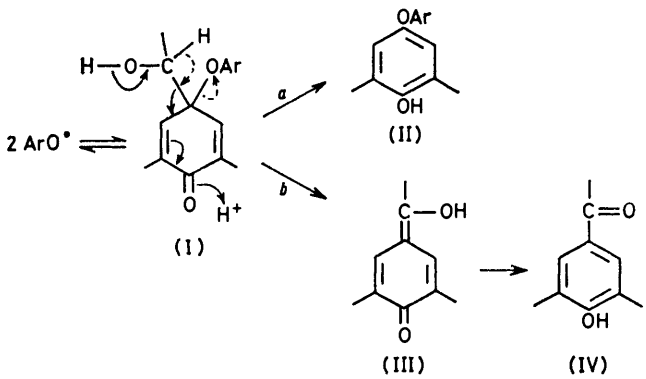
Formation of Diphenyl Ethers from Cyclohexa-2,5-dienones *via* 4-Phenoxy-4-(1-alkoxy)cyclohexa-2,5-dienones as Probable Intermediates

By **Matti Karhu**, Department of Chemistry, University of Helsinki, Vuorikatu 20, SF–00100 Helsinki 10, Finland

Acid-catalysed reactions of the cyclohexa-2,5-dienones (3) and (14) with phenol afford diphenyl ethers. Quinol ethers are considered to be intermediates in these reactions, with aromatisation of the cyclohexa-2,5-dienone ring by loss of the 4-(1-alkoxy) side-chain as an aldehyde constituting the driving force.

In enzymatic phenol oxidations [1] quinol ethers of type (I) are obvious intermediates in the formation of diphenyl ethers (II) by displacement of the side-chain as an aldehyde. The ketones (IV) isolated in these reactions could be formed from (I) through the quinone methide



Scheme

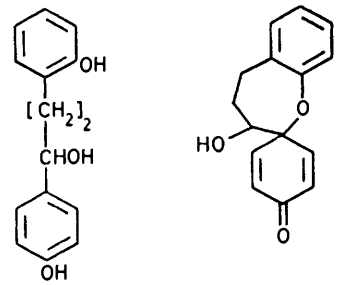
(III) by acid-catalysed elimination of phenol. An alternative route is the direct disproportionation of the phenoxyl radicals. In previous studies concerning the oxidation of phenols with α-hydroxy-side-chain [1] and α-carbonyl side-chain [2] (displacement of the side-chain as an acid), the diphenyl ethers were not isolated owing to their rapid further oxidation to *o*- and *p*-quinones. As a continuation [3] of our studies on the mechanism of phenol oxidation, we now have attempted to synthesize a quinol ether of type (I), to find out if ketones are formed in the acid hydrolysis of quinol ethers (path *b*, Scheme).

Results and Discussion

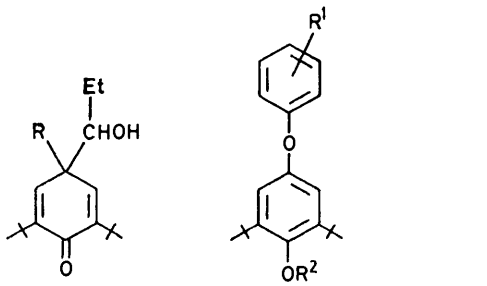
Alkaline ferricyanide oxidation of the diphenol (1), obtained by catalytic hydrogenation–hydrogenolysis of the dibenzyl ether of the corresponding chalcone over Raney nickel, gave a brown polymeric material and unchanged starting material. The desired quinol ether (2) could not be detected.

The formation of only a polymeric product may be explained in terms of different rates of oxidation of the two phenol rings of the diphenol (1). The oxidation potential is increased by the electronegative α-hydroxy-group [4] causing polymerization at the methylene-substituted phenol ring by intermolecular radical coupling.

Formation of 2,6-di-t-butyl-4-methoxyphenol [3] from the bromocyclohexadienone (3) and methanol clearly proceeds through methanolysis of (3), followed by acid-catalysed cleavage of the 1-alkoxy-side-chain of the resulting quinol ether (4) as propionic aldehyde. This

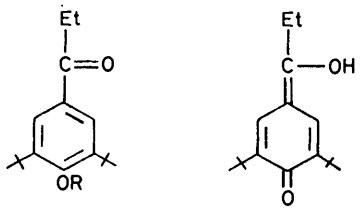


prompted us to examine the nucleophilic substitution of phenol for bromine in (3) in the hope of obtaining the quinol ether (5). On the basis of the products formed in



(3) R = Br
(4) R = MeO
(5) R = PhO
(6) R = OH

(7) R^1 = H, R^2 = H
(8) R^1 = *p*-MeO, R^2 = COMe
(9) R^1 = H, R^2 = COMe
(10) R^1 = *o*-MeO, R^2 = COMe

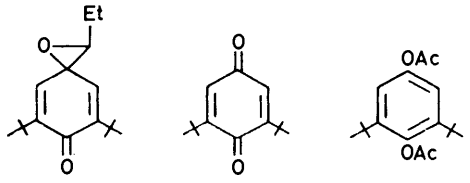


(11) R = H
(12) R = COMe

(13)

subsequent acidic hydrolysis of this intermediate quinol ether, it should be possible to decide which reaction pathway (*a* or *b*) is operating in the Scheme.

The dienone (3) was allowed to react with phenol in pyridine–nitromethane at room temperature. After disappearance of the starting material the diphenyl ether (7), the ketone (11), and the *p*-quinone (15) were observed on t.l.c. The formation of (7) indicates that the quinol ether (5) is formed in the reaction, though it is not stable



(14) (15) (16)

under the present reaction conditions. According to n.m.r. the isolated mixture of products contained the diphenyl ether and the ketone in a 1 : 1 ratio.

When the amount of pyridine was increased the diphenyl ether (7) and the ketone (11) (20 : 80) were obtained along with the *p*-quinone (15) and 4-bromo-2,6-di-t-butylphenol. The enhanced ratio of (11) to (7) suggests that the ketone (11) is formed by elimination of hydrogen bromide from the dienone (3) and tautomerization of the resulting quinone methide (13), rather than by acid-catalysed elimination of phenol from the quinol ether (5). This is supported by the observation that in nucleophilic substitutions of tertiary alkyl halides with phenol, the elimination becomes predominant when the amount of the base is increased in proportion to the phenol.[5]

Without solvent the ratio of the diphenyl ether (7) to the ketone (11) was 45 : 55.

To avoid the formation of the ketone (11) by elimination of hydrogen bromide, an alternative reaction was sought in which the quinol ether (5) would be formed as an intermediate. The oxiran (14) appeared to be a suitable starting material. Acid-catalysed reaction of (14) with phenol is expected to give (5) by selective cleavage of the C–O bond of the protonated epoxide to the more-substituted carbon atom.[6]

Reaction of the oxiran (14), obtained from the bromocyclohexadienone (3) by sodium methoxide, with phenol and concentrated sulphuric acid gave the *p*-quinone (15), the diphenyl ether (7), and the ketone (11) in a *ca.* 60 : 20 : 20 ratio. Since the t-butyl-substituted phenols tend to autoxidize to quinol hydroperoxides,[7] which are readily hydrolysed to the *p*-quinone,[8] the reaction time was shortened and acetic anhydride added before isolation of the products.

Acid-catalysed reactions of the oxiran (14) with 3 equiv. of phenol, *o*-methoxyphenol, and *p*-methoxyphenol are summarized in the Table. In each case the diphenyl ether was the main product. The highest amount of the diphenyl ether is achieved with the best nucleophile, the *p*-methoxyphenol. The lowest yield, obtained with *o*-methoxyphenol, is obviously due to the steric hindrance by the *o*-methoxy-group.

2,6-Di-t-butylhydroquinone, which was isolated as the diacetate (16), is formed in a similar reaction to the diphenyl ethers. The oxiran (14) is hydrolysed to the quinol (6) by the small amount of water present in the reaction mixture. Under acidic conditions this quinol

Acid-catalysed reactions of the oxiran (14) with phenols

	Yields of products (%)						
Phenol	(8)	(9)	(10)	(11)	(12)	(15)	(16)
p-$MeOC_6H_4OH$	76			6	6	5	7
PhOH		66		9	11	7	7
o-$MeOC_6H_4OH$			47	12	21	7	13

then rapidly loses its 1-hydroxypropyl group as propionic aldehyde,[9] giving the diacetate (16) in acetic anhydride. Carrying out the reaction without phenol gave the diacetate as the main product (62%), other products being the ketone (11) and its acetate (12) (28%), and the *p*-quinone (15) (10%).

Disproportionation of the phenoxyl radical, formed by homolytic dissociation of the ether linkage of the quinol ether (5), can not account for the formation of the ketone (11), since then equal amounts of the corresponding benzyl alcohol should be obtained.

The ketone might arise by acid-catalysed elimination of phenol from the quinol ethers. However, we believe that protonation of the oxiran (14) and subsequent deprotonation of the resonance-stabilized phenoxonium cation to give the enol (13), which is tautomerized to the ketone (11), is a more likely reaction pathway. Analogous formation of aromatic aldehydes has been reported in acid-catalysed reactions of several spirooxirancyclohexa-2,5-dienones.[10] Also, the fact that the amount of the ketone is increased with diminishing reactivity of the phenols (Table) supports the formation of the ketone directly from (14).

The amounts of the diphenyl ethers formed in the reactions of the oxiran (14) with phenols indicate that these reactions proceed mainly by side-chain displacement of the intermediate quinol ethers (path *a*, Scheme). The possibility of the ketone (11) being formed from quinol ethers (path *b*) can not be totally excluded on the basis of the above experiments. However, it seems unlikely that elimination of phenol from the quinol ether could compete with the formation of the diphenyl ether where aromatisation of the cyclohexa-2,5-dienone ring by loss of the side-chain as propionic aldehyde provides a strong driving force.

EXPERIMENTAL

M.p.s were determined with a m.p. microscope (Zeiss). I.r. spectra were recorded with a Perkin-Elmer 125 spectrophotometer and n.m.r. spectra with a JEOL JMN-PMX60 spectrometer for solutions in deuteriochloroform. Mass spectra were obtained with a JEOL JMS 01SG-2 instrument. G.l.c. was performed on a Carlo Erba 2150 instrument (20 m × 0.35 mm glass capillary column coated with liquid phase SP 100; carrier H_2, 5 ml min^{-1}; linear temperature programming 100—250 °C, heating rate 15 °C min^{-1}). Pre-coated, 2-mm thick plates (Merck Kieselgel 60 F_{254})

were used for preparative t.l.c. Light petroleum had b.p. 40—60 °C.

The composition of the crude mixtures of products was analysed by ^{1}H n.m.r. as described in a previous paper.[3] Absorption signals of the aromatic protons at δ 7.05 and 7.97 and the hydroxy-proton at δ 5.00 were used for evaluating the amount of 1,4-diacetoxy-2,6-di-t-butylbenzene (16), 4-acetoxy-3,5-di-t-butylpropiophenone (12), and 3,5-di-t-butyl-4-hydroxydiphenyl ether (7), respectively.

1-(4-*Hydroxyphenyl*)-3-(2-*hydroxyphenyl*)*propan*-1-*ol* (1).—A solution of 2,4′-bisbenzyloxychalcone [11] (2.1 g) in tetrahydrofuran (40 ml) and ethanol (40 ml) was hydrogenated at room temperature and atmospheric pressure over Raney nickel (*ca.* 3 g; eight weeks old) for 3 days. The catalyst was filtered off and the solvents evaporated under vacuum to give the *diphenol* (1) (1.3 g) as an oil which t.l.c. [cyclohexane–ethyl acetate (7 : 3)] showed to contain a trace of 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane.[11] An analytical sample was obtained by preparative t.l.c. [cyclohexane–ethyl acetate (1 : 1)] (Found: C, 68.1; H, 6.1. $C_{15}H_{16}O_3$ requires C, 68.1; H, 6.0%). Acetylation with acetic anhydride–pyridine gave the *triacetate* as an oil; $\nu_{max.}$ (neat film) 1 750 (broad) cm^{-1}; δ 7.47—6.88 (8 H, m, Ar-H), 5.72 (1 H, t, *J* 7 Hz, OCH), 2.77—1.87 (4 H, m, $ArCH_2CH_2$), and 2.23, 2.17 and 2.03 (each 3 H, s, COMe) (Found: C, 73.9; H, 6.8. $C_{21}H_{22}O_6$ requires C, 73.8; H, 6.8%).

The hydrogenation of the chalcone was slow. However, considerable amounts of 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane were formed when a more reactive catalyst was used. The reduction product was used for oxidation without purification.

Oxidation of the Diphenol (1) *with Alkaline Ferricyanide.*—The diphenol (1.2 g) in 2M sodium hydroxide (50 ml) and water (100 ml) was added dropwise during 2 h to a vigorously stirred mixture of potassium ferricyanide (5 g), water (400 ml), and light petroleum (700 ml) under nitrogen. From the organic layer 2,3,4,5-tetrahydro[2]benzoxepin-2-spirocyclohexa-2′,5′-dien-4′-one (10 mg), the oxidation product of the impurity of the diphenol (1), was isolated, m.p. 85—86 °C (lit.,[11] 85—86 °C). The pH of the alkaline water layer was adjusted to about 6 by addition of 2M hydrochloric acid. Extraction with ether gave the benzyl alcohol (1) (0.5 g) as a reddish oil whose acetylation product had identical i.r. and n.m.r. spectra to those of the triacetate described above.

Drying of the gelatinous mass formed between the layers of the oxidation mixture and during extraction of the neutralized water phase afforded a powdery, brown polymer (420 mg).

Reaction of the Dienone (3) *with Phenol.*—(a) *In nitromethane.* 2,6-Di-t-butyl-4-bromo-4-(1-hydroxypropyl)-cyclohexa-2,5-dienone [3] (400 mg) was dissolved in a solution of phenol (1.5 g) in pyridine (0.5 ml) and nitromethane (5 ml), and the mixture was left to stand at room temperature. After 8 h, t.l.c. [cyclohexane–ethyl acetate (10 : 1)] showed the diphenyl ether (7), the ketone (11), and the *p*-quinone (15) in the reaction mixture. Water was added and the products were extracted into ether–light petroleum (1 : 2). The extracts were washed with 2M sodium hydroxide, 2M hydrochloric acid, and water, and dried ($MgSO_4$). Evaporation of the solvent afforded a partly crystalline oil (220 mg). Analysis by n.m.r. revealed the diphenyl ether (7) (40%), the ketone (11) (40%), and the *p*-quinone (15) (20%). Preparative t.l.c. [cyclohexane–ethyl acetate (15 : 2)] gave the diphenyl ether (68 mg), m.p. 131—132 °C (from hexane) (lit.,[8] 132—133 °C); the ketone (42 mg), m.p. 136—137 °C (from light petroleum) (lit.,[12] 137 °C); and the *p*-quinone (18 mg), m.p. 64—65 °C (from ethanol) (lit.,[13] 65—66 °C).

When 1.5 ml of pyridine was used in the reaction a yellow oil (230 mg) was obtained, which n.m.r. showed to consist of the diphenyl ether (7) (16%), the ketone (11) (54%), 2,6-di-t-butyl-4-bromophenol (19%), and the *p*-quinone (15) (11%). 2,6-Di-t-butyl-4-bromophenol (23 mg) was isolated by preparative t.l.c. [cyclohexane–ethyl acetate (15 : 1)], m.p. 82—83 °C (lit.,[14] 81—82 °C).

(b) *Without solvent.* A solution of the dienone (3) (200 mg) in phenol (2.0 g) and pyridine (0.4 ml) was allowed to stand at room temperature for 16 h. Isolation as above gave a yellow solid (100 mg) which contained the diphenyl ether (7) and the ketone (11) in 45 : 55 ratio (n.m.r.).

5,7-*Di-t-butyl*-2-*ethyl*-1-*oxaspiro*[2,5]*octa*-4,7-*dien*-6-*one* (14).—To a stirred solution of the dienone (3) (680 mg) in methanol (20 ml), cooled in an ice-bath, was added sodium methoxide (108 mg) in methanol (2 ml). The mixture was stirred for a further 5 min and poured into water (50 ml). Extraction with light petroleum and evaporation of the washed (water) and dried ($MgSO_4$) extracts at room temperature under vacuum yielded a yellow oil (370 mg). Purification by preparative t.l.c. [cyclohexane–ethyl acetate–benzene (14 : 1 : 2)] gave the *spirodienone* (260 mg, 49.6%) as a viscous oil; $\nu_{max.}$ (neat film) 1 665, 1 635, and 1 618 cm^{-1}; δ 6.35 and 6.13 (1 H, d, W long-range coupling, *J* 2.5 Hz, ' dienone ' H), 3.35 (1 H, t, *J* 6 Hz, OCH), 1.95—1.57 (2 H, m, CH_2Me), 1.28 (18 H, s, CMe_3), and 1.08 (3 H, t, *J* 8 Hz, CH_2Me) (Found: C, 77.6; H, 9.7. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

Acid-catalysed Reaction of the Dienone (14) *with Phenol.*—A mixture of the dienone (14) (130 mg), phenol (280 mg), dimethoxyethane (6 ml), and concentrated sulphuric acid (2 drops) was stirred at room temperature for 30 min. Water was then added and the products extracted into light petroleum. Washing of the combined extracts with 2M sodium hydroxide, 2M hydrochloric acid, and water, followed by evaporation of the solvent under vacuum, gave a yellow oil (120 mg) which n.m.r. showed to consist of the *p*-quinone (15), the diphenyl ether (7), and the ketone, in the ratio 62 : 18 : 20.

Acid-catalysed Reaction of the Dienone (14) *in Acetic Anhydride.*—(a) *With phenol.* To a mixture of the dienone (14) (350 mg), phenol (290 mg), and dimethoxyethane (0.5 ml) was added concentrated sulphuric acid (2 drops), and the solution was stirred at room temperature for 5 min. Acetic anhydride (8 ml) was then added and the stirring continued for another 2 h. After hydrolysis of the excess of acetic anhydride with water, the mixture was extracted with light petroleum, and the extracts were washed with saturated sodium hydrogencarbonate solution and water. Evaporation of the solvent afforded a yellow oil (550 mg). The major product (116 mg) was isolated by preparative t.l.c. [cyclohexane–ethyl acetate (14 : 1)] and identified by its spectra as the *acetate* (9); $\nu_{max.}$ 1 670 cm^{-1}; δ 7.48—6.91 (5 H, m, Ar-H), 6.98 (2 H, s, Ar-H), and 2.35 (3 H, s, COMe) (Found: $M^{+\bullet}$, 340.203 5. $C_{22}H_{28}O_3$ requires *M*, 340.203 7). Reduction of the acetate with lithium aluminium hydride gave the phenol (7), m.p. 131—132 °C.

(b) *With* p-*methoxyphenol.* The dienone (14) (340 mg) and *p*-methoxyphenol (375 mg) were allowed to react as described above to give a yellow oil (650 mg). Preparative

t.l.c. afforded the *acetate* (8) (136 mg) as an oil; $\nu_{max.}$ 1 670 cm^{-1}; δ 6.91 (6 H, br s, Ar-H), 3.78 (3 H, s, OMe), 2.33 (3 H, s, COMe), and 1.32 (18 H, s, CMe_3) (Found: $M^{+\cdot}$, 370.213 9. $C_{23}H_{30}O_4$ requires *M*, 370.214 4).

(c) *With* o-*methoxyphenol.* Preparative t.l.c. [cyclohexane–ethyl acetate–benzene (12 : 2 : 1)] of the oil (540 mg) obtained from the dienone (14) (270 mg) and *o*-methoxyphenol (375 mg) by the above method afforded the *acetate* (10) (59 mg) as an oil; $\nu_{max.}$ 1 670 cm^{-1}; δ 7.12—6.92 (6 H, m, Ar-H), 3.88 (3 H, s, OMe), 2.33 (3 H, s, COMe), and 1.32 (18 H, s, CMe_3) (Found: $M^{+\cdot}$, 370.215 3. $C_{23}H_{30}O_4$ requires *M*, 370.214 4).

The composition of the crude products of the above reactions was analysed by gas chromatography (Table).

4-*Acetoxy*-3,5-*di-t-butylpropiophenone* (12).—Acetylation of 3,5-di-t-butyl-4-hydroxypropiophenone [12] (100 mg) with acetic anhydride (5 ml) and concentrated sulphuric acid (2 drops) gave a yellow oil (68 mg) which was purified by preparative t.l.c. [cyclohexane–ethyl acetate–benzene (7 : 1 : 1)] to afford the *acetate* (12) (47 mg) as an oil; $\nu_{max.}$ 1 760 and 1 685 cm^{-1}; δ 7.97 (2 H, s, Ar-H), 3.02 (2 H, q, *J* 7.5 Hz, CH_2Me), 2.38 (3 H, s, COMe), 1.40 (18 H, s, CMe_3), and 1.23 (3 H, t, *J* 7.5 Hz, CH_2Me) (Found: C, 75.4; H, 9.6. $C_{19}H_{28}O_3$ requires C, 75.0; H, 9.3%).

1,4-*Diacetoxy*-2,6-*di-t-butylbenzene* (16).—A solution of 2,6-di-t-butyl-*p*-quinone [13] in methanol (30 ml) was treated with sodium borohydride (0.3 g) for 5 min. The reaction mixture was acidified with 2M hydrochloric acid (20 ml) and extracted with ether. Evaporation of the extracts gave 2,6-di-t-butylhydroquinone (1.95 g). Acetylation as described earlier [15] afforded the diacetate (16) (2.25 g, 80.9%) as a white solid, m.p. 102.5—103.5 °C (from light petroleum) (lit.,[15] 101—103 °C); δ 7.05 (2 H, s, Ar-H), 2.35 and 2.28 (3 H, s, COMe), and 1.36 (18 H, s, CMe_3).

Acid-catalysed Reaction of the Dienone (14) *in Dimethoxyethane.*—To a solution of the dienone (14) (180 mg) in dimethoxyethane (0.5 ml) was added concentrated sulphuric acid (2 drops), and the mixture was stirred at room temperature for 5 min. Acetylation as above afforded a yellowish oil (117 mg) which n.m.r. showed to consist of the diacetate (16) (62%), the ketone (11) and its acetate (12) (28%), and the *p*-quinone (15) (10%). Crystallization from light petroleum gave the diacetate (16) (47 mg) as prisms, m.p. 101.5—102.5 °C, n.m.r. spectrum identical to that of the diacetate obtained by acid-catalysed acetylation of 2,6-di-t-butylhydroquinone, mixed m.p. 102.5—103.5 °C. Preparative t.l.c. [cyclohexane–benzene (1 : 3)] of the rest of the crude product gave the acetate (12) (11 mg), i.r. and n.m.r. spectra identical to those of the acetylation product of 3,5-di-t-butyl-4-hydroxypropiophenone.

The author wishes to thank Professor G. Brunow for helpful discussions, and the Research Foundation of Lääke Oy for financial support.

[0/274 *Received*, 18*th February*, 1980]

REFERENCES

[1] W. J. Connors, J. S. Ayers, K. V. Sarkanen, and J. S. Gratzl, *Tappi*, 1971, **54**, 1284.
[2] G. Brunow, *Acta Chem. Scand.*, 1969, **23**, 2537.
[3] M. Karhu, *J.C.S. Perkin I*, 1980, 1595.
[4] K. Kratzl, P. Claus, W. Lonsky, and J. S. Gratzl, *Wood Sci. Technol.*, 1974, **8**, 35.
[5] E. Gelles, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1954, 2918.
[6] R. A. Wohl, *Chimia*, 1974, **28**, 1.
[7] B. Miller, *J. Amer. Chem. Soc.*, 1967, **89**, 1685.
[8] D. A. Bolon, *J. Amer. Chem. Soc.*, 1966, **88**, 3148.
[9] E. Adler, K. Holmberg, and L.-O. Ryrfors, *Acta Chem. Scand.*, 1974, *B***28**, 883.
[10] B. Eistert, H. Fink, and A. Müller, *Chem. Ber.*, 1962, **95**, 2403.
[11] M. Karhu, *J.C.S. Perkin I*, 1979, 1661.
[12] J. Hamada and T. Fujisaki, *Nippon Kagaku Zasshi*, 1961, **82**, 898 (*Chem. Abs.*, 1963, **59**, 496h).
[13] C. R. H. I. DeJonge, H. J. Hageman, G. Hoentjen, and W. J. Mijs, *Org. Synth.*, 1977, **57**, 78.
[14] K. Ley, E. Müller, R. Mayer, and K. Scheffer, *Chem. Ber.*, 1958, **91**, 2670.
[15] D. H. R. Barton, P. G. Gorden, and D. G. Hewitt, *J. Chem. Soc.* (*C*), 1971, 1206.