

Hydroxymethylphenylnaphthoic Acid Lactones

Riaz Ahmed, T. L. Holmes and Robert Stevenson

Department of Chemistry, Brandeis University, Waltham, Mass. 02154

Received April 12, 1974

Reduction of 1-phenylnaphthalene-2,3-dicarboxylic anhydride (I) with zinc and acetic acid or lithium aluminium hydride yields a mixture of 1-phenyl-3-hydroxymethyl-2-naphthoic acid lactone (II) and 1-phenyl-2-hydroxymethyl-3-naphthoic acid lactone (III). Catalytic hydrogenation of (I) gave the tetrahydronaphthalene dicarboxylic anhydride (IV). Oxidation of the phenyldihydronaphthofuran (X), prepared by base-catalyzed cyclization of the ether (IX), also yielded lactones (II) and (III). The phenyltetrahydronaphthofuran (XII) was similarly prepared by cyclization of the phenylpropargyl cinnamyl ether (XI).

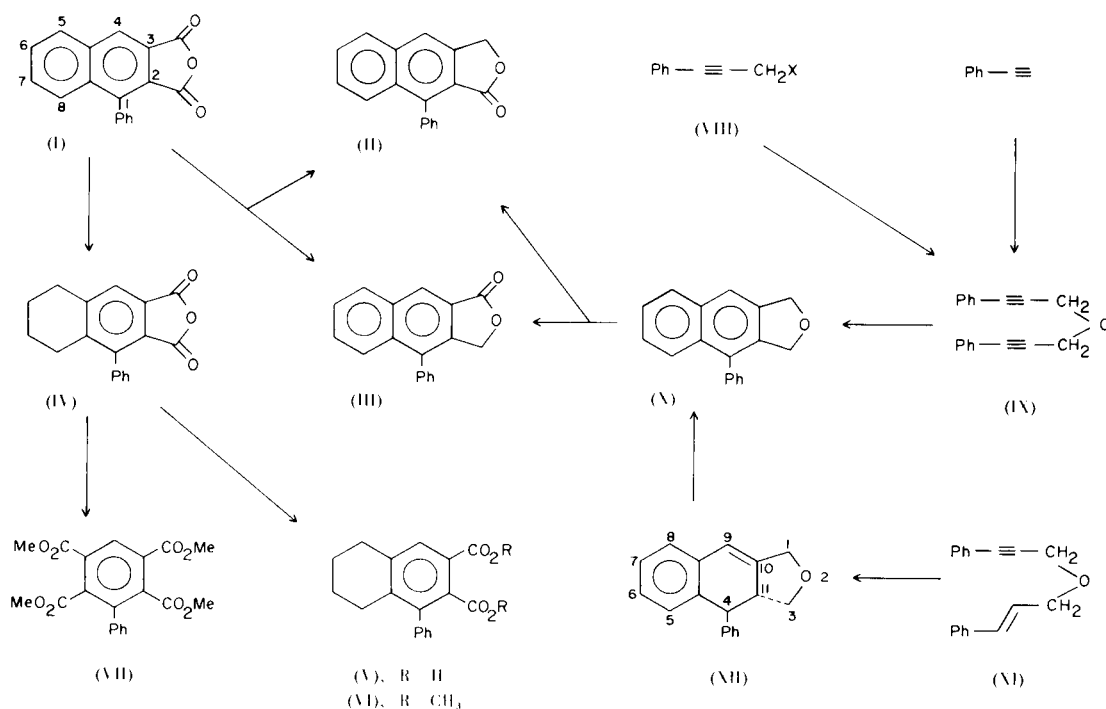
The self-condensation of phenylpropionic acid under the influence of acetic anhydride to give 1-phenylnaphthalene-2,3-dicarboxylic anhydride (I) (1,2) has been shown to have general applicability to substituted arylpropionic acids (3) and has been used as a key step in the synthesis of naturally-occurring phenyltetralin (4) and phenylnaphthalene lignans (5). Where the severity of the conditions promotes undesirable side-reactions, the use of *N,N'*-dicyclohexylcarbodiimide as condensing agent at low temperature was shown to be effective (6) and the scope and generality of these conditions have recently been demonstrated (7). We report here the reduction of the anhydride (I) as a model compound with the longer range view of the utility of these reduction procedures for lignan synthesis, particularly those with lactone functionality.

Three reports of the reduction of (I) with zinc and acetic acid exist from the period during which the structure of the anhydride was in doubt (8-10). Whereas Stobbe considered that the product was the 1,2,3,4-tetrahydronaphthalenedicarboxylic acid, Bucher concluded that it was a lactone or difficultly separable lactone mixture. We have repeated this reduction under Stobbe's conditions (zinc, acetic acid, water, sulphuric acid), purified the neutral fraction by thin layer chromatography, and isolated and identified the lactones (II) and (III), of which the former has recently been obtained by independent procedures (11,12). Proton magnetic resonance spectroscopy, which indicates that the lactones were formed in approximately equal amounts, is particularly useful for their identification. Thus, III has a downfield signal (δ 8.47) attributable to the H-4 aromatic proton deshielded by the *peri* lactone carbonyl group (characteristically $> \delta$ 8.0) and a lactone methylene signal (δ 5.23)

shielded by the ring-C aryl function (characteristic range δ 5.08-5.23). In contrast, lactone II has no low-field aromatic proton, (the H-4 aromatic proton being typically $< \delta$ 8.0) and a lactone methylene signal at δ 5.42 (characteristic range δ 5.32-5.54).

Lithium aluminium hydride reduction of a cyclic anhydride generally yields a diol, and only infrequently has been used for lactone preparation. We subjected the anhydride (I) to reduction with this reagent at low temperature. Examination of the infrared spectrum of the crude product indicated the presence of hydroxyl groups (over-reduction), lactone functionality, and unchanged anhydride. The nmr spectrum indicated, by integration of the lactone signals, that II and III were present in the ratio of 1:2, and these were separated and identified as previously. This provides another example of the interesting observation (13) that reduction occurs predominantly at that carbonyl site judged, if intermediate metal complex formation be ignored, to be the more hindered.

The conversion of some anhydrides to lactones by catalytic hydrogenation has been demonstrated (14). Hydrogenation of the anhydride (I) in acetic acid solution with platinum catalyst resulted in the uptake of two moles of hydrogen to give in quantitative yield a product whose ir spectrum indicated the retention of the anhydride group, and whose pmr spectrum (notably two benzylic methylene groups) indicated the structure (IV). It was characterized by base hydrolysis to the dicarboxylic acid (V), from which the anhydride was readily regenerated, and the corresponding dimethyl ester (VI) with fully consistent spectra. The ring-A reduced anhydride structure, was rigorously established by oxidation with alkaline potassium permanganate and diazomethane



esterification to yield the known biphenyl-2,3,5,6-tetracarboxylic acid tetramethyl ester (VII) (8).

The phenyl dihydronaphthofuran (X) has been reported (15) to be obtained in excellent yield by the action of potassium *t*-butoxide on bis(3-phenyl-2-propynyl) ether (IX), prepared from the sodium salt of phenylpropargyl alcohol (VIII, X = OH) and phenylpropargyl bromide (VIII, X = Br). We have obtained IX more conveniently by treatment of lithium phenylacetylide with bis(chloromethyl) ether and confirmed the cyclization as described to give X. Treatment of X with chromium trioxide in acetone yielded the lactones II and III (ratio *ca.* 1:2.7) in excellent yield, oxidation predominating in this instance at the less hindered benzylic site.

We have also prepared phenylpropargyl cinnamyl ether (XI) by treatment of cinnamyl bromide with sodium phenylpropargyl alkoxide, and subjected it to the potassium *t*-butoxide isomerization condition. The nmr spectrum of the product, readily isolated in 50% yield, indicated the phenyldihydronaphthalene cyclic ether structure (XII) and as expected *N*-bromosuccinimide dehydrogenation gave (X) (16,17). Attempted oxidation of XII, to yield a lactonic product, under the same conditions used for (X), was unsuccessful.

EXPERIMENTAL (18)

1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride (I).

Phenylpropionic acid (1 g.) was added to acetic anhydride (10 ml.) and the mixture heated under reflux for 6 hours. On

cooling, the anhydride separated as light straw-colored plates (0.45 g.), m.p. 259.5-263.5°. Two recrystallizations from methylene chloride raised the m.p. to 265-266°; ν (potassium bromide): 1828 and 1776 cm^{-1} (anhydride); $\text{uv } \lambda$ (cyclohexane): 252 (16000), 261 (18000), 300 (3900), 312 (3400) and 337 nm (1600); nmr: spectrum (complex ArH region, δ 8.55 s, C-4); mass spectrum: m/e 274 (M^+), 246 (M-CO^+), 230 (M-CO_2^+) and 202 ($\text{M-C}_2\text{O}_3^+$).

Action of Zinc and Acetic Acid on 1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride.

To a refluxing solution of the anhydride (1 g.) in acetic acid (40 ml.) was added zinc powder (8 g.) and aqueous sulfuric acid (25%, 8 ml.) in eight portions over 7 hours. The mixture was then allowed to stand at room temperature overnight, filtered, neutralized to litmus with saturated sodium bicarbonate solution, and extracted with ether. Evaporation of the dried extract gave a residual solid (no anhydride carbonyl absorption in ir) product, m.p. 95-140°, shown to be a mixture by tlc. A portion (0.5 g.) was chromatographed on a column (1 cm.) of silica gel (50 g.) and the eluted fractions monitored by tlc. Elution with petroleum ether-benzene (1:1, 1800 ml.) gave traces of an oil. The same eluent (800 ml.) then gave a product (57 mg.) which was crystallized once from petroleum ether-chloroform to give 1-phenyl-2-hydroxymethyl-3-naphthoic acid lactone (III) as prisms, m.p. 164.5-165.5°; ν (potassium bromide): 1761 cm^{-1} (lactone); $\text{uv } \lambda$ (ethanol): 242 (39600), 292 (3900) and 302 nm (4200); nmr: δ 5.23 s. (2H, lactone methylene), 7.33-8.17 m complex (9H, aromatic protons) and 8.47 s. (1H, C-4); m/e 260 (M^+), 231 (M-CHO), 215 weak (M-CHO_2) and 202 ($\text{M-C}_2\text{H}_2\text{O}_2$).

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{O}_2$: C, 83.06; H, 4.65. Found: C, 83.34; H, 4.76.

Continued elution with the same solvent (5200 ml.) yielded a lactone mixture (71 mg.) and with petroleum ether-benzene (2:3, 2000 ml.) a product (142 mg.) which was crystallized once from

petroleum ether-chloroform to give 1-phenyl-3-hydroxymethyl-2-naphthoic acid lactone (II) as short needles, m.p. 188-189°, [Lit. m.p. 185-186° (11), m.p. 186-187.5° (12)], ν (potassium bromide): 1761 cm^{-1} (lactone); $\text{uv } \lambda$ (ethanol): 242 (54200), 290 (4500) and 302 nm (4500); δ 5.42 d (2H, J 1.2 Hz, lactone methylene), 7.25-8.05 m complex (10 H, aromatic protons); m/e 260 (M^+), 231, 215 and 202.

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{O}_2$: C, 83.06; H, 4.65. Found: C, 83.30; H, 4.76.

Integration of the lactone methylene signals of the nmr spectrum of the crude lactone mixture indicated that (II) and (III) were produced in approximately equal amounts.

Catalytic Hydrogenation of 1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride.

The anhydride (604 mg.) was added to a suspension of platinum catalyst (pre-reduced from 70 mg. of platinum oxide) in acetic acid (250 ml.) and the mixture stirred in an atmosphere of hydrogen. After 3 hours, when the catalyst had coagulated and hydrogen uptake had ceased, a further 50 mg. of catalyst was added, the reduction continued and the catalyst addition repeated after a further 3 hours. When reduction had ceased, the catalyst was removed by filtration and the solvent removed under reduced pressure to give a residual solid (600 mg.), m.p. 179-183° with softening at 172°. Two recrystallizations from petroleum ether-chloroform gave 1-phenyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic acid anhydride (IV) as irregular prisms, m.p. 186.5-187°; ν (potassium bromide): 1832 and 1773 cm^{-1} (anhydride); $\text{uv } \lambda$ (cyclohexane): 228 (43000), 232 (44000), 246 sh. (15000), 297 (2500) and 307 nm (2800); nmr spectrum: δ 1.78 m. (4H, C-6 and 7), 2.58 m. (2H, C-8), 3.03 m. (2H, C-5), 7.08-7.57 m. (5H, C-2'-6') and 7.70 s. (1H, C-4).

Anal. Calcd. for $\text{C}_{18}\text{H}_{14}\text{O}_3$: C, 77.68; H, 5.07. Found: C, 77.78; H, 5.19.

1-Phenyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic Acid (V).

To a refluxing mixture of the anhydride (50 mg.) in water (25 ml.) and phenolphthalein (1 drop), sodium hydroxide solution was added dropwise to keep the solution pink colored. After 2½ hours, the solution was cooled, acidified with 2 *N* hydrochloric acid, and the precipitated solid (m.p. 230-234°) collected. Recrystallization from aqueous methanol gave the dicarboxylic acid as needles, m.p. 235-237°; nmr δ (DMSO- d_6): 1.63 m. (4 H C-6 and 7), 2.27 m. (2H, C-8), 2.82 m. (2H, C-5), 7.08-7.50 m. (5H, ArH) and 7.67 (1H, C-4); m/e 296 (M^+).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_4$: C, 72.96; H, 5.44. Found: C, 73.21; H, 5.64.

The dicarboxylic acid was refluxed with acetic anhydride for 2 hours, the solvent removed under reduced pressure, and the product recrystallized from chloroform-petroleum ether to yield the anhydride (IV) as prisms, m.p. and mixed m.p. 186-187°.

1-Phenyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic Acid Dimethyl Ester (VI).

Excess diazomethane in ether was added to a solution of the dicarboxylic acid (31 mg.) in methanol (4 ml.) and ether (5 ml.), allowed to stand at room temperature for 1 hour, diluted with ether (30 ml.) and extracted with sodium bicarbonate solution (1 ml., 10%). The ether solution was dried (sodium sulfate), evaporated and the residual oil crystallized from pentane to give the dimethyl ester as rhombohedra, m.p. 105-107°. It could be obtained as needles or prisms, m.p. 106-107° on recrystallization from aqueous ethanol; nmr δ (DMSO- d_6): 1.68 m.

(4H, C-6 and 7), 2.33 m. (2H, C-8), 2.85 m. (2H, C-5), 3.35 (3H, C-2 CO_2CH_3), 3.78 (3H, C-3 CO_2CH_3), 7.03-7.47 m. (5H, ArH) and 7.72 s. (1H, C-4).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_4$: C, 74.05; H, 6.2. Found: C, 73.97; H, 6.38.

Oxidation of 1-Phenyl-5,6,7,8-tetrahydronaphthalene-2,3-dicarboxylic Acid Anhydride (IV).

The anhydride (225 mg.) was dissolved in 10% sodium hydroxide solution (5 ml.), and the solution neutralized (to litmus) with hydrochloric acid. A solution of potassium permanganate (1.25 g.) in water (300 ml.) was then added portionwise over 5 hours to the refluxing solution and refluxing continued overnight. The mixture was then cooled, the precipitated manganese salts dissolved by addition of hydrochloric acid and solid sodium bisulfite, concentrated to half bulk and extracted with ether. The ether extract was dried (sodium sulfate) and evaporated. Treatment with diazomethane in the usual way and crystallization of the product from ethanol yielded biphenyl-2,3,5,6-tetracarboxylic acid tetramethyl ester (VII) as rhombs, m.p. 130-131°. Lit. m.p. 130-133° (8), m.p. 133-134.5° (11); nmr: δ 3.53 s. (6H, C-2 and 6 CO_2Me), 3.90 s. (6H, C-3 and 5 CO_2Me), δ 7.22-7.67 m. (5H, C-2'-6') and 8.65 s. (1H, C-4).

Action of Lithium Aluminum Hydride on 1-Phenylnaphthalene-2,3-dicarboxylic Acid Anhydride.

Lithium aluminum hydride (79 mg.) was heated under reflux with dry tetrahydrofuran (15 ml.) for 40 minutes, then the mixture cooled in an acetone-carbon dioxide bath. To this was added a solution of the anhydride (1.0 g.) in the same solvent (40 ml.) at -60 to -80° over a period of 45 minutes and the temperature allowed to rise to 0°. After being stirred overnight at this temperature, the reaction mixture was treated with hydrochloric acid (6 *N*), extracted with ether and worked up in the usual way. Infrared absorption spectral examination of the crude product indicated the presence of hydroxyl and anhydride functionality and the nmr spectrum indicated the presence (by their chemical shifts at δ 5.27 and 5.45) of the 3-naphthoic and 2-naphthoic acid lactones respectively in the ratios of ca. 2:1). Preparative thin layer chromatography of the crude product (100 mg.) on silica gel (Brinkman PF, 1 mm, 10 x 10 cm) with developing by 10% ethyl acetate in carbon tetrachloride and visualization of the products by ultraviolet irradiation indicated the presence of several fractions. Elution of the fraction with R_f 0.59 with chloroform yielded 1-phenyl-2-hydroxymethyl-3-naphthoic acid lactone (III) (30 mg.) m.p. 162-164°. Similarly, the fraction with R_f 0.27 yielded 1-phenyl-3-hydroxymethyl-2-naphthoic acid lactone (II) (16 mg.) m.p. 186-188°.

Bis(3-phenyl-2-propynyl) Ether (IX).

Methyl lithium (5 ml., 1.9 *M*) in ether was added to a solution of phenylacetylene (1.02 g.) in ether (50 ml.) at 0°. When gas evolution ceased, a solution of bis(chloromethyl)ether (0.55 g.) in ether (10 ml.) was added slowly with stirring, the mixture stirred overnight and then water was added. Washing and drying of the ether layer in the usual way, and distillation of a fraction, b.p. < 110°/0.8 mm. Hg., left the residual product (IX) as an oil with ir and nmr spectrum the same as that produced by previously described procedure (15); nmr: δ 4.50 s. (CH_2) and 7.1-7.5 m. (ArH).

4-Phenyl-1,3-dihydronaphtho[2,3-*c*]furan (X).

This compound prepared from IX as described (15) had m.p. 122-123°; nmr: δ (carbon tetrachloride): 4.91 (3- CH_2), 5.18

(1-CH₂), and 7.1-7.8 (ArH); Lit. m.p. 121.5-122.5°; nmr: δ (carbon tetrachloride): 5.07 and 5.33. A possible explanation for this chemical shift discrepancy would be an erroneous solvent attribution. To test this, the spectrum was also determined in deuteriochloroform and the values δ 5.03 and 5.28 found.

Oxidation of the Dihydronaphthofuran (X).

To a vigorously stirred solution of X (1 g.) in acetone (50 ml.) at 0° was added Jones' reagent (19) (25 ml.), the mixture stirred at room temperature for 1 day, concentrated to half bulk, then poured onto ice. Examination of the nmr spectrum of the dried and washed precipitate (0.9 g.) indicated the lactones II and III to be present in an approximate ratio of 2.6:1. Separation of a fraction (130 mg.) by thin layer chromatography (ethyl acetate-carbon tetrachloride, 1:4) gave two zones. Elution of the faster-running zone with chloroform and crystallization gave the lactone III (86 mg.), m.p. 166-168°. Similar treatment of the slower-running zone gave the lactone II (31 mg.), m.p. 185-186°.

4-Phenyl-1,3,4,11-tetrahydronaphtho[2,3-c]furan (XII).

To a solution of the salt formed from phenylpropargyl alcohol (5 g.) and sodium hydride in anhydrous dimethylformamide (100 ml.) was added cinnamyl bromide (9 g.), the mixture heated on the steam bath for 48 hours, then concentrated under reduced pressure. Water was then added, and the product extracted with ether and worked up in the usual way to give crude phenylpropargyl cinnamyl ether (XI) as an oil; nmr: δ 4.23 d. (J 6, C-C-CH₂), 4.33 s. (C \equiv C-CH₂), 5.9-6.8 m. (CH=CH) and 7.0-7.5 m. (ArH). The oil XI (2 g.) was dissolved in *t*-butyl alcohol (10 ml.), a solution of potassium *t*-butoxide (80 ml., prepared from 4 g. K) in the same solvent added, and the mixture heated with stirring on the steam bath for 6 hours. Solvent was then removed under reduced pressure, water added and extraction with ether performed. Crystallization of the washed and dried extract from ethanol gave the tetrahydronaphthofuran XII (17) as flakes (1 g.), m.p. 114-117°; nmr: δ 2.78 br. (C-3 CH₂O), 3.37 q. (J 15, 8; H-11), 4.18 br. (C-1 CH₂O), 4.57 d. (J 15, H-4, diarylmethine), 6.8-7.3 m. (H-9 vinyl and ArH).

Anal. Calcd. for C₁₈H₁₆O: C, 87.06; H, 6.50. Found: C, 87.25; H, 6.7.

Oxidation with Jones reagent as described for X, gave a complex product mixture in which lactone functions were absent (as determined by infrared spectrum).

Aromatization of Tetrahydronaphthofuran (XII or isomer) (17).

N-Bromosuccinimide (84 mg.) and benzoyl peroxide (few crystals) were added to a solution of (XII) (84 mg.) in carbon tetrachloride (20 ml.) and the mixture refluxed for 1 hour. Removal of the solvent and purification of the product by preparative tlc (using carbon tetrachloride-toluene (2:3)) and elution with chloroform yielded the dihydrofuran (X), (31 mg.), m.p. and mixed m.p. 122-123°.

Acknowledgment.

This investigation was supported by a research grant (GM 19566) from the National Institutes of General Medical Sciences U. S. Public Health Service.

REFERENCES

- (1) A. Michael and J. E. Bucher, *Ber.*, **28**, 2511 (1895).
- (2) A. W. Johnson, "Acetylenic Compounds," Vol. II, Edward Arnold Ltd., London, 1950, p. 77 reviews the polemics involved in the early work leading to the product structure elucidation.
- (3) F. G. Baddar, G. E. M. Moussa and M. T. Omar, *J. Chem. Soc.*, (C) 110 (1968) and preceding papers in series.
- (4) I. Maclean and R. Stevenson, *ibid.*, (C), 1717 (1966).
- (5) T. L. Holmes and R. Stevenson, *ibid.*, (C), 2091 (1971).
- (6) D. Brown and R. Stevenson, *J. Org. Chem.*, **30**, 1759 (1965).
- (7) P. A. Cadby, M. T. W. Hearn and A. D. Ward, *Aust. J. Chem.*, **26**, 557 (1973).
- (8) A. Michael and J. E. Bucher, *Am. Chem. J.*, **20**, 89 (1898).
- (9) H. Stobbe, *Ber.*, **40**, 3372 (1907).
- (10) J. E. Bucher, *J. Am. Chem. Soc.*, **30**, 1244 (1908).
- (11) L. H. Klemm, D. Hsu Lee, K. W. Gopinath and C. E. Klopfenstein, *J. Org. Chem.*, **31**, 2376 (1966).
- (12) E. Block and R. Stevenson, *J. Chem. Soc. (Perkin Trans I)* 308 (1973).
- (13) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967).
- (14) R. McCrindle, K. H. Overton and R. A. Raphael, *J. Chem. Soc.*, 4798 (1962).
- (15) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **12**, 1094 (1964).
- (16) On the basis of the large coupling constant (J 15 Hz) of the C-4 and C-11 protons, we conclude that these protons both have quasi-axial conformations, *i.e.* have a relative *trans* configuration.
- (17) Added in proof. Since this paper was submitted, a communication by A. J. Bartlett, T. Laird and W. D. Ollis, *J. Chem. Soc. (Chem. Comm.)*, 496 (1974) has appeared in which compound XI is reported to yield the Δ^4 (11) isomer rather than the Δ^9 isomer (XII). Until this ambiguity has been resolved, formulation XII should be regarded as tentative.
- (18) All melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Nmr spectra were determined in deuteriochloroform solution with tetramethylsilane as internal reference using a Varian A-60 spectrometer. For analytical tlc, silica gel G in 0.25 mm layers were used, and detection was effected by exposure to an iodine atmosphere.
- (19) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).