Oxidation of Alkoxyphenols. Part 27.[1] The Mechanism of Formation of Dibenzo[*d*,*f*][1,3]dioxepins

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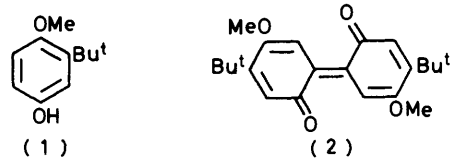
Electron spin resonance, kinetic evidence, and product isolation show that in the oxidation of 4-methoxy-3-t-butylphenol one of the initial products is 2-(4-methoxy-3-t-butylphenoxy)-4-methoxy-5-t-butylphenol. The radical of this compound reacts with another product, 5,5'-dimethoxy-4,4'-di-t-butyl-2,2'-diphenoquinone, to form 2',5,10'-trimethoxy-3',4,9'-tri-t-butylspiro(cyclohexa-3,5-diene-1,6'-dibenzo[*d*,*f*][1,3]dioxepin)-2-one. It is also shown that, depending on the oxidation procedure used, this reaction may provide the major pathway to this product. The other significant pathway involves the reaction of the diphenoquinone with unoxidized 4-methoxy-3-t-butylphenol.

In Part 26 [1] we showed that the first products that could be detected by F.T. n.m.r. in the oxidation of 4-methoxy-3-t-butylphenol (1) were the diphenoquinone (2) and the dioxepin (3). In order to cast more light on the mechanism of the oxidation, a flow system consisting of the phenol (1) in alkaline solution and aqueous potassium ferricyanide was arranged so that the reactants could be mixed at increasing distance from the cavity of an e.s.r. spectrometer through which the effluent flowed. Unfortunately, the only spectrum that could be positively identified was that of the phenoxy-radical derived from (1), which has been previously described by Stone and Waters.[2]

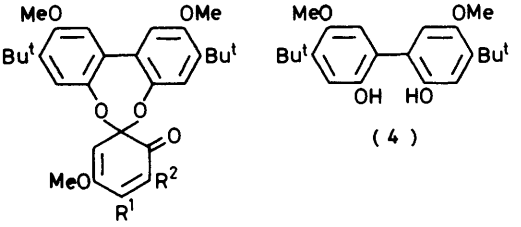
When, however, the phenol (1) was shaken in carbon tetrachloride solution with a large excess of silver oxide in a static system, the initial spectrum was that of a mixture of the phenoxy-radicals derived from the phenol (1) and its C–C coupled dimer (4). These signals were replaced on further shaking by a doublet of quintets, which could be reproduced exactly by similar oxidation of the phenoxyphenol (5), prepared as described below. In a similar experiment, in which phenol solutions were flowed through a bed of silver oxide in the cavity of an e.s.r. spectrometer, Huysmans and Waters [3] reported a quintet as the spectrum of the secondary radical derived from 4-methoxy-2-t-butylphenol, the hindered isomer of (1). Having isolated the phenoxyphenol (6) from this oxidation, we can now assign this signal to its radical. These and related e.s.r. data are presented in the Table, where it can be seen that the large doublet, where present, comes from splitting by a hydrogen *ortho* to the hydroxy, and the smaller multiplet from an equivalence between the splitting of the alkoxy-hydrogen and the *meta*-hydrogen of the phenolic ring.

The presence of the radical of the phenoxyphenol (5) as the oxidation of the phenol (1) is nearing completion has an obvious bearing on the mechanism of formation of the dioxepin (3). In an earlier paper [4] it was shown that oxidation of the mixed phenoxyphenol (7) in the presence of the biphenyldiol (4) gave a 90% yield of a mixed dioxepin (8). It seemed that a similar process might well supplement or override the more obvious oxidative coupling of (1) to (4) followed by coupling of a radical from the latter with another from the phenol (1) to give the dioxepin (3). Moreover, the phenoxyphenol (5) had never been isolated from oxidations of the phenol (1), and it must therefore be involved in a relatively rapid reaction. Indeed, addition of the hindered phenoxyphenol (6) to the diphenoquinone decolourized the latter in a much quicker reaction than the spontaneous trimerization of the quinone reported in Part 26.[1]

Oxidation of a mixture of this phenoxyphenol (6) and the biphenyldiol (4) in a 1 : 2 molar ratio gave a clean reaction, only the mixed dioxepin (8) being detectable by n.m.r. examination of the crude product; this provided a convenient system with which to study the involvement of phenoxyphenols in dioxepin formation. Although the reaction was found to be too fast to follow at concentrations suitable for

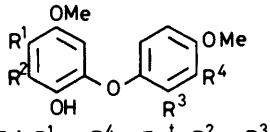


(1) (2)



(3) R^1 = Bu^t, R^2 = H
(8) R^2 = Bu^t, R^1 = H

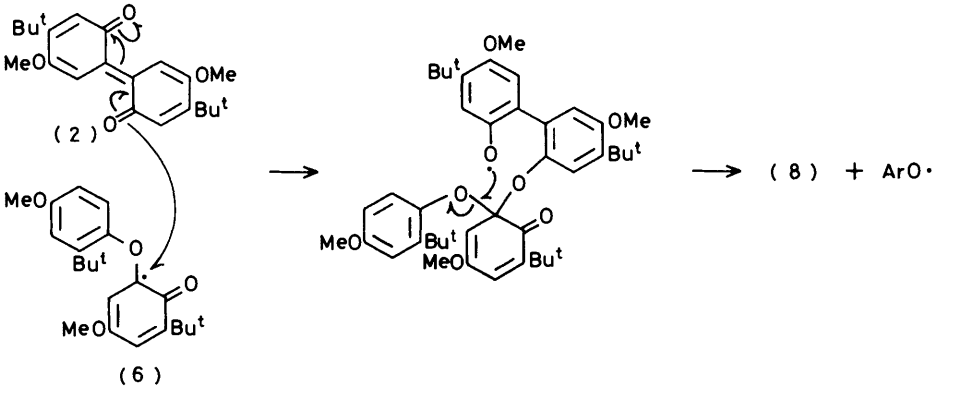
(4)



(5) R^1 = R^4 = Bu^t, R^2 = R^3 = H
(6) R^2 = R^3 = Bu^t, R^1 = R^4 = H
(7) R^2 = R^4 = Bu^t, R^1 = R^3 = H

Table. Hyperfine splitting constants (mT) from the e.s.r. spectra of aryloxyphenoxy-radicals

Phenol oxidized	Solvent	a_H (multiplicity)
(1)	CCl_4	0.41(2), 0.152(5)
(5)	CCl_4	0.41(2), 0.152(5)
4-Methoxy-2-t-butyl	CCl_4	0.140(5)
4-Methoxy-2-t-butyl	C_6H_6 [3]	0.13(5)
(6)	CCl_4	0.140(5)
4-Ethoxy-2-t-butyl	CCl_4	0.16(4)
(7)	CCl_4	0.140(5)



Scheme 1.

F.T. n.m.r. it was easily followed by visible absorption spectroscopy.

Oxidation of the diol (4) in the presence of an eight-fold excess of the phenoxyphenol (6) in carbon tetrachloride with alkaline ferricyanide gave a fairly rapid loss of colour, which was followed at 627 nm. A straight line plot of log (absorbance)$^{-1}$ against time showed that the reaction was first order in diphenoquinone. A similar experiment using a 1 : 1 mixture of (4) and (6) gave a loss of one tenth of diphenoquinone in 20 min, while with double the concentration of phenoxyphenol the same loss occurred in 10 min, showing that the reaction is also first order in phenoxyphenol and implying a rate equation of the form

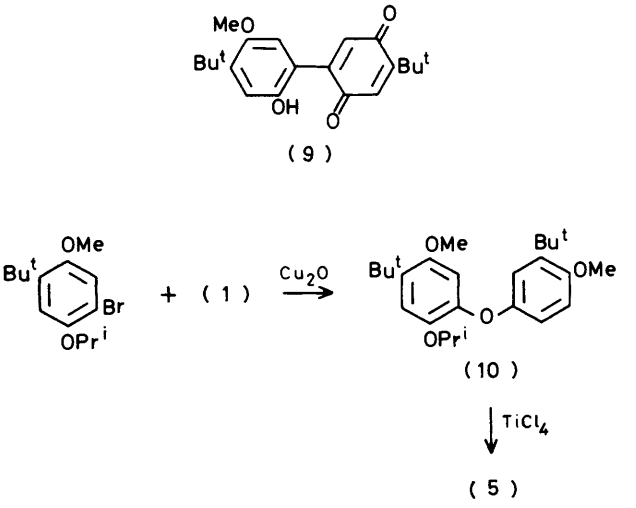
$$\frac{\mathrm{d[diphenoquinone]}}{\mathrm{d}t} = k[\text{diphenoquinone}][\text{phenoxyphenol}]$$

The rate was found to be dependent on the solvent used, and evaluation of k for carbon tetrachloride and dichloromethane solutions gave 5 900 and 7 500 l mol^{-1} s^{-1} respectively at 20 °C, taking the rate of loss of the first one tenth as approximating the initial reaction rate.

As the initial concentration of diphenoquinone produced in these experiments was unaffected by prior addition of the phenoxyphenol, even in a large excess, it is the diphenoquinone rather than its radical which is the species responsible for the cleavage of the phenoxyphenol. This is shown in Scheme 1. The radical (6) may be present largely in the form of an easily dissociable acetal dimer.

Using an extinction coefficient for the diphenoquinone (2) determined by oxidation of a dilute solution of the biphenyldiol (4) it was possible to estimate the initial concentration of (2) produced by vigorous oxidation of the phenol (1) in various solvents. In carbon tetrachloride a yield of 80% was obtained. If one assumes that the balance of the material, 20%, is the phenoxyphenol (5), which should react with the diphenoquinone to form the dioxepin (3) as in Scheme 1, then the stoicheiometry of the reaction implies a theoretical maximum yield of 60% dioxepin.

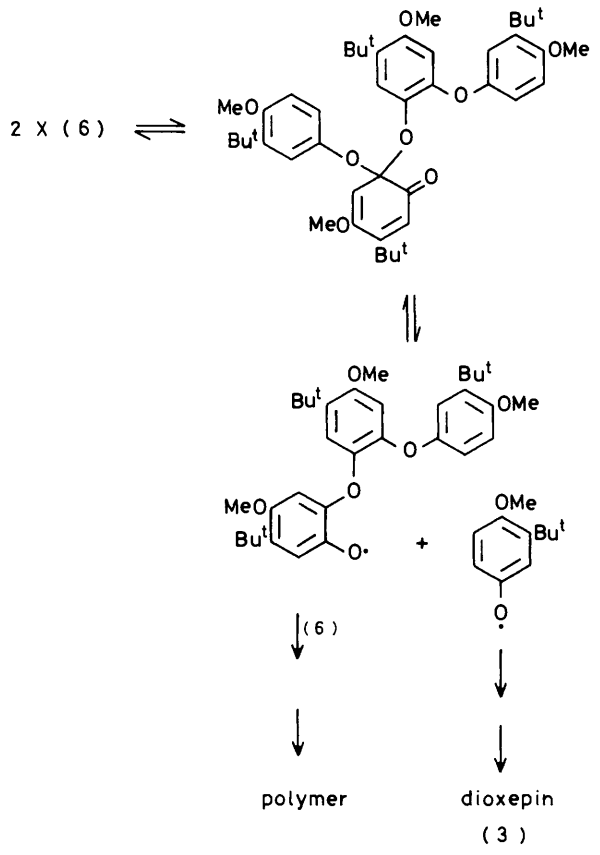
The fact that a yield of 76% dioxepin is readily obtained in large-scale work establishes the existence of an additional route. Rather than oxidative coupling of the phenol (1) with the biphenyldiol (4), the evidence suggests that this reaction may well be between the diphenoquinone (2) and the unoxidized monomer (1). In fact, a sample of a labelled dioxepin was produced by this reaction in Part 26.[1] This is a very rapid reaction at preparative concentrations, and it is reasonable to expect that it is significant in reactions where the oxidant is provided only in a slight excess. Oxidations for the purpose



Scheme 2.

of measuring visible absorption were, in contrast, carried out with a vast excess of oxidant, and initial oxidation was complete in 5 s or less.

The initial yield of the diphenoquinone (2) produced by oxidation of the phenol (1) was found to be surprisingly dependent on the solvent used. In dichloromethane this yield was only 44% which offered a good chance of identifying the balance of the material. In order to maximise the yield of the phenoxyphenol (5) the oxidation was performed on small, dilute batches of the phenol (1), and quenched to minimize dioxepin formation. Quenching was achieved by running the solution directly from the separating funnel into either methanol acidified with hydrochloric acid or ethanolic sodium borohydride. No more than 40 s elapsed between the commencement of oxidation and the final loss of blue colour. The products were separated by t.l.c. In the former case the diphenoquinone was converted into the hydroxyphenylquinone (9); in the latter to the diol (4). A trace (<3%) of the reduction product of the dioxepin (3), a trimeric diol, was isolated in the reductive quenching. As this is the only product formed in the reduction of the dioxepin by sodium borohydride, its detection in such small amounts indicates not only that dioxepin formation had been satisfactorily arrested, but also that direct oxidative coupling of the phenol (1) with the diol (4) is not a significant source of dioxepin.[5] Both systems produced an identical fraction in 25% yield of material that had spectroscopic properties consistent with those



Scheme 3.

expected for the phenoxyphenol (5), and the structure was confirmed by the synthesis outlined in Scheme 2, in which the isopropyl ether (10) was found to be identical with the isopropyl ether of the material obtained by oxidation.

Final proof of the phenoxyphenol–diphenoquinone pathway to the dioxepin was obtained by oxidizing the phenoxyphenol (5) and the diol (4) in a 1 : 2 molar ratio in carbon tetrachloride and observing *ca.* 90% conversion into the dioxepin (3) in the n.m.r. spectrum of the crude product. A slight cloudiness of the solution indicated the formation of a little polymeric material, as is seen in the oxidation of phenol (1). This appears to come from further oxidation of the phenoxyphenol, as prolonged shaking of the latter with alkaline ferricyanide produces polymeric material as the major product, the only other product detected being the dioxepin in yields of up to 30%.

The pathway to the polymer presumably involves a redistribution chain reaction, as in Scheme 3, of the type described for 2,6-disubstituted phenols by Bolon [6] and by Mijs *et al.*[7] This pathway appears to be of minor importance for the phenol (1) as the typical yield of polymer with vigorous oxidation is only 3%; moreover, the diphenoquinone is produced in considerable excess of the 2 : 1 ratio required for the reaction of Scheme 1.

In conclusion, it appears that the dioxepin is formed largely as shown in Scheme 1, but conditions may be so chosen as to allow additional dioxepin to be formed by reaction of the diphenoquinone with the monomer. The overall process may therefore be regarded as a trapping by the C–C coupled 2,2′-diphenoquinone of the C–O coupled phenoxyphenol radical which would otherwise polymerize.

Experimental

General details are as given in Part 26.[1]

Oxidation of 4-*Methoxy*-2-*t*-*butylphenol*.—A solution of 4-methoxy-2-t-butylphenol (7.2 g) in carbon tetrachloride (60 ml) was stirred with potassium ferricyanide (13.9 g) in 5% sodium hydroxide solution (60 ml) for 2 h. The entire mixture was filtered to remove most of the major product, the biphenyldiol (4). The organic layer was separated and evaporated and the residue was adsorbed on alumina. Ethyl acetate (5%) in hexane eluted 4-*methoxy*-2-(4-*methoxy*-2-*t*-*butylphenoxy*)-6-*t*-*butylphenol* (6) (0.65 g), m.p. (after recrystallization from methanol) 73—76 °C (Found: C, 73.6; H, 8.4. $C_{22}H_{30}O_4$ requires C, 73.7; H, 8.4%); δ (CCl_4) 1.42 (2 Bu^t), 3.53, 3.68 (OMe), 5.4 (OH), and 6.0—6.8 (5 ArH); M^+ 35.8. The structure was established by methylation, giving a product identical with the Ullmann condensation product of 2,5-dimethoxy-3-t-butyl-1-bromobenzene and 4-methoxy-2-t-butylphenol.[8]

Combined Oxidation of the Phenoxyphenol (6) *and the Biphenyldiol* (4).—A solution of the phenoxyphenol (6) (20 mg) and the biphenyldiol (4) (40 mg) in chloroform (3 ml) was shaken periodically with a solution of potassium ferricyanide (0.2 g) and sodium hydroxide (0.1 g) in water (5 ml) until the blue colour was no longer produced. After separation and evaporation of the organic layer, the n.m.r. spectrum of the residue showed only the mixed dioxepin (8), m.p. 213—216.5 °C (lit.,[9] 213—215.5 °C), undepressed when mixed with an authentic sample.

General Oxidation Procedure for Visible Absorption Study.—Standard solutions of the phenols to be examined were prepared in carbon tetrachloride or dichloromethane so that the absorbance after oxidation was *ca.* 1.5 in a 1-cm cell. Aliquots (5 ml) were oxidized by vigorous shaking for 5 s with 10 ml of a solution of potassium ferricyanide (2 g) and sodium hydroxide (2 g) in water (100 ml). The outlet of the separating funnel was lightly plugged with tissue paper so that the oxidized solution could be rapidly filtered directly into the spectrometer cell. The log extinction coefficient of 5,5′-dimethoxy-4,4′-di-t-butyl-2,2′-diphenoquinone (2) determined in this way was 4.10 in CCl_4 (627 nm) and 4.05 in CH_2Cl_2 (640 nm).

Quenched Oxidation of 4-*Methoxy*-3-*t*-*butylphenol* (1).—A solution of the phenol (1) (100 mg) in dichloromethane (800 ml) was shaken in 30 ml portions with a solution of potassium ferricyanide (5 g) and sodium hydroxide (2 g) in water (50 ml). Each portion was shaken vigorously for 10 s, then quickly drained into a stirred solution of sodium borohydride (1 g) in ethanol (100 ml). When the addition was complete the solution was shaken briefly with 2% sodium hydroxide solution (100 ml). The organic layer was separated and evaporated, and the products were chromatographed on silica. The first fraction was 4-methoxy-2-(4-methoxy-3-t-butylphenoxy)-5-t-butylphenol (5) (25 mg), an oil, the purity of which (75% as estimated by n.m.r.) was not improved by repeated chromatography on silica. Chromatography on Sephadex LH 20 gave a purity of 82%; δ ($CDCl_3$) 1.33 (2 Bu^t), 3.58, 3.73 (OMe), 5.1 (OH), and 6.3—7.0 (5 ArH); M^+ 358. The second fraction was 2-hydroxy-2′-(2-hydroxy-5-methoxy-4-t-butylphenoxy)-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (2 mg), identified by its n.m.r. spectrum.[10] The aqueous layer, after acidification, yielded 5,5′dimethoxy-4,4′-di-t-butylbiphenyl-2,2′-diol (4) (40 mg). In an alternative procedure, using methanol acidified with hydrochloric acid to quench the reaction, the diphenoquinone (2) was converted into the

purple hydroxyphenylquinone (9),[1] identified by its n.m.r. spectrum. This had a similar R_F value to the phenoxyphenol (5) and was separated from it by dissolving the combined fraction in methanol and then treating it with sodium borohydride. The solution became colourless and was shaken with an equal volume of 2% sodium hydroxide solution; on extraction with hexane it yielded the phenoxyphenol (5) (25 mg).

2-Isopropoxy-5-methoxy-4-t-butyl-1-bromobenzene.—A solution of t-butylhydroquinone (16.6 g) and 2-bromopropane (28 g) was stirred with sodium iodide (5 g) in dimethyl sulphoxide (50 ml) under nitrogen for 1 h. Sodium hydroxide (4.4 g) in water (5 ml) was added and stirring was continued overnight. Water (100 ml) was added and the mixture was extracted with hexane, the extract washed with water and evaporated. On crystallization from hexane, *4-isopropoxy-2-t-butylphenol* (10.9 g) was obtained, which on recrystallization had m.p. 78—79 °C (Found: C, 74.95; H, 9.8. Calc. for $C_{13}H_{20}O_2$: C, 75.1; H 9.6%);[11] δ (CCl_4) 1.30 (d, 2 Me, *J* 6.0 Hz), 1.45 (Bu^t), 4.25 (sept., 1 H, *J* 6.0 Hz), 5.1 (OH), and 6.2—6.7 (3 ArH); M^+ 208. This phenol (3 g) and dimethyl sulphate (2.7 g) were dissolved in acetone (20 ml) and refluxed with stirring under nitrogen for 1.5 h with a little aqueous sodium hydroxide. Water (30 ml) was added and the mixture was extracted with hexane, the extract washed with water and evaporated to give *5-isopropoxy-2-methoxy-t-butylbenzene* as an oil. A small sample was purified by silica t.l.c. (Found: C, 75.5; H, 9.9. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%); δ (CCl_4) 1.24 (d, 2 Me, *J* 6.0 Hz), 1.31 (Bu^t), 3.64 (OMe), 4.24 (sept., 1 H, *J* 6.0 Hz), and 6.2—6.7 (3 ArH); M^+ 208. Without purification this ether (3 g) was dissolved in carbon tetrachloride (30 ml) and bromine (2.4 g) in carbon tetrachloride (30 ml) was added dropwise. After stirring for 4 h, the solution was washed with aqueous sodium hydrogen carbonate and then water, and evaporated to give *2-isopropoxy-5-methoxy-4-t-butylbromobenzene* (3.7 g) as an oil. A small sample, purified by t.l.c. for analysis, did not crystallize (Found: C, 55.9; H, 7.3;Br, 26.6. $C_{14}H_{21}BrO_2$ requires C, 56.0; H, 7.0; Br, 26.4%); δ (CCl_4) 1.25 (d, 2 Me, *J* 6.0 Hz), 1.28 (Bu^t), 3.71 (OMe), and 4.23 (sept., 1 H, *J* 6.0 Hz); M^+ 300/302.

2-Isopropoxy-5-methoxy-4-t-butylphenyl 4-Methoxy-3-t-butylphenyl Ether (10).—(*a*) *By Ullmann condensation*. The bromide above (1.6 g), unpurified, and 4-methoxy-3-t-butylphenol (1) (1.4 g) were refluxed in 2,4,6-trimethylpyridine with cuprous oxide (1 g) and potassium carbonate (0.8 g) under nitrogen for 48 h. The reaction mixture in hexane was washed with hydrochloric acid, then water, and evaporated. The residue was adsorbed onto alumina. Hexane eluted a small amount of the bromide and some debrominated starting material. Ethyl acetate (1%) in hexane eluted an oil (0.43 g), a portion of which (100 mg) was further purified on silica t.l.c. to give the *diphenyl ether* (10) (46 mg) as an oil (Found: C, 74.9; H, 9.1. $C_{25}H_{36}O_4$ requires C, 75.0; H, 9.1%); δ ($CDCl_3$) 1.20 (d, 2 Me, *J* 6.0 Hz), 1.33 (Bu^t), 3.60, 3.72 (OMe), 4.28 (sept., H, *J* 6.0 Hz), and 6.45—6.95 (5 ArH); M^+ 400. On treatment with titanium tetrachloride in dichloromethane at 0 °C this gave the phenoxyphenol (5), identical with that obtained by the quenched oxidation of the phenol (1). Again a purity of only 75% was obtained after silica t.l.c.

(*b*) *By isopropylation of the phenoxyphenol* (5) *obtained by quenched oxidation of* 4-*methoxy*-3-*t-butylphenol* (1). The phenoxyphenol (5) (25 mg), prepared as previously described by oxidation of the phenol (1), was dissolved in dimethyl sulphoxide (5 ml) and stirred under nitrogen with 2-bromopropane (1 ml) and 10% sodium hydroxide (2 ml) for 4 h. The mixture was shaken with water and hexane, and the organic layer was separated and evaporated. The residue was chromatographed by silica t.l.c. to give the diphenyl ether (10) (15 mg), identical with that obtained above by Ullmann condensation.

Combined Oxidation of the Phenoxyphenol, (5) *and the Biphenyldiol* (4).—A sample of the phenoxyphenol (5) of 82% purity (28 mg) and a slight excess of the biphenyldiol (4) (50 mg) in carbon tetrachloride (6 ml) were shaken four times for 2 s at 10 min intervals with a solution of potassium ferricyanide (0.5 g) and sodium hydroxide (0.2 g) in water (8 ml). The organic layer was separated and evaporated. N.m.r. integration showed 80% of the crude product to be the dioxepin (3), implying a 90% conversion.

Oxidation of the Phenoxyphenol (5) *Alone*.—A solution of the phenoxyphenol (5) (19 mg) of 82% purity, prepared *via* the Ullmann condensation, was oxidized as described immediately above. N.m.r. integration of the crude product showed 30% conversion into the dioxepin (3). The only other product observed was polymeric; a portion of this material (6 mg) was filtered off, giving a fine white powder.

Acknowledgement

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