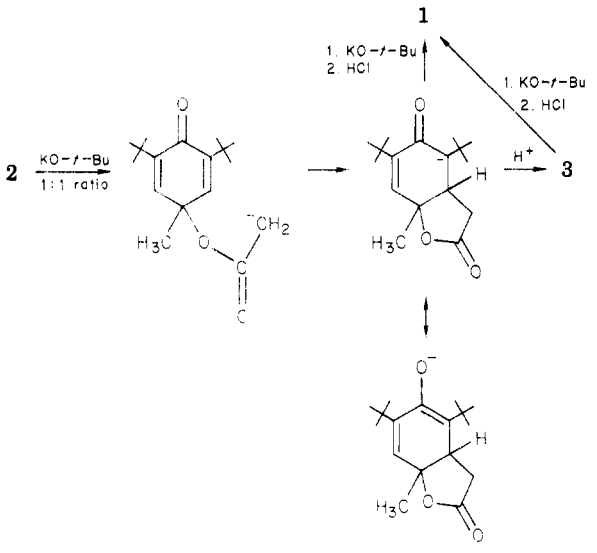
Table I. ^{13}C NMR Data for 3

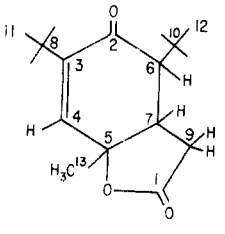
C atom	δ^a	mult[b]	C atom	δ^a	mult[b]
1	198.7	s	8	34.8	s
2	174.5	s	9	33.1	t
3	149.2	s	10	32.4	s
4	135.7	d	11	29.2	q
5	84.4	s	12	28.4	q
6	57.1	d	13	23.9	q
7	44.1	d			

[a] Downfield from ^{13}C signal of internal Me_4Si. [b] Off-resonance conditions.

Scheme I



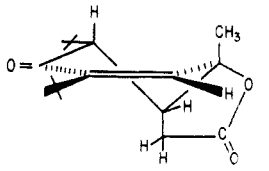
pling to attached protons. The ^{13}C NMR data, summarized in Table I, along with all the data above suggest structure **3**.



3

Clearly, **3** would be the expected intermediate in the rearrangement of **2** to **1**. Extraction by base of the acetoxy methyl proton of **2** and a subsequent Michael addition to the double bond, followed by protonation, would afford **3** (see Scheme I). However, all attempts to complete the rearrangement of **3** to **1** under acidic conditions (1, 6, or 12 M HCl in DMF, at 25 or 80 °C) led to unchanged **3**. When **3** was subjected to potassium *tert*-butoxide (≥1:1 ratio) under the original reaction conditions, followed by acidification with aqueous HCl, **1** was isolated in 95% yield. This suggests that a second equivalent of base is necessary to abstract the proton at C(7) of **3**, thus effecting elimination by either an E2 or E1cb mechanism, followed by aromatization.

The stereochemistry of **3** would then be important as to the ease by which an E2 elimination could occur. The ^1H NMR data show that the olefinic proton of **3** appears as a doublet (see above) indicating that it is long-range coupled to the proton at C(7). An examination of molecular models of **3** reveals that three different geometric configurations can exist at the ring fusions, assuming that the *tert*-butyl group exists in the equatorial position. However, only the geometry shown in **3a** places the two



3a

protons in a relationship approaching that of the "W" configuration,[4] thereby allowing for long-range coupling. The two leaving groups of **3a** are then in equatorial positions. However, there appears to be enough conformational flexibility at this end of the molecule to allow the leaving groups to become nearly diaxial during elimination without causing any substantial steric interactions in the remainder of the molecule.

Acknowledgment. The author thanks Dr. Jerry Westfahl for obtaining the NMR spectra, Mr. Tim Pratt for experimental assistance and Professor Leo Paquette for helpful discussions.

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Intramolecular Friedel-Crafts Acylation of a Lactone in Polyphosphoric Acid. Synthesis of 2-Phenylphenalen-1-one

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The tricyclic ring system of the antidepressant drug amitriptyline has inspired many endeavors toward molecular modifications.[1,2] During an SAR study of tetracyclic analogues, an attempt was made to synthesize 7*H*-benzo[5,6]cycloocta[1,2,3-*de*]naphthalen-7-one (**1**).[3] We report an intramolecular Friedel–Crafts acylation of 3-benzyl-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (**2**) in polyphosphoric acid (PPA). The reaction did not lead to the desired ketone **1**, providing instead a convenient route to 2-phenylphenalen-1-one (**3**).

A Perkin condensation (under the Gabriel–Weiss modification[4]) of 1,8-naphthalic anhydride and phenylacetic acid gave a mixture of 2-phenylphenalen-1,3-dione and (*Z*)-3-phenylmethylene-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (**4**).[5] The latter was separated and purified by column chromatography and recrystallization. Attempted reduction and hydrogenolysis of **4** with red phosphorous and boiling aqueous hydroiodic acid (57%) did not provide the expected 8-(2-phenylethyl)-1-naphthoic acid (**5**). Only reduction of the vinyl linkage occurred, giving **2** in 52%

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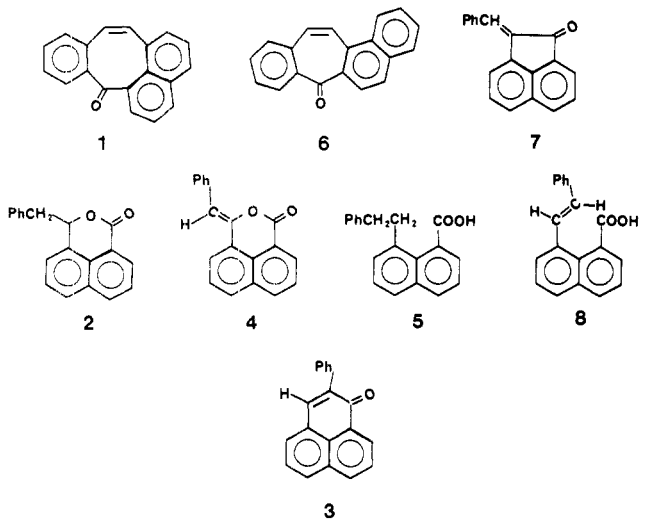

yield. Lactone **2** was preferably prepared and purified (68% yield) by the facile reduction of **4** with triethylsilane in trifluoroacetic acid.[6,7] It exhibited an A_2X pattern in the ^1H NMR spectrum at δ 3.16 (d, J = 6 Hz, 2 H) and 5.90 (t, J = 6 Hz, 1 H). Treatment of **2** with PPA at 180 °C for 3 h afforded **3** in 68% yield.[8] The cyclization could also be effected at 140 °C (4 h, 49% yield).

The structure of **3** was established as follows. The elemental analysis and the molecular ion in the mass spectrum indicate the formula $C_{19}H_{12}O$. The IR spectrum contains a highly conjugated carbonyl absorption at 1633 cm^{-1}. For comparison, in phenalenone the corresponding band appears at 1637 cm^{-1}.[9] The chemical shifts and the pattern of the ^1H NMR spectra of **3** strongly resembles those of phenalen-1-one and 3-phenylphenalen-1-one[10] (see Experimental Section). In $CDCl_3$, the lower field aromatic double doublet at 8.73 ppm (H-9) and the vinylic singlet at 7.87 ppm (H-3) should be noted. In the presence of trifluoroacetic acid, 1-hydroxy-2-phenylphenalenium cation is formed. Consequently, the aromatic absorption of the phenalenium system is resolved and shifted downfield, while the chemical shifts of the phenyl protons are hardly affected. The NMR and IR spectra rule out the alternative structures of **1**, **6**,[11] and 2-benzylideneacenaphthen-1-one (**7**).[12] Ketone **1** would have been formed by acylation of the phenyl system. Its conjugate acid could have rearranged to **6** under thermodynamically controlled conditions.[13] The ^{13}C NMR spectrum contained 16 signals, including six quaternary ones. The missing quaternary signal is probably due to the highly hindered C-9b. The carbonyl carbon appears at 183.9 ppm. For comparison, the corresponding absorption in phenalen-1-one is 185 ppm.[14]

Under the influence of PPA, lactone **2** may undergo ring opening and hydrolysis followed by dehydration to (*E*)-8-styryl-1-naphthoic acid (**8**). The remarkable step is the Friedel–Crafts cyclization (**8** → **3**) which involves an intramolecular acylation at a vinylic center. The regiospecific attack at the vinyl carbon rather than at the conventional aromatic nucleus is governed by spatial considerations. The *E* configuration in **8** prohibits the "aromatic" cyclization pathway. The proposed mechanism is supported by the cyclization of **8** to **3** in PPA (160 °C, 3.5 h, ^1H NMR (300 MHz), TLC, and melting point).

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 457 spectrometer. Electronic spectra were recorded on Cary-14 and Varian Techtron 635 spectrometers. The ^1H and ^{13}C NMR spectra were obtained by using Varian HA-100 and Bruker WH-300 spectrometers. ^1H and ^{13}C spectra were obtained by using internal locking, and the data are reported in parts per million, usually downfield from Me_4Si as internal reference (δ units). Mass spectra were measured on a Varian MAT 311 spectrometer.

3-Phenylmethylene-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (4). As described for the preparation of 3-benzylidenphthalide,[4a] a mixture of 1,8-naphthoic anhydride (50 g, 252 mmol), phenylacetic acid (35 g, 257 mmol), and freshly fused sodium acetate (2.0 g) was immersed in a silicon oil bath heated at 250 °C. Within 30 min the mixture melted, and carbon dioxide and water began to be evolved. After an additional hour at 250 °C, the resulting mixture was cooled to 200 °C, poured into a beaker containing ethanol and triturated. Filtration afforded 59.4 g of product. The diketone was removed by trituration in aqueous potassium carbonate (10%). The remaining product was chromatographed on a neutral alumina column (deactivated with 15% ethyl acetate). Elution with benzene gave **4**: 12.3 g (18%); mp 147–148 °C (ligroin) (lit.[4a] mp 146–148 °C); IR (KBr) 1730 (C=O) cm^{-1}; UV λ_{max} (EtOH) 384 nm (ϵ 15 100), 310 (15 800), 271 (14 000), 262 (18 200), 242 (25 100), 234 (24 500), 225 (23 400); ^1H NMR ($CDCl_3$) δ 6.55 (s, 1 H), 7.23–7.65 (m, 5 H), 7.77–8.07 (m, 5 H), 8.35 (d, J = 7.0 Hz, 1 H); mass spectrum m/e (relative intensity) 273 (21.4), 272 (M^+, 100), 271 (43.4), 215 (34.4), 126 (15.5).

3-Benzyl-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (2). A mixture of **4** (5.6 g, 20.6 mmol) and triethylsilane (7.6 mL, 80 mmol) was treated under magnetic stirring and anhydrous conditions with trifluoroacetic acid (7.6 mL, 60 mmol). The reaction mixture which turned red was kept at 70 °C for 65 h. After evaporation under vacuum, the crude product was washed with water, and the water was decanted. Recrystallization from ethanol afforded **2** (3.8 g, 67%) as colorless needles: mp 68–69 °C; IR (KBr) 1712 (C=O) cm^{-1}; UV λ_{max} (EtOH) 307 nm (ϵ 2540), 237 (26 400), 215 (81 200); ^1H NMR (CS_2) δ 3.16 (d, J = 6.0 Hz, 2 H), 5.90 (t, J = 6.0 Hz, 1 H), 6.74–7.15 (m, 6 H), 7.31–7.42 (m, 2 H), 7.72 (d, J = 9.0 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 8.05 (d, J = 7.0 Hz, 1 H); mass spectrum m/e (relative intensity) 274 (M^+, 2.0), 185 (13.5), 183 (100), 155 (7.6), 127 (19.8), 126 (4.4), 91 (2.9), 77 (3.4), 28 (3.8). Anal. Calcd $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.02; H, 5.15.

2-Phenylphenalen-1-one (3). At 180 °C and under anhydrous conditions, lactone **2** (3.3 g, 12 mmol) was added to polyphosphoric acid (Fluka, 125 mL). The red mass was kept at 180 °C with vigorous mechanical stirring for 3 h and then poured into ice–water. After the complex has completely disintegrated, the crude solid product was filtered and dried. Recrystallization from methanol afforded **3** as yellow-gold plates: mp 136 °C; yield 2.1 g (68%); IR (KBr) 1633 (C=O) cm^{-1}; UV λ_{max} (EtOH) 403 nm (ϵ 9400), 360 (8600), 253 (20 000), 232 (17 000); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.51 (m, 3 H, phenyl ring), 7.61–7.72 (m, 3 H, phenyl ring, H-5), 7.80–7.87 (m, 2 H, H-6(4), H-8), 7.874 (s, 1 H, H-3), 8.05 (d, J = 8.3 Hz, 1 H, H-4(6)), 8.24 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1 H, H-7), 8.73 (dd, J_1 = 7.3 Hz, J_2 = 1.0, 1 H, H-9); ^1H NMR ($CDCl_3$–CF_3COOH) δ 7.43–7.51 (m, 3 H, phenyl ring), 7.57–7.60 (m, 2 H, phenyl ring), 7.73 (t, J = 8.3 Hz, 1 H, H-5), 7.92 (t, J = 7.2 Hz, 1 H, H-8), 7.98 (d, J = 7.0 Hz, 1 H, H-6(4)), 8.02 (s, 1 H, H-3), 8.18 (d, J = 8.3 Hz, 1 H, H-4(6)), 8.38 (d, J = 7.8 Hz, 1 H, H-7), 8.85 (d, J = 7.8 Hz, 1 H, H-9); ^{13}C ($CDCl_3$) δ 183.9 (qt), 139.5, 139.3 (qt), 136.5 (qt), 134.5, 131.9 (qt), 131.3, 131.2, 130.9, 129.8 (qt), 129.0, 128.1, 128.0, 127.2, 127.1 (qt), 126.7; mass

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spectrum, m/e (relative intensity) 257 (9.9), 256 (M^+, 55.4), 255 (100), 227 (4.5), 226 (18.1), 225 (3.4), 224 (4.3), 200 (3.4), 128 (7.6), 127 (7.4), 114 (3.4), 113 (11.4), 112 (2.3), 101 (5.0), 100 (5.3). Anal. Calcd for $C_{19}H_{12}O$: C, 89.04; H, 4.72. Found: C, 89.25; H, 4.80.

(*E*)-8-Styryl-1-naphthoic acid (8). A mixture of **2** (0.8 g, 3 mmol), absolute ethanol (20 mL), and potassium hydroxide (0.2 g, 3.6 mmol) was gradually heated under nitrogen with magnetic stirring to 180 °C. Ethanol evaporated, and the mixture was kept at 180 °C for 2 h. After cooling to room temperature, the mixture was treated with sodium borohydride (0.034 g, 0.9 mmol) and dry THF (6 mL) followed by freshly distilled borontrifluoride etherate (0.17 g) in dry THF (2.5 mL). After 1 h at room temperature, second portions of sodium borohydride (0.034 g, 0.9 mmol) and borontrifluoride etherate (0.17 g) were added. After another hour at room temperature, the reaction mixture was treated with propionic acid (20 mL) and refluxed for 1 h. The solvents were removed under vacuum, and the residue was extracted with dichloromethane. The organic fraction was washed with hydrochloric acid and water and dried ($MgSO_4$), and the solvent was evaporated. Sublimation at 95 °C (0.05 mm) followed by recrystallization from benzene afforded **8** as colorless needles: mp 159-160 °C; 0.084 g (10.5% yield); IR (KBr) 1682 (C=O), 973 ((*E*)-CH=CH); UV λ_{max} (EtOH) 328 nm (ϵ 25 100), 272 (20 000), 231 (60 000); ^{1}H NMR (270 MHz, CD_2Cl_2) δ 6.98 (AB d, J = 16.7 Hz, 1 H, (*E*)-CH=CH), 7.32-7.43 (m, 3 H), 7.54-7.63 (m, 5 H), 7.68 (d, J = 7.5 Hz, 1 H), 7.79 (d, J = 7.5, 1 H), 7.93 (d, J = 8.2, 1 Hz), 8.08 (m, 1 H); mass spectrum, m/e (relative intensity) 275 (22.0), 274 (M^+, 100), 257 (14.0), 255 (19.8), 231 (14.3), 230 (M - CO_2, 48.0) 229 (38.3), 227 (14.4), 226 (22.3), 202 (11.4), 183 (53), 169 (10.8), 168 (57.6), 152(10.9), 128 (14.2), 127 (16.7), 114 (13.1), 113 (20.0), 107 (10.6), 105 (14.9), 77 (12.4). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 82.84; H, 5.16.

Acknowledgment. We thank the Israel Center for Psychobiology—Charles E. Smith Family Foundation for supporting this research.

Registry No. **2**, 73873-14-0; **3**, 73873-15-1; **4**, 73873-16-2; **8**, 73873-17-3; 1,8-naphthoic anhydride, 81-84-5; phenylacetic acid, 103-82-2.

Stereospecific Synthesis of the 6α- and 6β-Amino Derivatives of Naltrexone and Oxymorphone

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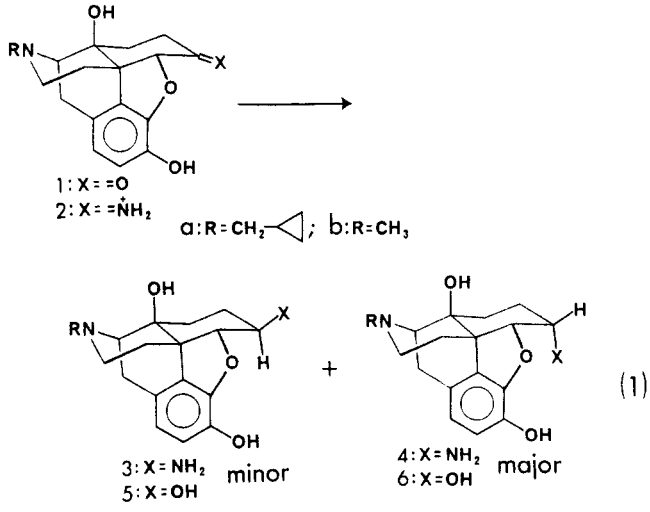
We have recently reported[1-4] on a group of affinity labeling agents as probes for opioid receptors. These ligands are all derivatives of β-naltrexamine **3a** or β-oxymorphamine **3b** in which an alkylating moiety is attached to the 6β-amino group. Because these compounds represent the first reported opioid receptor site-directed alkylating agents that are effective both in vitro and in vivo, we have devoted some effort to improving the synthesis of the amines **3** which are used as their precursors. The previously reported[5] synthesis of β-naltrexamine **3a**, which involved the $NaCNBH_3$ reductive amination of naltrexone **1a**, has the disadvantage of affording a mixture of C-6 epimers (**3a:4a** ~1:2), the separation of which is not very efficiently accomplished, especially on a large scale. This report describes a novel approach to the stereospecific synthesis of the 6β-amines (**3a,b**) and 6α-amines (**4a,b**).

Treatment of 6-keto opiates by various hydride reagents[6-12] or methyllithium[12,13] leads to the corresponding 6α-alcohol as the sole or major epimer. This fact, and the observed predominance of the 6α-amine (**4a**) from $NaCNBH_3$ reduction of the iminium species **2a**,[5] is explicable in terms of a chair-like conformation for ring C



(1)

(eq 1),[14] with hydride (or CH_3^-) transfer occurring mainly on the β face. The α face of ring C is sterically hindered due mainly to a 1,3-diaxial interaction with the aromatic ring.

On the other hand, it has been reported[2,3] that $NaCNBH_3$ reduction of the iminium salts **7a,b** stereospecifically affords the corresponding 6β-diethanolamino derivatives (**8a,b**). This was attributed[3] to ring C assuming a boat conformation (**7**) due to steric repulsion between the vicinal ether oxygen and the *syn*-CH_2CH_2OH group. There is ample precedent for similar steric effects (A strain) in cyclohexane systems.[15] With ring C in the boat conformation, hydride transfer from $NaCNBH_3$ occurs exclusively on the more accessible α face, thereby leading to the 6β isomers (**8a,b**).

Using a similar rationale, we have prepared amines **3a** and **3b** in a stereospecific fashion (eq 2). This involved formation of the dibenzyliminium salts (**9**) from the corresponding ketones (**1**) and dibenzylamine by azeotropic removal of water, followed by reduction with $NaCNBH_3$. Strictly anhydrous conditions must be observed or substantial amounts of the corresponding 6-hydroxy compounds **5** and **6** are produced. The intermediates **10a,b** were then debenzylated to the desired products by catalytic hydrogenolysis. None of the 6α epimers (**4a,b**) could be detected, even when the reaction sequence was performed

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