Table IV—Least-Squares Fits of Data in Fig. 5

n-Estimate	Slope $\times 10^{-22}$	Intercept $\times 10^{3}$
10^{19}	4.1	−4.2
2×10^{19}	6.7	−0.7
10^{20}	8.7	+2.2

Fig. 4, should be about 5% moisture, which is equivalent to 5×10^{19} molecules of water per tablet. This is the same order of magnitude as the number of sites, *i.e.*, the point where exactly one monolayer would be expected. Again, this is not a sensitive comparison, but it demonstrates on a rough scale the fact that the data and the model are compatible.

It is thus seen that the experimental data fit the model, whereas simpler models fail to be consistent with the data. Selecting a water-soluble substance has made possible a study of the contribution to drug degradation of the interaction of the drug in dissolved state with the main excipient. Less water-soluble substances might exhibit the same behavior, but it would be difficult to separate the contribution from the solution sorbed on the excipient from the solution sorbed on the drug. Here one might expect a combination of the model proposed above and the Leeson-Mattocks model.

The specific data presented here, of course, can only be claimed to hold for the thiamine-microcrystalline cellulose system. It appears to hold in the case of lactose-thiamine also, but quantitation of data is difficult in this system. It is believed that the type phenomenon described here is part of the overall mode of degradation in solid-dosage form.

SUMMARY

1. Thiamine, when tableted in a matrix of microcrystalline cellulose, initially will be less stable the more moisture is present. However, a point is reached where this trend reverses, and beyond this moisture content stability is enhanced with increased moisture content.

2. A model is proposed, which is believed to apply to many systems, whereby solutions of the drug are adsorbed on the main excipient and degradation is then confined to the first monolayer of the adsorbed solution.

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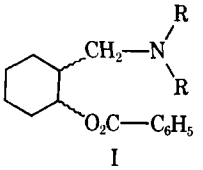
Conformational Aspects of Local Anesthetics

MARVIN R. BOOTS and SHARON G. BOOTS

Abstract □ The syntheses of two epimers of 3-*exo*-(*N*,*N*-dimethylaminomethyl-2-norbornanyl)4-*n*-butoxybenzoate are described. The results of several assays of local anesthetic activity are discussed.

Keyphrases □ Anesthetics, local—conformational aspects □ 3-*exo*-(*N*,*N*-Dimethylaminomethyl-2-norbornanyl)4-*n*-butoxybenzoate epimers—synthesis □ Pharmacological screening—local anesthetics □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Evidence in support of the concept of a receptor(s) being involved in blockage of nerve impulses by local anesthetics has been generated in recent years (1, 2). Numerous investigations have attempted to correlate a variety of physicochemical properties of the drug such as lipid solubility (3, 4), pKa′ values (5), electronic (4, 6), and steric factors (7, 8).



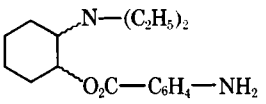
I

Mannich and Hong (9) evaluated a series of α-dialkylaminomethylcyclohexyl benzoates (I) and found one isomer (*cis* or *trans*?) to be very active.

This system (I) may exist as *cis-trans* isomers, conformational (axial or equatorial) isomers, and optical

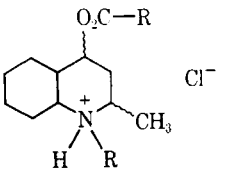
isomers. Therefore, in this case it is difficult to assign the observed differences in activity to a specific factor. However, in the cases studied optical isomerism has produced relatively small differences in activity between isomers (8, 10).

Heckel and Adams (11) observed very little difference in corneal anesthetic duration time for *cis* and *trans* isomers of substituted α-aminocyclohexyl benzoates (II).



II

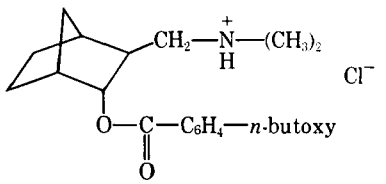
Russian workers have prepared and assayed seven of the eight theoretically possible stereoisomers of 1-alkyl-2-methyl-4-hydroxydecahydroquinoline (III) as various esters (7, 12, 13). In all types of local anesthesia, the compounds with both the methyl and benzoxyl groups in axial positions had the highest activity.



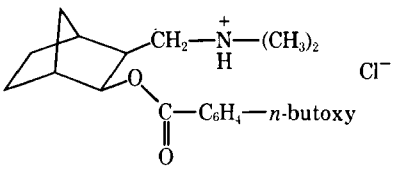
III

DISCUSSION

In order to obtain additional insight into the stereochemical requirements of local anesthetic activity a model system (IV) was investigated. Two epimers (IV*a*, IV*b*) were synthesized and several assays for local anesthetic activity were performed.



IVa

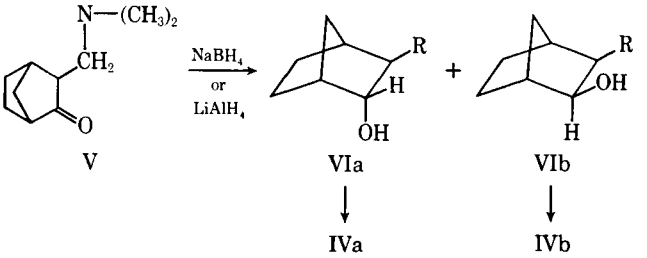


IVb

The synthetic approach to the desired epimers is outlined in Scheme I.

Sodium borohydride reduction of the ketone (V) afforded a mixture of alcohols (VI*a* and VI*b*) (14). Fractional crystallization afforded pure *endo* alcohol (VI*a*). The IR spectrum was identical with the published spectrum (14). The NMR spectrum of VI*a* showed N-$(CH_3)_2$ absorption at 2.18 p.p.m. and a multiplet at 3.72 p.p.m. for the *exo* proton at C-2. Treatment of VI*a* with 4-*n*-butoxybenzoyl chloride afforded the desired ester hydrochloride (IV*a*).

Lithium aluminum hydride reduction of the ketone (V) afforded a 75 : 25 (*exo* to *endo*) mixture of alcohols (VI*a* and VI*b*) as judged by the N-$(CH_3)_2$ absorption at 2.24 and 2.18 p.p.m. Seeding the mixture with pure *endo* alcohol (VI*a*) afforded a semisolid



Scheme I

(70 : 30 *exo* to *endo*) and a liquid (80 : 20 *exo* to *endo*). Treatment of the liquid mixture with 4-*n*-butoxybenzoyl chloride afforded the desired ester hydrochloride (IV*B*) after one recrystallization.

The stereochemistry of the dimethylaminomethyl group in ketone (V) has been shown to be *exo* (15) and this assignment is assumed to be maintained in the final product. Additional support for the assignment of the benzoxyl groups is based on the NMR spectra of the esters (IV*a* and IV*b*). The NMR spectrum of IV*a* showed a multiplet at 4.65 p.p.m. which is consistent with *exo* proton at C-2. The NMR spectrum of IV*b* showed a doublet (J = 7 c.p.s.) at 5.10 p.p.m. which is consistent with an *endo* proton at C-2. The lower field position of the C-2 proton of IV*b* with respect to the C-2 proton of IV*a* is unusual. The reason for this shift is not readily apparent. Therefore, assignment of the stereochemistry of the esters is based on the observed coupling of the C-2 protons.

Pharmacology[1]—The epimers (IV*a* and IV*b*) were evaluated with regard to (*a*) conduction block anesthesia in rats (see Table I) (16); (*b*) infiltration anesthesia in guinea pigs (see Table II) (17); (*c*) their irritation properties in rabbits (see Table III) (16); and (*d*) conduction-block anesthesia on isolated intact frog nerves (see Fig. 1) (18).

A comparison of the esters with regard to conduction block in rats (Table I) reveals that epimer IV*a* (0.25%) fails to provide a complete block while epimer IV*b* (0.25%) exhibits a rather potent block of long duration. In order to suggest that this is a conformational effect, the rate of absorption of the epimers must be considered. Since passive drug absorption has been shown to be dependent on the drug's partition coefficient, an evaluation of the partition coefficients (P) (1-octanol/pH 7.4 buffer) of the epimers was made (19). The log P of epimer IV*a* was 3.4 and of epimer IV*b* was 3.2. The IV*a*/IV*b* ratio is about 1.6. Thus, the difference in activity cannot be explained on the basis of different lipid solubilities since the more active isomer has the lower P value. The long duration of activity can be explained on the basis of the very high lipid solubility of the compounds.

Basicity of the epimers must also be considered since it is the nonionic form of the drug which is absorbed. The pKa's of the epimers were determined on the hydrochloride salts in 50% aqueous methanol and found to be 8.30 ± 0.05 pKa′ units.[2] Thus, the same amount of nonionic epimer is available for absorption.

The epimers exhibited marked differences in activity in infiltration anesthesia (Table II). In the case of epimer IV*a* its duration of activity was shorter than the standard drug lidocaine while the duration of activity of epimer IV*b* was much longer than either lidocaine or epimer IV*a*.

The compounds are extremely irritating as indicated by irritation index (Table III). The epimers produced erythema, edema, and necrosis in the guinea pig. However, this type of tissue response would not be expected to depend on any special stereochemical arrangement since many different types of compounds exert this activity. Therefore, the observed differences in activity would not be expected to be the result of differences in tissue irritation.

Different rates of metabolic degradation of the epimers could result in the alteration of activity. However, preliminary experi-

[1] The authors are indebted to Dr. H. Jack Adams, Drug Evaluation and Neuropharmacology Sections, Astra Pharmaceutical Products, Inc., for performing the pharmacological assays described in this paper.
[2] The authors are indebted to Professor B. van't Reit, Department of Chemistry and Pharmaceutical Chemistry, for these determinations. The pKa′ values were determined potentiometrically.

Table I—Data on Rat Sciatic Nerve Blocks[a]

Compd.[b] % Concn.	Onset, min.	Duration, min. RMT	Duration, min. LMT	Frequency of Complete Block[c] RMT	Frequency of Complete Block[c] LMT	Frequency of Partial Block[c] RMT	Frequency of Partial Block[c] LMT
IV*a* 0.25	—	—	—	0/5	0/5	5/5	3/5
IV*a* 0.5	2	1–2 days	98	2/5	1/5	3/5	1/5
IV*a* 1.0	2	8–13 days	159[d]	3/5	4/5	2/5	0/5
IV*a* 2.0	2	6–12 days	5–13 days	4/5	4/5	1/5	1/5
IV*b* 0.25	1	239[e]	214	4/5	2/5	1/5	2/5
IV*b* 0.4	2	1–8 days	—	5/5	0/5	0/0	4/5

[a] Onset and duration are for complete block only. [b] All concentrations are as base with epinephrine 1 : 100,000. [c] RMT = right mid-thigh; LMT = left mid-thigh. [d] Average of three; one blocked 11 days. [e] One block only; three blocked 1–5 days.

ments on isolated nerve (Fig. 1) tend to eliminate this factor as the primary reason for the differences in activity. The apparent reason for the failure of the intact nerve to return to an active state upon washing with Ringer's solution can be attributed to the very high partition coefficients of the epimers.

With this limited information, it appears that a conformational effect is being observed. However, additional chemical systems with well-defined stereochemistry must be studied in order to fully evaluate this effect.

Table II—Results of Intradermal Wheals in Guinea Pigs

Compd.[a] % Concn.	Onset, min.	Duration, min.[c]	Frequency
IV*a* 0.25	2	51 ± 18	12/12
Lidocaine 0.25[b]	2	86 ± 8	6/6
IV*a* 0.5	2	43 ± 37	12/12
Lidocaine 0.5	1	132 ± 43	6/6
IV*b* 0.25	2	102[d]	12/12
Lidocaine 0.25	2	34 ± 9	6/6
IV*b* 0.4	2	110[e]	12/12
Lidocaine 0.4	2	67 ± 12	6/6

[a] Epimer concentrations are as the base with epinephine 1 : 100,000. [b] Lidocaine (Xylocaine, Astra Pharmaceutical Products, Inc., Worcester, Mass.) concentrations are as the HCl salt with epinephine 1 : 100,000. [c] ± Standard deviations of the mean. [d] Average of two; other ten blocked over 145 min. [e] Average of three; other nine blocked over 170 min.

EXPERIMENTAL[3]

3-exo-N,N-Dimethylaminomethyl-endo-norbornanol-(2) (VIa)—A solution of 4.6 g. (0.12 mole) of sodium borohydride and 10.0 g. (0.06 mole) of 3-*exo*-*N,N*-dimethylaminomethyl-norbornanone-(2)[4] in 350 ml. of isopropyl alcohol was stirred at room temperature for 24 hr. Acetone (40 ml.) was added and the mixture was allowed to stir for an additional hour. The solvent was removed under reduced pressure and the residue was added to ether and water. The organic phase was washed with water, a saturated solution of sodium chloride, then was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 9.8 g. of an orange oil. The oil was dissolved in petroleum ether and cooled. This afforded 3.2 g. (0.019 mole), 32% of 3-*exo*-*N,N*-dimethylaminomethyl-*endo*-norbornanol-(2) as colorless needles, m.p. 66–70°, reported m.p. 69.5–70.5° (14). The IR spectrum was identical with the published spectrum (14). The NMR spectrum (carbon tetrachloride) showed a singlet for N-$(CH_3)_2$ absorption at 2.18 p.p.m. and a multiplet at 3.72 p.p.m. for the *exo* proton at C-2.

Reduction of 3-exo-N,N-Dimethylaminomethyl-norbornanone-(2) with Lithium Aluminum Hydride—To a suspension of 1.2 g. (0.03 mole) of lithium aluminum hydride in 50 ml. of anhydrous ether was added dropwise with stirring and cooling over a 30-min. period, 5.0 g. (0.03 mole) of 3-*exo*-*N,N*-dimethylaminomethyl-norbornanone-(2) in 50 ml. of anhydrous ether. The mixture was stirred at room temperature for 1 hr. then was poured onto ice containing a 5% sodium hydroxide solution. The mixture was extracted with ether. The organic phase was washed with water, a saturated sodium chloride solution, then was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 3.5 g. of a pale yellow liquid. Seeding with the pure *endo*-norbornanol (VI*a*) afforded 2.0 g. semisolid and 1.5 g. of a liquid.

Table III—Results of the Intradermal Wheal Irritation Test in Rabbits

Compd.[a] % Concn.	Total Score	Irritation Index
IV*a* 1.0	67	8.4
Lidocaine 1.0	2	.2
IV*a* 2.0	64	8.0
Lidocaine 2.0	34	4.2
IV*b* 0.25	70	8.8
Lidocaine 0.25	0	0
IV*b* 0.4	83	8.4
Lidocaine 0.4	14	1.8

[a] Epimer concentrations are as the base. Lidocaine concentrations are as the HCl salt.

The NMR spectrum (carbon tetrachloride) of the semisolid showed it to be 70 : 30 mixture of the *exo* to *endo* compounds as judged by the N-$(CH_3)_2$ absorption at 2.24 and 2.18 p.p.m. The NMR spectrum (carbon tetrachloride) of the liquid showed it to be an 80 : 20 mixture of the *exo* to *endo* compounds as judged by the N-$(CH_3)_2$ absorption at 2.24 and 2.18 p.p.m.

exo-3-(N,N-Dimethylaminomethyl)-endo-2-norbornanyl 4-n-Butoxybenzoate Hydrochloride (IVa)—A solution of 2.1 g. (0.012 mole) of 3-*exo*-*N,N*-dimethylaminomethyl-*endo*-norbornanol-(2) (VI*a*), 6.3 g. (0.03 mole) of 4-*n*-butoxybenzoyl

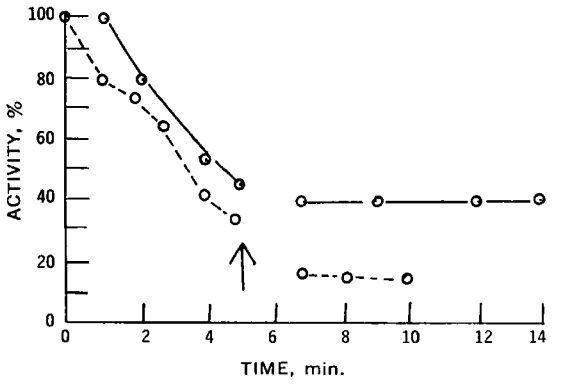


Figure 1—*Effects of IVa and IVb on isolated intact frog nerve. Key: —, IVa; - - - -, IVb. Changes in the amplitude of the action potential after treatment with compound and washing (→) with Ringer's solution are shown. The concentrations are 10 mM.*

[3] Melting points, determined with a Thomas-Hoover capillary apparatus, are uncorrected. The UV spectra were obtained with a Beckman DK-1A recording spectrophotometer using water as the solvent. The IR spectra were determined with a Perkin-Elmer 237 spectrophotometer. A Varian A-60 NMR spectrometer at an operating frequency of 60Mc./sec. was used. Tetramethylsilane was used as an internal standard.

[4] Aldrich Chemical Co.

chloride, and 60 ml. of chloroform was heated at reflux for 6 hr. The solvent was removed under reduced pressure and the residue was added to ether. This afforded 4.17 g. (0.011 mole), 92%, of *exo*-3-(*N*,*N*-dimethylaminomethyl)-*endo*-2-norbornanyl 4-*n*-butoxybenzoate hydrochloride as a white solid, m.p. 156–160°. Two recrystallizations from acetone afforded an analytical sample as white prisms, m.p. 165–167°. The IR spectrum (chloroform) showed absorption at 5.87 μ (C=O). The NMR spectrum (deuteriochloroform) showed absorption for one proton as a multiplet centered at 4.65 p.p.m. which is consistent with an *exo* proton at C-2. $\lambda_{max.}$ (H_2O) 262 mu, ϵ = 17,300.

Anal.—Calcd. for $C_{21}H_{32}ClNO_3$: C, 66.0; H, 8.4; N, 3.7. Found: C, 66.0; H, 8.2; N, 3.6.

exo-3-(N,N-Dimethylaminomethyl)-exo-2-norbornanyl 4-n-Butoxybenzoate Hydrochloride (IVb)—A solution of 1.5 g. (0.0089 mole) of the 80 : 20 liquid mixture of epimers obtained from the lithium aluminum hydride reduction, 4.6 g. (0.022 mole) of 4-*n*-butoxybenzoyl chloride, and 10 ml. of chloroform was allowed to stand at room temperature for 25 hr. The solvent was removed under reduced pressure, then ether was added to the residue. The mixture was chilled for 30 hr., then the white solid was removed by filtration. This afforded 3.3 g., m.p. 120–169°. Recrystallization from acetone afforded 1.8 g. of a white solid, m.p. 177–181°. An additional recrystallization from acetone afforded an analytical specimen of *exo*-3-(*N*,*N*-dimethylaminomethyl)-*exo*-2-norbornanyl 4-*n*-butoxybenzoate hydrochloride as white prisms, m.p. 177–181°. The IR spectrum (chloroform) showed absorption at 5.85 μ (C=O). The NMR spectrum (deuteriochloroform) showed absorption for one proton as a doublet centered at 5.10 p.p.m. (J=7 c.p.s.) which is consistent with an *endo* proton at C-2. $\lambda_{max.}$ (H_2O) 260 mμ, ϵ = 18,360.

Anal.—Calcd. for $C_{21}H_{32}ClNO_3 \cdot 1\ H_2O$: C, 63.1; H, 8.5; N, 3.5. Found: C, 63.5; H, 8.1; N, 3.5.

Partition Coefficients[5]—The method of Hansch (19) was slightly modified. Two milliliters of 1-octanol and 10 ml. of pH 7.4 buffer (0.05 *M* sodium monohydrogen phosphate, adjusted to pH 7.4 with 5 *M* sulfuric acid) were shaken for 24 hr. with 20–30 mg. of the compound. The aqueous layer was separated and its absorbance was determined at its $\lambda_{max.}$ The log *P* is reported as the mean of three determinations.

[5]The authors would like to thank Dr. K. Rogers, Department of Biochemistry, for aid in determining the partition coefficients.

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