Table I. γ-Radiolysis of **5b** (1 mM) To Release **1b** in Aqueous Solution (pH 7.0) under Various Conditions

conditions[a]	active species $G(^{\bullet}OH)$	$G(e^-_{aq})$	$G(^{\bullet}H)$	$G(CO_2^{\bullet-})$	decomposition: $G(-\mathbf{5b})$	release:[b] $G(\mathbf{1b})$
air	2.7	0[c]	0[d]	0	5.7	0.30 (5%)
Ar	2.7	2.7	0.55	0	4.5	0.72 (16%)
N_2O	5.4	0	0.55	0	4.1	0 (0%)
Ar + HCOONa	0	2.7	0	3.25	5.2	1.6 (31%)
N_2O + HCOONa	0	0	0	5.95	3.4	1.2 (35%)

[a] Solution of **5b** in triply distilled water, in the absence or presence of HCOONa (100 mM), was purged with Ar or N_2O for 20 min, except under aerated conditions. [b] The value in the parenthesis is the selectivity of **1b** release ($G(\mathbf{1b}) \times 100/G(-\mathbf{5b})$). [c] Scavenged by O_2 to yield superoxide radical anions ($O_2^{\bullet-}$). [d] Scavenged by O_2 to yield hydroperoxyl radicals ($HO_2^{\bullet}$), which are in equilibrium with $O_2^{\bullet-}$.

Successive anodic oxidation of **4a** at the anode–water interface would produce C(5) and C(6) cations [$\mathbf{4a}^+$(C(5)), $\mathbf{4a}^+$(C(6))], which undergo attack of water to yield **5a** and **6a**, respectively.

Characteristics of 5b. The present electrochemical method was effective in synthesizing a novel N(1)–C(5)-linked dimer of 5-fluorouracil (**1b**). On galvanostatic electrolysis (10 mA) of **1b** (1 mM) in aqueous solution (100 mL, 9 mM NaCl) in air, 87.6% of **1b** was converted over 2.5 h to produce a dimer 1-(5′-fluoro-6′-hydroxy-5′,6′-dihydrouracil-5′-yl)-5-fluorouracil (**5b**; 69.9 ± 1.6% at 0.5-h intervals).[10] No N(1)–C(6) linked dimer analogous to **6a** was detectable in this electrolysis. For isolation, an aqueous solution of 70 mM **1b** (100 mL; 18 mM NaCl) was also electrolyzed at 300 mA for 7 h and evaporated. The residue was dissolved in ice-cooled water (20 mL) and the insoluble solid was repeatedly recrystallized from methanol/water (1:2 v/v) to give **5b** as colorless prismatic crystals.

Table I shows the *G*-values[11] for decomposition of **5b** and release of **1b** in the γ-radiolysis of aqueous solution (pH 7.0) under various conditions. The radiation-activated release of **1b** favored oxygen-free conditions in Ar, showing 3 times higher selectivity (16%) over aerated conditions. Furthermore, the reducing species of hydrated electrons (e^-_{aq}) and carbon dioxide radical anions ($CO_2^{\bullet-}$) enhanced the **1b** release with 31–35% selectivity, while the oxidizing $^{\bullet}OH$ radicals induced no such a release. Hydrolysis of **5b** into **1b** did not occur at pH <8.0. Thus, radiolytic one-electron reduction of **5b** occurring more efficiently under oxygen-free conditions accounts for the **1b** release. The primary active species produced by radiolysis of intracellular water in hypoxic cells may be similar to those in Ar-saturated aqueous solution, suggesting the potential of **5b** as a prodrug that can be activated in the radiotherapy of hypoxic tumors.

A growth-delay assay of **5b** was performed using C3H/He mice (female, 8–10-weeks-old, 19–22 g, $n = 8$) bearing SCCVII tumors (1 cm in mean diameter) in the thigh. The tumor-volume-doubling times were 3.2 days for controls, 3.3 days for **5b** (50 mg/kg of body weight injected iv in the tail vein) alone, 8.0 days for 20-Gy radiation (10 MV X-rays at 5.6 Gy/min) alone, 9.2 days for **1b** (50 mg/kg iv) alone, 10.6 days for 20-Gy radiation combined with **5b** (50 mg/kg iv 20 min before irradiation), 13.1 days for 20-Gy radiation combined with **1b** (50 mg/kg iv 20 min before irradiation), and 13.8 days for 30-Gy radiation alone. Evidently, **5b** has no antitumor effect in contrast to **1b**, but can potentiate the radiotherapy to inhibit the tumor growth. This effect is presumably attributed to the radiation-activated release of **1b**.

Further synthesis and assay of related pyrimidine dimers that release **1b** as an antitumor drug component are in progress and will be reported in due course.

Acknowledgment. We thank Prof. C. von Sonntag for stimulating discussions and Messrs. H. Hisanaga and T. Yoshizawa for ^{19}F NMR measurement and mass spectrometry.

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(10) For **5b**: mp >190 °C dec; IR (KBr) 3300, 1720, 1675, 1280, 1140 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 5.36 (ddd, 1 H, J = 4.43, 4.42, 4.73 Hz), 7.15 (d, 1 H, J = 4.73 Hz), 8.18 (d, 1 H, J = 6.56 Hz), 8.49 (broad, 1 H), 10.67 (broad, 1 H), 12.21 (broad, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 74.31 (C(6), II, J = 29.34 Hz), 93.80 (C(5), II, J = 220.82 Hz), 124.78 (C(6), I, J = 5.13, 31.55, 5.13 Hz), 140.80 (C(5), I, J = 234.75 Hz), 148.22 (C(2), I), 151.79 (C(2), II), 156.70 (C(4), I, J = 26.41 Hz), 161.71 (C(4), II, J = 24.21 Hz); ^{19}F NMR (300 MHz, DMSO-d_6, TFA) δ 68.26 (C(5)-F, II), 86.30 (C(5)-F, I, J = 7.10 Hz); MS m/e 277 (M + 1). Anal. Calcd for $C_8H_6N_4O_5F_2$: C, 34.79; H, 2.19; N, 20.29; F, 13.76. Found: C, 35.03, H, 2.26; N, 20.31; F, 13.76.

(11) The number of molecules produced or changed per 100 eV of energy absorbed by the reaction system.

3-[4-[1-(6-Fluorobenzo[*b*]thiophen-3-yl)-4-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone: A New Atypical Antipsychotic Agent for the Treatment of Schizophrenia

The majority of clinically-effective antipsychotic agents in use today exhibit some propensity for the development of extrapyramidal side effects, either acutely (i.e., dystonia, akathisia, pseudo-Parkinsonism) or with a delayed onset (tardive dyskinesia). Clozapine has been classified as an "atypical" neuroleptic agent because this compound is almost devoid of extrapyramidal side-effect liability. However, clozapine demonstrates adverse hematological effects which require selective targeting and careful monitoring of patient populations.[1]

In a continuing program to discover and develop new safe antipsychotic agents with an atypical pharmacological

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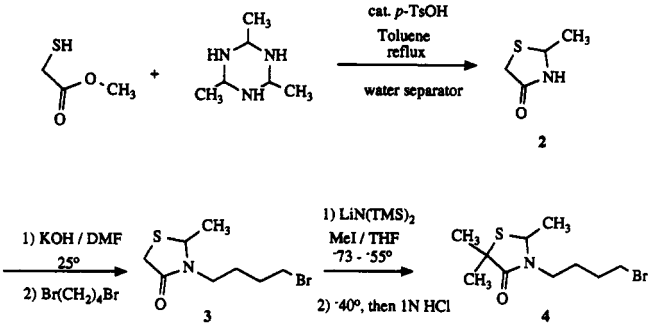
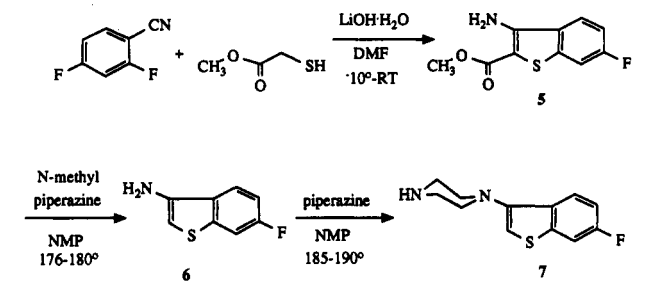
Scheme I



Scheme II



profile, we have prepared a series of 3-substituted-4-thiazolidinones. The lead compound in this series, P-9236 (HP-236, 3-[4-[1-(6-fluorobenzo[*b*]thiophen-3-yl)-4-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone, 1), displays a biological profile suggestive of potential atypical antipsychotic activity with a potency greater than that of clozapine, and has been selected for clinical development pending the outcome of its toxicological evaluation. We present here the synthesis of 1 and results of the key in vitro and in vivo pharmacological assays.

The synthesis of 1 is illustrated in Schemes I–III. Methyl thioglycolate is condensed with trimethyltriazine in refluxing toluene with removal of water to give 2-methyl-4-thiazolidinone 2 (previously reported via a different route[2]). This compound is alkylated with 1,4-dibromobutane to give compound 3, which is further alkylated in the α-position to provide key intermediate 4 [Anal. ($C_{10}H_{18}BrNOS$) C, H, N] (Scheme I).

Our preparation of the benzo[*b*]thiophene component is analogous to the method described by Beck.[3] Here, 2,4-difluorobenzonitrile is treated with the anion of methyl thioglycolate to provide the benzo[*b*]thiophene 5. Decarbomethoxylation of 5 gives the aminobenzo[*b*]thiophene 6 which is heated with piperazine [similarly to Perregaard's conversion of 3-hydroxyindoles to 3-(1-piperazinyl)indoles][4] to provide the other component of the target, key intermediate 7 [Anal. as maleate salt ($C_{16}H_{17}FN_2O_4S$) C, H, N] (Scheme II).

The two components, 4 and 7, are then combined to provide the target 1 (Scheme III), which is isolated as the maleate salt. Physical data for compound 1: ^{1}H NMR ($CDCl_3$, 200 MHz) δ (7.60 dd, 1 H, J = 5.0, 8.8 Hz), 7.50 (dd, 1 H, J = 2.3, 8.7 Hz), 7.15 (ddd, 1 H, J = 2.3, 8.8 and 8.8 Hz), 6.73 (s, 1 H), 6.30 (s, 2 H), 4.66 (q, 1 H, J = 6.1 Hz), 3.73–3.16 (m, 12 H), 1.87–1.65 (m, 4 H), 1.57–1.52 (2 s superimposed on d, 9 H); IR ($CHCl_3$) 3018 (m), 1710 (m), 1668 (s), 1470 (s), 1358 (s), 1190 (m) cm^{-1}; MS (EI, 70 eV) m/e 435 (m$^+$) (molecular weight of free base); mp 168–169 °C (uncorrected). Anal. ($C_{26}H_{34}FN_3O_5S_2$) C, H, N.

Scheme III

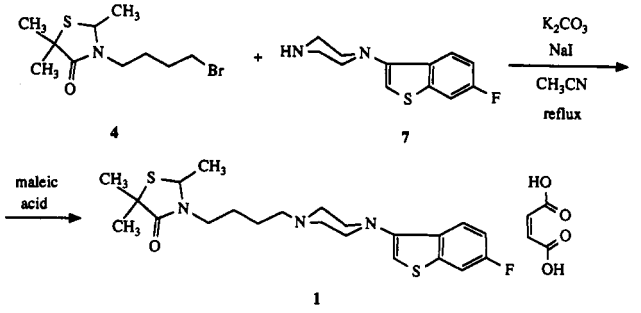


Table I. In Vitro Receptor Binding Profile of Compound 1

receptor	ligand/tissue	inhibn of ligand binding (K_I, μM)[a]
$5HT_{1A}$	[^{3}H]-8-OH-DPAT/hippocampus	0.04 ± 0.005
$5HT_2$	[^{3}H]spiperone/cortex	0.02 ± 0.002
D_2	[^{3}H]spiperone/striatum	0.52 ± 0.006
D_1	[^{3}H]SCH 23390/striatum	2.74 ± 0.77

[a] Values represent mean ± SEM of at least three determinations.

Table II. Comparison of Receptor Binding Affinity

	receptor binding affinity (K_I, μM)			ratio
	D_2	$5HT_2$	$5HT_{1A}$	$D_2/5HT_2$
haloperidol	0.01 ● 0.002	0.05 ± 0.009	5.75 ● 0.002	0.2
clozapine	0.79 ± 0.10	0.06 ± 0.03	0.64 ● 0.03	13.2
compound 1	0.52 ± 0.006	0.02 ● 0.002	0.04 ± 0.005	26.0

[a] Values represent mean ± SEM of at least three determinations.

The in vitro receptor binding profile of 1 reveals a greater affinity for serotonin $5HT_2$ and $5HT_{1A}$ receptors than for dopamine D_2 or D_1 receptors, as shown in Table I. Studies conducted with a large number of antipsychotic agents have shown that those agents which exhibit reduced extrapyramidal side effect liability in the clinic (clozapine, etc.) display a greater affinity for the $5HT_2$ receptor than for the D_2 receptor vs more typical agents (e.g., haloperidol). These observations led to the hypothesis that an atypical neuroleptic should display a K_I ratio for $D_2/5HT_2$ receptor binding of >1, whereas a typical neuroleptic would show a ratio of <1.[5,6] As shown in Table II, the ratio for haloperidol is 0.2, whereas clozapine's ratio is 13.2. Compound 1, with a ratio of 26.0, resembles clozapine in this aspect of its profile. In ex vivo studies, 1 inhibits striatal and nucleus accumbens $5HT_2$ receptor binding to a greater degree than D_2 receptor binding (56–100% vs 17–21%). The inhibition of $5HT_2$ receptor binding persists over time

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Table III. In Vivo Profile of Compound 1

	antagonism of apomorphine-induced climbing (mouse) (ED_{50}, mg/kg)[a]		antagonism of apomorphine-induced stereotypy (rat) (ED_{50}, mg/kg ip)	pole-climb avoidance (rat) (ED_{50}, mg/kg po)		intracranial self-stimulation (ED_{50}, mg/kg ip) (rat)
	ip	po		avoidance	escape failures	
haloperidol	0.194 ± 0.056 (2)	0.28 (0.27–0.29)	0.576 ● 0.148 (2)	1.1 (1.0–1.2)	14.1 (11.9–17.5)	0.077 (0.073–0.081)
clozapine	9.10 ● 1.77 (6)	23.2 (21.1–25.9)	>40	12.7 (11.1–14.1)	33.1 (29.1–39.9)	9.1 (8.5–9.7)
compound 1	2.5 ● 0.30 (2)	15.4 (14.41–16.57)	61.4 (54.2–69.6)	5.46 (4.57–6.37)	>20	4.7 (0.6–39.4)

[a] Values are mean ED_{50} + SEM (n) or ED_{50} and 95% confidence limits in parentheses.

and is still significant after 4 h.[7] This significant and long-lasting binding to $5HT_2$ receptors is also characteristic of clozapine and may be a factor in its atypical profile.[8]

It should be noted that compound 1 also displays potent affinity for the $5HT_{1A}$ receptor, although functional activity (agonism vs antagonism) has not been evaluated. Agonist activity at this receptor has been linked to antipsychotic activity. For example, the $5HT_{1A}$ agonist 8-OH-DPAT has been reported to demonstrate antipsychoticlike properties such as selective suppression of conditioned avoidance behavior without loss of escape response and a selective decrease in limbic vs neostriatal dopamine systhesis.[9] This agent and other $5HT_{1A}$ agonists such as buspirone and ipsapirone have been found to reverse haloperidol-induced catalepsy,[10] and a combination of $5HT_{1A}$ agonism and D_2 antagonism was the basis for the design of a series of potential atypical antipsychotic agents.[11]

The potential antipsychotic activity of compound 1 was confirmed in a number of animal models (Table III), including the pole-climb-avoidance assay[12] and intracranial self-stimulation assay[13] in rats. Compound 1 also inhibits apomorphine-induced climbing in mice,[14] and achieves this effect at doses significantly lower than those which inhibit apomorphine-induced stereotypic behavior in rats.[15] This indicates that 1 displays a measure of selectivity for limbic vs striatal brain regions. Such selectivity has been proposed as predictive of antipsychotic activity with reduced propensity for extrapyramidal side effects.[16,17]

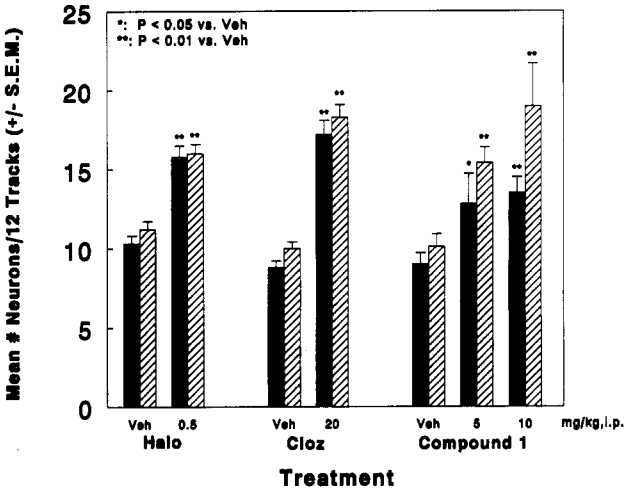

Figure 1. Dopamine single unit sampling, acute treatment: A10 pathway, solid; A9 pathway, hatched.

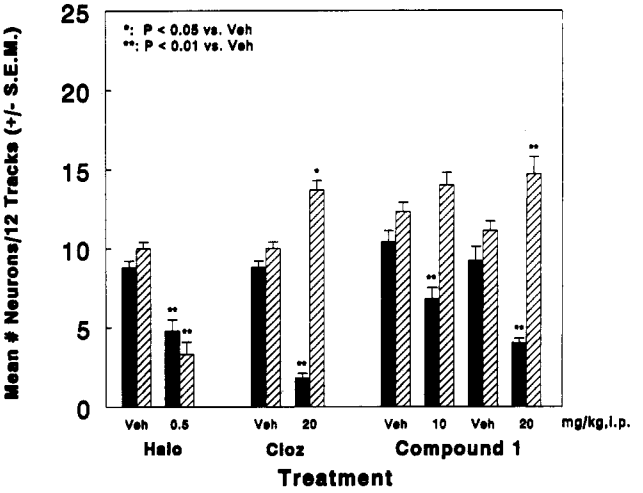

Figure 2. Dopamine single unit sampling, chronic (21 day) treatment: A10 pathway, solid; A9 pathway, hatched.

A key assay for evaluation of the potential EPS liability of an antipsychotic agent is the single unit dopamine neuron activity measurement developed by Chiodo and Bunney.[18] These investigators found that, on chronic administration, typical neuroleptics tended to reduce the

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number of spontaneously active dopamine neurons in both the A9 (nigrostriatal) and A10 (mesolimbic) dopamine pathways in the brain. In contrast, agents with reduced EPS liability selectively deactivated only the A10 pathway. Like haloperidol and clozapine, 1 increases the number of spontaneously active dopamine neurons on acute administration vs vehicle control (Figure 1). However, on chronic administration (Figure 2), haloperidol reduces the number of active neurons vs control in both the A9 and A10 pathways, while clozapine decreases activity selectively in the A10 pathway. Compound 1 also produces a selective decrease in the A10 dopamine neuron activity, displaying a clozapine-like profile indicative of atypical antipsychotic activity. In preliminary safety studies, 1 shows no prohibitive toxicological or cardiovascular effects.

In summary, the pharmacological profile of development candidate 1 both in vitro and in vivo suggests that this agent may prove to be an effective treatment for schizophrenia with reduced propensity for extrapyramidal side effects.[19]

Acknowledgment. We wish to thank Dana Hallberg and Anastasia Linville for spectral data. We also wish to thank Fakhra Arshad for additional biological assays.

Supplementary Material Available: The procedure for the dopamine single unit electrophysiology assay (1 page). Ordering information is given on any current masthead page.

(19) Portions of this work were presented at the 202nd American Chemical Society Meeting, New York, NY, August 1991; Abstract MEDI 85.

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Book Reviews

Clinical Applications of TGF-β. Ciba Foundation Symposium 157. Edited by Gregory R. Bock and Joan Marsh. John Wiley & Sons, Chichester, U.K. 1991. x + 254 pp. 15.5 × 23.5 cm. ISBN 0-471-92811-9. $69.50.

This volume is a collection of presentations and discussions deriving from a Ciba Foundation Symposium on the clinical applications of TGF-β held in London on June 12–14, 1990. The symposium focused on the clinical applications of transforming growth factor-β (TGF-β) in the control of cell differentiation and proliferation with special emphasis on the unique role of this group of peptides in the formation, remodeling, and destruction of the extracellular matrix. Particular attention is directed to the role of TGF-β in the pathogenesis of disease and as a mediator of inflammation and the repair of tissue injury. The important implications of the use of TGF-β or its antagonists in human therapeutics are stressed.

Topics addressed include the multiple forms of TGF-β; TGF-β receptors; mechanisms in TGF-β action; regulation of epithelial proliferation by TGF-β; molecular structure and mechanisms of action of latent forms of TGF-β; the role of TGF-β in the nervous system; the possible role of TGF-β in autocrine immune regulation and in wound healing; a stimulatory effect of TGF-β in tumor development; and the effects of TGF-β on bone, cardiac muscle cells, cell proliferation, fibrogenesis, glomerulonephritis, pulmonary fibrosis, normal and neoplastic hemopoiesis, and glioblastoma.

The book contains an adequate author and subject index. The volume should provide the reader with abundant evidence, obtained from molecular, cellular, and in vivo studies, to support the prediction of important clinical applications of TGF-β in medicine and surgery in years to come.

Staff

Drugs in Gastroenterology. Edited by P. C. Braga, M. Guslandi, and A. Titabello. Raven Press, New York. 1991. xi + 533 pp. 16 × 24 cm. ISBN 088167-864-3. $60.00.

This book reviews the pharmacology of various experimental and marketed drugs used to treat disorders of the gastrointestinal tract. The text is unique in that it brings under one cover a detailed compilation of both animal and clinical studies. Its intended purpose is to provide an information link between academic, pharmaceutical, and clinical scientists in the area of drug development for digestive disease.

The book is divided into 18 chapters primarily on the basis of pathophysiology. Chapters 1 and 2 review agents that are involved in the treatment of upper gastrointestinal disorders. Prokinetic drugs such as metoclopromide and cisapride are covered here. Chapters 3–6 deal with antiulcer and gastroprotective medications. A number of the top selling histamine(H_2)-receptor antagonists (e.g. cimetidine and ranitidine) are extensively reviewed in Chapter 4. In Chapter 7, the cytoprotective actions of misoprostol (a prostaglandin E_1 analog) against gastroduodenal lesions induced by nonsteroidal antiinflammatory drugs are examined. The remaining chapters review agents used to treat a variety of ailments including diarrhea (Octreotide), irritable bowel syndrome (hyoscine-N-butyl-bromide, cimetropium bromide), and inflammatory bowel disease (5-aminosalicyclic acid). Over 30 drugs in all are discussed.

Each chapter is dissected into several concise drug reviews. The general pharmacology of each drug is organized as follows: introduction, chemistry, animal studies (pharmacology, pharmacokinetics, metabolism), clinical studies, and safety. Tables are frequently used to summarize the literature of each compound and serve as a good reference source for dose selection. References as late as 1990 are noted, although some chapters appear more timely than others. An adequate subject index is included. One drawback of this text is that it contains numerous typographical, grammatical, and technical errors. Another limitation is that few of the authors appear to have been intimately involved with the research.

Overall, the book is a valuable source of information for those engaged in the study of gastrointestinal drugs. It is best suited for industrial and academic libraries as a reference book.

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Ring Enlargement in Organic Chemistry. By Manfred Hesse. VCH Verlagsgeselshaft mbH, Weinheim (Germany) and VCH Publishers, Inc., New York, NY. 1991. xi + 235 pp. 18 × 24.5 cm. ISBN 3-527-28182-7 (Weinheim), ISBN 0-89573-991-7 (New York). $85.00.

The ring enlargement reaction is a challenging concept in a complex field. Yet chemists who master the theory and the