

tinent details are given in the caption for Figure 2.

³¹P NMR Kinetic Measurements and Identification of 14/15. The procedure described¹⁸ for 2-CHA was applied to a solution of 9/13-CHA (1:1, 30 mg) in 1 M Tris buffer (1.8 mL, pH 7.4) diluted with D₂O (0.2 mL). The two starting material signals (δ 13.02 and 12.67, relative to external 25% H₃PO₄) in nine spectra that were recorded during 1 h of reaction at 37 °C were used to obtain plots of $\ln(\% P)$ vs. time, where $\% P = [(\text{starting material signal intensity})/(\text{total signal intensity})] \times 100$; for δ 13.02, slope = $-2.04 \times 10^{-2} \text{ min}^{-1}$, correlation coefficient = 0.987; for δ 12.67, slope = $-1.72 \times 10^{-2} \text{ min}^{-1}$, correlation coefficient = 0.999. After 76% reaction (average for 9-CHA and 13-CHA), the combined signal intensity for 14/15 (δ 29.45, 29.05) was 30% of the total signal intensity. The NMR sample was then saturated with NaCl and extracted with CHCl₃ (1 mL, 2 times); MS, m/z 338 and 340 for 14 and m/z 339 and 341 for 15.

Anticancer Screening Tests. Male BDF₁ mice (6 weeks old) were given an inoculum of 1×10^5 L1210 cells on day 0, and the test compounds were administered (ip) on day 2 using groups of

six to seven mice and either 10% aqueous Me₂SO or corn oil as the vehicle. At a dose of 100 mg/kg, 1 in either vehicle gave an increased life span (ILS) of ~64%, relative to the control groups (14-18 mice), which received ip injections of either vehicle (5 mL/kg) on day 2. Compound 7 in 10% aqueous Me₂SO gave ILS values of 11.0, -0.7, and 3.2% at doses of 75, 150, and 300 mg/kg, respectively; 9/13-CHA (1:1) in corn oil gave ILS values of 4.9, 1.5, and 1.7% at doses of 25, 50, and 100 mg/kg.

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Antiinflammatory Properties of 8-Aryl-5-isopropyl-2H-1,3-dioxolo[4,5-g]quinazolin-6(5H)-ones and -thiones

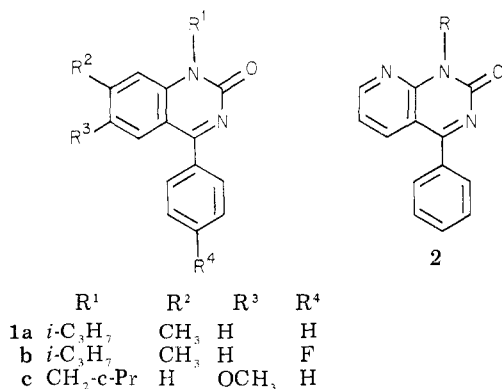
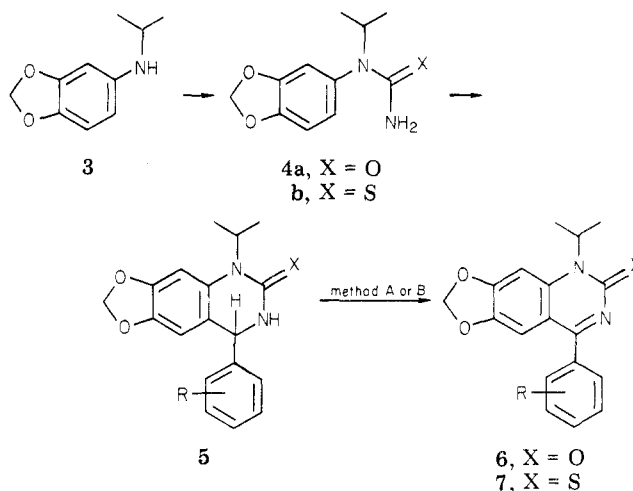
William J. Houlihan,* George Cooke, Richard Van Bochoven, John Perrine, Edward I. Takesue, and E. Jukniewicz

Sandoz, Inc., Preclinical Research, East Hanover, New Jersey 07936. Received February 16, 1982

A series of 8-aryl-5-isopropyl-2H-1,3-dioxolo[4,5-g]quinazolin-6(5H)-ones and -thiones was prepared and evaluated for antiinflammatory activity. The 8-phenyl-, 8-(3-fluorophenyl)-, and 8-(4-fluorophenyl)-2H-1,3-dioxolo[4,5-g]quinazolin-6(5H)-ones and the 8-phenyl-2H-1,3-dioxolo[4,5-g]quinazolin-6(5H)-thione were found to exhibit activity in the range of indomethacin and proquazone.

Since the early 1960's a considerable effort has been expended by medicinal chemists in developing aryl and aralkyl acids for use as nonsteroidal antiinflammatory drugs¹ (NSAIDs). In recent years a number of nonacidic agents, such as indoxole,² diftalone,³ and nictindole,⁴ have been found to exhibit an antiinflammatory profile similar to the acidic drugs.⁵ In our laboratories a search for nonacidic NSAIDs has led to the findings that 1-alkyl-4-aryl-2(1H)-quinazolinones^{6,7} (1) possess a good level of

Scheme I



antiinflammatory activity. From this series, the clinically useful proquazone⁸ (1a) and fluproquazone⁹ (1b) have been developed for treatment of rheumatoid arthritis and various types of pain, and the related ciproquazone¹⁰ (1c) has

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Table I. Carrageenin Edema Inhibition and Physical Properties for Compounds 6 and 7

no.	R	carr edema: ^a ED ₅₀ (%) inhibn, mg/kg, at 100 mg/kg po	method, ^a % yield	mp, °C (recrystn solvent) ^b	empirical formula	anal. ^c
6a	H	7	A, 86	193-194 (A)	C ₁₈ H ₁₆ N ₂ O ₃	C, H, N
6b	3-F	9	A, 78	182-183 (B)	C ₁₈ H ₁₅ FN ₂ O ₃	C, H, N
6c	4-F	8	A, 81	238-240 (C)	C ₁₈ H ₁₅ FN ₂ O ₃	C, H, N
6d	3,4-Cl ₂	(30)	A, 45	239-242 (D)	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₃	C, H, N
6e	2-CH ₃	65	A, 85	172-174 (A)	C ₁₉ H ₁₈ N ₂ O ₃	C, H, N
6f	4-CH ₃	(22)	A, 76	188-190 (A)	C ₁₉ H ₁₈ N ₂ O ₃	C, H, N
6g	3-OCH ₃	(12)	A, 78	189-191 (A)	C ₁₉ H ₁₈ N ₂ O ₄	C, H, N
6h	4-OCH ₂ C ₆ H ₅	(17)	A, 45	139-141 (C)	C ₂₅ H ₂₂ N ₂ O ₄	C, H, N
6i	3,4-OCH ₂ O	(21)	A, 80	234-235 (C)	C ₁₉ H ₁₆ N ₂ O ₅	C, H, N
6j	2-NO ₂	39	A, 80	191-193 (E)	C ₁₈ H ₁₅ N ₃ O ₅	C, H, N
6k	3-NO ₂	(28)	A, 70	218-219 (F)	C ₁₈ H ₁₅ N ₃ O ₅	C, H, N
6l	4-CO ₂ H	(33)	A, 62	277-280 (C)	C ₁₉ H ₁₆ N ₂ O ₅	C, H, N
7a	H	7	B, 52	202-205 (D)	C ₁₈ H ₁₆ N ₂ O ₂ S	C, H, N, S
7b	3-F	(36)	B, 45	214-216 (B)	C ₁₈ H ₁₅ FN ₂ O ₂ S	C, H, N, S
7c	4-F	(49)	B, 52	220-223 (D)	C ₁₈ H ₁₅ FN ₂ O ₂ S	C, H, N, S
7d	4- <i>i</i> -C ₃ H ₇	(10)	B, 51	169-170 (D)	C ₂₁ H ₂₂ N ₂ O ₂ S	C, H, N, S
7e	3-NO ₂	(0)	B, 40	193-196 (A)	C ₁₈ H ₁₅ N ₃ O ₄ S	C, H, N, S

^a See Experimental Section. ^b Recrystallization solvents: A, EtOAc; B, C₆H₆; C, *i*-PrOH; D, MeOH; E, Et₂O; F, EtOH.
^c Unless otherwise stated, the analyses are within ±0.4% of the theoretical value.

Table II. Carrageenan Edema Inhibition and Physical Properties for Compounds 5

no.	X	R	carr edema: ^a % inhibn at 100 mg/kg po	yield, %	mp, °C (recrystn solvent) ^b	empirical formula	anal. ^c
5a	O	H	59	52	175-177 (A)	C ₁₈ H ₁₈ N ₂ O ₃	C, H, N
5b	O	3-F	41	42	165-167 (B)	C ₁₈ H ₁₇ FN ₂ O ₃	C, H, N
5c	O	4-F	18	50	165-166 (A)	C ₁₈ H ₁₇ FN ₂ O ₃	C, H, N
5d	O	3,4-Cl ₂	3	44	155-157 (B)	C ₁₈ H ₁₆ Cl ₂ N ₂ O ₃	C, H, N
5e	O	2-CH ₃	50	64	155-157 (C)	C ₁₉ H ₂₀ N ₂ O ₃	C, H, N
5f	O	4-CH ₃	0	65	192-194 (B)	C ₁₉ H ₂₀ N ₂ O ₃	C, H, N
5g	O	3-OCH ₃	24	59	167-168 (B)	C ₁₉ H ₂₀ N ₂ O ₄	C, H, N
5h	O	4-OCH ₂ C ₆ H ₅	24	45	178-180 (D)	C ₂₅ H ₂₄ N ₂ O ₄	C, H, N
5i	O	3,4-OCH ₂ O	21	53	145-147 (E)	C ₁₉ H ₁₈ N ₂ O ₅	C, H, N
5j	O	2-NO ₂	0	56	202-205 (E)	C ₁₈ H ₁₇ N ₃ O ₅	C, H, N
5k	O	3-NO ₂	0	59	230-232 (A)	C ₁₈ H ₁₇ N ₃ O ₅	C, H, N
5l	O	4-CO ₂ H	0	58	270-271 (D)	C ₁₉ H ₁₈ N ₂ O ₅	C, H, N
5m	S	H	3	63	215-218 (B)	C ₁₈ H ₁₈ N ₂ O ₂ S	C, H, N, S
5n	S	3-F	26	55	200-203 (F)	C ₁₈ H ₁₇ FN ₂ O ₂ S	C, H, N, S
5o	S	4-F	5	39	197-200 (C)	C ₁₈ H ₁₇ FN ₂ O ₂ S	C, H, N, S
5p	S	4- <i>i</i> -C ₃ H ₇	4	64	152-155 (B)	C ₂₁ H ₂₄ N ₂ O ₂ S	C, H, N, S
5q	S	3-NO ₂	30	41	225-227 (G)	C ₁₈ H ₁₇ N ₃ O ₄ S	C, H, N, S

^a See Experimental Section. ^b Recrystallization solvent: A, 1-PrOH; B, MeOH; C, EtOAc; D, CH₂Cl₂-MeOH; E, Et₂O, F, dioxane-H₂O; G, C₆H₆. ^c See footnote c, Table I.

been reported to possess a useful antiinflammatory profile in animals.

Modification of the benzo ring in 1 to the pyrido analogue 2 resulted in considerable loss of activity relative to the carbon isosteres.¹¹

In the presence work we report that several 8-aryl-5-isopropyl-2*H*-1,3-dioxolo[4,5-*g*]quinazolin-6(5*H*)-ones (6) and -thiones (7) possess antiinflammatory activity in animals in the range of proquazone (1a).

Chemistry. Scheme I depicts the synthesis used to prepare the 8-aryl-5-isopropyl-2*H*-1,3-dioxolo[4,5-*g*]quinazolin-6(5*H*)-ones and -thiones reported in this paper. Treatment of the urea 4a or thiourea 5b with a benzaldehyde and a catalytic amount of methanesulfonic acid in refluxing toluene gave the 8-aryl-5-isopropyl-7,8-dihydro-2*H*-1,3-dioxolo[4,5-*g*]quinazolin-6(5*H*)-ones and -thiones 5 listed in Table II in 39-65% yields.¹² Oxidative

dehydrogenation of the 6-ones (5, X = O) with potassium permanganate (method A) in dioxane led smoothly to 6 (Table I) in 45-86% yields. The 6-thiones (5, X = S) were converted to 7 (Table I) by the use of activated manganese dioxide in methylene chloride.

Pharmacology. The antiinflammatory activity, as determined by the carrageenin foot edema¹³ assay for a series of selected derivatives of 5-7, is given in Tables I and II. The dihydro derivatives 5 at 100 mg/kg po in the rat are essentially devoid of activity, with the exception of compounds 5a (R = H) and 5e (R = 2-CH₃), where an ED₅₀ of ~100 mg/kg was found. Significant activity in the range of indomethacin and proquazone (1a) was found with several derivatives of 6 and 7. The compounds 6a

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(12) Additional examples and evidence for the mode of cyclization to 5 will be published by W. J. Houlihan, G. E. Cooke, M. Denzer, J. Nicoletti, and R. Van Bochoven.

(13) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).

Table III. Evaluation of the Antiinflammatory and Analgesic Activity of 8-Aryl-5-isopropyl-2H-1,3-dioxolo[4,5-*g*]quinazolin-6-(5H)-ones and -thiones^a

no.	carr edema, ^b mg/kg po		adjuvant arthritis, ^c mg/kg po	antibradycinin, ^d μ g/kg iv	Randall-Selitto, ^e mg/kg po
	normal	adrex			
6a	8	9	3	12	50
6b	9	14	9	50	11
6c	8	20	6	170	4
7a	7		6	47	
proquazone	5	6	1	10	1
indomethacin	5	6	0.1	320	4
phenylbutazone	25	30	5	> 1000	9

^a Numbers under columns are ED₅₀ values, except Randall-Selitto which is a minimum effect dose. ^b See Experimental Section. ^c Reference 14. ^d Reference 15. ^e Reference 16.

(R = H), **6b**, (R = 3-F), **6c** (R = 4-F), and **7a** (R = H) were selected for additional evaluation in order to define their spectrum of antiinflammatory activity (Table III). Antagonism of carrageenin-induced edema in adrenalectomized rats showed that compound **6a** had the same activity as seen in normal rats, while **6b** and **6c** suffered loss of activity, suggesting that some of their antiinflammatory activity may be mediated through the adrenals. All four compounds inhibited the development of adjuvant-induced polyarthritis in rats¹⁴ as effectively as phenylbutazone, but considerably weaker than indomethacin. The bronchoconstrictor effects of bradykinin¹⁵ were inhibited by **6a-c** and **7a** at doses considerably lower than those required by the three standard drugs. The nonnarcotic analgesic effects, as measured in the Randall-Selitto¹⁶ test, indicate that **6c** is as effective as indomethacin, **6b** was in the range of phenylbutazone, and **6a** was considerably weaker. Compound **6c** has been selected for further development as an antiinflammatory agent.

Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For all compounds listed in Tables I and II, ¹H NMR spectra were obtained on a Varian Associates A-60 spectrometer in CDCl₃ or Me₂SO-*d*₆, and IR spectra (KBr) were determined with a Perkin-Elmer Infracord. In all cases, the spectra were consistent with the assigned structure. Thin-layer chromatography (TLC) was carried out on compounds listed in Tables I and II using glass plates coated with silica gel HF-254 (E. Merck AG) with the solvent system CHCl₃-MeOH (9:1) for the purpose of establishing homogeneity.

N-Isopropyl-3,4-(methylenedioxy)aniline (3). A solution containing 24 g (0.20 mol) of 3,4-(methylenedioxy)aniline (mp 37 °C), 15.1 mL (26.7 g, 0.16 mol) of isopropyl iodide, 21.2 mL (15.4 g, 0.15 mol) of triethylamine, and 200 mL of CH₃OH was refluxed for 52 h. The solvent was removed in vacuo, and the residue was treated with 100 mL of H₂O and 150 mL of C₆H₆. The C₆H₆ layer was separated, dried with anhydrous MgSO₄, filtered, and distilled to give 19.5 g (74%) of **3** as an oil. Anal. (C₁₀H₁₃NO₂) C, H, N.

N-Isopropyl-N-[3,4-(methylenedioxy)phenyl]urea (4a). A solution of 14.7 g (0.08 mol) of **3** in 200 mL of HOAc maintained at 15 ± 5 °C was treated portionwise with 4.9 g (0.075 mol) of sodium isocyanate. After the solution was stirred for 15 h at room temperature, the solvent was removed in vacuo, and the solid residue was treated with 300 mL of 2 N NaOH and 250 mL of CHCl₃. The CHCl₃ layer was washed with H₂O, dried with anhydrous MgSO₄, and concentrated in vacuo to give 13.65 g (82%)

of **4a**, mp 116–119 °C (cyclohexane). Anal. (C₁₁H₁₄N₂O₃) C, H, N.

N-Isopropyl-N-[3,4-(methylenedioxy)phenyl]thiourea (4b). A mixture of 17.3 g (0.12 mol) benzoyl chloride and 13.6 g (0.17 mol) anhydrous sodium isothiocyanate was stirred and refluxed for ~3 h. The mixture was allowed to come to room temperature and then filtered, and the filtrate was treated dropwise with a solution of 28.6 g (0.16 mol) of **3** in 150 mL of dry C₆H₆. After the solution was stirred for ~30 min, the solid was filtered off and recrystallized from C₆H₆ to give 29 g (71%) of *N*-isopropyl-*N*-[3,4-(methylenedioxy)phenyl]-*N'*-benzoylthiourea (**8**), mp 152–154 °C. Anal. (C₁₈H₁₈N₂O₃S) C, H, N, S.

To a solution of 27 g (0.68 mol) of NaOH in 45 mL of dioxane and 200 mL of H₂O there was added portionwise 17 g (0.05 mol) of **8**. The mixture was stirred and refluxed for 48 h and then allowed to come to room temperature. The resultant solid was filtered off and recrystallized from C₆H₆ to give 8.9 g (75%) of **4b**, mp 149–151 °C. Anal. (C₁₁H₁₄N₂O₂S) C, H, N, S.

8-Aryl-5-isopropyl-7,8-dihydro-2H-1,3-dioxolo[4,5-*g*]quinazolin-6(5H)-ones and -thiones (5). General Procedure. A solution of 0.05 mol of **4a** or **4b**, 0.06 mol of benzaldehyde, 0.5 mL of CH₃SO₃H, and 250 mL of toluene was stirred and refluxed for ~21 h in a flask equipped with a Dean-Stark water separator. The cooled solution was washed with 200 mL of H₂O, dried with anhydrous MgSO₄, and filtered, and the filtrate was concentrated in vacuo. The resultant solid was decolorized if necessary in hot propanol with activated charcoal and then recrystallized from an appropriate solvent. Compounds **5a-q** prepared by this procedure are listed in Table II.

8-Aryl-5-isopropyl-2H-1,3-dioxolo[4,5-*g*]quinazolin-6(5H)-ones (6). General Procedures.¹⁷ **Method A.** A stirred solution of 0.025 mol of **5** (X = O) in 225 mL of dioxane was cooled to 10–15 °C and then was treated with a solution of 0.03 mol of KMnO₄ in 185 mL of H₂O. After the addition was completed, 2 mL of 37% formaldehyde was added, and the solids were removed by filtration. The filtrate was concentrated in vacuo, and the residue was dissolved in hot ethyl acetate, treated with charcoal, and recrystallized from the appropriate solvent (Table I). Compounds **6** prepared by this procedure are listed in Table I.

8-Aryl-5-isopropyl-2H-1,3-dioxolo[4,5-*g*]quinazolin-6(5H)-thiones (7). General Procedures.¹⁷ **Method B.** A mixture of 2.0 g of **5** (X = S), 4.0 g of activated MnO₂, and 50 mL of CHCl₃ was vigorously stirred for ~48 h at room temperature. The solids were filtered off, and the filtrate was concentrated in vacuo. The residue was crystallized from an appropriate solvent (Table I) or chromatographed on silica gel (C₆H₆ eluent) if unreacted **5** was detected by TLC analysis. Compounds prepared by this method are listed in Table I.

Carrageenin-Induced Paw Edema in Normal and Adrenalectomized Rats. The method described by Winter¹³ was employed. The compound to be evaluated was administered orally to male Wistar rats (150–175 g of body weight) in a suspension of 0.5% carboxymethylcellulose (CMC) 1 h before the subplantar injection of 0.1 mL of 1% Type 402 carrageenin (Marine Colloids, Springfield, NJ). The dose of the compound to be tested was administered on a milligram per kilogram basis in a volume of

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(17) G. A. Cooke and W. J. Houlihan, U.S. Patent 3 748 342 (1973).

1 mL per kilogram of body weight. Three hours later, the ensuing edema was measured by electronic plethysmographic procedures. The amount of paw swelling (3 h minus 0 h value) was determined for each rat, and the mean value in the substance-treated animals was expressed as a percentage of the mean value obtained in the vehicle-treated controls. The method described above was utilized with the exception that the rats were bilaterally adrenalectomized under ether anesthesia and allowed to recuperate for 7 days prior

to use. Adrenalectomized rats received 1.0% sodium chloride and 2.5% dextrose in their drinking water, together with the standard lab chow diet.

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Book Reviews

Concepts in Drug Metabolism. Parts A and B. Edited by Peter Jenner and Bernard Testa. Marcel Dekker, New York. Part A: 1980. xi + 409 pp. 16 × 24 cm. \$49.50. Part B: 1981. x + 627 pp. 16 × 24 cm. \$65.00.

Part A of this two-volume set contains a number of chapters that should be of particular interest to those medicinal chemists who include drug metabolism among their principal or ancillary activities. An extensive chapter (123 pages) by Testa and Jenner explores "A Structural Approach to Selectivity in Drug Metabolism and Disposition". Topics included in this presentation are substrate regioselectivity, substrate stereoselectivity, product regioselectivity, product stereoselectivity, and the application of quantitative structure-activity relationships in drug metabolism and disposition. Similarly, Trager's chapter entitled "Oxidative Functionalization Reactions" includes discussions of stereoselectivity and regioselectivity in monooxygenase-mediated reactions, as well as a rather detailed analysis of the concept of the oxenoid mechanism. An appreciation of the concepts presented in these two chapters, in conjunction with a knowledge of the potential toxicity of certain types of metabolites, should be of value to medicinal chemists who wish to incorporate metabolic principles into their approach to drug design.

Part A also contains a concise and useful review of the biochemistry and significance of conjugation reactions by Caldwell, as well as chapters on analytical techniques, extrahepatic drug metabolism, and developmental drug metabolism. The final chapter focuses upon the use of metabolite data in the evaluation of pharmacokinetics.

The first chapter of Part B is a review by Parke of the normal physiological functions of the endoplasmic reticulum (glycoprotein synthesis, lipid metabolism, cholesterol biosynthesis, etc.) and the pathological changes that occur when the endoplasmic reticulum is damaged as a result of aging or as a result of exposure to environmental chemicals. This chapter is followed by Mantering's comprehensive review (113 pages, 499 references) entitled "Hepatic Cytochrome P-450-Linked Drug-Metabolizing Systems". In this chapter the characteristics, functions, and interactions of the components of the monooxygenase system are considered with a particular emphasis being placed on cytochrome P-450 multiplicity.

The chapter titled "Toxication and Detoxification as a Result of Xenobiotic Metabolism" consists primarily of brief but lucid reviews of the metabolic activation and deactivation of paracetamol (acetaminophen), phenacetin, benzo[*a*]pyrene, 2-(acetylaminofluorene and allyl alcohol. This presentation provides a useful introduction to the principles of metabolic toxication but it is not an in-depth treatment of the subject. Other chapters in Part B emphasize such topics as the relevance of enzyme induction and inhibition of drug action, the genetic aspects of drug metabolism, evolutionary consideration of drug metabolism and drug toxicity, the in vivo assessment of hepatic drug disposition, and altered drug disposition in disease states. The authors of the latter chapter conclude that the effects of disease states on protein binding, absorption, distribution, and elimination may be of greater relevance to alterations of drug actions than are the effects of disease states on drug metabolism. The final chapter, a philosophical discourse entitled "Xenobiotic Metabolism:

Necessity, Chance, Mishap, or None of the Above?", raises some intriguing questions for which there may be no definitive answers.

There are certain topics that are covered in various degrees of depth in several chapters. Among the more prominent examples are induction and inhibition of cytochrome P-450, the multiplicity of cytochrome P-450, and metabolic activation as it relates to toxicity and carcinogenicity. As the editors point out in the preface, such overlap is unavoidable, and in some respects even desirable, if the goal of presenting a conceptual approach to major topics in drug metabolism and allied fields is to be achieved.

Both Parts A and B cover the literature through 1978 and a number of chapters cite papers that were published in 1979. These books constitute an important contribution to the literature of drug metabolism and they should serve as highly useful resources to anyone who is interested in the field. "Concepts in Drug Metabolism" is worthy of occupying space on the shelf next to the invaluable "Drug Metabolism: Chemical and Biochemical Aspects", which was published by Testa and Jenner in 1976.

Departments of Medicinal Chemistry Patrick E. Hanna
and Pharmacology
College of Pharmacy and
Medical School
University of Minnesota
Minneapolis, Minnesota 55455

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Calmodulin is a ubiquitous intracellular protein which binds calcium ions and functions as one of several pathways for the expression of Ca²⁺-mediated effects. Research interest in calmodulin is expanding at a rapid pace. This volume will certainly be the last to review the broad scope of calmodulin roles in under 500 pages at a price under \$100. We will no doubt look forward to future volumes, each of which will deal with only one of the 30 or so major aspects outlined in this work.

This volume provides a summary of the 1980 New York Academy of Sciences conference of the same name. As is the custom for the annals from such conferences, there are about 30 papers of substantial size (average size = 12 pages) and abstracts of poster sessions (44 in number). Papers have been divided into six sections: (1) Biochemistry of Calmodulin; (2) Calmodulin and Supramolecular Structures; (3) Protein Phosphorylation and Calmodulin; (4) Cyclic Nucleotides and Calmodulin; (5) Membrane Transport and Calmodulin; (6) Cellular Receptors and Calmodulin. The contributors are an absolutely outstanding collection of investigators in each of these areas, including C. Y. Cheung, one of two individuals credited with the "definitive" recognition of calmodulin.

Hypotheses for the involvement of calmodulin in cellular regulation abound. However, true to the inquisitive basis of science, more new questions are raised than are answered. For instance, the activation of phosphodiesterase activity and inhibition (or activation) of adenylate cyclase by calmodulin has fueled further interest in the complex manner in which these two