PROPHYLACTIC AND TREATMENT DRUGS FOR ORGANOPHOSPHORUS POISONING

ANNUAL REPORT

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The program is directed at the design and synthesis of treatment and prophylactic drugs as potential defenses against organophosphorus poisoning. During the past year, 11 compounds were submitted: one organophosphonate; one organophosphate; one physostigmine analog; 3-PAM iodide; one perfluoroalkyl alkyl hydroxylamine; one bis(pyridinyl)urea quaternary salt; two 1,3,4-oxadiazolones; one hydroxyimino-3-methylimidazolium salt; one propanesulfonate; and one 4,4-biphenylene-bis(morpholine).

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SUMMARY

The purpose of the contract is to maintain and operate a synthesis laboratory to provide chemical compounds needed in the development programs of the U.S. Army Medical Research Institute of Chemical Defense (ICD) Edgewood Area, Aberdeen Proving Ground, Maryland.

All compounds were assigned and prioritized by the Contracting Officer's Representative (COR). Eleven assignments were completed in the past year, as listed below.

No.	Name	Code No.	Wt., g[a]	Date Shipped
1.	2,2'-(4,4'-Biphenylene)-bis-[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide	CT-1-170-17	11	11/23/87
2.	3-(Diisopropylphosphato)-phenyltrimethylammonium iodide	CT-1-175	25	12/1/87
3.	4-Nitrophenyl dibutyl-phosphinate	CT-1-191	25	1/20/88
4.	4-Nitrophenyl 3-(benzoyl)-propanesulfonate	CT-1-236	7.5	2/26/88
5.	1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxyheptanoyl)]amino-ethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride	BSR-01-207 BSR-01-201	0.5 1.5	4/6/86 4/6/86
6.	5-Methoxy-3-(2-methoxy-phenyl)-1,3,4-oxadiazol-2(3H)-one	CT-1-287	24	5/5/88
7.	3-(2,3-Dihydro-2,2-dimethyl-benzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one	CT-1-288	22	5/5/88
8.	3-Pyridinealdoxime methiodide	CT-1-294	21	5/12/88
9.	[1-(Nonafluorobutyl)-pentylidene]hydroxylamine	CT-1-302	12	5/15/88
10.	N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide	CT-2-24	38	8/3/88
11.	1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide	CT-2-60	7	8/25/88

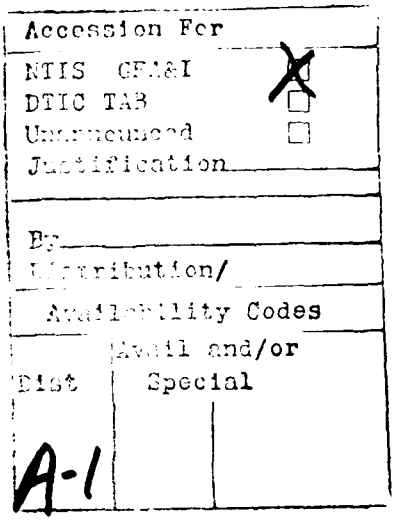
(a) A nominal five g sample was shipped also to WRAIR in all cases except for compounds 4 and 5.

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Acknowledgment

The timely advice and, assistance of Dr. Brennie Hackley, Jr., the Contracting Officers Technical Representative (COTR), and Mr. Claire Lieske of the ICD are gratefully acknowledged.



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PROPHYLACTIC AND TREATMENT DRUGS FOR ORGANOPHOSPHORUS POISONING

1. INTRODUCTION

The work reported herein represents a continuation of work performed since 1977 under a series of continuing contracts. The primary thrust over the years has been directed at the synthesis of prophylactic and treatment compounds for defense against nerve gas agents (GB,GD,VX). All of the work assignments on these preparative programs have been and continue to be made by the Contracting Officer's Representative (COR). In addition to candidate prophylactics and treatment drugs, the assignments have included intermediates and research compounds required by Army scientists for their in-house research programs directed at various aspects of organophosphorus (OP) poisoning.

Historically, starting October 1, 1977, work under the first two contracts (1,2), through January 27, 1981, was directed exclusively to the preparation of organophosphinate esters, 29 in all, as candidate prophylactics. The work was based on a concept delineated by C.N. Lieske and co-workers at the (then) Biomedical Laboratory at Edgewood, Maryland. Additional support in this early work was provided by the contractor in the form of kinetic studies to measure solvolysis half-lives at two pH levels.

In a third contract (3), this work was expanded to include the synthesis of compounds targeted to the synthesis of compounds other than the organophosphinate esters. This work covered the period September 1, 1981 to September 30, 1984, wherein a total of 48 compounds were prepared; of these, 25 compounds, 5 g each, were shipped also to Walter Reed Army Institute of Research (WRAIR). These 48 compounds included the following prophylactics: 25 organophosphinates (including one cyclic); a phosphinothioate; 3-nitrophenyl isopropyl methylphosphonate, and seven organocarbamates (including two ferrocenyl analogs). The other 14 assignments involved a variety of research compounds including two sugar oximes as acetylcholinesterase (AChE) reactivators; one INCAP; a cyclohexylpiperidine; γ-methyl-adenosine 5'-triphosphate; 2-aminoethylselenic and 2-aminoethyl-selenonic acids; monomethyl phosphate (purification); 2,3-dimethyl-3-hydroxybutylamine; pinacolyl dimethylphosphinate; and four compounds for the School of Public Health, University of Michigan.

Under the fourth and current contract starting October 1, 1984, the effort to improve our OP defensive capability in both the propylactic and treatment area was continued. Thus, in the first 3 years of the program (4,5,6), 50 assignments were completed: 20 organophosphinates, one organophosphonate, 13 phosphorinanes (cyclic phosphates), one phosphorothioate, four carbamates, three AChE reactivators, and six miscellaneous structures: suberyldicholine, a new tropate ester (two submissions), one (new) physostigmine analog, a nonanone oxime, a quaternary pyridine, and a tetraalkylquaternary iodide.

A number of the assigned compounds over the years have represented repeats which are requested by an Army or by another contract investigator via the COR. We note that while we do direct our attention to yield improvements in all assignments, the primary goal is to deliver the compound as expeditiously as possible. We note also that a few of the assigned compounds over the course of the work have been abandoned due either to synthetic problems which were not solvable in a reasonable time span or to the instability of a key intermediate or of the target compound.

In this, the fourth year of this contract, 11 compounds of varying structure were prepared, some new and interesting, as follows.

A new physostigmine analog bearing a carboxyheptanoyl group (compound 5).

Two 1,3,4-dioxazole structures: one bearing a 2-methoxyphenyl group on the 3-nitrogen atom (compound 6) and one bearing a 2,2-dimethylbenzofuran-7-yl group on the 3-nitrogen atom (compound 7).

A new hydroxylamine derived from n-nonafluorobutyln-butyl ketone (compound 9).

4-Nitrophenyl 3-benzoylpropanesufonate (compound 4,new) and a new difficult-to-prepare oxime derived from N-carboxypentyl-2-carboxaldehydo-3-methylimidazolium iodide (compound 11).

A bis(2-hydroxy-4-N-bromoethylmorpholino)-4,4-bis-biphenylene) dihydrobromide (compound 1).

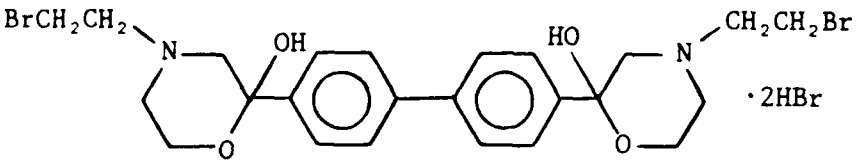
Four conventional-type structures: a diisopropyl-phosphate with a trimethylammonium phenoxy leaving group(compound 2), 4-nitrophenyl dibutylphos-phinate (compound 3), 3-PAM iodide (compound 8) and an N,N-bis(N-methyl-3-pyridinyl)urea diiodide (compound 10).

This years work brings the total number of submissions in the course of this contract to 61. Resyntheses (refills) were prepared as requested.

2. DISCUSSION OF WORK COMPLETED

The 11 assignments completed in the past year are discussed below.

2.1 2,2-(4,4-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide

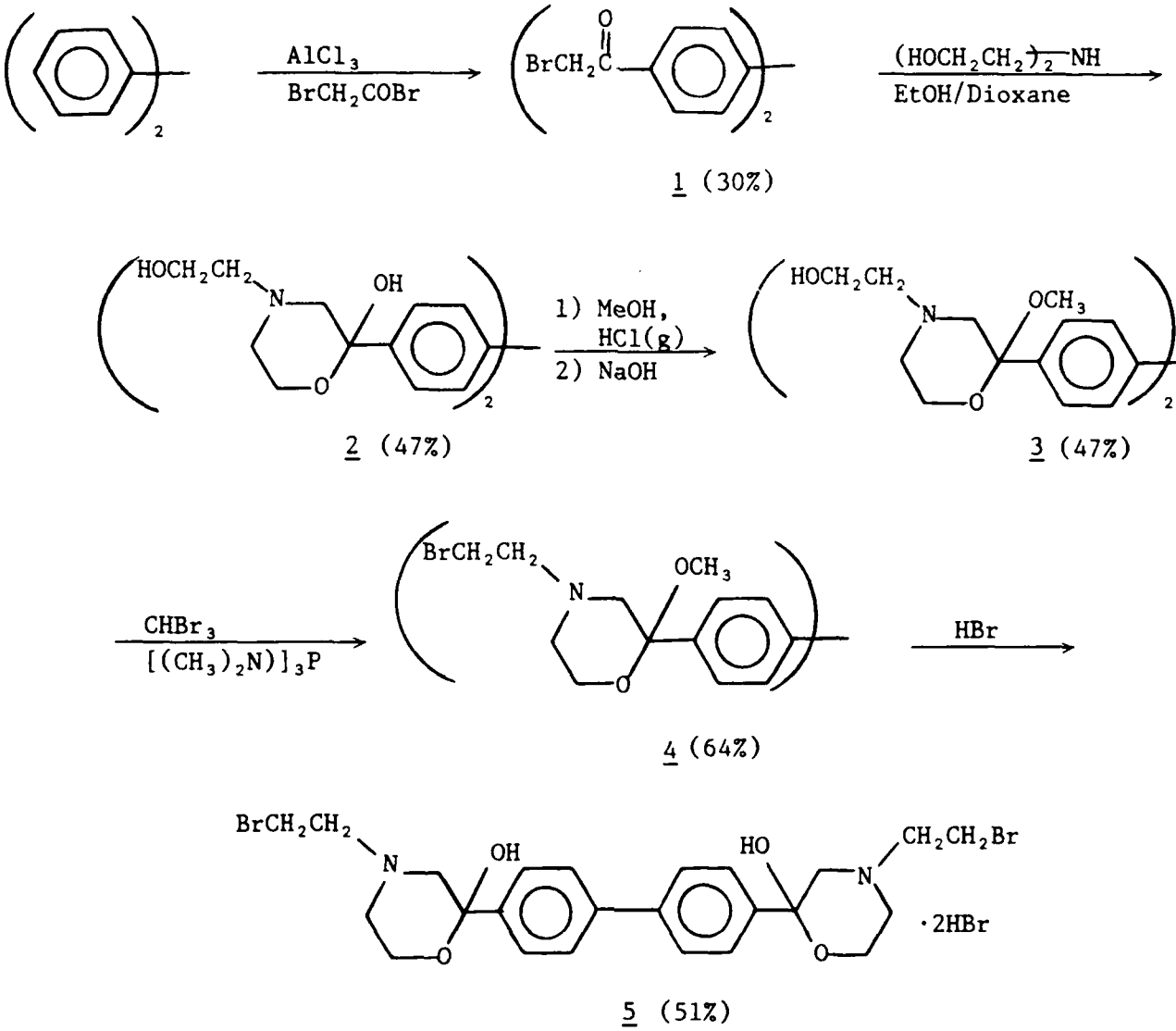


Synthesis of the title compound by a five-step reaction sequence has been reported in the literature (7). The same general sequence, shown in Chart No. 1, was used for the current resynthesis.

Condensation of α-bromoacetyl bromide with biphenyl in the presence of anhydrous aluminum chloride gave the bromoketone 1, isolated in two crops in 30% combined yield. Although the compound had a somewhat lower melting point than that reported in the literature, it was sufficiently pure for use in the next step. Treatment of intermediate 1 with excess diethanolamine in ethanol/dioxane as solvent gave the bis(hydroxymorpholine) 2 in 47% yield. Next, the literature reports the reaction of compound 2 with ethanol and hydrogen chloride to give a 36% yield of the 2-ethoxy analog of compound 3. Although the literature work was repeated successfully in these laboratories on small scale runs, the procedure required excessively large solvent volumes and product yields were not reproducible from one run to the next. Accordingly, the procedure was modified in that methanol was substituted for ethanol as the solvent. This allowed a five-fold reduction in the reaction volume and gave the bis(2-methoxymorpholine) 3 in 47% yield. Substitution of the primary hydroxyl group with a bromine was accomplished by treatment of compound 3 with tris(dimethylamino)phosphine and bromoform. The literature reports methylene chloride as the reaction solvent. In our hands, when methylene chloride was used as the solvent, the isolated product 4 was shown to contain 5-15% of the corresponding chloroethyl compound as an impurity. All attempts to remove this contaminant were unsuccessful. The problem was readily solved, however, by replacing methylene chloride with methylene bromide. This gave pure intermediate 4 in 64% yield. In the final step, the morpholine 2-ethoxy group was cleaved with acid to yield the title target compound 5. The literature work

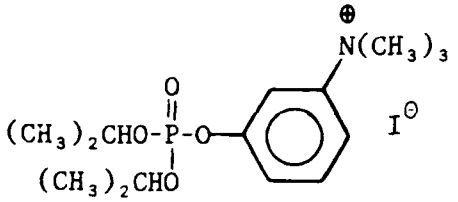
CHART NO. 1

2,2'-(4,4'-BIPHENYLENE)BIS[2-HYDROXY-4-(2-BROMOETHYL)-MORPHOLINE] DIHYDROBROMIDE



employed sulfuric acid for this hydrolysis. The crude product was then converted, via the free base, to a hydrochloride salt which was isolated in 27% yield. In the present study, the hydrolysis was accomplished with hydrobromic acid and product 5 was isolated as a hydrobromide salt in 51% yield. By this procedure, conversion of compound 5 to the free base was not necessary; thus was avoided any potential hydrolysis (or halogen exchange) of the reactive bromoethyl nitrogen mustard.

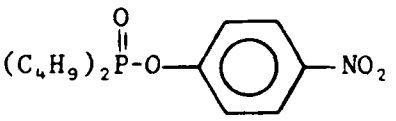
2.2 3-(Diisopropylphosphato)phenyltrimethylammonium iodide



Synthesis of the title compound, methylsulfate salt, has been reported in the literature (8). The same general synthesis sequence, shown in Chart No. 2, was used for the current resynthesis.

Diisopropyl phosphorochloridate was prepared by the action of sulfuryl chloride on diisopropyl phosphite, which, in turn, was prepared *in situ* from phosphorus trichloride and isopropanol. Treatment of chloridate 1 with 3-dimethylaminophenol gave the mixed phosphate triester 2. Purification of ester 2 has been reported (8) by distillation under high vacuum (10^{-6} mmHg). In the present work, the crude product 2 traveled as a single spot on thin-layer chromatography; accordingly, the compound was used as such, without purification, in the next step. Treatment of crude 2 with methyl iodide, in acetonitrile as solvent, gave the title quaternary iodide salt.

2.3 4-Nitrophenyl dibutylphosphinate



A sample of the title compound was prepared earlier by Ash Stevens Inc. (6). The same sequence, shown in Chart No. 3, was used for the current resynthesis.

Diethyl phosphite was treated with three equivalents of n-butylmagnesium bromide, and the product was oxidized with bromine according to a literature procedure (9) to give

CHART NO. 2

3-(DIISOPROPYLPHOSPHATO)PHENYLTRIMETHYLAMMONIUM IODIDE

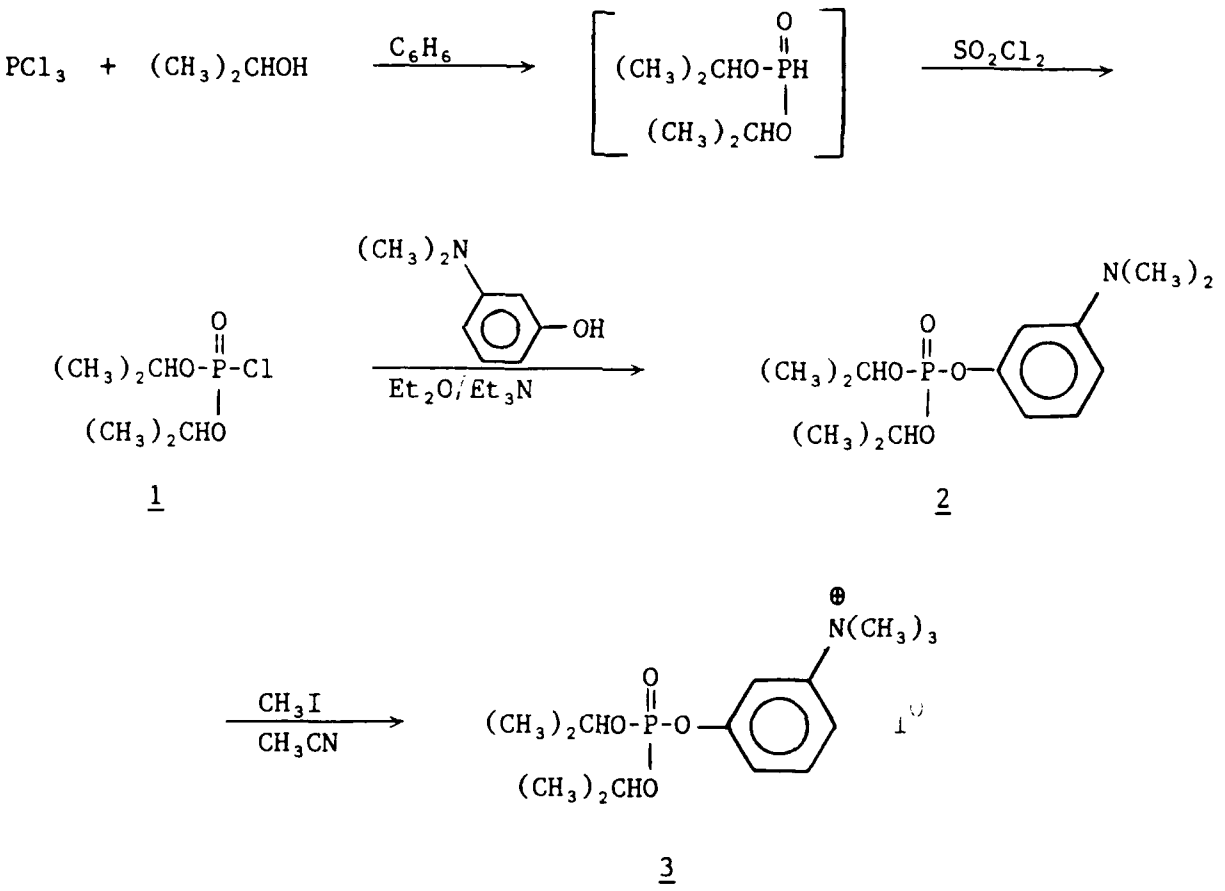
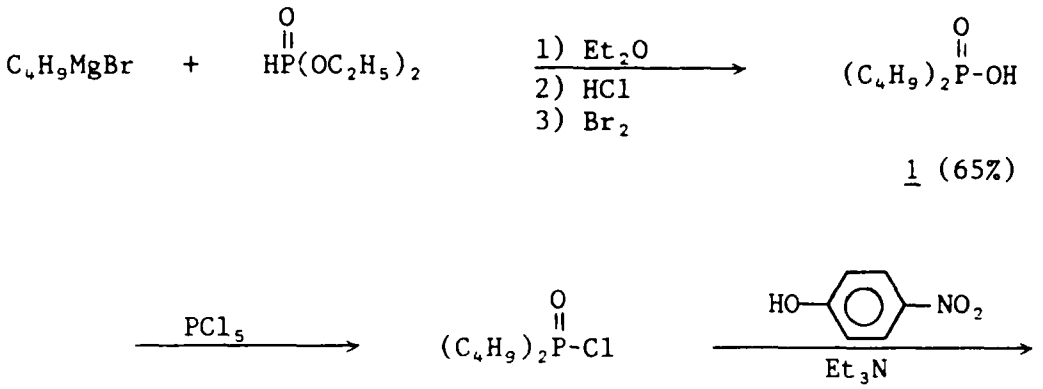
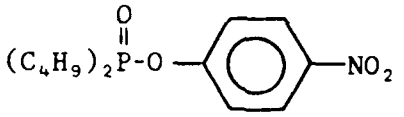


CHART NO. 3

4-NITROPHENYL DIBUTYLPHOSPHINATE

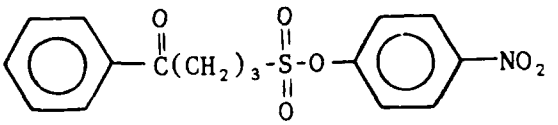




3 (65%)

dibutylphosphinic acid (1). The acid 1 was converted to phosphinic chloride 2 by treatment with phosphorus pentachloride. Chloride 2 was allowed to react with 4-nitrophenol and triethylamine to give the title compound 3, which was purified by column chromatography over acidic alumina. The yield of purified ester 3 depends in part on the quality of alumina used in the purification step. One batch of alumina used in the current work was not sufficiently acidic and caused considerable product decomposition.

2.4 4-Nitrophenyl 3-(benzoyl)propanesulfonate

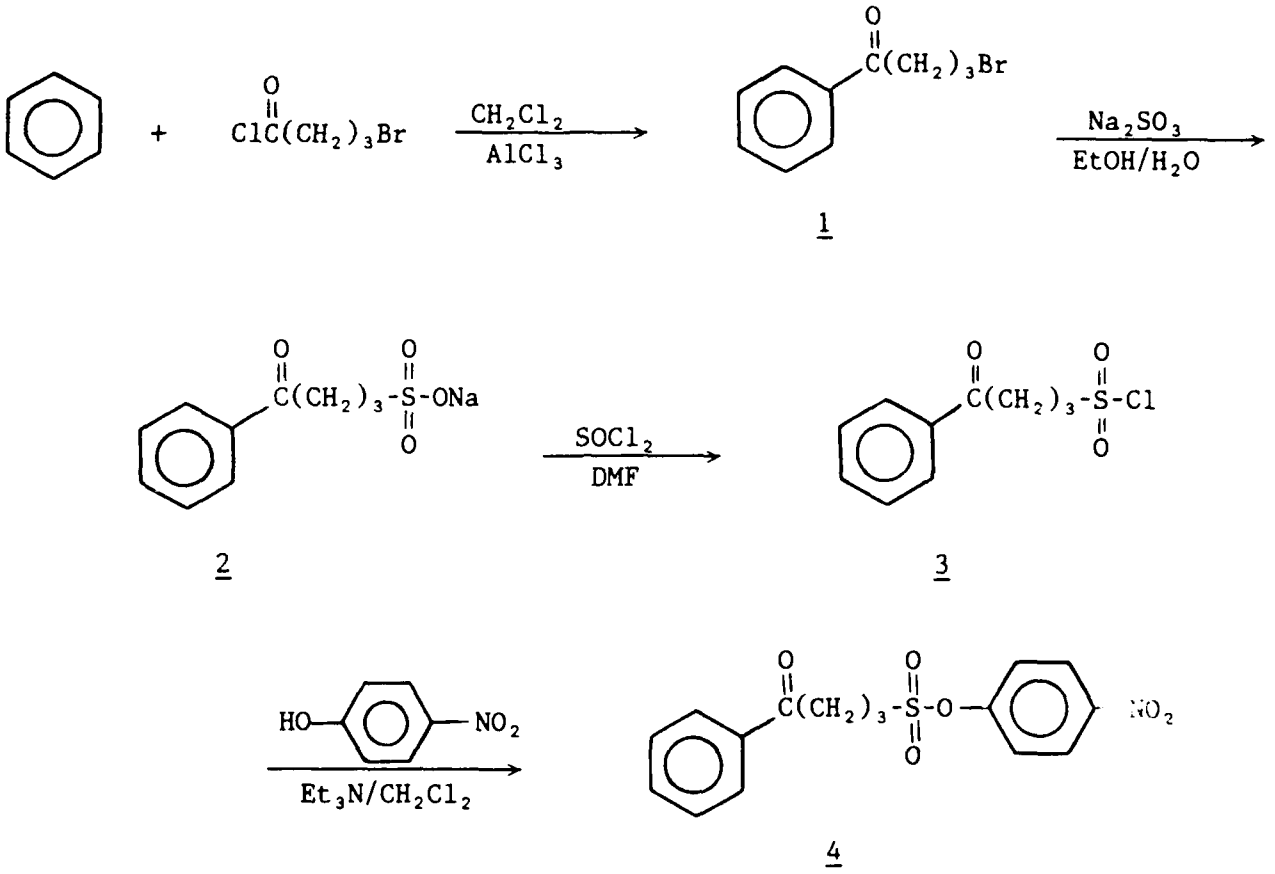


The title compound represents a new structure not reported in the chemical literature. The four-step synthesis route is shown in Chart No. 4.

Bromoketone 1 was prepared by the Friedel-Crafts acylation of benzene with bromopropionyl chloride as described in the literature (10). Treatment of compound 1 with sodium sulfite in aqueous ethanol as solvent gave the sulfonic acid sodium salt 2. In the initial studies, a sample of 2 was passed over a strong acid ion exchange resin to give the free sulfonic acid in the form of an oil, which rapidly darkened on standing. As a result, the stable sodium salt was used in all subsequent work. Treatment of compound 2 with a mixture of thionyl chloride and dimethylformamide gave a low yield of the desired sulfonyl chloride 3. Attempts to covert 2 to 3 using phosphorus pentachloride failed altogether. Thin-layer chromatography showed only decomposition products; none of the acid chloride could be detected. Last, the reaction of compound 3 with 4-nitrophenol in the presence of triethylamine gave a high yield of the desired title target structure 4.

CHART NO. 4

4-NITROPHENYL 3-(BENZOYL)PROPANESULFONATE



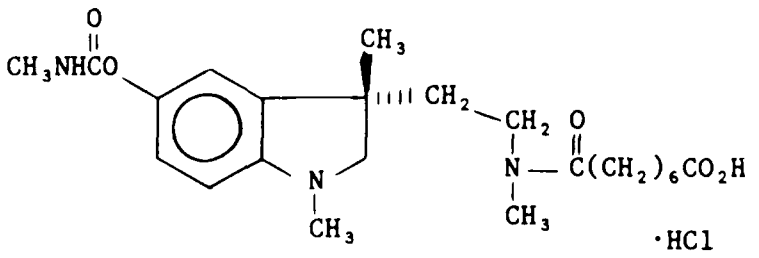
1

2

3

4

2.5 1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxyheptanoyl)]amino-ethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride

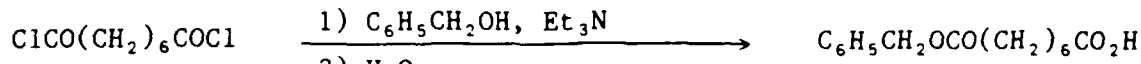


The synthesis route to the title compound is outlined in Chart No. 5, and is based on earlier work reported in the literature (11), which showed that reduction of eserethole, a close analog of physostigmine, with zinc and hydrochloric acid or catalytic hydrogenation in the presence of acetic acid cleaves the fused outside pyrrolle ring of the three-ring system. In the present study with physostigmine, the conditions were changed such that the acetic or hydrochloric acid was replaced with an acid chloride and sodium borohydride was used as the reducing agent.

The requisite acid chloride was prepared, as shown, by treating suberoyl chloride with 1 mol of benzyl alcohol; this was followed by hydrolysis to give suberic acid monobenzyl ester 1. After removal of some unreacted suberic acid and the dibenzyl ester, compound 1 was converted to acid chloride 2 with thionyl chloride. Next, the acid chloride was treated with physostigmine to give the presumed intermediate 3, which was reduced immediately with sodium borohydride to the substituted indole 4. The crude product was purified by column chromatography, then subjected to hydrogenolysis over palladium black to give compound 5, isolated as a hydrochloride salt. The structure of product 5 was confirmed by infrare and nuclear magnetic resonance spectra and elemental analysis.

CHART NO. 5

1,3-DIMETHYL-3-[2-[N-METHYL-N-(7-CARBOXYHEPTANOYL)]-AMINOETHYL]-5-(N-METHYLCARBAMOYLOXY)-2,3-DIHYDRO-INDOLE HYDROCHLORIDE



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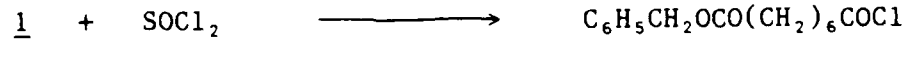

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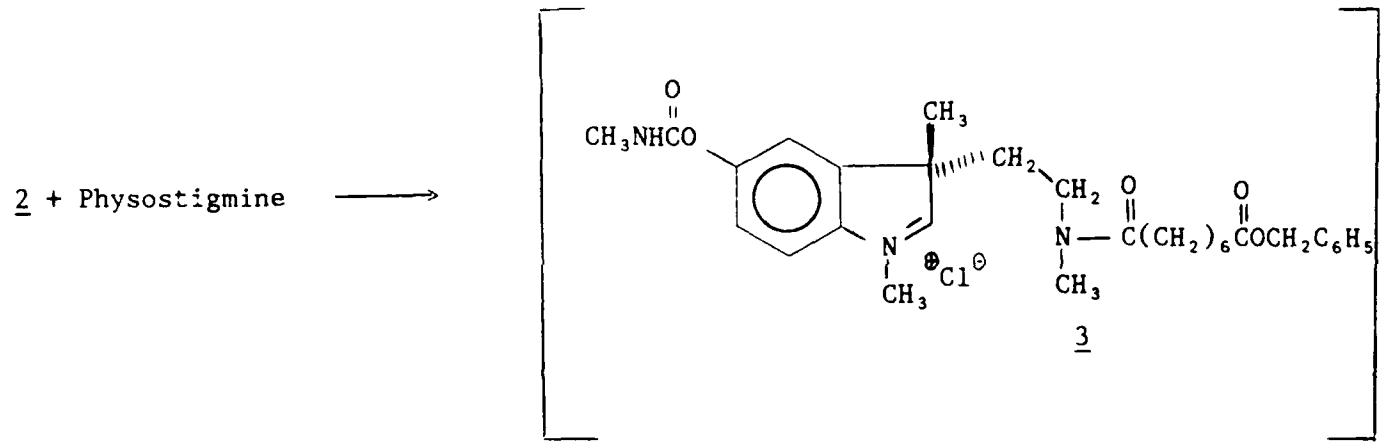

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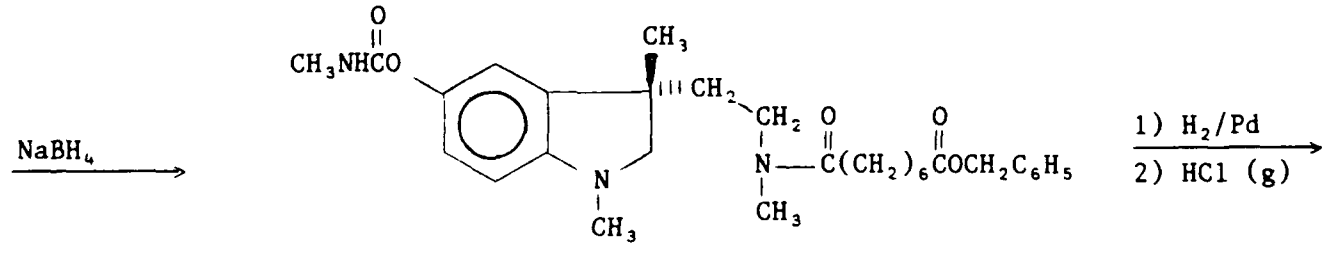
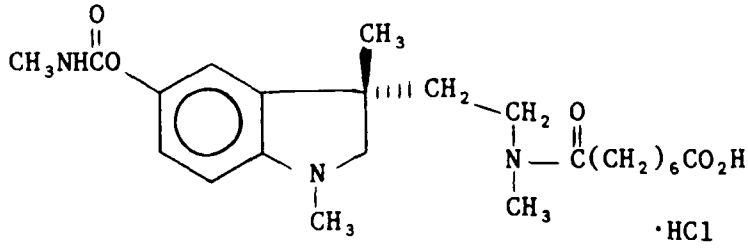
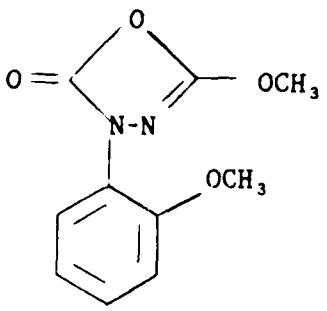


4 (73%)



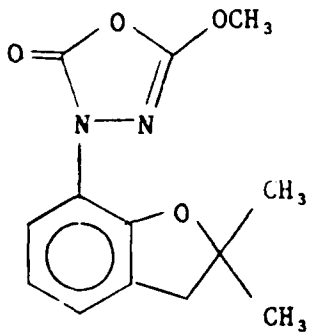
5 (85%)

2.6 5-Methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one



The title compound was prepared by a literature procedure (12,13) and is outlined in Chart No. 6. The required starting material, (2-methoxyphenyl)hydrazine (1), was prepared from o-anisidine by a standard reaction sequence involving diazotization followed by reduction with tin chloride. Treatment of compound 1 with methyl chloroformate gave the carbazate 2. Next, a benzene solution of 2 was treated with phosgene to give the chloro-carbonyl carbazate 3. In the literature procedure, this intermediate is isolated, then cyclized with sodium hydroxide to the desired product 4. In the current work, isolation of compound 3 was omitted. Instead, the reaction mixture containing crude 3 was treated directly with methanol and diisopropyl-ethylamine to give the desired title target compound. The yield for the two steps, although somewhat lower than the yield in the literature, was quite acceptable.

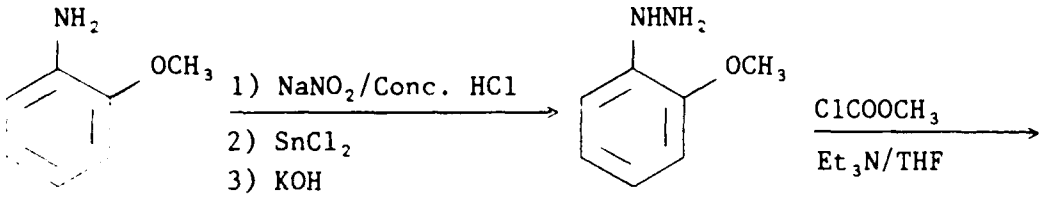
2.7 3-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one



The title compound was prepared by a general literature procedure (14,15), as outlined in Chart No. 7. As can e seen on Chart 7, 2-nitrophenol was treated with methallyl chloride in the presence of base to give the ether 1, which underwent thermal rearrangement at 185-250°C to yield the disubstituted phenol 2. Acid catalyzed cyclization of compound 2 to 7-nitrobenzofuran 3 followed by catalytic hydrogenation gave 7-amincbenzofuran 4.

CHART NO. 6

5-METHOXY-3-(2-METHOXYPHENYL)-1,3,4-OXADIAZOL-2(3H)-ONE



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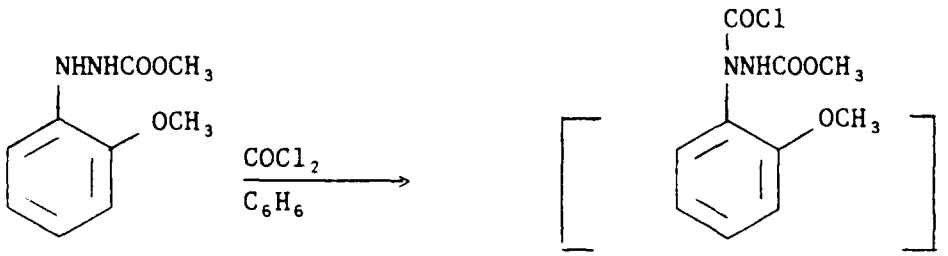
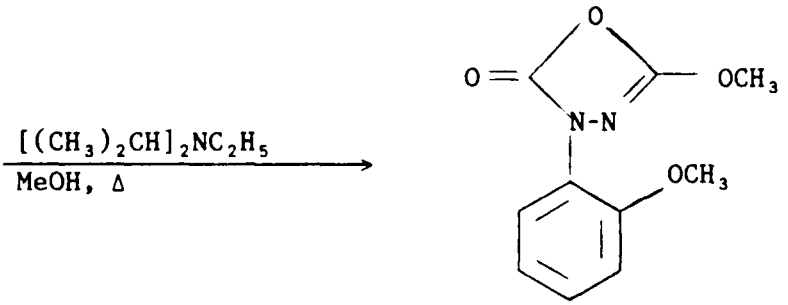


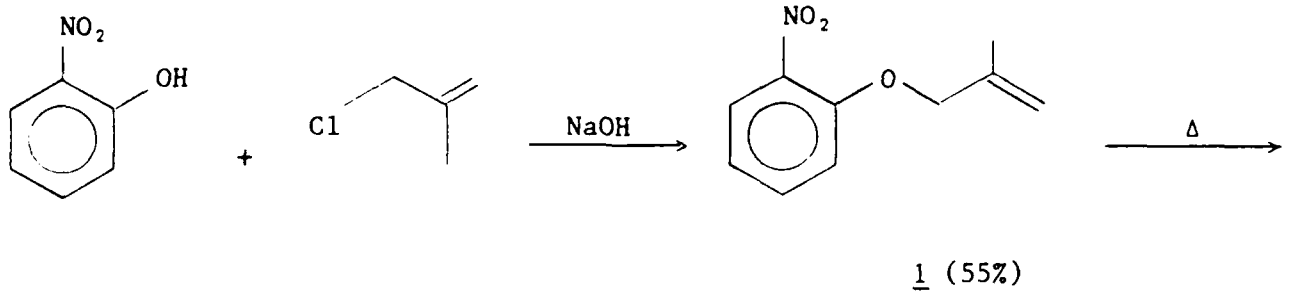
2 (88%) 3



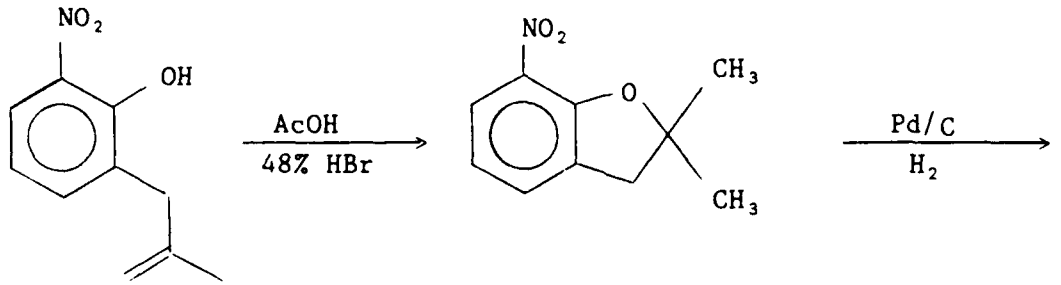
4 (68% from 2)

CHART NO. 7

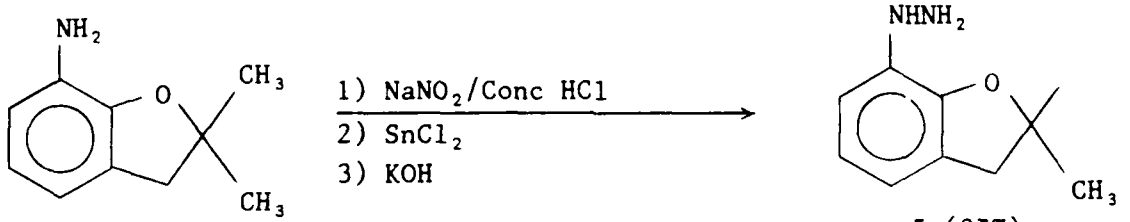
3-(2,3-DIHYDRO-2,2-DIMETHYLBENZOFURAN-7-YL)-5-METHOXY-1,3,4-OXADIAZOL-2(3H)ONE



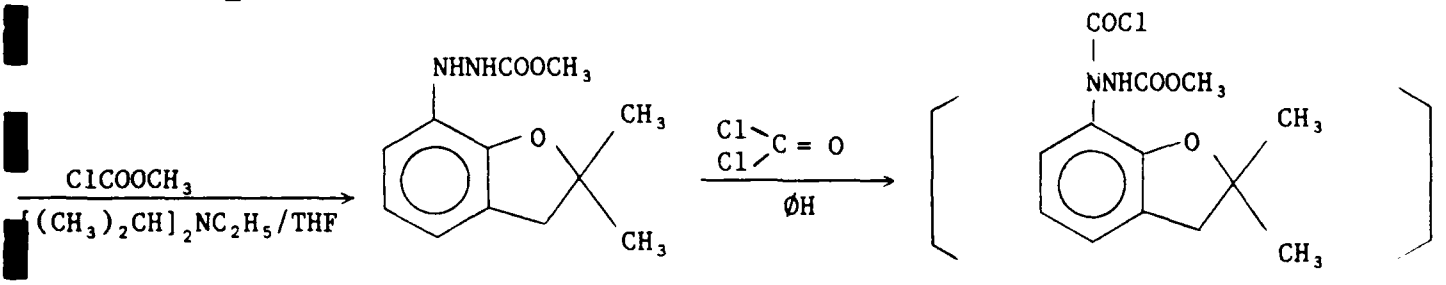
1 (55%)



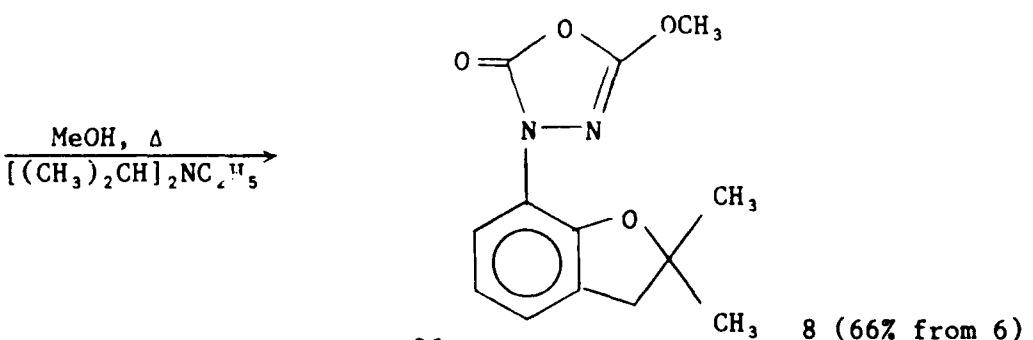
2 (48%) 3 (76%)



4 (100%) 5 (87%)



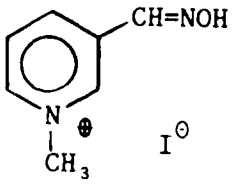
6 (74%) 7



8 (66% from 6)

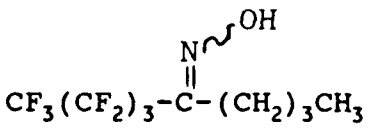
Compound 4 was converted to the hydrazine 5 by a standard diazotization reduction sequence, then treated with methyl chloroformate in the presence of diisopropylethylamine to give the crystalline intermediate 6. Finally, reaction of compound 6 with phosgene gave the N-chlorocarbonyl derivative 7 which was not isolated but was treated directly with methanol and diisopropylethylamine to give the title target compound 8. With the exception of intermediate 2, the yields throughout the sequence were good. No comparison could be made with the literature since no yields were reported.

2.8 3-Pyridinealdoxime methiodide



The title compound was prepared by the quaternarization of commercially available 3-pyridinealdoxime with methyl iodide. One recrystallization gave analytically pure title compound.

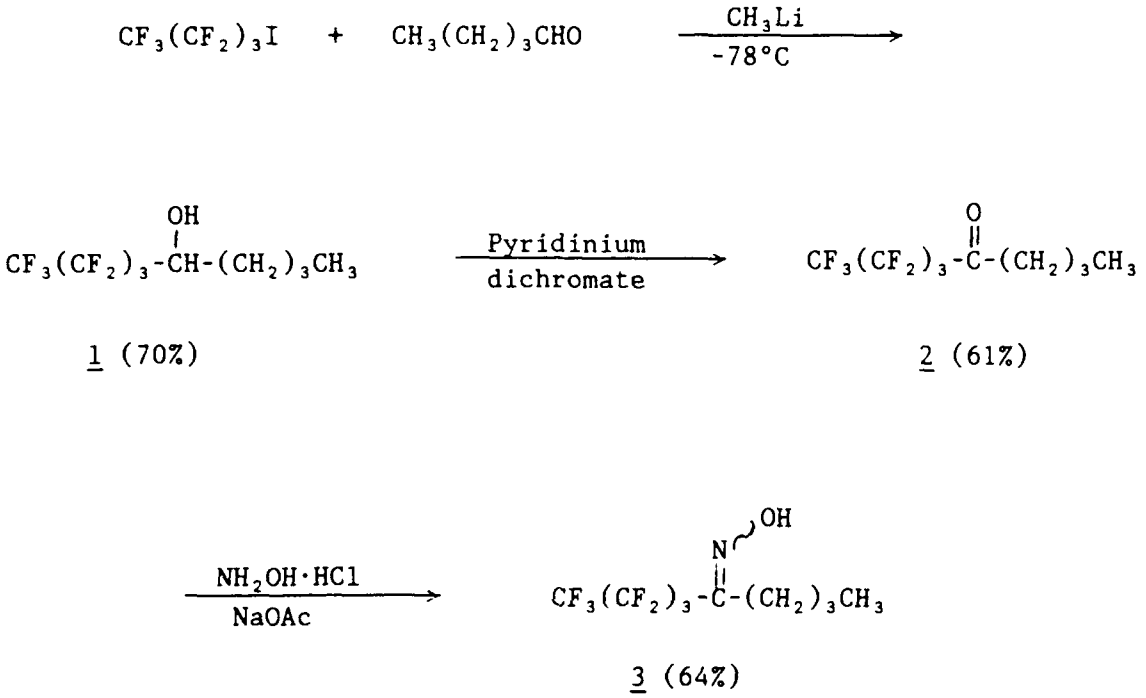
2.9 [1-(Nonafluorobutyl)pentylidene]hydroxylamine



The title structure is a new compound not reported in the chemical literature. Synthesis of this target was accomplished as shown in Chart No. 8. Alcohol 1 was prepared following a general literature procedure (16) by the coupling of perfluorobutyllithium, prepared *in situ*, with valeraldehyde. Oxidation of 1 with pyridinium dichromate in methylene chloride gave a satisfactory yield of ketone 2. In the last step, treatment of compound 2 with hydroxylamine gave the desired title oxime 3. NMR spectral evidence indicated that the compound was a mixture of the *syn* and *anti* oximes (with reference to the perfluorobutyl group) with one of the isomers predominating to the extent of 80-90%. No attempt was made to establish the configuration of the major isomer.

CHART NO. 8

[1-(NONAFLUOROBUTYL)PENTYLIDENE]HYDROXYLAMINE

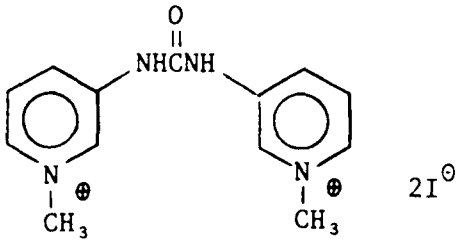


1 (70%)

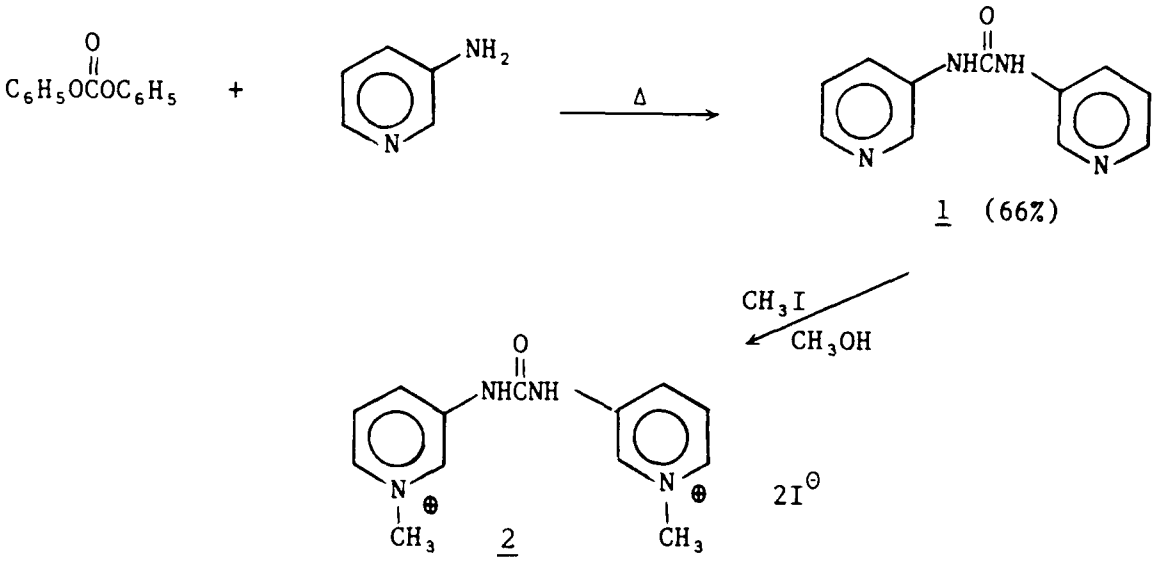
2 (61%)

3 (64%)

2.10 N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide

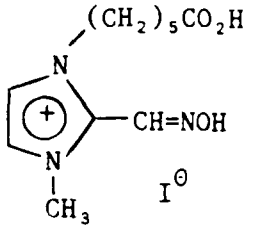


The title compound was prepared by a two-step reaction sequence as shown below.



Thus, diphenyl carbonate was heated neat with 3-aminopyridine to give urea 1. Treatment of compound 1 with excess methyl iodide in methanol solvent gave the title bisquaternary compound 2.

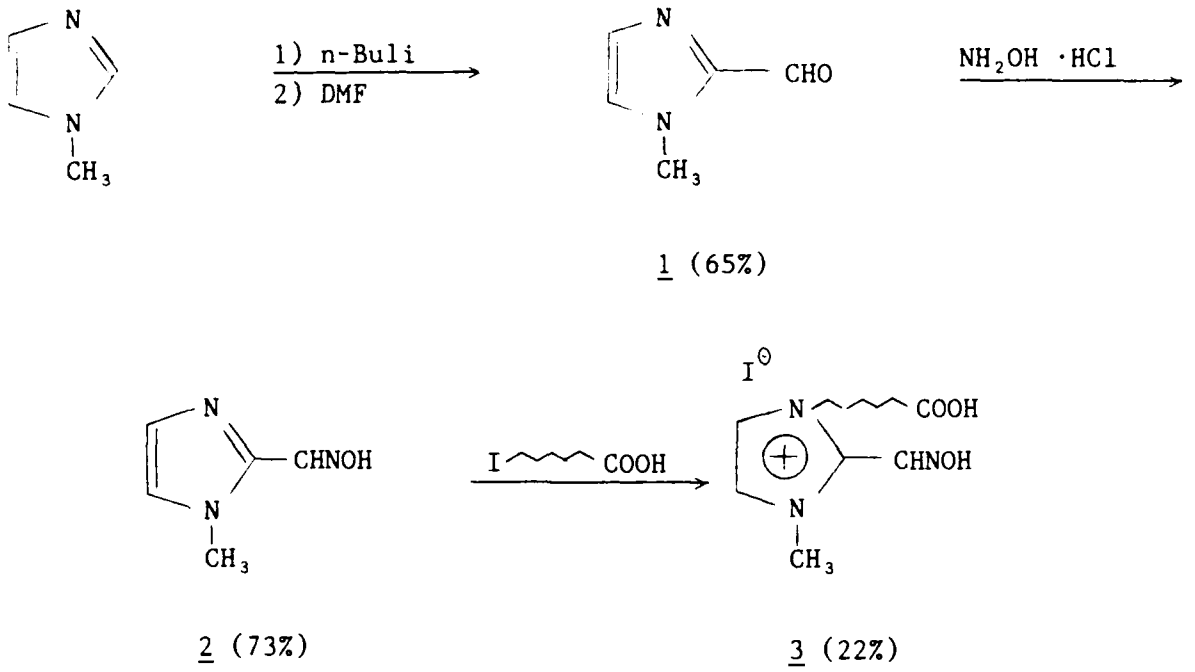
2.11 1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide



The title quaternary salt of 2-[(hydroxyimino)methyl]-imidazole was prepared by a three-step synthesis sequence as shown in Chart No. 9. Preparation of carboxaldehyde 1 followed a literature procedure (17) which involved formylation of the lithium salt of N-methylimidazole with dimethylformamide. Aldehyde 1, a low-melting solid, was isolated in 65% yield. Treatment of compound 1 with hydroxylamine hydrochloride in the presence of sodium bicarbonate gave a good yield (73%) of oxime 2. Quaternarization of compound 2 was attempted initially with 6-bromohexanoic acid. In the presence of a twofold excess of the acid, the reaction proceeded very slowly in refluxing tetrahydrofuran, acetone or acetonitrile solvents. Purification of one of the reaction mixtures by cellulose chromatography led to the isolation of a small amount of product identified as the quaternary bromide 3. In view of these poor results, the more reactive 6-iodohexanoic acid was substituted for the bromo acid. This change improved the reaction sufficiently to permit the isolation of crude product 3 in the form of a gummy solid. Purification was accomplished by simple recrystallization; chromatography was not required. Although the product yield was low (22%), it was adequate for the preparation of the requested 10 g of the title target compound.

CHART NO. 9

1-(5-CARBOXYPENTYL)-2-[(HYDROXYIMINO)METHYL]-3-METHYLIMIDAZOLIUM IODIDE



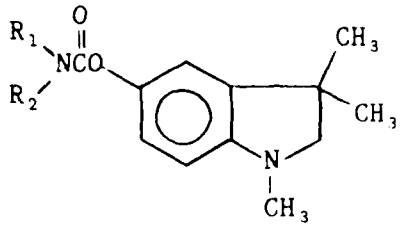
1 (65%)

2 (73%)

3 (22%)

3. WORK IN PROGRESS

3.1 5-(1,3,3-Trimethylindolinyl)N-alkylcarbamates



Preparation of the above N-methyl, N-ethyl, and N,N-diethylcarbamates has been initiated. Small scale exploratory synthesis of the key intermediate, 5-hydroxy-1,3,3-trimethyl-indoline via a route described in the literature has been completed (18). A repeat synthesis on a larger scale is in progress.

4. EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 273B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. Vapor-phase chromatography was performed using an F and M Model 810 with a flame ionization detector. NMR spectra, when required, were determined on a Varian Model T60 spectrometer. All thin layer chromatography was carried out using Analtech Uniplate silica gel GF 250μ plates with fluorescent indicator unless stated otherwise.

4.1 2,2'-(4,4-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide

The synthesis route to the title compound is shown in Chart No. 1.

α,α'-Dibromo-4,4'-biacetophenone (1): - Anhydrous aluminum chloride (450 g, 3.37 mol) was added to biphenyl (183 g, 1.19 mol) in carbon disulfide (1050 mL) at 0°C, followed by the dropwise addition of bromoacetyl bromide (600 g, 2.97 mol). The mixture was allowed to reflux gently until HBr evolution subsided (ca. 4 h). The mixture was cooled to room temperature; the carbon disulfide was decanted; and the remaining solid was broken up and hydrolyzed with a mixture of concentrated hydrochloric acid (90 mL) and water (3000 mL). The resulting solid was collected and washed with water (2 x 1500 mL). The solid was then transferred to a beaker, where it was thoroughly washed with ethanol (900 mL) to give a fluid slurry. After filtration and drying, a light brown powder (494 g) was obtained, mp 207-209°C. The powder was dissolved in dimethylformamide (2000 mL) and the solution was diluted with tetrahydrofuran (3000 mL). Filtration gave a light brown crystalline powder (248.9 g), mp 209-211°C. Recrystallization of this product from tetrahydrofuran gave a first crop, 91.6 g, mp 217-219°C, and a second crop, 63.4 g, mp 213-216°C. The second crop was recrystallized once more from tetrahydrofuran to give 51.6 g of product, mp 216-218°C; lit. mp 224-226°C (7). The combined yield was 143.2 g (30%). An earlier smaller scale run using 122 g of biphenyl gave 55.6 g (18%) of product, mp 217-219°C. NMR (dioxane-d_6) δ 4.64 (s, 4 H), 7.84 (d, 4 H, J=9 Hz), 8.14 (d, 4H, J=9 Hz).

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride	0.78	Homogeneous

2,2'-(4,4'-Biphenylene)bis[2-hydroxy-4-(2-hydroxyethyl)-morpholine] (2): - Diethanolamine (227.4 g, 2.16 mol) in ethanol (1.7 L) was added to a warm solution of α,α'-dibromo-4,4'-biacetophenone (180 g, 0.45 mol) in dioxane (2.4 L). The clear solution was allowed to stir at room temperature for 20 h. To this mixture was added water (4 L); the solution was acidified with hydrochloric acid to pH ca. 4 and was extracted with ether (2 x 2 L). The aqueous layer was made alkaline to pH 10 with 50% NaOH (w/v) and was extracted with methylene chloride (2 x 2 L). The combined methylene chloride extract was washed with water (2 x 2 L), dried ($MgSO_4$), and filtered. The filtrate was concentrated until the product began to crystallize; then, it was stored in a refrigerator overnight. The solid was collected to yield 93 g (46%) of product 2, mp 150-152°C; lit. mp 152-154°C (7).

2,2-(4,4-Biphenylene)bis[2-methoxy-4-(2-hydroxyethyl)-morpholine] (3): - Intermediate 2 (101 g, 0.227 mol) was dissolved in absolute methanol (2020 mL) containing 101 g of HCl gas. The mixture was heated at reflux for 2.5 h, then allowed to cool to room temperature. The precipitate was collected to give 115 g of off-white solid. The solid was dissolved in water (820 mL); the solution was adjusted to pH 10 with 50% aqueous sodium hydroxide and was extracted with methylene chloride (1 x 1200 mL, 1 x 500 mL). The combined methylene chloride extract was washed with water (800 mL), dried ($MgSO_4$), and concentrated to dryness to give a light-yellow solid, 98.3 g, mp 161-164°C. The solid was recrystallized five times from a mixture of tetrahydrofuran (4 mL/g) and petroleum ether (2 mL/g) to give 50.7 g (47%) of pure product, mp 175.5-177°C; NMR ($CDCl_3$) δ 2.00-3.20 (m, 12 H), 3.10 (s, 6 H), 3.67 (br t, 4 H, J=5 Hz), 3.80-4.40 (m, 4 H), 7.60 (s, 8 H).

Anal. Calcd for $C_{26}H_{36}O_6N_2$ (472.59): C, 66.08; H, 7.68; N, 5.93. Found: C, 65.91; H, 7.61; N, 6.12.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/tetrahydrofuran/methanol (5:3:2)	0.53	Homogeneous

2,2'-(4,4'-Biphenylene)bis[2-methoxy-4-(2-bromoethyl)-morpholine] (4): - Intermediate 3 (10 g, 21.2 mmol) was dissolved in methylene bromide (224 mL) containing bromoform (32 g, 126.6 mmol); the solution was blanketed with nitrogen and cooled to -30°C. Hexamethylphosphorous triamide (10.4 g, 63.7 mmol) was added dropwise. After the addition was completed, the mixture was stirred at -30°C for 1 h and at room temperature for 5 h; then, it was stored in a freezer overnight. Next day, the

mixture was washed with cold, 0.25% aqueous NaOH solution (1 x 220 mL) and then with water (3 x 220 mL); it was dried ($MgSO_4$) and concentrated to dryness. The residual solid was slurried with petroleum ether (220 mL) to give a beige powder (13 g). This material was purified by chromatography over silica gel (120 g) eluting with 1:1 methylene chloride/ether. The chromatographed compound was recrystallized from a mixture of tetrahydrofuran and petroleum ether to give 9.0 g (71%) of product, mp 156.5-157°C.

The reaction was repeated, starting with 25.7 g of intermediate 3, and gave 22 g of product, mp 156-157°C.

The combined product (31 g) was recrystallized from a mixture of tetrahydrofuran (15 mL/g) and petroleum ether (20 mL/g) to give pure intermediate 4, 29 g (64%), mp 156.5-157°C; NMR ($CDCl_3$) δ 2.00-3.23 (m, 12 H), 3.10 (s, 6 H), 3.27-3.67 (m, 4 H), 3.80-4.37 (m, 4 H), 7.56 (s, 8 H).

Anal. Calcd for $C_{24}H_{34}Br_2N_2O_4$ (598.39): C, 52.19; H, 5.73; Br, 26.71; N, 4.68. Found: C, 52.39; H, 5.94; Br, 26.59; N, 4.48.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (7:3)	0.53	Slight tailing

2,2'-(4,4'-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide (5): - Intermediate 4 (5.0 g, 8.36 mmol) was added to 48% hydrobromic acid (200 mL) and the mixture was stirred at room temperature overnight. The solvent was removed at room temperature and reduced pressure to give 6.8 g of crude product, a light-beige solid. Additional intermediate 4 (23 g, 38.4 mmol) was treated in a similar manner and gave 28.8 g of crude product. The combined solid (34.6 g) was recrystallized from a mixture of water, acetonitrile, and ether to give 17.2 g (51%) of pure title compound, a white crystalline solid, mp > 300°C (compounds turns black at 185°C and does not melt below 300°C). NMR (D_2O) δ 3.05-5.60 (m, 20 H), 7.78 (s, 8 H).

Anal. Calcd for $C_{24}H_{32}Br_4N_2O_4$ (732.18): C, 39.37; H, 4.41; Br, 43.66; N, 3.83. Found: C, 39.51; H, 4.52; Br, 43.45; N,4.06.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (7:3)	0.17	Slight tailing

4.2 3-(Diisopropylphosphato)phenyltrimethylammonium iodide

The synthesis sequence to the title compound is shown in Chart No. 2.

Diisopropyl phosphorochloridate (1): - A solution of isopropanol (90.15 g, 1.5 mol) in dry benzene (150 mL) was cooled to 5°C and treated dropwise with a solution of phosphorus trichloride (68.67 g, 0.5 mol) in dry benzene (150 mL) while maintaining the temperature at 7-10°C. After the addition was completed, the mixture was stirred at 7-10°C for 20 min, and a solution of sulfuryl chloride (67.49 g, 0.5 mol) in dry benzene (150 mL) was added dropwise while the temperature was maintained at 7-10°C. After the addition was completed, the solvent and low boilers were removed at room temperature and reduced pressure, and the residual liquid was distilled to give 92.5 g (92%) of the title compound, a colorless, clear liquid; bp 70-71°C/4 mmHg; lit. bp 48°C/1 mmHg (19); NMR ($CDCl_3$) δ 1.45 (d, 12 H, J=6 Hz), 4.43-5.17 (m, 2 H).

Diisopropyl 3-dimethylaminophenyl phosphate (2): - Sodium hydride (60% in mineral oil, 8.6 g, 0.215 mol) was suspended in ether (250 mL). The mixture was blanketed with nitrogen and cooled in an ice bath. A solution of 3-dimethylaminophenol (29.5 g, 0.215 mol) in ether (300 mL) was added; this was followed, after 20 min, by a solution of diisopropyl phosphorochloridate (43.2 g, 0.215 mol) in ether (300 mL). The cooled (ice bath) mixture was stirred for an additional 2 h; was washed successively with water (1 L), 0.5 N sodium hydroxide solution (2 x 500 mL) and water (3 x 500 mL); and was extracted with 1 N hydrochloric acid (2 x 500 mL). The combined acid extract was washed with ether (500 mL), basified to pH 10 with 50% aqueous sodium hydroxide, and extracted with methylene chloride (1 x 500 mL, 1 x 250 mL). The methylene chloride extracts were combined, washed with water (2 x 500 mL), dried ($MgSO_4$), and concentrated at reduced pressure (aspirator, water bath) to give 59 g (91%) of the title compound, a clear, light-brown oil; NMR ($CDCl_3$) δ 1.33 (d, 6 H, J=6 Hz), 1.38 (d, 6 H, J=6 Hz), 2.93 (s, 6 H), 4.43-5.06 (m, 2 H), 6.20-6.70 (m, 3 H), 6.83-7.37 (m, 1 H). This material was used as such in the next step.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ethyl ether (7:3)	0.55	Homogeneous

3-(Diisopropylphosphato)phenyltrimethylammonium iodide (3): - A mixture of diisopropyl 3-dimethylaminophenyl phosphate (25 g, 0.083 mol), methyl iodide (50 mL) and acetonitrile (25 mL) was stirred at room temperature for 22 h. The solvent and excess methyl iodide were removed (aspirator) to give crude product, a light-yellow solid. This material was slurried with n-hexane (300 mL), then recrystallized twice from ethyl acetate containing some acetonitrile to give 32.8 g (89%) of pure product as white crystals, mp 102-104°C; NMR ($CDCl_3$) δ 1.38 (d, 6 H, J=6 Hz), 1.40 (d, 6 H, J=6 Hz), 4.06 (s, 9 H), 4.43-5.13 (m, 2 H), 7.20-7.87 (m, 3 H), 7.87-8.23 (m, 1 H).

Anal. Calcd. for $C_{15}H_{27}INO_4P$ (443.27): C, 40.65; H, 6.14; I, 28.63; N, 3.16; P, 6.99. Found: C, 40.65; H, 6.12; I, 28.62; N, 3.34; P, 6.90.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/acetonitrile (1:1)	0.19	Homogeneous

4.3 4-Nitrophenyl dibutylphosphinate

The synthesis sequence to the title compound is shown in Chart No. 3.

Dibutylphosphinic acid (1): - A solution of diethyl phosphite (186.4 g, 1.35 mol) in anhydrous ether (160 mL) was added dropwise over a 75 min period to n-butylmagnesium bromide prepared from n-butyl bromide (616.6 g, 4.50 mol) and magnesium (109.4 g, 4.5 mol) in ether (985 mL). The mixture was heated at reflux for 2 h, then stirred at ambient temperature overnight. Ice water (975 mL) was added and the ether was removed by warming. The mixture was acidified with 6 N hydrochloric acid to pH 2 and was treated dropwise with bromine (239.7 g, 1.50 mol). After stirring for 30 min, the mixture was extracted with toluene (5 x 300 mL). The combined extract was washed with sodium thiosulfate and with water; it was dried ($MgSO_4$) and concentrated (aspirator) to dryness to give 202.6 g of a yellow solid. This material was dissolved in a mixture of petroleum ether (200 mL) and ligroin (200 mL) at 55C. The solution was filtered and the filtrate was stirred and cooled in an ice bath for 2 h. The solid was collected by filtration and washed with cold petroleum ether (100 mL) to give 134.7 g product, mp 66.5-68C.

Concentration and cooling of the mother liquor gave 37 g of second-crop product, mp 64-66°C. The combined material (171.2 g) was dissolved in a mixture of petroleum ether (175 mL) and ligroin (175 mL) at 55°C. The solution was filtered and cooled with stirring in an ice bath for 1 h. The solid was collected by filtration, was washed with cold petroleum ether, and was air-dried to give 150.9 g (63%) of pure product, mp. 66.5-68°C; lit. mp 71°C (20).

Dibutylphosphinic chloride (2): - Phosphorus pentachloride (35.1 g, 0.168 mol) was added to a solution of dibutylphosphinic acid (30 g, 0.168 mol) in toluene (60 mL). After the exotherm subsided, the mixture was heated at reflux for 2 h, cooled and concentrated (aspirator) to an oil. The oil was distilled twice to yield 30.4 g (92%) of pure acid chloride, bp 90°C/0.5 mmHg; lit. bp 163-166°C/22 mmHg (9), bp 143-145°C/16 mmHg (20).

4-Nitrophenyl dibutylphosphinate (3): - A solution of dibutylphosphinic chloride (30 g, 0.153 mol) in methylene chloride (30 mL) was added dropwise under nitrogen, to a solution of p-nitrophenol (21.28 g, 0.153 mol) and triethylamine (15.48 g, 0.153 mol) in methylene chloride (280 mL) with ice-cooling. The mixture was stirred at room temperature for 16 h, then heated at reflux for 1 h. After cooling to room temperature, the mixture was washed with cold 1 N hydrochloric acid (150 mL), cold saturated aqueous sodium bicarbonate (150 mL), brine (2 x 150 mL) and dried ($MgSO_4$). The solvent was removed (aspirator) to give a light yellow liquid which was purified by column chromatography (acidic alumina, 410 g) eluting with methylene chloride. The product-containing fractions were combined, dried ($MgSO_4$) and stripped to give a light yellow oil, 39.7 g (87%). Additional product, 10 g (22% yield) was prepared by the same procedure starting with 30 g of dibutylphosphinic chloride.

The combined product (39.7 g and 10 g) was purified further by column chromatography (acidic alumina, 410 g) eluting with methylene chloride. The product-containing fractions were combined, dried ($MgSO_4$) and concentrated to give a light yellow oil. The oil was dissolved in anhydrous ether (200 mL). The solution was treated with charcoal (4 g) and filtered through celite. The filtrate was concentrated at aspirator pressure and residual solvent was removed at 25°C/0.1 mmHg (18 h) to give 34.5 g (38%) of the title compound, a light yellow liquid. NMR ($CDCl_3$) δ 0.40-1.13 (m, 6 H), 1.13-2.33 (m, 12 H), 7.40 (d, 2 H, J = 9.5 Hz), 8.17 (d, 2H, J = 9.5 Hz).

Anal. Calcd for $C_{14}H_{22}NO_4P$ (299.31): C, 56.18; H, 7.41; N, 4.68; P, 10.35. Found: C, 56.05; H, 7.62; N, 4.78; P, 10.50.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ethyl acetate (4:1)	0.38	Trace of faster running impurity (UV negative)

4.4 4-Nitrophenyl 3-(benzoyl)propanesulfonate

The reaction sequence to the title compound is shown in Chart No. 4.

4-Bromo-1-phenyl-1-butanone (1): - A 250-mL three-necked flask equipped with a magnetic stirring bar, a septum, and a dropping funnel with a calcium chloride drying tube was charged with dry benzene (17.5 g, 0.22 mol). The flask was placed in an ice bath and a solution of aluminum chloride (15 g, 0.11 mol) and γ-bromobutyryl chloride (20 g, 0.11 mol) in methylene chloride (37.5 mL) was added dropwise. The mixture was stirred for 20 min then quenched by the addition of 0.5 N hydrochloric acid (100 mL). The layers were separated and the water layer was extracted with methylene chloride (2 x 50 mL). The combined organic layer was washed with water (5 x 100 mL), dried ($MgSO_4$) and concentrated (aspirator) to a clear, pale-yellow liquid which solidified in the freezer. The solid (23.5 g) was recrystallized from n-hexane (250 mL) to give 19.5 g (78%) of pure product as white plates, mp 33.5-35°C; lit. mp 34-35°C (10).

Sodium 3-(benzoyl)propanesulfonate (2): - A 1-L three-necked flask equipped with a dropping funnel, a reflux condenser, and a magnetic stirring bar was charged with sodium sulfite (11.1 g, 88 mmol) and water (150 mL). The solution was warmed to about 80°C and a solution of 4-bromo-1-phenyl-1-butanone (20 g, 88 mmol) in ethanol (150 mL) was added dropwise. The clear solution was heated at reflux for 5 h. Most of the ethanol was removed at reduced pressure (aspirator), and the residual aqueous solution was washed with ether (1 x 150 mL). The water was removed at reduced pressure to give a white solid (28.8 g), a mixture of sodium 3-benzoylpropanesulfonate (2), and sodium bromide. This mixture was used as such in the next step.

3-(Benzoyl)propanesulfonyl chloride (3): - A 100 mL round-bottomed flask equipped with a magnetic stirring bar and septum was charged with crude sodium 3-benzoylpropanesulfonate (5 g). The flask was flushed with nitrogen, and dry dimethylformamide (25 mL) was added through a syringe. The white suspension was cooled to -20°C and treated with a solution of thionyl chloride (9.5 g) in dry dimethylformamide (25 mL). The mixture was stirred at -20°C for 20 min, then ice water (50 mL) and methylene chloride (100 mL) were added. The layers were separated; the methylene chloride layer was washed successively

with cold solutions of brine (100 mL), sodium bicarbonate (2 x 100 mL), and brine (1 x 100 mL); then, it was dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue was chromatographed over silica gel (50 g), with methylene chloride as the eluent. The product-containing fractions were concentrated, and the residual solid was recrystallized from n-hexane to give white needles, 640 mg, mp 74-75°C.

The reaction was repeated using 59.6 g of crude compound 2 and gave 6.56 g of product. Both batches of the acid chloride were combined and recrystallized from n-hexane to give pure product 3, 6.9 g, mp 74-75°C; NMR ($CDCl_3$) δ 2.46 (m, 2 H, CH_2-C<u>H</u>$_2$-CH_2-), 3.26 (t, 2 H, J = 7 Hz, CO-C<u>H</u>$_2$-), 3.87 (t, 2 H, J = 7 Hz, C<u>H</u>$_2$-S), 7.20-7.63 (m, 3 H, Ar<u>H</u>), 7.77-810 (m, 2 H, Ar<u>H</u>).

<u>Anal</u>. Calcd for $C_{10}H_{11}ClO_3S$ (246.71): C, 48.68; H, 4.50; Cl, 14.37; S, 13.00. Found: C, 48.73; H, 4.63; Cl, 14.16; S, 13.04.

<u>Thin-Layer Chromatography</u>

<u>Eluent</u>	<u>Rf</u>	<u>Comment</u>
Methylene chloride	0.48	Slight tailing

<u>4-Nitrophenyl 3-(benzoyl)propanesulfonate (4):</u> - A solution of 3-(benzoyl)propanesulfonyl chloride (6.8 g, 27.6 mmol) in methylene chloride (200 mL) was added, under a nitrogen atmosphere, to a cooled mixture of 4-nitrophenol (3.83 g, 27.6 mmol) and triethylamine (2.93 g, 28.9 mmol) in methylene chloride (50 mL). The mixture was stirred at room temperature for 30 min, was washed with ice water (100 mL), and was dried ($MgSO_4$). The solution was treated with charcoal, was filtered, and was concentrated to dryness (aspirator). The residual solid was recrystallized from a mixture of acetonitrile/ether/n-hexane to yield 7.9 g (82%) of pure title compound as white needles, mp 113.5-114.5°C; NMR ($CDCl_3$) δ 2.44 (m, 2 H, CH_2-C<u>H</u>$_2$-CH_2), 3.42 (m, 4 H, C<u>H</u>$_2$-CH_2-C<u>H</u>$_2$), 7.20-7.70 (m, 5 H, Ar<u>H</u>), 7.80-8.14 (m, 2 H, COAr<u>H</u>), 8.33 (d, 2 H, NO_2Ar<u>H</u>, J=9Hz).

<u>Anal</u>. Calcd for $C_{16}H_{15}NO_6S$ (349.37): C, 55.01; H, 4.33; N, 4.01; S, 9.18. Found: C, 54.96; H, 4.45; N, 3.98; S, 8.97.

<u>Thin-Layer Chromatography</u>

<u>Eluent</u>	<u>Rf</u>	<u>Comment</u>
Methylene chloride	0.19	Homogeneous

4.5 1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxyheptanoyl)]amino-ethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride

The synthesis sequence to the title compound is shown in Chart No. 5.

Suberic acid monobenzyl ester (1): - Suberoyl chloride (24.7 g, 0.117 mol) was dissolved in dry tetrahydrofuran (120 mL), and the solution was blanketed with nitrogen and cooled in an ice-water bath. A mixture of benzyl alcohol (12.1 mL, 0.117 mol) and triethylamine (19.5 mL, 0.14 mol) in dry tetrahydrofuran (60 mL) was added dropwise over 1 h. The mixture was stirred at 25°C for 17 h, diluted with water (100 mL), and stirred for 1 h. The mixture was concentrated (aspirator) to a volume of ca. 150 mL, then treated with sodium hydroxide (0.5 N, ca. 400 mL) until it was basic. The mixture was extracted with ethyl acetate (300 mL), and the extract, in turn, was backwashed with sodium hydroxide (0.5 N, 200 mL). The aqueous layers were combined, acidified with acetic acid, and extracted with ethyl acetate (3 x 250 mL). The extract was dried ($MgSO_4$) and concentrated (aspirator, steam bath) to ca. 50 mL. Hexane (200 mL) was added and the solution was cooled to -10°C for 1 h. A precipitate was collected and identified as suberic acid. The filtrate was concentrated (aspirator) to dryness, and the residue was dried at 25°C/0.1 mmHg to give 11 g of a wax. The wax was crystallized from hexane/ethyl acetate (80 mL:8 mL). The resulting solid was triturated with methylene chloride (20 mL) to leave behind more of the poorly soluble suberic acid, which was removed by filtration. Hexane (60 mL) and ethyl acetate (6 mL) were added to the filtrate and the mixture was heated until the methylene chloride distilled out; then it was cooled to -10°C for 17 h. The resulting precipitate was collected, rinsed with hexane, and dried at 25°C/0.1 mmHg to give 7.9 g (26%) of the title ester, a white powder, mp 31-33°C. An earlier pilot run gave white crystals, mp 33-34°C. ^{1}HNMR ($CDCl_3$) δ 1.2-2.0 (m, 8 H), 2.2-2.6 (m, 4 H), 5.10 (s, 2 H), 7.33 (s, 5 H), 10.80 (br s, 1 H).

Anal. Calcd for $C_{15}H_{20}O_4$ (244.31): C, 68.16; H, 7.63. Found: C, 68.25; H, 7.73.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methylene chloride/methanol	0.43	Homogeneous

1,3-Dimethyl-3-[2-[N-methyl-N-(7-benzylcarboxyheptanoyl]-aminoethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole (4): - Suberic acid monobenzyl ester (2.5 g, 9.5 mol) and thionyl chloride (4 mL) were dissolved in toluene (30 mL), and the solution was warmed to 80°C for 45 min. The solution was concentrated (aspirator) to a gum, which was dried at 25°C/0.1 mmHg for 1 h. Dry tetrahydrofuran (50 mL) was added and the solution was cooled in an ice-water bath. Physostigmine (1.65 g, 6.0 mmol) was added in one portion; this was followed by a solution of sodium borohydride (500 mg) in ethanol (10 mL), added over a 15-min period. After 45 min, the suspension was warmed to 25°C for 15 min, then concentrated (aspirator/25°C) to a thick oil. The oil was dissolved in ether (100 mL), and the solution was washed with ammonium hydroxide (5%, 75 mL). The aqueous layer was backwashed with ether (100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (aspirator/25°C) to give 4 g of crude product. This material was combined with 3.6 g of crude product from a similar run and was applied onto a column of silica gel (100 g). The column was eluted with methylene chloride followed by methylene chloride/2% methanol and methylene chloride/5% methanol. The appropriate fractions were combined and concentrated (0-25°C/aspirator, then 0.1 mmHg) to give 4.6 g (73%) of the title compound, a pale-yellow oil. This product was used directly in the next step, due to its poor stability.

Thin-Layer Chromatography Analtech Silica Gel GF

Eluent	Rf	Comment
Methylene chloride/methanol (9:1)	0.77	Homogeneous

1,3-Dimethyl-3-[2-[N-methyl-N-(7-carboxyheptanoyl)]-aminoethyl]-5-(N-methylcarbamoyloxy)-2,3-dihydroindole hydrochloride (5): - The precursor benzyl ester (4.6 g, 8.8 mmol) was dissolved in anhydrous reagent ethanol (250 mL) in a Parr hydrogenation flask, and was hydrogenated at 50 psig with palladium-black catalyst (ca. 100 mg) for 20 h. The suspension was filtered, and the filtrate was concentrated (25°C/0.1 mmHg) to give 3.8 g of a gold oil. The oil was dissolved in a mixture of ether (250 mL) and methanol (7 mL). A small amount of suspended solid was removed by filtration through a sintered glass funnel. Ethereal hydrogen chloride (1.17 M, 75 mL) was added to the solution, which resulted in the formation of a gum. The solvent was decanted and the gum was dried (25°C/0.1 mmHg) to yield 3.5 g (85%) of an extremely hygroscopic, waxy powder. The solid was dried further over phosphorus pentoxide (25°C, 0.1 mmHg, 17 h). Combustion analysis of this material gave acceptable values after drying by the analyst (5.4% weight loss). High-resolution NMR suggested contamination with solvent. A-1 g sample of the material was dissolved in water (15 mL) and lyophillized to a glass, mp 75-80°C (turns to foam, which, in turn, slowly melts at

ca. 160°C). Analysis of this sample gave acceptable values as a 0.4 hydrate and as anhydrous when dried further by the analyst. Both samples were shipped to Edgewood. The complex ^{1}H NMR was consistent with the structure. ^{1}H NMR (D_2O) δ 1.22-1.47 (m, 11 H), 1.9-2.30 (m, 4 H), 2.34 (t, 2 H), 2.79 (s, 3 H), 2.94 (s, 3 H), 3.15-3.35 (m, 5 H), 3.83 (d, 1 H), 4.10 (d, 1 H), 7.22-7.32 (m, 2 H), 7.54-7.61 (m, 1 H).

Anal. Calcd for $C_{23}H_{36}ClN_3O_5$ (470.01): C, 58.78; H, 7.72; Cl, 7.54; N, 8.94. Found (first sample after drying at 120°C; 5.4% wt loss): C, 58.59; H, 7.92; Cl, 7.46; N, 8.74. Found (second sample after drying at 120°C, 1.5% wt loss): C, 58.79; H, 7.76; N, 8.68.

Calcd. for $C_{23}H_{36}ClN_3O_5 \cdot 0.4H_2O$: C, 57.89; H, 7.77; N, 8.81. Found (second sample undried): C, 57.85; H, 7.85; N, 8.85.

Thin-Layer Chromatography Analtech silica gel GF

Eluent	Rf	Comment
Methylene chloride/methanol (9:1)	0.27	Major
	0.70	Trace

4.6 5-Methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one

The synthesis sequence to the title commpound is shown in Chart No. 6.

(2-Methoxyphenyl)hydrazine (1): - A solution of sodium nitrite (35 g, 0.507 mol) in water (75 mL) was added dropwise to a slurry of o-anisidine (61.5 g, 0.5 mol) in concentrated hydrochloric acid. The dark brown suspension was stirred at 0°C for 40 min and then cooled to -25°C. A solution of stannous chloride (330 g, 1.74 mol) in concentrated hydrochloric acid (400 mL) was added dropwise. The mixture was stirred at -25°C for 3.5 h, then stored in a cold place (0 to -10°C) overnight. The precipitated stannous chloride-hydrazine complex was collected by filtration, sucked as dry as possible and decomposed without delay by stirring it into cold potassium hydroxide solution (1000 mL 25% w/v) covered with ether (1000 mL). After the mixture was shaken, the ethereal layer was separated and the aqueous layer was extracted with ether (2 x 1000 mL). The combined ether layer was washed with brine (1000 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the yellow residual solid was triturated with n-hexane (1 x 800 mL, 1 x 500 mL) to give a tan powder (48.8 g, 71%). The compound is unstable at room temperature and, therefore, it was used immediately in the next step.

Methyl 3-(2-methoxyphenyl)carbazinate (2): - Methyl chloroformate (34.4 g, 0.364 mol) was added, under nitrogen, to a cold (ice bath) solution of 2-methoxyphenylhydrazine (1) (48 g, 0.347 mol) and diisopropylethylamine (49.5 g, 0.382 mol) in tetrahydrofuran (600 mL). The mixture was stirred, with cooling for 30 min; then, it was stored in a freezer overnight. Next day, the mixture was diluted with water (300 mL) and extracted with ether (3 x 500 mL). The combined ether extract was washed with brine (2 x 500 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a light-grey solid (66.8 g). This material was chromatographed over silica gel (300 g, methylene chloride/ether, 4:1) and was recrystallized from benzene/hexane to give creamy fine crystals, 62.1 g (91%), mp 99-101°C.

Additional material (51 g, mp 99-101°C) was prepared from compound 1 (40 g) in a similar manner.

The combined product (62 g + 51 g) was recrystallized from benzene/n-hexane (400 mL:800 mL) to give fine white crystals, 110 g (88%), mp 99-101°C; lit. mp 102°C (12). NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.83 (s, 3 H), 5.80-6.40 (br m, 1 H), 6.67 (br s, 1 H), 6.87 (s, 4 H).

Anal. Calcd for $C_9H_{12}N_2O_3$ (196.21): C, 55.09; H, 6.17; N, 14.28. Found: C, 55.07; H, 6.32; N, 14.35.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (4:1)	0.70	Homogeneous

5-Methoxy-3-(2-methoxyphenyl)-1,3,4-oxadiazol-2(3H)-one (4): - A solution of methyl 3-(2-methoxyphenyl)carbazinate (2) (40 g, 0.204 mol) in benzene (400 mL) was added to a toluene solution of phosgene (106 mL, 0.204 mol). The solution was stirred at room temperature for 24 h, cooled in an ice bath, and treated with a mixture of methanol (200 mL) and diisopropylethylamine (79.1 g, 0.612 mol). The mixture was heated at reflux for 50 min, cooled, and concentrated (aspirator) to dryness. Water (250 mL) was added to the residue and the mixture was extracted with ether (3 x 500 mL). The combined ether extract was washed with water (2 x 500 mL), 1 N HCl (250 mL), and water (3 x 250 mL), and then dried ($MgSO_4$). The solvent was removed (aspirator), and the residual solid was recrystallized from ethanol/n-hexane (300 mL:1200 mL) to give pure product, 30.8 g (68%), mp 77-78°C; lit. mp 79°C (13). NMR ($CDCl_3$) δ 3.90 (s, 3 H), 4.07 (s, 3 H), 6.70-7.20 (m, 2 H), 7.20-7.60 (m, 2 H).

Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222.20): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.13; H, 4.44; N, 12.57.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (9:1)	0.67	Homogeneous

4.7 3-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one

The synthesis sequence to the title compound is shown in Chart No. 7.

1-(2-Methallyloxy)-2-nitrobenzene (1): - A 2-L three-necked flask equipped with a reflux condenser, a mechanical stirrer, and a dropping funnel was charged with acetone (400 mL), water (500 mL), o-nitrophenol (409 g, 2.5 mol, moist-solid containing 15% H_2O), and sodium hydroxide (105 g, 2.6 mol). The mixture was stirred and warmed until it became homogeneous. Initially, 113 g of methallyl chloride was added batchwise to the mixture; this was followed by an additional 113 g added dropwise. A total of 226 g (2.5 mol) of methallyl chloride was used. The mixture was stirred at room temperature for 2 h, then heated at gentle reflux overnight. After cooling, the upper organic layer was separated from the lower aqueous layer. The latter was diluted with water (500 mL) and extracted with cyclohexane (2 x 100 mL). The combined organic layer was washed with brine (5 x 200 mL), dried (K_2CO_3), and filtered. The filtrate was concentrated (aspirator, steam bath), and the residual oil was distilled to give 266.3 g (55%) of the title compound, a yellow liquid, bp 130°C/0.9 mmHg; lit. bp 99-100°C/0.42 mmHg (14). NMR ($CDCl_3$) δ, 1.85 (br s, 3 H), 4.55 (br s, 2 H), 5.00 (br s, 1 H), 5.13 (br s, 1 H), 6.67-7.13 (m, 2 H), 7.13-8.07 (m, 2 H).

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/benzene (7:3)	0.15	A trace of slower impurity

6-(2-Methallyl)-2-nitrophenol (2): - A 500-mL three-necked flask equipped with a magnetic stirring bar, a septum, a thermometer, and a reflux condenser was charged with 1-(2-methallyloxy)-2-nitrobenzene (50 g, 0.259 mol). After it was flushed with nitrogen, the flask was placed in an oil bath and preheated to 190°C. When the temperature of the mixture in the flask reached about 185°C, a very vigorous exothermic reaction took place and the temperature rose to 256°C. The temperature of the contents dropped slowly to 198°C, and was maintained at 198°C for 10 min. After cooling, the mixture was dissolved in minimum amount of chloroform and chromatographed over silica gel (700 g, hexane/ether, 4:1 as eluent) to give 24.2 g (48%) of pure product

and 9.5 g of a mixture of product and starting material.

A portion of the chromatographed material was sublimed (oil bath, 85°C/0.5 mmHg) to give analytically pure product, bright-yellow prisms, mp 50-51.5°C; lit. mp 51-51.5°C (14) NMR ($CDCl_3$) δ 1.77 (s, 3 H), 3.43 (s, 2 H), 4.70 (br s, 1 H), 4.87 (br s, 1 H), 6.90 (t, 1 H, J=8 Hz), 7.40 (m, 1 H), 7.98 (dd, 1 H, J=1.5 Hz, 8 Hz), 10.93 (s, 1 H).

Anal. Calcd for $C_{10}H_{11}NO_3$ (193.20): C, 62.16; H, 5.73; N, 7.25. Found: C, 62.22; H, 5.89; N, 7.40.

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/ether (4:1)	0.62	Homogeneous

In this manner, additional compound 1 (183.5 g) was processed to give 87.4 g (48%) of pure product 2 and 24.7 g of impure material.

2,3-Dihydro-2,2-dimethyl-7-nitrobenzofuran (3): - A mixture of 6-(2-methallyl)-2-nitrophenol (6 g, 31 mmol), acetic acid (40 mL), and 48% hydrobromic acid (12 mL) was heated at reflux for 1 h. After cooling, the contents were poured onto ice water (250 mL) and the mixture was extracted with ether (3 x 250 mL). The combined ether extract was washed successively with water (5 x 300 mL), with saturated aqueous $NaHCO_3$ (2 x 300 mL), and again with water (2 x 300 mL). The solution was dried ($MgSO_4$), treated with charcoal, filtered, and concentrated to dryness. The residual light-yellow solid (5.4 g) was recrystallized from n-hexane (containing some ether) to give 4.6 g (76%) of pure product, a creamy powder, mp 64.5-66°C; lit. mp 65-66°C (14). NMR ($CDCl_3$) δ 1.57 (s, 6 H), 3.10 (br s, 2H), 6.78 (br t, 1 H, J=8 Hz), 7.33 (m, 1 H), 7.83 (br d, 1 H, J=8 Hz).

Anal. Calcd for $C_{10}H_{11}NO_3$ (193.20): C, 62.16; H, 5.74; N, 7.25. Found: C, 61.93; H, 5.81; N, 7.45.

Thin-Layer Chromatography

Eluent	Rf	Comment
Hexane/benzene/acetonitrile (6:3:1)	0.47	Homogeneous

In this manner, an additional 138.7 g of compound 2 was processed to yield 109 g (79%) of product 3.

7-Amino-2,3-dihydro-2,2-dimethylbenzofuran (4): - Palladium-on-activated carbon (10%, 0.15 g) was added to a solution of 2,3-dihydro-2,2-dimethyl-7-nitrobenzofuran (4 g, 20.7 mmol) in tetrahydrofuran (18 mL) and the mixture was hydrogenated at 50 psig in a Parr apparatus for 30 min. After filtration through celite, the solvent was removed in vacuo to give 3.4 g (100%) of the title compound, a tan liquid; NMR ($CDCl_3$) δ 1.48 (s, 6 H), 2.98 (br s, 2 H), 3.50 (br s, 2 H), 6.60 (m, 3 H).

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/benzene/acetonitrile (6:3:1)	0.40	Homogeneous

In this manner, additional compound 3 (107 g) was hydrogenated to give 90.5 g (100%) of product 4.

2,3-Dihydro-2,2-dimethyl-7-hydrazinobenzofuran (5): - A solution of sodium nitrite (24.7 g, 0.36 mol) in water (50.8 mL) was added dropwise to a slurry of 7-amino-2,3-dihydro-2,2-dimethylbenzofuran (56.9 g, 0.35 mol) in concentrated HCl (425 mL) at 0°C. The dark brown suspension was stirred at 0°C for 10 min and then chilled to -25°C. A solution of stannous chloride (228 g, 1.2 mol) in concentrated HCl (274 mL) was added dropwise. The yellow suspension was stirred at -25°C for 3 h, then stored in a refrigerator overnight. The mixture was suction-filtered and the solid was sucked as dry as possible. The solid stannous chloride/hydrazine complex was decomposed without delay by stirring it into a cold potassium hydroxide solution (800 mL, 25% w/v) covered with ether (1000 mL). After the mixture was shaken, the ether layer was separated and the aqueous layer was extracted with ether (2 x 1000 mL). The combined ether extract was washed with brine (1000 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give 53.7 g (87%) of the title compound, a thick brown oil. The compound is unstable at room temperature and was used immediately in the next step.

Using the same procedure, additional compound 4 (33.6 g) was converted to 30.8 g (84%) of product 5.

Methyl 2-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)-hydrazinecarboxylate (6): - Methyl chloroformate (29.8 g, 0.315 mol) was added dropwise to a cold (ice bath) mixture of 2,3-dihydro-2,2-dimethyl-7-hydrazinobenzofuran (53.7 g, 0.30 mol), diisopropylethylamine (42.8 g, 0.33 mol) and tetrahydrofuran (500 mL). After the addition was completed, the cooled mixture was stirred for 30 min and the solvent was removed at reduced pressure. The residue was poured into water (500 mL), and the mixture was extracted with ether (1 x 1000 mL, 1 x 500 mL, 1 x 300 mL). The combined ether extract was washed with water (3 x

500 mL) and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed over silica gel (400 g, methylene chloride/ether, 4:1) to give 62.4 g of a light-yellow solid.

In the same manner, additional compound 5 (30.8 g) was processed to give 36.7 g of solid.

The combined solid (99.1 g) was recrystallized from a mixture of benzene (300 mL) and n-hexane (2.5 L) to give 82.6 g (74%) of pure product as white crystals, mp 100-101°C; lit. mp 101-102°C (15). NMR ($CDCl_3$) δ 1.47 (s, 6 H), 2.98 (s, 2 H), 3.70 (s, 3 H), 5.80 (br s, 1 H), 6.67 (s, 4 H).

Anal. Calcd for $C_{12}H_{16}N_2O_3$ (236.27): C, 61.00; H, 6.83; N, 11.86. Found: C, 61.27; H, 6.86; N, 11.89.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (4:1)	0.73	Homogeneous

3-(2,3-Dihydro-2,2-dimethylbenzofuran-7-yl)-5-methoxy-1,3,4-oxadiazol-2(3H)-one (8): - A toluene solution of phosgene (88 mL, 0.169 mol) was added to a solution of methyl 2-(2,3-dihydro-2,2-dimethylbenzofuran-7-yl)hydrazinecarboxylate (40 g, 0.169 mol) in benzene (600 mL). The turbid solution was stirred at room temperature for 3 h, warmed (oil bath, 55°C) until clear, then stored at room temperature for 24 h. The solution was cooled in an ice bath, treated with a mixture of methanol (200 mL) and N,N-diisopropylethylamine (65.5 g, 0.507 mol), and heated at reflux for 50 min. The solvents were removed at reduced pressure and the residue was poured into water (250 mL). The mixture was extracted witn ether (3 x 500 mL) and the combined extract was washed with water (2 x 500 mL), 1 N HCl (250 mL), and water (3 x 250 mL). The ether was dried ($MgSO_4$), treated with charcoal, and filtered. The solvent was removed (aspirator), and the residue was dissolved in warm petroleum ether (900 mL) containing sufficient ethyl ether to effect solution. The solution was decanted from a small amount of insoluble oil at the bottom, was seeded with a crystal of the product, and was stored in the refrigerator overnight. The solid was collected and dried to give 29 g (66%) of pure title compound, mp 56-57°C; lit. mp 52-54°C (15). NMR ($CDCl_3$) δ 1.52 (s, 6 H), 3.07 (br s, 2 H), 4.05 (s, 3 H), 6.50-7.30 (m, 3 H).

Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.27): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.57; H, 5.09; N, 10.75.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (9:1)	0.72	Homogeneous

4.8 3-Pyridinealdoxime methiodide

Methyl iodide (36.6 g, 258 mmol) was added to a solution of 3-pyridinealdoxime (10.5 g, 86 mmol) in acetone (400 mL). The mixture was stirred at room temperature overnight and filtered. The solid was dried to give 17.1 g of crude product, mp 153-155°C.

Additional material (12.6 g) with the same melting point was prepared in a similar manner.

The combined crude product was recrystallized from methanol/ethyl acetate (80 mL:250 mL) to give 27.3 g of pure product as light-yellow crystals, mp 155-157°C; lit. mp 154-155°C (21). NMR (CD_3OD) δ 4.5 (s, 3 H, N-C$\underline{H}_3$), 4.78 (br s, 1 H, C$\underline{H}$=N), 7.8-9.12 (m, 4 H, Ar$\underline{H}$).

Anal. Calcd for $C_7H_9IN_2O$ (264.06): C, 31.84; H, 3.43; I, 48.06; N, 10.61. Found: C, 32.02; H, 3.64; I, 48.11; N, 10.64.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/acetonitrile (1:1)	0.08	Streaks

4.9 [1-(Nonafluorobutyl)pentylidene]hydroxylamine

The synthesis sequence to the title compound is shown in Chart No. 8.

1-(Nonafluoro-n-butyl)-1-pentanol (1): - An ether solution of methyllithium (100 mL, 140 mmol) was added dropwise to a mixture of valeraldehyde (11.3 g, 131.2 mmol), perfluorobutyl iodide (50 g, 144.5 mmol), and anhydrous ether (300 mL) at -72°C under nitrogen. After the addition was completed, the clear solution was stirred at -72°C for 30 min, then treated with a mixture of 3 N HCl (500 mL) and ether (300 mL). The layers were separated and the aqueous layer was extracted with ether (300 mL). The organic layers were combined, washed with water (300 mL), and dried ($MgSO_4$). The solvent was removed (aspirator) and the residue was distilled to give 28 g (70%) of the title

compound, a light-pink liquid, bp 95-99°C/6.5 mmHg. NMR ($CDCl_3$) δ 0.40-1.15 (m, 3 H), 1.15-2.12 (m, 6 H), 2.53 (s, 1 H), 4.10 (m, 1 H).

Anal. Calcd for $C_9H_{11}F_9O$ (306.17): C, 35.30; H, 3.62; F, 55.85. Found: C, 35.54; H, 3.75; F, 55.48.

The reaction was repeated using 74 g of perfluorobutyl iodide and gave 39.4 g (67%) of product 1.

1,1,1,2,2,3,3,4,4-Nonafluoro-5-nonanone (2): - A solution of 1-perfluorobutyl-1-pentanol (27.5 g, 0.09 mol) and acetic acid (10.5 mL) in methylene chloride (150 mL) was added dropwise to a cold (ice bath) mixture of pyridinium dichromate (50.3 g, 0.134 mol), powdered molecular sieves (80 g), and methylene chloride (700 mL). After the addition was completed, the mixture was stirred at ambient temperature for 2 h and filtered. The solid was slurried with fresh methylene chloride (300 mL) and filtered. The combined methylene chloride solution was washed with water (3 x 600 mL) and dried ($MgSO_4$). The solvent was removed by distillation (oil bath 45-50°C), and the residue was slurried with ether (300 mL) and filtered. The filtrate was washed successively with cold 1 N HCl (2 x 50 mL), water (50 mL), and saturated aqueous $NaHCO_3$ (50 mL); then it was dried ($MgSO_4$) and treated with charcoal. After filtration, the solvent was removed by distillation; then the residual oil was chromatographed over silica gel (100 g, hexane/ether, 9:1) and distilled to give 16.7 g (61%) of pure product, a colorless, clear liquid, bp 71-73°C/ca. 10 mmHg. NMR ($CDCl_3$) δ 0.50-1.13 (m, 3 H), 1.13-2.17 (m, 4 H), 2.73 (br t, 2 H).

Anal. Calcd for $C_9H_9F_9O$ (304.16): C, 35.54; H, 2.98; F, 56.22. Found: C, 35.54; H, 2.88; F, 55.94.

Thin-Layer Chromatography

Eluent	Rf	Comment
Hexane/ether (9:1)	0.64	Homogeneous

An additional 14.8 g (38%) of compound 2 was prepared in this manner from 38.8 g of alcohol 1.

[1-(Nonafluorobutyl)pentylidene]hydroxylamine (3): - A solution of hydroxylamine hydrochloride (7.41 g, 106.6 mmol) in water (15 mL) was added to a solution of ketone 2 (28.5 g, 93.7 mmol) in ethanol (200 mL). To the resultant clear solution was added a solution of sodium acetate trihydrate (17.1 g, 125.7 mmol) in water (30 mL), and the mixture was heated at reflux for 2 h. After the mixture was cooled, ethanol was removed at reduced pressure (aspirator); then the residue was diluted with

water (100 mL) and extracted with methylene chloride (2 x 100 mL). The combined extract was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and water (100 mL) and was dried ($MgSO_4$). The solvent was removed (aspirator) and the residual liquid was distilled to yield 19.1 g (64%) of pure title compound, a mixture of the syn and anti isomers, bp 71-72°C/0.75 mmHg. NMR ($CDCl_3$) δ 0.50-1.18 (m, 3 H), 1.18-2.00 (m, 4 H), 2.00-2.90 (m, 2 H), 9.28 (br s, 0.3 H, exchangeable with D_2O), 9.66 (br s, 0.7 H exchangeable with D_2O).

Anal. Calcd for $C_9H_{10}F_9NO$ (319.19): C, 33.87; H, 3.16; F, 53.57; N, 4.39. Found: C, 33.82; H, 3.22; F, 53.33; N, 4.41.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/ether (4:1)	0.79	Homogeneous

4.10 N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide

N,N'-Di(3-pyridinyl)urea (1): - A mixture of diphenyl carbonate (84 g, 0.392 mol) and 3-aminopyridine (73.8 g, 0.784 mol) was heated, under nitrogen, in an oil bath (190°C) for 2 h. After cooling, the mixture was slurried with ether (3 x 500 mL) to give a light-tan powder, which was dissolved in ethanol (1200 mL) containing sufficient methylene chloride to effect solution. The solution was treated with charcoal and filtered. The filtrate was diluted with ether (900 mL) to give the title product (55.6 g, 66%) as light-tan crystals, mp 219.5-221.5°C; lit. mp 217-219°C (22). NMR (DMF-d_7) δ 7.08-7.50 (m, 2 H), 7.85-8.33 (m, 4 H), 8.75 (m, 2 H), 9.07 (br s, 2 H).

Anal. Calcd for $C_{11}H_{10}N_4O$ (214.23): C, 61.67; H, 4.71; N, 26.16. Found: C, 61.46; H, 4.79; N, 25.98.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/benzene/methanol (7:2:1)	0.17	Homogeneous

N,N'-Bis(1-methyl-3-pyridinyl)urea diiodide (2): - A suspension of N,N'-di(3-pyridinyl)urea (30 g, 0.14 mol) in methanol (1200 mL) was warmed in an oil bath (50°C bath temperature) to effect solution. Methyl iodide (119 g, 0.84 mol) was added and the solution was heated (50°C oil bath) for 21 h. The precipitated yellow solid was collected and recrystallized from methanol (3200 mL) to give 45 g (65%) of pure product, mp 270-272°C (dec). NMR (DMSO-d_6) δ 4.43 (s, 6 H), 7.98-8.37 (m, 2 H), 8.41-8.91 (m, 4 H), 9.25 (br s, 2 H), 10.26 (br s, 2 H).

Anal. Calcd for $C_{13}H_{16}I_2N_4O$ (498.11): C, 31.35; H, 3.24; I, 50.95; N, 11.25. Found: C, 31.32; H, 2.98; I, 51.03; N, 11.24.

Thin-Layer Chromatography

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (1:1)	0.08	Homogeneous

4.11 1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide

The synthesis sequence to the title compound is shown in Chart No. 9.

1-methyl-2-formylimidazole (1): - A 1-L three-necked flask equipped with a mechanical stirrer and rubber septa was charged with 1-methylimidazole (32.8 g, 400 mmol), tetrahydrofuran (160 mL), and ethyl ether (160 mL). The solution was chilled to -60 to -70°C, and a hexane solution of n-butyllithium (160 mL, 400 mmol) was added dropwise under a nitrogen stream. The total addition time was 30 min. The mixture was stirred at -60 to -70°C for 1 h and at room temperature for 2 h. The resultant solution was cooled to -70°C, and dimethylformamide (43.8 g, 600 mmol) was added in one portion. The mixture was stirred at -70°C for 3 h and stored in a freezer (-10°C) overnight. The mixture was warmed slowly to 0°C, and 4 N HCl (320 mL) was added with ice cooling. The layers were separated and the organic phase was extracted with 4 N HCl (70 mL). The combined aqueous layer was washed with ether (300 mL), adjusted with potassium carbonate (55 g) to about pH 8, and extracted with chloroform (2 x 300 mL, 1 x 200 mL). The combined chloroform extract was washed with water (200 mL) and dried ($MgSO_4$); then the solvent was removed at reduced pressure (aspirator). The residue was distilled at 86-98°C/5.5 mmHg to give 35.3 g of a clear, colorless liquid which solidified upon standing. One recrystallization from a mixture of ether (40 mL) and petroleum ether (60 mL) gave 28.7 g (65%) of pure product, mp 41-43°C (with prior softening at 38°C); lit. bp 89-95°C/12 mmHg, mp 38-39°C (17). NMR ($CDCl_3$) δ 4.00 (s, 3 H), 7.13 (s, 1 H), 7.18 (s, 1 H), 9.68 (s, 1 H).

Thin-Layer Chromatography

Eluent	Rf	Comment
Benzene/ethyl acetate (1:1)	0.33	Homogeneous

Using the same procedure, additional 1-methylimidazole (32.8 g) was converted to pure product (29.7 g, 67%).

2-[(Hydroxyimino)methyl]-1-methylimidazole (2): - An ethanol solution of 1-methyl-2-formylimidazole (57 g, 0.518 mol), hydroxylamine hydrochloride (39.6 g, 0.570 mol) and sodium bicarbonate (56.4 g, 0.671 mol) was heated at reflux for 1.5 h. The reaction mixture was filtered while hot, and the filtrate was concentrated (aspirator) to a white solid. The solid was dissolved in hot isopropyl alcohol (500 mL), and the solution was filtered through celite. The warm filtrate was allowed to cool slowly with stirring, while petroleum ether (3 x 100 mL) was added at 30-min intervals to deposit white crystals (52.8 g). One more recrystallization from a mixture of isopropyl alcohol (400 mL) and petroleum ether (300 mL) gave 47.5 g (73%) of pure product, mp 170-172°C; lit. mp 170-172°C (23). NMR (DMSO-d_6) δ 3.83 (s, 3 H), 7.00 (s, 1 H), 7.27 (s, 1 H), 8.10 (s, 1 H), 11.53 (s, 1 H).

Anal. Calcd for $C_5H_7N_3O$ (125.13): C, 47.99; H, 5.64; N, 33.58. Found: C, 48.05; H, 5.64; N, 33.56.

Thin-Layer Chromatography

Eluent	Rf	Comment
Benzene/ethyl acetate (1:1)	0.17	Homogeneous

1-(5-Carboxypentyl)-2-[(hydroxyimino)methyl]-3-methylimidazolium iodide (3): - A solution of 2-[(hydroxyimino)methyl]-1-methylimidazole (15.8 g, 0.126 mol) and 6-iodohexanoic acid 45.7 g, 0.189 mol) in acetonitrile (160 mL) was heated at reflux for 7 h under a nitrogen atmosphere. The solvent was removed (aspirator) and the brown gummy residue was triturated successively with methylene chloride (2 x 200 mL) and ether (200 mL). The residue was dissolved in acetonitrile (100 mL) and the solution was filtered. The filtrate was evaporated to dryness (aspirator), and the residue was triturated successively with tetrahydrofuran (700 mL) and ethyl acetate (2 x 200 mL). The residue was dissolved in acetonitrile (50 mL) and the solution was diluted with ethyl acetate (100 mL) to give a tan solid (13 g), which was recrystallized from a mixture of acetonitrile (160 mL) and ethyl acetate (160 mL) to yield a beige crystalline solid (11.4 g). One more recrystallization from a mixture of acetonitrile (140 mL) and ethyl acetate (180 mL) gave 10.3 g (22%) of pure product as light creamy crystals, mp 114-116°C. NMR (CD_3CN) δ 1.07-1.93 (m, 6 H), 2.30 (br t, 2 H, J=6 Hz), 3.90 (s, 3 H), 4.28 (t, 2 H, J=6 Hz), 7.50 (m, 2 H), 8.35 (s, 1 H).

Anal. Calcd for $C_{11}H_{18}IN_3O_3$ (367.19): C, 35.98; H, 4.94; I, 34.56; N, 11.44. Found: C, 36.09; H, 4.77; I, 34.42; N, 11.65.

Thin-Layer Chromatography

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (1:1)	0.47	Homogeneous

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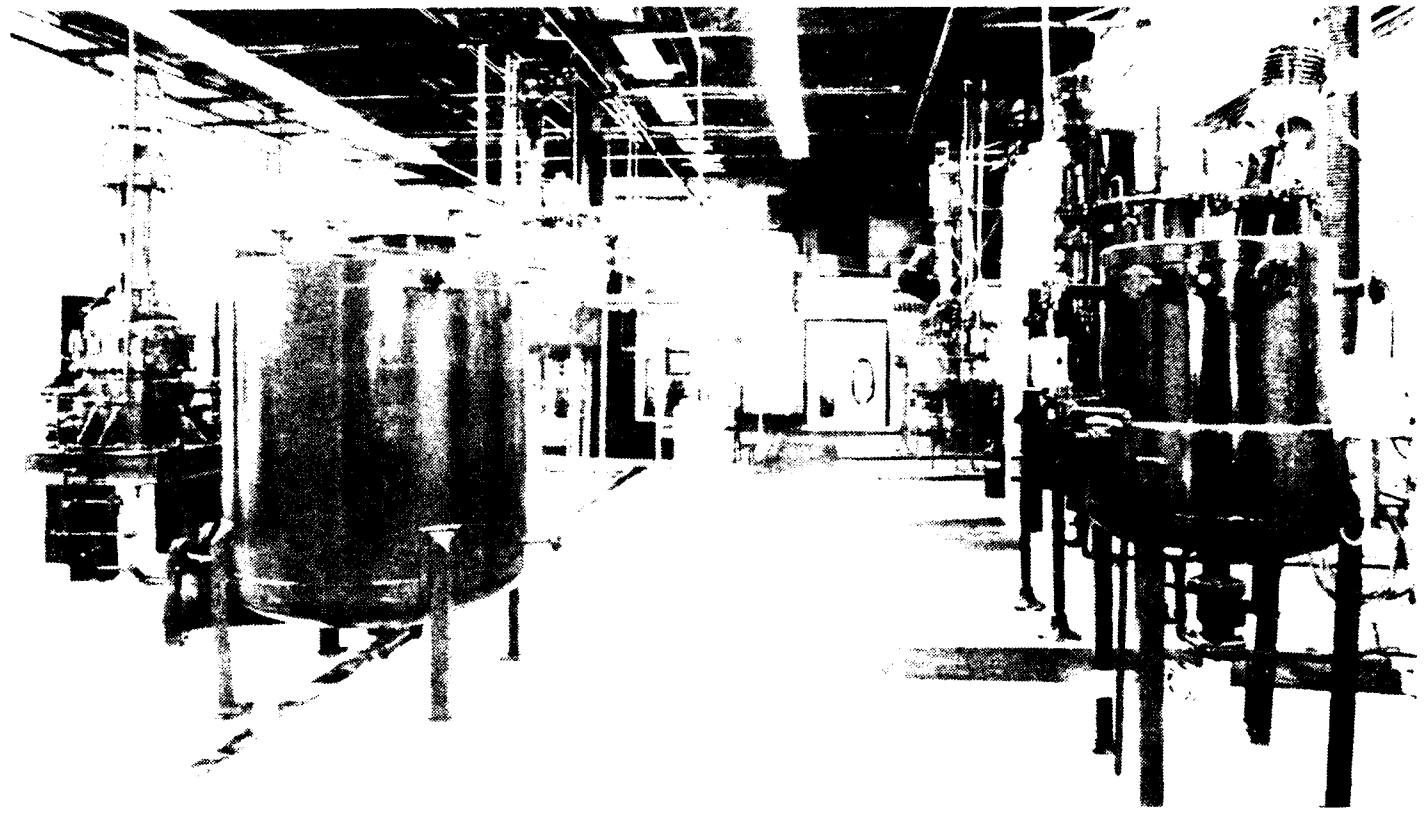

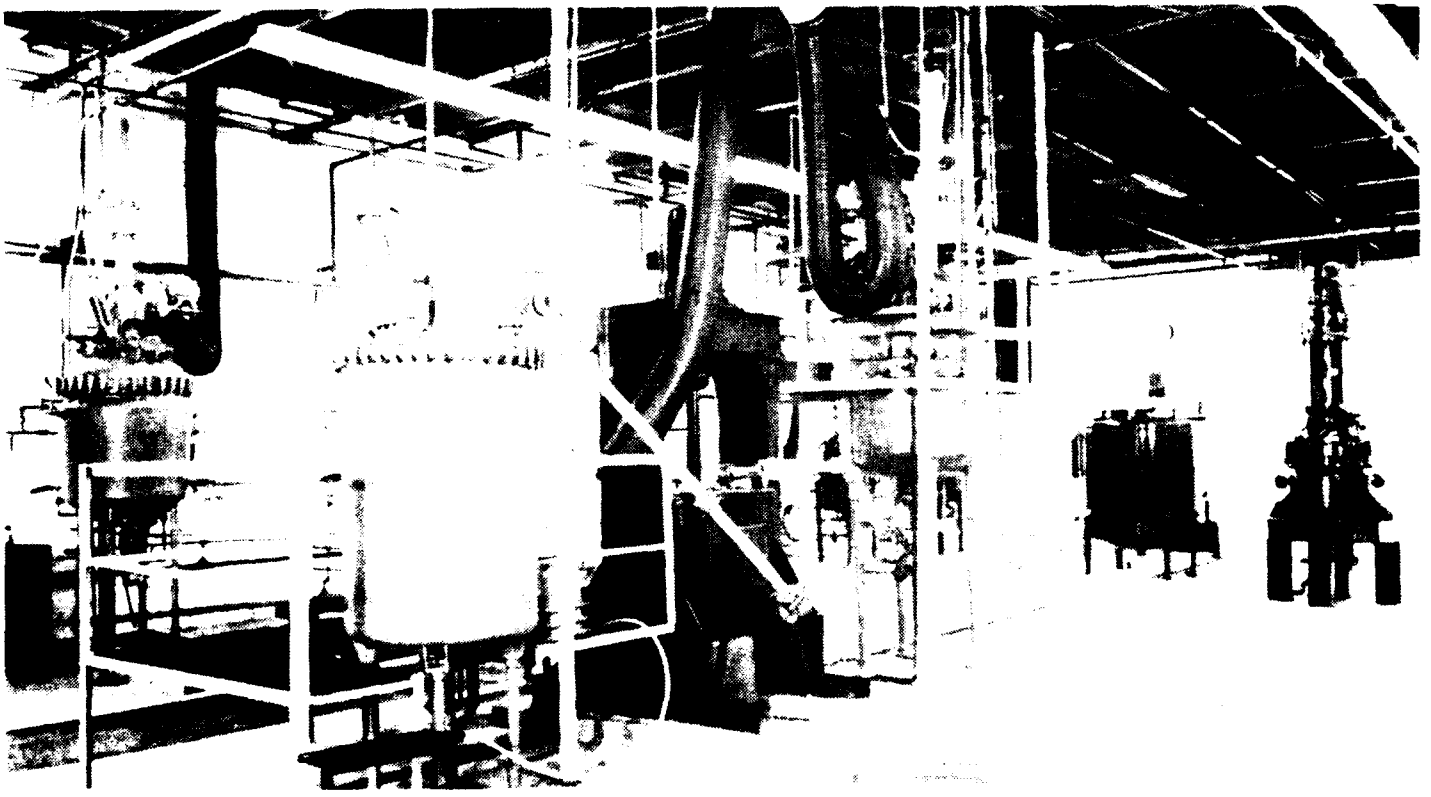

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