THE REACTION OF SOME INDOLES WITH SELENIUM DIOXIDE

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Summary

The reaction of selenium dioxide with indole in benzene gives 3,3′-diindolyl selenide. In separate experiments but with similar reaction conditions, 2-methylindole gave complex mixtures from which either 3,3′-di(2-methylindolyl) diselenide or the corresponding triselenide was isolated in low yield. 1,2-Dimethylindole gave 3,3′-di(1,2-dimethylindolyl) triselenide, also in low yield.

Some years ago, Witkop[1] studied the reaction of selenium dioxide with indole in benzene and obtained, in unspecified yield, a compound, m.p. 195°. Witkop did not propose a structure but the analytical figures, which corresponded to the empirical formula $C_{16}H_8N_2Se$, suggested that the compound did not contain an indole nucleus. We have reinvestigated this reaction and have isolated a product, m.p. 196–198° (presumably the above compound), but the yields were low (the highest being 23%) and were never reproducible. As the reaction proceeds, a fine precipitate of selenium metal is formed, which settles on the surface of the selenium dioxide, and appears to inhibit further reaction. The reaction also proceeded without a solvent but the yield was poor (7%).

Since the product (in methanol) exhibited ultraviolet maxima at 273 (inflexion), 280, and 288 mμ (log ϵ 4·06, 4·09, and 4·05 respectively), it appeared likely that the indole nucleus was intact. In addition, the intensities of the absorption maxima strongly suggested that two indole nuclei were present (indole exhibited maxima at 271, 277, and 288 mμ (log ϵ 3·78, 3·76, and 3·66 respectively)). The analytical figures for our compound were in good agreement with the empirical formula $C_{16}H_{12}N_2Se$ and therefore it appeared probable that the compound was a diindolyl selenide.

The infrared spectrum exhibited a sharp doublet at 3400 and 3408 cm^{-1} in the region expected for indole N–H stretching.[2] Additional doublets were also present at 1402 and 1409 cm^{-1} and at 1080 and 1095 cm^{-1}. Since all these infrared doublets occurred at practically the same frequencies as similar doublets found by Jardine and Brown[3] in the infrared spectrum of 3,3′-diindolyl sulphide, it seemed probable that the compound, m.p. 196–198°, was 3,3′-diindolyl selenide (I).

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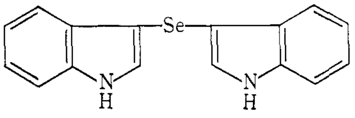
[1] Witkop, B., *Liebigs Ann.*, 1947, **558**, 106.

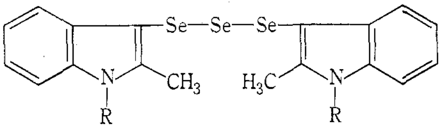
[2] Bellamy, L. J., "The Infrared Spectra of Complex Molecules." p. 251. (Methuen: London 1958.)

[3] Jardine, R. V., and Brown, R. K., *Can. J. Chem.*, 1964, **42**, 2626.

Aust. J. Chem., 1967, **20**, 359–64



(I)



(II) R = H (III) R = CH_3

The 60-Mc/s proton magnetic resonance spectra of indole and (I) were measured at the same concentration (0·3M) in acetone, dioxan, and dimethyl sulphoxide and the proton chemical shifts are shown in Table 1. The assignments for indole are based on the published 100-Mc/s spectrum of indole in acetone,[4] our chemical shift values being in good agreement with those of Black and Heffernan.[4] As can be seen from the table, the NH and C 2 proton shifts, which are in good agreement with those reported by Jardine and Brown for the same solvents,[5] are influenced by the nature of the solvent. The C 3 and C 4 proton shifts are practically unaffected by the nature of the solvent.

Table 1

CHEMICAL SHIFTS OF PROTONS OF 3,3′-DIINDOLYL SELENIDE AND OF INDOLE

Chemical shifts in τ values for 0·3M solutions. b, broad; vb, very broad; d, doublet; t, triplet; sx, sextet; m, multiplet

Proton	3,3′-Diindolyl Selenide			Indole		
	Dioxan	Me_2SO	Acetone	Dioxan	Me_2SO	Acetone
NH	0·37vb	−1·17b	−0·25vb	0·50vb	−1·02vb	−0·16vb
H 2	d 2·67*	d 2·43*	d 2·50†	t 2·93	t 2·70	t 2·75
H 3				sx 3·58	sx 3·59	sx 3·58
H 4 (m)	2·32	2·32‡	2·25	2·45	2·47	2·45

* J 2·6 c/s. † J 2·4 c/s. ‡ This signal is partly overlapped by the H 2 doublet.

The signal position for the NH proton of (I), which was readily assigned because the addition of deuterium oxide caused its disappearance, was influenced strongly by the solvent. The shift to lower fields, in the order dimethyl sulphoxide > acetone > dioxan, parallels that found for indole (Table 1) and other indole compounds.[5] The NH signal in dimethyl sulphoxide was much less broad than in the other two solvents.

The easily discernible sharp doublet (see Fig. 1(*a*)) collapsed to a sharp singlet (see Fig. 1(*b*)) (the sharpness of both doublet and singlet indicated a symmetrical structure) on the addition of deuterium oxide and was therefore coupled with the NH proton. The size of the coupling constant (J 2·6 c/s), which was practically the same as that (J 2·5 c/s) reported for coupling between the 1- and 2-protons of indole[4,6] and several substituted indoles[6] and greater than that (2·0–2·1 c/s) reported

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[4] Black, P. J., and Heffernan, M. L., *Aust. J. Chem.*, 1965, **18**, 357.

[5] Jardine, R. V., and Brown, R. K., *Can. J. Chem.*, 1963, **41**, 2067.

[6] Elvidge, J. A., and Foster, R. G., *J. chem. Soc.*, 1964, 981.

for coupling between the 1- and 3-protons,[4,6] suggested that the 2-position was unsubstituted. The sharp doublet occurred at a lower field in dimethyl sulphoxide than in dioxan, the difference (0·24 p.p.m.) being almost equivalent to that (0·26 p.p.m.) reported[3] for the sharp doublet (J 2·0 c/s) occurring in the spectrum of 3,3′-diindolyl sulphide when measured in the same two solvents. Except for the different coupling constant of the sharp doublet, the analogy between the latter compound and (I) is therefore extremely close. Supporting evidence that structure (I) is correct comes from the similarity of its p.m.r. spectrum in acetone (Fig. 1(*a*)) to the published spectrum of 3-selenocyanoindole[7] in acetone, in which however the sharp doublet occurs at lower field (τ 2·31), presumably as the result of the electronic effect of the more polar SeCN substituent.

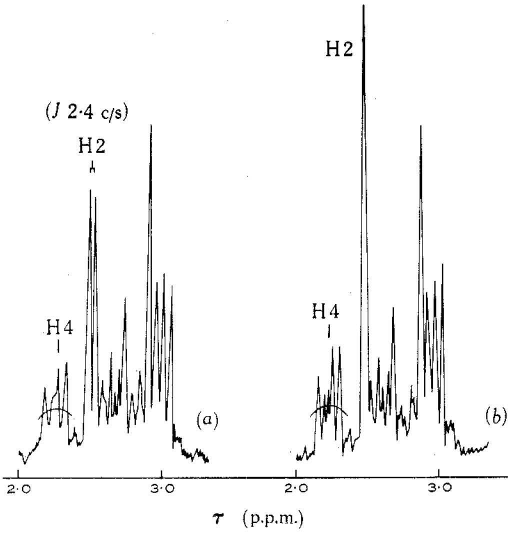

Fig. 1.—P.m.r. spectrum of 3,3′-diindolyl selenide. (*a*) 0·3M solution in acetone. (*b*) D_2O added to (*a*).

The low-field two-proton multiplet occurring in the p.m.r. spectrum of (I) (isolated from the rest of the spectrum except in dimethyl sulphoxide solution) was assigned to the protons at C 4 and C 4′ because it became less complex on the addition of deuterium oxide (the NH and C 2 protons of indole are weakly (0·8 c/s) coupled[4]). If this assignment is correct, it would be expected that a selenium atom located at the 3-position would exert an anisotropic deshielding effect on the neighbouring "*peri*" (C 4) proton.* Such a deshielding effect (greatest in acetone (0·20 p.p.m.)) relative to the C 4 proton of indole was indeed observed.

The corresponding reaction of selenium dioxide with 2-methylindole produced complex mixtures from which coloured crystalline products were isolated in low

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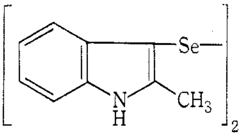
* Deshielding of the indole C 4 proton by carbonyl substituents located at the 3-position has been reported.[8,9]

[7] Agenas, L.-B., *Ark. Kemi*, 1964, **23**, 157.

[8] Remers, W. A., *J. Am. chem. Soc.*, 1964, **86**, 4608.

[9] Allen, G. A., Pidacko, C., and Weiss, M. J., *Chemy Ind.*, 1965, 2096.

yield by silica gel chromatography. Under similar reaction conditions, either the corresponding 3,3′-diselenide (IV) or the 3,3′-triselenide (II) was obtained. The former compound appeared to be the same as that described by Agenas.[7] The ultraviolet spectrum showed maxima at 222, 281, 286 (inflexion), and 335 mμ but the absorption intensities (log ε 4·73, 4·20, 4·17, and 3·79 respectively) were lower than those reported.[7] The first three maxima are due to the indole nucleus and the fourth maximum to the Se–Se group.[7,10] Supporting evidence for an intact indole nucleus was given by the infrared spectrum (maximum at 3390 cm^{-1} (NH)) and the p.m.r. spectrum (NH signal at τ −1·37 removed by the addition of deuterium oxide). The remaining protons were revealed as a complex multiplet centred at τ 2·83. The previous assignment of the sharp doublet in the p.m.r. spectrum of (I) to the proton at C2(2′) is strengthened by the absence of a similar doublet in the p.m.r. spectrum of (IV). Although the triselenide (II), unlike the diselenide (IV), decomposed rapidly in methanolic solution, an ultraviolet spectrum was obtained which revealed maxima at 280, 286 (inflexion), and 335 mμ. Because of this instability, the absorption intensities (log ε 4·25, 4·22, and 3·93 respectively) are probably not meaningful. The infrared spectra of (II) and (IV) were practically superimposable, showing that, as suggested by Agenas,[7] the addition of an extra selenium atom has negligible effect on the infrared spectrum of a diselenide. The reason for the formation of different products from similar reaction conditions is not clear, but it seems reasonable to suppose that the unstable triselenide (II) is formed first and decomposes to the diselenide (IV) either during the reaction or the subsequent silica gel chromatography (when the diselenide was obtained, more fractions (see Experimental) were taken and therefore the reaction product was in contact with the silica gel longer).



(IV)

Finally, the reaction of selenium dioxide with 1,2-dimethylindole in benzene gave, after silica gel chromatography, a triselenide, presumably 3,3′-di(1,2-dimethylindolyl) triselenide (III). This compound, which like (II) decomposed rapidly in methanolic solution, showed ultraviolet maxima at 282 and 331 mμ. Because of stability difficulties, the p.m.r. spectra of both triselenides ((II) and (III)) could not be measured.

The reactions described above form yet another example of the selenium insertion type well known[11,12] in reactions of selenium dioxide with other nitrogen-containing compounds, notably aromatic amines. With indoles, however, oxidation processes may also be occurring simultaneously and may be responsible for the complex mixtures obtained (only in the reaction with indole was starting material recovered).

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[10] Chierchi, L., and Passerini, R., *Boll. scient. Fac. Chim. ind. Univ. Bologna*, 1954, **12**, 131.

[11] Rabjohn, N., *Org. React.*, 1949, **5**, 331.

[12] Watkins, G. R., and Clark, C. W., *Chem. Rev.*, 1945, **36**, 256.

EXPERIMENTAL

(a) *General*

Benzene and light petroleum (b.p. 60–70°) used for chromatography were distilled and kept over sodium wire. Methylene chloride was distilled over potassium carbonate (kept for 24 hr in an oven at 120°). Column chromatography was carried out on Merck silica gel (0·2–0·5 mm) and thin-layer chromatography (solvent system benzene/light petroleum 3 : 2) on Merck silica gel G (spots were detected by iodine vapour). All melting points are uncorrected. The elementary analyses were carried out by the Australian Microanalytical Service, Melbourne. All analytical samples were dried *in vacuo* over P_2O_5 at 60° for 4 hr. Ultraviolet spectra were measured in methanol (Fisher "Spectroanalyzed") on a Beckmann DK-2 recording spectrophotometer. Infrared spectra (0·8% KBr disks) were measured on a Beckmann IR9 instrument. The 60-Mc/s p.m.r. spectra were obtained on a Varian A60 spectrometer (tetramethylsilane as internal standard).

(b) *Reactions of Selenium Dioxide*

(i) *With Indole in Benzene*

Finely ground selenium dioxide (May & Baker grade) (1 g) was added to a solution of indole (0·5 g) in benzene (20 ml) and the mixture warmed on the steam-bath. A fine red precipitate of selenium metal, which settled on the surface of the selenium dioxide, was quickly formed. After 2 hr reflux, the mixture was filtered hot (charcoal). The pale yellow filtrate was evaporated to 5 ml and hexane added until turbidity was observed. A pale yellow solid (129 mg; m.p. 192–194°) slowly crystallized. The filtrate gave a further quantity of solid (28 mg; m.p. 189–193°), making a total yield of 157 mg (23%). When crystallized from hexane/methylene chloride, *3,3′-diindolyl selenide* had m.p. 196–198° (Found: C, 61·5; H, 4·0; N, 8·8; Se, 27·3. $C_{16}H_{12}N_2Se$ requires C, 61·7; H, 3·9; N, 9·0; Se, 25·4%).

In another experiment, the reaction of selenium dioxide (5 g) with indole (5 g) in benzene (100 ml) gave the same product, m.p. 189–193° (raised to 196–198° on recrystallization from hexane/methylene chloride) in 7% yield (0·48 g). The filtrate from this product was chromatographed on silica gel (20 g). Elution with benzene/light petroleum (1 : 1) gave fractions containing indole (3·21 g). Elution with benzene containing increasing amounts of methylene chloride gave a series of fractions which contained reddish brown solids which appeared to be complex mixtures (thin-layer chromatography) from which no pure product could be isolated.

When an intimate mixture of indole (1 g) and selenium dioxide (1 g) was warmed on the steam-bath, a vigorous reaction occurred when the indole melted. After 15 min, the reaction was worked up as described above and a product (0·09 g; 7% yield), m.p. 187–192°, isolated. This compound was identical (mixed m.p. and i.r. spectrum) with the abovementioned compound.

(ii) *With 2-Methylindole in Benzene*

(1) Selenium dioxide (2 g) was added to a solution of 2-methylindole (1·12 g) in benzene (40 ml) and the mixture was boiled under reflux for 2 hr. The resultant mixture was filtered hot (charcoal) and the filtrate (reduced to 10 ml) chromatographed on a column of silica gel (15 g). The column was eluted with light petroleum containing increasing amounts of benzene, the fractions (each 100 ml) eluted with benzene/light petroleum (3 : 2) and benzene alone giving a solid (0·34 g; 16% yield), which appeared to be a single compound (thin-layer chromatography). Recrystallization from hexane/methylene chloride gave *3,3′-di(2-methylindolyl) triselenide* as orange-red plates, m.p. 194–197° (Found: C, 43·2; H, 3·5; N, 5·5; Se, 46·5. $C_{18}H_{16}N_2Se_3$ requires C, 43·5; H, 3·2; N, 5·6; Se, 47·6%).

(2) The reaction was carried out exactly as in (1) followed by chromatography on silica gel (15 g). Elution with benzene/light petroleum (3 : 2) (10 fractions, each 150 ml) gave a series of yellow solids (total 0·62 g). Recrystallization from hexane/benzene gave red-yellow plates (0·39 g; 22% yield), m.p. 175–178°. Recrystallization from aqueous acetone gave m.p. 180–182° (Found: C, 51·7; H, 4·0; N, 6·9; Se, 36·0. $C_{18}H_{16}N_2Se_2$ requires C, 51·7; H, 3·9; N, 6·7; Se, 37·8%). Agenas[7] gives m.p. 183–184° for 3,3′-di(2-methylindolyl) diselenide.

(iii) *With 1,2-Dimethylindole in Benzene*

As for 2-methylindole but with 1,2-dimethylindole (1·24 g). After the usual work-up, the product was chromatographed on silica gel (15 g). A series of fractions (each 100 ml) was eluted with light petroleum containing increasing amounts of benzene and were grouped together on the basis of thin-layer chromatography. The solid product (0·52 g; 23% yield) eluted with solvent mixtures ranging from light petroleum/benzene (9 : 1) to light petroleum/benzene (1 : 1) was crystallized from benzene/hexane to give *3,3′-di(1,2-dimethylindolyl) triselenide* as orange plates, m.p. 174–176° (Found: C, 45·7; H, 3·9; N, 5·3; Se, 43·4. $C_{20}H_{20}N_2Se$ requires C, 45·7; H, 3·8; N, 5·3; Se, 45·1%).

In the experiments described in (ii) and (iii), the complex mixtures (thin-layer chromatography) of reddish brown solids, which were eluted with solvent systems consisting of benzene and benzene containing increasing amounts of methylene chloride, were not investigated further.

ACKNOWLEDGMENTS

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