1-[(5-Arylfurfurylidene)amino]hydantoins. A New Class of Muscle Relaxants

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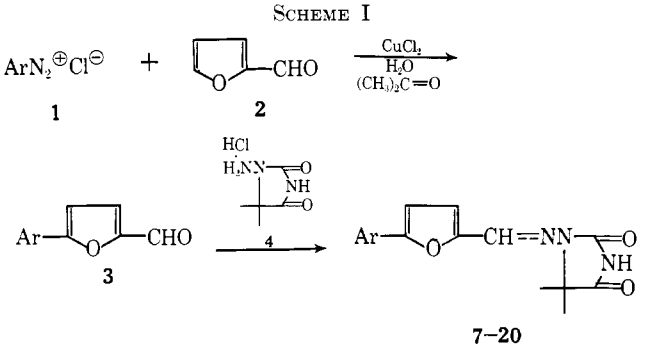
A series of 1-[(5-arylfurfurylidene)amino]hydantoins was synthesized and the compounds were screened for their effects on the flexor reflex in the anesthetized cat. These compounds were prepared by condensing 5-aryl-2-furaldehydes with 1-aminohydantoin hydrochloride. The intermediate aldehydes were made by coupling aryldiazonium chlorides with 2-furaldehyde in aqueous acetone using cupric chloride as a catalyst. The 1-aminoimidazolidinone derivative of 5-(4-nitrophenyl)-2-furaldehyde was prepared. The coupling of 4-nitrobenzenediazonium chloride with 2-thiophenecarboxaldehyde and 2-acetylfuran was accomplished. Screening data are presented together with a discussion of structure-activity correlations.

During the course of another investigation of substituted furans, 1-{[5-(*p*-nitrophenyl)furfurylidene]amino}hydantoin (**7**) was prepared and tested for its ability to alter the flexor reflex in the hind limb of the cat. It was found that **7** produced an inhibition of the polysynaptic pathway which was suggestive of centrally mediated muscle relaxant activity. Because of the nature and degree of activity of **7**, the synthesis of analogs to investigate structure-activity correlation was initiated.

Chemistry.—Utilizing the method of Akashi and Oda,[1] the appropriate aryldiazonium chlorides (**1**) and 2-furaldehyde (**2**) were coupled in aqueous acetone with cupric chloride as the catalyst (see Scheme I). Davis

SCHEME I



and Lougheed[2] demonstrated that the coupling of an aryldiazonium chloride (**1**, Ar = C_5H_4Br-*p*) with **2** did occur at the 5 position of 2-furaldehyde. The intermediate aldehydes **3** were condensed directly with 1-aminohydantoin hydrochloride (**4**)[3] to give the aminohydantoin derivatives **7–20**.

The unsubstituted arylhydantoin **5** was prepared from **4** and aldehyde **3** (Ar = C_6H_5) which was synthesized by the formylation of 2-phenylfuran.[2] The catalytic reduction of the nitrohydantoin derivative **7** in absolute ethanol proceeded smoothly to give the aminohydantoin **21** (see Scheme II). The 3-substituted derivatives of hydantoin **7** (**22**, **23**) were prepared by alkylating its sodium salt **6** with an appropriate alkyl halide. It was possible to synthesize hydantoin **24** by condensing **7** with 4-vinylpyridine in pyridine solution. Alkylation of **7** at position 3 of the hydantoin ring was indicated by an examination of the infrared spectra of **22–24**. These spectra all contained two absorption peaks in the 1700- and 1760–1780-cm^{-1} regions which are characteristic of hydantoins and N-substituted hydantoins.[4] The infrared spectrum of **7** also has carbonyl absorption peaks at 1710 and 1760 cm^{-1}.

Hydantoin derivatives **25–28** were made by condensing 5-(2-furyl)-2-furaldehyde,[5] 4-phenylbenzaldehyde,[6] 5-(4-nitrophenyl)-2-thiophenecarboxaldehyde, and 2-acetyl-5-(5-nitrophenyl)furan, respectively, with **4**. The reaction of aldehyde **3** (Ar = $C_6H_4NO_2$-*p*) with 1-aminoimidazolidinone-2[7] yielded the imidazolidinone derivative **29**.

Pharmacology.—All of the compounds were screened in the anesthetized cat by the method of Berger.[8] This procedure was used to detect inhibition of a polysynaptic pathway. Inhibition of this reflex has been considered by many investigators to be indicative of centrally mediated muscle relaxant activity.[8–10] The extremely low water solubility of these compounds prompted the use of dimethyl sulfoxide (DMSO) as a vehicle. Unfortunately, DMSO in doses of 0.2–0.3 ml/kg produced transient inhibition of the flexor reflex. Thus, compounds which transiently inhibit this reflex may have been masked by the vehicle. Since DMSO was used, its toxicity imposed another limiting factor and it was not possible to administer doses of test compounds larger than 20 mg/kg; a compound which might have been active at a larger dose appeared inactive in this test. Thus, an active compound was defined as one which produced greater inhibition of the reflex than was produced by the vehicle alone and which showed this activity at less than 20 mg/kg. The evaluation of mephenesin[11] by these rigid parameters might have resulted in classifying it as inactive. The results of the screening are shown in Table I in the form of a classification designated by + (group I), ++ (group II), and +++ (group III). For the purposes of this paper, the following definitions were used: group I (minimal activity) represents compounds which inhibited the reflex less than 30% or had an apparent duration of activity of less than 15 min; group II (moderate activity) represents com-

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(2) C. S. Davis and G. S. Lougheed, *J. Heterocyclic Chem.*, **4**, 153 (1967).
(3) W. Traube and E. Hoffa, *Ber.*, **31**, 167 (1898).
(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p 221.
(5) T. Reichstein, A. Grüssner, and H. Zschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).
(6) Available from Aldrich Chemical Co.
(7) J. G. Michels and G. Gever, *J. Am. Chem. Soc.*, **78**, 5349 (1956).
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(9) J. C. Burke, D. Papandrianos, L. J. Brannick, and G. L. Hassert, Jr., *Arch. Intern. Pharmacodyn.*, **134**, 216 (1961).
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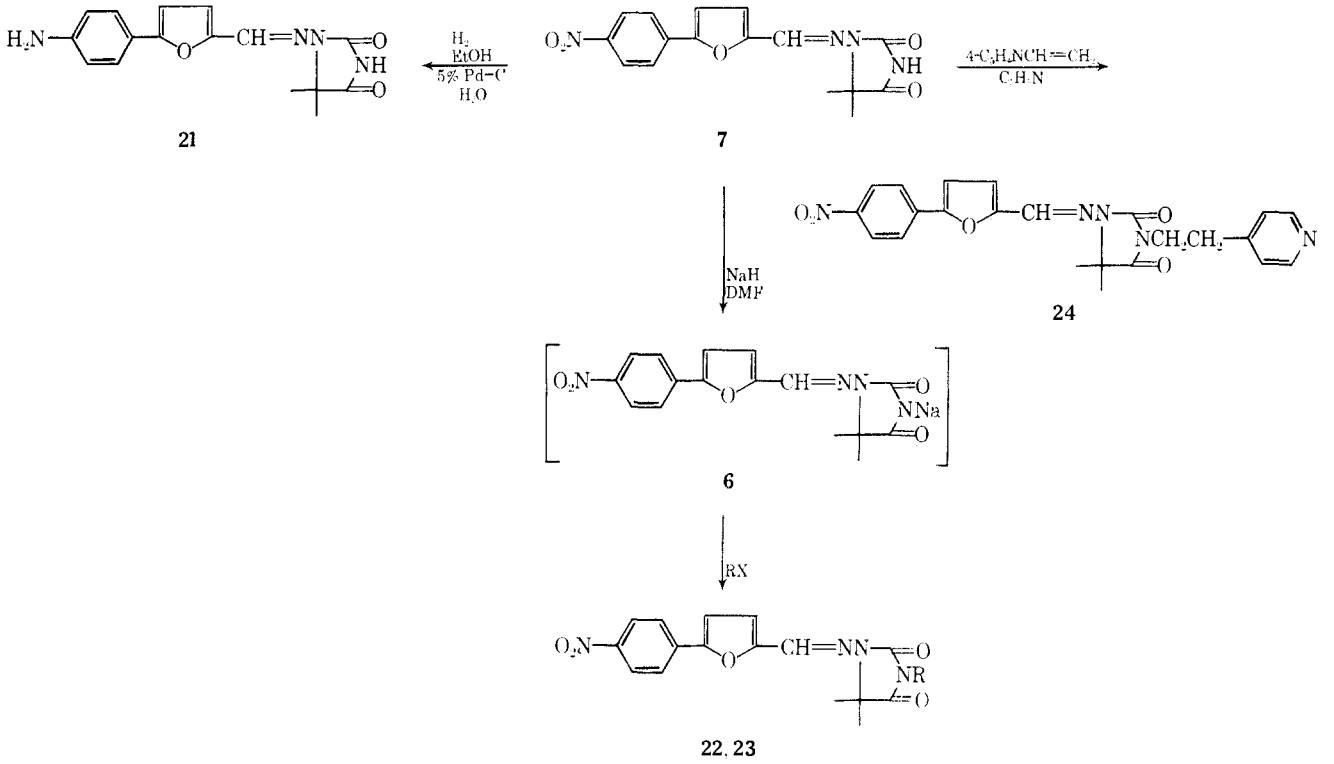
(11) Generic name for 3-*o*-toloxy-1,2-propanediol.

SCHEME II



pounds which inhibited the flexor reflex 30%, or greater, with durations greater than 15 min but less than 60 min; and group III (greatest activity) represents compounds which inhibited the flexor reflex 30%, or greater, with durations in excess of 60 min. The doses in Table I refer to the lowest level which produced the greatest inhibition using this rating system. All of the compounds in group III produced signs of muscle relaxation when administered intraperitoneally to mice.

Although these compounds appear to be centrally acting muscle relaxants, some degree of inhibition of the response to motor nerve stimulation was also observed. This inhibition of the response to motor nerve stimulation was always less than the inhibition observed following sensory nerve stimulation. Further work is necessary to clarify the contribution of this peripheral effect.

Structure–Activity Relationships.—Any modification of the basic structure of **7** resulted in a decrease in muscle relaxant activity (flexor reflex inhibition). While it was difficult to quantitate this activity, the following generalizations were made.

A. Position Isomers.—The position of the nitro group on the benzene ring greatly influenced activity. The *para* isomer (**7**) was the most active and the *meta* (**8**) and *ortho* (**9**) successively less active. Introduction of a second group into the *p*-nitrobenzene ring resulted in decreased activity (**10**, **11**).

B. Replacement of the *p*-Nitro Group.—Substitutions of this type reduced activity to a varying degree. The more active compounds contained the following groups: NH_2 (**21**), CN (**18**), and Cl (**12**). Although **12** was a fairly active compound, replacement with Br (**15**) and F (**16**) decreased activity markedly.

C. Modification of the Hydantoin Ring.—Substitutions on the hydantoin nitrogen in general significantly reduced activity (**22**–**24**). Replacement of the 4-carbonyl group of the hydantoin ring with methylene reduced activity only to a small degree (**29**).

D. Miscellaneous Structural Modifications.—When the *p*-nitrophenyl ring was replaced by a 2-furyl ring, there was considerable loss of activity (**25**). Substitution of the furyl ring in **7** for a thienyl ring resulted in a marked decrease in activity (**27**). A similar decrease in activity occurred when the aldehydic hydrogen of **7** was replaced by a methyl group (**28**). Finally, the use of a 4-phenyl(phenyl) group in the place of 5-(*p*-nitrophenyl)-2-furyl group diminished activity considerably (**26**).

The striking activity of **7** and its sodium salt **6** has prompted an intensive investigation into the mode of action of these compounds. Both of these compounds are undergoing evaluation as possible muscle relaxants.

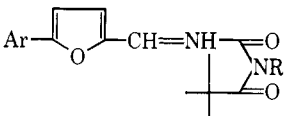
Experimental Section

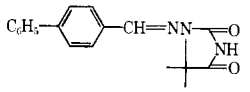
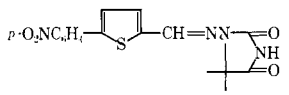
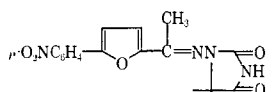
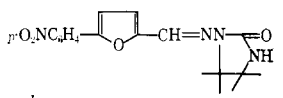
All melting points were taken on a hot stage (Mel-Temp) melting point apparatus and are corrected. The physical and analytical data for all compounds are reported in Table I. The infrared absorption curves were determined with a Perkin-Elmer Infracord.

1-{[5-(*p*-Cyanophenyl)furfurylidene]amino}hydantoin (18).—A suspension of *p*-aminobenzonitrile (50 g, 0.5 mole), water (100 ml), and concentrated HCl (75 ml) was heated until the solid dissolved. An additional amount (150 ml) of concentrated HCl was added and the suspension was cooled to below 0°. To the suspension was introduced $NaNO_2$ (35 g, 0.5 mole, in 200 ml of water). The material was stirred at 5° for 30 min, and then a solution of 2-furaldehyde (**2**) (48 g, 0.5 mole) in acetone was added followed by the addition of $CuCl_2$ (10 g) in water (300 ml). The temperature was allowed to rise to 15–20° while the solution was stirred for 4 hr. The solids were filtered and washed with water. The crude aldehyde was dissolved in DMF (800 ml) and slowly introduced to a solution of 1-aminohydantoin hydrochloride (**4**)[3] (91 g, 0.6 mole, in 1000 ml of water). The yellow solid was filtered and washed thoroughly with water.

TABLE I

1-[(5-ARYLFURFURYLIDENE)AMINO]HYDANTOINS



No.	Ar	R	Mp, °C	Yield, %	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Flexor reflex act. Dose,[c] mg/kg	Flexor reflex act. Rating[c]
5	C_6H_5[b]	H	258–260	94	D	$C_{14}H_{11}N_3O_3$	62.45	4.15	15.21	62.52	4.33	15.78	10.0	++
6	$C_6H_4NO_2$-*p*	Na	229–231 dec	61	..	$C_{14}H_9N_4O_5Na\cdot 4H_2O$	41.18	4.20	13.72	41.52	4.39	13.40	1.0	+++
7	$C_6H_4NO_2$-*p*	H	279–280	16	B	$C_{14}H_{10}N_4O_5$	53.50	3.21	17.83	53.28	3.16	17.77	1.0	+++
8	$C_6H_4NO_2$-*m*	H	246–247	33	D	$C_{14}H_{10}N_4O_5$	53.50	3.21	17.83	53.62	3.32	18.10	5.0	+++
9	$C_6H_4NO_2$-*o*	H	224–226	32	D	$C_{14}H_{10}N_4O_5$	53.50	3.21	17.83	53.33	3.07	17.69	5.0	++
10	$C_6H_3CH_3$-*o*-NO_2-*p*	H	256–259	45	A	$C_{15}H_{12}N_4O_5$	54.88	3.69	17.07	54.92	3.44	16.68	5.0	+++
11	C_6H_3Cl-*o*-NO_2-*p*	H	267–269	44	G	$C_{14}H_9ClN_4O_5$	48.22	2.60	16.07	48.42	2.61	15.86	2.5	++
12	C_6H_4Cl-*p*	H	275–277	44	D	$C_{14}H_{10}ClN_3O_3$	55.37	3.32	13.84	55.34	3.20	13.78	2.5	+++
13	$C_6H_3Cl_2$-*p*,*m*	H	274–276	62	D	$C_{14}H_{10}Cl_2N_3O_3$	49.72	2.68	20.97	49.93	2.68	21.03	5.0	+++
14	C_6H_3Cl-*o*-CF_3-*m*	H	244–246	97	F	$C_{16}H_{10}ClF_3N_3O_3$	48.47	2.44	11.30	48.56	2.72	11.18	5.0	++
15	C_6H_4Br-*p*[b]	H	284–285	42	A	$C_{14}H_{10}BrN_3O_3$	48.30	2.90	12.07	48.28	2.85	12.15	2.5	++
16	C_6H_4F-*p*	H	264–265	14	C	$C_{14}H_{10}FN_3O_3$	58.54	3.51	14.63	58.54	3.63	14.74	5.0	+
17	$C_6H_3CF_3$-*m*	H	205–207	40	B	$C_{15}H_{10}F_3N_3O_3$	53.42	2.99	12.46	53.40	3.35	12.43	5.0	++
18	C_6H_4CN-*p*	H	281–285 dec	65	G	$C_{15}H_{10}N_4O_3$	61.22	3.42	19.04	61.15	3.68	18.66	2.5	+++
19	$C_6H_4COCH_3$-*p*	H	269–270	57	B	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	61.58	4.47	13.36	2.5	++
20	$C_6H_4CO_2H$-*p*	H	320 dec	31	A	$C_{15}H_{11}N_3O_5$	57.51	3.54	13.41	57.71	3.75	13.25	10.0	++
21	$C_6H_4NH_2$-*p*	H	269–270	52	B	$C_{14}H_{12}N_4O_3$	59.15	4.25	19.71	59.24	4.33	19.98	5.0	+++
22	$C_6H_4NO_2$-*p*	CH_2CH_2OH	245.5–247	92	A	$C_{16}H_{14}N_4O_6$	53.63	3.94	15.64	53.58	3.98	15.61	2.5	++
23	$C_6H_4NO_2$-*p*	$(CH_2)_3CH_3$	201.5–202	92	E	$C_{18}H_{18}N_4O_5$	58.37	4.90	15.13	58.41	4.82	15.19	5.0	++
24	$C_6H_4NO_2$-*p*	CH_2CH_2-4-C_5H_4N	227–230	98	C	$C_{21}H_{17}N_5O_5$	60.14	4.09	16.70	59.70	4.01	16.57	5.0	++
25	2-C_4H_3O	H	241–243	83	C	$C_{12}H_{10}N_3O_4$	55.60	3.50	16.21	55.59	3.58	16.15	5.0	++
26			297–302	92	B	$C_{18}H_{13}N_3O_2$	68.81	4.69	15.12	68.91	4.62	15.09	5.0	++
27			295–298	13	C	$C_{14}H_{10}N_4O_4S$	50.90	3.05	16.96	50.90	3.14	16.89	2.5	+
28			287–288 dec	38	C	$C_{15}H_{12}N_4O_5$	54.88	3.69	17.01	54.81	3.82	16.89	2.5	+
29			283–284	45	A	$C_{14}H_{12}N_4O_4$	56.00	4.03	18.66	55.78	4.23	18.39	5.0	+++
Mephenesin[d]													30.0	++

[a] A = DMF, B = DMF–H_2O, C = DMF-95% ethanol, D = material was washed with acetone, E = 95% ethanol (SDA-30), F = acetonitrile, and G = DMF–60% aqueous ethanol. [b] See ref 2. [c] See text. [d] For comparison, administered in water.

In a similar manner **8–20** were prepared using the appropriate aniline. Compound **27** was synthesized by the above procedure starting with *p*-nitroaniline and substituting 2-thiophenecarboxaldehyde for aldehyde **2**. The use of 2-acetylfuran in place of **2** gave the hydantoin derivative **28**.

1-{[5-(*p*-Nitrophenyl)furfurylidene]amino}hydantoin (7).—To a solution of 5-(*p*-nitrophenyl)-2-furaldehyde[1] (40.0 g, 0.2 mole) in DMF was added an aqueous solution of **4** (30.0 g, 0.2 mole). The solution was chilled and diluted with water; the crude material was collected. The infrared absorption curve of a mineral oil mull displayed peaks at 1710 (C=O) and 1760 (C=O) cm^{-1}.

In a similar manner, **25** and **26** were prepared by using 5-(2-furyl)-2-furaldehyde[5] and 4-phenylbenzaldehyde.[6] The reaction of 5-(*p*-nitrophenyl)-2-furaldehyde and 1-aminoimidazolidinone-2[7] was carried out as above to yield **29**.

1-{[5-(*p*-Nitrophenyl)furfurylidene]amino}hydantoin Sodium Salt Tetrahydrate (6).—A slurry of **7** (20.0 g, 0.064 mole) in anhydrous methanol (200 ml) was treated with a solution of $NaOCH_3$ (3.7 g, 0.069 mole) in anhydrous methanol (200 ml). The resulting solution was stirred for 6 hr (precipitate was formed after 0.5 hr) before filtering. The orange product was air-dried for 18 hr. The infrared spectrum indicated the presence of water (band at 3450 cm^{-1}).

3-(2-Hydroxyethyl)-1-{[5-(*p*-nitrophenyl)furfurylidene]amino}hydantoin (22).—To a solution of **7** (62.8 g, 0.2 mole) in DMF (1000 ml) was added in small portions NaH (9.6 g, 0.2 mole, of a 50% mineral oil dispersion). After the sodium salt had precipitated, 2-bromethanol (50 g, 0.4 mole) was introduced. The temperature rose to 60° and was held there for 18 hr. The dark solution was then poured into ice water (4000 ml). The solid was filtered and air-dried overnight and then at 60° for 4 hr. The infrared absorption data of a mineral oil mull indicated peaks at 1710 (C=O) and 1760 (C=O) cm^{-1}.

In a similar manner, the N-butyl derivative **23** was prepared from **7** using *n*-butyl bromide as the alkylating agent. The infrared spectrum of **23** in a mineral oil mull had absorption peaks at 1700 (C=O) and 1780 (C=O) cm^{-1}.

1-{[5-(*p*-Nitrophenyl)furfurylidene]amino}-3-[2-(4-pyridyl)-ethyl]hydantoin (24).—A suspension of **7** (31.4 g, 0.1 mole), pyridine (170 ml), and 4-vinylpyridine (10.5 g, 0.1 mole) was refluxed for 27 hr. A clear solution resulted after 3–4 hr of refluxing. The solution was cooled and then poured into water and filtered. The filter cake was thoroughly washed with water and dried. The infrared absorption spectrum of a mineral oil mull showed peaks at 1730 (C=O) and 1780 (C=O) cm^{-1}.

1-{[5-(*p*-Aminophenyl)furfurylidene]amino}hydantoin (21).—Compound **7** (15.7 g, 0.05 mole) was suspended in absolute ethanol (SDA-32) (250 ml). To this suspension was added 5% Pd-C as a 50% mixture with water (3 g). The container was placed in a Parr hydrogenator and shaken under 2.8 kg/cm^2 hydrogen for about 1 hr (hydrogen absorption had ceased). The temperature rose to 34°. The reaction mixture was filtered and the filtrate was evaporated to yield the crude product.

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The Metabolic Fate of Some Silicon-Containing Carbamates[1]

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After ingestion, bis(hydroxymethyl)dimethylsilane dicarbamate (III), (hydroxymethyl)dimethyl-*n*-propylsilane carbamate (IV), and bis(hydroxymethyl)methyl-*n*-propylsilane dicarbamate (silameprobamate) (V) are absorbed and eliminated in the urine of rats. III is eliminated unchanged. IV is metabolized; bis(hydroxymethyl)tetramethyldisiloxane dicarbamate (VI) was isolated from the urine. V is also metabolized; two products isolated from the urine were a disiloxane VII as the minor component and bis(hydroxymethyl)(2-hydroxypropyl)methylsilane dicarbamate (VIII) as the major component. The data indicate that dealkylation is one of the metabolic paths for elimination of organosilicon compounds.

Although organosilicon compounds are used both in commerce and in medicine, little is known about their metabolic fate. Paul and Pover[3] have provided evidence that methyl ω-(trimethylsilyl)dodeconate and trimethylsilylhexadecane are absorbed from the gastrointestinal tract of rats. Dow Corning[4] has reported that [^{14}C]methylpolysiloxane is not excreted as $^{14}CO_2$. Our own interest in the metabolism of organosilicon compounds was stimulated by the lack of oral activity of silameprobamate (V), although it showed the same ED_{50} (rotating rod) as meprobamate (I) when it was dosed intraperitoneally.[5] It was felt that this difference in activity could be due either to a lack of absorption of the silicon compound when dosed orally or to a different detoxification pathway.

The metabolism of I itself has been studied by a number of investigators.[6] Oxidation of the propyl group provides the major pathway of detoxification. Carboxymeprobamate, ketomeprobamate, and hydroxymeprobamate (II) have been identified as metabolites (see Scheme I). The relative amounts of these metabolites vary with the species; however, the alcohol II is the major detoxification product.

SCHEME I

$$\underset{\text{I}}{CH_3CH_2CH_2C(CH_3)(CH_2OCONH_2)_2} \rightarrow \underset{\text{II}}{CH_3CHOHCH_2C(CH_3)(CH_2OCONH_2)_2} + CH_3COCH_2C(CH_3)(CH_2OCONH_2)_2 + HO_2CCH_2CH_2C(CH_3)(CH_2OCONH_2)_2$$

This study is concerned with the identification of the metabolites appearing in the urine arising from the oral dosing of some silacarbamates, bis(hydroxymethyl)dimethylsilane dicarbamate (III), (hydroxymethyl)dimethyl-*n*-propylsilane carbamate (IV), and silameprobamate (V).

$$\underset{\text{III}}{CH_3Si(CH_3)(CH_2OCONH_2)_2} \qquad \underset{\text{IV}}{n\text{-}C_3H_7Si(CH_3)_2CH_2OCONH_2}$$

$$\underset{\text{V}}{n\text{-}C_3H_7Si(CH_3)(CH_2OCONH_2)_2}$$

In our previous work,[5] we were able to show that III showed no pharmacological activity (rotating rod test) at intraperitoneal dose levels up to 500 mg/kg. In the present study, when III was orally dosed in rats, 53% of the ingested material was isolated from the urine as the crystalline unaltered compound. No metabolites were observed for this particular compound.

Compound IV showed an ED_{50} of 158 (148–169) mg/kg ip.[5] After oral dosing of IV in rats, about 90% of the ingested silicon could be detected in the urine within 4 days. In the ethyl ether extract of the urine, no unchanged IV could be detected. From an ethyl acetate extraction, there was obtained a silicon-containing oil, which was subjected to chromatographic separation. A white crystalline solid, mp 68–70°, was isolated. The nmr spectrum of this material showed two sharp singlets and a broad band, which, from the chemical shifts and areas under these bands, suggested that the solid is the disiloxane VI. The infrared spectrum and the elemental analysis of this material are in agreement with this structure assignment. This metabolite accounts for 29% of the silicon of the ingested silacarbamate IV. No other silicon metabolites were detected.

$$\text{IV} \longrightarrow \underset{\text{VI}}{NH_2COOCH_2Si(CH_3)_2OSi(CH_3)_2CH_2OCONH_2}$$

After oral dosing of silameprobamate, 60–90% of the ingested silicon was found in the urine within 3 days. Extraction and chromatographic separation afforded a solid material (mp 54–58°) and a viscous oil. Unfortunately, neither of these substances could be obtained in an analytically pure form.

(1) This research was supported by Public Health Research Grant GM13914 from the National Institute of General Medical Sciences.

(2) Alfred P. Sloan Fellow, 1965–1967.

(3) J. Paul and W. F. R. Pover, *Arch. Biochem. Biophys.*, **87**, 312 (1960).

(4) As reported in "The Bulletin," Vol. II, No. 4, Dow Corning Center for Aid to Medical Research, Midland, Mich., April 1960, p 15.

(5) R. J. Fessenden and Marvin D. Coon, *J. Med. Chem.*, **8**, 604 (1965).

(6) (a) B. J. Ludwig, J. F. Douglas, L. S. Powell, M. Meyer, and F. M. Berger, *J. Med. Pharm. Chem.*, **3**, 53 (1961); (b) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954); (c) B. W. Agranoff, R. M. Bradley, and J. Axelrod, *Proc. Soc. Exptl. Biol. Med.*, **96**, 261 (1957).