was obtained from New England Nuclear Corp., Boston, MA. Reserpine phosphate was from Ciba Pharmaceutical Co., Summit, NJ.

2-Benzyl-6-*endo*-hydroxy-6-*exo*-[3′,4′-bis(benzyloxy)-phenyl]-2-azabicyclo[2.2.2]octane (3). To a solution of *n*-butyllithium prepared[11b] from *n*-butyl bromide (77.0 g, 0.55 mol) and lithium metal (4.2 g, 0.60 g-atom) in anhydrous ether cooled at −70 °C was added a solution of 3,4-bis(benzyloxy)phenyl bromide (55.2 g, 0.149 mol) in 450 mL of anhydrous ether over a 1-h period. A white suspension was obtained. The resulting mixture was allowed to warm to −45 °C and diluted with an additional 100 mL of anhydrous ether. A solution of *N*-benzyl-2-azabicyclo[2.2.2]octan-6-one[14] (11.0 g, 0.051 mol) in 100 mL of anhydrous ether was added over a 30-min period at −40 °C. The mixture was allowed to warm to room temperature after the addition was complete, stirred overnight, and then treated at 0 °C with water until a clear solution resulted. The ether layer was separated, and the aqueous layer was extracted with ether. The organic phases were combined and extracted with 10% HCl (5 × 60 mL). The acidic aqueous layer and an oily material that separated from the ether phase and was insoluble in the aqueous phase were washed with ether (2 × 100 mL), neutralized with ammonium hydroxide, and extracted with ether (4 × 200 mL). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a residue. The residue was triturated with a minimum amount of anhydrous ether and filtered to give a white solid: yield 10.7 g (42%); mp 107–109 °C. An analytical sample was obtained by passing the solid through a silica gel column packed and eluted with ether–petroleum ether (1:2) to give white crystals: mp 108–110 °C; IR (CCl_4) 3420 (OH, associated) cm^{-1}. Anal. ($C_{34}H_{35}NO_3$) C, H, N.

2-Benzyl-6-[3′,4′-bis(benzyloxy)phenyl]-2-azabicyclo-[2.2.2]oct-5-ene (4). A solution of **3** (10.0 g, 0.0198 mol) in 100 mL of 2 N HCl in 1,4-dioxane was stirred at room temperature for 24 h and evaporated in vacuo to give a residue, which was then treated with water (150 mL), neutralized with ammonium hydroxide, and extracted with ether (3 × 150 mL). The combined extracts were dried over magnesium sulfate and evaporated to give a viscous oil. Chromatography of the oil on a silica gel column packed and eluted with ether–petroleum ether (1:3) gave pure **4**: yield 7.68 g (80%). Anal. ($C_{34}H_{33}NO_2$) C, H, N.

6-*endo*-(3′,4′-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (1). A solution of **5**[11b] (1.01 g, 0.003 mol) in 12 mL of 48% hydrobromic acid was refluxed under nitrogen for 1.5 h. The reaction mixture was cooled, neutralized with ammonium hydroxide, and extracted with chloroform–methanol (5:1) in three 20-mL portions. The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a residue, which was chromatographed on a silica gel column packed and eluted with 5% methanol/chloroform to give a blue solid, **7**. A solution of the solid in 0.5 mL of concentrated hydrochloric acid and 30 mL of ethanol was flushed with nitrogen, 10% palladium on charcoal (0.045 g) was added, and the mixture was hydrogenated at 3.15 kg/cm² at 45 °C for 2 days. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give a residue, which was chromatographed on a silica gel column packed and eluted with 5% methanol/chloroform to give 105 mg of unreacted intermediate and the desired product 1 as the hydrochloride salt (150 mg, 13% based on the starting **5**). Recrystallization of the HCl salt of 1 from methanol–chloroform gave white crystals, mp 265–267 °C. Anal. ($C_{13}H_{18}ClNO_2$) C, H, N.

6-*exo*-(3′,4′-Dihydroxyphenyl)-2-azabicyclo[2.2.2]octane (2). In a manner similar to that described for the preparation of 1, a solution of **6** (1.84 g, 0.0054 mol) in 35 mL of 48% hydrobromic acid was refluxed and worked up to give a dark residue, which was chromatographed to give a solid (**8**, 0.57 g), mp 132–136 °C. A mixture of the solid and 10% palladium on charcoal (0.09 g) in 50 mL of ethanol containing 0.5 mL of concentrated HCl was similarly hydrogenated, worked up, and purified to give a highly viscous hydrochloride salt of **2** (0.202 g, 15% yield based on starting **6**). The picrate was prepared in the normal manner, mp 219–220 °C. Anal. ($C_{19}H_{20}N_4O_9$) C, H, N.

Inhibition of [³H]Dopamine Uptake. The method was essentially that described by Horn and Snyder.[15] [³H]Dopamine was incubated at 0.1 μM with rat striatal homogenates. The ability of compounds 1, **2**, and the positive control, (±)-tranylcypromine hydrochloride, to inhibit [³H]dopamine uptake was tested at varying concentrations as shown in Figure 1. The ranges of concentration were chosen to include the half-maximally effective concentration (IC_{50}).

[³H]APO Binding Assay. (−)-[³H]Apomorphine hydrochloride was incubated at 0.5 nM with a subsynaptosomal membrane fraction (P_4) prepared from caudate nucleus tissue of calf brain. Experimental compounds were screened at 100 μM (N = 4). Tissue was recovered by filtration. The methods are described in detail elsewhere.[17,18]

Interactions with DA-Sensitive Adenylate Cyclase. Rat corpus striatum homogenates were evaluated with DA (50 μM) as a positive control. Concentrations of 1 and **2** were tested for ability to stimulate formation of cAMP as measured by a binding assay which has been described elsewhere.[19,20,22] Concentrations of 50, 100, 200, and 400 μM of test compounds were screened. There were only weak effects of 1 at 400 μM alone (Table II) and at 50 μM when combined with 50 μM DA (Table III).

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Aminotetralins as Narcotic Antagonists. 2. Synthesis and Opiate-Related Activity of 1-Phenyl-3-aminotetralins[1]

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The synthesis and analgetic agonist and antagonist activities of several 3-[*N*-(cyclopropylmethyl)-*N*-methylamino]-1-phenyltetralins are reported. The design of these agents was based partially on the possibility of two aryl receptor binding sites on the opiate receptor. The agents lack the phenolic hydroxyl and quaternary carbon functionalities generally associated with opiate activity; yet both the *cis*- and *trans*-1-phenyl-3-aminotetralins displayed significant agonist and antagonist activity. In preliminary studies, the trans isomer neither suppressed nor precipitated withdrawal signs in addicted monkeys.

The ultimate objective of the research described in this report is to discover, from among aminotetralin congeners, a mixed opiate agonist–antagonist and/or a pure narcotic antagonist. A mixed agonist–antagonist remains a prom-

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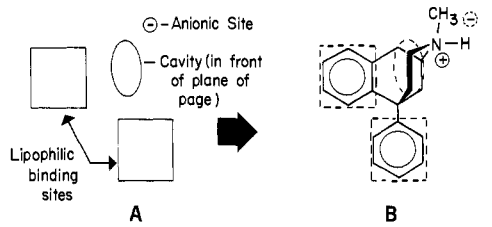
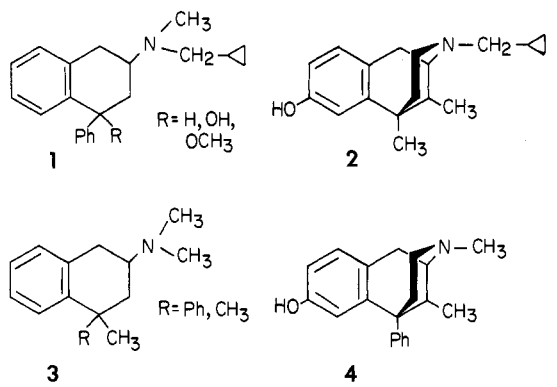


Figure 1. Depiction of a possible receptor surface containing two distinct aryl binding sites (A) and a 5-phenyl-6,7-benzomorphan superimposed on the binding site (B).

ising source for a nonaddicting, centrally acting, analgetic agent,[2] and narcotic antagonists have potential value in opiate addiction rehabilitation programs.[3,4] The present report describes the design, synthesis, and opiate-related activity of aminotetralins having structure 1.



The design of these compounds incorporates structure–activity features generally associated with mixed opiate agonist–antagonist activity. The aminotetralins are A,B ring analogues of morphine,[5] and their structural resemblance to the mixed agonist–antagonist cyclazocine[6] (2) is apparent. Evidence that the ethylenic bridge is not necessary for activity is provided by the aminotetralins (3) prepared by Martin and co-workers.[7-9]

The inclusion of the phenyl group at the C-1 position of 1 was modeled after the activity seen for 4.[10,11] The 5-phenyl substituent in 4 produces a compound which is twice as potent as the corresponding agents containing a methyl group at this position.[12,13] The increased activity of 5-phenylbenzomorphans could result from distribution-related effects or it may be due to specific binding of the 5-substituents to a hydrophobic binding site on the receptor. Dual or multiple aryl binding site hypotheses have been proposed by others[14-18] to explain the activities of a number of opiates. A representation of an opiate receptor surface containing two distinct aryl binding sites is shown in Figure 1. It is possible that agents such as 1 and 4 bind to opiate receptors having the topography represented in Figure 1. The investigation of compounds related to structure 1 should contribute information that will help in determining the validity of dual aryl receptor binding site hypotheses.

Scheme I

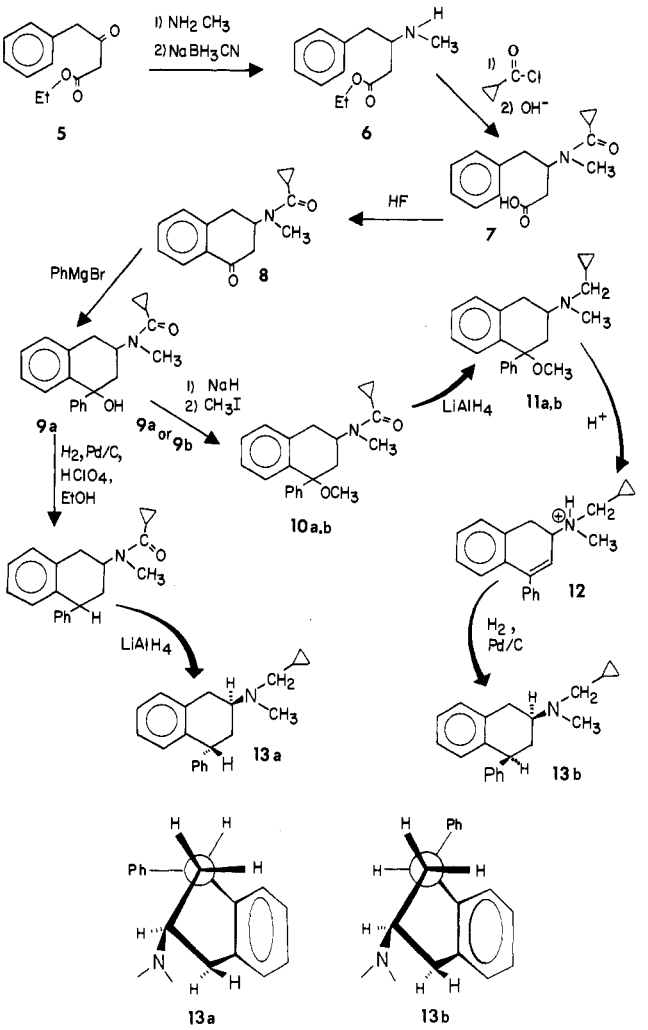


Figure 2. Projection formulas of 13a and 13b showing the conformational relationships of the C-1 and C-2 positions of the tetralin ring.

Chemistry. The synthesis of compounds of structure 1 was achieved by the sequence of reactions outlined in Scheme I. Ethyl 4-phenylacetoacetate (5) readily forms the corresponding enamine when treated with ammonia or methylamine, but these products proved difficult to reduce by catalytic hydrogenation. The methylenamine

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Table I. Analgetic and Narcotic-Antagonist Potencies of 3-[*N*-Methyl-*N*-(cyclopropylmethyl)amino]-1-phenyltetralins

compd	agonist:[b] ED_{50}, mg/kg	antagonist:[c] % inhibn dose: 30 mg/kg	10 mg/kg	3 mg/kg	1 mg/kg
12[a]	>50	not tested			
13a[a]	9.1 (5.2-15.9)[d]	0	54	100	60
13b[a]	6.3 (4.3-9.2)[d]			100	75
morphine sulfate	1.2				
codeine sulfate	7.5				
naloxone hydrochloride		0.031 (0.01-0.09)[e]			

[a] Tested as HCl salts of racemic mixtures. [b] Tested sc in mice by the hot-plate procedure (ref 21). Courtesy of Dr. A. Jacobson, NIAMDD, NIH. [c] The ability to reverse an ED_{80} dose of morphine when tested sc in mice by the tail-flick procedure (ref 22). Courtesy Dr. R. E. Willette, NIDA, ADAMHA. [d] Confidence interval (95%). [e] AD_{50} value and confidence interval.

could readily be reduced by sodium cyanoborohydride[19] to give the corresponding methylamino ester (**6**). Attempts to cyclize the carboxylic acids from **6** or **7** with polyphosphoric acid resulted in aromatization of the tetralin to α-naphthol. Azlactone formation resulted when attempts were made to prepare the acid chloride of **7**. Synthesis of tetralone **8** was achieved only in anhydrous HF, although considerable amounts of α-naphthol were formed in the reaction. Reaction of **8** with phenyllithium or phenylmagnesium bromide under a variety of conditions yielded α-naphthol as a major product. However, it was possible to isolate the diastereomeric alcohols **9a** and **9b** in low yields from the reaction of phenylmagnesium bromide and tetralone **8** in ether at room temperature. Methylation of alcohols **9a** and **9b** occurred readily, and the methoxy amides thus obtained (**10a** and **10b**) were reduced with $LiAlH_4$ to amines **11a** and **11b**. Attempts to prepare acid salts of the amines suitable for biological testing resulted in the elimination of MeOH to give **12**. Hydrogenation of **12** gave predominantly **13b**. Compound **12** proved to be surprisingly stable to acid treatment; however, when the free amine of **12** was reacted with CH_3I and refluxed in EtOH, it underwent elimination to give 1-phenylnaphthalene, thus confirming its structure. Hydrogenolysis of **9a** and subsequent amide reduction gave approximately a 9:1 mixture of diastereomers **13a** and **13b**.

The stereochemistries of the diastereomers of **13** were tentatively assigned from their NMR spectra. Assuming half-chair preferred conformations for the aminotetralins[20] as shown in Figure 2, it is reasonable to expect a triplet for the benzilic proton in the trans isomer (**13a**), since it is symmetrically disposed relative to the C-2 protons. A double doublet would be expected for the benzilic proton in the cis isomer (**13b**), since it is not syymmetrically disposed relative to the C-2 protons. This assignment requires that the nitrogen substituent be in nearly an equatorial conformation in both isomers of **13**. This contention is supported by examination of molecular models (Figure 2), which reveal that the angle defined by the phenyl and hydrogen on C-1 is essentially bisected by the aromatic portion of the tetralin ring. Thus, the phenyl at C-1 will exist in a pseudoaxial conformation and exhibit a 1,3-pseudodiaxial interaction with a C-3 axial substituent and in doing so force a bulky C-3 substituent into an equatorial conformation. For the cis diastereomer, the favored conformation is as drawn in Figure 2, and the expected double doublet centered at 420 Hz is observed for the benzilic proton. In the trans diastereomer, 1,3-pseudodiaxial interaction must occur either between the C-1 phenyl and C-3 hydrogen or the C-1 hydrogen and C-3 tertiary nitrogen. The steric bulk of the N-substituent is greater than that of the phenyl; thus, the conformation with the N-substituent equatorial (as drawn in Figure 2) is expected to be more stable. The NMR spectrum of **13a** substantiates this conformation, since the benzilic proton appears as a triplet centered at 455 Hz. In addition, the axial 3-N conformation has the *N*-alkyl substituents placed directly over the aromatic portion of the tetralin ring, and the NMR would show substantial upfield shifts for these groups. The fact that no such upfield shifts of *N*-alkyl absorptions are observed in the NMR spectrum of **13a** (relative to **13b**) supports the favorability of the equatorial 3-nitrogen conformation. The assigned stereochemistry is also consistent with the probability that catalytic hydrogenation of **12** occurred from the less hindered side of the molecule to yield *cis*-1-phenyl-3-aminotetralin (**13b**).

Pharmacology. The analgetic potencies of the compounds were determined in the mouse hot-plate procedure.[21] All compounds were tested as racemates, and results are recorded in Table I. The narcotic antagonist activities of **13a** and **13b** (Table I) were determined in the mouse tail-flick procedure.[22] The samples of **13a** and **13b** were depleted before antagonist AD_{50} values could be determined.

Preliminary studies in addicted monkeys[23] showed that **13a**, at 5 mg/kg im dose, neither suppressed nor precipitated the signs of opiate abstinence.

Discussion

The similar degrees and profiles of agonist and antagonist activities seen for diastereomers **13a** and **13b** and for previously reported aminotetralins[8] containing a 1-phenyl substituent would suggest that the conformation of the phenyl at C-1 is not a critical factor influencing opiate activity. However, the inactivity of **12** indicates that the 1-phenyl substituent may play a critical role in the drug–receptor interaction. Further studies which correlate the absolute stereochemistries of the enantiomers of compounds **13a** and **13b** with their activities will be required to determine the exact influence of the 1-phenyl substituent on opiate-related activity.

The chemical instability of intermediates in Scheme I has hindered the synthesis of large quantities or numbers of compounds related to structure **1**. To overcome the instability problem, we are now preparing 2,2-dimethyl analogues of **1**. These compounds cannot readily aromatize and thus are easier to synthesize and to test pharmacologically.

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The activities observed for **13a** and **13b** demonstrate that significant levels of opiate antagonist, as well as the agonist activity previously reported,[7-9] can be obtained from A,B ring analogues of morphine. The antagonist activity occurs even though the compounds lack the phenolic hydroxyl and quaternary central carbon atom that are generally accepted as necessary for substantial antagonistic activity.[24,25] The effect of the lack of these two structural features on the normal pharmacological profile observed for mixed agonist–antagonists[26,27] remains to be determined.

Experimental Section

Melting points were obtained in open capillary tubes with a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined as thin films or as KBr disks using a Perkin-Elmer Model 457 spectrophotometer. NMR spectra were taken on a JOEL Minimar 100-MHz instrument in $CDCl_3$ (Me_4Si) or D_2O (DDS). All spectral results are in agreement with the structures assigned. Analytical results were determined by MHW laboratories and where indicated by symbols of elements are within ±0.4% of their calculated values.

Ethyl 3-(Methylamino)-4-phenylbutyrate (6). Methylamine was passed into a stirred solution of ethyl 4-phenylacetoacetate (**5**; 32.5 g, 0.158 mol) in 250 mL of MeOH cooled in an ice bath. After 12 g (0.387 mol) of methylamine had been added to the ester solution, the bottle containing the solution was capped and allowed to stand overnight at 25 °C. The resulting solution was then concentrated on a rotary evaporator to a viscous oil (the NMR spectrum was consistent with the expected enamine structure). This crude product was dissolved in 200 mL of methanol and cooled with stirring in an ice bath. To this solution was added 1.0 mg of Bromcresol green and 15.8 g (0.25 mol) of $NaBH_3CN$. HCl gas was then passed into this solution at such a rate as to just maintain a green-yellow color.[19] When the solution turned yellow and this color persisted (about 2 h), the reaction mixture was poured into 500 g of ice and the pH was adjusted to 8 with 50% aqueous NaOH. The solution was then extracted with CH_2Cl_2 (4 × 100 mL). The combined CH_2Cl_2 layers were dried over anhydrous $MgSO_4$, filtered, and evaporated to a viscous oil (the NMR spectrum was consistent with structure **6**), which was used directly in the subsequent step without further purification.

3-(*N*-Methyl-*N*-cyclopropanecarboxamido)-4-phenylbutyric Acid (7). The crude **6** was dissolved in 300 mL of benzene containing 20 mL of dry pyridine. To this solution was added dropwise with stirring in an ice bath 20.0 g (0.19 mol) of cyclopropanecarbonyl chloride. The resulting reaction mixture was allowed to stand for 2 h at 25 °C and poured into 200 mL of H_2O. The H_2O layer was removed, and the benzene solution was washed with 2 × 100 mL of 10% aqueous HCl. The benzene layer was then isolated and dried over anhydrous $MgSO_4$. The benzene was removed on a rotary evaporator, and the residual oil was dissolved in 200 mL of THF. To this solution was added 200 mL of 0.2 N NaOH, and the resulting two-phase system was stirred for 1 h at 25 °C. The aqueous layer was then removed, washed with ether (2 × 50 mL), and acidified with concentrated HCl. The crystalline acid that formed was collected on a filter, dried, and recrystallized from benzene–heptane (4:1) to yield 17.0 g of **7** (overall yield from **5**, 41%), mp 115–116 °C. Anal. ($C_{15}H_{19}N_3$) C, H, N.

3-(*N*-Methyl-*N*-cyclopropanecarboxamido)-1-tetralone (8). A 10 g (0.038 mol) sample of **7** in 100 mL of anhydrous HF was allowed to stand for 10 h in a loosely capped, virmiculite-insulated polyethylene bottle. The reaction solution was poured into a polyethylene beaker and allowed to evaporate to 10–20 mL (about 10 h). Ice and then water were added to the remaining solution, and then the resulting solution was extracted with CH_2Cl_2 (2 × 50 mL). The CH_2Cl_2 extracts were combined and extracted with $NaHCO_3$ (10% solution). Acidification of the $NaHCO_3$ extracts gave 3.5 g of the starting acid. The CH_2Cl_2 was extracted with 1 N NaOH solution (2 × 50 mL) to remove α-naphthol, then dried ($MgSO_4$), and evaporated to an oil. When dissolved in Et_2O (10 mL) and stored at −20 °C for several days, the oil solidified to give 2.5 g (41%) of (±)-**8** (mp (65–75 °C dec). Several recrystallizations from Et_2O failed to raise the melting point or decrease the range. TLC of this product in several systems showed a single entity, and NMR and IR spectra were consistent with the assigned structure. Anal. ($C_{15}H_{17}NO_2$) C, H, N.

3-(*N*-Methyl-*N*-cyclopropanecarboxamido)-1-hydroxy-1-phenyltetralin (9a,b). To a solution of 4.3 g (0.018 mol) of **8** in 300 mL of anhydrous Et_2O at 25 °C was added over 2–3 min 0.06 mol of PhMgBr (commercial 2 N solution). A precipitate formed which later turned into a syrup. Six hours after the addition of the Grignard reagent, the reaction was quenched by adding 25 mL of 5% HCl. The Et_2O layer was quickly separated and extracted with 1 N NaOH solution (2 × 25 mL) to remove α-naphthol. Evaporation of the organic layer and crystallization of the residue from 10 mL of 95% EtOH gave 0.5 g of **9a** (mp 224–247 °C). Anal. ($C_{21}H_{23}NO_2$) C, H, N. The remaining EtOH solution was evaporated, and the residue was dissolved in 10 mL of CCl_4. While the solution was standing overnight at room temperature, 0.7 g of the diastereomeric alcohol **9b** (mp 155–157 °C was obtained: yield of (±)-**9a** plus (±)-**9b** was 21%. Anal. ($C_{21}H_{23}NO_2$) C, H, N.

3-(*N*-Methyl-*N*-cyclopropanecarboxamido)-1-methoxy-1-phenyltetralin (10a,b). To an anhydrous DMF solution (10 mL) of 0.5 g (0.156 mmol) of **9a** and 0.15 g of 50% NaH–mineral oil (washed with pentane) was added 2 mL of CH_3I. After stirring at 21 °C for 10 h, the reaction mixture was poured into H_2O (100 mL) and extracted with Et_2O (2 × 50 mL). The combined Et_2O extracts were dried over anhydrous $MgSO_4$. Removal of the solvent on a rotary evaporatory gave a white crystalline product, which was recrystallized from petroleum ether–CCl_4 (1:1) to give 0.45 g (86%) of (±)-**10a** as white needles, mp 132–134 °C. A similar reaction sequence starting with 0.5 g of **9b** and 0.2 g of NaH–mineral oil yielded 0.42 g (80%) of (±)-**10b**, mp 132–134 °C. Anal. ($C_{22}H_{25}NO_2$) C, H, N.

Although the melting points of **10a** and **10b** are identical, the IR spectra clearly indicate that they were not the same compound. In CCl_4, major absorptions between 1300 and 1000 cm^{-1}. **10a**: 1263, 1235, 1095, 1060 cm^{-1}; 10b: 1285, 1020, 1030 cm^{-1}.

***trans*-3-[*N*-Methyl-*N*-(cyclopropylmethyl)amino]-1-phenyltetralin Hydrochloride (13a·HCl).** Hydrogenolysis (50 psi) of the benzilic hydroxyl in **9a** (0.2 g, 0.62 mmol) in 50 mL of EtOH containing 0.5 g of 10% Pd/C in 10 drops of $HClO_4$ (60% solution) gave a diastereomeric mixture of 3-cyclopropanecarboxamido-1-phenyltetralins (as evidenced by IR and NMR spectra). This mixture was further reduced in THF solution with 0.075 g of $LiAlH_4$ and worked up to give a 9:1 mixture (based on integration of benzilic protons in the NMR spectrum) of **13a**/**13b**. The free base in Et_2O was treated with HCl gas and recrystallized from EtOH–Et_2O to yield 0.050 g (28%) of (±)-**13a**·HCl, mp 156–157 °C; EIMS, *m/e* 291 (M^+). Anal. ($C_{21}H_{25}N$) C, H, N.

3-[*N*-(Cyclopropylmethyl)-*N*-methylamino]-3,4-dihydro-1-phenylnaphthalene Hydrochloride (12·HCl). Ether **10a** was dissolved in 30 mL of anhydrous Et_2O and reduced with $LiAlH_4$ (0.2 g) at 25 °C for 8 h. Water was added dropwise while stirring until the aluminium and lithium salts coagulated to a granular solid. The solid residue was removed by filtration, and the resulting Et_2O solution was dried over anhydrous $MgSO_4$. The Et_2O was removed on a rotary evaporator to give a pale yellow oil (**11a**), which would not crystallize (the NMR and IR spectra were consistent with the assigned structure). This oil was redissolved in dry Et_2O, and HCl gas was passed over the solution. This immediately produced a gummy residue, which upon manipulation with a glass rod and standing for 30 min crystallized to a white solid, **12**·HCl, mp 176–177 °C. When **10b** was reduced with $LiAlH_4$ and the crude product **11b** was treated with HCl, a product identical with that obtained from **10a** was obtained. When **11a** or **11b** is dissolved in dilute HCl–D_2O solution, one can follow

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the elimination of MeOH and the formation of (±)-12·HCl in the NMR spectrum. Anal. ($C_{21}H_{24}ClN$) C, H, N.

A sample of this salt was treated with aqueous $NaHCO_3$ and extracted with Et_2O. The Et_2O solution was dried over anhydrous $MgSO_4$ and 1.0 mL of CH_3I was added. The reaction mixture was allowed to stand for 1 h at 21 °C and evaporated to dryness on a rotary evaporator (the NMR spectrum was consistent with the methyl iodide salt derived from structure **12**). This salt was refluxed in ethanolic KOH for 30 min. The reaction mixture was then added to H_2O and extracted with pentane. The pentane layer was dried and evaporated to an oily residue. The NMR and IR spectra of this residue are identical with that of an authentic sample of 1-phenylnaphthalene.[28]

(28) C. J. Pouchert and J. R. Cambell, "Aldrich Library of NMR Spectra", Vol 4, Aldrich Chemical Co., Milwaukee, WI, 1974, p 28C.

***cis*-3-[*N*-(Cyclopropylmethyl)-*N*-methylamino]-1-phenyltetralin Hydrochloride (13b·HCl).** Hydrogenation of a sample of 12·HCl (0.1 g) with 5% Pd/C in EtOH and workup by evaporation, conversion to the free amine with 5% $NaHCO_3$, and Et_2O extraction gave an oil which would not crystallize. The NMR spectrum indicated an approximate 9:1 mixture of **13b**/**13a**. This oil was dissolved in Et_2O, and HCl gas was passed into the flask. The resulting precipitate was recrystallized from ether–ethanol to give 0.06 g (60%) of **13b**·HCl: mp 152–154 °C; IR and NMR spectra differed from those of (±)-**13a** (see chemistry section for details); EIMS, *m/e* 291 (M^+).

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Ring-Hydroxylated Analogues of Lucanthone as Antitumor Agents

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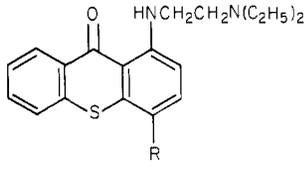
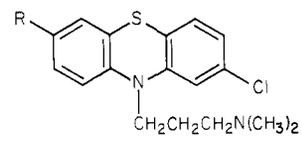
A series of ring-alkoxylated and ring-hydroxylated analogues of lucanthone was prepared and tested for antitumor activity. The most biologically interesting members of this group were the 7-hydroxylucanthone derivatives, **50** and **51**, which gave T/C values in the NCI P-388 antitumor screen of 188 and 265, respectively. The apparent association constants and ΔT_m values for a number of analogue–DNA complexes were determined to ascertain whether there was any quantitative correlation with biological activity. The most that can be said is that intercalation may be a necessary but far from sufficient condition for antitumor activity.

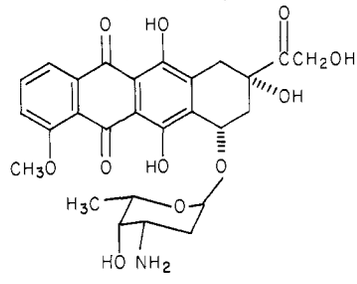
Several years ago Hirschberg reported that the antitumor activity of lucanthone (**1**) in L 1210 mice was abolished



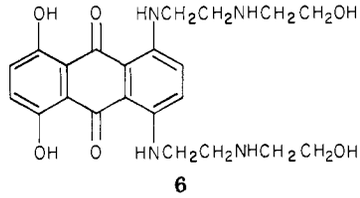
1 (lucanthone), R = CH_3
2 (hycanthone), R = CH_2OH



3 (chlorpromazine), R = H
4, R = OH



5 (adriamycin)



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by pretreatment of the animals with the mixed-function oxidase inhibitor SKF-525A.[1] This result indicated that biotransformation of **1** was required for in vivo antitumor activity. Several analogues of lucanthone were tested as antitumor agents, but none showed interesting activity. Some years ago it was reported that the active metabolite of lucanthone in schistosomiasis was the hydroxylated derivative, hycanthone (**2**).[2] This compound is an antitumor agent also, but, like lucanthone, the antitumor activity of **2** in L1210 mice was also abolished by pretreatment of the animals with SKF-525A.[1] The identity of the mysterious antitumor biotransformation product of lucanthone remains unknown to this day.

Chlorpromazine (**3**) bears a structural resemblance to lucanthone in the sense that both drugs have tricyclic aromatic systems, the middle ring of which contains divalent sulfur and a dialkylaminoalkyl group attached directly to one of the ring atoms. The metabolism of **3** has been well studied. Just as in the case of **1**, the corresponding sulfoxide is a metabolite and another major metabolite is the 7-hydroxy derivative (**4**).[3] It has been shown that lucanthone (**1**) and hycanthone (**2**) intercalate into DNA.[4] Many naturally occurring intercalating antitumor agents, such as dactinomycin and adriamycin (**5**),[5] as well as synthetic anthraquinones, such as **6**,[6] have oxygen substituents on their planar (or nearly planar) polycyclic ring systems. Ring hydroxylation increased the

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(2) D. Rosi, G. Perruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, and S. Archer, *J. Med. Chem.*, 10, 867 (1967).
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