

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

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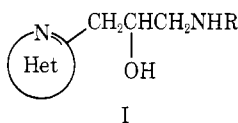
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A series of some 20 novel 2-propanolamines of type I was prepared by reaction of Het-CH₂Li with the properly substituted aminoacetonitrile, followed by hydrolysis and reduction. The most potent β -adrenergic blocking activity was found in the phenanthridine, 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 propranolol¹ with heterocycles, such as 1,2,5-thiadiazole,² pyridine,³ or thiazole.⁴

In the 1,2,5-thiadiazole series² 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-thiazoloxo)-2-propanol⁴ 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.

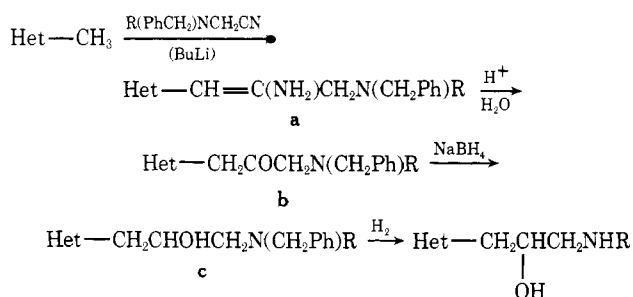
A few heterocyclic analogs of pronethalol⁵ have been reported,^{3,6} but to our knowledge there are no representatives in the literature in which the amino-2-propanol side chain of propranolol is directly attached to a nitrogen heterocycle on the carbon next to nitrogen (I).



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.

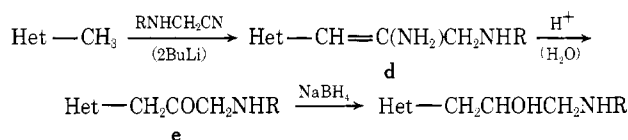
Chemistry. The synthesis of the above structure was accomplished by two procedures, A and B. Procedure A involves the reaction of the lithium derivative of the methyl heterocycle with *N*-benzyl-*N*-alkylaminoacetonitrile to give the enamine **a**, acid hydrolysis to the ketone **b**, and NaBH₄ reduction 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 ketone⁹ by reduction with NaBH₄ or from the heterocyclic aldehyde¹⁰ 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

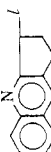
(a) *In Vitro.* The highest β -blocking activity was found in the phenanthridine series with **16**. The corresponding carbonyl compound **17** was about one-third as active. The pronethalol analog **26** showed cardiac toxicity and was found inactive. Considerably less active were the quinolines and 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 $\mu\text{g/kg/min}$ iv in the conscious dog resulted in heart rate increases from

[†] A very recent publication¹¹ 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 ₂ CHCH ₂ NHR OH									
No.	Het	R	β-Blocking activity ^a	Mp or bp (mm), °C ^b	Purification solvent ^c	Yield, % ^d	Pro- cedure	Empirical formula	Analyses
1	6-Methyl-2-pyridyl	<i>t</i> -Bu	1	89-91 (0.15)		91	A	C ₁₃ H ₂₂ N ₂ O	C, H, N
2	Trimethylpyrazinyl	<i>t</i> -Bu	1	130-135	A	45	A	C ₁₄ H ₂₃ N ₃ O·AcOH	C, H, N
3	2-Quinolyl	<i>i</i> -Pr	1	176-178	B	38	A	C ₁₅ H ₂₀ N ₂ O·2HCl	C, H, N
4	2-Quinolyl	<i>t</i> -Bu	3	83-84	C	28	A	C ₁₆ H ₂₂ N ₂ O	C, H, N
5	4-Methyl-2-quinolyl	<i>t</i> -Bu	17	62-64	C	45	B ^e		
6	6-Methyl-2-quinolyl	<i>t</i> -Bu	2	71-72	A	34	A	C ₁₇ H ₂₄ N ₂ O	C, H, N
7	7-Methyl-2-quinolyl	<i>t</i> -Bu	14	81-82	A-C	55	A	C ₁₇ H ₂₄ N ₂ O	C, H, N
8	6-Methoxy-2-quinolyl	<i>t</i> -Bu	0	195-200	D	59	A	C ₁₇ H ₂₄ N ₂ O ₂ ·2HCl	C, H, N
9	6-Dimethylamino-2-quinolyl	<i>t</i> -Bu	0	95-96	A-C	37	A	C ₁₈ H ₂₇ N ₃ O	C, H, N
10	3,4-Dimethyl-2-quinolyl	<i>i</i> -Pr	10	75-76	A	23	A	C ₁₇ H ₂₄ N ₂ O	C, H, N
11	3,4-Dimethyl-2-quinolyl	<i>t</i> -Bu	54	93-94	B	62	A	C ₁₇ H ₂₄ N ₂ O	C, H, N
12	3,4-Dimethyl-2-quinolyl	HV ^f	4	95-96	A-B	79	A	C ₁₈ H ₂₆ N ₂ O	C, H, N
13	4-Phenyl-2-quinolyl	<i>t</i> -Bu	9	63-64	A-C	27	A	C ₂₄ H ₃₀ N ₂ O ₃	C, H, N
14	6-Chloro-3-methyl-4-phenyl-2-quinolyl	<i>t</i> -Bu	0	175-180	B	77	A	C ₂₂ H ₂₆ N ₂ O·0.25H ₂ O	C, H, N; H ₂ O ^p
15	5,6-Benzo-2-quinolyl ^q	<i>t</i> -Bu	0	97-99	A-B	21	B	C ₂₃ H ₂₇ N ₂ OCl·2HCl	C, H, N
16	6-Phenanthridinyl	<i>t</i> -Bu	930	180-183	E	38	A	C ₂₀ H ₂₄ N ₂ O·(COOH) ₂	C, H, N
17	6-Phenanthridinyl	<i>t</i> -Bu ^h	382	225-230	E	15	<i>i</i>	C ₂₀ H ₂₂ N ₂ O	C, H, N
18	6-Phenanthridinyl	HV ^f	217	145-150	E	22 ^j	A	C ₂₈ H ₂₈ N ₂ O ₃ (COOH) ₂ ·0.5H ₂ O	C, H, N
19	1-Benzyl-2-benzimidazolyl	<i>t</i> -Bu	0	107-108	A	84	A	C ₂₁ H ₂₇ N ₃ O	C, H, N
20	2-Benzimidazolyl	<i>t</i> -Bu	1	158-159	B	64	<i>k</i>	C ₁₄ H ₂₁ N ₃ O	C, H, N
21	1-Methyl-2-benzimidazolyl	<i>t</i> -Bu	1	121-122	A	92	A	C ₁₅ H ₂₃ N ₃ O	C, H, N
22	1-Isoquinolyl	<i>t</i> -Bu	18	190-195	B	22	B	C ₁₆ H ₂₂ N ₂ O·2HCl	C, H, N
23	1-Isoquinolyl	HV ^f	0	140-143	E	29	B	C ₂₂ H ₂₆ N ₂ O ₃ (COOH) ₂	C, H, N
24	2-Quinolyl ^l	<i>i</i> -Pr	20	87-88	A	33	C	C ₁₄ H ₁₈ N ₂ O	C, H, N
25	2-Quinolyl ^l	<i>t</i> -Bu	9	85-86	A	35 ^m	C	C ₁₅ H ₂₀ N ₂ O	C, H, N
26	6-Phenanthridinyl ^l	<i>t</i> -Bu	0 ⁿ	70-75	F	38 ^o	C	C ₁₉ H ₂₃ N ₂ O·H ₂ O ^p	C, H, N; H ₂ O ^p
27		<i>t</i> -Bu	1	98-100	C	64	A	C ₁₈ H ₂₄ N ₂ O	C, H, N

^a Reference compound: propanolol = 100. ^b Melting points or boiling points were taken with a calibrated thermometer and are not corrected. ^c A, *i*-Pr₂O; B, *i*-PrOH; C, *n*-hexane; D, CH₃CN; E, EtOH; F, Et₂O. ^d Purified product. ^e Overall yield from quinaldine. ^f Homoveratryl or 3,4-dimethoxyphenethyl. ^g Benzo[*f*]quinol-3-yl. ^h Carbonyl side chain: -CH₂CO-NH₂; R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 383 (1949). ⁱ The heading should be: Het-CH(OH)CH₂NHR. ^m Overall yield from 2-bromoacetylquinoline hydrobromide. ⁿ Toxic at 10⁻⁵ M. ^o Overall yield from 6-phenanthridinaldehyde. ^p K. F. determination.

Table II. Intermediates for Procedure A

No. ^a	Enamine a			Amino ketone b			Amino alcohol c		
	Mp, °C	Yield, %	Formula	Analyses	Mp, °C	Yield, %	Formula	Analyses	Mp or bp (mm), °C
1	70-71	76	C ₂₀ H ₂₇ N ₃	C, H, N	b		C ₂₀ H ₂₃ N ₂ O	C, H, N	150 (0.3)
2	100-101	75	C ₂₁ H ₂₉ N ₄	C, H, N	b		C ₂₁ H ₂₅ N ₃ O	C, H, N	170 (0.2)
3	77-78	52	C ₂₂ H ₃₁ N ₃	C, H, N	69-70	66	C ₂₂ H ₂₇ N ₂ O	C, H, N	109-110
4	98-99	87	C ₂₃ H ₃₃ N ₃	C, H, N	100-102	82	C ₂₃ H ₂₉ N ₂ O	C, H, N	79-80
5	114-115	75	C ₂₄ H ₃₅ N ₃	C, H, N	126-127	92	C ₂₄ H ₃₁ N ₂ O	C, H, N	95-96
6	117-118	86	C ₂₄ H ₃₃ N ₃	C, H, N	111-112	94	C ₂₄ H ₂₉ N ₂ O	C, H, N	190-195 ^c
7	95.5-97	70	C ₂₄ H ₃₃ N ₃	C, H, N	108.5-110	95	C ₂₄ H ₂₉ N ₂ O	C, H, N	82-83
8	114-115	75	C ₂₄ H ₃₃ N ₃	C, H, N	126-127	93	C ₂₄ H ₂₉ N ₂ O	C, H, N	95-96
9	b	71	C ₂₄ H ₃₃ N ₃	C, H, N	108-109	87	C ₂₄ H ₂₉ N ₂ O	C, H, N	109-110
10	119-120	67	C ₂₄ H ₃₃ N ₃	C, H, N	129-130	91	C ₂₄ H ₂₉ N ₂ O	C, H, N	129-130
11	133-134	71	C ₂₅ H ₃₅ N ₃	C, H, N	129-130	87	C ₂₅ H ₃₁ N ₂ O	C, H, N	115-116
13	77-81	87	C ₂₉ H ₃₁ N ₃	C, H, N	104-105	91	C ₂₉ H ₂₇ N ₂ O	C, H, N	92-92.5
16	135-136	77	C ₂₇ H ₂₉ N ₃	C, H, N	151-152	89	C ₂₇ H ₂₅ N ₂ O	C, H, N	132-134
19	163-164	88	C ₂₈ H ₃₂ N ₄	C, H, N	102-103	82	C ₂₈ H ₂₈ N ₃ O	C, H, N	98-100
21	143-144	86	C ₂₈ H ₃₂ N ₄	C, H, N	69-70	81	C ₂₈ H ₂₈ N ₃ O	C, H, N	115-116
27	154-155	78	C ₂₅ H ₂₉ N ₃	C, H, N	93-94	89	C ₂₅ H ₂₅ N ₂ O	C, H, N	122-123

^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		Yield, %	Formula	Analyses
			(mm)	°C			
28	H	<i>t</i> -Bu	79	(12)	85	C ₈ H ₁₂ N ₂	a
29	H	HV			100	C ₁₂ H ₁₆ N ₂ O ₂	b
30	-CH ₂ Ph	HV	175	(0.2)	86	C ₁₉ H ₂₂ N ₂ O ₂	C, H, N
31	-CH ₂ Ph	<i>i</i> -Pr	90	(0.2)	90	C ₁₂ H ₁₆ N ₂	C, H, N
32	-CH ₂ Ph	<i>t</i> -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. Sugawara 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 μ g/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-phenylquinoline and 6-chloro-3-methyl-4-phenylquinoline,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 quinoline in 1.5 l. of absolute Et₂O was added gradually at 15° 1 mol of commercial BuLi in *n*-hexane under a N₂ 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 $\pm 0.4\%$ of the theoretical values.

(32) in 500 ml of Et₂O 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-H₂O added. The organic layer was washed with H₂O, 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 K₂CO₃. The product was taken up in PhH-Et₂O, washed with H₂O, and recrystallized from *i*-PrOH. The yield was 82%; ir (KBr) 3470 (broad), 1635 cm⁻¹; nmr (CDCl₃) 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 NaBH₄. After 4 hr it was heated to 60° for 0.5 hr, 200 ml of H₂O added, and EtOH evaporated *iv*. The product was taken up in Et₂O, washed with H₂O, and recrystallized from *i*-Pr₂O: 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/C¹⁹ and hydrogenated at 40-50 psi until the calculated amount of H₂ was taken up (2-4 hr). The product was isolated as a dihydrochloride which crystallized from *i*-PrOH: mp 180-182°. *Anal.* (C₁₆H₂₂N₂O·2HCl) C, H, N. It was converted to **4** by addition of excess aqueous K₂CO₃. Product was taken up in Et₂O, washed with H₂O, 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 Et₂O 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 Et₂O 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°. NaBH₄ 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 (CCl₄) 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 heterocycles²⁰ 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 5 α -androsterane yielded series of bisquaternary ammonio steroids, some of which proved to be potent neuromuscular blocking agents. One of the series, pancuronium bromide (3 α ,17 β -diacetoxy-2 β ,16 β -dipiperidino-5 α -androsterane 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 2 β -amino-3 α -hydroxy-5 α -androsteranes and derivatives¹ and the corresponding 3 α -amino-2 β -hydroxy isomers, Lewis, *et al.*,² observed that the corresponding monoquaternary salts possessed neuromuscular blocking activity, the most potent of these compounds being 3 α -acetoxy-2 β -piperidino-5 α -androsteran-17-one methobromide

(1) which has $\frac{1}{16}$ th the potency of *d*-tubocurarine. In this compound, 1, the 2 β -piperidino and 3 α -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 compression³ of ring-A substituents, the acetylcholine-like fragment of 1 resembles a specific molecular con-