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Synthesis of 2H-3,4-Dihydro-1,2-Benzoselenazin-3-One and Derivatives : a New Heterocyclic Ring System.

Pierre V. Jacquemin, Léon E. Christiaens and Marcel J. Renson*

Heterocyclic Organic Chemistry
Institute of Organic Chemistry - B6
University of Liège, Sart-Tilman, B-4000 Liège (Belgium)

Michel J. Evers and Norbert Dereu

Rhône-Poulenc Rorer
Centre de Recherches de Vitry-Alfortville
13 Quai Jules Guesdes F-94403 Vitry-sur-Seine (France)

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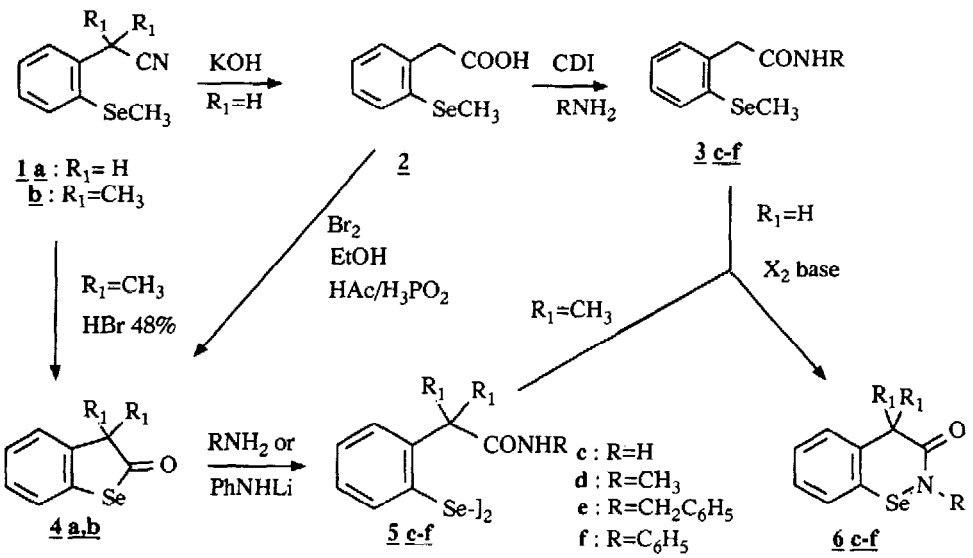
Abstract: *The synthesis of 2H-3,4-dihydro-1,2-benzoselenazin-3-ones which are six-membered homologues of Ebselen is described in order to evaluate their glutathione peroxidase-like activity. Spectral data of these new heterocycles are given.*

Glutathione peroxidase, a mammalian selenoenzyme which catalyzes the reduction of hydroperoxides by glutathione[1],acts through an active site containing the essential selenocysteine residue. Its activity is due to a catalytic cycle involving different oxidation states of selenium, among which a selenenic acid function plays the key role. Among molecules which would mimic the structure of the active site of the enzyme, N-phenyl-1,2-benzisoselenazolin-3-one (Ebselen^{INN})[2] is in fact the most prominent active and interesting compound. It contains a selenenic moiety stabilized by intramolecular cyclisation in a cyclic N-aroyl selenamide. Due to its strongly bound selenium moiety, demonstrated by a ^{75}Se-labeling study[3], Ebselen does not release selenium from the molecule, which probably accounts for its relative lack of toxicity. The discovery of its anti-inflammatory and glutathione peroxidase (GSH-Px)-like activity has prompted numerous biochemical and pharmacological investigations[4]. Similarly the study of the mechanism of the GSH-Px like activity of Ebselen has shown the formation in a catalytic cycle of various intermediates constituting different oxidation levels of the selenium atom[5]. The inactivity of the sulfur analog demonstrates the essential nature of the selenium moiety. Several structural modifications including substituent effect and isosteric replacement have been reported[6(a-c)]. For instance selenenylsulfides[6d] and

diselenides[6(e,f)] and the fundamental non benzo condensed isoselenazolidinone ring[6g] appeared recently in the literature. Ebselen is presently being investigated in clinical trials.

However, the poor solubility of Ebselen and its anlogues remains a problem for optimal development. We therefore have investigated the possibility of modifying the structure of Ebselen more fundamentally by incorporating a supplementary tetrahedral carbon (i.e.-CH_2- group) into the heterocycle, so that the non planar structure would lead to a less compact crystal lattice and therefore enhance solubility. The position of this -CH_2- must be carefully determined. This new structure must preserve: a)a selenium-$C_{aromatic}$ carbon bond , to avoid selenium release and maintain the low toxicity of Ebselen; b) a selenium-nitrogen bond, which is responsible for the GSH-Px like activity, and c) a nitrogen-carbonyl bond to stabilize the selenenamide structure. Therefore the sole possibility consists of inserting the -CH_2- group between the carbonyl function and the aromatic ring . This enlarged Ebselen-like ring compound is the hitherto unknown 2H-3,4-dihydro-1,2-benzoselenazin-3-one ring **6a**, which constitutes a new heterocyclic ring system. In addition to the basic heterocycle **6a** and its N-substituted derivatives **6a(d-f)** for which we suspected a low stability due in particular to its susceptibility to oxidation, that we subsequently demonstrated experimentally, we also were interested in the 4,4-dimethylated substituted heterocycles **6b(c-f)** whose enhanced stability has been demonstrated. To our knowledge, the corresponding 2H-3,4-dihydro-1,2-benzothiazin-3-ones have not been previously described. Chemically speaking, although the last step of the ring formation resembles the formation of the Ebselen ring, the formation of the precyclic intermediates is indiscutably novel. We though that a pentaatomic selenolactone ring system would be the best approach for the creation of this new heterocycle.



We started from o-methylselenophenylacetonitrile[7] **1a** and **1b**. Alkaline hydrolysis of nitrile **1 a** gave a nearly quantitative yield of phenylacetic acid **2**, however the alkaline hydrolysis of nitrile **1 b**, using various conditions led only to starting material with a minor amount of unidentified products. We circumvented these difficulties by first transforming **1b** into the selenolactone **4b**[8] followed by amidification either with the free amine or the corresponding anion in the case of the less nucleophilic aniline and

subsequent selenol oxidation into a diselenide[9]. The transformations are easy and give excellent yields of amides **5b(c-f)**.

The one pot conversion of the phenylacetic acid **2** into the amides **3c-f** using thionyl chloride and the amine was unsuccessful and led to undefined products. However **2** was easily transformed into amide **3** by the carbonyldiimidazole (CDI) method[10].

It is interesting to report that in contrast to transformation **1b** to **4b**, the selenolactone **4a** could not be obtained directly from **1a** using aqueous HBr. The synthesis of this selenolactone **4a** has been previously published starting from acid **2**[11].

Selenides **3**[12] and diselenides **5**[13] were cyclised into the 2H-3,4-dihydro -1,2-benzoselenazin-3-ones **6c-f**[14] by methods used for the syntheses of benzisoselenazolinones[15] namely transformation to a selenenylhalide ($SOCl_2$, SO_2Cl_2, Br_2) and dehydrohalogenation by a base (Et_3N, pyridine, Na_2CO_3).

(GSH-Px)-like activities and biological properties of heterocycles **6** will be reported elsewhere.

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7 - Compound **1a** is known : Christiaens L.; Renson M. *Bull. Soc. Chim. Belges* **1970**,*79*,235. Compound **1b** has been obtained in 70% yield by a two-fold methylation of **1a** (NaH, DMF, CH_3I).

8 - The selenolactone **4b** has been obtained in 80% yield by refluxing **1b** in azeotropic HBr for 24h. ^{1}H-NMR($CDCl_3$):1,4(s,6,CH_3);7.0-7.6(m,4,ArH).

9 - A THF solution of lactone **4b** is treated overnight with an excess of the free amine or 1 equiv. of C_6H_5NHLi. Usual work-up gives amide **5**.

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12 - Characterization of compounds **3c-f** [Yield % - M_p(°C) - ^{1}H-NMR($CDCl_3$/HMDSO) ppm]:**3c**: 85% - 160-162°C - 2,2(s,3,$SeCH_3$), 3,5(s,2,CH_2), 6,6-7,6(m,ArH + NH) - **3d**: 85% - 148-150°C - 2,2(s,3,$SeCH_3$), 2,7(d,3,$NHCH_3$), 3,7(s,2,CH_2), 6,9-7,5(m,4,ArH) - **3e**: 90% - 130-132°C - 2,2(s,3,CH_3), 3,7(s,2,CH_2), 4,3(d,2,CH_2NH), 7,1-7,3 m,9,ArH) - **3f**: 80% - 118-121°C - 2,2(s,3,CH_3), 3,8(s,2,CH_2), 6,7-8(m,10, ArH + NH).

13 - Characterization of compounds **5c-f**: [Yield % - M_p(°C) -^{1}H-NMR($CDCl_3$/HMDSO)ppm]:**5c**: 85% - 196-198°C - 1,4(s,6,CH_3), 6,5-7,9(m,4,ArH) **5d**: 85% - 164-167°C - 1,5(s,6,CH_3), 2,6(d,3,CH_3NH), 7,2-7,9(m,4,ArH) **5e**: 90% - 152-155°C - 1,5(s,6,CH_3), 4,3(d,2,CH_2NH), 6,5-7,9(m,9,ArH) **5f**: 60% - 232-236°C - 1,6(s,6,CH_3), 6,8-7,8(m,9,ArH)

14 - (a) All heterocycles are new, gave satisfactory elemental analysis within 0.1% and gave correct mass spectra (based on ^{80}Se). Heterocycles **6** were recrystallized from a mixture of ligroïne and toluene except for **6a,c** (CH_2Cl_2/toluene) and **6b,c** (CH_2Cl_2/ligroïne). The two latter molecules had to be crystallized without heating to prevent thermal decomposition. (b) - Characterization of heterocycles **6**: [Yield % - M_p(°C) - $\nu_{C=O}$(KBr) - ^{1}H-NMR($CDCl_3$/HMDSO)ppm]: **6a,c**: 40% - 142-145°C - 1639 cm^{-1} - 3,5(s,2,CH_2), 7,0-7,7(m,4,ArH) **6a,d**: 45% - 73-75°C - 1614 cm^{-1} - 3,2(s,3,CH_3), 3,7(s,2,CH_2), 7,2-7,6(m,4,ArH) **6a,e**: 60% - 74-75°C - 1611 cm^{-1} - 3,7(s,2,CH_2), 4,7(s,2,CH_2N), 6,8-7,6(m,9,ArH) **6a,f**: 20% - 155-157°C - 1650 cm^{-1} - 3,8(s,2,CH_2), 7,0-7,9(m,9,ArH) **6b,c**: 75% - 130-132°C - 1624 cm^{-1} - 1,5(s,6,CH_3), 6,8-8,0(m,4,ArH) **6b,d**: 45% - 106-109°C - 1618 cm^{-1} - 1,4(s,6,CH_3), 3,1(s,3,NCH_3), 7,1-7,5(m,4,ArH) **6b,e**: 60% - 86-87°C - 1626 cm^{-1} - 1,6(s,6,CH_3), 4,8(s,2,CH_2N), 7,0-7,6(m,9,ArH) **6b,f**: 75% - 90-92°C - 1630 cm^{-1} - 1,8(s,6,CH_3), 6,9-7,7(m,9,ArH).

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