INDOLE DERIVATIVES

LXXXVIII.* SYNTHESIS OF SOME O-(γ-ALKOXY-β-HYDROXYPROPYL) DERIVATIVES OF SEROTONIN

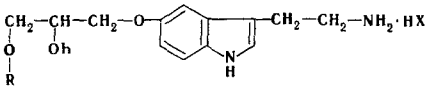
N. N. Suvorov, A. B. Shteinpress,
V. A. Gulyaev, M. V. Vasin,
and N. P. Kostyuchenko

UDC 547.751.07

The reaction of N-tritylserotonin with epichlorohydrin has given O-(β,γ-epoxypropyl)-N-tritylserotonin, the reaction of which with sodium alkoxides in the corresponding alcohols has given O-(γ-alkoxy-β-hydroxypropyl) derivatives of serotonin. It has been found that they possess a definite radioprotective action.

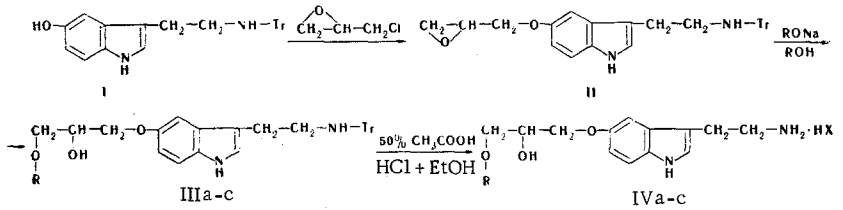
Serotonin possesses a considerable radioprotective activity [2]. Serotonin derivatives with an ester linkage (O-acyl and O-carbamoyl compounds) do not differ substantially in relation to the nature and duration of the radioprotective effect from serotonin itself. The length of the O-acyl residue has little influence on the radioprotective properties of these compounds [3]. For serotonin derivatives with an ether linkage (alkoxytryptamines), in contrast to the O-acyl derivatives, lengthening the hydrocarbon chain in position 5 of the indole ring of an alkoxytryptamine leads to an increase in the toxicity of the materials and to a loss of protective properties [4].

In view of the above facts, it appeared of interest to obtain some O-alkyl derivatives of serotonin containing functional groups in the side chain with the general formula



R = H; CH_3; C_2H_5; $CH_2(OH)-CH_2$; X = Cl; CH_3COO

The presence in the serotonin molecule of two reactive groups (NH_2 and OH) complicated the problem of introducing the appropriate groupings in position 5. Consequently, we used triphenylmethyl (trityl) protection of the amino group which, after the synthesis of the appropriate compounds, was removed under conditions not affecting the groupings introduced into position 5 of the indole ring. As the starting material we selected 5-benzyloxytryptamine, which is an intermediate in the synthesis of serotonin. After the protection of the amino group of the 5-benzyloxytryptamine, the benzyl residue was eliminated from the hydroxy group. The following route for the synthesis was selected:

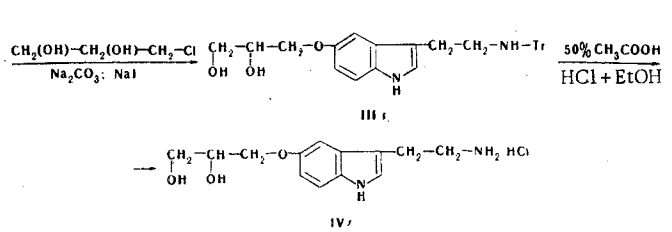


I II

IIIa-c IVa-c

* For Communication LXXXVII, see [1].

D. I. Mendeleev Moscow Institute of Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1515-1518, November, 1973. Original article submitted June 28, 1972.



a R = CH_3, b R = C_2H_5, c R = $CH_2(OH)-CH_2$, d R = H, Tr = $C(C_6H_5)_3$, X = Cl, CH_3COO

The synthesis of O-(β, γ-epoxypropyl)-N-tritylserotonin (II) was performed in isopropanol, which is the best solvent for the preparation of aryl glycidyl ethers [6]. When the reaction was performed in the presence of a fivefold molar excess of epichlorohydrin and with the stepwise addition of concentrated aqueous NaOH it was possible to obtain (II) with a yield of more than 60%. Compounds (IIIa-c) were obtained by the reaction of O(β,γ-epoxypropyl)-N-tritylserotonin with the appropriate alkali-metal alkoxides in an excess of the corresponding alcohols with yields of more than 80%. The analogous preparation of O-(β, γ-dihydroxypropyl)-N-tritylserotonin (IIId) by the reaction of O-(β, γ-epoxypropyl)-N-tritylserotonin with an aqueous solution of alkali with the addition of dioxane to create a homogeneous medium is complicated by the low yield and the difficulty of freeing the (IIId) from the byproducts of the reaction. A method of obtaining (IIId) from N-tritylserotonin (I) and glycerol monochlorohydrin according to Claisen [7] proved to be more successful, although the use of catalytic amounts of sodium iodide did not lead to satisfactory yields of O-(β, γ-dihydroxypropyl)-N-tritylserotonin. The use of an equimolar amount of sodium iodide and of methyl ethyl ketone as solvent enabled (IIId) to be obtained with a yield of more than 40%.

The structures of compounds (II) and (IIIa-d) were confirmed by their PMR and IR spectra.

Results of the Pharmacological Investigation

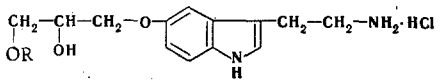
The tests of compounds (IVa-d) for antiradiation activity were performed on random-bred female white mice weighing 20-22 g. The animals were subjected to the action of ^{60}Co γ radiation in a dose of 800 r at a dose rate of 48.7-56.2 r/min. Solutions of the materials in distilled water were administered to the mice intraperitoneally or per os at the rate of 0.01 ml/g weight of the animal 5-10 min before irradiation. The radioprotective properties of the compounds were evaluated from the survival rate of the mice in the 30 days after irradiation and from the mean lifetimes (MLTs) of the animals that died. The results of the investigations are given in Table 1. It can be seen from this table that the addition of a glycerol residue (a β, γ-dihydroxypropoxy group) to tryptamine in position 5 of the indole ring somewhat increases the antiradiation effectiveness of the compound. The prophylactic use of substance (IVd) in the doses mentioned led to a 60% survival rate of the mice up to the 30th day after irradiation (with tryptamine protection, the survival rate was 35-55%, and in a control group the mortality was 91.9% after irradiation). The activity of (IVd) is better than that of mexamine. The alkylation by methyl and ethyl groups of the alcohol group of glycerol in the γ position of substance (IVd) did not increase the antiradiation properties of the compound. The addition of a hydroxyethyl group in the same position (substance IVc) destroyed the radioprotective effect.

EXPERIMENTAL

The PMR spectra were taken on JNM-4H-100 and C-60-HL instruments in deuterodimethyl sulfoxide and deuteroacetone. The PMR spectra are given in the δ scale, ppm. The following abbreviations have been used: d – doublet; q – quartet; m – multiplet; s – singlet; t – triplet. The IR spectra were taken on a UR-10 instrument in paraffin oil and in KBr. The alumina used was of activity grade II, and the eluent was chloroform.

O-(β, γ-Epoxypropyl)-N-tritylserotonin (II). A mixture of 4.18 g (0.01 mole) of N-tritylserotonin, 5.52 g (0.05 mole) of epichlorohydrin, and 2.75 g of isopropanol was heated with stirring to 70°C. Then a 38% aqueous solution of NaOH (0.011 mole) was added by drops to the solution over 10-15 min. The temperature was raised to 80°C and the mixture was stirred for another 1 h. Then it was cooled to room temperature, the sodium chloride that had deposited was filtered off, and the solution was evaporated in vacuum. The resulting viscous mass was treated with 50 ml of isopropanol and stirred. After some time, crystals of O-(β, γ-epoxypropyl)-N-tritylserotonin deposited. The reaction product was purified on a column of alumina and was recrystallized from isopropanol. This gave 2.89 g (61%) of (II), mp 135.5-137°C. Found: C 81.3; H 6.3; N 6.0%. $C_{32}H_{30}N_2O_2$. Calculated: C 80.9; H 6.4; N 6.0%. PMR spectrum: 3.77 (q,

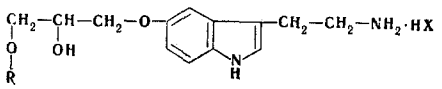
TABLE 1. Antiradiation Efficiency of the Materials on Parenteral Administration



Compound	R	Dose, mmole/kg	No. of mice	Survival rate, %	MLT, days
IVd	H	0,4	20	60,0±10,9	9,6±1,7
		0,15	10	60,0±15,5	11,0±3,7
IVa	CH_3	0,4	10	30,0±14,5	8,5±1,8
IVb*	C_2H_5	0,4	10	50,0±15,8	9,2±2,0
IVc	HOC_2H_4	0,4	10	0	8,2±1,3
Tryptamine hydrochloride		0,4	20	55,0±11,1	14,3±1,9
		0,15	30	36,6± 8,8	13,7±1,4
5-Methoxytryptamine (mexamine) hydrochloride		0,4	30	53,0± 9,1	14,2±2,3
		0,15	29	89,4± 5,7	18,6±4,1
Control group		—	34	8,9± 4,9	10,6±0,6

*Tested in the form of the acetate.

TABLE 2. Constants and Elementary Analyses of the Compounds of the General Formula



Compound	R	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	Cl	C	H	N	Cl	
IVa	CH_3	192—194 (dec.)	$C_{14}H_{21}N_2O_3Cl_1$	56,0	7,0	9,2	11,7	55,9	7,0	9,3	11,8	83
IVb	C_2H_5	137	$C_{17}H_{26}N_2O_5$	60,2	7,8	8,3	—	60,3	7,7	8,3	—	85
IVc	CH_2OHCH_2	149—150	$C_{15}H_{23}N_2O_4Cl_1$	54,2	7,2	8,4	10,6	54,4	7,1	8,5	10,7	80
IVd	H	156—157	$C_{13}H_{19}N_2O_3Cl_1$	54,5	6,7	9,6	12,5	54,4	6,7	9,8	12,4	67

α-CH_2), 4.18 (q, α-CH_2), J_{gem} = 11.1; J_{vic} = 6.2; J_{vic} = 3.0; 3.28 (m, β-CH); 2.5-2.9 (m, γ-CH_2), J_{gem} = 5.5, J_{vic} = 2.2, J_{vic} = 3.8. IR spectrum: 918 cm^{-1} (epoxide ring).

O-(β-Hydroxy-γ-methoxypropyl)-N-tritylserotonin (IIIa). A mixture of 2.84 g (6 mmoles) of (II) and a solution of 1.5 mmole of CH_3ONa in 50 ml of absolute methanol was boiled in a current of nitrogen for 10 h. After the end of the reaction, the solution was evaporated in vacuum. On cooling, the residue deposited crystals of O-(β-hydroxy-γ-methoxypropyl)-N-tritylserotonin. The reaction product was purified on a column of alumina and was recrystallized from methanol. This gave 2.68 (86%) of O-(β-hydroxy-γ-methoxypropyl)-N-tritylserotonin with mp 141-143°C. Found: C 78.1; H 6.8; N 5.6%. $C_{33}H_{34}N_2O_3$. Calculated: C 78.2; H 6.8; N 5.5%. PMR spectrum: 3.25 (s, CH_3O); 5.08 (d, OH), J = 5.8 Hz.

O-(γ-Ethoxy-β-hydroxypropyl)-N-tritylserotonin (IIIb). A mixture of 2.37 g (5 mmoles) of (II) and 1.25 mmole of C_2H_5ONa in 20 ml of absolute ethanol was boiled in a current of nitrogen for 5 h. After the end of the reaction the solution was evaporated and cooled. The crystals of (IIIb) that deposited were filtered off. The reaction product was purified on a column of alumina and was recrystallized from ethanol to give 2.2 g (84%) of (IIIb) with mp 69-70°C. Found: C 78.4; H 7.0; N 5.4%. $C_{34}H_{36}N_2O_3$. Calculated: C 78.5; H 7.0; N 5.4%. PMR spectrum: 3.67-4.10 (m, α, β-CH_2-CH); 1.11 (t, CH_3); 5.03 (d, OH), J = 4.6 Hz.

O-(β-Hydroxy-γ-hydroxyethoxypropyl)-N-tritylserotonin (IIIc). A mixture of 3.32 g (7 mmoles) of (II) and 1.75 mmole of sodium glycolate in 30 ml of ethylene glycol was stirred in a current of nitrogen at a bath temperature of 120-125°C for 5 h. After the end of the reaction, the solution was cooled, and distilled water was added. The white flocculant precipitate of (IIIc) that deposited was filtered off, dried, and freed from impurities on a column of alumina. A solution of (IIIc) in chloroform was evaporated to dryness in vacuum and the residue was recrystallized from methanol to give 3.08 g (82%) of product with mp 84-86°C. Found: C 76.2; H 6.7; N 5.3%. $C_{34}H_{36}N_2O_4$. Calculated: C 76.1; H 6.8; N 5.2%. PMR spectrum:

3.88 (m, α, β-CH_2—CH); 4.56 (t, OH on a primary carbon atom), J = 5.2 Hz; 5.07 (d, OH on a secondary carbon atom), J = 4.7 Hz.

O-(β,γ-Dihydroxypropyl)-N-tritylserotonin (IIId). A mixture of 1.25 g (3 mmoles) of N-tritylserotonin, 0.28 ml (3.35 mmoles) of glycerol monochlorohydrin, 0.42 g (3 mmoles) of potassium carbonate, 0.45 g (3 mmoles) of sodium iodide, and 6.5 ml of methyl ethyl ketone was boiled in a current of nitrogen for 25 h. After the end of the reaction, the inorganic salts were filtered off and the mother solution was evaporated to dryness in vacuum. The reaction product was chromatographed on a column of alumina with chloroform—methanol (10 : 1) as the eluent. The solution containing the (IIId) was evaporated to dryness in vacuum, and the residue was crystallized from ethanol. This gave 0.62 g (43%) of (IIId), mp 147-148°C. Found: C 78.1; H 6.6; N 5.7%. $C_{32}H_{32}N_2O_3$. Calculated: C 78.0; H 6.5; N 5.6%. PMR spectrum: 4.05 (m, α, β-CH_2—CH); 3.71 (d, β-CH); 4.61 (t, OH on a primary carbon atom), J = 6.5 Hz; 4.87 (d, OH on a secondary carbon atom), J = 6.5 Hz.

Removal of the Trityl Protection. To convert the compound (IIIa-d) into the form of salts (acetate or hydrochloride), 1.25 g of one of these substances was suspended in 32 ml of 50% acetic acid. The suspension was heated in a current of nitrogen with stirring up to a bath temperature of 140-150°C and was then stirred at this temperature for 5 min, after which the solution was cooled and the crystals of triphenylmethanol were filtered off. The mother solution was evaporated to dryness in vacuum and was dissolved in absolute methanol. In the preparation of the acetate of (IVb), dry ether was added to a solution of this salt and the mixture was cooled. The crystals of the acetate of (IVb) that separated out were filtered off and dried. In the preparations of compounds (IVa, c, d) in the form of the hydrochlorides, an excess of a titrated ethanolic solution of hydrogen chloride (1.1 mole of HCl per mole of substance) was added to an ethanolic solution of the acetate, and the solution was evaporated to dryness in vacuum. The dry residue was dissolved in 2-3 ml of absolute methanol, dry ether was added until the solution became turbid, and the mixture was cooled. The crystals that deposited were filtered off and dried. The constants and elementary analyses of the compounds obtained are given in Table 2.

LITERATURE CITED

1. N. N. Suvorov, V. S. Velezheva, and V. V. Vampilova, Khim. Geterotsikl. Soedin., 1512 (1973).
2. P. G. Zherebchenko, The Antiradiation Properties of Indolylalkylamines [in Russian], Atomizdat, Moscow (1971), p. 10.
3. L. M. Morozovskaya, G. N. Il'ina, M. É. Kaminka, M. D. Mashkovskii, and N. N. Suvorov, Khim.-Farmats. Zh., 3, 11 (1968).
4. I. G. Krasnykh, P. G. Zherebchenko, and V. S. Murasheva, Radiobiologiya, 2, 156 (1962).
5. N. N. Survorov, N. P. Sorokina, and G. N. Tsvetkova, Zh. Obshch. Khim., 34, 1595 (1964).
6. L. V. Skrylova and V. V. Safonova, USSR Authors' Certificate No. 138,028 (1960); Byul. Izobret., No. 9, 43 (1961).
7. L. I. Smith, H. H. Hoehn, and A. G. Whitney, J. Am. Chem. Soc., 62, 1863 (1940).