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Preparation of a New Immunosuppressant, 4,5-Bis(aminomethyl)acridine

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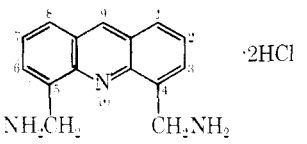
4,5-Bis(aminomethyl)acridine, useful as an immunosuppressant, was prepared in 31% overall yield by the reaction of acridine with *N*-(hydroxymethyl)phthalimide and subsequent decomposition with excess 6 *N* HCl. The drug was found to produce a suppression of the humoral antibody response comparable to several known immunosuppressive agents.

Certain acridine derivatives have been shown to have immunosuppressive properties.[1,2] In the course of studies on new compounds which can alter the immune response and avoid the disadvantages of drugs now in use,[3] we have synthesized and screened the title compound.



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As can be seen from Table I, the compound in the maximum tolerated doses produced a suppression of the humoral antibody response comparable to several of the known immunosuppressive agents. Significant reduction in the plaque-forming cells (PFC) followed the *in vivo* administration, both by the intraperitoneal and oral route.

Chemistry. Initially, the bis(aminomethyl)acridine was obtained from the 4-aminomethyl derivative, which in turn had been prepared earlier by a novel route from acridine under the conditions of the Tscherniac–Einhorn reaction.[4] However, it could be obtained more conveniently from acridine and an excess of the Tscherniac–Einhorn reagent (see Experimental Section). The structure was confirmed by elemental analysis and the nmr spectrum.

Biological Testing. The compounds were tested for their immunosuppressive properties by the hemolysin plaque-forming cell (PFC) test as described by Jerne.[5] A group of six mice were used for the test and control groups and the results of the drug-tested group were expressed as the mean percentage suppression of the total PFC/spleen as compared to the untreated immunized controls. All determinations were done in triplicate.

The question of dosage is difficult for immunosuppressive agents. For the known compounds with extensive pharmacological data, the dosage was chosen after reference to the published literature.[6–8] In the case of the new compounds with only limited toxicity data, it was chosen with reference to the acute LD_{50} and was, therefore, somewhat arbitrary. Usually we chose 20% of the acute LD_{50} by that route with a maximum single dose of 200 mg/kg if not found toxic on repeated application.

Experimental Section

Melting points were obtained on an Electrothermal melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument in the solvent stated with tetramethylsilane (TMS) as an internal standard. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and agreed with the theoretical values to within ±0.4%.

4,5-Bis(aminomethyl)acridine (1). Into 500 ml of concentrated H_2SO_4, cooled to 10–15°, *N*-hydroxymethylphthalimide (177 g, 1 mol) was introduced in small portions. After the compound was dissolved, acridine (90 g, 0.5 mol) was gradually added and the

Table I. Plaque-Forming Cell (PFC) Test in Mice

Compound	Dose, mg/kg (day −1 to day +3)	Route	% suppression of total PFC/spleen ± S.E.M.	LD_{50} ± S.E.M., mg/kg
4,5-Bis(aminomethyl)-acridine	10	ip	88 ± 4.4	54 ± 9 ip
	75	po	66.6 ± 8.6	>1000 po
	100	po	86 ± 3.7	
3,6-Diaminoacridine	200	po	20 ± 5.8	>1000 po
3-Methyl-3-hydroxy-1-(*p*-isopropylcarbamoyl-phenyl)triazene	150	ip	96.6	2505.4 ± 87 ip
	200	po	96.0	2747.0 ± 112 po
Cyclophosphamide	100	ip	99.9 ± 0.02	210 sc
Azathioprine	35	ip	39.2 ± 10.2	
	50	po	59.0 ± 20.0	350 sc
6-Mercaptopurine	50	ip	44.0 ± 9.5	100 sc
Antilymphocyte serum	3 ml/kg	ip	98 ± 0.4	

mixture was then stirred 1 week at room temperature. The dark solution was poured in a thin stream on 2 kg of ice and treated with 2 l. of concentrated NH_4OH solution (28%). After filtration and washing with H_2O, the wet precipitate was dissolved in 2 l. of $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and the volume was reduced to approximately 1 l. On cooling and subsequent filtration, 122 g of 4,5-bis(phthalimidomethyl)acridine was obtained as a whitish powder: mp 285–287°. From the filtrate a second crop of the same material was obtained after chromatography on silicic acid. Elution with benzene–ethyl acetate (95:5) afforded 14 g (total yield 136 g, 54%).

The 4,5-bis(phthalimidomethyl)acridine (136 g, 0.27 mol) was refluxed for 20 hr with 8 l. of 6 *N* HCl, then cooled to 0°, filtered, and washed with H_2O. The precipitate was suspended in 200 ml of MeOH, warmed to reflux, and then cooled to 10°. After filtration the yellow crystals were washed with MeOH to yield 49 g (58%) of crude material. An analytical sample was prepared by crystallization from water: mp >350°; pmr (DMF-d_7–D_2O) δ 4.8 (s, 4, $ArCH_2N$), 7.8 (comp m, 6, H-1, H-2, H-3, H-6, H-7, H-8), 9.1 (s, 1, H-9). *Anal.* ($C_{15}H_{15}N_3 \cdot 2HCl$) C, H, N, Cl.

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Book Reviews†

The Treatment of Parkinsonism with L-Dopa. By John Marks. American Elsevier, New York, N.Y. 1974. vii + 165 pp. 16 × 24 cm. $11.25.

The book is a compilation of reprints or translations of 12 "classical and original" papers, tracing the development of the use of levodopa in Parkinsonism, beginning with James Parkinson's 1817 essay on shaking palsy. The choice of the landmark contributions to the subject is defensible, although workers in the field might challenge the omission of other equally influential contributions. Some of the chapters are prefaced by an italicized brief historical outline or by a short interpretation of the findings described in the paper following. The book concludes with a terse italicized listing of "Further Problems" and a 3½ page appendix on current views on the clinical use of levodopa (unreferenced). While publication of the compilation of these 12 papers may be defended on the basis of historical value, all of them have appeared in print previously, and all are well known and are readily accessible in the original to the scientific community. The contribution of the author-editor-compiler (this reviewer is uncertain as to the proper designation) to the book seems minimal and, overall, the volume does not impress this reviewer as being useful or needed, either by active workers in the field or by those who might wish to gain knowledge of an insight into Parkinson's disease. Proofreading of the book has not been rigorous, as evidenced by misspelling of "vitamin" in the Index, p 165.

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Organic Reactions. Volume 21. William G. Dauben, Editor-in-Chief. Wiley, New York, N.Y. 1974. vii + 417 pp. 14.5 × 23 cm. $22.50.

This volume follows the pattern previously established with each chapter containing a discussion of selected reactions and their mechanisms followed by tables listing reactants, conditions, products, and the references for specific reactions in each general category. Both chapters of volume 21 discuss methods for the synthesis of fluorine-containing compounds. The titles of these chapters are "Fluorination by Sulfur Tetrafluoride" and "Modern Methods to Prepare Monofluoroaliphatic Compounds."

† Unsigned book reviews are by the editorial staff.

How Modern Medicines are Discovered. Edited by Frank H. Clarke. Futura, Mount Kisko, N.Y. 1973. ix + 177 pp. 15.5 x 23 cm. $10.00.

This is a book which is somewhat difficult to place in a category, either by content or by style. It does not fit the classification of a monograph or a journal, is not really a textbook, and yet its emphasis is more than historical. The editor and authors have attempted to tell the story of how new medicinal agents are developed, from the point of view of the medicinal researcher. They have chosen to go about this task by utilizing the rich historical framework from which the medicinal sciences have grown, by attempting to communicate the rewards and excitement as well as the disappointments which many have known during the progress of their work. They have also made every effort to highlight and put into perspective the considerable scientific insight and technological developments which have grown over the years. In my opinion, they have succeeded admirably.

The book begins with a chapter bearing the same title as the book, in which the editor eloquently describes the entire process involved in the creation of a new drug, from the initial concept to the final clinical trials. The interdisciplinary nature of the process is emphasized throughout. From this point, the story unfolds into chapters on the development of specific classes of medicinal agents, chosen mainly for their illustrative elegance. Chapter 2 relates the developments of the natural antibiotics, from the discovery of penicillin and chlortetracycline, through the testing methods to biosynthetic and chemical modifications. The third chapter is devoted to developments in the area of analgetics, again scanning the spectrum, this time from morphine to aspirin. Brief sections on narcotic antagonists and the development of the rational approach to analgetic drug design are also presented.

The fascinating story of the sulfa drugs is treated in chapter 4, from their origins in the dye industry to their use as antibacterials, diuretics, and antidiabetics. Chapter 5 deals with the progressive relationship in the early research in the areas of antimalarials and antihistamines which led to the discovery of the tranquilizers and antidepressants, represented best by the discovery of chlorpromazine. The chapter concludes with a short discussion of the function of the brain amines, particularly as related to mental illness and Parkinsonism. Chapter 6 contains a discussion of hormones and their analogs, touching on such topics as contraception and the sex hormones, steroidal antiinflammatory agents and other corticosteroids, and the polypeptide hormones insulin, ACTH, and oxytocin.

The next chapter is nominally concerned with the chemical transmitters in both the sympathetic and parasympathetic nervous system. The authors have approached the topic from a very current viewpoint, that of antihypertensive therapy. The balance in the autonomic nervous system is clearly, if somewhat simply,