homolysis (eq 1), whereas we implicate electron transfer (eq 2 and 3).

A rather different mechanism has been advanced by Iwaoka and Kondo.[13] In aqueous alcohol, dioxane, and glycerol, they find photoionization (from an upper triplet[13b]) to be a major process. However, photoionization is much less important in pure water or in aqueous acetonitrile,[13a] making the latter solvent much more suitable for the present investigation.

We conclude that the interaction of amines with photoexcited chlorophenothiazines 1 and 5 contributes to their photoreactivity. However, even in the absence of the side chain, 5 is still decomposed rather efficiently (ϕ = 0.2). This makes it relatively unlikely that a photostable drug of the chlorpromazine family can be synthesized merely by altering the constitution of the side chain of the drug. On photochemical grounds, substitution of the chlorine atom might be more fruitful.

Experimental Section

Fluorescence spectra were run in aerated solutions of aqueous acetonitrile and of isooctane at 23 °C using a Hitachi-Perkin-Elmer Model MPF-2A spectrophotofluorimeter. In the case of the drugs, supplied as salts, the free base was liberated from its salt with alkali. For the study in isooctane, the free base was then extracted into purified isooctane. Photolyses were carried out at 300 nm using a Rayonet Model RUL photoreactor. A "merry-go-round" was used to assure equal light absorption by samples irradiated in parallel. The samples were contained in Pyrex glass ampules, which were evacuated on a vacuum line where necessary using the freeze–pump–thaw technique. The progress of the reaction was followed by a potentiometric method (Orion Model 407A pIon meter and Orion Model 94-17A chloride-sensitive electrode). Because the solvent was CH_3CN–H_2O, it was necessary to make careful calibrations using solutions of known chloride concentration. Quantum yields of the reaction were made by comparison of the progress of the reaction with that of the ferrioxalate actinometer.[14]

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Aminotetralins as Narcotic Antagonists. Synthesis and Opiate-Related Activity of 1-Phenyl-2-aminotetralin Derivatives

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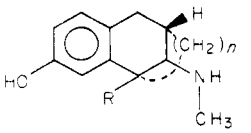
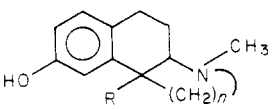
The synthesis and the opiate agonist and antagonist activities of three derivatives of *cis*-2-[methyl(cyclopropanemethyl)amino]-1-phenyltetralin are reported. The compounds were obtained by synthetic modification from 2-amino-1-tetralone. The 1-propionoxy derivative **4c** shows analgetic activity (ED_{50} = 17.8 mg/kg) one-half that of codeine, and the 1-methoxy derivative **4b** has weak antagonist activity (AD_{50} = 33.5 mg/kg). The compounds showed no other significant opiate-related activity.

Several reports on the 1-substituted 2-aminotetralin series with opiate activity have appeared. Freed et al.[1,2] have found the bridged aminotetralins of structure 1 to

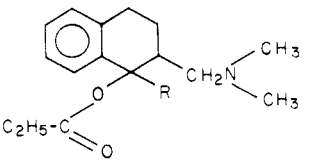


1, n = 4,5; R = Me, Et

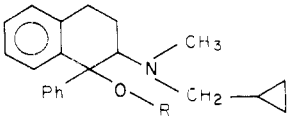


2, n = 2,3; R = Me, Et, Pr

be analgetic agonists and antagonists. In a similar series of compounds (**2**) synthesized by Takeda et al.,[3] analgetic activity in the range of codeine to morphine was found. Analgetic activities have also been reported for compounds of structure **3**.[4] Narcotic antagonist activity has not been



3, R = $CH_2C_6H_5$, $CH_2C_5H_4N$



4a, R = H
b, R = Me
c, R = OOCEt

reported for derivatives of **2** or **3**. Proper substitution of aminotetralin structures of this type could reasonably lead to compounds with mixed agonist–antagonist activity and possibly improved pharmacological properties over agents now available.

In the course of synthetic studies to prepare 1-substituted 3-aminotetralins,[5] several synthetic pathways were

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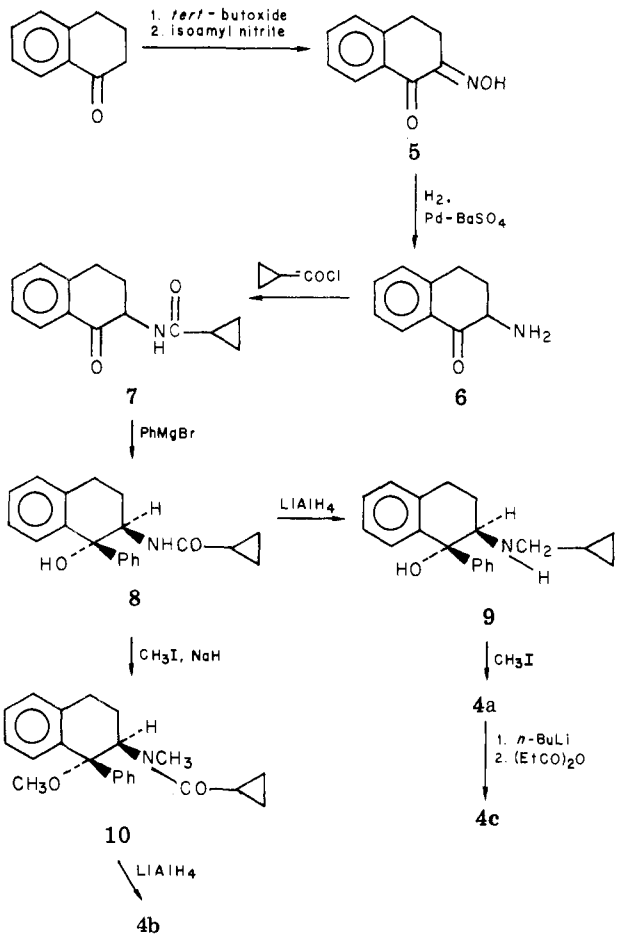
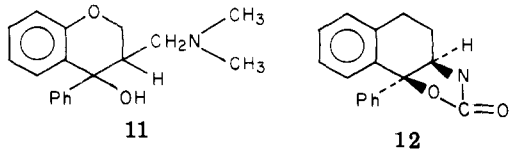
Scheme I



explored which led to 2-amino-1-tetralone.[6] This intermediate offered a relatively simple source for 1-substituted 2-aminotetralins. In this report, the preparation and opiate-related activities of several 1-phenyl-2-aminotetralin derivatives (**4a–c**) are described.

Chemistry. Several of the synthetic routes which were investigated in preparing aminotetralins led to 2-amino-1-tetralone.[6] The extension of one of these pathways (Scheme I) was used to synthesize the target compounds. Commercially available 1-tetralone was converted through 2-(hydroxyimino)-1-tetralone (**5**) to the 2-amino-1-tetralone (**6**).[7,8] Acylation of the amine with cyclopropanecarbonyl chloride provided the amide **7**. Grignard addition to **7** gave only one diasteriomer, **8**, which was reduced to the amine **9** and methylated to provide compound **4a**. Esterification of **4a** with propionic anhydride–butyllithium gave **4c**. The ether **4b** was obtained by O-methylation of **8** and reduction.

Attempts to prepare the ester **4c** by a 24-h reflux of the amino alcohol **4a** with propionyl chloride yielded a mixture of starting material and product **4c**. In a similar system (**11**), it has been reported that treatment of the *cis*-4-



hydroxy-3-hydro derivative with propionyl chloride in toluene at 60 °C for 2 h yielded the corresponding ester, returned some starting material, and gave no elimination product.[4] Under similar treatment the *trans*-4-hydroxy-3-hydro derivative (an arrangement favoring trans elimination of water) yielded the unsaturated chromane. Thus, the resistance to elimination shown by diasteriomer **4a** is indicative of a *cis*-1-hydroxy-2-hydro arrangement. Attempts to prepare the oxazolidine derivative **12** by treatment of **9** with diimidazolecarbonyl were not successful, consistent with a *cis*-hydroxy-2-hydro orientation.

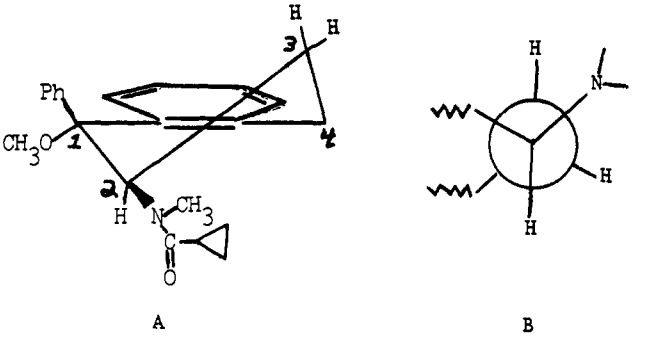


Figure 1. (A) Preferred conformation of substituted tetralins (ref 9). (B) Newman projection of the C-2 and C-3 portion of the tetralin ring showing the nonequivalence of the C-3 protons relative to the C-2 proton.

Table I. Opiate Agonist and Antagonist Activities of 1-Phenyl-2-aminotetralins

compd	ED_{50} (mg/kg, sc)[a]	AD_{50} (mg/kg, sc)[b]
4a·HCl	convulsant[c]	inact to 30
4b·HCl	inact to 50	33.5 (16.1-69.7)[d]
4c·HCl	17.8 (10.9-29.0)[d]	inact to 100
morphine	1.1 (0.8-1.5)[d]	

[a] Mouse hot-plate test for analgesia (ref 11). [b] Mouse-tail flick test for antagonism of morphine (6.5 mg/kg) (ref 12). [c] Compound was found to give fair analgesia at a dose of 50 mg/kg, but convulsant activity prevented an accurate assessment. [d] 95% confidence limits.

The half-chair conformation is considered energetically favorable for the tetralin system[9,10] with the 1-phenyl group existing in a quasiaxial configuration, as shown in Figure 1. The 2-amino functionality would prefer an equatorial orientation to avoid steric crowding with the 1-phenyl group. The proton NMR spectra of amide **10** shows a doublet of doublets for the C-2 proton centered at δ 5.70 with coupling constants of 4 and 14 Hz. These coupling constants are consistent with a C-2 axial proton being split by a C-3 equatorial proton and a C-3 axial proton, respectively. Thus, all of the diastereomers in this study are believed to have *cis*-1-phenyl-2-amino stereochemistry.

The insolubility of **8** in suitable solvents prevented the use of IR and NMR dilution studies to further confirm its stereochemistry.

Pharmacology. Compounds **4a–c** were tested for analgetic activity in the mouse hot-plate test.[11] Narcotic antagonist activities were determined in the mouse-tail flick procedure.[12] All pharmacological results are listed in Table I.

The low activities displayed by members of this series make questionable any structure–activity relationships with other analgetics. The degree of antagonist activity of **4b** is encouraging, since few compounds lacking the phenolic hydroxyl functionality (at position 7 of **4**) have been shown to possess narcotic antagonist activity.[13] Thus, it is likely that more potent opiate-related activity can be obtained from members of this series which are properly substituted. The preparation of phenolic derivatives of such agents is in progress.

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 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, Garden City, Mich., and, where indicated by symbols of elements, are within ±0.40% of their calculated values.

2-(Hydroxyimino)-1-tetralone (5). The procedure is essentially that of Thrift.[6] Potassium *tert*-butoxide (40.3 g, 0.36 mol) was added to a solution 100 mL of *tert*-butyl alcohol and 1.5 L of anhydrous Et_2O. The mixture was stirred and refluxed 12 h. 1-Tetralone (1) (51 g, 0.35 mol) was added over a period of 10 min, and then 57 mL (0.42 mol) of isoamyl nitrite was dripped slowly into the reaction mixture so as to maintain a gentle reflux. The reaction mixture was refluxed 1 h after the addition was completed. After cooling the reaction mixture, the voluminous precipitate that formed was filtered from the mixture, and the wet filter cake containing the product as the potassium salt was added to a beaker containing 500 mL of 2 N HCl and 500 mL of Et_2O. The organic layer was separated, dried (Na_2SO_4), and reduced in volume to 150 mL and on crystallization gave 24 g of **5** (mp 138–140 °C).

2-Aminotetralone Hydrochloride (6·HCl). The procedure of Zymalkowski and Rimek[7] was followed. A solution of **5** (15 g) in 150 mL of MeOH was added to a Paar hydrogenation bottle containing 0.5 g of Pd–$BaSO_4$ and a small volume of MeOH. A solution of 70 mL of 2 N HCl and 150 mL of MeOH was added and the mixture hydrogenated until H_2 uptake ceased (approximately 11 lb in 1.5 h). The reaction mixture was filtered, evaporated to 100 mL, washed with EtOAc, and evaporated to dryness. The residual HCl salt was crystallized from EtOH to give 11.0 g of **6** (mp 202–204 °C dec).

2-(Cyclopropanecarboxamido)-1-tetralone (7). Compound **6** (36.0 g; 0.184 mol) was treated with an equivalent amount of cyclopropanecarbonyl chloride under standard acylation condition. Workup and recrystallization from acetone gave 34.0 g of **7**, mp 155–158 °C. Anal. ($C_{14}H_{15}NO_2$) C, H, N.

1-Phenyl-1-hydroxy-2-(cyclopropanecarboxamido)-1-tetralone (8). A suspension of 4.0 g of **7** in 300 mL of anhydrous Et_2O was cooled to 0 °C, and 40 mL of 2 M phenylmagnesium bromide was added via syringe. The reaction mixture was stirred for 12 h while allowing the temperature to return to 25 °C. The reaction mixture was poured into an ice–NH_4Cl mixture, and the precipitate which formed was isolated by filtration to give 2.1 g of **8**. The Et_2O layer was separated, dried, and evaporated.

The residue was treated with petroleum ether and isolated by filtration to give 2.8 g of a solid material. Et_2O was added to the material and the insoluble portion was filtered off to give an additional 1.8 g of **8**. The Et_2O fraction was evaporated and the remaining 1.0 g of material was shown by NMR to be predominantly starting material with a small amount of product. The two crystallizations of product gave identical IR spectra and were homogeneous by TLC. A sample for analysis was recrystallized from acetone, mp 180–183 °C. Anal. ($C_{20}H_{21}NO_2$) C, H, N.

In other similar runs of this reaction, fractional crystallization of the product gave no indication of another diasteriomer being formed. Addition of the ketone to the Grignard reagent gave similar results. Reaction of the ketone with phenylmagnesium bromide in THF or phenyllithium in Et_2O yielded a mixture of starting material and decomposed compounds.

1-Phenyl-1-hydroxy-2-[(*N*-cyclopropanemethyl)amino]-tetralin (9). Compound **9** was prepared by reduction of **8** (8.0 g) in dry THF with $LiAlH_4$ (2.0 g) using standard procedures. The product (**9**·HCl) was isolated by crystallization from Et_2O–$CHCl_3$ (2:1) solution to yield 7.5 g of white solid, mp 209–210 °C. Anal. ($C_{20}H_{24}ClNO$) C, H, N.

1-Phenyl-1-methoxy-2-[*N*-methyl-*N*-(cyclopropanecarboxamido)]tetralin (10). Abstraction of the hydroxyl and amide protons from **8** (3.7 g; 0.012 mol) with NaH (0.036 mol) followed by stirring with excess MeI and standard workup procedures gave 3.1 g of **10**, mp 138–140 °C (from Et_2O–petroleum ether). Anal. ($C_{22}H_{25}NO_2$) C, H, N.

***c*-1-Phenyl-1-hydroxy-*r*-2-[*N*-methyl-*N*-(cyclopropanemethyl)amino]tetralin (4a).** A 5.3-g sample of **4** (0.018 mol) was dissolved in 100 mL of dry acetone, followed by the addition of 2.6 g (0.018 mol) of MeI and 5 g of anhydrous $KHCO_3$. The reaction mixture was stirred for 24 h at 25 °C. At the end of this time, the solvent was evaporated, and Et_2O–H_2O (100 mL of each) was added to the residue. The Et_2O layer was separated, dried, and evaporated to give 4.1 g of **4a** as an oil. The oil was crystallized from $CHCl_3$, mp 108–109 °C. Anal. ($C_{21}H_{25}NO$) C, H, N. HCl salt, mp 212–214 °C ($CHCl_3$–Et_2O). Anal. ($C_{21}H_{26}ClNO$) C, H, N.

***c*-1-Phenyl-1-propionyloxy-*r*-2-[*N*-methyl-*N*-(cyclopropanemethyl)amino]tetralin Hydrochloride (4c·HCl).** To a solution of 2.5 g of **4a** (0.008 mol) in 100 mL of dry THF was added 8 mL of 1.0 M butyllithium (0.008 mol), and the reaction mixture was allowed to stir for 0.5 h. To this mixture was then added dropwise 1.3 g (0.01 mol) of freshly distilled propionic anhydride in 30 mL of dry THF. The reaction mixture was allowed to stir for 12 h was then cooled, and 50 mL of water and 200 mL of Et_2O were added. The Et_2O layer was separated, washed twice with H_2O, dried, and evaporated to give an oil. The HCl salt of the oil was formed and crystallized from acetone to give 2.0 g of **4c**·HCl, mp 183–184 °C. Anal. ($C_{24}H_{30}ClNO_2$) C, H, N.

***c*-1-Phenyl-1-methoxy-*r*-2-[*N*-methyl-*N*-(cyclopropanemethyl)amino]tetralin Hydrochloride (4b·HCl).** To a solution of 3.1 g (0.009 mol) of **10** in 50 mL of THF was added 0.7 g of $LiAlH_4$ (0.01 mol), and the resulting mixture was refluxed overnight. The reaction mixture was then worked up by standard procedures to yield 2.0 g of **4b**·HCl, mp 189–190 °C (from $CHCl_3$–Et_2O). Anal. ($C_{22}H_{28}ClNO$) C, H, N.

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