Communications to the Editor

Hydroxylated 2,3,4,9-Tetrahydro-1*H*-carbazol-3-amines. A New Class of Experimental Cardiotonic Drugs

Sir:

We wish to report a new class of experimental cardiotonic drugs which has undergone extensive evaluation in our laboratories and which we believe holds considerable promise for eventual therapeutic application. The new drug structures (Table I) are tryptamine derivatives in which the aminoethyl side chain has been incorporated into a third ring to form a 3-aminotetrahydrocarbazole. An important structural feature is the presence of one hydroxyl group suitably located on the benzene ring. The parent structure 1, which lacks a hydroxyl group, has been evaluated in man as an antidepressant drug.[1] The results of the trial suggested that this substance possesses antidepressant properties.

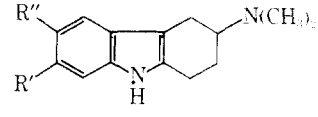
The evaluation of the cardiotonic properties of the tetrahydrocarbazoles was undertaken since it could be argued that their structures bear some resemblance to the structure of dopamine. Dopamine is an experimental cardiotonic drug with the disadvantages that it must be given intravenously and that it has a short duration of action.[2] Unlike dopamine, the tetrahydrocarbazoles do not possess the structural features required for transformation by monamine oxidase or catechol *O*-methyltransferase, the metabolizing enzymes which play a role in limiting the duration of action of dopamine.[3] We were also encouraged by the fact that 1 displays antidepressant activity, an effect which could be interpreted to result from an impact on central adrenergic function.[4] The increased polar character resulting from hydroxylation of 1 might be expected to yield compounds with a prominent peripheral adrenergic effect of an agonistic nature.

The carbazoles were prepared by the Fischer indole synthesis procedure. Condensation of 4-dimethylaminocyclohexanone hydrochloride[5] with phenylhydrazine hydrochloride in hot EtOH yielded 2,3,4,9-tetrahydro-*N*,*N*-dimethyl-1*H*-carbazol-3-amine hydrochloride (1), mp 253–255°.[6] Substitution of 4-benzyloxyphenylhydrazine and 3-benzyloxyphenylhydrazine for phenylhydrazine in the Fischer cyclization yielded the hydrochlorides of the corresponding 6-benzyloxy derivative, mp 209–212°, and the 7-benzyloxy derivative, mp 237–239°. Hydrogenolysis of the ethers in the presence of Pd/C in EtOH afforded 3-(dimethylamino)-2,3,4,9-tetrahydro-1*H*-carbazol-6-ol (2), mp 202–204°, and the hydrochloride of 3-(dimethylamino)-2,3,4,9-tetrahydro-1*H*-carbazol-7-ol (3), mp 286–288°.

The results of screening the compounds for their effect on cardiac force and heart rate in the anesthetized dog are presented in Table I. None of the compounds had a significant effect on heart rate at the indicated doses. The parent structure 1 had no significant effect on cardiac force. The 6-hydroxy derivative 2, however, was active when given by the intravenous route but was weakly active after administration by the intraduodenal route. The 7-hydroxy derivative 3 was active by both routes of administration. Although 3 was less active than dopamine on a mg/kg basis when administered by the intravenous route, it had a considerably longer duration of action. This compound did not have an appreciable effect on blood pressure at doses which resulted in a large increase in cardiac force and was chosen for further evaluation.

In the anesthetized dog, continuous infusion of 3 at 300 μg/kg/min iv caused a 36% increase in cardiac output and a similar increase in coronary blood flow at the time of the peak inotropic effect. Total peripheral resistance was reduced by approximately 18%. The positive inotropic effect of 3 was blocked by propanolol. Pretreatment with atropine did not unmask a chronotropic response. In unanesthetized dogs with chronically implanted strain gauges, 30 and 60 mg/kg of 3 given orally caused respectively a 36 and 96% increase in cardiac contractile force with little change in heart rate and blood pressure. The duration of cardiotonic action was more than 8 hr. In vitro, there was a strong positive effect on the isolated cat atria and papillary muscle

Table I. Cardiovascular Effects of the Aminotetrahydrocarbazoles in the Anesthetized Dog



Compd	R′	R″	Dose[a]/route[b]	N[c]	Cardiac force[d]	Heart rate[d]	Duration of effect on cardiac force
1	H	H	30/id	2	+23	−11	
			10/iv	3	+26	−15	
			20/iv	3	−26	−16	
2	H	OH	30/id	3	+34	−12	
			3/iv	4	+58	+8	13 min
			10/iv	4	+112	+29	45 min
3	OH	H	30/id	3	+65	+20	>4 hr
			3/iv	6	+80	+10	30 min
			0.3 (min)/iv[e]	8	+70	+15	30 min[f]
Dopamine			0.02/iv	4	+84	−3	2 min
			0.01 (min)/iv[e]	12	+160	+5	5 min[f]

[a] Mg/kg. [b] iv, intravenously; id, intraduodenally. [c] Number of dogs. [d] Peak effect, average percent change from control; ± ~25% is considered within control limits. [e] Infusion maintained at peak effect for 10 min. [f] Duration in the continuous infusion experiments is the interval from the time the infusion is stopped to the time the effect on cardiac force has become insignificant (<25%).

Table II. In Vitro Effects of 3 on the Isolated Cat Atria and Papillary Muscle

Dose, μg/ml	Right atrial rate[a]	Right atrial force[a]	Left atrial force[a]	Papillary muscle force[a]
3	3 ± 2.5[b]	3 ± 2.7	15 ± 4.1	37 ± 5.9
10	11 ± 1.2	19 ± 4.7	29 ± 4.0	54 ± 7.3
30	29 ± 5.7	33 ± 5.8	64 ± 7.1	75 ± 10.2
100	26 ± 8.0	58 ± 11.0	115 ± 15.2	84 ± 22.7

[a]Percent change from control. [b]Mean ± standard error.

force accompanied by a moderate increase in right atrial rate (Table II). Pretreatment with reserpine caused a complete abolishment of the in vitro inotropic effect of **3**. In vivo, pretreatment with reserpine caused a significant loss of the activity of small doses of **3** with no effect on larger doses. These experiments and others suggest that a portion of the drug's effect is mediated by endogenous catecholamine(s). The effect of dopamine on cardiac tissue has been characterized as mixed—both direct and indirect.[2] An explanation for the absence of an effect on heart rate at doses which cause a significant increase in cardiac force is not apparent. Experiments designed to further elucidate the mechanism of action of the drug are continuing.

References and Notes

(1) D. M. Gallant, M. P. Bishop, and R. Guerrero-Figueroa, *Curr. Ther. Res., Clin. Exp.*, 14, 61 (1972).
(2) L. I. Goldberg, *Pharmacol. Rev.*, **24**, 2 (1972).
(3) L. L. Iversen and B. A. Callingham, "Fundamentals of Biochemical Pharmacology", Z. M. Bacq, Ed., Pergamon, New York, N.Y., pp 276–279.
(4) H. S. Akiskal and W. T. McKinney, Jr., *Science*, **182**, 20 (1973).
(5) N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, **22**, 1146 (1957).
(6) All the new compounds described in this communication gave elemental analyses (C, H, N) within 0.4% of the calculated values and were further characterized by their NMR and ir spectra.

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Book Reviews

Bioactive Compounds from the Sea. Edited by Harold J. Humm and Charles E. Lane. (Volume 1 of a planned series of volumes entitled Marine Science.) Marcel Dekker, New York, N.Y. 1974. xiii + 251 pp. 22.8 × 15.2 cm. $18.75.

This book is a collection of 13 papers presented at a symposium held in St. Petersburg, Fla., in Nov 1971 entitled "Physiologically Active Compounds from Marine Organisms". The format of most chapters follows that of journal papers: referenced introductory information, experimental results, and brief discussion of the data. The majority of the papers deal with biological and pharmacological properties of extracts of marine organisms rather than with molecular structure investigations; few of the active materials discussed have been purified to the extent that detailed structural studies are possible. Individual chapters are devoted to investigations of the toxins or venoms from each of the following sources: an Australian jellyfish, a common Indo-Pacific sea urchin, a Caribbean sponge, dinoflagellates, a variety of echinoderms, nematocysts from assorted coelenterates, and sea snakes from Southeast Asia and the Far East. A comparison of the pharmacological actions of the potent marine toxins tetrodotoxin and saxitoxin is the subject of one paper, and the fascinating and potentially economically important discovery of prostaglandins in a gorgonian is discussed in another. The remaining chapters are devoted to the ciguatoxin problem and speculations regarding its causes, an investigation of some possible exogenous sources of puffer fish toxin, the use of seaweed extracts on terrestrial plants as growth stimulators and as an inhibitor of fruit decay, and an electron microscopy study which has yielded a detailed picture of the structure of the nematocysts from the well-known stinging jellyfish, the Portuguese man-of-war.

All of the chapters are of comparable length except Chapter 3 (sea urchin toxins) which constitutes one-fourth of the entire book and contains extensive data. Most of the other chapters also contain considerable experimental detail and graphic presentations of data, and hence the book will appeal and be of benefit largely to specialists, primarily pharmacologists, physiologists, and biochemists.

The stated purpose of the planned Marine Science series of books of which this monograph is Volume 1 is to disseminate knowledge of the ocean and its shorelines "to all the public—layman and scientists alike". Volume 1 is clearly directed to specialized scientists. In the reviewer's opinion, the title is somewhat misleading, since few discrete compounds are discussed. A shorter lapsed time between symposium date and monograph publication would be desirable if other similar symposia compilations are planned in this series.

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Principles of Medicinal Chemistry. Edited by William O. Foye and 37 other contributors. Lea and Febiger, Philadelphia, Pa. 1974. xviii + 857 pp. $29.50.

The main intent of this book is to provide a text for undergraduate pharmacy students. It does, however, provide an excellent introduction to the field of medicinal chemistry for graduate students in other chemical and biological disciplines. An effort has been made to correlate information about drug action from such fields as biochemistry, pharmacology, organic chemistry, and quantum chemistry, to name a few.

The volume consists of 37 chapters. The first six cover broad concepts of significance to medicinal chemistry: a historical background, physical–chemical properties and biological activity, molecular orbital theory in drug design, molecular structure and pharmacological action, drug metabolism, and receptor site theory. These six chapters alone (142 double-column pages) would serve as an excellent text for a one-semester graduate course in the subject, supplemented by selected readings from the remaining 31 chapters. These cover the usual pharmacodynamic and chemotherapeutic topics, plus some not usually treated separately in a text of this kind, on antifungal agents, pesticides, and respiratory tract drugs, all of great interest to practicing pharmacists.

The general approach to the special topics includes a description of the biochemical and/or physiological systems affected, the absorption, metabolism, and excretion of the drug, methods of evaluation, structure–activity relations, and synthetic methods. The