reaction Time (hr.)	Product of Reaction	Yield (%)
VIa	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	Ethanol	Picric acid	reflux	0.5	VIIa	62
		---	Nitrobenzene	80	5		44
		Ethanol	Oxygen	25	5		3
		Ethanol+ hydrochloric acid	Oxygen	25	5		45
		Ethanol+ potassium hydroxide	Oxygen	25	5		3
VIb	<i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	Ethanol	Picric acid	reflux	0.5	VIIb	72
		---	Nitrobenzene	80	5		35
		Ethanol	Oxygen	25	5		3
		Ethanol+ hydrochloric acid	Oxygen	25	5		46
		Ethanol+ potassium hydroxide	Oxygen	25	5		3

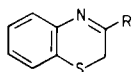
TABLE III

2,2'-Bi(3-aryl-2*H*-1,4-benzothiazines)

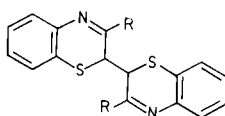
Compound	R	UV Data (a) m $\mu$ (log $\epsilon$ )	NMR Data (b)		MS Data m/e (relative intensity)
			Proton	$\delta$ -value	
VIIa	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Br	264 (4.52)	2	4.44 (s)	604 (0.39)
		292 (4.19)	16	6.8-7.9 (m)	302 (100)
		342 (4.04)			
VIIb	<i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	266 (4.34)	6	2.31 (s)	476 (1.5)
		289 (4.07)	2	4.50 (s)	238 (100)
		341 (3.90)	16	6.9-8.0 (m)	

(a) In 95% ethanol. (b) In deuteriopyridine at 100°.

2*H*-1,4-Benzothiazines were found to be more sensitive to oxidizing agents and the oxidative coupling of VIa and VIb (9) could be accomplished under milder conditions (Table II) than those employed for the thiazines IVa and IVb.



VI a, R = *p*-C<sub>6</sub>H<sub>4</sub>Br  
VI b, R = *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>



VII a, R = *p*-C<sub>6</sub>H<sub>4</sub>Br  
VII b, R = *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>

In addition to picric acid and nitrobenzene, the dimerization of benzothiazines VI could be also effected by using oxygen. As shown in Table II, in neutral or alkaline media the oxidation proceeded very smoothly, yielding the expected symmetrical dehydrodimers VII in very poor yield. However in the presence of acid the rate of reaction was considerably increased and about 45% of the starting material was converted into the corresponding, 2,2'-bibenzothiazines. The structure of the products obtained by oxidation of VIa and VIb was assigned on the basis of elemental analyses and spectral properties, the latter being summarized in Table III. Conclusive evidence for the symmetrical structures VIIa and VIIb was provided by the nmr spectra which showed the presence of a singlet, integrating for two protons, at 4.4 and 4.50  $\delta$ , respectively, attributable to the protons at C-2 and C-2' positions.

Although the dimerization of 1,4-thiazines and 1,4-benzothiazines should lead to the formation of a mixture

of the *meso*-form and the *dl*-pair, in all cases examined only one stereoisomer was isolated. X-ray analysis of compound VIIa (see Experimental section) which was obtained as monoclinic crystals (P2<sub>1</sub>/c) showed that only two molecules could be accommodated in the unit cell, thus indicating that the molecule had a centre of symmetry and therefore represents the optically inactive *meso*-compound.

Though the stereochemistry of the other dehydrodimers has not been investigated, it seems likely that the oxidative coupling of IVa, IVb and VIb also proceeds preferentially to give the *meso*-isomers Va, Vb and VIIb which are relatively less hindered than the corresponding *dl*-pairs.

## EXPERIMENTAL

Microanalyses were carried out by E. Thommen, Department of Organic Chemistry, University of Basel, Switzerland. Melting points were determined in capillaries and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Infracord 137E, uv spectra with a Bausch and Lomb (Spectronic 505) spectrophotometer and nmr spectra with a Varian A-60A spectrometer. Chemical shifts are expressed in ppm from TMS; s, singlet, m, multiplet. Mass spectra were measured by direct insertion technique with an A.E.I. MS 902 spectrometer (70 eV and 50  $\mu$  a) with a source temperature ca. 200°. Preparative thick-layer chromatography (PLC) was carried out on F<sub>254</sub> silica (E. Merck, A.G., Germany) and all solvents used for development and for elution were redistilled. Proportions given for mixed solvents are by volume. 2,2'-Bi(3,5-diphenyl-2*H*-1,4-thiazine) (Va).

## Method A.

A solution of 3,5-diphenyl-2*H*-1,4-thiazine (IVa) (0.9 g.) and picric acid (0.81 g.) in absolute ethanol (15 ml.) was refluxed for

15 minutes. After cooling, the precipitate was collected, washed with ethanol and dried to give 0.64 g. (71% yield) of Va. On recrystallization from benzene the compound had a melting point 214-215°; infrared  $\text{cm}^{-1}$ , 3030, 1592, 1553, 1511, 1333, 1316, 1299, 1258, 1193, 1183, 1170, 1156, 1073, 1056, 1027, 1000, 991, 971, 926, 885, 849, 833, 793, 790, 775, 746, 740, 689 (nujol).

*Anal.* Calcd. for  $\text{C}_{32}\text{H}_{24}\text{N}_2\text{S}_2$ : C, 76.76; H, 4.83; N, 5.59; S, 12.80. Found: C, 76.95; H, 5.03; N, 5.49; S, 12.62.

The uv, nmr and ms data are summarized in Table I.

#### Method B.

A solution of IVa (0.8 g.) in nitrobenzene (1 ml.) was heated at 140° for 10 hours. On cooling, a crystalline solid (0.1 g.) separated out. An additional 0.35 g. of the same material was obtained by evaporating the filtrate to dryness and by chromatographing the residue on a silica column (high grade silica gel 0.05-0.2 mm, Merck), using as the eluent petroleum ether-benzene (50:50), combined yield 57%. Recrystallization of the product from benzene gave analytically pure sample of Va which showed no melting point depression when mixed with that obtained above.

#### Method C.

To a well stirred solution of IVa (0.5 g.) in benzene (6 ml.), a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.45 g.) in benzene (40 ml.) was added dropwise over a period of ca. 1 hour. After the addition, the reaction mixture was allowed to stand at room temperature for 15 minutes, the solid was removed by filtration and washed several times with benzene. The combined filtrate and washings were evaporated to dryness *in vacuo* and the residue was chromatographed on a neutral alumina column (Woelm, grade III) eluted with petroleum ether-benzene (60:40). The first yellow band which emerged from the column was further purified by PLC over silica gel using as eluent petroleum ether-benzene (60:40). The band Rf 0.33 afforded 0.152 g. of Va (30% yield), identical in all respect with that obtained above.

2,2'-Bi[3,5-bis(*p*-tolyl)-2*H*-1,4-thiazine] (Vb).

#### Method A.

By the procedure outlined in Va, Method A, 1 g. of 3,5-bis(*p*-tolyl)-2*H*-1,4-thiazine (IVb) was oxidized with picric acid to give 0.78 g. (78% yield) of Vb. On recrystallization from benzene the product had the m.p. 254-255°; infrared  $\text{cm}^{-1}$ , 3030, 1613, 1587, 1558, 1520, 1316, 1299, 1285, 1263, 1193, 1179, 1111, 1064, 1036, 1017, 980, 893, 862, 848, 833, 819, 813, 794, 775, 757, 741, 714 (nujol).

*Anal.* Calcd. for  $\text{C}_{36}\text{H}_{32}\text{N}_2\text{S}_2$ : C, 77.65; H, 5.79; N, 5.03; S, 11.51. Found: C, 77.85; H, 6.02; N, 4.81; S, 11.30.

The uv, nmr and ms data are summarized in Table I.

#### Method B.

A solution of IVb (1 g.) in nitrobenzene (2 ml.) was heated at 140° for 10 hours and then filtered to give 0.46 g. of yellow solid (46% yield). After recrystallization from benzene, the product showed no melting point depression when mixed with a sample of Vb, obtained by the Method A.

#### Method C.

Oxidation of IVb (0.56 g.) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.37 g.) as outlined for IVa, gave 0.140 g. of Vb (25% yield) melting at 253-255°.

2,2'-Bi(3-*p*-bromophenyl)-2*H*-1,4-benzothiazine (VIIa).

#### Method A.

A solution of 3-(*p*-bromophenyl)-2*H*-1,4-benzothiazine (VIa) (2 g.) and picric acid (1.5 g.) in ethanol (50 ml.) was refluxed for 0.5 hours. After cooling, the crystalline precipitate was collected by filtration and washed with ethanol to give 1.25 g. of VIIa which was recrystallized from xylene, m.p. 230-231°; infrared  $\text{cm}^{-1}$ , 3030, 1605, 1587, 1550, 1490, 1316, 1263, 1220, 1170, 1125, 1105, 1075, 1008, 970, 943, 870, 855, 840, 826, 820, 775, 751, 720, 714 (nujol).

*Anal.* Calcd. for  $\text{C}_{28}\text{H}_{18}\text{Br}_2\text{N}_2\text{S}_2$ : C, 55.45; H, 2.99; N, 4.61; S, 10.57. Found: C, 55.83; H, 2.92; N, 4.42; S, 10.39.

The uv, nmr and ms data are summarized in Table III.

#### Molecular Symmetry Determination by X-rays.

A crystal was mounted on a X-ray diffraction apparatus for determining unit cell dimension. Weissenberg and precession photographs showed that the compound crystallized in the monoclinic system with unit cell parameters:  $a = 13.28$ ,  $b = 13.80$  and  $c = 6.79$  Å;  $\beta = 93^\circ.39'$ . The systematic absences were:

$$h\ 0\ l \quad \text{absent if} \quad l = 2n + 1$$

$$0\ k\ 0 \quad \text{absent if} \quad k = 2n + 1$$

thus the space group was  $P2_1/c$ . With two formula units in a unit cell the density was calculated to be 1.62 g./ $\text{cm}^3$  which was in good agreement with the measured density (by flotation technique) of  $1.63 \pm 0.01$  g./ $\text{cm}^3$ .

#### Method B.

A solution of VIa (0.45 g.) in 1.2 ml. of nitrobenzene was heated at 80° for 5 hours. The resulting precipitate was collected by filtration and dried to give 0.2 g. of VIIa, which was identical in all respects with that prepared by Method A.

#### Method C.

A stream of oxygen was bubbled at room temperature through a solution of 0.6 g. of VIa in ethanol (20 ml.) to which 1 ml. of concentrated hydrochloric acid was added. After 5 hours the oxidation was stopped and the precipitate was filtered and dried to give 0.27 g. of VIIa, identical in all respects with that obtained by Method A. Under similar conditions oxidation of VIa (0.61 g.) in neutral ethanol solution afforded 0.02 g. of VIIa. Similar yields were obtained when the oxidation was carried out in ethanol containing 1% of potassium hydroxide.

2,2'-Bi(3-*p*-tolyl)-2*H*-1,4-benzothiazine (VIIb).

#### Method A.

An ethanolic solution of 3-(*p*-tolyl)-2*H*-1,4-benzothiazine (VIb) (1 g.) was oxidized with picric acid by using the general procedure described in VIIa. After recrystallization from xylene, the product VIIb (0.72 g.) had m.p. 244-245°; infrared  $\text{cm}^{-1}$ , 3030, 1613, 1592, 1563, 1538, 1316, 1299, 1282, 1250, 1214, 1198, 1183, 1111, 1073, 1010, 941, 862, 840, 819, 769, 746, 725, 714 (nujol).

*Anal.* Calcd. for  $\text{C}_{30}\text{H}_{24}\text{N}_2\text{S}_2$ : C, 75.59; H, 5.07; N, 5.87; S, 13.45. Found: C, 75.84; H, 5.29; N, 5.77; S, 13.26.

The uv, nmr and ms data are summarized in Table III.

#### Method B.

By the general procedure outlined in VIIa, 1 g. of VIb was oxidized with nitrobenzene (3 ml.) to give 0.35 g. of VIIb showing no melting point depression when mixed with the product obtained above.

#### Method C.

Oxidation of VIb with oxygen in acidic, neutral and alkaline

ethanol solution was performed as described in VIIa. The yields are summarized in Table II.

Acknowledgment.

The authors wish to express their appreciation to Professor L. Mazzarella (Istituto Chimico, Università di Napoli) for assistance in the X-ray analysis.

REFERENCES

(1) This investigation was supported in part by a grant from Laboratorio per la Chimica e Fisica di Molecole di interesse biologico del C.N.R., Napoli.

(2) K. Fujii, *Yakugaku Zasshi*, **77**, 347 (1957); *Chem. Abstr.*, **51**, 12100 (1957).

(3) P. Bottex, B. Sillion, G. De Gaudemaris and J. J. Basselier, *Compt. Rend.*, **267C**, 186 (1968).

(4) M. Wilhelm and P. Schmidt, *J. Heterocyclic Chem.*, **6**, 635 (1969)

(5) R. A. Nicolaus, G. Prota, C. Santacroce, G. Scherillo and C. Sica, *Gazz. Chim. Ital.*, **99**, 323 (1969).

(6) G. Prota, *J. Invest. Dermatol.*, **50**, 82 (1970).

(7) G. Prota, G. Scherillo, O. Petrillo and R. A. Nicolaus, *Gazz. Chim. Ital.*, **99**, 1193 (1969).

(8) D. Sica, C. Santacroce and R. A. Nicolaus, *ibid.*, **98**, 17 (1968).

(9) C. Santacroce, D. Sica and R. A. Nicolaus, *ibid.*, **98**, 85 (1968).

Received June 9, 1970

Naples, Italy