Dibenzo[*c,h*]cinnoline Oxides

By W. H. Poesche

Dibenzo[*c,h*]cinnoline 5-oxide has been synthesised. The compound is not identical with the hydrogen peroxide oxidation product of dibenzo[*c,h*]cinnoline and the sodium sulphide reduction product of 1-nitro-2-*o*-nitrophenylnaphthalene, which must therefore be dibenzo[*c,h*]cinnoline 6-oxide, as previously supposed. Aside from steric interactions, electronic effects are made responsible for the exclusive formation of the 6-oxide in the latter two cases.

It has frequently been assumed that basisity and nucleophilicity of the nitrogen atom in nitrogen aromatics (a property of the nitrogen lone electron pair) can be correlated with calculated charge densities (a property of the π-electron cloud). Unsymmetrical heterocycles with more than one skeletal nitrogen atom in the molecule should be particularly suited to test this assumption. We have now established the site of attack in the *N*-oxidation of dibenzo[*c,h*]cinnoline (Figure 2) by comparison of the reaction product with authentic

dibenzo[*c*,*h*]cinnoline 5-oxide. The two compounds are not identical, showing that attack takes place in 6-position. Infrared spectroscopy revealed complete absence of the 5-oxide in the oxidation product; less than 5% could have been detected.

This result is in agreement with that of Corbett and Holt [1] who carried out the *N*-oxidation and obtained a single compound. This they suggested to be the 6-oxide on the basis of steric considerations: there is intramolecular overcrowding between an oxygen bound to N-5 and the hydrogen attached to C-4, whereas no such interference exists if the oxygen is in the alternate position (Figure 1). They did, however, not prove this structure since 1-amino-2-*o*-nitrophenylnaphthalene and 1-nitro-2-*o*-aminophenylnaphthalene (VI) needed for the unambiguous synthesis of the two *N*-oxides were not then available.

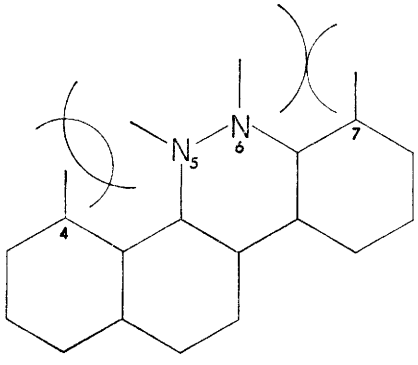


FIGURE 1. Steric interference in dibenzo[*c*,*h*]cinnoline 5- and 6-oxide. Assumed distances (Å): N–O, 1·24; C–H, 1·08; van der Waals radii: O, 1·4; H, 1·0

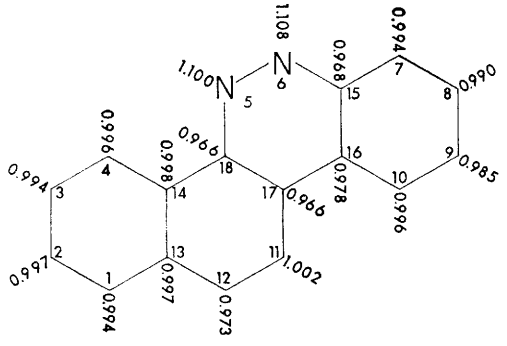
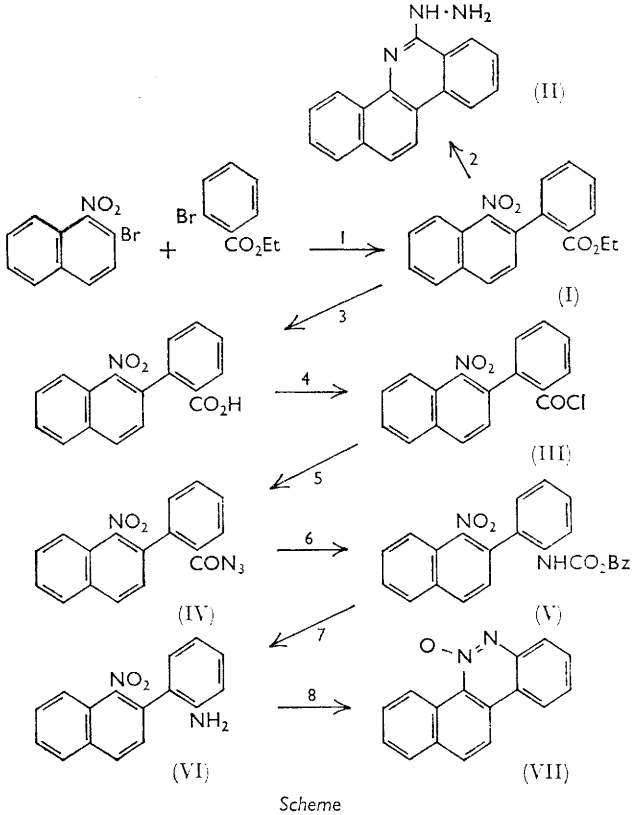


FIGURE 2. Hückel charge densities in dibenzo[*c*,*h*]cinnoline

Although the mentioned steric factors undoubtedly exist, we were able to prepare dibenzo[*c*,*h*]cinnoline 5-oxide in 80% yield from the nitro-amine (VI), of which we had prepared a larger quantity in the course of another investigation. The high yield indicates to us that the molecule cannot be severely strained, and it seemed therefore likely that electronic as well as steric factors must be made responsible for the exclusive formation of the 6-oxide. A molecular-orbital calculation confirmed this conclusion. It shows the N-6 atom to have a higher charge density than the N-5 atom (Figure 2). In addition, the total π-electron energy of the 6-oxide (30·484β) is calculated to be 0·024β higher than that of the 5-oxide (30·460β), indicating slightly greater resonance stabilisation in the observed product even if the 5-oxide could exist as a planar molecule.

Corbett and Holt [1] noted that the sodium sulphide reduction of 1-nitro-2-*o*-nitrophenylnaphthalene yielded the same dibenzo[*c*,*h*]cinnoline *N*-oxide as oxidation of dibenzo[*c*,*h*]cinnoline. We have confirmed this by using infrared spectroscopy. Again no 5-oxide could be detected. The same combination of steric and resonance effects as mentioned in the last paragraph would also account for this result. We may assume that the intermediate is dibenzo[*c*,*h*]cinnoline 5,6-dioxide, in analogy with the sodium sulphide reduction of *oo'*-dinitrobiphenyl where benzo[*c*]cinnoline 5,6-dioxide could be isolated when the amount of reducing agent was kept small.[2] On further reduction, the less tightly bound oxygen atom will be removed, which in our case is that attached to N-5.

The 2-*o*-aminophenyl-1-nitronaphthalene used in this work was prepared from 2-bromo-1-nitronaphthalene and ethyl *o*-bromobenzoate by the route shown in the Scheme. Conversion of the ester (I) into its hydrazide



Scheme

Reagents: 1, Ullmann (45%); 2, N_2H_4,H_2O; 3, NaOH (60%); 4, PCl_5 (100%); 5, NaN_3 (90%); 6, △, BzOH; 7, HBr–AcOH (50%); 8, $BzNMe_3^+ OH^-$ (80%)

failed; on heating with hydrazine, reduction of the nitrogroup and ring closure to the benzo[*c*]phenanthridine

[1] J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 1960, 3646.
[2] S. D. Ross, G. J. Kahan, and W. A. Leach, *J. Amer. Chem. Soc.*, 1952, **74**, 4122.

derivative (II) took place simultaneously. The acid chloride (III) could be converted into the azide (IV) with aqueous sodium azide solution. Compounds (III), (IV), and (V) were not analysed, but that the reactions had taken the expected course was shown by their infrared spectra and the fact that the nitro-amine (VI) and its acetyl derivative analysed correctly. For the condensation to the *N*-oxide (VII), a methanolic solution of benzyltrimethylammonium hydroxide [3] was used. This reagent generally seems to give a cleaner reaction than the hitherto employed alkali hydroxides.

The molecular-orbital calculations were carried out with the parameters recommended by Streitwieser: [4] $\alpha_N = \alpha_C + 0{\cdot}5\beta_{CC}$; $\alpha_{N^+} = \alpha_C + 2{\cdot}0\beta_{CC}$; $\alpha_O = \alpha_C + 1{\cdot}0\beta_{CC}$; $\beta_{CN} = \beta_{NN} = \beta_{CC}$; $\beta_{NO} = 0{\cdot}7\beta_{CC}$.

EXPERIMENTAL

Melting points are corrected. Microanalyses were carried out by W. Saschek, Chicago. Infrared spectra were recorded with a Perkin-Elmer 421 grating spectrometer.

Ethyl o-*bromobenzoate*. *o*-Bromobenzoic acid (173 g., 0·86 mole) dissolved in phosphorus oxychloride (450 g.) was treated with phosphorus pentoxide (173 g., 0·83 mole). After boiling under reflux for 1 hr., the phosphorus oxychloride was distilled off (oil-bath, 140°), and the distillation residue added to boiling ethanol (500 ml.). After boiling this mixture under reflux for 1 hr., it was fractionated. Ethyl *o*-bromobenzoate (185 g., 94%) distilled at 87°/0·8 mm., $n_D^{15.5}$ 1·5439 (lit.,[5] $n_D^{15{\cdot}4}$ 1·5455).

The ester could not be prepared by boiling *o*-bromobenzoic acid with triethyl orthoformate in ethanol in the presence of a catalytic amount of concentrated sulphuric acid.

1-*Nitro*-2-*bromonaphthalene*.[6a] 1-Nitro-2-naphthylamine [6b] (100 g., prepared from 2-acetamidonaphthalene [6c] *via* 1-nitro-2-acetamidonaphthalene [6d]) was dissolved in hot acetic acid (1·5 l.), cooled quickly to 20° and added to stirred nitrosylsulphuric acid (267 ml. 2M-solution of sodium nitrite in concentrated sulphuric acid [6a]) below 25°. This mixture was added to a stirred, ice-cooled solution of cuprous bromide (76·5 g.) in hydrobromic acid (1 l.; 48%). Next day the mixture was poured on to water (16 l.), the precipitate collected, air dried, and dissolved in hot chloroform (1 l.), the solution filtered, washed with sodium carbonate and water, and dried over calcium chloride. After removal of the chloroform, the compound was distilled, b. p. 110—115°/0·2 mm., yield 112 g. (83%) of a product melting at 102—103° (m. p. of pure compound 102—103° [6e]).

Ethyl o-(1-*nitro*-2-*naphthyl*)*benzoate* (I). To a stirred mixture of ethyl *o*-bromobenzoate (167·6 g., 0·72 mole) and 1-nitro-2-bromonapthalene (182 g., 0·72 mole) was added copper bronze at such a rate that the temperature did not exceed 145° (*ca.* 20 min.), and stirring continued for 28 hr. at 140°. The product was extracted three times with chloroform, the combined extracts were taken to dryness, taken up in boiling ethanol (500 ml.) and filtered hot. The residue consisted of 1,1′-dinitrobinaphthyl, (5·0 g.), m. p. 283—285° (lit.,[7] 284°). On cooling to room temperature, ethyl *o*-(1-nitro-2-naphthyl)benzoate (96·5 g.; m. p. 79—85°), and at −20°, 1-nitro-2-bromonapthalene (15·9 g.) separated. After this was removed, a further crop of ethyl *o*-(1-nitro-2-naphthyl)benzoate could be obtained from the filtrate. Total yield of recrystallised (ethanol) product was 103 g. (45%). Recrystallised once more from ethanol (charcoal) the compound formed greenish crystals, m. p. 105—106° (Found: C, 71·1; H, 4·8; N, 4·3. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·35%).

Since 1-nitro-2-bromonaphthalene and ethyl *o*-(1-nitro-2-naphthyl)benzoate have very similar m. p.s (103 and 106°, respectively), the identity of the isolated fractions was established by infrared spectroscopy (KBr disc). The latter compound showed strong absorption at 1720 cm.$^{-1}$ (C=O), missing in the former.

Reaction of ethyl o-(1-*nitro*-2-*naphthyl*)*benzoate with hydrazine hydrate*. The ester (1 g.) in n-butanol (2 ml.) was boiled under reflux with hydrazine hydrate (2 ml.) for 24 hr. After cooling, the precipitate was collected. Recrystallised twice from ethanol, it had m. p. 184·5—185°. Absence of carbonyl absorption in the infrared and the analysis identify the compound as 6-*hydrazinobenzo*[c]-*phenanthridine* (II) (Found: C, 78·6; H, 4·7. $C_{17}H_{13}N_3$ requires C, 78·75; H, 5·05%).

o-(1-*Nitro*-2-*naphthyl*)*benzoic acid*. Ethyl *o*-(1-nitro-2-naphthyl)benzoate (51·3 g., 0·16 mole) in hot ethanol (715 ml.) were boiled under reflux with 2N-aqueous potassium hydroxide (80 ml.) for 24 hr. The solvent was removed at room temperature, and the residue taken up in dilute potassium carbonate solution and extracted with ether. The clear aqueous layer was run into cooled, stirred hydrochloric acid (120 ml.; *d* 1·19) to yield, after drying, the acid (28·0 g., 60%; m. p. 210—211°), pure enough for the next step. Two further crystallisations from toluene gave the greenish yellow acid, m. p. 213—214° (Found: C, 69·7; H, 3·8. $C_{17}H_{11}NO_4$ requires C, 69·6; H, 3·8%).

o-(1-*Nitro*-2-*naphthyl*)*benzoyl azide* (IV). *o*-(1-Nitro-2-naphthyl)benzoic acid (25 g.) in benzene (470 ml.) was boiled under reflux with phosphorus pentachloride (19·6 g.) for 3½ hr. The benzene was distilled off, toluene (120 ml.) added, distilled off to remove last traces of phosphorus oxychloride, and the distillation residue dried completely in oil-pump vacuum, m. p. *ca.* 111°.

The acid chloride (III) (25·3 g.) was dissolved in acetone (330 ml.), and the stirred solution treated at −15° with 10% sodium azide solution (66 ml.). After 3 hr. the azide [23·0 g.; m. p. *ca.* 116° (decomp.)] was filtered off and dried over phosphorus pentoxide *in vacuo*. A further 2·3 g., m. p. 110—112°, was obtained from the filtrate on addition of water, $\nu_{max.}$ (KBr disc): 2140s (N_3), 1710s (C=O), 1530s, 1340m (NO_2).

Benzyl o-(1-*nitro*-2-*naphthyl*)*phenylcarbamate* (V). *o*-(1-Nitro-2-naphthyl)benzoyl azide (25·0 g.) was suspended in xylene (260 ml.), benzyl alcohol (13 ml.) added and the mixture carfully warmed with magnetic stirring. Evolution of nitrogen began at 57° and ceased at 75°, when all the solid had gone into solution. The temperature was raised to and kept for a short period at 140°, then the solvent removed *in vacuo*. The residual oil could not be induced to crystallise.

[3] J. W. Barton and J. F. Thomas, *J. Chem. Soc.*, 1964, 1265.
[4] A. Streitwieser, jun., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, London, 1961, p. 125.
[5] K. von Auwers, *Annalen*, 1921, **422**, 166.
[6] (*a*) Cf. H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1933, 1620; (*b*) C. R. Saunders and C. S. Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 638; (*c*) H. H. Hodgson and E. Kilner, *J. Chem. Soc.*, 1926, **7**; (*d*) W. W. Hartman and L. A. Smith, *Org. Synth.*, Coll. Vol. 2, 438; (*e*) V. Vesely, *Ber.*, 1905, **38**, 138.
[7] W. M. Cumming and G. Howie, *J. Chem. Soc.*, 1931, 3176.

1-*Nitro*-2-o-*aminophenylnaphthalene* (VI). The oil from the previous experiment was treated with hydrobromic acid in acetic acid (100 ml.; 30—32%).[8] After 2 hr., ether (1 l.) was added, and the solution refrigerated. Gradually, 1-nitro-2-*o*-aminophenylnaphthalene hydrobromide (17·2 g., 50% calc. on azide) separated as yellow cubes, m. p. 202—205°. The hydrobromide was treated with 1 : 1 concentrated ammonia: water–ether, the organic layer separated, the aqueous phase extracted with fresh ether, and the combined extracts dried (Na_2SO_4), and taken to dryness. 1-Nitro-2-*o*-aminophenylnaphthalene (12·5 g., 95%) remained as oil which crystallised only with great difficulty even if seeded. Crystals were obtained when an ether solution was left to evaporate slowly with occasional rubbing with a glass rod; yellow needles, m. p. 104—106° (Found: C, 72·3; H, 4·7. $C_{16}H_{12}N_2O_2$ requires C, 72·7; H, 4·6%). The *acetyl derivative* formed greenish-white, woolly needles, m. p. 188·5—189·5° (from toluene) (Found: C, 70·6; H, 4·8. $C_{18}H_{14}N_2O_3$ requires C, 70·6; H, 4·6).

Dibenzo[c,h]*cinnoline* 5-*oxide* (VII). 1-Nitro-2-*o*-aminophenylnaphthalene (0·529 g.) in ethanol (15 ml.) was boiled under reflux with a 40% methanolic solution of benzyltrimethylammonium hydroxide (10 ml.) for 7 hr., then concentrated to *ca.* 10 ml. Next day, the precipitate [0·39 g., 80%; m. p. 225—230° (decomp.)] was collected. Recrystallised from toluene, dibenzo[*c*,*h*]cinnoline 5-oxide formed long, thin, yellow plates, m. p. 232—235° (decomp.) Found: C, 78·1; H, 4·2; N, 11·25. $C_{16}H_{10}N_2O$ requires C, 78·05; H, 4·1; N, 11·4%), $\nu_{max.}$ (5% in $CHBr_3$) 1625w, 1609w, 1575m, 1550s, 1497m, 1468s, 1459m, 1409s, 1392s, 1361s, 1341s, 1320m, 1280s, 1244m, 1220w, 1201m, 1075w, 1035w, 1019w, 880w, 827s, 797w, 770s cm.$^{-1}$.

Sodium sulphide reduction of 1-*nitro*-2-o-*nitrophenylnaphthalene*. 1-Nitro-2-*o*-nitrophenylnaphthalene was prepared by the Ullmann reaction at 200°,[9] and purified by chromatography on aluminium oxide (eluent: benzene), followed by recrystallisation from ethanol, m. p. 185—186° (lit.,[9] 185—186°).

1-Nitro-2-*o*-nitrophenylnaphthalene (1·0 g.) suspended in boiling ethanol (200 ml.) was treated with sodium sulphide nonahydrate (2·0 g.) and sodium hydroxide (0·5 g.) in water (20 ml.). The mixture was boiled under reflux for 3 hr., concentrated, poured on to water, and the precipitate collected. The dried precipitate (0·54 g.) was dissolved in toluene (100 ml.) and chromatographed on a 50 × 1·5 cm. aluminium oxide (B.D.H.)–benzene column. Benzene–ethyl acetate (25 : 1) eluted a light brown oil (0·182 g.) which was not further investigated. Benzene–ethyl acetate (4 : 1) eluted dibenzo[*c*,*h*]cinnoline 6-oxide (0·325 g., 39%), m. p., after recrystallisation from toluene, 235—237° (decomp.), $\nu_{max.}$ (5% in $CHBr_3$) 1598w, 1584m, 1555w, 1498s, 1455s, 1433m, 1404m, 1385s, 1371s, 1360s, 1317s, 1275m, 1226s, 1211m, 1032w, 1015w, 962w, 890m, 821s, 798m, 771s, 765s cm.$^{-1}$.

N-*Oxidation of dibenzo*[c,h]*cinnoline*. Dibenzo[*c*,*h*]-cinnoline [10] (0·23 g.) in acetic acid (10 ml.) were stirred at room temperature with 30% hydrogen peroxide (0·5 ml.) for 10 hr. Next day, the yellow needles of dibenzo[*c*,*h*]-cinnoline 6-oxide (0·20 g.), m. p. 235—238° (decomp.) (lit.,[1] 232°), were collected. Evaporation of the filtrate to dryness yielded more dibenzo[*c*,*h*]cinnoline 6-oxide. Both were identified by their infrared spectra.

[*Note added in Proof.*—The decomposition points of the *N*-oxides depend on the rate of heating and are therefore not suitable for identification. On very slow heating, the 5- and 6-oxide decomposed at 226 and 221°, respectively].

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