was sought as described by Hansch.[12]

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References and Notes

(1) Established Investigator of the American Heart Association.
(2) Abbreviations used are COMT, catechol *O*-methyltransferase; SAM, *S*-adenosyl-L-methionine; 8-HQ, 8-hydroxyquinoline; DHB, 3,4-dihydroxybenzoic acid.
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(6) Using linear regression analyses (see Experimental Section), attempts were made to derive equations which could correlate the inhibitory activities of the 8-HQ's and various substituent parameters. Attempts to correlate the changes in inhibitory activities (pI_{50}'s) observed for the 5-substituted 8-HQ's with electronic (σ_5), inductive (F_5), or resonance parameters (R_5) were unsucessful.
(7) We have observed a tenuous correlation (see Experimental Section) between the hydrophobic character (π_7) and the inhibitory activities of the various 5- and 7-substituted 8-HQ's [pI_{50} = 4.61 (±0.12) + 0.44 (±0.14) π_7; n = 22; r = 0.82; s = 0.27; F test ($F_{1,20}$ = 42.38; $F_{1,20;\alpha\ 0.005}$ = 9.94)]. The π_7 values for iodide and bromide groups were taken from values listed for 2-substituted phenols[13] and the π_7 value for the nitro group was calculated from the experimentally determined log P value. The terms π_7^2, E_{s7}, and σ_{o7} were also used in attempts to obtain reasonable correlations but without significant success. Because of the small number of analogs with substituents in the 7 position, any correlation observed between the inhibitory activities and substituent parameters must be interpreted with care.
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Bridged Aminotetralins. 4. Resolution of Potent Analgesics of the Bridged Aminotetralin Type

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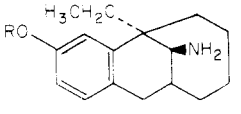
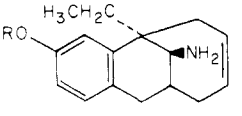
The resolution of three potent analgesics of the bridged aminotetralin type has been described, as well as the conversion of the enantiomers to the related phenols. Several of the compounds demonstrated analgesic activity up to 15 times that of morphine.

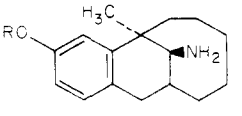
In previous reports[1,2] we described the synthesis and analgesic activity of a series of 1,3-bridged aminotetralins, including compounds with the potency level of morphine. Several of the more potent analgesics were selected for resolution into optical isomers. The compounds chosen were all β-epimers, in which the amine function is equatorially located relative to the tetralin ring and is trans to the alkyl function in the 5 position.[1] The resolution of these compounds (1-7) and the analgesic activities of the isomers are described herein.



1, R = CH_3
2, R = H



3, R = CH_3
4, R = H



5, R = CH_3
6, R = H
7, R = c-C_3H_5-C=O

Chemistry. The three methoxy derivatives **1**, **3**, and **5** were resolved by treatment with *d*- and *l*-tartaric acids and fractional crystallization of the tartrate salts from methanol to constant rotation. Both (+) and (-) rotamers were obtained. The resolved isomers **1** and **5** were demethylated to the corresponding phenols **2** and **6** in refluxing concentrated hydrobromic acid. The demethylation of **3** to **4** was carried out at low temperature with boron tribromide.

It was shown in a previous paper of this series[2] that acylation of the phenolic hydroxyl group gives derivatives of at least equivalent analgesic activity. Accordingly, the (-) rotamer of the phenol **6** was converted to its cyclopropylcarboxylate ester. This was done by the previously described route,[2] which involved blocking the primary amine with the benzyloxycarbonyl-protecting group, forming the ester of the phenolic OH, and then removing the blocking group by hydrogenation under acidic conditions.

Hydrogenation of the (+) rotamer of **3** over platinum oxide gave the (-) rotamer of **1**. Thus, despite the difference in signs of rotation, (-)-**1** and (+)-**3** are stereochemically related. In all likelihood, (-)-5 is also of the same relative configuration as (-)-**1**.

Pharmacology. The resolved compounds were tested for analgesic activity in the D'Amour-Smith rat tail flick test.[3] In Table I are shown the analgesic ED_{50}'s of these compounds when administered by ip, im, and po routes. The table shows that phenols are more active than the corresponding methoxy derivatives, while in the case of the one example reported (**7**), esterification of the phenolic function resulted in diminished activity.

It can also be seen that the most active compounds are (-)-**2**, (+)-**4**, and (-)-**6**, with potencies up to 15 times that of morphine. It was shown above that these compounds, despite the sign of rotation of (+)-**4**, are of the same relative stereochemistry. In the case of compound **6**, virtually all of the analgesic activity is exhibited by the (-) rotamer.

Table I. Analgesic Activities of Resolved Aminotetralins

Compd[a]	ED_{50}, mg/kg (95% SE limits) ip	im	po
(+)-1[b]	10[c]	10.0 (9.62-11.88)	30[c]
(-)-1[b]	3.3[c]	3.5 (2.81-4.75)	7.5[c]
(±)-1[b]	3.5 (1.17-4.91)	12.0 (10.99-12.85)	*d*
(+)-2[e]	7.5[c]	2.0 (1.61-3.18)	80[c]
(-)-2[e]	0.5 (0.31-0.82)	0.1 (0.072-0.225)	3.5 (2.21-4.65)
(±)-2[e]	3.7 (0.84-5.91)	0.25 (0.162-0.312)	10[c]
(+)-3[b]	3.75 (2.61-4.77)	12.5[c]	
(-)-3[b]	>6.25[f]		
(±)-3[b]	4.2 (3.62-4.91)		
(+)-4[b]	0.80[c]	0.195 (0.152-0.248)	5[c]
(-)-4[b]	9.0[c]	4.0 (3.125-5.25)	
(±)-4[b]	1.75[c]		
(+)-5[b]	>25[f]		
(-)-5[b]	2.0 (1.66-3.05)	4.5 (3.12-5.22)	3.5 (2.05-4.24)
(±)-5[b]	4.88 (2.67-7.01)		
(+)-6[g]	>100[f]	95[c]	
(-)-6[g]	0.53 (0.37-0.76)	0.12 (0.08-0.17)	2.05 (1.71-2.45)
(±)-6[g]	1.11 (0.14-2.17)	0.45 (0.382-0.492)	10[c]
(-)-7[b]	1.5[c]	0.45 (0.39-0.551)	
Morphine	4.43 (2.93-4.77)	1.57 (1.32-1.82)	15.9 (13.25-18.51)

[a] Compounds were administered in aqueous solutions or as suspensions in Tween-80 to groups of five to ten Charles River rats. Doses were calculated as milligrams of base per kilogram. [b] Hydrochloride salt. [c] Based on two doses. [d] Tested at one dose level (20 mg/kg); analgesic in 10/10 rats. [e] Free base. [f] Highest dose tested. [g] Hydrobromide salt.

This compound, (-)-**6**, was found to be the most potent of the group when administered orally, being about eight times as potent as morphine by this route. In acute toxicity studies in rats, (-)-**6** showed an oral LD_{50} of 200 mg/kg. A comparison of the agonist and antagonist activity of **6** [racemic, (+), and (-) rotamers] in the rat has been reported.[4] It was shown that in this compound there was no separation of activities on resolution. Both analgesic and narcotic antagonism were retained by the (-) rotamer.

Malis, Rosenthale, and Gluckman have reported[5] that in physical dependence studies carried out in our laboratories and those of the University of Michigan (-)-**6**, when administered intramuscularly to morphine-dependent Rhesus monkeys, caused the precipitation of withdrawal symptoms at doses of 0.5 and 1.0 mg/kg. At the higher dose (1.0 mg/kg) the effect persisted for over 10 h. The compound was judged to be a morphine antagonist slightly less potent but longer acting than nalorphine. The analgesic activity of (-)-**6** has also been demonstrated[5] in monkeys. In the monkey shock titration procedure (-)-**6** produced significant increases in shock threshold at doses as low as 0.06 mg/kg intramuscularly. When orally administered to monkeys (-)-**6** produced dose-related increases in shock thresholds over dose range from 0.25 to 12 mg/kg. This compound, (-)-**6**,[5] is currently undergoing clinical trials.

Experimental Section

Melting points were determined on the Thomas-Hoover Uni-Melt apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model IR-21 spectrophotometer. Ir spectra and microanalyses were determined under the supervision of Mr. B. Hofmann of Wyeth Laboratories, Inc. Rotations were determined on a Zeiss polarimeter LEP A2. The $[\alpha]_D$ values were calculated by extrapolation from instrument readings made at 578 and 546 μ.

Resolutions. A solution of 83 g (0.32 mol) of (±)-5,6,7,8,9,-10,11,12-octahydro-3-methoxy-5α-methyl-5,11-methanobenzocyclodecen-13β-amine (**5**) in 200 ml of MeOH was added to a solution of 57 g (0.38 mol) of *d*-tartaric acid in 500 ml of MeOH. The solution was diluted to 1 l. and allowed to stand for 2 days. Filtration gave 83.5 g of salt with mp 200–208° dec, $[\alpha]^{25}_D$ +14.8° (*c* 3, DMF). Further recrystallizations from MeOH to constant rotation gave 21 g of salt with mp 216–219° and $[\alpha]^{25}_D$ +43° (*c* 3, DMF). Anal. ($C_{17}H_{25}NO \cdot C_4H_6O_6$) C, H, N. The salt was treated with dilute NaOH, extracted with Et_2O, dried ($MgSO_4$), and concentrated to give 13 g of base. Preparation of the HCl salt in Et_2O–EtH gave a salt with mp 234–237° and $[\alpha]^{25}_D$ +46.0° (*c* 3, MeOH). Anal. ($C_{17}H_{26}NOCl$) C, H, N.

To obtain the opposite rotamer, the combined mother liquors from the above were concentrated and the residue was treated with dilute NaOH, extracted with ether, dried ($MgSO_4$), and concentrated to give 58 g of (-)-enriched base. This was added in MeOH to 38 g of *l*-tartaric acid in MeOH. The solution was diluted to 800 ml, allowed to stand for 4 days, and filtered to give 41.3 g of salt with mp 204–209°. Further recrystallizations to constant rotation gave 21.7 g, mp 216–218°, $[\alpha]^{25}_D$ -44° (*c* 3, DMF). Conversion of this salt to the base and subsequently to the HCl salt gave a salt with mp 234–237° and $[\alpha]^{25}_D$ -46.0° (*c* 3, MeOH). Anal. ($C_{17}H_{26}NOCl$) C, H, N.

In a similar manner, 5α-ethyl-6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine (**1**) was resolved to give a (+)-rotating tartrate salt with mp 209–211°, $[\alpha]^{25}_D$ +31.9° (*c* 1, DMF), and a (-)-rotating tartrate salt with mp 210–212°, $[\alpha]^{25}_D$ -32.8° (*c* 1, DMF). Conversion to the HCl salts in the usual manner gave the HCl salts as hydrates; the (+) isomer had mp 115–119°, $[\alpha]^{25}_D$ +44.5° (*c* 2, MeOH) [Anal. ($C_{17}H_{26}NOCl \cdot H_2O$) C, H, N], and the (-) isomer had mp 115–119°, $[\alpha]^{25}_D$ -44.1° (*c* 2, MeOH) [Anal. ($C_{17}H_{26}NOCl \cdot H_2O$) C, H, N].

The resolution of 5α-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine (**3**) using essentially the same procedure gave (+)-**3** tartrate with mp 210–211°, $[\alpha]^{25}_D$ +47.7° (*c* 3, DMF), and a (-)-tartrate with mp 209–211°, $[\alpha]^{25}_D$ -47.6° (*c* 3, DMF). Conversion in the usual manner to base gave (+)-**3** with mp 48–51°, $[\alpha]^{25}_D$ +84.3° (*c* 2, MeOH), and mp 50–53°, $[\alpha]^{25}_D$ -85.4° (*c* 2, MeOH) for the (-) rotamer. The HCl salts were prepared and showed mp 260–265°, $[\alpha]^{25}_D$ +69.3° (*c* 2, MeOH) [Anal. ($C_{17}H_{24}NOCl$) C, H, N], for the (+)-salt and mp 272–275°, $[\alpha]^{25}_D$ 69.6° (*c* 2, MeOH) [Anal. ($C_{17}H_{24}NOCl$) C, H, N], for the (-)-salt.

Preparation of Phenols. A. HBr Method. In a typical example, 6.5 g of (-)-5,6,7,8,9,10,11,12-octahydro-3-methoxy-5α-methyl-5,11-methanobenzocyclodecen-13β-amine [(-)-**5**] was refluxed for 0.5 h under N_2 in 48% HBr and then concentrated. The residue was recrystallized from H_2O to give 5.5 g of the HBr salt of the phenol (-)-**6** with mp 269–271° and $[\alpha]^{25}_D$ -41.7° (*c* 3, MeOH) [Anal. ($C_{16}H_{24}NOBr$) C, H, N].

Compounds (+)-**1** and (-)-**1** were demethylated in the same manner. After removal of the concentrated HBr, however, the residue obtained was treated with concentrated NH_4OH and the crystalline (+)- and (-)-bases were collected by filtration. Recrystallization of the bases [(+)-**2** and (-)-**2**] from EtOAc gave the (+) isomer, mp 194–196°, $[\alpha]^{25}_D$ +52.0° (*c* 2, MeOH) [Anal. ($C_{16}H_{23}NO$) C, H, N], and the (-) isomer, mp 194–196°, $[\alpha]^{25}_D$ -51.3° (*c* 2, MeOH) [Anal. ($C_{16}H_{23}NO$) C, H, N]. The (-) isomer of **2** was also converted to its HCl salt, which on recrystallization from CH_3CN had mp 245–270°, $[\alpha]^{25}_D$ -43.4° [Anal. ($C_{16}H_{24}NOCl$) C, H, N].

B. Boron Tribromide Method. A solution of 15 g of (+)-5α-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine [(+)-**3**] in 500 ml of CH_2Cl_2 was cooled to -20° under N_2. A solution of 15 ml of BBr_3 in 500 ml of CH_2Cl_2 was added with stirring and while maintaining the temperature at -20°. The mixture was allowed to come to room temperature while stirring was continued overnight. The reaction mixture was carefully treated with 100 ml of H_2O and stirred for 1 h. The aqueous phase was then separated, treated with

concentrated NH_4OH, and filtered to give 11.4 g of base product. This product was converted to its HCl salt in Et_2O–EtOH to give 12.0 g of (+)-4, mp 261–263°, $[\alpha]^{25}D$ +83.0° (c 2.5, MeOH). Anal. ($C_{16}H_{22}NOCl$) C, H, N.

In a similar manner, (−)-3 was converted to the corresponding phenol, (−)-4, which gave an HCl salt with mp 260–262°, $[\alpha]^{25}D$ −82.8° (c 2.5, MeOH). Anal. ($C_{16}H_{22}NOCl$) C, H, N.

Hydrogenation of (+)-3. A solution of 350 mg of (+)-3 ($[\alpha]^{25}D$ +69.3) in 75 ml of EtOH containing 0.5 ml of concentrated HCl was hydrogenated over 100 mg of PtO_2 in a Parr shaker at 23 psi. After 20 min, H_2 uptake was completed. The catalyst was filtered and the filtrate was concentrated to dryness. The residue was crystallized from H_2O to give 150 mg of product with mp 115–119° and $[\alpha]^{25}D$ −43.2° (c 2, MeOH). This product had an ir spectrum identical with that of (−)-1·HCl.

Preparation of the Ester Derivative (−)-13β-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol Cyclopropanecarboxylate (7). A mixture of 5.0 g of the HBr salt of (−)-6, 2.8 g of benzyl chloroformate, 200 ml of saturated $NaHCO_3$, and 200 ml of CH_2Cl_2 was stirred for 2 h. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and concentrated to give an oil. The oil was washed several times with hexane to remove the last traces of benzyl chloroformate. The resultant viscous material was dissolved in 200 ml of C_6H_6 containing 1.7 g of Et_3N. To this stirred solution was added slowly 1.7 g of cyclopropylcarboxoyl chloride in 15 ml of C_6H_6. The reaction mixture was stirred an additional 0.5 h, washed with H_2O followed by dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated to give an essentially pure ester derivative which still had the N-benzyloxycarbonyl-blocking group. This material was dissolved in 250 ml of THF containing 3.0 g of dry HCl and hydrogenated over 1.6 g of 10% Pd/C at 45 psi of H_2 for 3 h. The catalyst was filtered and the filtrate concentrated. The residue was crystallized from THF–Et_2O to give 2.3 g of the HCl salt of 7, mp 278°, $[\alpha]^{25}D$ −39.5° (c 2, MeOH). Anal. ($C_{20}H_{28}NO_2Cl$) C, H, N.

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(5) The complete animal pharmacology of this compound, designated in our laboratory as WY-16225, has been disclosed by J. L. Malis, M. E. Rosenthale, and M. I. Gluckman, *J. Pharmacol. Exp. Ther.*, **194**, 488 (1975).

3-Cyanocephems, and Carbon-13 Heterocyclic-Substituted Cephems via 1,3-Dipolar Cycloadditions[1]

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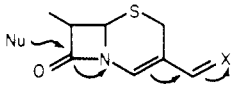
The transformation is described of 3-formylcephem 1 into its oxime, substituted oximes, and substituted hydrazones and, thence, into the 3-cyano, 3-diazomethyl, and 3-oxonitrilomethyl derivatives. These reactive 1,3-dipoles undergo 1,3-dipolar cycloadditions with various dipolarophiles to give C-3 heterocyclic-substituted cephems.

In the course of a program designed to produce cephems modified in the 3 position, analogues in which the dihydrothiazine ring contains proximate unsaturation seemed particularly attractive, because extension of the unsaturated system might increase the reactivity of the β-lactam; thus



The introduction of substituents at higher oxidation levels seemed especially interesting because they might provide enhanced reactivity. Extension of our interest in these compounds has led to the preparation of reactive 1,3-dipoles at the 3 position which have been utilized in the preparation of C-3 heterocyclic-substituted cephems by 1,3-dipolar cycloaddition. At the inception of this work, no examples of 1,3-dipoles directly attached to C-3 were known,[2-4] but recently the preparation and cycloaddition reactions of a 3-nitrone have been reported.[5]

Reaction of hydroxylamine with β-lactam antibiotics results in rapid cleavage of the β-lactam ring and has been used as a chemical assay method.[6] However, a suspension of the 3-formylcephem 1[7] reacted with 2 equiv of hydroxylamine hydrochloride in refluxing isopropyl alcohol within 10 min to give the 3-aldoxime **2**. The ester could be cleaved with TFA–anisole in the usual way to the free acid **3**.

The oxidation level of the 3-substituent could now be raised by simply dehydrating the oxime with thionyl chloride, producing the nitrile **11**, which was deblocked to the acid **12** with TFA–anisole. Both **3** and **12** underwent facile hydrolytic cleavage of the β-lactam upon raising the pH above 7.8.

An essentially similar condensation of **1** with aminooxyacetic acid hemihydrochloride produced the 3-[[[(carboxymethylene)oxy]imino]methyl]cephem **5**. Diazomethane treatment gave the corresponding 3-[[[(methoxycarbonylmethyl)oxy]imino]methyl] **6** in quantitative yield. Cleavage of the ester as before gave the free acid **7**. Analogously, formation of oximes **9** and **10** was achieved in ca. 50% yield by condensation of **1** with methoxyamine or benzyloxyamine in $CHCl_3$–MeOH at 25°.

Substituted hydrazines were also found to condense with **1** under conditions in which they were nucleophilic enough to react with the 3-formyl substituent and yet not basic enough to rupture the β-lactam ring. Thus, an equimolar solution of **1** and p-toluenesulfonylhydrazine in $CHCl_3$ gave the tosylhydrazone **13** quantitatively in 15 min at 25°. Subsequent reaction with diazomethane provided the N-methyl tosylhydrazone **14**. The condensation was found to be generally applicable, and cephems **17–20** were prepared using the appropriate hydrazines.

The preparation of diazoalkanes by pyrolysis of salts of p-tosylhydrazones has been reported.[8] A solution of the tosylhydrazone **13** in THF at −78° reacted with 1 equiv of