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PROPHYLACTIC AND TREATMENT DRUGS FOR ORGANOPHOSPHORUS POISONING

ANNUAL REPORT

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August 1, 1990

(For the Period of 30 September 1988 to 29 March 1990)

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21702-5012

Contract No. DAMD17-84-C-4235

ASH STEVENS INC.
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Detroit, Michigan 48202

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SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: ASH STEVENS INC. / 6b. OFFICE SYMBOL (If applicable)	7a NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): 5861 John C. Lodge Freeway, Detroit, Michigan 48202	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research and Development Command / 8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-84-C-4235
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21702-5012	10 SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 63002A; PROJECT NO. 3M2-63002D995; TASK NO. BA; WORK UNIT ACCESSION NO. 164

11. TITLE (Include Security Classification)

(U) Prophylactic and Treatment Drugs for Organophosphorus Poisoning

12. PERSONAL AUTHOR(S)

Blumbergs, P., C.C. Tseng, B.S. Ross, M.T. Budrick and C.L. Stevens

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Annual	FROM 9/30/88 TO 3/29/90	1990 August 1	72

15. SUPPLEMENTARY NOTATION

17 COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Organosphosphorus poisons, organophosphinates, organophosphonates, thiosulfonic acids, carbamates, synthesis.
06	15		
07	03		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The program is directed at the design and synthesis of treatment and prophylactic drugs as potential defenses against organophosphorus poisoning. During the past year, 23 compounds were submitted: three organophosphonates, eight carbamates, one organophosphinic acid, two sodium alkylthiosulfonates, thiotaurine and homothiotaurine, cis-4-chlorobuten-1-ol and 4-chlorobutanol, one alkylaryl disulfide, two chloroalky(aryl) carboxylic acids, 1,3,5-tris-2'-chloroethylbenzene and d_8-thiodiglycol.

20 DISTRIBUTION/AVAILABILITY OF ABSTRACT: ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	21 ABSTRACT SECURITY CLASSIFICATION: Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL: Mary Frances Bostian	22b TELEPHONE (Include Area Code): 301-663-7325 / 22c OFFICE SYMBOL: SGRD-RMI-S

DD Form 1473, JUN 86 Previous editions are obsolete. SECURITY CLASSIFICATION OF THIS PAGE

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). These following assignments were completed in the past year as listed below.

No.	Name	Code No. Bottle No.	Wt., g[a]	Date Shipped
1.	5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide	CT-2-98A (BL 55982)	17	11/09/88
2.	5-(1,3,3-Trimethylindolinyl)N-ethylcarbamate	CT-2-104 (BL 56050)	12	11/16/88
3.	5-(1,3,3-Trimethylindolinyl)N-methylcarbamate	CT-2-106 (BL 56210)	13	11/30/88
4.	d_8-Thiodiglycol	LVD-01-271 LVD-01-295	3 3.4	12/30/88 3/14/89
5.	5-(1,3,3-Trimethylindolinyl)N-heptylcarbamate hydrobromide	CT-2-118 (BL 56569)	17	1/12/89
6.	8-Chlorocaprylic acid	CT-2-161 (BL 57860)	7	3/20/89
7.	4-(2-Chloroethyl)benzoic acid	MB-02-136	6	3/30/89
8.	5-Carboxypentyl trifluoromethyl disulfide	CT-2-168	8.5	4/20/89
9.	cis-4-Chloro-2-buten-1-ol	CT-2-173 (BL 59202)	13	5/08/89
10.	Sodium ethanethiosulfonate	CT-2-179 (BL 58876)	11	5/18/89
11.	Thiotaurine	BSR-03-155 (BM 00400)	10	7/17/89

SUMMARY (Continued)

No.	Name	Code No. Bottle No.	Wt., g[a]	Date Shipped
12.	Sodium 1-propanethio-sulfonate	CT-2-195	10.5	7/17/89
13.	(S)(-)-5-(1,3,3-Trimethyl-indolinyl)-N-(1-phenyl-ethyl)carbamate	CT-2-192 (BM 03554)	8.5	8/08/89
14.	(R)(+)-5-(1,3,3-Trimethyl-indolinyl)-N-(1-phenyl-ethyl)carbamate	CT-2-197 (BM 00688)	12	8/08/89
15.	5-(1,3,3-Trimethylindo-linyl)-N-(3-chloro-phenyl)carbamate	CT-2-199 (BM 00679)	15	8/08/89
16.	Homothiotaurine	BSR-03-184 (BM 00660)	10	8/08/89
17.	4-Chlorobutanol	LVD-G1-406	20	9/05/89
18.	5-(1,3,3-Trimethyl-indolinyl)-N,N-dimethyl-carbamate hydrochloride	CT-2-220 (BM 01747)	30	9/25/89
19.	6-Aminohexylphosphonic acid, monopinacolyl ester	BSR-04-48	2.3	1/11/90
20.	1,3,5-Tris-2'-chloro-ethylbenzene	CT-2-295 (BM 03858)	2.5	2/20/90
21.	Methyl pinacolyl 4-(4-carboxybutanoylamino)-benzylphosphonate	CT-2-289 (BM 04257)	5.0	3/06/90
22.	Monopinacolyl 4-(4-carboxybutanoylamino)-benzylphosphonate	CT-2-298 (BM 04266)	2.5	3/06/89
23.	(5-Carboxypentyl)(3,3-dimethylbutyl)phosphinic acid	BSR-04-153	5.0	4/02/90

FOREWORD

The work described herein was performed under Contract No. DAMD17-84-C-4235 for the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Maryland. This Progress Report covers the period 30 September 1988 to 29 March 1990. Dr. C.L. Stevens served as Principal Investigator, Dr. P. Blumbergs as Associate Investigator, and Dr. A.B. Ash as Program Manager, phone (313) 872-6400.

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.

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 Officer's Representative (COR), 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 other than 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-methyladenosine 5'-triphosphate, 2-aminoethylselenic and 2-aminoethylselenonic 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 defense capability in both the prophylactic and treatment area was continued. Thus, in the first 4 years of the program (4,5,6,7), 61 assignments were completed: 22 organophosphinates, two organophosphonates, 13

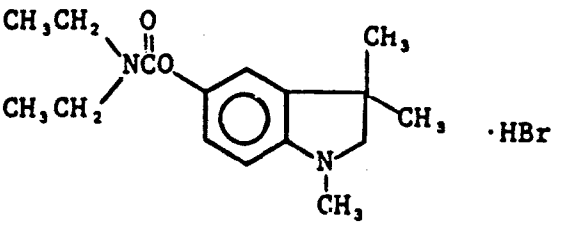
phosphorinanes (cyclic phosphates), one phosphorothioate, four carbamates, six AChE reactivators, suberyldicholine, a new tropate ester (two submissions), two (new) physostigmine analogs, a nonanone oxime, a quaternary pyridine, a tetraalkylquaternary iodide, two 1,3,4-diazol-2-ones, a bis(2-bromoethyl)morpholine, a (new) 3-(benzoyl)propane sulfonate, and a bis(1-methyl-3-pyridinyl)-urea.

In this, the final 18 months of the contract, a total of 23 assignments were completed, as follows: three organophosphonates, eight carbamates, one organophosphinic acid, two sodium alkylthiosulfonates, thiotaurine, homothiotaurine, cis-4-chlorobuten-1-ol and 4-chlorobutanol, one dialkyl disulfide, two chloroalky(aryl) carboxylic acids, 1,3,5-tris-2'-chlorcethyl-benzene and d_8-thiodiglycol. Thus, the 5-1/2-year total of submissions under the current contract was 83; small samples of each were submitted to WRAIR, when available, and data sheets were submitted to WRAIR for all submissions. These 83 compounds will be summarized in the Final Report, as specified in the contract.

2. DISCUSSION OF WORK COMPLETED

The 23 assignments completed in the past 18 months are discussed below.

2.1 5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide

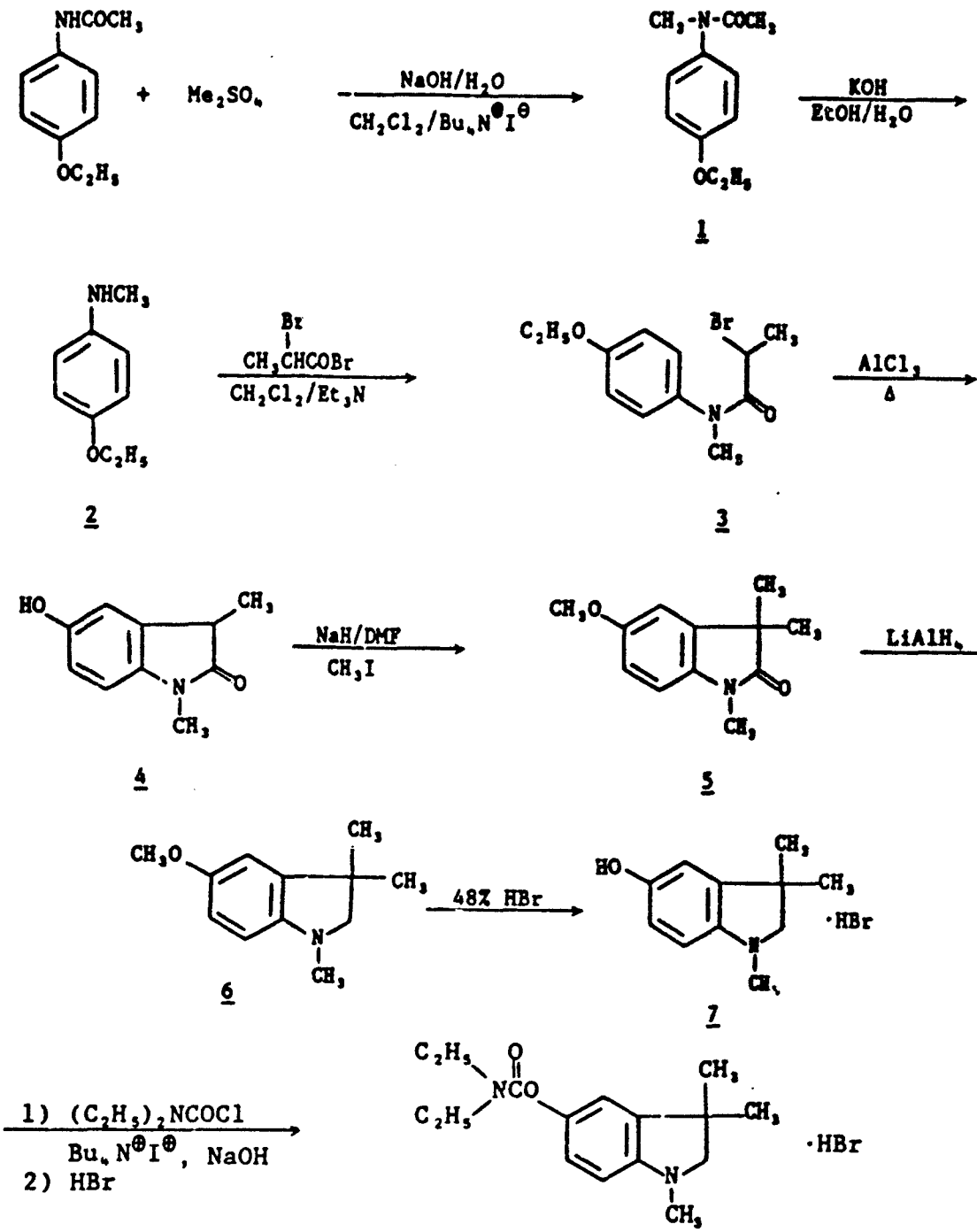


Synthesis of the N,N-dimethylcarbamate analog of the title compound was reported in 1965 by Ahmed and Robinson (8) and more recently by Chinese workers (9,10). The synthesis route used to prepare the desired diethylcarbamate is shown in Chart No. 1 and is the same as that described in the literature for closely related indolines (11,12).

N-Acetyl-p-phenetidine was treated with dimethyl sulfate and sodium hydroxide in a water/methylene chloride system using tetrabutylammonium iodide as a phase transfer catalyst to give the N-methylated intermediate 1. Base hydrolysis in aqueous ethanol gave N-methyl-p-phenetidine (2). Next, compound 2 was treated with α-bromopropionyl bromide to yield the N-acylated intermediate 3. In the literature procedure (11), excess N-methyl-p-phenetidine was used as the acid acceptor, whereas in the current work the readily available and less expensive triethylamine was the acid acceptor. Crude 3 was isolated in 97% yield. Cyclization of compound 3 with aluminum chloride gave 5-hydroxy-2-indolinone 4. The conversion of 4 to 5 by procedures reported in the literature involved two steps by which compound 4 was treated first with a dialkyl sulfate and aqueous base to give the 5-alkoxy derivative (11). This material was then treated with methyl iodide and sodium ethoxide to introduce the second methyl group at the 3-position of the indole ring. In the present work, this conversion was accomplished in one step by treating intermediate 4 with sodium hydride and methyl iodide in dimethylformamide as the solvent. Compound 5 was isolated in 67% yield. Reduction of the 2-keto group with sodium and n-butanol is reported (12) to give a low yield of the desired product. Accordingly, an alternative method (13) using lithium aluminum hydride was employed, and product 6 was isolated in 88% yield. Cleavage of the 5-methoxy group with aqueous hydrobromic acid gave a 95% yield of the crystalline key intermediate 7.

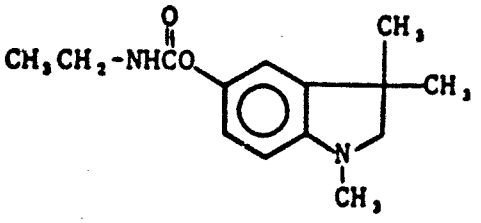
CHART NO. 1

5-(1,3,3-TRIMETHYLINDOLINYL)N,N-DIETHYLCARBAMATE HYDROBROMIDE



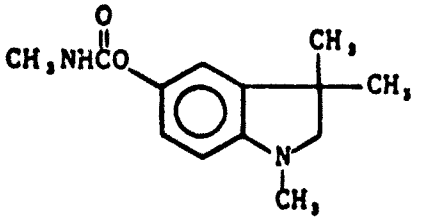
Finally, treatment of compound 7 with diethylcarbamoyl chloride and sodium hydroxide in a two-phase system (14) gave the title diethylcarbamate 8, isolated as the hydrobromide salt in 78% yield.

2.2 5-(1,3,3-Trimethylindolinyl)N-ethylcarbamate



The title new carbamate was prepared from intermediate 7 of Chart No. 1, section 2.1. The compound 7, hydrobromide salt was converted to the free base with sodium carbonate, then it was treated with ethyl isocyanate and a catalytic amount of sodium metal. The crystalline N-ethylcarbamate was isolated in 74% yield.

2.3 5-(1,3,3-Trimethylindolinyl)N-methylcarbamate



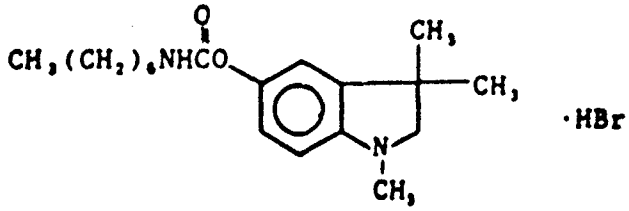
The title N-methylcarbamate was prepared from intermediate 7 of Chart No. 1 in the same manner as the N-ethylcarbamate described above. Thus, treatment of compound 7 free base with methyl isocyanate and catalytic sodium metal gave the crystalline carbamate in 90% yield.

2.4 d_8-Thiodiglycol

$$HOCD_2CD_2SCD_2CD_2OH$$

The title compound was prepared by a general literature procedure used for the synthesis of the radiolabeled product (15). Following this general procedure, hydrogen sulfide was treated with d_4-ethylene oxide at room temperature in the presence of a catalytic amount of sodium methoxide, and the result was a mixture of d_4-thioglycol and the desired product. The mixture was separated by distillation, and the thioglycol was treated with fresh d_4-ethylene oxide to yield additional product. The overall yield, based on d_4-ethylene oxide, was 65%.

2.5 5-(1,3,3-Trimethylindolinyl)N-heptylcarbamate hydrobromide



The title carbamate was prepared by treating the precursor 5-hydroxyindoline 7 shown in Chart No. 1, section 2.1, with n-heptyl isocyanate. The product was isolated as the crystalline hydrobromide salt in 70% yield.

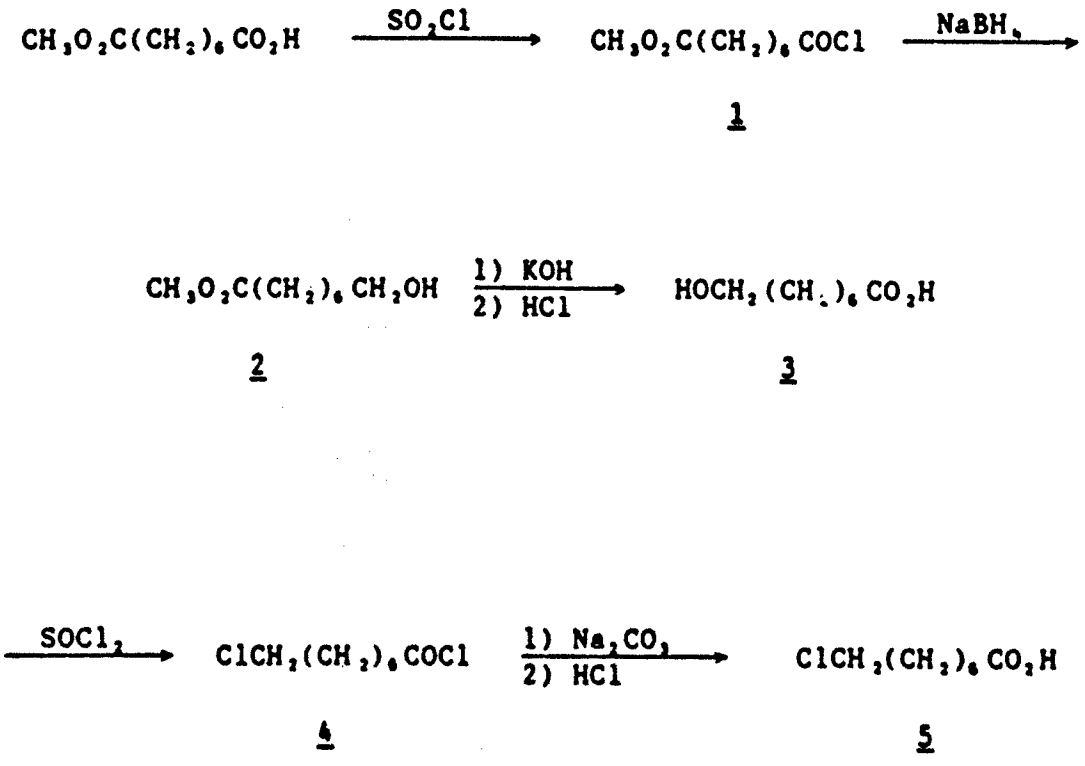
2.6 8-Chlorocaprylic acid

$$ClCH_2(CH_2)_6COOH$$

The synthesis sequence to this compound is shown in Chart No. 2. A shorter route to intermediate 3, i.e., the Baeyer-Villiger oxidation of cyclooctanone with peracetic acid, was considered by us, but it was discarded in view of a 1958 literature article (16) which states that the reaction proceeds in very low yield. A later article describes the successful conversion of cyclooctanone to 8-hydroxyoctanoic acid-lactone using trifluoroperacetic acid (17), but no yields are reported.

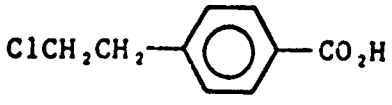
CHART NO. 2

8-CHLOROCAPRYLIC ACID



Turning to Chart No. 2, monomethyl suberate was treated with thionyl chloride to give acid chloride 1, which was reduced with sodium borohydride to 8-hydroxyoctanoic acid methyl ester (2). The ester was hydrolyzed with alcoholic base, and the product, hydroxy acid 3, was treated with thionyl chloride to give 8-chlorocapryloyl chloride (4). Mild base hydrolysis of the acid chloride gave the desired title chloroacid 5.

2.7 4-(2-Chloroethyl)benzoic acid



This assignment entailed a simple purification of commercially available material. Thus, recrystallization of the commercial product from toluene gave analytically pure title acid.

2.8 5-Carboxypentyl trifluoromethyl disulfide

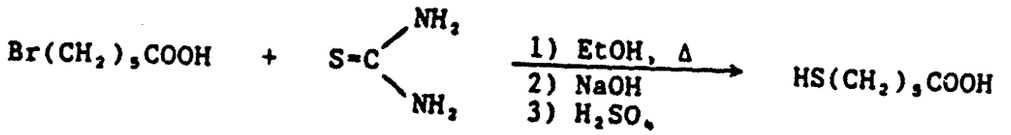
$$F_3CSS(CH_2)_5COOH$$

The title compound represents a new structure not previously reported in the chemical literature.

A number of synthesis procedures are available for the preparation of symmetrical disulfides, one of the simplest being the oxidation of thiols with iodine. When applied to the synthesis of unsymmetrical disulfides, these approaches give invariably mixtures of symmetrical and unsymmetrical disulfides. Accordingly, a thorough literature search was carried out in order to find methods useful for the preparation of mixed disulfides. Of the various approaches reported, several appeared applicable to the current problem. The method of disulfide bond formation chosen for the current synthesis work is the same as that reported in the literature (18) for the preparation of a similar mixed disulfide. The overall synthesis route is shown in Chart No. 3. The required precursor, compound 1, was prepared by the treatment of 6-bromohexanoic acid with thiourea to give a thiouronium salt, which was hydrolyzed directly with sodium hydroxide to 6-mercaptohexanoic acid. Next, the thioacid 1 was coupled with trifluoromethylsulfenyl chloride in methylene chloride as solvent. Thin-layer chromatography showed the formation of one major product contaminated with two impurities

CHART NO. 3

5-CARBOXYPENTYL TRIFLUOROMETHYL DISULFIDE



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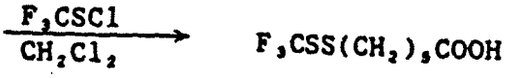

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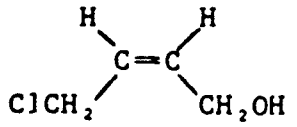
(the symmetrical disulfides). Purification was accomplished readily by distillation, and pure product 2 was obtained in 57% yield.

2.9 cis-4-Chloro-2-buten-1-ol



The title compound was prepared by a literature procedure (19) whereby cis-2-butene-1,4-diol was treated with one equivalent of thionyl chloride in the presence of pyridine. The product was purified by column chromatography and distillation. Although the product yield was low, sufficient material was obtained to fill the order; no effort was made to improve the yield.

2.10 Sodium ethanethiosulfonate

$$CH_3CH_2SO_2SNa$$

Preparation of the crystalline anhydrous potassium salt as well as the monohydrated sodium salt has been reported in the literature (20,21). For the current work, the same synthesis approach was used which involved the reaction of ethanesulfonyl chloride with aqueous sodium sulfide. Recrystallization of the crude product from ethanol gave pure anhydrous title compound. Recrystallization from water is reported to give monohydrated product (21).

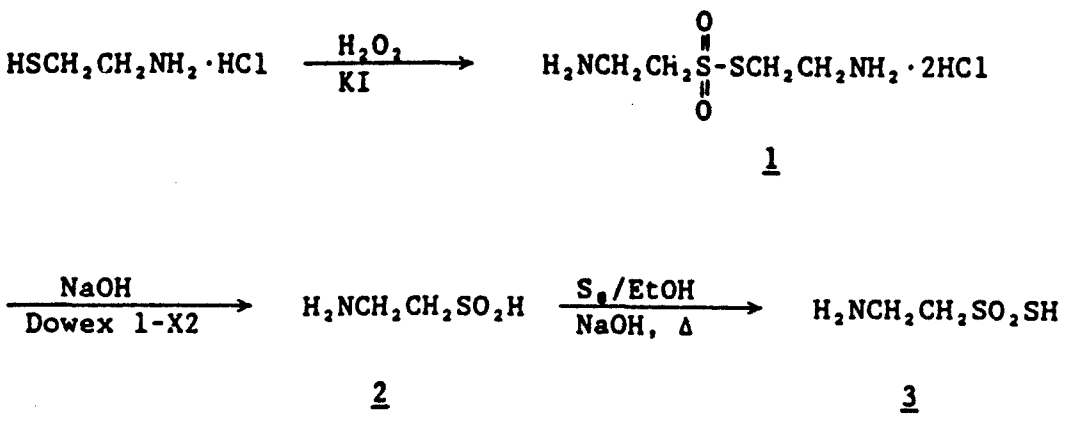
2.11 Thiotaurine

$$H_2NCH_2CH_2SO_2SH$$

The title compound was prepared by a standard literature procedure (22), as outlined in Chart No. 4. Thus, treatment of 2-aminoethanethiol hydrochloride with hydrogen peroxide in the presence of potassium iodide catalyst gave 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride (1). Compound 1 was dissolved in sodium hydroxide and applied to a column of Dowex 1-X2 ion-exchange resin. After washing with water, the column was eluted carefully with hydrochloric acid to give hypotaurine (2). Finally, treatment of intermediate 2 with elemental sulfur in ethanol solvent containing some sodium hydroxide gave the desired title target structure 3.

CHART NO. 4

THIOTAURINE

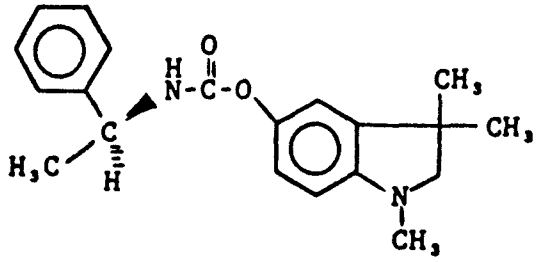


2.12 Sodium 1-propanethiosulfonate

$$CH_3CH_2CH_2SO_2SNa$$

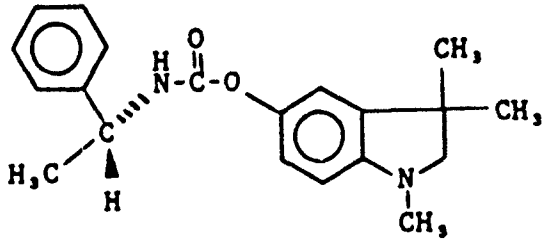
Synthesis of the potassium salt of 1-propanethiosulfonic acid has been reported in the literature (23). The title sodium salt was prepared by the same general procedure. Thus, treatment of 1-propanesulfonyl chloride with sodium sulfide in aqueous dimethoxyethane gave crude title product which was purified by recrystallization. No attempt was made to optimize product yield.

2.13 (S)(-)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate



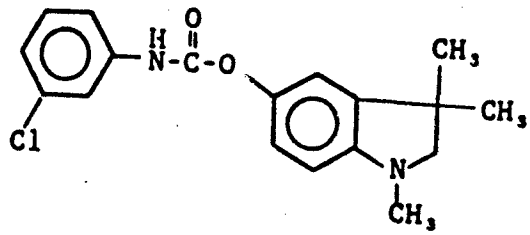
The title carbamate was prepared from intermediate 7 of Chart No. 1, section 2.1. A sample of this intermediate was converted with sodium carbonate to the free base, then it was treated with (S)(-)-1-phenylethyl isocyanate to yield the title carbamate. The yield of pure product was only fair (45%), but more emphasis was placed on product purity than yield.

2.14 (R)(+)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate



The title carbamate was prepared in the same manner as the enantiomer described in section 2.13 by treating intermediate 7, free base of Chart No. 1, section 2.1, with (R)(+)-1-phenylethyl isocyanate. Pure product was isolated in 54% yield.

2.15 5-(1,3,3-Trimethylindolinyl)-N-(3-chlorophenyl)carbamate



The title carbamate was prepared by treating intermediate 7, free base of Chart No. 1, section 2.1, with 3-chlorophenyl isocyanate. The yield of pure product was 73%.

2.16 Homothiotaurine

$$H_2NCH_2CH_2CH_2SO_2SH$$

Synthesis of homothiotaurine has been reported in the literature (24). The same general route, outlined in Chart No. 5, was used in the current work. Compound 1 was prepared by the successive treatment of N-(3-bromopropyl)phthalimide with sodium thiosulfate and iodine (25). Acid hydrolysis of this intermediate gave homocystamine dihydrobromide (2). Next, compound 2 was oxidized with hydrogen peroxide to a thiolsulfonate which was then cleaved with sodium hydroxide to homohypotaurine (3). By the literature procedure (24), the thiolsulfonate intermediate is not isolated but is treated directly with base to give compound 3, which is purified by chromatography over Dowex 50 ion-exchange resin. In the current work, crude thiolsulfonate dihydrobromide was isolated in the form of a crystalline solid, then it was treated with base and passed over a Dowex 1-X2 ion-exchange resin to give compound 3. In the last step, sulfinic acid 3 was treated with elemental sulfur in ethanol solvent containing some aqueous sodium hydroxide to yield the title target compound 4.

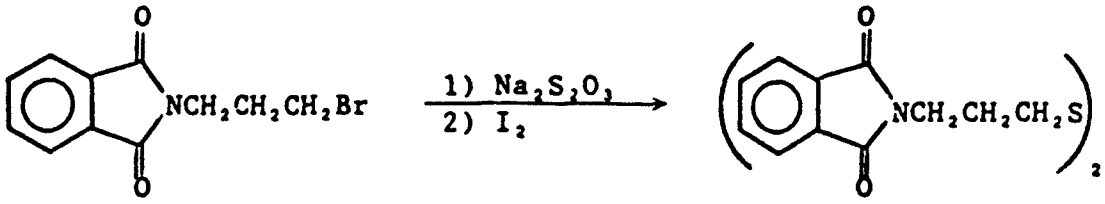
2.17 4-Chlorobutanol

$$ClCH_2CH_2CH_2CH_2OH$$

This assignment entailed the purification of commercially available material. Thus, technical 4-chlorobutanol (85%) was dried over potassium carbonate, then it was distilled through a 5-plate bubble plate column. The product analyzed for 99% 4-chlorobutanol containing 1% water.

CHART NO. 5

HOMOTHIOTAURINE



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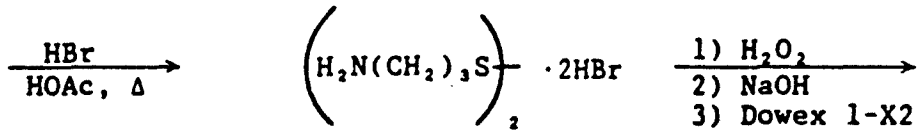

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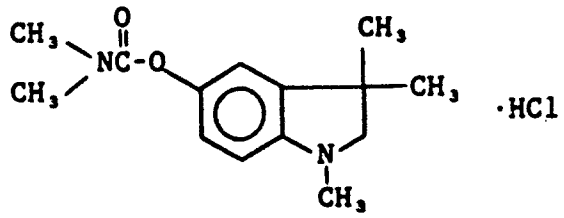
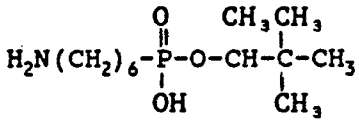
2.18 5-(1,3,3-Trimethylindolinyl)-N,N-dimethylcarbamate hydrochloride



Preparation of the title compound has been reported in the literature (8,9). For the current synthesis, compound 7 of Chart No. 1, section 2.1, was treated with dimethylcarbamoyl chloride in a two-phase system to give the title target structure, which was purified and characterized as a hydrochloride salt. The melting point of our product differs from that reported originally (8), but it is in agreement with the melting point reported in a more recent article (9). The elemental analysis and spectral data are in good agreement with the dimethylcarbamate structure.

2.19 6-Aminohexylphosphonic acid monopinacolyl ester



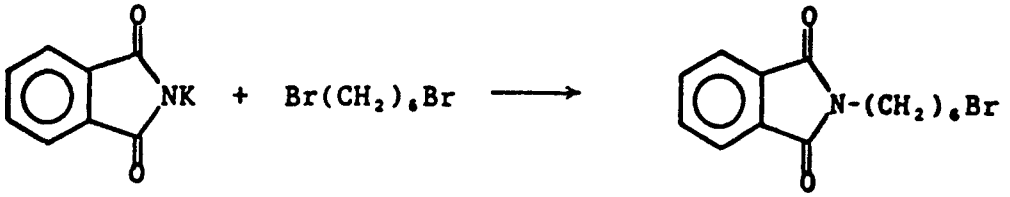
The title compound represents a new structure not reported in the chemical literature. The synthesis was accomplished via a five-step sequence as outlined in Chart No. 6.

6-Bromohexylphthalimide (1) was prepared by the reaction of 1,6-dibromohexane with potassium phthalimide (26). Treatment of compound 1 with excess triethyl phosphite at near reflux temperature gave the phosphonate ester 2.

In the next step, hydrolysis of ester 2 with acid or base was avoided in order to prevent the loss of the phthalimide. Instead, the ethyl groups were cleaved selectively with trimethylsilyl bromide to give phosphonic acid 3. Compound 3 was converted to a monochloridate with oxaloyl chloride, then it was esterified with pinacolyl alcohol to give a monopinacolyl ester, isolated as the sodium salt 4. In the last step, the phthalimide was cleaved with hydrazine to give the title target phosphinic acid 5. Thin-layer chromatography indicated that compound 5 was the major reaction product. However, purification of the crude material proved to be quite tedious, and pure 5 was isolated in 14% yield. A sufficient quantity of pure product was

CHART NO. 6

6-AMINOHEXYLPHOSPHONIC ACID, MONOPINACOLYL ESTER



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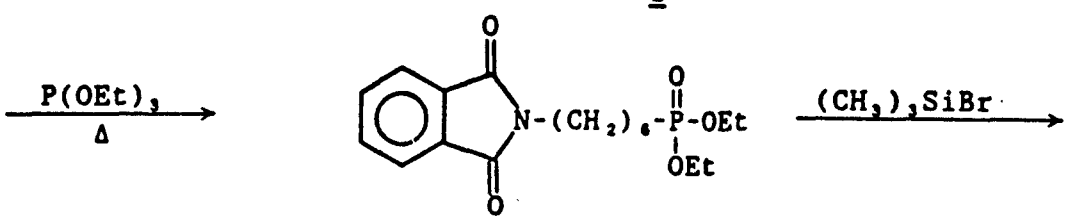

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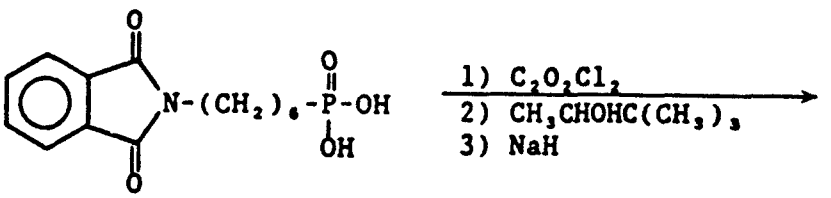

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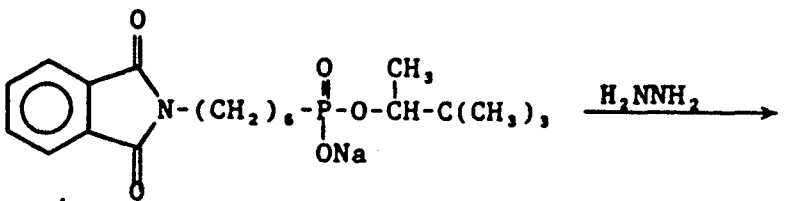

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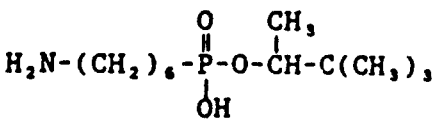

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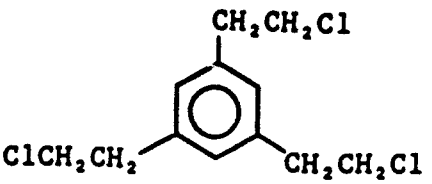
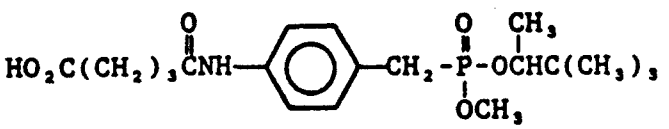
obtained to fill the request; accordingly, no attempt was made to optimize the yield.

2.20 1,3,5-Tris-2'-chloroethylbenzene



Synthesis of the title compound has been reported in the literature (27). The same approach, outlined in Chart No. 7, was used in the current work. By this route, 1,3,5-triacetylbenzene was treated with morpholine and sulfur to give the triacetic acid 1. Compound 1 was esterified with ethanol and the resulting triester 2 was reduced with lithium aluminum hydride to triol 3. Treatment of compound 3 with thionyl chloride and pyridine gave the desired title target compound 4.

2.21 Methyl pinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate

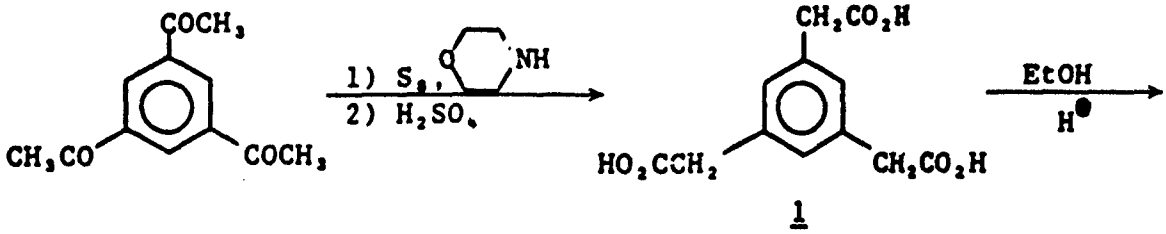


Synthesis of the title benzylphosphonic acid mono-α-phenethyl ester by a seven-step reaction sequence has been reported in the literature (28). Although the reaction conditions were given for each step, a detailed experimental procedure was not presented. The methyl pinacolyl ester shown above was synthesized via the same general sequence as shown in Chart No. 8.

Referring to Chart No. 8, diethyl 4-aminobenzylphosphonate was treated with trifluoroacetic anhydride to give the trifluoroacetamide 1. Next, the ethyl ester was cleaved by successive treatment with trimethylsilyl bromide and water to give phosphonic acid 2. Conversion of acid 2 to the dimethyl ester 3 was effected in the initial small scale runs with diazomethane. In a subsequent larger scale preparation, the procedure was changed in that the acid was treated first with phosphorus pentachloride to give a phosphonodichloridate, which was then

CHART NO. 7

1,3,5-TRIS-2'-CHLOROETHYLBENZENE



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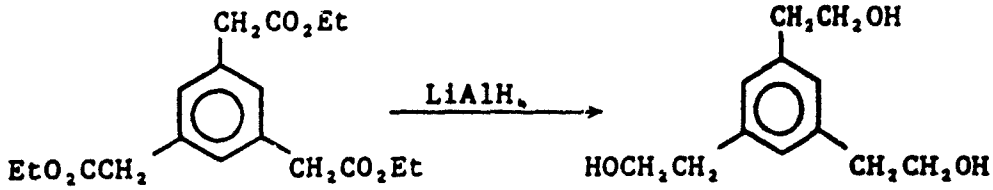

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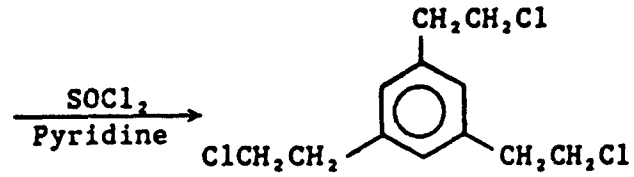

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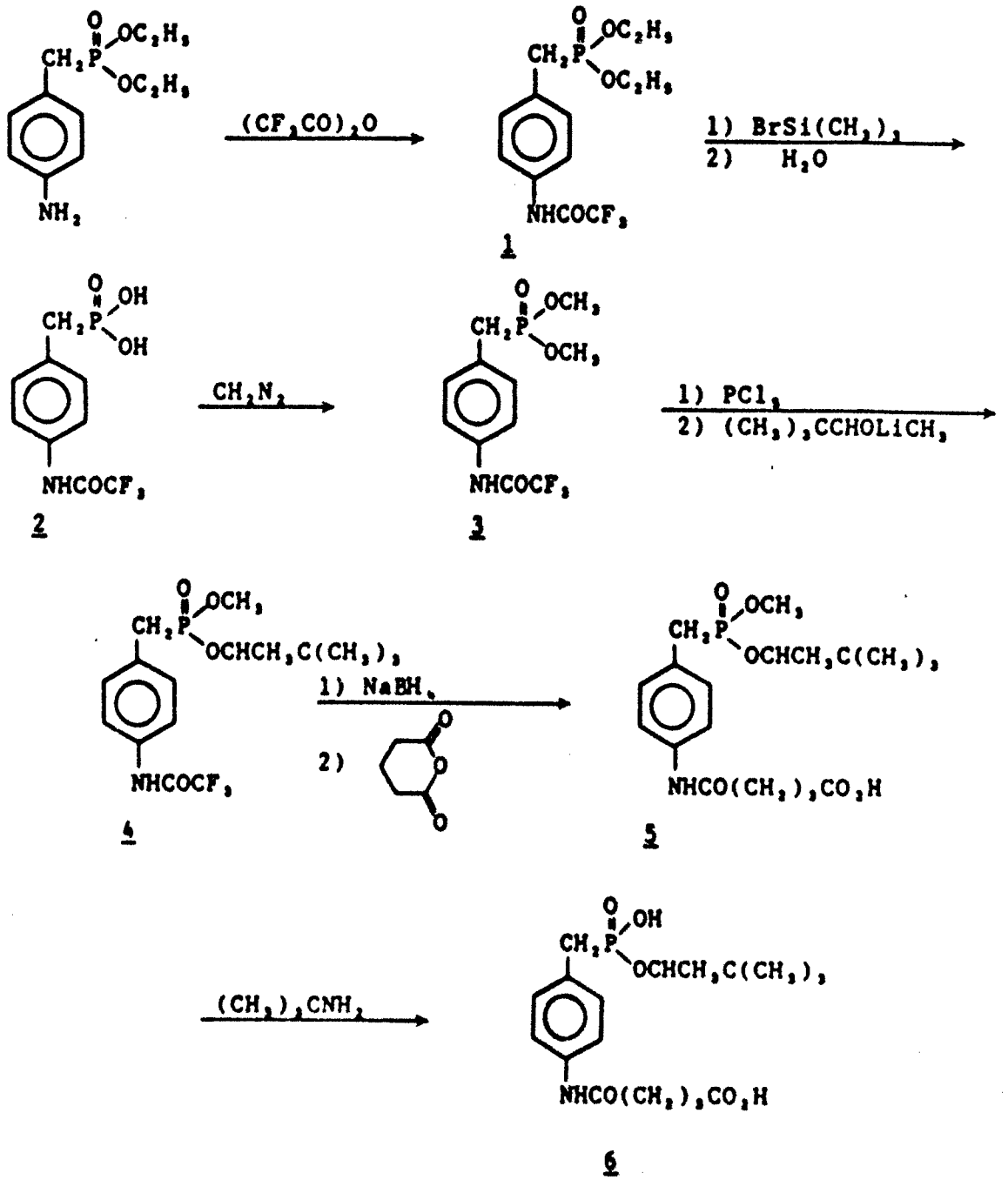
CHART NO. 8

METHYL PINACOLYL AND MONOPINACOLYL
4-(4-CARBOXYBUTANOYLAMINO)BENZYLPHOSPHONATE



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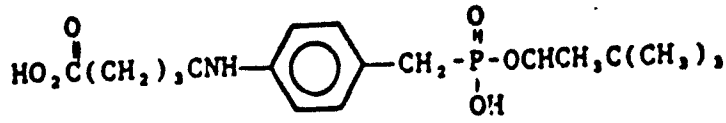
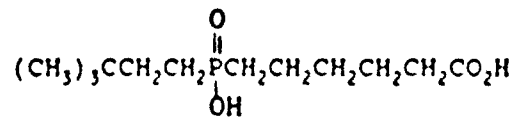
converted to ester 3 by the action of lithium methoxide in methanol. Treatment of phosphono diester 3 with one equivalent of phosphorus pentachloride converted it to a phosphonomonochloridate. The reaction of this acid chloride with the lithium salt of pinacolyl alcohol gave the mixed ester 4. The protecting trifluoroacetyl group was selectively removed with sodium borohydride, and the resulting amine was treated with glutaric anhydride to give the title target compound 5.

2.22 Monopinacolyl 4-(4-carboxybutanoylaminol)benzylphosphonate



The title phosphonic acid monoester was prepared as shown in Chart No. 8 by the selective hydrolysis of the mixed diester described in section 2.21 above. Thus, diester 5 was treated with tert-butylamine in acetonitrile at 55-60°C for 11 days to give monoester 6 as a tert-butylamine salt. Thin-layer chromatography (TLC) showed that this material was contaminated with a minor impurity which could not be removed by recrystallization. Passage of a small sample of this salt over ion-exchange resin gave pure free acid 6 as a crystalline solid. However, treatment of the remaining salt, in methanol, with the ion-exchange resin converted the carboxy group to a methyl ester. Accordingly, this material was treated with sodium carbonate to hydrolyze the carboxylic ester, then it was acidified with hydrochloric acid to give crude product 6. One recrystallization gave the pure title phosphonic acid monopinacolyl ester.

2.23 (5-Carboxypentyl)(3,3-dimethylbutyl)phosphinic acid

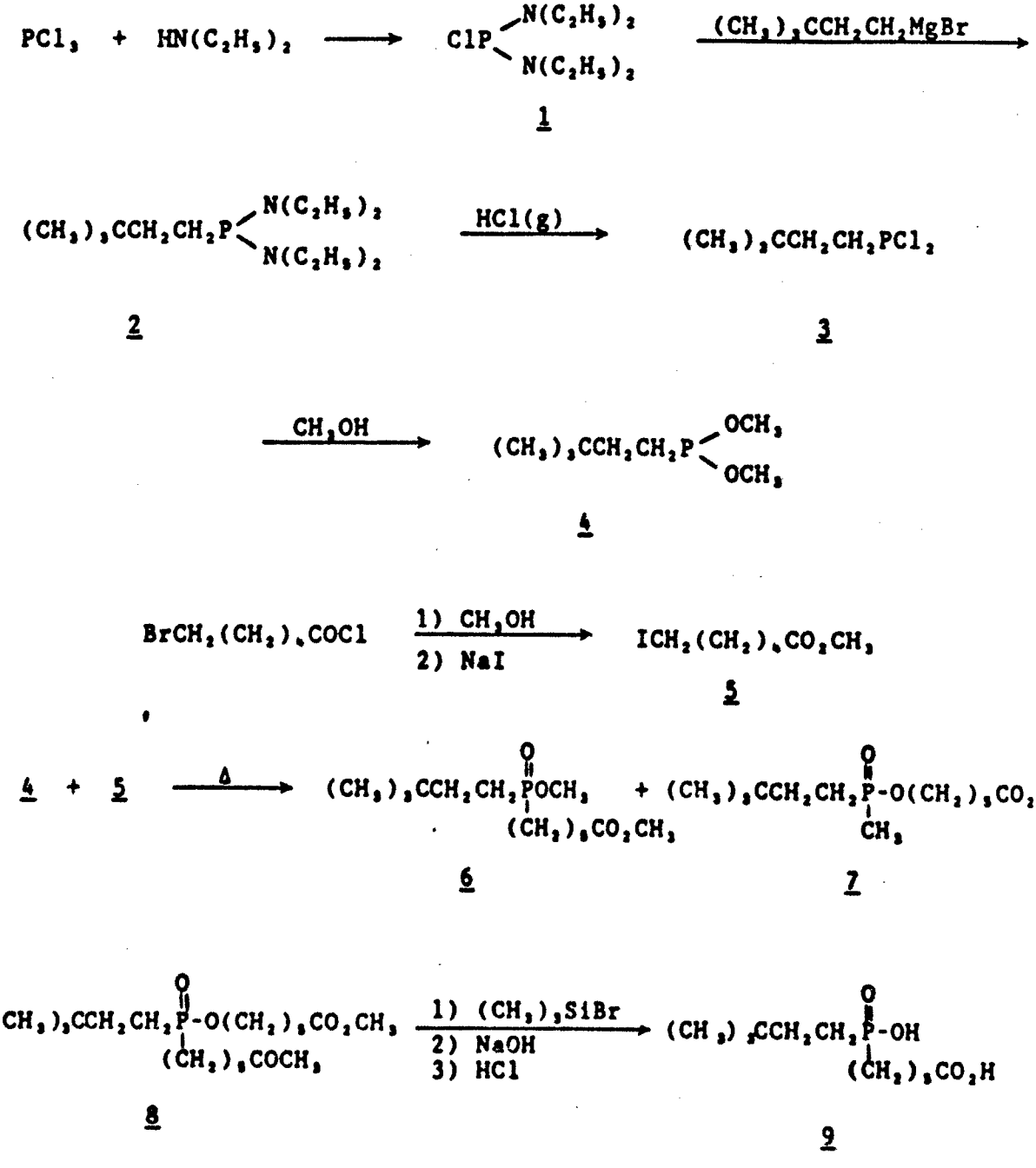


The title compound is a new structure not reported in the chemical literature. Synthesis of this target was accomplished as shown in Chart No. 9.

The phosphorodiamidous chloride 1 was prepared by a literature procedure (29). Treatment of compound 1 with 3,3-dimethylbutylmagnesium bromide gave the phosphonous diamide 2. Cleavage of the diethylamide groups was accomplished readily with

CHART NO. 9

(5-CARBOXYPENTYL)(3,3-DIMETHYLBUTYL)PHOSPHINIC ACID

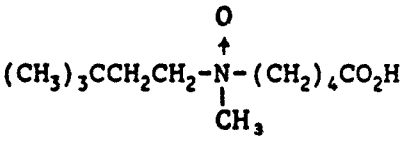


anhydrous hydrogen chloride, and the product, phosphonous dichloride 3, was converted to dimethyl phosphonite 4 by treatment with methanol and triethylamine. It was essential to handle compound 4 in an inert atmosphere, since it is readily oxidized in air to dimethyl 3,3-dimethylbutylphosphonate. Methyl 6-iodo-hexanoate was prepared from 6-bromohexanoyl chloride by treatment with methanol followed by sodium iodide in acetone. Next, phosphonite 4 was subjected to the Arbuzov reaction with iodohexanoate 5 to give a mixture of phosphinates 6 and 7. Attempts to improve product yield and purity were not successful. Variables studied included reaction time and temperature and the method of addition of the iodoester. Formation of phosphinate ester 7 was observed early in the reaction. Increasing the temperature or reaction time to drive the reaction to completion aided the formation of the undesired ester 7 and other impurities, including compound 8. Accordingly, the mixture of 6 and 7 was carried on to product 9. Successive treatment of the mixture with trimethylsilyl bromide and sodium hydroxide cleaved the ester groups to give product 9, isolated as the free acid and purified by recrystallization.

The synthesis sequence was satisfactory for the preparation of a 5-g sample of compound 9. For larger scale syntheses, improvements in the sequence would have to be made.

3. WORK IN PROGRESS

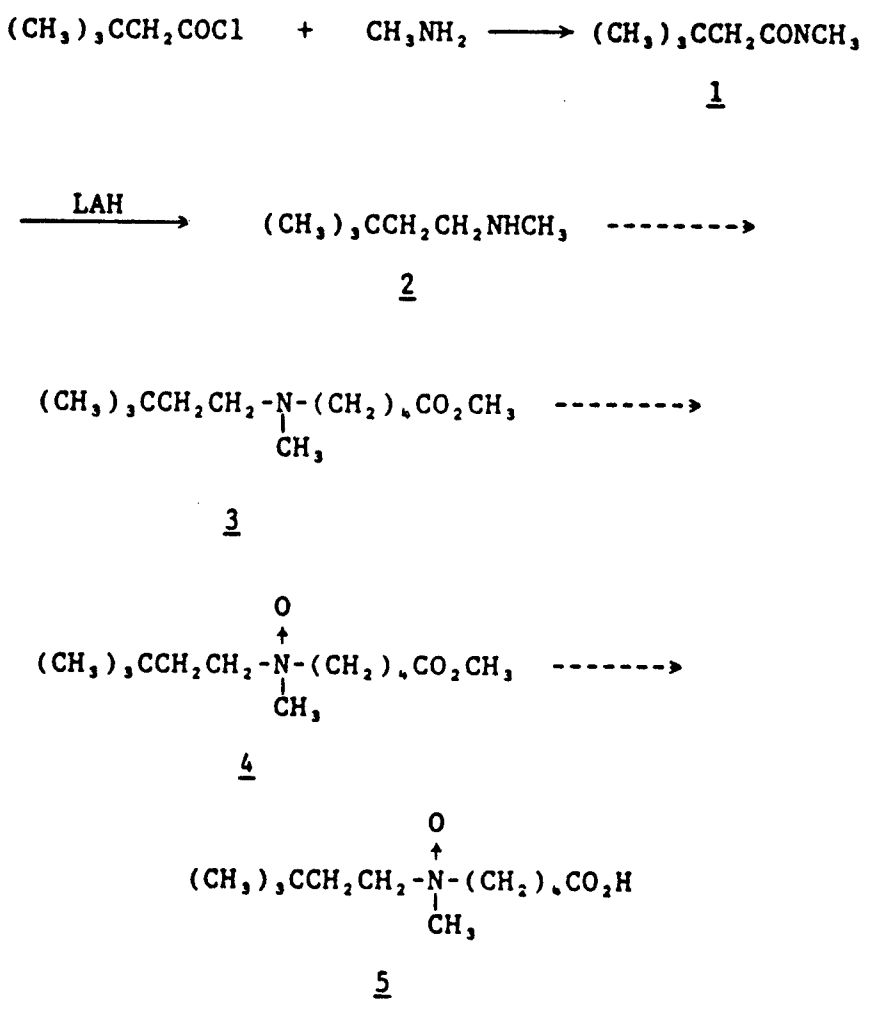
3.1 N-(4-Carboxybutyl)-N-(3,3-dimethylbutyl)methylamine N-oxide



A proposed synthesis route to the target compound is shown in Chart No. 10. At the time the contract expired, the sequence was completed to intermediate 2. Thus, tert-butylacetyl chloride was treated with methylamine to give amide 1. Reduction of this material with lithium aluminum hydride gave the secondary amine 2. The remainder of the sequence involved alkylation of 2 to give the tertiary amine 3, oxidation to the N-oxide 4, and hydrolysis to the target structure 5. None of these steps was investigated.

CHART NO. 10

N-(4-CARBOXYBUTYL)-N-(3,3-DIMETHYLBUTYL)METHYLAMINE N-OXIDE



4. EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1310 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. Nuclear magnatic resonance spectra (NMR) were determined on a Varian Model T60 Spectrometer. All thin-layer chromatography (TLC) was carried out using Analtech silica gel GF plates with fluorescent indicator, unless stated otherwise.

4.1 5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide

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

N-Acetyl-N-methylphenetidine (1): - A 3-L three-necked flask (equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel) was charged with N-acetyl-p-phenetidine (224 g, 1.25 mol), tetrabutylammonium iodide (11.5 g, 0.31 mol), and methylene chloride (1750 mL). Aqueous 50% sodium hydroxide (w/v, 500 g) was added dropwise to the stirred mixture followed, after 15 minutes, by the dropwise addition of dimethyl sulfate (189 g, 1.5 M). After the addition was completed, the mixture was heated at reflux for 3 h, cooled to room temperature, and diluted with water (600 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (1 x 600 mL). The combined organic phase was washed with water until the wash was neutral (3 x 1 L), then it was dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 250.4 g (103%) of a light tan liquid. Distillation gave 217.3 g (90%) of pure product as colorless clear liquid, bp 144-146°C/2.3 mmHg. NMR ($CDCl_3$) δ 1.43 (t, 3H, J=6.6 Hz), 1.87 (s, 3H), 3.23 (s, 3H), 4.07 (q, 2H, J=6.6 Hz), 6.63-7.30 (m, 4H).

Anal. Calcd for $C_{11}H_{15}NO_2$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.09; H, 7.91; N, 7.34.

Thin-Layer Chromatography

Eluent	Rf	Comment
Benzene/methanol (9:1)	0.42	Homogeneous

N-Methylphenetidine (2): - A solution of N-acetyl-N-methylphenetidine (848.3 g, 4.39 mol) and potassium hydroxide (591.1 g, 10.54 mol) in a mixture of ethanol (2 L) and water (212 mL) was heated at reflux for 6 h, then it was stirred under nitrogen at room temperature overnight. The ethanol was removed at reduced pressure (aspirator), and the residue was diluted with

water (1 L) and extracted with ether (3 x 400 mL). The combined extract was washed with water (600 mL), dried ($MgSO_4$), and concentrated (aspirator) to an oil. Distillation gave 526.4 g (79%) of pure product, bp 130°C/5 mmHg, lit. bp 138°C/18 mmHg (11).

N-(2-Bromopropionyl)-N-methylphenetidine (3): - A 2-L three-necked flask--equipped with a mechanical stirrer, a reflux condenser and a dropping funnel--was charged with N-methylphenetidine (111.6 g, 0.738 mol), triethylamine (78.4 g, 0.775 mol) and methylene chloride (500 mL). The mixture was cooled in an ice bath, and a solution of 2-bromopropionyl bromide (159.3 g, 0.738 mol) in methylene chloride (200 mL) was added dropwise under a nitrogen stream. The mixture was stirred at room temperature for 40 minutes, then it was washed successively with water (1 L), 0.5 N HCl (1 L), and brine (3 x 1 L). The organic phase was dried ($MgSO_4$), treated with charcoal, filtered, and concentrated (aspirator) to yield 204.8 g (97%) of product as a thick brown oil. This material was used as such in the next step. NMR ($CDCl_3$) δ 1.42 (t, 3H, J=7 Hz), 1.70 (d, 3H, J=6.2 Hz), 3.22 (s, 3H), 4.02 (q, 2H, J=7 Hz), 4.25 (q, 1H, J=6.2 Hz), 6.82 (d, 2H, J=8 Hz), 7.13 (d, 2H, J=8 Hz).

Thin-Layer Chromatography

Eluent	Rf	Comment
Benzene/ether (9:1)	0.3	Slight lower R_f impurity

1,3-Dimethyl-5-hydroxyindolin-2-one (4): - A 1-L Erlenmeyer flask equipped with a mechanical stirrer was charged with N-(2-bromopropionyl)-N-methylphenetidine (100 g, 0.349 mol). At room temperature, aluminum chloride (93.2 g, 0.698 mol) was added. After a few seconds, a reaction set in, becoming rather vigorous with copious evolution of ethyl chloride, the mass setting to a solid. Additional aluminum chloride (69.8 g, 0.524 mol) was added, and the mixture was heated at 210-220°C (oil bath temperature) for 1 h. After cooling, the dark solid was pulverized and treated with ice-cold water (1.8 L) containing concentrated hydrochloric acid (36 mL). After stirring for ca. 10 minutes, the solid was collected, washed with water (500 mL), and dissolved in tetrahydrofuran (600 mL). The solution was dried ($MgSO_4$), treated with charcoal, filtered, and concentrated to dryness (aspirator) to give 54.1 g (87.5%) of a beige solid.

Additional product, 119.6 g (87.6% yield), was prepared by the same procedure starting with 220.7 g of N-(2-bromopropionyl)-N-methylphenetidine. The combined product (173.7 g) was recrystallized from a mixture of reagent alcohol (1 L), tetrahydrofuran (1 L), and n-hexane (2 L) to yield 130 g (66%) of pure title compound as light tan crystals, mp 210-212°C, lit. mp 219°C

(11). NMR (DMSO-d_6) δ 1.28 (d, 3H, J=7.7 Hz), 3.08 (s, 3H), 3.42 (q, 1H, J=7.7 Hz), 6.75 (m, 3H), 9.05 (s, 1H).

Anal. Calcd for $C_{10}H_{11}NO_2$ (177.20): C, 67.78; H, 6.26; N, 7.91. Found: C, 67.64; H, 6.38; N, 7.89.

Thin-Layer Chromatography

Eluent	Rf	Comment
Toluene/ether (7:3)	0.18	Homogeneous

5-Methoxy-1,3,3-trimethylindolin-2-one (5): - A 2-L three-necked flask, equipped with a mechanical stirrer and septa, was charged with sodium hydride (29 g, 0.73 mol, 60% in oil) and dimethylformamide (138 mL). A solution of compound 4 (59 g, 0.33 mol) in dimethylformamide (460 mL) was added under a nitrogen stream with ice-cooling. The mixture was stirred at ambient temperature for 10 minutes, cooled (ice bath), and treated dropwise with methyl iodide (234.2 g, 1.65 mol). After the addition was completed, the mixture was stirred at room temperature for 1.5 h and quenched by the addition of water (400 mL). The mixture was extracted with ethyl ether (3 x 500 mL). The combined extract was washed with water (2 x 500 mL), and then it was dried ($MgSO_4$). The solvent was removed under reduced pressure to give 72.4 g of a light brown wet solid.

By the same procedure, an additional 84 g of crude product 5 was prepared from 67.9 g of intermediate 4.

The combined solid (156.4 g) was slurred with petroleum ether (300 mL) and collected and recrystallized from a mixture of ethyl ether (300 mL) and petroleum ether (800 mL) to yield 99 g (67%) of pure product 5 as beige crystals, mp 56-58°C; lit. mp 58.5-59°C (12). NMR ($CDCl_3$) δ 1.38 (s, 6H), 3.23 (s, 3H), 3.87 (s, 3H), 6.75-7.07 (m, 3H).

Anal. Calcd for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.34; H, 7.29; N, 6.85.

Thin-Layer Chromatography

Eluent	Rf	Comment
Toluene/ether (7:3)	0.45	Very slight lower R_f impurity

5-Methoxy-1,3,3-trimethylindoline (6): - A 3-L three-necked flask equipped with a mechanical stirrer and septa was charged with lithium aluminum hydride (26.9 g, 0.70 mol) and anhydrous tetrahydrofuran (900 mL). A solution of concentrated sulfuric acid (18.89 mL) in tetrahydrofuran (400 mL) was added

dropwise over 85 minutes at -15 to -5°C. While the temperature was maintained at -15 to -5°C, a solution of compound 5 (48 g, 0.23 mol) in tetrahydrofuran (400 mL) was added to the grayish suspension over a period of 60 minutes. The mixture was stirred at room temperature for 20 h, then quenched with saturated aqueous sodium sulfate (480 mL). The grey precipitate was removed by filtration and washed thoroughly with ethyl ether (1.5 L). The combined filtrate was separated from a water layer and dried ($MgSO_4$). After filtration, the solvent was removed (aspirator) to give 47 g of a brown liquid. Additional intermediate 5 (48 g) was processed in the same manner and gave 46.2 g of crude 6. The combined crude product (93.2 g) was distilled to give 78.9 g (88%) of pure product 6, a yellow clear liquid, bp 115-116°C/1.2 mmHg; lit. bp 118-120°C/6 mmHg (12). NMR ($CDCl_3$) δ 1.30 (s, 6H), 2.70 (s, 3H), 3.02 (s, 2H), 3.75 (s, 3H), 6.27-6.87 (m, 3H).

A sample of the product (0.7 g) was treated with concentrated hydrochloric acid (1 g) to give the hydrochloride salt (0.7 g, 84%), mp 202.5-204.5°C; lit. mp 203-203.5°C (12).

Anal. Calcd for $C_{12}H_{17}NO \cdot HCl$ (227.73): C, 63.49; H, 7.97; Cl, 15.57; N, 6.15. Found: C, 63.35; H, 7.78; Cl, 15.72; N, 6.12.

5-Hydroxy-1,3,3-trimethylindoline hydrobromide (7): - 5-Methoxy-1,3,3-trimethylindoline (39 g, 0.2 mol) was heated under nitrogen with 48% hydrobromic acid (217 g) at reflux for 4 h. The excess hydrobromic acid was removed under reduced pressure (aspirator, steam bath) followed by azeotropic distillation with benzene. The solid residue was slurred with a mixture of tetrahydrofuran (400 mL) and ethyl ether (100 mL) to give 51.6 g (100%) of crude 7, a light beige powder, mp 212-215°C. An additional 52.1 g (101%) of crude compound 7 was prepared from 39 g of compound 6. The combined crude product (103.7 g) was recrystallized from a mixture of ethanol (1 L) and ethyl ether (1.5 L) to give 98 g (95%) of pure compound 7 as off-white crystals, mp 212-214°C; lit. mp 212-212.5°C (12). NMR (CD_3OD) δ 1.43 (s, 6H), 3.27 (s, 3H), 3.77 (s, 2H), 6.73-7.57 (m, 3H).

Anal. Calcd for $C_{11}H_{15}NO \cdot HBr$ (258.17): C, 51.18; H, 6.25; Br, 30.95; N, 5.43. Found: C, 51.21; H, 6.27; Br, 30.72; N, 5.58.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.28	Slight tailing

5-(1,3,3-Trimethylindolinyl)N,N-diethylcarbamate hydrobromide (8a): - To a mixture of 5-hydroxy-1,3,3-trimethylindoline hydrobromide (22 g, 85.2 mmol), tetrabutylammonium iodide (880 mg), and diethylcarbamyl chloride (27.7 g, 204.5 mmol) in benzene (195 mL) was added dropwise 50% aqueous sodium hydroxide (44 g, 550 mmol). The mixture was heated at reflux for 1 h. After cooling, water (100 mL) was added. The water layer was separated and extracted with benzene (2 x 100 mL). The combined benzene layer was washed with brine (2 x 100 mL), dried ($MgSO_4$), and evaporated (aspirator). The residue was purified by chromatography twice over silica gel (1 x 480 g, 1 x 300 g) and eluted with chloroform/ethyl acetate (9:1). The product-containing fractions were combined and concentrated (aspirator) to give 23.1 g (98%) of compound 8a free base as a light brown liquid. A portion of this material (21.9 g) was dissolved in anhydrous ether (500 mL) and cooled in an ice bath, and hydrogen bromide gas was passed through the solution. The creamy solid thus obtained was recrystallized twice from a mixture of isopropyl alcohol and ether to give 22.5 g (78%) of pure product as white crystals, mp 169.5-171.5°C (dec). NMR (CD_3OD) δ 1.30 (br t, 6H, J=8 Hz), 1.50 (s, 6H), 3.20-3.82 (m, 4H), 3.38 (s, 3H), 3.90 (s, 2H), 7.13-7.90 (m, 3H).

Anal. Calcd for $C_{16}H_{24}N_2O_2 \cdot HBr$ (357.30): C, 53.79; H,7.05; Br, 22.36; N, 7.84. Found: C, 53.96; H, 6.97; Br, 22.55; N,7.76.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.45	Slight tailing

4.2 5-(1,3,3-Trimethylindolinyl)N-ethylcarbamate

To a stirred ice-cold solution of 5-hydroxy-1,3,3-trimethylindoline hydrobromide (22 g, 85.2 mmol) in water (200 mL) covered with ether (300 mL) was added sodium carbonate (4.5 g, 42.6 mmol). The mixture was stirred ca. 5 minutes, and the layers were separated. Additional sodium carbonate (4.5 g, 42.6 mmol) was added to the water layer, which was extracted again with ether (2 x 300 mL). The combined organic layer was washed with water (2 x 300 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator) and replaced with benzene (200 mL). The solution was stirred at room temperature, under a nitrogen blanket, and treated with ethyl isocyanate (12.1 g, 170.4 mmol) and a tiny piece of sodium metal (ca. 30 mg). After 24 h, the mixture was filtered, and the filtrate was evaporated (aspirator) to give 20.9 g (98.6%) of product as a light pink solid. The solid was purified by column chromatography (silica gel, 250 g), and eluting with chloroform/ether (4:1) resulted in a white solid. Recrystallization from a mixture of tetrahydrofuran (40 mL) and n-hexane (240 mL) yielded

15.6 g (73.6%) of pure title compound as white crystals, mp 105-107°C; NMR ($CDCl_3$) δ 1.18 (t, 3H, J=7.4 Hz), 1.30 (s, 6H), 2.77 (s, 3H), 3.12 (s, 2H), 3.38 (q, 2H, J=7.4 Hz), 5.00 (br s, 1H), 6.27-7.03 (m, 3H).

Anal. Calcd for $C_{14}H_{20}N_2O_2$ (248.32): C, 67.71; H, 8.12; N, 11.28. Found: C, 67.86; H, 7.90; N, 11.30.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.31	Homogeneous

4.3 5-(1,3,3-Trimethylindolinyl)N-methylcarbamate

5-Hydroxy-1,3,3-trimethylindoline hydrobromide (23 g, 89.1 mmol) was converted with aqueous sodium carbonate to the free base, as described in section 4.2. A solution of the free base in benzene (300 mL) was stirred at ambient temperature, under a nitrogen blanket, with methyl isocyanate (10.2 g, 178.2 mmol) and sodium metal (ca. 30 mg) for 24 h. The mixture was filtered, and the excess methyl isocyanate was removed at room temperature under reduced pressure (aspirator). The solution was concentrated (aspirator, 35-40°C) to yield a light pink solid (20.4 g). This material was chromatographed (silica gel, 250 g), and eluting with chloroform/ether (4:1) resulted in a white solid. Recrystallization from a mixture of tetrahydrofuran (60 mL) and n-hexane (300 mL) gave 18.9 g (90%) of pure title compound as white crystals, mp 141-143°C, lit. mp 144.5-145°C (12); NMR ($CDCl_3$) δ 1.28 (s, 6H), 2.70 (s, 3H), 2.78 (d, 3H, J=5 Hz), 3.04 (s, 2H), 5.05 (br s, 1H), 6.23-6.95 (m, 3H).

Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.29): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.83; H, 7.92; N, 12.10.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.33	Homogeneous

4.4 d_8-Thiodiglycol

Into a 200-mL Parr bottle immersed in dry ice/acetone was condensed d_4-ethylene oxide (4.1 g, 0.085 mol), followed by bubbling in hydrogen sulfide (2.4 g, 0.07 mol, 1.6 eq). After adding ca. 20 mg of sodium methoxide, the bottle was stoppered in the Parr apparatus and allowed to come to room temperature. After standing 6 days, the bottle was cooled again in dry ice/acetone. The bottle was opened, and the viscous liquid was subjected to short-path distillation (1 mmHg/25-210°C, oil bath).

Two fractions were collected. The first contained 2.4 g of a clear oil, bp 94-96°C/1 mmHg, which analyzed for d_4-thioglycol, and the second contained 3.3 g of the title compound, a yellow oil, bp 185-205°C/1 mmHg.

Anal. Calcd for $C_4H_2D_8O_2S$ (130.23): C, 36.89; O, 24.56; S, 24.62. Found: C, 38.65; O, 24.38; S, 24.38.

The above procedure was repeated, with the modification of using the above d_4-thioglycol as an additional reactant. Thus, into the 200-mL Parr bottle immersed in dry ice/acetone was condensed d_4-ethylene oxide (4.2 g, 87.5 mmol) followed by bubbling in hydrogen sulfide (0.9 g, 26.5 mmol, 1 eq). After adding the d_4-thioglycol (2.4 g, 29.2 mmol) and ca. 20 mg of sodium methoxide, the mixture was stoppered in the Parr apparatus and allowed to come to room temperature. After standing 6 days, distillation, as described above, gave two fractions. The second fraction 3.7 g, bp 115-128°c/0.5 mmHg, consisted of the title compound, a yellow oil. The combined yield of both runs was 65%, based on d_4-ethylene oxide.

Anal. Calcd for $C_4H_2D_8O_2S$ (130.23): C, 36.89; O, 24.56; S, 24.62. Found: C, 37.04; O, 24.44; S, 24.52.

4.5 5-(1,3,3-Trimethylindolinyl)N-n-heptylcarbamate hydrobromide

5-Hydroxy-1,3,3-trimethylindoline hydrobromide (21 g, 81.34 mmol) was converted to the free base, as described in section 4.2. A solution of the free base in benzene (300 mL) was stirred at ambient temperature, under nitrogen blanket, with n-heptyl isocyanate (11.49 g, 81.34 mmol) and sodium metal (ca. 30 mg) for 6 days, then it was heated at reflux for 30 h. After cooling, the mixture was filtered, and the solvent was removed under reduced pressure (aspirator) to give a light brown liquid, which was chromatographed (silica gel, 250 g) and eluted with chloroform/ether (4:1). The product-containing fractions were combined and concentrated (aspirator) to give a light yellow liquid. The liquid was dissolved in anhydrous ether (500 mL) and cooled in an ice bath, and anhydrous hydrogen bromide gas was bubbled through the solution. The cream-colored solid that precipitated was collected and recrystallized from a mixture of tetrahydrofuran (180 mL) and petroleum ether (300 mL) to give white crystals (23.8 g). Two additional recrystallizations from a mixture of tetrahydrofuran (165 mL) and petroleum ether (270 mL) yielded 22.8 g (70%) of pure title compound, mp 94-96°C; NMR (CD_3OD) δ 0.63-1.08 (m, 3H), 1.08-1.87 (m, 10H), 1.47 (s, 6H), 2.97-3.44 (m, 2H), 3.33 (s, 3H), 3.82 (s, 2H), 7.12-7.82 (m, 3H).

Anal. Calcd for $C_{19}H_{30}N_2O_2 \cdot HBr$ (399.38): C, 57.14; H, 7.82; Br, 20.01; N, 7.01. Found: C, 56.98; H, 7.72; Br, 19.86; N, 6.95.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.59	Slight tailing

4.6 8-Chlorocaprylic acid

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

7-Methoxycarbonylheptanoyl chloride (1): - A mixture of monomethyl suberate (20 g, 0.106 mol) and thionyl chloride (31.5 g, 0.265 mol) was heated at 50°C (oil bath temperature) for 2 h and at 110°C (oil bath temperature) for 1.5 h. The excess thionyl chloride was removed by distillation and the residue was distilled at reduced pressure to yield 21.1 g (96%) of pure product, a colorless clear liquid, bp 112°C/1.1 mmHg; NMR ($CDCl_3$) δ 1.03-2.10 (m, 8 H), 2.35 (br t, 2 H, J = 7 Hz), 2.95 (br t, 2 H, J = 7 Hz), 3.73 (S, 3 H).

Anal. Calcd for $C_9H_{15}O_3Cl$ (206.67): C, 52.31; H, 7.32; Cl, 17.15. Found: C, 52.37; H, 7.49; Cl, 16.89.

Additional acid chloride (87.9 g, 100%) was prepared in the same manner using 80 g of monoester 1.

Methyl 8-hydroxycaprylate (3): - A 2-L three-necked flask--equipped with a mechanical stirrer, a thermometer and a rubber septum--was charged with sodium borohydride (45.2 g, 1.19 mol) and dioxane (480 mL). The mixture was cooled to 0°C (dry ice-glycol), and a solution of 7-methoxycarbonylheptanoyl chloride (80 g, 0.387 mol) in dioxane (40 mL) was added dropwise at such a rate as to maintain the temperature at about 5°C. After the addition was completed, the milky suspension was heated at 50°C for 1 h. After cooling, water (240 mL) was added to the mixture with ice-cooling and stirring. The white precipitate was removed by filtration, and the filtrate was concentrated (aspirator) to about 150 mL and extracted with ether (3 x 300 mL). The combined ether extract was washed with water (2 x 300 mL) and dried ($MgSO_4$). After filtration, the solvent was removed (aspirator) to yield a clear faint yellow liquid, 52.2 g. A portion of this liquid (41.6 g) was distilled to give 29.1 g (54%) of pure product, bp 128-132°C/2.8 mmHg; NMR ($CDCl_3$) δ 1.03-2.03 (m, 1 OH), 2.33 (br t, 2 H, J = 7 Hz), 3.70 (S, 3 H), 3.33-3.97 (m, 3 H).

Anal. Calcd for $C_9H_{18}O_3$ (174.23): C, 62.04; H, 10.41. Found: C, 62.25; H, 10.48.

Additional acid chloride (87 g) was processed in this manner to give 43 g (59%) of pure product.

8-Hydroxycaprylic acid (4): - A mixture of methyl 8-hydroxycaprylate (55.2 g, 0.317 mol), potassium hydroxide (35.6 g, 0.634 mol), ethanol (160 mL), and water (62 mL) was heated at reflux for 3 h. Most of the solvent was removed at reduced pressure (aspirator), and the residue was dissolved in water (200 mL). The solution was acidified with concentrated sulfuric acid to pH 1 and extracted with ether (4 x 200 mL). The combined ether extract was washed with water (6 x 200 mL), dried ($MgSO_4$), treated with charcoal, and filtered. The filtrate was concentrated under reduced pressure (aspirator) to give a white solid (30.2 g). Recrystallization of the solid from a mixture of ether (150 mL) and hexane (400 mL) yielded 28 g (55%) of pure product as white crystals, mp 59-61°C; lit. mp 61-61.5°C (17); NMR ($CDCl_3$) δ 1.10-2.00 (m, 10 H), 2.37 (br t, 2 H, J = 7 Hz), 3.67 (br t, 2 H, J = 6.2 Hz), 7.10-7.43 (m, 2 H, D_2O exchangeable).

Anal. Calcd for $C_8H_{16}O_3$ (160.21): C, 59.98; H, 10.07. Found: C, 60.13; H, 10.18.

Thin-Layer Chromatography

Eluent	Rf	Comment
Hexane/methylene chloride/acetone/ acetic acid (6:2:2:0.5)	0.31	Homogeneous

8-Chlorocapryloyl chloride (5): - A mixture of 8-hydroxycaprylic acid (27.5 g, 0.172 mol) and thionyl chloride (81.7 g, 0.687 mol) was heated at 50-55°C (oil bath temperature) for 2 h. Excess thionyl chloride was removed at reduced pressure (aspirator, oil bath temperature 55°C), and the residue was distilled to yield 31.4 g (93%) of pure product as colorless clear liquid, bp 130-135°C/4 mmHg; lit. bp 113-114°C/1.4 mmHg (30); NMR (CCl_4) δ 1.10-2.13 (m, 10 H), 2.87 (t, 2 H, J = 6.7 Hz), 3.50 (t, 2 H, J = 6.7 Hz).

8-Chlorocaprylic acid (6): - To a cooled (ice bath) mixture of 8-chlorocapryloyl chloride (31 g, 0.157 mol), tetrahydrofuran (310 mL) and water (310 mL) was added sodium carbonate (18.3 g, 0.173 mol) in portions. After the addition was completed, the cloudy solution was stirred with cooling for 30 minutes and at room temperature for 16 h. The clear solution was concentrated at reduced pressure (aspirator) to about 310 mL and extracted with ether (310 mL). The aqueous layer was cooled in an ice bath, acidified to pH 1 with concentrated hydrochloric

acid (37 g), and extracted with ether (2 x 310 mL). The combined ether extract was washed with water (310 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator) to give a white semisolid (25.8 g). The material was chromatographed over silica gel (300 g) and eluted with a mixture of hexane/methylene chloride/tetrahydrofuran/acetic acid (6:2:2:0.5). The product-containing fractions were combined, and the solvent was removed at reduced pressure (aspirator). The residual solid was recrystallized from a mixture of ether (minimum) and n-hexane (150 mL) to yield 12.5 g (45%) of pure product, a white crystalline solid, mp 33-35°C; lit. mp 34.5-35°C (31). NMR ($CDCl_3$) δ 1.10-2.13 (m, 10 H), 2.13-2.90 (m, 2 H), 3.42-3.88 (t, 2 H, J = 6 Hz), 11.52 (br s, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_8H_{15}O_2Cl$ (178.66): C, 53.78; H, 8.46; Cl, 19.84. Found: C, 53.82; H, 8.37; Cl, 19.59.

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/methylene chloride/ tetrahydrofuran/acetic acid (6:2:2:0.5)	0.65	Homogeneous

4.7 4-(2-Chloroethyl)benzoic acid

As purchased, 4-(2-chloroethyl)benzoic acid (9.0 g, 0.048 mol) was dissolved in boiling toluene (90 mL). The solution was filtered, and the filtrate was cooled in an ice bath for 4 h. The solid was collected by filtration and washed with cold petroleum ether (50 mL). The washed solid was dried at 60°C/1 mmHg for 16 h to give 7.9 g (88% recovery) of pure product, mp 186-188°C.

Anal. Calcd for $C_9H_{10}ClO_2$ (185.63): C, 58.55; H, 4.91; Cl, 19.20. Found: C, 58.52; H, 4.67; Cl, 18.91.

Thin-Layer Chromatography

Eluent	Rf	Comment
Ethyl acetate/chloroform (3:7)	0.77	Homogeneous

4.8 5-Carboxypentyl trifluoromethyl disulfide

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

6-Mercaptohexanoic acid (1): - A mixture of 6-bromohexanoic acid (26.5 g, 0.136 mol) and thiourea (10.3 g, 0.136 mol) in ethanol (90 mL) was heated at reflux under nitrogen for 2 h. At the end of this period, sodium hydroxide (13.6 g, 0.34 mol) in water (140 mL) was added to the refluxing solution. The mixture was heated at reflux for an additional 2 h, cooled to room temperature, covered with benzene (200 mL), and acidified with dilute sulfuric acid (18 g concentrated sulfuric acid in 90 mL of water). The layers were separated, and the aqueous layer was extracted with benzene (1 x 200 mL). The combined benzene layer was washed with water (2 x 400 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure (aspirator), and the residue was stirred vigorously with n-hexane (100 mL). The white precipitate (1.0 g) was removed by filtration, and the filtrate was concentrated under reduced pressure (aspirator) to an oil. Distillation gave 14.3 g (71%) of pure title compound, a colorless clear liquid, bp 119-121°C/ 0.6 mmHg; lit. bp 112-116°C/0.8 mmHg (32). ^1H NMR ($CDCl_3$) δ 1.10-2.03 (m, 7 H), 2.03-2.87 (m, 4 H), 11.65 (s, 1 H).

Anal. Calcd for $C_6H_{12}O_2S$ (148.23): C, 48.62; H, 8.16; S, 21.63. Found: C, 48.72; H, 8.04; S, 21.83.

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/methylene chloride/ tetrahydrofuran/acetic acid (6:2:2:0.5)	0.51	Homogeneous

5-Carboxypentyl trifluoromethyl disulfide (2): - A solution of 6-mercaptohexanoic acid (9.4 g, 63.3 mmol) in methylene chloride (40 mL) was added dropwise to a solution of trifluoromethylsulfenyl chloride (9.5 g, 69.6 mmol) in methylene chloride (20 mL) at -40°C (cooling bath temperature) under a nitrogen atmosphere. The clear solution was stirred at -40°C for 1 h, at room temperature for 2 h, and heated at reflux for 1 h. After cooling, the reaction mixture was poured into ice water (60 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 60 mL). The combined methylene chloride layer was washed with water (5 x 90 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure (aspirator), and the residue was distilled twice to yield 8.9 g (57%) of pure product, a colorless clear liquid, bp 142°C/ 0.8 mmHg. ^1H NMR ($CDCl_3$) δ 0.97-2.10 (m, 6 H), 2.10-3.20 (m, 2 H), 2.63-3.20 (m, 2 H), 11.77 (s, 1 H).

Anal. Calcd for $C_{17}H_{11}F_3O_2S_2$ (248.30): C, 33.86; H, 4.47; F, 22.96; S, 25.83. Found: C, 34.09; H, 4.60; F, 22.88; S, 26.01.

Thin-Layer Chromatography

Eluent	Rf	Comment
n-Hexane/methylene chloride/ acetone/acetate acid (6:2:2:0.5)	0.59	Homogeneous

4.9 cis-4-Chloro-2-buten-1-ol

Thionyl chloride (82 mL, 134.5 g, 1.13 mol) was added dropwise to a mixture of 2-buten-1,4-diol (100 g, 1.13 mol) and pyridine (75 mL) in ether (175 mL). The temperature of the mixture was maintained at 0-5°C during the addition. After the addition was completed, the mixture was stirred at room temperature for 2 h, then poured into ice water (200 mL). The layers were separated and the aqueous layer was extracted with ether (1 x 200 mL). The combined organic layer was washed with water (3 x 200 mL), dried ($MgSO_4$), and filtered. The filtrate was treated with charcoal and filtered through celite. The ether was removed under reduced pressure (aspirator), and the residue was distilled. Fractions boiling in the range of 81-82°C/6 mmHg were collected and combined to give 28 g of crude product. The greyish green liquid was chromatographed over silica gel (100 g) and eluted with ether. Fractions containing the product were combined and concentrated (aspirator), and the residual liquid was triple-distilled to yield 13.8 g (11.5%) of pure product, a colorless clear liquid, bp 61-63°C/1.0 mmHg; lit. bp 50-52°C/ 0.4-0.5 mmHg (19). ^1H NMR ($CDCl_3$) δ 2.33-2.67 (br s, 1 H, exchangeable with D_2O), 3.83-4.67 (m, 4 H), 5.50-6.17 (m, 2 H).

Anal. Calcd for C_4H_7ClO (106.56): C, 45.09; H, 6.63; Cl, 33.27. Found: C, 44.99; H, 6.51; Cl, 33.16.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ether (3:2)	0.61	Homogeneous

4.10 Sodium ethanethiosulfonate

A 1-L three-necked flask--equipped with a reflux condenser, an inner thermometer, and septum--was charged with sodium sulfide nonahydrate (72.1 g, 0.3 mol). After flushing with nitrogen, deionized water (300 mL) was added. The clear solution was heated to 95-100°C, and ethanesulfonyl chloride (38.6 g, 0.3 mol) was added dropwise. The stirred mixture was

heated at reflux overnight, then it was concentrated (aspirator) to dryness. The solid residue was extracted with hot ethanol (500 mL) and filtered. The filtrate was stored in a refrigerator overnight and refiltered. The filtrate was concentrated under reduced pressure until a solid began to precipitate. The mixture was heated until homogeneous and seeded with a few crystals of the product. After cooling, the mixture was filtered to give 21.3 g of product, mp 276-279°C (dec). Concentration of the mother liquor gave an additional 9.5 g, mp 276-279°C (dec). The combined product (30.8 g) was slurried with toluene (400 mL) for 1.5 h and filtered. The solid thus obtained was recrystallized from ethanol (300 mL) to give 16.9 g (38%) of pure title compound as white scaly crystals, mp 279-281°C (dec). ^{1}H NMR (CD_3OD) δ 1.40 (t, 3 H, J=8 Hz), 3.23 (q, 2 H, J=8 Hz).

Anal. Calcd for $C_2H_5NaO_2S_2$ (148.18): C, 16.21; H, 3.40; Na, 15.51; S, 43.28. Found: C, 16.36; H, 3.32; Na, 15.48; S, 43.05.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/i-propanol/ acetic acid (8:2:0.5)	0.21	Homogeneous

4.11 Thiotaurine

The synthesis route to the title compound is shown in Chart No. 4.

2-Aminoethyl 2-aminothanethiolsulfonate dihydrochloride (1): - 2-Aminoethanethiol hydrochloride (100 g, 0.88 mol) and potassium iodide (1 g) were dissolved in water (200 mL). The solution was cooled in an ice water bath to ca. 5°C. Hydrogen peroxide (122.5 mL, 32.45%, 1.30 mol) was added dropwise to the stirred solution at a rate to maintain the temperature below 55°C (ca. 1 h). The dark solution was stirred at 20°C for 17 h. The now colorless solution was concentrated (aspirator, < 50°C) until a thick oil remained. Glacial acetic acid was added, and the solution was allowed to stand for 2 h at 25°C. The resulting precipitate was collected, washed with ether (3 x 100 mL), and redissolved in water (140 mL, 40°C). Ethanol (600 mL) was slowly added to the stirred solution. After standing for 1 h, the resulting precipitate was collected, and it was washed with ethanol (100 mL) and ether (2 x 100 mL). The precipitate was dried at 25°C/0.2 mmHg for 2 h to give 83.7 g of white solid, mp 174-175°C; lit. mp 168-170°C (33). A second crop of 15.7 g, mp 164-167°C, was also collected for a total of 99.4 g (88%).

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.60	Trace of hypotaurine at 0.88

Hypotaurine (2): - 2-Aminoethyl 2-aminoethanethiol-sulfonate dihydrochloride (20.0 g, 0.777 mol) was dissolved in 20% aqueous sodium hydroxide (20 mL) and applied onto a column of Dowex 1-X2 resin (hydroxide form, 660 mL, 0.46 mol eq.). The column was washed with water until the eluate was neutral (3.5 L). Then, the product was eluted with 2% hydrochloric acid. The product-containing fractions (just before the acid front) were combined and concentrated (50°C, 20 to 0.1 mmHg) to dryness to give 11.2 g of a solidified oil. The solid was suspended in hot methanol (40 mL), and water was added slowly until the solid dissolved (ca. 2-3 mL). Ether was added (10 mL) until cloudiness persisted. The solution was cooled in an ice bath for 10 minutes and filtered. The solid was rinsed with methanol (20 mL) and ether (20 mL), and then it was dried to give 6.9 g of white needles, mp 177-178°C; lit. mp 178-179°C (22). A second crop of 1.6 g, mp 174-176°C was collected also for a total of 8.5 g (75%). In a similar manner, 20.5 g of starting material was processed to yield 7.7 g of first crop product, mp 177.5-178°C . ^1H NMR (D_2O) δ 2.70 (t, 2 H), 3.83 (t, 2 H), 4.78 (s, 3 H, HOD).

Anal. Calcd for $C_2H_7NO_2S$ (109.15): C,22.00; H,6,47; N, 12.84; S,29.37. Found: C, 21.93; H, 6.48; N, 12.69; S, 29.47.

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.88	Homogenous

Thiotaurine (3): - Hypotaurine (15.4 g, 0.141 mol), sulfur powder (4.75 g, 0.148 mol), and sodium hydroxide solution (0.20 N, 70 mL) were added to ethanol (500 mL). The mixture was heated to reflux for 45 minutes, then cooled in an ice bath with stirring for 1 h. The resulting precipitate was collected, rinsed with ethanol (50 mL) and ether (50 mL), and dried (25°C/0.1 mmHg, 10 minutes) to yield 17.3 g of an off-white solid, mp 210-213°C. This material was dissolved in hot water (80 mL), the solution was filtered to remove a small amount of sulfur (ca. 200 mg), and the product was precipitated by the slow addition of ethanol (500 mL). After cooling in an ice bath for 1 h, the mixture was filtered, and the product was dried at 25°C/0.1 mmHg for 2 h to give 15.6 g (78%) of pure product as

white crystals, mp 212-213°C; lit. mp 213-214°C (22). ^{1}H NMR (D_2O) δ 3.68 (s, 4 H), 4.78 (s, 3 H, HOD).

Anal. Calcd for $C_2H_7NO_2S_2$ (141.21): C, 17.01; H, 5.00; N, 9.92; S, 45.51. Found: C, 17.21; H, 4.81; N, 9.80; S, 45.51.

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.85	Homogeneous

4.12 Sodium 1-propanethiosulfonate

A 1-L three-necked flask was equipped with a magnetic stirring bar, a dropping funnel, a reflux condenser, and a septum. The flask was charged with sodium sulfide nonahydrate (46.3 g, 0.193 M), water (125 mL), and dimethoxyethane (375 mL). With ice-cooling, a solution of 1-propanesulfonyl chloride (25 g, 0.175 M) in dimethoxyethane (100 mL) was added dropwise under a nitrogen stream. After the addition was completed, the light green homogeneous solution was heated at reflux for 1 h, then it was stored in a refrigerator overnight. The solvents were removedunder reduced pressure (aspirator). To the residue was added ethanol (200 mL), and the solution was concentrated to dryness (aspirator). This procedure was repeated using benzene (200 mL). The resultant dry residue was then extracted with hot ethanol (300 mL), and the solution was filtered. The filtrate was treated with charcoal and filtered again. The filtrate was concentrated under reduced pressure (aspirator) until solid began to precipitate, then diluted with a mixture of toluene (300 mL) and ether (100 mL). The precipitated solid was collected and dried to give creamy crystals (13.6 g). One recrystallization from isopropanol (200 mL) gave 10.7 g (38%) of pure product as white crystals, mp 260-262°C (dec). ^{1}H NMR (CD_3OD) δ 1.07 (t, 3 H, J=7 Hz), 1.60-2.37 (m, 2 H), 3.03-3.47 (m, 2 H).

Anal. Calcd for $C_3H_7NaO_2S_2$ (162.21): C, 22.21; H, 4.35; Na, 14.17; S, 39.54. Found: C, 22.43; H, 4.49; Na, 14.02; S, 39.50.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/methanol (4:1)	0.24	Homogeneous

4.13 (S)(-)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate

To an ice-cold, stirred mixture of 1,3,3-trimethyl-5-hydroxyindole hydrobromide (16 g, 61.97 mmol), water (140 mL), and ether (200 mL) was added sodium carbonate (3.28 g, 31 mmol). The mixture was transferred to a separatory funnel, and the layers were separated. Additional sodium carbonate (3.28 g) was added to the aqueous layer which was extracted with ether (2 x 200 mL). The combined ether layer was washed with water (2 x 200 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure (aspirator). The residue was dissolved in anhydrous benzene (250 mL) containing (S)(-)-1-phenylethyl isocyanate (9.58 g, 65.07 mmol) and a tiny piece of sodium metal (ca. 50 mg). The mixture was stirred at room temperature under a nitrogen blanket for 14 days, filtered, and the filtrate was poured into ice water (150 mL). The layers were separated, and the aqueous layer was extracted with ether (1 x 150 mL). The combined organic layer was washed with water (3 x 150 mL) and dried ($MgSO_4$). The solution was concentrated under reduced pressure (aspirator) to near dryness, and the residue was chromatographed over silica gel (1 kg) using chloroform/ethyl acetate (9:1) as eluent. Fractions containing product were combined and evaporated under reduced pressure to give a light yellow solid. One recrystallization from a mixture of ether (50 mL) and petroleum ether (200 mL) gave 13.2 g of product as white crystals. Thin-layer chromatography of this material showed a minor impurity. Accordingly, the solid was dissolved in ether (400 mL), and the solution was extracted with 1 N HCl (2 x 40 mL) and 3 N HCl (1 x 40 mL). The combined hydrochloric acid extract was washed with ether (2 x 250 mL) and basified with 50% sodium hydroxide solution (16 g). The precipitated product was extracted with ether (2 x 250 mL). The combined ether extract was washed with water (3 x 250 mL). The extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure (aspirator) to give a white solid. One recrystallization from a mixture of ether (60 mL) and petroleum ether (240 mL) gave 9.0 g (45%) of pure product as white crystals, mp 85-86°C. ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.53 (d, 3 H, J=7 Hz), 2.75 (s, 3 H), 3.09 (s, 2 H), 4.65-5.72 (m, 2 H), 6.28-6.60 (m, 1 H), 6.72-7.03 (m, 2 H), 7.43 (s, 5 H); $[\alpha]_D$ -88.4° (c = 1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{24}N_2O_2$ (324.42): C, 74.05; H, 7.46; N, 8.63. Found: C, 73.98; H, 7.37; N, 8.80.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.63	Homogeneous

4.14 (R)(+)-5-(1,3,3-Trimethylindolinyl)-N-(1-phenylethyl)-carbamate

1,3,3-Trimethyl-5-hydroxyindole hydrobromide (23 g, 89.1 mmol) was dissolved in water (200 mL) covered with ether (300 mL). With ice-cooling, sodium carbonate (4.72 g, 44.55 mmol) was added to the solution. After shaking, the aqueous layer was separated, and additional sodium carbonate (4.72 g, 44.55 mmol) was added. The resultant aqueous solution was extracted with ether (2 x 300 mL). The combined ether layer was washed with water (2 x 300 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure (aspirator), and the residue, 1,3,3-trimethyl-5-hydroxyindole free base, was dissolved in anhydrous benzene (200 mL) containing (R)(+)-1-phenylethyl isocyanate (15.7 g, 106.9 mmol) and a small piece of sodium metal (ca. 160 mg). The mixture was stirred at room temperature for 65 h, cooled in an ice bath, and diluted with ether (100 mL) previously saturated with water. The solution was filtered, and the filtrate was evaporated under reduced pressure (aspirator) to give a light pink solid (30.5 g). The solid was chromatographed over silica gel (300 g) with chloroform/ethyl acetate (9:1) as eluent. The product-containing fractions were concentrated, and the white residual solid (24.4 g) was recrystallized three times from a mixture of ether/petroleum ether (100 mL:300 mL) to yield 15.7 g (54%) of pure title compound as white crystals, mp 84-86°C; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.53 (d, 3 H, J=7 Hz), 2.75 (s, 3 H), 3.09 (s, 2 H), 4.65-5.72 (m, 2 H), 6.28-6.60 (m, 1 H), 6.72-7.03 (m, 2 H), 7.43 (s, 5 H). $[\alpha]_D$ +89.1° (c = 1.01, $CHCl_3$).

Anal. Calcd for $C_{20}H_{24}N_2O_2$ (324.42): C, 74.05; H, 7.46; N, 8.63. Found: C, 74.03; H, 7.54; N, 8.64.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.63	Homogeneous

4.15 5-(1,3,3-Trimethylindolinyl)-N-(3-chlorophenyl)carbamate

5-Hydroxy-1,3,3-trimethylindoline hydrobromide (23 g, 89.1 mmol) was converted to the free base, as described in section 4.14. A solution of the free base in anhydrous benzene (200 mL) containing 3-chlorophenyl isocyanate (16.4 g, 106.9 mmol) and triethylamine (0.5 mL) was stirred under a nitrogen blanket at room temperature for 18 h, then it was diluted with ether (300 mL). The mixture was washed with water (150 mL) and extracted with 5 N HCl (2 x 300 mL). The combined acid extract was washed with ether (3 x 150 mL) and basified with 50% aqueous sodium hydroxide to pH 11. The product was extracted with ether (3 x 300 mL). The combined ether extract was washed with water (2 x

300 mL), and then it was dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator). The residue was recrystallized three times from a mixture of ether and petroleum ether to give 21.5 g (73%) of pure title compound as white crystals, mp 116-118°C; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 2.76 (s, 3 H), 3.10 (s, 2 H), 6.30-7.67 (m, 8 H).

Anal. Calcd for $C_{18}H_{19}ClN_2O_2$ (330.81): C, 65.35; H, 5.79; Cl, 10.72; N, 8.47. Found: C, 65.41; H, 5.82; Cl, 10.60; N, 8.44.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ether (19:1)	0.59	Homogeneous

4.16 Homothiotaurine

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

Bis(3-phthalimidopropyl)disulfide (1): - A mixture of N-(3-bromopropyl)phalimide (304 g, 1.13 mol) and sodium thiosulfate pentahydrate (287 g, 1.16 mol) in 50% aqueous methanol (1.5 L) was heated at reflux for 1 h. The heat was removed and iodine (146 g, 0.575 mol) was added in ca. 5 g portions over 30 minutes. Water was added (1 L), and the oily suspension was cooled with stirring in an ice water bath. The resulting dense granular solid was collected and rinsed with water (3 x 500 mL). The solid was suspended in hot ethanol (1 L). Methylene chloride (500 mL) was added, and most of the solid was dissolved. The hot solution was gravity-filtered and stored at -10°C for 17 h. The resulting crystals were collected and washed with ethanol (3 x 150 mL). The washed crystals were dried at 25°C/0.1 mmHg for 17 h to give 224 g (90%) of product, mp 86-87°C; lit. mp 91°C (25). ^1H NMR ($CDCl_3$) δ 2.05 (m, 4 H), 2.76 (t, 4 H), 3.85 (t, 4 H), 7.85 (m, 8 H).

Anal. Calcd for $C_{22}H_{20}N_2O_4S_2$: C, 59.98; H, 4.58; N, 6.36; S, 14.56. Found: C, 59.74; H, 4.41; N, 6.30; S, 14.71.

Thin-Layer Chromatography Whatman silica gel MK6F

Eluent	Rf	Comment
Chloroform/methanol (9:1)	0.65	Homogeneous (streaks)

Homocystamine dihydrobromide (2): - A mixture of bis(3-phthalimidopropyl)disulfide (223 g, 0.506 mol), hydrobromic acid (115 mL, 48%), and glacial acetic acid (115 mL) was heated at

reflux for 22 h. After adding water (1 L), the suspension was cooled in ice water (30 minutes) and filtered. The solid (phthalic acid) was rinsed with water (3 x 100 mL). The combined aqueous layer was concentrated (aspirator, 50°C) to dryness, and the residual solid was resuspended in water (400 mL). The suspension was filtered, and the filtrate was concentrated as before. The residue was dissolved in hot ethanol (500 mL). Ether (250 mL) was added. The resulting solid was collected, washed with ether (2 x 150 mL), and pressed dry with a rubber dam. The solid was dried at 25°C/0.1 mmHg for 17 h to give 117 g of product, mp 228-231°C. A second crop was also collected for a total of 132 g (76%). ^{1}H NMR (D_2O) δ 2.18 (m, 4 H), 2.90 (t, 4 H), 3.20 (t, 4 H).

Thin-Layer Chromatography Analtech RPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.48	Trace impurity at Rf 0.14

Homohypotaurine (3): - Homocystamine dihydrobromide (116 g, 0.339 mol) and potassium iodide (1 g) were dissolved in water (300 mL). Hydrogen peroxide (61 mL, 32.45%, 0.644 mol) was added dropwise over 30 minutes. The solution was warmed in a boiling water bath, which initiated an exothermic reaction. After 10 minutes, the flask was cooled in an ice water bath, and the solution was decanted from a gum that had formed (ca. 10 g). The solution was concentrated (aspirator, 50°C) to a thick oil. Acetic acid (600 mL) was added, and the solution was stirred at 25°C for 1 h. The solid precipitate was collected, washed with ether (3 x 50 mL), and recrystallized from ethanol/ether. This resulted in five crops of crude intermediate thiolsulfonate (total 88.4 g) all melting within the range of 167-174°C. Without further purification, half of the thiolsulfonate (44 g, 0.117 mol) was dissolved in water (30 mL), and solid sodium hydroxide was added until pH 12 was reached (ca. 11 g). The solution was applied onto a Dowex 1-X2 resin column (660 mL, 0.46 mol eq. hydroxide form), and the column was washed with water until the eluate was neutral (3 L). The product was eluted with 3% acetic acid. The product-containing fractions were eluted before the acid front and were combined and concentrated (aspirator, 50°C) to dryness. The residual solid was triturated with hot ethanol (50 mL), collected, and washed with ethanol (10 mL) and ether (50 mL). The solid was dried at 25°C/0.1 mmHg for 2 h to give 9.3 g (45% from the disulfide) of product, mp 186-189°C; lit. mp 190-192°C (24). An additional 11.3 g of product was obtained in a similar manner from two other runs. ^{1}H NMR (D_2O) δ 2.00 (m, 4 H), 2.37 (t, 4 H), 2.96 (t, 4 H).

Anal. Calcd for $C_3H_9NO_2S$: C, 29.25; H, 7.37; N, 11.37; S, 26.03. Found C, 28.96; H, 7.36; N, 11.16; S, 26.12.

Thin-Layer Chromatography Analtech RPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.79	Homogeneous

Homothiotaurine (4): - Homohypotaurine (20.0 g, 0.162 mol), sulfur powder (5.46 g, 0.170 mol), and sodium hydroxide solution (0.20 N, 80 mL) were added to ethanol (500 mL), and the mixture was heated at reflux for 45 minutes, then cooled in an ice bath for 15 minutes. The solid precipitate was collected and rinsed with ethanol (50 mL) and ether (100 mL). The solid was mostly dissolved in boiling water (80 mL), and the solution was filtered to remove unreacted sulfur (ca. 300 mg). Hot ethanol (400 mL) was added to the filtrate, and the solution was cooled in ice for 30 minutes. The precipitated solid was collected and washed as before. It was dried at 25°C/0.1 mmHg for 17 h to give 17.8 g (71%) of pure product, mp 238-239°C (dec); lit. mp 226-231°C (24). ^1H NMR (D_2O) δ 2.36 (m, 4 H), 3.40 (m, 8 H).

Anal. Calcd for $C_3H_9NO_2S_2$ (155.23): C, 23.21; H, 5.84; N, 9.02; S, 41.31. Found: C, 23.42; H, 5.90; N, 8.79; S, 41.00.

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.86	Homogeneous

4.17 4-Chlorobutanol

Commercial 4-chlorobutanol [Aldrich, technical grade (85%), 250 mL] was dried over potassium carbonate, filtered, and distilled through a 5-plate bubble plate column. After a 50-mL forecut, the main fraction, 77 g, was collected, bp 77°C/10 mmHg. The elemental analysis indicated that the product contained a small amount of water.

Anal. Calcd for $C_4H_9ClO \cdot 0.07H_2O$: C, 43.74; H, 8.39; Cl, 32.28; O, 15.59. Found: C, 43.64; H, 8.45; Cl, 32.43; O, 15.60.

4.18 5-(1,3,3-Trimethylindolinyl)-N,N-dimethylcarbamate hydrochloride

A 1-L three-necked flask was equipped with a magnetic stirring bar, a reflux condenser, and rubber septa. The flask was charged with 1,3,3-trimethyl-5-hydroxyindole hydrobromide (45 g, 0.174 M) and tetrabutylammonium iodide (1.8 g). The flask was flushed with nitrogen, and a solution of dimethylcarbamyl chloride (22.5 g, 0.209 M) in benzene (400 mL) was added. The

suspension was stirred at room temperature while 50% sodium hydroxide solution (90 g, 1.125 M) was added dropwise. After the addition was completed, the mixture was heated at reflux for 1.5 h, cooled to room temperature, and diluted with water (200 mL). The layers were separated, and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic layer was washed with water (2 x 500 mL), and then it was dried ($MgSO_4$). The solvent was removed under reduced pressure (aspirator) to give a thick, light brown oil (46 g). The oil was dissolved in ether (500 mL), and hydrogen chloride gas was bubbled through the solution. The resulting white solid was collected and recrystallized from a mixture of isopropanol (400 mL)/methanol (minimum for solution)/ether (700 mL) to give white crystals (45 g). This solid was recrystallized two additional times from isopropanol (370 mL)/ether (600 mL) to give 36.9 g (74%) of pure product as white crystals, mp 188-190°C, lit. mp 111-112°C (8), mp 188-190°C (9). NMR (CD_3OD) δ 1.47 (s, 6 H), 2.98, (s, 3 H), 3.10 (s, 3 H), 3.28 (s, 3 H), 3.78 (s, 2 H), 7.05-7.78 (m, 3 H).

Anal. Calcd for $C_{14}H_{21}ClN_2O_2$ (284.79): C, 59.05; H, 7.43; Cl, 12.45; N, 9.84. Found: C, 58.99; H, 7.48; Cl, 12.62; N, 9.78.

Thin-Layer Chromatography

Eluent	Rf	Comment
Chloroform/ethyl acetate (9:1)	0.44	Homogeneous

4.19 6-Aminohexylphosphonic acid, monopinacolyl ester

The synthesis route to the title compound is shown in Chart No. 6.

N-(6-Bromohexyl)phthalimide (1): - A mixture of potassium phthalimide (50.0 g, 0.270 mol) and 1,6-dibromohexane (98 g, 0.401 mol) in acetone (250 mL) was heated at reflux under a nitrogen atmosphere for 20 h. The resulting suspension was cooled to 0°C, filtered, and concentrated (20°C/0.1 mmHg, 25-60°C) until no further excess dibromide was removed. Hexanes (500 mL) was added. The suspension was heated to reflux and filtered hot, and then ether was added until a homogeneous solution was formed (ca. 30 mL). The solution was cooled at -10°C for 1 h. The resulting precipitate was collected and washed with cold hexane (-10°C, 2 x 100 mL); it was dried at 25°C/0.2 mmHg for 4 h to give 53 g (63%) of white product, mp 52-54.5°C; lit. mp 52.5-55°C (26), mp 57°C (34).

Thin-Layer Chromatography Whatman Silica Gel MK6F

Eluent	Rf	Comment
Hexanes/ethyl acetate (4:1)	0.48	Homogeneous

Diethyl 6-phthalimidohexylphosphonate (2): N-(6-Bromohexyl)phthalimide (47.5 g, 0.153 mol) and excess triethyl phosphite (100 mL) were stirred in a flask equipped with a Dean-Stark trap and condenser under a nitrogen atmosphere. The mixture was heated to a point at which the phosphite (bp 156°C) condensed halfway up the trap arm. The generated ethyl bromide by-product was collected in the receiving trap until the theoretical volume (11.4 mL) was obtained (ca. 2 h). The excess phosphite was removed by distillation (aspirator), and the pot residue was subjected to kugelrohr distillation. The receiver was changed at 180°C/0.055 mmHg, and the product was collected at 180-185°C (oven temperature) to yield 49.7 g (88%) of a thick, pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 6 H), 1.2-2.0 (m, 10 H), 3.71 (t, 2 H), 4.18 (q, 4 H), 7.7-7.9 (m, 4 H).

Anal. Calcd for $C_{18}H_{26}NO_5P$ (367.37): C, 58.84; H, 7.13; N, 3.81; P, 8.43. Found: C, 58.90; H, 7.33; N, 3.80; P, 8.22.

Thin-Layer Chromatography: Whatman Silica Gel MK6F

Eluent	Rf	Comment
Ethyl acetate	0.45	Homogenous

6-Phthalimidohexylphosphonic acid (3): - A mixture of diethyl 6-phthalimidohexylphosphonate (33.2 g, 0.0904 mol) and bromotrimethylsilane (26.2 mL, 0.109 mol) in methylene chloride (300 mL) was stirred at 25°C for 17 h under a nitrogen atmosphere. Methanol (65 mL) was added, and after 20 minutes, the solution was concentrated (aspirator) to a thick oil. Ethyl acetate (200 mL) was added, and the emulsion was heated to reflux. Methanol was added until a solution formed (ca. 25 mL). The flask was cooled to -10°C for 1 h. The resulting precipitate was collected, washed with ethyl acetate (2 x 50 mL), and dried at 25°C/0.2 mmHg to give 18 g of analytically pure product as a white powder, mp 159-160°C. The filtrate was concentrated to 40 mL and cooled to give an additional 5.0 g of product, mp 158.5-160°C for a total of 23.0 g (82%). ^{1}H NMR ($CDCl_3/CD_3OD$) δ 1.2-1.9 (m, 10 H), 3.75 (br t, 2 H), 4.67 (s, 2 H), 7.90 (br s, 4 H).

Anal: Calcd for $C_{20}H_{30}NO_5P$ (395.43): C, 54.02; H, 5.83; N, 4.50; P, 9.95. Found: C, 54.06; H, 5.74; N, 4.45; P, 9.96.

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4-methanol (2:1)	0.80	Homogeneous

Phthalimidohexylphosphonic acid, monopinacolyl ester monosodium salt (4): - 6-Phthalimidohexylphosphonic acid (40.0 g, 0.129 mol) was suspended in dry tetrahydrofuran (500 mL) under a nitrogen atmosphere. The flask was cooled in an ice water bath. Oxalyl chloride (13.6 mL, 0.154 mol) was added dropwise over 15 minutes. The mixture was stirred for 15 minutes and pinacol (50 mL) was added in one portion followed by triethylamine (50 mL) over a 15 minutes period. The suspension was allowed to warm to 25°C for 45 minutes. Ether (1 L) was added, and the mixture was extracted successively with water (1 L) and sodium hydroxide solution (1 N, 1 L). The combined aqueous layer was carefully acidified to pH 1 with concentrated hydrochloric acid and extracted with ether (3 x 700 mL). An oil that separated from the ether (containing some starting material and by-products) was discarded. The ether layer was dried ($MgSO_4$) and concentrated to 20.7 g of a colorless foam. The foam was dissolved in a mixture of acetone (100 mL) and isopropanol (20 mL), and the solution was treated with sodium hydride (2.1 g, 60%). The suspension was concentrated, and the residue was dried at 25°C/0.1 mmHg for 2 h to give 22.3 g (42%) of a wax. This semipurified product was homogeneous on TLC and was used as is in the next step. In a probe run, the product precipitated from a solvent mixture of ether, ethyl acetate, isopropanol, and methanol (10:3:2:1) to give a very hygroscopic white solid which was dried at 25°C/0.1 mmHg to a white, granular solid, mp 200-240°C. ^1H NMR (CD_3OD) δ 0.88 (s, 9 H), 1.19 (d, 3 H), 1.3-2.0 (m, 10 H), 3.68 (t, 2 H), 4.11 (m, 1 H), 7.88 (br s, 4 H).

Anal. Calcd for $C_{20}H_{29}NNaO_5P$ (417.40): C, 57.55; H, 7.00; N, 3.36; P, 7.42. Found: C, 57.29; H, 7.09; N, 3.42; P, 7.29.

Thin-Layer Chromatography Whatman Silica Gel MK6F

Eluent	Rf	Comment
Methanol/ethyl acetate (1:1)	0.74	Homogenous

6-Aminohexylphosphonic acid monopinacolyl ester (5):- A mixture of 6-phthalimidohexylphosphonic acid monopinacolyl ester monosodium salt (22.3 g, 0.0533 mol, semipurified oil) and hydrazine (20 mL) in reagent ethanol (600 mL) was heated at reflux for 90 minutes, then cooled to 25 C. Acetic acid (20 mL) and water (100 mL) were added, and the suspension was concentrated to ca. 300 mL and filtered (ca. 5 g of

phthalhydrazide was collected). The filtrate was concentrated to a thick oil which was triturated with ethanol/acetone (1:1, 100 mL) to give more solid. The suspension was filtered, and the filtrate was concentrated to an oil which was dissolved in 50 mL of water. A tertiary amine resin column (AG3-X4A, 120 g dry, 336 meq) was washed successively with sodium hydroxide (1 N, 800 mL) and water (800 mL). The aqueous solution of crude product was applied onto the resin column, and the column was eluted with water. The initial basic fractions contained most of the impurities by reverse phase thin-layer chromatography (RPTLC). The product-containing, neutral fractions were combined and concentrated (aspirator) to dryness. The residual solid was recrystallized by dissolving in ethanol (35 mL) and adding ether (200 mL) to give 3.3 g of slightly contaminated product, mp 237-246°C. The impure fractions were recycled through the column and recrystallized as above to give an additional 0.9 g of similar purity product. This product was combined with the product obtained from an identical run for a total of 8.7 g. The combined product was dissolved in water (25 mL) and applied on the recycled resin column. The product-containing fractions were combined, concentrated, and the residual solid was recrystallized as above to give 6.0 g of a white powder, mp 245-253°C. This material was dissolved in hot water (20 mL), and the solution was allowed to cool slowly. After 1 h, acetone (6 mL) was added and the suspension was cooled to 5°C for 2 h. The precipitated solid was collected quickly on a cold funnel, rinsed with 50% acetone/water (-10°C, 2 x 10 mL) and acetone (2 x 10 mL), and dried at 80°C/0.1 mmHg for 2 h to give 2.3 g of analytically pure product as white crystals, mp 250-255°C. The mother liquors from the crystallizations described above (8.7 g and 6.0 g) were concentrated to give second crops of less pure product which, after multiple crystallizations, afforded an additional 1.4 g of pure material, mp 250-255°C, for a total of 3.7 g (14%). ^{1}H NMR (D_2O) δ 0.813 (s, 9 H), 1.114 (d, 3 H), 1.329 (m, 4 H), 1.464 (m, 4 H), 1.601 (m, 2 H), 2.919 (t, 2 H), 3.901 (m, 1 H).

Anal. Calcd for $C_{12}H_{28}NO_3P$ (265.32): C, 54.31; H, 10.63; N, 5.28; P, 11.67. Found: C, 54.16, H, 10.36, N, 5.25; P, 11.48.

Thin-Layer Chromatography Analtech HPTLC-RPSF (Reversed Phase)

Eluent	Rf	Comment
0.2 M NaH_2PO_4/methanol (2:1)	0.15	Homogenous, ninhydrin positive

4.20 1,3,5-Tris-2'-chloroethylbenzene

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

1,3,5-Benzentriacetic acid (1): - A mixture of 1,3,5-triacetylbenzene (25.4 g, 0.130 mol), morpholine (78.3 g, 0.90 mol), and sulfur (28.8 g, 0.90 mol) was heated at reflux for 18 h. The hot solution was poured into water (500 mL), and the mixture was stirred at ambient temperature for 30 minutes. The solid was collected by filtration and washed with water (100 mL). The moist solid was added to a mixture of water (600 mL), glacial acetic acid (100 mL), and sulfuric acid (100 mL). The mixture was heated at reflux for 7 h, cooled to ambient temperature, made basic with 1 N NaOH, and filtered. The aqueous filtrate was washed with ether (3 x 150 mL), concentrated (aspirator) to one half volume, and acidified with sulfuric acid to pH 1. The solution was extracted continuously for 4 days with ether in a liquid-liquid extractor. The ether extract was dried over magnesium sulfate and concentrated to dryness to give 17.4 g of a dark yellow solid. The solid was dissolved in hot acetic acid (70 mL, 110°C), and the solution was filtered. The filtrate was stored at ambient temperature for 5 h. The solid was collected by filtration and washed with cold acetic acid (20 mL). Then, it was air-dried to give 13.1 g of a yellow solid. The solid was dissolved in hot glacial acetic acid (65 mL, 110°C), and the solution was treated with charcoal (1 g) and filtered (celite). The filtrate was stored at ambient temperature for 4 h. The solid was collected by filtration, washed with cold glacial acetic acid (10 mL), and air-dried to give 10.4 g (32%) of the title compound, a pale yellow solid, mp 214-217°C, lit. mp 215-216°C (35).

Triethyl 1,3,5-benzenetriacetate (2): - A mixture of 1,3,5-benzenetriacetic acid (10 g, 0.040 mol), ethanol (110 mL), benzene (50 mL), and sulfuric acid (1 mL) was heated at reflux for 6 h, then it was stored at ambient temperature overnight. The mixture was neutralized with saturated sodium bicarbonate solution, diluted with water (160 mL), and extracted with ether (3 x 75 mL). The combined ether extract was washed with water (3 x 200 mL). The extract was dried ($MgSO_4$) and concentrated (aspirator) to give 8.3 g (69%) of a brown oil. This material was used as such in the next step.

1,3,5-Tris-2'-hydroxyethylbenzene (3): - To a suspension of lithium hydride (4.2 g, 0.111 mol) in ether (420 mL) at reflux was added a solution of triethyl 1,3,5-benzenetriacetate (8.3 g, 0.025 mol) in ether (83 mL) dropwise over a period of 30 minutes. The mixture was heated at reflux overnight, cooled to ambient temperature, quenched carefully with water (350 mL), and stirred at room temperature overnight. A portion of the quenched reaction mixture (50 mL) was extracted with a mixture of ethyl acetate (50 mL) and n-butyl alcohol (5 mL). The organic layer was separated and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure (aspirator). The residue was triturated with petroleum ether to give a creamy solid (0.5 g). One recrystallization from a mixture of isopropanol (ca. 1 mL)

and petroleum ether (ca. 5 mL) gave pure product (363 mg), mp 73-75°C, lit. mp 75°C (27).

An additional 3.3 g of compound 4, mp 73-75°C, was isolated from the remaining quenched reaction mixture (300 mL) by the same procedure. The combined yield of pure product was 3.66 g (70%). ^{1}H NMR (DMSO-d_6) δ 2.70 (t, 6 H, J=7 Hz), 3.65 (dt 6 H, J=5 Hz), 4.60 (t, 3 H, J=5 Hz, D_2O exchangeable), 6.97 (s, 3 H).

Anal. Calcd for $C_{12}H_{18}O_3$ (210.26): C, 68.54; H, 8.63. Found: C, 68.54; H, 8.81.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/methanol/ formic acid (9:1:0.3)	0.33	Homogeneous

1,3,5-Tris-2'-chloroethylbenzene (5): - A mixture of 1,3,5-tris-2-hydroxyethylbenzene (0.5 g, 2.38 mmol), thionyl chloride (2.5 g, 21 mmol), and pyridine (0.5 mL) in anhydrous benzene (20 mL) was heated at reflux for 2 h. The mixture was concentrated under reduced pressure (aspirator) to dryness. The residue was dissolved in ethanol (20 mL), and the solution was again concentrated to dryness. The residue was treated with ethyl acetate (30 mL), and the mixture was filtered. The filtrate was washed with brine (2 x 30 mL), and then it was dried ($MgSO_4$). After filtration, the solvent was evaporated to give a faint yellow solid (0.6 g). One recrystallization from a mixture of ethyl ether (3 mL) and petroleum ether (9 mL) gave white plates (0.43 g), mp 76-78°C. Additional product (3.8 g) was prepared from compound 4 (3 g) by the same procedure. The combined product (0.4 g and 3.8 g) was chromatographed over a short column of silica gel (50 g) and eluted with a mixture of ethyl ether and petroleum ether (1:1) to give a white solid (4.1 g). One recrystallization from a mixture of ethyl ether (20 mL) and petroleum ether (60 mL) gave 2.9 g (66%) of pure product as white crystals, mp 76-78°C; lit. mp 77°C (27); ^{1}H NMR ($CDCl_3$) δ 3.08 (t, 6 H, J=7 Hz), 3.78 (t, 6 H, J=7 Hz), 7.10 (s, 3 H).

Anal. Calcd for $C_{12}H_{15}Cl_3$ (265.61): C, 54.26; H, 5.69; Cl, 40.04. Found: C, 54.35; H, 5.73; Cl, 39.94.

Thin-Layer Chromatography

Eluent	Rf	Comment
Petroleum ether/ether (4:1)	0.61	Homogeneous

4.21 Methyl pinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate

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

Diethyl 4-trifluoroacetylaminobenzylphosphonate (1): - A 1-L three-necked flask was equipped with a dropping funnel, a magnetic stirring bar, and rubber septa. The flask was charged with diethyl 4-aminobenzylphosphonate (50 g, 0.206 mol). After flushing with nitrogen, methylene chloride (200 mL) containing triethylamine (21.8 g, 0.216 mol) was added. To this solution (chilled with ice) was added dropwise a solution of trifluoroacetic anhydride (45.3 g, 0.216 mol) in methylene chloride (200 mL). The mixture was stirred with ice-cooling for 40 minutes and stored in a refrigerator for 2 days. The solution was then washed successively with ice water (1 x 400 mL), 1 N HCl (1 x 400 mL), water (2 x 400 mL), and dried ($MgSO_4$). After filtration, the solution was evaporated (aspirator) to give a creamy solid (66.2 g). One recrystallization from ethyl acetate/petroleum ether (250 mL:500 mL) yielded 65 g (93%) of pure product as white crystals, mp 145-146°C; ^1H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J=8 Hz), 3.15 (d, 2 H, J=22 Hz), 4.09 (quintet, 4 H, J=8 Hz), 6.98-7.87 (m, 4 H), 10.63 (br s, 1 H).

Anal. Calcd for $C_{13}H_{17}F_3NO_4P$ (339.27): C, 46.03; H, 5.05; F, 16.80; N, 4.13; P, 9.13. Found: C, 46.23; H, 5.00; F, 16.63; N, 4.25; P, 8.97.

Thin-Layer Chromatography

Eluent	Rf	Comment
Tetrahydrofuran/ether (1:1)	0.47	Homogeneous

4-Trifluoroacetylaminobenzylphosphonic acid (2): - To a solution of diethyl 4-trifluoroacetylaminobenzylphosphonate (60 g, 0.177 mol) in chloroform (180 mL) was added a solution of bromotrimethylsilane (81.3 g, 0.531 mol) in chloroform (100 mL) at room temperature. The mixture was stirred at room temperature for 2 h and stored in a refrigerator overnight. The solvent was removed under reduced pressure (aspirator), and the residue was dissolved in acetone (518 mL). To the clear solution (chilled with ice) was added water (11.85 mL) dropwise. The yellow clear solution was stirred at room temperature for 1 h, then it was concentrated (aspirator) to dryness. The residue was dried at 25°C/0.1 mmHg overnight to give 50.1 g (100%) of the title compound. An analytical sample, mp 228-229°C, was prepared by recrystallization from acetone/ether. ^1H NMR (acetone-d_6) δ 3.10 (d, 2 H, J=22 Hz), 7.23-7.97 (m, 4 H), 9.30 (br s, 2 H), 10.30 (br s, 1 H).

Anal. Calcd for $C_9H_9F_3NO_4P$ (283.15): C, 38.18; H, 3.20; F, 20.13; N, 4.95; P, 10.94. Found: C, 38.33; H, 3.25; F, 20.38; N, 4.87;; P, 10.86.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/methanol/formic acid (8:2:1)	0.47	Slight tailing

Dimethyl 4-trifluoroacetylaminobenzylphosphonate (3)

A. Diazomethane procedure: - To an ether solution of diazomethane (prepared from 21.5 g, 0.1 mol of Diazald and cooled in ice) was added 4-trifluoroacetylaminobenzylphosphonic acid (4.1 g, 17.2 mmol) in portions. The mixture was stirred for 1 h with ice-cooling. After destroying the excess diazomethane with acetic acid, the solution was concentrated (aspirator) to dryness to give a creamy solid (4.6 g). An additional 13.3 g of product was prepared by the same procedure from 12 g of phosphonic acid. The combined product (17.9 g) was dissolved in ethyl acetate (300 mL). The solution was washed with saturated aqueous sodium bicarbonate (150 mL) and brine (150 mL). The solution was dried ($MgSO_4$), and the solvent was removed (aspirator) to give 16.4 g of a light creamy solid. One recrystallization from a mixture of tetrahydrofuran/petroleum ether (70 mL:140 mL) gave 15.6 g (88%) of pure product as white crystals, mp 128-130°C. ^1H NMR ($CDCl_3$) δ 3.18 (d, 2 H, J=22 Hz), 3.77 (d, 6 H, J=11 Hz), 7.07-7.87 (m, 4 H), 10.26 (br s, 1 H).

Anal. Calcd for $C_{11}H_{13}F_3NO_4P$ (311.20): C, 42.46; H, 4.21; F, 18.32; N, 4.50; P, 9.95. Found: C, 42.66; H, 3.99; F, 18.25; N, 4.50; P, 10.09.

Thin-Layer Chromatography

Eluent	Rf	Comment
Tetrahydrofuran/ether (1:1)	0.41	Homogeneous

B. Acid chloride method: - A 1-L round-bottomed flask equipped with a magnetic stirring bar was charged with phosphorous pentachloride (64.7 g, 0.310 mol) and alcohol-free chloroform (400 mL). To this solution was added in portions 4-trifluoroacetylaminobenzylphosphonic acid (40 g, 0.141 mol). After the addition was completed, the milky suspension was heated at reflux for 3 h. The solvent and low-boiling materials were removed by distillation (initially at atmospheric, then at reduced pressure). To the residual solid was added a mixture of dry tetrahydrofuran (200 mL) and hexamethylphosphoramide (10 mL) under nitrogen. The clear solution was cooled in an ice bath and

treated with a solution of lithium methoxide, prepared from lithium metal (2.15 g, 0.36 mol) and methanol (150 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure (aspirator), and the residue was dissolved in a mixture of methylene chloride (250 mL) and brine (250 mL). After shaking, the aqueous layer was separated and extracted with methylene chloride (1 x 250 mL). The combined methylene chloride layer was washed with brine (1 x 250 mL) and dried ($MgSO_4$). After filtration and evaporation (aspirator), the residue was purified by chromatography over silica gel (160 g) and eluted with a mixture of ether and tetrahydrofuran (1:1). The product-containing fractions were combined and concentrated (aspirator) to give a light yellow solid. One recrystallization from tetrahydrofuran/petroleum ether (40 mL:160 mL) gave 32.3 g (74%) of product as light yellow crystals, mp 128-130°C.

Methyl pinacolyl 4-trifluoroacetylaminobenzylphosphonate (4): - A mixture of dimethyl 4-trifluoroacetylaminobenzylphosphonate (2.8 g, 9 mmol) and phosphorous pentachloride (2.25 g, 10.8 mmol) in methylene chloride (30 mL) was heated at reflux for 3 h. The solvent and low-boiling point materials were removed by distillation (atmospheric, then in vacuo). To the residual solid was added a cold (-5 to -10°C) solution of lithium pinacolylate prepared from n-butyllithium (32.4 mmol in hexane, 13 mL) and pinacolyl alcohol (6.62 g, 64.8 mmol) in tetrahydrofuran (30 mL). The clear, light brown solution was stirred at room temperature for 2 h. The solvents were removed under reduced pressure (aspirator), and the residue was dissolved in a mixture of ethyl acetate (200 mL) and water (100 mL). After shaking, the aqueous layer was separated and extracted with ethyl acetate (100 mL). The combined ethyl acetate layer was washed with saturated aqueous sodium bicarbonate (1 x 100 mL), brine (2 x 100 mL), and dried ($MgSO_4$). After filtration, the solution was concentrated to dryness (aspirator), and the residue was triturated with petroleum ether to give 2.4 g of a yellow solid, mp 139-141°C. Additional product, 9.7 g, mp 138-140°C, was prepared by the same procedure from 12.7 g of dimethyl phosphonate. The combined solid, 12.1 g, was recrystallized from tetrahydrofuran (20 mL)/ ether (20 mL)/petroleum ether (120 mL) to give 9.5 g of pure product as white crystals, mp 141-143°C; ^1H NMR ($CDCl_3$) δ 0.87, 0.90 (two s, 9 H), 1.07, 1.27 (two d, 3 H, J=7 Hz), 3.12 (d, 2 H, J=22 Hz), 3.65, 3.67 (two d, 3 H, J=11 Hz), 4.20 (m, 1 H), 6.98-7.73 (m, 4 H), 10.08 (br s, 1 H).

Anal. Calcd for $C_{16}H_{23}F_3NO_4P$ (381.34): C, 50.40; H, 6.08; F, 14.95; N, 3.67; P, 8.12. Found: C, 50.68; H, 6.24; F, 14.79; N, 3.89; P, 8.11.

Concentration of the crystallization mother liquors gave an additional 2.2 g of product, mp 140-142°C for a total yield of 11.7 g (62%).

Thin-Layer Chromatography

Eluent	Rf	Comment
Tetrahydrofuran/ether (1:1)	0.58	Homogeneous

Methyl pinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate (5): - Methyl pinacolyl 4-trifluoroacetylaminobenzylphosphonate (4, 8.9 g, 23.3 mmol) was stirred with sodium borohydride (5 g, 132 mmol) in ethanol (90 mL) for 1 h. The solvent was removed under reduced pressure (aspirator), and the residue was dissolved in a mixture of ether (90 mL) and water (90 mL). After shaking in a separatory funnel, the water layer was separated and extracted with ether (1 x 90 mL). The combined ether layer was washed with water (2 x 90 mL) and extracted with 1 N HCl (3 x 40 mL). The combined acid extract was washed with ether (1 x 40 mL) and basified with aqueous 50% NaOH to about pH 11. The basic solution was extracted with ether (3 x 90 mL). The combined ether extract was washed with water (2 x 90 mL), then it was dried ($MgSO_4$). After filtration, the solvent was removed (aspirator) to give a clear, faint yellow oil (5.4 g, 18.9 mmol). This oil was stirred with glutaric anhydride (1.94 g, 17 mmol) and triethylamine (1.72 g, 17 mmol) in dry benzene (60 mL) overnight. The mixture was concentrated (aspirator) to remove most of benzene, then it was diluted with methylene chloride (120 mL). The solution was washed with 1 N HCl (1 x 60 mL), water (2 x 60 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 120 g) using a mixture of ethyl acetate and methanol (7:3) as eluent. The product-containing fractions were combined, and the solvent was removed at reduced pressure (aspirator). The residue was dissolved in methylene chloride (150 mL), and the solution was washed with water (2 x 75 mL). The washed solution was dried ($MgSO_4$), and the solvent was removed (aspirator). The residual thick oil was dried at 60°C (oil bath) and 0.25 mmHg overnight to give 5.7 g (61% from 4) of pure product as a yellow gum. ^1H NMR ($CDCl_3$) δ 0.90 (s, 9 H), 1.15, 1.25 (two d, 3 H, J=7 Hz), 1.67-2.72 (m, 6 H), 3.17 (d, 2 H, J=22 Hz), 3.67, 3.70 (two d, 3 H, J=11 Hz), 4.30 (br s, 1 H), 7.00-7.70 (m, 4 H), 8.60 (br s, 1 H), 8.80 (br s, 1 H).

Anal. Calcd for $C_{19}H_{30}NO_6P$ (399.43): C, 57.13; H, 7.57; N, 3.51; P, 7.75. Found: C, 56.93; H, 7.49; N, 3.44; P, 7.90.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/methanol/ acetic acid (9:1:0.1)	0.40	Trace of a faster impurity

Using the same procedure, an additional 11.5 g of intermediate 4 was processed to give 5.2 g (41%) of product 5.

4.22 Monopinacolyl 4-(4-carboxybutanoylamino)benzylphosphonate

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

A mixture of methyl pinacolyl 4-(4-carboxybutanoylamino)-benzylphosphonate (5.0 g, 11.98 mmol) and t-butylamine (2.74 g, 37.5 mmol) in acetonitrile (10 mL) was heated at 55-60°C (oil bath temperature) for 11 1/2 days. The solvent and low boilers were removed under reduced pressure (aspirator) to give an off-white solid (6.7 g). The solid (6.5 g) was slurried with acetonitrile (200 mL), then recrystallized from a mixture of methanol (10 mL)/i-propanol (15 mL)/acetonitrile (65 mL) to give 3.3 g (first crop) and 1.7 g (second crop) of a white solid. The combined solid (5 g) was dissolved in methanol (10 mL), and the solution was passed through a column of ion-exchange resin (amberlite, IR-120 plus, 190 mL) and eluted with methanol. The methanol was removed under reduced pressure (aspirator), and the residue was recrystallized from a mixture of tetrahydrofuran (2 mL)/ethyl acetate (5 mL)/petroleum ether (18 mL) to give white crystals (3.4 g), mp 69-70°C. This material was the carboxylate methyl ester of the desired product. The solid (3.4 g) was heated at reflux with sodium carbonate (7 g, 66 mmol) in water (60 mL) for 1 h. After cooling, the solution was covered with ethyl acetate (50 mL) and acidified to pH 1-2 with concentrated hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate (1 x 50 mL). The combined ethyl acetate layer was washed with brine (1 x 50 mL). The washed solution was dried ($MgSO_4$), and the solvent was removed at reduced pressure to give 3.1 g of a light yellow solid. One recrystallization from ethyl acetate (30 mL)/petroleum ether (100 mL) gave 2.7 g (59%) of pure product, mp 145-147°C. ^1H NMR (DMSO-d_6) δ 0.84 (s, 9 H), 1.12 (d, 3 H, J=7 Hz), 1.43-2.63 (m, 6 H), 3.03 (d, 2 H, J=22 Hz), 4.13 (m, 1 H), 7.00-7.83 (m, 4 H), 9.93* (br s, 1 H), 10.21* (br s, 2 H).

*Exchangeable with D_2O.

Anal. Calcd for $C_{18}H_{28}NO_6P$ (385.40): C, 56.10; H, 7.32; N, 3.64; P, 8.04. Found: C, 56.09; H, 7.30; N, 3.61; P, 7.80.

Thin-Layer Chromatography

Eluent	Rf	Comment
Methylene chloride/methanol/formic acid (9:1:0.3)	0.29	Homogeneous

4.23 (5-Carboxypentyl)(3,3-dimethylbutyl)phosphinic acid

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

Tetraethylphosphorodiamidous chloride (1): - Phosphorous trichloride (112 g, 0.816 mol) was dissolved in hexanes (2 L), and the solution was cooled in a dry ice-acetone bath under a nitrogen atmosphere. With vigorous mechanical stirring, diethylamine (238.6 g, 3.26 mol) was added at a rate to maintain the internal temperature below -50°C (ca. 2 h). The mixture was allowed to warm to 25°C. The salt was removed by filtration and washed with hexanes (3 x 300 mL). The combined filtrate was concentrated under a nitrogen atmosphere to an oil. The oil was distilled through a 4-inch vacuum-jacketed, helices-filled column to give 83.2 g (48%) of product, bp 85-87°C/0.3 mmHg; lit. bp 59-60°C/0.25 mmHg (29). The product is very hygroscopic and air-sensitive.

3,3-Dimethylbutyl-N,N,N',N'-tetraethylphosphonous diamide (2): - 1-Bromo-3,3-dimethylbutane (122.9 g, 0.7445 mol) was added to freshly crushed magnesium turnings (19.6 g, 0.806 mol) in ether (600 mL) under nitrogen at a rate to maintain a steady reflux (ca. 45 minutes). The solution was heated at reflux for an additional 30 minutes, then it was cooled in a dry ice-acetone bath. Tetraethylphosphorodiamidous chloride (130.7 g, 0.620 mol) was added at a rate to keep the temperature below -30°C. Due to the thick salt formation, the stirring was stopped after two-thirds of the addition to prevent damage to the stirring shaft. After warming to 25°C for 17 h, the suspension was stirred for 1 h. Radical inhibitor, 3-tert-butyl-4-hydroxy-5-methylphenyl-sulfide (50 mg) was added and the salts were removed by filtration and washed with ether (2 x 250 mL). The combined filtrate was concentrated under a nitrogen atmosphere. The residual oil was distilled through a 4-inch vacuum-jacketed, helices-filled column to give 114.8 g (71%) of product, bp 85-87°C/0.2 mmHg. The product is very hygroscopic and air-sensitive. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9 H), 0.9-1.3 (m, 14 H), 2.8-3.6 (m, 8 H).

Anal. Calcd for $C_{14}H_{33}N_2P$ (260.39): C, 64.57; H, 12.77; N, 10.76; P, 11.89. Found: C, 64.42; H, 12.93; N, 10.87; P, 11.87.

3,3-Dimethylbutylphosphonous Dichloride (3): - In a dry flask, ethereal hydrogen chloride (2.25 M, 880 mL, 2.0 mol) containing 3-tert-butyl-4-hydroxy-5-methylphenylsulfide (50 mg) was cooled in a dry ice-acetone bath under a nitrogen atmosphere. 3,3-Dimethylbutyl-N,N,N',N'-tetraethylphosphonous diamide (121.7 g, 0.467 mol) was added dropwise with stirring over 1 h. The suspension was stored at 25°C for 17 h. The suspended solid was removed by filtration and washed with hexanes (2 x 150 mL).

The combined filtrate and wash was concentrated under nitrogen. The residual oil was distilled through a 4-inch vacuum-jacketed, helices-filled column to give 65.1 g (74%) of product, bp 58-59.5°C/3.5 mmHg. The product is very hygroscopic and air-sensitive.

Dimethyl 3,3-Dimethylbutylphosphonite (4): - 3,3-Dimethylbutylphosphonous dichloride (73.0 g, 0.390 mol) and 3-tert-butyl-4-hydroxy-5-methylphenylsulfide (50 mg) were dissolved in dry ether (600 mL), and the solution was cooled in a dry ice-acetone bath under a nitrogen atmosphere. A mixture of methanol (33.2 mL, 0.82 mol), triethylamine (115 mL, 0.82 mol) and dry ether (100 mL) was added over 1 h. The mixture was stored at 25°C for 17 h. More methanol (10 mL) was added, and the salt was removed by filtration and washed with hexanes (2 x 150 mL). The combined filtrate was concentrated under nitrogen. The residual oil was distilled through a 4-inch vacuum-jacketed, helices-filled column to give 56.5 g (81%) of product, bp 56-58.5°C/3 mmHg. ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9 H), 1.2-1.6 (m, 4 H), 3.65 (d, J=11 HZ, 6 H). If the product is exposed to oxygen, the resulting phosphonate will show a downfield peak at δ 3.76 (d, J=12 Hz, 6 H).

Methyl 6-Iodohexanoate (5): - 6-Bromohexanoyl chloride (100 g, 0.468 mol) was dissolved in dry ether (300 mL) under a nitrogen atmosphere, and the solution was cooled in an ice water bath. Methanol (100 mL) was added dropwise over 30 minutes. After warming to 25°C for 1 h, the solution was concentrated to an oil. Sodium iodide (77.2 g, 0.515 mol) and reagent acetone (300 mL) were added, and the suspension was stirred for 20 h at 25°C. The salts were removed by filtration and washed with ether (3 x 50 mL). The combined filtrate was concentrated to an oil. The oil was dissolved in ether (200 mL). The solution was filtered, and the filtrate was concentrated at reduced pressure (aspirator). The residual oil was distilled through a short-path apparatus to give 115.6 g (96%) of product, bp 70-75°C/0.2 mmHg. ^{1}H NMR ($CDCl_3$) δ 1.3-2.1 (m, 6 H), 2.03 (t, 2 H), 3.25 (t, 2 H), 3.73 (s, 3 H).

Anal. Calcd for $C_7H_{13}IO_2$ (256.07): C, 32.83; H, 5.12; I, 49.56. Found: C, 32.78; H, 5.16; I, 49.35.

Thin-Layer Chromatography Whatman Silica Gel MK6F

Eluent	Rf	Comment
Hexanes\ethyl acetate (4:1)	0.70	Homogeneous

Methyl (5-Carbomethoxypentyl)(3,3-dimethylbutyl)phosphinate (6): - Methyl 6-iodohexanoate (88 g, 0,34 mol) and 3-tert-butyl-4-hydroxy-5-methylphenylsulfide (50 mg) were placed in a 250-mL three-neck flask equipped with an addition funnel, magnetic stirrer, and a short-path distillation head with a collection bulb in a dry ice-acetone bath. A vigorous stream of nitrogen gas was allowed to flow through the system in order to facilitate the removal of the generated methyl iodide. The flask was placed in an oil bath preheated to 120°C. Dimethyl 3,3-dimethylbutylphosphonite was added over 20 minutes. After an additional 20 minutes, the mixture was allowed to cool and distilled in a kugelrohr apparatus. The product-containing fraction was collected, bp 120-130°C (oven temperature)/0.1 mmHg to give 17.5 g (33% yield) of a 3:1 mixture of product and the isomer 5-carbomethoxypentyl (methyl)(3,3-dimethylbutyl)-phosphinate (7). Higher temperatures or longer reaction times resulted only in higher yields of the undesired isomer 7. A 2.8-g fraction collected at 140-170°C contained mostly compound 8. ^{1}H NMR of the product ($CDCl_3$) δ 0.93 (s, 9 H), 1.2-2.0 (m, 12 H), 2.33 (br t, 2 H), 3.69 (s, 3 H), 3.71 (d, J=11 Hz, 3 H). ^{1}H NMR of the analytically pure side product 7, ($CDCl_3$) δ 0.91 (s, 9 H), 1.35-1.47 (m, 4 H), 1.43 (d, J=13 Hz, 3 H), 1.60-1.75 (m, 6 H), 2.32 (t, 2 H), 3.65 (s, 3 H), 3.96 (ap q, 2 H).

Thin-Layer Chromatography

Eluent	Rf	Comment
Ethyl acetate	0.47	Streaks

(5-Carboxypentyl)(3,3-dimethylbutyl)phosphinic acid (9): - A 3:1 mixture of compounds 6 and 7 described above (15.1 g, containing 0.0387 mol of 6) was dissolved in dry methylene chloride (100 mL) under a nitrogen atmosphere and cooled in an ice water bath. Bromotrimethylsilane (15 mL, 0.113 mol) was added in one portion. After 1 h, the solution was allowed to stand at 25°C for 17 h. Methanol (30 mL) was added, and the solution was concentrated to a thick oil. The oil was redissolved in methanol (40 mL). Sodium hydroxide solution (1 N) was added until the pH was 13 (ca. 170 mL). After stirring for 20 minutes, the aqueous solution was washed with ether (150 mL) and acidified to pH 2 with 6N HCl. The acidic solution was extracted with ether (2 x 150 mL). The combined ether extract was dried ($MgSO_4$), then it was concentrated. The residue was dried at 25°C/0.2 mmHg for 2 h to give 15.6 g of a colorless oil. The oil was dissolved in warm ether (80 mL). Hexanes was added until cloudiness (ca. 50 mL). The solution was seeded and stored at -10°C for 5 h. The solid was collected, washed with cold hexanes (3 x 20 mL), and dried at 25°C/0.2 mmHg for 1 h to give 8.0 g of crude product, mp 50-60°C. The product was combined with 0.8 g of similar material. The mixture was recrystallized by triturating with 70 mL ether, removing the undissolved solid

by filtration (0.5 g, mp 74-76 C). Hexanes (45 mL) was added, and the mixture was cooled to -10°C. This procedure was repeated. The resulting solid was triturated with cold ether (30 mL, -10°C), collected by quick filtration, and washed with hexanes (2 x 20 mL). It was dried immediately at 25°C/0.2 mmHg for 17 h to give 5.3 g (46%) of pure product as white crystals, mp 66-67°C. The product is hygroscopic. ^{1}H NMR ($CDCl_3$) δ 0.896 (s, 9 H), 1.42-1.50 (m, 4 H), 1.60-1.77 (m, 8 H), 2.339 (t, 2 H), 10.95-11.00 (m, 2 H).

Anal. Calcd for $C_{12}H_{25}PO_4$ (264.29): C, 54.53; H, 9.53; P, 11.72. Found: C, 54.50; H, 9.70; P, 11.58.

Thin-Layer Chromatography Whatman Silica Gel MK6F

Eluent	Rf	Comment
Methanol/ethyl acetate 1:1	0.59	Homogeneous

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