The Addition of Carbanions and Metal–Organic Compounds to Quinone Methides

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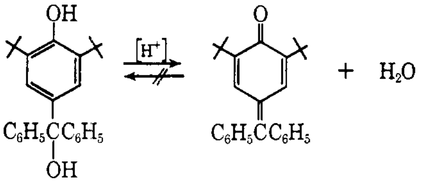
Quinone methides are known to undergo both acid-catalyzed and base-catalyzed addition reactions with a variety of nucleophiles.[1] The synthetic usefulness of these addition reactions leading to new phenols has been pointed out recently in a paper describing the base-catalyzed condensation of hydroxybenzyl alcohols involving the intermediate formation of quinone methides.[2]

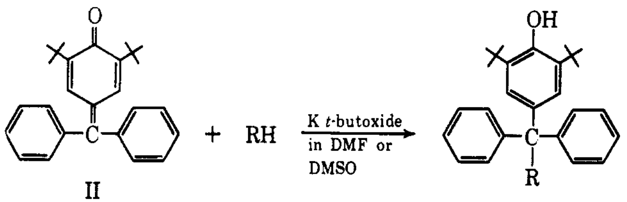
In the course of an investigation of the photochemical reaction of benzophenone with 2,6-di-*t*-butylphenol, we observed that α,α-diphenyl-2,6-di-*t*-butyl-1,4-benzoquinone methide (II) (henceforth called 3,5-di-*t*-butylfuchsone) was formed in an acid-catalyzed elimination reaction from 3,5-di-*t*-butyl-4-hydroxytriphenylcarbinol[3] (I) (eq 1). 3,5-Di-*t*-butylfuchsone resisted all our attempts to bring about acid-catalyzed addition reactions (by nonphotochemical means) with nucleophiles such as water, alcohols, or phenols, presumably because of the stability of the corresponding triphenylmethyl cation.[4]



I II

(1)

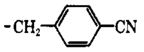
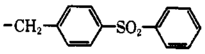
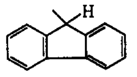
We have now found, however, that 3,5-di-*t*-butylfuchsone readily undergoes addition reactions with carbanions. Using dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) as solvents and potassium *t*-butoxide as base, 3,5-di-*t*-butylfuchsone rapidly adds acetonitrile, dimethyl sulfoxide, dimethyl sulfone, phenyl *p*-tolyl sulfone, *p*-tolunitrile, and fluorene, thus giving the hindered phenols III in good yields (eq 2) (see Table I).



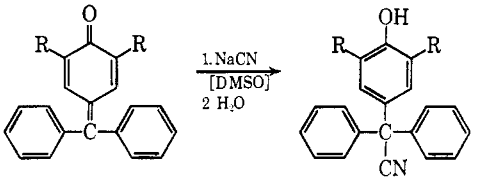
II III

(2)

TABLE I

III	R	Solvent	Yield, %
a	$-CH_2CN$	DMF	97
b	$-CH_2SOCH_3$	DMSO	90
c	$-CH_2SO_2CH_3$	DMSO	77
d		DMF	99
e		DMSO	83
f		DMF	82

DMSO was also found to be an excellent solvent for the reaction of cyanide ion with fuchsones. Sodium cyanide, dissolved in DMSO, rapidly reacted with fuchsone (IVa), 3,5-di-*t*-butylfuchsone (IVb), and 3,5-diphenylfuchsone (IVc) (eq 3). The resulting nitriles V were isolated in excellent yields (see Table II).



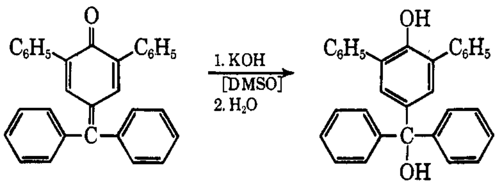
(3)

IV V

TABLE II

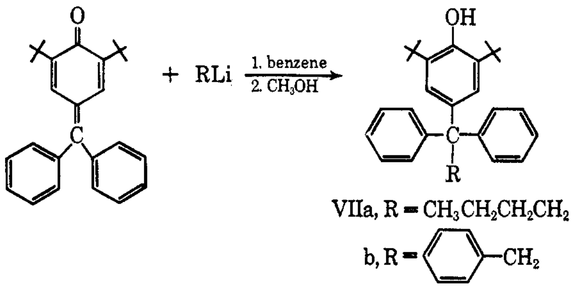
V	R	Yield, %
a	H	80
b	*t*-Butyl	91
c	Phenyl	91

3,5-Diphenylfuchsone (IVb) was also found to react with hydroxide ion in DMSO solution, giving 3,5-diphenyl-4-hydroxytriphenylcarbinol (VI)[5] (eq 4). In a manner similar to the 1,6-addition of carbanions, the reaction of 3,5-di-*t*-butylfuchsone proceeds with *n*-butyllithium and benzyllithium, yielding the hindered phenols VIIa (65%) and VIIb (90%) (eq 5). To our surprise, however, the reaction of phenyllithium with 3,5-di-*t*-butylfuchsone took an entirely different course. Reaction of 3,5-di-*t*-butylfuchsone with phenyllithium, followed by treatment of the reaction product with methanol and hydrochloric acid, gave an essentially quantitative yield of 3,5-di-*t*-butyl-4-phenylmethoxytri-



(4)

IVc VI



(5)

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[1] For a recent review on quinone methides, see A. B. Turner, *Quart. Rev.* (London), **18**, 347 (1964).

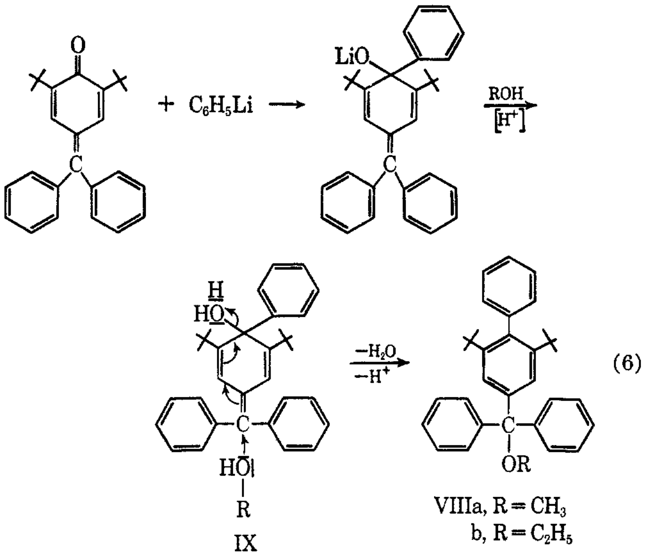
[2] A. Merijan and P. D. Gardner, *J. Org. Chem.*, **30**, 3965 (1965).

[3] H-D. Becker, *ibid.*, **32**, 2115 (1967).

[4] H-D. Becker, *ibid.*, **32**, 2131 (1967).

[5] This compound was of interest with respect to the photosensitized addition of phenols to quinone methides.[4]

phenylmethane (VIIIa) (eq 6). Obviously, phenyllithium does not react with 3,5-di-*t*-butylfuchsone in a 1,6-addition as observed in all addition reactions described above, but adds to the carbonyl function of the fuchsone (1,2-addition).[6] The formation of VIIIa is then readily understood. Elimination of water from the protonated carbinol (IX) and addition of methanol according to the outlined mechanism leads to the observed product. As expected, the corresponding ethoxy compound VIIIb was formed, when ethanol was used as a solvent for the protonation of the phenyllithium adduct of 3,5-di-*t*-butylfuchsone.



Finally, it is worth mentioning that all 2,6-di-*t*-butyl-substituted phenols prepared in the course of this investigation were found to be oxidized with active manganese dioxide[7] in benzene solution, thus giving stable phenoxy radicals of either green[8] or blue[9] color. Attempts to isolate the phenoxy radicals or study their chemical reactions were not undertaken.

Experimental Section

Materials.—DMF was distilled under reduced pressure before use. DMSO was dried over calcium hydride and distilled from calcium hydride at about 1 mm pressure. Potassium *t*-butoxide was a commercial product (MSA Research Corp., Callery, Pa.). 3,5-Diphenylfuchsone has been described.[7b] Melting points were taken on a Fisher-Johns melting point apparatus and are not corrected. Molecular weights were determined by thermoelectric measurements in solvents as indicated in each case.

2,6-Di-*t*-butyl-4-(α,α-diphenyl-β-cyano)ethylphenol (IIIa).—Potassium *t*-butoxide (672 mg, 6 mmoles) was added to a suspension of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) in DMF (10 ml) and acetonitrile (0.36 ml, 6.8 mmoles) agitated by a stream of nitrogen. The reaction mixture was placed in an oil bath at 120° for 3 min and the dark solution was then poured into 100 ml of water. Addition of 100 ml of methanol to the milky solution gave a colorless crystalline precipitate: yield, 1.20 g (97%); mp 151-152°. Recrystallization by dissolving in hot methanol and adding water raised the melting point to 154–155°.

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.04; mol wt, 411.59. Found: C, 84.62; H, 7.88; N, 3.13; mol wt (chloroform), 411.

2,6-Di-*t*-butyl-4-(α,α-diphenyl-β-methylsulfinyl)ethylphenol (IIIb).—3,5-Di-*t*-butylfuchsone (3.7 g, 10 mmoles) was added to a solution of potassium *t*-butoxide (4.48 g, 40 mmoles) in 40 ml of dimethyl sulfoxide. The reaction mixture was kept in a water bath at 85° for 30 min and agitated by a stream of nitrogen, giving a green solution. Under stirring were then added very slowly 250 g of ice and 150 ml of water, yielding a colorless precipitate which was removed by filtration, washed with water, and recrystallized from aqueous methanol: yield, 4.3 g; mp 172°. Recrystallization by dissolving in hot chloroform and addition of petroleum ether (bp 30–60°) raised the melting point to 175–176°; yield, 4.05 g (90%).

Anal. Calcd for $C_{29}H_{36}O_2S$: C, 77.36; H, 8.09; S, 7.13; mol wt, 448.68. Found: C, 77.55; H, 8.17; S, 6.84; mol wt (benzene), 451.

2,6-Di-*t*-butyl-4-(α,α-diphenyl-β-methylsulfonyl)ethylphenol (IIIc).—3,5-Di-*t*-butylfuchsone (1.85 g, 5 mmoles) was added to a solution of dimethyl sulfone (1.8 g, 9.6 mmoles) and potassium *t*-butoxide (1.12 g, 10 mmoles) in dimethyl sulfoxide kept on a water bath at 75–80° and agitated by a stream of nitrogen. The reaction mixture turned first green and then deep red. After 20 min, 150 ml of ice water was added slowly under stirring, giving a colorless precipitate, which was filtered, washed with water, and dried at 100°: yield of crude product, 2.1 g; mp 220–225°. Recrystallization by dissolving in a little warm benzene and adding methanol gave 1.8 g (77%), mp 234–235°.

Anal. Calcd for $C_{29}H_{36}O_3S$: C, 74.96; H, 7.81; S, 6.90; mol wt, 464.68. Found: C, 75.14; H, 8.08; S, 6.90; mol wt (benzene), 468.

2,6-Di-*t*-butyl-4-[α,α-diphenyl-β-(*p*-cyanophenyl)]ethylphenol (IIId).—Potassium *t*-butoxide (672 mg, 6 mmoles) was added to a solution of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) and *p*-tolunitrile (702 mg, 6 mmoles) in dimethylformamide (20 ml) which was kept in an oil bath at 95° and agitated by a stream of nitrogen. After 5 min, ice water (50 ml) and methanol (10 ml) were added to the dark reaction mixture, yielding a light yellow precipitate, 1.45 g (99%), mp 175–178°. Recrystallization from boiling methanol gave colorless crystals: yield, 1.37 g (94%); mp 180–181°.

Anal. Calcd for $C_{35}H_{37}NO$: C, 86.19; H, 7.64; N, 2.87; mol wt, 483.66. Found: C, 86.15; H, 7.30; N, 3.00; mol wt (chloroform), 490.

2,6-Di-*t*-butyl-4-[α,α-diphenyl-β-(*p*-phenylsulfonylphenyl)]-ethylphenol (IIIe).—3,5-Di-*t*-butylfuchsone (1.110 g, 3 mmoles) was added to a solution of phenyl *p*-tolyl sulfone (1.392 g, 6 mmoles) and potassium *t*-butoxide (1.12 g, 10 mmoles) in 20 ml of dimethyl sulfoxide. The reaction mixture was agitated by a stream of nitrogen for 4.5 hr at room temperature. Slow addition of 150 ml of ice water caused precipitation of a tan crystalline product which was treated with 50 ml of boiling methanol in order to remove excess phenyl *p*-tolyl sulfone. The residue was recrystallized by dissolving it in 10 ml of hot chloroform and adding 50 ml of methanol: yield, 1.55 g (83%); mp 207–208°.

Anal. Calcd for $C_{40}H_{42}O_3S$: C, 79.70; H, 7.02; S, 5.32; mol wt, 602.85. Found: C, 79.42; H, 6.98; S, 5.19; mol wt (benzene), 606.

2,6-Di-*t*-butyl-α,α-diphenyl-α-(β-fluorenyl)-*p*-cresol (IIIf).—Potassium *t*-butoxide (678 mg, 6 mmoles) was added to a solution of 3,5-di-*t*-butylfuchsone (1.85 g, 5 mmoles) and fluorene (1 g, 6 mmoles) in dimethylformamide (50 ml), which was kept at 75° and agitated with a stream of nitrogen. After 15 min, ice was added slowly to the green reaction mixture, yielding an almost colorless crystalline precipitate. The reaction mixture was acidified with a little aqueous hydrochloric acid and filtered. The light yellow crystalline residue was dissolved in 100 ml of boiling benzene and the solution was diluted with about 400 ml of methanol, causing precipitation of colorless crystals: yield, 2.2 g (82%); mp 240–243° (decomposes, depending on the rate of heating). Recrystallization by dissolving in hot benzene and adding methanol did not raise the melting point.

Anal. Calcd for $C_{40}H_{40}O$: C, 89.51; H, 7.51; mol wt, 536.77. Found: C, 89.56; H, 7.53; mol wt (benzene), 523.

α,α-Diphenyl-α-cyano-*p*-cresol (Va).—A suspension of fuchsone (1.25 g, 5 mmoles) and sodium cyanide (1.5 g, 15 mmoles) in DMSO (10 ml) was heated under N_2 agitation at 130–140° (oil bath) for 5 min. The by then very pale yellow solution was poured into 300 ml of wster. The milky solution was filtered the next day, yielding 1.16 g (80%) of white powder, mp 188–190°. Recrystallization from aqueous methanol raised the melting point to 191–192°.

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(6) A similar 1,2-addition has been observed previously in the reaction of phenylmagnesium bromide with anthrafuchsone; see P. L. Julian and W. J. Gist, *J. Am. Chem. Soc.*, **57**, 2030 (1935).

(7) (a) *cf.* H-D. Becker, *J. Org. Chem.*, **29**, 3068 (1964); (b) *ibid.*, **32**, 2493 (1967).

(8) Deep green phenoxy radicals were formed by oxidation of IIIa–f and VIIa–b.

(9) Phenols I and Vb formed blue radicals upon oxidation.

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91; mol wt, 285.35. Found: C, 84.12; H, 5.25; N, 4.80; mol wt (chloroform), 300.

2,6-Di-*t*-butyl-*α*,*α*-diphenyl-*α*-cyano-*p*-cresol (Vb).—Sodium cyanide (980 mg, 20 mmoles) was added to a suspension of 3,5-di-*t*-butylfuchsone (1.85 g, 5 mmoles) in dimethyl sulfoxide (50 ml) which was agitated by a stream of nitrogen and kept in an oil bath at 75°. After 15 min a clear, light red solution had formed. Slow dilution with cold water yielded a colorless crystalline precipitate (mp 155°) which was recrystallized from hot methanol: yield, 1.81 g (91%); 156–157°.

Anal. Calcd for $C_{28}H_{31}NO$: C, 84.59; H, 7.86; N, 3.52; mol wt, 397.57. Found: C, 84.64; H, 7.82; N, 3.69; mol wt (benzene), 392.

2,6-Diphenyl-*α*,*α*-diphenyl-*α*-cyano-*p*-cresol (Vc).—Sodium cyanide (950 mg, 20 mmoles) was added to a suspension of 3,5-diphenylfuchsone (2.05 g, 5 mmoles) in dimethyl sulfoxide (50 ml) which was kept in an oil bath at 75°. After agitation with a stream of nitrogen, a clear light yellow solution had formed. The reaction mixture was poured into 300 ml of water and the white suspension was diluted with 50 ml of methanol. The resulting colorless precipitate was removed by filtration and recrystallized from boiling methanol: yield, 2.0 g (91%); mp 160–161°.

Anal. Calcd for $C_{32}H_{23}NO$: C, 87.84; H, 5.29; mol wt, 437.55. Found: C, 88.09; H, 5.34; mol wt (benzene), 440.

3,5-Diphenyl-4-hydroxytriphenylcarbinol (VI).—3,5-Diphenylfuchsone (1.025 g, 2.5 mmoles) was added to a mixture of sodium hydroxide (2.0 g), water (5 ml), and dimethyl sulfoxide (25 ml) which was kept in an oil bath at 90° and agitated by a stream of nitrogen. After 10 min the clear light yellow reaction mixture was poured into 500 ml of water. Filtration after 5 hr gave a colorless crystalline residue which was recrystallized from petroleum ether (bp 30–60°): yield, 500 mg (47%) of colorless to light yellow crystals; mp 141–142°.

Anal. Calcd for $C_{32}H_{24}O_2$: C, 86.89; H, 5.65; mol wt, 428.54. Found: C, 86.83; H, 5.64; mol wt (benzene), 414.

2,6-Di-*t*-butyl-4-(*α*,*α*-diphenyl)pentylphenol (VIIa).—*n*-Butyllithium (5.5 ml of a 1.6 *M* solution in hexane) was added under nitrogen to a solution of 3,5-di-*t*-butylfuchsone (1.85 g, 5 mmoles) in benzene (15 ml). The deep red reaction mixture was refluxed for 5 min. Evaporation of the solvent *in vacuo* and treatment the oily residue with 15 ml of aqueous methanol yielded light yellow crystals. The mixture was acidified with 2 ml of methanol containing 0.3 ml of concentrated hydrochloric acid and kept in the refrigerator for several hours. Filtration gave 1.4 g (65%) of light yellow crystals, mp 95–96°. Recrystallization by dissolving in a little ether and the addition of methanol raised the melting point to 97–98°.

Anal. Calcd for $C_{31}H_{40}O$: C, 86.86; H, 9.41; mol wt, 428.67. Found: C, 86.60; H, 9.24; mol wt (benzene), 414.

2,6-Di-*t*-butyl-4-(*α*,*α*,*β*-triphenyl)ethylphenol (VIIb).—Tetramethylethylenediamine (0.8 ml) was added to a solution of butyllithium (4 mmoles, in hexane) in toluene (30 ml). The orange reaction mixture was kept under nitrogen for 10 hr. Addition of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) gave a deep red reaction mixture which was quenched after 5 min with 5 ml of methanol. Evaporation *in vacuo* yielded light yellow crystals (1.38 g), mp 163–164°. Recrystallization by dissolving in hot chloroform and the addition of methanol raised the melting point to 169–170°, yield, 1.25 g (90%).

Anal. Calcd for $C_{34}H_{38}O$: C, 88.26; H, 8.28; mol wt, 462.68. Found: C, 88.24; H, 8.55; mol wt (benzene), 450.

3,5-Di-*t*-butyl-4-phenylmethoxytriphenylmethane (VIIIa).—Phenyllithium (3.3 mmoles, in benzene–ether solution) was added under nitrogen to a solution of 3,5-di-*t*-butylfuchsone (1.11 g, 3 mmoles) in benzene (10 ml). The pale yellow reaction mixture was evaporated *in vacuo* after 3 min and the resulting yellow oil was dissolved in 25 ml of methanol. Dropwise addition of 2 ml of concentrated hydrochloric acid under rapid stirring gave a colorless crystalline precipitate (1.38 g), mp 150–153°. Recrystallization by dissolving in a few milliliters of ether and the addition of methanol gave colorless needle-shaped crystals: yield, 1.31 g (95%); mp 156–157°.

Anal. Calcd for $C_{34}H_{38}O$: C, 88.26; H, 8.28; mol wt, 462.60. Found: C, 88.51; H, 8.44; mol wt (benzene), 455.

3,5-Di-*t*-butyl-4-phenylethoxytriphenylmethane (VIIIb).—The phenyllithium addition to 3,5-di-*t*-butylfuchsone was carried out with the same amounts and in the same manner as described above. The oily product, however, was dissolved in 20 ml of ethanol. Addition of 40 ml of concentrated hyrochloric acid under stirring gave 1.32 g of colorless crystalline product, mp 150–152°. It was recrystallized by dissolving in ether and adding ethanol, giving 1.10 g (77%) of colorless crystals, mp 155–156°.

Anal. Calcd for $C_{35}H_{40}O$: C, 88.19; H, 8.46; mol wt, 476.71. Found: C, 87.98; H, 8.41; mol wt (benzene), 464.

Registry No.—IIIa, 13343-49-2; IIIb, 13343-50-5; IIIc, 13319-99-8; IIId, 13343-51-6; IIIe, 13343-52-7; IIIf, 13343-53-8; Va, 13343-54-9; Vb, 13343-55-0; Vc, 13343-56-1; VIIa, 13343-57-2; VIIb, 13343-58-3; VIIIa, 13343-59-4; VIIIb, 13343-60-7;

Azepinoindoles. III.[1a]

3,4,5,6-Tetrahydro-1H-azepino[4,3,2-*cd*]indoles

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As a continuation of our study of indole derivatives which might possess interesting activity in the central nervous system,[1b] we prepared a series of 3,4,5,6-tetrahydro-1H-azepino[4,3,2-*cd*]indoles. The sodium hydroxide catalyzed condensation[2] of diethyl malonate with 4-nitrogramine (**1**)[3,4] gave the expected yellow adduct (**2**) (Scheme I). In our initial experiments catalytic reduction of **2** in ethanol with nickel, palladium, or platinum catalysts followed by chromatography of the crude product on neutral alumina (activity grade I)[5] with ether–chloroform mixtures gave the lactam (**3**) directly in 26–41% yield. It was later found, however, that the initial product of this reaction is the amine (**4**) which could be isolated as the hydrochloride in better than 90% yield. Pyrolysis of this hydrochloride at 200° under reduced pressure gave **3** in good yield. The structure of **3** was supported by spectral data. Its infrared spectrum ($\nu_{\max}$ 3360, 3200, 1723, and 1655 cm^{-1}) was in good agreement with the proposed NH, ester, and amide fractions. The nmr spectrum[6a] had singlets at 656 and 613 cps for the protons on nitrogen, a broad multiplet at 429–393 cps for the aromatic protons, a triplet centered at 62 cps and a quartet centered at 241.5 cps (apparent $J = 7$ cps) for the ethyl group of the ester, and an AB_2[7] pattern with peaks centered at about 226 and 193 cps ($J \cong 5$ cps) for the C-4 and C-3 protons, respectively.

Conversion of **3** to the amine (**5**) was accomplished without difficulty. Mild alkaline hydrolysis of the ester (**3**) gave the corresponding acid which without purification was transformed to lactam **6** by pyrolytic

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(1) (a) Part II: J. B. Hester, Jr., *J. Org. Chem.*, **32**, 3804 (1967); (b) J. B. Hester, Jr., A. H. Tang, H. H. Keasling, and W. Veldkamp, *J. Med. Chem.*, in press.

(2) E. E. Howe, A. J. Zambito, H. R. Snyder, and M. Tishler, *J. Am. Chem. Soc.*, **67**, 38 (1945).

(3) J. B. Hester, *J. Org. Chem.*, **29**, 1158 (1964).

(4) G. Berti and A. DaSettimo, *Gazz. Chim. Ital.*, **90**, 525 (1960).

(5) H. Brockmann and H. Schodder, *Chem. Ber.*, **74**, 73 (1941).

(6) The nmr spectra were determined at 60 Mc in one of the following solvents: (a) deuteriodimethyl sulfoxide or (b) deuterium oxide. The peaks are reported in cycles per second downfield from tetramethylsilane.

(7) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, p 15.