Synthesis and Acylation of 2-Nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin

William K. Hagmann*, Laura A. O'Grady, Conrad P. Dorn and James P. Springer

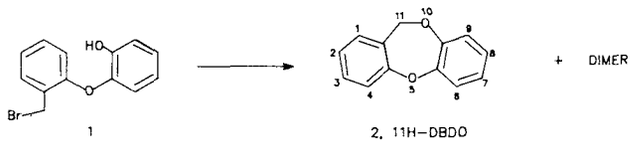
Merck Sharp and Dohme Research Laboratories,
Rahway, New Jersey 07065

Received October 1, 1985

A one-pot synthesis of the 11*H*-dibenzo[*b*,*e*][1,4]dioxepin ring system from catechol and an *o*-chlorobenzyl chloride is described. Friedel-Crafts acylation occurs at the 7-position as shown by X-ray analysis.

J. Heterocyclic Chem., **23**, 673 (1986).

The synthesis of aryl tricyclic compounds having two benzo groups fused around a central seven-membered ring has been important to the development of two classes of drugs, the antidepressants [1] and the non-steroidal antiinflammatory drugs (NSAIDS) [2]. Many heterocycles have appeared in the central ring. Substituted 11*H*-dibenzo-[*b*,*e*][1,4]dioxepins (11*H*-DBDO) were synthesized for use as antidepressants [3]. More recently, the 11*H*-DBDO ring system has appeared as the aromatic nucleus in aryl acetic acids with potent antiinflammatory activities [4]. A new

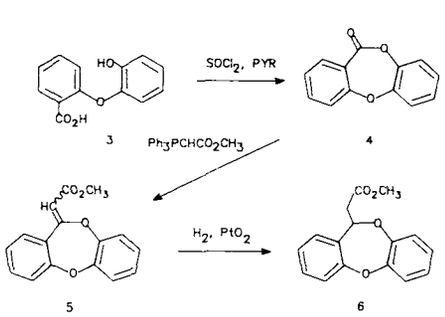


one-pot synthesis of this tricyclic system has been described. In this paper, we will examine the details of this new synthetic approach to the 11*H*-DBDO ring system as well as the selectivity of the acylation of the 2-nitro derivative.

The first preparation of the parent 11*H*-DBDO was described by Inubushi [5]. The final step to 11*H*-DBDO **2**, also known as depsidan, was the cyclization of 2-hydroxyphenyl-2'-bromomethylphenyl ether **1** in the presence of base. However, the major product of the reaction was a dimer; which was a result also obtained by other researchers [6].

There are many reports of the chemistry of 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-ones (11*H*-DBDO-11-one), commonly referred to as depsidones [7]. As shown in Scheme I, the cyclization of 2-(2-hydroxyphenoxy)benzoic acid **3** with thionyl chloride and pyridine gave

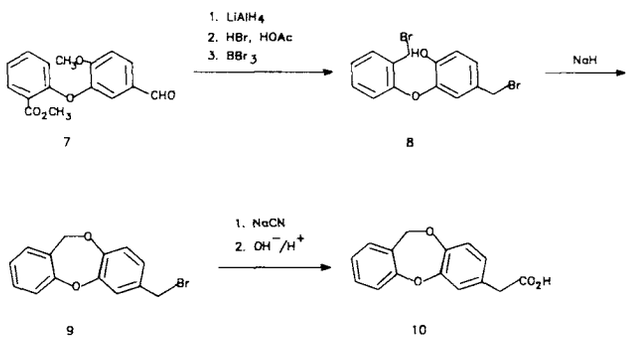
SCHEME I



11*H*-DBDO-11-one **4** in nearly quantitative yield [8]. (Carbomethoxymethylene)triphenylphosphorane was added to the carbonyl of **4** to give a mixture of double bond isomers **5**. These were subsequently reduced by catalytic hydrogenation to the 11-acetic ester **6** [3].

In our syntheses of other 11*H*-DBDO acetic acids [4], the initial preparation of the ring system paralleled that of Inubushi (Scheme II). For example, 4-methoxy-3-(2'-methoxycarbonyl)phenoxy-benzaldehyde **7**, prepared from

SCHEME II



the sodium salt of isovanillin and methyl 2-bromobenzoate, was reduced with lithium aluminum hydride. The resultant diol was converted to the corresponding dibromide with hydrogen bromide in glacial acetic acid, then demethylated with boron tribromide to give 2-hydroxy-5-bromomethylphenyl 2'-bromomethylphenyl ether **8**. A cold, dimethylformamide solution of **8** was treated with sodium hydride followed by slow warming to give 7-bromomethyl-11*H*-DBDO **9** in poor yield. The acetic acid **10** was prepared from **9** by reaction with cyanide followed by hydrolysis.

The synthetic strategy for the preparation of 11*H*-DBDO's has generally begun with the formation of the diaryl ether bond followed by ring closure of the benzylic ether bond to form the triyclic system (Figure 1, path

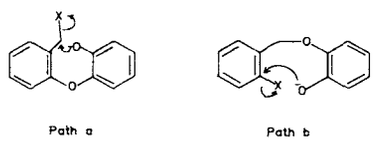
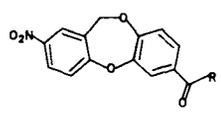


FIGURE 1 Synthetic Strategies for Cyclizations to 11H–DBDO

Table I

7-Acyl-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepins (15)



Compound	R	yield (%)	mp (°C)
15a	CH_3	43	155.5-156.5
15b	Ph	65	166-168
15c	2-Furyl	57	151-152
15d	$CH_3O_2C(CH_2)_2$	46	179-181

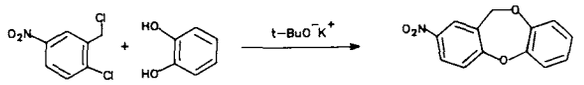
Table II

Fractional Coordinates for Atoms in **15a** [a]

Atom	X	Y	Z
C1	2961(13)	4017(2)	7052(3)
C2	2769(14)	4503(2)	7500(3)
C3	4123(16)	4524(2)	8235(3)
C4	5684(16)	4040(2)	8544(3)
C4A	5874(13)	3547(2)	8103(3)
O5	7671(10)	3090(1)	8426(2)
C5A	6338(13)	2529(2)	8437(3)
C6	7252(13)	2226(2)	9091(3)
C7	6260(13)	1654(2)	9184(3)
C8	4332(14)	1390(2)	8598(3)
C9	3425(14)	1692(2)	7947(3)
C9A	4405(13)	2260(2)	7846(3)
O10	3236(9)	2505(2)	7178(2)
C11	5025(14)	2999(2)	6898(3)
C11A	4574(13)	3528(2)	7356(3)
N12	1022(13)	5018(2)	7178(3)
O13	−75(13)	5008(2)	6522(2)
O14	763(15)	5439(2)	7589(3)
C15	7358(14)	1352(2)	9895(3)
O16	9096(11)	1594(2)	10395(2)
C17	6307(16)	7380(2)	9995(3)
H1	198(7)	401(1)	655(2)
H3	398(8)	486(1)	849(2)
H4	664(7)	404(1)	909(2)
H6	865(7)	243(1)	947(1)
H8	367(7)	100(1)	865(2)
H9	228(7)	151(1)	754(2)
H11A	407(8)	306(1)	639(2)
H11B	745(8)	390(1)	688(2)
H17A	723(8)	59(1)	1050(2)
H17B	712(8)	51(1)	960(2)
H17C	421(8)	66(1)	1001(2)

[a] The standard deviations of the least significant figures are given in parentheses. Values of non-hydrogen atoms are times 10^4 and for hydrogen atoms are times 10^3.

a). In our other approach, the benzylic ether bond was initially formed followed by cyclization *via* the diaryl ether (Figure 1, path b). This methodology was developed for the preparation of 11*H*-DBDO-7-acetates [4]. In the presence of two equivalents of potassium *t*-butoxide,

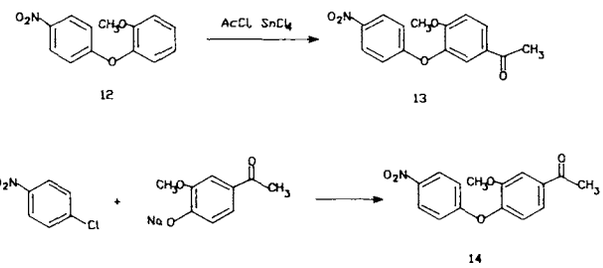


11

catechol reacted with 2-chloro-5-nitrobenzyl chloride to form 2-nitro-11*H*-DBDO **11**. The benzylic chloride is displaced first to form the benzylic ether. Additional base forms the second potassium salt which adds to the aromatic ring and, upon heating, subsequently displaces the aryl chloride. Despite only moderate yields for this particular reaction (28%), the overall yields and savings in chemical manipulations represent a significant improvement in the synthesis of this ring system.

The Friedel-Crafts acylation of **11** was expected to occur at the 7-position. The nitro group at the 2-position is strongly electron withdrawing and reduces the tendency for electrophilic substitution in that ring. The electron donating effects of alkyl ethers is greater than that of aryl ethers as shown in an analogous acyclic compound. The Friedel-Crafts acylation of 2-methoxyphenyl phenyl ether by acetyl chloride in the presence of aluminum chloride was reported to give substitution *para* to the methoxy group as well as *para* to the phenyl ether in the other aromatic ring [9].

SCHEME III

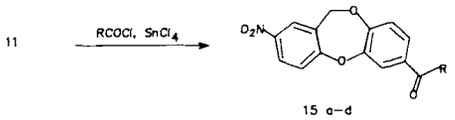


12 13

14

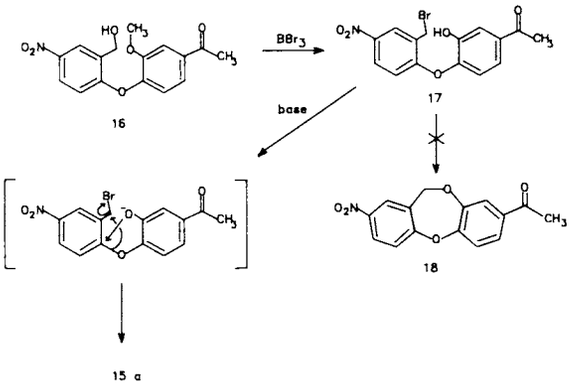
This selectivity was confirmed with the aromatic acylation of 2-methoxyphenyl 4-nitrophenyl ether **12** with acetyl chloride in the presence of stannic chloride to give **13** as the only characterizable product (Scheme III). The other isomer **14**, having the acetyl group *para* to the phenyl ether oxygen, was prepared from the sodium salt of acetovanillone and 4-chloronitrobenzene for comparison with **13**.

Acylation of **11** under the conditions described above gave a single characterizable product. Direct ^{1}H-nmr analysis of its structure was not straightforward. It was presumed to be 7-acetyl-2-nitro-11*H*-DBDO **15a**, yet there was still the possibility that the 8-acetyl had been formed.



15 a-d

SCHEME IV



Other acyl chlorides were reacted with **11** and the results are shown in Table I.

A sample of the 8-acetyl isomer **18** was needed for comparison with the 7-acetyl isomer **15a**. The sodium salt of acetovanillone was reacted with 2-chloro-5-nitrobenzyl alcohol to form diaryl ether **16**, which was subsequently demethylated with boron tribromide to form **17** (Scheme IV). Cyclization of **17** with sodium hydride gave the same product **15a** obtained by acylation of **11**! Either the presumption that the direction of acylation of **11** would follow that of the acyclic analog **12** was incorrect or the cyclization of the phenolic oxygen to the benzylic bromide of **17** was not direct.

Direct structural information as to the location of the acetyl group in **15a** was obtained by X-ray crystallography (Figure 2). The crystallographic analysis of **15a** confirmed

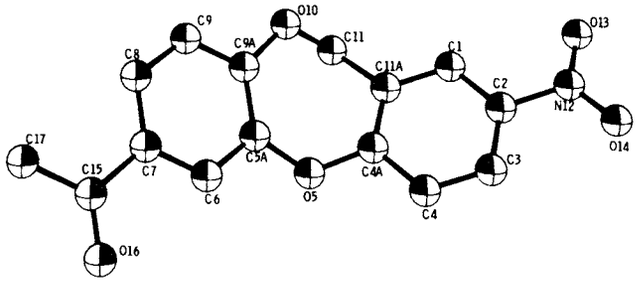


Figure 2. ORTEP Representation of the X-Ray Crystal Structure of **15a**.

that the acetyl group was indeed at the 7-position as predicted by the acyclic model (**12** → **13**). Therefore, the cyclization of **17** did not occur directly, but rather underwent a very mild Smiles rearrangement [11] to give the same isomer **15a**.

The inherent symmetry of the 11*H*-DBDO ring system introduces complexities into its synthesis. Subtle side reactions, such as the observed Smiles reaction, may go undetected. The one-pot synthesis provides for the unambiguous preparation of this ring system with a minimum of chemical manipulations. Subsequent acylation gives a single product substituted at the 7-position, providing a handle for further chemical elaboration.

Table III

Bond Distances and Bond Angles of **15a** [a]

Bond Distances (Angstroms)

C1	C2	1.378(7)	C7	C8	1.386(7)
C1	C11A	1.388(7)	C7	C15	1.477(7)
C2	C3	1.373(8)	C8	C9	1.373(7)
C2	N12	1.470(7)	C9	C9A	1.384(7)
C3	C4	1.372(8)	C9A	O10	1.361(6)
C4	C4A	1.385(7)	O10	C11	1.447(7)
C4A	O5	1.376(6)	C11	C11A	1.483(7)
C4A	C11A	1.384(7)	N12	O13	1.210(6)
O5	C5A	1.400(6)	N12	O14	1.223(7)
C5A	C6	1.377(7)	C15	O16	1.219(6)
C5A	C9A	1.397(7)	C15	C17	1.491(8)
C6	C7	1.392(7)			

Bond Angles (Degrees)

C2	C1	C11A	118.8(5)	C1	C2	C3	122.7(5)
C1	C2	N12	118.7(5)	C3	C2	N12	118.6(5)
C2	C3	C4	118.9(5)	C3	C4	C4A	119.0(5)
C4	C4A	O5	116.3(5)	C4	C4A	C11A	122.3(5)
O5	C4A	C11A	121.2(5)	C4A	O5	C5A	122.2(4)
O5	C5A	C6	113.8(4)	O5	C5A	C9A	126.0(4)
C6	C5A	C9A	120.1(5)	C5A	C6	C7	121.4(5)
C6	C7	C8	118.4(4)	C6	C7	C15	118.8(4)
C8	C7	C15	122.8(5)	C7	C8	C9	120.1(5)
C8	C9	C9A	122.2(5)	C5A	C9A	C9	117.9(4)
C5A	C9A	O10	126.9(4)	C9	C9A	O10	115.2(4)
C9A	O10	C11	118.7(4)	O10	C11	C11A	112.5(4)
C1	C11A	C4A	118.2(5)	C1	C11A	C11	121.9(4)
C4A	C11A	C11	119.8(4)	C2	N12	O13	118.9(5)
C2	N12	O14	118.1(5)	O13	N12	O14	123.0(5)
C7	C15	O16	121.3(5)	C7	C15	C17	118.9(5)
O16	C15	C17	119.9(5)				

[a] The standard deviations of the least significant figures are given in parentheses.

EXPERIMENTAL

General Procedures.

Melting points were determined on a Thomas-Hoover Melting Point Apparatus and are uncorrected. The ^{1}H-nmr spectra were obtained in deuteriochloroform with tetramethylsilane as internal standard on a Varian EM-390 spectrometer and are given in δ units. Infra-red spectra were obtained on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined on a LKB 9000 mass spectrometer. Analytical results were determined on a Control Equipment Elemental Analyzer 240X. Preparative hplc were performed on a Waters Prep LC-500 with Prep PAK 500 silica gel cartridges. X-ray diffraction experiments were carried out using a Enraf Nonius CAD-4 four circle diffractometer.

2-Nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**11**).

Catechol was reacted with potassium *t*-butoxide and 2-chloro-5-nitrobenzyl chloride according to the method described to give **11** [4]. Potassium *t*-butoxide (26.1 g, 0.23 mole) was added to an ice cooled solution of catechol (25.6 g, 0.23 mole) in dry dimethylformamide (200 ml). After stirring at 0° for 30 minutes, 2-chloro-5-nitrobenzyl chloride (47.8 g, 0.23 mole) was added and stirring continued at room temperature for 1 hour. Potassium *t*-butoxide (26.1 g, 0.23 mole) was added and stirring continued at room temperature for 1 hour. Dimethylformamide (500 ml) was added and the solution refluxed for 5 hours. After cooling to 0°, water (100 ml) was added and the mixture successively extracted with ethyl acetate/ether (1:1, 3 x 400 ml). The combined extracts were washed with water (5 x 700 ml) and brine (1 x 200 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation to give a thick black residue which was purified by rapid filtration through a silica gel pad eluted with 50% ether in hexanes. The filtrate was concentrated by rotoevaporation and the residue recrystallized from hot ethyl acetate in give **11** (14.2 g). The mother liquors were concentrated and purified by column chromatography on silica gel eluted with 7% ether in hexanes to give additional **11** (1.7 g). The product was obtained as a bright yellow solid (15.9 g, 28% yield, mp 127-128°); ^{1}H-nmr: 5.21 (2H, s), 6.76-7.33 (5H, m), 8.13 (1H, s), 8.20 (1H, dd, J = 11, 3 Hz); ir (thin film): 1620, 1580, 1520 cm^{-1}; ms: m/e 243.

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.19; H, 3.72; N, 5.75. Found: C, 64.03; H, 3.54; N, 5.46.

2-Methoxyphenyl 4'-Nitrophenyl Ether (**12**).

A solution of the sodium salt of guaiacol (1.46 g, 10 mmoles) and 4-chloronitrobenzene (1.57 g, 10 mmoles) in dimethylformamide (10 ml) containing fine copper metal (0.1 g) was refluxed for 8 hours. After cooling to room temperature, ether/ethyl acetate (1:1, 100 ml) was added and the mixture filtered. The filtrate was successively washed with water (3 x 25 ml), 1*N* sodium hydroxide solution (3 x 25 ml), and water (3 x 25 ml). The solution was dried over anhydrous magnesium sulfate and the solvent removed by rotoevaporation. The residue was recrystallized from ethyl acetate/hexanes to give **12** as an orange solid (2.0 g, 82% yield). An analytical sample was prepared as deep orange plates by recrystallization from methanol (mp 102-103°); ^{1}H-nmr: 3.76 (3H, s), 6.83 (2H, d, J = 9 Hz), 6.93-7.16 (4H, m), 8.08 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.53; N, 5.71. Found: C, 63.30; H, 4.45; N, 5.58.

5-Acetyl-2-methoxyphenyl 4'-Nitrophenyl Ether (**13**).

A solution of **12** (0.25 g, 1 mmole) in nitromethane (2 ml) was added to a solution of acetyl chloride (0.21 ml, 3 mmoles) and tin(IV) chloride (0.35 ml, 3 mmoles) in nitromethane (3 ml) at 0°. The solution was stirred at room temperature for 2 hours. Ethyl acetate (50 ml) was added and the solution washed successively with water (4 x 20 ml) and saturated salt solution (20 ml). After drying the solution over anhydrous magnesium sulfate, the solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with 50% ether in hexanes. The product was recrystallized from methanol to give **13** as pale orange needles (mp 125-126°); ^{1}H-nmr: 2.55 (3H, s), 3.86 (3H, s), 6.86 (2H, d, J = 9 Hz), 7.01 (1H, d, J = 8 Hz), 7.66 (1H, d, J = 2 Hz), 7.83 (1H, dd, J = 8, 2 Hz), 8.15 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.47; H, 4.59; N, 4.83.

4-Acetyl-2-methoxyphenyl 4'-Nitrophenyl Ether (**14**).

A solution of the sodium salt of acetovanillone (1.76 g, 10 mmoles) and 4-chloro-nitrobenzene (1.57 g, 10 mmoles) in dry dimethylformamide (10 ml) containing fine copper metal (0.1 g) was refluxed for 7 hours. After cooling to room temperature, ethyl acetate (50 ml) was added and the solution washed successively with water (3 x 20 ml), 1*N* sodium hydroxide solution (3 x 20 ml), water (3 x 20 ml), and saturated salt solution (20 ml). The solution was dried over anhydrous magnesium sulfate and the solvent removed by rotoevaporation. The residue was purified by column chromatography on silica gel eluted with 20% ethyl acetate in hexanes. The product was recrystallized from methanol as a pale orange solid (1.1 g, 38% yield, mp 104-105°); ^{1}H-nmr: 2.63 (3H, s), 3.83 (3H, s), 6.88 (2H, d, J = 9 Hz), 7.08 (1H, d, J = 8 Hz), 7.46 (1H, dd, J = 8, 1.5 Hz), 7.56 (1H, d, J = 1.5 Hz), 8.1 (2H, d, J = 9 Hz).

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.54; H, 4.53; N, 4.80.

General Procedure for the Acylation of 2-Nitro-11*H*-dibenzo[*b*,*e*][1,4]-dioxepin (**15**).

Typically, to a solution of acid chloride (1.2 mmoles) and tin(IV) chloride (1.2 mmoles) in dry nitromethane (1 ml) at 0° under dry nitrogen atmosphere was added **11** (1 mmole). The dark solution was stirred at room temperature overnight. Water was added and the mixture extracted with ethyl acetate (3 x 25 ml). The combined extracts were successively washed with water (3 x 20 ml) and saturated salt solution (1 x 20 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with ethyl acetate/hexanes. The product was recrystallized from hot ethyl acetate.

7-Acetyl-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**15a**).

Compound **15a** was prepared from acetyl chloride and **11** in 43% yield as described (mp 155.5-156.5°) [4].

7-Benzoyl-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**15b**).

Compound **15b** was prepared from benzoyl chloride and **11** in 65% yield (mp 166-168°); ^{1}H-nmr: 5.33 (2H, s), 7.00 (1H, d, J = 9 Hz), 7.20-7.85 (8H, m), 8.15 (1H, s), 8.20 (1H, d, J = 9 Hz); ir (thin film): 1655, 1605 cm^{-1}; ms: m/e 347, 270, 105.

Anal. Calcd. for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03. Found: C, 68.86; H, 3.79; N, 3.88.

7-(2-Furoyl)-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**15c**).

Compound **15c** was prepared from 2-furoyl chloride and **11** as off white needles in 57% yield (mp 151-152°); ^{1}H-nmr: 5.37 (2H, s), 6.60 (1H, dd, J = 3.6, 1.8 Hz), 7.03 (1H, d, J = 8.7 Hz), 7.23-7.43 (2H, m), 7.63-7.80 (2H, m), 7.93 (1H, d, J = 2.4 Hz), 8.20 (1H, s), 8.24 (1H, dd, J = 8.7, 2.7 Hz); ir (thin film) 1740, 1610, 1555 cm^{-1}; ms: m/e 337, 95.

Anal. Calcd. for $C_{18}H_{11}NO_6$: C, 64.09; H, 3.28; N, 4.15. Found: C, 64.13; H, 3.66; N, 4.30.

7-(3-Carbomethoxypropionyl)-2-nitro-11*H*-dibenzo[*b*,*e*][1,4]dioxepin (**15d**).

Compound **15d** was prepared from 3-carbomethoxy propionyl chloride and **11** in 46% yield (mp 179-181° [dec]); ^{1}H-nmr: 2.73 (2H, t, J = 7 Hz), 3.23 (2H, t, J = 7 Hz), 3.70 (3H, s), 5.26 (2H, s), 6.95 (1H, d, J = 8 Hz), 7.28 (1H, dd, J = 9, 1.5 Hz), 7.6 (1H, dd, J = 9, 1.5 Hz), 7.83 (1H, d, J = 1.5 Hz), 8.16 (1H, s), 8.25 (1H, dd, J = 9, 1.5 Hz); ir (thin film) 1730, 1675, 1602 cm^{-1}; ms: m/e 357, 326, 270.

Anal. Calcd. for $C_{18}H_{15}NO_7$: C, 60.50; H, 4.23; N, 3.92. Found: C, 60.26; H, 4.22; N, 3.96.

X-ray Diffraction Studies of **15a**.

Suitable crystals of **15a** for X-ray diffraction studies were formed from ether with space group symmetry of $P2_1/c$ with a = 3.953(1)Å, b = 23.100(4)Å, c = 17.683(6)Å and β = 93.94(3)° for Z = 4. Of the 2177 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1702 were observed ($I \geq 3\sigma I$). The structure was solved with a multi-solution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques [11]. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. A badly disordered molecule of ether was found in the crystal lattice which was modeled by thirteen atoms with occupancies of 0.25. The function $\Sigma\omega(|F_o|-|F_c|)^2$ with $\omega = 1/(\alpha F_o)^2$ was minimized to give an unweighted residual of 0.057. The atomic parameters are given in Tables II and III.

4-Acetyl-2-methoxyphenyl 2'-Hydroxymethyl-4'-nitrophenyl Ether (**16**).

Sodium hydride (60% oil dispersion, 8.4 g, 0.21 mole) was added to an ice cooled solution of acetovanillone (35 g, 0.21 mole) in dry dimethylformamide (200 ml) under a dry nitrogen atmosphere. After stirring at 0° for 30 minutes, 2-chloro-5-nitrobenzyl alcohol (37.5 g, 0.20 mole) was added. The solution was refluxed for 48 hours after which additional sodium salt of acetovanillone (5 g) was added. The solution was refluxed for an additional 24 hours, then cooled to room temperature. Water (100 ml) and ethyl acetate (500 ml) were added and the mixture was washed successively with water (3 x 100 ml), 2.5*N* sodium hydroxide solution (3 x 100 ml), water (3 x 100 ml), and saturated salt solution (100 ml). The solution was dried over anhydrous sodium sulfate, then filtered through a pad of silica gel (200 g) which was subsequently washed with fresh ethyl acetate (100 ml). The combined filtrates were rotoevaporated and the residue purified by preparative hplc eluted with 70% ether in hexanes. The product was recrystallized from ether/hexanes to give **16** as a yellow solid (10.1 g, 16% yield, mp 117-118.5°); ^{1}H-nmr: 2.61 (3H, s), 2.91 (H, br s, disappears upon addition of deuterium oxide), 3.81 (3H, s), 6.60 (1H, d, J = 9 Hz), 7.08 (1H, d, J = 8 Hz), 7.40-7.60 (2H, m), 7.93 (1H, dd, J = 9, 3 Hz), 8.31 (1H, d, J = 3 Hz); ir (thin film) 3400, 1680, 1585 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.72; H, 4.56; N, 4.88. Found: C, 62.54; H, 4.53; N, 4.80.

4-Acetyl-2-hydroxyphenyl 2'-Bromomethyl-4'-nitrophenyl Ether (**17**).

A 1.0*M* solution of boron tribromide in methylene chloride (110 ml) was slowly added to a stirred solution of **16** (8.9 g, 0.028 mole) in methylene chloride (100 ml) at −78°. The dark solution was stirred at −78° for 2 hours, then warmed to 0° for 2 hours. Water (30 ml) was cautiously added and the mixture extracted with ethyl acetate (300 ml). The mixture was successively washed with water (3 x 50 ml) and saturated salt solution (50 ml). The solvent was removed by rotoevaporation to give **17** as a dark oil which was used directly in the subsequent cyclization; ^{1}H-nmr: 2.55 (3H, s), 4.68 (2H, s), 6.61 (1H, d, J = 9 Hz), 6.68 (1H, d, J = 8 Hz), 7.38 (1H, dd, J = 8, 1.5 Hz), 7.53 (1H, d, J = 1.5 Hz), 7.93 (1H, dd, J = 9, 3 Hz), 8.2 (1H, d, J = 3 Hz); ir (thin film): 3050, 1680, 1585 cm^{-1}.

Cyclization of 4-Acetyl-2-hydroxyphenyl 2'-Bromomethyl-4'-nitrophenyl Ether **17**.

Sodium hydride (60% oil dispersion, 1.12 g, 28 mmoles) was added to a solution of **17** (~8 g, ~22 mmoles) in dry dimethylformamide (50 ml) at −60° under a dry nitrogen atmosphere. The solution was stirred at this temperature for 30 minutes, then slowly warmed to 0° over a one hour period and stirred at 0° for 2 hours. Water (30 ml) and ethyl acetate (300 ml) were added and the thick emulsion filtered through a pad of Celite which was subsequently washed with fresh ethyl acetate (100 ml). The combined filtrates were successively washed with water (3 x 100 ml) and saturated salt solution (100 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotoevaporation and the residue purified by column chromatography on silica gel eluted with 40% ether in hexanes to give **15a** (0.30 g, 4.8% yield) as the only characterizable product.

Acknowledgements.

The authors would like to acknowledge the contributions of the members of the Department of Analytical Chemistry for obtaining the chemical analyses and mass spectra.

REFERENCES AND NOTES

[1] C. Kaiser and P. E. Setler, in "Burger's Medicinal Chemistry", 4th Ed, Part III, M. E. Wolff, ed, John Wiley and Sons, Inc., New York, 1981, pp 1031-1081.

[2] T. Y. Shen, *idem.*, pp 1237-1241.

[3] C. Malen and J. -C. Poignant, French Patent 2,480,283 (1980); *Chem. Abstr.*, **96**, 142901a (1982).

[4] W. K. Hagmann, C. P. Dorn, R. F. Frankshun, L. A. O'Grady, P. J. Bailey, A. Rackham and H. W. Dougherty, *J. Med. Chem.*, in press.

[5] Y. J. Inubushi, *J. Pharm. Soc. Japan*, **72**, 1223 (1952); *Chem. Abstr.*, **47**, 12408 (1953).

[6] M. Tomita, T. Ujiie, and S. Tanaka, *Yakugaku Zasshi*, **80**, 358 (1960); *Chem. Abstr.*, **54**, 18432 (1960).

[7] C. E. Pawloski, in "Chemistry of Heterocyclic Compounds", Vol 26, A. Rosowsky, ed, Wiley-Interscience, New York, 1972, pp 357-69.

[8] D. S. Noyce and J. W. Weldon, *J. Am. Chem. Soc.*, **74**, 401 (1952).

[9] S. Kimoto and S. Kishi, *J. Pharm. Soc. Japan*, **73**, 509 (1953); *Chem. Abstr.*, **48**, 3355 (1954); M. Tomita, I. Keitmatsu, and T. Asada, *ibid.*, **68**, 156 (1948); *Chem. Abstr.*, **48**, 3920 (1954).

[10] W. E. Truce, E. M. Kreider, and W. W. Brand, in "Organic Reactions", Vol 18, Robert K. Kieger Publishing Co, Huntington, N. Y., 1978, Chapter 2, pp 99-215.

[11] The following library of crystallographic programs was used: MULTAN 80, P. Main *et al.*, University of York, York, England (1980); ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1970); SDP+V1.1, Y. Okaya *et al.*, B. A. Frenz and Associates, College Station, Texas (1984).