80. K. Kobayashi, S. Miyanzawa, and A. Terehara, Tetrahedron Lett., 537-540 (1976).
81. S. Singer and K. Sharpless, J. Org. Chem., 43, 1448-1455 (1978).
82. G. Tunicliff, T. Ngo, and A. Barbeau, Experientia, 33, 20-22 (1977).
83. D. Tsui, D. Gorecki, C. Charington, et al., Eur. J. Pharmacol., 38, 189-192 (1976).
84. G. Johnston, in: GABA in Nervous System Function, E. Roberts, T. N. Chase, and D. W. Towers, eds., New York (1976), pp. 395-411.
85. G. Johnson, P. Krogsgaard-Larsen, A. Stephanson, et al., J. Neurochem., 26, 1029-1032 (1976).
86. P. Krogsgaard-Larsen, G. Johnston, D. Lodge, et al., Nature, 268, 53-55 (1977).
87. P. Krogsgaard-Larsen, K. Thyssen, and K. Shaumburg, Acta Chem. Scand., B32, 327-334 (1978).
88. G. Johnston, P. Krogsgaard-Larsen, and A. Stephanson, Nature, 258, 627-628 (1975).

ANALGESIC AND ANTI-INFLAMMATORY ACTION OF CERTAIN ORGANOSILICON COMPOUNDS

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We have already shown the presence of anti-inflammatory and analgesic activity in certain organosilicon compounds [1-3]. We found that compounds containing the silicon atom in the ring or a silicon atom joined to three lower alkyl radicals have the most marked analgesic action. In continuation of our study on the relationship between the chemical structure and the anti-inflammatory and analgesic activity, we studied in this direction the organosilicon derivatives of γ-hydroxyvaleric acid and hydroxybenzyl alcohols, synthesized at the Department of Organic Chemistry of the Perm University.

The ethyl esters of γ-trialkylsiloxyvaleric acid were obtained by the reaction between equimolecular amounts of ethyl levulinate and trialkylsilane [4].

$$CH_3COCH_2CH_2COOC_2H_5 + HSiRR'_2 \xrightarrow{Ni} CH_3CH(OSiRR'_2)CH_2CH_2COOC_2H_5$$

$R = R' = C_2H_5$; $R = C_2H_5$; $R' = C_4H_9$

Ethyldibutylsilyl ester of levulinic acid was synthesized by the reaction between equimolecular amounts of levulinic acid and ethyldibutylsilane

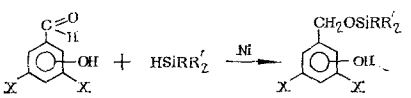
$$CH_3COCH_2CH_2COOH + HSi(C_2H_5)(C_4H_9)_2 \xrightarrow[-H_2]{Ni} CH_3COCH_2CH_2COOSi(C_2H_5)(C_4H_9)_2$$

The trialkylsilyl esters of γ-trialkylsiloxyvaleric acid were obtained by the reaction of trialkylsilyl ester of levulinic acid with equimolecular amount of trialkylsilane

$$CH_3COCH_2CH_2COOSiRR'_2 + HSiRR'_2 \xrightarrow{Ni} CH_3CH(OSiRR'_2)CH_2CH_2COOSiRR'_2$$

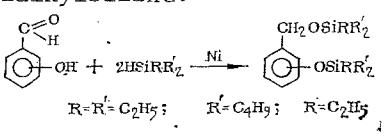
$R = R' = C_2H_5$; $R = C_2H_5$; $R' = C_4H_9$

Hydroxybenzyloxytrialkylsilanes were synthesized by the reaction between equimolecular amounts of trialkylsilane and hydroxybenzaldehyde.



$R = R' = C_2H_5$; $R = C_2H_5$, $R = C_4H_9$; $X = H$, tert·C_4H_9

Trialkylsiloxybenzyloxytrialkylsilanes were obtained by the reaction of hydroxybenzaldehyde with a 2.5-fold amount of trialkylsilane.



$R = R' = C_2H_5$; $R' = C_4H_9$; $R = C_2H_5$

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TABLE 1. Physicochemical Characteristics of Organosilicon Derivatives of γ-Hydroxyvaleric Acid and Hydrobenzyl Alcohols

Compound	Formula	Yield, %	bp, °C	d_4^{20}	n_D^{20}	Found, %		Empirical formula	Calculated, %		IR spectra, ν, cm^{-1}		
						Si	MR_D		Si	MR_D	C=O	O—H	Si—O—C
I	2-$HOC_6H_4CH_2OSiC_2H_5(C_4H_9)_2$	53	143—4 (2)	0,8929	1,4580	9,35	91,58	$C_{17}H_{30}O_2Si$	9,54	89,20		3400	1060
II	2-$HOC_6H_4CH_2OSi(C_2H_5)_3$	42	112—4 (1)	0,9906	1,4977	11,54	70,50	$C_{13}H_{22}O_2Si$	11,78	70,61	—	3400	1070
III	3-$HOC_6H_4CH_2OSi(C_2H_5)_3$	59	141—3 (4)	0,9787	1,4903	11,68	70,47	$C_{13}H_{22}O_2Si$	11,78	70,61	—	3350	1075
IV	3,5-(tert-$C_4H_9)_2$-4-$HOC_6H_2CH_2OSi(C_2H_5)_3$	70	190 (5)	0,9417	1,4977	7,84	108,50	$C_{21}H_{38}O_2Si$	8,01	107,79	—	3630	1080
V	3,5-(tert-$C_4H_9)_2HOC_6H_2CH_2OSiC_2H_5(C_4H_9)_2$	79	225—7 (5)	0,9301	1,4898	6,84	126,40	$C_{25}H_{46}O_2Si$	6,91	126,38	—	3650	1090
VI	2-$(C_2H_5)_3SiOC_6H_4CH_2OSi(C_2H_5)_3$	47	148—50 (1)	0,9405	1,4861	15,98	107,60	$C_{19}H_{36}O_2Si_2$	15,93	107,34	—	—	1075 920
VII	2-$C_2H_5(C_4H_9)_2SiOC_6H_4CH_2OSiC_2H_5(C_4H_9)_2$	37	208—10 (1)	0,9123	1,4795	12,06	144,60	$C_{27}H_{52}O_2Si_2$	12,11	144,52	—	—	1075 915
VIII	3-$(C_2H_5)_3SiOC_6H_4CH_2OSi(C_2H_5)_3$	61	175 (3)	0,9327	1,4805	15,78	107,50	$C_{19}H_{36}O_2Si_2$	15,93	107,34	—	—	1075 965
IX	3-$C_2H_5(C_4H_9)_2SiOC_6H_4CH_2OSiC_2H_5(C_4H_9)_2$	49	213—5 (1)	0,9138	1,4810	11,96	144,70	$C_{27}H_{52}O_2Si_2$	12,11	144,52	—	—	1075 965
X*	$CH_3CHCH_2CH_2COOC_2H_5$ $OSi(C_2H_5)_3$												
XI*	$CH_3CHCH_2CH_2COOC_2H_5$ $OSi(C_2H_5)_2H$												
XII*	$CH_3CHCH_2CH_2COOC_2H_5$ $OSi(C_4H_9)_2C_2H_5$												
XIII	$CH_3CHCH_2CH_2COOSi(C_2H_5)_3$ $OSi(C_2H_5)_3$	86	145—6 (2)	0,9251	1,4500	16,00	100,8	$C_{17}H_{38}O_3Si_2$	16,20	101,77	1725	—	1090
XIV	$CH_3CHCH_2CH_2COOSi(C_4H_9)_2C_2H_5$ $OSi(C_4H_9)_2C_2H_5$	90	190—1 (1)	0,8999	1,4555	12,00	138,60	$C_{25}H_{54}O_3Si_2$	12,24	138,95	1725	—	1090
XV	$CH_3COCH_2CH_2COOSi(C_4H_9)_2C_2H_5$	75	128—30 (1)	0,9341	1,4455	9,78	81,72	$C_{15}H_{30}O_3Si$	9,80	82,08	1725 1710	—	1080
XVI	$C_2H_5CHCH_2CH_2COOC_2H_5$ $OSi(C_2H_5)_3$	52	162—4 (3)	0,9796	1,4905	8,68	95,28	$C_{18}H_{38}O_3Si$	8,71	94,08	1740	—	1095

*The physicochemical characteristics have already been published in [4].

The physicochemical characteristics of the compounds synthesized are listed in Table 1.

EXPERIMENTAL(CHEMICAL)

The IR spectra of the compounds were taken in the form of a thin film on an IKS-22 spectrophotometer (USSR).

The ethyl esters of γ-trialkylsiloxyvaleric acid are obtained by the method already described in [4].

Ethyldibutylsilyl Ester of Levulinic Acid. A mixture of levulinic acid (0.1 mole) dissolved in 25 ml of THF and ethyldibutylsilane (0.1 mole) is heated at the boiling point of the reaction mixture for 6 h, with stirring, in the presence of colloidal nickel [5]. At the end of the reaction, the solvent is distilled off, and the product distilled *in vacuo*.

Trialkylsilyl Esters of γ-Trialkylsiloxyvaleric Acid. A mixture of trialkylsilyl ester of levulinic acid (0.1 mole) and trialkylsilane (0.1 mole) is heated for 4 h at 110°C in the presence of colloidal nickel. At the end of the reaction, the product is isolated and purified *in vacuo*.

Hydroxybenzyloxytrialkylsilanes. A mixture of trialkylsilane (0.2 mole), hydroxybenzaldehyde (0.2 mole) and colloidal nickel is heated in a round-bottomed flask fitted with a stirrer, reflux condenser and thermometer for 2.5-3 h, with gradual increase in temperature. At the end of the reaction, the mixture is cooled and separated from the catalyst, and the reaction product is isolated by distillation *in vacuo*.

Trialkylsiloxybenzyloxytrialkylsilanes. A mixture of trialkylsilane (0.25 mole), an aromatic hydroxy aldehyde (0.1 mole) and colloidal nickel is heated in a round-bottomed flask, fitted with a reflux condenser, for 3-3.5 h at the boiling point of the reaction mixture. The reaction mixture is cooled, the catalyst separated, and the reaction product isolated and purified by distillation *in vacuo*.

EXPERIMENTAL(PHARMACOLOGICAL)

The biological activity of the oxygen-containing organosilicon compounds was studied in experiments on nonpedigree white mice of both sexes weighing 17-20 g each, and on the Vistar line rats, weighing 160-200 g, grown at the Stolbovaya nursery.

We first determined the tentative toxicity in intraperitoneal administration to white mice. The degree of toxicity of the preparations was determined according to the classification of K. P. Sidorov [6].

The anti-inflammatory activity of the compounds was studied on a model of a formalin-induced inflammation. The value of the inflammatory reaction was determined oncometrically [7]. The analgesic action of the compounds studied was found by the "hot plate" method [8]. Amidopyrine was used as the standard of the anti-inflammatory and analgesic action.

The compounds studied were administered intraperitoneally to the experimental animals in the form of a suspension in 2% starch mucilage in a dose equal to 1/10 and 1/5 LD_{50}. Equal volumes of starch mucilage were injected to the control animals. Amidopyrine was administered intraperitoneally in a dose of 100 mg/kg. The experimental results were processed statistically and were considered reliable at $P < 0.05$ [9].

RESULTS AND DISCUSSION

The experimental results of the study of the toxicity, anti-inflamatory activity, and analgesic activity of the oxygen-containing organosilicon compounds are listed in Table 2, which shows that the LD_{50} of the compounds tested exceeds 800-1000 mg/kg. Hence, the compounds belong to a class of slightly toxic and practically nontoxic materials [6].

Of the compounds tested, those belonging to the group of the derivatives of hydroxybenzyl alcohol (compounds I-IX) and γ-hydroxyvaleric acid (compounds X-XIV, XVI) exhibited anti-inflammatory and analgesic activity.

In the first group of compounds, the trialkylsilyl derivatives of salicylic alcohol (I, II) had an anti-inflammatory action, not inferior to that of amidopyrine. However, the silylation products of o-hydroxybenzyloxytrialkylsilanes, the o-trialkylsiloxybenzyloxytrialkylsilanes (VI, VII), and the corresponding meta-derivatives (VIII, IX) had no anti-inflammatory activity.

TABLE 2. Analgesic and Anti-Inflammatory Activity of Organosilicon Derivatives of γ-Hydroxyvaleric Acid and Hydroxybenzyl Alcohols

E Compound	LD_{50}, mg/kg	Increment in volume of foot of rat, % with respect to initial volume				Time (M±m) of defence reflex in sec (at peak of action) in mice	P
		after 3 h	P	after 6 h	P		
I	80 >800	40	<0,001	48,5	<0,001	—	
II	80 >800	52,6	<0,001	57,8	<0,001	—	
III	>1000 200	75	>0,5	85	<0,5	16,3±2,1	<0,1
IV	>1000 200	79,2	<0,5	76,4	<0,02	14±3,0	<0,5
V	>1000 200	84	<0,1	105	>0,5	14,7±1,0	<0,1
VI	>800 80	68,2	>0,5	93,2	>0,5		
VII	>1000 200	72,2	>0,5	99,3	>0,5	16±2,4	<0,1
VIII	>1000 200	71,0	<0,5	87,6	<0,25	29,5±5,5	<0,001
IX	>800 80	64,6	<0,05	93,8	<0,5	15±0,9	<0,05
X	>800 80	76,0	>0,5	91,0	<0,1	18,0±0,3	<0,001
XI	>800 80	92	>0,5	102	<0,05	18,8±0,4	<0,001
XII	>800 80	89,0	>0,5	101,6	<0,01	26,8±1,9	<0,001
XIII	>800 80	46,2	<0,001	54,2	<0,001	17,5±1,8	<0,02
XIV	>800 160	54,4	<0,001	59,2	<0,001	23,5±2,9	<0,001
XV	>800 160	45	<0,001	54	<0,001	19,2±0,8	<0,001
XVI	>1000 200	47,4	<0,001	53,4	<0,001	14,8±1,6	<0,02
Control (starch mucilage		74,0		97,5		12,1±0,8	
Standard (amidopyrine)		37,0		45,0		36,4±4,3	

Note. P was calculated with reference to control.

In the second group of compounds, trialkylsilyl esters of γ-trialkylsiloxyvaleric acid (XIII, XIV) and the ethyl ester of γ-phenyl-γ-triethylsiloxybutyric acid (XVI) caused an inhibition of the inflammatory reaction. Esters of γ-di- and trialkylsiloxyvaleric acid (X, XI, XII) did not have any anti-inflammatory activity. The analysis of the data obtained showed that the difference in the anti-inflammatory activity of the compounds studied, to a certain extent, was the result of the chemical structure. It was found that a change in the nature of the radicals of the ethyl esters of γ-di- and trialkylsiloxyvaleric acid in the siloxy group (X, XI, XII) does not lead to an appreciable change in the anti-inflammatory action. However, substitution of the ethyl radical in the ethyl ester of γ-trialkylsiloxyvaleric acid (X, XII) by triethylsilyl or ethyldibutylsilyl group (XIII, XIV), and also of the methyl radical in the ethyl ester of γ-triethylsiloxyvaleric acid (X) by phenyl (XVI) leads to pronounced anti-inflammatory activity.

An intensification of the anti-inflammatory action was also noted in the presence of a hydroxyl group in the o-position of hydroxybenzyloxytrialkylsilanes.

The organosilicon derivatives of γ-hydroxyvaleric acid and hydroxybenzyl alcohols studied had a weakly marked analgesic action. In the series of the organosilicon derivatives of hydroxybenzyl alcohols, the most distinct anesthetic action was that of m-triethylsiloxybenzyloxytriethylsilane (VIII), and in the series of the organosilicon derivatives of γ-hydroxyvaleric acid, that of the ethyl ester of γ-ethyldibutylsiloxyvaleric acid (II) and ethyldibutylsilyl ester of γ-ethyldibutylsiloxyvaleric acid (XIV).

The analysis of the analgesic action in the series of ethyl and trialkylsilyl esters of γ-di- and trialkylsiloxyvaleric acid (X-XIV) showed that the ethyldibutylsiloxy group gives

a greater contribution to the analgesic action than the diethylsiloxy- and triethylsiloxy groups (compare X with XII and XI, XIII with XIV). Substitution of the methyl radical in the ethyl ester of γ-triethylsiloxyvaleric acid (X) by phenyl (XVI), and the ethyl group in the ethyl ester of levulinic acid (19.2 ± 1.2) by the ethyldibutylsiloxy group (XV) did not change the analgesic action. Substitution of ethyl radicals in triethylsiloxy group by two butyl radicals led to an appreciable intensification of the analgesic activity (compare X with XII and XIII with XIV). The contribution of the ethyl group of the carboethoxysilyl radical to the analgesic action of the preparation is the same as that of the $OSi(C_2H_5)_3$- and $OSi(C_4H_9)_2C_2H_5$ groups.

It is known that the importance of the anti-inflammatory agents increases with the presence of anesthetic properties in them. To obtain preparations with both types of activity, active groups responsible for such an activity must be present.

We took into account the above discovered regularities in the relationship between the chemical structure and the analgesic and anti-inflammatory action, and synthesized the ethyldibutylsilyl ester of γ-ethyldibutylsiloxyvaleric acid, containing the two groupings responsible for the anesthetic and analgesic action. Table 2 shows that this compound has both anti-inflammatory and analgesic activity.

LITERATURE CITED

1. E. L. Pidèmskii, I. I. Lapkin, et al., Izv. Estestestvennanauchn. Inst. Permsk. Gos. Univ., 15, 3-6 (1974).
2. L. M. Obvintseva, E. L. Pidèmskii, B. A. Bargteil', et al., in: Study of Biological Action of Products of Organic Synthesis and Natural Compounds [in Russian], Perm (1976), pp. 56-63.
3. E. L. Pidèmskii, A. F. Goleneva, I. I. Lapkin, et al., Deposited at All-Union Institute of Scientific and Technical Information [VINITI] (1973), No. 3552-78.
4. I. I. Lapkin and V. V. Dvinskikh, Zh. Obshch. Khim., 48, 2509-2511 (1978).
5. Yu. I. Khudobin, V. N. Dolgov, and N. P. Kharitonov, in: Chemistry and Practical Use of Organosilicon Compounds [in Russian], No. 6, Leningrad (1961), p. 155.
6. K. P. Sidorov, in: Toxicology of New Industrially Produced Chemical Compounds [in Russian], No. 13, Moscow (1973), pp. 47-51.
7. L. S. Salyamon, in: Medicinal Regulation of the Inflammatory Process [in Russian], Leningrad (1958), pp. 11-43.
8. N. B. Eddy and D. J. Leimbach, J. Pharmacol. Exp. Ther., 107, 385-393 (1953).
9. M. L. Belen'kii, Elements of Quantitative Estimation of Pharmacological Effect [in Russian], 2nd edn., Leningrad (1963).