Amides of Silicon-Containing Aromatic Carboxylic Acids

IGAL BELSKY, DAVID GERTNER, AND ALBERT ZILKHA

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

Received November 10, 1967

Various amide derivatives of *o*- and *p*-trimethylsilylbenzoic acid, *p*-trimethylsilylphenylacetic acid, and *p*-trimethylsilylhydrocinnamic acid were prepared starting from the corresponding acids. Preliminary pharmacological evaluation of seven compounds showed that they had some activity as central nervous system depressants; *p*-trimethylsilylphenylacetylurea was more active than its analog without silicon.

Many amides, ureides, and hydrazides of aromatic acids such as benzoic, phenylacetic, salicylic, and substituted benzoic acids are known to be CNS depressants.[1,2] As part of a program for the preparation of silicon-containing compounds with potential biological activity[3,4] we have prepared some amides of trimethylsilyl-substituted aromatic acids. The introduction of organosilicon into these compounds seemed interesting, since besides the fact that silicon, although abundant in nature, is rarely present in biological systems, the physical properties of the compounds such as solubility, partition coefficient, and permeability to physiological membranes are expected to be different from the analogous carbon compounds.

The silicon-containing acids used were *o*- and *p*-trimethylsilylbenzoic acid,[5] *p*-trimethylsilylphenylacetic acid,[6] and *p*-trimethylsilylhydrocinnamic acid. The latter was prepared by hydrolysis and decarboxylation of diethyl *p*-trimethylsilylbenzylmalonate.[7]

The acyl chlorides of the acids were prepared by reaction with $SOCl_2$. In the case of trimethylsilylphenylacetic and hydrocinnamic acid the reaction was carried out in the presence of calcium carbonate to minimize cleavage of the Si–Ar bond under the acid conditions.

The amides (Table I) were obtained by addition of the acyl chlorides to 2 equiv of the amine in suitable solvents at room temperature. *p*-Trimethylsilylphenylacetylurea was obtained by reaction of *p*-trimethylsilylphenylacetyl chloride and urea in benzene at 80°.[8] *p*-Trimethylsilylphenylacetyl hydrazide was prepared by reaction of *p*-trimethylsilylphenylacetic acid and hydrazine under azeotropic conditions in the presence of 1-butanol and alumina.[9]

Preliminary Pharmacological Evaluation.—A number of the amides synthesized were selected for pharmacological screening. The compounds were tested for their sedative and anticonvulsant activity. They were administered orally in fine suspensions of 3% acacia by stomach tube to 18-hr fasted mice receiving water *ad libitum*.

Supramaximal electroshock tests[10] (Table II) were carried out on groups of four male mice (22–24 g) per dose level and maximal volume administered did not exceed 0.2 ml/20 g. In order to determine time of maximum effect, groups of animals were tested at different time intervals following administration of compounds. Prevention of full tonic limb extension (T.Ex.) was considered as protection against supramaximal electroshock.

Maximal pentylenetetrazole seizure tests[11] were also carried out (Table III). The compounds were administered at different time intervals prior to the subcutaneous injection of 100 mg of pentylenetetrazole/kg. Death rate was chosen as index for protective effects. Methylphenylhydantoin, phenobarbital sodium, and phenylacetylurea were administered as reference drugs.

In blood pressure, respiration rate, and heart rate tests (Table IV) male cats (2–3 kg) anesthetized with pentobarbital sodium (35 mg/kg) intraperitoneally were used. Blood pressure was measured from the left carotid artery and recorded on a kymograph. Respiration rate and heart rate were recorded on the physiograph with impedance electrodes and an ECG transducer, respectively. Time was recorded. Substances were injected through a cannula in the left femoral vein.

The results showed that full protection against convulsions, as measured by the supramaximal electroshock, was shown by compounds I, VIII, and IV at a dose of 100 mg/kg at 2 hr following their administration. Compound IV exhibited an anticonvulsant activity at a dose range comparable to that of the reference compounds and was more effective in this respect than phenylacetylurea and showed a longer duration of action. It was also the only compound having an anticonvulsant effect in the antipentylenetetrazole test.

To find out whether IV had any psychotropic properties, autonomic as well as behavioral changes in mice were observed and conditioned avoidance response tests in rats[12] were carried out. No special psychotropic effects were noted even at doses up to 600 mg/kg.

None of the compounds in Table II tested showed any sedative activity or other abnormalities in gross behavior of mice after doses up to 100 mg/kg. All compounds investigated, except VIII, caused a drop in blood pressure and a concomitant increase in respiration rate.

(1) (a) O. C. Wilson and O. Gisvold, "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 3rd ed, J. B. Lippincott Co., Philadelphia, 1956, p 152; (b) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, The Macmillan Co., New York, N. Y., 1965, p 330.

(2) (a) R. B. Moffett, P. H. Seay, and W. B. Reid, *J. Med. Pharm. Chem.*, **2**, 179 (1960); (b) W. B. Horrom and E. T. Lynes, *ibid.*, **6**, 528 (1963).

(3) I. Belsky, D. Gertner, and A. Zilkha, *ibid.*, **11**, 92 (1968).

(4) A. Rotman, M.Sc. Thesis, submitted to The Hebrew University of Jerusalem, 1967.

(5) R. S. Benkeser and H. R. Krysiak, *J. Am. Chem. Soc.*, **76**, 599 (1954).

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

(7) M. Frankel, I. Belsky, D. Gertner, and A. Zilkha, *ibid.*, 493 (1966).

(8) M. A. Spielman, A. O. Greiszler, and W. J. Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948).

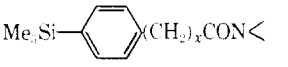
(9) J. Rabini and G. Vita, *J. Org. Chem.*, **30**, 2486 (1965).

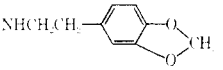
(10) J. E. P. Toman and G. M. Everett in "Evaluation of Drug Activities: Pharmacometrics," Vol. 1, D. R. Laurence and A. L. Bachrach, Ed., Academic Press Inc., New York, N. Y., 1964, p 287.

(11) L. S. Goodman, M. S. Grewal, W. C. Brown, and E. A. Swinyard, *J. Pharmacol. Exptl. Therap.*, **108**, 168 (1953).

(12) D. Bovet, L. Gatti, and M. Frank, *Sci. Rept. Ist. Super. Sanita*, **1**, 127 (1961).

TABLE I
AMIDES OF SILICON-CONTAINING AROMATIC CARBONYLIC ACIDS



No.	x	—NR	Reaction solvent[a]	Yield, %	Mp or bp (mm), °C	Formula[c]
V	0	α-$NHC_{10}H_7$	A	88	141	$C_{20}H_{21}NOSi$
VI	0	NH-*n*-C_4H_9	B	76	66	$C_{14}H_{23}NOSi$
VII	0		B	84	170–174 (2)	$C_{15}H_{23}NOSi$
VIII	0	NHC_6H_4COOEt-*p*	A	91	104	$C_{19}H_{23}NO_3Si$
IX	0	$NHCH(CH_3)CH_2N(CH_3)_2$	A	90	74	$C_{15}H_{26}N_2OSi$
X	0	$NHCH_2CH_2C_6H_3$-3,4-$(OMe)_2$	A	87	104[b]	$C_{20}H_{27}NO_3Si$
XI	1	NH_2	C[c]	89	107	$C_{11}H_{17}NOSi$
XII	1		A	93	172–174 (2)	$C_{15}H_{23}NO_2Si$
XIII	1	$NHCH_3$	C[c]	82	100	$C_{12}H_{19}NOSi$
XIV	1	$NHCH_2CH{=}CH_2$	D	94	102	$C_{14}H_{21}NOSi$
XV	1	$NHCH_2C_6H_4SiMe_3$-*p*	A	90	118	$C_{21}H_{31}NOSi_2$
XVI	1		A	94	130	$C_{19}H_{23}NOSi$
XVII	2	NH_2	C[c]	83	98	$C_{12}H_{19}NOSi$
XVIII	2		A	93	45	$C_{16}H_{25}NO_2Si$
XIX	1[d]		A	78	70	$C_{21}H_{27}NO_3Si$

[a] The reaction was carried out in A, $CHCl_3$; B, THF; C, H_2O; D, CCl_4. [b] *ortho* isomer. [c] NH_4OH or amine was used. [d] The amide of $Me_3SiCH_2C_6H_4CH_2COOH$: A. Shenhar, Ph.D. thesis, submitted to the Hebrew University, 1967. [e] All compounds were analyzed for C, H, N, Si.

TABLE II
SUPRAMAXIMAL ELECTROSHOCK[a]

Compd	Dose, mg/kg	No. unprotected against T.Ex.[b] 0.5 hr after injection	1 hr after injection	2 hr after injection	3 hr after injection
I	100	3	0	0	1
	50	4	3	0	2
	25	3	3	3	4
IV	100	1	0	0	0
	50	2	1	0	1
	25	3	2	0	3
VIII	100	4	2	0	3
	50	4	2	3	4
	25	4	3	3	4
IX	100	0	1	1	...
	50	3	3	4	...
	25	3	4	4	...
XIV	100	3	1	2	1
	50	3	2	2	1
	25	3	2	1	1
XV	100	4	4	...	...
	50	4	3	...	...
	25	4	4	...	...
Phenylacetylurea	100	2	0	1	...
	50	1	1	4	...
	25	3	3	4	...
Methylphenylhydantoin	25	...	0[c]	...	...
	10	...	3[c]	...	...
Phenobarbital Na	20	...	0	...	...

[a] The compounds were administered to groups of four male mice (22–24 g) per dose level and the maximal volume administered did not exceed 0.2 ml/20 g. [b] Prolonged full tonic limb extension. [c] Time after administration was 1.5 hr.

TABLE III
ANTIPENTYLENETETRAZOLE TESTS[a]

Compd[b]	Dose, mg/kg	No. of survivors Time after administration, hr 0.5	1	2
IV	100	2	2	2
	50	2	1	1
	25	1	0	0
Phenylacetylurea	100	2	2	2
	50	0	1	0
	25	1	1	0
Mesantoin	100	4	4	
	50	2	3	
	25	2	2	
Phenobarbital Na	25		4	

[a] Experiments were carried out on groups of four mice. [b] In experiments on compounds I, VIII, IX, XIV, and XV no survivors were left in the above conditions.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

***p*-Trimethylsilylhydrocinnamic Acid.**—Diethyl *p*-trimethylsilylbenzylmalonate[7] (32.2 g, 0.1 mole) was added with stirring to a solution of Na (4.6 g, 0.2 g-atom) in absolute EtOH (100 ml) and heated to reflux. H_2O (5 ml) was added, and the reaction mixture was refluxed for 15 min and cooled. The disodium salt (31 g, 100%) was filtered and washed with petroleum ether (bp 40–60°); mp >300°. It was dissolved in H_2O (200 ml) and the solution was acidified with HCl to pH 4. The malonic acid derivative was extracted with ether and dried ($MgSO_4$). The ether was driven off, and the acid was heated at 40 mm for 6 hr at 160–180°. It solidified (18 g, 83%) on cooling; mp 103° after recrystallization from petroleum ether. *Anal.* ($C_{12}H_{18}O_2Si$) C, H, Si, mol wt (on titration with 0.1 *N* $KOCH_3$ in C_6H_6–MeOH using thymol blue as indicator).

***p*-Trimethylsilylphenylacetyl Chloride.**—To a stirred solution of *p*-trimethylsilylphenylacetic acid (10.4 g, 0.05 mole) in C_6H_6 (10 ml), containing anhydrous $CaCO_3$ (15 g), freshly distilled $SOCl_2$ (10 ml) was added and the mixture was refluxed for 2 hr. It was filtered and distilled, bp 117° (4 mm). *Anal.* ($C_{11}H_{15}ClOSi$) C, H, Cl.

TABLE IV
EFFECTS ON BLOOD PRESSURE AND RESPIRATION RATE[a]

Compd[b]	Dose, mg/kg	Blood pressure Decrease, mm	Blood pressure Duration, min	Respiration rate increase, % of control
I	1	0		14
	2	5	1	30
	4	5	1	36
	6	130	3	50
VIII	1	0		0
	2	0		5
	4	0		6
	6	0		60
IX	1	30	4	22
	2	40	4	35
	4	70	20	83
	6	100	60	81
XIV	1	20	2	41
	2	30	2	40

[a] Figures represent mean values obtained from at least two separate experiments for each dose level. No change in the heart rate was observed in all experiments. [b] Compound III did not cause any significant drop in blood pressure.

***p*-Trimethylsilylhydrocinnamoyl chloride** was similarly obtained in 75% yield, bp 112–114° (2 mm). *Anal.* ($C_{12}H_{17}ClOSi$) C, H, Cl.

Typical examples for the preparation of the amides are given below; the rest are summarized in Table I.

***p*-Trimethylsilylbenz-*p*-anisidide (I).**—A solution of *p*-trimethylsilylbenzoyl chloride[5] (2.12 g, 0.01 mole) in $CHCl_3$ (10 ml) was dropped into a cooled solution of *p*-anisidine (2.46 g, 0.02 mole) in dry $CHCl_3$ (30 ml) and stirred for 20 hr. The $CHCl_3$ was driven off *in vacuo*, and Me_2CO was added to the residue. The precipitated *p*-anisidine hydrochloride was filtered off and washed thoroughly (Me_2CO). The combined Me_2CO solutions were evaporated *in vacuo*, H_2O was added, and I was filtered off and washed (5% HCl, H_2O); yield 2.7 g (90%), mp 126° (from EtOH–H_2O). *Anal.* ($C_{17}H_{21}NO_2Si$) C, H, N, Si.

***p*-Trimethylsilylphenylacetylpiperidide (II).**—A solution of *p*-trimethylsilylphenylacetyl chloride (2.26 g, 0.01 mole) in $CHCl_3$ (15 ml) was dropped into a cooled solution of piperidine (1.68 g, 0.02 mole) in $CHCl_3$ (25 ml) and stirred for 15 hr at room temperature. The solvent was driven off *in vacuo* and the residue was taken up in ether and H_2O. The ethereal layer was separated, washed (dilute HCl, NaOH), and dried ($MgSO_4$). The ether was removed *in vacuo* and II (2.4 g, 87%) was collected at 164–166° (1 mm). *Anal.* ($C_{16}H_{25}NOSi$) C, H, N, Si.

***p*-Trimethylsilylphenylacetyl Hydrazide (III).**—A mixture of *p*-trimethylsilylphenylacetic acid (10.4 g, 0.05 mole), 1-butanol (15 ml), hydrazine hydrate (4 ml), and activated alumina (2 g) (100–150 mesh) were stirred and heated to reflux. C_6H_6 (10 ml) was then added, and the mixture was distilled azeotropically for 5 hr, the temperature being kept below 95° by occasional addition of C_6H_6. The hot reaction mixture was filtered and evaporated *in vacuo*. Petroleum ether (bp 40–60°) was added to the residue and III (8.2 g, 80%) crystallized out; mp 118° (from EtOH–H_2O). *Anal.* ($C_{11}H_{18}N_2OSi$) C, H, N, Si.

***p*-Trimethylsilylphenylacetylurea (IV.)**—A solution of *p*-trimethylsilylphenylacetyl chloride (2.26 g, 0.01 mole) in C_6H_6 (3 ml) was heated with urea (2 g, 0.033 mole) until reaction set in, and then on a steam bath for 2 hr. The C_6H_6 was driven off *in vacuo*, and H_2O was added to the residue, which was filtered off and washed (NaOH, H_2O); yield 1.9 g (76%), mp 176° (from EtOH–H_2O). *Anal.* ($C_{12}H_{18}N_2OSi$) C, H, N, Si.

Acknowledgment.—We wish to express our thanks to "Yissum" Research Development Co. for the grant which enabled us to carry out this research. We wish to thank Dr. H. Edery and Dr. Y. Grunfeld of the Israel Institute for Biological Research, Ness-Ziona, and the Pharmacological Institute of the National Council for Research and Development for carrying out the pharmacological tests.

Syntheses and Hypotensive Activities of 3-Amino-4H-pyrrolo[3,4-*c*]isoxazoles and Derivatives

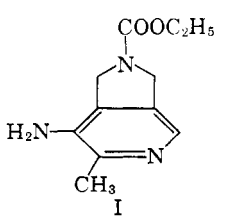
SHREEKRISHNA M. GADEKAR, SOPHIA NIBI, BERNARD D. JOHNSON, ELLIOTT COHEN, AND JOHN R. CUMMINGS

Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

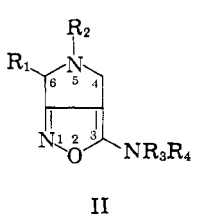
Received October 28, 1967

A series of novel 3-amino-4H-pyrrolo[3,4-*c*]isoxazoles and their derivatives have been synthesized and evaluated for their biological activity. Some of the compounds caused hypotension, tyrosine hydroxylase inhibition, and catecholamine and serotonin depletion.

Previous reports[1] from these laboratories have disclosed the chemistry and pharmacology of a series of pyrrolo[3,4-*c*]pyridines, which included 7-amino-2-carbethoxy 6-methylmerimine (I). Since it is known[2] that isoxazoles and pyridines exhibit many similar chemical properties (*e.g.*, basicities, polarities, boiling points, and dielectric constants), it was decided to prepare derivatives of 3-amino-4H-pyrrolo[3,4-*c*]isoxazoles (II) for pharmacological evaluation.

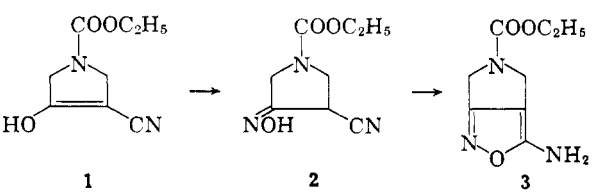


I



II

Chemistry.—Utilizing a key intermediate in the synthesis of merimines, ethyl 3-cyano-4-hydroxy-3-pyrroline-1-carboxylate (**1**)[3] was condensed with hydroxylamine to afford the oxime (**2**), which following



1 2 3

(1) (a) W. B. Wright, Jr., J. S. Webb, and J. M. Smith, Jr., *J. Am. Chem. Soc.*, **79**, 2199 (1957); (b) S. M. Gadekar, J. L. Frederick, J. Semb, and J. R. Vaughan, Jr., *J. Org. Chem.*, **26**, 468 (1961).

(2) N. K. Kuchetkov and S. D. Sokolov, *Advan. Heterocyclic Chem.*, **2**, 365 (1963).

(3) J. Song, U. S. Patent 3,024,243 (1962).