

Unexpected Synthesis of *trans*-2,3-Dimethoxy-3-(*p*-formylphenylamino)-4'-nitroflavanones

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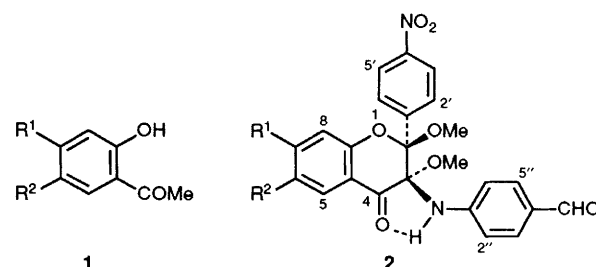
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The reaction of *o*-hydroxyacetophenones **1a–c** with *p*-nitrobenzaldehyde in aqueous methanolic KOH leads to the formation of *trans*-2,3-dimethoxy-3-(*p*-formylphenylamino)-4'-nitroflavanones **2a–c**, two of which have been structurally characterized by X-ray crystallography.

The Claisen–Schmidt reaction between *o*-hydroxyacetophenones and nitrobenzaldehydes, which is usually performed in aqueous ethanolic alkali, is allowed to take place over a very short time^{1,2} to avoid formation of unwanted amorphous materials.² In connection with a recent study³ involving two hydroxynitrochalcones, we undertook an investigation of the reaction between the aforesaid classes of compounds under conditions wherein the solvent, alkali concentration, and time were varied. The present communication deals with a novel type of condensation product encountered in the course of these experiments.

Each of the *o*-hydroxyacetophenones **1a–c** was treated with *p*-nitrobenzaldehyde (mole ratio 1 : 1) in aqueous methanolic KOH at room temperature. In contrast to the usual situation, a precipitate began to appear after *ca.* 15 min. Chromatography of the precipitate collected after 20 h in each case furnished the major component, which exhibited several striking spectral features.[†] Although the presence of (i) two aliphatic methoxy groups, (ii) one aldehyde and one keto carbonyl, and (iii) one *p*-XC₆H₄NH– moiety could be readily ascertained, the most conspicuous feature of the ¹H NMR spectra was the appearance of a four-proton very broad signal that could be rationalized only after observing the spectrum of the product from **1c** at various temperatures. Thus, three broad two-proton signals (δ 6.47, 7.74 and 8.08) observed at 20.7 °C (in CD₃SOCD₃) changed to three clean doublets (*J* 9 Hz) at higher temperatures (59.9 and 74.7 °C), making it clear that two *para*-disubstituted benzene rings are actually present and they interact sterically. Careful analysis of all aspects of the spectral data of the three analogous products

isolated, and finally X-ray crystallographic analysis of two of them,[‡] established their structures and relative stereochemistries as **2a–c**. A view of the solid-state conformation of **2b** as an example is provided in Fig. 1. In both compounds, the heterocyclic ring has a half-chair conformation[§] with pseudo-axial *trans*-methoxy substituents. The arylamino nitrogen atom in each molecule is intramolecularly hydrogen bonded to the carbonyl oxygen atom at C(4) thereby forming a pseudo-five-membered ring [H(7'')...O(13) = 2.32(2) Å, **2b**; 2.10(5) Å, **2c**]. In crystals of **2b**, molecules are associated *via* a weak intermolecular N–H...O hydrogen bond involving the



a: R¹ = R² = H; b: R¹ = OMe, R² = H; c: R¹ = H, R² = OMe

[†] **2a**: m.p. 226–227 °C; IR (Nujol): ν /cm^{−1} 3375, 1710 and 1685; ¹H NMR (CDCl₃): δ 2.98 (s, 3H), 3.10 (s, 3H), 5.74 (s, 1H), 6.23 (d, *J* 9 Hz, 2H), 7.14–7.30 (m, 4H), 7.68 (dt, *J* 9 and 2 Hz, 1H), 7.96 (dd, *J* 9 and 2 Hz, 1H), 7.50–8.30 (br, 4H) and 9.61 (s, 1H); ¹³C NMR (CDCl₃): δ 50.99 (OMe), 51.74 (OMe), 87.99 (C-3), 106.23 (C-2), 114.82 (C-2'', 6''), 117.62 (C-8), 118.39 (C-4a), 122.76 (C-3', 5'), 123.13 (C-6), 127.67 (C-5), 127.77 (C-4''), 130.45 (br, C-2', 6'), 130.85 (C-3'', 5''), 137.01 (C-7), 140.77 (C-1'), 148.83 (C-4'), 149.41 (C-1''), 155.75 (C-8a), 189.49 (C-4) and 190.25 (CHO); MS: *m/z* 448 (M⁺).

2b: m.p. 253–254 °C; IR (Nujol): ν /cm^{−1} 3375, 1702 and 1690; ¹H NMR (CDCl₃): δ 2.97 (s, 3H), 3.11 (s, 3H), 3.94 (s, 3H), 5.76 (br s, 1H), 6.22 (d, *J* 9 Hz, 2H), 6.62 (d, *J* 2 Hz, 1H), 6.74 (dd, *J* 9 and 2 Hz, 1H), 7.29 (d, *J* 9 Hz, 2H), 7.90 (d, *J* 9 Hz, 1H), 7.60–8.35 (br, 4H) and 9.67 (s, 1H); ¹³C NMR (CDCl₃): δ 51.02 (OMe), 51.60 (OMe), 55.82 (OMe), 87.88 (C-3), 101.39 (C-8), 106.30 (C-2), 110.58 (C-6), 111.80 (C-4a), 114.85 (C-2'', 6''), 123.04 (C-3', 5'), 127.60 (C-4''), 129.42 (C-5), 130.53 (C-2', 6'), 130.76 (C-3'', 5''), 140.94 (C-1'), 148.78 (C-4'), 149.60 (C-1''), 157.90 (C-8a), 166.98 (C-7), 187.80 (C-4) and 190.14 (CHO); MS: *m/z* 478 (M⁺).

2c: m.p. 214–215 °C; IR (Nujol): ν /cm^{−1} 3335, 1702 and 1690; ¹H NMR (CDCl₃): δ 3.00 (s, 3H), 3.10 (s, 3H), 3.90 (s, 3H), 5.72 (s, 1H), 6.23 (d, *J* 9 Hz, 2H), 7.10 (d, *J* 9 Hz, 1H), 7.23–7.33 (m, 3H), 7.38 (d, *J* 2 Hz, 1H), 7.70–8.40 (br, 4H) and 9.60 (s, 1H); ¹H NMR (CD₃SOCD₃, 20.7 °C): δ 2.94 (s, 3H), 3.03 (s, 3H), 3.84 (s, 3H), 6.47 (br, 2H), 7.03 (br s, 1H), 7.20–7.26 (m, 2H), 7.34–7.40 (m, 3H), 7.74 (br, 2H), 8.08 (br, 2H) and 9.53 (s, 1H).

[‡] Crystal data: **2b**, C₂₅H₂₂N₂O₈, *M* = 478.46, triclinic, space group *P* $\bar{1}$ (No. 2), *a* = 11.117(1), *b* = 13.110(1), *c* = 8.937(1) Å, α = 91.88(1), β = 112.45(1), γ = 75.27(1)° (from 25 orientation reflections, 35° < θ < 39°), *U* = 1161.2(3) Å³, *Z* = 2, *D*_c = 1.368 g cm^{−3}, μ (Cu-K α radiation, λ = 1.5418 Å) = 8.3 cm^{−1}, sample dimensions 0.10 × 0.10 × 0.30 mm; **2c**, C₂₅H₂₂N₂O₈, *M* = 478.46, monoclinic, space group *C*2/c (No. 15), *a* = 18.521(2), *b* = 11.232(1), *c* = 22.334(2) Å, β = 100.85(1)° (from 25 orientation reflections, 35° < θ < 40°), *U* = 4563(1) Å³, *Z* = 8, *D*_c = 1.393 g cm^{−3}, μ (Cu-K α radiation) = 8.4 cm^{−1}, sample dimensions 0.07 × 0.13 × 0.26 mm. Intensity data (+*h*, $\pm k$, $\pm l$, 4753 non-equivalent reflections for **2b**; +*h*, +*k*, $\pm l$, 4045 non-equivalent reflections for **2c**) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-K α radiation, graphite monochromator, θ_{\max} = 75°); the usual Lorentz and polarization corrections were applied. Both crystal structures were solved by direct methods (MULTAN11/82). Initial non-hydrogen atom positions were derived from *E*-maps; hydrogen atoms were located in difference Fourier syntheses. Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; isotropic H) converged at *R* = 0.048 (*R*_w = 0.065; max. $\Delta\rho$ = 0.32, min. $\Delta\rho$ = −0.24 e Å^{−3}) and *R* = 0.038 (*R*_w = 0.050, max. $\Delta\rho$ = 0.17, min. $\Delta\rho$ = −0.16 e Å^{−3}) over 2801 and 1888 reflections with *I* > 3.0 σ (*I*), respectively, for **2b** and **2c**. Crystallographic calculations were performed by use of the Enraf-Nonius Structure Determination Package (SDP). Atomic coordinates, bond lengths and angles, and thermal parameters for **2b** and **2c** have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

[§] Endocyclic torsion angles (ω_{ij} , σ 0.3–0.4°) about the bonds between atoms *i* and *j* in **2b**, with corresponding values for **2c** in parentheses, follow: $\omega_{1,2}$ 51.4(49.0), $\omega_{2,3}$ −63.1 (−65.5), $\omega_{3,4}$ 44.8(50.7), $\omega_{4,4a}$ −15.2(−19.1), $\omega_{4a,8a}$ −0.5(−2.0), $\omega_{8a,1}$ −18.7(−14.0)°

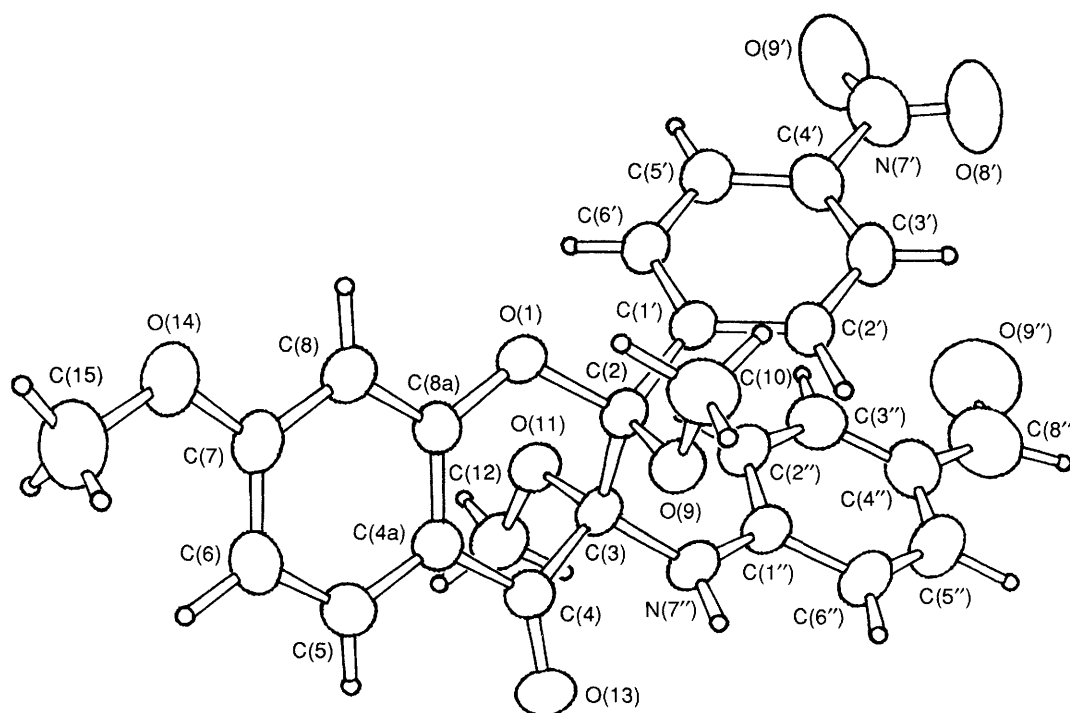
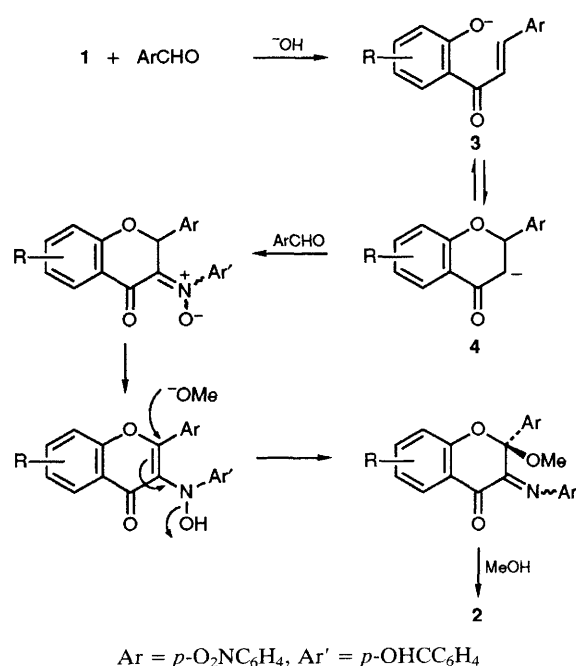


Fig. 1 ORTEP diagram showing the structure and solid-state conformation of one enantiomer of **2b**; small circles represent hydrogen atoms

oxygen atom of a methoxy group in a molecule related by a crystallographic centre of symmetry [$N(7'') \cdots O(9) = 3.280(4)$ Å, $H(7'') \cdots O(9) = 2.51(4)$ Å, $N(7'')-H(7'') \cdots O(9) = 168(2)^\circ$] whereas crystals of **2c** lack any like interactions. These dissimilarities in packing arrangements result in significant differences between the conformations[¶] adopted about the $C(3)-N(7'')$ and $N(7'')-C(1'')$ bonds of **2b** and **2c** in the solid state while the orientations of their nitrophenyl substituents about the $C(2)-C(1')$ bond show less variation. In accord with the demands of the structures, when the reactions were performed in 10% alkali the yields of **2a-c** were found to increase significantly (from 10–15%^{||} to 45–52%) on changing the mole ratio of *o*-hydroxyacetophenone **1** to *p*-nitrobenzaldehyde from 1 : 1 to 1 : 2; at other alkali concentrations (e.g. 5, 15 and 20%), **2a-c** were also formed, albeit in somewhat lower yields.

A plausible mechanism for formation of **2** is delineated in Scheme 1. The ability of a mixture of 2'-hydroxy-4-nitrochalcone and *p*-nitrobenzaldehyde to generate **2a** under the same reaction conditions supports this mechanism. It is noteworthy that intramolecular attack of a flavanone 3-anion on a 2'-nitro group is not without precedent.⁴ Our attempts to isolate products analogous to **2** by condensing each of 2'-hydroxychalcone, 2'-hydroxy-3-nitrochalcone, flavanone and 3'-nitroflavanone with *p*-nitrobenzaldehyde, as well as 2'-hydroxy-4-nitrochalcone with each of *p*-nitrotoluene and *m*-nitrobenzaldehyde, however, did not meet with success. The combination of **4** and *p*-nitrobenzaldehyde, therefore, follows



Scheme 1

[¶] Torsion angles (σ 0.3–0.5°) characterizing the conformations of the $C(2)$ and $C(3)$ substituents in **2b**, with values for **2c** in parentheses, follow: $C(3)-C(2)-C(1')-C(2') = -91.6(-86.2)^\circ$, $C(3)-C(2)-C(1')-C(6') = 84.2(93.7)^\circ$, $O(11)-C(3)-N(7'')-C(1'') = 49.9(28.6)^\circ$, $C(3)-N(7'')-C(1'')-C(2'') = -22.0(22.0)^\circ$.

^{||} Based on the amount of *p*-nitrobenzaldehyde.

an intriguing mechanism which is the subject of current investigations.

Finally, it should be stressed that the reaction exhibits a high degree of stereoselectivity, and, moreover, that the products **2a-c** have potentially interesting physiological activities^{5,6} which have yet to be explored.

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