New Compounds

Cobalt Derivatives of Schiff Bases of Aliphatic Amines as Antitumor Agents

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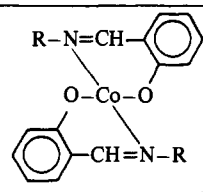
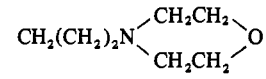
Some Schiff bases, R'CH=NR, are known to slow the growth of several animal tumors.[1,2] Some metal chelates have shown good antitumor activities against animal tumors.[1,3] Metal ions are known to affect the antitumor activities of the bis(thiosemicarbazones) of pyruvaldehyde[4] and of 3-ethoxy-2-oxobutyraldehyde (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.

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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

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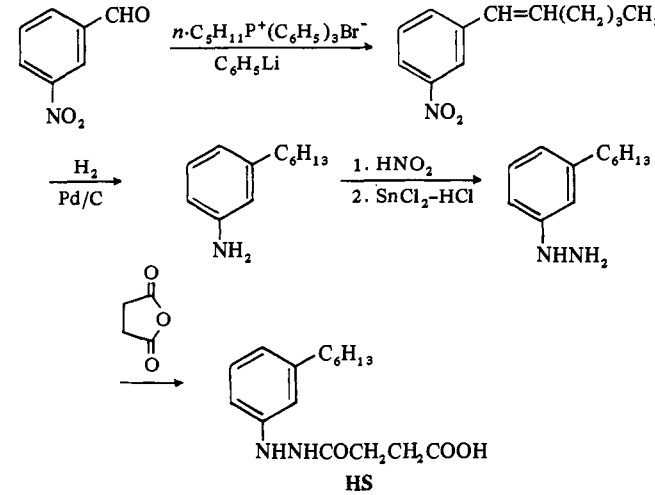
An interesting antibiotic, spinamycin, was isolated by Umezawa and his group from cultures of a new organism, *Streptomyces albospinus.*[1] Physical data and synthesis of the hexahydro derivative (HS) demonstrated the structure to be 1-(*m*-1,3,5-hexatrienylphenyl)-2-succinoylhydrazine.[2] In connection 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]



HS

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

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