

## Trimeric Aldolization Product of 1,4-Benzothiazine

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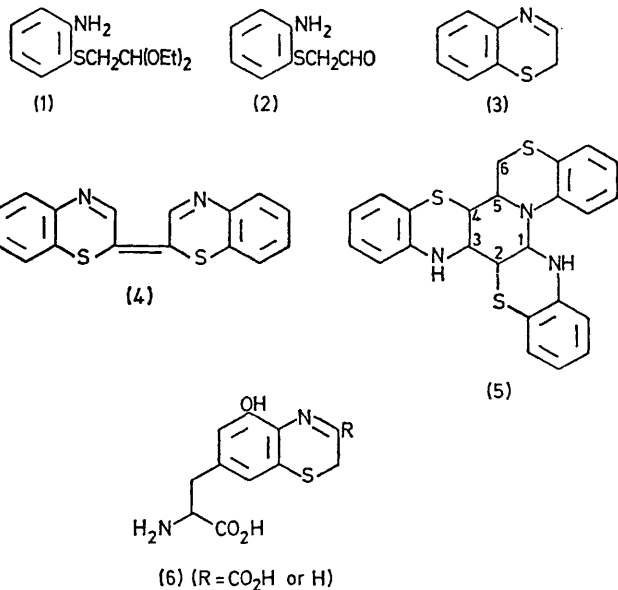
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**Summary** 2*H*-1,4-Benzothiazine, the parent system of the mammalian phaeomelanin pigments, is a highly unstable molecule which readily undergoes a reversible aldolization to form, mainly, the cyclic trimer (5).

WHEREAS synthetic and natural 2*H*-1,4-benzothiazines of varying structural complexity have become well known in recent years,<sup>1</sup> the parent compound (3) has remained elusive. A previous attempt<sup>2</sup> to obtain (3) by cyclisation of the amino-aldehyde (2), generated *in situ* by treatment of the acetal (1) with HCl in methanol, resulted in the isolation of the conjugated dimer (4), arising from a ready acid-catalysed coupling of the corresponding monomer by the action of atmospheric oxygen. We report now that the reaction of the same acetal (1) with aqueous HCl, *e.g.* 0.5 M, in the absence of air, gives a mixture of polymeric aldolization products, the major one, isolated in crystalline form (after t.l.c. on silica), being formulated as the cyclic trimer (5) on the following grounds.

The product, m.p. 222–224 °C (decomp.) (C<sub>6</sub>H<sub>6</sub>-light petroleum), λ<sub>max</sub> (MeOH) 234, 266, and 311 nm (log ε 4.64, 4.08, and 3.87), ν<sub>max</sub> (CHCl<sub>3</sub>) 3360 cm<sup>-1</sup> (broad), showed M<sup>+</sup> at *m/e* 447 (C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>S<sub>3</sub><sup>+</sup>) and relevant fragment ions at *m/e*



298 ( $C_{16}H_{14}N_2S_2^+$ ) and 149 ( $C_8H_7NS^+$ , base peak), formed by loss of one and two benzothiazine molecules, respectively.

Distinguishing features of the  $^1H$  n.m.r. spectrum ( $C_6D_5N$ ) were an ABX system (partially overlapped with other signals) suggesting a cyclic  $-CH_2-CH-$  grouping and a low-field  $^1H$  doublet at  $\delta$  5.92, attributable to a methine group linked to two nitrogen atoms. These assignments were substantiated by the  $^{13}C$  n.m.r. spectrum ( $C_6D_5N$ ) showing, in addition to aromatic carbons, only six  $sp^3$ -carbons at  $\delta$  66.9 (d, C-1), 54.9 (d, C-5), 53.9 (d, C-3), 46.5 (d, C-4), 42.8 (d, C-2), and 31.4 (t, C-6) p.p.m., assigned as shown using known chemical shifts rules, and  $^1H$  single-frequency off-resonance. The deuteration effect<sup>3</sup> (ca. -0.08 p.p.m.)<sup>†</sup> was also detected for C-1 and C-3, located adjacent to the NH groups. These data suggested that the product had the cyclic structure (5) arising by aldol condensation of three benzothiazine molecules.

Supporting evidence for this conclusion followed from the characteristic behaviour of the trimer in acid media. When a solution of (5) in MeOH-HCl was left at room temperature in the presence of air, it rapidly became intensely violet, and work-up of the mixture led to the isolation of the conjugated dimer (4) (35% yield), whose

formation may be rationalized as involving an initial conversion of the trimer into the monomeric 1,4-benzothiazine, followed by oxidative coupling at the C-2 position. More directly, the acid-catalysed conversion of (5) into (3) could be observed by monitoring the  $^1H$  n.m.r. spectrum of a solution of the trimer in trifluoroacetic acid, showing after a few minutes a  $^1H$  triplet at  $\delta$  8.64 ( $J$  5.2 Hz) and a  $^2H$  doublet at  $\delta$  4.04 ( $J$  5.2 Hz), attributable to the methine and methylene protons of the monomeric heterocyclic ring.<sup>4</sup>

From this study it can be concluded that 2*H*-1,4-benzothiazine behaves similarly to other heterocyclic enamines<sup>5</sup> in forming reversible aldolization products. An important implication of this result is that the polymerization of the postulated benzothiazine intermediates, e.g. (6), of phaeomelanin biosynthesis<sup>1a,c</sup> may proceed *via* aldol condensation more than by oxidative coupling involving positions 2 and 8, as previously suggested.<sup>6</sup>

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<sup>†</sup> Such a small shift could be clearly observed by partial D-exchange resulting in the splitting of the original singlet.

<sup>1</sup> For reviews see: (a) R. H. Thomson, *Angew. Chem. Internat. Edn.*, 1974, **13**, 305; (b) G. Prota, in 'Organic Compounds of Sulphur, Selenium, and Tellurium,' Vol. 3, Specialistic Periodical Reports, Senior Reporter, D. H. Reid, The Chemical Society, 1974, Ch. 3; (c) G. Prota and R. H. Thomson, *Endeavour*, 1976, **35**, 32.

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