Chemistry of Heterocyclic Compounds, Vol. 33, No. 2, 1997

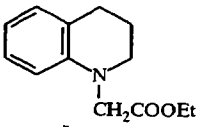
SILYL MODIFICATION OF BIOLOGICALLY ACTIVE COMPOUNDS. 4.* DERIVATIVES OF AMINO ACIDS IN THE TETRAHYDROQUINOLINE, TETRAHYDROISOQUINOLINE, AND TETRAHYDROSILAISOQUINOLINE SERIES

E. Lukevics, S. Germane, I. Segal, and A. Zablotskaya

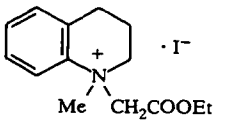
A series of derivatives of (1,2,3,4-tetrahydro-1-quinolyl)-, (1,2,3,4-tetrahydro-2-isoquinolyl)-, and (1,2,3,4-tetrahydrosila-2-isoquinolyl)acetic acid, which are structural analogs of glycine, were synthesized. The psychotropic activity and the acute toxicity of the compounds were studied.

The investigation of synthetic amino acids with small side chains has demonstrated the expediency of studying the essential and sufficient requirements for the manifestation of activity in many peptides and proteins [1, 2]. It is also known that alkylsilyl groups secure nonpolar and hydrophobic properties during the search for biologically active compounds [3]. Therefore, speculating on the participation of synthetic amino acids in the biological process with their inclusion into peptides, we supposed that such properties as increased tissue absorption and proteolytic activity would appear, due to the hydrophobicity of the molecule and the size of the substituents.

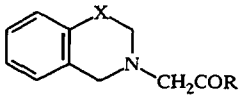
In a continuation of researches into the organosilicon derivatives of amino acids [4-6] we synthesized derivatives of amino acids (N,N-disubstituted glycines) in which the nitrogen atom is included in the cyclic tetrahydroquinoline (Ia) or tetrahydroisoquinoline (IIa, c, e, IIIa) system and also the methiodides (Ib, IIb, IIIb) [7]. In addition, compound (IIId) with a silatetrahydroisoquinoline substituent, containing the *p*-aminobenzoic fragment instead of glycine, was obtained.



Ia

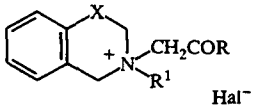


Ib



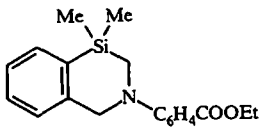
IIa, c, e; IIIa

II X = CH_2, a R = OEt, c R = NH_2, e R = ONa; III X = $SiMe_2$, a R = OEt

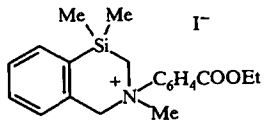


IIb, d; IIIb

II X = CH_2, b R = OEt, R^1 = Me, Hal = I, d R = OH, R^1 = H, Hal = Cl; III X = $SiMe_2$, b R = OEt, R^1 = Me, Hal = I



IIIc



IIId

*For Communication 3, see [6].

Latvian Institute of Organic Synthesis, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 270-274, February, 1997. Original article submitted October 10, 1996.

0009-3122/97/3302-0234$18.00

TABLE 1. Neurotropic Activity of Derivatives of (1,2,3,4-Tetrahydro-1-quinolyl)-, (1,2,3,4-Tetrahydro-2-isoquinolyl)-, and (1,2,3,4-Tetrahydrosila-2-isoquinolyl)acetic and Benzoic Acids

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg			$M \pm m$, % of control (100%)				
		Test							
		Rotating rod	Tube	Rectal temperature	Hypoxic hypoxia	Hexenal narcosis	Ethanol narcosis	Corazol convulsion	Phenamine hyperactivity
IId	815 (567...1110)	>500	178 (136...596)	447 (313...596)	135,3*	121,1	89,3	334,1*	45,2*
IIe	3550 (2020...5080)	>500	>500	>500	140,9*	184,7*	132,5*	270,3*	83,2
IIc	447 (313...597)	103 (67...138)	109 (41...206)	170 (73...332)	101	149,9*	133,8*	144,3*	67,0
Ib	41 (27...55)	>25	>25	>25	184,4*	156,2*	120,2*	104,9	75,8*
IIb	129 (84...179)	3 (1...5)	21 (15...29)	6 (3...8)	110,9	164,9*	131,2*	169,6*	121,4
IIIb	45 (31...60)	33 (22...46)	>25	21 (15...29)	182,6*	150,0*	113,2	155,4*	106,8
IIId	>1000	65 (44...89)	73 (26...137)	82 (57...111)	111,2	109,5	154,8*	140,9*	100,8

*Differences in relation to the control are statistically reliable at $P < 0.05$.

Ethyl (1,2,3,4-tetrahydro-1-quinolyl)- and (1,2,3,4-tetrahydro-2-isoquinolyl)acetates (Ia) and (IIa) were obtained by heating tetrahydroquinoline and tetrahydroisoquinoline respectively with ethyl acetate. The organosilicon analog of the tetrahydroisoquinoline derivative with a silicon atom in the ring (IIIa) was synthesized by the reaction of dimethylchloromethyl(2-bromomethylphenyl)silane with glycine ethyl ester in the presence of triethylamine. Similarly, ethyl (4,4-dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)benzoate (IIIc) was obtained by the reaction of the above-mentioned silane with ethyl *p*-aminobenzoate. The reaction of the ethyl esters (Ia, IIa, IIIa, IIIc) with methyl iodide resulted in the formation of their methiodides. Treatment of the ester (IIa) with a concentrated aqueous solution of ammonia under a small pressure and also its reaction with concentrated hydrochloric acid gave the amide (IIc) and the hydrochloride (IId) of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid respectively.

The sodium salt (IIe) was obtained as a result of the successive reaction of tetrahydroisoquinoline with monochloroacetic acid and sodium hydroxide.

A comparative investigation of the synthesized compounds was made with a view to determining the effect of the organosilicon substituent on the biological activity in the [1,2,3,4-tetrahydro(iso)quinolyl]acetic acid series and on the psychotropic activity of the synthesized compounds.

The results from study of the activity of the synthesized compounds are given in Table 1. The stimulating activity of the derivatives of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid in the "rotating rod" and "tube" tests depends on the nature of the substituent at the carbonyl group. Thus, the greatest stimulating activity is exhibited by the amide of tetrahydroisoquinolylacetic acid (IIc). The action of the hydrochloride of tetrahydroisoquinolylacetic acid (IId) is somewhat less clearly defined, while the sodium salt (IIe) does not have stimulating properties at doses of up to 500 mg/kg.

Among the methiodides (Ib, IIb, IIIb, IIId) the methiodide of ethyl (1,2,3,4-tetrahydroisoquinolyl)acetate (IIb) has the highest stimulating activity. The corresponding derivative of tetrahydroquinoline (Ib) does not have stimulating properties, while the compounds with a dimethylsilyl group at position 4 of the isoquinoline structure (IIIb, d) are significantly less active. The benzoic acid derivative (IIId) has half the stimulating activity of the corresponding derivative of acetic acid (IIIb).

With respect to the hypothermic effect (the rectal temperature test) approximately the same relationships were obtained as in the previous tests.

None of the investigated compounds exhibits stimulating characteristics in the "cross-bar" test. They also do not exhibit analgesic properties and do not prevent convulsion caused by maximum electric shock.

With respect to the corazol convulsion it was established that the strongest anticonvulsive activity is exhibited by the hydrochloride of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid (IId), which increases the corazol dose leading to a lethal outcome in mice by 3.34 times. This is followed, in decreasing order, by the corresponding sodium salt (IIe) and the amide (IIc), which increase the corazol dose by 2.7 and 1.4 times. In the series of methiodides the highest anticorazol activity is exhibited by the methiodide of ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIb). The organosilicon derivatives (IIIb, IIId) have somewhat lower anticonvulsive activity, while the methiodide of ethyl (1,2,3,4-tetrahydro-1-quinolyl)acetate (Ib) does not have any protective properties at all in corazol convulsions. Nearly all the derivatives of tetrahydro(iso)quinolylcarboxylic acids except compounds (IId, IIId) at a dose of 5 mg/kg increase the duration of hexenal narcosis by 1.5-1.85 times. With respect to ethanol narcosis it was established that the action of the investigated compounds was less well defined (by 20-55%). Except for the methiodides of ethyl [1,2,3,4-tetrahydro(sila)-2-isoquinolyl]acetates (IIb, IIIb) and benzoates (IIId) the studied compounds reduce phenamine hyperactivity by 15-55%. In this case the hydrochloride of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic (IId) is more active. The methiodide of ethyl tetrahydroquinolylacetate (Ib), unlike the other investigated methiodides (IIb, IIIb, IIId), has antiphenamine activity.

The antihypoxia activity of the investigated compounds is most clearly defined in the methiodide of ethyl (4,4-dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIIb) and in the methiodide of ethyl (1,2,3,4-tetrahydro-1-quinolyl)acetate (Ib), which increase the life duration of mice by 1.83 and 1.85 times respectively. The hydrochloride (IId) and the sodium salt of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid (IIe) have somewhat lower antihypoxia activity.

The sodium salt (IIe), amide (IIc), and methiodide (IIb) of ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate at a dose of 5 mg/kg facilitate the healing process in animals and prevent retrograde amnesia due to electric shock by 83.3, 83.3, and 66.7% respectively (control 16,6%).

During the investigation of acute toxicity it was established that the sodium salt (IIe) had the highest lethal dose, while the toxic characteristics of the hydrochloride (IId) and the amide (IIc) of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid were increased by 4.3 and 7.9 times respectively. The highest toxicity in the series of methiodides is given by the methiodide of ethyl (1,2,3,4-tetrahydroquinolyl)acetate (Ib). The corresponding methiodide of the ethyl ester of the tetrahydroisoquinolyl derivative

(IIb) has 3.1 times lower toxicity. The appearance of the dimethylsilyl group at position 4 of the tetrahydroisoquinoline structure (IIIb) in turn increases the acute toxicity of the compound by 2.9 times. Substitution of the acetic acid residue by benzoic acid (IIId) appreciably reduces the toxic characteristics of the compound.

As a result of the investigations it was established that the methiodide of ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate has the highest stimulating activity.

The antihypoxia action is most clearly defined in the methiodides of ethyl (1,2,3,4-tetrahydro-1-quinolyl)- and (4,4-dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)acetates.

All the investigated compounds are capable to one degree or other of prolonging the hexenal and ethanol narcosis and have clearly defined anticonvulsive activity with corazol.

The lowest toxicity among the investigated derivatives is possessed by sodium (1,2,3,4-tetrahydro-2-isoquinolyl)acetate and the methiodide of ethyl *o*-(4,4-dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)benzoate. The latter exhibits comparatively high stimulating activity, while the sodium salt prolongs hexenal narcosis most among the investigated compounds and exhibits high anticorazol activity.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90/DS instrument in deuterochloroform or DMSO-d_6 with TMS as internal standard. The error of the measurement was ± 0.05 ppm. The IR spectra were recorded on a Perkin-Elmer 580 B instrument in Vaseline oil. Gas-liquid chromatography was conducted on a Chrom 4 chromatograph with a flame-ionization detector. A glass column (1.2 m × 3 mm) with 5% of OV-17 on Chromosorb W-HP (80-100 mesh) was used.

The elemental analyses for C, H, N, and Cl agreed with the calculated data.

Ethyl (1,2,3,4-Tetrahydro-1-quinolyl)acetate (Ia), the methiodide of ethyl (1,2,3,4-tetrahydro-1-quinolyl)acetate (Ib), ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIa), the methiodide of ethyl (1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIb), (1,2,3,4-tetrahydro-2-isoquinolyl)acetamide (IIc), the hydrochloride of (1,2,3,4-tetrahydro-2-isoquinolyl)acetic acid (IId), sodium (1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIe), and the methiodide of ethyl (4,4-dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)acetate (IIIb) were obtained by the procedure in [7].

Methiodide of Ethyl *p*-(4,4-Dimethyl-4-sila-1,2,3,4-tetrahydro-2-isoquinolyl)benzoate (IIId) ($C_{19}H_{23}INO_2Si$). To a mixture of 2.48 g (15 mmole) of ethyl *p*-aminobenzoic acid and 4.5 ml (3.3 g, 32 mmole) of triethylamine in 15 ml of benzene, while stirring, we added dropwise 4.2 g (15 mmole) of dimethylchloromethyl(2-bromomethylphenyl)silane. The reaction mixture was heated at 75°C for 2 h and left at room temperature for 17 h. The precipitate was filtered off and washed with benzene. The filtrate was evaporated. To the obtained ester (IIIc) (2.03 g) in the form of a thick viscous mass we added 1.5 ml (3.4 g, 24 mmole) of methyl iodide. The reaction mixture was heated for 4 h and kept at room temperature for 3 days. The precipitate was separated by decantation and recrystallized from absolute alcohol. The yield of compound (IIId) was 0.25 g; mp 183-186°C. PMR spectrum (deuterochloroform, ppm): 6.99-8.18 (8H, m, Ar + Ar), 4.62 (2H, s, $ArCH_2N$), 4.30 (2H, q, OCH_2), 3.38 (2H, s, $SiCH_2$), 1.36 (3H, t, CH_3), 0.50 (6H, s, $SiMe_2$).

Biological Section [6]. A comparative assessment was made of the action of the substances on hypoxia, hexenal and ethanol narcosis, phenamine hyperactivity, corazol convulsions, learning, and the Porsolt test. The trials were performed on groups of animals, consisting of six individuals. The investigated substances were administered at dosages of 5 mg/kg in the form of aqueous solutions or aqueous suspensions prepared with Tween 80 and were injected intraperitoneally 1 h before the test was set up. The control animals were injected in the abdominal cavity with the same volume of distilled water.

The authors express their gratitude to the Latvian Scientific Council for grant No. 96 443 for the investigation.

REFERENCES

1. J. Gante, Angew. Chem. Int. Ed. Engl., **33**, 1699 (1994).
2. H. Josien, S. Lavielle, A. Brunissen, M. Saffroy, Y. Torrens, J. C. Beraujouan, J. Glowinski, and G. Chassaing, J. Med. Chem., **37**, 1586 (1994).
3. E. Lukevics and A. Zablotskaya, Metalloorg. Khim., **6**, 263 (1993).

4. A. Zablotskaya, S. Germane, I. Segal, and E. Lukevics, Latv. Ķīm. Ž., No. 1, 79 (1993).
5. E. Lukevics, A. Zablotskaya, S. Germane, and I. Segal, Latv. Ķīm. Ž., No. 4, 472 (1994).
6. E. Lukevics, I. Segal, A. Zablotskaya, and S. Germane, Khim. Geterotsikl. Soedin., No. 6, 793 (1996).
7. E. Lukevics, I. Segal, A. Zablotskaya, and S. Germane, Molecules, in press.