Preparation of N-Substituted Maleimides by Direct Coupling of Alkyl or Aralkyl Halides with Heavy Metal Salts of Maleimide[1]

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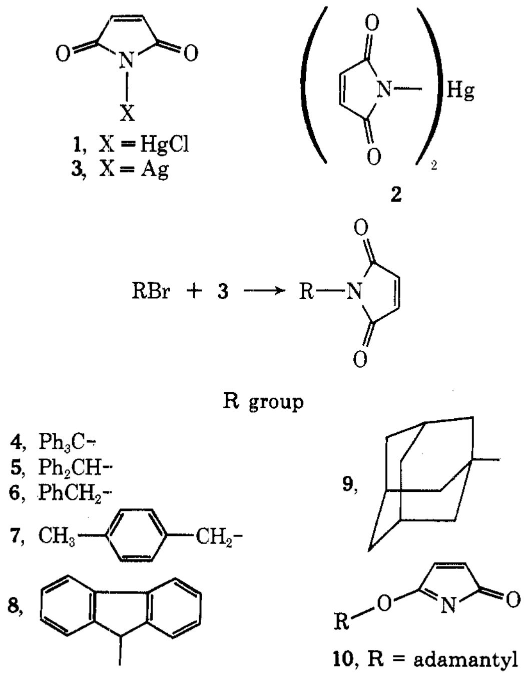
A new procedure for the preparation of some *N*-alkyl- and *N*-aralkylmaleimides has been developed. This procedure uses the reaction of a heavy metal salt of maleimide with alkyl and aralkyl halides in an inert solvent. Silver maleimide (**3**) was found to be far more reactive than mercuric maleimide (**2**). Compound **3** was prepared by treatment of maleimide with silver nitrate and sodium hydroxide in a mixture of ethanol and dimethyl sulfoxide. Compound **2** was prepared by treatment of maleimide with mercuric chloride and sodium hydroxide in ethanol-water. The latter reacted with trityl chloride in refluxing toluene to give a 60% yield of *N*-tritylmaleimide (**4**). The reaction of **3** with trityl chloride in benzene at room temperature increased the yield to 95%. Compound **3** was treated with benzhydryl bromide, benzyl bromide, α-bromo-*p*-xylene, and 9-bromofluorene in benzene under reflux to yield *N*-benzhydrylmaleimide (**5**, 57%), *N*-benzylmaleimide (**6**, 38%), α-*N*-maleimidyl-*p*-xylene (**7**, 17%), and *N*-(9-fluorenyl)maleimide (**8**, 55%), respectively. *N*-(1-Adamantyl)maleimide (**9**) was prepared in refluxing toluene in a 51% yield. When this last reaction was run at room temperature, *O*-(1-adamantyl)maleimide (**10**) was obtained in nearly quantitative yield. This compound represents the first synthesis of an *O*-alkylmaleimide and it can easily be distinguished from **9** and other N-substituted maleimides by nmr, ir, and uv spectroscopy, and by tlc. Compound **10** was converted to **9** in a 55% yield by heating the compound in toluene in the presence of silver bromide.

N-Alkyl- or *N*-arylmaleimides have been prepared by reaction of amines with maleic anhydride to give maleamic acids, which, after isolation, are then cyclized in such mixtures as refluxing acetic anhydride–sodium acetate or hot phosphoric acid.[2] A careful survey of the literature revealed that some amines did not afford good yields of maleimides after condensation with maleic anhydride because the cyclization of the maleamic acids proceeded poorly.[3,4] We, therefore, decided to attempt the preparation of a heavy metal salt of maleimide and to condense this with simple alkyl or aralkyl halides, a method that has been of use in the synthesis of nucleosides.[5] What we wish to report is the first synthesis of N-substituted maleimides by direct coupling of heavy metal salts of maleimide with organic halides in an inert solvent.

Attempted preparation of chloromercurimaleimide (**1**, Chart I) always led to the formation of mercuric maleimide (**2**), regardless of the relative molar quantities of maleimide, sodium hydroxide, and mercuric chloride used. Compound **2** was coupled with trityl chloride in hot toluene to afford a 60% yield of *N*-tritylmaleimide (**4**). However, this procedure was not useful for the synthesis of other N-substituted maleimides. A better reagent for this purpose was silver maleimide (**3**), easily prepared by treatment of maleimide with silver nitrate and sodium hydroxide.

Chart I



Silver maleimide was treated with a number of organic halides in hot benzene or toluene. In general, benzene was the most satisfactory solvent. When silver maleimide was placed in warm polar solvents, such as dimethylformamide or acetonitrile, it rapidly decomposed. An advantage of this procedure is best demonstrated by the synthesis of *N*-(9-fluorenyl)maleimide (**8**) in 55% yield, whereas the older reaction sequence starting from 9-aminofluorene gave **8** in an overall yield of only 8%.[4] This procedure is particularly advantageous in cases where the amine is not readily available, such as in the synthesis of α-*N*-maleimidyl-*p*-xylene (**7**). Starting from α-bromo-*p*-xylene, the yield of **7** was only 17%. However, this direct single-step coupling precluded the necessity of preparing the amine. Reaction of **3** with benzyl bromide in toluene at reflux gave **6** in a significantly lower yield (11%) and maleimide and α-phenylxylenes were identified in the mixture. Such compounds were not detected when the same reaction was performed in benzene.

When silver maleimide was treated with 1-bromoadamantane in benzene at room temperature, a nearly quantitative yield of *O*-(1-adamantyl)maleimide (**10**) was obtained as a solid, representing the first reported synthesis of an O-substituted maleimide. The structure of **10** was clearly differentiated from *N*-(1-adamantyl)maleimide (**9**) and other N-substituted maleimides by nmr and ir spectroscopy. The nmr spectra of all of the N-substituted maleimides studied in this investigation had a sharp singlet between τ 3.19 and 3.45, which was expected because of the symmetrical environment of the two olefinic protons. This was also true of maleimide itself and for the two heavy metal salts, **2** and **3**, which was an important proof of structure for the latter. On the other hand, the nmr spectrum of **10** revealed two doublets for the same protons in the form of a nearly classical AB pattern at τ

Table I
Ultraviolet Spectra of Some Maleimide Derivatives

Compd	λ, nm (ε)[a] Maxima	Minima
N-Ethylmaleimide	297 (637)	243 (55)
N-(1-Adamantyl)maleimide (**9**)	301 (643)	251 (121)
O-(1-Adamantyl)maleimide (**10**)	310 (678)	276 (432)

[a] Spectra determined in 1,2-dichloroethane.

3.21 and 3.59 (J = 5.2 Hz). This indicated that the bond between the adamantane and maleimide was linked through one of the oxygen atoms of maleimide. The downfield shift of one of the peaks relative to that obtained for **9** at τ 3.43 may be due to an induced ring current, resulting in a deshielding effect. A fully conjugated planar structure such as **10** would be expected to produce such a ring current. The results of this conjugated planar geometry is also evident in the observed differences in the uv spectra of **10**, **9**, and *N*-ethylmaleimide (Table I).

Infrared spectra were also of important diagnostic value in studying the maleimides. Usually, the carbonyl peak near 1700 cm^{-1} has been utilized for structural purposes. However, an out-of-plane deformation at 678 cm^{-1} for maleimide was reported[6] which appears near 690 cm^{-1} in N-substituted maleimides. The phenyl C-H in phenyl-substituted maleimides is fully resolved at slightly higher wave numbers. Freedom from contamination with maleimide was verified by the absence of a peak at 678 cm^{-1} in addition to tlc data. Another strong band which was characteristic of the maleimides studied appeared between 820 and 850 cm^{-1} and has not yet been assigned to a bond. Compound **10** exhibited a strong infrared band at 1042 cm^{-1}, which was not present in **9** or the other maleimides, and which is due to an ether linkage. The conjugated C=C and C=N bands were also evident at 1600 and 1530 cm^{-1} and the C-H bending vibration at 694 cm^{-1} was shifted to 720 cm^{-1}. All of this evidence clearly identified **10** as *O*-(1-adamantyl)maleimide.

An examination of O → N isomerization was now undertaken with **10**, using mercuric bromide, a reagent often used to effect such transformations in pyrimidines[7] and other diazines.[8] When **10** was treated with mercuric bromide in boiling benzene, **9** was isolated in 34% yield. It was probable that in the coupling reaction **10** was the product first formed and that silver bromide, the by-product, catalyzed the O → N isomerization *in situ*. Treatment of **10** with an "activated" silver bromide[9] (prepared from *tert*-butyl bromide and silver succinimide) in hot toluene afforded a 55% yield of **9**. Compound **10** would not rearrange to **9** when heated under reflux without the heavy metal salts. A study of the course of the coupling reaction by tlc revealed that after 1 hr the only new product was **10** and that all of the 1-bromoadamantane had been consumed by silver maleimide. After an additional 3 hr, **10** and **9** were both observed and after 30 hr the only product was **9**. Presumably, the other coupling reactions proceeded by a similar pathway. A reinvestigation by tlc and ir spectroscopy of earlier periods in some of the reactions reported above or reactions at lower temperatures gave good evidence that this was the case, except in the synthesis of *N*-tritylmaleimide (**4**).

It is interesting to note that during attempts to purify **10** by sublimation above 90°, a small quantity of **9** was detected in the sublimate only. Since the residue did not contain any **9**, it was concluded that the rearrangement proceeded by a free-radical process in the vapor phase.[10] It was mentioned above that a mixture of α-phenylxylenes and maleimide appeared to be the major products during a synthesis of *N*-benzylmaleimide (**6**) in boiling toluene. It now seemed quite probable that these products arose *via* a free-radical process propagated by homolytic dissociation of *O*-benzylmaleimide, resulting in benzyl and maleimidyl free radicals. Earlier we had thought that such a reaction was initiated by homolytic decomposition of **3**, but, when **3** was suspended alone in boiling toluene, no decomposition took place.

Experimental Section[11]

Mercuric Maleimide (2). A solution of maleimide (15.0 g, 0.154 mol) in 100 ml of water was mixed with a solution containing 21.0 g (0.077 mol) of mercuric chloride in 80 ml of ethanol and to this stirring mixture was added 385 ml of 0.4 *N* sodium hydroxide solution, dropwise. Compound **2** (23.9 g, 80%) was isolated as a slightly off-white solid by filtration, washing with water, ethanol, and acetone in succession, and drying in a vacuum desiccator ($CaCl_2$, 20 mm): ir 3050, 1650 (br), 1345, 1175, 1165, 1080, 1008, 827, 770, 694, and 665 cm^{-1}; nmr τ 3.15 (sharp singlet). An analytical sample was prepared by recrystallization from dimethyl sulfoxide.

Anal. Calcd for $C_8H_4HgN_2O_4$: C, 24.47; H, 1.02; Hg, 51.07; N, 7.13. Found: C, 24.36; H, 1.13; Hg, 50.94; N, 6.97.

Silver Maleimide (3). A solution of silver nitrate (24.8 g, 0.146 mol) in 100 ml of DMSO was added to a solution of maleimide (14.2 g, 0.146 mol) in 600 ml of absolute ethanol and to this mixture was added, dropwise, 365 ml of 0.4 *N* ethanolic sodium hydroxide solution over a period of 2 hr while the mixture was vigorously stirred. The off-white solid was isolated by suction on filter paper[12] and thoroughly washed with absolute ethanol. The precipitate was suspended in water, stirred vigorously for several minutes, filtered, and washed again with ethanol. This process was repeated in acetone and the solid was dried in a vacuum desiccator (20 mm) for 48 hr, yielding 27 g (91%) of **3**: ir 3080, 1727, 1610, 1560, 1370, 1310, 1080, 990, 831, 710, 703 (sh), and 660 cm^{-1}; nmr (DMSO-d_6) τ 3.45 (sharp singlet); nmr (pyridine-d_5) τ 4.06 (sharp singlet).

Anal. Calcd for $C_4H_2AgNO_2$: C, 23.56; H, 0.99; Ag, 52.90; N, 6.87. Found: C, 23.62; H, 1.13; Ag, 53.04; N, 6.85.

Prior to the utilization of **5** it was further dried at 0.05 mm over P_2O_5 at room temperature for at least 24 hr. During the preparation and handling of **3**, precautions were taken to exclude light.

***N*-Tritylmaleimide (4). Method A. From Mercuric Maleimide (2).** From a mixture containing 0.57 g (1.5 mmol) of **2**, 0.3 g of Celite-545, and 28 ml of toluene, 12 ml of toluene was removed by distillation. Trityl chloride (0.40 g, 1.4 mmol) was added to it and the mixture was stirred at reflux for 4 hr. The precipitated solids were removed by filtration and washed with several portions of hot chloroform. The solvents were removed by evaporation and the residue was dissolved in 30 ml of ethyl acetate, washed with 30% aqueous potassium iodide (4 × 20 ml), and dried. Evaporation of the solvent left 0.72 g of a moist yellow solid which upon trituration with ethyl ether afforded 0.28 g (60%) of **4** as a white powder, mp 225-227°. Crystallization from a mixture of hexane and benzene produced the analytical sample: mp 225-228°; ir 3000, 1706, 1340, 1323, 836, 694, and 690 cm^{-1}; nmr τ 2.78 (m, 15 aromatic H), 3.44 (sharp singlet, 2 olefinic H).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.29; H, 5.06; N, 4.08.

Method B. From Silver Maleimide (3). Trityl chloride (0.72 g, 2.6 mmol) was dissolved in 22 ml of benzene and treated with 0.55 g (2.7 mmol) of **3** at 25°. After 4 hr, the mixture was filtered and the filtrate was evaporated to a white powder (0.81 g, 95%), mp 226-229°. The product was identical to that obtained by method A, as determined by ir spectroscopy and tlc.

***N*-Benzyhydrylmaleimide (5).** Benzhydryl bromide (4.4 g, 0.018 mol) and **3** (4.0 g, 0.020 mol) were stirred in 240 ml of dry benzene at reflux for 1.7 hr. The silver salts were removed by filtration and washed with methylene chloride. Evaporation of the solvent afforded a light-tan solid which was crystallized from 100 ml of ethanol, giving 2.7 g (57%) of **5**: mp 147-151°; ir 3050, 1698, 1357, 831, 698, 690 cm^{-1}; nmr τ 2.66 (sharp singlet, 10 aromatic H), 3.31 (sharp singlet, 2 olefinic H), 3.46 (s, benzylic H). Recrystallization from ethanol afforded the analytical sample.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.83; H, 5.07; N, 5.27.

***N*-Benzylmaleimide (6). Method A.** Compound **3** (10.0 g, 49 mmol) was added in five equal portions at 0.5-hr intervals to a stirring solution of 7.8 g (45 mmol) of benzyl bromide in 145 ml of benzene maintained at 60°. The mixture was then heated to reflux for 15.5 hr, and the silver salts were removed by filtration and washed thoroughly with benzene. Evaporation of the benzene gave an amber-colored residue which was dissolved in 150 ml of carbon tetrachloride and washed with water (3 × 200 ml). The organic layer was dried and the solvent was evaporated, leaving 3.2 g (38%) of a liquid which almost completely solidified upon standing. Crystallization from ethanol and sublimation gave white crystals of **6**: mp 69–72° (lit.[13] mp 70–72°); ir 3060, 1701, 840, 697 (sh), 690 cm^{-1}; nmr τ 2.67 (sharp singlet, 5 aromatic H), 3.34 (sharp singlet, 2 olefinic H), 5.33 (sharp singlet, 2 benzylic H).

Method B. A repeat of the above reaction in toluene under reflux gave an oil which was separated by preparative tlc in benzene on 20 × 20 cm silica gel F-254 plates of 2-mm thickness (E. Merck, Darmstadt). The product having R_f 0.15 was identified as **6** (mp 67–68°) and the spectra of the faster moving substance (R_f 0.58) indicated that it could be a mixture of α-phenylxylenes: ir (film) 3000, 2900, 1602, 1515, 1495, 1455, 742, 722, 696 cm^{-1}; nmr τ 2.80 (m, 9 aromatic H), 6.00 and 6.05 (two singlets for two positional isomers, 2 methylene H), and 7.80 and 7.87 (2 singlets for two positional isomers, 3 methyl H).

***α-N*-Maleimidyl-*p*-xylene (7).** A mixture consisting of α-bromo-*p*-xylene (12.0 g, 0.065 mol), **3** (13.3 g, 0.066 mol) and 500 ml of dry benzene was refluxed for 16 hr. The silver salts were removed by filtration. Evaporation of the solvent left a tacky, amber-colored residue which was vigorously stirred in 200 ml of ether for 3 hr. After filtration, the solvent was evaporated, leaving a light-tan semisolid which was sublimed at 110° (0.02 mm). A small amount of an oily contaminant was removed from the sublimate (**7**) by sandwiching it between porous plates. Additional **7** was obtained by treatment of the residue as above. The combined solids were dissolved in 80 ml of benzene and washed with water (4 × 75 ml) to remove maleimide. The benzene solution was dried and evaporated to afford a white, crystalline solid. Sublimation (0.02 mm, 104°) produced 2.2 g (17%) of an analytically pure material: mp 101–104°; ir 3080, 3010, 2910, 1706, 1342, 1335, 825, 692 cm^{-1}; nmr τ 2.76 and 2.79 (two singlets, 4 aromatic H), 3.27 (sharp singlet, 2 olefinic H), 5.34 (sharp singlet, 2 methylene H), 7.67 (sharp singlet, 3 methyl H).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.78; H, 5.66; N, 6.72.

***N*-(9-Fluorenyl)maleimide (8).** To a suspension of **3** (6.1 g, 0.030 mol) in 50 ml of benzene was added, with stirring, a solution of 7.1 g (0.029 mol) of 9-bromofluorene in 200 ml of benzene and the mixture was refluxed for 2.5 hr. Solids were removed by filtration, and the solvent was evaporated, leaving a yellow solid. This material was stirred for 3 hr in 25 ml of ether and a white powder was isolated by filtration and washed with 10 ml of ice-cold ether. The solid was dissolved in 250 ml of benzene and washed with water (4 × 200 ml). Drying of the benzene layer and evaporation of the solvent left a white solid which was crystallized from heptane–benzene to give 4.2 g (55%) of white needles of **8**, mp 176–179°. Further purification was effected by sublimation (0.02 mm, 140–145°): mp 174–177° (lit.[4] mp 174–175°); ir 3080, 2880, 1355, 1350, 1704, 1686, 827, 738, 692 cm^{-1}; nmr τ 2.07–2.81 (m, 8 aromatic H), 3.28 (sharp singlet, 2 olefinic H), 3.83 (s, 1 aliphatic H).

***N*-(1-Adamantyl)maleimide (9).** A mixture of **3** (1.37 g, 6.7 mmol), 1-bromoadamantane (1.12 g, 5.2 mmol), and toluene (24 ml) was heated at reflux for 4 hr. Filtration and evaporation of the solvent left 0.83 g of a light-orange, waxy solid. Sublimation (0.3 mm, 110°) afforded 0.62 g (51%) of a white, crystalline material which was homogeneous by tlc, mp 120° (with sublimation). An analytical sample was prepared by recrystallization from petroleum ether (bp 30–60°): mp 118–121°; ir 3040, 2880, 1709, 1689, 1351, 828, 694, and 678 cm^{-1}; nmr (CCl_4, internal TMS) τ 3.57 (sharp singlet, 2 olefinic H), 7.67 (s, 6 methylene H), 7.88 (m, 3 bridgehead H), 8.28 (s, 6 methylene H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.38; N, 5.99.

***O*-(1-Adamantyl)maleimide (10).** A mixture of 1-bromoadamantane (3.2 g, 1.5 mmol), **3** (3.2 g, 1.6 mmol), and benzene (80 ml) was stirred at room temperature for 18 hr. The silver bromide was filtered off and the filtrate was evaporated to dryness to yield 3.4 g (98%) of **10**: mp 132–140° dec; ir 3080, 2900, 1745, 1732, 1600, 1530, 1383, 1378, 1355, 1042, 887, 822, 728, 720, and 662 cm^{-1}; nmr τ 3.21 and 3.59 (AB quartet, 2 olefinic H, J = 5.2 Hz), 7.67 (s, 6 methylene H), 7.83 (s, 3 bridgehead H), 8.29 (s, 6 methylene H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.52; H, 7.33; N, 5.74.

Rearrangement of 10 to 9. To a solution of *tert*-butyl bromide (0.24 g, 1.8 mmol) in 17 ml of toluene was added 0.33 g (1.6 mmol) of silver succinimide[14] and the mixture was stirred for 20 min. The silver bromide which precipitated was washed by decantation with nine 15-ml portions of toluene. At this point the toluene wash no longer gave a positive alcoholic silver nitrate test. The silver bromide was suspended in 15 ml of fresh toluene and a solution of **10** (0.31 g, 1.4 mmol) in 15 ml of toluene was added. The mixture was stirred at reflux for 4.5 hr and the salt was removed by filtration. After evaporation of the solvent, carbon tetrachloride was added and evaporated three times. Sublimation of the residue *in vacuo* (0.02 mm, 40–100°) produced 0.17 g (55%) of **9** which was shown to be identical with previous preparations by melting point and tlc and by ir and nmr spectroscopy.

Registry No. 2, 42867-29-8; **3,** 42867-30-1; **4,** 42867-31-2; **5,** 32620-66-9; **6,** 1631-26-1; **7,** 42867-34-5; **8,** 7702-44-5; **9,** 42867-36-7; **10,** 42867-37-8; maleimide, 541-59-3; trityl chloride, 76-83-5; benzhydryl bromide, 776-74-9; benzyl bromide, 100-39-0; α-bromo-*p*-xylene, 104-81-4; 9-bromofluorene, 1940-57-4; 1-bromoadamantane, 768-90-1.

References and Notes

(1) (a) This work was supported by Grant No. CA 12205 from the National Cancer Institute, National Institutes of Health. (b) A communication of some of these results was reported by the above authors at the 165th National Meeting of the American Chemical Society, Dallas, Tex., April 1973, ORGN 115.

(2) N. B. Mehta, A. P. Phillips, F. F. Lui, and R. E. Brook, *J. Org. Chem.*, **25**, 1012 (1960); Y. Kanaoka, T. Sekine, M. Machida, Y. Soma, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull.*, **12**, 127 (1964).

(3) K.-C. Tsou, R. J. Barnett, and A. M. Seligman, *J. Amer. Chem. Soc.*, **77**, 4613 (1955); T. M. Pyriadi, *J. Org. Chem.*, **37**, 4184 (1972).

(4) H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **26**, 2244 (1961).

(5) J. A. Montgomery and H. J. Thomas, *Advan. Carbohyd. Chem.*, **17**, 301 (1962); J. J. Fox and I. Wempen, *ibid.*, **14**, 283 (1959).

(6) P. Bassignana, C. Cogrossi, G. Polla Mattiot, and M. Gillio-Tos, *Spectrochim. Acta*, **18**, 809 (1962).

(7) T. L. V. Ulbricht and G. T. Rogers, *J. Chem. Soc.*, 6125 (1965); D. Thacker and T. L. V. Ulbricht, *ibid.*, 333 (1968).

(8) D. Heller and G. Wagner, *Pharmazie*, **27**, 427 (1972). For examples with pyridones see D. Heller and G. Wagner, *ibid.*, **27**, 290 (1970), and references cited therein.

(9) Silver bromide, prepared from silver nitrate and potassium bromide in water, gave greatly lowered yields in this reaction.

(10) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1960, pp 733, 736.

(11) Melting points were determined on a Kofler micro hot stage and are corrected values. Infrared spectra were obtained from KBr pellets on a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were recorded on a Beckman DK-2 spectrophotometer in 1.0-cm silica cuvettes. Nmr spectra of N- and O-substituted maleimides were recorded as $CDCl_3$ solutions (99.8%, internal TMS) and heavy metal salts of maleimide as DMSO-d_6 solutions (99.5%, internal TMS) on a Varian A-60 spectrophotometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn., or the Spang Microanalytical Laboratory, Ann Arbor, Mich. Solvent evaporations were carried out on a rotary evaporator under reduced pressure and at a bath temperature under 50°. Moist organic solutions were dried over anhydrous magnesium sulfate. Thin layer chromatography (tlc) was performed on silica gel F-254 precoated plates (E. Merck, Darmstadt) of 0.25 mm thickness. Spots were visualized with an ultraviolet lamp or in an iodine chamber.

(12) The use of a sintered-glass funnel causes the salt to turn dark at the salt-glass interface.

(13) R. Lukes and M. Pergan, *Collect. Czech. Chem. Commun.*, **27**, 1387 (1962).

(14) J. Ley and K. Schaefer, *Ber.*, **39**, 1259 (1906).