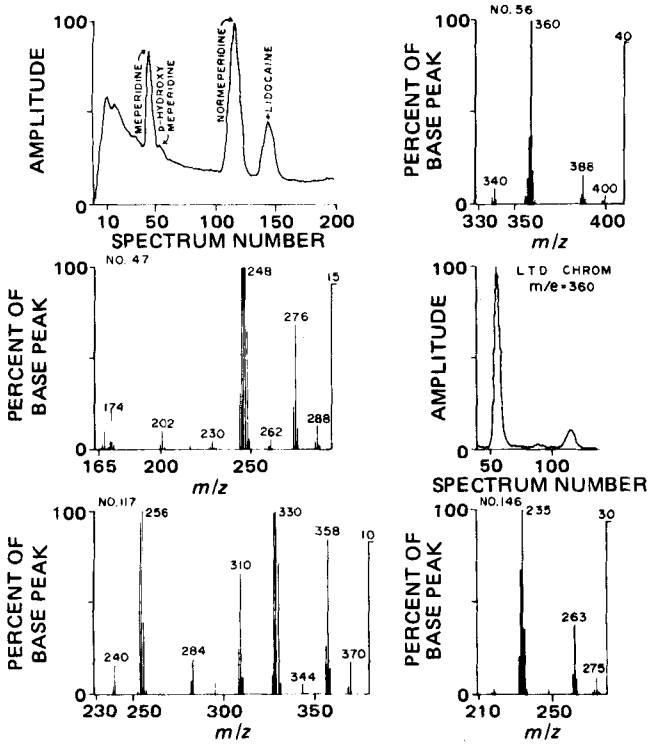

Figure 3—*GLC–mass spectrometric chromatogram, as trifluoroacetyl derivatives, of the 24-hr urinary extract of a rat administered meperidine. Key: upper left, integrated total ion current chromatogram; middle right; limited chromatogram at m/z 360; spectrum 47, meperidine; spectrum 56, p-hydroxymeperidine; spectrum 117, normeperidine; and spectrum 146, lidocaine (added internal standard).*

56 showed *m/z* 388 $(M + 29)^+$, 360 $(M + 1)^+$, and 340 $(M -$ fluoride ion$)^+$. The identity of *p*-hydroxymeperidine and normeperidine as metabolites thus was established and confirmed the observation of Lindberg *et al.* (5) that *p*-hydroxymeperidine is a metabolite of meperidine in the rat.

Urinary Excretion of Meperidine and Its Metabolites in Rats—A preliminary determination of the urinary excretion of meperidine and its metabolites in the rat indicated meperidine (6.1%), *p*-hydroxymeperidine (0.36%), total meperidinic acid (16.1%), normeperidine (24%), and total normeperidinic acid (3.9%) of administered meperidine hydrochloride (35 mg/kg). A detailed study of the urinary disposition of meperidine and its metabolites in several mammalian species will be reported in a separate paper.

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Electrokinetic Studies of Magnesium Hydroxide

HANS SCHOTT

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Abstract □ The electrophoretic mobility of magnesium hydroxide was studied as a function of the concentration of its potential-determining ions, namely, of the magnesium ions, and of the hydroxide ions or pH. The zero point of charge was located at ~10.8. The ζ-potential of magnesium hydroxide below this pH was positive. The addition of magnesium nitrate to magnesium hydroxide suspensions increased the positive ζ-potential and lowered the pH. The low solubility of magnesium hydroxide in water prevented the attainment of substantial concentrations of magnesium ions in solution. Increasing the hydroxide-ion concentration or the pH produced charge inversion. The largest negative ζ-potential was attained at pH 11.5. Further increases in pH produced no significant increase in the negative value of the ζ-potential.

Keyphrases □ Magnesium hydroxide—electrophoretic mobility in aqueous solution □ Electrophoretic mobility—magnesium hydroxide in aqueous solution □ Zero point of charge—magnesium hydroxide

Even though magnesium hydroxide suspensions are used extensively as antacids and laxatives, the information available on their electrokinetic properties is meager. Two sets of limited data, based on electro-osmosis and electrophoresis, were published in 1917 and 1934, respectively, for magnesium hydroxide that was precipitated with little

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Table I—Electrophoretic Mobility Values of Magnesium Hydroxide in Various Media

Suspension	Electrolytes and Concentrations	Mobility ± *SEM*[a], (μm/sec)/(v/cm)	Specific Conductance, millimho/cm	pH
1	0.0200 *M* $NaNO_3$	1.60 ± 0.06	2.43	9.6
2	0.0200 *M* $NaNO_3$[b]	1.29 ± 0.06	2.23	9.6
3	0.0100 *M* $NaNO_3$[b,c]	1.36 ± 0.07	1.15	10.2
4	0.00666 *M* Na_2SO_4	1.64 ± 0.05	—	9.5
5	0.0100 *M* $NaNO_3$ + 0.00333 *M* $Mg(NO_3)_2$	1.91 ± 0.09	1.89	9.4
6	0.00666 *M* $Mg(NO_3)_2$	2.07 ± 0.10	1.49	9.0
7	0.00666 *M* $Mg(NO_3)_2$[b]	1.85 ± 0.05	1.49	9.5
8	0.00333 *M* $Mg(NO_3)_2$[c]	2.75 ± 0.07	0.74	9.8
9	0.0195 *M* $NaNO_3$ + 0.0005 *M* NaOH	1.36 ± 0.07	—	10.2
10	0.0180 *M* $NaNO_3$ + 0.0020 *M* NaOH	−1.62 ± 0.04	2.08	11.2
11	0.0150 *M* $NaNO_3$ + 0.0050 *M* NaOH	−1.95 ± 0.04	2.97	11.5
12	0.0100 *M* $NaNO_3$ + 0.0100 *M* NaOH	−1.96 ± 0.05	3.72	11.8
13	0.0200 *M* NaOH	−1.99 ± 0.04	5.00	12.2

[a] Average of 10 measurements ± *SEM*. [b] Contained approximately 10 times more suspended magnesium hydroxide. All other suspensions contained 0.1 g/liter of magnesium hydroxide. [c] At an initial ionic strength of 0.0100 *M*, *i.e.*, one-half of that of other suspension media.

or no subsequent purification (1, 2). The ionic strength of the suspensions apparently was not controlled.

This paper reports the electrophoretic properties of magnesium hydroxide with emphasis on the effect of potential-determining ions on its electrophoretic mobility.

BACKGROUND

Potential-determining ions are ions whose concentration in solution determines the ψ_0-potential of the suspended particles, *i.e.*, the electric potential at the particle surface (3–5). For magnesium hydroxide, the potential-determining ions are the magnesium ions and hydroxide ions. Since these ions determine the potential at the particle surface rather than the ζ-potential at the plane of shear within the electric double layer, they affect the colloidal properties of magnesium hydroxide suspensions more strongly than other ions, which cannot become an integral part of the particle surface.

The state of aggregation of colloidal dispersions and coarse suspensions depends on the magnitude of the electrostatic repulsion between particles that opposes the omnipresent interparticle London–van der Waals attraction. The former, in turn, depends on the ψ_0- and ζ-potentials. Thus, the state of aggregation of suspended magnesium hydroxide is strongly pH dependent because the hydrogen-ion concentration in aqueous media varies inversely with the concentration of the potential-determining hydroxide ions.

Slightly soluble hydroxides $M^{z+}(OH)_z^-$ of polyvalent cations are amphoteric; z represents the valence of the cation. The surface charge of the hydroxide particles depends on the composition of their surface layer, $[M^{z+}(OH)_n]^{z-n}$. At relatively low pH values where $z > n$, a positive charge results because, in the case of magnesium hydroxide, the ratio of the concentration of magnesium ions to that of hydroxide ions in the surface layer exceeds 1:2. Alternatively, the positive charge may be ascribed to proton adsorption on a neutral surface. At high pH values where $z < n$, a negative surface charge results.

At an intermediate pH where $z = n$, the particles have a zero net surface charge. At this pH, known as the zero point of charge or isoelectric point (3–6), the surface layer has the same 1:2 ratio of magnesium-ion concentration to hydroxide-ion concentration as the bulk of the particles. Since the surface layer is electrically neutral, the ψ_0- and ζ-potentials of the magnesium hydroxide particles are zero.

Because an electric surface charge is absent, the suspensions are flocculated more extensively at the zero point of charge than at any other pH, as was demonstrated by maxima in the rate and volume of sedimentation and in viscosity (3–5). Hence, the tendency toward caking is smallest at the zero point of charge. Old electro-osmosis (1) and electrophoresis (2) measurements indicated a zero point of charge of ~12 for nonpurified magnesium hydroxide, while recent correlations placed the zero point of charge of pure magnesium hydroxide at 12.0 (7) and at 12.3 (8).

EXPERIMENTAL

Materials—All chemicals were ACS reagent grade. The water was double distilled and free of carbon dioxide. Magnesium hydroxide was precipitated by the action of sodium hydroxide on magnesium sulfate, using a literature procedure (9) with the following two modifications. The sodium hydroxide was prepared first as a 50% solution, which was filtered to remove any traces of sodium carbonate. A slurry of the precipitated magnesium hydroxide was prepared in water, filtered, and washed extensively with water on the filter. This procedure was performed eight times.

Methods—The electrophoretic mobility of magnesium hydroxide suspensions was determined by microelectrophoresis using a commercial instrument[1] with an acrylic cell equipped with a cylindrical molybdenum anode and a platinum–iridium strip cathode. The cell constant and equations for calculating specific conductance of the suspension from current intensity, electrophoretic mobility from velocity of migration, and ζ-potential from electrophoretic mobility were reported previously (10). The ionic strength was maintained constant at 0.0200 *M* for most measurements and at 0.0100 *M* for the others.

Most suspensions for electrophoretic measurements were prepared by diluting 0.5 ml of 2.0% (w/v) magnesium hydroxide stock suspensions with 99.5 ml of the various electrolyte solutions. The final magnesium hydroxide concentration is 10 times higher than its solubility in water.

The electrophoresis cell was filled with two aliquots from each diluted suspension, and five particles were tracked for each aliquot. All electrophoretic measurements were made within 30 min of mixing but, in the two instances tested, aging for 4 hr did not alter the results.

The pH of each diluted suspension aliquot was measured before and after the mobility determinations. The differences between the two readings were 0.2 pH unit or less.

RESULTS

The results are presented in Table I. Negative values of the electrophoretic mobility indicate that the particles were negatively charged and migrated to the anode.

Preliminary measurements indicated that the concentration of magnesium hydroxide present in a suspension had some effect on electrophoretic mobility. Comparison of Suspensions 1 and 2 and of 6 and 7 shows that higher magnesium hydroxide concentrations resulted in lower mobilities. These decreases were about an order of magnitude greater than the increase in apparent viscosity resulting from the higher magnesium hydroxide concentration, indicating that viscosity increases did not cause the drop in mobility. Subsequent measurements were made at the constant magnesium hydroxide concentration of 0.10 g/liter.

Suspensions 1 and 4, in which the supporting electrolytes were sodium nitrate and sodium sulfate of identical ionic strengths, respectively, had the same electrophoretic mobility within experimental error. This fact indicates that there was no specific interaction between magnesium hydroxide and either anion. Specific anion effects are due exclusively to the hydroxide ion.

Effect of Magnesium Ion—Comparison of the electrophoretic mobility of Suspensions 1 and 5 shows that the addition of the potential-determining magnesium ions as the soluble nitrate increased the positive electrophoretic mobility or the positive ζ-potential by ~20%. Evidently, this addition forced more magnesium ions into the particle surface, increasing the positive surface-charge density. However, because of the low solubility product of magnesium hydroxide (1.6×10^{-11}), the concen-

[1] Zeta-Meter, Zeta Meter Inc., New York, N.Y.

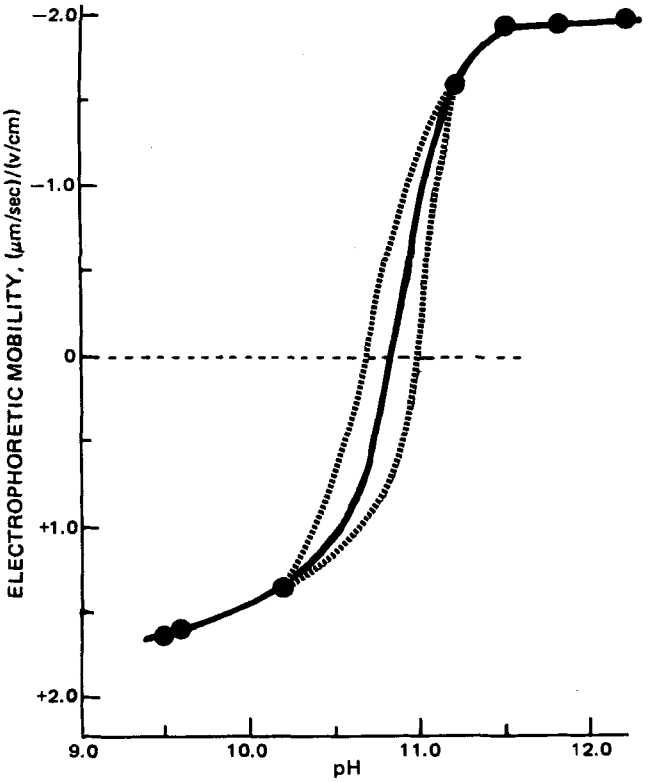

Figure 1—*Electrophoretic mobility of magnesium hydroxide as a function of pH. The conditions were ionic strength of 0.0200* M *and no added soluble magnesium salt.*

tration of magnesium ions in solution cannot exceed 10^{-4} *M*. All or most of the magnesium added as magnesium nitrate to make Suspension 5 must have precipitated as magnesium hydroxide.

Further addition of magnesium nitrate, which occurred when going from Suspension 5 to Suspension 6, produced only a minor change in electrophoretic mobility which was not statistically significant. Evidently, the incorporation of excess magnesium ions from solution into the surface layer of magnesium hydroxide particles became increasingly more difficult as their ζ-potential became more positive because the increasingly greater excess of magnesium ions over hydroxide ions in the surface layer resulted in greater positive surface-charge density, which, in turn, caused increased electrostatic repulsion of the added magnesium ions and increased attraction for the hydroxide ions (5).

The replacement of sodium nitrate by equivalent amounts of magnesium nitrate caused the pH to drop from 9.6 (before such replacement, Suspension 1) to 9.4 (when half of the sodium nitrate was replaced by magnesium nitrate, No. 5) to 9.0 (when all of the sodium nitrate was replaced, Suspension 6). Similarly, Suspension 8, with one-half of the concentration of added magnesium nitrate as Suspension 6, had a pH that was 0.8 unit higher. The decreases in pH produced by the addition of magnesium nitrate were probably due to the adsorption of hydroxide ions from solution onto the surface of positively charged magnesium hydroxide particles, especially of those particles that freshly precipitated as a result of the addition of magnesium nitrate in amounts exceeding the magnesium hydroxide solubility.

An equivalent explanation for this decrease in pH is the hydrolysis of most of the added magnesium nitrate according to the equilibrium $Mg^{2+} + 2H_2O \rightleftharpoons Mg(OH)_2(s) + 2H^+$. In view of the low solubility product of magnesium hydroxide and the high pH, the bulk of the magnesium ions added as magnesium nitrate must have precipitated as magnesium hydroxide with the simultaneous formation of hydrogen ions, shifting the equilibrium forward.

Effect of Hydroxide Ion—While the magnesium-ion concentration cannot be raised much in the vicinity of the zero point of charge because of precipitation of magnesium hydroxide, the concentration of the hydroxide ions can be raised considerably. With an increasing concentration of added hydroxide ions and an increasing pH at a constant ionic strength of 0.0200 *M*, the electrophoretic mobility became less positive (Suspensions 1 and 9), went through zero, and, after charge inversion, became negative (Suspensions 10–13).

Comparison of the electrophoretic mobilities of Suspensions 10–13 was made by the *F* test (11). When Suspension 10 was included, the differences between the four mobility values were statistically significant. Without Suspension 10, the differences between the three mobility values of Suspensions 11–13 were not significant, despite the trend of increasingly greater negative mobility values with increasing pH. At constant ionic strength, hydroxide-ion concentrations above those corresponding to pH 11.5 did not increase the negative value of the ζ-potential of magnesium hydroxide. This observation may indicate that the surface layer of the magnesium hydroxide particles consisted of a monomolecular layer of extra hydroxide ions at pH $\geq$11.5 (5).

Zero Point of Charge—*Direct determination of the zero point of* charge as the pH corresponding to zero mobility was unsuccessful. At pH 10.8 and an ionic strength of 0.0200 *M*, many particles did not move in the electric field, some particles moved sluggishly toward the anode, and others migrated toward the cathode.

Therefore, the zero point of charge was estimated by graphical interpolation of the electrophoretic mobility values obtained at a constant ionic strength of 0.0200 *M* in the absence of added magnesium nitrate (Suspensions 1, 4, and 9–13). These points (Fig. 1) form the familiar S-shaped curve (12). The best zero point of charge estimate, corresponding to the smoothest and most symmetric curve (solid line), is 10.8. The extreme values (dotted lines) are 10.7 and 10.9. The zero point of charge value of 10.8 is certainly accurate within a range of ±0.2.

This 10.8 value is more than one pH unit below the published zero point of charge values. The 1917 and 1934 publications (1, 2) did not indicate how extensively the magnesium hydroxide samples were purified or whether they were separated from the mother liquor, nor did they specify the ionic strength of the suspensions or whether the ionic strength was controlled.

The addition of magnesium nitrate to magnesium hydroxide suspensions, which may be considered analogous to purifying precipitated magnesium hydroxide incompletely, increased the positive value of the electrophoretic mobility and lowered the pH. However, it is doubtful that these changes could increase the zero point of charge by a full pH unit.

DISCUSSION

There are probably two reasons why the nitrate and sulfate anions produced no specific effects on the ζ-potential. First, these anions do not form complexes with magnesium ions in aqueous solution, thereby making their uptake by the magnesium hydroxide particles unlikely. By analogy with aluminum hydroxide (13, 14), the chloride and citrate anions, being better ligands, are probably chemisorbed to some extent by magnesium hydroxide, affecting its colloidal properties.

Second, magnesium nitrate and magnesium sulfate are very soluble in water as opposed to the phosphates, fluoride, and carbonate of magnesium, which range from very slightly soluble to insoluble. If the latter anions were present in magnesium hydroxide suspensions, they probably would be bound extensively to the surface layer of the particles, possibly acting as potential-determining ions, and affect their colloidal properties considerably.

The observation that mobility values depended on the solids content of the magnesium hydroxide suspensions may be due to impurities, or even to somewhat soluble magnesium hydroxo complexes (15), released from the suspended solids during electrophoresis. It is impossible to wash gelatinous precipitates such as magnesium hydroxide completely free of adsorbed ions. The product used in the present experiments was similar to that of commercial magnesium hydroxide pastes used to manufacture milk of magnesia, except that it was washed more extensively. Thus, the present data are applicable to the formulation of antacid and laxative suspensions based on magnesium hydroxide.

Precipitated magnesium hydroxide purified further by electrodialysis–electrodecantation or magnesium hydroxide prepared in the absence of anions other than hydroxide, *e.g.*, by the reaction of water with magnesium amalgam or with dialkyl magnesium compounds, could well exhibit zero point of charge values at variance with the present estimate.

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Molecular Requirements of the Active Site of Cholinergic Receptors XV: Synthesis and Biological Activity of 2,3-Dehydrodeoxamuscarone and 2,3-Dehydrodeoxamuscarines

PIERO ANGELI, LIVIO BRASILI, DARIO GIARDINÀ, and CARLO MELCHIORRE ˣ

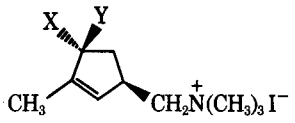
Received June 30, 1980, from the *Institute of Pharmaceutical Chemistry, University of Camerino, 62032 Camerino (MC), Italy.* Accepted for publication October 10, 1980.

Abstract □ To elucidate the molecular requirements of the active sites of cholinergic receptors, 3-methyl-4-oxo-1-(*N,N*-dimethylaminomethyl)cyclopent-2-ene methiodide (2,3-dehydrodeoxamuscarone) and *cis*- and *trans*-3-methyl-4-hydroxy-1-(*N,N*-dimethylaminomethyl)cyclopent-2-ene methiodides (*cis*- and *trans*-dehydrodeoxamuscarines) were synthesized and tested. The results, compared with those of the corresponding oxygenated compounds, seem to indicate that 2,3-dehydrodeoxamuscarines and muscarine bind at the same site while 2,3-dehydrodeoxamuscarone interacts with the site normally occupied by muscarone. Furthermore, the previously suggested hypothesis that the unpolar site might somehow incorporate that of muscarone was considered.

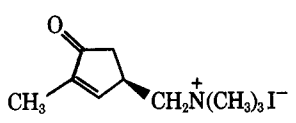
Keyphrases □ Cholinergic receptors—molecular requirements of active sites, synthesis of 2,3-dehydrodeoxamuscarone and *cis*- and *trans*-dehydrodeoxamuscarines □ Structure–activity relationships—2,3-dehydrodeoxamuscarone and *cis*- and *trans*-dehydrodeoxamuscarines, molecular requirements of cholinergic receptors, dualism of receptor active sites □ 2,3-Dehydrodeoxamuscarone and 2,3-dehydrodeoxamuscarine—synthesis and biological activity

To investigate the molecular requirements of cholinergic receptors, many compounds incorporating a cyclopentane nucleus were synthesized in the past few years (1). As a consequence of these studies, the hypothesis of Triggle and Triggle (2) concerning an accessory site of reduced polarity and low steric demand of the cholinergic receptor gained further support (3–5). In fact, most of these compounds, although lacking oxygenated functions, are fairly active on both nicotinic and muscarinic receptors. However, their specificity is generally low when compared with the corresponding oxygenated compounds (*i.e.*, muscarine).

To gain more information on the dualism of the active site of the cholinergic receptors, *cis*- and *trans*-3-methyl-4-hydroxy-1-(*N,N*-dimethylaminomethyl)cyclopent-2-ene methiodides (*cis*- and *trans*-2,3-dehydrodeoxamuscarines, I*a* and I*b*) and 3-methyl-4-oxo-1-(*N,N*-dimethylaminomethyl)cyclo-pent-2-ene methiodide (2,3-dehydrodeoxamuscarone, II) were synthesized and tested. Their pharmacological results were compared with those of 3-methyl-1-(*N,N*-dimethylaminomethyl)cyclopent-2-ene methiodide (III), because it incorporates a



I*a*: X = H, Y = OH
I*b*: X = OH, Y = H
III: X = Y = H



II

double bond at the same position 2 of the cyclopentyl moiety as a basic feature and is one of the most active compounds among those lacking oxygenated functions (5).

EXPERIMENTAL

Melting points[1] were taken in sealed capillaries and are uncorrected. NMR spectra were recorded on a 90-MHz apparatus[2] with tetramethylsilane or 3-(trimethylsilyl)propanesulfonic acid sodium salt as the internal standard. Chromatographic separations were performed on silica gel (Kieselgel[3] 60, 0.063–0.200 mm) columns. Organic solutions were dried over anhydrous sodium sulfate.

3-Methyl-4-oxo-1-carbomethoxycyclopent-2-ene (VI)—Bromine (7.56 ml) in carbon tetrachloride (100 ml) was added to a vigorously stirred solution of V (21.9 g) (6) in carbon tetrachloride (100 ml) at room temperature. After the reaction started, the addition was continued with cooling at 0°. The solvent then was evaporated to give an oil, which was kept at 120° for 15 min under 50 mm pressure and then distilled, bp 130–135°/30 mm (12.7-g yield); IR[4] (liquid film): 1640 (C=C), 1710 (C=O), and 1735 (COO) cm^{-1}; NMR (chloroform-*d*): δ 1.70 (broad s, 3H, 3-CH_3), 2.60 (d, 2H, 5-H_2), 3.70 (s, 3H, OCH_3), 3.50–4.00 (m, 1H, 1-H), and 7.13 (m, 1H, 2-H) ppm.

Anal.—Calc. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.20; H, 6.60.

***cis*- and *trans*-3-Methyl-4-hydroxy-1-carbomethoxycyclopent-2-enes (VII*a* and VII*b*)**—The overall procedure recommended by Brown and Hess (7) was followed. Thus, a solution of 0.55 *M* 9-borabicyclo[3.3.1]nonane in tetrahydrofuran[5] (36.5 ml) was added dropwise over 2 hr to a stirred and cooled (0°) solution of VI (3 g, 19.5 mmoles) in dry tetrahydrofuran (5 ml) under a dry nitrogen stream. After 4 hr at 0°,

[1] Büchi SMP-20 apparatus.
[2] Model EM-390, Varian.
[3] Merck.
[4] Perkin-Elmer 297 spectrophotometer.
[5] Aldrich.

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