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THE TRANSFORMATIONS OF ARYLOXYSULFONIUM CATIONS—I

MECHANISM STUDIES AND CATALOGUE OF REARRANGEMENTS

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Abstract—The reaction of phenols with dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of both a proton donor and a proton acceptor yields a remarkable variety of product types (including *ortho* and *para*-thiomethoxymethyl substituted phenols, O-thiomethoxymethyl phenols, alkylated dienones, and 5,6-benzo-1,3-oxathians) all of which are derived from an initially formed aryloxysulfonium cation.

SOME YEARS ago in an attempt to devise a simple and practical synthesis of *p*-hydroxybenzyl phosphate, we treated *p*-cresol with dicyclohexylcarbodiimide (DCC) and H_3PO_4 in dimethyl sulfoxide (DMSO); but, instead of the desired product, we isolated two unexpected thiomethoxymethyl substituted phenols. In efforts to extend this discovery, we found the course of the reaction was extraordinarily sensitive to the structure of the starting phenol and that several classes of products could be obtained. A preliminary account of our work including some mechanistic suggestions has appeared[2] and related independent studies by Burdon and Moffatt[3] were published simultaneously by mutual agreement. The latter author's work has since been fully described.[4,5] Here and in the following paper[6] we present the results and conclusions of our own efforts. Though there has been some duplication, many of the substrates we have used are different from those of Burdon and Moffatt leading to variations in reaction pathway along with some divergences in mechanistic interpretation. Recent widespread interest in the rearrangements of the simple allyl sulfonium salts[7] and other heteroatom analogues[8] of our primary reaction intermediate also spurs us to the complete publication of our experimental data and expansion of our initial communication.

The most often encountered transformation of phenols on treatment with DCC and DMSO in the presence of anhyd. H_3PO_4 is exemplified by the reaction of *o*-cresol which yields, as major product, 2-thiomethoxymethyl-6-methylphenol (I).‡ along with the expected by-product, dicyclohexylurea (DCU).

* Abstracted from the Ph.D. Thesis of J.P.M.[1]

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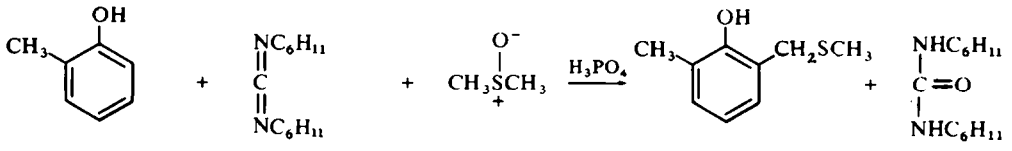
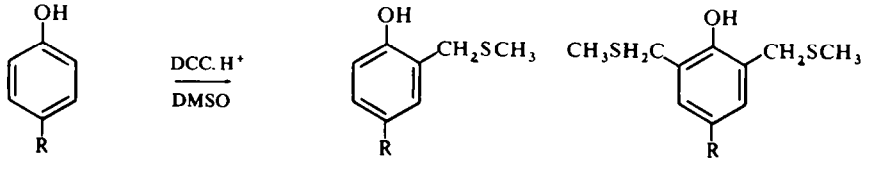
‡ For brevity and because of the simplicity of product identification in this work, structural evidence will only be presented in the Experimental without comment here. Additional structure proof and discussion along with more complete experimental data including reproductions of spectra may be found in the thesis of J.P.M.[1]



DCC I DCU

Experiments[1] designed to maximize the formation of I showed that the best yields were obtained when the reaction was carried out between 0° and room temp. and that optimum reaction time was from 3–18 hr depending on acid catalyst used. Also, the total yield did not change significantly between a DMSO concentration of 1:4 DMSO-C_6H_6 and neat DMSO. Although the product yields did not change drastically as the ratio of DCC to *o*-cresol was varied, maximum yields were obtained when this ratio was between 2:1 and 3:1. The final and most crucial parameter varied in this study of reaction conditions was the acid catalyst. The reaction did not take place in the absence of a proton donor nor did it occur in the presence of strong mineral acids. These latter observations are of special significance in the mechanistic discussion. Of the several mild acid catalysts tested, anhyd. H_3PO_4 and pyridinium trifluoroacetate proved to be the two most effective; the best catalyst to phenol ratio was between 0·3 and 0·5. Cleaner reactions and easier work-up procedures were found with H_3PO_4, but reaction times tended to be longer probably because of this acid's relative insolubility in a DMSO-C_6H_6 medium. Although pyridinium trifluoroacetate ordinarily afforded higher yields of phenolic products, work-up was complicated by the presence of two by-products, N-trifluoroacetyl-N,N'-dicyclohexylurea and N-cyclohexyltrifluoroacetamide, derived from a side reaction (of which many examples are known[9]) initiated by formation of an intermediate isourea adduct between DCC and trifluoroacetate. The best isolated yield of I was 65%.

The reaction of phenol with DMSO and DCC in the presence of pyridinium trifluoroacetate afforded both the mono- and di-*o*-substituted phenols (II, 30%, and IV, 20%) and *p*-cresol was similarly converted to III (18%) and V (20%).



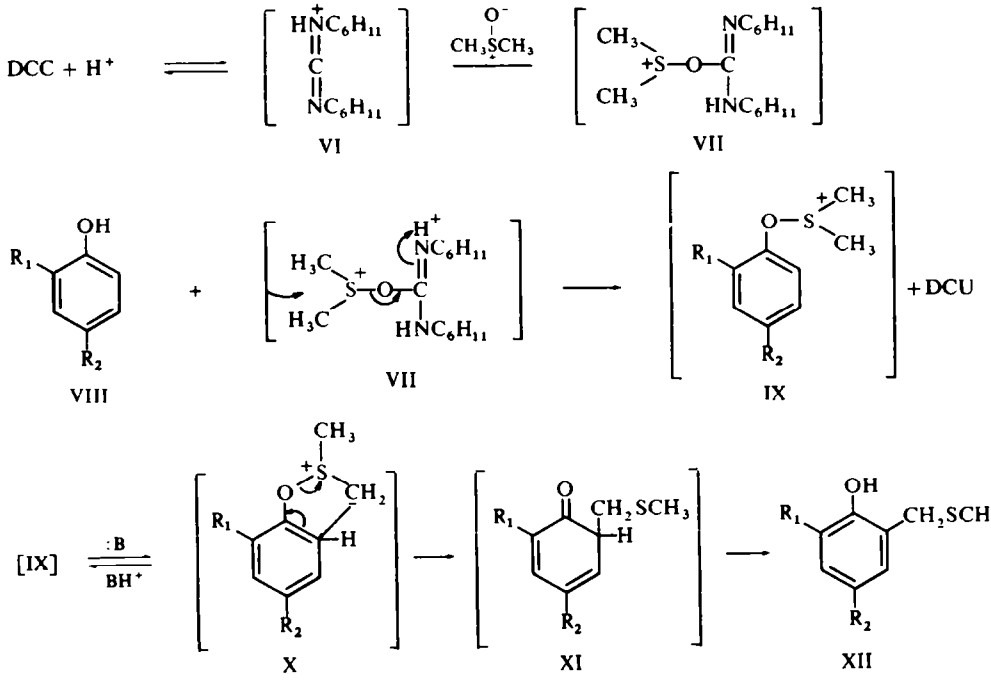
II (R = H)
III (R = CH_3)

IV (R = H)
V (R = CH_3)

It is important to note no *para* substituted phenols were isolated from the *o*-cresol or the phenol experiments. These have been synthesized by other means[6] and would have been isolated if present in the reaction mixture. The reactions thus are all examples of specific *ortho* substitution on a phenol ring of one or more thiomethoxymethyl groups. Before considering other possible substrates it is useful to examine our postulated mechanism for this transformation (Scheme A).

DCC is first reversibly protonated yielding an activated carbodiimide (VI) which

SCHEME A

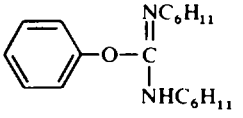


is later attacked by DMSO to generate an oxysulfonium cation (VII). This isourea intermediate then undergoes backside displacement on the S atom by the OH of the phenolic substrate (VIII) to give a molecule of DCU and the new aryloxysulfonium cation (IX). The steps outlined to this point are identical to the initial stages of the mechanism previously proposed and verified by Pfitzner and Moffatt[10] for the oxidation of alcohols to aldehydes or ketones with DCC-DMSO-H^+, the only difference being that in the present system ROH is a phenol instead of a simple alcohol. Other schemes for oxidizing alcohols to carbonyl compounds employing DMSO as the oxidant[11] have also been shown to proceed *via* an intermediate alkoxysulfonium cation. The suggested geometry of the displacement process in which the aryloxysulfonium cation (IX) is formed from VII and VIII is based on Johnson's studies of the stereochemistry of displacement reactions on alkoxysulfonium cations.[12] Direct involvement of the phenolic OH in our pathway was further established by the fact that neither anisole nor *m*-dimethoxybenzene could be substituted with a thiomethoxymethyl group under the experimental conditions. A mechanistic variation involving the discrete intermediacy of the methylmethylenesulfonium cation (XIII) followed by reaction of this with the phenol (VIII) to yield the cation (IX) or derived ylid (X) has been excluded by treating preformed XIII (synthesized by another route) with VIII (see accompanying paper[6]).

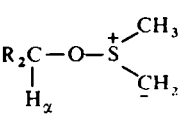
$$\underset{\text{VII}}{} \rightarrow \underset{\text{XIII}}{[CH_2 = \overset{+}{S}CH_3]} + \text{DCU}$$

$$\underset{\text{XIII}}{} + \underset{\text{VIII}}{\text{Phenol}} \rightarrow \underset{\text{IX}\quad\text{X}}{\text{Aryloxysulfonium Cation or Ylid}}$$

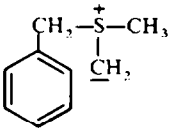
It has long been known that phenols react with carbodiimides to yield isoureas[13,14] but this species could be shown not to be a reaction intermediate by treating XIV with DMSO in the presence of H_3PO_4 under standard conditions. No 2-thiomethoxymethylphenol (II) was detected in this control experiment.



XIV



XV



XVI

The next step in Scheme A is a second equilibrium in which the newly formed aryloxysulfonium cation (IX) loses a proton to produce an aryloxysulfonium ylid (X). Although the acidity of these systems cannot be measured, an estimate can be made from studies in related species. Hydrogens in trimethylsulfonium cation are easily exchanged in NaOD-D_2O solutions[15] and the aryloxysulfonium cation (IX) should be more acidic by many powers of ten because the electron-releasing Me group has been replaced by the strongly electron-withdrawing aryloxy group.[16] The intervention of an oxysulfonium ylid (XV) in the related oxidation of alcohols has been demonstrated by deuterium labeling experiments.[12,17] The postulated deprotonation step is also in accord with our observation that the phenol reaction only takes place in mildly acidic media. No thiomethoxymethylphenols are obtained in the presence of strong acid catalysts or in the absence of any acidic species suggesting that any proposed pathway should include steps catalyzed by both acids and bases. The mechanism (Scheme A) fulfills this requirement; in the initial step an acid catalyst is needed to activate the DCC while in the process now under discussion (IX → X) a basic catalyst is demanded to activate the alkylating agent.

The next step in the alcohol oxidation mechanism is internal abstraction of the proton H_α in XV by the carbanion 5 atoms removed followed by cleavage to yield the carbonyl compound. In our intermediate ylid (X) this pathway is no longer available. The site equivalent to H_α is the ring *ortho* position and the stage is now set for attack here by the carbanion in X to generate the cyclohexadienone (XI). The intramolecularity of this conversion is forcefully verified by the absence of *para* products from the thiomethoxymethylation of *o*-cresol and phenol. In a final step XI undergoes enolization to give the product (XII), a main driving force for this process being formation of the aromatic system.

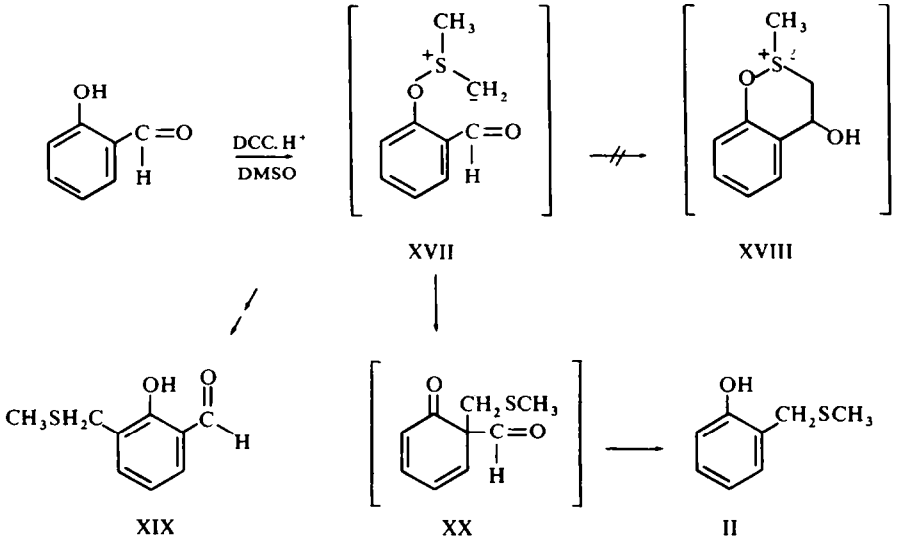
A reaction which closely resembles the internal *ortho* shift depicted in Scheme A is the Stevens–Hauser rearrangement[18] in which benzyldimethylsulfonium cation on treatment with strong base is converted to 2-thiomethoxymethyltoluene *via* the ylid (XVI). Our rearrangement occurs under much milder conditions because of the greatly increased acidity of the S-Me protons (*vide supra*).

The formation of the di-*ortho*-alkylated phenols from phenol and *p*-cresol is easily explained by a simple recycling of the monosubstituted derivatives through the general rearrangement mechanism. Note that the reaction is usually carried out in the presence of a large excess of carbodiimide.

In order to obtain additional and more conclusive evidence for the hypothesis elucidated in Scheme A, we next undertook an investigation of the reactions of other

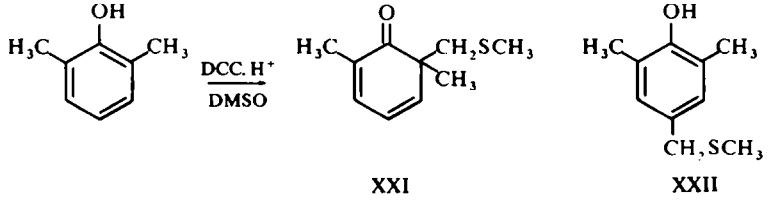
phenols with DCC-DMSO-H$^+$. We especially hoped to test the accuracy of our mechanistic view by utilizing it as a tool for predicting the course of other more complex transformations.

As our first model substrate we chose salicylaldehyde in the hope that we could trap the expected intermediate ylid (XVII) by reaction of the carbanionic site with the electrophilic aldehyde carbon suitably situated 6 atoms away (→XVIII → products). The actual reaction, however, took a different path and the two main products



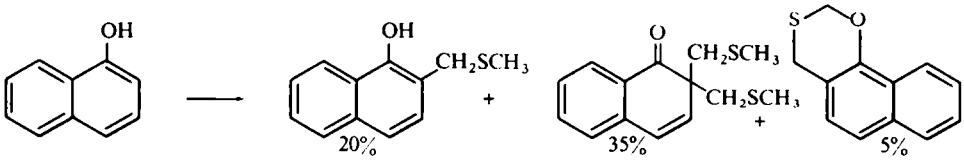
were 3-thiomethoxymethyl-2-hydroxybenzaldehyde (XIX, 18%) and 2-thiomethoxymethylphenyl (II, 16%) along with much recovered salicylaldehyde. No evidence for the presence of products derived from XVIII was found. It would appear that the reaction behaves as predicted in that the ylid (XVII) is formed. Now, however, instead of adding to the carbonyl it attacks the two possible *ortho* ring positions generating the two possible dienones. Enolization of one of these yields the standard rearrangement product (XIX). The other dienone intermediate (XX) lacks the requisite proton to permit this final transformation. Since XX is a β-keto aldehyde it can, however, be converted to II by a reverse Claisen type condensation with the aid of an appropriate nucleophile in the reaction medium.

We next decided to examine the reaction of 2,6-dimethylphenol with DCC-DMSO since from analogy with the intermediate (XX) in the salicylaldehyde reaction, the dienone (XXI) should be formed.



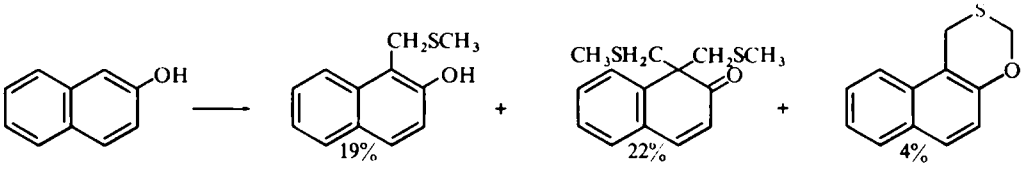
However, in this case the previously described pathways for completing the rearrangement and rearomatizing the ring are no longer available to XXI and it might be anticipated that this species would be the final product.* However, in our hands, the reaction mixture did find a way to yield an aromatic system; the product surprisingly was the *p*-substituted phenol (XXII). The mechanism of this *para*-thiomethoxymethylation reaction is the subject of the accompanying paper.[6]

In other attempts to generalize the *o*-thiomethoxymethylation reaction, we have treated 1-naphthol and 2-naphthol with DMSO-DCC. The single phenolic product from the 1-naphthol experiment was the anticipated 2-thiomethoxymethyl-1-naphthol (XXIII). The most interesting products were isolated from the neutral fraction and identified as 2,2-di-thiomethoxymethyl-3,4-dehydro-1-tetralone (XXIV)† and 5,6-[2,1-naphtho]-1,3-oxathian (XXV). The reaction of 2-naphthol gave the



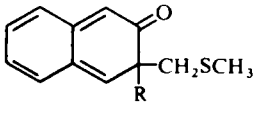
XXIII XXIV XXV

same classes of products: the substituted naphthol (XXVI), the dienone (XXVII)†, and the oxathian (XXVIII). The isolation of the mono-substituted naphthols (XXIII and XXVI) is easily rationalized using the general rearrangement mechanism. The



XXVI XXVII XXVIII

formation of the 2,2- and 1,1-disubstituted dienones (XXIV and XXVII) can readily be explained by a pathway involving the recycling of XXIII and XXVI once again through this same scheme. The lack of substitution in the 3-postion of 2-naphthol is not surprising since reaction in this sense would require the intermediacy or



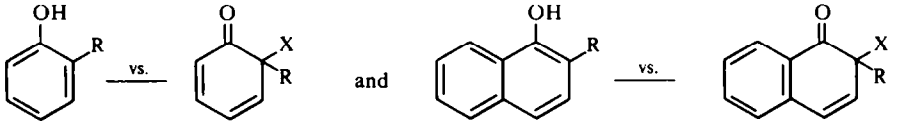
R = H or $-CH_2SCH_3$

XXIX

* This compound (XXI) has been isolated by Burdon and Moffatt under somewhat different reaction and work-up conditions; and has been converted to the *p*-substituted phenol with acid. We have isolated related dienones (*vide infra*).

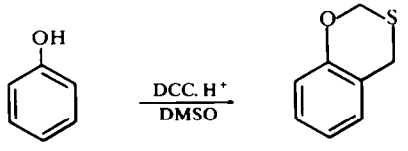
† Part of the structure proof for both the dienones (XXIV and XXVII) depends on their conversion in high yield with acid to XXIII and XXVI, respectively.

isolation of a species possessing the highly destabilized *o*-quinonoid system (XXIX). It is worthwhile to speculate on the fact that dienones are easily isolated from the naphthol reactions but not from the reaction of 2,6-dimethylphenol with DMSO-DCC (*vide supra*). In the latter example the benzene resonance is lost in the intermediate (XXX *vs.* XXXI) whereas the naphthol transformations only require the smaller energy change from a naphthalene to a benzene system (XXXII *vs.* XXXIII).



XXX XXXI XXXII XXXIII

The pathway required for the formation of the naphtho oxathians (XXV and XXVIII) is not easily elucidated and our experiments directed toward this end are described in the next paper.[6] It is however, appropriate to note here that when the reaction of phenol itself with DCC-DMSO was re-examined it proved possible to isolate a

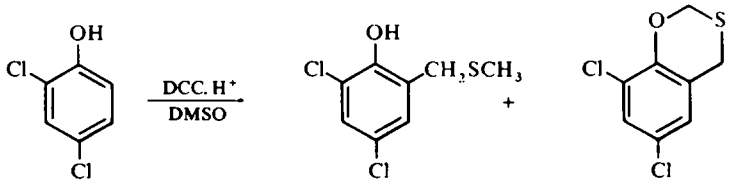


XXXIV

4% yield of the parent ring system, 5,6-benzo-1,3-oxathian (XXXIV). NMR evidence for the presence of trace quantities of similar products in the neutral fractions from the reactions of other simple phenols with DMSO-DCC was also obtained but the compounds were not isolated.

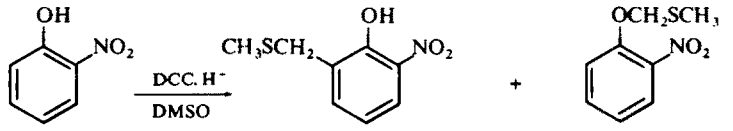
Since most of the phenolic substrates employed so far have approximately the same pK_a's (8–10), we next began an examination of the reactions of a few more acidic phenols in the expectation that the product distribution would change.

When 2,4-dichlorophenol (pK_a = 7·5) was reacted with DCC-DMSO, only 7% of 2,4-dichloro-6-thiomethoxymethylphenol (XXXV) was isolated and 5,6-(3',5'-dichlorobenzo)-1,3-oxathian (XXXVI. 10%) was the only neutral phenol derived product.



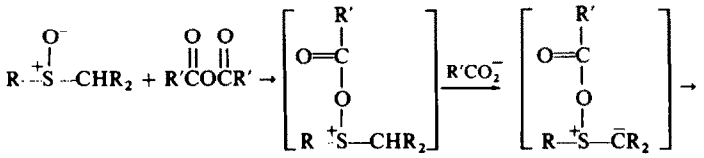
XXXV XXXVI

o-Nitrophenol (pK_a = 7·23) yielded the expected 2-nitro-6-thiomethoxymethylphenol (XXXVII, 40%) but the only neutral reaction product isolated was from a new compound class, 2-nitro-O-thiomethoxymethylphenol (XXXVIII, 5%).

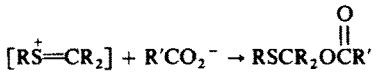


XXXVII XXXVIII

We suggest that the formation of the O-alkylated phenol occurs by a process similar to the Pummerer rearrangement[19] in which sulfoxides on treatment with acid anhydrides are converted to thiomethoxymethyl esters (XLII). Mechanistic

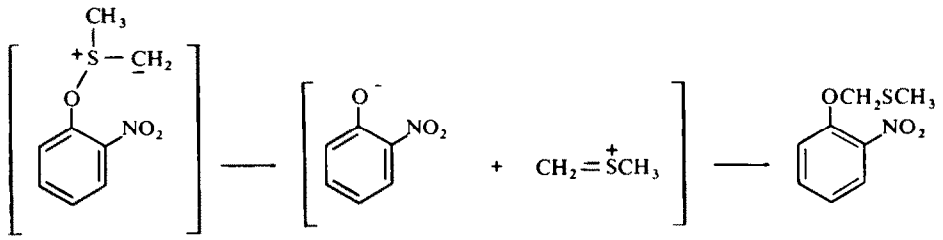


XXXIX XL



XLI XLII

studies indicate that this reaction proceeds by initial generation of the cation (XXXIX) followed by proton abstraction to yield the ylid (XL), fragmentation to the methylenesulfonium cation (XLI), and readdition of carboxylate to afford the product (XLII).[20] In our work the species equivalent to XL would be the aryloxysulfonium ylid (XLIII), the key intermediate in the formation of the *o*-thiomethoxymethylphenol (XXXVII). Breakdown of XLIII to *o*-nitrophenoxide and the cation (XIII) followed by recombination would give XXXVIII. If this mechanism is correct

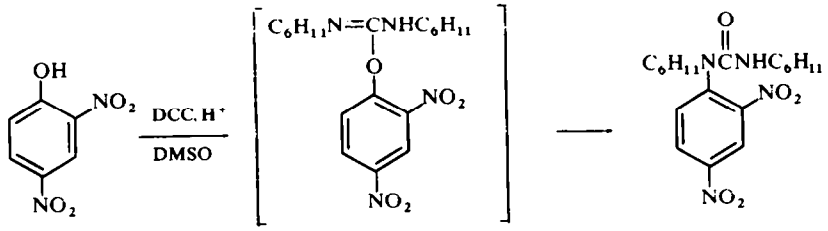


XLIII XIII XXXVIII

the lack of O-thiomethoxymethylated products from the reactions of the less acidic phenols is in accord with expectations. From the primary aryloxysulfonium ylid intermediate it is possible to get either elimination (to give XIII) or *ortho* substitution (normal rearrangement). The first reaction will become more important in systems where the phenolate is a better leaving group i.e. the phenol is more acidic (nitrophenol *vs.* phenol).*

* Note that the highest yield of O-thiomethoxymethyl product (60%) was obtained[5] with an even more acidic phenol, pentachlorophenol. The non reaction of 1,3-dimethoxybenzene with DCC-DMSO-H^+ would seem to eliminate the initial DCC-DMSO adduct (VII) as a source of XIII; see earlier discussion and following paper.[6]

The last phenolic substrate to be reacted with DCC-DMSO-H^+ was 2,4-dinitrophenol. This very acidic phenol (pK_a = 4·1) behaved in a very different manner—the predominant product being N,N'-dicyclohexyl-N-(2,4-dinitrophenyl)-urea (XLV).[14] This compound is formed by the reaction of the phenol with DCC to generate

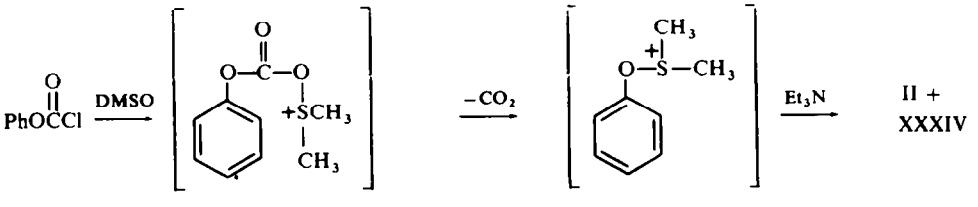


XLIV XLV

an intermediate isourea (XLIV) which spontaneously rearranges to the urea. Rearrangements like that of XLIV to XLV have long been known in the reactions of phenols bearing strongly electron withdrawing substituents with DCC or the related ketenimines and iminochlorides.[14*] The thiomethoxymethylation reactions of phenols with DCC-DMSO are thus limited in scope to systems in which the phenol is not so acidic it reacts too rapidly itself with the DCC.

During our studies, we made at attempt to investigate the behavior of an aryloxysulfonium cation, which did not have any ionizable protons on carbon α to S by treating diphenylsulfoxide with DCC and *p*-cresol in the presence of a proton donor in the hope that diphenyl-*p*-tolyloxysulfonium cation would be formed. However, only *p*-cresol was present in the product phenol fraction and diphenylsulfoxide was recovered in essentially quantitative yield.

Other attempts to prepare aryloxysulfonium cation intermediates by alkylation of sulfenyl esters with oxonium cations, by replacement of N_2 in aryl diazonium cations by DMSO, and by addition of DMSO to benzyne were unsuccessful as were efforts to generate nitrogen analogues of aryloxysulfonium cations.[1] A final scheme involved the adaptation of Barton's method[11] for the oxidation of alcohols with alkyl chloroformates in DMSO. In an exploratory experiment phenyl chloroformate was slowly decomposed in DMSO at room temperature; CO_2 evolution occurred.



XLVII

* In this context it is appropriate to correct here a recent report by Hawtrey[21] of the isolation of an isourea in the reaction of picric acid with DCC. The product has been isolated previously from the same reaction and conclusively assigned the correct N-aryl structure.[14] Hawtrey was obviously unaware both of the earlier work and the possibility of an O → N aryl migration.

and after addition of Et_3N, the reaction mixture was worked up and 5% of 2-thiomethoxymethylphenol (II) and 6% of 5,6-benzo-1,3-oxathian (XXXIV) were obtained. The reaction is believed to occur by the mechanism pictured. Efforts to obtain XLVII as a crystalline salt (Ph_4B^-, $SbCl_6^-$) failed and the isolation of an aryloxysulfonium cation thus remains a challenge.

EXPERIMENTAL

M.ps were taken in soft glass capillary tubes using a calibrated thermometer. IR spectra were measured on either a Perkin–Elmer 137 or a Beckman IR-5 Spectrophotometer and UV spectra were taken on a Cary Model 14 Spectrophotometer. A Varian Model A-60 was used to record NMR spectra (internal TMS standard). Mass spectral data was obtained with an MS-902 High Resolution or a Nuclide Low Resolution Mass Spectrometer.

Solvents and reactants were of the best commercial grade available and were used without further purification unless specified. Anhyd. H_3PO_4 was prepared by adding the appropriate amount of P_2O_5 to 85% H_3PO_4. All large scale PLC was carried out on one meter by 20 cm plates coated with Silica Gel PF 254 (Merck Darmstadt).

Reaction of o-*cresol with DCC-DMSO.** A soln of 10·8 g (0·1 mol) *o*-cresol and 60 ml (0·9 mol) DMSO was placed in a 500 ml 3-neck flask fitted with a mechanical stirrer and drying tube. The flask was cooled in ice-water and 51·5 g (0·25 mol) DCC dissolved in C_6H_6 (50 ml) was added with stirring, followed by 4·8 g (0·025 mol) crystalline pyridinium trifluoroacetate (prepared by the slow addition of TFA to a dilute ether soln of py, at 0°). After 15 min DCU began to precipitate from the yellow soln. The ice-bath was removed an hr later and stirring continued for 3 hr at room temp. To hydrolyze the unreacted DCC, a mixture of 100 ml H_2O, 100 ml Et_2O, and excess oxalic acid was added slowly to the stirred mixture. Vigorous evolution of gas occurred causing much foaming. After hydrolysis was complete, DCU was filtered and washed thoroughly with Et_2O. The ether layer was washed with 3 × 150 ml H_2O and 1 × 150 ml sat $NaHCO_3$ aq. The phenolic products were extracted from the Et_2O soln with 3 × 100 ml of 10% aq NaOH. The alkaline extract was cooled in ice-water and slowly acidified to Congo Red with *ca.* 70 ml conc HCl. Finally the phenolic products were extracted with 2 × 150 ml Et_2O, dried over Na_2SO_4 filtered and evaporated to yield 10 g of yellow oil.

TLC of the oil on Silica Gel developed in C_6H_6 revealed starting phenol (R_f = 0·3) and product (R_f = 0·45). Separation and isolation of the phenols was accomplished by subjecting the oil to PLC (3 g oil per plate coated to a 2 mm thickness, developed twice with 1:1 C_6H_6:$CHCl_3$). Each phenol was extracted from adsorbent by stirring in 1:1 $CHCl_3$:MeOH; and filtering. The filtrates were dried over Na_2SO_4 and evaporated *in vacuo*. The 2-methyl-6-thiomethoxymethylphenol was further purified by distillation; b.p. 71°/0·4 mm; yield: 9·0 g (59%); NMR(τ) CCl_4: 3·0–3·4 (m), 3·53 (s), 6·41 (s), 7·83 (s), 8·19 (s); ratio: 3:1:2:3:3; IR(μ) CCl_4: 3·05; UV(mμ) λ_{max} (ε)MeOH: 278 (2200), + aq NaOH: 283 (2000). (Found: C, 64·23; H, 7·21; S, 18·90. $C_9H_{12}OS$ requires: C, 64·24; H, 7·19; S, 19·10%).

Desulfurization of the product was accomplished in 90% yield by stirring the phenol in MeOH with excess Raney Ni at room temp for 1 hr. The 2,6-dimethylphenol (m.p. 45–46°, lit. 49°) was identical with an authentic sample.

Two neutral by-products were isolated by fractional crystallization from the original Et_2O solution after the acidic, basic, and H_2O soluble compounds had been removed. The predominant species was shown to be N-trifluoroacetyl-N,N'-dicyclohexylurea by comparison with a sample obtained from the reaction of CF_3CO_2H with DCC (m.p. 138–139°); MS: Mol. wt. 320 (1%), P-81 (base peak, 100%). (Found: C, 56·39; H, 7·32; N, 8·54. $C_{15}H_{23}F_3N_2O_2$ requires: C, 56·30; H, 7·20; N, 8·70%).

The other by-product was proven by independent synthesis (CF_3COCl + $C_6H_{11}NH_2$) to be N-cyclohexyl trifluoroacetamide; m.p. 93–94°; MS: Mol. wt. 195 (2%), P-113 (100%). (Found: C, 49·45; H, 6·12. $C_8H_{12}F_3NO$ requires: C, 49·23; H, 6·19%).

Reaction of phenol with DCC-DMSO. Pyridinium trifluoroacetate (4·8 g, 0·025 mol) was added with cooling to a mixture of phenol (9·4 g, 0·1 mol) and DCC (51·5 g, 0·25 mol) in 100 ml C_6H_6 and 100 ml DMSO and stirred for 1 hr in an ice-bath and 3 hr at room temp. After hydrolysis of the DCC as above the separated ethereal solution (300 ml) was washed with 3 × 150 ml H_2O, 2 × 100 ml sat. $NaHCO_3$ aq.

* For a modified procedure which also yields some *p*-substituted phenol and discussion see following paper.[6]

and 1 × 150 ml H_2O. The phenolic products were extracted from the Et_2O with 4 × 100 ml 2N NaOH. The pre-cooled alkaline extracts were acidified to Congo Red with conc HCl and the phenols extracted with 2 × 200 ml Et_2O. Evaporation of Et_2O afforded 12 g of oil which was divided and applied to 3 PLC plates developed twice in C_6H_6. The fastest moving band, R_f = 0·6, was 2,6-di-thiomethoxymethylphenol (4·8 g, 20%); b.p. 119–120°/0·3 mm; NMR(τ) CCl_4: 2·9–3·4 (m), 6·34 (s), 8·12 (s); ratio: 4:4:6; IR(μ) CCl_4: 3·02. (Found: C, 56·40; H, 6·60; S, 30·10. $C_{10}H_{14}OS_2$ requires: C, 56·03; H, 6·58; S, 29·92%).

Directly behind the disubstituted phenol was 4·4 g (30%) of 2-thiomethoxymethylphenol; R_f = 0·4; b.p. 73–74°/0·3 mm; NMR(τ) CCl_4: 2·8–3·4 (m), 6·38 (s), 8·12 (s); ratio: 5:2:3; IR(μ) CCl_4: 3·0–3·1; MS: mol. wt. 154 (32%), P-SMe (100%). (Found: C, 62·56; H, 6·57; S, 21·00. $C_8H_{10}OS$ requires: C, 62·30; H, 6·54; S, 20·79%).

The original Et_2O soln containing the non-phenolic material was dried over Na_2SO_4 and conc *in vacuo* to yield 8·3 g of yellow oil. Addition of n-pentane and n-hexane ppt. some of the previously described by-products containing a trifluoroacetyl residue. The residual oil (3·5 g) was applied to 2 PLC plates, developed twice in 1:1 cyclohexane:C_6H_6. Only the fastest moving compound (R_f = 0·78, C_6H_6) was isolated in a pure enough state for identification: 5,6-benzo-1,3-oxathian; 0·62 g (4%); b.p. 100° at 4 mm (bath temp in a short path apparatus); NMR(τ) CCl_4: 3·0–3·3 (m), 4·88 (s), 6·25 (s); ratio: 4:2:2; MS: mol. wt. 152·0296 (calc 152·0289) parent is 100% peak, P-CH_2S (54%), P-74 (94%). (Found: C, 63·23; H, 5·35; S, 21·30. C_8H_8OS requires: C, 63·13; H, 5·30; S, 21·08%).

Reaction of p-*cresol with DCC-DMSO.* When 0·2 mol (21·6 g) *p*-cresol, 0·5 mol (103 g) DCC, and 0·06 mol (11·6 g) pyridinium trifluoroacetate were reacted in 285 ml DMSO and 150 ml C_6H_6 (*vide supra*), nearly equal amounts of 2-thiomethoxymethyl-4-methylphenol (18%) and 2,6-di-thiomethoxymethyl-4-methylphenol (20%) were obtained. The neutral products from this reaction were not separated or characterized.

Separation of a portion of the phenolic products was accomplished by chromatographing 3·4 g of crude oil on 2 PLC plates with a 1:1 C_6H_6:cyclohexane soln (2 developments). The R_f values for *p*-cresol, the monosubstituted cresol, and the disubstituted cresol on TLC (C_6H_6) were 0·2, 0·3 and 0·4, respectively. Total recovery from the chromatographic plates was 96% (3·2 g). 2-Thiomethoxymethyl-4-methylphenol (0·95 g) was isolated as a yellow oil: NMR(τ) CCl_4: 3·1–3·4 (m), 6·39 (s), 7·82 (s), 8·12 (s); ratio: 4:2:3:3; IR(μ) CCl_4: 3·02. (Found: C, 63·80; H, 7·06. $C_9H_{12}OS$ requires: C, 64·24; H, 7·19%).

2,6-Di-thiomethoxymethyl-4-methylphenol (1·4 g) was also isolated as a viscous yellow oil; NMR(τ) CCl_4: 3·05–3·3 (m), 6·37 (s), 7·82 (s), 8·09 (s); ratio: 3:4:3:6; IR(μ) CCl_4: 3·04. (Found: C, 57·88; H, 7·14. $C_{11}H_{16}OS_2$ requires: C, 57·85; H, 7·06%).

Non-reaction of anisole or 1,3-*dimethoxybenzene with DCC-DMSO.* When anisole or 1,3-dimethoxybenzene was treated with DCC and H_3PO_4 in DMSO under the usual reaction conditions, no products containing thiomethoxymethyl groups on these substrates were isolated (comparison sample available[6]).

Non-reaction of N,N′-*dicyclohexyl*-O-*phenylisourea with DMSO.* A mixture of N,N′-dicyclohexyl-O-phenylisourea[14] (1 eq), DMSO (10 eq) and H_3PO_4 (0·5 eq) was diluted with C_6H_6 and stirred overnight at room temp (no DCU precipitated). Half was taken up in Et_2O and washed with H_2O and 5% NaOH. The alkaline extracts were acidified with conc HCl and extracted with Et_2O, evaporation gave 0·4 g of phenolic residue. TLC showed only the presence of phenol and no substituted phenols. The base-washed neutral fraction contained mostly the starting isourea and some DCU (TLC). The same results were obtained with the other half of the reaction mixture which was heated to 80° for 3 hr and worked up as described above.

Reaction of salicylaldehyde with DCC-DMSO. To a mixture of 12·2 g (0·1 mol) salicylaldehyde, 61·8 g (0·3 mol) DCC, 60 ml DMSO, and 100 ml C_6H_6 was added 4·8 g (0·025 mol) pyridinium trifluoroacetate. Reaction and isolation as described previously. After Et_2O extracts containing the phenolic products had dried over $MgSO_4$ and been evaporated, a purple oil (14 g) remained. Most of the unreacted salicylaldehyde was removed by vacuum distillation (55–60°/10 mm) and the distillation residue (7·5 g) was chromatographed on 3 PLC plates with 1:1 C_6H_6:cyclohexane. The wider of the 2 main bands afforded 3·3 g (18%) of 3-thiomethoxymethyl-2-hydroxybenzaldehyde (R_f = 0·4, C_6H_6); b.p. 97° at 0·4 mm; NMR(τ) CCl_4: −1·28 (s), 0·26 (s), 2·5–3·3 (m), 6·36 (s), 8·04 (s); ratio 1:1:3:2:3; IR(μ) CCl_4: 3·0–3·4 (complex, broad), 3·66, 5·83 (long); UV (mμ) λ_{max} (ε) MeOH: 333 (3200), 257 (9500); +NaOH: 390 (7200); MS: mol. wt. 182 (48%), P-SMe (100%). (Found: C, 59·63; H, 5·85. $C_9H_{10}O_2S$ requires: C, 59·26; H, 5·93%).

Raney Ni desulfurization of the above phenol yielded 2-hydroxy-3-methylbenzaldehyde (40%), identified by NMR: 0·22 (s), 2·60–3·32 (m), 5·12 (broad s), 7·88 (s); ratio 1:3:1:3; $CDCl_3$; and also oxidized with $KMnO_4$ to 2-hydroxy-3-methylbenzoic acid (m.p. 162–164°, lit.[22] 163–164°).

The other product (R_f = 0·32, C_6H_6) was shown to be 2-thiomethoxymethylphenol (2·5 g, 16%) by comparison with another sample (*vide supra*).

Reaction of 1-*naphthol with DCC-DMSO.* Under usual conditions, 7·2 g (0·05 mol) recrystallized 1-naphthol was reacted with 25·8 g (0·125 mol) DCC, 50 ml DMSO and 3·9 g (0·02 mol) pyridinium trifluoroacetate in 50 ml C_6H_6. After the usual workup, 5 g phenols and 6·4 g neutral compounds were isolated.

The phenolic mixture was distributed between 2 plates developed in C_6H_6. After extraction of the bands, 2 compounds were isolated, 1 naphthol (R_f = 0·27), and 2-thiomethoxymethyl-1-naphthol (R_f = 0·48). 2·0 g (20%); NMR(τ) CCl_4: 2·3–3·1 (m), 6·29 (s), 8·22 (s); ratio: 7:2:3; IR(μ) CCl_4: 3·05. (Found: C, 70·24 H, 5·92. $C_{12}H_{12}OS$ requires: C, 70·54; H, 5·92%). Raney Ni desulfurization gave 2-methyl-1-naphthol (m.p. 62–64°, lit.[23] 63–64°) in high yield.

PLC of the neutral fraction on 2 plates developed twice in 2:1 C_6H_6:cyclohexane yielded 2 pure products (R_f = 0·67, R_f = 0·33, C_6H_6). The major neutral compound was 2,2-di-thiomethoxymethyl-3,4-dehydro-1-tetralone (4·2 g, 32%); m.p. 49–50° (recrystallized from *n*-hexane); NMR(τ) CCl_4: 1·96–2·9 (m); 3·28 (d), 3·88 (d), 7·12 (s), 8·04 (s); 4:1:1:4:6; IR(μ) CCl_4: 5·96, 6·05; MS: mol. wt. 264 (24%), P-108 (97%), P-156 (100%). (Found: C, 63·87; H, 5·85. $C_{14}H_{16}OS_2$ requires: C, 63·62; H, 6·10%). This was easily converted to 2-thiomethoxymethyl-1-naphthol (70%) by refluxing for 1 hr in 1N HCl and MeOH.

The faster and minor component was 5,6-[2,1-naphtho]-1,3-oxathian (m.p. 62°, recrystallized from MeOH), isolated in *ca.* 5% yield (0·5 g); NMR(τ) CCl_4: 1·8–3·2 (m), 4·72 (s), 6·19 (s); ratio: 6:2:2. (Found: C, 71·55; H, 4·97; S, 16·04. $C_{12}H_{10}OS$ requires: C, 71·25; H, 4·98; S, 15·89%).

Reaction of 2-*naphthol with DCC-DMSO.* When 0·1 mol (14·4 g) 2-naphthol was reacted with 0·3 mol (61·8 g) DCC, 100 ml DMSO, and 0·05 mol (9·6 g) pyridinium trifluoroacetate under the usual conditions, 3 products analogous to those from 1-naphthol were obtained by the isolation and purification procedures above.

From the phenolic fraction 5 g (35%) of 2-naphthol and 3·9 g (19%) of 1-thiomethoxymethyl-2-naphthol (nondistillable oil) were obtained; NMR(τ) CCl_4: 2·05–3·6 (m), 5·91 (s), 8·09 (s); ratio: 7:2:3; IR(μ) CCl_4: 3·04. (Found: C, 70·39; H, 5·88; S, 15·30. $C_{12}H_{12}OS$ requires: C, 70·57; H, 5·92; S, 15·69%).

The major product was 1,1-di-thiomethoxymethyl-3,4-dehydro-2-tetralone; m.p. 69·71° from pet ether; 5·8 g (22%); NMR(τ) CCl_4: 2·5–2·8 (m), 3·74 (d), 6·89 (s), 8·25 (s); ratio: 5:1:4:6; IR(μ) CCl_4: 6·00, 6·14. (Found: C, 63·76; H, 6·01; S, 24·40. $C_{14}H_{16}OS_2$ requires: C, 63·60; H, 6·10; S, 24·25%).

From the neutral fraction 0·75 g (4%) of 5,6-[1,2-naphtho]-1,3-oxathian (R_f = 0·8, C_6H_6, m.p. 65–66°, from MeOH) was also isolated; NMR(τ) CCl_4: 2·16–3·1 (m), 4·80 (s), 5·92 (s); ratio: 6:2:2. (Found: C, 71·05; H, 4·92; S, 15·80. $C_{12}H_{10}OS$ requires: C, 71·25; H, 4·98; S, 15·89%).

Reaction of 2,4-*dichlorophenol with DCC-DMSO.* A mixture of 16·3 g (0·1 mol) 2,4-dichlorophenol, 51·5 g (0·25 mol) DCC, 70 ml DMSO, 100 ml C_6H_6, and 9·65 g (0·05 mol) pyridinium trifluoroacetate was reacted and worked up as usual to give 7·3 g of phenolic compounds and 15·6 g of a neutral fraction.

The 7·3 g of phenols was distributed between 2 PLC plates, developed in C_6H_6. Although there was no band separation, 2 distinct zones were observed. The slower, major zone was 2,4-dichlorophenol. The very impure top zone was first rechromatographed in C_6H_6 and then again in $CHCl_3$, after which 1·6 g (7%) of pure 2,4-dichloro-6-thiomethoxymethylphenol was isolated as a viscous oil; NMR(τ) CCl_4: 2·7–3·0 (m), 4·18 (s), 6·33 (s), 7·98 (s); ratio: 2:1:2:3; IR(μ) CCl_4: 2·87, 3·10. (Found: C, 43·46; H, 4·00. $C_8H_8Cl_2OS$ requires: C, 43·07; H, 3·61%).

A portion (3·5 g) of the neutral fraction was chromatographed on a plate developed in C_6H_6. Only the fastest moving component, 5,6-(3′,5′-dichlorobenzo)-1,3-oxathian (R_f = 0·7), was isolated in a pure state free of DCU derivatives; m.p. 131–133° (from hexane); total reaction yield 2·2 g (10%); NMR(τ) CCl_4: 2·8–3·1 (m), 4·71 (s), 6·20 (s); ratio 2:2:2. (Found: C, 43·06; H, 2·87. $C_8H_6Cl_2OS$ requires: C, 43·46; H, 2·74%).

Reaction of o-*nitrophenol with DCC-DMSO.* The standard procedure was followed with 13·9 g (0·1 mol) *o*-nitrophenol, 51·5 g (0·25 mol) DCC, 9·65 g (0·05 mol) pyridinium trifluoroacetate, 60 ml DMSO, and 100 ml C_6H_6. The phenol fraction, a red-brown solid (16·2 g), afforded 2-nitro-6-thiomethoxymethylphenol as a yellow solid after recrystallizations from cyclohexane:pet ether, 8 g (40%); m.p. 78–79°; NMR(τ) CCl_4: −0·96 (s), 1·85–3·2 (m), 6·20 (s), 7·91 (s); ratio: 1:3:2:3; IR(μ) CCl_4: 3·10. (Found: C, 48·50; H, 4·08. $C_8H_9NO_3S$ requires: C, 48·42; H, 4·06%).

A portion (3 g) of the neutral fraction, a dark red oil (9·5 g), was chromatographed on 2 plates developed in C_6H_6. The only pure compound isolated was the fastest moving component (R_f = 0·6). 2-nitro-O-thiomethoxymethylphenol (1 g, 5% total yield, yellow oil); NMR(τ) CCl_4: 2·2–3·15 (m), 4·77 (s), 7·75 (s); ratio: 4:2:3; MS: mol. wt. 199 (1%), P-SMe (3%); P-138 (100%). (Found: C, 48·41; H, 4·71. $C_8H_9NO_3S$ requires: C, 48·22; H, 4·56%).

Reaction of 2,4-*dinitrophenol with DCC-DMSO.* To a mixture of 9·2 g (0·05 mol) 2,4-dinitrophenol, 31 g (0·15 mol) DCC, 80 ml DMSO, and 35 ml C_6H_6 was added 2·4 g (0·012 mol) pyridinium trifluoroacetate under the usual conditions. The phenolic fraction (1·15 g) yielded only starting material. The neutral ether fraction 6 g) was divided between 2 plates, developed once in C_6H_6. The top zone afforded 3 g of yellow amorphous possibly polymeric solid (darkened, 250°, turned purple 270°, and dec 290°) structure not determined. The smaller yellow band, which was immediately above the starting line, yielded 2 g of a yellow flakey solid (m.p. 138–140°, lit.[14] 142°), shown to be N-(2,4-dinitrophenyl)-N,N'-dicyclohexylurea; NMR(τ) CS_2: 1·3–2·8 (m), 5·7–7·0 (m), 8·0–9·3 (m); ratio: 3:3:20; IR(μ) KBr: 3·04, 6·04; UV(mμ) λ_{max} (ε) MeOH: 345 (4600).

Reaction of p-*cresol with diphenylsulfoxide and DCC.* Anhyd. H_3PO_4 (2 g, 0·02 mol) was added with stirring to a mixture of 4·32 g (0·04 mol) *p*-cresol, 20·2 g (0·1 mol) Ph_2SO, and 16·5 g (0·08 mol) DCC in 150 ml CH_3CN. The mixture was refluxed for 4 hr, cooled, the DCU filtered, and filtrate conc. to a yellow oil. TLC of oil showed only starting phenol and sulfoxide, NMR analysis indicated a nearly quantitative recovery.

Reaction of phenyl chloroformate with DMSO. Phenyl chloroformate (7·83 g, 0·05 mol) was added dropwise to a stirred 0° mixture of 34 ml DMSO and 30 ml C_6H_6. CO_2 was detected in effluent gas by allowing it to pass into a saturated soln of $Ba(OH)_2$. Et_3N (8·4 ml, 0·06 mol) was then slowly dropped into the orange mixture and CO_2 evolution became markedly more vigorous. Stirring was continued for an additional hr. Then the Et_3NHCl was completely precipitated with Et_2O and filtered. The filtrate (200 ml) was washed with 1 × 100 ml dilute HCl, 2 × 100 ml H_2O, and 2 × 50 ml 10% NaOH. The pre-cooled alkaline extracts were acidified to Congo Red with conc HCl and extracted with 2 × 100 ml Et_2O. This latter extract was dried over Na_2SO_4 and conc. *in vacuo* to yield 3·5 g of a yellow oil distributed between 2 plates and developed in 1:4 C_6H_6:$CHCl_3$. Elution of the larger band (R_f = 0·3, $CHCl_3$) afforded 1·7 g (36%) of phenol. The faster moving component (R_f = 0·47, $CHCl_3$) was 2-thiomethoxymethylphenol (0·4 g, 5%).

The neutral fraction (1·2 g) was subjected to PLC in C_6H_6. Only the fastest moving component, 5,6-benzo-1,3-oxathian (0·35 g, 6%), (R_f = 0·8), was isolated in a pure enough state for identification.

NMR(τ) CS_2: 1·3–2·8 (m), 5·7–7·0 (m), 8·0–9·3 (m); ratio: 3:3:20; IR(μ) KBr: 3·04, 6·04; UV(mμ) λ_{max}

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