

E. Campaigne\* and Richard F. Weddleton [1]

Department of Chemistry, Indiana University,  
Bloomington, IN 47405  
Received April 18, 1986

Reaction of 1-naphthol with 2-chlorocyclohexanone in alkaline alcohol gave as the major product 5-(2'-oxocyclohexyl)-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran (**1**), which could be converted to the title compound **5** by reduction and dehydrogenation. This product arises from ambident alkylation of 1-naphthol at the 2- and 4-positions. *Via* the 2'-oxocyclohexyl ether, **5** was also synthesized from 4-phenyl-1-naphthol.

*J. Heterocyclic Chem.*, **23**, 1625 (1986).

Some years ago, we reported the synthesis of 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran in low yield by the reaction of 2-chlorocyclohexanone with 1-naphthol in ethanol containing potassium carbonate [2]. However, the major product of this reaction was a ketone, C<sub>22</sub>H<sub>22</sub>O<sub>2</sub>, obtained in about 50% yield [3]. We wish to report here the characterization and identification of this ketone.

It is evident that a delicate balance exists between carbon alkylation and oxygen alkylation in ambident anions derived from phenols or naphthols. Such factors as the structure of the alkylating agent, the anion, the solvent polarity and hydrogen bonding power have been found to markedly influence the ratio of carbon to oxygen alkylation, and the position of alkylation of carbon. Wenkert, Youssefyeh and Lewis [4] have shown that 2-naphthoxide can give either oxygen or 1-carbon alkylation, or both, depending on the alkylating agent. In addition, they found that the 1-carbon alkylated compound can be further alkylated to give a 1,1-dialkyl derivative or a 1-alkyl-2-alkoxy derivative.

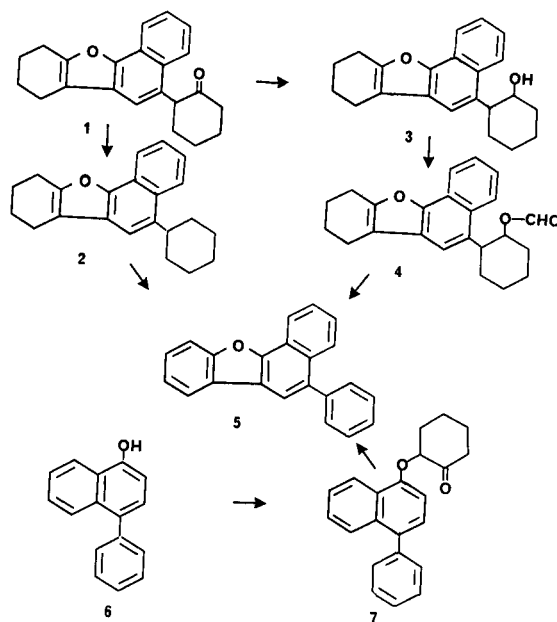
Kornblum, Berrigan and LeNoble [5] observed both *ortho*- and *para*-alkylation of phenoxide ion. They later observed [6] that a hindered 2,6-dialkylphenol gave 88% oxygen alkylation with methyl iodide, but 100% *para*-alkylation with the bulkier isopropyl iodide. Thus *para*-alkylation is favored for bulkier alkylating agents when the two *ortho*-positions are substituted by large groups. In the reaction of 2-naphthoxide with benzyl bromide, Kornblum reported [7] that strong hydrogen-bonding solvents increased the amount of 1-carbon alkylation of 2-naphthol, while high dielectric constant of the solvent favors *O*-alkylation.

From the reaction of 2-chlorocyclohexanone with 2-naphthol and potassium carbonate, Mousseron [8] isolated a hemiketal, formed by 1-carbon alkylation, followed by hemiketal formation. The yield is good, as shown by dehydration of the crude ketal to form 8,9,10,11-tetrahydronaphtho[2,1-*b*]benzofuran in 61% yield [2]. This indicates a preference for carbon alkylation by 2-chlorocyclohexanone, at least in this case.

In the synthesis of 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran previously reported [2], it was assumed that 1-naphthol reacted with 2-chlorocyclohexanone to yield the 2-alkylated product which readily cyclized to the hemiketal on isolation. Distillation of the crude oil led to dehydration, forming the product isolated in low yield. The residual tars were intractable on attempts to distill other products. Oxygen alkylation would have formed a keto-ether, not likely to cyclize under the conditions employed.

Reaction of 1-naphthol with 2-chlorocyclohexanone in alcohol in the presence of potassium carbonate, followed by treatment with picric acid, gave a mixture of two picrates, which could be separated by fractional crystallization. The more soluble picrate, obtained in about 8% yield, proved to be the 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran derivative [2]. The less soluble picrate, obtained in about 75% crude yield, was neutralized to give the

Scheme 1



ketone,  $C_{22}H_{22}O_2$ , which we have now proved to have structure **1** (Scheme 1).

Ketone **1** was reduced *via* the Huang-Minlon route to a cyclohexyl derivative **2**, or by lithium aluminum hydride to the alcohol **3**. An attempt to dehydrate the alcohol with 99% formic acid led instead to the formyl ester **4**. Either **2** or **4**, when treated with powdered selenium, were converted to 5-phenylnaphtho[1,2-*b*]benzofuran **5**. The structure of **5** was confirmed by an alternate synthesis from 4-phenyl-1-naphthol (**6**). Compound **6** was alkylated on oxygen following the suggestions of Kornblum [6], using the dry sodium salt of **6** and 2-chlorocyclohexanone in DMF, to give **7**. Cyclization of **7** with phosphorus pentoxide in dry xylene, followed by dehydrogenation of the crude product with selenium produced **5**.

The structures of **2** and **5** are supported by comparison of the ultraviolet spectra with known analogs (Table 1). The uv maxima of 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran and 5-cyclohexyl-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran are compared in the first two columns of Table 1. It is clear that these two spectra are nearly congruent, with a bathochromic shift of 3 to 6  $m\mu$  for the alkyl substituted compound. This same bathochromic shift of 5  $m\mu$  is observed in comparing the spectra of naphthalene and 1-cyclohexylnaphthalene [9]. The spectra of naphtho[1,2-*b*]benzofuran and **5** are compared in the last two columns of Table 1. Here again the two spectra are very similar, with a bathochromic shift of about 5-6  $m\mu$  for most of the peaks for the phenyl substituted derivative. Peaks at 280, 289 and 297  $m\mu$  are nearly the same for these two compounds, however. These shifts are quite consistent with comparable shifts in the spectra of naphthalene and 1-phenylnaphthalene [9].

Table 1

Comparison of UV Spectra of  
7,8,9,10-Tetrahydronaphtho[1,2-*b*]benzofuran (**A**) with **2** and  
Naphtho[1,2-*b*]benzofuran (**B**) with **5**.

| <b>A</b>                        | <b>2</b>                        | <b>B</b>                        | <b>5</b>                        |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| $\lambda$ max (log $\epsilon$ ) | $\lambda$ max (log $\epsilon$ ) | $\lambda$ max (log $\epsilon$ ) | $\lambda$ max (log $\epsilon$ ) |
| 205 (4.35)                      | 208 (4.30)                      | 236 (4.39)                      | 242 (4.47)                      |
| 248 (4.73)                      | 253 (4.67)                      | 242 (4.45)                      | 247 (4.52)                      |
| 255 (4.78)                      | 260 (4.71)                      | 250 (4.65)                      | 255 (4.59)                      |
| 278 (3.90)                      | 284 (3.78)                      | 257 (4.95)                      | 263 (4.79)                      |
| 288 (3.90)                      | 293 (3.79)                      | 280 (4.10)                      | 281 (4.17)                      |
| 296 (3.70)                      | 302 (3.62)                      | 289 (4.21)                      | 288 (4.28)                      |
| 326 (3.09)                      | 329 (3.13)                      | 297 (4.28)                      | 297 (4.28)                      |
| 341 (2.94)                      | 344 (3.03)                      | 323 (3.67)                      | 329 (3.68)                      |
|                                 |                                 | 339 (3.91)                      | 344 (3.72)                      |

It is interesting to speculate on the reasons why 2,4-dialkylation occurs preferentially in the reaction of 1-naphthol anion with 2-chlorocyclohexanone in alcohol,

even when the reagents are in a ratio of 1:1. The preference for carbon alkylation of 2-chlorocyclohexanone has already been noted [8]. Also *para*-alkylation is favored in hindered phenols [6]. Therefore it is possible that 4-alkylation is the preferred site for the 1-naphthoxide anion. However, once alkylated at the 4-position, the product can be alkylated a second time at the now more reactive 2-position, leading to a 2,4-di(2'-oxocyclohexyl)-1-naphthol which is quenched from further reaction by formation of the hemi-ketal. The hemi-ketal is then dehydrated on work-up, giving **1** as the major product. The lesser amount of initially 2-alkylated product is quenched from further reaction by cyclization to the hemi-ketal, and is isolated as 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran [2]. However, no 4-monoalkylated product was observed.

Therefore, it is probably more reasonable that alkylation at the 2-position occurs first. In this case, it must be assumed that the 2'-oxocyclohexyl-1-naphthoxide ion reacts more readily at the 4-position because of hindrance at the 2-position, and gives the 2,4-dialkylated product. The increased reactivity of the substituted 1-naphthol is confirmed by the fact that 47% of 1-naphthol was recovered from the reaction of 1-naphthol and 2-chlorocyclohexanone in equivalent amounts [2].

## EXPERIMENTAL

The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer with 1 cm quartz cells in 95% ethanol solution. Infrared spectra were obtained on a Perkin-Elmer Model 137-B infrared spectrometer. All melting points were recorded using the same calibrated thermometer and are uncorrected. Elementary analyses were performed by Midwest Microlab, Indianapolis, Indiana.

5-(2'-Oxocyclohexyl)-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran (**1**).

A three-necked flask equipped with stirrer and condenser was swept out with nitrogen and in it were placed 28.8 g (0.2 mole) of 1-naphthol (redistilled, mp 95-96°), 26.4 g (0.2 mole) of 2-chlorocyclohexanone, 150 ml of 95% ethanol and 27 g (0.2 mole) anhydrous potassium carbonate. The mixture was heated to reflux under nitrogen until carbon dioxide evolution ceased (about 2 hours), and poured into 1.5 l of cold water with vigorous stirring. The gummy organic layer was washed with three 500 ml portions of cold water and then dissolved in a minimum amount of hot 95% ethanol. A solution of 45.8 g (0.2 mole) of picric acid in 200 ml of 95% ethanol was added, and the mixture heated to boiling, filtered and cooled. A first fraction of red microcrystals (10.3 g, mp 164-172°) was collected, and the mixture cooled to 5°. A second crop (6.7 g) melting at 175-179° was collected, and the mother liquor concentrated to one-half volume. On cooling, a third crop of red crystals (23.0 g, mp 143-165°) was collected. These three fractions were combined to give 40 g (74% based on 2-chlorocyclohexanone) of the crude picrate.

On cooling overnight in a refrigerator, a fourth fraction, melting at 110-125° (7.3 g, 8.1% based on 1-naphthol) was obtained. Two recrystallizations from 95% ethanol gave 2.43 g (2.7% based on 1-naphthol) of red microcrystals melting at 130-132°, which proved to be the picrate of 7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran [2], by mixture melting point and congruency of its spectra.

The combined first three fractions of picrate precipitate were dissolved in a minimum amount of hot acetone, and added, with vigorous stirring, to 600 ml of 28% ammonium hydroxide. The precipitate was collected and washed with two 50 ml portions of cold water, to give 10.5 g (33% based on 2-chlorocyclohexanone) of a tan precipitate, melting at 105-118°. After several recrystallizations from ethanol, white needles of **1**, melting at 146-147°, were obtained; ir (potassium bromide): 3100, 2910, 2840, 1700, 1263, 1125  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 210 (4.41), 252 (4.67), 259 (4.70), 282 (3.82), 292 (3.83), 300 (3.64), 328 (3.15) and 345  $\text{m}\mu$  (3.04).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_2$ : C, 82.98; H, 6.96. Found: C, 82.96; H, 6.97.

This ketone formed a semicarbazone [10] as white crystals, melting at 229-231° after two recrystallizations from ethanol.

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_2$ : C, 73.91; H, 6.71. Found: C, 73.53; H, 6.45.

#### 5-Cyclohexyl-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran (**2**).

Using the Huang-Minlon modification of the Wolff-Kishner reduction [11], 10.0 g (31.5 mmoles) of **1**, 5.6 g (100 mmoles) of potassium hydroxide, and 5.0 g (150 mmoles) of 95% hydrazine were refluxed in 50 ml of diethylene glycol for six hours (at about 226°). After cooling, 50 ml of water was added, the mixture poured into 30 ml of 6 *N* hydrochloric acid, and extracted with three 50 ml portions of ether. The ether layers were combined, washed with water, dried (anhydrous sodium sulfate), and evaporated, giving a yellow oil. It was dissolved in hot ethanol, treated with Norite, filtered and cooled, to give 8.0 g (84%) of white needles, melting at 82-83°; ir (potassium bromide): 3080, 2940, 2850, 1263, 1140  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 208 (4.30), 253 (4.67), 260 (4.71), 284 (3.78), 293 (3.79), 302 (3.63), 329 (3.13), and 344  $\text{m}\mu$  (3.03).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{24}\text{O}$ : C, 86.80; H, 7.95. Found: C, 86.89; H, 7.76.

#### 5-(2'-Hydroxycyclohexyl)-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran (**3**).

Using the Soxhlet extractor technique described by Vogel [12], 5.0 g (15.7 mmoles) of **1** was reduced with 3.0 g (79 mmoles) of lithium aluminum hydride in ether. After refluxing 21 hours, the mixture was cooled in an ice bath, and 20 ml of ethyl acetate added slowly. The contents of the reaction flask was then poured slowly into 200 ml of 10% sulfuric acid, cooled, and the white precipitate collected and washed with water. After drying, the product was recrystallized twice from ethanol to give 4.2 g (84%) of white prisms, melting at 141-143°; ir (potassium bromide): 3530, 3050, 2910, 2850, 1263, 1152  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 209 (4.18), 253 (4.57), 261 (4.62), 284 (3.67), 293 (3.67), 304 (3.49), 328 (3.04) and 345  $\text{m}\mu$  (2.93).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{24}\text{O}_2$ : C, 82.46; H, 7.55. Found: C, 82.49; H, 7.68.

#### 5-(2'-Formyloxycyclohexyl)-7,8,9,10-tetrahydronaphtho[1,2-*b*]benzofuran (**4**).

A mixture of 500 mg (1.5 mmoles) of **3** and 1 ml of 99% formic acid was heated for 15 minutes on a steam bath, poured into water, and extracted with three 20 ml portions of benzene. The benzene solution was washed with water, dried, and evaporated to give a yellow oil which was recrystallized three times from ethanol to give 305 mg (56%) of white needles, melting at 135-135.5°; ir (potassium bromide): 1710, 1200 and 1120  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 206 (4.35), 253 (4.83), 260 (4.86), 284 (3.89), 293 (3.89), 304 (3.70), 330 (3.27) and 344  $\text{m}\mu$  (3.13).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{24}\text{O}_3$ : C, 79.28; H, 6.94. Found: C, 79.01; H, 6.94.

#### 5-Phenylnaphtho[1,2-*b*]benzofuran (**5**).

##### Method A.

Using a method previously described [2], 200 mg (0.64 mmole) of **4** were treated with 400 mg (5.1 mmoles) of powdered selenium for 2 hours at 360°. When no further evolution of hydrogen selenide was observed, the mixture was cooled, washed out with ethanol, treated with Norite, evaporated to dryness and recrystallized twice from 70% ethanol to give 50 mg (26%) of colorless plates of **5**, melting at 121.5-122°.

##### Method B.

In the same way, 500 mg (1.65 mmoles) of **2** was treated with 1.30 g (16.5 mmoles) of powdered selenium. Work-up as above gave 67 mg (14%) of colorless plates, melting 121-121.5°, identical in all respects to the product from method A.

##### Method C.

A mixture of 352 mg (1.12 mmoles) of **7**, 1.75 g (12.3 mmoles) of phosphorus pentoxide, and 3.5 g (22.8 mmoles) of phosphorus oxychloride in 14 ml of dry xylene was heated to reflux for 19 hours (a dark green color formed, changed to deep violet and faded as the reaction was completed). The reaction mixture was poured into 50 ml of water, extracted with three 50 ml portions of ether, and the ethereal solution washed with 50 ml of 10% sodium hydroxide, twice with water, and dried. Evaporation gave a crude yellow oil; ir (liquid film): 1175 (aryl CO) and 1120  $\text{cm}^{-1}$  (cyclic CO), but no absorption in the carbonyl region (1650-1800  $\text{cm}^{-1}$ ).

The crude oil was dehydrogenated with 300 mg of powdered selenium, and worked-up as for method A, to give 89 mg (27%) of colorless plates of **5**, melting at 120-121°; ir (potassium bromide): 3060, 1175 and 1120  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 242 (4.47), 247 (4.52), 255 (4.59), 263 (4.79), 281 (4.17), 288 (4.28), 329 (3.68) and 344  $\text{m}\mu$  (3.72).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{14}\text{O}$ : C, 89.77, H, 4.79. Found: C, 89.46; H, 4.81.

#### 4-Phenyl-1-naphthol (**6**).

This compound was prepared as described by Johnson and Goldman [13], and was obtained as white needles melting at 139-140° in 84% yield. The ir spectrum exhibited bands at 3380 (OH), 3060 (aryl CH), 1620 and 1580 ( $\text{C}=\text{C}$ ) and 1175  $\text{cm}^{-1}$  (aryl CO).

Compound **6** formed a *p*-nitrobenzoate in good yield as yellow plates melting at 146-146.5°.

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{15}\text{NO}$ : C, 74.79; H, 4.09. Found: C, 74.62; H, 4.12.

Treatment of **6** with diphenylcarbonyl chloride in dry pyridine produced the diphenylurethane in 58% yield, melting at 189-190° after recrystallization from ethanol.

*Anal.* Calcd. for  $\text{C}_{29}\text{H}_{21}\text{NO}_2$ : C, 83.83; H, 5.10. Found: C, 83.65; H, 5.48.

#### 4-Phenyl-1-naphthyl 2'-Oxocyclohexyl Ether (**7**).

The sodium salt of **6** was prepared [14] from 4.6 g (21 mmoles) of **6** in 10 ml of methanol and 0.84 g (21 mmoles) of sodium hydroxide in 10 ml of 85% aqueous methanol. Evaporation *in vacuo* at 50°, followed by drying for 24 hours in a vacuum oven, gave 4.9 g (97%) of the sodium salt.

A saturated solution of 4.9 g (20 mmoles) of the sodium salt of **6** in DMF at 35° was added to a solution of 2.6 g (20 mmoles) of 2-chlorocyclohexanone in DMF at 35°. The mixture was maintained at 35° under nitrogen for 19 hours, poured into 1 l of water, and extracted with three 500 ml portions of ether. The ether solution was washed with 10% sodium hydroxide, then water, dried and evaporated to yield an oily solid. Two recrystallizations from ethanol gave 2.32 g (37%) of white crystals, melting at 143-143.5°; ir (potassium bromide): 1700, 1160 and 1115  $\text{cm}^{-1}$ ; uv:  $\lambda$  max (log  $\epsilon$ ) 214 (4.31), 236 (4.18) and 302  $\text{m}\mu$  (3.69).

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{20}\text{O}_2$ : C, 83.51; H, 6.37. Found: C, 83.50; H, 6.57.

Compound **7** readily formed a 2,4-dinitrophenylhydrazone, melting at 175-176° after two recrystallizations from ethyl acetate.

*Anal.* Calcd. for  $\text{C}_{28}\text{H}_{24}\text{N}_4\text{O}_5$ : C, 67.73; H, 4.87; N, 11.28. Found: C, 67.42; H, 4.94; N, 10.93.

## REFERENCES AND NOTES

- [1] Taken from a thesis submitted by R. F. W. for the degree Master of Science at Indiana University, June, 1963.
- [2] E. Campaigne and S. W. Osborn, *J. Heterocyclic Chem.*, **5**, 655

- (1968).
- [3] S. W. Osborn, Ph. D. Thesis, "Polycyclic Midring Heterocycles", submitted to Indiana University, 1962.
- [4] E. Wenkert, R. D. Youssefyeh and R. G. Lewis, *J. Am. Chem. Soc.*, **82**, 4675 (1960).
- [5] N. Kornblum, P. J. Berrigan and W. J. LeNoble, *J. Am. Chem. Soc.*, **82**, 1257 (1960).
- [6] N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961).
- [7] N. Kornblum, R. Seltzer and P. Haberfield, *Chem. Eng. News*, Sept. 24, 1962, p 50.
- [8] M. Mousseron, 1-(2-oxocyclohexyl)- $\beta$ -naphthol, U. S. Patent 2,882,201 (1959); *Chem. Abstr.*, **53**, 17084i (1959).
- [9] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds", John Wiley and Sons, Inc., New York, NY, 1951.
- [10] N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis", 2nd Ed, Interstate Publishers, New York, NY, 1957.
- [11] Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
- [12] A. I. Vogel, "Practical Organic Chemistry", 3rd Ed, Longmans, Green and Co. Ltd., London, 1956, pp 878-879.
- [13] W. S. Johnson and A. Goldman, *J. Am. Chem. Soc.*, **67**, 430 (1945).
- [14] N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).