SYNTHESIS OF α-AMINO ALCOHOLS OF THE SELENOPHENE SERIES

N. N. Magdesieva, T. A. Balashova, and G. M. Dem'yanova

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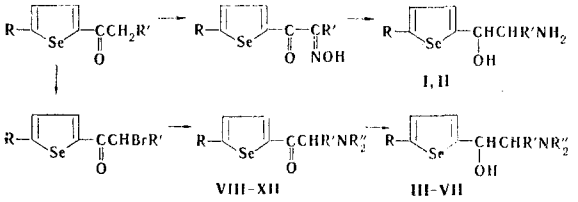
(2-Selenienyl)ethanolamines were synthesized by the reduction of the corresponding amino ketones and isonitroso ketones.

Continuing our search for new physiologically active compounds of the selenium series, we have synthesized a series of α-amino alcohols (I-VII, Table 2) by using readily accessible ketones of the selenophene series as starting materials. For obtaining amino alcohols with unsubstituted NH_2 groups (I, (II) the starting ketones were nitrosated with butyl nitrite, and the resulting α-nitroso ketones were reduced with lithium aluminum hydride. Amino alcohols with a tertiary amino group were obtained by reduction of the corresponding α-amino ketones (VIII-XII, Table 1) – the products of the condensation of the bromo ketones with amines. The starting bromo ketones were obtained by bromination of the ketones with dioxane dibromide. It is expedient to carry out the synthesis of the α-amino alcohols without isolation of the corresponding α-amino ketones.



The resulting α-amino alcohols of the selenophene series, which are similar in structure to ephedrine, have (like ephedrine) adrenomimetic activity according to the evidence of preliminary pharmacological tests on animals.

EXPERIMENTAL

2-(ω-Bromoaceto)selenophene. A 36.8-g (0.23 mole) sample of bromine was added in 40 min at 20° to a solution of 30 g (0.17 mole) of 2-acetoselenophene [1] in a mixture of 70 ml of ether and 35 ml of dioxane, and the mixture was stirred at 20° for another 40 min and poured into an ether–water mixture (65 ml of each). The ether layer was separated, washed several times with water, and dried with sodium sulfate. The ether was removed by distillation to give 27 g (69%) of a product with mp 48-49° (from methanol). Found: C 28.9; H 2.2%. C_6H_5BrOSe. Calculated: C 28.6; H 2.0%.

5-Methyl-2-(ω-bromoaceto)selenophene. This compound [14.4 g (51%)] was obtained in the same way as the above compound from 20 g (0.11 mole) of 5-methyl-2-acetoselenophene [1] and 22.4 g (0.14 mole) of bromine and had mp 45° (from methanol). Found: C 31.7; H 2.7%. C_7H_7BrOSe. Calculated: C 31.6; H 2.6%.

2-(Isonitrosoaceto)selenophene. A 6.2-g (0.06 mole) sample of butyl nitrite and 10 g (0.06 mole) of 2-acetoselenophene were added to an ice-cooled solution of sodium ethoxide obtained from 1.4 g (0.06 g-atom) of sodium in 30 ml of absolute ethanol. The mixture was allowed to stand in a tightly sealed vessel

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TABLE 1. Amino Ketones (VIII-XII) and Their Hydrochlorides*

Compound	R	R′	NR″₂	Bp, °C (mm)	n_D^{20}	Yield, %	Hydrochlorides of VIII-XII: mp (dec.), °C	empirical formula	found, % C	found, % H	calc., % C	calc., % H
VIII	H	H	$N(CH_3)_2$	105—106(3)	1,5775	30	173—174	$C_8H_{11}NOSe \cdot HCl$	37,8	5,2	38,0	4,8
IX	CH_3	H	$N(CH_3)_2$	110—111(2)	1,5717	21,5	159—160	$C_9H_{13}NOSe \cdot HCl$	41,0	5,6	40,5	5,3
X	H	H	$N(CH_2)_5$	166—167(7)	1,5810	42	205—210	$C_{11}H_{15}NOSe \cdot HCl$	44,8	5,6	45,1	5,5
XI	CH_3	H	$N(CH_2)_5$	145—146(1)	1,5790	47	193—196	$C_{12}H_{17}NOSe \cdot HCl$	46,6	6,2	46,7	5,9
XII	H	H	Morpholino	163—164(2)	1,5910	41,4	175—180	$C_{10}H_{13}NO_2Se \cdot HCl$	41,1	4,8	40,8	4,8

* Because of the instability of the amino ketones, their hydrochlorides were analyzed. The yields of hydrochlorides were quantitative. They were purified by reprecipitation from absolute methanol solutions by the addition of absolute ether.

TABLE 2. Amino Alcohols (I-VII) and Their Hydrochlorides

Compound	R	R′	NR_2''	Mp, °C (from absolute ether)	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, %*	Hydrochlorides of I-VII, mp (dec.) °C
I	H	H	NH_2	74—75	C_6H_9NOSe	37,4	5,0	37,9	4,8	57	143—144
II	H	CH_3	NH_2	70—71	$C_7H_{12}NOSe$	41,3	5,8	41,0	5,9	55,4	169—170
III	H	H	$N(CH_3)_2$	104 (3)†	$C_8H_{13}NOSe$	44,1	6,5	44,0	6,0	12,6	154—155
IV	CH_3	H	$N(CH_3)_2$	48‡	$C_9H_{15}NOSe$	46,3	6,8	46,6	6,5	14	oil
V	H	H	$N(CH_2)_5$	79—80	$C_{11}H_{17}NOSe$	51,5	6,9	51,2	6,6	35	192—193
VI	CH_3	H	$N(CH_2)_5$	74—75	$C_{12}H_{19}NOSe$	53,0	7,3	52,8	7,0	43	172—173
VII	H	H	Morpholino	98—99	$C_{10}H_{15}NO_2Se$	46,6	5,9	46,2	5,8	45	183—184

* The yields of III-VII were calculated on the basis of the starting bromo ketone. The yields of the hydrochlorides were quantitative. The composition of the hydrochlorides (B · HCl) was confirmed by determining the percentage of C and H. The compounds were purified by crystallization from acetone.
† This is the boiling point; n_D^{20} 1.5560.
‡ Bp 106° (2 mm), n_D^{20} 1.5492.

at 20-25° for 24 h. The resulting precipitate was removed by suction filtration, washed with ether, and dissolved in 50-60 ml of water. The solution was neutralized with concentrated hydrochloric acid, and the resulting precipitate was removed by suction filtration to give 2 g (17%) of a product with mp 93-94° (from benzene–petroleum ether). Found: C 35.7; H 2.80%. $C_6H_5NO_2Se$. Calculated: C 35.6; H 2.5%.

2-(ω-Dimethylaminoaceto)selenophene (VIII). A dry solution of 4.5 g (0.1 mole) of dimethylamine in 80 ml of benzene was added with stirring in the course of 20 min to a solution of 5 g (0.02 mole) of 2-(ω-bromoaceto)selenophene in 30 ml of dry benzene, and the mixture was allowed to stand at 20-25° for 10 h. The precipitate was removed by suction filtration and washed with benzene. The combined benzene filtrates were treated with 2 N HCl, and the aqueous layer was separated and made alkaline with saturated aqueous sodium carbonate solution. The liberated amino ketone was extracted with ether, and the extract was dried with potassium carbonate and vacuum distilled in a stream of nitrogen to give 1.25 g (30%) of VIII. The hydrochloride of VIII was obtained by the reaction of dry ether solutions of hydrogen chloride and of the amino ketone. The yield was quantitative.

2-(ω-Morpholinoaceto)selenophene (XII). A solution of 5 g (0.02 mole) of 2-(ω-bromoaceto)selenophene in 30 ml of absolute ether was added with stirring in the course of 20 min to a solution of 3.5 g (0.04 mole) of morpholine in 10 ml of absolute ether, and the mixture was allowed to stand at 20-25° for 10 h. The precipitate was removed by suction filtration and washed with ether. The combined ether solutions were treated with 2 N HCl. The aqueous layer was made alkaline with saturated aqueous sodium

carbonate solution and extracted with ether. The ether solution was dried with potassium carbonate and vacuum distilled under nitrogen to give 2.1 g (41.4%) of XII with mp 48.5-49.5°.

2-(α-Hydroxy-β-aminopropyl)selenophene (II). A solution of 7 g (0.0324 mole) of 2-(α-isonitrosopropyl)selenophene [2] in 25 ml of absolute ether was added with stirring in the course of 1 h to 3.2 g (0.08 mole) of lithium aluminum hydride in 70 ml of absolute ether, and the mixture was refluxed for 3 h and decomposed with water. The precipitate was removed by suction filtration and washed three times with ether. The combined ether solutions were dried with potassium carbonate, and the solvent was vacuum evaporated to give 3.7 (55.4%) of II with mp 70-71° (from absolute ether).

2-(α-Hydroxy-β-dimethylaminoethyl)selenophene (III). A dry ether solution of VIII, obtained by the method described above from 20 g (0.08 mole) of 2-(ω-bromoaceto)selenophene, was evaporated in vacuo to 100 ml and added with stirring in the course of 1 h to 3.8 g (0.1 mole) of lithium aluminum hydride in 100 ml of absolute ether. The mixture was refluxed for 3 h, cooled, and decomposed with water. The precipitate was removed by suction filtration and washed with ether. The filtrate was extracted with 2 N HCl, and the aqueous layer was separated, made alkaline, and extracted thoroughly with ether. The precipitate on the filter paper was dissolved in 2 N HCl, and 32 g of tartaric acid was added. The mixture was made alkaline and extracted with ether, and the combined ether solutions were dried with potassium carbonate and vacuum distilled to give 2.1 g of III (12.6% based on the starting bromoketone).

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