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Heterocyclic Synthesis of Crowded Aposafranones: Structure of 1-Methyl-8-dimethylamino-10-phenylphenazin-2-(10*H*)one and Related Compounds

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Oxidative condensation of three *p*-phenylenediamines with 3-hydroxy-2-methyl-*N*-(phenylamino)benzene gives new coloured aposafranones. 2-Methylresorcinol is easy to convert into the asymmetric building block 3-hydroxy-2-methyl-*N*-(phenylamino)benzene with aniline. The aposafranones are sterically crowded because of the 1-methyl and *N*-phenyl groups. The UV/Vis absorption maxima are in the range 530–545 nm.

Introduction

One of the earliest phenazinones is known as an aposafranone and was reported by Kehrmann in 1896 and 1924[1–6] along with work by Fischer and Hepp.[7–8] In comparison with phenazines, methods for making aposafranones are less well developed and typically have low yields and harsh reaction conditions. Some synthetic methods for making aposafranone **3** involve acid-catalysed condensation of *o*-phenylenediamines by benzoquinones[9] or naphthoquinones,[10] aposafranone **5** by the iron(III)-trichloride-catalysed intramolecular condensation of *o*-phenylenediamines,[11] and aposafranone **8** by multi-step reactions from *o*-fluoronitrobenzenes (Scheme 1).[12] A route to aposafranone-*N*-oxides **11** involving enamines combines traditional nucleophilic substitution chemistry with an unusual intramolecular condensation onto a nitro group (Scheme 2).[13] Methods for making 10-alkylphenazinones are also known.[14]

The more highly derivatised compounds **12**–**14** which are substituted with an amino group have not been reported. However, compound **14** has been prepared by the synthesis shown in Scheme 3.[15]

Results and Discussion

Our attempts to make building block **16** by the selective condensation of aniline/aniline hydrobromide with resorcinol were unsuccessful. We always obtained 1,3-bis(phenylamino)benzene **18** (Scheme 4).[16] However, the same reaction of aniline/aniline hydrobromide with readily available 2-methylresorcinol **19** gave 2-methyl-*N*-(phenylamino) benzene **20** (Scheme 5). The steric bulk of the product appears to disfavour a second substitution reaction so differentiation of the two hydroxy groups is easily accomplished in this substrate. The Knoevenagel studies used iodine as a catalyst.[16] Iodine presumably liberates HI as the acid catalyst, but we got cleaner reactions without adding iodine.

The condensation products or aposafranones **24**–**26** were formed from the condensation of building block **20** with *p*-phenylenediamines **21**–**23**, respectively, using the strong oxidant potassium dichromate under mildly acidic conditions (Scheme 6). A solvent mixture of water and acetone was used to solubilise compound **20**. We developed this method previously for some related mauveine derivative syntheses.[17] The crude yields are about 8–10%. A small fraction of this was purified by chromatography on silica gel to get material pure enough for spectroscopic characterisation. The primary amino group and the tertiary amino group are conjugated to the carbonyl group, which explains the bathochromic shift in the absorption maximum to 530–545 nm. The compounds are purple coloured. The characterisation data is that which would be expected. All three compounds exhibit a red-shifted carbonyl group around 1600 cm^{-1} owing to the strong conjugation. In the 400 MHz proton NMR spectrum, the proton at position 9 appears at about 6.00 ppm owing to buttressing by the adjacent phenyl ring as is seen in mauveine chromophores.[18] In the 400 MHz ^{13}C NMR spectrum, each compound exhibits a carbonyl group peak at about 184 ppm.

The data analysis was confirmed by an X-ray single crystal structure determination (Figure 1) for compound **25**.

The tricyclic fused ring system in compound **25** is slightly puckered as indicated by the dihedral angle between the rings C1–C6 and C1/C6/N2/C7/C12/N1 (r.m.s. deviation = 0.015 Å) of 3.279(9)°; the equivalent angle for C7–C12 and C1/C6/N2/C7/C12/N1 is 0.936(4)° and the dihedral angle between the C1–C6 and C7–C12 rings is 3.820(9)°. The C3–O1, C4–C5 and C6–N2 bond lengths of 1.2532(15), 1.3387(18) and 1.3150(16) Å, respectively, are consistent with predominant double bond

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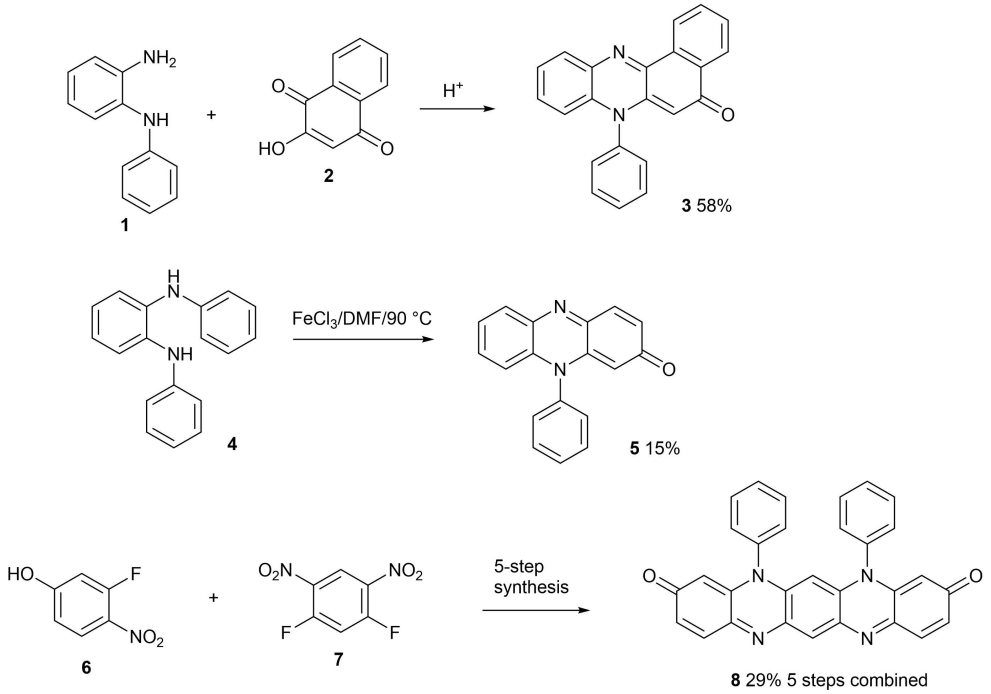
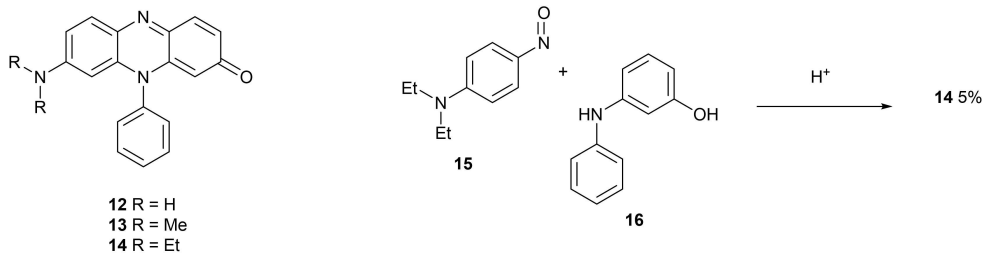
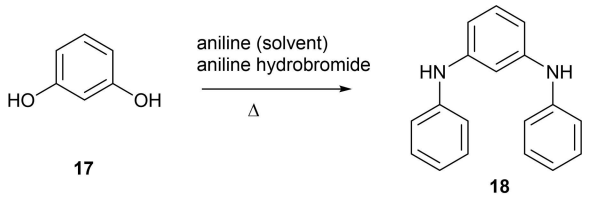


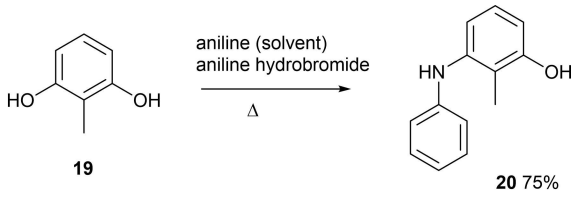
Scheme 1. Traditional syntheses of aposafranones.



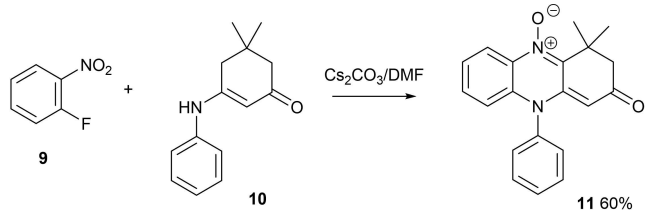
Scheme 3. Compounds **12**–**13** have not been reported. A synthesis of compound **14** is shown.



Scheme 4. Attempted synthesis of compound **16** gives compound **18** instead.[16]

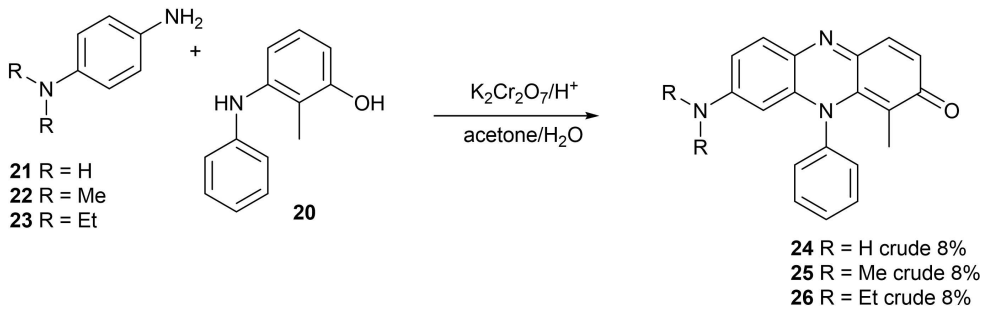


Scheme 5. Synthesis of a key building block **20**.



Scheme 2. A route to aposafranone-*N*-oxides.

character and the Scheme 6 shown above presumably represents the major resonance form for compound **25**. The pendant C13–C18 phenyl group attached to N1 is almost perpendicular to the central ring [dihedral angle = 73.97(4)°] and C19 deviates significantly from its attached C1–C6 ring by −0.178(2) Å, presumably due to steric crowding with the adjacent phenyl group. The bond-angle sum at N3 of 359.9° indicates sp^2 hybridisation and the shortened C10–N3 bond length of 1.3573(15) Å suggests some conjugation of the N3 lone pair with the π system and carbonyl group of the fused rings. In the extended structure, two weak C–H···O hydrogen bonds may



Scheme 6. Synthesis of compounds **24**–**26**.

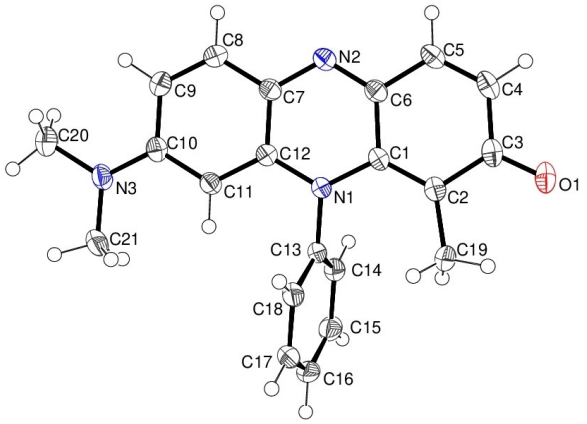


Figure 1. The molecular structure of compound **25** showing 50% displacement ellipsoids.

help to establish the packing. The 8-amino groups are close to planarity indicative of their strong conjugation to the carbonyl group. The carbonyl group IR stretch is also low down at about 1600 cm^{-1}, rather than 1700 cm^{-1}, owing to this and the aromatic ring fusion.

The spectroscopic data for each compound are similar with a UV/Vis absorption around 530 nm for compound **24** and 545 nm for compounds **25** and **26**. The HOMO-LUMO gaps for compounds **24**, **25** and **26** are 226, 221 and 219 kJ mol^{-1}, respectively, calculated from the UV/Vis spectrum, λ_{max} 530, 542 and 545 nm, via $\Delta E = Nhc/\lambda$ where N = Avogadro's number, h = Planck's constant and c = velocity of light. The *N*-phenyl ring shields the 9H proton, moving it upfield to about 6 ppm in the 400 MHz NMR spectrum, which is typical for these systems. There is steric compression between the *N*-phenyl group and the 1-methyl group as these two groups are not parallel and are similar to other 1,8-disubstituted naphthalenes. The steric crowding in these molecules has not inhibited their synthesis or the extensive conjugation they exhibit.

Scheme 7 shows a possible mechanism for the synthesis of compound **25** applicable to compounds **24** and **26**. *para*-Phenylenediamines like **22** and related compounds are electron rich and easily oxidised.[19] Electrophile **27** could react with electron-rich amine **20** to give adduct **28** which will easily oxidise to dye intermediate **29**. Although the *ortho*-phenylamino group is entropically set up to cyclise, the chromophore will be quite stable and oxidation of the diarylamino group to the delocalised free radical **30** will probably be required to facilitate cyclisation and dehydrogenation forming product **25**. Hence, steric hindrance will stabilise the free radical and might even favour cyclisation by an effect known as the Thorpe-Ingold effect.[20]

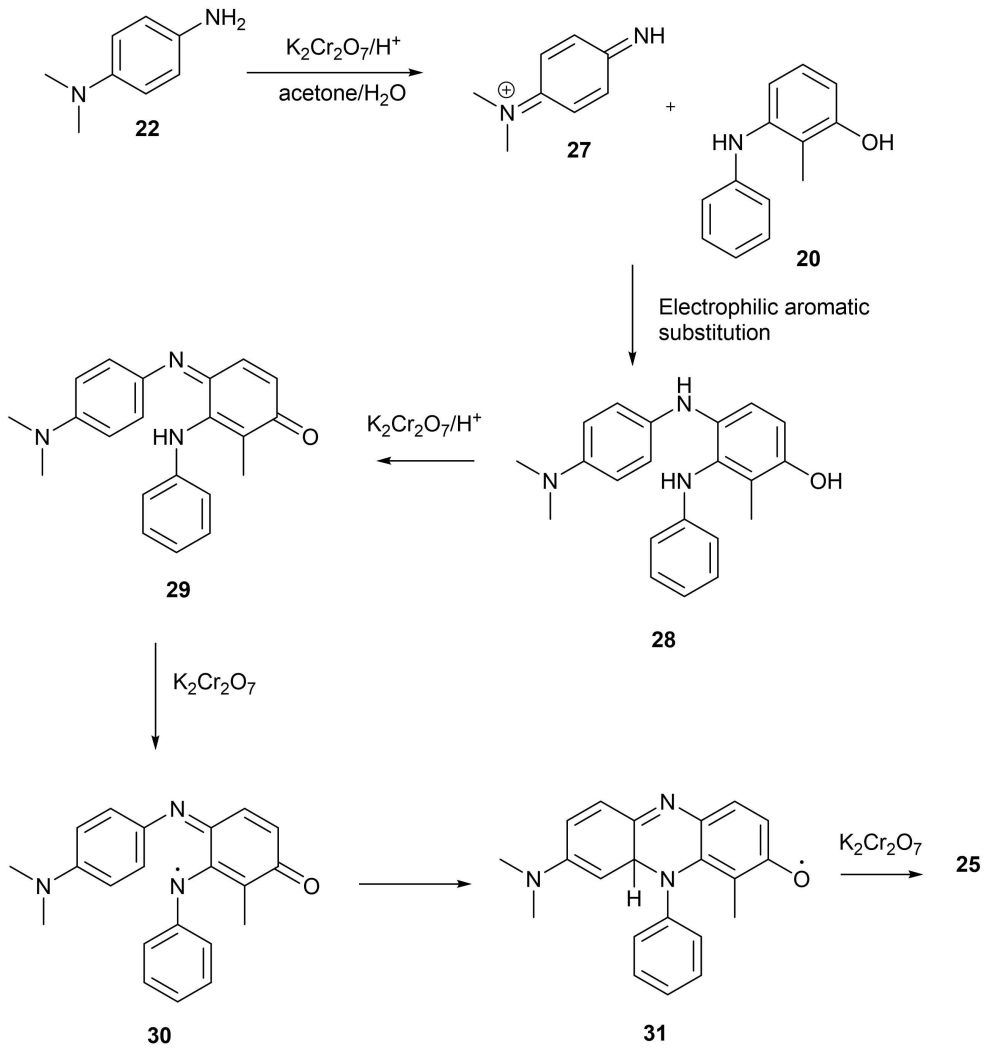
The molecular strain may be new for heterocyclic dyes but does bear resemblance to the common structure of other 1,8-disubstituted naphthalenes such as 1-methyl-8-phenylnaphthalene **27**,[21–23] naphthalene-1,8-dicarbonitrile **28**[24] and others (Scheme 8).[25]

Conclusion

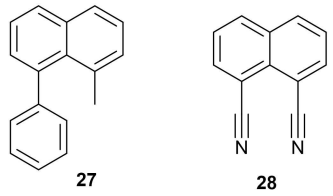
Condensation of aniline hydrobromide in aniline with 2-methylresorcinol **19** gives **3**-hydroxy-2-methyl-*N*-(phenylamino)benzene **20** in which only one of the hydroxy groups has been replaced by a phenylamino group. This allows for a selective derivatisation to give a useful heterocyclic building block **20**. Building block **20** can be condensed with *p*-phenylenediamines **21**–**23** under oxidative conditions in a mixture of water and acetone to give aposafranones **24**–**26**, respectively. The acetone and water mixture is able to dissolve building block **20**. Small amounts of the crude reaction mixture were purified by chromatography so that the column was not overloaded. The building block **20** is useful for chromophore synthesis because the symmetry of 2-methylresorcinol has been broken with a novel reaction that only gives a monosubstituted product. A mechanism is included to explain why the products form.

Experimental Section

IR spectra were recorded on a diamond-attenuted total reflection (ATR) Fourier transform infrared (FTIR) spectrometer. UV-Vis spectra were recorded using a Perkin Elmer Lambda 25 UV-Vis spectrometer with EtOH as the solvent. The term sh means shoulder. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 and 100.5 MHz, respectively, using a Varian 400 spectrometer. Chemical shifts, δ, are given in ppm and measured by comparison with the residual solvent. Coupling constants, *J*, are given in Hz. High-resolution mass spectra were obtained at the University of



Scheme 7. A possible mechanism for the synthesis of compound **25**.



Scheme 8. Structures of two related sterically crowded molecules.

Wales, Swansea, using an Atmospheric Solids Analysis Probe (ASAP) (positive mode) instrument: Xevo G2-S ASAP. Melting points were determined on a Kofler hot-stage microscope.

3-Hydroxy-2-methyl-N-(phenylamino)benzene 20

2-Methylresorcinol **19** (5.0 g, 40.3 mmol) and aniline hydrogen bromide (5.0 g, 29 mmol) were refluxed in neat aniline for 24 h. After cooling, the mixture was diluted with approximately 5 M dilute hydrochloric acid (200 mL). The crude product was filtered off (6.4 g 75%). A small fraction of the product (250 mg) was purified by chromatography on silica gel. Elution with CH_2Cl_2 gave the title compound (200 mg, 80%) as a white solid, mp 142–143 °C (from dichloromethane:light petroleum ether). λ_{max} (EtOH)/nm 219 (log ε 4.2) and 282 (4.19); λ_{max} (diamond)(cm^{-1}) 3465–3150w, 1618w, 1593 s, 1523 s, 1497 s, 1471 s, 1319 s, 1294 s, 1171 s, 1070 s, 927w, 774 s, 694vs and 503 s; δ_H (400 MHz; $CDCl_3$) 2.16 (3H, s), 6.51 (1H, d, J=8.0), 6.87 (1H, d, J=8.0), 6.93 (1H, t, J=8.0 and 8.0), 6.97 (2H, d, J=8.0), 7.02 (1H, t, J=8.0 and 8.0) and 7.28 (2H, t, J=8.0 and 8.0); δ_C (100.1 MHz; $CDCl_3$) 9.7, 109.1, 112.2, 114.9, 117.7, 120.5, 126.7, 129.3, 142.7, 144.3 and 154.4; *m/z* (Orbitrap ASAP) 200.1066 ($M+H^+$, 100%), $C_{13}H_{13}NO+H^+$ requires 200.1070.

8-Amino-1-methyl-10-phenylphenazin-2-(10H)-one 24

General Procedure

Crude 2-methyl-N^1-phenylamino-3-hydroxybenzene **20** (1.0 g, 5.0 mmol) and *p*-phenylenediamine **21** (0.875 g, 8.1 mmol) were dissolved in water (200 mL) containing conc. H_2SO_4 (10 drops) and acetone (100 mL). The mixture was treated with $K_2Cr_2O_7$ (3.1 g, 10.5 mmol) and heated in a beaker at 60 °C for 5 h without stiring. The beaker was covered with a petri dish. After removing the lid, the mixture was stirred with heating in a fume hood air flow which evaporates the acetone. After this and cooling, the mixture was filtered and washed with water to give a crude product (200 mg,

13.2%). A small fraction of the dried product was purified by chromatography on silica gel. Elution with Et_2O/MeOH (90:10) then Et_2O/MeOH (70:30) gave the pure title compound (18 mg, 1.2%), mp > 200 °C (from dichloromethane:light petroleum ether). λ_{max} (EtOH)/nm 530 (log ε 4.1) and 280 (4.2); λ_{max} (diamond)(cm^{-1}) 3177w, 1594 m, 1483 s, 1434 s, 1383 s, 1288 s, 1194w, 1120s, 1021 s, 824 s, 760s, 697 s and 568 s; δ_H (400 MHz; $CDCl_3$) 1.40 (3H, s), 4.43 (2H, s, NH_2) 5.90 (1H, d, J = 4.0), 6.68 (1H, dd, J = 8.0 and 4.0), 6.99 (1H, d, J = 8.0), 7.38–7.42 (2H, m), 7.52 (1H, d, J = 8.0), 7.56–7.59 (3H, m) and 7.69 (1H, d, J = 8.0); δ_C (100.1 MHz; $CDCl_3$) 11.7, 97.3, 110.2, 113.5, 129.3, 129.5, 129.7, 130.0, 132.2, 132.4, 133.9, 135.3, 136.3, 140.7, 143.5, 150.8 and 184.4; *m/z* (Orbitrap ASAP) 302.1295 ($M+H^+$, 100%), $C_{19}H_{15}N_3O+H^+$ requires 302.1293

8-(Dimethylamino)-1-methyl-10-phenylphenazin-2-(10H)-one 25

Following the general procedure with *N*,*N*-dimethyl-*p*-phenylenediamine. Crude yield (264 mg, 16%). A small fraction of the dried product was purified by chromatography on silica gel. Elution with Et_2O/MeOH (95:5), then Et_2O/MeOH (90:10), then Et_2O/MeOH (80:20) gave the pure title compound (20 mg, 1.2%), mp > 200 °C (from dichloromethane:light petroleum ether). λ_{max} (EtOH)/nm 544 (log ε 4.6) and 280 (4.6); λ_{max} (diamond)(cm^{-1}) 3598–3139w, 1603vs, 1514vs, 1455vs, 1382vs, 1357vs, 1199w, 1125vs, 1034w, 798 s, 767w, 705w, 625w, 498w and 426; δ_H (400 MHz; CD_3OD) 1.48 (3H, s), 3.01 (6H, s), 5.88 (1H, s), 7.05 (1H, d, J = 8.0), 7.16 (1H, d, J = 8.0), 7.58 (2H, m), 7.69 (1H, d, J = 8.0), 7.73 (2H, m), 7.83 (1H, d, J = 8.0) and 8.59 (1H, s); δ_C (100.1 MHz; D_7DMF) 10.9, 39.6, 94.5, 109.2, 111.5, 128.5, 129.7, 129.9, 130.5, 131.1, 131.8, 134.0, 135.6, 136.5, 142.3, 152.9 and 182.9; *m/z* (Orbitrap ASAP) 330.1605 ($M+H^+$, 100%), $C_{21}H_{19}N_3O+H^+$ requires 330.1601.

8-(Diethylamino)-1-methyl-10-phenylphenazin-2-(10H)-one 26

Following the general procedure with *N*,*N*-diethyl-*p*-phenylenediamine. Crude yield (322 mg 18%). A small fraction of the dried product was purified by chromatography on silica gel. Elution with Et_2O/MeOH (90:10), then Et_2O/MeOH (70:30) gave the pure title compound (23 mg, 1.3%), mp > 200 °C (from dichloromethane:light petroleum ether). λ_{max} (EtOH)/nm 545 (log ε 3.9) and 285 (4.1); λ_{max} (diamond)(cm^{-1}) 2972w, 1603vs, 1514vs, 1481vs, 1455vs, 1413vs, 1399vs, 1277 s, 1123vs, 1021 s, 825 s, 797 s, 566w, 494w and 430w; δ_H (400 MHz; $CDCl_3$) 1.07 (6H, t, J = 8.0), 1.46 (3H, s), 3.27 (4H, q, J = 8.0), 5.74 (1H, d, J = 4.0), 6.78 (1H, dd, J = 8.0 and 4.0), 7.02 (1H, d, J = 8.0), 7.43 (2H, d, J = 8.0), 7.54 (1H, d, J = 8.0), 7.57-7.62 (3H, m) and 7.72 (1H, d, J = 8.0); δ_C (100.1 MHz; $CDCl_3$) 11.8, 12.4, 45.0, 94.3, 110.1, 110.8, 128.4, 129.4, 129.6, 129.9, 131.4, 132.1, 133.6, 135.2, 136.7, 141.0, 142.2, 150.4 and 183.9; *m/z* (Orbitrap ASAP) 358.1918 ($M+H^+$, 100%), $C_{23}H_{23}N_3O+H^+$ requires 358.1919

Single-crystal diffraction

The crystal structure of compound **25** (brown block 0.14 × 0.09 × 0.06 mm) was established using intensity data collected on a Rigaku CCD diffractometer (Cu Kα radiation, λ = 1.54178 Å) at 100 K. The structure was routinely solved by dual-space methods using SHELXT [26] and the structural model was completed and optimized by refinement against $|F|^2$ with SHELXL-2018.[27] The hydrogen atoms were placed geometrically (C–H = 0.95–0.99 Å) and refined as riding atoms; the methyl groups were allowed to rotate, but not to tip, to best fit the electron density. The constraint $U_{iso}(H) = 1.2U_{eq}$(carrier) or $1.5U_{eq}$(methyl carrier) was applied in all cases. Full details of the structure and refinement are available in the deposited CIF (Deposition number 2220912). Crystal data for compound **25** ($C_{21}H_{19}N_3O$): M_r = 329.39, orthorhombic, space group *Pccn* (No. 56), a = 13.8108(3) Å, b = 13.8896(3) Å, c = 17.7129(4) Å, V = 3397.80(13) Å^3, Z = 8, T = 100 K, μ = 0.641 mm^{-1}, ρ_{calc} = 1.288 g cm^{-3}, 17682 reflections measured ($9.0 \le 2\theta \le 153.3°$), 3436 unique ($R_{int}$ = 0.018), $R(F)$ = 0.040 [2941 reflections with $I > 2\sigma(I)$], $wR(F^2)$ = 0.117 (all data), $\Delta\rho_{min,max}$ (e Å^{-3}) = −0.23, +0.57.

Supporting Information Summary

Deposition Number 2220912 (for **25**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service. The proton and carbon NMR data for all compounds in the experimental section are reported in the supplemental section.

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Conflict of Interest

Funding The authors received no financial support for the research, authorship and/or publication of this article.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: aposafranone · chromophores · phenazinone · safranone · X-ray crystallography

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