The Photolysis of a 5-Oxo Steroid Derivative

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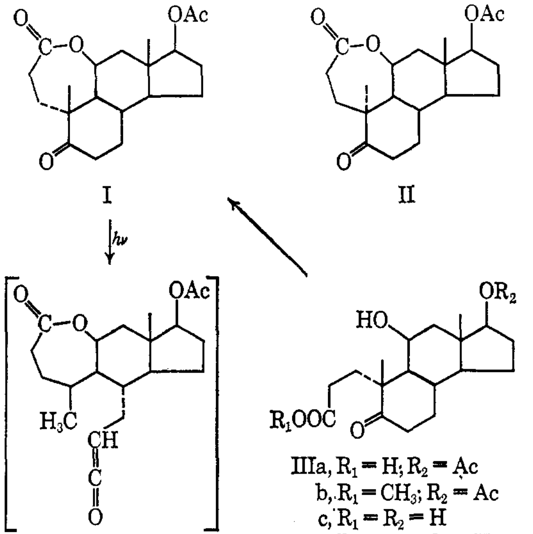
Received October 11, 1967

The ultraviolet irradiation of 17-oxo steroids in organic solvents is known to invert the configuration of the C-13 angular methyl group, giving rise to the corresponding lumi steroids in which rings C and D are *cis* fused.[2] In this connection, we were interested in the possibility that irradiation of the 5-oxoandrostane derivative I might yield the corresponding C-10 epimer II.

The synthesis of I was accomplished readily by utilizing 11β-hydroxytestosterone 17-acetate[3] as starting material. Ozonolysis of the latter compound gave the keto acid IIIa as an amorphous solid[4] which was characterized by conversion into its methyl ester IIIb and the corresponding 17β-hydroxy derivatives IIIc and IIId. Compound IIIa gave the lactone I by heating in benzene with *p*-toluenesulfonic acid or by heating with acetic anhydride containing a trace of sodium acetate.[5] Hydrolysis of the lactone I also gave IIIc, which was identical with the acid obtained by hydrolysis of IIIa.



I

II

IV

IIIa, $R_1 = H; R_2 = Ac$
b, $R_1 = CH_3; R_2 = Ac$
c, $R_1 = R_2 = H$
d, $R_1 = CH_3; R_2 = H$

Va, $R = H$
b, $R = CH_3$
c, $R = C(CH_3)_3$

VIa, $R = H$
b, $R = CH_3$

The major product isolated from the irradiation of I in aqueous dioxane was the acid Va, which was characterized as its methyl ester Vb. The latter compound was converted into the diacid VIa and the dimethyl ester VIb. Irradiation of I in *t*-butyl alcohol gave the *t*-butyl ester Vc, which on hydrolysis also gave the diacid VIa.

Quinkert and coworkers[6] and recently Meinwald and Schneider[7] have demonstrated that prolonged ultraviolet irradiation of nonconjugated ketones gives rise to carboxylic acids or carboxylic acid derivatives *via* ketene intermediates. Similarly, the intermediate ketene IV seems likely as the primary product of the photolysis of I.

Experimental Section[8]

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid 17-Acetate (IIIa) and Methyl Ester (IIIb).—A solution of 5.0 g (0.0144 mol) of 11β-hydroxytestosterone 17-acetate,[3] 6 ml of glacial acetic acid, and 114 ml of ethyl acetate was ozonized in a bath of Dry Ice and acetone for 16 min (Welsbach T-23 Laboratory Ozonator, pressure 8.0 psi, rotameter float 0.08 S. C. F. M.). The resulting yellow solution was flushed at −78° with oxygen for 5 min and with nitrogen for 25 min. The solution was then treated at 0° with 100 ml of glacial acetic acid, 20 ml of water, and 8 ml of 30% hydrogen peroxide. The colorless solution was allowed to stand at 5° overnight and was then concentrated under reduced pressure to a total weight of 15.8 g, the water bath being kept at 40–50°. The residue was distributed between 200 ml of benzene and 350 ml of a 7% sodium carbonate solution by shaking for 15 min. The benzene layer was then extracted with two 100-ml portions of 10% sodium carbonate solution. The combined sodium carbonate extracts were poured into an excess of ice-cold 6 *N* hydrochloric acid solution and the resulting mixture was extracted with ethyl acetate. These extracts were dried and evaporated to give 4.95 g (94%) of crude IIIa which could not be crystallized: $\nu_{max}^{CHCl_3}$ 3615, 1710, 1255, and 1045 cm^{-1}; ν_{max} (piperidine–chloroform) 3620, 1730, 1705, 1625, 1565, 1495, 1480, 1257, and 1045 cm^{-1}.

In another experiment on the same scale, the final ethyl acetate extracts were concentrated to a total weight of 6.64 g. This residue (containing some acetic acid), dissolved in 20 ml of methanol, was treated at 0° with an excess of diazomethane in ether. The solvents were evaporated and the residue was chromatographed on 100 g of silica gel. The ethyl acetate–benzene (10:90) fraction was crystallized from ether–hexane to yield 3.68 g of methyl ester IIIb, mp 107–108°. Several recrystallizations from the same solvent system gave the analytical sample: mp 108–109°; $[\alpha]^{25}D$ +47.0° (*c* 1.0 in ethanol); $\nu_{max}^{CHCl_3}$ 3620, 1735, 1710, 1255, and 1045 cm^{-1}; nmr ($CDCl_3$), δ 1.10 (18-CH_3), 1.37 (19-CH_3), 2.03 ($OCOCH_3$), and 3.66 ($COOCH_3$).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.56; H, 8.20.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid ε-Lactone 17-Acetate (I). A.—A solution of 7.89 g of the crude keto acid IIIa and 430 mg of *p*-toluenesulfonic acid monohydrate in 630 ml of benzene was heated under reflux for 1.5 hr (Dean–Stark apparatus). The resulting solution was extracted once with dilute sodium bicarbonate solution, once with water, dried, and evaporated to give 6.27 g of crude I. Column chromatography on 65 g of silica gel and elution with ethyl acetate–benzene (10:90) gave a fraction which was crystallized from ethyl

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[8] Melting points were determined in a capillary tube and are corrected. The infrared spectra were recorded on a Beckman IR 9 spectrophotometer and the nmr spectra on a Varian A-60 instrument using tetramethylsilane as an internal reference standard. The organic solutions were dried over anhydrous sodium sulfate. Column chromatography was carried out on 0.2–0.5-mm silica gel manufactured by E. Merck AG, Darmstadt.

acetate–hexane to yield 4.1 g of lactone I, mp 245–246° (under vacuum). Recrystallization from the same solvent gave the analytical sample: mp 245.5–246.5° (under vacuum); $[\alpha]^{25}\mathrm{D}$ $-26.4°$ (*c* 1.0 in dioxane); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1720, 1250, and 1040 cm^{-1}; nmr (CDCl$_3$), δ 1.02 (18-CH$_3$), 1.35 (19-CH$_3$), and 2.05 (OCOCH$_3$).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.93; H, 8.02.

B.—The crude acid IIIa (9.9 g) and 2.25 g of fused sodium acetate were heated under reflux in 900 ml of acetic anhydride for 2 hr (nitrogen atmosphere). The solution was then filtered from undissolved sodium acetate and was concentrated under reduced pressure. The residue was dissolved in methylene chloride and this solution was washed with dilute sodium bicarbonate solution, water, dried, and evaporated. The residue was chromatographed on 200 g of silica gel. Elution with ethyl acetate–benzene (10:90) and crystallization from ethyl acetate–hexane gave 2.9 g of crude lactone I, mp 232–237°. Further crystallization yielded 1.87 g of the pure compound, mp 245–246° (under vacuum), identical with the product obtained by method A.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid (IIIc). A. From I.—The lactone I (250 mg) was hydrolyzed by heating under reflux for 10 min with a solution of 250 mg of potassium hydroxide, 0.25 ml of water, and 5 ml of methanol. The reaction mixture was then evaporated under reduced pressure and the residue was dissolved in water. The resulting solution was acidified at 0° with dilute hydrochloric acid solution. The precipitate was filtered, washed with water, and dried, yielding 198 mg (85%) of keto acid IIIc, mp 224.5–226° dec. Several recrystallizations from aqueous acetone gave the analytical sample: mp 225–226° dec; $[\alpha]^{26}\mathrm{D}$ $+69.9°$ (*c* 1.1 in ethanol); $\nu_{\max}^{\mathrm{KBr}}$ 3535, 3380, 1690, 1240, and 1050 cm^{-1}; $\nu_{\max}$ (piperidine–chloroform) 3620, 1705, 1625, 1565, and 1400 cm^{-1}; nmr (dimethylformamide-d_7), δ 1.05 (18-CH$_3$), 1.37 (19-CH$_3$).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.58; H, 8.78.

B. From IIIa.—In a similar manner the crude acetate IIIa (4.26 g) was hydrolyzed by heating under reflux for 10 min with a solution of 4.6 g of potassium hydroxide, 5 ml of water, and 50 ml of methanol. The reaction mixture was then evaporated and the residue was dissolved in 20 ml of water. This solution was acidified at 0° with dilute hydrochloric acid solution. After standing in the refrigerator overnight, the resulting precipitate was filtered, washed with cold water, and recrystallized twice from aqueous acetone (charcoal) yielding 2.26 g of keto acid IIIc, mp 224–225° dec, identical with the sample obtained by hydrolysis of the lactone I.

11β,17β-Dihydroxy-5-oxo-3,5-seco-A-norandrostan-3-oic Acid Methyl Ester (IIId).—Treatment of IIIc (0.75 g) with diazomethane in methanol–ether, followed by crystallization from ethyl acetate–hexane, gave 0.43 g of the methyl ester IIId, melting at 93.5–96°, resolidifying at 98°, and remelting at 121.5–122°; $[\alpha]^{26}\mathrm{D}$ $+66.6°$ (*c* 1.0 in ethanol); $\nu_{\max}^{\mathrm{CHCl_3}}$ 3620, 1730, and 1708 cm^{-1}; nmr (CDCl$_3$), δ 1.07 (18-CH$_3$), 1.38 (19-CH$_3$), and 3.70 (COOCH$_3$).

Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.43; H, 8.74.

Irradiation of I in Aqueous Dioxane. Preparation of 9β-Acetoxydodecahydro-5,9aβ-dimethyl-2-oxo-2H-indeno[5,6-*b*]-oxepine-6α-propionic Acid (Va) and Methyl Ester (Vb).—A solution of 2.57 g (7.38 mmol) of I in 200 ml of dioxane and 10 ml of water was irradiated (Corex filter) for 7.5 hr at 25–30°.[9] After evaporation of the solvents the residue was dissolved in benzene. The acidic reaction products were extracted by shaking this solution three times with 60-ml portions of 10% sodium carbonate solution. (Thin layer chromatography indicated the presence of some I and several other products in the resulting benzene layer.) The sodium carbonate extracts were combined and acidified at 0° with dilute hydrochloric acid solution. The resulting precipitate was filtered, washed with water, and dried to give 1.08 g of crude acid Va. Crystallization from aqueous acetone gave 0.761 g of Va, mp 108–111°. Several recrystallizations from ethyl acetate gave the analytical sample: mp 100–101° dec; $[\alpha]^{26}\mathrm{D}$ $-30.6°$ (*c* 0.8 in dioxane); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1725, 1265, 1160, and 1034 cm^{-1}; $\nu_{\max}$ (piperidine–chloroform) 1725, 1625, 1565, 1385, 1265, 1160, and 1030 cm^{-1}; nmr (CDCl$_3$), δ 1.08 (9a-CH$_3$), 1.12 (doublet, 5-CH$_3$), and 2.05 (OCOCH$_3$).

Anal. Calcd for $C_{20}H_{30}$: C, 65.55; H, 8.25. Found: C, 65.49; H, 8.36.

The crude acid Va (1.95 g) was treated with excess diazomethane, followed by column chromatography of the product on silica gel. The product was eluted with ethyl acetate–benzene (15:85) and was crystallized several times from ether–hexane to give 0.76 g of the methyl ester Vb: mp 112–112.5°; $[\alpha]^{25}\mathrm{D}$ $-27.1°$ (*c* 0.9 in dioxane); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1730, 1260, 1160, and 1030 cm^{-1}; nmr (CDCl$_3$), δ 1.08 (9a-CH$_3$), 1.10 (doublet, J = 7 cps, 5-CH$_3$), 2.02 (OCOCH$_3$), and 3.70 (COOCH$_3$).

Anal. Calcd for $C_{21}H_{32}O_6O_6$: C, 66.30; H, 8.48. Found: C, 66.23; H, 8.66.

Irradiation of I in *t*-Butyl Alcohol. Preparation of 9β-Acetoxydodecahydro-5,9aβ-dimethyl-2-oxo-2H-indeno[5,6-*b*]oxepine-6α-propionic Acid *t*-Butyl Ester (Vc).—A solution of 3.32 g (9.55 mmol) of I in 310 ml of *t*-butyl alcohol was irradiated (Corex filter) for 7 hr at 50–60° and for an additional 3 hr at 30–40°.[8] After evaporation of the solvent the residue was chromatographed on 100 g of silica gel. Elution with ethyl acetate–benzene (4:96) gave Vc along with a small amount of a less polar by-product. The latter compound was removed readily by one recrystallization from ether–hexane to give 0.85 g of *t*-butyl ester Vc, mp 125–126°. (Further elution with ethyl acetate–benzene (8:92) gave an additional 1.45 g of Vc containing a trace of a more polar by-product which could not be removed by crystallization from ether–hexane.) Crystallization of the 0.85 g sample from ether–hexane gave the analytical sample: mp 129–130°; $[\alpha]^{26}\mathrm{D}$ $-24.1°$ (*c* 0.8 in dioxane); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1725, 1370, 1260, and 1150 cm^{-1}; nmr (CDCl$_3$), δ 1.08 (9a-CH$_3$), 1.10 (doublet, J = 7 cps, 5-CH$_3$), 1.45 (COOC(CH$_3$)$_3$), and 2.03 (OCOCH$_3$).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 67.96; H, 9.00.

***trans*-4α-(2-Carboxyethyl)hexahydro-1β,6β-dihydroxy-γ,7aβ-dimethylindan-5β-butyric Acid (VIa). A. From Vb.**—A solution of Vb (200 mg), 300 mg of potassium hydroxide, 0.3 ml of water, and 5 ml of methanol was heated under reflux for 20 min. The reaction mixture was then evaporated and the residue was dissolved in water. The aqueous solution was acidified with dilute hydrochloric acid solution and was extracted four times with ethyl acetate. The dried extracts were evaporated and the residue was crystallized twice from acetone–ether to give 103 mg (57%) of the dicarboxylic acid VIa, mp 187.5–188° dec; $[\alpha]^{26}\mathrm{D}$ $+57.0°$ (*c* 1.0 in ethanol). Crystallization from the same solvent mixture gave the analytical sample: mp 189.5–190° dec; $[\alpha]^{25}\mathrm{D}$ $+58.0°$ (*c* 1.0 in ethanol); neutralization equivalent 167; $\nu_{\max}^{\mathrm{KBr}}$ 3540, 3450, 1715, 1465, 1420, 1285, 1270, 1200, 1185, and 1030 cm^{-1}; $\nu_{\max}$ (piperidine–chloroform) 1630, 1570, 1400, and 1390 cm^{-1}; nmr (dimethylformamide-d_7), δ 1.00 (7a-CH$_3$), 1.02 (doublet, γ-CH$_3$).

Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.39; H, 9.03.

B. From Vc.—A solution of 0.20 g of Vc, 0.4 g of potassium hydroxide, 0.40 ml of water, and 4.0 ml of methanol was heated under reflux for 5 hr. Working up as described for the hydrolysis of Vb gave 0.094 g (58%) of the dicarboxylic acid VIa, mp 188.5–189° dec, $[\alpha]^{26}\mathrm{D}$ $+58.7°$ (*c* 1.0 in ethanol), identical with the product obtained by hydrolysis of Vb.

***trans*-4α-(2-Carboxyethyl)hexahydro-1β,6β-dihydroxy-γ,7aβ-dimethylindan-5β-butyric Acid Dimethyl Ester VIb.**—The dicarboxylic acid VIa (1.70 g) was treated with an excess of diazomethane in ether. Several recrystallizations from acetone–hexane gave 1.05 g of the dimethyl ester VIb: mp 117.5–118.5°; $[\alpha]^{25}\mathrm{D}$ $+53.4°$ (*c* 1.0 in ethanol); $\nu_{\max}^{\mathrm{CHCl_3}}$ 3620, 1730, 1460, 1440, 1260, 1175, and 1020 cm^{-1}; nmr (CDCl$_3$), δ 1.00 (7a-CH$_3$), 1.02 (doublet, γ-CH$_3$), and 3.68 (COOCH$_3$).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.50; H, 9.01.

Registry No.—I, 15983-73-0; IIIa, 15983-71-8; IIIb, 15983-72-9; IIIc, 15983-69-4; IIId, 15983-70-7; Va, 15983-82-1; Vb, 15983-83-2; Vc, 16031-71-3; VIa, 15983-84-3; VIb, 15983-85-4.

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[9] Irradiations were carried out using a Hanovia 200-W high pressure mercury vapor lamp. The lamp was placed in a water-cooled quartz immersion well, which was in turn fitted inside a water-jacketed Pyrex reaction vessel of slightly larger diameter. The reaction mixture was flushed with nitrogen for 30 min prior to irradiation which was then carried out with magnetic stirring under a slow stream of nitrogen. The dioxane and *t*-butyl alcohol were purified by distillation over sodium.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses, and to Mr. S. Traiman and Dr. E. Billeter for the infrared and nmr spectra, respectively. We are also indebted to Mr. C. Angevine and Mrs. A. Kahn for technical assistance.

Preparation of 1-Deuteriobenzaldehydes by Lithium Aluminum Deuteride Reduction of N-*t*-Butylbenzamides

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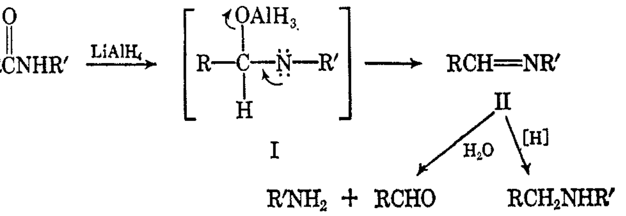
Received August 31, 1967

The normal product resulting from the treatment of an amide with lithium aluminum hydride is the corresponding amine.[2] However, numerous investigators have reported the concomitant formation of significant amounts of aldehyde[3] and alcohols[4] under the reaction conditions. Often the formation of aldehydes becomes the major course of the reaction.[5-7] This is readily understandable if one views the reaction as proceeding by the addition of the hydride reagent to the amide carbonyl group to give a derivative of a geminal amino alcohol (I). Elimination from this intermediate yields an aldimine (II) which on hydrolysis affords the aldehyde or, on further reduction, produces the amine.



The need for 1-deuteriobenzaldehydes in connection with other work led us to investigate procedures for the preparation of labeled aldehydes from amides. The recognized[8] sensitivity of hydride reductions to steric factors suggested the possibility that the reduction could be arrested at the aldimine stage if the effective hydride source (I) and the intermediate (II) contained sufficiently bulky substituents close to the reaction site. The lithium aluminum deuteride reduction of N-*t*-butylbenzamides proved to be a convenient route to the desired 1-deuteriobenzaldehydes. The necessary amides were readily prepared by the reaction of the corresponding acid chlorides with *t*-butylamine.

Optimum yields of aldehyde were obtained when equimolar amounts of lithium aluminum deuteride and amide in ether solution were heated under reflux for 15 hr. The use of a lower ratio of deuteride to amide resulted in the recovery of much unconverted amide, while increased reaction time appears to have a negligible, if any, effect on the yields. Increasing the molar ratio of deuteride to amide to 1.5 causes the complete reduction of the imine to the corresponding N-*t*-butylbenzylamine and no aldehyde is obtained when the reduction product is treated with 5% HCl.

Several methods[9] are available for the preparation of benzaldehyde-1-*d*. The method described in the present work has been successfully applied to the synthesis of the following 1-deuteriobenzaldehydes with the indicated yields: anisaldehyde (57%), *p*-tolualdehyde (58%), and benzaldehyde (33%). The convenience of this method compares favorably with the alternate procedures.

Experimental Section[10]

The following procedure is typical.

N-*t*-butylanisamide.—To a cooled, stirred solution of *t*-butylamine (16.4 g, 0.22 mol) in 60 ml of ether was added a solution of anisoyl chloride (17.1 g, 0.10 mol) in 60 ml of ether over a period of 2 hr. The precipitated amine hydrochloride was removed by filtration and the ethereal solution containing the amide was washed with water and dried over anhydrous sodium sulfate. Removal of the ether gave 19.2 g of crude material which was recrystallized from hexane–chloroform to afford 12.6 g (60%) of N-*t*-butylanisamide, mp 116–117°.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.41; H, 8.18; N, 6.85.

N-Anisylidene-*t*-butylamine.—To a stirred slurry of lithium aluminum deuteride (1.26 g, 0.030 mol) in 100 ml of anhydrous ether was added a solution of N-*t*-butylanisamide (5.18 g, 0.025 mol) in 150 ml of anhydrous ether over a 30-min period. The reaction mixture was heated under reflux for 15 hr after which the reaction was quenched by the cautious addition of 5 ml of water followed by 3 ml of 10% sodium hydroxide. The ether layer was concentrated on a rotary evaporator to give 4.78 g of a colorless oil. The nmr spectrum of the oil indicated its composition to be 90% aldimine (CH_3 singlet, 1.28 ppm), 5% unreacted amide (CH_3 singlet, 1.46 ppm), and 5% amine (CH_3 singlet, 1.16 ppm).

Anisaldehyde-1-*d*.—The crude aldimine (4.78 g) obtained from the lithium aluminum deuteride reduction was stirred at 70° with 60 ml of 5% hydrochloric acid for 30 min. The imine hydrochloride which precipitated initially was gradually converted to an insoluble oil. The reaction mixture was cooled to room temperature and extracted with 75 ml of ether. The ether extract was washed with 5% sodium hydroxide, followed by water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give 2.43 g (71%) of a colorless oil. The nmr spectrum showed this material to be essentially pure anisaldehyde-1-*d*. Distillation gave a colorless oil (1.96 g, 57%), bp 76° (0.6 mm). The infrared spectrum showed a C–D stretching doublet at 2050 and 2100 cm^{-1} and no aldehyde proton could be detected by nmr analysis.

Registry No.—Lithium aluminum deuteride, 14128-54-2.

Acknowledgment.—This work was supported in part by grants from The City College Research Committee, The City University of New York, and the National Science Foundation Undergraduate Research Participation Program.

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[10] Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectophotometer. Nmr spectra were determined with a Varian Associates A-60 spectrometer and absorptions are reported in parts per million (ppm) relative to tetramethylsilane for 15% solutions in deuteriochloroform.