Silicon Heterocyclic Compounds. III. Silicon-Substituted Spirobarbiturates[1]

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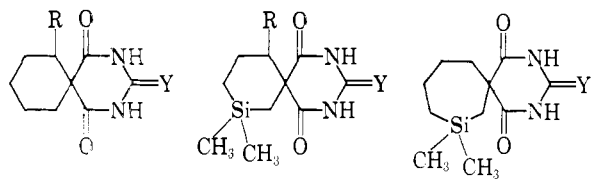
A group of silicon-containing spirobarbiturates of the general structures II and III have been prepared by the classical reaction between a substituted malonic ester, 3,3-dicarbethoxy-1-silacycloalkane, and a urea or thiourea. The toxicities and the ED_{50} for the loss of the righting reflex have been evaluated for these compounds.

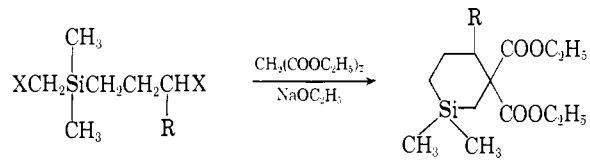
Spirobarbiturates[2] have attracted the attention of investigators since the first report in 1921.[3] Studies of these interesting compounds have been limited by the relative unavailability of the starting dicarbethoxycycloalkanes and by the poor yields in the preparation of the spiranes. As medicinal agents, spirobarbiturates show activity similar to that of the 5,5-dialkylbarbiturates. Although the parent cyclohexyl ring system (I, R = H; Y = O or S) does not show "narcotic activity,"[4] the alkyl-substituted rings (I, R = alkyl; Y = O or S) do show activity, "therapeutic ratios"[5] up to 5.18 having been reported (I, R = *n*-C_3H_7).[6]



I II III

Since, in our study of silicon heterocyclic compounds,[7] a synthetic route was developed allowing the preparation of silicon-substituted dicarbethoxycycloalkanes (V), it seemed opportune to synthesize these diesters and convert them to silicon-substituted spirobarbiturates.

Synthesis.—The dicarbethoxysilacycloalkanes used in this study were prepared by the ring closure of a dihalosilaalkane (IV) and malonic ester. The dihalosilaalkanes used for the preparation of silacyclohexanes and silacycloheptanes have been previously reported.[7] The yields in the ring closure reactions varied from 25% (dicarbethoxysilacycloheptane) to 50% (dicarbethoxysilacyclohexanes).



IV V

The silicon-substituted spirobarbiturates and spirothiobarbiturates were prepared using the classical reaction between a urea and a substituted malonic ester.[8] The reaction of urea or thiourea with 3,3-dicarbethoxy-1,1-dimethyl-1-silacyclohexane (V, R = H) gave reasonable yields (45%) of the spirobarbiturate II (R = H; Y = O or S). In agreement with the observations of other investigators, the yields were substantially lower (0–18%) when the 4-alkyl-substituted silacyclohexanes (V, R = alkyl) were used in the reaction (see Table I). None of the alkyl-substituted spirothiobarbiturates could be isolated.

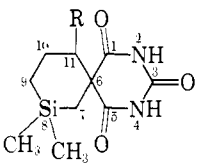
The only cycloheptane diester available was 3,3-dicarbethoxy-1,1-dimethylsilacycloheptane, which was converted to the spirobarbiturate (III, Y = O) and to the spirothiobarbiturate (III, Y = S) in 53 and 28% yields, respectively.

It was also of interest to include in this study the N-substituted spirobarbiturates. Using the method of Bose,[9] the reaction of dicyclohexylcarbodiimide with cyclohexane-1,1-dicarboxylic acid gave the expected N,N'-dicyclohexylspirobarbiturate in 38% yield. However, when the reaction was attempted using 1,1-dimethyl-1-silacyclohexane-3,3-dicarboxylic acid, a mixture of products was obtained.

The ultraviolet spectra of the silaspirobarbiturates in ethanol both in neutral and in basic solution were recorded. As has been noted with the 5,5-dialkylbarbiturates,[10] the spectra of these spirobarbiturates

(1) (a) This investigation was supported in part by Public Health Service Research Grant GM 10122, from the Institute of General Medical Sciences. (b) Taken in part from the M.S. Thesis of James G. Larsen, San Jose State College, 1963.

(2) The term, spirobarbiturate, is used in this report to emphasize the relationship of these compounds to the 5,5-dialkylbarbiturates, as well as for simplicity. The numbering system and the generic name for this group of compounds are as follows.



2,4-diaza-11-alkyl-8,8-dimethyl-8-silaspiro[5.5]undecane-1,3,5-trione

(3) (a) A. W. Dox and L. Yoder, *J. Am. Chem. Soc.*, **43**, 1366 (1921); (b) A. C. Cope, P. Kovacic, and M. Burg, *ibid.*, **71**, 3658 (1949); (c) O. Wichterle and O. Nemeck, *Chem. Listy*, **37**, 381 (1943); *Chem. Abstr.*, **45**, 561 (1951); (d) E. van Heyningen, *J. Am. Chem. Soc.*, **76**, 2241 (1954); (e) R. Ya Levina, N. N. Godovikov, and F. K. Velichko, *Zh. Obshch. Khim.*, **25**, 2522 (1955); *Chem. Abstr.*, **50**, 9430 (1956); (f) R. Ya Levina and N. N. Godovikov, *Zh. Obshch. Khim.*, **25**, 986 (1955); *Chem. Abstr.*, **50**, 3458 (1956); (g) R. Ya Levina, N. N. Mezentsova, and O. V. Lebedev, *Zh. Obshch. Khim.*, **25**, 1097 (1955); *Chem. Abstr.*, **50**, 3257 (1956).

(4) The term "narcotic activity" has been used by previous workers in this area[3b] to describe the dose at which 50% of the test animals failed to right themselves when struck on the tail by a forefinger. This study used the righting reflex as the sub-lethal test of activity and the values are reported as effective dose for 50% of the group (ED_{50}) (see Table III).

(5) The term "therapeutic ratio" has been defined by previous workers in this area[3b] as the ratio of "narcotic dose" to the toxic dose (ND_{50}/LD_{50}). When the term is used in connection with the compounds prepared in this study, the value refers to the ratio of the effective dose for the loss of the righting reflex to the toxic dose (ED_{50}/LD_{50}).

(6) See ref. 3b.

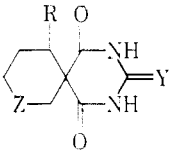
(7) (a) R. J. Fessenden and M. C. Coon, *J. Org. Chem.*, **29**, 1069 (1964); (b) *ibid.*, **29**, 2499 (1964).

(8) J. B. Dickey and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 60.

(9) A. K. Bose and S. Garratt, *J. Am. Chem. Soc.*, **84**, 1310 (1962).

TABLE I

SPIROBARBITURATES



Compd.	Z	R	Y	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	CH_2	H	O	46	279.5–281[a]							
2	CH_2	H	S	60	239–240[b]							
3	$Si(CH_3)_2$	H	O	45	244–245	$C_{10}H_{16}N_2O_3Si$	49.96	50.01	6.72	6.57	11.66	11.05
4	$Si(CH_3)_2$	CH_3	O	18	209–210	$C_{11}H_{18}N_2O_3Si$[c]	51.93	51.72	7.15	7.14	11.01	10.85
5	$Si(CH_3)_2$	C_2H_5	O	13	209.5–210.5	$C_{12}H_{20}N_2O_3Si$[d]	53.69	53.88	7.53	7.42	10.44	10.18
6	$Si(CH_3)_2$	H	S	45	196–197	$C_{10}H_{16}N_2O_2SSi$[e]	46.83	47.02	6.30	6.19	10.93	11.15
7	$CH_2Si(CH_3)_2$	H	O	53	175–176	$C_{11}H_{18}N_2O_3Si$	51.93	51.96	7.15	7.02	11.01	11.19
8	$CH_2Si(CH_3)_2$	H	S	28	191–193	$C_{11}H_{18}N_2O_2SSi$[f]	48.85	48.81	6.72	6.60	10.36	10.24

[a] Lit.[3b] 279–280.6°. [b] Lit.[3b] 243.2–243.8°. [c] *Anal.* Calcd.: Si, 11.04. Found: Si, 11.22. [d] *Anal.* Calcd.: Si, 10.46. Found: Si, 10.61. [e] *Anal.* Calcd.: S, 12.50. Found: S, 12.26. [f] *Anal.* Calcd.: S, 11.86. Found: S, 11.74.

TABLE II

SPECTRAL DATA FOR THE SPIROBARBITURATES

Compd.	Ultraviolet: Neutral λ_{max}, Å.	Ultraviolet: Neutral ϵ_{max}	Ultraviolet: 0.01 *N* NaOH λ_{max}, Å.	Ultraviolet: 0.01 *N* NaOH ϵ_{max}	Infrared, μ: N–H	Infrared, μ: C=O
1	End	...	2470	8340	3.12, 3.25	5.70, 5.76, 5.92
2	2860	20,700	...	...	3.17	5.85, 5.97, 6.55
	2350	8550				
3	End	...	2400	9050	3.10, 3.22	5.68, 5.89
4	End	...	2410	9105	3.10	5.65, 5.80, 5.85, 5.95
5	End	...	2405	8750	3.05, 3.10	5.70, 5.80, 6.00
6	2370	7850	...	...	3.18	5.89, 6.40
7	End	...	2415	9020	3.12, 3.25	5.65, 5.79, 5.91
8	2880	22,500	...	...	3.20	5.72, 5.79, 5.90, 6.51
	2370	7850				

in neutral solutions showed only end absorption, while those in basic solutions (0.01 *N* NaOH) exhibited absorption in the 2400-Å. region (see Table II).

Pharmacology.—The results of the pharmacological studies are summarized in Table III. The cyclohexylspirobarbiturate (I, R = H; Y = O) and the sulfur analog (I, R = H; Y = S) were synthesized and included in this portion of the study.

The desirable high "therapeutic ratios" (2.4 to 5.18) reported for the cyclohexylspirobarbiturates (I, R = alkyl; Y = O) were not observed with the silacyclohexylspirobarbiturates (II), in which cases the range was 1.0 to 1.8. The sulfur analog of the silaspirobarbiturate (II, R = H; Y = S) showed a greatly increased toxicity, an effect not observed with I (R = H; Y = S).

These differences between the cyclohexylspirobarbiturates (I) and the corresponding silicon compounds (II) may be due to the *gem*-dimethyl group in the silicon compounds, distortion of the cyclohexyl ring by the substitution of a silicon atom in the ring, or a combination of these effects. Unfortunately, the direct carbon analogs of II are not readily available for comparison.

Special note of the silacycloheptanespirobarbiturate (III) should be taken. Compound III (Y = O), which showed the most rapid onset of action of the compounds studied, also exhibited the highest "therapeutic ratio" (3.0) of the group (see Table III). Conversely, III (Y = S) showed a belated onset and exhibited the greatest toxicity of any of the compounds studied.

Experimental[11]

3,3-Dicarbethoxy-1-silacycloalkanes. Halomethyl-(ω-haloalkyl)dimethylsilanes.—The general procedure used to obtain the starting dihalogen intermediates has been published elsewhere.[7] The compounds used were purified prior to ring closure but were not completely characterized. The new dichlorosilaalkanes prepared in this study are: chloromethyl(γ-chlorobutyl)dimethylsilane, 39–77%, b.p. 88° (8 mm.), $n^{20}D$ 1.4660; chloromethyl(γ-chloropentyl)dimethylsilane, 44–56%, b.p. 60–64° (1.5 mm.), $n^{24}D$ 1.4630; chloromethyl(γ-chlorohexyl)dimethylsilane, 19%, b.p. 89–90° (2.0 mm.), $n^{28}D$ 1.4632.

Ring Closure.—The following general procedure was used to obtain the cyclic diesters. In a three-neck round-bottom flask were placed 200 ml. of absolute ethanol (freshly distilled from sodium), 0.15 mole of the dihalogen compound, and 0.15 mole of malonic ester. The mixture was heated to reflux and 0.33 mole of sodium ethoxide in 200 ml. of ethanol was added in one portion followed by 0.05 mole of sodium iodide. The mixture was refluxed for 20 hr. At the end of the reflux period, the mixture was cooled, filtered, then concentrated to *ca.* 200 ml. and diluted with an equal volume of water and extracted with

(10) L. R. Goldbaum, *Anal. Chem.*, **24**, 1604 (1952).

(11) All melting points are corrected and were taken on a Fisher-Johns melting point stage. Analyses were performed by the Berkeley Microanalytical Laboratory except for the silicon analyses, which were performed in this laboratory. Infrared spectra were run using a Beckman IR-4 spectrophotometer and the ultraviolet spectra were obtained using a Cary spectrophotometer.

TABLE III

PHARMACOLOGICAL ACTION OF SILABARBITURATES AND RELATED COMPOUNDS[a]

Compd.	Loss of the righting reflex ED_{50} (95% confidence levels), mg./kg.	Toxicity LD_{50} (95% confidence levels), mg./kg.	Induction period,[b] hr.	Duration of activity,[c] hr.
1	...[d]	1000[e]	...	..
2	...[f]	600[g] (440 to 830)	6	..
3	670 (500 to 880)	1000	2	1
4	...[h]	230 (165 to 320)	1	..
5	240 (185 to 320)	450 (330 to 530)	2	6
6	140 (100 to 200)	230 (165 to 320)	1	2
7	230 (165 to 320)	670 (500 to 880)	0.2	3
8	...[f]	140 (100 to 200)	6	..

[a] Female Webster Swiss white mice, 15–20 g., were used. The compounds were introduced intraperitoneally as corn oil suspensions using 25 animals per compound. The values reported were calculated by the method of J. T. Litchfield and F. Wilcoxon [*J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949)]. [b] The induction period is defined as the time elapsed from injection to the loss of the righting reflex. [c] The duration of activity is defined as the time in which the surviving animals were without the righting reflex. [d] No activity was noted at 1000 mg./kg. [e] Lit.[3b] LD_{50} 800 mg./kg. (i.p. as the sodium salt). [f] All animals who lost the righting reflex died. [g] Lit.[3b] LD_{50}, 1200 mg./kg. (i.p. as the sodium salt). [h] The value obtained, 190 (135 to 270) mg./kg., is not considered to differ significantly from the toxicity.

three 100-ml. portions of ether. The ethereal extracts were washed with water, dried ($MgSO_4$), then fractionally distilled to obtain the cyclic diester. The analytical samples of the diesters were obtained using gas phase chromatography. The data for the diesters are summarized in Table IV.

Spirobarbiturates.—The following general procedure was employed for the preparation of the compounds which are summarized in Table I. In a 50-ml. round-bottom flask were placed 0.02 mole of the appropriate diester, 0.02 mole of urea (or thiourea), and 0.02 mole of sodium ethoxide dissolved in 15 ml. of absolute ethanol. The mixture was heated at reflux for 12 hr., cooled to room temperature, and acidified with 12 ml. of 2 *N* HCl. It was then filtered and the solid material was washed with two 25-ml. portions of water. The product was crystallized from 95% ethanol and, in general, a recrystallized sample was used for analysis.

The following exceptions and observations were made using this procedure. The reflux period for **4** was 24 hr.; for **5**, 17 hr. The starting diester was recovered (46–47%) from the reactions leading to compounds **4** and **5**. The procedure failed to yield solid material in the attempted reactions of 3,3-dicarbethoxy-4-propyl-1,1-dimethyl-1-silacyclohexane with urea and of 3,3-dicarbethoxy-1,1,4-trimethyl-1-silacyclohexane with thiourea.

2,4-Dicyclohexyl-2,4-diazaspiro[5.5]undecane-1,3,5-trione (IV).—A solution of 1.65 g. (8.0 mmoles) of dicyclohexylcarbodiimide in 20 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) was mixed with a solution of 0.70 g. (4.0 mmoles) of cyclohexane-1,1-dicarboxylic acid[12] in 20 ml. of tetrahydrofuran. The mixture was allowed to stand at room temperature for 1 hr. and was then filtered, yielding 0.90 g. (100%) of *N,N'*-dicyclohexylurea, m.p. 227–230° (lit.[13] 231–232°). The tetrahydrofuran was removed from the filtrate using a roto evaporator and the solid residue was crystallized from ether–petroleum ether (b.p. 30–60°), yielding 0.55 g. (39%) of the product, m.p. 134–134.5°; infrared spectrum 5.59, 5.95, and 5.85 (sh) μ.

Anal. Calcd. for $C_{21}H_{32}N_2O_4$: C, 69.95; H, 8.96; N, 7.77. Found: C, 70.18; H, 8.81; N, 7.80.

In one run, the product was crystallized from ethanol. Initial crystallization occurred; however, after the mixture was allowed to stand overnight, an oil was obtained. The infrared spectrum showed bands at 3.0 (N–H), 5.90, and 6.10 μ (C=O), an indication that cleavage had occurred.

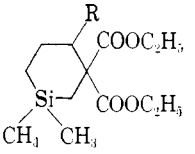
Attempted Synthesis of 2,4-Dicyclohexyl-2,4-diaza-8,8-dimethyl-8-silaspiro[5.5]undecane-1,3,5-trione. 1,1-Dimethyl-1-silacyclohexane-3,3-dicarboxylic Acid.—In a 100-ml. round-bottom flask were placed 13.6 g. (0.05 mole) of 3,3-dicarbethoxy-1,1-dimethyl-1-silacyclohexane, 40 g. (0.70 mole) of KOH, and 30 ml. of water. Upon warming, a vigorous, exothermic reaction ensued, which required an ice bath for control. After the reaction had subsided, the reaction mixture was cooled to room temperature and added slowly to a sulfuric acid–ice mixture The white precipitate was extracted with three 100-ml. portion of ether. The ether was removed using a roto evaporator, and the diacid, 9.7 g. (90%), was crystallized from petroleum ether (b.p. 30–60°), m.p. 156.5–158° dec.

Anal. Calcd. for $C_9H_{16}O_4Si$: C, 50.00; H, 7.40; neut. equiv., 108.1. Found: C, 49.96; H, 7.53; neut. equiv., 107.9.

Reaction with Dicyclohexylcarbodiimide.—Repeated attempts to prepare the N-substituted silaspirobarbiturate using the pro-

TABLE IV

DICARBETHOXYSILACYCLOHEXANES



R	Yield, %	B.p., °C. (mm.)	n_D (°C.)	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Silicon, % Calcd.	Silicon, % Found
H	50	115 (3.2)	1.4567 (26)	$C_{13}H_{24}O_4Si$	57.35	57.26	8.82	8.73	...	...
CH_3	34	114 (1.8)	1.4584 (26)	$C_{14}H_{26}O_4Si$	58.34	58.47	9.71	9.68	9.75	9.89
C_2H_5	50	117 (1.5)	1.4589 (27)	$C_{15}H_{28}O_4Si$	...	...	...	...	...	...
C_3H_7	21	130 (2.0)	1.4607 (27)	$C_{16}H_{30}O_4Si$	61.09	60.98	9.63	9.55	8.93	9.04

An analytical sample of the 4-ethyldicarbethoxysilacyclohexane was not obtained. Gas phase chromatography of the distillation fractions indicated the presence of a close-boiling impurity (not identified) and gas chromatographic purification of this compound was not successful due to thermal decomposition on the column. The impure diester was used for the preparation of the spirobarbiturate.

The only silacycloheptane diester prepared was 3,3-dicarbethoxy-1,1-dimethyl-1-silacycloheptane, b.p. 113° (0.8 mm.), $n^{25}D$ 1.4621, which was obtained in 25% yield using bromomethyl(δ-bromobutyl)dimethylsilane as the starting dihalogen compound.

Anal. Calcd. for $C_{14}H_{26}O_4Si$: C, 58.34; H, 9.71. Found: C, 58.70; H, 9.89.

(12) The diacid, m.p. 184–188°, was obtained from the saponification of dicarbethoxycyclohexane, b.p. 102° (3 mm.), $n^{24}D$ 1.4472; V. P. Gollmov [*Zh. Obshch. Khim.*, **22**, 1944 (1952); *Chem. Abstr.*, **47**, 9267 (1963)] reports b.p. 100° (2 mm.), $n^{20}D$ 1.4482.

(13) A. K. Bose, S. Garratt, and J. J. Pelois, *J. Org. Chem.*, **28**, 730 (1963).

cedure described above failed. Reaction conditions were varied from ice temperature for 2 hr. to reflux temperature for 1 hr. In one run a small amount (*ca.* 10% by weight of the material subjected to the reaction) of crystalline substance, m.p. 171–173°, was obtained after elution chromatography of the oily residue. The infrared spectrum of this material showed bands at 3.0 (N–H), 6.03 (C=O), and 8.1 μ (Si-CH_3). The structure of this material was not determined.

Ultraviolet Spectra.—The sample was dissolved in 70% aqueous ethanol. Since the spectra of these spirobarbiturates change with time, the solutions were used within 1–2 hr. For the neutral solutions an aliquot was diluted to the proper volume with 70% ethanol. For the basic solutions, an aliquot was diluted to the proper volume using NaOH (70% ethanol solution; 0.01 *N* final volume). These latter solutions were run within 5 min. of mixing. The spectra were run from 3500 to 2150 Å. The ultraviolet data obtained are summarized in Table II. The data obtained for diethylbarbital were: neutral solution, end absorption; 0.01 *N* NaOH, λ_{max} 2400 Å. (ϵ_{max} 9650).

Infrared Spectra.—The infrared spectrum for each of the spirobarbiturates was run as a mineral oil mull. The bands observed in the N–H region (2.7 to 3.3 μ) and in the C=O region (5.5 to 6.2 μ) are summarized in Table II. For the spirothiobarbiturates, the bands in the 6.5-μ region (C=S) are also tabulated.

The Effect of Piperidinecarboxamide Derivatives on Isolated Human Plasma Cholinesterase. II. Variations in the Amide Function[1]

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A series of carbamoylpiperidine derivatives has been prepared. The inhibitory activity of these and similar derivatives[2,3] upon isolated human plasma cholinesterase was determined. The results are discussed primarily in terms of the effect on biochemical response elicited by variations in the amide function.

In previous investigations, we have explored the effect of compounds of several series of carbamoylpiperidines (piperidinecarboxamides) upon isolated human plasma pseudo-cholinesterase,[2] and the respective relationships with surface-active properties.[4] The very interesting results obtained in these studies prompted additional synthetic[3] and physicochemical[5,6] investigations designed to elucidate further the influence that structural variations in the inhibitor molecules have on isolated cholinesterase systems. We have prepared additional mono- and bis(carbamoylpiperidino)ethanes and -decanes, reported here and in an earlier paper,[3] for the evaluation of their inhibitory characteristics.

Our earlier work[2] yielded data reflecting responses effected by (1) the nature and degree of alkyl substitution on the amido function, (2) the mono- and the corresponding bis(carbamoylpiperidino) substitution on the alkane homologs, (3) the number and arrangement of the methylene units in the alkane component attached to the ring nitrogen(s), and (4) unsaturation in the piperidine ring.

This article deals primarily with the effect of structural variation in the amide function upon biochemical response. More specifically, we were interested in the effect such molecular modification might elicit on the latter response in terms of (1) the electron densities around the carbonyl function,[7] and (2) the lyophobic–lyophilic nature of substituents.[8]

Experimental

Synthetic Work.[9,10]—The chemistry of some of our piperidinecarboxamide derivatives has been reported previously.[3]

3-(Piperidinoformyl)pyridine (XXI).[11]—This compound was prepared from nicotinic acid. It distilled at 115–118° (0.15 mm.).

3-(Morpholinoformyl)pyridine (XXII).[12]—This compound was also prepared from nicotinic acid. It distilled at 138–140° (0.4 mm.).

The compounds described in Table I were prepared by the following procedures.

Procedure A.[13] **1-Decyl-3-(N-ethylcarbamoyl)piperidine Hydrobromide (III).**—N-Ethylnicotinamide (50 g., 0.332 mole) and 1-bromodecane (73.4 g., 0.332 mole) were heated at 150° for 7 hr. After cooling the reaction mixture, the solid product was dissolved in aqueous ethanol, and the solution was subjected to hydrogenation in the presence of 1 g. of platinum oxide at maximum pressures of 3.16–3.51 kg./cm.^{2} (45 to 50 p.s.i.). When absorption of hydrogen ceased, the catalyst was removed by filtration and the solvent was removed *in vacuo* utilizing a rotary evaporator. Residual traces of moisture were removed from the oily product by azeotropic distillation with absolute ethanol and/or benzene, and the product was purified by recrystallization.

Procedure B. 1-Decyl-3-(piperidinoformyl)piperidine Hydrobromide (XII).—3-(Piperidinoformyl)pyridine (25 g., 0.131 mole) and 1-bromodecane (73 g., 0.330 mole) were dissolved in 200 ml. of anhydrous benzene, and the solution was refluxed for 53 hr. The oily precipitate produced in the reaction was dissolved in 150 ml. of water, and the solution was washed with benzene, treated with charcoal, and filtered. The solution was

(1) This investigation is being supported by grants from the National Institute of Mental Health (USPHS MY-2072,'MH-04379), the Geschickter Fund for Medical Research, Inc., and the National Science Foundation (GB-2381/B-15989).

(2) A. Lasslo, J. G. Beasley, G. G. Nelms, and G. J. Epperson, *J. Med. Chem.*, **6**, 811 (1963).

(3) R. P. Quintana and W. A. Shrader, *J. Pharm. Sci.*, **52**, 1186 (1963).

(4) R. P. Quintana, *ibid.*, **53**, 1221 (1964).

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