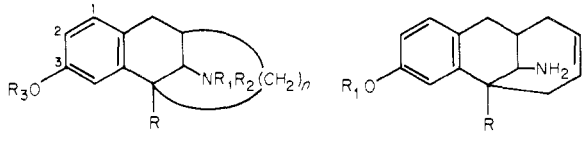
Analgesic Agents. 3. New Bridged Aminotetralins[1]

Meier E. Freed,* John R. Potoski, Elisabeth H. Freed, George L. Conklin, and Stanley C. Bell

Medicinal Chemistry Section, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087. *Received April 7, 1975*

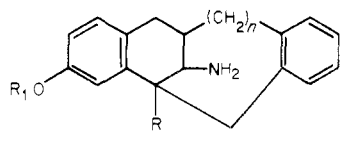
A number of new bridged aminotetralins have been synthesized. Several modifications not previously examined have been tested for their effect on the analgesic properties. A number of the compounds prepared demonstrated analgesic activity on the order of morphine.

In previous reports we described the synthesis and analgesic properties of a series of 1,3-bridged aminotetralins I.[2,3] It was suggested that for optimum activity



I

II



III

of these compounds the amine function should be unsubstituted and oriented equatorially relative to the tetralin ring (β-epimer) and that the aromatic substituent ($R_3 = CH_3 < H$) should be located meta to the quaternary carbon. Steric crowding about the amine function, which is dependent on the size of the alkyl group at the 5 position (Me < Et) and on bridge size ($n = 3 < 4 < 5$), is an important feature of the molecular geometry.

The goal of the present investigation was to develop analgesics having superior pharmacologic properties and to better define the required features for analgesic activity. This led to the synthesis of molecular modifications in which the polarity of the compounds was altered by introduction of ester groups at the 3 position or by conversion of the tertiary amine to its *N*-oxide. The conformational flexibility of the 1,3 bridge was restricted by unsaturation (II) and by increasing the bulk (i.e., increasing the steric crowding about the amine function) by including an aromatic moiety (III). Compounds which exemplified each of these new structural variations were synthesized and pharmacologically evaluated. Although these modifications did not produce compounds with significantly enhanced analgesic properties, a number had potency in the range of morphine.

Chemistry. The synthetic routes utilized for the preparation of the required compounds are described in Schemes I–III.

Treatment of a 1-alkyl-7-methoxy-2-tetralone (**I**) with excess *cis*-1,4-dichlorobutene in the presence of potassium *tert*-butoxide yielded **2** (X = O) (Scheme I). The oxime **2** (X = NOH) was obtained by refluxing **2** (X = O) with methanolic NH_2OH–AcOH. Reduction of this oxime with lithium aluminum hydride ($LiAlH_4$), a reagent which generally does not attack the isolated double bond, led to a somewhat surprising ring closure[4] with formation of a tetracyclic amine (**3** or **4**). The absence of absorption in the area of 5 μ in the ir of the hydrochloride indicated that the product was not a primary amine. In the NMR the base showed no vinylic protons and only one exchangeable proton. Mass spectral analysis was carried out and showed *m/e* at 243 (mol wt for $C_{16}H_{21}NO$, 243). Addition of the amine function to the bridge double bond occurred at the 7 or 8 position, but not both. This conclusion is supported by the fact that the product was obtained in 98% purity by GLC (hence is either **3** or **4**). The structure of the tetracyclic system was not established unequivocally since from the available data we were unable to distinguish between these two isomers.

Under Bouveault–Blanc conditions[5] (Na–EtOH) the oxime **2** (X = NOH) was reduced, with retention of the double bond, to the β-epimer of **5**. The orientation of the epimer was established by low-pressure hydrogenation of **5b** over PtO_2 to the known β-epimer **6b**.[2] With the butenyl-bridged amine now in hand, *N*-methyl and *N*,*N*-dimethyl derivatives were prepared. Treatment of **5b** with methyl iodide gave the monomethyl derivative **7b**. The *N*,*N*-dimethyl product **8b** was obtained from the primary amine by use of HCOOH–HCHO.[6] Demethylation of **5** was accomplished by means of BBr_3, yielding the phenols **9**.

For the preparation of the benzo-bridged products a similar route was employed (Scheme II). 1-Substituted 7-methoxy-2-tetralones,[2] on treatment with *o*-xylyl dibromide and potassium *tert*-butoxide in *tert*-butyl alcohol, formed the tetracyclic ketone **10**. Under the same reaction conditions the use of 2-bromo-1-(*o*-bromomethylphenyl)ethane, prepared from isochroman and HBr by the method of Colonge and Boisde,[7] gave the higher homologue **10a** ($n = 2$).[8] Oximation of **10** (pyridine–NH_2OH–HCl) to **10** (X = NOH) was next carried out. Reduction of the oxime with Raney nickel–H_2 in the presence of NH_4OH gave an epimeric mixture of amines (**11**), which were separated by fractional crystalization of the HCl salts. Conversion of **11** to **12** was readily accomplished by refluxing with aqueous HBr. In this group the compounds could not be assigned to one or the other of the epimeric series (axial or equatorial NR_2).

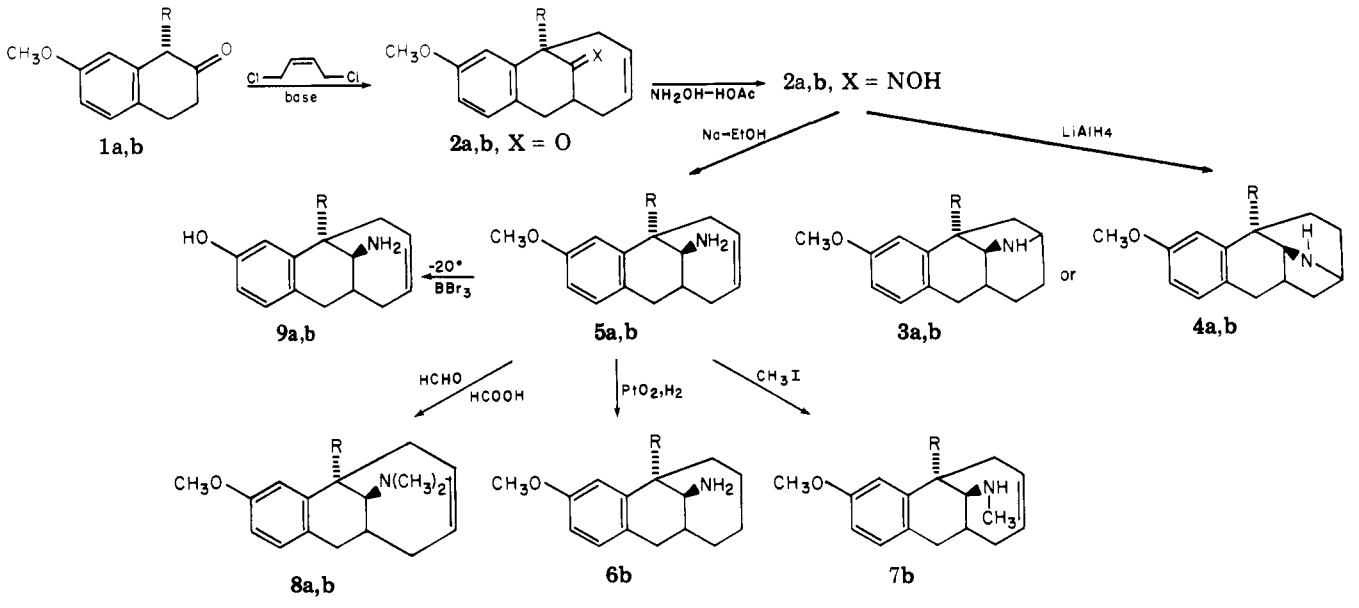
An analgesic (**13**, R = H), selected from the series of 4-bridged aminotetralins previously described,[2] was converted to the *O*-acetyl and *O*-cyclopropylcarbonyl derivatives. The preparation of these compounds (Scheme III) required blocking of the amino function of **13**, for which the carbobenzyloxy group was utilized. Treatment of **13** (R = Cbz) with the appropriate acylating agents yielded the *O*-esters **14**. Hydrogenolysis (Pd/C) removed the blocking group giving **15**. Oxidation of **16** with *m*-CPBA gave the *N*-oxide **17**. The compounds prepared are shown in Schemes I–III.

Pharmacology. The compounds were screened for analgesic activity by the D'Amour and Smith[9] rat tail flick test. Selected results appear in Table I. Comparisons are made with morphine, *d*-propoxyphene, **13** (R = H), and **16**.

From these results some conclusions with regard to structure–activity relationships can be made. Introduction of the benzo group (III), which both restricted conformational flexibility and increased the bulk of the bridging moiety, led generally to compounds less active than the simpler analogues (I). Since, in this series, the question of epimeric assignment has not been established, further conclusions do not seem to be warranted.

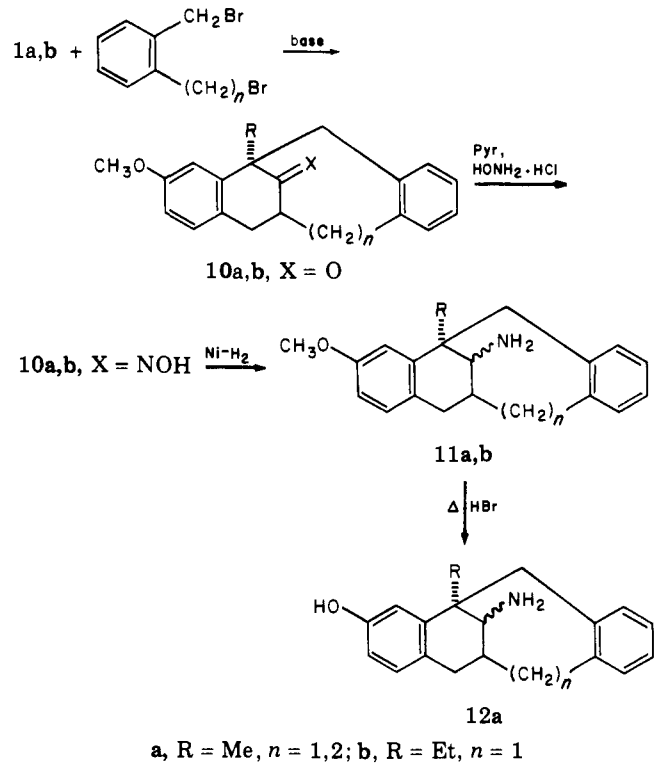
Introduction of the 7,8 double bond (II), which retained

Scheme I



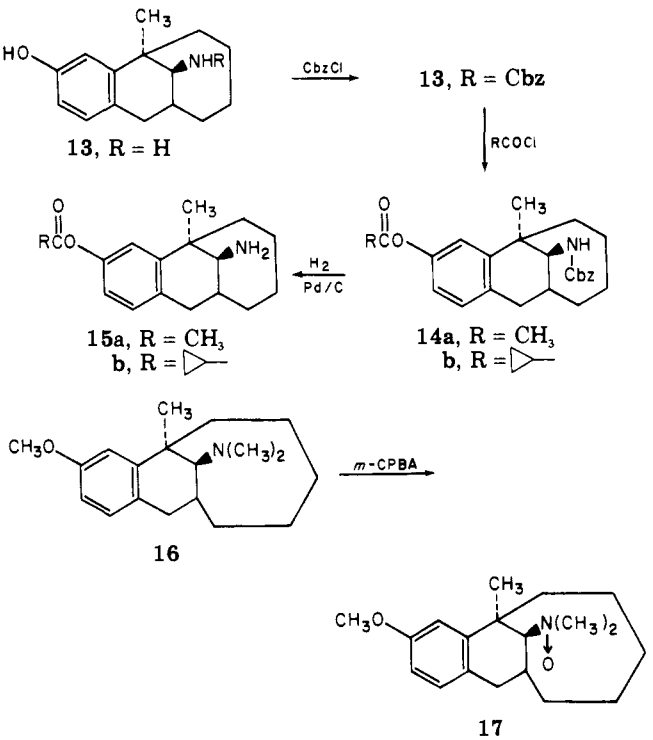
a, R = Me; b, R = Et

Scheme II



a, R = Me, n = 1,2; b, R = Et, n = 1

Scheme III



the conformational rigidity but not the bulk of the benzo series, led to a number of compounds with activity equal to or greater than that of the comparable parent series (I, n = 4). Comparisons made within this series showed that, with regard to the variables examined (R, R_1, R_2, R_3), primary amines were more active than their secondary or tertiary derivatives. Replacing the 3-methoxy with 3-hydroxy led to superior analgesic properties as did increasing the size of the 5-alkyl group from methyl to ethyl. These observations correlate well with those reported earlier.[2]

Esterification of the 3-hydroxy group led to little variation in activity. The *N*-oxide 17, prepared from **16**, also demonstrated activity equivalent to the more basic tertiary amine.

The modifications introduced in this study (esters, *N*-oxides, butenyl and benzo bridges) all produced compounds with significant analgesic properties, the most active being **9b**. Previously elucidated structure–activity relationships have received some further support, and several new ones have been examined.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Ir spectra were obtained on either a Varian A-60 or Jeolco HL60 spectrometer. Ir and NMR spectra and microanalyses were determined under the supervision of Mr. B. Hofmann of Wyeth Laboratories, Inc. GLC were obtained on a Perkin-Elmer 881 instrument using a 3% OV-1 column. GLC–mass spectra were obtained on a Perkin-Elmer Model 27 mass spectrometer. High-resolution mass spectra were obtained on a Model MS-902 AEI instrument. GLC and mass spectra were

Table I. Analgesic Activity of Bridged Aminotetralins

Compd	ED_{50},[a] mg/kg ip	Potency × morphine[b]	ED_{50}, mg/kg po[c]
5a[d]	16.5[e]	0.27	6.25, 2/6[f]
5b[d]	4.2 (3.62-4.91)[g]	1.05	6.25, 2/6
7b[h]	25, 1/6		
8a[d]	50, 0/6		
8b[d]	50, 0/6		
9a[d]	6.25[e]	1.26	
9b[i]	1.75[e]	2.53	6.25, 2/6
11a (n = 1)[d,j]	14.5 (12.21-16.95)	0.31	
11a (n = 1)[d,k]	25, 2/6		
11a (n = 2)[l]	25, 0/6		
11b (n = 1)[d]	50, 4/6		
12a (n = 1)[m]	12.5 (11.21-14.62)	0.35	
12a (n = 2)[m]	25, 1/6		
13 (R = H)[m]	7.4 (6.27-9.61)	0.60	
15a[d]	10.0 (7.21-12.85)	0.44	40[e]
15b[d]	5.5 (5.11-5.97)	0.81	16.5[e]
16[d]	10.0 (9.14-12.51)	0.44	
17[d]	10.0 (8.11-12.52)	0.44	16.5[e]
Morphine	4.43 (2.93-4.77)	1.00	15.9 (13.25-18.51)
d-Propoxyphene	10.36 (10.22-10.50)		

[a] Compounds were administered intraperitoneally in aqueous solutions or as suspensions in Tween-80 to groups of six or ten Charles River rats. Doses were calculated as milligrams of base per kilogram. [b] Potency of morphine taken as unity. [c] Oral dose. [d] Hydrochloride salt. [e] Based on two doses. [f] Dose, number of rats showing analgesia/number of rats tested. [g] 95% SE limits in parentheses. [h] Hydroiodide salt. [i] Free base. [j] Epimer with mp 312-314°. [k] Epimer with mp 298-299°. [l] Fumarate salt. [m] Hydrobromide salt.

determined under the supervision of Dr. T. Chang of Wyeth Laboratories, Inc.

Butenyl-Bridged Ketones (2a). In a typical procedure, a solution of 40 g (0.21 mol) of 1-methyl-7-methoxy-2-tetralone (**1a**) was added to a solution of freshly prepared K-t-BuOH (from 9.8 g of K) in 400 ml of t-BuOH. The resultant solution was stirred 1 h and then added slowly, under N_2, to a stirred solution of 53 g (0.42 mol) of *cis*-1,4-dichloro-2-butene in 150 ml of t-BuOH. The mixture was stirred for 18 h and a second solution of K-t-BuOH (from 15 g of K) in 400 ml of t-BuOH was added slowly. The mixture was refluxed 6 h, allowed to stand at room temperature overnight, poured into 4 l. of H_2O, and extracted with C_6H_6. The C_6H_6 solution was washed twice with H_2O, dried ($MgSO_4$), concentrated, and distilled to give 36 g of 6,9,10,11-tetrahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12-one (**2a**), bp 155–165° (0.5 mm). A portion was crystallized from heptane, giving a product with mp 79–81°. Anal. ($C_{16}H_{18}O_2$) C, H.

Benzo-Bridged Ketones (10a, n = 1). In a typical procedure, a solution of 19.1 g (0.1 mol) of 1-methyl-7-methoxy-2-tetralone (**1a**) in 150 ml of t-BuOH was added to a solution of K-t-BuOH (from 4.3 g of K) in 100 ml of t-BuOH. The solution was stirred 1 h and then added to a solution of 39.5 g (0.15 mol) of o-xylyl dibromide in 300 ml of t-BuOH. After 20 h of stirring under N_2 a second solution of 12 g of K-t-BuOH in 100 ml of t-BuOH was added and stirring was continued for another 3 days. The mixture was concentrated and the residue was treated with 300 ml of H_2O and 300 ml of Et_2O. Filtration of the mixture and recrystallization from C_6H_{12} gave 5.8 g of 6,11,12,13-tetrahydro-3-methoxy-5-methyl-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-one (**10a**, n = 1) with a mp of 138–140°. The ether portion, after being dried ($MgSO_4$) and concentrated, gave a second crop which, after recrystallization from C_6H_{12}, had mp 134–137°. The total yield was 13 g (45%). Anal. ($C_{20}H_{20}O_2$) C, H.

n = 2. In the same manner described above for n = 1, 22 g (0.115 mol) of 1-methyl-7-methoxy-2-tetralone was allowed to react with K-t-BuOH (from 5 g of K) and 32 g (0.115 mol) of α-(β-bromoethyl)benzyl bromide in 500 ml of t-BuOH. After 1 day a second charge of 22 g (0.2 mol) of commercial K-t-BuOH was added. The usual work-up gave a viscous oil, which was chromatographed on 1.5 kg of alumina. Elution was started with 100% hexane, gradually changed to varying ratios of hexane and benzene, and finally concluded with 100% benzene. Elution with 80 and 100% benzene gave 9.5 g of reasonably pure 5,6,7,8,13,14-hexahydro-2-methoxy-14-methyl-6,14-methanodibenzo[*a*,*e*]-cyclodecen-15-one (**10a**, n = 2). Crystallization of this product from MeOH gave 8.0 g with mp 98–103°. A small portion was further recrystallized from MeOH to give a product with mp 102–105°. Anal. ($C_{21}H_{22}O_2$) C, H.

Oximes (2a,b). Method A for Butenyl-Bridged Oximes. A solution of 23 g of NaOAc in 150 ml of MeOH was mixed with a solution of 19.5 g of NH_2OH–HCl in 200 ml of MeOH and after 1 h the resultant mixture was filtered. To the filtrate was added 13.5 g of **2a** in 50 ml of MeOH. The solution was refluxed 4 h, allowed to stand overnight, and concentrated. The residue was stirred with H_2O and filtered, giving 14.2 g of 6,9,10,11-tetrahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12-one oxime (**2a**), mp 122–125°. Recrystallization from 2-propanol gave 11.7 g, mp 124–126°. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

The oxime of 5-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12-one (**2b**), prepared in the same manner, had mp 151–153°. Anal. ($C_{17}H_{21}NO_2$) C, H, N.

Method B for Benzo-Bridged Oximes (10a, n = 1). A mixture of 7 g of **10a** (X = O, n = 1), 15 g of NH_2OH–HCl, and 80 ml of pyridine was refluxed for 20 h. The mixture was concentrated and the residue was treated with dilute HCl and H_2O, and filtered, giving 7.4 g of 6,11,12,13-tetrahydro-3-methoxy-5-methyl-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-one oxime (**10a**, n = 1), mp 188–190°. Anal. ($C_{20}H_{21}NO_2$) C, H, N.

In the same manner were prepared 5-ethyl-6,11,12,13-tetrahydro-3-methoxy-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-one oxime (**10b**, n = 1), mp 173–175° [Anal. ($C_{21}H_{23}NO_2$) C, H, N], and 5,6,7,8,13,14-hexahydro-2-methoxy-14-methyl-6,14-methanodibenzo[*a*,*e*]cyclodecen-15-one oxime (**10a**, n = 2), mp 228–232° [Anal. ($C_{21}H_{23}NO_2$) C, H, N].

Reduction of Butenyl-Bridged Oximes with Lithium Aluminum Hydride (3a,b–4a,b). A solution of 10 g (0.039 mol) of 6,9,10,11-tetrahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12-one oxime (**2a**) in 100 ml of THF was added slowly to a stirred mixture of 8.2 g (0.21 mol) of $LiAlH_4$ and 200 ml of THF under N_2. The mixture was refluxed for 20 h and then cooled, and to it was added 33 ml of H_2O. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in a mixture of ether and dilute HCl. The aqueous phase was separated, then basified with dilute NaOH, and extracted with ether, and the ether extracts were dried ($MgSO_4$) and concentrated to give 7.0 g (75% yield) of oil which was 98% pure by GLC. The NMR spectrum of the oil showed no olefinic protons and only one exchangeable proton. Mass spectral analysis showed m/e 243 (mol wt for $C_{16}H_{21}NO$, 243). Conversion of the oil to an HCl salt in ether and recrystallization of the salt from i-PrOH gave a salt with mp 276–278°. Anal. ($C_{16}H_{22}NOCl$) C, H, N. The ir spectrum showed no salt band characteristic for primary amines at 5.0 μ.

In a similar manner, $LiAlH_4$ reduction of 5-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12-one oxime (**2b**) gave essentially a single product whose mass spectrum showed m/e 257 (mol wt for $C_{17}H_{23}NO$, 257) and NMR spectrum showed one exchangeable and no olefinic protons.

Reduction of Butenyl-Bridged Oximes with Sodium and Ethanol (5a,b). Under a N_2 atmosphere, 4.4 g of sodium pellets

was added to a stirred, refluxing solution of 2.5 g of **2a** (X = NOH) in 2.5 ml of EtOH. Reflux was continued for 1 h. The mixture was then cooled, diluted with 25 ml of EtOH, and refluxed again. When sodium pellets were no longer visible, the solution was cooled and diluted with 200 ml of ice water. The EtOH was removed in vacuo and the remaining aqueous mixture was extracted with Et_2O. The ether portion was dried ($MgSO_4$) and concentrated to give an oil which was found on GLC analysis to be essentially a single compound, 6,9,10,11-tetrahydro-3-methoxy-5α-methyl-5,10-methano-5*H*-benzocyclononen-12β-amine (**5a**). The product showed two olefinic protons at δ 5.5 and 5.1 (triplets) and two exchangeable protons in its NMR spectrum. Preparation of the HCl salt in Et_2O and recrystallization from MeOH–H_2O gave 1.6 g of product with mp 300–302°. Anal. ($C_{16}H_{22}NOCl$) C, H, N, Cl. The ir spectrum showed salt bands at ~5 μ characteristic of primary amine hydrochlorides.

In a similar manner, the sodium and alcohol reduction of **2b** (X = NOH) gave a single amine product 5α-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine (**5b**) which, as free base, had mp 77–78° [Anal. ($C_{17}H_{23}ON$) C, H, N] and two olefinic protons centered at δ 5.2 (broad multiplet) in its NMR spectrum. The HCl salt of the base prepared in Et_2O had mp 285–286°. Anal. ($C_{17}H_{24}ONCl$) C, H, N.

Hydrogenation of Bridged Double Bond (6b). A solution of 50 mg of 5α-ethyl-6,9,10,11-tetrahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine (**5b**) in 25 ml of EtOH containing 1 ml of concentrated HCl was hydrogenated over 10 mg of PtO_2 for 15 min. The catalyst was filtered and the filtrate concentrated. The residue was recrystallized from MeOH–MeCN to give 30 mg of 5α-ethyl-6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12β-amine (**6b**) hydrochloride with mp 252–254° (lit.[1] mp 253–256°; mixture melting point showed no depression and ir spectra were identical).

Reduction of Benzo-Bridged Oximes (11a,b, n = 1, 2). A mixture of 25 g of **10a** (n = 1) oxime, 50 ml of concentrated NH_4OH, and 250 ml of EtOH was hydrogenated at 45 psi over 50 g of Raney nickel. After the uptake of H_2 stopped, the catalyst was filtered and the filtrate concentrated. The residue was converted to its HCl salt in Et_2O, giving 20 g of mixture of α- and β-amino epimers. Recrystallization from a solution of 400 ml of H_2O and 150 ml of MeOH gave 11.5 g of an epimer of 6,11,-12,13-tetrahydro-3-methoxy-5-methyl-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-amine hydrochloride (**11a**, n = 1), mp 312–314°. Anal. ($C_{20}H_{24}NOCl{\cdot}0.5H_2O$) C, H, N. Concentration of the mother liquors to 150 ml gave 6.2 g of solid, which was recrystallized from MeOH–MeCN (1:3) to give the second amino epimer of 6,11,12,13-tetrahydro-3-methoxy-5-methyl-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-amine hydrochloride (**11a**, n = 1) with mp 298–299°. Anal. ($C_{20}H_{24}NOCl$) C, H, N.

Carried out in a like manner, hydrogenation of **10a** (n = 2) oxime gave essentially a single epimer of 5,6,7,8,13,14-hexahydro-2-methoxy-14-methyl-6,14-methanodibenzo[*a*,*e*]cyclodecen-15-amine (**11a**, n = 2). The fumaric acid salt was prepared and had, on recrystallization from EtOH, mp 224–226°. Anal. ($C_{21}H_{25}NO{\cdot}C_4H_4O_4{\cdot}0.5C_2H_5OH$) C, H, N.

Reduction of **10b** (n = 1) oxime by the same procedure gave a mixture of the two amino epimers of 5-ethyl-6,11,12,13-tetrahydro-3-methoxy-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-14-amine (**11b**, n = 1), only one of which could be isolated as a crystalline HCl: mp 305–308°. Anal. ($C_{21}H_{26}NOCl$) C, H, N.

***N*-Methyl Butenyl Bridge (7b).** A solution of 2.6 g (0.01 mol) of **5b** and 1.5 g (0.011 mol) of methyl iodide in 60 ml of acetone was refluxed for 2.5 h. The mixture was cooled and filtered to give 1.3 g of the HI salt of 5α-ethyl-6,9,10,11-tetrahydro-3-methoxy-*N*-methyl-5,10-methano-5*H*-benzocyclononen-12β-amine (**7b**), mp 260–262°. Anal. Calcd for $C_{18}H_{26}NOI$: C, 54.14; H, 6.56; N, 3.51. Found: C, 53.60; H, 6.81; N, 3.47.

***N*,*N*-Dimethylamine (8a,b).** To a stirred solution of 5.0 g of **5a** in 5.2 g of formic acid was added 4.5 ml of 40% formalin. The solution was heated to 70°, at which temperature gas evolution began. When the temperature began to drop, heat was again applied and the temperature was maintained at 90° for 8 h. The solution was concentrated and the residue was treated with 150 ml of H_2O and then made strongly alkaline with concentrated NaOH. The mixture was extracted with Et_2O and the Et_2O layer was dried (Na_2SO_4) and concentrated to give 4.8 g of *N*,*N*-dimethyl-6,9,10,11-tetrahydro-3-methoxy-5α-methyl-5,10-methano-5*H*-benzocyclononen-12β-amine (**8a**) as an oil. The HCl salt was prepared and on recrystallization from EtOH amounted to 3.5 g: mp 228–230°. Anal. ($C_{18}H_{26}NOCl$) C, H, N.

In a similar manner, *N*,*N*-dimethyl-6,9,10,11-tetrahydro-3-methoxy-5α-ethyl-5,10-methano-5*H*-benzocyclononen-12β-amine (**8b**) was prepared as the HCl salt: mp 236–237°. Anal. ($C_{19}H_{28}NOCl$) C, H, N.

Preparation of Phenols (9a,b). BBr_3 Method. A solution of 6.7 g of BBr_3 in CH_2Cl_2 was added slowly to a stirred solution of 3.0 g of **5b** in 100 ml of CH_2Cl_2 at –20° under N_2. The mixture was allowed to come to room temperature and was stirred overnight. The mixture was cooled to 0°, 150 ml of H_2O was added, and the mixture was stirred 1 h. The H_2O layer was separated, basified with concentrated NH_4OH, and filtered to give 2.1 g of 12β-amino-5α-ethyl-6,9,10,11-tetrahydro-5,10-methano-5*H*-benzocyclononen-3-ol (**9b**) with mp 178–186°. Recrystallization from MeOH gave a product with mp 216–218°. Anal. ($C_{16}H_{21}NO$) C, H, N.

12β-Amino-5α-methyl-6,9,10,11-tetrahydro-5,10-methano-5*H*-benzocyclononen-3-ol (**9a**), prepared in similar manner, was converted to the HCl salt which on crystallization from EtOH had mp 180° dec. Anal. ($C_{15}H_{20}NOCl{\cdot}C_2H_5OH$) C, H, N.

HBr Method (12a, n = 1, 2). A solution of 1.3 g of **11a** (n = 2) in 30 ml of 48% HBr was refluxed for 45 min and concentrated. Recrystallization from EtOH–Et_2O gave 0.90 g of the HBr salt of 15-amino-5,6,7,8,13,14-hexahydro-14-methyl-6,14-methanodibenzo[*a*,*e*]cyclodecen-2-ol (**12a**, n = 2), mp 310° dec. Anal. ($C_{20}H_{24}NOBr{\cdot}0.5H_2O$) C, H, N.

In a similar manner, **11a** (n = 1, the epimer with mp 312–314°) was converted to 14-amino-6,11,12,13-tetrahydro-5-methyl-5,12-methano-5*H*-dibenzo[*a*,*e*]cyclononen-3-ol (**12a**, n = 1). The HCl salt was prepared and on crystallization from H_2O had mp 345–347° dec. Anal. ($C_{19}H_{22}NOCl{\cdot}0.5H_2O$) C, H, N.

Preparation of *O*-Esters (15a,b). *N*-Benzyloxycarbonyl Derivative (13, R = Cbz). A mixture of 15 g of **13** (R = H), 11.6 g of carbobenzyloxy chloride, 100 ml of saturated $NaHCO_3$, and 100 ml of CH_2Cl_2 was stirred for 1 h. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and concentrated. The residue was triturated with EtOAc–pentane and filtered to give 24 g of crude product. Recrystallization from EtOAc–cyclohexane gave 18.3 g of carbobenzyloxylated amine, **13** (R = Cbz), with mp 103–110°, suitable for the next step.

Preparation of Acetate Ester (15a). A solution of 5 g of **13** (R = Cbz), 10 ml of acetic anhydride, and 50 ml of pyridine was allowed to stand overnight. The solution was diluted with water and extracted with Et_2O. The Et_2O extracts were washed with dilute HCl, dried ($MgSO_4$), and concentrated to give 5.1 g of acetate derivative **14a** as a viscous oil which was pure by TLC analysis. The acetate derivative was dissolved in 100 ml of THF containing 1.3 g of dry HCl and was hydrogenated over 250 mg of 10% Pd/C at 40 psi H_2 for 90 min. The catalyst was filtered and the filtrate concentrated. Crystallization of the residue from THF–Et_2O gave 1.35 g of the HCl salt of 12β-amino-6,7,8,9,-10,11-hexahydro-5α-methyl-5,10-methano-5*H*-benzocyclononen-3-ol acetate (**15a**), mp 269° dec. Anal. Calcd for $C_{17}H_{24}NO_2Cl$: C, 65.90; H, 7.81; N, 4.52. Found: C, 65.38; H, 7.28; N, 4.48.

Preparation of Cyclopropylcarbonyl Ester (15b). A solution of 2.0 g of **13** (R = Cbz) and 2 ml of cyclopropanecarboxoyl chloride in 10 ml of pyridine was allowed to stand overnight. The solution was diluted with H_2O and extracted with ether. The ether extracts were washed with dilute HCl, dried ($MgSO_4$), and concentrated to give a viscous oil. The oil was chromatographed on 70 g of alumina. Elution with Et_2O gave 1.5 g of oil which crystallized from EtOAc–hexane to give 1.2 g of cyclopropylcarboxylate ester **14b**, mp 104–109°. This ester was hydrogenated in THF–HCl over 10% Pd/C, as described above, to give 0.45 g of the HCl salt of 12β-amino-6,7,8,9,10,11-hexahydro-5α-methyl-5,10-methano-5*H*-benzocyclononen-3-ol cyclopropanecarboxylate (**15b**), mp 225–257°, on crystallization from THF–Et_2O. Anal. ($C_{19}H_{26}NO_2Cl{\cdot}0.25H_2O$) C, H, N.

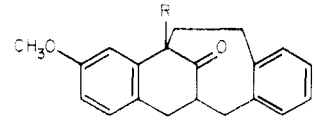
Preparation of the *N*-Oxide (17). To a cold (0°) solution of 1.5 g of **16** in 20 ml of THF was added 1.0 g of *m*-chloro-

perbenzoic acid in 10 ml of THF. The solution was stirred at 0–10° for 30 min. EtOH (2 ml) saturated with dry HCl was added. After crystallization occurred, 30 ml of Et_2O was added and the mixture was filtered to give 1.7 g of the HCl salt of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-*N*,*N*,5α-trimethyl-5,11-methanobenzocyclodecen-13β-amine *N*-oxide (**17**), mp 170–173° dec. Anal. Calcd for $C_{19}H_{30}NO_2Cl$: C, 67.13; H, 8.90; N, 4.13. Found: C, 66.61; H, 9.04; N, 3.98.

Acknowledgment. The authors are indebted to Mr. J. Malis and Mrs. E. Hernadi of the Wyeth Laboratories Pharmacology Department for their work in the determination of the biological activity of the compounds reported.

References and Notes

(1) The "butenyl-bridged" compounds are named as benzocyclononenes and the "benzo-bridged" compounds as dibenzo[a,e]cyclononenes and decenes in the Experimental Section in accordance with Chemical Abstracts recommendations.
(2) M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, and J. L. Malis, *J. Med. Chem.*, **16**, 595 (1973).
(3) M. E. Freed, J. R. Potoski, E. H. Freed, M. I. Gluckman, and J. Malis, *Adv. Biochem. Psychopharmacol.*, 137 (1974).
(4) While not pertinent to the current investigation, this reaction is mentioned since there seems to be little precedent for it in the chemical literature. A somewhat related cyclization was described by H. Hodjat, A. Lattes, J. P. Laval, J. Moulines, and J. J. Perie, *J. Heterocycl. Chem.*, **9**, 1081 (1972). The tetracyclic amine showed analgesic action (in 2/6 rats at 25 mg/kg ip) but was toxic (5/6 deaths at 50 mg/kg ip).
(5) L. Bouveault and G. Blanc, *C. R. Acad. Sci.*, **136**, 1676 (1903).
(6) R. N. Icke, B. B. Wisegarver, and G. A. Alles, *Org. Synth.*, **25**, 89 (1945).
(7) J. Colonge and P. Boisde, *Bull. Soc. Chim. Fr.*, 1337 (1956).
(8) We considered the alternate structure



to be improbable since we have found that 1-alkyl-β-tetralones are preferentially alkylated at the 1 position. This, plus the well-established fact that benzyl halides are far more reactive than the corresponding phenethyl halides, indicates that the intermediate first formed is 1-methyl-1-[o-(2-bromoethyl)]benzyl-2-tetralone, which on cyclization gives **10a** (n = 2) as indicated in Scheme II.
(9) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).

Azaparacyclophanes. A Novel Class of Conformationally Rigid Analogs of Phenylethylamine and Phenylpropylamine[1]

Kent E. Opheim,*[2] Adolph P. Roszkowski, Marshall B. Wallach, and Ian T. Harrison

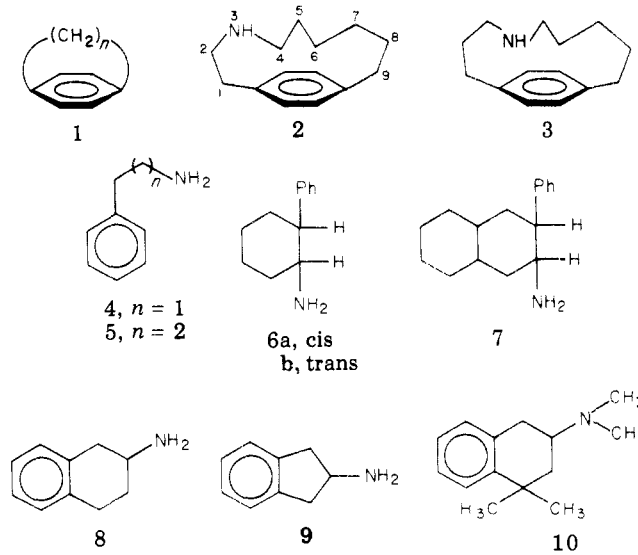
Institutes of Organic Chemistry and Clinical Medicine, Syntex Research, Palo Alto, California 94304. *Received July 3, 1975*

Aza[9]paracyclophanes **2** and **3**, analogs of phenylethylamine and phenylpropylamine, have been prepared and tested for pharmacological activity. Compound **3** was found to induce mydriasis without signs of sympathomimetic or anticholinergic activity.

The [n]paracyclophanes (**1**) represent a class of aromatic compounds in which the para positions of a benzene ring are incorporated into a bridging ring system.[3,4] The inclusion of a biologically active moiety into the conformationally rigid paracyclophane framework might lead not only to a unique class of drugs but also, because of its rigidity, could provide information concerning the stereochemical requirements of the biological receptor for that drug.

Most paracyclophanes (**1**) with values of n between 7 and 16 have been reported.[5] As the value of n decreases below 10, the benzene ring is increasingly distorted into a boat shape. For example, when n = 7, the para aromatic carbons are almost 20° above the usual benzene plane,[5] and this is reflected in the red shift of the ultraviolet spectrum of the benzene absorption.[3,5] Examination of CPK molecular models shows that rotation of the bridge about the aromatic nucleus is restricted at $n \approx 10$. This is consistent with the observed rotational barrier for an analogous group of bridged compounds, the [m,n]paracyclophanes.[4] Thus, at $n < 10$ the bridge is in a fixed conformation above the aromatic ring and cannot become coplanar with it.

We have prepared the paracyclophane analogs, 3-aza[9]paracyclophane (**2**) and 4-aza[9]paracyclophane (**3**), of phenylethylamine (**4**) and phenylpropylamine (**5**), respectively. The amine-containing bridge in **2** and **3** is restricted to conformations which place it above and in close proximity to the aromatic ring. Such restrictions would be expected to modify the spectrum of biological activity displayed by the corresponding open-chain analog



by limiting interaction with receptor sites that require simultaneous binding of the amine group and aromatic system. A further effect could arise from pK_a changes induced by the proximity of the aromatic system and the amine group. The conformations imposed by the paracyclophane structure are very different from those indicated to be important in structure–activity theories based on molecular orbital,[6] solid state,[7] and solution[8] studies.

The biological properties of various conformationally restrained analogs of phenylethylamine (**4**) have been