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°.

Acknowledgments. The authors acknowledge Dr. K. M. J. McErlane for help in the study of the decarboxylation of **4** and **5** and Drs. E. L. May (National Institutes of Health, Bethesda) and P. A. J. Janssen (Janssen Pharmaceutica, Beerse, Belgium) for pharmacological data relating to mice and rats, respectively.

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Bridged Aminotetralins† as Novel Potent Analgesic Substances

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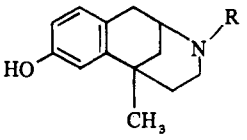
Forty-nine bridged aminotetralins have been synthesized. Structure–activity relationships were investigated by varying a number of the structural parameters. Several of the resulting compounds had analgesic activity on the order of morphine.

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]



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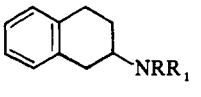
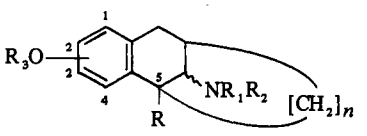


II



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.

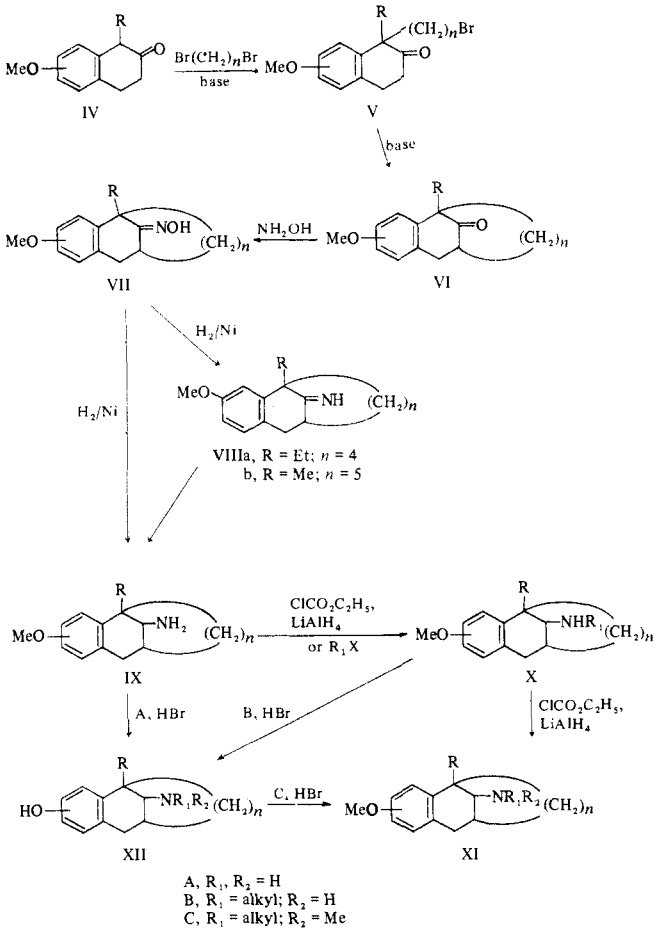
Chemistry. In order to vary the groups R, R_1, R_2, R_3, and *n* (bridge size), as well as the position of the aromatic substituent R_3, the synthetic route shown in Scheme I was employed.

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]

Scheme I



crystallization and/or chromatography.

Hydrogenation of oximes VIIa and VIIb could be halted at the intermediate imine stage VIII. These imines could be isolated as hydrochloride salts and were characterized by ir, nmr, and mass spectra. Secondary amines X were obtained by treating the appropriate primary amine with an alkyl halide under standard conditions. Primary and secondary amines IX and X were monomethylated *via* chloroformylation and $LiAlH_4$ reduction. By briefly heating the methyl ethers with 48% HBr, phenols XII were obtained. The bridged aminotetralins prepared are listed in Table II.

Assignment of Amine Epimers. Identification of the α and β epimers XIII and XIV was made by comparison of the nmr spectra of $-NCH_3$ derivatives (Table III). Dreiding models show that in the α epimer (XIII) the NCH_3 group is located below the plane of the aromatic ring and should be shielded by the local magnetic field due to the aromatic ring current. For each epimeric pair, the NCH_3 group found at higher field was assigned the α configuration and the downfield NCH_3 the β (XIV). This argument is analogous to that used in establishing the configuration (at C-9) of *N*,5,9-trimethyl-6,7-benzomorphan.[8]

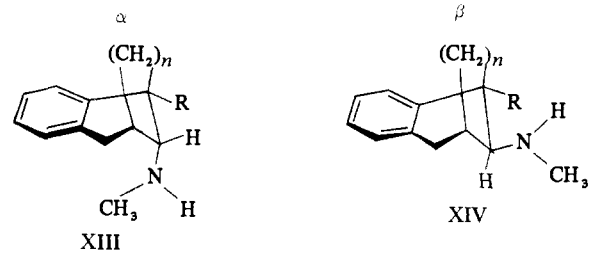
The compounds were screened for analgesic activity by the D'Amour and Smith rat tail flick test.[9] The 95% confidence intervals (Table IV) were calculated by the Probit analysis method of Finney.[10]

Table I. Per Cent of α- and β-Amines *via* Hydrogenation of Oximes[a]

n	R	% α	% β
3	Me	60	40
4	Me	25	75
4	Et	15	85
5	Me	5	95

[a] All oximes for this table had a 3-CH_3O substituent.

As a result of this investigation a number of structure-activity relationships emerged. (1) It was found that activity resided largely in the β epimer (XIV), in which the amine is in an equatorial position relative to the half chair conformation of the tetralin ring. This is similar to the results implied in the reports of Martin, *et al.*, and Pai, *et al.*,[6,11] in which axial aminotetralins were found to be less active than related equatorial ones. (2) Primary amines were found to be more active than secondary or tertiary, although in general potent analgesics derived from morphine contain tertiary nitrogen.[4] (3) Variation of the position of the CH_3O substituent in the aromatic ring showed that analgesic activity exists only in those compounds where this group is in a position meta to the quaternary carbon. (4) As expected, when the CH_3O was replaced by HO–, enhanced activity resulted. These findings (3 and 4) correlate with previous work in the analgesic field.[4,12,13] (5) Examination of models indicated that steric crowding about the β-amine depends on bridge length ($n = 3 < 4 < 5$) and size of the alkyl group at the 5 position (Me < Et). This is supported chemically from the observed increasing difficulty of oximation, which is of the same order, and from the unusual stability of imines VIIIa and VIIIb. As seen from Tables II and IV, these factors (increased bridge length and size of the 5-alkyl group) lead to compounds with increasing activity. It may be concluded that a sterically crowded amine function may be a requisite for optimal activity in this series.



In Table IV are shown the ED_{50}, potency relative to morphine, and therapeutic index (as measured by the ratio of LD_{50} or CD_{50} to ED_{50}) of six of the more active compounds. Comparisons are also shown with codeine and *d*-propoxyphene.

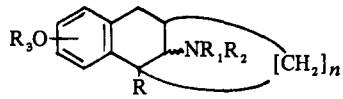
We have thus successfully synthesized a new series of morphine level analgesics having a high therapeutic index. This series incorporates structural features significantly different from those of previously reported agents. Additional work is being carried out and will be the subject of a future report.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model IR-21 spectrophotometer. Nmr 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. Gc–ms were obtained on a Perkin-Elmer Model 270 mass spectrometer. High-resolution mass spectra were obtained on a Model MS-902 AEI instrument. Glc and mass spectra were determined under the supervision of Drs. S. Schrader and T. Chang of Wyeth Laboratories, Inc. The various methoxy-1-alkyl-2-tetralone starting materials IV were either obtained commercially or prepared routinely by literature procedures.[14–18]

1-Haloalkyl-2-tetralones (V). Method A. In a typical procedure, NaH (37.1 g, 0.84 mol of a 54.5% dispersion in mineral oil), washed free of mineral oil and suspended in a little C_6H_6, was added to a stirred solution of 150 g (0.788 mol) of 7-methoxy-1-methyl-2-

Table II. Amines



Amine	R	R_1	R_2	R_3	Position of R_3	Epimer α or β	Mp, °C	Formula[a]
					$n = 3$			
1	Me	H	H	Me	3	α	270–272	$C_{15}H_{21}NO \cdot HCl$
2	Me	H	H	Me	3	β	300–302	$C_{15}H_{21}NO \cdot HCl$
3	Me	H	H	H	3	α	277–280	$C_{14}H_{19}NO \cdot HBR \cdot 0.5C_2H_5OH$
4	Me	H	H	H	3	β	305–310	$C_{14}H_{19}NO \cdot HBr$
5	Me	Me	H	Me	3	α	254–255	$C_{16}H_{25}NO \cdot HCl$
6	Me	Me	H	Me	3	β	266–267	$C_{16}H_{23}NO \cdot HCl$
7	Me	Allyl	H	Me	3	α	162–164	$C_{18}H_{25}NO \cdot HCl$
8	Me	$(CH_3)_2CCHCH_2$	H	Me	3	α	166–169	$C_{20}H_{29}NO \cdot HCl$
9	Me	Phenethyl	H	Me	3	α	228–229	$C_{23}H_{29}NO \cdot HCl$
10	Me	Me	Me	Me	3	α	221–223	$C_{17}H_{25}NO \cdot HCl$
11	Me	Me	Me	Me	3	β	224–226	$C_{17}H_{25}NO \cdot HCl$
12	Me	Me	Me	H	3	α	268–271	$C_{16}H_{23}NO \cdot HBr$
13	Me	Allyl	Me	Me	3	α	163–165	$C_{14}H_{27}NO \cdot HCl$
14	Me	$(CH_3)_2CCHCH_2$	Me	Me	3	α	136–138	$C_{21}H_{31}NO \cdot C_4H_4O_4 \cdot 0.25H_2O$
15	Me	Phenethyl	Me	Me	3	α	149–151	$C_{24}H_{31}NO \cdot C_4H_4O_4 \cdot 0.25H_2O$
					$n = 4$			
16	Me	H	H	None	None	β	>315	$C_{15}H_{21}N \cdot HCl$
17	Me	H	H	Me	3	β	307–308	$C_{16}H_{23}NO \cdot HCl$
18	Me	H	H	Me	3	α	237–240	$C_{16}H_{23}NO \cdot HCl$
19	Me	H	H	H	3	β	246–248	$C_{15}H_{21}NO \cdot HBr \cdot C_3H_7OH$
20	Me	H	H	H	3	α	130–134	$C_{15}H_{21}NO \cdot HBr \cdot 0.25CH_3CN$
21	Me	H	H	Me	2	β	284–287	$C_{16}H_{25}NO \cdot HCl$
22	Me	H	H	H	2	β	299–303	$C_{15}H_{21}NO \cdot HBr$
23	Me	H	H	Me	1	β	308–309	$C_{16}H_{23}NO \cdot HCl$
24	Me	H	H	H	1	β	245–250	$C_{15}H_{21}NO \cdot HBr$
25	Et	H	H	Me	3	β	253–256	$C_{17}H_{25}NO \cdot HCl \cdot H_2O$
26	Et	H	H	Me	3	α	185–187	$C_{17}H_{25}NO \cdot HCl$
27	Et	H	H	H	3	β	205–209	$C_{16}H_{23}NO$
28	Et	H	H	H	3	α	266–270	$C_{16}H_{23}NO \cdot HBr$
29	Prop	H	H	Me	3	β	226–227	$C_{15}H_{27}NO \cdot C_4H_4O_4$
30	Benzyl	H	H	Me	3	β	144–147	$C_{22}H_{27}NO \cdot HCl \cdot H_2O$
31	Benzyl	H	H	H	3	β	312–316	$C_{21}H_{25}NO \cdot HCl$
32	Me	Me	H	Me	3	β	295–298	$C_{17}H_{25}NO \cdot HCl$
33	Me	Me	H	Me	3	α	249–250	$C_{17}H_{25}NO \cdot HCl$[b]
34	Me	Allyl	H	Me	3	β	200–202	$C_{19}H_{27}NO \cdot HCl$
35	Me	$(CH_3)_2CCHCH_2$	H	Me	3	β	225–226	$C_{21}H_{31}NO \cdot HCl$
36	Me	Phenethyl	H	Me	3	β	243–245	$C_{24}H_{30}NO \cdot HCl$
37	Et	Me	H	Me	3	β	282–284	$C_{18}H_{27}NO \cdot HCl$[c]
38	Et	Me	H	Me	3	α	258–260	$C_{18}H_{27}NO \cdot HCl \cdot 0.25H_2O$
39	Me	Me	Me	Me	3	β	207–209	$C_{18}H_{27}NO \cdot HCl \cdot 0.25H_2O$
40	Me	Me	Me	Me	3	α	200–202	$C_{18}H_{27}NO \cdot HCl$[d]
41	Et	Me	Me	Me	3	β	162–165	$C_{19}H_{29}NO \cdot HCl$
42	Me	$(CH_3)_2CCHCH_2$	Me	Me	3	β	108–110	$C_{22}H_{23}NO \cdot C_4H_4O_4 \cdot 0.5H_2O$
					$n = 5$			
43	Me	H	H	None	None	β	>315	$C_{16}H_{25}N \cdot HCl$
44	Me	H	H	Me	3	β	311–312	$C_{17}H_{25}NO \cdot HCl$
45	Me	H	H	H	3	β	269–270	$C_{16}H_{23}NO \cdot HBr$
46	Me	Me	H	Me	3	β	303–305	$C_{18}H_{27}NO \cdot HCl$[e]
47	Me	Me	Me	Me	3	β	195–198	$C_{18}H_{27}NO \cdot HCl \cdot H_2O$
48	Me	Me	Me	H	3	β	243–245	$C_{18}H_{27}NO \cdot HBr$
49	Me	H	H	Me	3	α	207–208	$C_{17}H_{25}NO \cdot HCl \cdot 0.25H_2O$[f]

[a] All compounds were analyzed for C, H, and N. [b] C: calcd, 69.01; found, 68.53. [c] C: calcd, 69.76; found, 69.29. [d] C: calcd, 69.76; found, 69.28. [e] C: calcd, 69.76; found, 69.27. [f] N: calcd, 4.67; found, 4.05.

tetralone and 707 g (3.06 mol) of 1,5-dibromopentane in 600 ml of DMF under N_2. The temperature of the mixture was kept below 20° during the addition. After stirring 3.5 hr, the mixture was diluted with H_2O and acidified with dilute acid. Et_2O extraction, drying ($MgSO_4$), concentration, and distillation gave 182 g (68%) of 1-(5-bromopentyl)-7-methoxy-1-methyl-2-tetralone, bp 185–198° (1 mm).

Method B. A solution of 238 g (2.14 mol) of K *tert*-BuOH and 366 g (1.91 mol) of 7-methoxy-1-methyl-2-tetralone in 1.3 l. of *tert*-BuOH under N_2 was stirred for 45 min. This solution was added over 30 min to a stirred solution of 1.330 kg (5.76 mol) of 1,5-dibromopentane and 1.0 g of NaI in 1.5 l. of *tert*-BuOH under N_2. The mixture was stirred 2 hr, concentrated to 1.5 l., and diluted with H_2O, and the organic layer was separated. The aqueous layer was extracted with C_6H_6 and the combined organic portions were washed with dilute acid followed by H_2O, dried ($MgSO_4$), concentrated, and distilled to give 443 g of 1-(5-bromopentyl)-7-methoxy-1-methyl-2-tetralone, bp 160–195° (0.7 mm).

Bridged Ketones (VI). In a typical procedure, a solution of 92 g (0.271 mol) of 1-(5-bromopentyl)-7-methoxy-1-methyl-2-tetralone in 250 ml of DMF was added slowly to a stirred mixture of NaH (12.6 g, 0.299 mol of a 57% dispersion in mineral oil) washed free of mineral oil and 500 ml of DMF. The reaction mixture was warmed at 85° for 3 hr. Dilution of the mixture with H_2O followed by Et_2O extraction, drying ($MgSO_4$), and distillation gave 45.6 g (65%) of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5-methyl-5,11-methanobenzocyclodecen-13-one, bp 150–175° (0.5 mm). The distillate solidified. A portion was recrystallized from *n*-hexane and had mp 68–76°. *Anal.* ($C_{17}H_{22}O_2$) C, H.

Oximes (VII). Method A. In a typical procedure, a mixture of 52 g of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5-methyl-5,11-

Table III. Nmr Data on *N*-Methylamines

Compd	*n*	R	δ for NCH_3[a]	Epimer α or β
		Secondary Amines		
5	3	Me	2.32	α
6	3	Me	2.40	β
33	4	Me	2.34	α
32	4	Me	2.42	β
38	4	Et	2.33	α
37	4	Et	2.46	β
b	5	Me	2.38	α
46	5	Me	2.48	β
		Tertiary Amines		
10	3	Me	2.25	α
11	3	Me	2.54	β
40	4	Me	1.90	α
39	4	Me	2.45	β
41	4	Et	2.44	β
47	5	Me	2.51	β

[a] Range of δ NCH_3 for α, 1.90–2.38. Range of δ NCH_3, for β, 2.40–2.54. [b] This compound was not isolated. Data were obtained on mixture of α and β.

methanobenzocyclodecen-13-one, 70 g of $NH_2OH \cdot HCl$, and 370 ml of C_6H_5N was refluxed for 1 day. The mixture was diluted with H_2O and extracted with Et_2O. The Et_2O extracts were washed with dilute acid, dried ($MgSO_4$), and concentrated. The residue was recrystallized from *i*-PrOH to give 25 g of oxime with mp 161–163°. *Anal.* ($C_{17}H_{23}NO_2$) C, H, N.

Method B. A solution of NH_2OH was prepared by mixing $NH_2OH \cdot HCl$ (14 g, 0.2 mol) and NaAc (16.5 g, 0.2 mol) in 450 ml of MeOH. After 1 hr, the mixture was filtered and the filtrate was treated with 10 g (0.04 mol) of 6,7,8,9,10,11-hexahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12-one. After 5 hr of reflux the solution was concentrated to 200 ml, and upon cooling and filtering, 8.0 g of oxime, mp 174–176°, was obtained. *Anal.* ($C_{16}H_{21}NO_2$) C, H, N.

Primary Amines (IX). A. Reduction Procedure. In a typical reduction, a mixture of 18.5 g of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5-methyl-5,11-methanobenzocyclodecen-13-one oxime, 3 tsp of Raney Ni (W R Grace No. 28), 100 ml of EtOH, and 50 ml of concentrated NH_4OH was hydrogenated in a Parr apparatus at 45 psi and 50°. The catalyst was removed and the filtrate was concentrated and distilled to give 13.1 g of oil, bp 140–143° (0.2 mm). Gc–ms analysis showed two isomers (95:5). Conversion to the HCl salt gave, after recrystallization from H_2O, 9.5 g of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5α-methyl-5,11-methanobenzocyclodecen-13β-amine HCl (**44**), mp 311–312°.

B. Separation Procedures. (1) In the manner described above, hydrogenation of 35 g of 6,7,8,9,10,11-hexahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12-one oxime gave 31 g of oil which was found by glc to be a mixture of amine epimers. This was treated with HCl in Et_2O to give 32 g of HCl salt with mp 257–267°. Recrystallization of the salt from 500 ml of H_2O gave 20 g of 17 with mp 307–308° (β-amino isomer). Fractional crystallization from the mother liquors yielded 5.9 g of salt with mp 231–236°. Recrystallization from acetone–MeOH gave 4.5 g of 18 with mp 237–240° (α isomer).

(2) An 8:1 (glc) mixture of epimers (70 g) of 5-ethyl-6,7,8,9,10,-11-hexahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12-amine was crystallized from 1100 ml of dilute HCl to give 64 g of 25, mp 253–256° (β isomer). The filtrate was basified (NaOH), extracted with Et_2O, dried ($MgSO_4$), and concentrated. The residue was chromatographed on 300 g of silica gel. Elution of the silica gel with a 1:1 C_6H_6–$CHCl_3$ solution gave additional β isomer. Further elution with 1:3 C_6H_6–$CHCl_3$ gave 3.0 g of α isomer. Conversion of a portion of this to its HCl salt in Et_2O gave HCl salt 26, mp 182–185°.

Isolation of Imines (VIII). A. Hydrogenation of 3.5 g of unpurified 5-ethyl-6,7,8,9,10,11-hexahydro-3-methoxy-5,10-methano-5*H*-benzocyclononen-12-one oxime gave, on distillation, 1.6 g of oil, bp 150–160° (0.5 mm). Its ir spectrum showed C=NH at 6.1 μ and its mass spectrum had a molecular ion at 242. Conversion of the oil to a HCl salt gave, after recrystallization from EtOH–Et_2O, 1.1 g, mp 252–253° (VIIIa). The ir spectrum of the salt showed $C=N^+H_2$ at 5.9 μ. *Anal.* ($C_{17}H_{23}NOCl$) C, H, N. Hydrogenation of this imine in the usual way gave the amine 25.

B. In a large-scale hydrogenation of 200 g of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5-methyl-5,11-methanobenzocyclodecen-13-one oxime, a small amount of imine was detected by gc–ms (M^+ 257) and isolated by fractional crystallization from H_2O as the HCl salt (VIIIb), mp 235–238° (ir showed $C=N^+H_2$ at 5.9 μ; mass spectrum M^+ 257).

Alkylation of Primary Amines Using R'X. In a typical procedure, 1.7 g of 6,7,8,9,10,11-hexahydro-3-methoxy-5α-methyl-5,10-methano-5*H*-benzocyclononen-12β-amine, 0.85 g of allyl bromide, and 1.3 g of ethyl diisopropylamine were refluxed in 10 ml of C_6H_6 for 3 hr. The mixture was diluted with Et_2O and filtered. Concentration and distillation gave 1.3 g, bp 144–146° (0.2 mm). Treatment with ethereal HCl gave 1.3 g of the HCl salt of *N*-allyl-6,7,8,9,10,11-hexahydro-3-methoxy-5-methyl-5,10-methano-5*H*-benzocyclononen-12β-amine (34), mp 200–202°

N-Methylations. In a typical procedure, a mixture of 8.0 g of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-5-methyl-5,11-methanobenzocyclodecen-13β-amine, 100 ml of saturated $NaHCO_3$, 100 ml of CH_2Cl_2, and 10 ml of $ClCO_2C_2H_5$ was stirred for 4 hr. The organic layer was washed with dilute HCl, dried ($MgSO_4$), and concentrated to give 8.5 g of oil. This was refluxed with 2.5 g of $LiAlH_4$ in THF for 20 hr. The usual $LiAlH_4$ work-up gave an oil which was converted to 5.5 g of the HCl salt of 5,6,7,8,9,10,11,12-octahydro-3-methoxy-*N*,5α-dimethyl-5,11-methanobenzocyclodecen-13β-amine (**46**), mp 303–305°.

Cleavage of CH_3O Group. In a typical procedure, 3.0 g of 5,6,7,-8,9,10,11,12-octahydro-3-methoxy-5α-methyl-5,11-methanobenzocyclodecen-13β-amine was refluxed 30 min in 60 ml of 48% HBr under N_2. The solution was concentrated and the residue recrystallized from H_2O (treated with activated C) to give the phenol 45, mp 269–270°. In the case of 27, the HBr salt was converted to the

Table IV. Analgesic Activity of Bridged Aminotetralins

Compd	ED_{50},[a] mg/kg ip	95% confidence intervals	Potency × morphine[b]	LD_{50} or CD_{50}/ED_{50}[e]
45	1.11	2.17–0.14	2.77	>200
25	3.50	4.91–1.17	0.88	57
27	3.70	5.91–0.84	0.83	>50
44	4.88	7.01–2.67	0.63	>50
19	7.40	10.12–3.47	0.54	8
48	7.64	9.97–5.12	0.40	
46	7.85	15.46–4.89	0.39	
20	9.78	15.23–4.26	0.31	
4	13.56	21.70–8.91	0.22	
26	18.33	44.70–8.91	0.16	
18	22.29	66.18–15.89	0.13[c]	
3	22.29	66.18–15.89	0.13[c]	
Morphine	3.08	3.98–2.11	1	75[f]
Codeine	5.42	8.68–3.56	0.56[d]	22[f]
d-Propoxyphene	9.89	26.21–5.29	0.31	5.1

[a] Compounds were tested as salts; 27 was tested as the "inner salt." Route of administration was intraperitoneally and groups of ten Charles River rats were tested at four dose levels. Doses were calculated as milligrams per kilogram of base. [b] Potency of morphine taken as unity. [c] Only two doses of ten rats each. [d] This value is specific for this route of administration (intraperitoneally) in rats. [e] Ratio based on either LD_{50} or CD_{50} (convulsant dose 50), whichever was lower. [f] LD_{50} used to calculate ratio.

zwitterion by treatment with NH_4OH and recrystallized from EtOAc, mp 205–209°.

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Metabolism of Dimethoxymethylphenobarbital in Mice. Relationship between Brain Phenobarbital Levels and Anticonvulsant Activity

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The relationship between the anticonvulsant activity of DMMP and its metabolism to phenobarbital was investigated in mice. Brain, blood, and whole-body phenobarbital levels were determined at various times by gas–liquid chromatography. The brain levels of phenobarbital 3 hr after oral administration of the ED_{50} of DMMP, 42 mg/kg, were 24.6 ± 2.3 μg/g. An equivalent dose of sodium phenobarbital, 31 mg/kg, produced brain phenobarbital levels of 25.4 ± 2.9 μg/g. Blood and whole-body phenobarbital levels paralleled those in the brain. A metabolite of DMMP, *N*-methoxymethylphenobarbital (MMP), was found in the brain when either 120 or 200 mg/kg of DMMP was given alone or when SKF-525A was given prior to DMMP. This intermediate appears to have anticonvulsant activity. These data indicate that in the mouse the activity of DMMP, after a single dose, is a result of its metabolism to phenobarbital.

Several new alkoxymethyl derivatives of barbiturates have recently been synthesized and evaluated as possible anticonvulsants.[1,2] The most potent of these, 1,3-bis(dimethoxymethyl)phenobarbital (DMMP), has been reported to protect mice against induced seizures in a manner similar to phenobarbital but without the initial hypnotic side effects often noted with the parent compound. The oral ED_{50} of DMMP has been reported in the range of 14 mg/kg for protection against maximal electroshock seizures (MES). The pattern of toxicity in mice and rats showed a progressive CNS depression which finally resulted in death due to respiratory paralysis.

Several investigators have demonstrated that N-substituted anticonvulsants are dealkylated *in vivo* and that the dealkylated products are as active or more active as anticonvulsants than the original drug. Craig and Shideman[3] found in rats that mephobarbital (*N*-methylphenobarbital) is metabolized to phenobarbital and that the anticonvulsant potency of mephobarbital is approximately one-third that of the demethylated product. Swinyard, *et al.*,[4] found mephobarbital to be one-half as potent as phenobarbital in mice. Butler[5] studied the metabolism of 1,3-dimethylbarbital in dogs and showed that it was metabolized to barbital. It is possible that DMMP, like other N-substituted barbiturates, is metabolized to phenobarbital *in vivo* and that this metabolite is responsible for the anticonvulsant activity. This series of experiments was designed to determine the concentrations of phenobarbital in blood, brain, and whole body following a single oral dose of DMMP and sodium phenobarbital. The findings indicate that the anticonvulsant activity of DMMP in mice is the result of its metabolism to phenobarbital.

Methods

Peak Time of Anticonvulsant Activity of DMMP and Phenobarbital. National Institutes of Health general purpose albino mice weighing 20–30 g were used throughout the study. The mice were housed in community plastic cages (18 × 11.5 × 6.5 in.), kept in diurnal lighting, and given food and water *ad lib* until used. In general, the MES assay was conducted as described by Toman[6] and Swinyard.[7,8] The day after arrival in the laboratory, each animal was subjected to 50-mA alternating current for 0.2 sec using a stimulus generator (Wahlquist Instrument Co., Salt Lake City, Utah) *via* saline dampened corneal electrodes. This procedure is necessary to establish a base line for the assay.[9] Animals were then used within 3 days of the initial electrical stimulation.

Mice, which had been fasted overnight, were given either sodium phenobarbital or DMMP directly into the stomach *via* a blunt 18 gauge needle introduced transesophageally; the volume administered was 0.01 ml/g of body weight. DMMP, which is insoluble in water, was suspended in 5% acacia. Sodium phenobarbital was dissolved in the same vehicle. In all experiments, control animals received a weight determined volume of 5% acacia only.

The time of peak anticonvulsant effect was determined for orally administered DMMP and sodium phenobarbital by giving a dose which will protect approximately 50% of the mice at 3 hr. This dose was given to a series of mice which were then shocked at 0.5, 1, 2, 3, and 6 hr. A total of 30 mice were used for each time point.

The ED_{50} for both drugs was then determined at the time of peak anticonvulsant effect. Protection was considered positive when the tonic extensor phase of the convulsion