β-Adrenergic Blocking Agents. Nitrogen Heteroaryl-Substituted 2-Propanolamines and Ethanolamines

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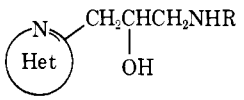
A series of some 20 novel 2-propanolamines of type I was prepared by reaction of Het-CH_2Li with the properly substituted aminoacetonitrile, followed by hydrolysis and reduction. The most potent β-adrenergic blocking activity was found in the phenanthridine, quinoline, and isoquinoline series, the phenanthridine being almost ten times as active as propranolol. Some ethanolamine homologs of the phenanthridine and quinoline series were prepared for comparison, the former being toxic, the latter somewhat more active than the corresponding 2-propanolamine.

Some efforts have been made recently to replace the aryl portion of propranolol[1] with heterocycles, such as 1,2,5-thiadiazole,[2] pyridine,[3] or thiazole.[4]

In the 1,2,5-thiadiazole series[2] a number of derivatives are potent adrenergic blocking agents of short duration and with some sympathomimetic activity. On the other hand, 1-isopropylamino-3-(2-thiazoloxy)-2-propanol[4] is a selective myocardial β stimulant, producing a marked increase in heart rate and force of contraction at a dose as small as 0.1 mg/kg iv.

A few heterocyclic analogs of pronethalol[5] have been reported,[3,6] but to our knowledge there are no representatives in the literature in which the amino-2-propanol side chain of propranolol is directly attached to a nitrogen heterocycle on the carbon next to nitrogen (I).

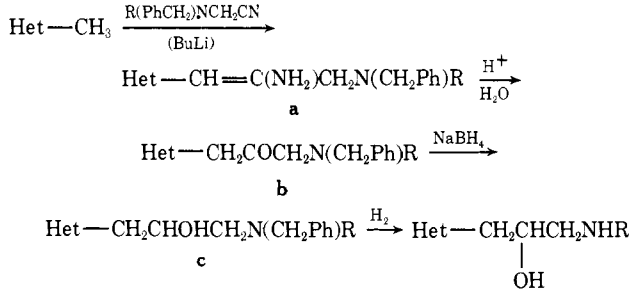


I

The ir shows intramolecular hydrogen bonding in this type of structure. The hydroxyl group has the possibility of hydrogen bonding with the weakly basic heterocyclic nitrogen, forming a six-membered ring, or with the strongly basic secondary amine nitrogen, forming a five-membered ring. Hydrogen bonding was also found in the amino ketone intermediates.

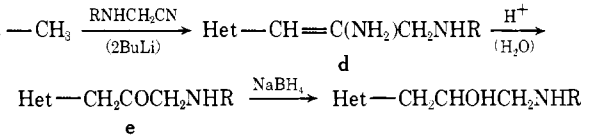
Chemistry. The synthesis of the above structure was accomplished by two procedures, A and B. Procedure A involves the reaction of the lithium derivative of the methyl heterocycle with *N*-benzyl-*N*-alkylaminoacetonitrile to give the enamine **a**, acid hydrolysis to the ketone **b**, and $NaBH_4$ reduction to the protected amino alcohol **c**, followed by catalytic debenzylation. The intermediates in this reaction sequence usually were obtained in high yields and were easily purified, but the debenzylation step was troublesome and gave mixtures, if the heterocycle was sensitive to hydrogenation. The amino ketone **17** was obtained by catalytic debenzylation of the amino ketone **16b**, before procedure B was developed.

procedure A



Procedure B circumvents the above debenzylation step but requires 2 equiv of BuLi for the formation of the enamine **d** because of the acidity of the secondary aminoacetonitrile. The enamine **d** was not isolated because of instability. The α-amino ketone **e** may be isolated as a hydrochloride but darkens quickly on addition of base.

procedure B



In the quinoline and phenanthridine series, the homologous pronethalol analogs **24, 25,** and **26** were prepared from the corresponding oxiranes.[7,8] These were used crude and were prepared from the corresponding 2-bromo ketone[9] by reduction with $NaBH_4$ or from the heterocyclic aldehyde[10] by treatment with dimethylsulfonium methylide.†

The final products are listed in Table I and the intermediates in Tables II and III.

Pharmacological Evaluation. β-Blocking activity was evaluated using *in vitro* guinea pig atrial preparations (n = 2) and determining isoproterenol dose-response curves for heart rate. The dose-response curves following β blockade were shifted to the right of the control curves proportional to the degree of isoproterenol inhibition. The degree of inhibition determined for propranolol was arbitrarily assigned a value of 100, and all test compounds were referenced to this (Table I).

Results

(a) *In Vitro.* The highest β-blocking activity was found in the phenanthridine series with **16.** The corresponding carbonyl compound **17** was about one-third as active. The pronethalol analog **26** showed cardiac toxicity and was found inactive. Considerably less active were the quinolines and isoquinolines related to **16.** In the quinoline series methyl substitution generally increased activity: **5, 7, 10,** and **11.** Surprisingly, the pronethalol analogs **24** and **25** were more active than the corresponding homologs **3** and **4.** The isoquinoline analog **22** is about six times as potent as the corresponding quinoline analog **4.** Other heterocyclic analogs were practically inactive.

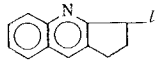
Amino substitution was limited to *i*-Pr, *t*-Bu, and 3,4-dimethoxyphenethyl. Some of the intermediates, the *N*-benzyl tertiary amines, were inactive.

(b) *In Vivo.* Isoproterenol infusion of 0.3 μg/kg/min iv in the conscious dog resulted in heart rate increases from

† A very recent publication[11] describes an elegant synthesis of some 6-(α-hydroxy-β-*N*,*N*-dialkylaminoethyl)phenanthridines *via* the Mannich reaction which would have been applicable also.

Table I

Het—CH_2CHCH_2NHR (OH)

No.	Het	R	β-Blocking activity[a]	Mp or bp (mm), °C[b]	Purification solvent[c]	Yield, %[d]	Procedure	Empirical formula	Analyses
1	6-Methyl-2-pyridyl	*t*-Bu	1	89–91 (0.15)		91	A	$C_{13}H_{22}N_2O$	C, H, N
2	Trimethylpyrazinyl	*t*-Bu	1	130–135	A	45	A	$C_{14}H_{25}N_3O \cdot AcOH$	C, H, N
3	2-Quinolyl	*i*-Pr	1	176–178	B	38	A	$C_{15}H_{20}N_2O \cdot 2HCl$	C, H, N
4	2-Quinolyl	*t*-Bu	3	83–84	C	28	A	$C_{16}H_{22}N_2O$	C, H, N
						45	B[e]		
5	4-Methyl-2-quinolyl	*t*-Bu	17	62–64	C	34	A	$C_{17}H_{24}N_2O$	C, H, N
6	6-Methyl-2-quinolyl	*t*-Bu	2	71–72	A	55	A	$C_{17}H_{24}N_2O$	C, H, N
7	7-Methyl-2-quinolyl	*t*-Bu	14	81–82	A–C	59	A	$C_{17}H_{24}N_2O$	C, H, N
8	6-Methoxy-2-quinolyl	*t*-Bu	0	195–200	D	37	A	$C_{17}H_{24}N_2O_2 \cdot 2HCl$	C, H, N
9	6-Dimethylamino-2-quinolyl	*t*-Bu	0	95–96	A–C	23	A	$C_{18}H_{27}N_3O$	C, H, N
10	3,4-Dimethyl-2-quinolyl	*i*-Pr	10	75–76	A	62	A	$C_{17}H_{24}N_2O$	C, H, N
11	3,4-Dimethyl-2-quinolyl	*t*-Bu	54	93–94	B	79	A	$C_{18}H_{26}N_2O$	C, H, N
12	3,4-Dimethyl-2-quinolyl	HV[f]	4	95–96	A–B	6[e]	A	$C_{24}H_{30}N_2O_3$	C, H, N
13	4-Phenyl-2-quinolyl	*t*-Bu	9	63–64	A–C	27	A	$C_{22}H_{26}N_2O \cdot 0.25H_2O$	C, H, N; H_2O[p]
14	6-Chloro-3-methyl-4-phenyl-2-quinolyl	*t*-Bu	0	175–180	B	77	B	$C_{23}H_{27}N_2OCl \cdot 2HCl$	C, H, N
15	5,6-Benzo-2-quinolyl[g]	*t*-Bu	0	97–99	A–B	21	B	$C_{20}H_{24}N_2O$	C, H, N
16	6-Phenanthridinyl	*t*-Bu	930	180–183	E	38	A	$C_{20}H_{24}N_2O \cdot (COOH)_2$	C, H, N
17	6-Phenanthridinyl	*t*-Bu[h]	382	225–230	E	15	*i*	$C_{20}H_{22}N_2O$	C, H, N
18	6-Phenanthridinyl	HV[f]	217	145–150	E	22[j]	A	$C_{28}H_{20}N_2O_3(COOH)_2 \cdot 0.5H_2O$	C, H, N
19	1-Benzyl-2-benzimidazolyl	*t*-Bu	0	107–108	A	84	A	$C_{21}H_{27}N_3O$	C, H, N
20	2-Benzimidazolyl	*t*-Bu	1	158–159	B	64	*k*	$C_{14}H_{21}N_3O$	C, H, N
21	1-Methyl-2-benzimidazolyl	*t*-Bu	1	121–122	A	92	A	$C_{15}H_{23}N_3O$	C, H, N
22	1-Isoquinolyl	*t*-Bu	18	190–195	B	22	B	$C_{16}H_{22}N_2O \cdot 2HCl$	C, H, N
23	1-Isoquinolyl	HV[f]	0	140–143	E	29	B	$C_{22}H_{26}N_2O_3(COOH)_2$	C, H, N
24	2-Quinolyl[l]	*i*-Pr	20	87–88	A	33	C	$C_{14}H_{18}N_2O$	C, H, N
25	2-Quinolyl[l]	*t*-Bu	9	85–86	A	35[m]	C	$C_{15}H_{20}N_2O$	C, H, N
26	6-Phenanthridinyl[l]	*t*-Bu	0[n]	70–75	F	38[o]	C	$C_{19}H_{22}N_2O \cdot H_2O$[p]	C, H, N; H_2O[p]
27		*t*-Bu	1	98–100	C	64	A	$C_{18}H_{24}N_2O$	C, H, N

[a] Reference compound: propranolol = 100. [b] Melting points or boiling points were taken with a calibrated thermometer and are not corrected. [c] A, i-Pr_2O; B, i-PrOH; C, n-hexane; D, CH_3CN; E, EtOH; F, Et_2O. [d] Purified product. [e] Overall yield from quinaldine. [f] Homoveratryl or 3,4-dimethoxyphenethyl. [g] Benzo[*f*]quinol-3-yl. [h] Carbonyl side chain: CH_2CO-CH_2NH-*t*-Bu. [i] See Experimental Section. [j] Overall yield from 6-methylphenanthridine, as no intermediates crystallized. [k] **20** was made from **19** by debenzylation with Na in liquid NH_3: R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 383 (1949). [l] The heading should be: Het $CH(OH)CH_2NHR$. [m] Overall yield from 2-bromoacetylquinoline hydrobromide. [n] Toxic at 10^{-5} *M*. [o] Overall yield from 6-phenanthridinealdehyde. [p] K. F. determination.

Table II. Intermediates for Procedure A

	Enamine **a**				Amino ketone **b**				Amino alcohol **c**			
No.[a]	Mp, °C	Yield, %	Formula	Analyses	Mp, °C	Yield, %	Formula	Analyses	Mp or bp (mm), °C	Yield, %	Formula	Analyses
1	70–71	76	$C_{20}H_{27}N_3$	C, H, N	*b*				150 (0.3)	54	$C_{20}H_{28}N_2O$	C, H, N
2	100–101	75	$C_{21}H_{30}N_4$	C, H, N	*b*				170 (0.2)	72	$C_{21}H_{31}N_3O$	C, H, N
3	77–78	52	$C_{22}H_{25}N_3$	C, H, N	69–70	66	$C_{22}H_{24}N_2O$	C, H, N	109–110	89	$C_{22}H_{28}N_2O$	C, H, N
4	98–99	87	$C_{23}H_{27}N_3$	C, H, N	100–102	82	$C_{25}H_{26}N_2O$	C, H, N	79–80	83	$C_{23}H_{28}N_2O$	C, H, N
5	114–115	75	$C_{24}H_{29}N_3$	C, H, N	126–127	92	$C_{24}H_{28}N_2O$	C, H, N	95–96	88	$C_{24}N_{30}N_2O$	C, H, N, Cl
6	117–118	86	$C_{24}H_{29}N_3$	C, H, N	111–112	94	$C_{24}H_{28}N_2O$	C, H, N	190–195[c]	82	$C_{24}H_{30}N_2O \cdot 2HCl \cdot CH_3CN$	C, H, N
7	95.5–97	70	$C_{24}H_{29}N_3$	C, H, N	108.5–110	95	$C_{24}H_{28}N_2O$	C, H, N	82–83	90	$C_{24}H_{30}N_2O$	C, H, N
8	114–115	75	$C_{24}H_{29}N_3$	C, H, N	126–127	93	$C_{24}H_{28}N_2O$	C, H, N	95–96	86	$C_{24}H_{30}N_2O$	C, H, N
9	*b*	71			108–109	87	$C_{25}H_{31}N_3O$	C, H, N	109–110	92	$C_{25}H_{33}N_3O$	C, H, N
10	119–120	67	$C_{24}H_{29}N_3$	C, H, N	129–130	91	$C_{24}H_{28}N_2O$	C, H, N	129–130	96	$C_{24}H_{30}N_2O$	C, H, N
11	133–134	71	$C_{25}H_{31}N_3$	C, H, N	129–130	87	$C_{25}H_{30}N_2O$	C, H, N	115–116	93	$C_{25}H_{32}N_2O$	C, H, N
13	77–81	87	$C_{29}H_{31}N_3$	C, H, N	104–105	91	$C_{29}H_{38}N_2O$	C, H, N	92–92.5	80	$C_{29}H_{42}N_2O$	C, H, N
16	135–136	77	$C_{27}H_{29}N_3$	C, H, N	151–152	89	$C_{27}H_{28}N_2O$	C, H, N	132–134	92	$C_{27}H_{40}N_2O$	C, H, N
19	163–164	88	$C_{28}H_{32}N_4$	C, H, N	102–103	82	$C_{28}H_{31}N_3O$	C, H, N	98–100	87	$C_{28}H_{33}N_3O$	C, H, N
21	143–144	86	$C_{22}H_{28}N_4$	C, H, N	69–70	81	$C_{22}H_{27}N_3O$	C, H, N	115–116	73	$C_{22}H_{29}N_3O$	C, H, N
27	154–155	78	$C_{25}H_{29}N_3$	C, H, N	93–94	89	$C_{25}H_{28}N_2O$	C, H, N	122–123	69	$C_{25}H_{30}N_2O$	C, H, N

[a] The numbers correspond to the numbers of the final compounds listed in Table I, the letters **a**–**c** to the intermediates in procedure A. [b] This compound was used crude in the next step. [c] **6c** was converted to the dihydrochloride. Recrystallization from MeCN gave a solvate with 1 mol of MeCN.

Table III. Aminonitriles Intermediates

No.	R_1	R_2	Bp (mm), °C	Yield, %	Formula	Analyses
28	H	*t*-Bu	79 (12)	85	$C_6H_{12}N_2$	*a*
29	H	HV		100	$C_{12}H_{16}N_2O_2$	*b*
30	$-CH_2Ph$	HV	175 (0.2)	86	$C_{19}H_{22}N_2O_2$	C, H, N
31	$-CH_2Ph$	*i*-Pr	90 (0.2)	90	$C_{12}H_{16}N_2$	C, H, N
32	$-CH_2Ph$	*t*-Bu	95 (0.2)	82	$C_{13}H_{18}N_2$	C, H, N

[a] R. Madronero, *An. Real. Acad. Farm.*, **34** (2), 173 (1968); *Chem. Abstr.*, **70,** 105857h (1969). [b] S. Sugasawa and K. Mizukami, *Chem. Pharm. Bull.*, **6,** 359 (1958).

a resting rate of 86 beats/min to a stressed rate of 169 beats/min. This response to isoproterenol was blocked following doses of the phenanthridine analog **16** and propranolol; **16** was three times more potent than propranolol in this test.

Experimental Section‡

Pharmacology. (a) *In Vitro.* Guinea pigs of either sex weighing 500–700 g were stunned by a blow to their head, the heart was removed, and the intact left and right atria were dissected free. Tissues were maintained in separate jacketed baths, using a modified Krebs solution (pH 7.4) at 37°. Using 4:0 silk anchored on both auricular appendages, the atria were suspended between a stationary glass rod and a Grass force displacement transducer (FT03). Recordings from the spontaneously beating atria were made on direct writing oscillographs. Tissues were allowed to stabilize for 1.5 hr before adding 1 ml of either vehicle (control runs) or vehicle plus test compound. After 30 min, cumulative isoproterenol dose–response curves were determined with concentrations of 2×10^{-9}, 6×10^{-9}, 2×10^{-8} *M*, etc. Isoproterenol response was represented by an increase in heart rate; values were calculated and plotted as per cent maximum response *vs.* concentration of isoproterenol in the Krebs solution. Antagonist concentration was either 10^{-6} or 10^{-5} *M*.

(b) *In Vivo.* To evaluate *in vivo* potency of the most active compound **16**, heart rate response in the conscious dog was monitored before and after administration of the β blocker and compared to results obtained with propranolol. Four dogs were tested with each compound on separate days; control heart rates were established and then control heart rate response to isoproterenol infusion of 0.3 μg/kg/min iv for 13 min. Both β blockers were dosed at 0.01, 0.04, 0.08, and 0.16 mg/kg iv at 20-min intervals. Five minutes after each dose, isoproterenol infusion was begun and the heart rate again monitored. The heart rate increase was compared to the control response and expressed as per cent maximum response. All results were graphed.

Chemistry. Most starting materials were commercially available. The others were prepared according to the references cited: 2-bromoacetylquinoline,[9] phenanthridine-6-aldehyde,[10] 2,3,4-trimethylquinoline, 4-phenylquinaldine and 6-chloro-3-methyl-4-phenylquinaldine,[12] 6-methylphenanthridine,[13] 1-benzyl-2-methylbenzimidazole,[14] 1,2-dimethylbenzimidazole,[15] 1-methylisoquinoline,[16] 2,3-trimethylenequinoline.[17] The aminoacetonitrile intermediates in Table III were prepared by reaction of glycolonitrile with the appropriate amine.[18] Routine ir and nmr spectra are consistent with the structures shown for these compounds. Nmr shifts are given in δ (parts per million) from TMS.

Preparation of 4 by Procedure A. *N*^{1}-**Benzyl**-*N*^{1}-*tert*-**butyl**-**3**-(**2-quinolyl**)-**2-propene**-**1,2-diamine** (**Enamine 4a**). To a stirred solution of 1 mol of freshly distilled quinaldine in 1.5 l. of absolute Et_2O was added gradually at 15° 1 mol of commercial BuLi in *n*-hexane under a N_2 blanket. After 3 hr it was cooled in ice and a solution of 1 mol of (benzyl-*tert*-butylamine)acetonitrile

‡ The melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. A Beckman IR-9 spectrophotometer was used to determine the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

(32) in 500 ml of Et_2O added rapidly. The reaction mixture was allowed to stand for 15 hr at 25°. It was cooled in ice and slowly 600 ml of ice-H_2O added. The organic layer was washed with H_2O, evaporated iv, and recrystallized from *i*-PrOH to give a yield of 87% of pure **4a**. Nmr indicated an enamine structure rather than an imine by showing a singlet at 5.1 representing the H on the olefinic α-C. This singlet ranging from 4.8 to 5.8 was typical for all enamines a, except enamine **27a** (which carries an alkyl substituent on the α-C); ir (KBr) 3420 (sharp singlet), 1630, 1600 cm^{-1}.

1-(Benzyl-*tert*-butylamino)-3-(2-quinolyl)-2-propanone (Amino Ketone 4b). A mixture of 0.2 mol of 4a and 250 ml of 3 *N* HCl was heated at 80° for 0.5 hr. It was treated in the cold with an excess of K_2CO_3. The product was taken up in PhH-Et_2O, washed with H_2O, and recrystallized from *i*-PrOH. The yield was 82%; ir (KBr) 3470 (broad), 1635 cm^{-1}; nmr ($CDCl_3$) 6.6 and 6.8 (d, 1 H), 5.9 ppm (s, 1 vinylic H); uv max (MeOH) 408 nm.

1-(Benzyl-*tert*-butylamino)-3-(2-quinolyl)-2-propanol (Amino Alcohol 4c). To a stirred solution of 0.2 mol of **4b** in 1.5 l. of EtOH was added gradually at 25° 0.5 mol of $NaBH_4$. After 4 hr it was heated to 60° for 0.5 hr, 200 ml of H_2O added, and EtOH evaporated iv. The product was taken up in Et_2O, washed with H_2O, and recrystallized from *i*-Pr_2O: yield 83%.

1-(*tert*-Butylamino)-3-(2-quinolyl)-2-propanol (4). A solution of 0.2 mol of **4c** in 650 ml of MeOH was treated with 2 g of 20% Pd/C[19] and hydrogenated at 40–50 psi until the calculated amount of H_2 was taken up (2–4 hr). The product was isolated as a dihydrochloride which crystallized from *i*-PrOH: mp 180–182°. *Anal.* ($C_{16}H_{22}N_2O \cdot 2HCl$) C, H, N. It was converted to 4 by addition of excess aqueous K_2CO_3. Product was taken up in Et_2O, washed with H_2O, and crystallized from *n*-hexane: yield 28%.

Preparation of 4 by Procedure B. To a solution of 0.25 mol of quinaldine in 500 ml of Et_2O was added at 15° 0.5 mol of BuLi. After 1 hr it was cooled with ice and 0.25 mol of (*tert*-butylamino)acetonitrile was added and allowed to stand for 20 hr. The resulting brown solution was diluted with Et_2O to 2 l. and cooled. Introduction of excess HCl gave a yellow hygroscopic amorphous powder. Solution in 2 l. of 85% EtOH was allowed to stand for 5 hr at 25°. $NaBH_4$ reduction as described in the preparation of **4c** and recrystallization from *n*-hexane gave 29 g (45%) of 4: ir (KBr) sharp absorption peak at 3272 cm^{-1} superimposed on broad absorption; ir (CCl_4) 3400 cm^{-1} (broad).

1-(*tert*-Butylamino)-3-(6-phenanthridinyl)-2-propanone Oxalate (17). A mixture of 0.1 mol of **16b**, 0.2 mol of concentrated HCl, and 1 g of 20% Pd/C in 350 ml of MeOH was hydrogenated at 50 psi. The product was converted to the oxalate: uv max (MeOH) 415, 395, 252, 242 nm. This amino ketone and others in Table II are characterized by a strong uv absorption between 390 and 450 nm [the uv max (MeOH) for **19b** is at 345 nm], typical of similar β-keto heterocycles[20] stabilized by intramolecular H bonding.

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Pancuronium Bromide and Other Steroidal Neuromuscular Blocking Agents Containing Acetylcholine Fragments

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Incorporation of acetylcholine-like fragments into rings A and D of 5α-androstane yielded series of bisquaternary ammonio steroids, some of which proved to be potent neuromuscular blocking agents. One of the series, pancuronium bromide (3α,17β-diacetoxy-2β,16β-dipiperidino-5α-androstane dimethobromide, Pavulon), has proved a clinically useful agent of medium duration of action. It is proposed that its potency and lack of side effects are associated with the individual geometries and electronic structures of its two acetylcholine-like fragments and that the ring D fragment in particular contributes to the high potency and medium duration of action of this agent. The preparation of these amino steroids and structure-activity relationships within the series are also described.

In the course of investigating the synthesis and pharmacology of 2β-amino-3α-hydroxy-5α-androstanes and derivatives[1] and the corresponding 3α-amino-2β-hydroxy isomers, Lewis, *et al.*,[2] observed that the corresponding monoquaternary salts possessed neuromuscular blocking activity, the most potent of these compounds being 3α-acetoxy-2β-piperidino-5α-androstan-17-one methobromide (1) which has $\frac{1}{16}$th the potency of *d*-tubocurarine. In this compound, **1**, the 2β-piperidinio and 3α-acetoxy groups are almost certainly both pseudo-equatorial due to the twisted boat conformation of ring A.[1] We assume that in this preferred conformation, which may be rigid due to steric compression[3] of ring-A substituents, the acetylcholine-like fragment of **1** resembles a specific molecular con-