(αR)-erythro-α-Methylepinephrine [(αR,βS)-3]. Concentrated ammonium hydroxide (2.3 mL, 35 mmol) was added to an ice-cold solution of (±)-*erythro*-α-methylepinephrine hydrochloride [(±)-3·HCl; 2.00 g, 8.56 mmol) in water (5 mL) containing sodium bisulfite (50 mg/100 mL). After the solution had been refrigerated for 4 h, a light tan precipitate was collected by centrifugation. Washing of the precipitate with water, acetone, and finally ether gave (±)-1 (1.50 g, 89%). The free base (0.84 g, 4.3 mmol) was mixed with (+)-*o,o'*-dibenzoyltartaric acid monohydrate (1.69 g, 4.49 mmol) in boiling water (150 mL). Refrigeration overnight gave a purple precipitate (1.10 g, 93%). Two recrystallizations of this precipitate from water (charcoal) gave the pure salt with a pale purple color (0.51 g, 43%): mp 128–131 °C dec; $[\alpha]^{25}_D$ +99° (*c* 0.66, CH_3OH). Further recrystallization of the salt from water did not change its specific rotation. The salt (0.20 g, 0.36 mmol) in water ($NaHSO_3$ added) was treated with concentrated ammonium hydroxide as described above. The solution was frozen for 2 days[7] and then allowed to thaw to about 4 °C. The precipitate was collected by centrifugation. Washing with water, acetone, and finally ether gave pure (αR,βS)-3 (50 mg, 70%): mp 195–196 °C dec; $[\alpha]^{25}_D$ +34° (*c* 0.40, 0.2 N HCl).

(αS)-erythro-α-Methylepinephrine [(αS,βR)-3]. The mother liquor remaining after the initial crystallization of the (+)-*o,o'*-dibenzoylbitartrate salt above was evaporated at reduced pressure. The solid, purple residue (1.10 g, 93%) was treated in water ($NaHSO_3$ added) with concentrated ammonium hydroxide. After refrigeration, the precipitated amine (0.30 g, 77%, 1.5 mmol) was collected by centrifugation and was then mixed with (−)-*o,o'*-dibenzoyltartaric acid monohydrate (0.60 g, 1.6 mmol) in boiling water (60 mL). Refrigeration of this solution and recrystallization of the resulting precipitate from water (charcoal) gave the pure salt with a pale purple color (0.38 g, 45%): mp 129–132 °C dec; $[\alpha]^{25}_D$ −99° (*c* 0.61, CH_3OH). Further recrystallization of the salt from water did not change its specific rotation. The salt (0.20 g, 0.36 mmol) was decomposed in water ($NaHSO_3$ added) with concentrated ammonium hydroxide. The solution was frozen for 4 days and then allowed to thaw to about 4 °C.[7] The precipitate was collected by centrifugation. Washing the precipitate with water, acetone, and finally ether gave pure (αS,βR)-3 (50 mg, 70%): mp 195–196 °C dec; $[\alpha]^{25}_D$ −33° (*c* 0.40, 0.2 N HCl).

(R)-Norepinephrine [(R)-5]: mp 213–215 °C dec; $[\alpha]^{25}_D$ −48° (*c* 0.17, 0.2 N HCl) [lit.[11] mp 215–217 °C; $[\alpha]^{18}_D$ −36.8° (*c* 5% w/v in 0.1 N HCl)].

(R)-Epinephrine [(R)-6]: mp 203–204 °C dec; $[\alpha]^{25}_D$ −53° (*c* 0.18, 0.2 N HCl) [lit.[12] mp 211–212 °C; $[\alpha]^{17}_D$ −50.6° (*c* 0.3 g in 1.56 mL of 1 N HCl plus 2.44 mL of H_2O)].

(αS)-erythro-N-Salicylidene-α-methylnorepinephrine [(αS,βR)-7] was formed in situ: CD (CH_3OH, *c* 0.029) $[\theta]_{500}$ ±0, $[\theta]_{470}$ ±0, $[\theta]_{403}$ +1500, $[\theta]_{360}$ +600, $[\theta]_{345}$ +1000; CD (CH_3OH, *c* 0.0029) $[\theta]_{345}$ ±0, $[\theta]_{315}$ +3600, $[\theta]_{292}$ ±0, $[\theta]_{273}$ +18000, $[\theta]_{250}$ ±0, $[\theta]_{230}$ −18000, $[\theta]_{225}$ −15000; CD (CH_3OH, *c* 0.00057) $[\theta]_{220}$ −18000.

(R)-N-Salicylidenenorepinephrine [(R)-8] was formed in situ: CD (CH_3OH, *c* 0.027) $[\theta]_{500}$ ±0, $[\theta]_{435}$ ±0, $[\theta]_{397}$ −620, $[\theta]_{355}$ ±0, $[\theta]_{345}$ +400; CD (CH_3OH, *c* 0.0027) $[\theta]_{345}$ ±0, $[\theta]_{315}$ +2800, $[\theta]_{280}$ +1000, $[\theta]_{263}$ +3000, $[\theta]_{246}$ ±0, $[\theta]_{230}$ −8400, $[\theta]_{225}$ ±0; CD (CH_3OH, *c* 0.00055) $[\theta]_{225}$ ±0, $[\theta]_{220}$ ±0.

Competition for [^{3}H]Prazosin Binding Sites. A crude homogenate of rat forebrain was prepared and incubated with [^{3}H]prazosin (17.1 Ci/mmol, New England Nuclear) in a total volume of 2 mL. The incubation media (pH 7.7) contained the following: Tris (50 mM), EDTA (1 mM), $MgCl_2$ (6 mM), and protein (1.0 mg). After 30 min at 25 °C, each incubation was rapidly filtered by suction using glass-fiber filters (Whatman GF/B). The radioactivity remaining on the filters was measured in a liquid scintillation counter to estimate the amount of [^{3}H]prazosin bound to membrane fragments. Saturation binding was performed in each homogenate in order to obtain a K_d value for K_i calculations.[5,20] Norepinephrine (0.1 mM) was used to define nonspecific binding at each ligand concentration and was 10–20% of total bound counts. To a series of such incubations, progressively increasing concentrations of the competing catecholamines containing a single concentration of [^{3}H]prazosin were added so as to obtain competition binding curves. The EC_{50} values were estimated from a plot of total bound counts vs. concentrations of competing catecholamines. Each incubation was performed in triplicate in four different membrane preparations.

Acknowledgment. This study was supported by NIH Grant HL-14192. (±)-*erythro*-α-Methylnorepinephrine, (αR)- and (αS)-*erythro*-α-methylnorepinephrine, and (±)-*erythro*-α-methylepinephrine hydrochloride were generously donated by Sterling-Winthrop Research Institute, Rensselaer, NY.

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A Novel Approach for Heavy Metal Poisoning Treatment, a Model. Mercury Poisoning by means of Chelating Microspheres: Hemoperfusion and Oral Administration

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The chelating drugs BAL (2,3-dimercaptopropanol), EDTA (ethylenediaminetetraacetic acid), and penicillamine (2-amino-3-mercapto-3-methylbutanoic acid), which are used for metal poisoning, are toxic and there is a real need for alternatives, especially for severe cases. A novel approach for treatment of heavy-metal poisoning is under investigation in our group. The approach utilizes the synthesis of chelating microspheres specific for the desired metallic compound. The microspheres are suggested for use in severe cases by means of hemoperfusion, as a first aid, and then by oral administration. As a model this approach was tired for mercury poisoning. Polymercaptal microspheres of 0.8 μm average size were synthesized. The microspheres have a high surface area, have a high affinity toward organic and inorganic mercury compounds, and can compete easily with albumin and cysteine in the ability to bind mercury compounds. These microspheres also were encapsulated with agarose—a blood compatible polymer—and were tried successfully for plasma perfusion (in 10 min, 40% of CH_3HgCl and of $HgCl_2$ were removed from 20 ppm of poisoned plasma).

Heavy metals (Hg, As, Pb, Zn, Fe, etc.) exert their toxic effects by binding with one or more reactive groups, SH, SS, NH_2, etc., that are essential for normal physiological function.[1] Chelating drugs, such as EDTA (ethylenedi-

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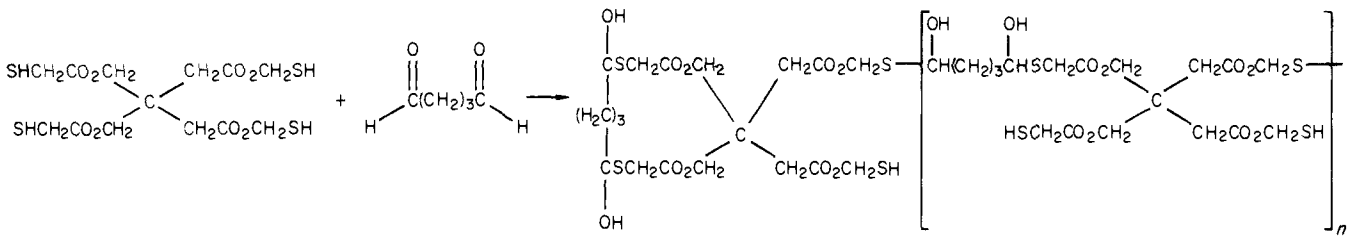
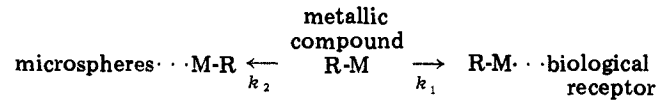
Scheme I



Scheme II[a]



[a] $k_2 >> k_1$.

aminetetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), BAL (2,3-dimercaptopropanol), and penicillamine (2-amino-3-mercapto-3-methylbutanoic acid), are still the therapy of choice in cases of heavy-metal poisoning.[2] They form stable complexes with the metallic compounds and thereby prevent or reverse the binding of the metallic compounds to the biological receptors. However, these chelating drugs are toxic, cause serious side effects, and are limited in the amount that can be administered. There is a real need to find alternative ways for the treatment of metal poisoning, especially for severe cases. Our suggestion for the treatment of heavy-metal poisoning is to synthesize chelating microspheres specific for the desired metal and to use them extracorporeally (hemoperfusion) and orally (has to be nonabsorbable and not toxic). Chelating microspheres have the advantage of high surface area. Therefore, using them orally reduces meaningfully the dose that has to be administered and might greatly increase the fecal excretion of the metallic compounds.[3] The use of the chelating microspheres by means of hemoperfusion has the advantage of preventing the administration of the drugs into the body and may be used as a first aid for severe metal poisoning cases.

As a model, mercury poisoning was chosen to be investigated. Mercury compounds are an environmental and agricultural hazard.[4] Mercury compounds emerged as environmental pollutants with the advent of the industrial revolution (about 12000 tons of mercury are released worldwide each year).[5] It is possible that in the future high levels of these metallic compounds will be a health hazard. Polymercaptal microspheres of 0.8 μm average size were synthesized and tested for mercury fast intake under different conditions. Moreover, these microspheres were encapsulated by agarose—a blood compatible polymer[6]—and a column containing the encapsulated beads was tried successfully for plasma perfusion.

Results and Discussion

Chelating Microspheres: A New Oral Drug. The formation of the chelating compound is based on the reaction of the thiol groups of pentaerythritol tetrathioglycolate and the aldehyde groups of glutaraldehyde.[7] The

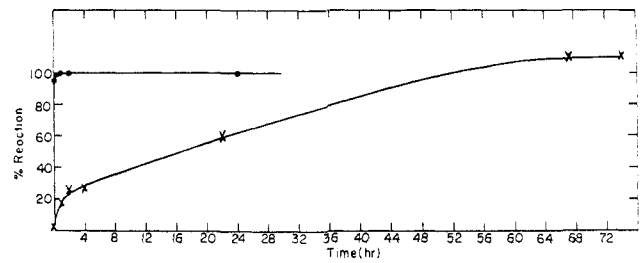


Figure 1. Comparison of the rate of intake of mercuric chloride by chelating microspheres and agglutinated chelating microspheres. The reaction was carried out by stirring 10^{-4} M $HgCl_2$ (20 ppm) and 20 mg of the chelating polymer in 50 cm^3 of PBS solution: (O) chelating microspheres; (x) agglutinated chelating microspheres.

assumed reaction is shown in Scheme I. The structure of the produced microspheres is under continued investigation for future publication. It appears that the C(OH)S groups and free thiol groups of the microspheres bind the mercury compounds and reverse the binding from the biological receptors to the microspheres (Scheme II).

Many of the heavy metallic compounds are excreted by the liver via the bile duct and intestinal tract, but a great part of the metallic compound (approximately 90% of methylmercury chloride) is reabsorbed by the intestine. Therefore, there is a possibility that nonabsorptive binding materials administered orally might bind the metallic cmpound secreted in the bile and thereby prevent the reabsorption of the metal and greatly increase its fecal excretion. Several investigators[3,8,9] showed that oral administration of indigestible, unabsorbable resin which bind methylmercury enhances the fecal excretion of methylmercury from animals. It also was observed[3] that nonabsorbable polythiol resin given by mouth can substantially reduce blood, brain, kidney, and liver levels of methylmercury. Furthermore, during an epidemic of methylmercury poisoning in Iraq[10] a group of scientists reported that oral administration of the same polythiol resin to human beings decreased their whole body mercury levels. The rate of mercury intake (for diffusion-controlled cases) is directly proportional to the surface area of the mercury binder resin. For a resin with a spherical shape, the rate is directly proportional to the ratio $1/r$

$$v \alpha n \pi r^2 = \left(\frac{3V}{4\pi r^3}\right)\pi r^2 = 0.75V\left(\frac{1}{r}\right) = k\left(\frac{1}{r}\right)$$

where v is the rate of mercury intake, V is the spheres volume, and n is the number of spheres with radius r. For example, spheres with a 1 μm radius will intake mercury 100 times faster than the same spheres with a radius of

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Table I. Rate of Intake of Methylmercury Compounds by Chelating Microspheres[a]

microspheres, mg	time, min	reaction, %
4.6	10	84
4.6	90	84
4.6	360	86
60	10	85
60	45	93
60	120	96

[a] The reaction was carried out by stirring the mercury compounds (10^{-4} M or 20 ppm of Hg) with chelating microspheres in 80 cm^3 of PBS solution.

Table II. Rate of Intake of $HgCl_2$ by Chelating Microspheres[a]

metallic compds	pH	microspheres, mg	time, min	reaction, %
$HgCl_2$	2.0	40	10	98
$HgCl_2$	2.0	40	120	100
$HgCl_2$	7.2	20	15	56
$HgCl_2$	7.2	20	90	98
$HgCl_2$	7.2	60	5	61
$HgCl_2$	7.2	60	60	100
$HgCl_2$ + $CaCl_2$ (10^{-2} M)	7.2	60	15	100
$HgCl_2$ + NaCl (0.15 M)	7.2	60	15	100

[a] The reaction was carried out by stirring the mercury compounds (10^{-4} M or 20 ppm of Hg) with chelating microspheres in 80 cm^3 of aqueous solution (pH 2.0 and 7.2).

100 μm. The dramatic effect of the high surface area of the chelating microspheres (radius of 0.4 μm in comparison to hundreds of micrometers of the polythiol resin) is clearly shown in Figure 1. In 30 min an intake of 100% of the mercuric chloride was accomplished by the microspheres, while for the same period of time the agglutinated microspheres bound only 5% of the mercuric chloride. The chelating microspheres were found to bind heavy metals, especially mercury, lead, and cadmium compound, and did not react with alkali and alkaline earth metallic compounds. The microspheres in PBS solution showed a higher reactivity toward organic and inorganic mercury compounds than the commerical mercury resins Srafion NMRR[11a] and Chalex 100.[11b] They intake mercury compounds over a broad pH range (Tables I and II) and can reverse and bind mercury compounds already bound to albumin or cysteine (Table III). The chelating microspheres were found to have low toxicity, LD_{50} (orally) = 1 mg/g of body weight, and may be useful as an oral drug for mercury posioning. The removal of other heavy metals by these microspheres is under investigation.

Hemoperfusion for Metal Poisoning Treatment. Hemoperfusion and hemodialysis are the main tools useful for an extracorporeal purification of blood from poisonings.[12] An extracorporeal complexing hemodialysis system for treatment of methylmercury poisoning was described previously.[13] This system is based on the fact that

Table III. Rate of Intake of Mercury Compounds from Albumin and from Cysteine in PBS Solution[a]

microspheres mg	Hg compds, ppm	reaction with albumin, %	reaction with cysteine, %
48	5 ($HgCl_2$)	81	
60	5 (CH_3HgCl)	75	
50	20 ($HgCl_2$)		97
20	20 (CH_3HgCl)		91

[a] The reaction was carried out by stirring the mercury compounds for 2 h with 60 cm^3 of 4% human albumin and 10^{-2} M cysteine in PBS solution. Then the chelating microspheres were added and the solution was stirred for another 1 h. [b] In control experiments (the reactions were carried out in the same way but without chelating microspheres) the loss of mercury compounds was negligible.

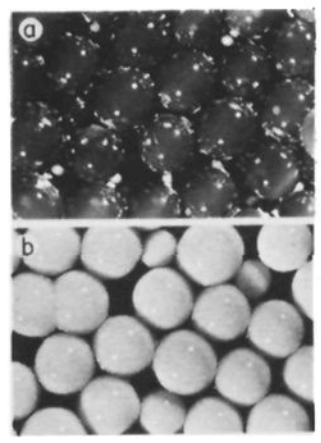

Figure 2. Photomicrograph of encapsulated chelating beads (10×): (a) control; (b) encapsulated chelating beads.

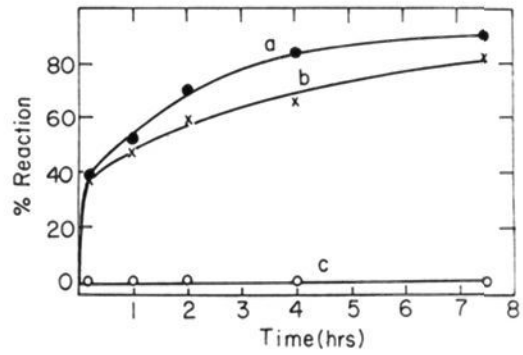

Figure 3. Plasma perfusion with encapsulated beads. The reaction was carried out by circulating 40 cm^3 of human poisoned plasma (20 ppm of $HgCl_2$ and 20 ppm of CH_3HgCl were shaken for 2 h with the plasma) through a column containing 4 g of wet encapsulated beads, with a mean flow rate of 6 mg/cm^3: (a) detoxification of $HgCl_2$; (b) detoxification of CH_3HgCl; (c) control, the reaction was carried in the same way (with $HgCl_2$ and CH_3HgCl) but the agarose did not contain the chelating microspheres.

methylmercury readily equilibrates between blood and other tissues.[14] Therefore, removal of mercury from the blood will decrease the mercury levels of the whole body. However, for treatment of most poisonings, hemoperfusion is simpler, faster, less expensive, and more effective than hemodialysis.[12] The hemoperfusion technique was tried for detoxification of different circulating toxic substances, such as certain uremic toxin, salicylates and barbiturates, different drugs, and circulating antigens.[12] Hemoperfusion treatment apparently has not been tried for severe heavy-metal poisoning. Our suggestion is to adopt and try

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this technique also for severe cases of metal poisoning. For these purposes the chelating microspheres were encapsulated with agarose, which is known to be a blood compatible polymer[6] with high porosity. The encapsulated beads (Figure 2) are very effective toward mercury compounds; e.g., by shaking 0.8 g of wet encapsulated beads with 20 ppm of $HgCl_2$ in 20 cm^3 of PBS solution, after 10 min, 93% of the mercury was intaken by the beads. In a preliminary experiment, 40 mL of human plasma was poisoned with 20 ppm of $HgCl_2$ and CH_3HgCl. Plasma perfusion through a column containing the encapsulated beads was then carried out successfully (Figure 3). For example, in 10 min, 40% of $HgCl_2$ and 40% of CH_3HgCl were removed from the poisoned plasma, and in 7.5 h, 80% of CH_3HgCl and 85% of $HgCl_2$ were intaken. In the future, more study on plasma perfusion will be carried out and then the research will be expanded for hemoperfusion.

In conclusion, in cases of severe mercury poisoning an hemoperfusion treatment as a first aid is suggested. Following this, administration of the chelating microspheres or the other mercury binder drugs [BAL, penicillamine, polythiol resins, or possibly the new recently reported water-soluble drugs 2,3-dimercaptosuccinic acid,[15] dithiocarbamate compounds,[16] or dimercaptopropanesulfonate (unithiol)], is advised. A success in this approach for the treatment of severe mercury poisoning will lead to further research related to other metal poisoning, using the same techniques with the appropriate chelating microspheres (selectivity for the desired metal). In case of success in vitro, experiments in vivo are planned to be carried out.

Experimental Section

Glutaraldehyde (25%) was purchased from Fluka, pentaerythritol tetrathioglycolate from Evans Chemtic Inc., Agarose from Pharmacia Fine Chemicals, and poly(oxyethylene)sorbitan monolaurate (Tween 20) from Sigma. The analytical grade reagents H_2SO_4, HCl, $SnCl_2$, $NH_2OH{\cdot}HCl$, $KMnO_4$, and deionized H_2O showed very small Hg blank and could be used without further purification. The stock solution of $HgCl_2$ and of CH_3HgCl and the appropriate dilutions were prepared in 10% HCl. The glassware used for Hg analysis was soaked in concentrated HNO_3 for several hours before use.

Phosphate-buffered saline solution (PBS, 0.1 M, pH 7.2) was prepared by adding Na_2HPO_4 solution (0.1 M) to an aqueous solution of NaH_2PO_4 (0.1 M) until pH of 7.2 was reached. Then the solutions were diluted 10 times with distilled water, and sodium chloride was added to obtain a concentration of 0.15 M.

Mercury Analysis. Mercury was determined by cold vapor atomic absorption (Varian Model 1200) with a cold vapor analyzer kit attached, according to the procedure described by Campe et al.[17]

Binding of Mercury Compounds to Plasma. Normal human plasma was shaken for 2 h with 20 ppm of CH_3HgCl and $HgCl_2$. The binding was determined in two ways: with $HgCl_2$, plasma samples were placed into ultrafiltration membranes (Amicon 2100, CF-50), which were centrifuged for 5 min at 1000 rpm; with CH_3HgCl, ultrafiltration of plasma samples through a dialysing membrane with a permeability corresponding to molecular weights of 10 000 was carried out. In both techniques, mercury was not recovered in the ultrafiltrate, which means that the mercury compounds were bound to the plasma completely.

Chelating Microspheres.[18] An aqueous solution containing 0.2% (v/v) Tween 20 as surfactant and 5% (v/v) pentaerythritol tetrathioglycolate was stirred vigorously for several hours until stable aqueous micelles of pentaerythritol tetrathioglycolate were produced. Thereafter, 5.5 mL of glutaraldehyde (25%) was added to the emulsion solution, which was shaken for another 12 h. The reaction product contained a solid sticky compound resulting from the agglutination of chelating microspheres and another part (60%) containing monodisperse chelating microspheres. The microspheres were separated by decantation from the sticky part and then cleaned from impurities by either dialysis or slow spinning. The size of the microspheres was determned by looking under a light microscope (Zeiss, magnification 1000×). The monodisperse microspheres moved in a Brownian motion. They are quite uniform with a 0.8 μm average size.

Toxicity. The acute median lethal dose [LD_{50} (orally)] to 40 ICR mice of the chelating microspheres was found to be 1 mg/g of body weight.

Reaction of the Chelating Microspheres and Mercury Compounds. The chelating microspheres were added to a stirred PBS solution containing the mercury compounds. Samples tested for mercury concentration were taken and spun at 2100g to separate the solution from the microspheres. Control experiments were carried out in the same way but without the presence of chelating microspheres. (Spinning of the control samples did not show any precipitation of the mercury compounds.)

Encapsulated Beads.[18] The encapsulated beads were obtained according to a procedure described by Losgan et al.[6] A solution containing 1.25 g of agarose, 0.12 mL of Tween 20, and 25 mL of H_2O was heated to 85 °C until the gel had melted into a clear solution. Then, 8 mL of pentaerythritol tetrathioglycolate was added, and the solution was stirred for 15 min in order to produce stable micelles of pentaerythritol tetrathioglycolate. The temperature was then decreased to 70 °C and 9 mL of glutaraldehyde (25%) was added to the solution, which was stirred for another hour. The mixture was then drawn into a disposable syringe and injected dropwise into a tall vessel containing an ice-cold solvent mixture made of toluene, chloroform, and hexane in the ratio 10:4:2. The encapsulated beads were separated from the solvent mixture in a crude sieve and then washed several times with dioxane and finally with distilled water.

Acknowledgment. I thank Mr. J. Hirsh and Mrs. H. Rosin for their help in doing some of this research.

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