Studies on Simplified Ergoline Derivatives. A General Six-Step Synthesis of Phenyl-Substituted 4-Methyl-3,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-1-(2*H*)-one Analogs (1)

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This communication outlines the development of a novel, general synthetic route to substituted α-tetralones **5**, their subsequent conversion to the α,β-unsaturated ketones **11**, and an improved, one-step transformation of **11** to the tricyclic title compounds **1**. Thus, substituted derivatives of **1** can be prepared in six steps from simple benzaldehydes, or, in three steps from more readily available α-tetralones.

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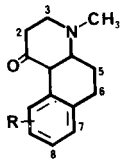
Introduction

As part of our studies on the structure-activity relationships of agents which interact with dopamine and serotonin receptors (*e.g.* see references 2 and 3), it becomes necessary to prepare a series of synthetic intermediates, *i.e.* phenyl-substituted 4-methyl-3,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-1(2*H*)-ones (**1**), which would be useful for the synthesis of molecular subfragments of (+)-lysergic acid diethylamide (LSD). The requisite tricyclic ring system has been prepared by a variety of synthetic routes (4-6); however, few of these methods readily lend themselves to the present requirements, which include a *trans* configuration of the ring junction at position 4a and 10b, sufficient generality to enable the incorporation of the desired phenyl substituents, overall simplicity and acceptable yields.



	R
a	7, 10-$(OCH_3)_2$
b	7, 10-$(OCH_3)_2$; 8-CH_3
c	H
d	7-OCH_3
e	8-OCH_3
f	9-OCH_3

1a-f

Horii, *et al* (7); have prepared **1c** in two steps from the corresponding α,β-unsaturated methyl ketone **11c**. Although an overall yield of only 11% was reported, the product exhibited a *trans* ring fusion; furthermore, the starting ketone **11c** appeared adaptable to the design of a general synthesis whereby phenyl-substituted analogs could be prepared from simple precursors.

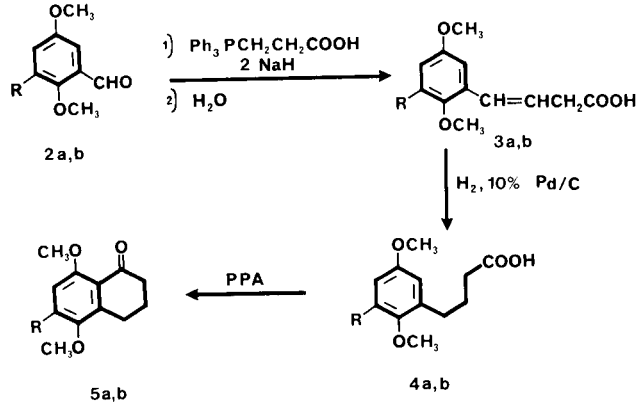
We now wish to report a general synthesis of substituted derivatives of **11**, *via* the tetralones **5**, as well as an improved, single-step transformation of **11** to the tricyclic products **1**.

Results and Discussion.

Synthesis of α-Tetralones **5**.

The choice of α-tetralones as precursors of **11** was made on the basis of the ready availability of several analogs (**5c-f**) from commercial sources. Furthermore, tetralones **5a** (8) and **5b** (9) have been previously reported, even though their literature preparations are lengthy and insufficiently general to suit our requirements. Consequently, a route was sought which might produce good yield of the tetralones from readily accessable precursors. Several potential routes were investigated. For example, the reaction of 1-ethoxy-1-(trimethylsilyloxy)cyclopropane with aromatic aldehydes in the presence of titanium tetrachloride has recently been reported to give 4-hydroxy-4-phenylbutyrate esters in good yield (10). Hydrogenolysis, followed by ester hydrolysis and cyclization, would result in the desired α-tetralone. However, in our hands, the chain homologation reaction failed, resulting in nearly quantitative recovery of the starting aldehyde.

The route which eventually proved successful is shown in Scheme I. Treatment of the benzaldehyde **2** and the appropriate Wittig reagent with two equivalents of base, followed by hydrolysis of the resulting betaine, gave 82-87% yields of the 4-phenyl-3-butenoic acids **3**. Catalytic hydrogenation of the crude isomeric mixtures of olefins **3** to the saturated acids **4**, followed by cyclization in polyphosphoric acid, afforded the desired α-tetralones **5**

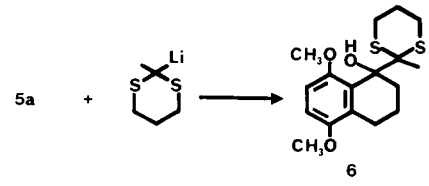


Scheme I

in good yield. Thus, the reaction sequence from aldehyde to tetralone consists of only three high-yielding steps, with only one intermediate being isolated and characterized.

Synthesis of 1-Acetyl-3,4-dihydronapthalenes **11**.

The conversion of the tetralone derivatives **5** to the unsaturated ketones **11** required that a masked, nucleophilic carbonyl equivalent attack the kentone carbonyl of the tetralone to give a tertiary benzylic alcohol, which could then be subjected to endocyclic dehydration. One such reagent which has been used extensively is the lithiated derivatives of a cyclic dithioacetal, such as the 1,3-dithianes (11).When tetralone **5a** was treated with 2-lithio-2-methyl-1,3-dithane as shown in Scheme II, the dithianyl adduct **6** was isolated in good yield. Dehydration, followed by hydrolysis to the ketone (or, alternatively, the reverse order of reactions) would be expected to give the unsaturated methyl ketone **11a**. Unfortunately, **6** proved unreactive to mild dehydration conditions, and decomposed under more stringent conditions. Similarly, all attempts to hydrolyze the dithiane ring using a variety of reagents and reaction conditions, resulted in decomposition. Since most of the dehydration or hydrolytic reagents which induced decomposition were either proton or Lewis acids, it was apparent that the acid sensitivity of **6** precluded its use as an intermediate.



Scheme II

Table I

Physical and Analytical Data for 4-Methyl-3,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-1(2*H*)-ones

Compound	Yield % (a)	Mp °C, Recrystallization Solvent (b)	Reaction Time (hours)	Formula	Analyses % Calcd./Found C	H	N
1a	67 (45)	223-225(c)/E	10	$C_{16}H_{21}NO_3 \cdot HCl$	61.63	7.11	4.49
					61.70	7.15	4.45
1b	22 (67)	83-85/P	6	$C_{17}H_{23}NO_3 \cdot$	68.08	8.18	4.09
				3/5EtOAc (d)	68.23	8.34	3.71
1c	78 (35)	86-89(e)/H	10	$C_{14}H_{17}NO$			
1d	54 (43)	86-88/H	6	$C_{15}H_{19}NO_2$	73.44	7.81	5.71
					73.25	7.85	5.67
1e	20 (44)	84-87/H	3	$C_{15}H_{19}NO_2$	73.44	7.81	5.71
					73.31	7.88	5.69
1f	51 (45)	90-92/H	6	$C_{15}H_{19}NO_2$	73.44	7.81	5.71
					73.48	7.82	5.70

(a) Yield based on unrecovered starting material, followed by % recovered starting material, in parenthesis. (b) E = ethanol/ethyl ether; P = petroleum ether, bp 40-60°; H = hexane. (c) Hydrochloride salt; free base is an oil. (d) Compound **1a** (free base), like **1b**, analyzed correctly with a partial mole of solvent (ethyl acetate); whereas **1a** could be converted to a hydrochloride salt, contact of **1b** with hydrochloric or oxalic acid resulted in decomposition. Results of high resolution mass spectrum for **1b** are as follows: M^+ (for $C_{17}H_{23}NO_3$), calcd. mass = 289.1677; determined mass 289.1675. (e) Literature (7) mp 89-90°.

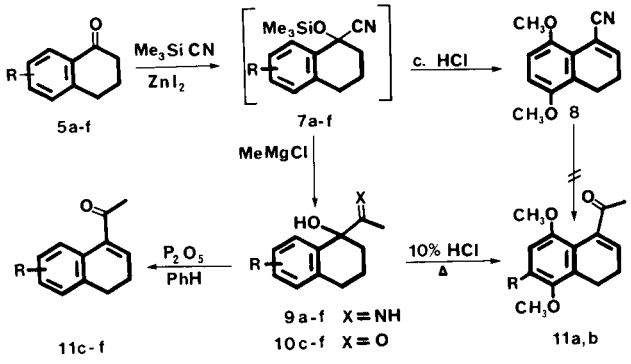
Table II

Proton Magnetic Resonance Data for Derivatives of **1** (a)

Compound	N-CH_3	(C_2-C_5)H	(C_6)H	Aromatics	(C_{10a})H
1a	2.55 (s)	2.20-3.38 (m, 7H)	1.50-1.95 (m, 2H)	3.63 (s, 3H, OCH_3)	4.15 (d)
				3.72 (s, 3H, OCH_3)	
				6.63 (s, 2H)	
1b	2.60 (s)		1.65-3.34 (m, 9H)	2.28 (s, 3H, CH_3)	4.15 (d)
				3.63 (s, 3H, OCH_3)	
				3.68 (s, 3H, OCH_3)	
				6.52 (s, 1H)	
1c	2.43 (s)		1.65-3.15 (m, 9H)	6.75-7.20 (m, 4H)	3.75 (d)
1d	2.42 (s)	2.25-3.15 (m, 7H)	1.65-2.10 (m, 2H)	3.80 (s, 3H, OCH_3)	3.75 (d)
				6.42-7.15 (m, 3H)	
1e	2.45 (s)	2.25-3.20 (m, 7H)	1.60-2.05 (m, 2H)	3.73 (s, 3H, OCH_3)	3.58-3.80 (m)
				6.50-6.88 (m, 3H)	
1f	2.41 (s)	2.28-3.20 (m, 7H)	1.58-2.05 (m, 2H)	3.68 (s, 3H, OCH_3)	3.55-3.85 (m)
				6.37-7.15 (m, 3H)	

(a) Solvent = (deuteriochloroform).

Another nucleophilic carbonyl equivalent which could be useful is cyanide ion. Thus, dehydration of the appropriate cyanohydrin adduct of **5**, followed by conversion of the nitrile to a methylketone *via* an organometallic reagent, should result in formation of the unsaturated ketones **11**. Although the cyanohydrin adducts of α-tetralones are unstable (12), this problem may be circumvented by formation of the silyl ether derivatives **7** through treatment of the tetralone with trimethylsilylcyanide in the presence of zinc iodide (13) as shown in Scheme III. Treatment of **7a** with concentrated hydrochloric acid brought about dehydration to the α,β-unsaturated nitrile **8**. However, reaction of **8** with methylmagnesium halides afforded none of the expected **11a** upon hydrolysis; the ir spectrum of the crude product exhibited weak absorption at 2230 cm^{-1}, characteristic of an unconjugated nitrile and indicative of 1,4-addition of the Grignard reagent to the endocyclic double bond. Alternatively, when **8** was allowed to react with methyl lithium, extensive decomposition was observed, with no formation of **11a**.

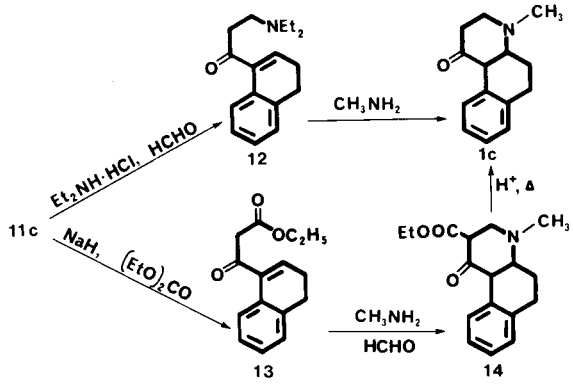


Scheme III

If, on the other hand, the silylcyanohydrins **7** were treated *in situ* with a methylmagnesium halide, followed by hydrolysis with 10% aqueous hydrochloric acid, the α-hydroxy imines **9** were formed. For compounds **9c-f**, the imines were not isolated, but underwent hydrolysis directly to the acyloins **10**; dehydration by phosphorus pentoxide in refluxing benzene gave good yields of the unsaturated ketones **11c-f**. An exception was noted in the case of the 6-methoxy analog. Here, the acyloin adduct **10e** underwent spontaneous dehydration under the condition of hydrolysis to give the unsaturated compound **11e** directly. The intermediate imines **9a** and **9b** proved to be unusually stable; no significant hydrolysis was observed in 10% aqueous hydrochloric acid at room temperature even after several hours. However, refluxing in 10% aqueous hydrochloric acid for several hours resulted not only in hydrolysis, but also in dehydration to the desired ketones **11a** and **11b** as well.

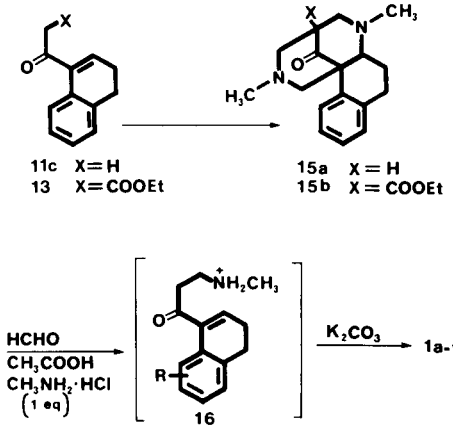
Formation of the Tricyclic Products **1**.

The two-step reaction sequence employed by Horii, *et al* (7), for the preparation of **1c** is represented in Scheme IV. Displacement of the tertiary amine from the initially formed Mannich base **12** by methylamine, followed by internal Micheal addition to the conjugated double bond, brings about formation of the third ring of **1c**. In later communication (6), the Mannich reaction and ring closure were accomplished in one step; however, **11c** was first converted to the β-keto ester **13**. The resultant tricyclic compound **14** was then decarboxylated to give **1c**. Although the reported yields were quite poor in both instances, the tricyclic products **1c** and **14** were shown to have formed exclusively *trans* at the 4a,10b ring juncture. Thus, the possiblity of carrying out a one-step ring closure of **11**, using the reaction conditions reported for the formation of **14**, appeared reasonable.



Scheme IV

It had been reported that when equimolar amounts of **13**, formaldehyde, and methylamine were allowed to react in aqueous ethanol, the tetracyclic compound **15b** was isolated as the predominant product, whereas a three-fold excess of aldehyde and amine gave exclusively the ex-



Scheme V

pected **14** (6); Scheme V. Attempted conversion of **11c** to **1c**, using either of the above conditions, resulted in the exclusive formaton of **15a**. Because **15** is presumably formed after conjugate attack of the initial Mannich base on the double bond, and, before protonation can occur, by reaction with another molecule of the iminium ion $CH_2\overset{+}{N}HCH_3$, it would be expected that any excess of formaldehyde and methylamine, as well as a *p*H near neutrality, would favor the tetracyclic products **15**. Conversely, equimolar amounts of all reactants, as well as an acidic reaction medium (which could "trap" the initial Mannich product as its salt **16** until any excess iminum ion is removed during work-up) might favor formation of the desired tricyclic compounds **1**. Indeed, when the Mannich reaction was carried out in a glacial acetic acid with equivalent amounts of **11**, formaldehyde and methylamine hydrochloride, **1a-f** (Table I) were isolated, for the most part, in good yield, with little or no formation of the tetracyclic compounds. Two exceptions were noted: compounds **11b** and **11e** underwent extensive decomposition under standard reaction conditions, such that very low yields of **1b** and **1e** were obtained. This result may de due to the electron-donating substituents on the phenyl ring being *para* to the ketone carbonyl group which augments the latter's acid lability. Nonetheless, the reaction provides a convenient, one step transformation of the unsaturated ketones **11** to the heterotricyclic compounds **1**.

The entire synthesis of **1a-f** from simple benzaldehyde precursors required only six steps. More importantly, the preparation is sufficiently general that it should find utility in the synthesis of other desired phenyl-substituted analogs, the only limitation being the sensitivity of the substituents to the reaction conditions.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained on Beckman Acculab 8 or Perkin-Elmer 710B grating spectrophotometers; ^{1}H-nmr spectra were recorded on Hitachi Perkin-Elmer R-24 or Varian EM360A 60 MHz instruments. Mass spectra were determined on a Finnigan 4015 gas chromatograph/mass spectrometer at 70 eV. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta GA.

Column chromatography was carried out using 70-230 mesh Merck silica gel 60. Trimethylsilylcyanide (Silar Laboratories) was distilled before use; all other reagents were used as received.

A solution of 2,5-dimethoxybenzaldehyde (**2a**) (3.58 g, 21.5 mmoles) and 2-carboxyethylphosphonium chloride (14) (8 g, 21.5 mmoles) in a 1:1 mixture of THF/DMSO (50 ml) was added in one portion to dry (99%) sodium hydride (1.05 g, 43.7 mmoles) at 0° under an atmosphere of dry nitrogen. The resulting suspension was then stirred at room temperature for 15 hours. After cooling the dark red mixture to 0°, water (100 ml) was added. The solution was washed with ether (3 × 100 ml), acidified to ~ *p*H 2 with concentrated hydrochloric acid, and extracted with ether (2 × 100 ml). The combined ether extracts were washed with water (5 × 200 ml), dried (magnesium sulfate) and evaporated to a gummy yellow solid. Trituration with anhydrous ether gave 3.99 g (82%) of 4-(2,5-dimethoxyphenyl)-3-butenoic acid (**3a**) as yellow crystals, mp 102-108°; ir (melt): 1710 (acid C=O), 1490 cm^{-1} (ether C-O); nmr (deuteriochloroform): δ 3.15 (d, 2, CH=CH-CH_2); 3.75 (s, 6, OCH_3), 6.0-7.0 (m, 5, Ar-H and Ar-CH=CH), 9.85 (s, 1, COOH). A solution of **3a** (1g, 4.46 mmoles) in absolute ethanol (70 ml) was shaken with 10% palladium on charcoal (0.15 g) for 20 minutes under an atmosphere of hydrogen on a Parr hydrogenator. The solution was then filtered and the filtrate evaported to give 0.92 g (91%) of **4a** as a white solid, mp 62-64°, lit (15) mp 65.5°.

4-(2,5-Dimethoxy-3-methylphenyl)butanoic Acid (**4b**).

The intermediate alkene 4-(2,5-dimethoxy-3-methylphenyl)-3-butenoic acid (**3b**) was prepared from the appropriate benzaldehyde derivative **2b** (16) using the same procedure described in the preparation of **3a** to give 87% of **3b** as a visous orange oil; ir (neat): 1710 (C=O), 1480 cm^{-1} (ether C-O); nmr (deuteriochloroform): δ 2.10 (s, 3, $ArCH_3$), 3.10-3.45 (m, 2, CH=CH-CH_2), 3.60 (d, 6, OCH_3), 6.40-6.85 (m, 4, ArH and ArCH=CH), 10.40 (s, 1, COOH). Catalytic hydrogenation of crude **3b** was carried out as for **3a** to give 77% of the saturated acid **4b** as white crystals from hexane, mp 38.5-40°, lit (9) mp 39.5-40.5°.

5,8-Dimethoxy-1-tetralone (**5a**).

A mixture of **4a** (3.0 g, 13.26 mmoles) and polyphosphoric acid (50 g) was stirred for 30 minutes at 85°. The dark mixture was then poured onto cracked ice (200 g) and water (50 ml) and extracted with ether (3 × 150 ml). The combined extracts were washed with 5% aqueous sodium bicarbonate (200 ml) and water (200 ml), dried (sodium sulfate/magnesium sulfate) and evaporated to give a dark red oil. Vacuum distillation afforded 2.0 g (72%) of **5a** as a pale yellow liquid, bp 120-125°/0.1 mm, which crystallized to a yellow solid, mp 59-61°, lit (8) mp 58-62°.

5,8 Dimethoxy-6-methyl-1-tetralone (**5b**).

This compound was prepared form **4b** according to the same procedure as **5a** to give 87% of **5b** as a viscous yellow oil, by 119-122° 0.05 mm; lit (9) bp 149-150°/0.1 mm.

1-Hydroxy-1-2-(2-methyl)-1,3-dithianyl-5,8-dimethoxy-1,2,3,4-tetrahydronapthalene (**6**).

A hexane solution of *n*-butyllithium (3.5 ml, 5.25 mmoles) was added dropwise over a 5 minute period to a solution of 2-methyl-1,3-dithiane (17) (0.7 g, 5.2 mmoles) in THF (10 ml) at -38°, and the resulting clear solution stirred at that temperature for 1,5 hours. The solution was then cooled to -78° and a solution of **5a** (1.0 g, 5 mmoles) in THF (5 ml) was added dropwise over a 5 minute period. Stirring was continued at -78° for 3 hours; the solution was warmed to 0° and water (10 ml) was added. The organic solvents were evaporated and the aqueous residue was extracted with dichloromethane (3 × 10 ml). The combined extracts were washed with 8% sodium hydroxide (15 ml) and water (15 ml), dried and evaporated to give a white solid. Recrystallization from petroleum ether (bp 60-70°) gave 1.3 g (76%) of **6** as white needles, mp 112-114°; ir (chloroform): 3225 (O-H), 1460 cm^{-1} (ether C-O); nmr (deuteriochloroform): δ 1.50-3.50 (m, 15, aliphatic CH), 3.85 (d, 6, OCH_3), 6.03 (s, 1, OH), 6.73 (s, 2, - ArH).

Anal. Calcd. for $C_{17}H_{24}O_3S_2$: C, 59.97; H, 7.10; S, 18.83. Found: C, 59.99; H, 7.12; S, 18.79.

1-Cyano-5,8-dimethoxy-3,4-dihydronapthalene (**8**).

A solution of **5a** (0.104 g, 0.5 mmoles),trimethylsilylcycanide (0.055 g, 0.55 mmoles), and several crystals of zinc iodide in chloroform (5 ml) was refluxed for 2 hours. Upon cooling, the solvent was evaporated, and concentrated hydrochloric acid (2 ml) was added. The stirred mixture was heated at 80° for 2 hours, cooled, and ether (10 ml) was added. The layers were separated and the aqueous phase was extracted with ether (2 × 5 ml). The combined organic portions were washed with water (10 ml), dried (magnesium sulfate), and evaporated to give a white solid.

Recrystallization from 95% ethanol yielded 0.07 g (64%) of **8** as white needles, mp 77-80°, lit (8) mp 85-86°.

1-Hydroxy-1-acetyl-1,2,3,4,-tetrahydronapthalene (**10c**).

To a solution of **5c** (0.83 g, 5.67 mmoles) and zinc iodide (5 mg) in benzene (1 ml, distilled from calcium hydride) was added the trimethylsilylcyanide (0.62 g, 6.24 mmoles) all at once under an atmosphere of nitrogen. The stirred mixture was maintained at 50° for 2 hours, cooled to room temperature and an additional 5 ml benzene was added, followed by a solution of methylmagnesium chloride in THF (4.05 ml of a 2.8 *M* solution, 11.25 mmoles). The stirred mixture was heated at reflux for 18 hours, cooled to room temperature, and 10% aqueous hydrochloric acid (10 ml) was slowly added. The mixture was stirred for 1 hour, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic portions were washed with 5% aqueous sodium bicarbonate (10 ml) and water (10 ml), dried (magnesium sulfate) and evaporated to give a yellow oil. Distillation afforded 0.61 g (56%) of **10c** as a colorless liquid, bp 84-88°/0.025 mm; ir (neat): 3455 (O-H), 1710 cm^{-1} (C=O); nmr (deuteriochloroform); δ 1.70-2.05 (m, 4, CH_2CH_2), 2.00 (s, 3, -$COCH_3$), 2.69-2.98 (m, 2, Ar-CH_2), 4.55 (s, 1, OH), 6.74-7.25 (m, 4, ArH).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.62; H, 7.48.

5-Methoxy-1-hydroxy-1-acetyl-1,2,3,4-tetrahydronapthalene (**10d**).

This compound was prepared from tetralone **5d** by the same method as **10c** to give, after recrystallization from hexane, 62% of **10d** as white prisms mp 53-55°; ir (potassium bromide): 3410 (O-H), 1715 cm^{-1} (C=O). nmr (deuteriochloroform); δ 1.80-2.17 (m, 4, CH_2CH_2), 2.00 (s, 3, $COCH_3$), 2.40-3.25 (m, 2, $ArCH_2$), 3.83 (s, 3, OCH_3), 4.55 (s, 1, OH), 6.40-7.38 (m, 3, ArH).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.93; H, 7.36.

7-Methoxy-1-hydroxy-1-acetyl-1,2,3,4-tetrahydronapthalene (**10f**).

This compound was prepared from tetralone **5f** by the same method as **10c** to give, after distillation, 54% of **10f** as a pale yellow oil, bp 120-123°/0.43 mm; ir (neat): 3460 (O-H); 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.80-2.03 (m, 4, CH_2CH_2), 2.04 (s, 3, $COCH_3$), 2.63-2.92 (m, 2, $ArCH_2$), 3.68 (s, 3, OCH_3), 4.56 (s, 1, OH), 6.36-7.30 (m, 3, ArH).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.70; H, 7.36.

1-Acetyl-3,4-dihyronapthalene (**11c**).

To a solution of **10c** (6.3 g, 33.1 mmoles) in dry benzene (100 ml) was added phosphorous pentoxide (6.3 g, 44.4 mmoles). The stirred mixture was heated at reflux for 20 minutes, then cooled to room temperature. The clear benzene solution was decanted, and the black gummy residue was thoroughly washed with benzene (3 × 25 ml). The combined benzene portions were evaporated to afford a yellow oil. Distillation gave 5.20 g (91%) of **11c** as a colorless liquid, bp 93-96°/0.025 mm, lit (18) bp 108-109°/0.9 mm.

1-Acetyl-5-methoxy-3,4-dihydronapthalene (**11d**).

Dehydration was accomplished using the procedure described for **11c**, starting with the appropriate acyloin **10d**. Recrystallization from hexane gave 68% of **11d** as pale yellow flakes, mp 82-84°C; ir (neat, before crystallization): 1675 cm^{-1} (C=O); nmr (deuteriochlorofrom) δ 2.15-2.95 (m, 4, $ArCH_2CH_2$), 2.40 (s, 3, $COCH_3$), 3.78 (s, 3, OCH_3), 6.70-7.32 (m, 4, ArH and C=CH).

Anal. Calcd. For $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.09; H, 6.99.

1-Acetyl-7-methoxy-3,4-dihydronapthalene (**11f**).

Prepared from **10f** by the procedure described for **11c** to give, after distillation, 82% of **11f** as a pale yellow liquid, bp 112-114°/0.01 mm. ir (neat): 1675 cm^{-1} (C=O); (deuteriochloroform): δ 2.05-2.80 (m, 4, $ArCH_2$-CH_2), 2.42 (s, 3, $COCH_3$), 3.78 (s, 3, OCH_3), 6.60-7.45 (m, 4, ArH and C=CH).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.07; H, 7.02.

1-Acetyl-6-methoxy-3,4-dihydronapthalene (**11e**).

This compound was isolated directly from the Grignard reaction of **5e**, following hydrolysis of the imine **9e**. Recrystallization from hexane afforded a 61% overall yield of **11e** from **5e**, mp 76-78°; ir (neat, before crystallization): 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.10-2.85 (m, 4, $ArCH_2CH_2$), 2.45 (s, 3, $COCH_3$), 3.77 (s, 3, OCH_3), 6.59-6.95 (m, 3, ArH and C=CH), 7.56-7.80 (m, 1, ArH).

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 6.99.

1-Acetyl-5,8-dimethoxy-3,4-dihydronapthalene (**11a**).

Tetralone **5a** was subjected to the reaction conditions described for **10c**; however, the organic portion of the acid hydrolysis mixture contained no significant amount of product. A small portion of the aqueous layer (A) was neutralized (potassium carbonate); and the oil which separated was taken up in ether, washed with brine, dried (magnesium sulfate) and evaporated to afford a yellowish solid. Recrystallization from ethyl acetate gave the imine **9a** as white plates, mp 158-160; ir (chloroform): 3530 (O-H, N-H), 1650 cm^{-1} (C=N); nmr (deuteriochloroform): δ 1.65-3.20 (m, 11, CH_2, OH, NH); 3.72 (s, 3, OCH_3), 3.80 (s, 3, OCH_3); 6.72 (s, 2, ArH); Ms: m/e 249 (M^+), 207 (M^+ -C_2H_4N).

Anal. Calcd. for $C_{14}H_{19}NO_3 \cdot \frac{1}{4}$ EtOAc: C, 66.40; H, 7.80; N, 5.16. Found: C, 66.11; H, 7.75; N, 5.57.

The acidic, aqueous portion (A) was stirred and heated at reflux for 3 hours, causing a yellow oil to separate. The cooled mixture was thrice extracted with ethyl acetate, the combined extracts washed once with saturated aqueous sodium bicarbonate, once with water, dried magnesium sulfate) and evaporated to give a yellow oil which crystallized. Recrystallization from petroleum ether (bp 40-60°) afforded **11a** in 53% overall yield from **5a** as white prisms, mp 75-76.5°; ir (potassium bromide): 1690 cm^{-1} (C=O); nmr (deuteriochloroform); δ 2.21 (s, 3, $COCH_3$), 2.30 (t, 2, $ArCH_2$), 2.60-2.90 (m, 2, $ArCH_2CH_2$), 3.70 (s, 3, OCH_3), 3.80 (s, 3, OCH_3); 6.42 (t, 1, C=CH); 6.77 (s, 2, ArH).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.34; H, 6.94.

1-Acetyl-6-methyl-5,8-dimethoxy-3,4-dihydronapthalene (**11b**).

This compound was prepared by the same reaction as the described for **11a**, although the intermediate imine **9b** was not isolated and characterized. The crude product was purified by column chromatography, eluting **11b** with chloroform as a pale yellow oil in an overall yield of 62% from **5b**; ir (neat): 1690 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.12-2.45 (m, 2, $ArCH_2CH_2$), 2.20 (s, 3, $COCH_3$), 2.27 (s, 3, $ArCH_3$), 2.55-2.92 (m, 2, $ArCH_2$), 3.60 (s, 3, OCH_3), 3.68 (s, 3, OCH_3) 6.32 (t, 1, C=CH), 6.55 (s, 1, ArH).

Anal. Calcd. for $C_{15}H_{18}O_3 \cdot \frac{1}{4}H_2O$: C, 71.83; H, 7.43. Found: C, 71.88; H, 7.69.

13-Oxo-2,6-dimethyl-2,3,4,5,6,6a,7,8-octahydro-4,12b-methano-1*H*-napthо[2,1-*b*][1,5]diazocine (**15a**).

A stirred solution of **11c** (0.25 g, 1.3 mmoles) and methylamine hydrochloride (0.26 g, 4.9 mmoles) in aqueous formaldehyde (37%, 2 ml) and ethanol (2 ml) was heated overnight on a steam bath. Upon cooling, the solution was washed with ether (2 × 10 ml), and 5% aqueous sodium bicarbonate (10ml) was added. The solution was extracted with ether (2 × 10 ml); the combined extracts were washed with water (10 ml), dried (magnesium sulfate) and evaporated to give a yellow oil. Kugelrohr distillation afforded 0.25 g (71%) of a viscous yellow syrup which crystallized to a yellowish solid, mp 114-116°; ir (neat): 1720 cm^{-1} (C=O); nmr (deuteriochlorofrom): δ 1.80-3.70 (complex m, 18, singlets at 2.35 and 2.47), 7.05-7.40 (m, 4, ArH).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.51; H, 8.18; N, 10.36. Found: C, 75.45; H, 8.21; N, 10.33.

Preparation of Heterotricyclic Compounds **1**.

The general reaction procedure may be illustrated as follows: Methylamine hydrochloride (1 mmole) dissolved in 37% aqueous formaldehyde solution (1 mmole) was added in one portion to a solution of **11** (1 mmole) in glacial acetic acid (1.5 ml). The stirred solution was heated

(see reaction time, Table I) at 120° for 6-10 hours, cooled to room temperature and diluted with water (3 ml). The solution was saturated with solid potassium carbonate and the resulting oily suspension heated on a steam bath for 1 hour, extracted with ethyl acetate, dried (magnesium sulfate) and evaporated to an oil. The oil was dissolved in a minimal amount of chloroform and applied to a column packed with silica gel (30 g). Elution with a gradient from chloroform to 10% methanol in chloroform gave unreacted **11** in the initial fractions, followed by **1**. Evaporation of the solvent and recrystallization gave pure **1**. (see Tables I and II).

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