was washed successively with ether (2 × 25 mL), $NaHCO_3$ solution (20 mL, half saturated), and water and dried. Crystallization from methanol afforded 0.6 g (40%) of product, mp >300 °C. Anal. ($C_{15}H_{12}N_2O_5S_2$) C, H, N, S.

11-Chloro-8-methoxycarbonyl-6-sulfamyldibenzo[*b,f*]-[1,4]thiazepine (11). A mixture of **10** (0.90 g, 2.5 mmol) and $POCl_3$ (15 mL) was refluxed for 16 h. The resulting solution was cooled, diluted with ether, and filtered to yield 0.7 g (74%) of solid, mp 224–246 °C. Crystallization from ethyl acetate afforded 0.5 g (53%) of product, mp 257–258 °C. Anal. ($C_{15}H_{11}ClN_2O_4S_2$) C, H, N.

10,11-Dihydro-8-methoxycarbonyl-6-sulfamyldibenzo-[*b,f*][1,4]thiazepine (12). To a stirred suspension of **10** (2.2 g, 6.04 mmol) in dry dioxane (60 mL) was added dropwise at ambient temperature 16.5 mL (16.5 mmol) of a 1 M BH_3–THF solution. After ca. 8 h, the reaction was quenched with a mixture of dilute HCl and acetone and allowed to stir overnight. Adjustment of the pH to 7 with sodium bicarbonate, followed by removal of the solvent and addition of water, afforded 2.2 g of crude product. Trituration of this solid with 150 mL of ethyl acetate, followed by filtration (to remove ca. 0.4 g of **10**) and concentration of the filtrate to 50 mL, yielded 0.66 g (31%) of product, mp 243–245 °C. Anal. ($C_{15}H_{14}N_2O_4S_2$) C, H, N. Evaporation of the filtrate and crystallization of the residue from 2-propanol and ethanol afforded **20**, mp 212–213 °C dec. Anal. ($C_{14}H_{14}N_2S_2O_3$) C, H, N, S.

A mixture of **11** (10 g, 26.1 mmol), 10% Pd/C (2 g), 250 mL of dry THF, and 5 mL of glacial HOAc was hydrogenated at 50 psi, 55–60 °C, for 4–5 h. Cooling, filtration of the catalyst, and removal of the solvent followed by $NaHCO_3$ wash afforded **12** in essentially quantitative yield.

8-Carboxy-10,11-dihydro-6-sulfamyldibenzo[*b,f*][1,4]-thiazepine (13). A mixture of **12** (0.66 g, 1.88 mmol), water (10 mL), methanol (10 mL), and 50% sodium hydroxide solution (2 mL) was refluxed for 0.5 h. The solvent was removed in vacuo and the residue dissolved in water and filtered. Acidification with concentrated HCl afforded 0.5 g (80%) of pure yellow product, mp >300 °C. Anal. ($C_{14}H_{12}N_2O_4S_2$) C, H, N, S.

Methyl 4-(2-Methoxycarbonylphenoxy)-3-nitro-5-sulfamylbenzoate (16). **15** (2.0 g, 5.8 mmol) was suspended in 10.4 mL of concentrated HCl. A solution of 0.5 g of $NaNO_2$ (7.2 mmol) in 1.1 mL of H_2O was added, maintaining the temperature below 0 °C. The cold diazonium salt solution was poured at room temperature with stirring into a mixture of 14 mL of SO_2 saturated glacial acetic acid, 0.21 g of $CuCl_2$, and 0.42 mL of water. After stirring 80 min water was added and the mixture was extracted three times with $CHCl_3$; the combined $CHCl_3$ solutions were washed three times with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in 10 mL of $CHCl_3$; after addition of 2.9 g of $(NH_4)_2CO_3$ the mixture was refluxed for about 1 h. The reaction was cooled, the mixture evaporated under reduced pressure, and the residue washed with water and then treated with methanol. The resulting precipitate was filtered and recrystallized from methanol to yield 1.0 g (45%), mp 202–204 °C. Anal. ($C_{16}H_{13}N_2O_9S$) C, H, N.

8-Methoxycarbonyl-6-sulfamyldibenz[*b,f*][1,4]oxazepin-11(10*H*)-one (17). A mixture of **16** (7.8 g, 22.5 mmol), 10% Pd/C (1.2 g), and 2.5 mL of concentrated HCl in 200 mL of THF was hydrogenated 7 h at 45 °C at 45 psi. The mixture was cooled and filtered and the mother liquor evaporated under reduced pressure. The resulting residue was suspended in 150 mL of methanol with 12 drops of concentrated H_2SO_4 and refluxed overnight. The crystalline precipitate was filtered and washed with a small amount of methanol to give 6.0 g (90%). Recrystallization of 1.5 g from acetone–methanol gave 1.2 g, mp >300 °C. Anal. ($C_{15}H_{12}N_2O_6S$) C, H, N, S.

10,11-Dihydro-8-methoxycarbonyl-6-sulfamyldibenz-[*b,f*][1,4]oxazepine (18). To a stirred slurry of 2.0 g (5.75 mmol) of **17** in 100 mL of absolute THF was added 40 mL (40 mmol) of 1 M BH_3–THF at 0 °C over 20 min. The mixture was allowed to come to room temperature and was kept there for 5 h. After cooling to 15 °C, 40 mL of 3 N HCl was added slowly. The THF was removed by distillation at aspirator pressure and the aqueous phase was neutralized with saturated $NaHCO_3$ solution. The precipitated product was filtered, washed with water, and dried to yield 1.5 g of crude material which was chromatographed on silica gel with $CHCl_3$–MeOH (95:5) as eluent to yield 0.5 g (26%) of product, mp 242–244 °C. Anal. ($C_{15}H_{14}N_2O_5S$) C, H, N, S.

8-Carboxy-10,11-dihydro-6-sulfamyldibenz[*b,f*][1,4]oxazepine (19). A solution of 450 mg (1.4 mmol) of **18** in 17 mL of CH_3OH–H_2O (1:1) and 1.2 mL of 33% NaOH was refluxed for 0.5 h. After cooling, the solution was acidified with concentrated HCl. The resulting colorless precipitate was filtered, washed with water, and dried to yield 380 mg (88%) of product, mp 280–282 °C. Anal. ($C_{14}H_{12}N_2O_5S$) C, H, N, S.

Acknowledgment. The authors wish to express their gratitude to Mr. Marc N. Agnew for determination of NMR spectra and to Mr. Jeffrey C. Wilker and his group for pharmacological testing. The assistance of Miss Linda Cuiskelly in the preparation of this manuscript is gratefully acknowledged.

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1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]-1*H*-imidazole Nitrate, a New Potent Antifungal Agent[1]

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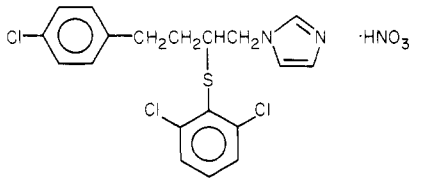
The preparation and antifungal properties of 1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]-1*H*-imidazole nitrate **1** are described. It is particularly effective against in vivo *Candida albicans* infections (mice), maintaining good activity down to 0.25% formulation strength and showing unusually low reinfection rates after treatment is ended.

Many antifungal compounds containing an imidazole group are known and largely fall into two general classes: the (poly)arylmethylimidazoles[2] (e.g., clotrimazole) and the arylethylimidazoles[3] (e.g., miconazole). As the result of

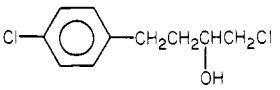
0022-2623/78/1821-0840$01.00/0

a search for new antifungal agents having improved activity against candidiasis, we wish to describe here the preparation and properties of a potent new anticandidal agent based on the 1-(phenylbutyl)imidazole skeleton, namely, 1-[4-(4-chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]-1*H*-imidazole nitrate (**1**).

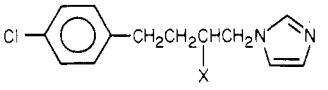


1

Chemistry. The chlorohydrin **2** was obtained by re-



2



3a, X = -OH
b, X = -Cl

action of *p*-chlorobenzylmagnesium chloride with epichlorohydrin in ether and converted to the crystalline alcohol **3a** by reaction with sodium imidazole (1.1 equiv) in dimethylformamide. Reaction of **3a** with thionyl chloride gave the chloro compound **3b**, which was converted to **1** (free base) with 2,6-dichlorothiophenol and anhydrous potassium carbonate in acetone. Isolation and purification as the nitrate salt gave **1**. The free base is also crystalline and can be obtained by neutralization of **1** with aqueous potassium carbonate.

Biological Data. The in vitro profile of **1** is similar to that of related antifungal agents. However, the compound shows marked superiority over known agents in in vivo assays vs. *Candida albicans*, its activity being characterized by consistently high cure rates and minimal recurrence of infection after treatment is ended.

In preliminary in vitro antimicrobial screening, **1** showed complete inhibition of growth at the concentrations (μg/mL) indicated against the following representative fungi and bacteria. Agar dilution assay[4,5] (fungi) (comparable values for miconazole in parentheses): *Trichophyton mentagrophytes* (two strains) 1, 5 (0.5, 0.5); *Trichophyton rubrum* (two strains) 0.5, 0.05 (0.5, 0.5); *Trichophyton tonsurans* (two strains) 5, 5 (0.5, 0.5); *Trichophyton concentricum* 0.05 (0.5); *Microsporum gypseum* (two strains) 5, 0.05 (5, 0.05); *Microsporum canis* (two strains) 0.5, 0.1 (0.5, 0.5); *Epidermophyton floccosum* 5 (5). Broth dilution assay[4] (fungi): *Candida albicans* (ATCC 10231) 30 (30); *C. albicans* (ATCC 14053) 10 (30); *Cryptococcus neoformans* ≤1 (≤0.3). Broth microdilution assay[6] (bacteria): *Staphylococcus aureus* (No. 6538 P) 6.25 (6.25); *Staph. aureus* (No. 14154) 12.5 (12.5); *Streptococcus faecalis* (No. 8043-2) 3.12 (3.12); *Strept. pyogenes* (No. 8668) 0.0016 (≤0.0008).

The in vivo activity of **1** was evaluated using an experimentally induced *C. albicans* vaginal infection in mice.[7] Ten or more animals per test compound were treated vaginally b.i.d. for 4 days and cultured for remaining organisms at the end of treatment ("day 4") and 3 days later ("day 7").[8] Whereas **1** (1% formulation in a modified PEG 400 solution[9]) effected clearance in 90% of the animals at the end of treatment, with 80% of the treated animals remaining free of infection 3 days later, commercial miconazole (2% formulation) in the same assay cleared only 33% of the animals at day 4 with all animals exhibiting reinfection 3 days later. In a similar assay using 20 animals/group a solution of **1** (1%) in neat PEG 400 solution cleared 95% of the infected animals, with 83% of treated animals remaining clear 3 days later. Clotrimazole (1%) and nystatin (100 000 U/g) in the same assay (commercial formulations) showed 85 and 10% clearing, respectively, at the end of treatment, with 55 and 0%, respectively, of treated animals remaining uninfected 3 days later. In a dose response study of **1** against miconazole, **1** was found to have activity at 0.25% concentration[10] comparable to that of miconazole at 4% concentration.[11] The results are presented in Table I.

Table I. In Vivo Activity against *C. albicans* (Pure Culture) in Mice

formulation concn, %	% noninfected animals			
	1		miconazole	
	day 4[a]	day 7	day 4	day 7
4	–[b]	–	75	70
2	85	85	50	37
1	90	95	60	25
0.5	80	75	30	25
0.25	75	75	–[b]	–
placebo[c]	0	0	0	0

[a] Twenty animals/group. Treatment (4 days b.i.d.) ends on day 4. Animals cultured on day 4 (6-h posttreatment) and day 7. [b] A minus (–) indicates not tested. [c] Ten animals/group.

Table II. In Vivo Activity against a Mixed Infection of *C. albicans* (Ten Strains) in Mice

formulation concn, %	% noninfected animals			
	1		miconazole	
	day 4[a]	day 7	day 4	day 7
2	–[b]	–	10	15
1	84	83	20	25
0.5	65	60	20	11
0.2	60	63	15	20
0.1	35	40	–	–
placebo	0	0	5	5

[a] See footnote *a*, Table I. [b] A minus (–) indicates not tested.

In an extended assay it was further shown that mice with negative cultures at the end of treatment with **1** remained free of infection until the assay was terminated (21 days posttreatment).

Because there remained a possibility that the pure culture of *C. albicans* used in the above in vivo assays might be unduly sensitive to compound **1**, a further assay was run using a mixed culture of ten distinct strains of *C. albicans*. In this assay, 60% of those animals treated with **1** (1% formulation in modified PEG 400 solution[9]) were free of infection at the end of treatment, with 55% of all treated animals remaining uninfected 3 days later. Miconazole (2% commercial cream formulation) showed only 33% clearance of infection at the end of treatment, with 25% of treated animals remaining uninfected 3 days later. The untreated controls remained infected throughout the study. Repetition of this assay using different formulation concentrations gave the results presented in Table II, again showing **1** at 0.2% formulation strength to be more active than 2.0% miconazole in the commercial formulation.

Although developed specifically as an anticandidal agent, **1** demonstrates good activity against the representative dermatophyte *T. mentagrophytes* in an in vivo guinea pig model.[12] Groups of ten animals were treated with the test compound once daily for 5 days, starting 3 days post-challenge. Animals were cultured after one treatment (day 4), at the end of treatment (day 7), and 7 days later (day

14). Treatment with 1 (0.5% formulation[13]) gave 60% clearance at day 4 and 90% clearance at day 7, with 40% of treated animals remaining free of infection 7 days later. Miconazole (0.5% formulation[13]) in the same assay gave figures of 70, 80, and 10%, respectively, at days 4, 7, and 14.

Preliminary acute toxicity studies (single dose) show 1 to be remarkably nontoxic, having LD_{50} values of >3200 mg/kg po and >1600 mg/kg ip in mice and >3200 mg/kg po (male), 1720 mg/kg po (female), and 940 mg/kg ip in rats.

Compound 1 was assayed for mutagenicity in the Ames test[14] using *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 and *Saccharomyces cerevisiae* strain D4 directly and in the presence of liver microsomal enzyme preparations from Arochlor induced rats.[15] No mutagenicity was detected toward any strain of *S. typhimurium* at doses of 0.1, 1, 10, or 100 μg/plate or toward *S. cerevisiae* at a dose of 0.1 μg/plate. However, 1 was lethal to all strains of *S. typhimurium* at a dose of 500 μg/plate and toward *S. cerevisiae* at doses of 1–500 μg/plate.

Compound 1 is currently undergoing further development for use in antimycotic therapy.[16]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were determined in methanol with a Cary 14 instrument. Infrared spectra were obtained in KBr with a Perkin-Elmer 237B spectrometer. NMR spectra were obtained with Varian A-60 and HA-100 instruments, and mass spectra were determined with a Varian-MAT CH4 spectrometer. Elemental analyses were performed by the analytical department of Syntex Research, Institute of Organic Chemistry, and are within ±0.4% of calculated values.

1-Chloro-4-(4-chlorophenyl)-2-butanol (2). A solution of *p*-chlorobenzylmagnesium chloride [from α,*p*-dichlorotoluene (40 g, 0.248 mol) and magnesium (6 g, 0.25 mol)] in diethyl ether (180 mL) was added dropwise with stirring to epichlorohydrin (23 g, 0.25 mol) in ether (100 mL) at a sufficient rate to maintain gentle reflux. After the addition was complete (1 h) reflux was maintained by warming for about 1 h and the mixture let stand overnight. After the addition of ice, water, and sufficient dilute sulfuric acid to dissolve solids, the product was isolated by separation of the organic phase, ether extraction of the aqueous phase, washing the combined ethereal solutions with water, drying ($MgSO_4$), and evaporation. The product was distilled in vacuo, that fraction boiling between 111 (0.3 mm) and 125 °C (0.15 mm) being collected and used directly in the next step: yield 38.7 g; GC purity ca. 89%.

1-[4-(4-Chlorophenyl)-2-hydroxy-*n*-butyl]imidazole (3a). A solution of sodium imidazole was prepared by the portionwise addition of sodium hydride [50% dispersion in mineral oil (7.89 g, 0.164 mol)] to a cooled stirred solution of imidazole (12.0 g, 0.176 mol) in dry dimethylformamide (120 mL). The mixture was then stirred at room temperature, until the evolution of hydrogen ceased, and warmed to approximately 60 °C. A solution of 1-chloro-4-(4-chlorophenyl)-2-butanol (**2**, 38.6 g) in dimethylformamide (30 mL) was added dropwise with stirring, maintaining the temperature around 60 °C. The mixture was stirred overnight at room temperature, treated with hexane (100 mL), and gradually diluted with cold water until crystallization of the product was complete. Filtration and washing of the residue with hexane and water gave 32.2 g of pure **3a**: yield, 51.7% from α,*p*-dichlorotoluene. The analytical sample from ethyl acetate had mp 106–109 °C. Anal. ($C_{13}H_{15}ClN_2O$) C, H, N.

1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-*n*-butyl]imidazole Nitrate (1). A solution of 1-[4-(4-chlorophenyl)-2-hydroxy-*n*-butyl]imidazole (**3a**, 6.0 g, 0.024 mol) in thionyl chloride (30 mL) was warmed at 65–70 °C for 1 h and evaporated to dryness. The residue was dissolved in dichloromethane and basified with aqueous potassium carbonate and the organic phase was washed with water, dried ($MgSO_4$), and evaporated to give 1-[4-(4-chlorophenyl)-2-chloro-*n*-butyl]imidazole (**3b**) as an amber gum. After evacuation to remove traces of dichloromethane, acetone (100 mL) was added, followed by 8.5 g (0.047 mol) of 2,6-dichlorothiophenol[17] and 6.4 g (0.046 mol) of anhydrous potassium carbonate, and the mixture was stirred under reflux overnight. After removal of the solvent 100 mL of water was added and the product extracted with 300 mL of ether. The extract was washed twice with water, dried ($MgSO_4$), and treated dropwise with 70% nitric acid (d = 1.42) until precipitation was complete. The resulting nitrate salt was recrystallized from acetone–ethyl acetate to give **1** as colorless blades (9.6 g, 84%): mp 162–163 °C (foaming). Anal. ($C_{19}H_{18}Cl_3N_3O_3S$) C, H, N. The free base prepared by neutralization of a suspension of 1 in ether with aqueous potassium carbonate and recrystallization from cyclohexane had mp 68–70.5 °C (foaming). Anal. ($C_{19}H_{17}Cl_3N_2S$) C, H, N.

Acknowledgment. The authors wish to thank Mr. William F. Taylor and Ms. Elizabeth Manoukian for technical assistance in preparing the formulations and Dr. Duane Hallesy of the Syntex Department of Toxicology for the toxicity experiments.

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(8) Twenty mice were used as positive controls. All of these and those animals treated with placebo formulation remained infected throughout the study.
(9) The formulation contained PEG 400, PEG 4000, water, glycerine, and Tween 80.
(10) The formulation contained PEG 400, PEG 4000, water, glycerine, benzyl alcohol, benzalkonium chloride, EDTA-Na_2, and BHA.
(11) Miconazole was formulated in the published[18] commercial formulation (4%). The 2% formulation was obtained commercially and diluted to 1 and 0.5% using the above published formula.
(12) R. S. Gordee and T. R. Matthews, *Antimicrob. Agents Chemother.*, 378 (1967).
(13) The formulation contained steryl alcohol, cetyl alcohol, Span 60, Tween 60, propylene glycol, mineral oil, and water.
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(15) The assay was performed by Litton Bionetics Laboratory, Kensington, Md.
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structure–activity relationships of compounds related to 1 will appear in a future publication.
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Book Reviews

Biological Activity and Chemical Structure. Pharmacochemistry Library. Volume 2. Edited by J. A. Keverling Buisman. Elsevier Scientific, Amsterdam. 1977. x + 314 pp. 17.5 × 25 cm. $44.60.

This is a compilation of papers presented and discussions held at the IUPAC–IUPHAR Symposium of the same name, held in Noordwijkerhout, The Netherlands, Aug 30–Sept 2, 1977, and is Volume 2 of the "Pharmacochemistry Library", a series to be devoted to quantitative structure–activity methods.

The stated purpose of the symposium was to "bring chemists and pharmacologists into close contact with each other in the field of quantitative structure–activity relationships of bioactive compounds". A variety of pharmacologic topics is addressed; however, some chapters are short and do not provide adequate coverage to the imposing title of the chapter. Some of the authors elected to follow a broad, philosophical approach to structure–activity research, which makes enjoyable reading, but transmits relatively little that is new and provides little new insight. Indeed, more authors than not have written largely retrospectively and have described work which is already in print or which they state to be "in press" elsewhere. Some of the chapters seemed to this reviewer to be only marginally consistent with the "QSAR" theme of the conference.

Four chapters dealing with hydrophobic bonding/interactions were scattered throughout the volume. Together, these seem to comprise a useful account of current thought on hydrophobic interactions in SAR. It would have seemed logical to group these chapters together, rather than dispersing them through the book.

The volume ends with a summary of "round table discussions" by selected participants in the conference. It is the prejudice of this reviewer that these types of discussions only extremely rarely read well when translated into print, regardless of how stimulating they were when they were heard by the auditors of the discussion.

Stimulating, interesting symposia do not always make equally valuable reading material. One must question the wisdom of what seems to be a trend of publishing in book form the verbatim accounts of all possible international (and, even, national and regional) symposia in medicinal chemistry and/or pharmacology. The high cost of this volume, coupled with the fact that it is bound in a delicate hard-cover paper binding which appears to be unequal to the challenge of hard or prolonged usage, may discourage many researchers from purchasing it.

The University of Iowa **Joseph G. Cannon**

Psychopharmacology: A Generation of Progress. Edited by M. A. Lipton, A. DiMascio, and K. F. Killam. Raven Press, New York, N.Y. 1978. xxviii + 1731 pp. $49.50.

This volume was developed by the American College of Neuropsychopharmacology (ACNP) to provide a comprehensive survey of progress in their field. It clearly summarizes the current understanding of the uses and modes of action of psychotropic drugs. This volume is enormous in both scope and size, with over 250 authors contributing to 149 chapters.

The first section of the book deals with ethical and methodological issues in basic and clinical psychopharmacology. Subsequent sections review the mechanisms of drug action on a basic, molecular level viewing the neuroanatomical, histochemical, and neurophysiological aspects of psychoactive drugs. Other sections present the biochemical pharmacology of all the putative CNS neurotransmitters and their receptors as well as the response of peptides and neuroendrocrine regulation to psychotropic agents. Behavioral pharmacology is dealt with in several sections which discuss drug experiments in both animal and human models where attention is directed toward an understanding of mental or emotional illness. Several chapters cover the pharmacology of memory and learning, neurological disorders, and electrophysiological indicators of drug action.

After discussion of the interface between basic studies and clinical observations, an examination is made of the methodological, design, and statistical features that are necessary for drug assessments in patient populations. A number of the chapters in this section deal with the metabolism and kinetics of drug activity in patients, with an aim to providing some scientific bases for understanding individual variations in drug response. The current thinking about the etiology and therapeutic approaches to anxiety, the affective disorders, and schizophrenia is covered as well as the special cases of pediatric and geriatric psychopharmacology.

The final sections of the volume present some of the unforeseen hazards associated with the advent of modern psychopharmacology—the adverse effects that these agents produce in individuals who ingest psychotropic drugs for therapeutic or recreational purposes and the problems produced for society and the individual by those who misuse or abuse the drugs. Reviews of the drugs of abuse provide a useful perspective of recent developments and future trends.

This volume provides pertinent background material for all who are interested in the study and use of psychotropic drugs. Despite the scope of the book the topics are well organized and clearly written. This book represents a sequel to the ACNP's "Psychopharmacology: A Review of Progress 1957–1967", edited by the late Daniel Efron. A comparison of the two volumes readily illustrates the quantum leaps of progress seen in the 20 years since modern neuropsychopharmacology has emerged as a discipline. While the cost of this book does not lend itself as an easy purchase, it is clearly the most complete and thorough review of the field that has been published.

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Modern Pharmacology-Toxicology. Volume 11. Receptors in Pharmacology. Edited by John R. Smythies and Ronald J. Bradley. Marcel Dekker, New York and Basel. 1978. viii + 506 pp. 16 × 23.5 cm. $45.00.

This volume is the most recent in a pharmacology-oriented series. However, each edition is clearly independent of its predecessors.

"Receptors in Pharmacology" contains 11 chapters. Seven of these provide reviews of research progress on specific receptor systems (AcCh, β-adrenergic, opiate, progesterone, amino acid, etc.). The remaining four chapters are broadly applicable to receptor studies. The inclusion of the latter serves to unify the text and enhance its value beyond a mere collection of individually authored review articles.

The opening chapter, "Receptor Theory" by D. J. Triggle, sets an appropriate tone by defining the behavior expected from various models of receptor organization. It is clear that few receptors are available in isolated preparations of sufficient purity to judge the validity of one model vs. another. More importantly the state of purified receptors may not reflect relevant physiologic