Selenium Derivatives in the Indole series

I. On the Synthesis of 3-Selenocyanoindole and 3,3'-Diindolyl Diselenide

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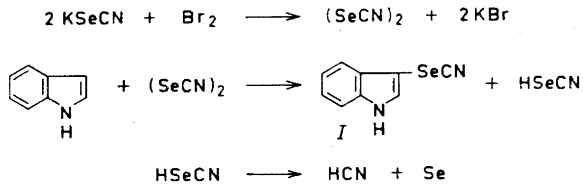
Among the aromatic selenium derivatives described in the literature, those related to the simple heterocyclics are most sparsely occurring. It was found that no selenium derivative of indole has been previously described. As a part of an investigation on different types of organic selenium compounds at this Institute, attempts have been made to prepare some heterocyclic selenium derivatives. This paper deals with the preparation of 3-selenocyanoindole (I) and 3,3'-diindolyl diselenide (II).

Many methods used in the preparation of organic sulphur compounds are applicable to the corresponding selenium compounds. In 1960 Grant and Snyder [1] reported the preparation of 3-thiocyanoindole by reacting indole with thiocyanogen, and 3,3'-diindolyl disulphide by hydrolysis of the thiocyano compound. The use of the selenocyanation method has been restricted by the fact that selenocyanogen is a most instable substance, hardly possible to isolate. Birckenback and Kellermann [2] have reported that they managed to isolate it, but its disproportionation into the corresponding mono- and triseleno compounds is described by many authors, *e.g.* Kaufmann and Kögler [3].

However, Challenger *et al.* [4], after attempting the isolation of selenocyanogen, found that it was possible to use triseleno dicyanide in the selenocyanation of aniline and dimethylaniline. Later some other methods have been tried, and Müller *et al.* [5] have recently prepared 1-hydroxy-2,6-di-*t*-butyl-4-selenocyanate in 33 % yield by dissolving 2,6-di-*t*-butylphenol and potassium selenocyanate in methanol and adding bromine at room temperature. A third method of performing the selenocyanation has now been tried in the preparation of 3-selenocyanoindole, following the method of Grant and Snyder on 3-thiocyanoindole. A suspension of potassium selenocyanate in methanol was allowed to react with bromine at −60°. To the yellow suspension thus obtained, a methanolic solution of indole was added without allowing the temperature to rise above −50°. After completion of the reaction, the temperature was allowed to rise to zero. At about −30° a quantity of red selenium was liberated. The reaction mixture was worked up by pouring it onto ice followed by ether extraction. The selenium obtained was collected and found to correspond to 90–95 % of the theoretical amount in Scheme 1. In the same way the crude organic product corresponded to the theoretical amount and after recrystallization yielded 70 % of 3-selenocyanoindole.



Scheme 1

Considering the amounts of elemental selenium and 3-selenocyanoindole obtained, there is reason to believe that at the temperature at which the reaction was performed selenocyanogen exists. The amounts of product further indicate that the reaction proceeds as indicated. Without further proof this convenient method of selenocyanation is communicated.

When recrystallizing the crude material, a high-melting by-product was obtained. It was possible to identify it as 3,3'-diindolyl diselenide by infra-red spectroscopy.

The selenocyano compound was found to be even more easily hydrolyzable than the corresponding thiocyano compound earlier described [1]. The hydrolysis was complete when dissolving the 3-seleno-

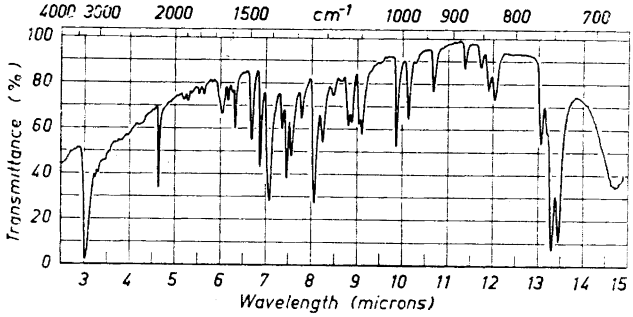
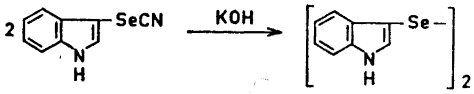


Fig. 1. Infra-red spectrum of 3-selenocyanoindole (I) in KBr. 2.5—15 μ.

cyanoindole in methanol and on addition of methanolic potassium hydroxide solution. At once the yellow solution adopted a darker colour and when adding water, the diselenide was precipitated in quantitative yield. After recrystallization from methanol-water an analytical sample was obtained.



Scheme 2 II

However, it was found that in some cases it was impossible to obtain the analytically pure diselenide. Certain products contained too much selenium and the selenium percentage increased after each recrystallization. The product was also somewhat darker coloured. On the other hand, in some cases the selenium percentage was too low preventing purification of the product. These complications occurred for instance when the selenocyano compound was not carefully purified. The cause is possibly a disproportionation of the diselenide into mono- and triselenide. This is known to happen under certain circumstances with diselenides of different types [6-7], as well as with selenocyanogen, mentioned above. In a further communication on this and similar diselenides the investigation of the disproportionation will be considered in detail.

Experimental. 3-Selenocyanoindole. (I). A suspension of 30 g (0.208 mole) of potassium selenocyanate in 50 ml of absolute methanol was prepared and cooled to —70°. A solution of 5.2 ml (16.2 g; 0.102 mole) of bromine in 80 ml of absolute methanol was prepared and added to the suspension at such a rate that the temperature did not exceed —50°. A solution of 12 g (0.102 mole) of indole in 80 ml of absolute methanol was then added to the yellow reaction mixture, not allowing the temperature to exceed —50°. The mixture was stirred for 1 hour at —60° to complete the

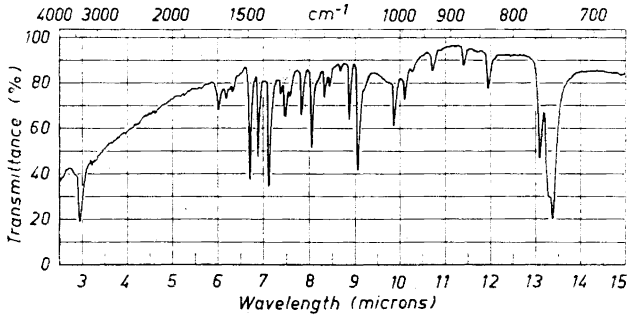


Fig. 2. Infra-red spectrum of 3,3′-diindolyl diselenide (II) in KBr. 2.5—15 μ.

reaction, and the temperature then allowed to rise to 0°. At about −30° a large amount of red selenium was liberated. The reaction mixture was poured onto ice, the ice allowed to melt and the mixture was filtered. The yellow filtrate was extracted with ether and the solid material boiled repeatedly with ether until the solvent remained colourless. The combined ether extracts were dried over sodium sulphate and the ether removed by distillation. The residual ether was removed in a vacuum desiccator. A yellow, crystalline product was obtained. Yield 22.0 g (97.5 %). M.p. 80−85°.

The red selenium was boiled with alcohol and water. The grey selenium thus obtained was filtered off and dried. Yield 7.6 g (46.5 % of the introduced amount in the form of potassium selenocyanate, or 93 % of the calculated amount according to Scheme 1).

The product was dissolved in methylene chloride, boiled with *norite*, and, after filtering, the solution was concentrated to 100 ml and diluted with 100 ml of light petroleum (b.p. 30−65°). Upon standing in a refrigerator the solution gave 15.7 g (70 %) of pale yellow crystals in three crops, m.p. 91−96°. After two more recrystallizations the product melted at 98.5−100°.

(Found: Mol. wt., ebullioscopically in benzene 239; C 48.92; H 2.77; N 12.52; Se 35.56. Calc. for $C_9H_6N_2Se$: Mol. wt. 221.1, C 48.89; H 2.74; N 12.67; Se 35.71.).

3,3'-Diindolyl diselenide (II) A solution of 10.8 g (0.049 mole) of 3-selenocyanoindole in 100 ml of methanol was prepared. To this solution were added *ca* 50 ml of a 5 % methanolic solution of potassium hydroxide. The reaction mixture immediately became yellow-brown. After standing at room temperature for a few minutes, the solution was diluted with *ca* 200 ml of water. A bright yellow precipitate was obtained, that was filtered off and dried in a desiccator. The yield was 9.5 g (100 %), m.p. 167−172°. After two recrystallization from methanol-water, the product was obtained as bright yellow needles. M.p. 178−179.5°.

(Found: Mol. wt., ebullioscopically in benzene 384; C 49.57; H 3.18; N 7.10; Se 40.29. Calc. for $C_{16}H_{12}N_2Se_2$: Mol. wt. 390.2, C 49.25; H 3.10; N 7.18; Se 40.47.)

The selenium analyses were carried out according to Fredga [8].

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Specific Activities of Free, Neutral-Salt Soluble and Insoluble Hydroxyproline after Administration of ^{14}C-Proline to Chick Embryos

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Since the investigations of Stetten [1], it has been known that the hydroxyproline of collagen is not derived from free hydroxyproline but from proline that is hydroxylated during the synthesis of collagen. It has been shown, however, that in carrageenan granuloma [2] and polyvinyl sponge implants [3] considerable amounts of free hydroxyproline are present even during early stages of the development of connective tissue. Tissues of chick embryos likewise have a relatively high content of free hydroxyproline [4-6]. Mitoma *et al.*[7] found that free hydroxyproline could be incorporated in small amounts into collagen in chick embryos, but the later work of Prockop *et al.*[8] indicated that free hydroxyproline cannot be a significant source for collagen hydroxyproline even in rapidly developing chick embryos. Therefore they suggested that the free hydroxyproline of