Effects of Phosphonium Compounds on *Schistosoma mansoni*

Patrick R. McAllister, Mary J. Dotson, Samuel O. Grim, and Gilbert R. Hillman*

Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77550, and Department of Chemistry, University of Maryland, College Park, Maryland 20742. *Received September 4, 1979*

A new series of phosphonium salts was examined for effects on the cholinergic nervous system of *Schistosoma mansoni*. Studies were conducted using both an activity-monitoring and fluorescent-labeling technique. The activity method gave more definitive results, indicating that some poly(methylene)bis(triphenylphosphonium) salts and some [3-(alkylamino)propyl]triphenylphosphonium salts have strong anticholinergic effects. Hexyltriphenylphosphonium bromide has very marked effects both in the motility and the fluorescence test, but these effects cannot immediately be ascribed to cholinergic actions.

It has been believed for several years[1] that acetylcholine (ACh) has a role as a neurotransmitter in the nervous system of schistosomes. However, some drugs, such as muscarine, nicotine, and *d*-tubocurarine, which are highly active at vertebrate cholinergic synapses appear to have little effect on schistosomes. Other drugs, such as hycanthone,[2] behave as ACh antagonists in schistosomes but not in vertebrate preparations. It seems possible, therefore, that schistosome-specific anticholinergic drugs can be identified. Such drugs might be selectively toxic to the schistosome in the presence of the host animal and, therfore, might be useful in the therapy of schistosomiasis.

For the purpose of studying the neuropharmacologic actions of antischistosomal drugs, we have developed two methods of examining drug effects. One method consists of recording the body movements of schistosomes kept alive in vitro in cell culture medium.[3,4] Serotonin (5HT) causes large stimulatory effects in this system, and ACh or carbachol (CCh) causes dramatic paralytic effects. The effect of new drugs on these responses constitutes our test system.

The second method consists of labeling schistosomes with a fluorescent ACh analogue. The assumption[5-7] was made that the labeled sites are physiological binding sites but are not necessarily postsynaptic receptors for ACh. In support of this assumption, we have found that labeling occurs at anatomical regions expected to contain nerve endings, that dansyl compounds unrelated to ACh (e.g., dansylglycine) do not cause labeling, and that several anticholinergic drugs block the fluorescent labeling.

In the present paper, a new series of phosphonium compounds (Table I) is tested by these methods. The compounds bear a resemblance to known anticholinergic ammonium compounds and might therefore be expected to exhibit some anticholinergic activity.

Results and Discussion

The effects of the compounds on schistosome motility are shown in Table II. Several of the compounds cause a significant block of the paralytic response to CCh. Compounds **14–17** are particularly effective in this regard. These compounds represent a structurally related group of poly(methylene)bis(triphenylphosphonium) salts. Compounds **4–6**, a group of [3-(alkylamino)propyl]triphenylphosphonium derivatives, were also effective at a highly significant level.

Compounds **7–9**, which constitute a group of *n*-alkyltriphenylphosphonium salts, also form a group with respect to their effects on motility. These compounds stimulated motor activity but blocked the stimulatory action of 5HT to varying degrees. Compound **9**, the most biologically active of the group, caused paralysis after prolonged exposure (1 h) (Figure 1). The paralytic effect of compound **9** was reversed by incubating the worms for 1 h in drug-free medium. Because compounds **7–9** interfered with 5HT stimulation and altered the basal motility rate, it was difficult to obtain a measurement of the drugs' effects on CCh paralysis. This difficulty was most evident in the case of compound **9**, which itself caused complete paralysis.

Compounds **1–3** and **13** were relatively inactive in this test; these drugs constitute a group of (aminoalkyl)triphenylphosphonium salts. Compound **12**, a cyanoalkylphosphonium salt, also had low activity. The bromoalkyl compound, **11**, had some activity in this experimental protocol.

All compounds were tested at 10^{-5} M for their ability to block the labeling of schistosomes by 5-(dimethylamino)-*N*-[2-(dimethylamino)ethyl]naphthylenesulfonamide hydrochloride (DDNS). Only compound **9** produced significant blockage (Figure 2), though compounds **2–4** showed slight effects. Compound **3**, **6**, and **14** (representing low, high, and intermediate activity in the motility monitor) were also tested at 10^{-4} M; they did not affect labeling significantly at this higher concentration. This group of compounds, therefore, does not have pronounced effects in the fluorescence test. No correlation appears to exist between the motility effects, except that compound **9** had the largest effect of all tested compounds in both experimental protocols. This observation suggests that motility effects and fluorescence effects may reflect binding at different sites, which could represent functionally different subdivisions of the cholinergic nervous system.

The present studies indicate that some of these phosphonium compounds have a pronounced effect on the muscular activity of adult schistosomes. Of the various chemical structures tested, the following two classes of compounds emerge as having significant activity.

(a) *n*-Alkyltriphenylphosphonium Compounds. These drugs cause reduced response to 5HT stimulation, paralysis, and reduction of fluorescent labeling by DDNS, a fluorescent acetylcholine analogue. In view of our limited understanding of the neuropharmacology of schistosomes and the severe technical restrictions in the measurements that can be made with schistosomes (for example, a single-cell neurophysiological recording has never been

* Address correspondence to this author at the University of Texas Medical Branch.

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Table I. Phosphonium Salts Employed in This Study

no.	formula	compd name
1	$[C_6H_5)_3P(CH_2)_5NH_3]Br_2$	(5-aminopentyl)triphenylphosphonium bromide hydrobromide
2	$[(C_6H_5)_3P(CH_2)_3NH_2(C_2H_5)]Br_2$	[3-(ethylamino)propyl]triphenylphosphonium bromide hydrobromide
3	$[(C_6H_5)_3P(CH_2)_3NH_2(C_3H_7)]Br_2$	[3-(propylamino)propyl]triphenylphosphonium bromide hydrobromide
4	$[(C_6H_5)_3P(CH_2)_3NH_2(C_4H_9)]Br_2$	[3-(butylamino)propyl]triphenylphosphonium bromide hydrobromide
5	$[(C_6H_5)_3P(CH_2)_3NH_2(C_5H_{11})]Br_2$	[3-(pentylamino)propyl]triphenylphosphonium bromide hydrobromide
6	$[(C_6H_5)_3P(CH_2)_3NH_2(C_6H_{13})]Br_2$	[3-(hexylamino)propyl]triphenylphosphonium bromide hydrobromide
7	$[(C_6H_5)_3PCH_3]Br$	methyltriphenylphosphonium bromide
8	$[(C_6H_5)_3PC_2H_5]Br$	ethyltriphenylphosphonium bromide
9	$[(C_6H_5)_3PC_6H_{13}]Br$	hexyltriphenylphosphonium bromide
10	$[(C_6H_5)_3PCH_2C_6H_5]Br$	triphenyl(phenylmethyl)phosphonium bromide
11	$[(C_6H_5)_3P(CH_2)_3Br]Br$	(3-bromopropyl)triphenylphosphonium bromide
12	$[(C_6H_5)_3P(CH_2)_3CN]Br$	(3-cyanopropyl)triphenylphosphonium bromide
13	$[(C_6H_5)_3P(CH_2)_2NH_3]Br_2$	(2-aminoethyl)triphenylphosphonium bromide hydrobromide
14	$[(C_6H_5)_3P(CH_2)_2P(C_6H_5)_3]Br_2$	1,2-ethanediylbis(triphenylphosphonium) dibromide
15	$[(C_6H_5)_3P(CH_2)_3P(C_6H_5)_3]Br_2$	1,3-propanediylbis(triphenylphosphonium) dibromide
16	$[(C_6H_5)_3P(CH_2)_5P(C_6H_5)_3]Br_2$	1,5-pentanediylbis(triphenylphosphonium) dibromide
17	$[(C_6H_5)_3P(CH_2)_6P(C_6H_5)_3]Br_2$	1,6-hexanediylbis(triphenylphosphonium) dibromide

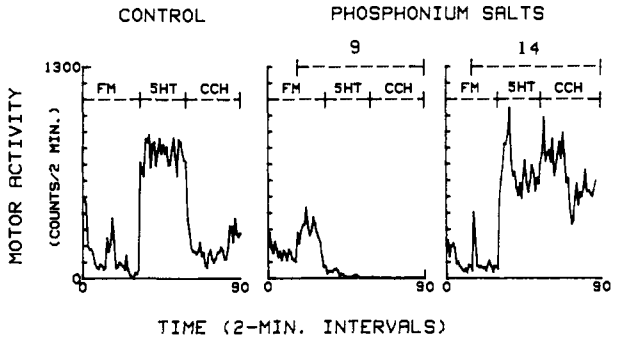

Figure 1. Effect of phosphonium salts on schistosome motor activity. Schistosome movements per 2 min were recorded automatically (see text). After a period in drug-free Fischer's medium (FM), serotonin (5HT) was added at 10^{-3} M, followed by carbamylcholine (carbachol, CCH) at 10^{-4} M. Left: normal response to 5HT and CCh, with no other drug treatment. Center and right: response to 5HT and CCh with compound **9** and **14** salts added at 10^{-4} M during the periods shown. Compound **9** causes paralysis; **14** antagonizes the paralysis normally caused by CCh.

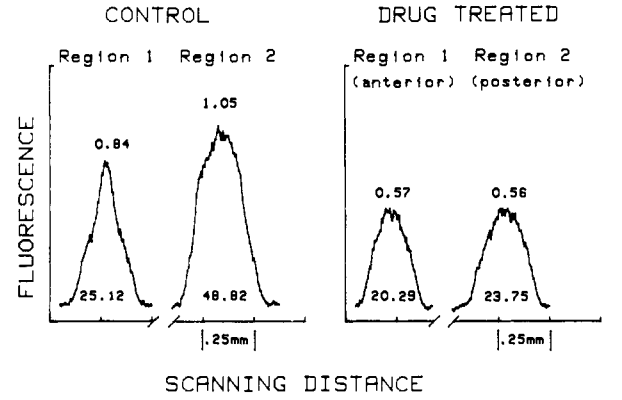

Figure 2. Effect of phosphonium compound **9** on the fluorescent labeling of *S. mansoni* by a dansylcholine derivative (DDNS). Each graph shows scans across two regions of the parasite (see text) after treatment with DDNS, 10^{-5} M, for 1 h. The area under each curve and the height of the peak are indicated below and above the curves. The left tracing shows a normal DDNS-treated worm; the one on the right shows a worm treated with compound **9** (10^{-5} M) before and during DDNS treatment. Fluorescence is expressed in arbitrary units. Compound **9** causes approximately 50% reduction of the fluorescence in region 2.

achieved), one cannot interpret these findings unambiguously in terms of a neurochemical mechanism of drug action. However, paralysis of the schistosomes, including resistance to stimulation by 5HT, is an effect produced by

Table II. Effects of Phosphonium Salts on Carbachol-Induced Paralysis Response to Carbachol[a]

no.	phosphonium treated[b]	control	% reduction in carbachol response[c]	p[d]
1	−81.3 ± 10.6	−93.6 ± 4.2	13.1	<0.05
2	−72.0 ± 10.8	−88.4 ± 11.2	18.6	<0.05
3	−71.7 ± 5.2	−72.4 ± 11.5	0.97	NS
4	−70.3 ± 6.6	−91.1 ± 2.3	22.8	<0.001
5	−31.8 ± 7.3	−76.0 ± 12.3	58.2	<0.001
6	−35.4 ± 9.0	−94.1 ± 5.1	62.4	<0.0001
7[e]	−22.9 ± 11.6	−79.3 ± 15.6	71.1	<0.001
8[f]	−63.8 ± 11.3	−87.5 ± 10.2	27.0	<0.02
9[g]				
10	−55.1 ± 14.7	−75.6 ± 11.9	27.1	<0.05
11	−35.0 ± 4.8	−64.0 ± 16.5	45.3	<0.01
12	−73.0 ± 13.6	−81.4 ± 9.7	10.3	NS
13	−67.8 ± 15.6	−79.4 ± 10.6	14.6	NS
14	+13.3 ± 14.7	−74.6 ± 10.5	117.8	<0.001
15	+2.0 ± 26.8	−77.0 ± 5.8	102.6	<0.001
16	−19.7 ± 10.1	−82.5 ± 12.2	76.1	<0.001
17	−4.6 ± 20.6	−81.1 ± 20.6	94.3	<0.001

[a] Response = [(motility after CCh − motility before CCh)/motility before CCh] × 100. [b] All phosphonium salts were tested at 10^{-4} M. Mean and standard deviation are shown. [c] Percent reduction = [(response with test drug − control CCh response)/control CCh response] × 100. SD = standard deviation of percent reduction, determined in at least three experiments. [d] p = probability that phosphonium had no effect on CCh response; from nonpaired Student's t test. NS = no significant difference between test and control. [e] Slight stimulation of worm activity when exposed to compound 7. Reduction in 5HT response. [f] Stimulation of worm activity when exposed to compound 8. Reduction in 5HT response. [g] Strong stimulation of activity when exposed to compound 9. Abolished 5HT response. No CCh effect could be measured.

acetylcholine-like drugs such as carbachol;[1] possibly, these phosphonium analogues exert a cholinomimetic action. Serotonin antagonists also produce effects of this type,[8] and one cannot rule out this mode of action as well.

(b) Alkanediylbis(phosphonium) Compounds and (Aminoalkyl)phosphonium Compounds. These compounds bear a structural resemblance to diquaternary ammonium compounds, such as decamethonium, which are recognized as neuromuscular and ganglionic anticholinergic agents. In the schistosomal motility test system, these compounds also behave as ACh antagonists, although

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one still cannot ignore the possibility of other neurochemical interactions as well. This group of compounds was inactive in the fluorescence-blocking test, indicating that the two test systems are not redundant and measure interactions at different populations of binding sites. Apparently, some drugs, such as the present ones, can affect only one of these systems, while other drugs, such as hycanthone,[2] act upon both systems.

Experimental Section

Synthesis of Phosphonium Salts. *n*-Alkyltriphenylphosphonium salts were prepared by the reaction of triphenylphosphine in benzene solution with the corresponding 1-bromoalkane.[9]

(ω-Bromoalkyl)triphenylphosphonium salts were prepared by the reaction of triphenylphosphine with excess α,ω-dibromoalkane.[10,11]

Poly(methylene)bis(triphenylphosphonium) salts were prepared by the reaction of triphenylphospine with α,ω-dibromoalkane (2:1 molar ratio) in boiling 1-butanol.[12]

Phosphonium quaternary ammonium salts have been previously prepared,[13] as have aminoalkylphosphonium salts,[9,14,15] although the salts prepared in this study are previously unreported. Two straightforward methods are available: (a) the reaction of a (haloalkyl)triphenylphosphonium salt with an amine, or (b) the reaction of a haloalkylamine hydrohalide with a tertiary phosphine. The syntheses of the phosphonium ammonium salts are described in the following paragraphs. All reactions were carried out in a nitrogen atmosphere.

(5-Aminopentyl)triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_5NH_3]Br_2$). 5-Bromopentylamine hydrobromide (10.0 g, 40.6 mmol), prepared as previously described,[16] and Ph_3P (20.0 g, 76.5 mmol) in 80 mL of *n*-BuOH were stirred magnetically and heated at 118 °C for 6 h. After the reaction mixture cooled to room temperature, 100 mL of C_6H_6–Et_2O (50:50) was added. The upper layer was decanted and the lower layer which contained a viscous oil was stirred and washed several times with Et_2O. The remaining product was dissolved in EtOH and reprecipitated with Et_2O to give 15 g (70%) of product (mp 94–96 °C) which apparently contains an EtOH of solvation. Anal. ($C_{25}H_{34}Br_2NOP$) C, H, Br, N.

A sample of $[Ph_3P(CH_2)_5NH_3]Br_2$·EtOH was dissolved in EtOH–H_2O and treated with an EtOH solution of $NH_4[Cr(SCN)_4(NH_3)_2]$ to produce a precipitate of $[Ph_3P(CH_2)_5NH_3][Cr(SCN)_4(NH_3)_2]_2$ by metathesis. The derivative was purified by recrystallization from acetone by the addition of $CHCl_3$. The final product melted at 142–144 °C. Anal. ($C_{31}H_{40}Cr_2N_{13}PS_8$) C, H.

[3-(Ethylamino)propyl]triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_3NH_2(C_2H_5)]Br_2$). (3-Bromopropyl)triphenylphosphonium bromide, $[Ph_3P(CH_2)_3Br]Br$ (5.0 g, 11.8 mmol), in 30 mL of *n*-BuOH was cooled to −30 °C and $EtNH_2$ (10.0 g, 222 mmol) was added to the above solution. The mixture was stirred magnetically as the reaction flask was allowed to warm to room temperature. A dry ice–acetone condenser was employed to return the $EtNH_2$ to the reaction vessel. After 6 h, the excess $EtNH_2$ was removed by heating and addition of Et_2O to the remaining solution caused precipitation of the product, which was recrystallized from absolute EtOH by the slow addition of Et_2O. After washing the collected precipitate with Et_2O, it was dried overnight at 65 °C (1 mmHg). The pure product, mp 263–264 °C, weighed 4.6 g (84%). Anal. ($C_{23}H_{28}Br_2NP$) C, H, Br, N.

[3-(Propylamino)propyl]triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_3NH_2(C_3H_7)]Br_2$). This compound was prepared from *n*-propylamine and compound 11 in absolute EtOH at 90 °C for 6 h. Purification as before yielded a white solid, mp 259–260 °C, in 73% yield. Anal. ($C_{24}H_{30}Br_2NP$) C, H, N, P.

[3-(Butylamino)propyl]triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_3NH_2(C_4H_9)]Br_2$). This compound, mp 255–257 °C, was prepared in 57% yield by the reaction of compound 11 and *n*-butylamine in *n*-BuOH at 118 °C for 6 h and with purification as indicated above. Anal. ($C_{25}H_{32}Br_2NP$) N, P; Br: calcd, 29.7; found, 29.2.

[3-(Pentylamino)propyl]triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_3NH_2(C_5H_{11})]Br_2$). This compound, mp 245–246 °C, was prepared in 39% yield from *n*-pentylamine and compound 11 in *n*-BuOH at 118 °C for 5 h, and with purification as described before, except that a longer time was required for the semisolid product to crystallize after the addition of Et_2O. Anal. ($C_{26}H_{34}Br_2NP$) Br, N, P.

[3-(Hexylamino)propyl]triphenylphosphonium Bromide Hydrobromide ($[(C_6H_5)_3P(CH_2)_3NH_2(C_6H_{13})]Br_2$). This compound was prepared from *n*-hexylamine and compound 11 in *n*-BuOH at 118 °C for 6 h. EtOH was added slowly to the cooled solution with stirring until an oil precipate formed. Subsequent heating at reflux caused the oil to solidify. The solid was collected by filtration and reprecipitated four times from dry $CHCl_3$ by the addition of Et_2O. A final recrystallization was made from *i*-PrOH and Et_2O. The final product, mp 227–228 °C, represented a 57% yield. Anal. ($C_{27}H_{36}Br_2NP$) C, H, Br, N, P.

[3-(Cyclohexylamino)propyl]triphenylphosphonium Bromide Hydrobromide. This salt, mp 227–228 °C, was prepared in 60% yield from cyclohexylamine and compound 11 in *n*-BuOH at 118 °C for 7 h. Anal. ($C_{27}H_{34}Br_2NP$) Br, N, P.

Triphenyl[3-[(phenylmethyl)amino]propyl]phosphonium Bromide Hydrobromide. This compound, mp 295–296 °C, was prepared in 77% yield from benzylamine and compound 11 in *n*-BuOH at 118 °C for 7 h. After cooling and stirring the solution for 1 day, the addition of ether caused crystallization of the viscous semisolid mixture. The precipitate was recrystallized from abosulte EtOH. Anal. ($C_{28}H_{30}Br_2NP$) Br, N, P.

Preparation of schistosomes. A mouse–snail cycle of *Schistosoma mansoni* maintained by S. K. File and J. H. Smith of the University of Texas Medical Branch, Pathology Department, in Galveston, was used to supply us with infected mice. After 45–60 days of development, the adult paired schistosomes were removed from the infected mice. The mice were injected with heparin and anesthetized with ether before being sacrificed by cervical dislocation. Using gentle hook dissection, the adult paired schistosomes were removed from the portal and mesenteric veins. The worms were maintained at 37 °C and pH 7.4 in Fischer's cell culture medium (FM) (Grand Island Biological Co.), with added antibiotics and buffering.[17] At least 1 mL of FM was allowed for maintaining each worm pair.

Fluorescence Studies. All of the schistosomes for one fluorescent scanning experiment were taken from the same host mouse. The worm pairs from a mouse were divided into test and control groups.

The fluorescent compound used to label the schistosomes was 5-(dimethylamino)-*N*-[2-(dimethylamino)ethyl]naphthylenesulfonamide hydrochloride (DDNS), synthesized by S.-H. Chu as described previously.[6] This compound is a more lipid-soluble analogue of DNS-chol, a fluorescent probe of acetylcholine receptors.[18]

The control worms were incubated in a FM solution of DDNS, 10^{-5} M, at 37 °C for 60 min. The test worms were incubated for 30 min in the test phosphonium salt solution at a concentration of 10^{-5} or 10^{-4} M; then DDNS was added and the incubation continued for another 60 min. After incubation, the worms were rinsed with saline and placed under a cover slip on a microscope slide. The mounted schistosome was placed on the microscope stage and the head of the male worm aligned in the field of view.

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The microscope is an Olympus Model BHB with vertical fluorescence illumination. Emitted fluorescent light, returning through the microscope objective, is directed to the camera port at the top of the microscope. A Farrand MSA microscope spectrum analyzer with an adapted Aminco potted 1P21 photomultiplier tube is mounted on the camera port. The photomultiplier is connected to an Aminco J-22A photometer. The movement of the image of the worm across the light-sensitive spot of the photometer is controlled by a small synchronous motor attached to the microscope stage controls. As the stage moves, the fluorescence as a function of distance across the specimen is recorded from the output of the photometer directly into a Hewlitt-Packard 9825A computer for interpretation. The computer automatically records 500 fluorescence values for each scan, locates the fluorescent peak, and determines the height and area of the fluorescent region of the scan.

The fluorescence labeling of the schistosome was evaluated as described previously.[7] Schistosomes are routinely scanned twice: once across the esophageal region (region 1) and once across the region of maximal brightness posterior to the esophagus (region 2). The data obtained include the peak height or maximum recorded fluorescence intensity at any point in the scanned region and the peak area or total fluorescence over the scanned region. Both the esophageal and central region of the head were evaluated by these parameters. Only male schistosomes were scanned, due to the small size of females.

Motor Activity Studies. A specially constructed "activity cage" described in previous reports[3,4] was used to measure the motor response of *S. mansoni* to test compounds. This apparatus contains four chambers mounted in a temperature-regulated block. Two worm pairs are placed in each glass-bottomed cell located above the array of fiber optics which are connected to photocells. Movement of the worms in the cells obscures a light beam. The photocells register the light-intensity fluctuations due to these movements. The resultant electronic changes are translated into numerical "counts" which are proportional to the amount of movement. The resulting counts for each chamber accumulate for a 2-min period and the data are automatically transferred to a Hewlett-Packard 9825A computer. The data are plotted automatically by the computer to give a graph of overall movement and patterns.

A typical experiment involves the use of two cells as control chambers and two cells as test chambers. The control chambers are perfused at 37 °C with FM solutions of serotonin (5HT) and carbachol (CCh) in the absence of test compound, and the test chambers are perfused with the same drugs in the presence of the test compound. The effects of various concentrations and lengths of exposure to the compounds are reported.

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Conformationally Restricted Tricyclic Antidepressants. 1. Octahydrodibenzazepinonaphthyridines as Rigid Imipramine Analogues

Arnold R. Martin,* Vidyadhar M. Paradkar, Geoffrey W. Peng,

Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, Arizona 85721

Robert C. Speth, Henry I. Yamamura,

Department of Pharmacology and Psychiatry, University of Arizona Health Sciences Center, Tucson, Arizona 85724

and Alan S. Horn

Department of Pharmaceutical and Analytical Chemistry, State University, Groningen, The Netherlands.
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The stereoselective synthesis and structure elucidation of the racemic 2-methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b,f*]azepino[5,4a,4-*bc*]-2,7-naphthyridine ring-fusion isomers (**1a** and **1b**) are described. Photocyclization of *N*-(1-methyl-1,2,5,6-tetrahydronicotinyl)-10,11-dihydro-5*H*-dibenzazepine (**3**) in methanol vs. tetrahydrofuran stereoselectively gave, respectively, the cis (moderate yield) or the trans (poor yield) pentacyclic lactams (**4a** or **4b**). Equilibration of **4a** in base gave a 1:2 mixture of **4a** and **4b**, which was separated by column chromatography. Borane reductions of **4a** and **4b** gave **1a** and **1b** without epimerization. The racemic ring-fusion isomers were compared with imipramine in rodents as inhibitors of (-)-norepinephrine uptake in vitro and in vivo, as inhibitors of serotonin uptake in vitro, and as inhibitors of the binding of the muscarinic cholinergic antagonist [^{3}H]quinuclidinylbenzilate (QNB), the α-adrenergic antagonist [[[2-(2′,6′-[^{3}H]dimethoxyphenoxy)ethyl]amino]methyl]benzodioxane (WB 4101), and the dopaminergic antagonist [^{3}H]spiperone at their respective membrane binding sites in homogenates obtained from rat brain. Both **1a** and **1b** inhibited (-)-norepinephrine uptake in a rat brain synaptosomal preparation; **1b** was slightly more potent than **1a** but somewhat less potent than imipramine. Imipramine was more than twice as effective as **1b** as an inhibitor of the neuronal uptake of the norepinephrine synthesis inhibitor 4,α-dimethyl-*m*-tyramine (H77/77) in vivo, while **1a** appeared to potentiate rather than prevent the norepinephrine depleting action of H77/77. Both **1a** and **1b** were virtually inactive as inhibitors of synaptosomal serotonin uptake. Imipramine and **1b** were nearly equipotent as inhibitors of [^{3}H]QNB binding and significantly more active than **1b**. In the [^{3}H]spiperone binding assay, **1a** was comparable to chlorpromazine in potency. Imipramine and **1b** were much less effective. The amine uptake and receptor binding results are rationalized on the basis of conformational structure–activity relationships.

The mechanism by which the clinically effective tricyclic antidepressants (thymoleptics) alleviate symptoms in depressed patients remains to be unequivocally established. The various tricyclics exhibit a bewildering variety of pharmacological properties,[1] which may include inhibition of neuronal uptake of norepinephrine and/or serotonin, antagonism of reserpine's actions, an anticholinergic (antimuscarinic) action, antihistaminic actions, cardiotoxic effects, and antipsychotic effects. The majority of thymoleptics in current clinical use are flexible molecules consisting of a condensed three ring system and a secondary or tertiary amino group connected by a three carbon chain. There is considerable freedom of rotation

(1) G. L. Klerman and J. O. Cole, *Pharmacol. Rev.*, 17, 101 (1965).

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