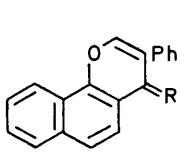
Coumarins and Related Compounds. Part XXI.[1] A Reinvestigation of the Reaction between 1-Naphthol and 2-Formyl-2-phenylacetonitrile

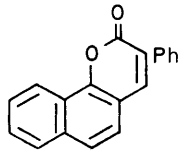
By **Arun K. Das Gupta,* Rabindra M. Chatterje,** and **Sailendra N. Choudhuri,** Department of Chemistry, Research Division, East India Pharmaceutical Works Ltd., Calcutta-700 060, India

Controversy arose between Baker and Ghosh over whether a compound of m.p. 169—170° obtained in the title reaction was 3-phenylnaphtho[1,2-*b*]pyran-2-one (2) or the corresponding naphthopyran-4-one (1). Synthesis of compounds (1) and (2) showed that both these authors were wrong. The reaction has now been repeated and found to give a mixture of 3-(4-hydroxy-1-naphthyl)-2-phenylacrylonitrile (5), 3-hydroxy-3-(4-hydroxy-1-naphthyl)-2-phenylpropiononitrile (9), and 3,4-dihydro-4-(4-hydroxy-1-naphthyl)-3-phenylnaphtho[1,2-*b*]-pyran-2-one (11). Thermal condensation between 1-naphthol and 2-formyl-2-phenylacetonitrile gave exclusively the naphthopyranone (2) in moderate yield.

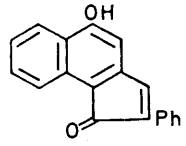
THE condensation product from 1-naphthol and 2-formyl-2-phenylacetonitrile reported by Jacobson and Ghosh to be the naphthopyran-4-one (1) has been the subject of much controversy.[2-4] Compound (1) was synthesised unambiguously by Venkataraman [5] and found to be different from Ghosh's product of m.p. 169—170°. In wrong have been noted.[7-9] To clarify the situation we repeated the condensation under precisely the original conditions,[3] and obtained a yellow material, m.p. 135°, in quantitative yield, originally claimed by Ghosh [2] to be the imine hydrochloride (3). Ghosh's report that the free imine (4), m.p. 115—130°, could be isolated is



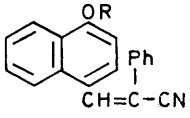
(1) R=O
(3) R=NH,HCl
(4) R=NH



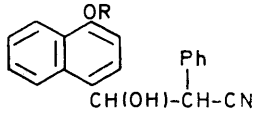
(2)



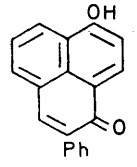
(7)



(5) R=H
(6) R=Me



(9) R=H
(10) R=Me



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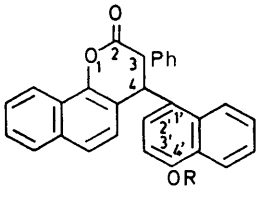
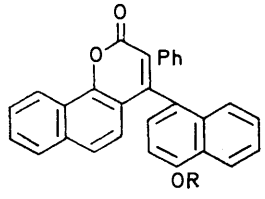


(11) R=H
(12) R=Me



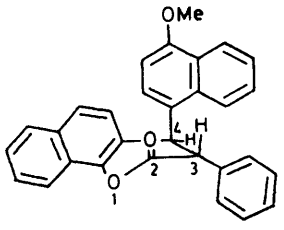
(13) R=H
(14) R=Me

Part XIX we reported [6] a synthesis of the naphthopyran-2-one (2), which excluded the possibility, suggested by Baker,[3] that this was the product of the title reaction. Other cases where Baker's corrected assignments were surprising, since our product was partly soluble in sodium carbonate and wholly so in sodium hydroxide. Moreover, the compound did not respond to a test for halogen.

[1] Preliminary report, Part XX, A. K. Das Gupta, R. M. Chatterje, and S. N. Choudhuri, *Tetrahedron Letters*, 1973, 4203.
[2] S. Jacobson and B. N. Ghosh, *J. Chem. Soc.*, 1915, **107**, 424. 959, 1051; B. N. Ghosh, *ibid.*, 1916, **109**, 105.
[3] W. Baker and R. Robinson, *J. Chem. Soc.*, 1925, 1981; W. Baker, *ibid.*, 1925, 2349.
[4] Elsevier's Encyclopaedia of Organic Chemistry, ed. F. Radt, Elsevier, New York, 1953, vol. 12B, pp. 3486—3487.
[5] H. S. Mahal, H. S. Rai, and K. Venkataraman, *J. Chem. Soc.*, 1934, 1120; V. R. Sathe and K. Venkataraman, *Current Sci.*, 1949, **18**, 373.
[6] A. K. Das Gupta and R. M. Chaterje, *J.C.S. Perkin I*, 1973, 1802.
[7] W. Borche and U. Wannagat, *Annalen*, 1950, **569**, 81.
[8] D. Pillon and J. Massicot, *Bull. Soc. chim. France*, 1954, 26.
[9] A. K. Das Gupta and K. R. Das, *Indian J. Chem.*, 1973, **11**, 1245.

Hydrolysis with dilute sulphuric acid gave a gum instead of the reported compound with m.p. 169—170°. Chromatography of the gum over silica gel gave a yellow compound, m.p. 205—206°, not identical with the naphthopyranone (2). This contained nitrogen, and its i.r. spectrum showed strong OH and C≡N absorptions (3 350 and 2 225 cm^{-1}) and no carbonyl band. Methylation gave a product identical [6] with 3-(4-methoxy-1-naphthyl)-2-phenylacrylonitrile (6); hence the compound of m.p. 205—206° was 3-(4-hydroxy-1-naphthyl)-2-phenylacrylonitrile (5).

These observations led us to reinvestigate thoroughly the work of Ghosh. We noted that solvent of crystallisation had always been taken into account to meet the analytical requirements for compounds (1), (3), and (4).[2] T.l.c. showed that the reaction mixture contained several compounds besides the starting materials, and by chromatography over deactivated alumina four materials were isolated: (i) 1-naphthol, (ii) a non-nitrogenous compound, m.p. 248—249°, (iii) the nitrile (5), and (iv) a nitrogenous compound, m.p. 224—225°. The material of m.p. 248—249° was assigned structure (11) on the basis of spectral evidence, including mass spectra, which ruled out two other possible structures, (7) and (8), which might have been formed by Hoesch condensation [10] followed by cyclisation. Methylation of compound (11) gave the methoxy-derivative (12), *m/e* 430 ($C_{30}H_{22}O_3$). The n.m.r. spectrum of compound (12) showed a sharp singlet at δ 3.90 (3 H, OCH_3) and a weakly coupled pair of AB doublets centred at δ 4.52 and 5.35 (J_{AB} 4—5 Hz, H-3 and -4). The protons *meta* and *ortho* to the methoxy-group (H-2′ and -3′) gave rise to an AB quartet (δ_A 6.80, δ_B 6.58m J_{AB} 7—8 Hz) and the rest of the aromatic protons (15 H) appeared as a complex multiplet at δ 7.15—8.44. A Drieding model indicated the most



(12a)

stable conformation as (12a), with the two aromatic substituents *trans* to each other in a half-boat δ-lactone ring. In this conformation the torsion angle between H-3 and -4 (*ca.* 90°) is supported by the observed low coupling constant between them. Compound (11) is probably formed by condensation of 1-naphthol with the nitrile (5). Dehydrogenation [6] of the lactone (12) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) yielded the naphthopyranone (14) in high yield. Demethylation [6] of (14) with pyridine hydrochloride afforded the naphthopyranone (13). The product of m.p. 224—225° showed i.r. bands characteristic of nitrile (2 240 cm^{-1}) and hydroxy- (3 360 cm^{-1}) groups and no carbonyl absorption. If the chromatographic separation was carried out on silica gel rather than alumina, this nitrile was isolated in negligible amount and the proportion of compound (5) was much greater; this seemed to indicate some relationship between the two substances. The empirical formula ($C_{19}H_{15}NO_2$) indicated that the nitrile of m.p. 224—225° contained two more hydrogen atoms and one more oxygen atom than compound (5); this led us to believe that it might be the intermediate hydroxy-nitrile (9) which could undergo dehydration on silica gel. Indeed treatment with toluene-*p*-sulphonic acid in boiling benzene afforded the nitrile (5). Methylation of (9) gave 3-hydroxy-3-(4-methoxy-1-naphthyl)-2-phenylpropiononitrile (10), which on dehydration gave the expected methoxy-nitrile (6).

Having been unable to substantiate the observations of Ghosh, we studied the condensation of 1-naphthol with 2-formyl-2-phenylacetonitrile in the presence of Lewis acids [11] (zinc chloride and aluminium chloride). By use of zinc chloride in dry ether at 0 °C, the expected naphthopyran-2-one (2) was obtained in poor yield, together with compounds (5) and (11). Similar condensation in the presence of aluminium chloride and dry hydrogen chloride at 150—170 °C gave a mixture from which compounds (2), (5), and (11) could be isolated in very poor yield. Variation of temperature, solvent, *etc.*, produced no essential improvement.

Lastly, thermal condensation of 1-naphthol with 2-formyl-2-phenylacetonitrile or the corresponding ester yielded exclusively the naphthopyran-2-one (2) rather than the naphthopyran-4-one (1), in moderate yield. This appears to be the best and simplest method for the synthesis of compound (2).

EXPERIMENTAL

N.m.r. spectra were measured for solutions in [^{2}H]chloroform with a Varian XL-100 spectrophotometer. Mass spectra were measured with an A.E.I. MS9 instrument. Chromatography was carried out with silica gel (B.D.H. 60—120 mesh) or alumina (B.D.H.). T.l.c. was performed with silica gel G (Merck) with (A) benzene–dioxan–acetic acid (90 : 25 : 4) and (B) benzene–chloroform (90 : 10) as eluants; spots were located by exposure to iodine vapour. Unless otherwise stated u.v. spectra were determined for solutions in methanol and i.r. spectra for Nujol mulls.

Condensation between 2-Formyl-2-phenylacetonitrile and 1-Naphthol.—(A) *With glacial acetic acid and hydrogen chloride.* Into an ice-cold suspension of 2-formyl-2-phenylacetonitrile (3 g) and 1-naphthol (3 g) in glacial acetic acid (6 ml) dry hydrogen chloride was passed for 1 h. The mixture was left at room temperature for 2 days, and the resulting solution was poured into crushed ice containing hydrochloric acid. A yellow powder (6 g), m.p. 130—135°, separated out which could not be further purified by crystallisation. A portion (1 g) was heated under reflux with 10% sulphuric acid (30 ml) for 3 h, and the mixture was then cooled and filtered to give a brown powder (0.8 g), m.p. 180—200°. Chromatography over silica gel afford 3-(4-hydroxy-1-naphthyl)-2-phenylacrylonitrile (5) as yellow

[10] P. E. Spoerri and A. S. DuBois, *Org. Reactions*, 1949, **5**, 387.
[11] A. K. Das Gupta, R. M. Chatterje, and M. S. Paul, *J. Chem. Soc.* (*C*), 1971, 3367.

needles, m.p. 205—206° (from methanol), R_F (A) 0.62, $\nu_{max.}$ 3 340 (OH), 2 220 (CN), 1 615, and 1 565 cm^{-1} (aromatic), $\lambda_{max.}$ 245sh, and 375 nm (log ε 4.35 and 4.25) (Found: C, 84.1; H, 5.1; N, 5.3. $C_{19}H_{13}NO$ requires C, 84.1; H, 4.85; N, 5.15%). Methylation of the nitrile (5) with dimethyl sulphate and potassium carbonate in dry acetone gave the methyl ether as needles, m.p. 129—130° (from ethanol), R_F (B) 0.62, $\nu_{max.}$ 2 227 (CN), 1 613, and 1 565 cm^{-1} (aromatic), $\lambda_{max.}$ 244 and 360br nm (log ε 4.3 and 4.2) (Found: C, 84.0; H, 5.5. Calc. for $C_{20}H_{15}NO$: C, 84.2; H, 5.3%), identical (mixed m.p., i.r. and u.v. spectra, and t.l.c.) with authentic 3-(1-methoxy-4-naphthyl)-2-phenylacrylonitrile (6).

T.l.c. of the crude condensation product indicated the presence of several components. The mixture (4 g) was chromatographed on deactivated alumina (200 g), with as eluants, (*a*) benzene–hexane (3 : 2) and benzene–ether [(*b*) 9 : 1, (*c*) 8 : 2, (*d*) 7 : 3, (*e*) 6 : 4, and (*f*) 1 : 1]. Fraction (*a*) gave a trace of an oil * which was not homogenous on t.l.c. and showed ν_{CO} 1 720 cm^{-1}. Fraction (*b*) gave a semi-solid which afforded needles, m.p. 92—93° (from hexane), of 1-naphthol. Fraction (*c*) yielded *3,4-dihydro-4-(4-hydroxy-1-naphthyl)-3-phenylnaphtho*[1,2-b]*pyran-2-one* (11) (400 mg), m.p. 248—249° (from methanol), R_F (B) 0.18 (Found: C, 83.7; H, 4.95. $C_{29}H_{20}O_3$ requires C, 83.65; H, 4.85%), M^+ 416, $\nu_{max.}$ 3 340 (OH) and 1 745 cm^{-1} (lactone); $\lambda_{max.}$ 239, 296br, and 327 nm (log ε 4.7, 4.1, and 3.9), giving a positive reaction with iron(III) chloride. Methylation of the lactone (11) (250 mg) with dimethyl sulphate (0.5 ml) in the presence of anhydrous potassium carbonate (1 g) and dry acetone (10 ml) gave the *methoxy-compound* (12), m.p. 258—259° (from toluene), R_F (B) 0.69 (Found: C, 83.5; H, 5.25. $C_{30}H_{22}O_3$ requires C, 83.7; H, 5.15%), M^+ 430; $\nu_{max.}$ 1 770 cm^{-1} (lactone); $\lambda_{max.}$ (dioxan) 244, 292, 302, and 323sh nm (log ε 4.4, 4.16, 4.1, and 3.7), δ 7.15—8.44 (15 H, m, aromatic), 6.80 (1 H, q, 2′-H), 6.58 (1 H, q, 3′-H), 5.36 (1 H, d, 4-H), 4.52 (1 H, d, 3-H), and 3.90 (3 H, s, OCH_3).

Fraction (*d*) gave the nitrile (5) (200 mg), m.p. 204—205°. Fraction (*e*) afforded *3-hydroxy-3-(4-hydroxy-1-naphthyl)-2-phenylpropiononitrile* (9)† (400 mg), m.p. 224—225° (from benzene), R_F (A) 0.40 (Found: C, 78.6; H, 5.35; N, 4.5. $C_{19}H_{15}NO_2$ requires C, 78.8; H, 5.25; N, 4.85%). $\nu_{max.}$ 3 360 (OH), 2 240 (CN), 1 600, and 1 505 cm^{-1} (aromatic), $\lambda_{max.}$ 242, 310, and 328 nm (log ε 4.4, 4.0, and 3.9). Treatment of this nitrile (100 mg) with toluene-*p*-sulphonic acid (40 mg) in boiling benzene (20 ml) for 3 h gave the nitrile (5) (70 mg), identified by mixed m.p., i.r. spectrum, and t.l.c. Methylation of the nitrile (9) in the usual way gave the methoxynitrile (10), m.p. 227—228°, $\nu_{max.}$ 3 350 (OH), 2 245 (CN), 1 620, and 1 580 cm^{-1} (aromatic), dehydration of which with toluene-*p*-sulphonic acid as described earlier gave the nitrile (6), m.p. and mixed m.p.[6] 129—130°. Fraction (*f*) gave a solid (1.2 g) which was not homogeneous (t.l.c.). Rechromatography over alumina yielded traces of compounds (5) and (11) and a powder (1 g) which could not be purified further by rechromatography over alumina or silica gel or by fractional crystallisation.

(B) *With zinc chloride in ether.* Dry hydrogen chloride was passed into an ice-cold mixture of 1-naphthol (3 g), 2-formyl-2-phenylacetonitrile (3 g), and zinc chloride (3 g) in dry ether (30 ml) with stirring for 4 h. The mixture was kept for 2 days at 0 °C, then the ether was decanted and the solid was decomposed with ice-cold dilute hydrochloric acid. The product (5.4 g) was chromatographed on silica gel (150 g) with benzene–hexane [(*a*) 1 : 3, (*b*) 1 : 1, and (*c*) 2 : 1], (*d*) benzene, and benzene–chloroform [(*e*) 3 : 1 and (*f*) 1 : 1] as eluants. Fraction (*a*) afforded an oil (50 mg) shown to be a complex mixture by t.l.c. Fraction (*b*) (60 mg) was identical with authentic 3-phenylnaphtho[1,2-*b*]pyran-2-one (2), m.p. 208—210° (mixed m.p., i.r. spectrum, and t.l.c.). Fraction (*c*) (900 mg) was 1-naphthol, m.p. 90—92°. Fraction (*d*) (280 mg) was identical with the lactone (11), m.p. 247—248° (mixed m.p. and t.l.c). Fraction (*e*) gave the nitrile (5) (65 mg), m.p. 204—205° (mixed m.p. and t.l.c). Fraction (*f*) gave a mixture (1.5 g) which could not be further purified by repeated chromatography.

3-Phenylnaphtho[1,2-b]*pyran-2-one* (2).—(a) *From 2-formyl-2-phenylacetonitrile.* An intimate mixture of 1-naphthol (5 g) and 2-formyl-2-phenylacetonitrile (5 g) was placed in a preheated silicone bath at 220 °C and maintained at that temperature for 15 min. (These conditions were the best of several investigated.) When cold, the residue was treated with water containing a few drops of hydrochloric acid and heated on a steam-bath for 0.5 h. The mixture was then extracted with ether and the extract was washed with dilute alkali and water and evaporated. Treatment of the residue with acetone gave the naphthopyranone (2) as fine yellow needles (1.9 g), m.p. 210—211° (lit.,[6] 212—213°), $\nu_{max.}$ (Nujol) 1 720, 1 470, 1 240, 865, 822, and 780 cm^{-1}, R_F (B) 0.49, identical (i.r. and u.v. spectra and mixed m.p.) with an authentic [6] sample. From the mother liquor, by chromatography over alumina, another crop (75 mg) was isolated.

(b) *From methyl 2-formyl-2-phenyl acetate.* 1-Naphthol (6.5 g) and methyl 2-formyl-2-phenylacetate [12] (6.5 g) were heated at 260—270 °C for 20 min (optimal conditions). The product was worked up as in (a) to give the naphthopyranone (2) (2.1 g) as light yellow needles, m.p. 212—213°.

Dehydrogenation of the Dihydronaphthopyranone (12).—Compound (12) (400 mg) was refluxed with DDQ (400 mg) in freshly distilled dioxan (40 ml) with a crystal of toluene-*p*-sulphonic acid until the reaction was complete (16 h). The separated solid was filtered off, the dioxan was removed under reduced pressure, and the residue was passed through a column of alumina with chloroform as eluant. Crystallisation from methylene chloride–methanol gave *4-(4-methoxy-1-naphthyl)-3-phenylnaphtho*[1,2-b]*pyran-2-one* (14) (250 mg), m.p. 231—232°, R_F (B) 0.52 (Found: C, 84.2; H, 4.9. $C_{30}H_{20}O_3$ requires C, 84.1; H, 4.7%), $\nu_{max.}$ (KBr) 1 730 cm^{-1} (α-pyrone), $\lambda_{max.}$ (dioxan) 246, 283, 313, 324, and 360 nm (log ε 4.5, 4.5, 4.2, 4.2, and 4.0).

Demethylation of the Naphthopyranone (14).—A mixture of freshly distilled pyridine hydrochloride (1 g) and compound (14) (100 mg) was refluxed at 260—270 °C for 20 min. It was then cooled, treated with water containing a few drops of hydrochloric acid, and warmed on a steam-bath for 15 min. The pale yellow solid (80 mg), m.p. 280—281°, which separated was crystallised twice from benzene to afford *4-(4-hydroxy-1-naphthyl)-3-phenylnaphtho*[1,2-b]*pyran-2-one* (13), m.p. 288—289°, R_F (A) 0.61 (Found: C, 84.25; H, 4.45. $C_{29}H_{18}O_3$ requires C, 84.05; H, 4.4%), $\nu_{max.}$ 3 360br

* When a 10 g batch was chromatographed, 3-phenylnaphtho-[1,2-*b*]pyran-2-one (2), m.p. 208—210°, was isolated from this oil by rechromatography and crystallisation, and identified by mixed m.p. and t.l.c.

† When the chromatography was performed on silica gel (B.D.H.), the nitrile (9) could not be isolated; however, the yield of the nitrile (5) was greatly increased.

[12] J. E. Gowan, S. P. MacGiolla Riogh, G. J. MacMohan, S. O'Cleirigh, E. M. Philbin, and T. S. Wheeler, *Tetrahedron*, 1958, **2**, 116.

(OH) and 1 705 cm^{-1} (α-pyrone), $\lambda_{max.}$ (dioxan) 245, 282, 315, 325, and 360 nm (log ε 4.36, 4.44, 4.16, 4.16, and 4.04).

Synthesis of 3-(4-*Hydroxy*-1-*naphthyl*)-2-*phenylacrylonitrile* (5).—A mixture of freshly distilled pyridine hydrochloride (12 g) and the methoxy-nitrile [6] (6) (2.5 g) was refluxed for 15—20 min under anhydrous conditions, at 250—260 °C. The mixture was then cooled, treated with water containing a few drops of hydrochloric acid, and heated on a steam-bath for 30 min. Filtration gave a yellow compound which was dissolved in dilute sodium hydroxide; the solution was filtered and acidified with dilute hydrochloride acid to give the nitrile (5) (2.2 g), m.p. 205—206° (from methanol), identical (mixed m.p., i.r. spectrum, and t.l.c.) with the sample described earlier.

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