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A Reinvestigation of the Structure of the Erythro and Xanthoapocyanine Dyes: Some Unusual Aspects of Quinoline Chemistry

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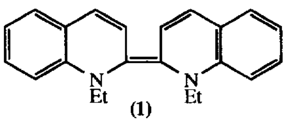
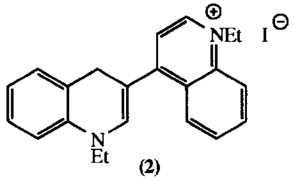
Abstract: The products of the base treatment of N-ethylquinolinium iodide are shown to be the ethiodides of 1-ethyl-3-(2'-quinolyl)-1,4-dihydroquinoline and 3-methyl-5,6-benzoindazolino[1,2-c]quinoline. Copyright © 1996 Elsevier Science Ltd

The formation of mixtures of red and yellow dyes by treatment of N-methyl or N-ethylquinolinium salts with conc. aqueous methanolic alkali was first disclosed in a German patent of 1903.[1] Initially, the structure (1) was suggested for the red product from N-ethylquinolinium iodide[2] and it was christened erythroapocyanine on the basis of its strong red colour. Later, the structures (2) and (3) were proposed for erythroapocyanine and its yellow xanthoapocyanine counterpart respectively,[3] still without any supporting evidence apart from elemental composition. The structural evidence for erythroapocyanine (2) was later provided as follows: oxidation of (2) with either iodine[2] or potassium permanganate[4] yielded a compound formulated as diethiodide (4). Conversion of (4) to the corresponding chloride salt and subsequent heating *in vacuo* eliminated ethyl chloride and provided the biquinolyl (5).[4] Treatment of (5) with ethyl iodide reformed (4). The structure of (5) was established by an apparently unambiguous synthesis from ethyl 4-quinolylpyruvate and 2-aminobenzaldehyde.[4] Although the same workers reported an analogous synthesis of the isomeric biquinolyl (6), no chemical correlation with xanthoapocyanine was reported. Further investigation on these compounds has been restricted to the preparation of a number of derivatives bearing substituents such as methyl, chloro, amino and methoxy groups in the benzenoid ring.[5] A later incidental preparation of these dyes[6] showed that erythroapocyanine with $\lambda_{max} = 516$ nm (ε 31,600) and xanthoapocyanine with $\lambda_{max} = 461$ nm (ε 19,900) have very distinctive absorption spectra. More recently, the corresponding dimethyl erythroapocyanine was encountered as a degradation product of the trimeric species formed on treatment of N-methylquinolinium methanesulphonate with cold dilute aqueous alkali.[7]



(1)



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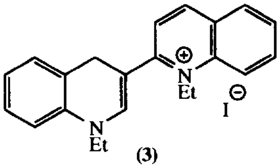

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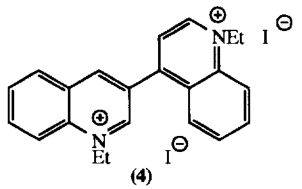

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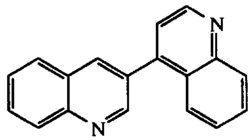
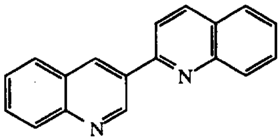
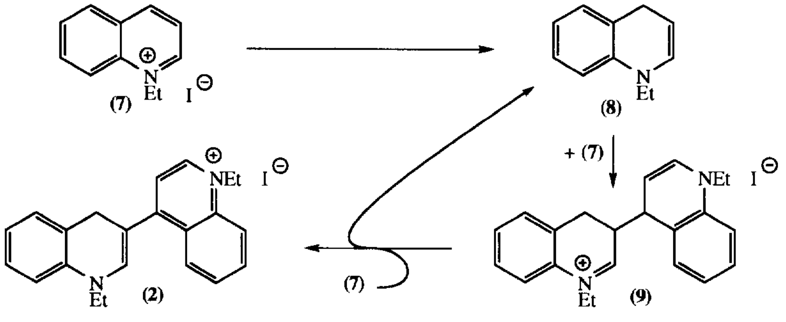


(5)



(6)

A possible mechanism for the formation of erythroapocyanine (**2**) from N-ethyl quinolinium iodide (**7**) is outlined in Scheme 1. Presumably, the sequence starts by reduction of (**7**) to the 1,4-dihydroquinoline (**8**). This is not an unusual step since fairly mild conditions can be used for reduction of pyridinium and quinolinium salts to their corresponding dihydro derivatives.[8] The methanolic solvent is crucial to this step since we have shown that when the reaction is conducted in tert-butanol using potassium tert-butoxide as base, no erythro dye was obtained as indicated by both nmr and UV analysis of the reaction mixture. However, we did obtain small quantities of the xantho dye under this condition. Reduction of (**7**) to (**8**) is followed by reaction of (**8**) with another molecule of (**7**) forming intermediate (**9**). Oxidation of (**9**) to (**2**) could either be aerobic or, more economically, coupled with the reduction of more (**7**) to (**8**).



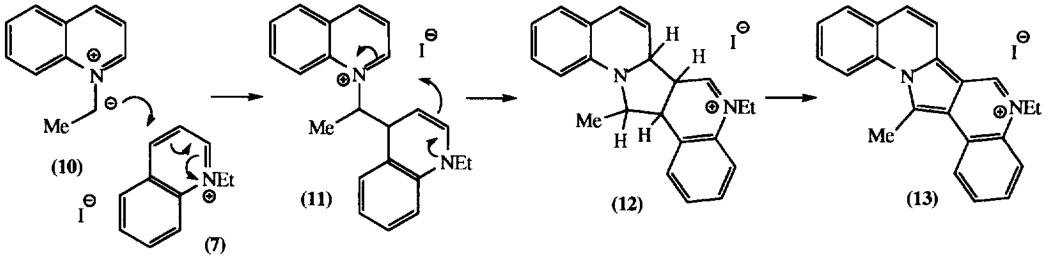
Scheme 1

The limited literature concerning the chemistry of 1,4-dihydroquinolines prompted the following investigation of the chemistry of the erythro and xanthoapocyanines. We repeated some of the preparation procedures and performed some of our own experiments to investigate if the proposed structures were correct.[9] In our hands, the quantities of erythro and xanthoapocyanine formed depended upon the molar ratio of the the base (potassium hydroxide) to N-ethylquinolinium iodide in the methanolic medium. With only 0.25 mole equivalent of base, the combined yield of the dyes isolated at the end of reaction was very modest (17%) from which no xanthoapocyanine could be isolated. With 0.5 mole equivalent of base (stoichiometric quantity) the combined yield of dyes rose to 40%. With 0.75 mole equivalent of base, the combined yield of the dyes was 56%. With an even larger proportion of base (1.0 mole equivalent), the reaction is more complex and although the combined yield of the dyes is slightly improved (61%), the quality of the material is poor with many impurities present. In each experiment, xanthoapocyanine comprised 10-15% of the combined dye mass.

The composition of the resulting red dye (erythroapocyanine) as an iodide salt of $C_{22}H_{23}N_2$ was confirmed by accurate mass measurement (FAB). The proton and carbon nmr spectra are fully compatible with structure (**2**) for this compound.[10] Thus, there are clearly two ethyl groups in different chemical environments. doublets for H-2 and H-3 protons of the quinolinium ring are observed at 8.95 and 7.51 ppm, J = 6.9 Hz. The anticipated singlet for H-2 of the 1,4-dihydroquinoline ring is observed at 7.50 ppm along with a two proton singlet at 4.30 ppm for H-4 protons. The corresponding methylene is observed at 28.7 ppm in ^{13}C spectrum.

In contrast, accurate mass determination of the corresponding xanthoapocyanine revealed that its correct composition is $C_{22}H_{19}N_2I$ so that is not merely the positional isomer (**3**) of erythroapocyanine (**2**) as previously suggested. Proton nmr shows the presence of only one ethyl group as a triplet at 1.60 ppm and a quartet at 4.81 ppm consistent with the presence of an ethyl quinolinium function. Furthermore, there is also present a three proton singlet at 3.45 ppm consistent for a methyl group attached to an aromatic ring. Ten of the remaining protons absorbed between 7.76 and 8.94 and last remaining proton absorbed as a singlet at 10.2 ppm. The ^{13}C spectrum displayed signals at 14.8 ppm and 17.8 ppm together with a methylene carbon at 51.6 ppm and a further 19 signals between 108.6 ppm and 133.1 ppm attributed to the carbons in the aromatic rings.

Consideration of this spectroscopic information and transformations that are likely to occur under the reaction conditions led us to propose structure **(13)** for xanthoapocyanine resulting from the route in Scheme 2. The sequence commences with deprotonation of the N-ethyl group of **(7)** to afford ylide **(10)**. Although such deprotonation of quinolinium salts is usually associated with methylene groups bearing electron withdrawing groups,[11] it is well established that N-methylpyridinium salts readily form the corresponding ylides.[12] Subsequent addition of ylide **(10)** to the 4-position of another molecule of **(7)** provides intermediate **(11)**, which is optimally aligned for cyclisation to **(12)**. Such a situation would not arise if the addition of **(10)** occurred at the 2-position of **(7)**. Aromatisation of **(12)** *via* loss of four hydrogens results in xanthoapocyanine, **(13)**.



Scheme 2

Additional evidence for structure **(13)** was provided by NOE experiments. Thus irradiation of the ring substituted methyl protons at 3.45 ppm results in substantial enhancement of the signals at 8.69 ppm (d, J = 8.7 Hz) and 8.46 ppm (dd, J = 6.7 and 1.5 Hz) only. Irradiation of the methylene protons at 4.81 leads to the significant enhancement of the signal at 10.27 ppm (s) only.

In summary, whereas the previously reported structure **(2)** for erythroapocyanine is fully consistent with its spectroscopic properties, its supposed isomer xanthoapocyanine is shown to have a totally different composition and structure for which we propose **(13)**. These two compounds originate by fundamentally different pathways. Both types of reaction open up wider synthetic possibilities which we hope to explore in the near future.

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REFERENCES

1. Farbwerke Meister Lucius & Brünning, Ger. Pat. 154448 (Sept 20, 1903).
2. Kaufmann, A; Strübin, P. *Chem. Ber.* **1911**, 44, 690.
3. Konig, W. *Chem. Ber.* **1922**, 55, 3293.
4. Mills, W. H.; Ordish, J. B. *J. Chem. Soc.* **1928**, 81.
5. Browning, C. H.; Cohen, J. B.; Ellingworth, S.;Gulbransen, R. *Proc. Roy. Soc. (London) Sec. B* **1924**, 96, 317.
6. Hamer, F. M. *J. Chem. Soc.* **1956**, 1480.
7. Vorsanger, H.; Ferrand, F.; Mazza, M.; Vorsanger, J.-J. *Bull. Chim. Soc. Fr.* **1970**, 593.
8. Birch, A. J.; Lehman, P. G. *J. Chem. Soc. Perkin Trans. 1*, **1973**, 2754. Bunting, J. W.; Meathrel, W. G. *Tetrahedron Lett.*, **1971**, 10, 133.
9. Ethylquinolinium iodide (14.0 g, 49 mmol) was dissolved in methanol (10 mL) and the solution was set to reflux. A 10% solution of potassium hydroxide in methanol (14 mL) was added in two portions (10 minute interval) and reflux was continued for 5 hours. The dark solution was left to cool to room

temperature and then more methanol (50 mL) was added and the mixture was left overnight at 4 °C. The precipitates was filetered off on a buchner funnel and air dried (4.30 g). Nmr analysis showed that this solid mass contains erythroapocyanine and small quantities of the xanthoapocyanine and starting material. Solid mass was dissolved in hot methanol (200 mL per 1.05 g). Upon cooling, yellow crystals of xanthoapocyanine precipitated and were filtered off and air dried (0.13 g, 12%). The supernatant was reduced in volume to secure a crop of erythroapocyanine. Erythroapocyanine : m.p. 157-159 °C; δ_H (360 MHz, DMSO-d_6) 1.27 (3H, t, J = 7.1 Hz), 1.50 (3H, t, J = 7.1 Hz), 3.94 (2H, q, J = 7.1 Hz), 4.04 (2H, s), 4.82 (2H, q, J = 7.1 Hz), 8.19 (1H, t, J = 9.7 Hz), 7.19 (1H, d, J = 7.5 Hz), 7.24-7.29 (2H, m), 7.50 (1H, s), 7.52 (1H, d, J = 6.9 Hz), 7.84 (1H, t, J = 7.3 Hz), 8.12 (1H, dt, J_d = 1.2, J_t = 7.0 Hz), 8.33 (1H, d, J = 8.5 Hz), 8.49 (1H, d, J = 7.3 Hz), 8.93 (1H, d, J = 6.9 Hz); δ_C (90.6 MHz, DMSO-d_6) 13.71 (q), 14.77 (q), 28.67 (t), 45.76 (t), 50.47 (t), 102.06 (s), 113.3 (d), 113.89 (d), 117.89 (d), 123.07 (d), 124.25 (d), 125.03 (s), 127.63 (d), 127.74 (d), 129.19 (d), 129.47 (d), 133.96 (d), 136.25 (s), 137.52 (s), 144.65 (d), 146.93 (d), 154.41 (s); HRMS Calcd for $C_{20}H_{17}N_2^+$ (M-Et$^+$) 285.1392, found 285.1391.

Xanthoapocyanine : m.p. 315-317 °C (Lit.[2] 320 °C); δ_H (360 MHz, DMSO-d_6) 1.61 (3H, t, J = 7.1 Hz), 3.48 (3H, s), 4.84 (2H, q, J = 7.1 Hz), 7.79 (1H, t, J = 7.3), 7.88-7.94 (3H, m), 8.19 (2H, t, J = 9.0 Hz), 8.33 (1H, dd, J = 3.3, 6.4 Hz), 8.51 (1H, d, J = 9.0 Hz), 8.71 (1H, dd, J = 3.3, 6.3 Hz), 8.88 (1H, d, J = 8.8 Hz), 10.25 (1H, s); δ_C (90.6 MHz, DMSO-d_6) 14.87 (q), 17.89 (q), 51.65 (t), 115.44 (d), 118.37 (s), 119.32 (d), 119.43 (d), 122.35 (s), 123.74 (s), 125.69 (d), 127.04 (s), 127.11 (d), 127.83 (d), 128.08 (s), 128.76 (d), 129.21 (d), 129.65 (d), 129.72 (d), 132.60 (s), 133.21 (s), 133.32 (s), 146.59 (d); HRMS Calcd for $C_{22}H_{19}N_2^+$ (M$^+$) 311.1641, found 311.1615.

10. ^{1}H and ^{13}C N.m.r spectra were recorded in deutrated DMSO solutions on a Bruker AM360 spectrometer operating at 360 MHz and 90.6 MHz respectively. The solvents' residual proton signals were used as internal reference. Mass spectra were obtained on a Jeol AX505W mass spectrometer using electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques.
11. Kröhnke, F.; Zecker, W. *Angew Chem. Int. Ed. Engl.* **1962**, 1, 626. Kröhnke, F. *Angew Chem. Int. Ed. Engl.* **1963**, 2, 225 and 380.
12. Ratts, K. W.; Howe, R. K.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, 91, 6115.

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