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Synthesis and Pharmacology of Some 2-Aminotetralins. Dopamine Receptor Agonists†

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A series of 2-amino-1,2,3,4-tetrahydronaphthalene compounds bearing substituents on the nitrogen and in the aromatic ring was synthesized from β-tetralone intermediates. Compounds were screened *in vivo* for dopaminergic activity using tests in which apomorphine was especially active. It was found that apparent dopaminergic activity is inherent in 2-dialkylaminotetralins, the dipropylamine substitution being the most consistently productive amine group studied. Activity was greatly enhanced by proper substitution in the aromatic ring. The 5,6-dihydroxy group was the best potentiating group found. These data support the idea that the extended conformation for the phenylethylamine moiety of ampmorphine and dopamine is favorable for dopaminergic agonist activity. They also suggest that an unetherified catechol group may not be essential for such activity.

The report[1] of the marked anti-Parkinson activity of apomorphine (APM) has encouraged research in the development of drugs which mimic this agent. It is currently believed that APM is a dopaminergic agonist and presumably it is through this mechanism that this agent is effective clinically. Unfortunately, APM has a relatively short duration of action and is a particularly powerful emetic in man. Hence, it would be desirable to discover longer acting, nonemetic dopaminergic agonists.

By inspection of the structure of APM and dopamine, the 2-aminotetralins suggest themselves as candidates for possession of dopaminergic activity. This relationship has been noted by Cannon and coworkers[2,3] as the rationale for synthesis of some 5,6-dioxy-2-aminotetralins, and, indeed, agonist activity was found. We have expanded considerably this series of compounds by various substitutions on the nitrogen and the aromatic ring and have examined more fully the recent conclusion[4] that the emetic pharmacophore of APM necessarily includes an unetherified catechol group. It will be shown below that this requirement does not necessarily hold for properly modified fragments of APM, a finding which has significance in the characterization of central dopamine receptors.

Chemistry. Several general routes to 2-amino-5,6-dioxytetralins can be envisioned. The use of 5,6-dimethoxy-2-amino-1-tetralone as an intermediate has been reported.[3] For simplicity of introduction of as wide as possible a variety of amino groups into the 2 position we hoped that the β-tetralone **4** would offer greater versatility as an intermediate. Its synthesis had not been reported, but it was obtained easily from the known 1,2,6-trimethoxynaphthalene **3**. Our synthesis is shown in Scheme I. This route to **3** is somewhat shorter than the other pertinent schemes[5,6] which have been used.

The use of Fremy's radical for the oxidation of **1** to **2** gave very unpredictable results in the phosphate buffers employed by Teuber and Gotz[7] for this reagent. From our study of this reaction we have concluded that the pH must be controlled to the range 4.0–4.5 (litmus). For this purpose a phthalate buffer was effective. At lower pH the oxidation slowed and the radical decomposed rapidly. At higher pH a faster reaction occurred, but pure **2** could not be obtained from the complex products.

The trihydroxynaphthalene formed by reduction of **2** was very sensitive to air oxidation in solution, so the reduction–methylation of **2** to **3** was performed without isolation of this intermediate. Reduction of **3** to **4** was done by the method of Robinson and coworkers.[8] An identical route was used for 5,8-dimethoxy-2-tetralone and 7,8-dimethoxy-2-tetralone starting from 1,6-dihydroxynaphthalene and 2,7-dihydroxynaphthalene, respectively. Other 2-tetralones were available commercially or were made from commercial 2-methoxynaphthalenes.

These 2-tetralones proved convenient as intermediates and were used for reductive alkylation of primary amines by standard methods.[9] The less reactive secondary amines required forcing dehydration to intermediate enamines, which were subsequently reduced to the tertiary amines **6**. For introduction of secondary amines not commercially available, secondary amines **5** were alkylated by simple methods. Cleavage of the ether groups was generally successful using HI–acetic acid. Difficulty was frequently encountered in purifying the resulting hydroiodides, so these were converted to HCl salts, which were easier to obtain as colorless, crystalline solids.

An additional structural variation which at one point we decided to pursue was the homologation of one of the hydroxy groups in **7**, preferably the 5-hydroxy group. This attempt was prompted by persistent emesis in the tetralins, which we attributed initially to the presence of the catechol function. To this end we devised Scheme II.

In order to secure placement of the hydroxymethyl group in the 5 position rather than the 7 position, it was necessary

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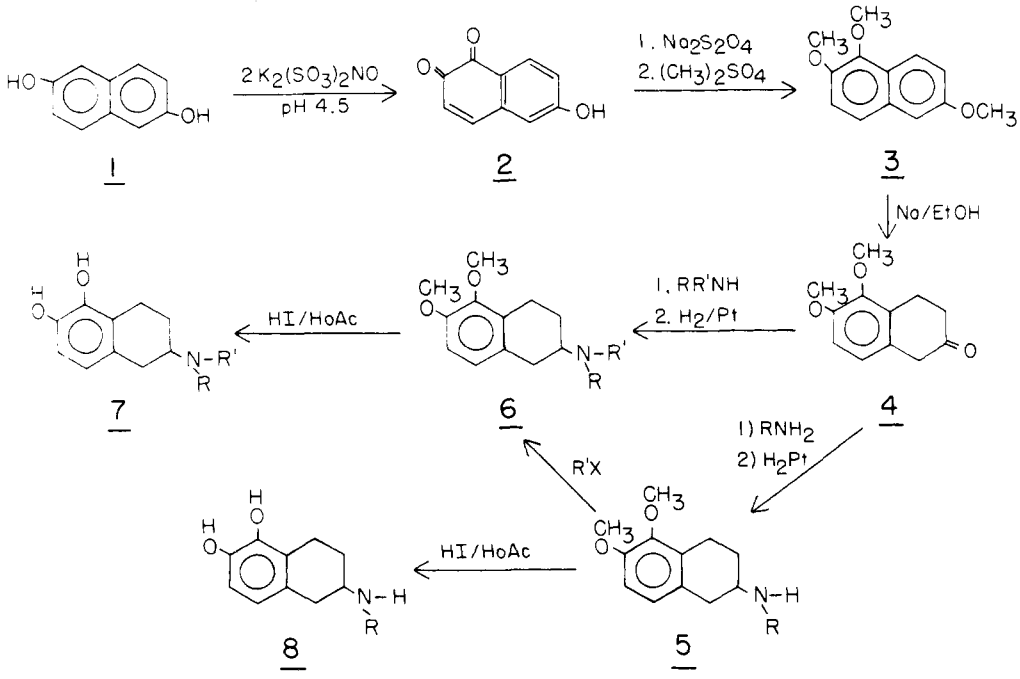
Scheme I



to insert this group in some form while the naphthalene was still fully aromatic. However, the functionalized methyl group had to be one which would survive the subsequent sodium–alcohol reduction. The hydroxymethyl group in **10**, for example, was cleanly cleaved to yield **12** by these conditions. Only an aminomethyl group seemed to fulfill this requirement. The aldehyde **9** was a suitable starting point for this sequence. Its transformation to the dimethylaminomethyl compound **11** was conveniently done by the method of Borch[10] with dimethylamine and $NaBH_3CN$. Reductive amination of **12** and **13** gave **34** and **14**, respectively. The benzylic amino group of **14** was converted to acetoxy, **35**, by refluxing in acetic anhydride. We were unable to cleave the methyl ether in either **14** or **35** without decomposition.

The 1-methyl-2-dipropylaminotetralin (compound **75** in Table I) was made by alkylation of the enamine from 2-tetralone and dipropylamine, followed by catalytic reduction ($Pt-H_2$) of the resulting immonium intermediate. The stereochemistry was not determined but was presumed to be cis.[11]

The octahydrobenzo[*f*]quinolines, **76** and **77** (Table I), were made *via* the enamine lactams,[12] **15**, which were prepared from β-tetralone, primary amine, and ethyl acrylate (Scheme III). The ring junction in **76** and **77** was presumed to be cis.

Scheme II

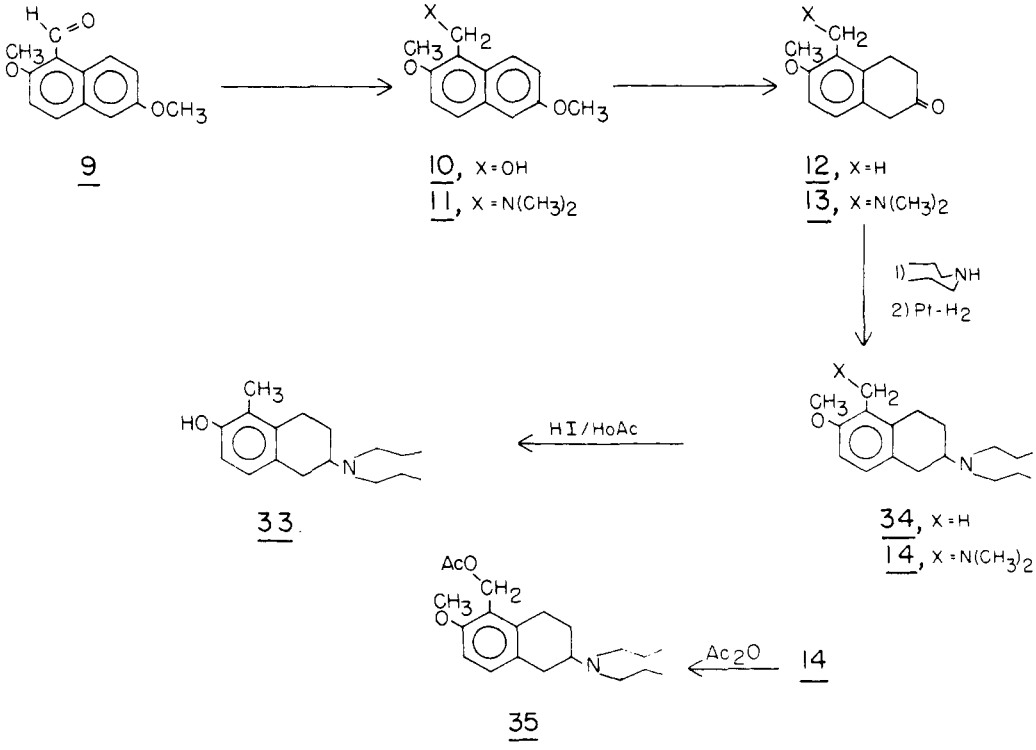
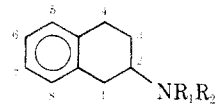
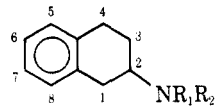


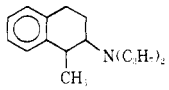
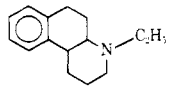
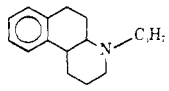
Table I. Pharmacological Evaluation of 2-Aminotetralins



No.	Aromatic substitution	R_1	R_2	Mp, °C[a] (HCl salt)	E,[b] μg/kg	S,[c] mg/kg	R,[d] mg/kg
Apomorphine					26	0.5	1
16	5,6-$(OH)_2$	H	H	295 dec	>34	–[l]	21
17	5,6-$(OH)_2$	CH_3	CH_3	220[f]	13	0.2	0.2
18	5,6-$(OH)_2$	C_2H_5	C_2H_5	174–175[g]	0.48	3	1
19	5,6-$(OH)_2$	C_3H_7	CH_3	197–203 dec	<2.6	4	0.9
20	5,6-$(OH)_2$	C_3H_7	C_3H_7	208 dec	0.57	0.03	0.08
21	5,6-$(OH)_2$	C_4H_7	C_4H_7	155–156.5	53	4	2
22	5,6-$(OH)_2$	$CH_2C_6H_5$	$CH_2C_6H_5$	224–225	>900	–	–
23	7,8-$(OH)_2$	CH_3	CH_3	187–189 dec	64	–	0.8
24	7,8-$(OH)_2$	C_3H_7	C_3H_7	160.5–163	18	4	4
25	5,6-$(OCH_3)_2$	H	H	285 dec[p]	NT[m]	–	4
26[k]	5,6-$(OCH_3)_2$	H	H	235 dec[q]	NT	–	4
27	5,6-$(OCH_3)_2$	C_2H_5	C_2H_5	177–179	440	22	44
28	5,6-$(OCH_3)_2$	C_3H_7	CH_3	178–179	880[e]	9	22
29	5,6-$(OCH_3)_2$	C_3H_7	C_3H_7	178–179	900[e]	0.5	5
30	5,6-$(OCH_3)_2$	$CH_2CH_2OCH_3$	CH_3	149–151[h]	>770	–	–
31	5,6-$(OCH_3)_2$	$CH_2CH_2C_6H_5$	CH_3	209–212	>900	–	–
32	5,6-$(OCH_3)_2$	$CH_2C_6H_5$	$CH_2C_6H_5$	195–198	>800	–	–
33	5-CH_3, 6-OH	C_3H_7	C_3H_7	215–216	57	5	5
34	5-CH_3, 6-OCH_3	C_3H_7	C_3H_7	182.5–183.5	88	25	–
35	5-CH_2OCOCH_3, 6-OCH_3	C_3H_7	C_3H_7	157–159	67	25	–
36	5,6-$(OC_2H_5)_2$	C_3H_7	C_3H_7	152[h]	320[e]	0.5	1
37	5,6-$(OH)_2$	C_3H_7	H	231–233 dec	<3.4	0.2	2
38	5,6-$(OCH_3)_2$	C_3H_7	H	227–229	NT	22	44
39	5,6-$(OH)_2$	C_6H_{13}	H	92–94	NT	–	44
40	5,6-$(OCH_3)_2$	$CH_3(CH)CH_2CH_3$	H	215–217	>260	–	–
41	5,6-$(OCH_3)_2$	$CH(CH_3)_2$	H	244–245	>260	–	–
42	5,6-$(OH)_2$	$CH_2C_6H_5$	H	278 dec	NT	–	–
43	5,6-$(OCH_3)_2$	$CH_2C_6H_5$	H	277–280	NT	–	–
44	5,6-$(OCH_3)_2$	$CH_2CO_2C_2H_5$	H	186.5–189	>260	–	–
45	5,6-$(OH)_2$	$-(CH_2)_4-$		290 dec	<3500	–	–
46	5,6-$(OCH_3)_2$	$-(CH_2)_4-$		258 dec	NT	–	–
47	5,6-$(OH)_2$	$-(CH_2)_5-$		279 dec	>2600	–	22
48	5,6-$(OCH_3)_2$	$-(CH_2)_5-$		269–271 dec	NT	–	–
49	5,6-$(OH)_2$	$-CH_2CH_2OCH_2CH_2-$		292 dec	>880	–	44
50	5,6-$(OCH_3)_2$	$-CH_2CH_2OCH_2CH_2-$		254–256	NT	–	44
51	5,6-$(OH)_2$	$-CH_2CH_2N(CH_3)CH_2CH_2-$		267–272[i] dec	NT	–	–
52	5,6-$(OCH_3)_2$	$-CH_2CH_2N(CH_3)CH_2CH_2-$		256–258[i] dec	NT	–	–
53	6-OH	$-CH_2CH_2OCH_2CH_2-$		270–272	>860	–	43
54	5-OCH_3	$-CH_2CH_2OCH_2CH_2-$		240–241	>260	–	–
55	7-OH	$-CH_2CH_2OCH_2CH_2-$		230[g] dec	>300	–	–
56	7-OCH_3	$-CH_2CH_2OCH_2CH_2-$		252–253 dec	>300	–	–
57	5,8-$(OH)_2$	$-CH_2CH_2OCH_2CH_2-$		310–312 dec	>300	–	–
58	5,8-$(OCH_3)_2$	$-CH_2CH_2OCH_2CH_2-$		277–278 dec	>300	–	–
59	7,8-$(OH)_2$	$-CH_2CH_2OCH_2CH_2-$		232–235[f]	>250	–	–
60	7,8-$(OCH_3)_2$	$-CH_2CH_2OCH_2CH_2-$		237–238 dec	>260	–	–
61		C_4H_9	H	216–218[o]	>850	–	–
62		C_4H_9	CH_3	126–128	>260	–	–
63		C_2H_5	C_2H_5	145–147	55	8	43
64		C_3H_7	C_3H_7	154–154.5[n]	55	4	43
65		$CH_2CH_2OCH_3$	H	159–160	>260	–	–
66		CH_2CH_2OH	CH_3	93.5–95[j]	>700	–	–
67		CH_2CO_2H	H	207–210	>850	–	–
68		$CH_2CH_2OCH_3$	CH_3	103–104[h]	>220	–	–
69		$CH_2CH_2OCH_3$	C_2H_5	147–148	>880	4	–
70		$CH_2CH_2OCH_3$	C_3H_7	144–146	500	5	–
71		$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	150[h]	>4000	–	–
72		$-CH_2CH_2OCH_2CH_2-$		270 subl	>2500	–	38
73		$-(CH_2)_6-$		247–249	>258	–	–
74		$-(CH_2)_7-$		214–216	>260	–	43

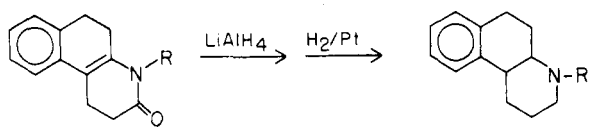
Table I *(Continued)*



No.	Aromatic substitution	R_1	R_2	Mp, °C[a] (HCl salt)	E,[b] μg/kg	S,[c] mg/kg	R,[d] mg/kg
75				138–140	>260	22	–
76				212–213.5	–	–	–
77				208–209	–	–	–

[a]All new compounds gave satisfactory analyses for C, H, and N. [b]Minimum emetic dose in the dog expressed as μg/kg im. [c]Minimum dose sc required to induce stereotyped behavior for 30–50 min in the rat. [d]Minimum dose sc required to block the tonic emg of the reserpinized rat for 10–20 min. [e]These agents proved to be extremely emetic when administered po. [f]Monohydrate, confirmed by Karl Fischer analysis. [g]HI salt. [h]HBr salt. [i]2HCl salt. [j]Hydrogen oxalate salt. [k]Fully aromatic naphthalene, not a tetralin. [l]Compound inactive at the highest dose tested; see methods for dose limits. [m]NT, not tested. [n]Lit.[21] mp 154–155°. [o]Lit.[21] mp 217°. [p]Lit.[3] mp 270–272°. [q]Lit.[3] mp 243–244°.

Scheme III



15

76 R = C_2H_5

77 R = C_3H_7

Pharmacological Tests. The pharmacological activity of these 2-aminotetralins was assessed in three animal tests in which apomorphine has proven to be active at low doses.

The ability to induce stereotyped behavior[13] was determined in Sprague–Dawley male rats. The minimum effective dose was defined as the sc dose which induced stereotyped behavior for 30–40 min. Three animals were used per dose and the maximum dose tested was 50 mg/kg.

Antitremor activity was evaluated in rats pretreated iv with reserpine and α-chloralose, 5 mg/kg and 80 mg/kg, respectively, which resulted in a tonic electromyogram (EMG).[14] The EMG was monitored using Grass needle electrodes inserted into the gastrocnemius muscle and connected to a Tektronix storage oscilloscope. The minimum effective dose was defined as the sc dose required to abolish the tonic EMG for 10–15 min. Test drugs were administered 3–4 hr after reserpine and α-chloralose treatment. A minimum of two animals were used per dose and the doses ranged from the stereotyped behavior threshold dose to a maximum dose of 50 mg/kg.

Minimum emetic doses were determined im in the dog. Drugs were administered at an initial dose of 0.033 mg/kg. Subsequent doses were increased by a factor of 3.3 or 1.65, usually to a maximum of 1 mg/kg, or decreased by a factor of 1.65 until emesis or the lack of it was observed. The lowest emetic dose and the highest nonemetic dose were confirmed in two to four additional animals and the emetic threshold was defined as the average between the two doses. Tests were always performed 30 min following the mid-day feeding and the animals observed for emetic responses every 10 min up to 3 hr after drug and again 20 hr after drug. Animals received drugs no more frequently than every fifth day. Saline and apomorphine were tested once a month to safeguard against possible development of conditioning and/or tolerance, respectively.

Drugs were administered in saline solution and activities are expressed as mg/kg of free base.

Results and Discussion

Results are shown in Table I. 5,6-Dihydroxy compounds, **17–21**, were all in the potency range of APM. The optimum substitution pattern seemed to be that found in compound **20** which was approximately 50 times more potent than APM. Increasing the size of the substituents on the nitrogen resulted either in a dramatic decrease in potency, **21**, or loss of activity, **22**.

Surprisingly, 7,8-dihydroxy compounds, **23** and **24**, retained dopaminergic agonist activity and though less potent than the 5,6-dihydroxy congeners, compound **24** was clearly more potent than APM as an emetic and only eight times less potent on the other two tests.

Replacement of hydroxy groups with alkoxy substituents, **27–29** and **36**, resulted in a marked decrease in potency compared to compounds **18–20**. However, the alkoxy analogs proved to be extremely potent emetics when administered orally. In this respect **29** was 100 times more potent than APM following oral administration. These findings suggest that either the alkoxy derivatives are dopaminergic agonists and possess better absorption following the oral rather than the im route, or the compounds are dealkylated in the gut or liver to yield the potent hydroxy compounds.

The authors attach some significance to the observation that **33**, a 5-methyl-6-hydroxy derivative of **29**, retained respectable potency in all three tests. This clearly suggests that both hydroxyl groups are not mandatory for dopaminergic agonist activity.[2,4]

Secondary amines, **37–44**, with one exception, were for the most part inactive. The exception, **37**, though similarly potent on the stereotyped behavior and reserpine tests, was at least ten times more potent than APM as an emetic. As with the tertiary amines, replacing hydroxyls with alkoxy groups, **38**, resulted in a marked diminution in potency.

Cyclic amines, **45–60**, regardless of the type and position of substitution on the aromatic ring, were inactive.

An additional interesting finding, as regards the molecular requirements for dopaminergic activity, was obtained in the group of tetralins unsubstituted in the aromatic ring,

61–74. As pointed out earlier in this section, alkyl groups larger than C_3H_7, cyclized compounds, and secondary amines were virtually inactive. However, **63** and **64**, respective analogs of **18** and **20**, unsubstituted in the aromatic ring, retained activity in all tests. In addition, stereotyped behavior following **63** or **64** was not blocked by pretreating the animals with α-methyltyrosine and reserpine. This latter finding strongly suggests that **63** and **64** are direct acting dopaminergic agonists. Additional support for this conclusion was derived from the observation that small doses of haloperidol, a dopaminergic antagonist, blocked the emesis and stereotyped behavior induced by **63**, **64**, and APM.

It is concluded that properly substituted 2-aminotetralins are dopaminergic agonists. However, the emetic activity inherent in the 2-aminotetralin molecule could not be removed without simultaneously losing activity in the other pharmacological tests.

In addition, the conclusion by Cannon and coworkers[2,4] that the emetic pharmacophore of APM necessarily includes an unetherified catechol group does not apply to the simpler analogs of APM studied here. Our studies would suggest that the unetherified catechol group enhances the emetic activity of the tetralin pharmacophore which by itself possesses respectable emetic potency. This conclusion is paralleled by the recent finding[15] that aporphines lacking a catechol group can still induce *in vivo* dopaminergic activity characteristic of apomorphine.

Experimental Section

Melting points were determined in open capillaries using a Thomas-Hoover oil bath apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR8 spectrophotometer. Proton magnetic resonance spectra were obtained on a Varian T60. Spectral data on all compounds were consistent with the proposed structures. Where elemental analyses are indicated, results obtained were within ±0.4% of the theoretical values.

6-Hydroxy-1,2-naphthoquinone (2). A solution of 84 g (0.32 mol) of potassium nitrosodisulfonate in 3000 ml of water and 1350 ml of phthalate buffer, pH 4.5, was cooled to 5°. With stirring, 20.6 g (0.13 mol) of 2,6-dihydroxynaphthalene dissolved in 700 ml of methanol was added rapidly. The solution changed rapidly from a clear purple to murky red. After stirring 1 hr in an ice bath the tiny red crystals of **2** were collected and washed sparingly with cold water. The filter cake was digested with 750 ml of hot methanol and filtered hot and the filtrate was cooled eventually in a Dry Ice bath. The yield was 17 g (76%) of pure **2**, whose spectral data agreed with the reported values.[7]

1,2,6-Trimethoxynaphthalene (3). A solution containing 26.6 g (0.153 mol) of the quinone **2** in 615 ml of DMF was washed for 20 min with N_2. To this solution was added a freshly prepared solution of 54 g (0.31 mol) of $Na_2S_2O_4$ in 250 ml of H_2O, resulting in warming and a color change to light yellow. After stirring for 20 min in the presence of N_2, 80 g (0.58 mol) of anhydrous K_2CO_3 was added, followed by 50 g (0.40 mol) of dimethyl sulfate. This addition of K_2CO_3 and dimethyl sulfate was repeated twice at 20-min intervals, followed by stirring an additional 1 hr. The reaction was then poured into ice water, and the resulting solid was collected and washed with H_2O. The crude product was eluted through a short column of 300 g of activity III alumina with 80% hexane–20% benzene, yielding 30.6 g (91%) of pure **3** as a nearly colorless solid, mp 55° (lit.[5] 55°).

3,4-Dihydro-5,6-dimethoxy-2-(1*H*)-naphthalenone (4). This tetralone was prepared from **3** in 70% yield by the method of Robinson.[8] It was isolated and stored as the $NaHSO_3$ adduct, from which it was released as needed with aqueous K_2CO_3. An analytical sample was purified by recrystallization from hexane: mp 61–63° (lit.[16] 64–65°). It gave an intense Tetralone Blue test.

Secondary 2-Aminotetralins from β-Tetralones. Under N_2, a solution of the appropriately substituted β-tetralone (10 mmol), primary amine (30 mmol), acetic acid (30 mmol), and ethanol (25 ml) was allowed to stand 2 hr over 2.5 g of 3A molecular sieves. The solution was decanted into a Parr reduction bottle and the sieves were rinsed with ethanol. To the combined solution was added 100 mg of PtO_2, and hydrogenation was performed at about 2 atm. Uptake of the theoretical amount of H_2 was generally complete in a few minutes. The amine-containing fraction was isolated and the excess primary amine removed at reduced pressure. The crude residue was decolorized, if necessary, and an addition salt prepared and recrystallized to chromatographic and analytical purity. Yields were generally 75–90%.

***tert*-2-Aminotetralins from β-Tetralones.** Under N_2, a solution of the appropriately substituted β-tetralone (10 mmol), secondary amine (40 mmol), *p*-toluenesulfonic acid monohydrate (1 mmol), and benzene (60 ml) was refluxed with continuous water removal until an aliquot showed little or no carbonyl in the infrared spectrum. This time ranged from 5 min in the case of pyrrolidine to 48 hr for dipropylamine. In the case of higher boiling amines (*e.g.*, dibutylamine) advantage was found in the use of toluene as solvent. If the amine was lower boiling than benzene (dimethyl- or diethylamine), the reaction was performed in a steam-heated pressure bottle containing 4 g of 3A molecular sieves. The solution was diluted with an equal volume of ethanol and hydrogenated over platinum as above. The nonvolatile amine fraction was routinely eluted through a short activity I alumina column. Addition salts were then prepared and recrystallized, usually from methanol–ethyl acetate. Yields were generally 70–85%.

***tert*-2-Aminotetralins, by Alkylation of *sec*-2-Aminotetralins.** This procedure, which was used for introduction of secondary amino groups not available commercially, is exemplified by 2-[*N*-(β-methoxyethyl)-*N*-propylamino]-1,2,3,4-tetrahydronaphthalene (**70**).

A solution of 2-[*N*-(β-methoxyethyl)amino]-1,2,3,4-tetrahydronaphthalene (2.8 g, 13.6 mmol) and *n*-propyl iodide (6.8 g, 40 mmol) in 20 ml of benzene was placed over a solution of K_2CO_3 (4 g) in 7 ml of water. The mixture was refluxed 48 hr, following the progress by tlc of aliquots. The benzene layer was removed, washed, dried, and evaporated. The residue was freed of starting secondary amine by treatment at room temperature with 0.25 g of phenyl isocyanate, destroying excess isocyanate with hot methanol. The tertiary amine (acid soluble fraction) was eluted through a column of 45 g of activity I alumina with 75% hexane–25% ethyl acetate. The nearly colorless oil thus obtained was converted to its HCl salt and recrystallized from MeOH–EtOAc. The yield was 2.4 g of **70** · HCl (62%), mp 144–146°.

When a methyl group was added to a secondary amine, the Baltzly procedure[17] for the Eschweiler–Clarke reaction was used.

Cleavage of Methyl Ethers. In an ice bath under nitrogen, 7.0 g (26 mmol of HI, 206 mmol of H_2O) of 47% HI was added to 4.4 mmol of catecholamine dimethyl ether, followed by dropwise addition of 18.4 g (180 mmol) of acetic anhydride. This was heated to gentle reflux for 1 hr and then cooled to room temperature. The HI salt of the product was generally less soluble than that of the starting ether and occasionally precipitated during this process. If not, the solution was triturated with ether or ethyl acetate. The HI salts so obtained were frequently brown and difficult to recrystallize effectively, so the HCl salts were generally prepared by the simple halogen exchange method of Phillips.[18] If the HCl salt did not crystallize from methanol, ethyl acetate was added and boiled until the methanol had been driven off. Overall yields were generally 60–70%.

2,6-Dimethoxy-1-naphthaldehyde (9). To a mixture of 5.5 g (41 mmol) of *N*-methylformanilide and 6.4 g (42 mmol) of $POCl_3$ was added 6.8 g (36 mmol) of 2,6-dimethoxynaphthalene. This was heated 5 hr on a steam bath under a drying tube with occasional shaking. The reaction was diluted with 25 ml of DMF and poured into 400 ml of chilled 1 *N* HCl and stirred thoroughly. The resulting suspension of solid **1** was filtered and washed with water, yielding 7.55 g of red solid, mp 81–84°. This was recrystallized once from 2-propanol (charcoaling) and once from hexane, yielding 4.6 g (59%) of **9**, mp 88–90.5° (lit.[19] mp 90°).

2,6-Dimethoxy-1-hydroxymethylnaphthalene (10). This was prepared by sodium borohydride reduction of **9** (4.4 g, 20 mmol) in ethanol in the usual way, yielding 4.3 g of crude **10**, mp 121°. Recrystallization from 50% hexane–50% 2-propanol gave 3.3 g (75%) of pure **10**, mp 123–125° (lit.[20] mp 124–125°).

3,4-Dihydro-6-methoxy-5-methyl-2(1*H*)-naphthalenone (12). By the Robinson procedure[8] 3.3 g (15 mmol) of **10** was treated with 2.8 g (120 mmol) of sodium in 30 ml of ethanol, and a $NaHSO_3$ adduct of the product was obtained. The β-tetralone as released from its adduct was a solid (mp 52°) which gave a Tetralone Blue test. The pmr and ir spectra confirmed that the hydroxyl group had been lost.

5-Acetoxymethyl-1-2-dipropylamino-6-methoxy-1,2,3,4-te-

trahydronaphthalene (35). Acetic acid (about 10 ml) was added to a solution of 6.0 g (133 mmol) of dimethylamine in 100 ml of methanol until a pH of 6.4 (moist litmus) was reached. To this was added 5.2 g (24 mmol) of **9** and 0.8 g (13 mmol) of $NaBH_3CN$. After some transient bubbling had subsided, another 0.3 g (5 mmol) of $NaBH_3CN$ was added and the clear solution was stirred 1 hr. The reaction was then diluted with 200 ml of 1 *N* HCl and stirred 20 min, and some insoluble solid was filtered off. The filtrate was made strongly basic and extracted with CH_2Cl_2, which was in turn dried (Na_2SO_4) and evaporated, leaving 5.3 g (90%) of 2,6-dimethoxy-1-dimethylaminomethylnaphthalene (**11**) as a clear oil which was not purified further.

By the Robinson procedure[8] 5.2 g (21 mmol) of **11** was treated with 4.5 g (20 mmol) of sodium in 48 ml of ethanol. After acidification and refluxing, 150 ml of water was added and the solution was washed with benzene. The aqueous part was made basic and extracted with CH_2Cl_2, which was washed, dried (Na_2SO_4), and evaporated, leaving 4.6 g (95%) of crude, faintly yellow oil **13.** This material was identified by its ir and pmr spectra. It could not be purified in the usual way because it did not form an isolable $NaHSO_3$ adduct. The tlc showed small amounts of contaminants present, but the material was taken for the next step unpurified. The contaminants were evidently removed in subsequent steps.

Reductive alkylation of dipropylamine with 4.3 g of the β-tetralone **13,** by the procedure outlined above, gave 3.8 g of the crude product 5-dimethylaminomethyl-6-methoxy-2-dipropylamino-1,2,3,4-tetrahydronaphthalene (**14**) as a dark oil. This was chromatographed on 75 g of activity I alumina, eluting with hexane. The purified **14** was an oil having consistent pmr and ir spectra and was homogeneous by tlc (silica, various solvents).

A solution of 0.50 g (1.6 mmol) of **14** in 50 ml of acetic anhydride was refluxed under a drying tube 4 hr. It was evaporated at reduced pressure and then treated at room temperature with excess $NaHCO_3$. The product was extracted into ether, which was washed, dried (Na_2SO_4), and evaporated. The residual oil was chromatographed on 10 g of activity I alumina, eluting with 10% benzene–90% hexane. The product was 275 mg (55%) of colorless oil **34,** homogeneous by tlc. It was converted to its HCl salt and crystallized from ethyl acetate–ether: mp 159–160°. *Anal.* ($C_{20}H_{30}ClNO_3$) C, H, N.

1-Methyl-2-dipropylamino-1,2,3,4-tetrahydronaphthalene (75). Under nitrogen, a solution of 3.0 g (20 mmol) of β-tetralone, 4.0 g of dipropylamine, 0.10 g (0.50 mmol) of *p*-toluenesulfonic acid hydrate, and 50 ml of benzene was refluxed 48 hr with continuous water removal. The benzene and excess dipropylamine were then removed at reduced pressure and replaced with a solution of 8.5 g (60 mmol) of methyl iodide in 25 ml of ethanol. Refluxing 18 hr removed the enamine (tlc), and new bands appeared in the ir at 1635 (immonium group) and 1710 cm^{-1} (hydrolysis to carbonyl). The solution was then hydrogenated over 150 mg of PtO_2. Within 2 hr uptake of hydrogen ceased at 42% of theory. From this reaction 1.8 g (36%) of crude amine was isolated by acid–base treatment and chromatographed on 20 g of activity I alumina, eluting with 90% hexane–10% benzene. From the oil so obtained a HCl salt was prepared and recrystallized from methanol–ethyl acetate: 1.4 g (24%); mp 138–140°. *Anal.* ($C_{17}H_{28}ClN$) C, H, N. No evidence of more than one isomer was found[11] using silica gel tlc and a variety of solvents.

4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (77). A solution of 2.0 g (14 mmol) of β-tetralone and 2.0 g (20 mmol) of *n*-propylamine in 100 ml of toluene was refluxed with removal of water, rapidly giving complete conversion to the imine. Toluene and excess propylamine were removed at reduced pressure and replaced with 3.0 g (30 mmol) of ethyl acrylate in 50 ml of ethylene glycol and refluxed 18 hr. The intermediate enamino lactam was obtained by distillation of solvent at reduced pressure, taking the resulting oil into CH_2Cl_2, washing, drying evaporating, and chromatographing on silica gel (90% hexane–10% ethyl acetate) in 45% yield.

This enamino lactam was reduced to an oily enamine free of carbonyl by refluxing in ether with excess $LiAlH_4$. This crude enamine was hydrogenated in ethanol over PtO_2 at 2 atm, taking up the theoretical amount of hydrogen in 15 min. An HCl salt was prepared from the resulting amine and recrystallized from ethanol–ethyl acetate, yielding 860 mg (25% overall) of slightly yellow crystals, mp 208–209°. *Anal.* ($C_{16}H_{24}ClN$) C, H, N. Silica gel tlc (several solvents) gave no evidence of more than one isomer.

The HCl salt of 4-ethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**76**) was prepared in the same way, mp 212–213.5°. *Anal.* ($C_{15}H_{22}ClN$) C, H, N.

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