4-Phenylsulfenyl-*o*-phenylenediamine (3b). A solution of 2-amino-4-phenylsulfenylnitrobenzene (**2b**) (1.8 g, 0.007 mol) in methanol (160 ml) and water (40 ml) containing ferrous sulfate heptahydrate (1.0 g, 0.004 mol) was refluxed and treated with iron powder (2.0 g). Two further portions of iron were added at 2 and 4 hr. The reaction was finished in ~5–6 hr, when insoluble material was filtered off. The filtrate was evaporated and the residue taken up in benzene. The benzene solution was filtered and evaporated, leaving the diamine **3b** as a gum (1.4 g, 90%) which later crystallized: mp ~53–55°.

Methyl 5(6)-Phenylsulfenyl-2-benzimidazolecarbamate (1b). 4-Phenylsulfenyl-o-phenylenediamine (**3b**) (0.7 g, 0.0032 mol) was treated with 1,3-bis(methoxycarbonyl-*S*-methyl)isothiourea (110%), as described for the preparation of the sulfoxide **1a**. Recrystallization from methanol–chloroform gave the benzimidazole **1b**: mp 243° dec. Anal. ($C_{15}H_{13}N_3O_2S$) C, H, N.

2-Amino-4-phenylsulfonylnitrobenzene (2c). A mixture of 5-chloro-2-nitroaniline (2.0 g, 0.011 mol) and sodium benzenesulfinate (5.0 g, 0.03 mol) in dimethylformamide was heated at ~150–160° for 3.5 hr. After cooling, the mixture was diluted with water and the product filtered off: mp 180–182.5° (3.0 g, 98%).

4-Phenylsulfonyl-*o*-phenylenediamine (3c). A solution of the nitroamine **2c** (1.9 g, 0.007 mol) in methanol was hydrogenated at 3 atm of pressure in the presence of Raney nickel catalyst for 2 hr at 20°. The catalyst was filtered off and the filtrate evaporated. The residue was recrystallized from benzene, yielding pure diamine **3c** (1.53 g, 90%): mp 112.5–113.5°.

Methyl 5(6)-Phenylsulfonyl-2-benzimidazolecarbamate (1c). 4-Phenylsulfonyl-o-phenylenediamine (**3c**) (0.75 g, 0.03 mol) was treated with 1,3-bis(methoxycarbonyl-*S*-methyl)isothiourea (0.68 g, 0.033 mol), as described above for the preparation of **1a**. Recrystallization from methanol–chloroform gave the pure benzimidazole **1c**: mp >320° (0.86 g, 87%). Anal. ($C_{15}H_{13}N_3SO_4$) C, H, N. This compound may also be prepared by the oxidation of the sulfoxide **1a** or the sulfide **1b** with peracetic acid (1 and 2 equiv, respectively) in chloroform–acetic acid. Solvent is removed by evaporation under vacuum and the residue treated with sodium bicarbonate solution. The product is filtered off, washed with water, and recrystallized from methanol–chloroform.

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(7) Inserted in an oil bath at ~250°, the melting point is ~253° dec, followed by resolidification, then remelting at ~275–278°; the initial decomposition at ~253° is not apparent if the sample is inserted in the oil bath below about 245°.

Synthesis and Antibacterial Properties of Methylsulfinyl and Methylsulfonyl Analogs of Some Nitrofurans[1]

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The sulfoxides 5-methylsulfinyl-2-furaldehyde semicarbazone (**2**) and 1-[(5-methylsulfinyl-2-furfurylidene)amino]hydantoin (**3**) as well as the sulfones 1-[(5-methylsulfonyl-2-furfurylidene)amino]hydantoin (**1**) and 1-(5-methylsulfonyl-2-furyl)-2-(6-amino-3-pyridazyl)ethylene hydrochloride (**4**) have been prepared and tested for antibacterial activity against a number of gram-negative and gram-positive organisms. The compounds are much less active than the corresponding 5-nitrofuran derivatives, possibly because their reduction potentials are too negative for them to interfere with reductive enzyme systems within the bacteria.

During the past three decades, numerous derivatives of 5-nitrofuran substituted at the 2 position have been prepared, many of them with high antibacterial activity.[2] More recently, analogs of the more active nitrofurans have been prepared in which the nitro group has been replaced by other electronegative groups such as trifluoromethyl,[3] aryl-, aralkyl- and alkylsulfonyl,[4-6] cyano[7,8] and sulfo, sulfamoyl, carboxyl, methoxycarbonyl, and carbamoyl.[8] None of these compounds were reported to possess significant antibacterial activity, although bactericidal properties have been claimed for the methylsulfonyl analog of nitrofurantoin (**1**) and certain of its derivatives.[9]

Nitrofurans are reduced by a number of enzyme systems present in bacteria[10,11] and the ease of reduction of the nitro group may be correlated to the antibacterial activity.[12] We considered that analogs of nitrofurans containing a reducible group with similar electronic properties to nitro might possess antibacterial activity and have therefore prepared two compounds containing a sulfoxide group, namely the methylsulfinyl analogs of nitrofurazone and nitrofurantoin (compounds **2** and **3**), respectively. The methylsulfonyl analogs of nitrofurantoin and nifurprazine, a nitrofuran of the vinylogous imine type with enhanced bacterial activity,[13] have also been prepared (compounds **1** and **4**, respectively).

Synthesis. The nitrofurazone and nitrofurantoin analogs (Table I) were prepared by condensing the appropriate furaldehyde with semicarbazide or 1-aminohydantoin.[14] In order to prepare 5-methylsulfinyl-2-furaldehyde (**5**), 5-bromo-2-furaldehyde was converted to the methylmercaptan[4] which was oxidized to the sulfoxide with sodium periodate. The methylsulfonyl analog of nifurprazine (**4**, Table I) was prepared by condensing 5-methylsulfonyl-2-furaldehyde[5] with 3-acetamido-6-methylpyridazine[15] in the presence of $AcOH–Ac_2O$ followed by removal of the acetyl group by acidic hydrolysis. An attempt to prepare the methylsulfinyl analog of nifurprazine by this procedure was unsuccessful.

Antibacterial Activity. The compounds were tested for antibacterial activity in vitro using a standard agar dilution technique[16] against a number of gram-negative and gram-positive organisms including *Escherichia coli*, *Klebsiella*

Table I. Methylsulfinyl and Methylsulfonyl Analogs of Nitrofurans

R_1–(furan)–$CH{=}R_2$

Compd	R_1	R_2	Mp, °C	Purificn solvent	Formula	Analyses
1	CH_3SO_2	N-(2,5-dioxoimidazolidin-1-yl) (N=)	273–276[a]	DMF–H_2O		
2	CH_3SO	$NNHCONH_2$	177–179	CH_3OH	$C_7H_9N_3O_3S$	C, H, N, S
3	CH_3SO	N-(2,5-dioxoimidazolidin-1-yl) (N=)	223–224	CH_3OH	$C_9H_9N_3O_4S$	C, H, N, S
4	CH_3SO_2	CH–(6-amino-3-pyridazinyl) (NH_2)	247–250 dec[b]		$C_{11}H_{11}N_3O_3S \cdot HCl$	C, H, N, S, Cl

[a]Reference 9, mp 275–276°. [b]Hydrochloride.

pneumoniae, *Proteus vulgaris*, *Diplococcus pneumoniae*, *Staphylococcus Oxford*, and *Streptococcus faecalis*. None of the compounds possess significant antibacterial activity.

Discussion

Aryl sulfoxides and aryl sulfones are known to undergo electroreduction to the corresponding thioethers and arylsulfinic acids, respectively.[17] However, the reactions are less facile than electroreduction of nitroaryls since the polarographic half-wave potentials of the sulfoxides and sulfones are of the order of −2 V,[17] which is appreciably more negative than those of nitro compounds.[12] Thus, even if methylsulfinyl and methylsulfonyl analogs of antibacterially active nitrofurans are able to reach and bind with the essential enzymes within the bacteria, their reduction potentials may be too negative for them to interfere with the reductive enzyme systems.

Experimental Section

Melting points were determined in open glass capillaries on a Büchi apparatus and are uncorrected. Elemental analyses within ±0.4% of the theoretical values are indicated by the symbols of the elements. The structures of the compounds were supported by their ir spectra (KBr) recorded on a Perkin-Elmer Model 720 spectrophotometer. Mass spectra were recorded on a LKB 9000 instrument at 70 eV and the NMR spectra on a Varian T-60 instrument with Me_4Si as internal standard. TLC was carried out on precoated Merck silica gel F_{254} plates.

Preparation of Azomethines 1–3. General Procedure. An aqueous solution of the hydrochloride of the appropriate *N*-amino compound was buffered to pH 4–5 by addition of NaOAc and an equivalent amount of aldehyde dissolved in H_2O or EtOH was added. The solution was stirred at room temperature until the product had crystallized, whereupon it was collected by filtration and recrystallized from a suitable solvent (Table I). Yields varied from 50 to 80%.

5-Methylsulfinyl-2-furaldehyde (5). 5-Methylthio-2-furaldehyde[4] (3.3 g, 0.023 mol) was added to a solution of sodium periodate (5.2 g, 0.024 mol) in 50 ml of H_2O and the mixture stirred at 0°C for 20 hr and then at room temperature for 2 hr. The suspension was filtered and the filter cake washed with CH_2Cl_2. After extraction of the filtrate with CH_2Cl_2, the organic phase was combined with the washings and washed with $NaHCO_3$ solution and H_2O and then dried over Na_2SO_4. On evaporation of the solvent, a pale yellow oil remained which was distilled in vacuo and a fraction, bp 130–140° (0.2 mm) (1.7 g, 49%), was collected which crystallized on standing: mp 38–40°. Two recrystallizations from toluene raised the mp to 43–44°: ir 1680 (aldehyde C=O), 1050 cm^{-1} (sulfoxide); NMR ($CDCl_3$) δ 3.03 (s, 3, CH_3), 7.11 and 7.34 (AB system, 2, J = 3.5 Hz, furan H), and 9.79 ppm (s, 1, aldehyde H). Anal. ($C_6H_3O_3S$) C, H, S.

1-(5-Methylsulfonyl-2-furyl)-2-(6-acetamido-3-pyridazyl)ethylene (6). A solution of 5-methylsulfonyl-2-furaldehyde[5] (1.15 g, 6.6 mmol) and 3-acetamido-6-methylpyridazine[15] (1.0 g, 6.6 mmol) in a mixture of 9 ml of AcOH and 9 ml of Ac_2O was heated at 160° for 3 hr. After removal of the solvent in vacuo, the residue was dissolved in H_2O and neutralized with $NaHCO_3$ solution containing a little concentrated aqueous NH_3. The precipitate was collected by filtration and dried in vacuo. The solid was triturated with boiling dioxane. The dioxane solution was treated with active charcoal and concentrated and EtOAc was added, whereupon a precipitate was formed: mp 270–272° (0.19 g, 10%); ir 3400 (NH), 1690 (amide I), 1520 (amide II), 1320, 1125 cm^{-1} (SO_2); mass spectrum *m/e* (rel intensity) 307 (M^+, 13), 265 (5), 228 (6), 186 (100), 158 (7), 131 (18), 102 (11), 77 (6), 63 (5), 51 (8), and 43 (34). On TLC (EtOAc–Me_2CO, 1:1) the product gave one spot (R_f 0.5). It was hydrolyzed directly without further purification.

1-(5-Methylsulfonyl-2-furyl)-2-(6-amino-3-pyridazyl)ethylene Hydrochloride (4). Compound 6 (0.20 g, 0.65 mmol) was heated at 100° with 6 ml of 5 *N* HCl for 1 hr. The resulting solution was cooled in an ice bath whereupon the product crystallized and was collected by filtration and dried in vacuo: yield 0.10 g (51%); TLC of the free base (EtOAc–Me_2O, 1:1) showed one spot (R_f 0.2); mass spectrum *m/e* (rel intensity) 265 (M^+, 24), 186 (100), 158 (9), 131 (41), 102 (5), 77 (11), 63 (15), and 51 (13); NMR (Me_2SO-d_6) δ 3.38 (s, 3, CH_3), 7.04 and 7.37 (AB system, 2, J = 3.5 Hz, furan H), 7.20 and 7.58 (AB system, 2, J = 16.5 Hz, *trans*-CH=CH), and 7.61 and 8.28 ppm (AB system, 2, J = 9.5 Hz, pyridazine H).

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Book Reviews

Insect Hormones and Bioanalogues. By K. Sláma, M. Romaňuk, and F. Šorm. Springer-Verlag. New York and Vienna. 1974. 477 pp. $45.90.

This important book includes a synthesis of insect endocrinology based on years of thinking about insect hormones by Karel Sláma of the Entomological Institute of the Czechoslovak Academy of Sciences. It is written in three sections: a survey of the neuroendocrine system in insects, a discussion of the chemistry and physiology of juvenoid compounds, and a similar, shorter discussion of ecdysoids. Sláma covers the biological material while the chemistry is described by Romaňuk and Šorm. The book ends with an appendix giving the effects of 353 juvenoids on a variety of insects in the laboratory. Much of this is previously unpublished material. This book should be a valuable reference for those considering the use of insect hormones as pesticides since, in addition to a comprehensive listing of bioanalogs, it also describes bioassays in detail.

Sláma's observations on insect endocrinology are clearly based on a vast amount of experience. He strongly emphasizes the point that the role of the juvenoids and ecdysoids in insect development is concerned with the expression of information already programmed at the cellular level and that these hormones serve chiefly to align the insect's developmental processes with the external environment. That is, that the ecdysoids and juvenoids are timing rather than scheduling devices.

In this respect it may be noted that in a recent paper [*J. Insect Physiol.*, **21**, 921–955 (1975)] he attacks a popular concept, that the kind of morphogenesis which occurs in an insect depends primarily on the level of juvenile hormone at the time of a moult (a concept which would allow easy reversal of differentiation), and cites instead experiments which show that in insects, as in vertebrates, differentiation proceeds in the direction of progressive limitation of the options available to a cell.

Other valuable aspects of this book include Sláma's discussions of insect endocrinology in terms of a wide variety of insect types, a technique which separates the idiosyncratic results from general principals of insect physiology, and the extensive bibliographies which include European references often overlooked in American reviews.

Since this is a valuable (and expensive) book for workers in the field of insect hormones, it is unfortunate that the proofreading is sloppy and that ungrammatical phrases are allowed to mar an otherwise powerful exposition. Material discussed in this book covers papers published up to the year 1971 with additional references for 1972.

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Drug Disposition and Pharmacokinetics. By Steven H. Curry. Blackwell Scientific Publications, Oxford, London, Edinburgh, and Melbourne. 1975. 214 pp. 15.5 × 23 cm. $17.50.

This book summarizes much of the literature in the areas of drug metabolism and pharmacokinetics. It is intended to be useful to a diversified audience, from students to active researchers concerned with the rational investigation and application of drugs. The text discusses numerous aspects of drug disposition such as bioavailability, compartmental behavior, drug interactions, protein binding, and the factors which influence renal excretion. It has several worthwhile chapters describing the qualitative features of these and related topics. However, other characteristics of the book limit its utility. These include: (1) a style of referencing which makes it very difficult to locate sources of information; (2) a pharmacokinetics section which contains few detailed derivations and dwells upon the calculation of absorption rate constants while neglecting useful approaches to data analysis and blood level prediction such as superposition and clearance concepts; and (3) a chapter which summarizes metabolic reactions but does not identify the animal species in which the transformation was observed or state the relative importance of the pathway being discussed.

For these reasons, this book would seem to be a satisfactory guide to researchers who need to appreciate the qualitative aspects of pharmacokinetics and drug metabolism. Furthermore, it would be useful as a text in an introductory course in these fields. However, it seems to lack the quantitative detail and referencing necessary for use in more advanced courses. The book itself is reasonably free of typographical errors and the chapters are arranged in a logical fashion.

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Advances in Drug Research. Volume 9. Edited by N. J. Harper and A. B. Simmonds. Academic Press, London, New York, San Francisco. 1974. 142 pp. 23.5 × 15.5 cm. $12.25.

Six contributors, including R. Howe of the Imperial Chemical Industries, E. M. Jepson of the Central Middlesex Hospital, D. Kritchevsky of the Wistar Institute, J. R. Parrott of the Royal College, University of Strathclyde, E. M. V. Williams of the University of Oxford, and K. W. Walton of the University of Birmingham, have reviewed the physiological, pharmacological, and clinical aspects of ischemic heart disease in this volume. The first chapter (6 pp) by Jepson is concerned with the clinical management of the disease and involves a discussion of risk factors, clinical management of hyperlipoproteinemia, and preventive measures. Although most of the information found in this section is also available in greater detail in other works, this chapter represents a concise discussion of what is generally known about the management of a very complicated disease state.

The chapter by Howe on hypolipidemic agents (37 pp) follows. After a brief discussion concerning the significance of serum lipoproteins, the important clinically useful drugs as well as many of those having theoretical significance are discussed. Compounds are generally classified according to their "possible" modes of action and the enzyme systems which they are known to affect. This section is well referenced through 1971 and partially into 1972 but should not be considered as complete or exhaustive. Reasons why certain compounds did not become clinically useful are presented. Many of the interesting stereostructure–activity relationships are summarized. Since the more recent literature is not considered in this chapter, readers of this monograph would find it beneficial to reevaluate certain proposed mechanisms of action in light of more recent reports. Also, many of the results of the Coronary Drug Project Research Group are now available. This chapter could serve as an excellent starting point for investigators who previously have not worked in this area and are interested in the design and synthesis of antilipidemic drugs.

Next, Kritchevsky discusses various animal models for atherosclerosis (13 pp). Medicinal chemists will find the summary of various animal models, including dogs, rats, chickens, pigeons, pigs, rabbits, and primates, interesting and informative. When applicable, disadvantages to a particular model are described. Clearly, no animal model meets the needs of every objective. As Kritchevsky points out, "the search for a suitable animal model . . . continues;