DL-β-N,N-Dialkylaminoethyl Esters of Substituted α-Trimethylsilylphenyl-β-hydroxypropionic Acids

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Six substituted DL-α-trimethylsilylphenyl-β-hydroxypropionic acids were prepared starting from sodium *p*- or *m*-trimethylsilylphenylacetate which was converted to the Ivanov reagent with isopropylmagnesium chloride and treated with aldehydes or ketones. β-N,N-Dimethyl- and β-N,N-diethylaminoethyl esters were prepared from the acids with the corresponding β-N,N-dialkylaminoethyl chloride in boiling 2-propanol. Preliminary pharmacological evaluation showed that these esters have anticholinergic activity and some of them have protective effects against organophosphate poisoning.

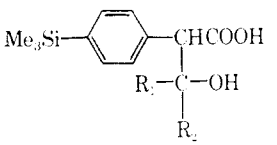
Aminoalkyl esters of carboxylic acids[1,2] such as benzoic acid, *p*-aminobenzoic acid, and tropic and substituted-tropic acids[3] are known to have local anesthetic and anticonvulsant activity. Rhone and Cason[4] reported that aminoalkyl esters of *p*-trimethylsilylbenzoic acid have local anesthetic and analgetic activity.

As part of a program for the preparation of silicon-containing compounds with potential biological activity[5,6] we have prepared DL-β-N,N-dialkylaminoethyl esters of substituted α-trimethylsilylphenyl-β-hydroxypropionic acids. They were synthesized from *p*- or *m*-trimethylsilylphenylacetic acid.[7]

The dry sodium salt of these acids was added to an ethereal solution of isopropylmagnesium chloride to yield the Ivanov reagent[8] (I) which on treatment with aldehydes or ketones and subsequent hydrolysis led to the formation of substituted DL-α-trimethylsilylphenyl-β-hydroxypropionic acids (II) (Table I). DL-α-*p*-Trimethylsilylphenyl-β-hydroxypropionic acid (DL-*p*-trimethylsilyltropic acid) was obtained on treatment of I with anhydrous formaldehyde.

Table I

DL-α-*p*-Trimethylsilylphenyl-β-hydroxy-β,β-dialkylpropionic Acids



R_1	R_2	Mp, °C	Yield, %	Formula[c]
H[a]	H	140	64	$C_{12}H_{18}O_3Si$
C_6H_5	H	184	64	$C_{18}H_{24}O_3Si$
C_6H_5[b]	CH_3	102	78	$C_{19}H_{24}O_3Si$
-$(CH_2)_4$-		148	80	$C_{16}H_{24}O_3Si$
-$(CH_2)_5$-		185	90	$C_{17}H_{26}O_3Si$[d]

[a] Paraformaldehyde, dried *in vacuo* over P_2O_5, was heated to 180–200°, and the generated gaseous formaldehyde was introduced to the Ivanov reagent. [b] *m*-Trimethylsilylphenylacetic acid[7] was used. [c] All compounds were analyzed for C, H, Si, and their molecular weights were determined. [d] C: calcd, 66.93; found, 66.39. H: calcd, 8.55; found, 8.12.

β-N,N-Dimethylaminoethyl and β-N,N-diethylaminoethyl esters (III) of II were obtained as the water-soluble hydrochlorides by heating the acids in 2-propanol with the corresponding β-N,N-dialkylamino-ethyl chlorides (Table II) (see Scheme I).

Scheme I

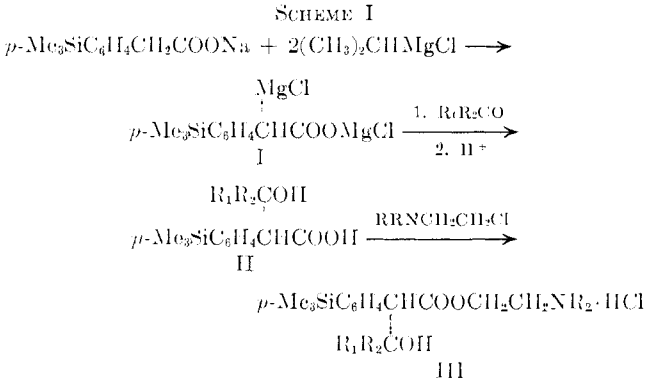
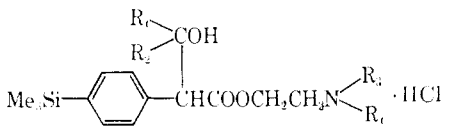


Table II

DL-β-N,N-Dialkylaminoethyl Esters of Substituted *p*-α-Trimethylsilylphenyl-β-hydroxypropionic Acids



No.	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Formula[b]
2	CH_3	CH_3	C_2H_5	C_2H_5	145–147	87	$C_{20}H_{36}ClNO_3Si$
3	CH_3	CH_3	CH_3	CH_3	153–155	84	$C_{18}H_{32}ClNO_3Si$
4	-$(CH_2)_4$-		CH_3	CH_3	139–141	90	$C_{20}H_{34}ClNO_3Si$
5	-$(CH_2)_5$-		CH_3	CH_3	150–152	87	$C_{21}H_{36}ClNO_3Si$

[a] Determined in a sealed tube. [b] All compounds were analyzed for C, H, N, Si.

Preliminary pharmacological results show that the compounds are moderately toxic. All of them possess some anticholinergic activity, but in no case is the activity higher than that of atropine. Compound **2** appears to be the most active in this series. In the mydriatic test, **4** was the most active. This is the silicon-containing analog of cyclopentolate which is in use as an ophthalmic drug.[9]

Experimental Section

Typical procedures for the preparation of substituted α-trimethylsilylphenyl-β-hydroxypropionic acids and of their β-N,N-dialkylamino esters are given below; the rest are summarized in

(1) L. S. Goodman and A. Gilman, Ed., "The Pharmacological Basis of Therapeutics," 3rd ed, The MacMillan Co., New York, N. Y., 1965, p 532.

(2) C. O. Wilson and O. Gisvold, "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 3rd ed, J. B. Lippincott Co., Philadelphia, Pa., 1965, p 343.

(3) F. Blicke and J. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952).

(4) L. F. Cason and J. R. Rhone, U. S. Patent 2,789,122 (1957).

(5) I. Belsky, D. Gertner, and A. Zilkha, *J. Med. Chem.*, **11**, 92 (1968).

(6) A. Rotman, M.Sc. Thesis, Hebrew University of Jerusalem, 1966.

(7) M. Frankel, M. Broze, D. Gertner, and A. Zilkha, *J. Chem. Soc., C*, 379 (1966).

(8) D. Ivanov and A. Spassov, *Bull. Soc. Chim. France*, **49**, 19 (1931).

(9) Reference 1, p 526.

TABLE III

DOSE RANGE FINDING EXPERIMENTS AND GROSS BEHAVIORAL CHANGES[a]

Compd	Dose, mg/kg	General changes
1	25	No obvious abnormalities.
	50	Spontaneous motility reduced; piloerection.
	100	During first 0.5 hr ataxia, followed by almost complete cessation of spontaneous activity; decreased sensibility to touch; intermittent myoclonic jerks; hypothermia; symptoms lasting about 2 hr.
	200	All animals died within 15 min; death was preceded by convulsions.
2	25	No obvious abnormalities.
	50	Spontaneous motility slightly reduced; slight piloerection.
	100	During first 0.5 hr slight ataxia, followed by decrease in spontaneous motility; brief intermittent convulsions; ptosis; hypothermia; symptoms lasting about 3 hr.
	200	Four animals died within 60 min; death was preceeded by strong clonic convulsions.
3	25	No obvious abnormalities.
	50	Slight piloerection; slight ptosis.
	100	During first 0.5 hr clonic convulsions, followed by decreased spontaneous motility; reduced sensibility to touch; dyspnea; symptoms lasting for about 3 hr.
	200	All animals died within 10 min following strong convulsions.
4	25	No obvious abnormalities.
	50	Piloerection.
	100	Slight ptosis; slight decrease in spontaneous motility; during first 15 min following injection brief strong myoclonic jerks and writhing.
	200	Ataxia followed by decreased spontaneous activity; ptosis; symptoms lasting for about 2 hr.
5	25	No obvious abnormalities.
	50	Within 5 min following injection, strong myoclonic jerks and writhing, lasting several min; slight piloerection.
	100	Slight ptosis; piloerection.
	200	Considerable reduction in spontaneous motility; ptosis; 3 animals died within 18 hr.

[a] Groups of five mice of 22–25 g for each dose level were used.

Tables I and II. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Where analytical results are indicated only by the symbols of the elements, the observed values differed from the calculated values by not more than ±0.4%.

Sodium *p*-Trimethylsilylphenylacetate.—*p*-Trimethylsilylphenylacetic acid[7] (20.8 g, 0.1 mole) in absolute EtOH (40 ml) was added dropwise with stirring to a solution of Na (2.3 g, 0.1 g-atom) in absolute EtOH (60 ml). The reaction mixture became neutral to litmus, was cooled in an ice–salt mixture for several hours, filtered, and washed with cold absolute EtOH. The salt was dried at 120°, yield 20.5 g (89%). An additional crop of 2.5 g (11%) was isolated on evaporation of the filtrate. *Anal.* ($C_{11}H_{15}NaO_2Si$) Si, mol wt (titration with 0.1 *N* HCl using methyl orange).

DL-α-*p*-Trimethylsilylphenyl-β-hydroxy-β,β-dimethylpropionic Acid.—To a solution of isopropylmagnesium chloride [from isopropyl chloride (8 g, 0.1 mole) and Mg (2.4 g, 0.1 g-atom)] in dry Et_2O (50 ml), solid sodium *p*-trimethylsilylphenylacetate (11.1 g, 0.05 mole) was added in small portions, and the reaction mixture was heated under reflux for 5 hr and then cooled to 0°. Dry Me_2CO (5.8 g, 0.1 mole) in dry Et_2O (30 ml) was added dropwise, and the reaction mixture was heated for an additional 2 hr and cooled to 0°. H_2O (25 ml) followed by (1:1) HCl (50 ml) was added cautiously with stirring, and the mixture was stirred until two clear layers were formed. The aqueous layer was extracted (Et_2O) and the combined ethereal layers were extracted with dilute NaOH. The basic solution was acidified (HCl) and extracted (Et_2O). The ethereal extract was dried ($MgSO_4$) and the ether was driven off *in vacuo*, leaving 11.3 g (83%) of product, mp 157° (from C_6H_6–petroleum ether (bp 40–60°)). *Anal.* ($C_{14}H_{22}O_3Si$) C, H, Si, mol wt (anhydrous titration with KOMe).

DL-β-N,N-Diethylaminoethyl α-*p*-Trimethylsilylphenyl-β-hydroxypropionate Hydrochloride (1).—DL-α-*p*-Trimethylsilylphenyl-β-hydroxypropionic acid (2.38 g, 0.01 mole) and β-N,N-diethylaminoethyl chloride (1.35 g, 0.01 mole) were refluxed in dry *i*-PrOH (15 ml) for 10 hr. The reaction mixture was filtered and the solvent was driven off *in vacuo*. The residue solidified on trituration with dry Et_2O, yield 3 g (80%), mp 118° (sealed tube) (from EtOAc–petroleum ether). *Anal.* ($C_{18}H_{32}ClNO_3Si$) C, H, N, Si.

Preliminary Pharmacological Evaluation.—The DL-β-N,N-dialkylaminoethyl ester hydrochlorides (Table II) were tested as anticholinergics. Atropine sulfate was used as reference drug. All compounds were dissolved in saline and, regardless of route of administration, the maximal volume administered to mice never exceeded 0.2 ml/20 g.

For dose range finding experiments and gross behavioral changes in mice (Table III), the compounds were administered intraperitoneally to groups of five animals for each dose level. Observations were made for not more than 24 hr following injection.

In vitro acetylcholine antagonism (Table IV) tests were carried out.[10]

TABLE IV

IN VITRO ACETYLCHOLINE ANTAGONISM. GUINEA PIG ILEUM[a]

		% redn in ht of contraction elicited by acetylcholine in presence of exptl compd				
Concn, μg/ml	Atropine	1	2	3	4	5
0.04	95	···	70	···	···	···
0.1	100	···	95	···	···	···
0.2	···	···	100	···	···	10
0.4	···	···	···	85	80	85
0.6	···	···	···	···	···	80
1	···	70	···	95	90	100
2	···	70	···	100	100	···

[a] Figures represent mean values of three experiments for each compound. None of the compounds showed any antagonistic effects toward contractions elicited by histamine or bradykinin.

Effects on blood pressure, respiration rate, heart rate, and antagonism to hypotension elicited by acetylcholine were also studied (Table V). Male cats (2–3 kg) anesthetized with pentobarbital sodium (35 mg/kg) intraperitoneally were used. Blood pressure was measured from the left carotid artery with a Hg manometer or a statham pressure transducer and recorded on a kymograph or physiograph, respectively. Respiration rate and heart rate were recorded on the physiograph with impedance electrodes and an ECG transducer, respectively. Substances were injected through a cannula in the left femoral vein.

In antiarecoline tests in mice[11] (Table VI), the compounds were injected intraperitoneally followed 30 min later by the subcutaneous administration of arecoline (4 mg/kg). For mydriatic tests in mice[12] (Table VII) the compounds were injected subcutaneously. The diameter of the pupils was measured with a micrometer under a stereoscopic microscope at 15-min intervals, twice before and four times after injection.

Since the combination of atropine and pyridine-2-aldoxime methanesulfonate (P2S) constitutes the standard treatment against organic phosphate poisoning, the possibility of replacing atropine by these compounds was considered. The compounds in combination with a standard dose of P2S (90 mg/kg) were administered intraperitoneally to mice. TEPP (tetraethyl pyrophosphate) was injected subcutaneously to these animals 5 min

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(11) A. Herz, *Arch. Exptl. Pathol. Pharmacol.*, **242**, 414 (1962).
(12) P. Pulewka, *ibid.*, **242**, 307 (1962).

TABLE V

ANTAGONISM TO HYPOTENSION ELICITED BY ACETYLCHOLINE AND EFFECTS ON BLOOD PRESSURE, RESPIRATION RATE, AND HEART RATE[a,b]

Compd	Dose, mg/kg	Blood pressure Decrease, mm	Blood pressure Duration, min	Respiration rate Increase, % of control	Respiration rate Duration, min
1	1	10	0.5	20	2
	2	50	2	60	2
	4	100	4	65	3
2	1	20	1	20	1
	2	50	2.5	35	1
	4	80	4	85	3
3	2	50	2.5	70	2
	4	80	6	75	3
4	1	40	3	25	2
	2	80	3	30	3
	4	90	6	45	5
5	1	50	2	45	1.5
	2	80	3	50	3
	4	90	8	55	5

[a] Figures represent mean values obtained from at least three separate experiments. No antagonism to depressor effect of acetylcholine at doses up to 10 mg was observed. [b] No effect on the heart rate was observed for any compound.

TABLE VI

ANTIARECOLINE TEST.[a] MICE

Compd	Dose, mg/kg	Av antiarecoline action[b]
Atropine	0.5	++
	1	++++
	10	++++
1	0.5	0
	1	++
	10	++
2	0.5	0
	1	+
	10	+++
3	0.5	0
	1	0
	10	++
4	0.5	0
	1	++
	10	+++
5	0.5	0
	1	++
	10	++

[a] Groups of eight mice (20–25 g) were used for each dose level. [b] Rating scale: 0 = no antiarecoline action; + = very slight, turning of head sidewards or backwards, no biting clamp; ++ = slight, briefly biting clamp; +++ = medium, intermittent attempt to remove clamp; ++++ = strong, immediate, strong, and continuous attempt to remove clamp.

later and the number of survivors was recorded (Table VIII). Observations for mortality were made for not more than 24 hr after the administration of TEPP. In this test, 2 was the most active.

TABLE VII

MYDRIATIC ACTION.[a] MICE

Compd	Dose, mg/kg	Av % increase in pupilary width 15 min	30 min	45 min	60 min
Atropine	0.1	36	150	112	137
	1	200	200	233	216
1	0.1	14	10	0	0
	1	10	0	0	0
	10	0	0	0	0
2	0.1	14	14	0	0
	1	14	0	0	0
	10	25	12	12	0
3	0.1	0	0	0	0
	1	0	0	0	0
	10	0	12	0	0
4	0.1	0	0	0	0
	1	0	0	0	0
	10	33	116	12	0
5	0.1	0	0	0	0
	1	0	28	28	0
	10	0	20	0	0

[a] Groups of four mice (20–23 g) for each dose level were used.

TABLE VIII

PROTECTIVE EFFECTS OF COMPOUNDS AGAINST ORGANOPHOSPHATE POISONING[a]

Compd	Dose, mg/kg	TEPP (Multiples of LD_{50})	Survivors
Pyridine-2-aldoxime Methanesulfonate (Control)	90	5	3
P2S (Control)	90	10	0
Atropine (Control)	25	5	5
Atropine (without P2S)	25	5	0
1	50	5	3
2	50	5	5
	25	5	5
	10	5	5
	50	10	5
	25	10	5
	10	10	3
2 without P2S	50	5	0
3	50	(+)[b]	0
4	50	(+)[b]	0
5	50	5	5
	50	10	2
5 without P2S	50	5	0

[a] The test compounds were injected together with 90 mg/kg of pyridine-2-aldoxime methanesulfonate (P2S) 5 min before TEPP into groups of five mice per dose level. Mortality was recorded up to 24 hr after injection. [b] +, animals died within 5 min after the combined injection of P2S and the test compound, prior to the injection of TEPP.

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