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SYNTHESIS OF BIOLOGICALLY ACTIVE DERIVATIVES OF CYCLOPENTENO[d]-SELENAZOLE AND THEIR THIOANALOGS

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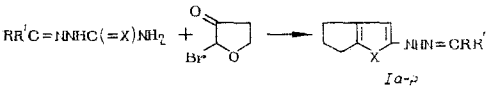
In an earlier paper [1], we reported the preparation of a number of biologically active 2-hydrazinoselenazoles. Continuing this work on the chemistry and biology of urea and semicarbazide selenium derivatives, we have prepared the 2-R-ylidenehydrazinocyclopenteno[d]selenazoles (Ia — h; Table 1) by the condensation of selenosemicarbazones of aromatic and heterocyclic aldehydes and ketones with α-bromocyclopentanone. To study the effect of the selenium atom on antimicrobial activity, the 2-R-ylidenehydrazinocyclopenteno[d]thiazoles (Ii-p; Table 1) were also prepared, using the corresponding thiosemicarbazones as thioamide component:



Ia-h, X = Se; Ii-p X = S

a, i: R = H, R′ = C_6H_5
b, j: R = H, R′ = CH = $CHC_6H_4NO_2$-2′
c, k: R and R′ =
d, l: R = H, R′ = $C_6H_3OCH_3$ 3′, CH_3-4′
e, m: R = H, R′ = α-furyl
f: R = H, R′ = α-thienyl
g, n: R = H, R′ = C_6H_3OH-1′, Br-5′
h, o: R = R′ = CH_3; p: hydrobromide I_o

It should be remembered that the carbon—selenium bond in the acyclic compounds is weaker than the carbon—sulfur bond, so that the preparation of compounds Ia-h is often accompanied by the separation of elemental selenium. The best yield (83%) of 2-benzylidenehydrazinocyclopenteno[d]selenazole Ia was obtained by refluxing a mixture of the starting compounds for 5-10 min in ethanol in the presence of fused sodium acetate and a small quantity of glacial acetic acid (method A).

The preparation of 2-isopropylidenehydrazinocyclopenteno[d]selenazole Ih presents some difficulties because of its increased solubility and instability on storage; it can be converted to Ia-g by reaction with aromatic carbonyl compounds (method B).

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TABLE 1. 2-R-Ylidenehydrazinocyclopenteno[d]thiazoles and Selenazoles

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				R_f (acetone hexane)	Yield, % (method A)
		C	H	N	Se (S)		C	H	N	Se (S)		
Ia	218—9	53,67	4,42	14,38	27,09	$C_{13}H_{13}N_3Se$	53,82	4,51	14,48	27,21	0,61 (1:1)	89
Ib	198—9	46,45	3,79	15,42	21,27	$C_{15}H_{14}N_4O_2Se$	46,55	3,91	15,51	21,85	0,60 (1:1)	93
Ic	251—3	50,72	3,60	18,80	23,70	$C_{14}H_{12}N_4OSe$	50,77	3,65	16,91	23,84	0,65 (1:1)	61
Id	214—5	49,85	4,38	12,38	23,40	$C_{14}H_{15}N_3O_2Se$	50,01	4,50	12,50	23,48	0,42 (1:1)	62
Ie	191—3	47,03	3,88	14,88	27,98	$C_{11}H_{11}N_3OSe$	47,15	3,96	15,00	28,18	0,54 (1:1)	69
If	193—5	44,48	3,59	14,22	26,08	$C_{11}H_{11}N_3SSe$	44,60	3,74	14,18	26,65	0,52 (1:1)	75
Ig	211—2	40,38	3,09	10,88	20,43	$C_{13}H_{12}BrN_3OSe$	40,54	3,14	10,91	20,50	0,66 (1:1)	89
Ih	154—6	44,52	5,41	17,20	—	$C_9H_{13}N_3Se$	44,63	5,39	17,35	—	0,37 (1:1)	52
Ii	239—41	64,28	5,25	17,17	(13,01)	$C_{13}H_{13}N_3S$	64,17	5,38	17,27	13,18	0,52 (1:1)	81
Ij	220—2	51,24	4,29	17,91	(9,95)	$C_{15}H_{14}N_4O_2S$	51,31	4,49	17,82	10,20	0,59 (1:1)	78
Ik	222—3	58,20	5,32	14,49	(10,99)	$C_{14}H_{15}N_3O_2S$	58,11	5,23	14,52	(11,08)	0,58 (2:1)	76
Il*	258—60	58,93	4,39	19,52	(11,09)	$C_{11}H_{12}N_4OS$	59,13	4,25	19,70	(11,27)	0,68 (2:1)	61
Im	215—7	55,54	4,87	17,98	(13,90)	$C_{11}H_{11}N_3OS$	56,63	4,75	18,01	(13,74)	0,72 (2:1)	60
In	220—1	46,36	3,72	12,30	(9,49)	$C_{13}H_{12}BrN_3OS$	46,17	3,57	12,42	(9,48)	0,70 (2:1)	90
Io	159—61	55,40	6,82	21,33	(16,25)	$C_9H_{13}N_4S$	55,36	6,71	21,52	(16,42)	0,42 (1:1)	62
Ip	230	39,23	4,98	15,15	(10,60)	$C_9H_{11}BrN_3S$	39,14	5,11	15,21	(11,61)	—	73

*Compound obtained by method B.

Compounds Ii-p were prepared either by the direct condensation of the thiosemicarbazone with α-bromocyclopentanone, or by the substitution of the isopropylidene group of Io by a carbonyl compound residue with a higher molecular weight. Compound Io was most conveniently obtained as the hydrobromide Ip by mixing acetone thiosemicarbazone in acetone with α-bromocyclopentanone in ether.

Compounds Ia-o are colored (from yellow to red-orange) crystalline substances; they melt with decomposition at temperatures generally above 200°; they are soluble in aromatic hydrocarbons and dioxane, and insoluble in water and aliphatic hydrocarbons. Compound Ip is a white crystalline substance. Chromatography was carried out using silica gel type L5/40 μ (thickness of layer, 0.8 mm) in acetone—hexane (1:1). In UV light, the compounds are yellowish green or exhibit a green fluorescence.

The antimicrobial activity of 16 derivatives of cyclopenteno[d]selenazole and their thioanalogs was studied.

The minimum bacteriostatic (MBsC) or microstatic (MMsC) concentrations were determined by the method of double serial dilution in Hottinger's broth (or Sabouraud's medium). *Staphylococcus aureus* 209 P, *E. coli* 675, and the fungal dermatophyte *Microsporum canis* (*lanosum*) were used as test microorganisms. The microbial loading was $2.5 \cdot 10^5$ μg/ml for bacteria, and $5 \cdot 10^5$ reproductive bodies/ml for fungi. The maximum concentration studied was 200 μg/ml.

The activities of the substances were rated according to the following MBs and MMs concentrations: highly active, MBsC $\leqslant$1.65 — 3.1 μg/ml, MMsC $\leqslant$ 6.2 μg/ml; moderately active, MBsC = 6.2-25 μg/ml, MMsC = 12.5—50 μg/ml; weakly active, MBsC = 50-200 μg/ml, MMsC = 100-200 μg/ml; inactive, MBsC and MMsC > 200 μg/ml.

As can be seen from Table 2, at concentrations of 200 μg/ml, not one of the derivatives of cyclopentenone[d]thiazole suppressed the growth of the test organisms; these compounds were therefore described as inactive antimicrobial agents.

On the other hand, the cyclopenteno[d]selenazole derivatives did exhibit some bacteriostatic activity. All the compounds in this group inhibited the growth of fungi to some degree; in addition, compounds Ib and c were moderately active, and Id, g, and h were weakly active towards stapphylococcus. Moderately active were Ib-d and f-h (by degree of activity). Compounds Ia and b were weakly active towards microsporum. At concentrations of 200 μg/ml,

TABLE 2. Antimicrobial Activity of 2-R-Ylidenehydrazinocyclopenteno[d]-thiazoles and Selenazoles

Compound	Staphylococcus aureus 109-P	Escherichia coli 675	Microsporum canis
	MBsC or MMsC, μg/ml		
Ia	>200	>200	200
Ib	25	>200	50
Ic	25*	>200	50
Id	50	>200	12,5†
Ie	>200	>200	100
If	>200	>200	50
Ig	200	>200	50
Ih	50	>200	25
Ii	200	>200	>200
Ij	>200	>200	>200
Ik	200	>200	>200
Il	>200	>200	>200
Im	>200	>200	>200
In	>200	>200	>200
Io	>200	>200	>200
Ip	>200	>200	>200

*MBsC of preparations of hemolytic Streptococcus pneumococcus, diphtheria bacillus, and anthracoid bacillus were respectively 25, 12.5, 100, and 200 μg/ml.

†MMsC of activated aspergillase and candidase was more than 200 μg/ml.

all of the compounds suppressed the growth of *E. coli*. A comparison of activity and chemical structure shows that an alkylidene group exerts more effect than an arylidene group (including furfurylidene). The significant contributions of the nitro group and the phenolhydroxyl group were noted.

Thus, it was found that the cyclopenteno[d]selenazole derivatives were more effective antimicrobial agents than their thioanalogs.

EXPERIMENTAL CHEMICAL SECTION

2-Isopropylidenehydrazinocyclopenteno[d]selenazole (Ih). A mixture of 1.78 g (0.01 mole) of acetone selenosemicarbazone and 1.64 g (0.02 mole) of fused sodium acetate was dissolved in 20 ml of ethanol by heating under reflux, the solution cooled to 40-45°, and 1.63 g (0.01 mole) of α-bromocyclopentanone and a small quantity of glacial acetic acid added. The reaction mixture was refluxed for 1 h, cooled, a negligible amount of elemental selenium filtered off, and the filtrate evaporated at 90-95°. The brown oil which separated was treated with water to give a resinous material which crystallized within 2 days. It was purified by precipitation from toluene solution with hexane.

2-Benzylidenehydrazinocyclopenteno[d]selenazole (Ia). Method A. To a suspension of 2.26 g (0.01 mole) of benzaldehyde selenosemicarbazone, and 1.64 g (0.02 mole) of fused sodium acetate in 25 ml of ethanol was added a small quantity of glacial acetic acid and 1.63 g (0.01 mole) of α-bromocyclopentanone. The mixture was refluxed and after about 2-3 min a yellow precipitate separated. This was filtered off and washed on the filter with warm water until the filtrate gave a negative bromide-ion reaction.

Compounds Ia-g were prepared in the same way.

Method B. To a solution of 0.24 g (0.001 mole) of 2-isopropylidenehydrazinocyclopenteno[d]selenazole (Ih) in 10 ml of glacial acetic acid was added 1.06 g of benzaldehyde and 2-3 drops of glacial acetic acid. The mixture was refluxed for 30 min, filtered hot and the filtrate treated with saturated sodium acetate solution to give a flocculant yellow precipitate (41% yield).

2-Benzylidenehydrazinocyclopenteno[d]thiazole (Ii) was prepared by the method given in [2]. Compounds Ij-n were prepared in the same way. Compound Ii was prepared by method B.

The toxicity of the compounds was obtained from a determination of the maximum endurable dose on subcutaneous injection into non-pedigree white mice; the animals were observed for a period of 14 days.

Derivatives of arylidenehydrazinocyclopenteno[d]selenazole containing a heterocyclic substituent (compounds Ib, c, and g) were characterized by low toxicity. The maximum endurable doses for white mice ranged from 500 to 1000 μg/ml and greater. The introduction of two methyl groups (compound Ih) led to a sharp increase in toxicity.

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