Synthesis, Stereochemistry, and Analgesic Activities of Diastereoisomeric Esters of 3-Allyl-4-phenyl-4-piperidinol

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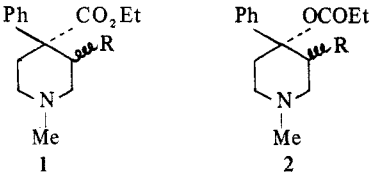
The α and β isomers of 3-allyl-1-methyl-4-phenyl-4-propionyloxypiperidine and related compounds (synthesized from 3-allyl-4-piperidones) have been assigned the configurations *c*-3-allyl and *t*-3-allyl-*r*-acyloxy(hydroxy), respectively, on the basis of ^{1}H nmr evidence and the behavior of the parent 4-piperidinols toward dilute hydrochloric acid. Cyclic products resulting from the action of hot 16% HCl–H_2O upon α-3-allyl-1-methyl-4-phenyl-4-piperidinol are described. In mice (hot-plate test) the above named α-propionate was 13 times and the β isomer 0.1 times as active as morphine, while in rats the α-ester was 60 times morphine (tail-withdrawal test) and behaved as a typical narcotic analgetic. The effects of 3-allyl contrasted with those of 3-methyl substituents by comparing their analgesic activity to that of 1-methyl-4-phenyl-4-propionyloxypiperidine (the reversed ester of pethidine).

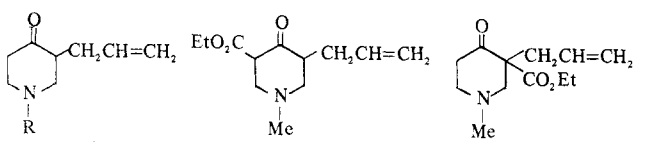
This work forms part of our studies of asymmetric analogs of pethidine (**1a**) and its reversed ester **2a**.[1-4] When R in **1**



1 **2**

a, R = H
b, R = Me
c, R = $CH_2CH{=}CH_2$

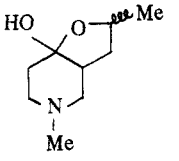
and **2** is methyl, the *t*-3-methyl-*r*-4-CO_2Et (or OCOEt) isomer (designed β) is more potent an analgesic than the corresponding *c* diastereoisomer (α), as judged by animal tests, and this is true also for analogs of **2b** in which the 1 and 4 substituents are varied.[5,6] The report of the α isomer of the 3-allyl analog **2c** being the more potent analgesic[7,8] appears exceptional but its stereochemistry was based only on ir spectral data which led to an incorrect assignment of the relative geometry of the α- and β-prodine (**2b**). The correct assignment of these configurations, based on X-ray and nmr studies, was subsequently reported[9,10] and a further study of the diastereoisomers (**2c**) and related compounds has now been made.



3 **4** **5**

a, R = CH_2Ph
b, R = Me

The intermediate 4-piperidone **3a** was made in low yield by alkylating the sodium salt of 1-benzyl-4-piperidone with allyl bromide according a method Conia[11] applied to cyclohexanones. Similar alkylation of the stronger base 1-methyl-4-piperidone failed and the 1-methyl analog **3b** was made by the method of Ziering and others.[7] In this procedure, decarboxylation of the Dieckmann cyclization product (**4** and/or **5**) must be effected by dilute hydrochloric acid; use of 20% acid led to a nonketonic solid which had a melting point (after sublimation) close to that of a product similarly obtained by McElvain and Barnett from **5**.[12] The hemiacetal structure **6** of this solid originally proposed from ir and analytical evidence[12] is now confirmed from its mass spectrum, while the presence of a pair of methyl doublets in its ^{1}H nmr spectrum (δ 1.40 and 1.36, $^3J \sim 7$ Hz in $CDCl_3$) shows that the product is a diastereoisomeric mixture. Formation of **6** from **4** (or **5**) probably proceeds *via*



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hydration of the terminal carbon–carbon double bond, a reaction facilitated by a rise in the acid concentration. Treatment of the 4-piperidone **3** with phenyllithium and acylation of the products gave the corresponding 4-phenyl-4-piperidinols and their esters; isomers were separated by fractional crystallization and/or column chromatography (details in the Experimental Section).

Assignment of the configurations *c*-3-allyl-*r*-4-hydroxy(acyloxy) to α and *t*-3-allyl to β isomers is made from consideration of ^{1}H nmr characteristics of isomeric esters and the behavior of isomeric alcohols toward dilute hydrochloric acid. The chemical shifts of the acyloxy protons of diastereoisomeric pairs differ, and the α and β values are similar to those of α- and β-3-methyl analogs, respectively (Table I);

Table I. ^{1}H Nmr Chemical Shifts of Some 4-Acyloxy-4-phenylpiperidine Hydrochlorides in Deuteriochloroform

Structure	Isomer	Chemical shifts of acyloxy (OCOR) protons[a]		
		Me[b]	CH_2Me[c]	CH_2Me[d]
2c	α		2.63 (2.75)	1.26 (1.32)
	β		2.41 (2.58)	1.08 (1.17)
Acetoxy analog of 2c	α	2.31		
	β	2.08		
N-Benzyl analog of 2c	α		2.50	1.15
	β		2.30	1.00
2b[e]	α		2.59	1.22
	β		2.38	1.07
Acetoxy analog of 2b[e]	α	2.27		
	β	2.09		

[a]Chemical shifts in δ units with tetramethylsilane as internal standard; values in parentheses refer to spectra run in D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard; δ values of corresponding bases differed little from those of the salts. [b]Singlet. [c]Quartet, $^3J \sim 7$ Hz. [d]Triplet, $^3J \sim 7$ Hz. [e]Data from ref 1.

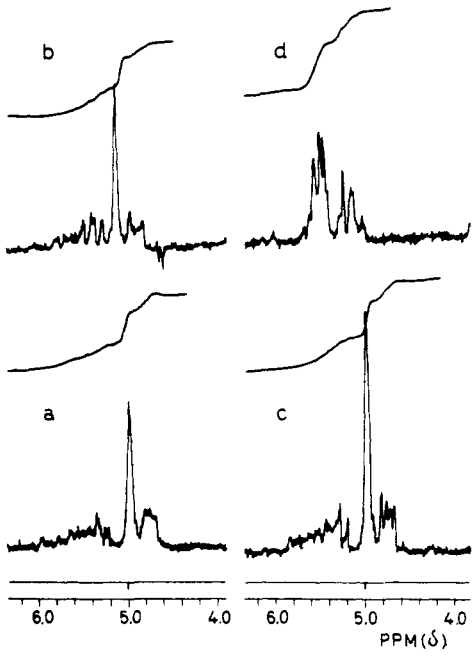
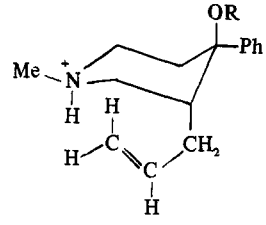


Figure 1. Resonance region of the CH_2=CH portion of the 3-allyl group: a, α-2c base; b, α-2c hydrochloride; c, β-2c base; d, β-2c hydrochloride.

the stereochemistry of the latter compounds (2b and the related acetoxy derivative) is established[10] (see same reference for interpretation of the differences in isomeric δ_{OCOR} values). In α-esters, the terminal methylene signal of the 3-allyl group (m near δ 5 in $CDCl_3$) suffers little change when the ring nitrogen atom is protonated (Figure 1a,b); in contrast, the corresponding signal of β-bases moves downfield in the salts to overlap the broad methine (CH_2=C*H*) resonance (Figure 1c,d). Similar effects are seen in spectra of the parent 4-piperidinols and these results support the assigned configurations because the methylene protons in question would only be expected to approach charged nitrogen closely enough to fall under its deshielding influence when the 3-allyl substituent is axial as in 7. Examples



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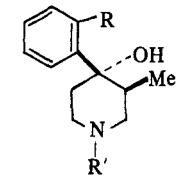
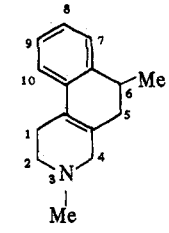
of protons deshielded through space by a charged nitrogen center were reported previously.[10,13] The β-OCOR signals were also higher field than the corresponding resonances of the α-esters in spectra run in D_2O and in a similar degree to differences seen in $CDCl_3$ (Table I). Hence, the preferred conformations of the protonated esters 2c are likely to be similar in the two solvents. The terminal methylene resonance of the 3-allyl group of β-2c hydrochloride moved upfield when $CDCl_3$ was replaced by D_2O, due probably to a modification of the shielding influence of charged nitrogen consequent upon this solvent change.†

Further stereochemical evidence was obtained from the action of 16% aqueous hydrochloric acid (24 hr at 50°) on the isomeric 4-piperidinols related to 2c. It has been shown that the 3-*t*-methyl-4-*r*-hydroxypiperidines 8a and 8b are extensively dehydrated, whereas the 3-*c*-methyl isomers are unchanged after this treatment.[6,15] In the present case,



8a, R = H
b, R = Me
(R' = Me, Et, or CH_2Ph)

both isomers suffered partial hydration of the allylic double bond, as shown by a secondary methyl resonance (d, δ 1.23, $^3J \sim 7$ Hz) in ^1H nmr spectra of the products, but only the β form underwent significant dehydration: a well-resolved triplet (δ 5.9, line separation 4 Hz) appeared in the β spectrum which was typical of vinylic protons in 4-aryl-1,2,5,-6-tetrahydropyridines.[16] More vigorous treatment of the α-3-allyl-4-piperidinol (16% HCl, 6 hr of reflux) gave a mixture from which two products were isolated, identified as the benzoisoquinoline 9 and the tetrahydrofuran 10, respectively, on the basis of evidence detailed in the Experimental Section. The derivative 10 is most likely formed by a mechanism similar to that leading to the hemiacetal compound 6, *i.e.*, hydration of the allylic double bond and ring



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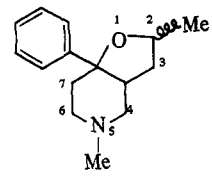

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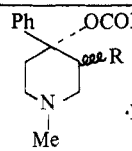
closure through H_2O elimination of the intermediate diol. When hydration of the allylic double bond is followed by dehydration of the piperidinol, the central carbon atom (with carbonium ion character) of the propyl substituent of the intermediate tetrahydropyridine would then cycloalkylate the neighboring aromatic ring leading to 9.

Pharmacology and Discussion. In mice (hot-plate test), α-2c was about 13 times and β-2c about one-tenth as active as morphine (Table II). These results confirm the superiority of the α form as an analgesic but the potency of the β isomer is much less than the value reported earlier (α-2c 11 times, β-2c 3 times morphine, mice, tail pressure method).[7,8] In rats, by the tail-withdrawal test,[17] our sample of α-2c was over 60 times as active as morphine [ED_{50} (mg/kg) 0.08, morphine 5.0] while the acetoxy analog of α-2c (ED_{50} 0.16) was half as active as the propionate. Both α-esters may confidently be classified as narcotic analgesics since they caused typical morphine-like effects in rats, notably lead-pipe rigidity of the back and the hind limbs and loss of the pinna and cornea reflexes.[17] In the same test, β-2c was slightly active at 10 mg/kg. These findings agree with those of the hot-plate test and confirm that α-2c is over 100 times as active as β-2c.

Assuming (1) that receptor events are the chief cause of activity differences between α- and β-2c (differences in the brain concentrations of the two isomers are unlikely to be

†The β-3-methyl (axial) resonance of β-prodine and related salts also moves upfield after the same solvent change.[1] This result was previously attributed to a conformational change but recent ^{13}C nmr studies of β-prodine discount such an explanation.[14]

Table II. Hot-Plate Activities in Mice[a] of Some Reversed Esters of Pethidine



No.	R (isomer)	ED_{50}, mg/kg sc[b] (95% confidence limits)	Rel potency (morphine = 1)
2a	H	0.85 (0.64–1.11)[c]	1.4
2b	α-Me	0.92[d]	1.3
2c	α-$CH_2CH{=}CH_2$	0.09 (0.07–0.10)	13.3
2b	β-Me	0.18[d]	6.7
2c	β-$CH_2CH{=}CH_2$	11.7 (9.4–14.6)	0.1
Morphine HCl		1.2 (0.9–1.3)	1.0

[a] A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965). [b] Data obtained from Dr. E. L. May of the Department of Medicinal Chemistry, National Institutes of Health, Bethesda, Md. [c] Reference 4. [d] A. F. Casy and K. McErlane, *J. Pharm. Pharmacol.*, 23, 68 (1971).

large)‡ and (2) that the "active" conformation of the reversed esters does not differ significantly from the preferred geometry, it must be concluded that an equatorially placed 3-allyl function markedly enhances receptor association when compared to the desallyl analog, whereas the axially placed 3-allyl function lowers the activity of the parent ester (Table II, **2a**, α-**2c**, and β-**2c**). Results upon the isomers **2c** contrast sharply with the effect of inserting (e)- and (a)-methyl groups into the 3 position of the unsubstituted ester (Table II, **2a**, α-**2b**, and β-**2c**). Comparative data upon 3-ethyl and 3-propyl analogs of α- and β-**2c** are presently gathered and a further discussion of the effects of the 3-alkyl substituents upon analgesic activity in reversed esters of pethidine is deferred until this information is available.

Experimental Section§

3-Allyl-1-benzyl-4-piperidone (3a). A solution of Na (1 g) in *tert*-amyl alcohol (20 ml) was evaporated and then treated with xylene (15 ml), followed successively by 1-benzyl-4-piperidone (6.1 g) and allyl bromide (4 g). The mixture was heated under reflux for 3 hr, then cooled, and shaken with excess of 16% HCl-H_2O. The H_2O phase was made alkaline with NH_3-H_2O and extracted with Et_2O. The residue from Et_2O was chromatographed over silica gel (0.08 mm) and eluted with petroleum ether (bp 30–50°)-Et_2O (1:1). The second fraction was **3a** (0.9 g) characterized as a picrate, mp 114° from EtOH. *Anal.* ($C_{21}H_{22}N_4O_8$) C, H, N.

Isomeric 3-Allyl-1-benzyl-4-phenyl-4-propionyloxypiperidines. The 4-piperidone **3a** (0.9 g) was treated with PhLi in Et_2O, prepared from Li (0.1 g) and PhBr (1.1 g) in the usual manner,[4,5] and the crude mixture of 4-piperidinols obtained esterified with $(PrCO)_2O$ (3 ml) and pyridine (0.3 ml) in xylene (10 ml) by a 3-hr reflux period. The product was evaporated and the residue shaken with Et_2O and NH_3-H_2O. The Et_2O phase (dried, Na_2SO_4) was evaporated and chromatographed over silica gel (0.08 mm) with petroleum ether (bp 30–50°)-Et_2O (2:1) as eluent. The β isomer (more readily eluted) gave a hydrochloride (mp 213°) and the α isomer gave a hydrochloride (mp 219°), both from EtOH-Me_2CO. *Anal.* (both isomers) ($C_{24}H_{30}ClNO_2$) C, H, N.

3-Allyl-1-methyl-4-piperidone (3b). Diethyl α-allyl-β,β'-(methylimino)dipropionate[7] (50 g) was added to NaOEt [freshly prepared from Na (5 g) and EtOH (100 ml), excess of solvent evaporated] in xylene (250 ml). About 70 ml of solvent, containing most of the EtOH formed during the reaction, was distilled and the remaining mixture heated under reflux for 4 hr. The cold product was shaken with 8% HCl-H_2O, the organic phase washed with more of the same acid, and the combined HCl-H_2O extract heated under reflux for 4 hr. The extract was concentrated *in vacuo*, made alkaline with 40% NaOH-H_2O, and extracted with Et_2O. The Et_2O phase (dried, Na_2SO_4) was evaporated and the residue distilled to give **3b** (16 g): mp 98° (10 mm) [lit.[7] bp 117–122° (31 mm)]: $n^{20}D$ 1.4820; picrate mp 148–150° from EtOH. *Anal.* ($C_{15}H_{18}N_4O_8$) C, H, N.

When the Dieckmann cyclization product **4-5** was decarboxylated with 20% HCl-H_2O, the product was a diastereoisomeric mixture of 2,5-dimethyl-7a-olperhydrofuro[3,2-*c*]pyridine (**6**): mp 98–100° (lit.[12] mp 95–96°); mol wt (from mass spectrum) 171 (as required for $C_9H_{17}NO_2$); methiodide mp 177–180° from Me_2CO (lit.[12] mp 176–179°). Fractional crystallization of the sublimed [80° (0.1 mm)] mixture from Me_2CO-hexane gave a pure isomer **6**: mp 119–120°; ^1H nmr δ 4.37 (center of m, 1, methine proton adjacent to O), 1.27 (d, ^3J = 7 Hz, 3, CMe). *Anal.* ($C_9H_{17}NO_2$) C, H, N.

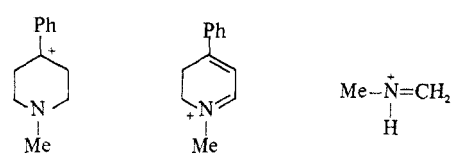
Isomeric 3-Allyl-1-methyl-4-phenyl-4-piperidinols and Esters. The 4-piperidone **3b** (10 g) was added to PhLi in Et_2O, prepared from Li (1.5 g) and PhBr (10.5), and the total 4-piperidinols (11.3 g) were isolated as usual. The α isomer separated from the mixture in petroleum ether (bp 30–50°)-Et_2O, mp 110–111°[7] (hydrochloride mp 169–171° from EtOH). *Anal.* ($C_{15}H_{22}ClNO$) C, H, N. The residue from the α-base mother liquors was esterified with $(PrCO)_2O$ (5 ml) (10 hr, steam). The total propionate bases were distilled [bp 120–130° (0.05 mm), short path] and chromatographed on silica gel. Elution with Et_2O gave β-**2c** hydrochloride, mp 207–208° from Me_2CO (lit.[7] mp 205–206°). *Anal.* ($C_{18}H_{26}ClNO_2$) C, H, N. Further elution with Et_2O-MeOH (9:1) gave α-**2c** hydrochloride, mp 185–186° from Me_2CO (see ref 7). *Anal.* ($C_{18}H_{26}ClNO_2$) C, H, N. α-**2c** was also obtained from the α-piperidinol after $(PrCO)_2O$-pyridine treatment. A mixture of β-**2c** (200 mg), 8% NaOH-H_2O (3 ml), and EtOH (3 ml) heated under reflux for 3 hr and extracted with Et_2O gave the β-4-piperidinol, mp 85° from hexane (lit.[7] mp 85–86°), hydrochloride mp 197° from EtOH-Et_2O. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N. Treatment of the piperidinols (0.5 g) with Ac_2O (3 ml), pyridine (0.3 ml), and toluene (5 ml) at reflux temperature (3 hr) gave the 4-acetoxy analogs of **2c**: α-hydrochloride, mp 213–214° from EtOH-Me_2CO [*Anal.* ($C_{17}H_{24}ClNO_2$) C, H, N]; β-picrate, mp 155–157° from EtOH [*Anal.* ($C_{23}H_{26}N_4O_9$) C, H, N]. (β-Hydrochloride was hydroscopic.)

Reaction of α-3-Allyl-1-methyl-4-phenyl-4-piperidinol with Hot HCl-H_2O. The α-4-piperidinol (700 mg) was heated under reflux for 6 hr with 16% HCl-H_2O (10 ml), and the free base was recovered as usual. This base was chromatographed on alumina (neutral, activity 3) and two compounds were eluted with petroleum ether (bp 30–50°)-Et_2O (2:1). The first, an oil (darkened in the light), distilled at 70–80° (0.05 mm) (short path) to give **3,6-dimethylbenz[h]-1,2,3,-4,5,6-hexahydroisoquinoline (9)** (200 mg): hydrochloride mp 231–232° from EtOH-Me_2CO; uv λ_{max} 263 nm (ε 9280 in EtOH) (styrene chromophore); ^1H nmr δ 7.2 (s, 4, aryl H), 1.2 (d, ^3J = 7 Hz, 3, CMe); mass spectrum *m/e* (rel intensity) 213 (100) (molecular ion, M^+, abundant in accord with the conjugated aromatic structure 9), 212 (92) (M − 1), 198 (20) (M − 15). *Anal.* ($C_{15}H_{20}ClN$) C, H, N. The second fraction, a solid purified by sublimation [80° (0.7 mm)], was **2,5-dimethyl-7a-phenylperhydrofuro[3,2-c]pyridine (10)** (250 mg), mp 67°; uv λ_{max} 257 nm (ε 473 in EtOH) (nonconjugated phenyl chromophore); ^1H nmr δ 7.3 (center of m, 5, aryl H), 4.47 (center of m, 1, methine adjacent to O), 2.3 (s, 3, NMe), 1.23 (d, ^3J = 7 Hz, 3, CMe); mass spectrum *m/e* (rel intensity) 231 (37) (M^+), 174 (45), 172 (48), 44 (100).# *Anal.* ($C_{15}H_{21}NO$) C,

‡ Close identity of the pK_a values of the two isomers (α, 7.37; β, 7.29 ± 0.06 in 1:1 EtOH-H_2O) further indicates that their distribution patterns are likely to be similar.

§ Melting points (uncorrected) were taken in a Büchi-Tottoli capillary melting point apparatus. Analyses were performed by the Microanalytical department (Istituto Superiore di Sanità) under the direction of Dr. I. Zavattiero. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value. ^1H nmr spectra were recorded on Varian HA-100 and Varian T-60 spectrometers in $CDCl_3$ (TMS). Mass spectra were determined on a Perkin-Elmer 270 spectrometer, ionizing energy 70 eV. All spectroscopic details are restricted to those of diagnostic value.

#Probable structure of fragments (see ref 18 for an example of a related fragment).



m/e 174 172 44

H, N. The hydrochloride gave mp 250–251° from EtOH–Me_2CO. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N [sample dried at 120° (0.5 mm) prior to analysis].

pK_a Measurement. The pK_a values were determined potentiometrically as described by Albert and Serjeant[19] by titration of of the HCl salts (0.25 mmol) in 50% EtOH–H_2O (47.5 ml) against 0.05 *N* KOH at 25°.

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Bridged Aminotetralins† as Novel Potent Analgesic Substances

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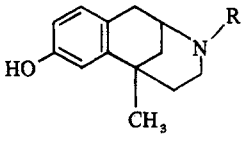
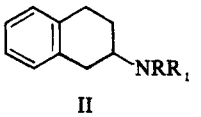
Forty-nine bridged aminotetralins have been synthesized. Structure–activity relationships were investigated by varying a number of the structural parameters. Several of the resulting compounds had analgesic activity on the order of morphine.

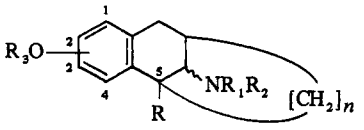
The search for synthetic analgesics with superior pharmacologic properties has led to the discovery of a considerable number of active morphinans and benzomorphan I derivatives.[1–4] Analgesic activity has also been reported in less complex tetralins having an exocyclic amino function (II).[5,6]



I



II



III

We undertook the synthesis of a new molecular modification III which combines the tricyclic feature of I with the exocyclic amino function of II. A key feature of the derived structure III is that the carbon bridge about the amine group has the effect of forming a pair of epimeric amines differing only in the orientation (α,β) of the amine function. The structure III has a quaternary carbon, as well as an aromatic substituent R_3O- (R_3 = CH_3, H), as do most strong analgesics in the benzomorphan class.[4] Compounds of formula III were synthesized and pharmacologically evaluated.‡ A number were analgesics having a potency on the order of morphine.

Chemistry. In order to vary the groups R, R_1, R_2, R_3, and *n* (bridge size), as well as the position of the aromatic substituent R_3, the synthetic route shown in Scheme I was employed.

By treatment of a 1-alkyl-2-tetralone (IV) with an excess of an α,ω-dibromide in the presence of either NaH in DMF or potassium *tert*-butoxide in *tert*-butyl alcohol, the bromoalkyl moiety was introduced, forming V. Cyclization to VI was accomplished with NaH in DMF. Preparation of the oxime derivative VII was effected by refluxing the tetralone with NH_2OH in either MeOH or pyridine. Oximes VII where R = CH_3CH_2, *n* = 4 and R = CH_3, *n* = 5 could be obtained only under the more vigorous pyridine conditions. Reduction to a bridged aminotetralin IX was conveniently carried out by hydrogenation over Raney nickel catalyst. Both α- and β-amines were formed in ratios which varied in a regular manner with increased steric crowding about the oximino group (Table I). The amines IX formed hydrochloride salts from which pure α and β epimers were separated by fractional

†These compounds are named as benzocyclooctenes, -nonenes, and -decenes in the Experimental Section in accordance with Chemical Abstracts recommendations.

‡Subsequent to the inception of our work, the synthesis by an alternate route of a related propano-bridged aminotetralin was reported. This compound lacked the aromatic substituent as well as the quaternary carbon. No pharmacology was indicated.[7]