FORMATION OF *PERI*-FUSED HETEROCYCLES BY INTRAMOLECULAR DISPLACEMENT OF HALIDE

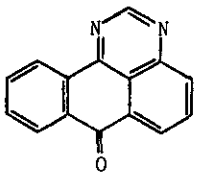
John M. Herbert,[a] Paul D. Woodgate,[a]* and William A. Denny [b]

a. Department of Chemistry, University of Auckland, New Zealand

b. Cancer Research Laboratory, University of Auckland, New Zealand

Abstract - The preparation of phthaloperin-12-one and naphtho[1,8-de]-1,3-thiazine using copper-assisted displacement of aryl halogen is described.

The literature contains very few examples wherein a *peri*-fused heterocyclic system is formed by a process involving nucleophilic aromatic substitution, and to date almost all of the instances reported have involved nucleophilic addition at a carbonyl group of the anthraquinone nucleus, to form a new ring system such as benzo[e]perimidin-7-one (1).[1] We now report the preparation of phthaloperin-12-one (2) and naphtho[1,8-de]-1,3-thiazine (3) by copper-assisted[2] nucleophilic substitution of aryl halogen.



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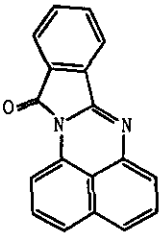

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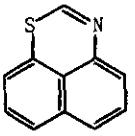

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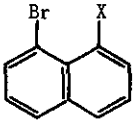

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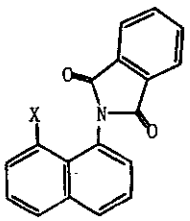
a: X = NH_2

b: X = COOH c: X = Br

The common intermediate in the preparation of both 2 and 3 was 8-bromo-1-naphthalenamine (4a), which was obtained from 8-bromo-1-naphthoic acid (4b),[3] either directly using a Schmidt reaction, or indirectly *via* 1,8-dibromonaphthalene (4c) formed by Hunsdiecker bromodecarboxylation of 4b.[4] The *peri* dibromide 4c was in turn treated with potassium phthalimide (2 molar equivalents) in refluxing dimethylformamide containing copper(I) iodide[5] to give the monosubstitution product, the phthalimidonaphthalene (5a), which was not isolated but was instead cleaved with hydrazine hydrate to give 8-bromo-1-naphthalenamine (4a, 68%) and phthalazine-1,4-dione. The presence of one bulky phthalimido group evidently creates considerable steric hindrance to attack of a second phthalimide

anion at a *peri* position of intermediate 5a, and as a result the formation of 1,8-bis(phthalimido)naphthalene (5b) was not observed. The *peri* bromine atom could, however, be displaced from the sterically less congested bromo-amine 4a. Thus, treatment of 4a with potassium phthalimide and copper(I) iodide in refluxing dimethylformamide gave phthaloperin-12-one (2, 57%) *via* intermediate 5c, in a process analogous to those used previously to prepare phthaloperin-12-one from 8-nitro-1-phthalimidonaphthalene (5d),[6] and from 8-azido-1-phthalimidonaphthalene (5e).[7] Proof of the structure of (2) was provided by independent synthesis from 1,8-naphthalenediamine (6) and phthalic anhydride at 180°C.[8]



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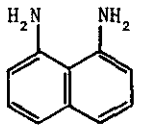
a: X = Br b: X = phthalimido

c: X = NH_2 d: X = NO_2

e: X = N_3



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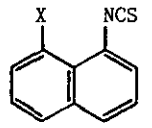

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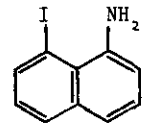
a: X = I b: X = Br



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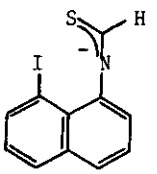
A related approach was used to prepare naphtho[1,8-de]-1,3-thiazine (3) from 8-halo-1-isothiocyanatonaphthalenes 7a and 7b, using a sequence analogous to previously reported[9] cyclisations of aliphatic *vic*-iodoisothiocyanates to furnish 2-substituted thiazolines; similar cyclisations of *o*-bromo- and iodo- thiobenzamidobenzene to give benzothiazoles have been reported also.[10] To this end, the isothiocyanates 7a and 7b were obtained by treatment of the corresponding amines, 8[11] and 4a respectively, with carbon disulphide in the presence of dicyclohexylcarbodiimide in pyridine. In both cases the yield obtained was better than 80%. Treatment of 8-iodo-1-isothiocyanatonaphthalene (7a) with lithium triethylborohydride gave the anion 9, which on subsequent exposure to copper(I) iodide in dimethylformamide cyclised to give naphtho[1,8-de]-1,3-thiazine (3, 86%). The conversion of 8-bromo-1-isothiocyanatonaphthalene (7b) into 3 occurred under essentially the same conditions, although not surprisingly the reaction time required was very much longer and the yield obtained was considerably lower.

Following an attempt to recrystallise 3 from aqueous ethanol, a product resulting from nucleophilic attack of water at the imine carbon followed by air oxidation was isolated, and was identified as naphtho[1,8-de]-1,3-thiazin-2-one (10, mp > 300°C). However, attempts to purify

this compound only led to further decomposition. The behaviour of the pure thiazine 3 on melting is of interest. Immediately above its melting point it resolidified to give crystals which remained unmelted at 300°C, probably as a consequence of air oxidation to form 10. The perimidinyl anion (11), which is isoelectronic with 3, also oxidises readily in air.[12]



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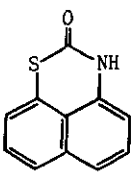

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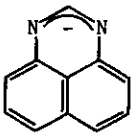

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EXPERIMENTAL

8-Bromo-1-naphthalenamine (4a)

(A) A suspension of 1,8-dibromonaphthalene (143 mg, 0.5 mmol), potassium phthalimide (185 mg, 1.0 mmol), and copper(I) iodide (191 mg, 1.0 mmol) in dimethylformamide was heated under reflux with vigorous stirring for 10 min under a nitrogen atmosphere. The hot suspension was added to aqueous hydrochloric acid (50 ml, 4 mol l^{-1}), and the resulting mixture cooled to room temperature and filtered to give a grey solid, which was extracted with boiling dichloromethane (2 x 20 ml). The combined extracts were filtered, and the solvent was evaporated to leave a light brown crystalline residue (135 mg), which was redissolved in dry ethanol (20 ml). Hydrazine hydrate (0.25 ml) was added to this solution, followed by concentrated hydrochloric acid (1.0 ml). The white precipitate of 1,4-phthalazinedione was removed by filtration, following which the filtrate was made alkaline with aqueous ammonia and extracted with chloroform (3 x 20 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give 4a (75 mg, 68%) as a brown solid which was distilled (Kugelrohr) at 98°C/0.08 mmHg to give white needles, mp 85-89°C (lit.[13] mp 87-88°C). ν_{max}(KBr) 3450, 1630 (NH_2), 1560 cm^{-1} (C=C). δ_H($CDCl_3$) 4.84 (br s, 2H, NH_2), 6.70 (dd, J_o 9.5 Hz, J_m 2.5 Hz, 1H, H2), 6.90-7.33 (m, 3H, H3, H4, H6), 7.46-7.76 (m, 2H, H5, H7). *m/z* 223, 221 (M, 64, 70 %), 142 (M-Br, 17), 115 (142-HCN, 100).

(B) Sodium azide (228 mg, 3.5 mmol) was added during 10 min to a stirred suspension of 8-bromo-1-naphthoic acid (146 mg, 0.58 mmol) in concentrated sulphuric acid (0.5 ml) and chloroform (0.5 ml) at 45°C, each successive portion of sodium azide being added after the effervescence resulting from the previous addition had subsided. The mixture was stirred for 90 min at 45°C, and

added to water (10 ml). The mixture was made alkaline with aqueous ammonia, and extracted with chloroform (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 4a (117 mg, 91%).

Phthaloperin-12-one (2)

A stirred suspension of 8-bromo-1-naphthalenamine (143 mg, 0.64 mmol), copper(I) iodide (124 mg, 0.64 mmol), and potassium phthalimide (121 mg, 0.64 mmol) in dried dimethylformamide (8 ml) was heated under argon at130°C for 15 min, after which time no starting material remained (t.l.c.). The mixture was diluted with chloroform (40 ml) and filtered through a pad of alumina. Evaporation of the filtrate gave a dark red solid which was recrystallised from glacial acetic acid to give 2 (99 mg, 57 %), as red needles, mp 233-234°C (lit.[6] 229-230°C). ν_{max}(KBr) 1725 cm^{-1} (C=O). $\delta_H(CF_3COOH)$ 7.30-8.62, m, 10H. *m/z* 270 (M, 100%), 242 (M-CO, 21), 241 (242-H, 12). This material was spectroscopically identical to, and did not depress the melting point of, a sample of 2 prepared by the method of Sachs.

8-Iodo-1-isothiocyanatonaphthalene (7a)

A solution of 8-iodo-1-naphthalenamine[11] (1.86 g, 4.0 mmol) in pyridine (1.0 ml) was added slowly under nitrogen to a stirred solution of dicyclohexylcarbodiimide (0.824 g, 4.0 mol) in carbon disulphide (2.4 ml). After stirring the mixture for 24 h at room temperature, 1,3-dicyclohexylthiourea was removed by filtration, and the filtrate was evaporated under reduced pressure to give a brown oil. Chromatography of this material on silica gel in acetone-hexane (1:4) gave 7a (1.085 g, 87%) as a white solid which was recrystallised from hexane, mp 78-79°C. *Anal*. Calcd. for $C_{11}H_6NIS$: C, 42.5; H, 1.9; N, 4.5; I, 40.8; S, 10.3. Found: C, 42.6; H, 1.9; N, 4.6; I, 41.0; S, 10.4%. ν_{max}(KBr) 2070 cm^{-1} (N=C=S). $\delta_H(CDCl_3)$ 7.12 (t, *J* 7.5 Hz, 1H, H6), 7.37-7.94 (m, 4H, H2, H3, H4, H7), 8.26 (dd, J_o 7.5 Hz, J_m 1 Hz, 1H, H5). *m/z* 311 (M, 100%), 184 (M-I, 60), 140 (184-CS, 85).

8-Bromo-1-isothiocyanatonaphthalene (7b)

Prepared from 8-bromo-1-naphthalenamine under the conditions described above, 7b (81%) was obtained as a light brown oil which crystallised on standing. Recrystallisation from hexane gave colourless needles, mp 52.5-53°C, bp (Kugelrohr) 82°C/0.08 mmHg. *Anal*. Calcd. for $C_{11}H_6BrNS$: C, 50.0; H, 2.3; N, 5.3; S, 12.1. Found: C, 50.1; H, 2.3; N, 5.6; S, 12.1%. ν_{max}(KBr) 2060 cm^{-1} (N=C=S).

$\delta_H(CDCl_3)$ 7.08–7.98 (m, 6H). *m/z* 265, 263 (M, 64, 64 %), 184 (M-Br, 64), 140 (184-CS, 100).

Naphtho[1,8-de]-1,3-thiazine (3)

A solution of lithium triethylborohydride in tetrahydrofuran (2.2 ml of 0.94 mol l^{-1}, 2.1 mmol) was added under nitrogen to a solution of 8-iodo-1-isothiocyanatonaphthalene (643 mg, 2.1 mmol) in tetrahydrofuran (10 ml) at 0°C. The resulting yellow solution was left to stand at 0°C for 1 h, then added to a suspension of copper(I) iodide (88 mg, 0.46 mmol) in dimethylformamide (5 ml) under nitrogen at 0°C. The mixture was stirred for 10 min to give an orange-brown solution which was diluted with water (50 ml). Tetrahydrofuran was removed under reduced pressure and the aqueous mixture was saturated with sodium chloride and extracted with ethyl acetate (3 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 3 (327 mg, 86%) as green needles, mp 104–110°C, resolidifying at *ca.* 140°C to give prisms, mp >320°C. *Anal.* Calcd. for $C_{11}H_7NS$: M^+, 185.0300. Found: M^+, 185.0308. ν_{max}(KBr) 1675 (C=N), 1610 cm^{-1} (C=C). $\delta_H(CDCl_3)$ 6.78 (dd, J_o 7 Hz, J_m 2 Hz, 1H, H9), 6.93–7.47 (m, 5H, H4, H5, H6, H7, H8), 8.05 (s, 1H, H2). *m/z* 185 (M, 100%), 158 (M-HCN, 23), 153 (M-S, 10), 141 (M-CS, 13), 114 (141-HCN, 19).

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