Synthesis of 3-Hydroxy-1-[(methylcarbamoyl)oxy]naphthalene

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The synthesis of 3-hydroxy-1-[(methylcarbamoyl)oxy]naphthalene, a suspected metabolite of the insecticide Sevin, is reported.

Keywords: *3-Hydroxy-1-[(methylcarbamoyl)oxy]naphthalene; Sevin; carbaryl; hydroxycarbaryl*

INTRODUCTION

Sevin, common name carbaryl, is metabolized by plants, mammals, and insects to yield, among other products, hydroxycarbaryls. Synthesis of unsymmetrical hydroxycarbaryls by carbamoylation of the unsymmetrical diols is complicated by lack of regioselectivity as shown in Scheme 1.

Reports of all possible regioisomers exist in the literature (Durden, 1971; Kuhr and Casida, 1967; Leeling and Casida, 1966; Sugiyama et al., 1972). However, not all have had their structures fully elucidated.

This paper describes the synthesis of 3-hydroxy-1-[(methylcarbamoyl)oxy]naphthalene, a suspected metabolite of the insecticide Sevin, in four steps and its complete ^1H and ^{13}C NMR spectral data.

RESULTS AND DISCUSSION

After treatment of 1,3-dihydroxynaphthalene with methyl isocyanate, Durden (1971) reported the identification of 1-hydroxy-3-[(methylcarbamoyl)oxy]naphthalene by visualization of a TLC plate with Gibbs reagent. Gibbs reagent reacts specifically with phenols and naphthols with open hydroxy in the peri positions. This experiment was repeated so the structure could be confirmed by NMR techniques. Isolation of this material by column chromatography found it be a 3:1 mixture of the two possible isomers, **1** and **2**. From 2D NMR experiments, it was found that 3-hydroxy-1-[(methylcarbamoyl)oxy]naphthalene, **1**, was the major product. Separation of the isomers could not be achieved.

Selective hydrolysis of the biscarbamate, **3**, with one equivalent of isopropylamine again gave a mixture, but this time the ratio of isomers **1**:**2** was 1:3.8. By comparison of the ^1H and ^{13}C NMR of the two reaction mixtures, we were able to identify two sets of isomer signals by relative intensity.

Assignment of the two isomers **1** and **2** was made by analysis of HETCOR, LRHETCOR conducted on the mixture of the two products (D. G. McIntyre, A. Lopes, M. J. Glen, and A. A. Ribero, unpublished data) and of the pure product, **1**.

A synthetic strategy was then developed based on the regioselective deprotection of a 1,3-bis-protected-dihydroxynaphthalene. Selection of the appropriate protecting group centered upon its preferential removal in the presence of a carbamate moiety. Scheme 2 depicts the successful execution of such a strategy.

Commercially available 1,3-dihydroxynaphthalene was bis-protected with methyl chloroformate and triethylamine in methylene chloride to provide the desired bis-carbonate, **4**, in 95.5% yield. Since the 1-position of the biscarbamate was more susceptible to amine nucleophiles, as aforementioned, it was assumed that the biscarbonate would suffer a similar fate. Reaction of compound **4** with isopropylamine gave a mixture of the two regioisomers, **6** and **7**. Compound **6** was isolated in 29.6% yield by fractional crystallization from carbon tetrachloride and confirmed to be one isomer by NMR. Confirmation that **6** was isolated and not **7** was unknown until the final product had been characterized. Compound **6** was converted to **8** by reaction with methyl isocyanate and catalytic triethylamine by the procedure of Durden (1971) in 60.2% yield. Deprotection of **8** to 3-hydroxy-1-[(methylcarbamoyl)oxy]naphthalene, **1**, was accomplished by refluxing with 1 N HCl in methanol in 56.4% yield.

The structure of 3-hydroxy-1-[(methylcarbamoyl)oxy]-naphthalene, **1**, was established by ^1H and ^{13}C NMR, HETCOR, and LRHETCOR. The key to the structure elucidation lies in the assignment of C-2 and H-2. Long-range correlations of C-2 and H-2 to H-4, 3-OH, C-1, and C-3 unambiguously reveal **1** as the correct regioisomer.

The ^1H NMR of **1** shows a singlet at 9.9 ppm and is assigned as the 3-OH proton. The LRHETCOR shows three correlations of the OH proton with carbons at 155, 111.3, and 106.3 ppm. The 155 signal, which was established as a quaternary carbon from the HETCOR, is assigned as C-3. The carbons at 111.3 and 106.3 ppm (C-2 or C-4) are unambiguously assigned below. The HETCOR shows a correlation of the carbon at 111.3 ppm with a proton at 6.9 ppm, either H-2 or H-4, while the carbon at 106.3 ppm shows a correlation with the proton at 7.04 ppm, either H-2 or H-4.

The ^{13}C NMR shows three signals in the 147–155 ppm range. The 155 ppm (C-3) signal was assigned above. The LRHETCOR shows a correlation of the CH_3 protons at 2.73 ppm to the carbon at 154.7 ppm and is assigned as the carbonyl (C-11). The remaining signal at 147.5 ppm is therefore C-1 and is supported by literature precedent (Granger and Mangras, 1975). The LRHETCOR shows a correlation of C-1 with two protons, one at 6.9 ppm, confirming it as H-2, and one at 7.75 ppm, which can only be H-8. The HETCOR shows a correlation of the proton at 6.9 ppm with the carbon at 111.3 ppm, thus confirming it as C-2. The remaining carbon at 106.3 ppm is thus assigned as C-4. The literature (Granger and Mangras, 1975; Wang et al., 1984) supports the assignment of H-8 as the furthest downfield aromatic proton.

This unique solution unambiguously confirms the structure of 3-hydroxy-1-[(methylcarbamoyl)oxy]naphthalene.

EXPERIMENTAL PROCEDURES

All solvents and reagents were used as received from the supplier. Melting points were determined using a Thomas-

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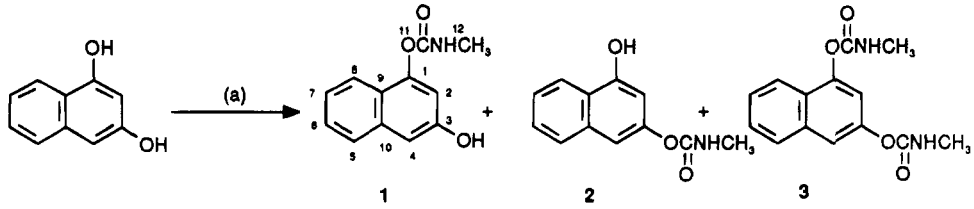
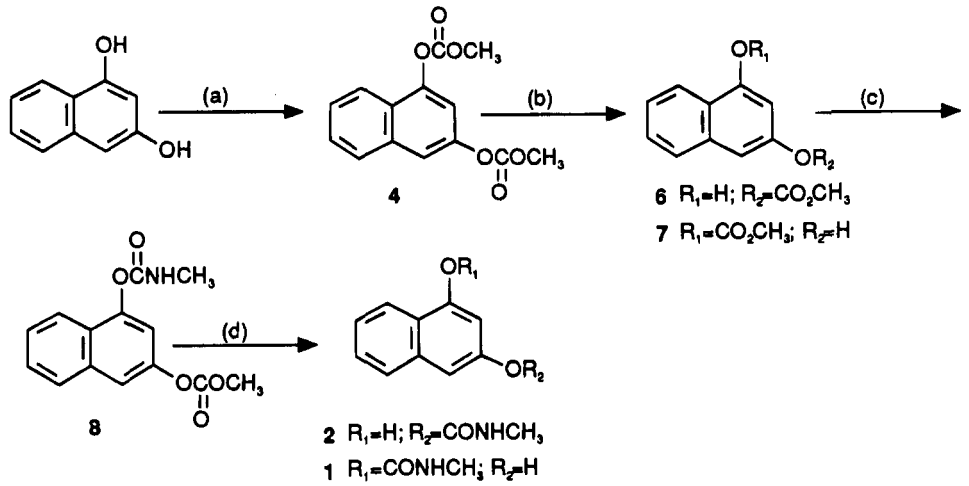
Scheme 1[a]



[a] Key: methyl isocyanate, TEA, acetone.

Scheme 2[a]



[a] Key: (a) methyl chloroformate, TEA, CH_2Cl_2; (b) isopropylamine, CH_3CN; (c) CH_3NCO, TEA, acetone; (d) 1 N HCl, MeOH.

Hoover capillary melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was used to monitor reactions. TLC was conducted on 5 × 10 cm Merck silica gel (UV 254). ^1H and ^{13}C NMR spectra were determined on a Bruker AC-P300 or a Varian Gemini-300 spectrometer in the solvent noted with tetramethylsilane (TMS) as an internal standard. Spectra run in DMSO were referenced versus the solvent at 39.50 ppm (^{13}C) and 2.50 ppm (^1H). Chemical shifts are reported in parts per million. ^1H NMR data are reported in the following order: chemical shift, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, and assignment. Mass spectra were determined on a Hewlett-Packard Model 5995 spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Purity was conducted on either a Hewlett-Packard gas chromatograph Model 5890, equipped with a Quadrex 1.5 M methyl phenyl (5%) silicone column, program 70 °C 0 min 15 °C/min 280 °C 5 min, or a Waters 900 HPLC with photodiode array detector equipped with two each Zorbax (5 μm) C-8 columns (4 × 80 cm) in series. Mobile phase: (A) 0.1% trifluoroacetic acid in H_2O and (B) 0.1% trifluoroacetic acid in CH_3CN. Gradient program (flow 1.8 mL/min): 0 min %A:%B, 90:10; 0.10 min %A:%B, 90:10; 15.0 min %A:%B, 0:100; 21.10 min %A:%B, 90:10.

All reactions are unoptimized.

1,3-Bis[(methoxycarbonyl)oxy]naphthalene, 4. Methyl chloroformate (362.8 g, 3.84 mol) was added dropwise to a solution of 1,3-dihydroxynaphthalene (300 g, 1.87 mol) and triethylamine (389 g, 3.84 mol) in methylene chloride (6 L) under N_2 at 15 °C. After 2 h, the reaction was washed once with H_2O (1.5 L), once with saturated $NaHCO_3$ (1.5 L), and once with brine (1.5 L). The organic portion was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2 as the eluent to give 493 g (95.5%) of pure **4**: mp 83–84.5 °C, off-white crystals. Found: C, 60.42, H, 4.48, O, 32.65%. Calcd for $C_{14}H_{12}O_6$: C, 60.87, H, 4.38, O, 34.75%. ^1H NMR ($CDCl_3$) δ 3.94 (3H, s, CH_3), 3.97 (3H, s, CH_3), 7.32–7.99 (6H, m, aromatic *H*s).

1-Hydroxy-3-[(methoxycarbonyl)oxy]naphthalene, 6. Isopropylamine (1.05 g, 1.78 mol) was added dropwise to a solution of **4** (492 g, 1.78 mol) and CH_3CN (2.5 L) under N_2 at 15 °C. After stirring at room temperature for 24 h, the solvent was removed under reduced pressure to give a brown residue. The residue was crystallized from CCl_4 to give 114.8 g (29.6%) of pure **6**: mp 114–115 °C, tan crystals. Found: C, 65.67, H, 4.79, O, 29.20%. Calcd for $C_{12}H_{10}O_4$: C, 66.05, H, 4.62, O, 29.33%. ^1H NMR ($CDCl_3$) δ 3.95 (3H, s, CH_3), 6.10 (1H, s, O*H*), 6.64 (1H, s, aromatic *H*), 7.21 (1H, s, aromatic *H*), 7.46 (1H, dd, aromatic *H*), 7.37 (1H, dd, aromatic *H*), 7.73 (1H, d, J = 7.8 Hz, aromatic *H*), 7.98 (1H, d, J = 8.2 Hz, aromatic *H*). MS *m/e* 218.

3-[(Methoxycarbonyl)oxy]-1-[(methylcarbamoyl)oxy]naphthalene, 8. A solution of **6** (106.6 g, 0.49 mol), triethylamine (5 drops), and methyl isocyanate (32.0 g, 0.56 mol) in acetone (1 L) was stirred at room temperature for 24 h in an autoclave. The solvent was removed under reduced pressure and the residue crystallized from ethyl acetate/hexane to give 81.2 g (60.2%) of pure **8**: mp 135–136 °C, white needles. Found: C, 61.56, H, 4.86, N, 5.09%. Calcd for $C_{14}H_{13}N_1O_5$: C, 61.09, H, 4.76, N, 5.09%. ^1H NMR ($CDCl_3$) δ 2.93 (3H, d, J = 4.9 Hz, CH_3NH), 3.93 (3H, s, CH_3CO), 5.2 (1H, bs, N*H*), 7.25 (1H, s, aromatic *H*), 7.4–7.5 (3H, m, aromatic *H*), 7.80 (1H, d, aromatic *H*), 7.87 (1H, d, aromatic *H*). MS *m/e* 275.

3-Hydroxy-1-[(methylcarbamoyl)oxy]naphthalene, 1. A solution of **8** (62.1 g, 0.22 mol) in methanol (800 mL) and 1 N HCl (124 mL) was heated under reflux for 3 days. The methanol was removed under reduced pressure and the solution poured into H_2O and extracted with ethyl acetate. The solvent was removed under reduced pressure to give a pink residue. The residue was crystallized from ethyl acetate to give 27.0 g (56.4%) of pure **1** (99.5% by HPLC): mp 157–159 °C, light pink crystals. Found: C, 66.04, H, 5.14, N, 6.33%. Calcd for $C_{12}H_{11}N_1O_3$: C, 66.35, H, 5.10, N, 6.45%. ^1H NMR (DMSO) δ 2.73 (3H, d, J = 4.6 Hz, CH_3), 6.90 (1H, d, *H2*), 7.03 (1H, d, *H4*), 7.29 (1H, t, *H7*), 7.41 (1H, t, *H6*), 7.70 (2H, d, *H5*), 7.85 (1H, q, N*H*), 7.79 (1H, d, *H8*), 9.90 (1H, s, 3-O*H*). ^{13}C NMR (DMSO) δ 27.20 (C-12), 106.22 (C-4), 111.23 (C-2), 121.08 (C-8), 121.91 (C-9), 122.94 (C-7), 126.18 (C-5), 126.68 (C-6), 134.98 (C-10), 147.69 (C-1), 154.82 (C-11), 155.01 (C-3). MS *m/e* 218.

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