Carcinogenic Nitrogen Compounds. Part LXVIII.[1] A New Class of Pseudoazulenes: [1]Benzoselenino[4,3-*b*]indoles

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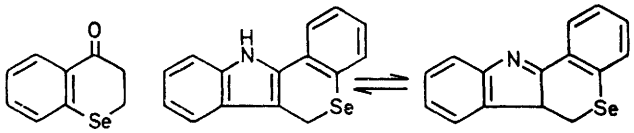
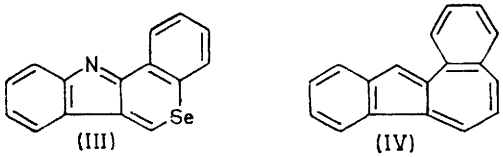
A new family of pseudoazulenes, mono- and di-benzo-derivatives of [1]benzoselenino[4,3-*b*]indole, have been prepared by dehydrogenation of the corresponding dihydro-compounds obtained from 2,3-dihydro-1-benzoselenin-4-one arylhydrazones. The properties of the pseudoazulenes are compared with those of their sulphur analogues.

We have previously [2] reported the synthesis and properties of sulphur-containing pseudoazulenes derived from [1]benzothiopyrano[4,3-*b*]indole; these pseudoazulenes were readily formed by photo-oxidation or treatment with picric acid of indoles derived from thiochroman-4-one. We have now attempted similar syntheses of the [1]benzoselenino[4,3-*b*]indole group, starting from 2,3-dihydro-1-benzoselenin-4-one (I).[3]



(I) (II) (IIa)

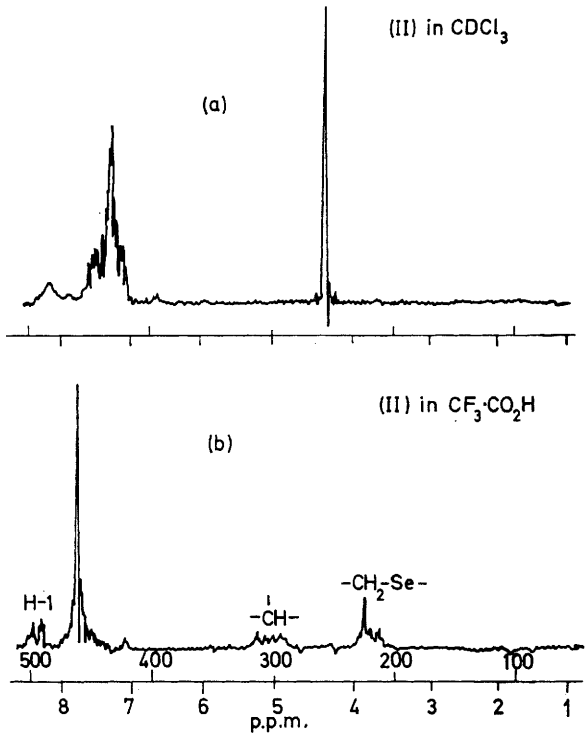
The indolisation of 2,3-dihydro-1-benzoselenin-4-one phenylhydrazone (best achieved with a solution of hydrogen chloride in acetic acid) afforded 6,11-dihydro-[1]benzoselenino[4,3-*b*]indole (II). As shown by n.m.r. spectroscopy, this compound possessed the normal indole structure (II) in neutral solvents [Figure (a)] [δ 4·25 (s, CH_2), 7·3—7·7 (8H, complex, aromatic), and 8—8·35 (NH) p.p.m.] However, like its sulphur analogue,[4] 6,11-dihydro[1]benzothiopyrano[4,3-*b*]indole, it exhibited 1*H*-indole ⇌ 3*H*-indole tautomerism in trifluoroacetic acid; its n.m.r. spectrum in this solvent [Figure (b)] showed the presence of a non-aromatic proton at position 6a and is consistent with the structure (IIa) (note the highly deshielded angular 1-proton). Compound (II) was readily dehydrogenated with picric acid in hot acetic acid to give the orange-red pseudoazulene (III) which, as expected, was a base, giving



(III) (IV)

yellow salts with hydrochloric and perchloric acids. Compound (III) is iso-π-electronic with dibenz[*a*,*e*]-azulene (IV).

The α- and β-naphthylhydrazones of ketone (I) afforded, respectively, the 6,13-dihydro-compounds (V) and (VII) (the sulphur analogue of the latter possesses



N.m.r. spectra of compound (II)

carcinogenic activity [5]). These indoles could also be readily dehydrogenated with picric acid to give the corresponding red pseudoazulenes (VI) and (VIII); (VI) is an analogue of dibenz[*c*,*h*]acridine, and (VIII) of dibenz[*a*,*h*]acridine, which is carcinogenic,[6] and is iso-π-electronic with benzo[*e*]naphtho[2,1-*a*]azulene.

The aromatic character of these selenium-containing pseudoazulenes is shown in their behaviour under electron impact; in the mass spectra of all three, the base peak corresponds to the molecular ion, and intense peaks corresponding to the doubly charged molecular

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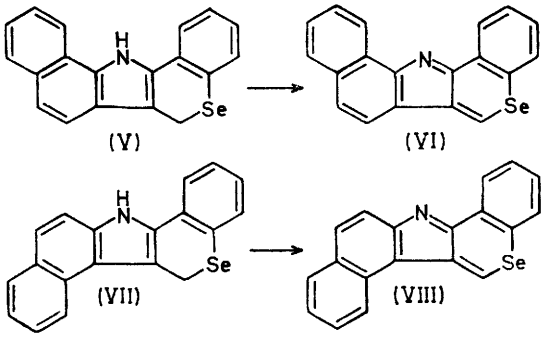
[2] N. P. Buu-Hoï, A. Croisy, A. Ricci, P. Jacquignon, and F. Périn, *Chem. Comm.*, 1966, 269; N. P. Buu-Hoï, A. Martani, A. Croisy, P. Jacquignon, and F. Périn, *J. Chem. Soc.* (*C*), 1966, 1787; N. P. Buu-Hoï, P. Jacquignon, A. Croisy, A. Loiseau, and F. Périn, *ibid.*, 1969, 1422.
[3] *Cf.* A. Ruwet and M. Renson, *Bull. Soc. chim. belges*, 1968, **77**, 465.
[4] N. P. Buu-Hoï, V. Bellavita, G. Grandolini, A. Ricci, and P. Jacquignon, *Compt. rend.*, 1966, **262**, 1204.
[5] N. P. Buu-Hoï and Dr. F. Zajdela, unpublished results.
[6] E. Boyland and A. M. Brues, *Proc. Roy. Soc.*, 1937, *B* **122**, 429; G. Barry, J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger, and E. L. Kennaway, *ibid.*, 1935, *B* **117**, 318; A. Lacassagne, N. P. Buu-Hoï, F. Zajdela, and R. Daudel, *Adv. Cancer Res.*, 1956, **4**, 315.

ion are observed (Table). The main mode of fragmentation consists of loss of the selenium heteroatom; this, in compound (III), gives rise to the indeno[1,2-*b*]indole species (IX), in compound (VI) to the benz[*g*]indeno-[1,2-*b*]indole species (X), and in compound (VIII) to



the benz[*e*]indeno[1,2-*b*]indole species (XI). The aromaticity of these hitherto unreported heterocycles (IX), (X), and (XI) is indicated by the fact that they, too,

Main peaks in mass spectra of compounds (III), (VI), and (VIII)

(III)

m/e	% of base peak	Species
283	100	M^+(^{80}Se)
281	52·6	M^+(^{78}Se)
204	13·1	
203 [a]	66·0	(IX)$^+$
202	12·8	[(IX) − H]$^+$
176	3·9	[(IX) − HCN]$^+$
141·5	11·8	M^{2+}(^{80}Se)
140·5	6·5	M^{2+}(^{78}Se)
101·5	7·9	(IX)$^{2+}$

[a] *m** 146 [*M* ⟶ (IX) + ^{80}Se].

(VI)

m/e	% of base peak	Species
333	100	M^+(^{80}Se)
331	52	M^+(^{78}Se)
254	25	
253 [a]	50	(X)$^+$
252	8·7	[(X) − H]$^+$
251	8·5	[(X) − 2H]$^+$
226	6·5	[(X) − HCN]$^+$
166·5	17·5	M^{2+}(^{80}Se)
165·5	8·7	M^{2+}(^{78}Se)
127	19·6	
126·5	21·5	(X)$^{2+}$
126	17	

[a] *m** 193 [*M* ⟶ (X)$^+$ + ^{80}Se].

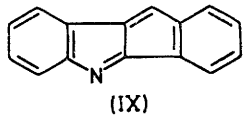
(VIII)

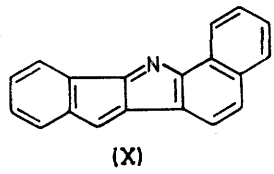
m/e	% of base peak	Species
333	100	M^+(^{80}Se)
331	53·5	M^+(^{78}Se)
254	22·3	
253 [a]	40	(XI)$^+$
252	8·3	[(XI) − H]$^+$
251	7·5	[(XI) − 2H]$^+$
226	4·7	[(XI) − HCN]$^+$
166·5	17·7	M^{2+}(^{80}Se)
165·5	7·7	M^{2+}(^{78}Se)
127	11·7	
126·5	12·3	(XI)$^{2+}$

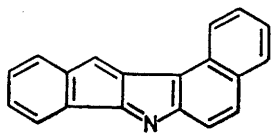
[a] *m** 193 [*M* ⟶ (XI)$^+$ + ^{80}Se].

give intense doubly charged ion peaks and undergo relatively little further fragmentation through extrusion of hydrogen cyanide.

Like their sulphur analogues,[7] the pseudoazulenes and their dihydro-derivatives reported here display strong activity as inducers of the microsomal enzyme zoxazolamine hydroxylase in rats; these results and those of carcinogenicity tests will be reported elsewhere.







EXPERIMENTAL (with Miss R. PÊCHEUR)

2,3-*Dihydro*-1-*benzoselenin*-4-*one*.—This ketone (22 g.), b.p. 114°/0·8 mm., m.p. 38°, was obtained by cyclisation of β-(phenylseleno)propionic acid (65 g.) with 85% phosphoric acid (107 c.c.) and phosphorus pentoxide (161 g.). Its *phenylhydrazone* was prepared (87%) by heating under reflux for 15 min. a solution of the ketone (1·2 g.) and phenylhydrazine (0·6 c.c.) in methanol (6 c.c.); the product gave yellowish prisms, m.p. 104—105° (from ethanol, then from benzene) (Found: C, 59·5; H, 4·4. $C_{15}H_{14}N_2Se$ requires C, 59·7; H, 4·6%) $\nu_{max.}$ (Nujol) 2400—3100, 1350, and 1650 cm.$^{-1}$.

6,11-*Dihydro*[1]*benzoselenino*[4,3-b]*indole* (II).—The foregoing hydrazone (1 g.) was indolised (89%) by briefly boiling its solution in acetic acid (25 c.c.) saturated with hydrogen chloride; cooling and dilution with water gave the *product* (II) which yielded pale yellow needles, m.p. 153° [from cyclohexane–benzene (1 : 1)] (Found: C, 63·5; H, 3·8; N, 5·1. $C_{15}H_{11}NSe$ requires C, 63·4; H, 3·9; N, 4·9%), $\nu_{max.}$ (Nujol) 3350 cm.$^{-1}$ (NH). The n.m.r. spectra were taken with a Varian A-60 spectrometer (internal reference $SiMe_4$). The *picrate* formed deep violet needles (ethanol) which, when heated on a copper Maquenne bloc, melted at 140—145° and were converted (resolidified) into the picrate of compound (III) (Found: N, 11·1. $C_{21}H_{14}N_4O_7Se$ requires N, 10·9%). Indolisation could also be achieved by use of polyphosphoric acid, but the yield was only 32—64% and a less pure product was obtained.

[1]*Benzoselenino*[4,3-b]*indole* (III).—A solution of the picrate (0·6 g.) of the 6,11-dihydro-derivative and an excess of picric acid (0·5 g.) in acetic acid (10 c.c.) was heated under reflux until a yellowish brown compound, the *picrate* of the dehydrogenated base (III) (*ca.* 70%), was precipitated. Recrystallisation from acetic acid afforded yellow prisms (0·3 g.), m.p. 234—236° (instantaneous; decomp. >200°) (Found: N, 10·9. $C_{21}H_{12}N_4O_7Se$ requires N, 11·0%). The picrate (0·25 g.) was decomposed with aqueous ammonia, the free base was taken up in ether, the ethereal solution was dried (K_2CO_2) and filtered, and the filtrate was treated with an ethereal solution of hydrogen chloride, to give a precipitate of the *hydrochloride* of the indole (III), which yielded yellow needles (0·15 g.) (from aqueous hydrochloric acid), m.p. 208—209° (instantaneous; decomp. >150°) (Found: N, 4·6. $C_{15}H_{10}ClNSe$ requires N, 4·4%). The free *base*, obtained in poor yield by decomposition of the hydrochloride with aqueous sodium hydroxide, gave orange-red prisms, m.p. 161—162° [from cyclohexane–benzene (2 : 1)] (Found: C, 63·8; H, 3·2. $C_{15}H_9NSe$

[7] N. P. Buu-Hoï, D.-P. Hien, A. Ricci, and P. Jacquignon, *Compt. rend.*, 1967, *D*, **265**, 714.

requires C, 63·8; H, 3·2%). The *perchlorate* was prepared by dehydrogenation of the 6,11-dihydro-indole (II) (1·3 g.) in solution in warm acetic acid (13·5 c.c.) by use of triphenylmethyl perchlorate [8] (1·6 g.) under nitrogen atmosphere. After the dehydrogenation reagent had dissolved a yellow crystalline precipitate formed, which was washed with acetic acid, then anhydrous ether, and dried *in vacuo* (Found: C, 46·7; H, 3·0. $C_{15}H_{10}ClNO_4Se$ requires C, 47·1; H, 2·6%).

6,13-*Dihydrobenzo*[g][1]*benzoselenino*[4,3-b]*indole* (V).—A solution of the ketone (I) (2·1 g.), α-naphthylhydrazine hydrochloride (1·9 g.), and sodium acetate (0·7 g.) in ethanol (150 c.c.) was heated under reflux for 2 hr., then cooled. The precipitate was washed with water and recrystallised from ethanol to give 2,3-dihydro-1-benzoselenin-4-one α-naphthylhydrazone (3 g.), pale yellow needles, m.p. 195°. Indolisation as before afforded *compound* (V) as pale yellow needles (2 g.), m.p. 205° (from cyclohexane) (Found: C, 68·5; H, 3·9; N, 4·1. $C_{19}H_{13}NSe$ requires C, 68·3; H, 3·9; N, 4·2%); the *sesquipicrate* gave violet needles (from ethanol), m.p. 172—175° (instantaneous), with resolidification owing to dehydrogenation (Found: N, 11·7. $C_{56}H_{35}N_{11}O_{28}Se_2$ requires N, 11·4%).

Benzo[g][1]*Benzoselenino*[4,3-b]*indole* (VI).—Dehydrogenation of compound (V) (1·5 g.) with picric acid (3 g.) as before, afforded the *picrate* of (VI), as brown-red leaflets (2·5 g.) (from acetic acid), m.p. 275—280° (instantaneous; decomp. >240°) (Found: N, 10·1. $C_{25}H_{14}N_4O_7Se$ requires N, 10·0%). The *hydrochloride* formed red needles (from aqueous ethanol), m.p. 198—200° (instantaneous; decomp. >170°) (Found: N, 3·7. $C_{19}H_{12}ClNSe$ requires N, 3·8%); decomposition with aqueous sodium hydroxide furnished the free *base*, red microprisms, m.p. 209—210° (from cyclohexane), for which carbon determinations were unreliable (Found: H, 3·6; N, 4·1. $C_{19}H_{11}NSe$ requires H, 3·4; N, 4·2%).

6,13-*Dihydrobenzo*[e][1]*benzoselenino*[4,3-b]*indole* (VII).—Similarly prepared by indolisation of 2,3-dihydro-1-benzoselenin-4-one β-naphthylhydrazone (1·5 g.) [yellow needles, m.p. 189—190° (from ethanol)], this *indole* formed pale yellow needles (1 g.), m.p. 207° (from cyclohexane) (Found: C, 67·9; H, 3·9; N, 4·1%); the *picrate* gave brown-violet needles (from ethanol), m.p. 160—165° (instantaneous), with resolidification to form the picrate of (VIII) (Found: N, 9·8. $C_{25}H_{16}N_4O_7Se$ requires N, 9·9%).

Benzo[e][1]*benzoselenino*[4,3-b]*indole* (VIII).—The *picrate* gave orange-brown leaflets (from acetic acid), m.p. 278—280° (instantaneous; decomp. >190°) (Found: N, 9·8%); the *hydrochloride* yielded red needles (from aqueous ethanol), m.p. 187—190° (instantaneous; decomp. >160°) (Found: N, 4·0%). The free *base* formed crimson-red microprisms (from cyclohexane), m.p. 193—195° (instantaneous; decomp. >185°) (Found: H, 3·7; N, 4·5%); this substance, like its isomer (VI), failed to give reliable figures in carbon determinations.

Mass Spectra.—These were taken with an A.E.I. MS9 spectrometer [70 ev; insertion temperature 180° for compound (III), 190° for compound (VI), and 200° for compound (VIII)]; we thank Dr. B. Das and also Mr. G. Bérenger for help with this work.

[9/1982 *Received*, *November* 18*th*, 1969]

[8] *Cf.* T. E. Young and P. H. Scott, *J. Org. Chem.*, 1966, **31**, 343.