TABLE VII

EFFECT OF COMPOUND **66** AND INTERACTIONS WITH EPINEPHRINE, NOREPINEPHRINE, ISOPROTERENOL, TYRAMINE, EPHEDRINE, AND AMPHETAMINE ON CAT BLOOD PRESSURE AND NICTITATING MEMBRANE (NM) CONTRACTION TO PREGANGLIONIC CERVICAL SYMPATHETIC NERVE STIMULATION

Expt no.	Dose, mg/kg iv	Response[a] (min)	Change[b] in the responses of Norepinephrine	Isoproterenol	Epinephrine	Tyramine	Ephedrine	Amphetamine	NM
1	2.5	+40 (5)	0	−10	+16	...	...	...	+20
2	5.0	+80 (2)	−20	−33	...	...	...	...	0
		−50 (2)							
3	10.0	+84 (2)							
		−40 (50)	−100	...	+25	−100	...	...	...
4	10.0	+60 (2)							
		−100 (>60)	−50	−75	0	...	...	−50	...
5	10.0	+70 (2)							
		−60 (>60)	−50	...	+50	...	−50	...	...
6	12.0	+70 (2)							
		−70 (60)	−100	−100	+66	...	−100	...	...

[a] Millimeter rise (+) or fall (−). [b] % augmentation (+) or antagonism (−).

of monomethoxy (**19**), dimethoxy (**65**), or chloro (**17**) groups in place of the hydroxy function, as also the substitution of a β-naphthyl (**13**) or indolyl (**15**) residue in place of the dihydroxyphenyl group led to a complete loss of this activity. The corresponding 3-deamino compound (**5**) also had greatly reduced activity. 4-(3,4-Dihydroxyphenethyl)amino-3-aminoquinoline (**53**), however, showed significant hypotensive activity. In the corresponding 2-(3,4-dihydroxyphenethyl)amino-3-aminopyridine (**36**) there was a complete loss of the hypotensive activity, while the 3-(3,4-dihydroxyphenethyl)amino-4-aminopyridine (**31**) showed vasopresser activity.

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Silicon-Containing Barbiturates

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Three 5-(*p*-trimethylsilylphenyl)barbiturates and one related thiobarbiturate were prepared starting from *p*-trimethylsilylphenylacetic acid, which was converted to diethyl alkyl-*p*-trimethylsilylphenylmalonates and condensed with urea or thiourea. Preliminary pharmacological evaluation of these barbiturates, as well as of two 5-(*p*-trimethylsilylbenzyl)barbiturates, showed them to have low sedative activity. Some of the compounds showed anticonvulsant activity.

Recently, work was reported on the preparation and biological evaluation of some silicon-containing analogs of biologically active organic compounds.[1] This interest was aroused by the fact that, although silicon is the main constituent of the earth's crust, it only rarely appears in living organisms.[2] Spirobarbiturates containing silicon in a cyclohexyl ring have been prepared and found to have narcotic activity.[3] Several silicon-containing barbituric acids having a trimethylsilylmethyl group have also been synthesized.[4] We have recently prepared 5-(*p*-trimethylsilylbenzyl)barbiturates,[5] and we wish now to report the synthesis of 5-(*p*-trimethylsilylphenyl)barbiturates and their preliminary pharmacological evaluation.

The barbiturates were prepared from *p*-trimethylsilylphenylacetic acid,[6] which was converted to the ethyl ester under mild conditions.[7] The ethyl ester was condensed with diethyl carbonate in the presence of sodium ethoxide[8] to yield diethyl *p*-trimethylsilylphenylmalonate. This was treated, in absolute ethanol in the presence of sodium ethoxide, with ethyl iodide or allyl bromide yielding diethyl *p*-trimethylsilylphenylethyl- or -allylmalonate, respectively. Condensation of the malonate derivatives with urea or thiourea in absolute ethanol in the presence of sodium ethoxide yielded the silicon-containing barbiturates (Table I).

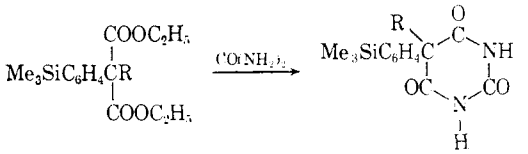

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TABLE I

5-(*p*-TRIMETHYLSILYLPHENYL)BARBITURATES

Compd	X	R	Mp, °C	Yield, %	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Silicon, % Calcd	Silicon, % Found	λ_{max}, mμ	ϵ_{max}	N–H, μ	CO, μ
1	O	H	210	67	$C_{13}H_{16}N_2O_3Si$	56.46	56.09	5.84	5.80	10.14	10.44	10.16	10.24	272	18,500	3.15, 3.27	5.75, 5.86
2	O	Ethyl	224	58	$C_{15}H_{20}N_2O_3Si$	59.19	58.85	6.62	6.44	9.20	8.67	9.23	9.42	265[a]	960	3.08, 3.25	5.80, 5.85
3	O	Allyl	259	64	$C_{16}H_{20}N_2O_4Si$	60.73	61.02	6.37	6.35	8.85	8.82	8.88	9.12	220,[a] 262[a]	18,000, 940	3.12, 3.23	5.79, 5.87
4	S	Allyl	202	71	$C_{16}H_{20}N_2O_2SSi$	57.80	57.60	6.06	5.76	8.43	8.59	8.45	8.33	234, 246,[a] 302	15,000, 10,000, 21,500	3.15	5.73, 5.85, 6.60 (C=S)

[a] Shoulder.

TABLE II

DOSE-RANGE FINDING EXPERIMENTS AND GROSS BEHAVIORAL CHANGES[a]

Compd	Dose, mg/kg	General changes
6	100[b]	Piloerection, sedation, ptosis, lasting about 1 hr.
	50	Slight sedation during 45 min.
2	200	Slight sedation, piloerection lasting about 30 min.
	100	Slight sedation.
5	50	Same. Death at about 1 hr.
	25	Ptosis, reduction of spontaneous motility, intermittent brief seizures, piloerection. After 2 hr fully recovered.
	10	Spontaneous motility reduced.
3[c]		
4[c]		

[a] Groups of five male mice (23–25 g) for each dose level were used. Observations were made for no longer than 24 hr after administration. [b] This was the maximal dose which could be tested. As for higher doses, the compound could not be dissolved properly in propylene glycol at volumes suitable for injection. [c] Doses up to 100 mg/kg showed no obvious gross behavioral changes.

The barbiturates prepared are insoluble in water, cold ethanol, and carbon tetrachloride. They are soluble in hot ethanol, acetone, and dilute sodium hydroxide.

Preliminary Pharmacological Evaluation.—Some of the silicon-containing barbiturates were evaluated for their sedative and anticonvulsant activity in mice. The compounds were dissolved in propylene glycol and injected intraperitoneally. Maximum volume injected did not exceed 0.05 ml/20 g. Control groups of mice received solvent only.

The compounds investigated were 5-(*p*-trimethylsilylphenyl)-5-ethylbarbituric acid (**2**), 5-(*p*-trimethylsilylphenyl)-5-allylbarbituric acid (**3**), 5-(*p*-trimethylsilylphenyl)-5-allyl-2-thiobarbituric acid (**4**), 5-(*p*-trimethylsilylbenzyl)-5-ethylbarbituric acid (**5**), and 5-(*p*-trimethylsilylbenzyl)-5-acetamidobarbituric acid (**6**). Dose-range finding experiments and gross behavioral changes are given in Table II.

Supramaximal electroshock tests[9] (Table III) were carried out on groups of 10–20 mice for each dose level. Animals were submitted to maximal electroshock provoked by 70 v, 30 min after injection of test material. The following parameters were recorded: brief-tonic limb flexion (TF), prolonged full-tonic limb extension (TEx), and death. 5-Ethyl-3-methyl-5-phenylhydantoin (mesantoin) and an analogous barbiturate not containing silicon, *viz.*, sodium phenobarbital, were taken as reference drugs. Prevention of tonic limb extension was considered as protection against supramaximal electroshock. Maximal, pentylenetetrazole-seizure tests[10] (Table III) were conducted on groups of 10–20 mice for each dose level. Maximum volume injected did not exceed 0.05 ml/20 g, and 30 min following injection of test compounds, pentylenetetrazole (100 mg/kg) was injected subcutaneously. Protection against tonic seizures was noted, but death rate was chosen as the index for protective effects.

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TABLE III

ANTICONVULSIVE ACTIVITY

Compd	No. of mice tested	Dose, mg/kg	Supramaximal electroshock[a] TEx	Dead	Antipentylenetetrazole test, survivors
Saline	20	0.05 ml/20 g	16	4	0
Propylene glycol	30	0.05 ml/20 g	26	2	7[b]
Mesantoin	20	25	0	0	20
	20	10	9	0	
Phenobarbital	20	25	0	0	20
	20	10	2	0	16
2	20	50	2	0	17
	20	25	8	0	17
	20	10	10	0	11
3	10	50	0		5
	10	25	4		2
	10	10	6		1
4	10	50	4		2
	10	25	6		0
	10	10	10		
5	20	25	0	0	2
	20	10	9	0	0
6	20	50	0	0	16
	20	25	2	0	9
	20	10	5	0	5
	20	5	11	0	

[a] Brief tonic limb flexion was observed with all the test compounds and at the doses given. TEx = prolonged, full-tonic limb extension. [b] Tested on a group of 40 mice.

The preliminary pharmacological results show that the compounds had only a weak sedative activity. Part of the compounds showed significant anticonvulsant activity, although less than that of phenobarbital or mesantoin. In the electroshock tests, **6** showed activity similar to phenobarbital, while **2**, **3**, and **4** showed lower activity. Compound **5** was investigated up to a dose of 25 mg/kg due to its toxicity, and at this dose it showed full protection against electroshock.

In the antipentylenetetrazole test, **6** and **2** were the most active, while **3** showed medium activity at a relatively high dose. Compounds **5** and **4** were essentially inactive.

Experimental Section

Melting points were determined using a Fisher-Johns apparatus. Uv spectra were carried out in EtOH (J. T. Baker alcohol reagent) using a Beckman DU spectrophotometer. The ir spectra (KBr) were taken on a 337 Perkin-Elmer grating spectrophotometer.

Ethyl *p*-Trimethylsilylphenylacetate.—Purified $SOCl_2$ (18 g, 0.153 mole) was dropped into cold absolute EtOH (60 ml) at −20°. The mixture was stirred in the cold for another 15 min, and solid *p*-trimethylsilylphenylacetic acid (31.2 g, 0.15 mole) was added in small portions, care being taken that the temperature did not rise above −15°. The reaction mixture was stirred in the cold for another hour, and left to warm to room temperature. It was cooled again to −15° and neutralized with 10% NaOH solution. The mixture was diluted with H_2O and the ester was extracted with Et_2O and washed (H_2O, 5% bicarbonate), dried, and distilled giving an oil (32 g, 93%), bp 137° (5 mm), $n^{25}D$ 1.493.

Anal. Calcd for $C_{13}H_{20}O_2Si$: C, 66.10; H, 8.47; Si, 11.86. Found: C, 66.05; H, 8.31; Si, 12.04.

Diethyl *p*-Trimethylsilylphenylmalonate.—Ethyl *p*-trimethylsilylphenylacetate (20 g, 0.11 mole) and dry redistilled diethyl carbonate (75 ml, excess) were heated to boiling and a solution of NaOEt, prepared by dissolving Na (2.8, 0.12 g-atom) in absolute EtOH (50 ml), was dropped in during about 1 hr (at the same rate as the EtOH distilled), followed by C_6H_6 (60 ml) which was also distilled. The mixture was heated for another 30 min, cooled to 0°, diluted with H_2O, and acidified to pH 2. It was extracted with Et_2O, and the extract was dried and distilled. The oily malonate (28.8 g, 85%) boiled at 168–169° (5 mm) (176–177°, 8 mm), $n^{25}D$ 1.491.

Anal. Calcd for $C_{16}H_{24}O_4Si$: C, 62.31; H, 7.84; Si, 9.10. Found: C, 62.33; H, 7.70; Si, 8.83.

Diethyl Ethyl-*p*-trimethylsilylphenylmalonate.—Ethyl *p*-trimethylsilylphenylmalonate (13 g, 0.042 mole) and EtI (6.6 g, 0.042 mole) were stirred and heated to about 80°, and a solution of Na (1.15 g, 0.05 g-atom) in absolute EtOH (25 ml) was dropped in during 40 min. The mixture was stirred and heated for 1 hr. The alcohol was driven off *in vacuo*, H_2O was added, and the ester was taken up in Et_2O, washed, dried, and distilled. The oily ester (11.5 g, 82%) boiled at 160–162° (2–3 mm), $n^{25}D$ 1.492.

Anal. Calcd for $C_{18}H_{28}O_4Si$: C, 64.25; H, 8.39; Si, 8.34. Found: C, 64.20; H, 8.39; Si, 8.47.

Diethyl Allyl-*p*-trimethylsilylphenylmalonate.—Diethyl *p*-trimethylsilylphenylmalonate (15.4 g, 0.05 mole) was added to a solution of Na (1.15 g, 0.05 g-atom) in absolute EtOH (60 ml). Allyl bromide (7.3 g, 0.06 mole) in absolute EtOH (20 ml) was added dropwise, and the reaction mixture was stirred at room temperature until neutral toward litmus (about 5 hr). EtOH and excess allyl bromide were evaporated *in vacuo*, and the residue was diluted with H_2O and extracted with Et_2O. The Et_2O was washed with water, dried ($MgSO_4$), and distilled to give product (13.4 g, 77%), bp 170–172° (6 mm), $n^{25}D$ 1.496.

Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.44; H, 7.91.

5-(*p*-Trimethylsilylphenyl)barbiturates.—The compounds listed in Table I were prepared by the following general procedure. To a solution of Na (0.01–0.02 g-atom) in absolute EtOH (20 ml), diethyl *p*-trimethylsilylphenylmalonate (0.01 mole) and dry urea (0.01–0.015 mole) were added, and the reaction mixture was heated with stirring under reflux for 7–20 hr. EtOH was distilled *in vacuo*, H_2O was added, and the solution was filtered and acidified to pH 2. The mixture was left in the cold for several hours, and the precipitated barbiturate was filtered. It was recrystallized from EtOH–H_2O.

The 2-thiobarbiturate was prepared by the same procedure using thiourea instead of urea.

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