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SYNTHESIS AND PHOTOCHROMISM OF $\Delta^{2,2'}$-BI-(2H-1,4-BENZOTHIAZINE)

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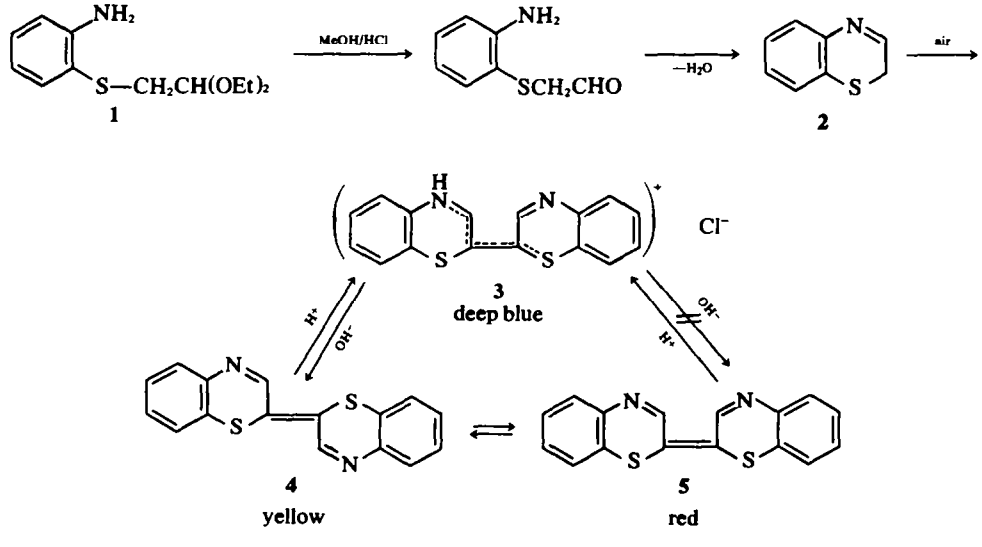
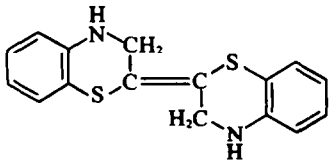
Abstract—$\Delta^{2,2'}$-Bi- (2H-1,4-benzothiazine) (**4**), the parent ring system of a group of amino-acid pigments (trichosiderins) from red hair and feathers, has been synthesized by a simple and novel method involving air oxidation of 2H-1,4-benzothiazine, generated *in situ* by treatment of 1-(*o*-aminophenylthio)-2,2-diethoxyethane (**1**). This procedure yields only the yellow *trans*-isomer **4**, which in solution exhibits marked photochromism, being reversibly converted into the red unstable *cis*-form **5** on brief irradiation with sunlight.

Our interest in the chemistry of trichosiderins, a group of $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) pigments occurring in red hair and feathers,[1-3] has led us to look for a synthesis for the parent ring system. Unfortunately, the earlier synthetic procedure[4] involving oxidative coupling of 3-substituted-2H- 1,4-benzothiazines could not be adapted to the preparation of $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) itself, because of the inaccessibility of the starting material, which on account of its high instability has so far never been isolated. Notably, a recent study[5] has shown that the product which is formed by condensation of 2-aminothiophenol and 1,2-dibromoethylene, is 2-methylbenzothiazole and not 2H-1,4-benzothiazine, as previously reported by Langlet.[5]

Another attempt[5] to prepare 2H-1,4-benzothiazine by a more unambigous route, namely by hydrolysis of 1-(*o*-aminophenylthio)-2,2-diethoxyethane (**1**), also resulted in the isolation of 2-methylbenzothiazole which, as suggested, presumably arises by ring contraction of the 2H-1,4-benzothiazine formed initially. The plausible intermediacy of the elusive 2H-1,4-benzothiazine in the hydrolysis of **1** led us to re-examine this route in the hope that, under milder controlled conditions, it could be possible to limit to some extent the rearrangement of the thiazine ring. In fact, under most of the conditions we tried acid treatment of **1** afforded, along with some 2-methylbenzothiazole, a deep yellow substance which, surprisingly, was found to correspond to the desired $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) (**4**), arising most probably by air oxidation of 2H-1,4-benzothiazine (**2**), generated *in situ* (Scheme 1).

After several trials, a satisfactory, simple and





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reproducible method was developed for the preparation of 4 in 52% yield, involving treatment of a methanolic solution of 1 with conc HCl at room temperature in the presence of atmospheric oxygen. Subsequent concentration of the dark blue mixture gave a microcrystalline precipitate (3) corresponding to the hydrochloride of $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine), which, after neutralization with $NaHCO_3$aq, gave the remarkably stable free base 4 as yellow-orange prisms, subliming above 185° and melting at 298–300° without appreciable decomposition. The identification of this compound followed principally from the molecular formula $C_{16}H_{10}N_2S_2$ (elemental analysis and mass spectroscopy), and from the characteristic pH-dependence of the visible spectrum (Table 1), showing a large reversible bathochromic shift on acidification, typical of the $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) chromophore.[1,7] On treatment with $NaBH_4$ or LAH, 4 underwent selective reduction at the azomethine double bonds yielding a colourless tetrahydroderivative (6), $C_{16}H_{14}N_2S_2$, which was readily reoxidized in nitrobenzene at 140° or better by oxygen in acid media at room temp to give the starting product, thus regenerating the fully conjugated chromophoric system.

The assignment of the stereochemistry of $\Delta^{2,2'}$-bi-(2H-1,4-benzothiazine) was assisted by the observation that in solution it exhibits a pronounced photochromism. When a dilute solution of 4 in dioxan or benzene is exposed to sunlight at room temperature it turns immediately from deep yellow to pale red, showing a new broadened maximum at 480 nm of markedly lower intensity and an isosbestic point at 492 nm (Fig 1). In the dark the process reverses

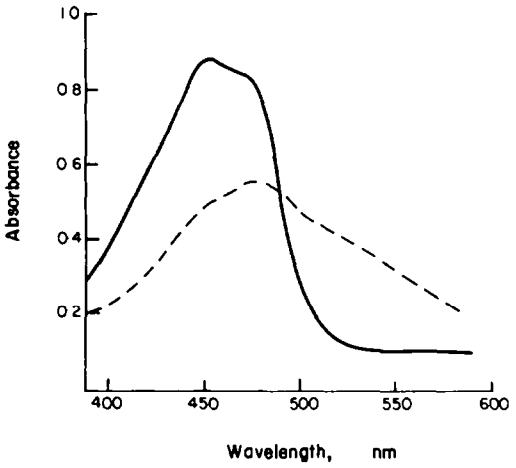

Fig 1. Visible spectra of $\Delta^{2,2'}$-bi-(2H-1,4-benzothiazine) in dioxan before (——) and after (– – –) brief (30 sec) irradiation with direct sunlight.

slowly at room temperature, but rapidly above 60°, to regenerate the original spectrum while preserving the same isosbestic point, thus indicating that a photochemical equilibrium between the stable yellow $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) and its red photoproduct has been attained by irradiation.

Unfortunately, the exceedingly low solubility of $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) in most suitable solvents precluded a PMR study of the photoequilibrium. Slow evaporation of a benzene solution of 4, exposed to direct sunlight, allowed the isolation of the photoproduct which, as expected, was found to be isomeric with the starting material. On heating the photoisomer in the solid state for 5 min at 175°, an almost quantitative reconversion to the stable yellow form occurred. In solution, in addition to the photochemical and thermal reconversion, the red isomer could also be transformed into the *trans*-isomer 4 by protonation with dilute HCl to give the corresponding deep-blue mesomeric ammonium-

Table 1. Absorption spectra of the two isomeric $\Delta^{2,2'}$-bi-(2H-1,4-benzothiazines)

Structure	λ_{max}^{dioxan}	nm(log ε)	$\lambda_{max}^{MeOH/H^{+a}}$	nm(log ε)	$\lambda_{max}^{6N\,HCl}$	nm(log ε)
4[b]	470 sh	(4·32)	562	(4·34)	597	(4·53)
	454	(4·34)	366	(3·87)	402	(3·73)
	274	(4·65)	292 sh	(4·13)	313	(4·17)
	267 sh	(4·47)	272	(4·45)	303	(4·17)
					275	(4·38)
5[c]	480	(4·05)	562	(4·34)	597	(4·53)
	298	(4·25)	366	(3·87)	402	(3·73)
	274	(4·40)	292 sh	(4·13)	313	(4·17)
	267 sh	(4·37)	272	(4·45)	303	(4·17)
					275	(4·38)

[a] MeOH/conc HCl (99:1, v/v).
[b] The blue shift is reversible on neutralization
[c] Neutralization of acid solution give the spectrum of 4

thionium cation from which 4 was obtained by neutralization (Scheme 1).

The facile interconversion of the two isomers, together with their relative stabilities, led us to conclude that the yellow stable form of $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) had the *trans*-configuration 4 around the inter-ring double bond, and that its red photoproduct was the *cis*-form 5. This is consistent with the ratio between the extinction coefficients of the visible absorption maxima of 4 and 5 (Table 1), indicating that the chromophore of the former possesses a higher degree of planarity with respect to the latter, in which interactions between the hydrogens at C-3 and C-3' are expected to cause strong disturbance of the coplanarity of the conjugated system.

Thus, the photochromism of $\Delta^{2,2'}$-bi-(2H-1,4-benzothiazine) can be ascribed to the *cis-trans* isomerization about the central double bond, which appears to be characterized by a rather low energy barrier to interconversion. An important implication of this result is that the photochemical colour changes observed[8] in some natural $\Delta^{2,2'}$-bi- (2H-1,4-benzothiazine) pigments, can now be explained similarly, thus permitting the stereochemistry of the stable forms to be defined as *trans*.

EXPERIMENTAL

M.ps were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Infracord 137 E, UV spectra with a Perkin-Elmer 402 spectrophotometer and PMR spectra with a Perkin-Elmer R-12 A spectrometer. Chemical shifts are expressed in δ values (ppm) downfield from TMS as internal reference. Mass spectra and exact mass measurements were measured by the direct insertion technique with an AEI-MS 902 spectrometer (70 eV) with the lowest source temperature which produced a definite spectrum. Besides the molecular ion the most abundant ions in the mass spectrum (above *m/e* 100) are given with their relative intensities. Analytical TLC was carried out on Merck silica GF_{254} using either (a) ether: benzene (90:10) or (b) chloroform: ethyl acetate (80:20) as solvent systems.

trans-$\Delta^{2,2'}$-*Bi*- (2*H*-1,4-*benzothiazine*), 4

To a soln of 1[5] (500 mg) in MeOH (80 ml), conc HCl (20 ml) was added, and the mixture was left at room temp overnight under a stream of air. The resulting dark-blue soln was concentrated *in vacuo* to a small volume (20 ml) and the microcrystalline ppt 3, which formed on cooling, was collected by filtration, washed with MeOH, and suspended in $NaHCO_3$ aq to give the free base 4, crystallizing from toluene as orange-red prisms (160 mg), homogeneous on TLC (solvent (a); $R_f = 0{\cdot}41$). After recrystallization from DMF the product had m.p. 298–300°, and gave consistent analytical data. (Found: C, 65·95; H, 4·02; N, 9·15; S, 22·12; $C_{16}H_{10}N_2S_2$ requires: C, 65·30; H, 3·40; N, 9·52; S, 21·76%); *m/e* 294 (M^+, 100), 261 (17), 249 (8), 230 (5), 159 (10), 147 (13), 120 (8%); λ_{max}: see Table 1; ν_{max}($CHCl_3$) 1620 and 1603 cm^{-1}.

cis-$\Delta^{2,2'}$-*Bi*- (2H-1,4-*benzothiazine*), 5

A saturated soln of 4 (50 mg) in benzene was exposed to direct sunlight until UV and TLC (solvent (a), (b)) examination demonstrated the complete conversion of starting compound into its red isomer. The resulting soln was then concentrated under reduced pressure at 30° to a volume of 15 ml, thus obtaining 35 mg of 5, dark red prisms, homogeneous on TLC (solvent (a), $R_f = 0{\cdot}79$) sparingly soluble in organic solvents. (Found: C, 64·52; H, 3·78; N, 9·36; S, 22·40. $C_{16}H_{10}N_2S_2$ requires: C, 65·30; H, 3·40; N, 9·52; S, 21·76%). The molecular formula $C_{16}H_{10}N_2S_2$ was confirmed by high resolution mass spectrometry, λ_{max}: see Table 1; ν_{max}($CHCl_3$) 1621 and 1603 cm^{-1}. The mass spectrum was virtually identical with that of the *trans* isomer 4.

Reduction of trans-$\Delta^{2,2'}$-bi- (2H-1,4-*benzothiazine*), 4

(A) A mixture of 4 (100 mg) $NaBH_4$ (120 mg) and DMF (15 ml) was stirred at 80° for 6 hr. After cooling the mixture was diluted with water and extracted 3 times with EtOAc. Evaporation of combined extracts gave a microcrystalline residue which was recrystallized from dioxan to give 31 mg of *trans*- 6, colourless prisms, homogeneous on TLC (solvent (b), $R_f = 0{\cdot}37$; detection: UV light), m.p. 230–231° (dec); *m/e* 298 (M^+, 100), 265 (14), 232 (5), 174 (36), 162 (25), 149 (39), 142 (22), 136 (47), 130 (20%); (Found: M^+ 298·0581; $C_{16}H_{14}N_2S_2$ requires M 298·0598); λ_{max} (dioxan) 247, 278, and 313 nm (logϵ 4·40, 4·06, 4·12); ν_{max} (Nujol) 3279 and 1603 cm^{-1}; δ (DMSO–d_6) 6·82 (8H, cm, aromatic), 6·11 (2H, br, NH, removed by D-exchange), 3·89 (4H, d, $J = 2{\cdot}5$ Hz, NH–CH_2, collapsed to a singlet on addition of D_2O).

(B) To a soln of 4 (100 mg) in THF (20 ml, distilled from LAH), an excess of LAH was added slowly and the mixture was refluxed, with constant stirring in an atmosphere of N_2 for 20 min and then left at room temp for 2 hr. The colour of the soln changed from yellow to colourless. The excess of hydride was destroyed by dropwise addition of EtOAc followed by MeOH. After dilution with water, the mixture was extracted 3 times with EtOAc. Evaporation of the combined extracts gave a residue which was crystallized from dioxan to give 20 mg of 6, identical in all respects with that obtained above.

Reoxidation of trans-$\Delta^{2,2'}$-bi- (3,4-*dihydro*-2H-1.4- *benzothiazine*), 6

(A) A stream of oxygen was bubbled at room temp through a soln of 6 (40 mg) in dioxan (30 ml) containing 6 ml of 2N HCl. After 3 hr the purple red oxidation mixture was neutralized with $NaHCO_3$ aq (20 ml) and extracted with EtOAc. The residue obtained after evaporating the organic layer was crystallized from DMF to give 30 mg of 4 melting at 298–300°.

(B) A soln of 6 (50 mg) in nitrobenzene (6 ml) was heated at 140° for 1 hr. After cooling, the mixture was diluted with MeOH, the resulting yellow ppt filtered off and thoroughly washed with MeOH, to give, 37 mg of 4, m.p. 298–300° (from DMF), identical in all respects with that obtained above.

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