

NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. LIV.*

2-(2-THIENYLSELENOMETHYL)BENZOIC ACID AND ITS TRANSFORMATIONS

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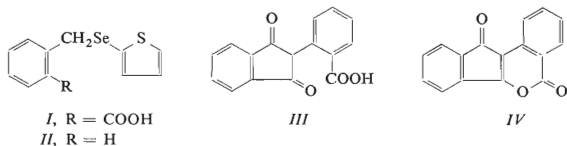
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2-Thiophenselenol obtained in the reaction of 2-thienylmagnesium iodide with elementary selenium was converted to 2-(2-thienylselenomethyl)benzoic acid (*I*) by reacting with phthalide and sodium ethoxide in ethanol. A by-product of the reaction was the dioxo acid *III* which, on heating, is converted to the orange-red benz[*d*]indeno[1,2-*b*]pyran-5,11-dione (*IV*). When attempting to cyclize the acid *I* with polyphosphoric ester, decarboxylation to selenide *II* and cleavage of the C—Se bond with concomitant formation of the oxoenol-lactone *IV* took place.

The high antihistaminic activity of 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*b*]benzo[*e*]thiepin (dithiadene)¹⁻⁴ and the interesting results of our studies⁵⁻⁷ on the selenium isosters of three series of sulfur-containing psychotropic agents provoked the attempt to prepare the selenium isoster of dithiadene, *i.e.* a compound containing the unknown tricyclic system *cf.* thieno[2,3-*b*]benzo[*e*]selenepin. The attempt was unsuccessful but some interesting reactions were observed. Reaction of 2-thienylmagnesium iodide^{3,8} with elementary selenium in ether resulted in the unstable 2-thiophenselenol which was in a crude state treated with phthalide⁹ in a solution of sodium ethoxide in boiling ethanol. A mixture of two compounds of acidic character was obtained, the principal component having been isolated in pure state by crystallization from benzene and light petroleum. It has the structure of 2-(2-thienylselenomethyl)benzoic acid (*I*) (compare the analogous reactions of thiophenols¹⁰⁻¹³, 1-thionaphthol¹, 2-thiophenol^{1,3} and selenophenols⁶). The minor product has the empirical formula C₁₆H₁₀O₄ which shows that the compound was not formed by a simple condensation of two phthalide molecules but that an oxidative reaction has taken place simultaneously. Its UV spectrum indicates a considerable degree of conjugation and the IR spectrum points to the presence of carboxyl and of a conjugated keto group. On heating, this compound is dehydrated to the orange-red substance C₁₆H₈O₃, the molecular weight of which was determined by mass spectrometry. Its UV spectrum indicates further intensification of conjugation, the NMR spectrum contains only signals of aromatic protons and

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the IR spectrum displays bands of a conjugated keto group in a five-membered ring and of an enol- δ -lactone.



Irrespective of the mechanism of the transformations that may have taken place the following were considered as possible structures of the compounds with formulae $C_{16}H_{10}O_4$ and $C_{16}H_8O_3$: 2-(2-carboxyphenyl)-1,3-indandione (*III*) and benz[*d*]indeno[1,2-*b*]pyran-5,11-dione (*IV*). Compounds *III* and *IV* were described by Pailer and coworkers¹⁴. Compound *III* was obtained by the authors either by condensation of phthalaldehydic acid with phthalide in the presence of sodium ethoxide, or by rearrangement of hydrodiphtalyl^{15,16} with sodium ethoxide. On heating above 190°C or in the presence of acetic anhydride the red enol-lactone *IV* is formed, with a melting point corresponding to the value of our product. Reference¹⁴ gives no spectral data on *III* and *IV* and a direct comparison was not attempted; nevertheless, the identity of our products as *III* and *IV* appears to be incontestable.

Under different conditions we attempted to cyclize acid *I* to 9 H-thieno[2,3-*b*]benzo[*e*]selenepin-4-one with polyphosphoric acid or ester, *i.e.* by reactions proceeding smoothly in the sulfur-containing series^{1,3}. The products of these attempts were rather complex mixtures, the only substance containing both selenium and sulfur that has been isolated being 2-thienyl benzyl selenide (*II*) formed apparently by decarboxylation of acid *I*. Another product isolated here was the red enol-lactone *IV*, the formation of which indicates that in the attempts at cyclization the Se—C bond was also cleaved.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol) in a Unicam SP 200 G spectrophotometer.

2-(2-Thienylselenomethyl)benzoic Acid (*I*)

Grey selenium (38 g) was added under stirring in a nitrogen atmosphere over a period of 45 min to a solution of 2-thienylmagnesium iodide (prepared by reaction of 103.5 g 2-iodothiophene⁸ with 13.25 g magnesium in 450 ml ether) and the mixture was refluxed for 2 h. After standing overnight it was decomposed under cooling with 200 ml 20% HCl, after separation the aqueous phase was extracted with ether and the ether solutions were combined. The product was extracted twice with 200 ml 10% NaOH, the alkaline aqueous solution was separated and overlaid with benzene and, under cooling, made acid with concentrated HCl. After shaking, the benzene phase was separated, dried (Na_2SO_4) and evaporated at reduced pressure. A total of 43 g (55%) crude 2-thiopheneselenol was obtained which could not be redistilled without

decomposition and therefore was used for further work as such. The whole residue was dissolved in a solution of sodium ethoxide (from 6.07 g sodium and 100 ml ethanol), 35.4 g phthalide⁹ was added and the mixture was refluxed for 4 h. Ethanol was evaporated, the crystalline residue was dissolved in 500 ml water, the solution was washed with benzene, filtered with charcoal and made acid with concentrated hydrochloric acid. The precipitated product was filtered, washed with water, dried and crystallized from a mixture of benzene and light petroleum whereupon 5.0 g of an insoluble substance separated. The solution gave rise to 48 g acid *I* which was further crystallized from aqueous ethanol, m.p. 127–128°C. For C₁₂H₁₀O₂SSe (297.2) calculated: 48.49% C, 3.39% H, 26.57% Se; found: 48.38% C, 3.43% H, 27.07% Se.

2-(2-Carboxyphenyl)-1,3-indandione (*III*)

The fraction (5.0 g) obtained in the preceding experiment and insoluble in benzene–light petroleum was recrystallized from aqueous ethanol. It has a diffuse melting point at 180–230°C, being converted to an orange-red compound which then melts at 261–263°C. UV spectrum: λ_{\max} 221 nm (log ϵ 4.58), 250 nm (4.18), 282 nm (3.93), 340 nm (3.70). IR spectrum: 756 (1,2-C₆H₄), 1589 and 1602 (Ar), 1695 (Ar—COOH), 1730 and 1749 (1,3-indanedione), 3170 cm⁻¹ (COOH). For C₁₆H₁₀O₄ (266.2) calculated: 72.18% C, 3.79% H; found: 72.05% C, 3.92% H. Pailer and coworkers¹⁴ described the preparation of this compound by authentic methods but did not report its analysis and characterized it only by its behaviour on heating which is in good agreement with the behaviour of the present sample.

Benz[*d*]indeno[1,2-*b*]pyran-5,11-dione (*IV*)

Compound *III* (0.825 g) was heated for 3 h to 200°C and the product was recrystallized from a mixture of benzene and ethanol; 0.65 g red needles, m.p. 261–262°C. UV spectrum: λ_{\max} 233 nm (log ϵ 4.49), 246 nm (4.55), 273 nm (4.47), 348 nm (3.86). IR spectrum: 759 (1,2-C₆H₄), 1606 (Ar), 1626 (Ar—C=C), 1705 (Ar—CO in a five-membered ring), 1763 cm⁻¹ (enol-lactone with a six-membered ring). NMR spectrum (CF₃COOH) shows only signals of aromatic protons. Molecular weight determined by mass spectrometry: 248. For C₁₆H₈O₃ (248.2) calculated: 77.41% C, 3.25% H; found: 77.80% C, 3.20% H. Pailer¹⁴ described the compound as red needles melting at 257°C.

Attempts at Cyclization of Acid *I*

A. Ethanol (11.7 ml) was added dropwise under stirring to a mixture of 21.3 g phosphorus pentoxide and 300 ml toluene. After 30 min a total of 27.4 g acid *I* was added and the mixture was refluxed under stirring for 6 h. After standing overnight it was decomposed with 250 ml water, the insoluble fraction was filtered off and the filtrate was separated. The toluene layer was washed with 5% NaOH and evaporated at reduced pressure. From the residue (16.0 g) one-half was distilled. The lowest-boiling fraction (2.15 g, b.p. 92–96°C/0.3 Torr) was chromatographically homogeneous and was redistilled before analysis: b.p. 87°C/0.01 Torr. According to the analysis, we are dealing here with 2-thienyl benzyl selenide (*II*). For C₁₁H₁₀SSe (253.2) calculated: 52.18% C, 3.98% H, 31.18% Se; found: 51.74% C, 3.70% H, 31.49% Se. The second fraction (2.25 g, b.p. 160–175°C/0.2 Torr) crystallized to 30 mg red needles melting at 261–262°C (benzene) which were identified as compound *IV*. The distillation residue is a mixture of at least five compounds.

B. Acid *I* (9.0 g) was treated analogously to procedure (*A*) but benzene was used instead of toluene. Similar treatment yielded 5.9 g of a red product which was extracted with hot ethanol to yield 1.9 g compound *IV* (red needles), m.p. 261–262°C.

The mass spectrum of compound IV was kindly recorded by Prof. H. Budzikiewicz, Technische Hochschule, Braunschweig. The NMR spectrum of the same compound was recorded by Dr B. Kákáč and Dr J. Holubek in the department of physical chemistry of this institute. The analytical determinations were done at the analytical department of this institute (head Dr J. Körbl) by Mr K. Havel, Mrs V. Šmidová and Dr J. Čech.

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