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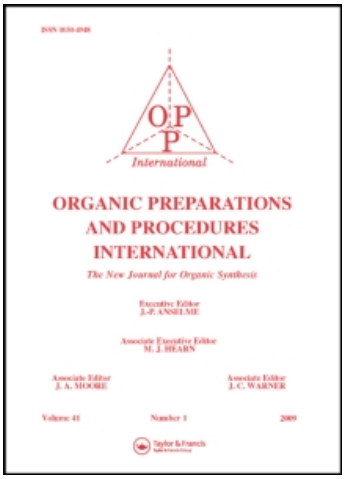

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ADIPOYLATION OF 2-METHOXYNAPHTHALENE

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ADIPOYLATION OF 2-METHOXYNAPHTHALENE

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In the course of a project examining the utility of alkanoic acids incorporating a 6-substituted naphthoyl group as fluorescent probes of biological membranes, it was necessary to adipoylate 2-methoxynaphthalene (**1**). The literature on acylation of **1** indicated that yields are generally poor and the distribution of isomers variable.[1] In weakly polar or apolar media, acylation α to the methoxy apparently predominates,[2] while in polar solvents such as nitrobenzene, the incoming group is highly solvated and thus is so sterically demanding that not only is α substitution less prevalent but substitution occurs mainly at position 6, which is conjugated with the methoxy group.[2] Several attempts have been made to employ these solvent effects in the preparation of 1-acyl-2-methoxynaphthalenes[3] or 2-acyl-6-methoxynaphthalenes.[4] In practice however, the isomer distribution varies considerably even for reactions in the same or similar solvents. This is attributable to secondary demethylation[5,6] or condensation reactions of either isomer, the latter reactions affording tarry side-products that complicate isolation and purification. A procedure has recently been described which, by virtue of the reversibility of the acylation reaction, allows the thermodynamically more stable 2-acyl-6-methoxynaphthalenes to be obtained almost exclusively.[7]

Among the few references dealing with the preparation of keto acids of 2-methoxynaphthalene, the best yields (46%) of 2,6-disubstituted compounds containing fewer than four carbon atoms in the acyl side-chain have been obtained by acylation with the anhydride in nitrobenzene.[5,8] For the corresponding compounds with five or more carbon atoms, acylation using the diacid monochloride monoester in dichloromethane affords up to 37% yield of the 2,6-derivative.[8] In this work, we examined the adipoylation of 2-methoxynaphthalene in dichloromethane, nitrobenzene and a mixture of these two solvents, using methyl 5-(chlorocarbonyl)pentanoate (**2**) in the presence of aluminum chloride. In addition to methyl 6-(6-methoxy-2-naphthyl)-6-oxohexanoate (**3**) as the major product, unreacted **1** was isolated along with monomethyl adipate (the hydrolysis product of **2**), and two side-products, methyl 6-(2-methoxy-1-naphthyl)-6-oxohexanoate (**4**) and, in some cases, methyl 6,6-*bis*(6-methoxy-2-naphthyl)-5-hexenoate (**5a**). The fact that **3** was the major product regardless of the solvent used (Table) suggests even the unsolvated acyl complex was bulky; thus attack at position 1 is sterically hindered, both by the 2-methoxy substituent and also by H-8 (the peri effect). Methyl

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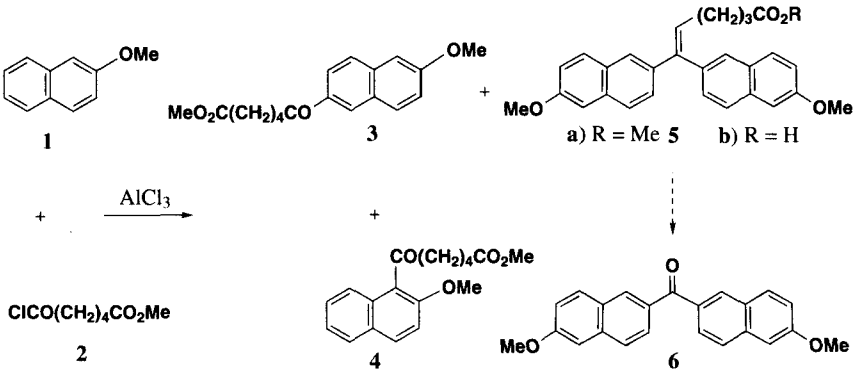

6,6-*bis*(6-methoxy-2-naphthyl)-5-hexenoate (**5a**), was isolated in 16% and 27% yield in nitrobenzene and nitrobenzene/dichloromethane respectively; these yields would suggest that **3** is formed in roughly 40% yield, if **5a** is derived from **3**. Compound **5a** was unequivocally identified from its spectroscopic data and those of the corresponding acid, **5b**, and by its conversion to the diarylketone **6**. Although **5a** has not been described previously, formation of 1,1-diarylalkenes during acylation of methoxyarenes with acid chlorides is well documented ("abnormal Gatterman reaction").[9] In the naphthalene series, we found only one pertinent reference by Buu-Hoï,[10] in which 2-methoxynaphthalene was propionylated. Formation of these diarylalkenes may be explained by an electrophilic aromatic substitution mechanism involving acid-catalyzed attack of the activated aryl compound by the initially formed ketone, followed by dehydration of the tertiary alcohol.

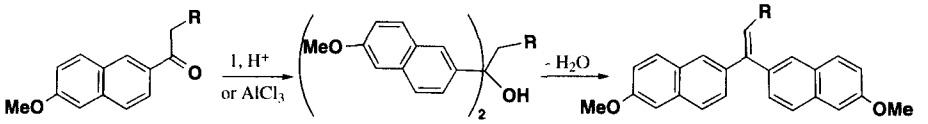

Table. Yields[a] of Adipoylation[b] of **1** in Different Solvent Systems

Solvent	3	4	5a
Nitrobenzene	29%	traces	16%
Nitrobenzene+CH_2Cl_2	28%	traces	27%
CH_2Cl_2	40%	9%	—

a) Of isolated products, based on starting **1**. b) RT, 12 hrs.

In order to check these hypotheses, the reaction in dichloromethane was quenched at various times, and the ratio of acylated products **3** and **4** determined by ^1H NMR in the crude mixture. The increase proportion of **3** formed for longer reaction times, may be attributed to the reversibility of the reaction leading to **4** and the greater thermodynamic stability of **3**.[7] However, **3** was always the major product, despite the observations of Giordano and Villa,[7] who noted that for other acylating agents,

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attack at position 1 led to the kinetic product. The ratio of **3** to **4** in CH_2Cl_2 as determined by ^1H NMR of the crude mixture, was 66:34, 70:30 and 81:19 after 1, 2 and 12 hrs respectively.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined on a Reichert Kofler Thermopan. IR spectra were obtained on a Perkin Elmer FTIR 1640 spectrometer. ^1H NMR spectra were recorded on a Bruker AMX-300 spectrometer, with TMS as internal standard. Column chromatography was done using silica gel 60 Merck (70-230 mesh). Elemental analyses were performed on a Perkin Elmer 240 apparatus (Microanalysis Service, University of Santiago).

Preparation of Methyl 6-(6-Methoxy-2-naphthyl)-6-oxohexanoate (3).- *In Dichloromethane.*- Methyl 5-(chlorocarbonyl)pentanoate (**2**) (11.3 g, 63.3 mmol) was slowly added to a vigorously stirred suspension of $AlCl_3$ (16.7 g, 125 mmol) in CH_2Cl_2 (180 mL). After 15 min. had elapsed, a solution of 2-methoxynaphthalene (10 g, 63.3 mmol) in CH_2Cl_2 (100 mL) was added, and the mixture was stirred for 12 hrs. Crushed ice and then concentrated HCl (100 mL) were added, the organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2 (2 x 100 mL). The organic extracts were combined, washed with 5% $NaHCO_3$ (200 mL) and dried (anhydrous Na_2SO_4), and the solvent was evaporated *in vacuo*, leaving 18 g of a brown, tarry residue. It was chromatographed on a column of silica gel, using CH_2Cl_2 as eluent, to afford unreacted **1** (2.4 g, 24%), **4** (1.5 g, 9%) and **3** (6.9 g, 40%). Further elution of the column with CH_2Cl_2/EtOAc (8:2) afforded monomethyl adipate (1.20 g).

Compound **3**, mp. 81-83° (from toluene). IR (KBr): 2930, 1733, 1672, 1624, 1480, 1291, 1256, 1220, 1168, 1019 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.39 (1H, virtual s, 1-H); 8.00 (1H, dd, $J_{3,4}$ = 8.62 Hz, $J_{3,1}$ = 1.66 Hz, 3-H); 7.86 (1H, d, $J_{8,7}$ = 8.87 Hz, 8-H); 7.77 (1H, d, $J_{4,3}$ = 8.62 Hz, 4-H); 7.20 (1H, dd, $J_{7,8}$ = 8.87 Hz, $J_{7,5}$ = 2.30 Hz, 7-H); 7.15 (1H, d, $J_{5,7}$ = 2.30 Hz, 5-H); 3.95 (3H, s, OCH_3); 3.67 (3H, s, CO_2CH_3); 3.10 (2H, t, J = 6.80 Hz, $COCH_2$); 2.40 (2H, t, J = 7.01 Hz, CH_2CO_2); 1.80-1.76 (4H, m, $(CH_2)_2$).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.26; H, 7.38

Compound **4**, colorless oil. IR (film): 2949, 1732, 1689, 1622, 1508, 1253. cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.86 (1H, d, $J_{4,3}$ = 9.10 Hz, 4-H); 7.79 (1H, virtual d, $J_{5,6}$ = 7.94 Hz, 5-H); 7.63 (1H, virtual d, $J_{8,7}$ = 8.24 Hz, 8-H); 7.45 (1H, ddd, $J_{7,8}$ = 8.24 Hz, $J_{7,6}$ = 6.90 Hz, $J_{7,5}$ = 1.05 Hz, 7-H); 7.35 (1H, ddd, $J_{6,5}$ = 7.94 Hz, $J_{6,7}$ = 6.90 Hz, $J_{6,8}$ = 1.30 Hz, 6-H); 7.26 (1H, d, $J_{3,4}$ = 9.10 Hz, 3-H); 3.95 (3H, s, OCH_3); 3.66 (3H, s, CO_2CH_3); 2.94 (2H, t, J = 6.94 Hz, $COCH_2$); 2.37 (2H, t, J = 7.11 Hz, CH_2CO_2); 1.80-1.72 (4H, m, $(CH_2)_2$).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.30; H, 7.46

In Nitrobenzene.- To a vigorously stirred solution of **1** (10 g, 63.3 mmol) and **2** (14 g, 78.4 mmol) in nitrobenzene (62.5 mL), finely powdered $AlCl_3$ (10 g, 75 mmol) was added in small portions. The reaction was stirred for 12 hrs at room temperature. The mixture was acidified with 6N HCl (50 mL), the nitrobenzene was removed by steam distillation, and the acidic, aqueous residue was extracted several times with CH_2Cl_2. The combined extracts were washed and dried (see preparation above) and

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the solvent was evaporated, leaving 12 g of a brown paste. This was chromatographed on silica gel, using CH_2Cl_2 as eluant and monitoring the eluatte by t.l.c, to afford unreacted **1** (0.86 g), methyl 6,6-*bis*(6-methoxy-2-naphthyl)-5-hexenoate (**5a**) (2.2 g, 16%), **4** (traces) and **3** (5.15 g, 29%). Further elution with CH_2Cl_2/EtOAc (8:2) afforded monomethyl adipate (0.9 g).

Compound **5a**. IR (KBr): 3421, 1734, 1653, 1267, 1200 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75 (1H, d, $J_{4,3}$ = 8.45 Hz, 4-H); 7.74 (1H, d, $J_{4',3'}$ = 9.35 Hz, 4'-H); 7.64 (1H, d, $J_{8,7}$ = 8.30 Hz, 8-H); 7.63 (1H, virtual s, 1-H); 7.59 (1H, d, $J_{8',7'}$ = 9.24 Hz, 8'-H); 7.49 (1H, virtual s, 1'-H); 7.45 (1H, dd, $J_{3,4}$ = 8.45 Hz, $J_{3,1}$ = 1.80 Hz, 3-H); 7.27 (1H, dd, $J_{3',4'}$ = 9.35 Hz, $J_{3',1'}$ = 1.60 Hz, 3'-H); 7.19 (1H, virtual s, 5-H); 7.18 (1H, dd, $J_{7,8}$ = 8.30 Hz, $J_{7,5}$ = 2.27 Hz, 7-H); 7.10 (1H, virtual s, 5'-H); 7.08 (1H, dd, $J_{7',8'}$ = 9.24 Hz, $J_{7',5'}$ = 2.54 Hz, 7'-H); 6.21 (1H, t, J = 7.46 Hz, =CH); 3.95 (3H, s, OCH_3); 3.91 (3H, s, OCH_3); 3.59 (3H, s, CO_2CH_3); 2.32 (2H, t, J = 7.54 Hz, CH_2CO_2); 2.25 (2H, virtual quad., J = 7.42 Hz, =CHC<u>H</u>$_2$); 1.82 (2H, virtual quint., J = 7.33 Hz, $CH_2C\underline{H}_2CH_2$).

Anal. Calcd. for $C_{29}H_{28}O_4$: C, 79.07; H, 6.41. Found: C, 79.00; H, 6.48

In Nitrobenzene/dichloromethane.- To a mixture of **1** (10 g, 63.3 mmol) and suspended $AlCl_3$ (11.2 g, 84 mmol) in nitrobenzene (2 mL) and CH_2Cl_2 (24 mL), **2** (11.3 g, 63.3 mmol) was slowly added. The reaction was stirred for 12 hrs at room temperature. The mixture was acidified with 6N HCl (40 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined and washed successively with 5% $NaHCO_3$, and water and then dried (anhydrous Na_2SO_4) and the solvent was evaporated *in vacuo*, leaving 16 g of a brown paste. This was chromatographed on a column of silica gel, using CH_2Cl_2 as eluant and monitoring the eluate by t.l.c., to afford, in order of elution, unreacted **1** (2.8 g), **5a** (3.7 g, 27%), **4** (traces) and **3** (4.97 g, 28%). Further elution of the column with CH_2Cl_2/EtOAc (8.2) afforded monomethyl adipate (1.5 g).

Preparation of 6,6-*bis*(6-Methoxy-2-naphthyl)-5-hexenoic Acid (5b).- Ester **5a** (1 g, 2.3 mmol) was saponified by refluxing in a mixture of 2N NaOH (1.5 mL) and methanol (8 mL) for 6 hrs. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was dissolved in water, which was extracted with diethyl ether. Then, the aqueous phase was acidified with 6N HCl (10 mL) and further extracted with diethyl ether, and this ethereal extract was washed with water and dried (anhydrous Na_2SO_4). Evaporation of the ether left a solid residue (0.74 g) that was recrystallized from toluene to afford pure **5b**, mp. 93-94°. IR (KBr): 2924, 1705, 1628, 1601, 1483, 1388, 1267, 1201, 1161, 1031 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.98 (1H, s, exchang. in D_2O, CO_2H); 7.75 (1H, d, $J_{4,3}$ = 8.51 Hz, 4-H); 7.73 (1H, d, $J_{4',3'}$ = 8.89 Hz, 4'-H); 7.64 (1H, d, $J_{8,7}$ = 8.39 Hz, 8-H); 7.64 (1H, virtual s, 1-H); 7.58 (1H, d, $J_{8',7'}$ = 9.34 Hz, 8'-H); 7.50 (1H, virtual s, 1'-H); 7.45 (1H, dd, $J_{3,4}$ = 8.51 Hz, $J_{3,1}$ = 1.77 Hz, 3-H); 7.27 (1H, dd, $J_{3',4'}$ = 8.89 Hz, $J_{3',1'}$ = 1.66 Hz, 3'-H); 7.19 (1H, virtual s, 5-H); 7.17 (1H, dd, $J_{7,8}$ = 8.39 Hz, $J_{7,5}$ = 2.50 Hz, 7-H); 7.10 (1H, virtual s, 5'-H); 7.08 (1H, dd, $J_{7',8'}$ = 9 .34 Hz, $J_{7',5'}$ = 2.50 Hz, 7'-H); 6.21 (1H, t, J = 7.44 Hz, =CH); 3.94 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 2.34 (2H, t, J = 7.47 Hz, C<u>H</u>$_2CO_2H$); 2.27 (2H, virtual quad., J = 7.40 Hz, =CHC<u>H</u>$_2$); 1.83 (2H, virtual quint., J = 7.32 Hz, $CH_2C\underline{H}_2CH_2$).

Anal. Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14. Found: C, 78.66; H, 6.28

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Preparation of *bis*(6-Methoxy-2-naphthyl) Ketone (6).- A mixture of ester **5a** (0.90 g, 2 mmol) and sodium dichromate (2 g, 7.6 mmol) in acetic acid (10 mL) was refluxed for 5 min. Then, the crude mixture was poured over crushed ice, and the solid that precipitated was filtered out and washed with cold water. This precipitate was dissolved in EtOAc, and the solution was washed with 5% $NaHCO_3$ and then dried (anhydrous Na_2SO_4). Evaporation of the solvent in vacuo left a solid residue (0.55 g) that was recrystallized from EtOAc to afford pure **6**, mp. 199-200°. (Lit.,[10] 198°) IR (KBr): 1652, 1623, 1477, 1387, 1267, 1221, 1197, 1164, 1028 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.26 (1H, virtual s, 1-H); 7.97 (1H, dd, $J_{3,4}$ = 8.50 Hz, $J_{3,1}$ = 1.65 Hz, 3-H); 7.85 (1H, d, $J_{4,3}$ = 8.50 Hz, 4-H); 7.82 (1H, d, $J_{8,7}$ = 9.49 Hz, 8-H); 7.22 (1H, dd, $J_{7,8}$ = 9.49 Hz, $J_{7,5}$ = 2.47 Hz, 7-H); 7.21 (1H, d, $J_{5,7}$ = 2.47 Hz, 5-H); 3.98 (3H, s, OCH_3).

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