Journal of Medicinal Chemistry, 1972, Vol. 15, No. 3 339

New Compounds

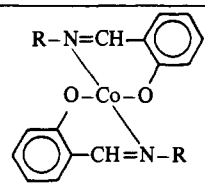
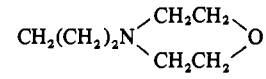
Cobalt Derivatives of Schiff Bases of Aliphatic Amines as Antitumor Agents

Ernest M. Hodnett* and William J. Dunn, III

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma. *Received September 21, 1971*

Some Schiff bases, R'CH=NR, are known to slow the growth of several animal tumors.[1,2] Some metal chelates have shown good antitumor activities against animal tumors.[1,3] Metal ions are known to affect the antitumor activities of the bis(thiosemicarbazones) of pyruvaldehyde[4] and of 3-ethoxy-2-oxobutyraldehyde (ketoxal).[5] New information has been obtained on some Co II derivatives of Schiff bases of salicylaldehyde that were prepared earlier,[1] including their activities against the im Walker sarcoma of the rat.[6] Results of screening tests on these compounds (Table I) show that most of these compounds have significant activity in this tumor system. The antitumor activities of these compounds are measured with difficulty because of their low solubilities in both aqueous and organic media. Since they are administered as suspensions, the particle size may affect their antitumor activities.

Table I. Activity against Intramuscular Walker Sarcoma of the Rat[a]

R	Dose,[b] mg/kg	T/C
		
$(CH_2)_2CH_2OH$	37.5	0.21
	18.8	0.38
	9.4	0.62
$C(CH_3)_2CH_2OH$	100	0.24
	50	0.55
	25	0.64
	12.5	0.89
$C(CH_3)(CH_2OH)_2$	100	0.56
	50	0.78
$C(C_2H_5)(CH_2OH)_2$	200	0.38
	100	0.61
	50	0.60
$CH_2CH_2OC_2H_5$	100	0.43
	50	0.97
$CH_2(CH_2)_2NH(CH_2)_2OH$	100	0.43
	50	0.85
	25	0.92
	50	0.29
	25	0.76
	12.5	0.93

[a]The screening data were supplied through the kindness of Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. Assays were performed according to CCNSC specifications.[6] [b]One dose daily for 4 days, administered ip.

Acknowledgment. We thank Joyce Wan and John Lay for preparing and analyzing some of these compounds and the American Cancer Society for financial support through an Institutional Grant to Oklahoma State University.

References

(1) E. M. Hodnett and W. Willie, *Proc. Okla. Acad. Sci.*, **46**, 107 (1966).
(2) J. H. Billman, F. Koehler, and R. May, *J. Pharm. Sci.*, **58**, 767 (1969); E. M. Hodnett and W. J. Dunn, *J. Med. Chem.*, **13**, 768 (1970); E. M. Hodnett and P. D. Mooney, *ibid.*, **13**, 786 (1970).
(3) S. Kirschner, Y.-Y. Wei, D. Francis, and J. G. Bergman, *ibid.*, **9**, 369 (1966).
(4) H. G. Petering, H. H. Buskirk, and J. A. Crim, *Cancer Res.*, **27**, 1115 (1967).
(5) J. G. Cappuccino, S. Banks, G. Brown, M. George, and G. S. Tarnowski, *ibid.*, **27**, 968 (1967).
(6) Cancer Chemotherapy National Service Center (CCNSC), *Cancer Rep.*, **25**, 1 (1962).

An Improved Synthesis of the Antibiotic, Hexahydrospinamycin

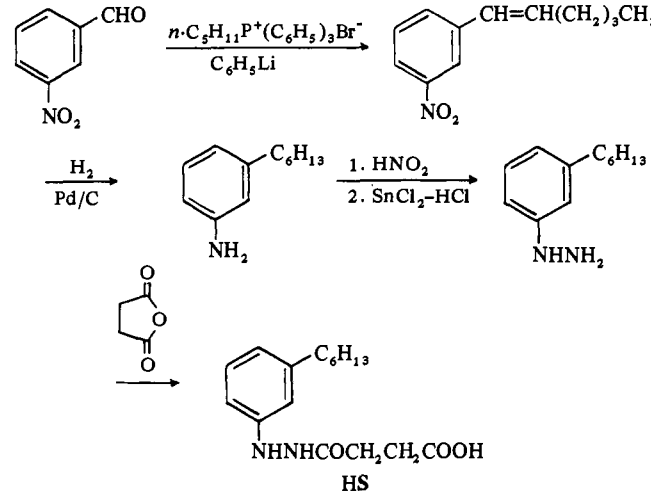
Tetsuo Miyadera† and Edward M. Kosower*

Department of Chemistry, State University of New York, Stony Brook, New York 11790. *Received August 6, 1971*

An interesting antibiotic, spinamycin, was isolated by Umezawa and his group from cultures of a new organism, *Streptomyces albospinus.*[1] Physical data and synthesis of the hexahydro derivative (HS) demonstrated the structure to be 1-(*m*-1,3,5-hexatrienylphenyl)-2-succinoylhydrazine.[2] In connection with efforts to learn something about the mechanism by which spinamycin exerts its antibiotic effect,[3] we have developed an improved synthesis of the hexahydro derivative. The antifungal activity of hexahydrospinamycin and analogs has been described in the accompanying paper.[3] Our synthesis is not only simpler, shorter and more effective than that previously reported,[2] but is suitable for the preparation of alkyl group variants.

The synthetic scheme is outlined below.

Structures were confirmed by ir and nmr spectra. The melting point and solubility behavior of hexahydrospinamycin agreed with that reported.[2]



Experimental Section

3-Nitro-(1-hexenyl)benzene. PhLi [from Li (0.160 g-atom, 1.11 g) and PhBr (0.08 mole, 12.56 g)] in Et_2O (75 ml) was added to a suspension of *n*-pentyl triphenylphosphonium bromide (0.08 mole, 33.04 g) in THF (200 ml). A soln of 3-nitrobenzaldehyde (0.08 mole, 12.08 g) in THF (50 ml) was added to the phosphorane soln with ice cooling. After stirring for 24 hr, H_2O and Et_2O were

†On leave from Central Research Laboratories, Sankyo Co., Tokyo, Japan.

added, the org layer was sepd, shaken with satd $NaHSO_3$ soln, and then washed (H_2O). The Et_2O layer was dried (Na_2SO_4), the solvent removed, petr ether added, the soln filtered from insol material, the solvent evapd, and the residue distd to give an oil. Redistn gave a pale yellow oil (8.20 g, 50%), bp 120–124° (0.7 mm).

3-*n*-Hexylaniline. 1-(3-Nitrophenyl)hexene-1 (7.60 g) was hydrogenated over 10% Pd/C (300 mg) in EtOH (50 ml). The mixt was worked up as usual to give a colorless oil (6.05 g, 92%), bp 108° (0.7 mm).

3-*n*-Hexylphenylhydrazine. (Standard procedures give much lower yields.) A soln of $NaNO_2$ (9.94 mmoles, 686 mg) in H_2O (2 ml) was added to a mixt of 3-*n*-hexylaniline (9.81 mmoles, 1.737 g), ice (*ca.* 3 g), and concd HCl (2.5 ml) while cooling in ice–salt bath. The resulting soln was added all at once to a well-cooled soln of $SnCl_2$ (4.45 g) in concd HCl (25 ml) with vigorous stirring. Et_2O and H_2O were added, and the Et_2O layer was sepd. The ext was washed with H_2O and dil NaOH soln and dried (NaOH). The solvent was removed, and the residue distd to give a pale yellow liquid (1.468 g, 78%), bp 135–140° (bath temp) (0.25 mm), which solidified on standing in the freezer (−30°); HCl salt, mp 155–156° (from EtOAc). The hydrazine, although described,[2] has not been previously isolated. The air-sensitive material can be stored under N_2 at −30°.

Hexahydrospinamycin[2-*N*-succinoyl-1-(3-*n*-hexylphenyl)-hydrazine] (HS). A soln of 3-*n*-hexylphenylhydrazine (1.244 g) and succinic anhydride (0.650 g) in abs EtOH (20 ml) was allowed to stand for 24 hr at 0°. The reaction mixt was poured into ice water, and the ppt filtered, washed with H_2O and hexane and dried, mp 100–101°, yield 1.75 g (93%). Recrystn from $CHCl_3$–hexane gave colorless crystals, mp 100–101°.

Acknowledgment. The authors are grateful for support from the Petroleum Research Fund and the Army Research Office (Durham, N. C.).

References

(1) E. L. Wang, M. Hamada, Y. Okami and H. Umezawa, *J. Antibiot., Ser. A*, 19, 216 (1966).
(2) H. Naganawa, T. Takita, K. Maeda, and H. Umezawa, *ibid.*, 21, 241 (1968).
(3) E. M. Kosower and T. Miyadera, *J. Med. Chem.*, 15, 307 (1972).

Book Reviews

Steroid-Protein Interactions. Ulrich Westphal. Springer-Verlag, New York, N. Y. 1971. xiii + 567 pp. 23.8 × 16.3 cm. $24.90

Like all other hormones–and as far as that goes, all drugs–steroids must interact with a specific receptor protein at a cell wall or intracellular membrane, or inside a cell, or with an enzyme protein resulting in an allosteric change of its conformation and a modification of its enzymatic activity. Or else, the interaction may be with a nuclear protein or a repressor molecule. Although some receptor proteins are believed to have been recognized in cytoplasm and nucleus, they cannot yet be studied in pure form. By contrast, many serum proteins have been purified adequately and have become useful tools in understanding ligand-protein interactions. Plasma albumin especially has provided much of our basic knowledge of these reactions. The present book summarizes physical and biological methods of determining steroid-protein complexing and binding. It discusses the influence of molecular structure on human serum albumin-steroid binding, and devotes attention particularly to corticosteroid-globulin combinations. Other steroids, including sex hormones, and other proteins are also included, and immunoglobulins and enzymes are treated prominently. This book should serve well to unify the views of the mechanisms of action of steroids expressed by variously trained researchers.

University of Virginia **Alfred Burger**
Charlottesville, Virginia

The Alkaloids. Vol. 1. A Review of the Literature, 1969–June 1970. Edited by J. E. Saxton. The Chemical Society, London W1V OBN. xiii + 505 pp. 22 × 14.5 cm. $26.00

This volume, which covers some background material but essentially mostly the literature published during a 1.5-year period, attests to the renewed vigor of alkaloid chemistry attained during the last decade. Two chapters on biosynthesis of different alkaloids and especially terpenoid indole compounds open the discussions. Then follow systematic progress reports on 22 or more groups of alkaloids; as expected, the indole, bisindole, and diterpene derivatives occupy the lion's share of these chapters but not at the scientific expense of other types. E. Schlittler writes skillfully about pharmacologically and clinically interesting alkaloids, including hallucinogens, ergot alkaloids, analgetic and antiinflammatory compounds, antihypertensive and cardiovascular drugs, curare, quinuclidine, emetine, and tumor-inhibitory types. The sophisticated natural-products chemist who wants to be brought up-to-date in these areas by 14 distinguished "reporters" will not wish to be without this book.

University of Virginia **Alfred Burger**
Charlottesville, Virginia

Snake Venoms and Envenomation. Edited by Sherman A. Minton, with 13 contributors. Marcel Dekker, New York, N. Y. 1971. ix + 188 pp. 23.5 × 16 cm. $12.50.

Herpetologists are interested in all facets of snaky phenomena, *i.e.*, the morphology, genetics, habitat, nutrition, reproduction, behavior, etc. of snakes. Pharmacologists and biochemists have become increasingly concerned with snake venoms, not only because of the toxicity of such excreta, but also because of potential therapeutic applications of venoms and their mode of action. Clinicians and toxicologists share in these interests and want to understand snake venoms when patients or domestic animals are to be treated for the acute syndrome of snake bite. The present book, originally published in *Clinical Toxicology*, 3, No. 3 (1970), contains the following review articles: identification of poisonous snakes; salivary glands of snakes; biochemistry and pharmacology of snake venoms; detection of venoms in tissue; elapid neurotoxins and their mode of action; and 3 articles on snake bite treatment. Chemists use snake venoms as a source of various enzymes, and have made progress in identifying the polypeptide structures of some snake neurotoxins and even establishing structure-activity relationships. The action of several neuromuscular-blocking toxins at the motor end-plate or by presynaptic blockade has aided us in separating such events in experimental neuropharmacology. The diverse areas that profit directly or indirectly from these studies should assure the book a wide readership.

University of Virginia **Alfred Burger**
Charlottesville, Virginia

Foreign Compound Metabolism in Mammals. Vol. 1. A Review of the Literature Published between 1960 and 1969. D. E. Hathway, Senior reporter; S. S. Brown, L. F. Chasseaud, D. H. Hudson, reporters. The Chemical Society, London W1V OBN. 1971. xvii + 455 pp. 14.3 × 22.4 cm. £11.00

Several good books on the biological metabolism of foreign chemicals in mammals have appeared, mostly authorized by investigators who have pioneered in this field and have presented their experiences with understandable bias. The present volume is a review of factual observations, gathered over the last decade when the study of the biotransformation of drugs, pesticides, food additives, etc. became a major force in medicinal research. The metabolic routes of hundreds of drugs are listed, albeit hard to locate in the absence of a subject index. Unfortunately, the listing is not reliably complete as shown by a quick spot-check of several important drugs whose metabolism has been published in the literature. Nomenclature and spelling are British but do not offer obstacles to the American reader. A long chapter is devoted to general considerations of mechanisms of biotransformation, perhaps the most valuable educational feature of the book. The novice is introduced to the subject by general sections on drug transport, techniques using isotopically labeled compounds, and the kinetics of absorption, distribution, metabolism, and excretion. The inhibition of drug metabolism and the interaction of drugs with each other are dealt with briefly. The final chapter is concerned with species, strain, and sex differences in metabolism.

University of Virginia **Alfred Burger**
Charlottesville, Virginia