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NEW BENZOXAZINE AND BENZOTHIAZINE DYES

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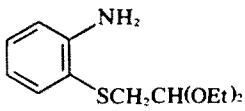
Abstract—2*H*-1,4-benzoxazine can be generated *in situ* from 1-(*o*-aminophenoxy)-2,2'-dimethoxyethane in trifluoroacetic acid whence further reaction leads to the benzoxazine dye **7**. The benzothiazine dye **9** can be derived in similar fashion from 1-(*o*-aminophenylthio)-2,2-diethoxyethane.

In a previous paper[1] we reported an attempt to prepare the unknown 2*H*-1,4-benzothiazine **3** by cyclisation of the amino-aldehyde **2** which was generated from the acetal **1**. In fact, under various mild acid conditions, the isomeric 2-methylbenzothiazole was formed together with the conjugated dimer **4**. $\Delta^{2,2'}$-Bi-(2*H*-1,4-benzothiazine) **4** was best obtained from **1** by treatment with cold aqueous methanolic hydrochloric acid in a stream of air.



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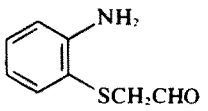

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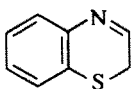

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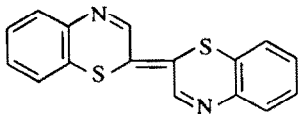

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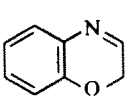
The parent 2*H*-1,4-benzoxazine **5**, is also unknown and we have attempted its synthesis by a similar approach. This has also failed but once again we have obtained a new chromophoric system.[2] The acetal **6** (R = Me) was derived by reduction of the corresponding nitro compound which was obtained by condensation of sodium *o*-nitrophenoxide with bromoacetaldehyde dimethyl acetal. Efforts to convert this into **5** with aqueous mineral acids under various conditions met with no success and gave only intractable polymeric products. However, when the amino-acetal **6** (R = Me) was dissolved in anhydrous trifluoroacetic acid, formation of the benzoxazine **5** was apparent after a few minutes from the NMR spectrum which showed a one-proton triplet at δ 8.67 (J = 3.2 Hz) arising from H-3 and a two-proton doublet at δ 5.50 (J = 3.2 Hz) from H-2. Methanol (δ3.60, s) was also formed, and was rapidly converted into methyl trifluoroacetate (δ4.00, s). After a short time (~15 min) the signals from **5** disappeared as further reaction took place and from the violet solution we isolated a red benzoxazine dye, $C_{18}H_{12}N_2O_2$. This compound obviously contains two benzoxazine moieties, and the molecular formula corresponds to the oxygen analogue of **4** with the addition of a C_2H_2 fragment. We formulate this unexpected product as **7**. Like **4** it undergoes a marked bathochromic shift in acid solution (λ_{max} 465 → 544 nm) which is reversible. The NMR spectrum consists of an aromatic multiplet (8H), and two singlets (each 2H) at δ 7.80 and 6.06 which arise respectively, from the two pairs of cyclic and exocyclic methine protons. On catalytic hydrogenation it formed an octahydro derivative **8** isolated as an amorphous mixture of two stereoisomers showing λ_{max} 298 nm, ν_{max} 3370 cm^{-1}, and the appropriate NMR spectrum (see Experimental).



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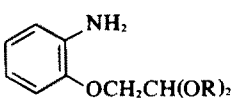

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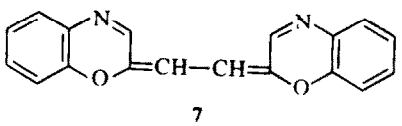

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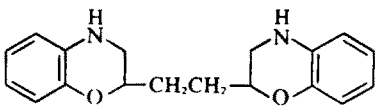

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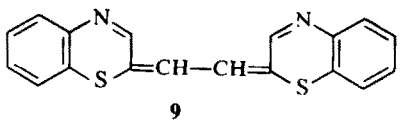

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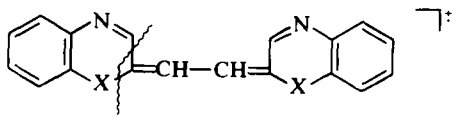
The aminothioacetal **1** behaved similarly in TFA solution and was completely converted into the relatively more stable thiazine **3** within five minutes. Its NMR spectrum was characterised by a triplet (1H) at δ 8.64 (J = 5.2 Hz, H-3) and a doublet (2H) at δ 4.04 (J = 5.2 Hz, H-2); the signals persisted for up to 40 min before disappearing. The formation of methanol followed by esterification was again observed. After working up the reaction mixture the red thiazine dye **9** was isolated. It was similar to **7** and showed a large reversible bathochromic shift in acid solution (507 → 620 nm). The tendency for a benzo-1,4-thiazine/oxazine to ring contract to a benzothiazole/oxazole appears to be reflected in the mass spectra of these dyes. In the spectra of both **7** and **9** the molecular ion forms the base peak and there is relatively little fragmentation. In both spectra the second strongest

peak is at M^+–C_7H_5NX (X = S or O) formed by loss of a benzothiazolyl or benzoxazolyl radical ion (see **10**). Additional peaks at M^+–C_7H_5NS–C_2H may arise from subsequent fragmentation, by direct cleavage of the central C–C bond, or, less likely (because of the high intensity), they may represent $M^+/2e$ ions. The principal peaks in the mass spectrum of **4**[1] are *m/e* 294(M^+, 100%), 159(M^+–C_7H_5NS, 10%) and 147(13%).



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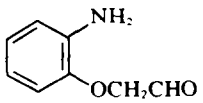
The mechanism of formation of **7** is puzzling. We considered first the possibility that the central C_2H_2 moiety might be derived from formaldehyde which could arise by oxidation of the methanol formed by decomposition of the acetal **6** (R = Me). However this is excluded by the formation of **7** from **6** (R = Et) in similar yield, by the formation of **9** from **1**, and when **6** (R = Me) was treated with TFA in the presence of methanol-d_4 there was no incorporation of deuterium into the benzoxazine dye **7**. Alternatively the central portion of **7** and **9** might originate from glyoxal which could conceivably be formed in various ways from **1** or **6**, or from the enamine tautomer of **3** or **5**. This does not seem likely because separate experiments showed that the ether link in compounds of type $ArOCH_2CH(OMe)_2$ is stable under the reaction conditions, and attempts to improve the yield of **7** by adding glyoxal or hydroxyacetaldehyde to the reaction mixture had the opposite effect.

NMR evidence indicates that **5** is formed quickly and then reacts further, so another possibility is that **5** (in the tautomeric enamine form) condenses with **11** (derived from **6**) to form the enol ether **12**, and hence the aldehyde **13**. Reaction of the latter with **5** would lead to the formation of the dye **7**.

This of course is speculative, and difficult to test since present knowledge of benzoxazine chemistry discourages attempts to prepare **13**. So far as is known all 2*H*-1,4-benzoxazines without a substituent at C-3 are unstable. Moreover the reactions leading to the formation of **7** appear to be very complex, very sensitive to any variation in the conditions, and the dye is obtained in poor yield.



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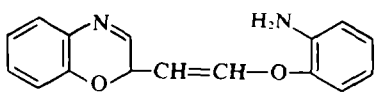

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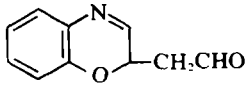

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EXPERIMENTAL

2,2-Dimethoxy-1-(o-nitrophenoxy)ethane

To a solution of sodium *o*-nitrophenoxide (8.1 g) in anhydrous DMSO (40 ml) chloroacetaldehyde dimethyl acetal (12 ml) was added, dropwise, with stirring, and the mixture was kept at 100° for 18 h. After cooling, and dilution with water, the mixture was extracted 3 times with Et_2O, and the extract was washed with 2N NaOH, and water, dried and evaporated. The residual nitro-acetal crystallised from EtOH as needles, m.p. 36–37° (Found: C, 52.81; H, 5.76; N, 6.20. $C_{10}H_{13}NO_5$ requires: C, 52.89; H, 5.80; N, 6.17%); $\delta(CCl_4)$ 7.3 (4H, m, ArH), 4.62 (1H, t, J = 5Hz, $-CH_2CH<$), 4.02 (2H, d, J = 5 Hz, $-CH_2CH<$), and 3.40 (6H, s, –OMe); *m/e* 227 (M^+, 0.24), 226(0.92), 196(16), 122(24), 106(20), and 75(100%).

2,2-Diethoxy-1-(o-nitrophenoxy)ethane

By the procedure above sodium *o*-nitrophenoxide (8.5 g) was condensed with bromoacetaldehyde diethyl acetal (10 ml) in DMSO at 100°. The crude product was purified by column chromatography on silica gel in C_6H_6–Et_2O (90:10) to give the nitro-acetal as a pale yellow oil (10.2 g), (Found: C, 56.40; H, 6.97; N, 5.68. $C_{12}H_{17}NO_5$ requires: C, 56.46; H, 6.72; N, 5.49%); $\delta(CCl_4)$ 7.8–6.8 (4H, m, ArH), 4.73 (1H, t, J = 5 Hz, $-CH_2CH<$), 3.99 (2H, d, J = 5 Hz, $-CH_2CH<$), 3.68 (2H, q, J = 7 Hz, $-OCH_2CH_3$), 3.64 (2H, q, J = 7 Hz, OCH_2CH_3) and 1.17 (6H, t, J = 7 Hz, $-OCH_2CH_3$)(the non-equivalence of the $-OCH_2-$ protons is also observed in the spectrum of bromo-acetaldehyde diethyl acetal); *m/e* 210(M^+–OEt, 13), 122(38), 106(60), 103(100) and 75(98%).

1-(o-Aminophenoxy)-2,2-dimethoxyethane, **6** (R = Me)

A solution of 2,2-dimethoxy-1-(*o*-nitrophenoxy)ethane (1.62 g) in methanol (20 ml) was hydrogenated at 3 atmospheres over 10% Pd/C (90 mg) for 12 h. Removal of catalyst and solvent left **6** (R = Me)(1.2 g) as a pale yellow oil, homogeneous on TLC, which darkened in air. It distilled at 90°/0.02 mm but was used without further purification. $\delta(CCl_4)$ 7.65 (4H, m, ArH), 4.63 (1H, t, J = 5 Hz, $-CH_2CH<$), 3.98 (2H, bs, removed by D-exchange, NH_2), 3.92 (2H, d, J = 5 Hz, $-CH_2CH<$) and 3.63 (6H, s, $-OCH_3$); *m/e* 197(M^+, 100), 166(10), 165(18), 134(56), 109(72) and 108(50%), (Found: C, 60.62; H, 7.70; M^+, 197.1054 · $C_{10}H_{15}NO_3$ requires: C, 60.95; H, 7.67%; M, 197.1051).

1-(o-Aminophenoxy)-2,2-diethoxyethane, **6** (R = Et)

Catalytic hydrogenation of 2,2 - diethoxy - 1 - (*o* - nitro - phenoxy)ethane, as above, gave the corresponding amine **6** (R = Et) as a pale yellow oil which darkened in air. It was homogeneous by TLC and distilled at 110°/0.02 mm, but was used without further purification. $\delta(CCl_4)$ 7.3 (4H, m, ArH), 4.68 (1H, t, J = 5 Hz, $-CH_2CH<$), 3.87 (2H, d, J = 5 Hz, $-CH_2CH<$), 3.72 (2H, bs, removed by D-exchange, NH_2), 3.57 (2H, q, J = 7 Hz, $-OCH_2CH_3$), 3.52 (2H, q, J = 7 Hz, $-OCH_2CH_3$) and 1.16 (6H, t, J = 7 Hz, $-OCH_2CH_3$); *m/e* 225(M^+, 65), 179(9), 134(36), 108(35) and 103(100%), (Found: C, 63.92; H, 8.42%; M^+, 225.1369 · $C_{12}H_{19}NO_3$ requires: C, 63.96; H, 8.49%; M, 225.1364).

Benzoxazine dye, **7**

(a) A solution of **6** (R = Me) (400 mg) in anhydrous TFA (10 ml) was stirred vigorously for 10 min and then boiled under reflux for 20 min. After cooling, the deep violet mixture was concentrated *in vacuo*, diluted with $CHCl_3$ (15 ml), washed with aqueous $NaHCO_3$, dried, and evaporated. Fractionation of the residue (185 mg) on a polyamide column (2 × 50 cm) in C_6H_6 afforded **7** (65 mg, 33% based on 3 mol of aminoacetal), red needles (from EtOAc), m.p. 251–254° (Found: C, 75.16; H, 4.05; N, 9.74%; M^+, 288.0899. $C_{18}H_{12}N_2O_2$ requires: C, 75.04; H, 4.20; N, 9.72%; M, 288.0898), λ_{max} (MeOH) 267 and 465 nm (log ϵ 4.44 and 4.52), λ_{max} (MeOH–H^+) 267, 350br and 544 nm (log ϵ 4.36, 3.84 and 4.49), $\delta(CDCl_3)$ 7.80 (2H, s, cyclic =CH–), 7.8–6.2 (8H, m, ArH) and 6.06 (2H, s, exocyclic =CH–); *m/e* 289(16), 288(M^+, 100), 287(5), 259(9), 169(16) and 144(5%).

(b) When the diethyl acetal **6** (R = Et) was treated in the same way a 15% yield of the same benzoxazine dye **7** was obtained.

(c) A mixture of **6** (R = Me) (200 mg) in TFA (5 ml) and MeOH-d_4 (0.5 ml) was stirred at room temperature for 10 min and then refluxed for 20 min. Workup as in (a) afforded 25 mg of **7**, m.p. 251–253° with no deuterium incorporation (MS evidence).

Reduction of the benzoxazine dye, **7**

A suspension of **7** (20 mg) in MeOH (15 ml) was hydrogenated at 2 atmospheres over 10% Pd/C (5 mg) for 12 h. Removal of catalyst and solvent left the octahydro derivative **8** as an amorphous mixture of two diastereoisomers (TLC evidence) which was not purified further. ν_{max} ($CDCl_3$) 3370 cm^{-1}; δ(CCl_4) 6.5 (8H, m, ArH), 4.04 (2H, bm, $-OCH<$), 3.24 (6H, bm, cyclic-CH_2- and NH) and 1.82 (4H, bm, exocyclic -CH_2-); *m/e* 296(M^+, 100), 188(72), 161(92) and 148(76%).

Benzothiazine dye, **9**

A solution of **1**[3] (440 mg) in anhydrous TFA (10 ml) was stirred for 2 days. The resulting greenish-blue mixture was concentrated *in vacuo*, diluted with $CHCl_3$ (15 ml), washed with aqueous $NaHCO_3$, dried, and evaporated. Crystallisation of the residue from EtOAc gave **9** (36 mg, 19%) as deep red needles, m.p. 264–265°. (Found: C, 67.12; H, 3.94; N, 8.49; S, 19.76. $C_{18}H_{12}N_2S_2$ requires: C, 67.50; H, 3.78; N, 8.74; S, 20.0%), λ_{max} (MeOH) 283, 330br and 507 nm (log ϵ 4.40, 4.08 and 4.45), λ_{max} (MeOH–H^+) 285, 360br and 620 nm (logϵ 4.34, 3.94, 4.46), δ($CDCl_3$) 7.93 (2H, s, cyclic =CH–), 7.7–6.9 (8H, cm, ArH), and 6.35 (2H, s, exocyclic =CH–); *m/e* 320(M^+, 100), 319(24), 185(30), and 160(18%). The yield of 30% quoted in Ref. 2 was achieved under different conditions and was difficult to reproduce.

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