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Stereochemical Preferences for Curarimimetic Neuromuscular Junction Blockade II: Enantiomeric Bisquaternary Amines as Probes

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Abstract □ Two pairs of bisquaternary enantiomeric neuromuscular junction blocking agents as well as their diastereomeric *meso*-forms were prepared in which the carbon asymmetry is adjacent to the quaternary center. The tertiary amines from which the blocking species were obtained by methyl iodide treatment were *N*-methylpavine and 1,1′-dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline). Blocking potencies were determined by the mouse inclined screen assay and by the cat tongue–hypoglossal nerve technique. The mouse assay showed no statistical difference between the enantiomeric probes derived from *N*-methylpavine and only a modest superiority of the *(R–R)* isomer over the *(S–S)* isomer in the case of the tetrahydroisoquinoline compounds. The cat assay showed a modest statistically significant *(R–R)* > *(S–S)* difference in potencies in both kinds of probes. The diastereomeric *meso*-compounds were less active than the enantiomers in mice but were of intermediate activity in the cat determination. Acetylcholinesterase-inhibiting activity was determined for each probe to discount potency differences from this source, and no significant differences in blocking potency attributable to preferential enzyme inhibition by the probes were noted.

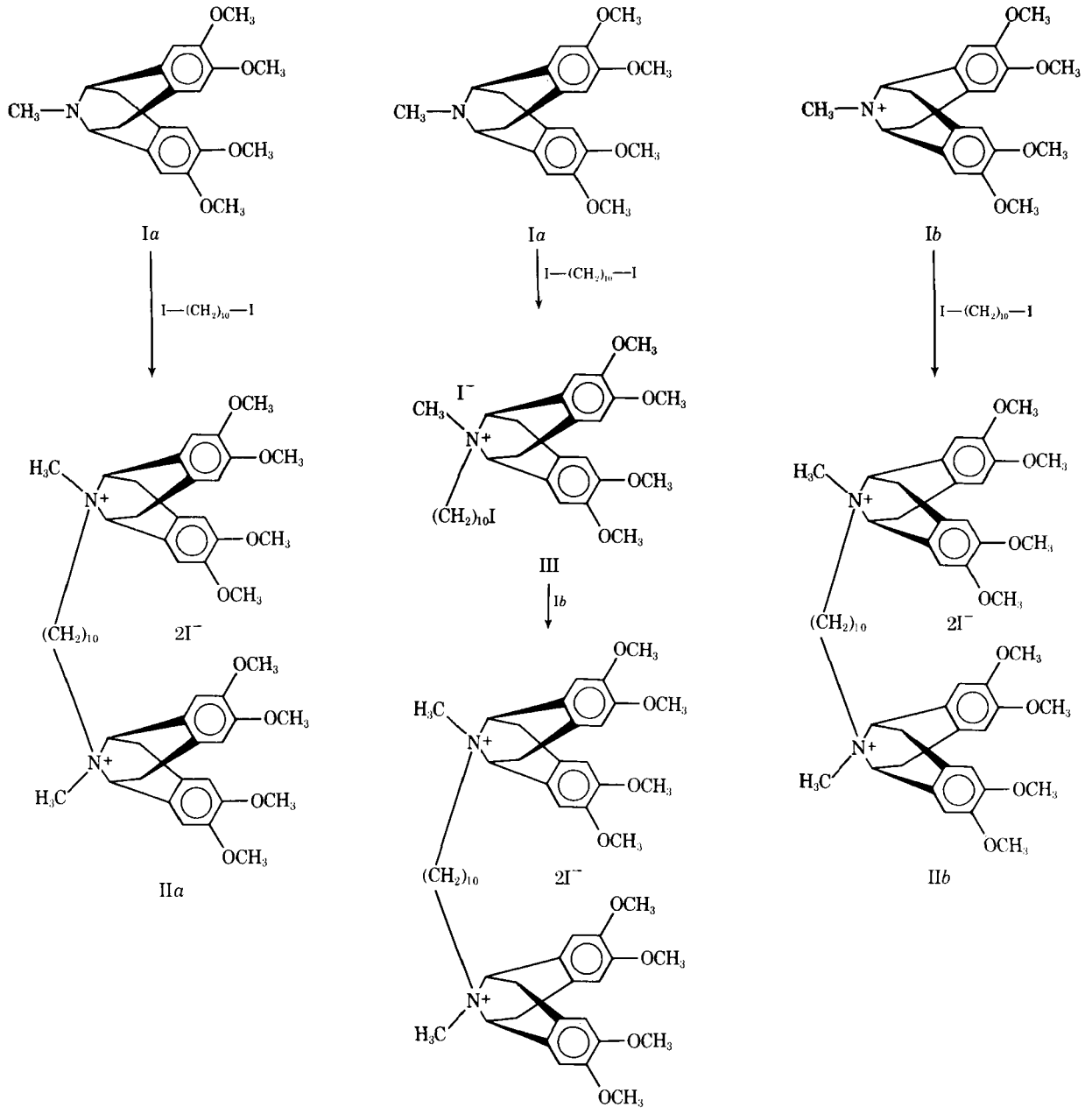
Keyphrases □ Curarimimetic neuromuscular junction blockade—stereochemical preferences, enantiomeric bisquaternary amines as probes □ Neuromuscular junction blockade, curarimimetic—stereochemical preferences, enantiomeric bisquaternary amines as probes □ *N*-Methylpavine (enantiomeric bisquaternary amines)—probes for stereochemical preferences for curarimimetic neuromuscular junction blockade □ 1,1′-Dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (enantiomeric bisquaternary amines)—probes for stereochemical preferences for curarimimetic neuromuscular junction blockade

The initial report (1) from these laboratories concerning the possibility of stereochemical preferences being exhibited at the neuromuscular junction toward nondepolarizing blocking agents of the curare type was concerned with several monoquaternary enantiomeric probes derived from alkaloids related to tetrahydroisoquinoline. These studies examined the possibility that the exclusive, but modest, *(S)* > *(R)* (about 1.8:1) blocking potency difference shown by the cat assay could have been due to stereopreferential binding of the probes by blood components and/or by stereoselective acetylcholinesterase inhibition since other factors such as absorption, excretion, and metabolism differences were unlikely due to the rapid onset of block. The blood binding studies on both plasma protein and red blood cells indicated a low order of binding and a reversed order from that which might account for potency differences. The stereoselective inhibition of acetylcholinesterase, while it had the correct orientation in some cases, was of such a low order of activity and so random in its focus that it could not be seriously considered as causal for the observed potency differences.

DISCUSSION

Since neuromuscular junction blockers have traditionally been thought of as bisquaternaries, in spite of the recent disclosure that (+)-tubocurarine is actually a monoquaternary (2), it seemed appropriate to test neuromuscular junction stereochemical preferences on these types to see whether the preferences determined for monoquaternaries extended to the bisquaternaries. Unpublished observations in these laboratories had shown that quaternization of (±)-*N*-methylpavine (I) with 1,10-diiododecane produced a potent neuromuscular junction blocking agent (II) comparable in activity to (+)-tubocurarine. Therefore, the enantiomeric forms (II*a* and II*b*) of this quaternary blocker as well as the *meso*-form (II*c*) were considered to be suitable probes in the determination of stereochemical preferences at the neuromuscular junction for blocking agents.

Stereochemical preferences can only be considered valid when made between enantiomeric forms since diastereomers have different physical and chemical properties whereas enantiomers only differ in rotatory effect on polarized light. On the other hand, the fact that enantiomers may be operating in an asymmetric biological environment necessitates giving attention to preferential plasma protein and/or red blood cell binding as well as to stereopreferential acetylcholinesterase inhibition. Previous studies (1) demonstrated that blood components probably need not be considered as causal for differences in activity. However, acetylcholinesterase inhibition cannot be ruled out as a possible factor, even though it was inoperative in the case of the monoquaternaries, because it is



Scheme I

well known that benzoquinonium[1], a bisquaternary, has marked enzyme inhibitory properties (3).

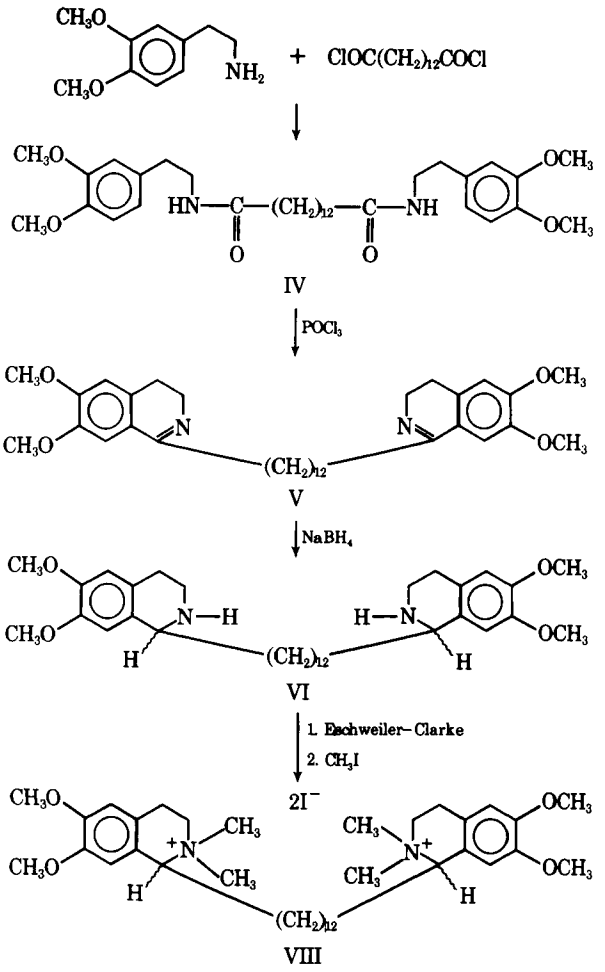
The *N*-methylpavine enantiomers were prepared according to the procedures elaborated in the literature (4, 5). The enantiomeric quaternary probes (II*a* and II*b*) were prepared by treatment of the appropriate enantiomer with 1,10-diiododecane; the preparation of the *meso*-form (II*c*) required the intermediate preparation of (+)-*(R)*-*N*-methylpavine-*N*-(10-iododecane) iodide (III), which was then reacted with (−)-*(S)*-*N*-methylpavine to achieve the desired *meso*-product (II*c*). The reactions are summarized in Scheme I.

The selection of the quaternary derivative derived from 1,1′-dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) (VIII) as a useful probe was based on the report of its activity by Smith *et al.* (6) and the obvious opportunity to use it as an enantiomeric probe. Smith *et al.* indicated only that activity differences existed between two fractions from the synthetic process which had differing solubilities, obviously the racemic pair and the *meso*-form. The possibility for exploring enantiomeric differences of the racemate as well as the fact that this paper has been cited as an example of such differences (7) suggested that it be an appropriate candidate.

The chemical preparation of VIII (said to be in press) has not appeared to date, although it is apparent that these kinds of compounds are readily prepared through the reactions shown in Scheme II with, initially, formation of an appropriate diamide (IV) by condensation of 1,12-dodecanedicarboxylic acid chloride with homoveratrylamine. Under Bischler–Napieralski ring closure conditions (8), the bis ring closure occurs to yield the appropriate 3,4-dihydroisoquinoline (V). Reduction of V with methanolic sodium borohydride and conversion to the hydrochloride salt led to a mixture of racemic and *meso*-1,1′-dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) dihydrochlorides (VI). The separation of the two forms was not as easily accomplished by simple water recrystallization to effect separation on a solubility basis as was suggested by Smith *et al.* (6). The experience of the present authors was that absolute ethanol was a far better differentiating agent in a solubility sense, as indicated by the experimental results.

To distinguish between the *meso* and racemic fractions, the free

[1] Mytolon.



Scheme II

base of each was regenerated and converted to the bi[(−)-*O,O*-di-*p*-toluoyltartrate] salt and then subjected to recrystallization from different solvents and solvent combinations. Only the salts from the racemic form (arbitrarily designated as the A fraction) showed marked changes in both melting point and optical rotation when recrystallized from a specific solvent mixture [ethanol–ethyl acetate–acetone (1:2:2)], and it was concluded that this form was the one that could be resolved. Indeed, continued recrystallization of this salt from the same solvent system resulted in a product that had no change in melting point or rotation and which, when treated appropriately with base, yielded the (+)-isomer (VI*a*) as an oil. Treatment of the mother liquors by formation of the bitartrate of the isomeric (+)-*O,O*-di-*p*-toluoyltartaric acid, using the same recrystallization methods, resulted in the enantiomeric salt being obtained, which yielded the corresponding (−)-isomer (VI*b*) as an oil in the same manner.

At this point, the observations of Battersby and Edwards (9) were pertinent to the problem of determining the absolute configurations of the two enantiomers. The experience of these authors indicated rather convincingly that a correlation exists between optical rotation and absolute configuration if it can be shown that a specific shift in rotation can be correlated with a change in solvent polarity. In short, if a positive shift in rotation under the specified conditions can be identified, the compound has an *(S)*-configuration and vice versa. Table I shows the results obtained with the two isomers under consideration and certainly indicates that the (+)-isomer possesses the *(R)*-configuration and that the (−)-isomer possesses the *(S)*-configuration. Establishment of the absolute configurations led to the *N*-methylation of the corresponding secondary amines (VI*a* and VI*b*) by the Eschweiler–Clarke method to the corresponding oily enantiomers, which were then converted to the desired probes (VIII*a* and VIII*b*) by treatment with methyl iodide. Similar treatment of the *meso*-form (Fraction B) yielded the necessary quaternary probe (VIII*c*).

Table I—Effect of Solvent Polarity on Optical Rotation of Enantiomeric 1,1′-Dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines)

	Molecular Rotation in			
Enantiomer	C_6H_6	$CHCl_3$	CH_3OH	Amine·2HCl CH_3OH
VI*a*	+16.6	+15.5	+2.8	0.0
VI*b*	−16.0	−12.1	−2.5	0.0

The pharmacological results encompass both a mouse inclined screen test and the cat tongue–hypoglossal nerve assay method. The mouse test (10) was initially preferred because it was simple, relatively inexpensive, reasonably fast, and adaptable to statistical analysis. However, cat data may be more meaningful (1). The relative potency ratios were calculated using 100 as the standard potency of (+)-tubocurarine. Analyses of the dose–response data for each individual compound showed no significant deviation from parallelism of the dose–response curves observed among the three compounds in each series or between each compound and (+)-tubocurarine. The test for parallelism was important since nonparallelism would imply a different mechanism of action which would, of course, negate any finding of potency differences.

Tables II and III give the ED_{50} values and potency ratios (based on ED_{50}) for (+)-tubocurarine and the compounds synthesized for this study. The results show that, in mice, no significant difference for the *N*-methylpavine-derived probes could be detected between the enantiomers, although both were significantly more potent than the *meso*-isomer. With the 1,1′-dodecamethylenebis(6,7-dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium) iodides, the *(R–R)*-isomer was approximately twice as potent as its enantiomer and both were more potent than the *meso*-form [*i.e.*, the *(R–S)* form]. In the cat assay (Table III), a more definitive predominance of the *(R–R)*-enantiomer was evident although, again, the ratio approximates 2:1. It is interesting that, in the cat assay, the diastereomeric *(R–S)* form adopts a potency position intermediate between the enantiomers that is significantly different than the mouse assay data, which show the *(R–S)* forms being less active in both cases.

Assessing all data presented in these experiments leads to the inescapable conclusions that the *(R–R)* bisquaternaries tend to have a greater neuromuscular junction blocking potency than the *(S–S)* forms and that the potencies of the diastereomeric *(R–S)* forms are dependent on the animal used for assay.

The differences in cited activity were also examined in the light of the ability of these compounds to inhibit acetylcholinesterase which, undoubtedly, could influence the gross measurement of neuromuscular junction blocking activity. The methods were described previously (1), and it was determined that there were no significant differences in blocking ability by the various isomers (Table IV). On this basis, it must be concluded that there is a modest but significant predominance in blocking activity by the *(R–R)* absolute configuration in these types of bisquaternaries. This finding is exactly the reverse of the findings with monoquaternary enantiomeric probes (1). The significance of this difference is not apparent at this time.

EXPERIMENTAL[2]

Preparation of Enantiomeric *N*-Methylpavines—The *N*-methylpavines (I) were prepared according to the published procedure (3, 4). The racemic base was resolved by (+)-L-tartaric acid

[2] Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. TLC was conducted on Eastman chromagram sheet 6060 silica gel, and visualization was done with both UV lamp and iodine vapor. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR spectra were determined in mineral oil or KBr with a Perkin-Elmer 237B grating IR spectrophotometer. NMR spectra were measured with a Varian Associates model A-60D NMR spectrometer. Mass spectral determinations were performed by Mass Spectrometry Laboratory Services, Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, using an AEI-MS30 mass spectrometer or a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

Table II—ED_{50} and Potency Ratios in the Mouse Assay for Neuromuscular Junction Blocking Potency

Compound	ED_{50}, mg/kg	Potency Ratios [(+)-Tubocurarine = 100]
(+)-Tubocurarine	0.34	100
II*a*	0.45	76
II*b*	0.42	81
II*c*	0.72	47
VIII*a*	2.00	17
VIII*b*	3.80	9
VIII*c*	5.60	6

to afford (+)-*(R)*-*N*-methylpavine (I*a*), mp 150–151°, $[\alpha]_D^{25}$ +211° (c 1.0, C_2H_5OH), and by (−)-D-tartaric acid to afford (−)-*(S)*-*N*-methylpavine (I*b*), mp 151–153°, $[\alpha]_D^{25}$ −210° (c 1.0, C_2H_5OH). These values were in excellent agreement with literature values (4).

***N,N'*-Decamethylenebis[(+)-*(R)*-*N*-methylpavinium Iodide] (II*a*)**—1,10-Diiododecane (1 g, 0.0025 mole) and (+)-*N*-methylpavine (3.5 g, 0.01 mole) were dissolved in dry benzene (30 ml) and then refluxed in an oil bath at 95° for 5 days. Ethanol was occasionally added dropwise to keep the reaction mixture homogeneous, and then the mixture was cooled in a refrigerator for 2 days. The solid cake which separated was obtained by decantation, crushed, and washed twice with cold benzene. Attempted crystallization by dissolving in methanol and adding ether failed to give a crystalline product; but the resulting gummy precipitate, when rubbed with a glass rod, consistently gave a white solid, mp 178–181° dec., $[\alpha]_D^{25}$ +186° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{52}H_{70}I_2N_2O_8$: C, 56.52; H, 6.34; N, 2.54. Found: C, 56.25; H, 6.41; N, 2.42.

***N,N'*-Decamethylenebis[(−)-*(S)*-*N*-methylpavinium Iodide] (II*b*)**—This compound was prepared in the same manner as the (+)-isomer by refluxing 1,10-diiododecane (1.0 g, 0.0025 mole) and the (−)-*N*-methylpavine (3.5 g, 0.01 mole) in dry benzene for 5 days to give 2.0 g of product, mp 181–182° dec., $[\alpha]_D^{25}$ −190° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{52}H_{70}I_2N_2O_8$: C, 56.52; H, 6.34; N, 2.54. Found: C, 56.26; H, 6.20; N, 2.36.

(+)-*(R)*-*N*-Methylpavine-*N*-(10-iododecane) Iodide (III)—(+)-*N*-Methylpavine (1.0 g) was dissolved in anhydrous benzene (10 ml) and added dropwise to a refluxing solution of 1,10-diiododecane (5 g) in dry benzene (30 ml) in an oil bath at 95° with vigorous stirring and refluxing. The addition was completed in 6 hr; the reaction mixture was allowed to reflux for 2 days, cooled to room temperature, and stored in a refrigerator for 2 days. The solid layer was separated by decantation, crushed, washed twice with cold benzene, filtered, and dried. The solid residue was lixiviated with methanol–ether (1:1), and the insoluble residue was removed by filtration. Evaporation of the filtrate and recrystallization of the residue by dissolving in methanol and dropping into a large excess of ether yielded 0.6 g of a white crystalline powder, mp 129–132° (prior softening at 115°), $[\alpha]_D^{25}$ +150° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{31}H_{45}I_2NO_4$: C, 49.66; H, 6.01; I, 33.9; N, 1.87. Found: C, 50.34; H, 6.21; I, 33.1; N, 2.13.

This was the best analysis achieved and was not improved by additional attempts at purification.

***meso*-*N,N'*-Decamethylenebis(*N*-methylpavinium Iodide) (II*c*)**—Compound III (0.4 g, 0.00053 mole) was dissolved in ethanol together with (−)-*N*-methylpavine (1.0 g, 0.0028 mole), refluxed in an oil bath for 4 days at 95°, cooled, and added dropwise to a large excess of ether. The precipitate was collected, dissolved in methanol, and added dropwise to a large excess of ether. The process was repeated three times to yield 0.3 g of a white powder, mp 179–181° (with decomposition and prior softening at 165°) $[\alpha]_D^{25}$ +26.7° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{52}H_{70}I_2N_2O_8$: C, 56.52; H, 6.34; I, 23.0; N, 2.54. Found: C, 56.41; H, 6.28; I, 23.2; N, 2.47.

1,12-Dodecamethylenebis[2-(3',4'-dimethoxyphenyl)ethylamide] (IV)—2-(3',4'-Dimethoxyphenyl)ethylamine (36 g, 0.2 mole) was dissolved in benzene (500 ml) in a 2-liter flask fitted with a condenser, a mechanical stirrer, and an addition funnel containing 1,12-dodecanedicarboxylic acid chloride [prepared from 1,12-dodecanedicarboxylic acid (26 g) and thionyl chloride (70 ml) in benzene]. The acid chloride solution was added dropwise to the amine solution with vigorous stirring and, after the addition was completed, the reaction mixture was allowed to cool to room temperature and filtered. The residue was recrystallized twice from ethanol to yield 54.6 g of white crystals (93%), mp 152–153°; IR (cm^{-1}): 1642 (C=O) and 3310 (N—H).

Table III—ED_{50} and Potency Ratios in Cat Assay for Neuromuscular Junction Blocking Potency

Compound	ED_{50}[a], mg/kg	Potency Ratios [(+)-Tubocurarine = 100]	ED_{50} Potency Ratio of Isomers[b] (Most Potent = 1)
(+)-Tubocurarine	0.15	100	—
II*a*	0.010	1500	1.0
II*b*	0.021	714	2.1
II*c*	0.019	790	1.9
VIII*a*	0.320	47	1.0
VIII*b*	0.780	19	2.4
VIII*c*	0.530	28	1.7

[a] These values are with a 95% confidence limit. [b] A statistical comparison was made between the line elevations of the isomers to evaluate the significance of the difference in ED_{50} values. For the series II*a*, II*b*, and II*c*, the values of F_{el} (*dF'*, *dF*) were 1.95 (2, 36); for the series VIII*a*, VIII*b*, and VIII*c*, the values were 0.83 (2, 32). In both cases the slopes between the isomers were not statistically different and, thus, the observed potency ratios are real and statistically different.

Anal.—Calc. for $C_{34}H_{52}N_2O_6$: C, 69.86; H, 8.90; N, 4.79. Found: C, 70.08; H, 8.75; N, 4.82.

1,1'-Dodecamethylenebis(6,7-dimethoxy-3,4-dihydroisoquinoline) (V)—The preceding diamide (IV) (50 g, 0.086 mole) was dissolved in dry chloroform (300 ml), and phosphorus oxychloride (50 ml) was added. The mixture then was refluxed in an oil bath at 75° for 3 hr and poured into ice water. The mixture was made alkaline with 10% aqueous sodium hydroxide and then extracted with chloroform (5 × 250 ml). The chloroform extract was washed with water, dried, and evaporated to dryness. The residue was recrystallized from benzene to yield 40 g (85%) of white crystals, mp 104–105°. The IR and NMR data were compatible with the expected structure.

Anal.—Calc. for $C_{34}H_{48}N_2O_4$: C, 74.45; H, 8.76; N, 5.11. Found: C, 74.51; H, 8.69; N, 5.21.

1,1'-Dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) Dihydrochlorides (VI)—Compound V (35 g) was dissolved in methanol containing 1% water (300 ml), and the resulting solution was then cooled in an ice bath. Sodium borohydride (30 g) was added to this solution in small portions with stirring while not allowing the temperature to rise above 5°. Upon completion of the addition, the continuously stirred solution was allowed to stand at room temperature for 30 min and then refluxed on a steam bath for 2 hr. It was then cooled to room temperature

Table IV—Acetylcholinesterase Inhibition by Enantiomeric Neuromuscular Junction Blockers

Compound	Wilkinson K_i[a], $\times 10^{-4}$ *M*	Wilkinson V_{max}, mole/unit/min	K_i Ratio between Enantiomers
Acetylcholine	2.56 ± 0.02 (K_m)	1.008 ± 0.05	
(+)-Tubocurarine	4.29 ± 0.40	1.55 ± 0.70	
II*a*	0.75 ± 0.10	0.53 ± 0.10	0.914:1.00
II*b*	0.82 ± 0.08	0.55 ± 0.05	
VIII*a*	8.27 ± 0.04	0.26 ± 0.01	0.779:1.00
VIII*b*	10.62 ± 0.06	0.31 ± 0.03	

[a] Determined by calculation from computer program (Wilkinson) generated, altered K_m values.

and the solvent was removed under reduced pressure. The residue was suspended in water (100 ml), made alkaline with 10% aqueous sodium hydroxide, and extracted with chloroform (5 × 150 ml). The chloroform extract was washed with water, dried, and stripped of solvent under reduced pressure to leave an oily residue (33.7 g, 96%) which, when stored in a refrigerator overnight, was converted into a soft solid. This soft solid, dissolved in 200 ml of anhydrous ether, was treated with dry hydrogen chloride gas with continuous stirring until precipitation ceased. The precipitate was removed by filtration and recrystallized from ethanol to yield 33.0 g of white crystals, mp 142–144°.

Anal.—Calc. for $C_{34}H_{54}Cl_2N_2O_4$: C, 65.28; H, 8.64; Cl, 11.36; N, 4.48. Found: C, 65.40; H, 8.59; Cl, 11.51; N, 4.39.

Separation of *meso* and Racemic 1,1′-Dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) Dihydrochlorides (VI)—The separation was carried out be repeated recrystallizations of the VI dihydrochloride salt from absolute ethanol until no further change in the melting points of the differently soluble fractions was observed. The fraction least soluble in absolute ethanol (A), mp 199–201°, provided a yield of 6.0 g; the more soluble fraction (B), mp 138–141°, provided a yield of 5.4 g.

Identification of the Racemic and *meso* Species—The free bases of Fractions A and B were obtained by dissolving 5 g of each salt separately in 50 ml of water and then alkalinizing with 10% aqueous sodium hydroxide followed by ether extraction (4 × 50 ml) to give an ethereal solution which was dried and stripped of solvent. Each oily residue (2.0 g, 0.0036 mole) was dissolved in ethanol (15 ml) and added to 15 ml of a hot alcoholic solution of (−)-*O,O*-di-*p*-toluoyltartaric acid (2.8 g, 0.0072 mole), and the resulting mixture was allowed to cool overnight in a refrigerator. The solid cake in each case was then separated and dried. The salt from Fraction A was a white solid, mp 133–135°, $[\alpha]_D^{25}$ −79.5° (c 1.0, CH_3OH); the salt of Fraction B was a semisolid and solidified only after several washings with ether to give a product, mp 130–132°, $[\alpha]_D^{25}$ −77.9° (c 1.0, CH_3OH).

Recrystallization of both salts from ethanol–ethyl acetate–acetone (1:2:2) separated a nicely crystalline solid only from the salt of Fraction A, whereas the salt from Fraction B always formed a soft semisolid cake. Repeated recrystallization of the salt of Fraction A finally resulted in 0.6 g of a white crystalline solid (VI-A), mp 155–157°, $[\alpha]_D^{25}$ −65.8° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{74}H_{88}N_2O_{20}$: C, 67.07; H, 6.65; N, 2.11. Found: C, 66.96; H, 6.61; N, 2.02.

(+)-1,1′-Dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) (VI*a*)—Compound VI-A (0.5 g) was suspended in water, alkalinized with 10% aqueous sodium hydroxide, and extracted with ether. The ethereal extract was then washed with water, dried, and evaporated to dryness, leaving 0.2 g of an oily residue, $[\alpha]_D^{25}$ +2.5 ± 0.1° (c 1.0, $CHCl_3$). Its dihydrochloride showed a melting point of 199–201° and $[\alpha]_{365}^{25}$ of −421 ± 0.5° (c 1.0, CH_3OH).

(−)-1,1′-Dodecamethylenebis(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) (VI*b*)—The mother liquors left from the recrystallization of VI-A were collected and stripped of solvent; the residue was dissolved in water, alkalinized with 10% aqueous sodium hydroxide, and extracted with ether. The ethereal extract was washed and dried, and the solvent was evaporated to leave an oily residue (1.5 g). This oily residue was dissolved in 15 ml of ethanol, added to 15 ml of a hot alcoholic solution of (+)-*O,O*-di-*p*-toluoyltartaric acid (2 g), and then left overnight in a refrigerator. The solid cake which formed was separated and recrystallized extensively in the same way as for VI-A to give 0.7 g of white crystalline solid, mp 154–156°, $[\alpha]_D^{25}$ +66.1° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{74}H_{88}N_2O_{20}$: C, 67.07; H, 6.65; N, 2.11. Found: C, 67.10; H, 6.70; N, 2.21.

The free base was obtained in exactly the same way as for VI*a* to give 0.3 g as an oily residue, $[\alpha]_D^{25}$ −2.3 ± 0.1° (c 1.0, $CHCl_3$). Its dihydrochloride showed a melting point of 198–200° and a $[\alpha]_{365}^{25}$ of +395 ± 0.5° (c 1.0, CH_3OH).

(+)-1,1′-Dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) (VII*a*)—Compound VI*a* (0.2 g) was dissolved in a cold mixture of 5 ml of 90% formic acid and 4 ml of 40% aqueous formaldehyde, and the solution was then heated on a steam bath for 16 hr. The reaction mixture was cooled to room temperature, treated with 5 ml of 4 *N* HCl, and evaporated to dryness under reduced pressure. The residue was then dissolved in water, made alkaline with 10% aqueous potassium hydroxide, and extracted with ether. The ethereal extract was washed, dried, and evaporated to leave an oily residue (0.18 g), $[\alpha]_D^{25}$ +3.2 ± 0.1° (c 1.0, CH_3OH).

Quaternization of VII*a* with methyl iodide in methanol afforded VIII*a* as a pale-yellow powder, which started decomposing at 220° and charred at about 350°, $[\alpha]_D^{25}$ +2.8° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{38}H_{62}I_2N_2O_4$: C, 52.78; H, 7.17; I, 29.38; N, 3.24. Found: C, 52.53; H, 7.3; I, 29.2; N, 3.25.

(−)-1,1′-Dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) (VII*b*)—Compound VI*b* (0.3 g) was methylated with formic acid and formaldehyde in the same manner as was VI*a* to yield finally 0.25 g of an oily product, $[\alpha]_D^{25}$ −3.1 ± 0.1° (c 1.0, CH_3OH).

Quaternization of VII*b* with methyl iodide gave VIII*b* as a pale-yellow powder, which started decomposing at 220° and charred at about 360°, $[\alpha]_D^{25}$ −2.8° (c 1.0, CH_3OH).

Anal.—Calc. for $C_{38}H_{62}I_2N_2O_4$: C, 52.78; H, 7.17; I, 29.38; N, 3.24. Found: C, 52.91; H, 7.05; I, 29.1; N, 3.29.

***meso*-1,1′-Dodecamethylenebis(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) (VII*c*)**—The *meso*-base was methylated in the same manner as VI*a* to yield an oily residue.

Quaternization with methyl iodide gave VIII*c* as a white powder, which started decomposing at about 210° and charred at about 340°.

Anal.—Calc. for $C_{38}H_{62}I_2N_2O_4$: C, 52.78; H, 7.17; I, 29.38; N, 3.24. Found: C, 52.99; H, 7.30; I, 29.20; N, 3.11.

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