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Some 2-Iminoselenazolidin-4-ones and related compounds

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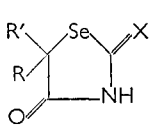
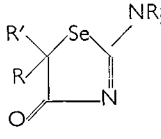
A series of 2-iminoselenazolidin-4-ones, selenazolidine-2,4-diones and some 2-alkylidenehydrazones have been synthesised. Wide-range screening for biological activity failed to reveal any compounds of promise.

OXAZOLIDINONES, thiazolidinones and the closely related rhodanines have been extensively investigated for their biological properties, including antibacterial and antifungal activity (Clarke-Lewis, 1958; Brown, 1961). A recent review (Dingwall, 1962) has shown that comparatively little is known about the properties of their selenium isosteres.

Among the selenazolidin-4-ones, the 2-imino-derivative (I, X=NH; R=R′=H), its 5-methyl homologue (I, X=NH; R=Me; R′=H) (Hofmann, 1889; Frerichs, 1903) and a number of 2-dialkylamino-2-selenazolin-4-ones (II) have already been described (Zingaro, Bennett & Hammar, 1953) but not examined for biological activity. A series of 5-alkyl-2-iminoselenazolidin-4-ones (I, X=NH; R=alkyl; R′=H) and the corresponding 5-alkylselenazolidine-2,4-diones (I, X=O; R=alkyl; R′=H) were therefore prepared for examination. Since the ultra-violet



I



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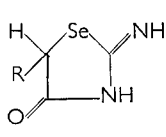
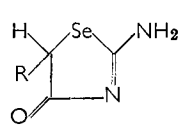


III



IV

and infra-red absorption spectra of the former, which are potentially capable of imino–amino tautomerism (III ⇌ IV), favours the imino-structure (Comrie, Dingwall & Stenlake, 1963), nomenclature consistent with this evidence is used throughout.

5-Alkyl(or aryl)-2-iminoselenazolidin-4-ones were prepared by condensing α-halogenocarboxylic acids with selenourea in ethanol (Comrie, Dingwall & Stenlake, 1963). Acid hydrolysis of the parent 2-imino-compound conveniently gave the 5-alkylselenazolidine-2,4-diones (I, X=O, R=alkyl; R′=H), which could be prepared alternatively by condensing the α-halogenocarboxylic acid with selenourea in water. Nucleophilic reactivity of the methylene carbon atom in selenazolidine-2,4-dione (I; X=O; R=R′=H) was shown by the ready formation of 5-arylidene derivatives (I; X=O; RR′=ArCH:) with aromatic aldehydes in the presence of base.

Selenazolidine-2,4-dione 2-alkylidene(or arylidene)hydrazones (I; X = N·N:CHR) were easily prepared by a base-catalysed condensation of α-halogenocarboxylic acids and the selenosemicarbazones of acetone or

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benzaldehyde. The relatively greater insolubility of 5-ethylselenazolidine-2,4-dione 2-benzylidenehydrazone (I, X = N·N:CHPh; R=Et; R′=H) compared with that of the corresponding 2-isopropylidenehydrazone (I, X=N·N:CMe_2; R=Et; R′=H) probably accounts for its formation from the latter and benzaldehyde.

Alkyl halides and selenourea gave the appropriate isoselenouronium halide. With alkali, *Se*-benzylselenouronium chloride was transformed in air into dibenzyl diselenide and it would appear, therefore, that hydrolysis to benzyl selenomercaptan takes place, since this substance is readily oxidised to the diselenide (Painter, 1941). Attempted cyclisation of *Se*-benzylselenouronium chloride as a step in a reaction sequence designed to obtain the unknown isomeric selenohydantoins failed, as did other methods which have been successfully applied to hydantoins (Jack, 1959) and thiohydantoins. Condensation of 2-iminoselenazolidin-4-one with sulphonyl chlorides in pyridine gave the corresponding 2-sulphonamido-2-selenazolin-4-ones (Roy & Guha, 1945).

Experimental

Selenium was determined spectrophotometrically (Dingwall & Williams 1961).

TABLE 1. 5-ALKYL-2-IMINOSELENAZOLIDIN-4-ONES (I; X=NH; R′=H)

Compound	R	M.p.°C	Yield %	Formula	Found %		Requires %	
					N	Se	N	Se
2-Imino-5-propyl-selenazolidin-4-one*	Pr^n	184–6	80	$C_6H_{10}N_2OSe$	13·9	38·3	13·7	38·5
2-Imino-5-isopropyl-selenazolidin-4-one	Pr^i	211–3	61	$C_6H_{10}N_2OSe$	13·7	38·4	13·7	38·5
5-Butyl-2-iminoselenazolidin-4-one hydrobromide	Bu	179–81 (decomp.)	43	$C_7H_{13}BrN_2OSe$†	9·5	26·0	9·3	26·6
2-Imino-5-phenyl-selenazolidin-4-one	Ph	200–4	60	$C_9H_8N_2OSe$	11·6	32·6	11·7	33·0

* Recrystallised from ether.
† Found: C, 28·2; H, 4·7; Br, 26·4; requires C, 28·0; H, 4·4; Br, 26·6%. *Base* m.p. 178–9° (decomp.) (from ethanol) Found: N 12·85; Se, 35·6; $C_7H_{12}N_2OSe$ requires N, 12·8; Se, 36·0%. *Picrate* m.p. 126–30° (from methanol) Found: N, 15·4; Se, 17·2; $C_{13}H_{15}N_5O_8Se$ requires N, 15·6; Se, 17·6%.

2-Iminoselenazolidin-4-ones (Table 1). Equimolecular quantities of α-halogenocarboxylic acids and selenourea were refluxed together in ethanol for 30 min to give the product as the hydrohalide (Comrie, Dingwall & Stenlake, 1963). The *bases* were liberated by neutralizing aqueous solutions of the salts and purified by recrystallising from ethanol unless otherwise stated.

Selenazolidine-2,4-diones (Table 2). (*a*) The α-halogenocarboxylic acid (0·01 mole) and selenourea (0·01 mole) were heated together in water (10 ml) for 2 hr on a boiling water-bath. Cooling the reaction mixture followed by ether extraction (5 × 10 ml) gave the *product*, usually as a pale-yellow oil, on removing the solvent. Purification was achieved by crystallisation from ethanol or aqueous ethanol, by distillation or by sublimation under a high vacuum.

TABLE 2. 5-SUBSTITUTED SELENAZOLIDINE-2,4-DIONES (I; X=O)

Compound	R	R′	M.p.°C	Yield %	Formula	Found %		Requires %	
						N	Se	N	Se
5-Methylselenazolidine-2,4-dione	Me	H	74–5	82	$C_4H_5NO_2Se$*	7·9	43·9	7·9	44·35
5-Ethylselenazolidine-2,4-dione	Et	H	69–71	75	$C_5H_7NO_2Se$†	7·4	41·6	7·3	41·1
5-Propylselenazolidine-2,4-dione	Pr^n	H	55–6	67	$C_6H_9NO_2Se$	6·7	38·1	6·8	38·3
5-Isopropylselenazolidine-2,4-dione	Pr^i	H	73–4	73	$C_6H_9NO_2Se$	6·9	37·9	6·8	38·3
5-Butylselenazolidine-2,4-dione	Bu	H	92–3	89	$C_7H_{11}NO_2Se$	6·3	35·3	6·4	35·9
5-Phenylselenazolidine-2,4-dione	Ph	H	160–2	60	$C_9H_7NO_2Se$	5·9	32·6	5·8	32·7
5,5-Dimethylselenazolidine-2,4-dione	Me	Me	82·5–83·5	68	$C_5H_7NO_2Se$	7·4	40·9	7·3	41·1

* Found: C, 26·6; H, 3·1; requires C, 27·0; H, 2·8%.
† Found: C, 31·6; H, 4·1; requires C, 31·3; H, 3·7%.

(*b*) The corresponding 2-iminoselenazolidin-4-one (*ca* 1 g) was refluxed in a mixture of hydrochloric acid (2 ml) and water (25 ml) for 2 hr. Isolation and purification of the *product* was carried out as in method (*a*).

5-*Benzylideneselenazolidine*-2,4-*dione*. Selenazolidine-2,4-dione (1·64 g), benzaldehyde (1·48 g), anhydrous sodium acetate (1·3 g) and acetic anhydride (10 drops) were refluxed together in glacial acetic acid (4 ml) at 160–70° for 3 hr. The *product* (1·93 g) which separated on cooling gave pale-yellow needles, m.p. 250–2° (decomp.) (from ethanol). Found: C, 47·5; H, 3·1; N, 5·6; Se, 30·75; $C_{10}H_7NO_2Se$ requires C, 47·6; H, 2·8; N, 5·6; Se, 31·3%.

5-*Salicylideneselenazolidine*-2,4-*dione* was similarly obtained as a yellow amorphous solid, m.p. 214–6° (from ethanol) in 61% yield from the dione and salicylaldehyde. Found: N, 5·3; Se, 29·15; $C_{10}H_7NO_3Se$ requires N, 5·3; Se, 29·45%.

Selenazolidine-2,4-*dione* 2-*isopropylidenehydrazone*. Acetone selenosemicarbazone (0·82 g) and chloroacetic acid (0·64 g) were refluxed together in 95% ethanol (15 ml) for 1 hr. The *product* (0·66 g) which separated on cooling was washed with ethanol and hot water and recrystallised from aqueous ethanol to give plates, m.p. 181–3°. Found: Se, 35·95; $C_6H_9N_3OSe$ requires Se, 36·2%.

5-*Ethylselenazolidine*-2,4-*dione* 2-*isopropylidenehydrazone*, m.p. 103–6° (from ethanol), was similarly obtained in 69% yield from acetone selenosemicarbazone and α-bromobutyric acid. Found: C, 38·3; H, 5·6; N, 16·8; Se, 31·8; $C_8H_{13}N_3OSe$ requires C, 39·0; H, 5·3; N, 17·1; Se, 32·1%.

5-*Phenylselenazolidine*-2,4-*dione* 2-*isopropylidenehydrazone*. Acetone selenosemicarbazone and α-chloro-α-phenylacetic acid were condensed as above. Water was added to the reaction mixture, which was then neutralised to pH 8 with concentrated ammonia solution and extracted with ether. Removal of the solvent gave the *product* (39%), m.p. 208° (from ethanol). Found: C, 48·5; H, 4·8; N, 13·9; Se, 26·8; $C_{12}H_{13}N_2OSe$ requires C, 49·0; H, 4·45; N, 14·3; Se, 26·8%.

Selenazolidine-2,4-*dione* 2-*benzylidenehydrazone*. Benzaldehyde selenosemicarbazone (0·26 g), chloroacetic acid (0·11 g) and anhydrous sodium acetate (0·2 g) were refluxed together in 95% ethanol (10 ml) for 10 min. The *product* (0·23 g, m.p. 254–6° decomp.) (from glacial acetic acid) separated on cooling. Found: Se, 30·1; $C_{10}H_9N_3OSe$ requires Se, 29·7%.

5-*Ethylselenazolidine*-2,4-*dione* 2-*benzylidenehydrazone* (64%, m.p. 200–2°, from ethanol) was similarly obtained from benzaldehyde selenosemicarbazone and α-bromobutyric acid. (Found: Se, 26·9; $C_{12}H_{13}N_3OSe$ requires Se, 26·8%). The same product was formed from 5-ethylselenazolidine-2,4-dione 2-isopropylidenehydrazone and benzaldehyde in glacial acetic acid,

Se-*Benzylselenouronium chloride*, Selenourea (0·88 g) and benzyl chloride (1·0 g) were refluxed together for 30 min in dry ethanol (10 ml), access of moisture being prevented by a calcium chloride guard tube. The reaction mixture was filtered, concentrated and cooled, giving the *product* (1·42 g), m.p. 194–6° (from ethanol, charcoal). Found: N,11·2; Se, 31·4; $C_8H_{11}ClN_2Se$ requires N, 11·2; Se, 31·6%. *Picrate*, m.p. 173–4° (from water). Found: N, 14·65; Se, 16·3; $C_{14}H_{13}N_5O_7Se:2H_2O$ requires N, 14·6; Se, 16·4%. *Toluene*-p-*sulphonate*, m.p. 172–3° (from ethanol). Found: N, 7·1; Se, 21·2; $C_{15}H_{18}N_2O_3SSe$ requires N, 7·4; Se, 20·8%.

Se-*Methylselenouronium iodide*, m.p. 113–5° (from ethanol-ether), was similarly obtained in 79% yield from selenourea and methyl iodide. Found: N, 10·7; Se, 30·2; $C_2H_7IN_2Se$ requires N, 10·6; Se, 29·8. *Picrate*, m.p. 218–20° (from ethanol). Found: N, 18·8; Se, 21·3; $C_8H_9N_5O_7Se$ requires N, 19·1; Se, 21·6%.

2-*Toluene*-p-*sulphonamido*-2-*selenazolin*-4-*one*. 2-Iminoselenazolidin-4-one hydrochloride (0·64 g) and toluene-*p*-sulphonyl chloride were heated together in pyridine (5 ml) for 2 hr. Extraction gave the *sulphonamide* (0·35 g), m.p. 209–11° (from ethanol). Found: N, 8·8; Se, 24·8; $C_{10}H_{10}N_2O_3SSe$ requires N, 8·8; Se, 24·9%. 2-Iminoselenazolidin-4-one hydrochloride and benzenesulphonyl chloride similarly gave 2-*benzenesulphonamido*-2-*selenazolin*-4-*one*, m.p. 168° (from ethanol), in 46% yield. Found: N, 9·0; Se, 26·4; $C_9H_8N_2O_3SSe$ requires N, 9·3; Se, 26·1%.

Biological results

In view of the diverse biological activity of the oxygen and sulphur analogues, general pharmacological screening of selected compounds was carried out (Table 3). For test procedures in mice the compounds were suspended in a 5% acacia mucilage at various concentrations depending on the dose employed; the dose volume was 0·5 ml/20 g weight. The only activity observed was weak antihistamine and parasympatholytic activity.

Antibacterial activity of 5-ethyl-2-iminoselenazolidin-4-one hydrobromide, 5-ethylselenazolidine-2,4-dione and its 2-isopropylidenehydrazone, and 5-benzylideneselenazolidine-2,4-dione was negligible against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, and *Proteus vulgaris*.

TABLE 3. BIOLOGICAL RESULTS

Test	Animal	Route	5-Ethylselenazolidine-2,4-dione	5-Ethyl-2-iminoselenazolidin-4-one hydrobromide
Dose range	Mouse	Oral	LD50: 24 mg/kg Severe clonic convulsions before death.	LD50: 250 mg/kg Depression 125 mg/kg. Death after several hours.
		s.c.	LD50: 24 mg/kg. Severe clonic convulsions before death.	LD50: 750 mg/kg. Depression 125 mg/kg
Analgesic	Mouse	s.c.	−ve at 10 mg/kg	−ve at 10 mg/kg
Max. electro-shock seizure ..	Mouse	Oral	−ve at 10 mg/kg	−ve at 100 mg/kg
Conditioned response ..	Rat	Oral	−ve at 9·6 mg/kg	−ve at 100 mg/kg
Max. leptazol seizure	Mouse	Oral	sl. +ve at 10 mg/kg (3/5 protected)	−ve at 100 mg/kg
Antihistamine	Guinea-pig (ileum)		+ve at 100 μg in 20 ml	+ve at 100 μg in 20 ml
Anti-amphetamine	Mouse	Oral	−ve at 1–9 mg/kg	−ve at 10–90 mg/kg
Anti-Tremorine	Mouse	Oral	−ve at 9·6 mg/kg	−ve at 100 mg/kg
Sympathetic block	Cat	s.c.	sl. +ve at 5 mg/kg	−ve at 50 mg/kg
Diuretic	Rat	Oral	−ve at 1–9 mg/kg	−ve at 10–90 mg/kg
Parasympatholytic	Guinea-pig (ileum)		−ve at 100 μg in 20 ml	+ve at 100 μg in 20 ml

Conclusion

The 2-iminoselenazolidin-4-ones and selenazolidine-2,4-diones tested exhibited negligible biological activity.

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