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PHOTOLYSIS OF CHLOROACETAMIDES AS A ROUTE TO NEW 2,8-BRIDGED ISOQUINOLINE DERIVATIVES. X-RAY CRYSTAL STRUCTURE OF 8,13-DIHYDRO-2-METHOXY-4,6- ETHANODIBENZ[*c,f*]AZONINE-5,7-DIONE

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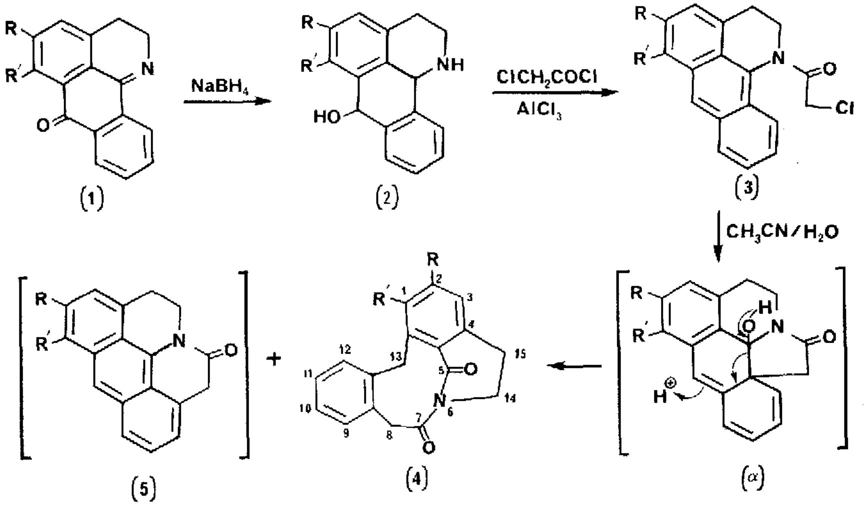
ABSTRACT: Photolysis of 1-chloroacetyl-2,3-dihydro-5-methoxy-1*H*-dibenzo[*de,h*]quinoline (3a) and the corresponding 5,6-dimethoxy derivative (3b) in aqueous acetonitrile gave good yields of 8,13-dihydro-2-methoxy- and 8,13-dihydro-1,2-dimethoxy-4,6-ethanodibenz[*c,f*]-azonine-5,7-dione, (4a) and (4b), respectively. These represent the first examples of 2,8-bridged isoquinoline derivatives. The structure of (4a) was confirmed by X-ray crystallography.

There is currently considerable interest in bridged aromatic systems and derivatives, particularly those with short bridging chains[1-3]. Such systems are of interest for studying strain effects on physical and chemical properties; they could also provide potentially useful rigid models for the assessment of structure-pharmacological property relationships. Our involvement in this general area has focussed on heterocyclophanes and reduced derivatives[3-4], with heteroatoms in the aromatic system and/or the bridge. In this regard we wish to report the synthesis of the first 2,8-bridged isoquinoline derivatives (4a,b) with a five-carbon atom bridging chain.

The derivatives (4a,b) were obtained from the *N*-chloroacetyl compounds (3a,b), these precursors being prepared in turn from the dibenzo[*de,h*]quinolones (1a,b)[5]; reduction ($NaBH_4$, MeOH,0-20°) of (1a,b) gave the 2,3,7,11b-tetrahydro-1*H*-dibenzo[*de,h*]quinolin-7-ols (2a[5],b[6]), which on treatment with chloroacetyl chloride and then aluminium chloride gave the 1-chloroacetyl-2,3-dihydro-1*H*-dibenz[*de,h*]quinolines (3a,b)[7].

Photolysis of (3a) in acetonitrile/water (1:1 v/v; $1.9x10^{-3}M$) for 1.5 hr (Hanovia 450W Hg arc lamp; Corex filter sleeve λ >250nm) gave, after filtration through silica gel and then p.t.l.c. (silica gel; CH_2Cl_2), the 2,8-bridged isoquinoline derivative (4a, colourless crystals from Et_2O, m.p. 183-183.5°)[8] in 85% yield, together with a small amount of impure gummy material tentatively identified as the lactam (5a)[9]; (5a) could not be isolated when more dilute solutions ($10^{-3}M$ and $4.6 \times 10^{-4}M$) were irradiated, although the yield of (4a) was barely affected. The structure of (4a) was initially determined by spectroscopic means. Only six aromatic CH carbon resonances appeared in the ^{13}C NMR spectrum, while two new signals at 170.83 ppm and 170.59 ppm were attributed to the two carbonyl groups; this was supported by the IR spectrum which showed two bands at 1730 and 1672 cm^{-1} consistent with an imide group. Photolysis of (3b) ($4.25 \times 10^{-4}M$ solution) under the same conditions as for (3a) afforded the dimethoxy analogue (4b, colourless crystals from Et_2O, m.p. 197-199°)[10] in 79% yield; no (5b) could be isolated from the photolysate.

Unequivocal confirmation of the structure of (4a) was forthcoming from a single crystal X-ray structure determination.[11] The structure obtained is shown in Figure 1 and non-hydrogen atom co-ordinates are given in Table 1. The molecule adopts a general chair shape[12] with bending around atoms 8 and 13, as is indicated also in solution by NMR spectroscopy.[13] No other 2,8-bridged isoquinoline derivatives appear to have been described previously.



a) R = MeO, R' = H b) R = R' = MeO

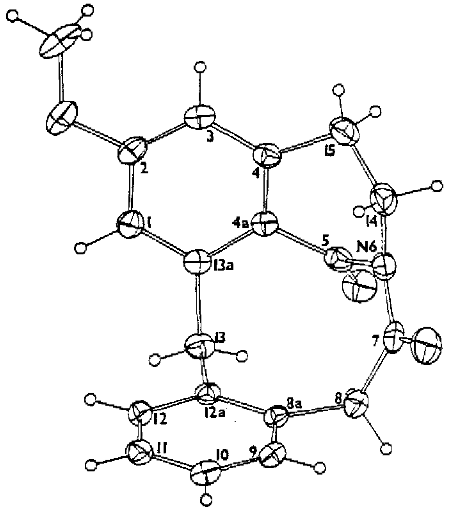


Figure 1: Structure of (4a), with the molecule, projected normal to the aromatic ring plane; 20% thermal ellipsoids are shown for the non-hydrogen atoms, together with skeletal ring numbering. Hydrogen atoms have arbitrary radii of 0.1Å.

Table 1. Non-hydrogen atom coordinates

Atom	x	y	z
C(1)	0.4142(3)	0.3369(4)	0.4171(2)
C(2)	0.5435(3)	0.3380(3)	0.4353(2)
O(2)	0.6156(2)	0.2734(3)	0.5140(1)
C(21)	0.7479(3)	0.2846(5)	0.5408(2)
C(3)	0.5903(3)	0.3921(3)	0.3743(2)
C(4)	0.5082(3)	0.4566(3)	0.2972(2)
C(4a)	0.3833(2)	0.4728(3)	0.2857(2)
C(5)	0.3032(3)	0.5476(3)	0.2042(2)
O(5)	0.2284(2)	0.6479(2)	0.1977(1)
N(6)	0.3133(2)	0.4818(3)	0.1278(1)
C(7)	0.2129(3)	0.3989(4)	0.0732(2)
O(7)	0.2200(2)	0.3285(3)	0.0114(1)
C(8)	0.0982(3)	0.3836(4)	0.0980(2)
C(8a)	0.1117(2)	0.2454(3)	0.1566(2)
C(9)	0.0837(3)	0.1061(3)	0.1126(2)
C(10)	0.0874(3)	−0.0276(4)	0.1547(2)
C(11)	0.1195(3)	−0.0276(4)	0.2438(2)
C(12)	0.1498(3)	0.1062(4)	0.2907(2)
C(12a)	0.1483(2)	0.2458(3)	0.2486(2)
C(13)	0.1906(3)	0.3836(4)	0.3095(2)
C(13a)	0.3324(2)	0.4039(2)	0.3409(2)
C(14)	0.4422(3)	0.4404(4)	0.1349(2)
C(15)	0.5409(3)	0.5032(4)	0.2200(2)

Mechanistically, the formation of (4) probably arises from initial electron transfer from the anthracene ring to the halogen followed by chloride ion loss and subsequent intramolecular radical coupling to give a methoxy-stabilised carbocation[14]. Trapping of this ion by nucleophilic addition of water could give a neutral intermediate (α) after loss of a proton. An acid-catalysed Grob-type cleavage[15,16] would then afford the structure (4).

Opportunities exist for generalisation of this cleavage process for the synthesis of other new bridged and strained heterocyclic systems. Further functional group manipulations should also provide access to 2,8-isoquinolinophane derivatives of potential biological interest.

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5) G.N. Walker and R.J. Kempton, *J. Org. Chem.*, *36*, 1413 (1971). Compounds (1a) and (1b) were made by a modification of Walker and Kempton's procedure. *The crude viscous, oily* dimethoxyphenylethylamino phthalide (1g) in CH_2Cl_2 (10 ml) was adsorbed on silica gel (2g), the solvent evaporated, and the resulting powder added portionwise to polyphosphoric acid (10g) at 100°C with stirring; stirring was continued at 100°C for 20 min. The usual general work-up and p.t.l.c. (silica gel/$CHCl_3$) gave (1a, 66%, m.p. 168-169°C dec.), (1b, 3%; 41% (60°C, 10 min.), m.p. 151-152°C dec.), and (1, R=MeO, R'=OH, *11%, m.p. 173-174°C dec.). Compound* (1b): ^1H NMR (300 MHz, $CDCl_3$)* δ:8.31 (dd, J 7.5, 1.5Hz, 1H), 8.23 (dd, J 7.5, 1.5Hz, 1H), 7.70-7.58 (m, 2H), 7.02 (s, 1H), 4.08 (t, J 7.5 Hz, 2H), 3.98 (s, OMe), 3.97 (s, OMe), 2.87 (t, J 7.5 Hz, 2H): ^{13}C NMR ($CDCl_3$)* δ:184.42(CO), 156.87, 156.28, 148.99, 135.89, 134.07, 133.91, 133.69 (ArH), 131.34 (ArH), 127.48 (ArH), 124.85 (ArH), 124.53, 120.48, 116.48 (ArH), 62.14 (OMe), *56.96 (OMe), 48.27* (CH_2-N), *26.39* (CH_2-Ar); *MS: m/z 293* (M^+; *100%; Calcd. for* $C_{18}H_{15}NO_3$, 293.1052, found 293.1050), 278 (35), 264 (65), 263 (25); Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%, found: C, 73.59,; H, 5.13; N, 4.81%; IR (Nujol) : 1660, 1596, 1580 cm^{-1}. *All NMR spectra were run on solutions in $CDCl_3$ at 300MHz (^1H) or 75.5 MHz (^{13}C).

6) Compound (2b): Colourless gum, ^1H *NMR*, δ: *7.73* (d, J 7.2 Hz, 1H), 7.42 (d, J 7.2 Hz, 1H), 7.25-7.13 (m,2H), 6.44 (s, 1H), 5.55 (s, 1H), 4.26 (s, 1H), 3.80 (s, OMe), 3.68 (s, OMe), 3.28-3.19 (m, 1H), 3.02-2.93 (m, 1H), 2.73-2.62 (m, 1H), 2.54-2.48 (m, 1H); MS: m/z 297 (M^+, 15), 296 (M-1, 30%; Calcd. for $C_{18}H_{18}NO_3$ 296.1285, found 296.1294) 293(50), 279(80), 264(100); IR ($CHCl_3$) 3432 cm^{-1} (v.br.).

7) Compounds (3a) and (3b): To a suspension of (2a) (100 mg) in dry CH_2Cl_2 (12 ml) was added dropwise $ClCH_2COCl$ (128 mg), at 0°C. Stirring was continued at 0°C for 15 min, and then $AlCl_3$ (150 mg) was added in one portion. The mixture was stirred at R.T. for an additional 1 h, and then quenched with ice/water (10 ml); CH_2Cl_2 (60 ml) was added to the mixture, and the organic layer was washed with water (2x10 ml), and dried with Na_2SO_4. The solvent was removed *in vacuo* and p.t.l.c. (silica gel: CH_2Cl_2) of the residue gave (3a) as pale yellow needles (96 mg, m.p. 137-138°C, 79%), after recrystallization from diethyl ether. ^1H NMR δ: 8.17 (s, 1H), 7.93-7.87 (m, 2H), 7.47-7.40 (m, 2H), 7.07 (s, 1H), 6.98 (s, 1H), 5.29-5.24 (m, 1H), 4.02 (d, J 13.6 Hz, 1H), 3.92 (s, OMe), 3.64 (d, J 13.6 Hz, 1H), 3.57-3.46 (m, 1H), 3.38-3.28 (m, 1H), 3.05-3.00 (m, 1H); ^{13}C NMR δ: 168.66 (CO), 157.89, 134.68, 133.21, 132.85, 132.25, 129.14 (ArH), 126.47 (ArH), 126.31 (ArH), 124.52, 124.29 (ArH), 122.88 (ArH), 120.89, 120.33 (ArH), 102.68 (ArH), 55.86 (OMe), 45.41 (CH_2-N)*, 43.47 (CH_2-CO-)* 31.19 ($ArCH_2$); MS: m/z 325 (M^+, 100%, Calcd. for $C_{19}H_{16}NO_2{}^{35}Cl$ 325.0868, found 325.0874), 327(33), 289(10), 248(90), 247(52), 204(28); Anal. Calcd. for $C_{19}H_{16}NO_2Cl$: C, 70.05; H, 4.95; N, 4.30%, found : C, 70.19; H, 5.03; N, 4.33%; IR (Nujol) : 1670, 1630 cm^{-1}. Compound (3b) was prepared similarly in 33% yield, m.p. 101-102°C (recrystallized from diethyl ether). ^1H NMR, δ: 8.52 (s, 1H), 7.95-7.92 (m, 1H), 7.83-7.80 (m, 1H), 7.43-7.33 (m, 2H), 7.12 (s, 1H), 5.25-5.20 (m, 1H), 3.99

(s, OMe), 3.95 (s, OMe), 3.96 (d, J 13.7 Hz, 1H), 3.55 (d, J 13.7 Hz, 1H), 3.65–3.51 (m, 1H), 3.46–3.35 (m, 1H), 3.12–3.06 (m, 1H); ^{13}C NMR δ: 168.77 (CO), 147.70, 141.14, 132.65, 132.32, 129.98 (ArH), 129.62, 128.36, 127.04 (ArH), 126.38 (ArH), 124.83, 122.79 (ArH), 121.20, 119.91 (ArH), 117.01 (ArH), 61.95 (OMe), 57.91 (OMe), 45.68 (CH_2–N)*, 43.55 (–CH_2–CO–)*, 31.28 (ArCH_2); MS : m/z 355 (M^+, 100%; Calcd. for $C_{20}H_{18}NO_3{}^{35}Cl$ 355.0972, found 355.0981), 357(33), 340(45), 319(82), 304(80), 278(50), 262(70), 261(55), 232(40); Anal. Calcd. for $C_{20}H_{18}NO_3Cl$: C, 67.51; H, 5.10; N, 3.94%, found: C, 67.44; H, 5.18; N, 3.90%; IR (thin film from $CHCl_3$): 1658, 1620 cm^{-1}. (*These assignments may be interchanged.)

8) Compound (4a): ^{1}H NMR δ: 7.38–7.35 (m, 1H), 7.20–7.17 (m, 1H), 7.13–7.04 (m, 2H), 6.85 (d, J 1.95 Hz, 1H), 6.49 (d, J 1.95 Hz, 1H), 4.77 (d, J 13.2 Hz, 1H), 4.72 (d, J 13.3 Hz), 3.80 (s, OMe), 3.82–3.76 (m, 1H), 3.64 (d, J 13.3 Hz, 1H), 3.37 (d, J 13.2 Hz, 1H), 3.22–3.13 (m, 1H), 3.03–2.91 (m, 1H), 2.83–2.76 (m, 1H); ^{13}C NMR δ: 177.83 (CO), 170.59 (CO), 162.82, 142.23, 140,01, 139.91, 134.25 (ArH), 132.53, 131.77 (ArH), 129.11, 128.63 (ArH), 127.70 (ArH), 113.03 (ArH), 109.98 (ArH), 56.17 (OMe), 44.39 (CH_2–N), 40.14 (CH_2–CO), 37.67 (Ar–CH_2–Ar), 28.38 (CH_2–Ar); MS: m/z 307 (M^+, 70%; Calcd. for $C_{19}H_{17}NO_3$ 307.1206, found 307.1208) 264(100), 263(50), 236(30); Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56%, found: C, 74.33; H, 5.63; N, 4.66%; IR (Nujol): 1730, 1672, 1602 cm^{-1}.

9) The ^{1}H NMR indicated six aromatic protons, three methylene groups, and one methoxy group for the main component; this was confirmed by the ^{13}C NMR and a resonance at 167.87 ppm was ascribed to the amide carbonyl (IR, thin film from $CHCl_3$: 1672, 1633 cm^{-1}); MS: m/z 289 (M^+, 100%; Calcd. for $C_{19}H_{15}NO_2$ 289.1101, found 289.1109).

10) Compound (4b): ^{1}H NMR δ: 7.55–7.50 (m, 1H), 7.36–7.32 (m, 1H), 7.10–7.01 (m, 2H), 6.51 (s, 1H), 4.76 (d, J 13.48 Hz, 1H), 4.36 (d, J 13.12 Hz, 1H), 4.18 (d, J 13.12 Hz, 1H), 3.98 (s, OMe), 3.83 (s, OMe), 3.82–3.75 (m, 1H), 3.36 (d, J 13.48 Hz, 1H), 3.22–3.12 (m, 1H), 2.99–2.88 (m, 1H), 2.74–2.72 (m, 1H); ^{13}C NMR δ: 177.51 (CO), 170.78 (CO), 155.99, 146.48, 142.49, 134.11, 133.93 (ArH), 132.49 (ArH), 132.17, 131.96, 129.17, 128.59 (ArH), 127.59 (ArH), 108.74 (ArH), 62.27 (OMe), 56.54 (OMe), 44.51 (CH_2–N), 40.21 (CH_2–CO), 30.99 (Ar–CH_2–Ar), 27.88 (ArCH_2); MS: m/z 337 (M^+, 100%; Calcd. for $C_{20}H_{19}NO_4$ 337.1312, found 337.1290) 294(75), 293(30), 263(20), 235(30); Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%, found: C, 71.17; H, 5.64; N, 4.16%; IR (thin film from $CHCl_3$) : 1732, 1678, 1594 cm^{-1}.

11) Structure Determination: $C_{19}H_{17}NO_3$, M = 307.3. Monoclinic, $P2_1/c$, a=11.493(7), b=8.823(4), c=16.361(9)Å. β=112.02(4)°, U=1538(1)Å^3. Dc($\underline{Z}$=4) 1.33 g.cm^{-3}. F(000)=648. The structure was refined to R=0.045, R' (statistical weights)=0.042 for 1554 'observed' diffractometer reflections out of 2730 independent reflections to $2\theta_{max}$ = 50° (Mo $K\alpha$ radiation). Anisotropic thermal parameters were refined for C, N, O; (x, y, z, Uiso)$_H$ were estimated. Non-hydrogen interatomic distances, interbond angles, and anisotropic thermal parameters, as well as hydrogen atom parameters and S.F. amplitudes are available from the Cambridge Crystallographic Data Centre.

12) Macrocycle torsion angles (degrees) for the number-denoted atoms in (4a) are as follows: 13a–4a–5–6 (–119.4); 4a–5–6–7 (108.6); 5–6–7–8 (0.2); 6–7–8–8a (–89.4); 7–8–8a–12a (100.7); 8–8a–12a–13 (–4.5); 8a–12a–13–13a (–90.4); 12a–13–13a–4a (80.1); 13–13a–4a–5 (9.9).

13) Dipole-dipole (through space) interaction between one of the protons on C13 with both protons on C8 was indicated by a NOESY experiment, with a mixing time delay of 1s ≈ T_1 for the involved protons.

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