Pyridinium Ylides in Syntheses of Naphthopyrandiones and in Regioselective Syntheses of Acylated Anthraquinones Related to Fungal and Bacterial Metabolites[1]

Michael F. Aldersley, Shuhid H. Chishti, Francis M. Dean*, Mark E. Douglas, and David S. Ennis
The Robert Robinson Laboratories, The University of Liverpool, Liverpool L69 3BX

Improvements have been made in the use of acylated pyridinium ylides for the transformation of 2-methyl-1,4-naphthoquinone into derivatives (**15**) and (**16**) of naphtho[2,3-*c*]pyran-5,10-dione, containing furan and thiophene groups. The substitution and cyclisation steps can be combined effectively by using 2-phenoxymethyl- instead of 2-methyl-naphthoquinone. The use of better leaving groups than phenoxy (especially 4-nitrophenoxy) allows the quinone to react with two proportions of ylide and leads regiospecifically to 1-aroyl-2-arylanthracene-9,10-diones such as (**20a**). If the leaving group is nuclear bromine as in 2-bromo-3-methyl-1,4-naphthoquinone, another reaction with 2 mol equiv. of ylide leads to complex red intermediates of type (**31**) which in contact with alumina are quantitatively converted into the regioisomeric 2-aroyl-3-arylanthracene-9,10-diones such as (**22a**).

The structures have been determined by standard methods but special features of the NMR spectra are reported including a case of extreme line broadening by traces of iron. Mechanisms are suggested for the diverse reactions between the quinones and the ylides.

A small but significant group of natural products is based upon the naptho[2,3-*c*]pyran nucleus and contains members with antitumour and/or antibacterial activities.[2] We have improved and extended the route to such compounds from naphthoquinones and pyridinium ylides,[3] and found that it can be extended to regiospecific syntheses of acylated anthraquinones similar to antibiotic X-14881 C (*Streptomyces*) and altersolanol B[4] and related to some of the highly physiologically active naphthacene quinones.[5]

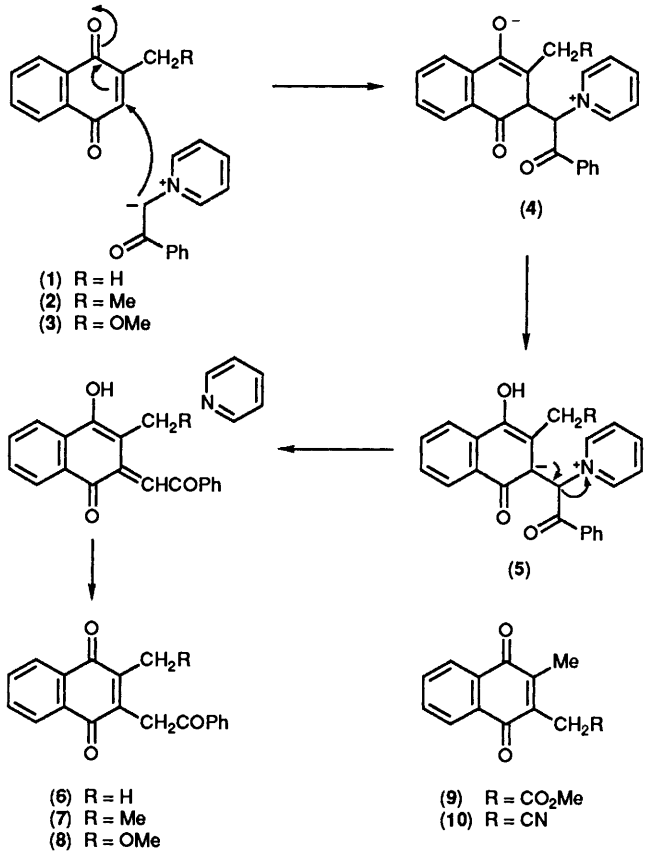
Results and Discussion

In the previous studies, the ylides were formed *in situ* from pyridinium salts by adding triethylamine, and the solvent used was generally ethanol. For this study, we have usually preferred to preform the ylide by extracting it from aqueous base into dichloromethane and to use acetonitrile instead of ethanol for the reaction medium. Using this technique, the yield of (isolated) 2-methyl-3-phenacyl-1,4-naphthoquinone (**6**) improves from less than 70% to more than 80%. An additional advantage of a preformed ylide is that the basicity of the reaction mixture does not exceed that of the ylide which is low, (pK_a values for the conjugate acids[6] are in the range 8–10) although such compounds remain effective nucleophiles.

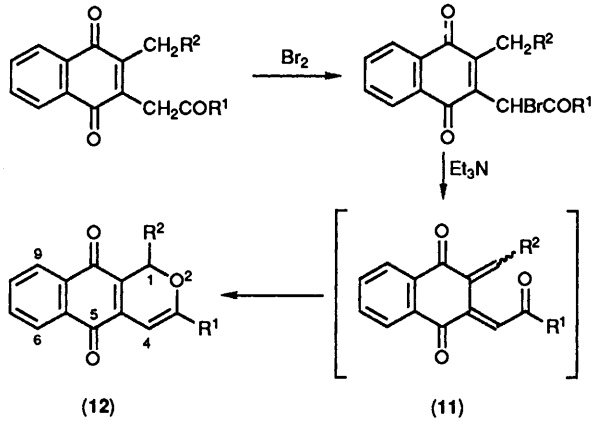
The introduction of phenacyl groups into quinones has already been modified for alkyl instead of aryl groups, *i.e.* methyl and t-butyl groups.[3] We have found that the appropriate ylides will also yield the ester (**9**) and the cyanide (**10**) (Scheme 1) but that the ester cannot be cyclised to a naphthopyran as in Scheme 2 and that the cyanide is too sensitive to be of any use for synthetic purposes.

When thiophene and furan derivatives were employed instead of phenacyl ylides the substitutions into methylnaphthoquinone occurred smoothly making (**13**) and (**14**) readily available. Moreover, the bromination–dehydrobromination sequence was also effective in converting these into (**15**) and (**16**) respectively, notwithstanding the possibility of nuclear substitution; evidently the heterocycles are sufficiently deactivated by the attached carbonyl groups to allow the methylenic (enolic) bromination to take precedence.

On the other hand, the bromination step failed unexpectedly



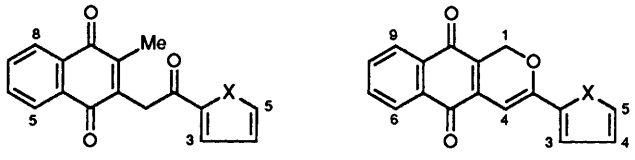
Scheme 1.



(12) (11)

a; R^1 = Ph; R^2 = H; **b**; R^1 = 4 - BrC_6H_4; R^2 = H; **c**; R^1 = Ph; R^2 = Me

Scheme 2.

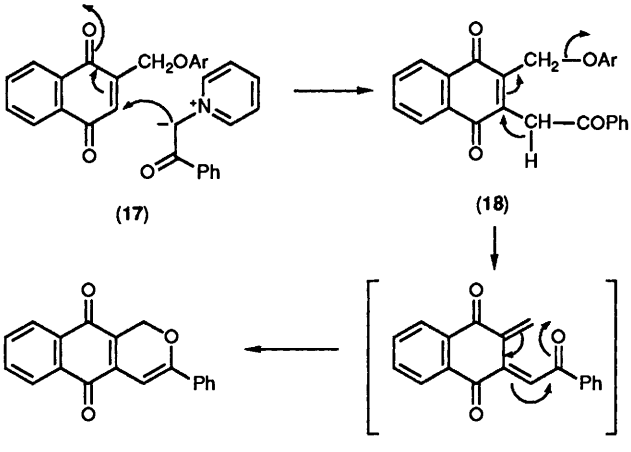


(13) X = S
(14) X = O

(15) X = S
(16) X = O

in a simple homologous quinone. 2-Ethyl-1,4-naphthoquinone (**2**) reacted smoothly with phenacylpyridinium ylide to give the desired product (**7**) (Table 2), but this reacted with bromine only with difficulty. Several variations were tried and traces of (**12c**) were identified but clearly some major difficulty was being encountered. Since an electronic effect seems very unlikely we think a steric effect is responsible and suggest that the extra methyl group hinders enolisation. Although models give only moderate support to this view, other results described below are consistent with it.

In order to increase the utility of the method we therefore sought a mode of access to the quinone methides (**11**) of Scheme 2 which did not depend upon bromination, and turned to those naphthoquinones in which a good leaving group was already present. The literature was devoid of general routes to suitable



(17) (18)

(12a) (19)

Ar

a; Ph
b; 4 - ClC_6H_4

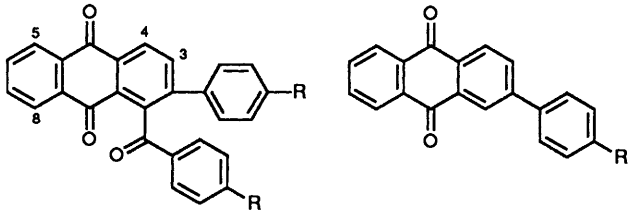
Ar

c; 2, 4, 5 - $Cl_3C_6H_3$
d; 4 - $O_2NC_6H_4$

Scheme 3.

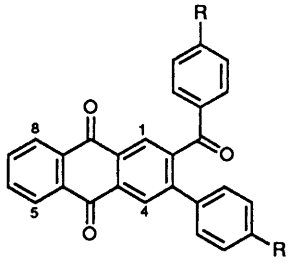
halogenomethyl quinones but indicated that equivalent alkoxy- and aryloxy-quinones were readily available so we used these.[7] Because the methoxy group is a poor leaving group the interaction with phenacylpyridinium ylide stopped at the production of the disubstituted naphthoquinone (**8**) from 2-methoxymethyl-1,4-naphthoquinone (**3**). But when 2-phenoxymethyl-1,4-naphthoquinone (**17a**) was used the parallel product (**18a**) smoothly eliminated phenoxide to form the quinone methide (**19a**) and thence the naphthopyrandione (**12a**) in excellent yield (Scheme 3).

Leaving groups which were even moderately better than phenoxide disclosed a new possibility. With phenacylpyridinium ylide, 2-(4-chlorophenoxymethyl)-1,4-naphthoquinone (**17b**) gives only a moderate yield of the naphthopyrandione (**12a**), the rest of the material being accounted for by the presence of 1-benzoyl-2-phenyl-9,10-anthraquinone (**20a**) (Scheme 4). The identity of this compound was initially suggested by the isolation from related reactions of small amounts of 2-phenyl-9,10-anthraquinone (**21a**), a well documented compound,[8] and then confirmed by the usual analytical and spectroscopic methods. The only feature requiring immediate comment is the orientation, which was established by the presence in the ^1H NMR spectrum (Table 4) of a simple AB quartet unaffected by *meta* splitting. Because the synthetic components of the system 2-benzoyl-3-phenyl-9,10-anthraquinone (**20a**) can also be arranged so as to form the isomer (**22a**), we sought for this in the product but did not find it.



(20a) R = H
(20b) R = Br

(21a) R = H
(21b) R = Br



(22a) R = H
(22b) R = Br

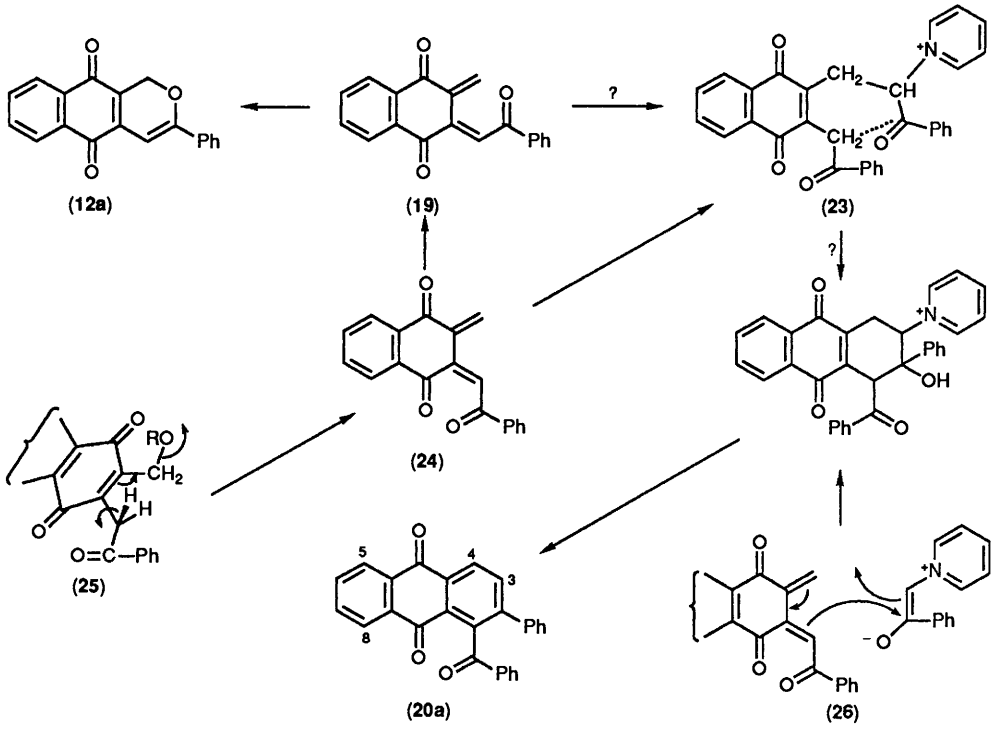
Anthraquinone formation increases as the leaving-group ability of the aryloxy substituent increases. Table 1 lists yields for reactions between various aryloxymethylnaphthoquinones and phenacylpyridinium bromide in a molar ratio 1.0:1.1 which does not favour anthraquinone formation, as this latter requires 2 mol equiv. of ylide. The results show that with the better leaving groups anthraquinone formation is markedly preferred to naphthopyran formation. When the molar ratio is 1:2, anthraquinone formation becomes almost exclusive, so providing the first general and regiospecific route to such compounds.

Scheme 4 outlines a simple way in which the formation of the anthraquinone derivative might be accounted for. Essentially a second mol equiv. of ylide adds to the quinone methide (**19**) before this has time to cyclise to the naphthopyrandione (**12a**); the subsequent aldol and elimination reactions leading to the

Table 1. Effect of aryloxy leaving group in (**17**) on phenacylpyridinium ylide reactions.[a]

Aryloxy group	Yields[b] (g) Naphthopyran (**12a**)	Anthraquinone (**20a**)	(**17**) Accounted for (%)
PhO	0.42	0.00	87
4-ClC_6H_4	0.29	0.14	83
2,4,5-$Cl_3C_6H_2$	0.14	0.32	78
4-$O_2NC_6H_4$	0.08	0.34	69

[a] Naphthoquinone derivative (**17**) (1.67 mmol) in acetonitrile (5 ml) and pyridinium salt (0.52 g, 1.87 mmol) in acetonitrile (5 ml) with triethylamine in acetonitrile under nitrogen. [b] Isolated by chromatography.



Scheme 4.

anthraquinone (**20a**) are all familiar. However, such an explanation does not readily account for the regiospecificity of the aldol reaction [dotted line in (**23**)] nor does it explain why anthraquinone formation should over-ride naphthopyran formation when both reactions appear to require the identical quinone methide intermediate.

Intramolecular electrocyclic reactions in systems of the correct geometry are commonly very fast, and in any case, are much faster than reactions between two species which have to collide first. It follows that if indeed the quinone methide intermediate has the *E* geometry shown [(**19**), Scheme 4] it would inevitably cyclise before the second ylide arrived and anthraquinone derivatives could never be formed. Therefore we suggest that the quinone methide intermediate is initially produced in the alternative *Z* configuration (**24**), also shown in Scheme 4, and has to invert before it can give a pyran (**12a**), although it can add an ylide immediately. Inversion is probably easy because the *Z* configuration cannot be both planar and free from strain, and the reaction mixture contains species (including phenoxide ion) that could enable inversion by addition–elimination routes. The relatively strained *Z* configuration is merely a result of *trans* elimination in the least strained conformation of the precursor as shown by diagram (**25**). (The situation recalls the difficulty of brominating the ethylnaphthoquinone mentioned earlier). A need for inversion could also explain why the best yields of naphthopyran are obtained only some time (depending upon R) after the initial reaction appears to be complete. Direct evidence for the *Z* configuration is presented below.

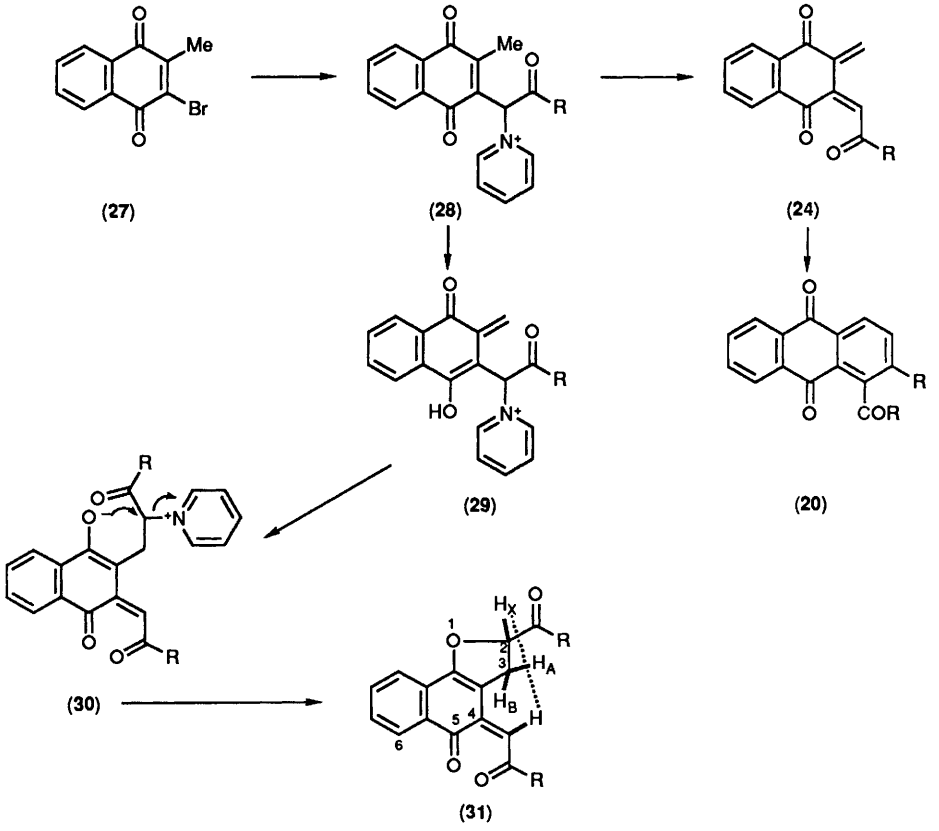
The regiospecific nature of the aldol ring closure could likewise be a consequence of the *Z* configuration so long as this configuration (or conformation) holds, but we prefer to regard it as the result of a mechanism having the character of an electrocyclic addition between the quinone methide and (enolic) ylide as indicated by diagram (**26**). For this mechanism there is no equivalent leading to the alternative anthraquinone orientation in (**22a**).

Yet more new reactions were disclosed by having a leaving group, bromine, attached to the naphthoquinone nucleus as in (**27**) (Scheme 5). The behaviour of such quinones with nucleophiles is known to be ambiguous in that amines can either replace the halogen by addition–elimination or add at the methyl group after enolisation to form a quinone methide.[9] Both modes are necessary in the present transformations, with the bromine displacement coming first to give intermediates (**28**). Since one of the two major products is always an acylated anthraquinone of type (**20a**) it is obvious that the intermediates (**28**) can eliminate pyridine to give the quinone methide (**24**)

Table 2. Proton chemical shifts (δ) for 1,4-naphthoquinone derivatives in $CDCl_3$ at 220 MHz.[a]

	Naphthoquinone nucleus			Aromatic substituents (benzenoid)				
Comp.	5(8)	6(7)	3	2(6)	3(5)	4	CH_2	CMe
(2)	8.06	7.69	6.77t (1.5)				2.50m	1.19t (8)
(7)	*ca.* 8.07	7.70		*ca.* 8.06	7.21	7.62t	2.64q 4.37 br s	1.14t
(8)	*ca.* 8.10	*ca.* 7.61					4.50 (CH_2CO) 4.54(CH_2O)	3.28(OMe)
(9)	8.08	7.72					3.71	2.17
(10)	8.09	7.73					3.74	2.33
(17a)	8.12, 8.16	7.77, 7.86	7.18t (2)	6.98	7.32	6.98	5.07d (2)	
(17b)	8.11, 8.14	7.76, 7.79	7.17t (2)	6.95d (7)	7.30d (7)		5.05d (2)	
(17c)	8.16	7.79	7.27t (2)				5.10t (2)	
(17d)[d]	8.06	7.92	7.02t (1.6)	7.34d (5.1)	8.25d (5.1)		5.28d (1.6)	
				(heterocyclic)				
				3	4	5		
(13)[c]	*ca.* 8.09	*ca.* 7.25		7.92d (3.8)	7.19dd (4.3, 3.8)	*ca.* 7.25	4.34	2.21
(14)[c]	*ca.* 8.08	*ca.* 7.70		7.33d (3.6)	6.60dd (3.2, 1.2)	7.65br	4.26	2.29

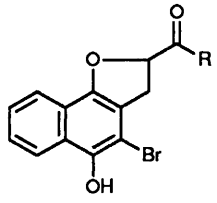
[a] Relative intensities are appropriate to assignments; coupling constants (Hz) are given in parentheses when first-order analysis seemed meaningful. [b] In [$^2H_6$]DMSO at 250 MHz. [c] At 200 MHz(FT).



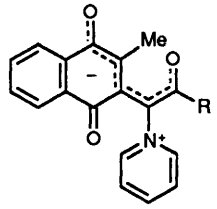
a; R = Ph; **b**; R = 4 - BrC_6H_4

Scheme 5.

discussed above, but a second mode of reaction must be available to allow for the second of the major products which are red naphthofuranones with structures (**31**) (Scheme 5). It may be that if pyridine elimination from (**28**) is comparatively slow enolisation can intervene giving (**29**) which can add the second ylide and undergo internal nucleophilic substitution as in (**30**) eventually forming the final product (**31**). We cannot be precise about the order of some of these events, but note that the enolisation–ylide addition must come after the bromine displacement otherwise the bromoquinols (**32**) would be formed and further reaction prevented. Importantly, the enedione configuration in (**31a**) is proved to be *Z* by NMR methods described below, justifying some of the mechanistic proposals made above.



(**32**)



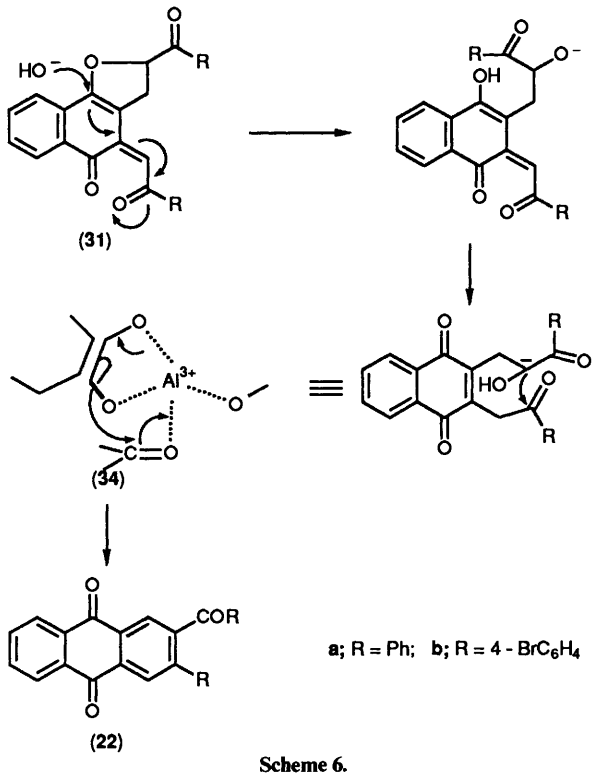
(**33**)

Small amounts of other products accompany the red naphthofuranones. The known alkaline hydrolysis of acylated ylides [10] probably accounts for the presence of small amounts of benzoic or other acids along with simple 2-arylanthraquinones (**21a,b**). Such by-products can be minimised by keeping reaction times short and excluding moisture. It is likely that such side reactions would be more prominent but for the fact that some of the intermediates have very acidic protons and would exist mainly as salts; *e.g.* (**28a**) would exist mainly as the ion (**33**) which would resist hydrolytic attack while still being vulnerable to enolisation; since this latter only involves the carbonyl group not involved in stabilising the anion.

The red naphthofuranones (**31a,b**) are somewhat sensitive to hydrolytic conditions and are best handled in non-protic solvents. They can be isolated by rapid chromatography on silica columns but lose their colour in a few minutes in contact with alumina. The process is a transformation into acylated anthraquinones isomeric with those obtained before, *e.g.* (**31a**) changes into (**22a**). Since hydrolysis in the absence of alumina furnishes only an unsatisfactory mixture (not analysed in detail) the specific nature of the reaction appears to depend upon the aluminium cation. Scheme 6 indicates a possible route, with diagram (**34**) showing how co-ordination of aluminium with carbonyl and ketol (enediol) groups could both catalyse the condensation and control its direction.

The transformation of the red naphthofuranones occurs with high efficiency and with complete regiospecificity thus supplying an excellent route to acylated anthraquinones of this orientation. Currently the method is limited by the rather low yields (not better than 33%) of the red naphthofuranones, a state that pilot experiments indicate can be improved. Other work indicates the possibility of introducing mixed substituents by using two different ylides and of using (acylated) hydroxynaphthoquinones instead of brominated compounds. These modifications will greatly extend the scope of the synthesis, and allow some naturally occurring quinones to be used as starting materials.[11]

Similar reactions were conducted with heterocyclic nuclei (furan, thiophene) instead of phenyl and bromophenyl nuclei and gave essentially similar results. In reactions with the appropriate pyridinium ylides the bromonaphthoquinone (**27**) supplied the 1-acyl-2-heteroaryl anthraquinones (**35a,b**) along



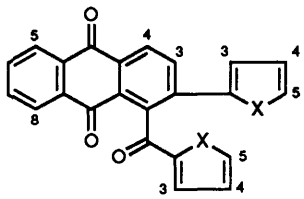
a; R = Ph; **b**; R = 4-BrC_6H_4

Scheme 6.

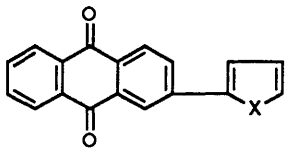
with smaller amounts of furoic and thiophene-2-carboxylic acids and also (in one case) the corresponding 2-heteroarylanthraquinone (**36b**); red naphthofuranones (**37a,b**) were the other major products. As before, these red naphthofuranones were rapidly transformed into 2-acyl-3-heteroaryl anthraquinones (**38a,b**) when left in contact with alumina. Anthraquinones bearing acyl groups as described here are not common, and these heterocyclic examples appear to be of new kinds, there having been no rational synthesis available for them previously.

In one case, that of the pyridinium ylide derived from thiophene, we observed the formation of a product assigned the indolizine structure (**39**) no part of which is derived from the naphthoquinone itself. The indolizine had the molecular formula $C_{13}H_8N_2OS$ and IR bands indicating cyanide and carbonyl groups. The mass spectrum suggested the loss of thiophene and carbonyl groups and was supported by the NMR spectra which again suggested a thiophene nucleus and another aromatic nucleus possessing one proton that appeared at the exceptionally low fields characteristic of acylated indolizines.[12] It is evident that structure (**39**) could originate from a pyridinium ylide by reacting (twice) with acetonitrile solvent, along with elimination of HCN and appropriate oxidations. These oxidations are performed by the quinone for in its absence no indolizine is produced. Cognate indolizine syntheses from pyridinium ylides are already known although they do not have acetonitrile as a component.[13]

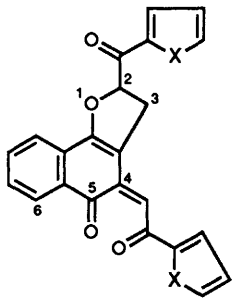
Structural Studies and Notes on ^{1}H NMR *Spectra.*—The products of these reactions generally contained several carbonyl groups for which no specific IR assignments could be made; the red naphthofuranones (**31**) and (**37**) exhibited a series of unusually strong, well resolved bands in the carbonyl region that outnumber the carbonyl groups present and must include polarised alkene and combination frequencies. Similarly, the mass spectra conformed to the structures but usually without any special feature; all the compounds show a series of losses of



(35)

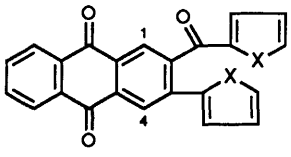


(36)

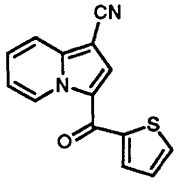


(37)

a; X = O; b; X = S



(38)



(39)

Table 3. Proton chemical shifts (δ) for derivatives of 1*H*-naphtho[2,3-*c*]pyran in $CDCl_3$ at 250 MHz.[a]

	Compounds			
Site	(12a)	(12c)	(15)	(16)[b]
Pyran nucleus				
1	5.32	5.91q (7)	5.31	5.28
4	6.74	6.71	6.61	6.66
Naphthoquinone nucleus				
6(9)	8.10m	8.11m	8.09m	8.12m
7(8)	7.80m	7.83m	7.72m	7.71m
Furan/thiophene nuclei				
3			7.48d (5)	6.86d (3.3)
4			7.12dd (5, 1)	6.51dd (3.3, 1.5)
5			7.57d (1)	7.56 (br)
Phenyl substituent				
2(6)	7.70m	*ca.* 7.72m		
3(5)	7.44m	*ca.* 7.46m		
4	7.44m	*ca.* 7.46m		
C-Me		1.49d (7)		

[a] Coupling constants (Hz) are given in parentheses where first-order analysis appeared meaningful. [b] At 200 MHz(FT).

28 and/or 29 units corresponding to carbonyl or enol hydroxy groups along with other fragmentations corresponding to loss of aryl and/or aroyl groups. For the naphthoquinones (**13**) and (**14**) the fragmentation to aroyl is so strong as to be almost the only visible one, although of the two fragments only the aroyl fragment is actually seen. The red naphthofuranones tend to lose 18 units initially, suggesting an early transformation into the expected acylated anthraquinones obtained from them chemically, but as the rest of the spectra show many differences in detail some other process is likely. As usual, compounds containing bromine exhibited isotope peaks and strong bands corresponding to loss(es) of halogen.

The NMR spectra were more informative. However, many compounds listed in Tables 3–5 display nearly coincident multiplets, so making it difficult to deduce unique assignments even when chemical shifts and couplings can be determined satisfactorily. For the present purposes it has been generally unnecessary to know (for example) which of two nearly coincident signals should be assigned to the proton at position 8 of an anthraquinone nucleus and which to that at position 5, and in such respects assignments are tentative. For similar reasons many coupling constants are also tentative, notwithstanding the use of decoupling and other techniques. Precision in these matters was often unnecessary for purely structural work and was not pursued assiduously.

The most important result was the stereochemistry assigned to the red naphthofuranones (**31**) and (**37**). These compounds signal both an ABX spin system and a solitary methine proton all giving discrete unambiguous peaks (Table 5). A study of nuclear Overhauser effects (NOE) in (**31a**) showed that irradiation of the solitary proton produces a positive effect at H_a but a negative one at H_x, a very strong indication that all three protons lie on or very close to a straight line.[14] It is clear, therefore, that the enedione link has the *Z* configuration as shown. The arrangement does not permit the aroyl part to achieve planarity, and models suggest that the aroyl group as a unit rotates out of plane to some extent. When the aryl part now rotates about its link to carbonyl its *ortho* protons have to sweep through the shielding cones of the various adjacent double bonds; a smaller effect occurs at the *meta* protons. Since the other aroyl group at position 2 remains free to adopt the usual conformation (because at position 2 it is not hindered) we can assign to it the standard chemical shifts, reserving the upfield shifts for the hindered group (Table 5). NOE measurements confirm this assignment; irradiation of the solitary methine proton strongly affects only the upfield *ortho* signals and again there is a negative effect at the adjacent *meta* protons which are collinear with the others and can therefore be assigned uniquely. Conversely, irradiation of the X proton affects only the downfield *ortho* signals. The stereochemistry of the other red naphthofuranone derivatives was decided on the basis of parallel chemical shifts only.

During the first attempts to study the red naphthofuranone (**31b**) from 4-bromophenacylpyridinium bromide we failed to obtain any ^1H NMR spectrum whatsoever from the product except at very high concentrations of substrate when a weak spectrum did appear. Changes in solvent and temperature did not improve the result. The sample gave no ESR signal, but atomic absorption spectrometry disclosed the presence of iron (17 ppm) and manganese (5 ppm). The spectrum was not improved by treating the sample with iron chelating agents except that repeated washing with caesium fluoride solutions gradually led to the appearance of a spectrum at normal concentrations. A wash with an iron-containing solution immediately destroyed the spectrum again; it also destroyed the spectra of the other red naphthofuranones. The iron appears to have originated from the 4-bromophenacyl bromide used to make the pyridinium salt although these compounds gave normal spectra. The red naphthofuranones may have an affinity for iron because of the enedione groups they possess in conjunction with the (known) ability of iron to form complexes with *ortho*-quinone methides.[15]

Amongst anthraquinone derivatives (Table 4) those with the 1-aroyl-2-aryl arrangement display a characteristic feature in which protons at positions 5 and 8 fall into two quite separate groups. One type of proton resonates at the usual field, *i.e.* 8.30 ± 0.03, the other at a higher field, 8.10 ± 0.04. We assign

Table 4. Proton chemical shifts (δ) for anthraquinone derivatives.[a]

	Anthraquinone nucleus						Phenyl substituent			Benzoyl substituent				
Compd.	1	3	4	5	6(7)	8	2(6)	3(5)	4	2(6)	3(5)	4	Solvent	Field[d] (MHz)
(21a)	8.52d (1.5)	8.00dd (8, 1.5)	8.34d (8)	8.30m	7.80m	8.30m	7.75dd (8, 1.5)	7.49m	7.49m				$CDCl_3$	220CW
(21b)	8.48d (2)	7.97dd (8.2)	8.37d (8)	8.32m	7.80m	8.32m	7.61dt (8, 1.5)	7.59dt (8, 1.5)					CCl_4	220CW
(20a)		7.83d (7.9)	8.51d (7.9)	8.31m (7.9, 1.6)	*ca.* 7.8	8.12m (7.9, 1.6)	*ca.* 7.25		*ca.* 7.25	7.67dd (7.2, 1.5)	7.30dd (7.2, 1.5)	7.43dd (7.2, 1.5)	CD_2Cl_2	200FT
(20b)		7.73d (8)	8.44d (8)	8.27dd (7.5, 1.5)	*ca.* 7.6	8.07dd (7.5, 1.5)	7.38 ?	7.40 ?		7.38d (8.5)	7.06d (8.5)		CCl_4	220CW
(22a)	8.40s		8.36s	*ca.* 8.29	*ca.* 7.9	*ca.* 8.29	*ca.* 7.3	*ca.* 7.3	*ca.* 7.3	7.67m	*ca.* 7.3	7.51m	CD_2Cl_2	200FT
(22b)	8.38s		8.37s	8.34m	7.85m	8.34m	7.44d (8.5)	7.22d (8.5)		7.54d (8.5)	7.52d (8.5)		$CDCl_3$	220CW
							Heteroaryl substituent			Heteroaroyl substituent				
							3	4	5	3	4	5		
(38)	8.52d (2)	8.04dd (8.1, 1.6)	8.31d (8.1)	*ca.* 8.3	*ca.* 7.8	*ca.* 8.3	7.49dd (5.2, 1.5)	7.20dd (5.2, 3.6)	7.63d (3.6)				CD_2Cl_2	250FT
(37a)[b]		8.27d (7.0)	8.47d (7.9)	8.29dd (7.4, 1.6)	7.79, 7.84dt (7.4, 1.6)	8.14 (7.4, 1.6)	6.71d (3.8)	6.44d (3.8, 1.3)	7.50d (1.3)	6.95dd (3.8)	6.50dd (3.8, 1.3)	7.57br	CD_2Cl_2	250FT
(37b)[b,c]	8.64s	8.02d (8.14)	8.48d (8.14)	8.32dd (7.5, 1.3)	7.79, 7.84dt (7.5, 7.4)	8.14 (7.5, 1.3)	7.16dd (3.8, 1.3)	6.97dd (4.8, 3.7)	7.37dd (5.1, 1.2)	7.17dd (3.8, 3.7)	6.99dd (4.8, 1.3)	7.64dd (4.9, 1.2)	CD_2Cl_2	250FT
(38a)[b]	8.49s		8.32s	*ca.* 8.3	*ca.* 7.8		6.85d (3.6)	6.55dd (3.6, 1.5)	7.58d (1.5)	7.66d (1.4)	6.54dd (3.7, 1.4)	7.01d (3.7)	CD_2Cl_2	250FT
(38b)			8.35s	*ca.* 8.3	*ca.* 7.9		7.41d (5.3)	7.02dd (5.0, 3.5)	7.23d (3.4)	7.76d (5.3)	7.06dd (3.8, 5.3)	7.33d (3.4)	CD_2Cl_2	250FT

[a] Multiplicities are given in descending order of size of splitting. Most of the splittings (quoted in parentheses) are first-order only; minor splittings are ignored and non-diagnostic overlapping systems have not been analysed in detail. [b] Couplings confirmed by double irradiation experiments. [c] Correlations confirmed by COSY experiment. [d] CW ≡ continuous wave mode; FT ≡ Fourier Transform mode.

Table 5. Proton chemical shifts[a] (δ) for derivatives of naphtho[1,2-*b*]furan-5(4*H*)-one in CD_2Cl_2.

Compd.	Naphthofuran nucleus: ABX System 2	3a	3b	Benzene ring protons 6	7	8	9
(31a)[b]	6.47dd (AB 15,	3.71dd AX 10,	3.18dd BX 2.5)	8.15dd (7.5, 1.5)	7.73td (7.5, 7.2)	7.76td (7.5, 1.5)	8.11dd (8, 1.5)
(31b)	6.38dd (AB 15,	3.68dd AX 10,	3.10dd BX 2.5)	*ca.* 8.1 (8,2)	*ca.* 7.8 (7,8)	*ca.* 7.8 (7,8)	*ca.* 8.1 (8,2)
(37a)	6.29dd (AB 15,	3.58dd AX 10,	2.89dd BX 2.8)	*ca.* 8.1	*ca.* 7.8	*ca.* 7.8	*ca.* 8.1
(37b)	6.35dd (AB 15,	3.65dd AX 10,	3.03dd BX 3.1)	*ca.* 8.1	*ca.* 7.8	*ca.* 7.8	*ca.* 8.1

Compd.	Aroyl substituents: 2-Benzoyl group 2(6)	3(5)	4	4-Benzoylmethylene 2(6)	3(5)	4	=CH=	Field (MHz) mode
(31a)	8.05dd (8, 1.5)	7.47td (8, 7, 1)	7.39dt (7.5, 1.5)	7.71dd (8, 1.5)	7.38td (7.5, 1)	7.39dt (7.5, 1)	6.75s	400FT
(31b)	7.88d (8.6)	7.61d (8.6)		7.50d (*ca.* 8)	7.45d (*ca.* 8)		6.76s	250FT
	2-(C_4H_3X) Group 3	4	5	4-(C_4H_3X)CO Group 3	4	5		
(37a)	7.27d (3.5)	6.53dd (3.5, 2)	*ca.* 7.55m ?	6.64d (3.5)	6.41d (3.5, 2)	*ca.* 7.55m ?	6.65s	220CW
(37b)	7.80d (4.2)	*ca.* 7.1 ?	7.46d (4.3)	7.69d (4.5)	*ca.* 7.1 ?	7.46d (4.3)	6.63s	220CW

[a] Coupling constants are given in parentheses. [b] Assignments supported by double irradiation and NOE experiments.

the latter resonance to the proton at position 8 because this will be shielded to some extent by the aroyl group which cannot be co-planar and must rotate both to relieve steric congestion and to minimise repulsion between the carbonyl groups. We have been unable to make useful assignments to the substituent aryl protons in these compounds. The various groups shield each other and for the aroyl group this results in the downfield shifts, usual in carbonyl compounds, being compensated by upfield shifts so that aryl and aroyl group protons can no longer be distinguished easily.

Experimental

UV Spectra were recorded by means of a Pye-Unicam SP8-100 spectrophotometer with solutions *ca.* 10^{-4} M in 95% ethanol. IR spectra were obtained using a Perkin-Elmer 21B machine in most cases and an Alpha Centauri FT-IR 13 machine in others; only bands more intense than the average are recorded. ^1H NMR spectra were obtained using a Perkin-Elmer R34 instrument at 220 MHz(CW), a Varian R12 instrument operating at 240 MHz(FT), or a Bruker WM instrument operating at 250 MHz(FT); throughout, relative intensities are those required by the proposed assignments. Molecular weights were determined by mass spectrometry with either AEI MS12 or VG Analytical 7070E spectrometers; in all cases, molecular weights are quoted with significant figures indicating the accuracy of the technique used. M.p.s are uncorrected.

Petroleum refers to light petroleum b.p. 60–80 °C. Triethylamine was distilled from potassium hydroxide pellets before use. Ether and acetonitrile were stored over molecular sieve drying agents.

Reaction of 2-Methyl-1,4-naphthoquinone (**1**) *with Preformed Ylides.*—The details given for (pyridinio)benzoylmethanide (Scheme 1) are typical. Phenacylpyridinium bromide (2.77 g, 0.01 mol) in water (10 ml) over dichloromethane (20 ml) was treated with aqueous potassium hydroxide (0.56 g, 0.01 mol) at 0 °C and the deep yellow organic layer was at once separated and dried over sodium sulphate whilst being refrigerated at −2 °C. The filtered solution was added gradually to 2-methyl-1,4-naphthoquinone (1.7 g, 0.01 mol) in acetonitrile (100 ml) under nitrogen. The green colour initially produced changed to red and then orange during 24 h, after which removal of volatile materials under reduced pressure left a solid that crystallised from ethanol–petroleum mixtures to give 2-methyl-3-phenacyl-1,4-naphthoquinone (**6**) as yellow needles (2.37 g, 82%), identical with an authentic specimen.[3]

Methyl (3-*Methyl*-1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)*acetate* (**9**).—2-Methyl-1,4-naphthoquinone (1.79 g) reacted with *N*-(methoxycarbonylmethyl)pyridinium chloride (1.78 g) in acetonitrile (100 ml) when triethylamine (1 g) was added dropwise, with stirring, under nitrogen. After 24 h, removal of volatile materials under reduced pressure left a brown solid which was purified by flash chromatography on silica from dichloromethane–pentane (10:1, v/v) to give the *acetate* as fine yellow plates (from methanol) (2.03 g, 85%), m.p. 122.5–123.5 °C; ν_{max}(Nujol) 1 745, 1 660, 1 635, 1 585, 1 600, 1 300, 742, 698, and 645 cm^{-1} (Found: C, 68.9; H, 4.9%; *M*, 244. $C_{14}H_{12}O_4$ requires C, 68.8; H, 4.95%; *M*, 244).

(3-*Methyl*-1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)*acetonitrile* (**10**).—2-Methyl-1,4-naphthoquinone (3.4 g) and *N*-(cyanomethyl)pyridinium bromide (4.0 g) in acetonitrile (100 ml) under

nitrogen were treated with triethylamine (2 g) and the reaction mixture was left for 12 h before filtration and removal of solvent under reduced pressure. The residue was dissolved in dichloromethane and washed copiously with water, dried (Na_2SO_4) and recovered for crystallisation from ethanol–hexane which supplied the *nitrile* as dark yellow-brown prisms (1.56 g, 37%), m.p. 158–162 °C, ν_{max} 2 254, 1 672, 1 659, 1 620, 1 585, 730, 700, and 675 cm^{-1} (Found: C, 71.3; H, 4.8; N, 7.0%; *M*, 211.0633. $C_{13}H_4NO_2$ requires C, 73.9; H, 4.3; N, 6.6%; *M* 211.0758).

2-(3-*Methyl*-1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)*acetylthiophene* (**13**).—After the dropwise addition of bromine (56 g) to 2-acetylthiophene (42 g) in stirred tetrachloromethane (300 ml) the mixture was refluxed for 40 min and the solvent removed under reduced pressure. The residue in ether (sodium dried, 200 ml) was added to pyridine (32 g) also in ether (300 ml) and stirred for 5 min after which tarry material was removed by filtration through a loose glass-wool plug. The filtrate slowly deposited a yellow solid during 2 days (more quickly on refluxing) and this was crystallised from ethanol to give 2-oxo-2-(2-thienyl)ethylpyridinium bromide as irregular, cream-coloured prisms (68 g, 71%), m.p. 200–202 °C; ν_{max} 1 660, 1 620, 1 360, and 790 cm^{-1}; δ(220 MHz; D_2O) 9.12 (2 H, d, *J* 6 Hz, 2-,6-H), 8.72 (1 H, t, *J* 7.5 Hz, 4-H), 8.27 (2 H, br t, 3-,5-H, all pyridinium protons), 8.22 (2 H, d, 3-,5-H), 7.37 (1 H, t, *J* 4.5 Hz, 4-H, all thiophene protons), and 6.59 (2 H, s, CH_2N^+) [Found (cation only): M^+, 204.02. $C_{11}H_{10}NOS$ requires M^+, 204.05].

2-Methyl-1,4-naphthoquinone (1.79 g, 0.01 mol) in acetonitrile (100 ml) was allowed to react with the ylide preformed from the thienylpyridinium bromide (2.84 g, 0.01 mol) and contained in dichloromethane. Removal of the solvents under reduced pressure after 24 h left an oil that was taken up in dichloromethane and washed repeatedly with 2 M hydrochloric acid followed by water. The product was recovered in the usual manner as a tarry brown solid; the tar was washed away with a little methanol and the residue crystallised from methanol–petroleum mixtures to give the *title compound* (**13**) as bright yellow prisms (1.34 g, 45%), m.p. 121–123 °C; ν_{max} 1 670, 1 660, 1 483, 1 250, and 710 cm^{-1} (Found: C, 68.8; H, 4.0%; *M*, 296.07. $C_{17}H_{12}O_3S$ requires C, 68.9: H, 4.1%; *M*, 296.05).

3-(2-*Thienyl*)-1H-*naphtho*[2,3-c]*pyran*-5,10-*dione* (**15**).—The foregoing thiophene derivative (**13**) (0.5 g) in dichloromethane (30 ml) was treated with bromine (0.27 g) also in dichloromethane (10 ml) with exclusion of light. After 40 min the solution turned pale yellow and removal of volatile materials under reduced pressure left a sticky mass with spectroscopic properties consistent with the required bromo ketone but which was not purified. The whole of this mass was dissolved in dichloromethane and kept under nitrogen while cyclisation was effected by adding triethylamine (0.171 g). After 1 h the product was purified by chromatography on silica from dichloromethane in the dark. (The deep red compound becomes pale pink when adsorbed on silica and exposed to diffuse daylight). The product was crystallised from ethanol–trichloromethane to give the *naphthopyrandione* (**15**) as reddish black prisms (0.3 g, 60%), m.p. 205–207 °C; $\nu_{max}(CCl_4)$ 1 660, 1 635, 1 561, and 1 530 cm^{-1} (Found: C, 69.1; H, 3.3%; *M*, 294.04. $C_{17}H_{10}O_3S$ requires C, 69.4; H, 3.4; *M*, 294.04).

3-(2-*Furyl*)-1H-*naphtho*[2,3-c]*pyran*-5,10-*dione* (**16**).—2-Acetylfuran (22 g) was converted into 2-bromoacetylfuran by an established method [16] and that part of the product distilling at 120 °C was immediately treated with pyridine (15.8 g) in ether (250 ml) under gentle reflux. After 16 h a tar had adhered to the flask leaving the desired material suspended in the ether. This solid was collected and purified from ethanol giving 2-(2-*furyl*)-2-*oxo-ethylpyridinium bromide* as prisms (12.6 g, 24%), m.p. 208–210 °C, ν_{max} 1 691, 1 470, 1 380, and 750 cm^{-1}, δ(220 MHz; [$^2H_6$]DMSO), 9.20 (2 H, d, *J* 6 Hz, 2-, 6-H), 8.80 (1 H, t, *J* 7.5 Hz; 4-H), 8.34 (2 H, t, 3-, 5-H, pyridinium bands), 8.26 (1 H, d, 1.5 Hz, 5-H), 7.76 (1 H, d, *J* 4 Hz, 3-H), 6.90 (1 H, m, 4-H), (furan bands), and 6.53 (2 H, s, CH_2N^+) (Found: M^+, 188.06. $C_{11}H_{10}NO_2$ (cation only) requires M^+, 188.07).

2-Methyl-1,4-naphthoquinone (1.72 g) was alkylated by the ylide obtained externally from the furylpyridinium bromide (1.88 g) as in the foregoing example. The product after removal of pyridine by acid washing formed a brownish mass that separated from ethyl acetate–petroleum mixtures giving 2-(3-*methyl*-1,4-*dioxo*-1,4-*dihydro*-2-*naphthyl*)*acetylfuran* (**14**) as fluffy, faintly yellow needles (1.07 g, 65%), m.p. 119–121 °C, ν_{max} 1 660, 1 630, 1 390, 750, and 690 cm^{-1} (Found: C, 72.6; H, 4.2%; *M*, 280.09. $C_{17}H_{12}O_4$ requires C, 72.8; H, 4.3%; *M*, 280.08).

This dioxo-naphthylacetylfuran (0.21 g) in dichloromethane (15 ml) was treated with bromine (0.14 g) also in dichloromethane (10 ml) in the absence of light and after 30 min all volatile materials were removed under reduced pressure at 10 °C. The residue was at once dissolved in dichloromethane and kept under nitrogen while triethyl-amine (0.085 g) was added. The mixture became reddish black immediately. The product was isolated after 15 min in the usual manner and purified by chromatography on silica from dichloromethane with protection from light and when crystallised from chloroform–ethanol gave the *naphthopyrandione* (**16**) as very dark red prisms (0.13 g, 53%), m.p. 205–206 °C, $\nu_{max}(CCl_4)$ 1 660, 1 635, and 1 320 cm^{-1} (Found: C, 73.1; H, 3.5%; *M*, 278.06. $C_{17}H_{10}O_4$ requires C, 73.4; H, 3.6; *M*, 278.06).

2-*Ethyl*-3-*phenacyl*-1,4-*naphthoquinone* (**7**).—Triethylamine (1.11 g, 11 mmol) was added to a solution of 2-ethyl-1,4-naphthoquinone (1.79 g, 10 mmol) and phenacylpyridinium bromide (3.10 g, 11 mmol) in acetonitrile (100 ml) under nitrogen. The mixture was at first green but later became red-brown and after it had been kept in the dark for 24 h it was filtered and diluted with dilute hydrochloric acid (30 ml) and water (200 ml), which precipitated a yellow product that crystallised from methanol giving the *ethylphenacylquinone* as fine needles (1.89 g, 68%), m.p. 151–152 °C, ν_{max} 1 670, 1 657, 1 621, 1 580, 752, 718, and 688 cm^{-1} (Found: C, 78.8; H, 5.25%; *M*, 304.11. $C_{20}H_{16}O_3$ requires C, 78.9; H, 5.3%; *M*, 304.12).

1-*Methyl*-3-*phenyl*-1H-*naphtho*[2,3-c]*pyran*-5,10-*dione* (**12c**).—When 1,8-diazabicyclo[5.4.0]undec-7-ene (0.1 ml) was added to 2-ethyl-3-phenacyl-1,4-naphthoquinone (0.03 g) in acetonitrile (5 ml) the solution became yellow-brown and was at once treated with bromine (0.1 ml) and left for 1 h. The entire reaction solution was then filtered through a short column of silica giving a red solution which was concentrated under reduced pressure until a red solid was deposited on the side of the flask. This solid did not crystallise readily and did not give wholly satisfactory results in elementary analysis but the ^1H NMR spectrum (Table 3) was that expected from the title compound and the mass spectrum exhibited the requisite molecular ion peak at *m*/*z* 302.

Preparation of 2-*Aryloxymethyl*-1,4-*naphthoquinones*.[7]—In the course of 1 h a solution of ammonium peroxydisulphate (13.7 g) in water (80 ml) was added to a stirred solution of 1,4-naphthoquinone (7.7 g, 0.05 mol), the requisite aryloxyacetic acid (0.05 mol), silver nitrate (1 g), and water (10 ml) in acetonitrile (150 ml), maintained at 60–65 °C. After a further 5 min at that temperature the mixture was filtered and cooled to −5 °C to complete the crystallisation of the product. The solid was collected, and crystallised from water to give the aryloxymethylnaphthoquinones in yields between 38 and 49%. 2-(4-*Chlorophenoxy*)*methyl*-1,4-*naphthoquinone* (**17b**) formed

bright yellow needles, m.p. 167–169.5 °C (Found: *M*, 298, 300. $C_{17}H_{11}ClO_3$ requires *M*, 298, 300). 2-(2,4,5-*Trichlorophenoxy*)-*methyl*-1,4-*naphthoquinone* (**17c**) separated from aqueous ethanol as yellow crystals, m.p. 204–206 °C (Found: C, 55.1; H, 2.4%. $C_{17}H_9Cl_3O_3$ requires C, 55.5; H, 2.5%). 2-(4-*Nitrophenoxy*)*methyl*-1,4-*naphthoquinone* (**17d**) formed yellow crystals, m.p. 204.5–205 °C (Found: *M*, 309. $C_{17}H_{11}NO_5$ requires *M*, 309). 2-Phenoxymethyl-1,4-naphthoquinone (**17a**) has been described previously.[7] NMR spectra are noted in Table 2.

2-*Methoxymethyl*-3-*phenacyl*-1,4-*naphthoquinone* (**8**).—Interaction of triethylamine (5.5 mmol) and 2-methoxymethyl-1,4-naphthoquinone (0.96 g, 5.5 mmol) with phenacylpyridinium bromide (1.44 g, 5 mmol) in acetonitrile (100 ml) as in the previous experiment led to a dark red, oily product that was obtained by dilution with water, extraction into dichloromethane, washing of the extract with dilute hydrochloric acid and then water, and isolation in the usual way. The oil slowly crystallised when kept and could then be recrystallised from wet methanol giving the *methoxymethylquinone* (**8**) as orange-yellow needles, (1.52 g, 67%), m.p. 91.5–92.5 °C, ν_{max} 1 685, 1 660, 1 655, 1 624, 1 590, 1 095, 756, 732, and 691 cm^{-1} (Found: C, 75.2; H, 5.0%; *M*, 320.20. $C_{20}H_{10}O_4$ requires C, 75.0; H, 5.0%; *M*, 320.12).

Reactions with 2-*Aryloxymethyl*-1,4-*naphthoquinones*.—In general, the relevant 2-aryloxymethyl-1,4-naphthoquinone (1.67 mmol) and phenacylpyridinium bromide (0.52 g, 1.87 mmol) were treated in acetonitrile (100 ml) with a slight excess (0.28 ml) of triethylamine under nitrogen and with exclusion of light. The yields usually increased with reaction time up to *ca.* 5 h. The reactions were terminated by removing solvent and catalyst under reduced pressure and at 20 °C, and the products isolated by flash chromatography on silica from chloroform. Yields are presented in Table 1. Only two products were obtained, one being 3-phenyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**12a**), identical with authentic material. The other was 1-*benzoyl*-2-*phenyl*-9,10-*anthraquinone* (**20a**), which separated from ethanol as yellowish needles which tended to redden in light, m.p. 226–228 °C; ν_{max} 1 660, 1 575, 755, 750, 720, 710, and 685 cm^{-1} (Found: C, 83.3; H, 4.1%; *M*, 388. $C_{27}H_{16}O_3$ requires C, 83.5; H, 4.1%; *M*, 388).

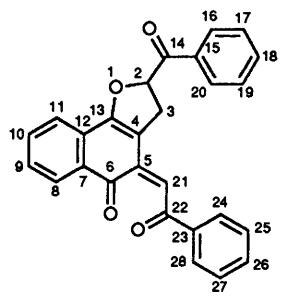
2-*Benzoyl*-3-*benzoylmethylene*-2,3-*dihydronaphtho*[1,2-b]-*furan*-5-*one* (**31a**).—2-Bromo-3-methyl-1,4-naphthoquinone (4.7 g, 190 mmol) and phenacylpyridinium bromide (10.5 g, 38 mmol) were dissolved in the minimum acetonitrile and then a further amount (10 ml) of the solvent was added. The solution was treated with triethylamine (7.9 ml) in acetonitrile (10 ml) added dropwise at 15 °C; the immediate and green colour was replaced by red after 5 min; after 10 h the solvent and catalyst were removed under reduced pressure at 25 °C and the residue chromatographed as rapidly as possible on a column of silica from dichloromethane–petroleum mixtures. The first fractions were pale yellow and supplied a solid that crystallised from trichloromethane–heptane giving 2-phenyl-9,10-anthraquinone (**21a**) as fine yellow needles (0.5 g), m.p. 162–163 °C (lit.,[5] 161 °C), $\nu_{max}(CCl_4)$ 1 675, 1 595, 1 325, and 1 300 cm^{-1} (Found: C, 84.3; H, 4.5%; *M*, 284. Calc. for $C_{20}H_{12}O_2$: C, 84.5; H, 4.3%; *M*, 284). Subsequent fractions were also pale yellow but turned red in light and upon the usual work-up furnished 1-benzoyl-2-phenyl-9,10-anthraquinone (2.7 g, 38%) identical with samples from earlier preparations.

The next fractions were intensely red and careful removal of solvent under reduced pressure left a red oil which crystallised when kept with a little ether, and then, on crystallisation from toluene, produced the *naphthofuranone* (**31a**) as fine red needles (2.5 g, 33%), m.p. 180–182 °C, λ_{max}(EtOH) 246, 297, 310sh, and 497 nm (log ε 4.21, 4.24, 4.22, and 3.86), ν_{max}(KBr) 1 680, 1 670, 1 615, 1 587, 1 577, 1 540br, vs, 1 490, 1 475, 1 442, 1 387, 1 335, 1 260, 1 060, 995, 766, 756, 715, 705, 687, and 677 cm^{-1} [Found (sample dried for 2 h at 80 °C/0.01 mmHg): C, 79.8; H, 4.6%; *M*, 406. $C_{27}H_{18}O_4$ requires C, 79.8; H, 4.5%; *M*, 406]. (^{13}C NMR data presented in Table 6).

Table 6. ^{13}C NMR spectra (δ) for the naphthofuranone derivative (**31a**).[a]

Shift	Mult.[b]	Site
40.388	td	3
70.582	dd	2
92.539	d	21
125.606	st	4
125.907	dd	9
126.523	dd	11
128.245	dt	25, 27
128.369	dd	17, 19
128.473	dd	8
128.667	dd	16, 20
130.843	dt	24, 28
131.795	s	12
132.711	?	5
132.780	s	7
133.161	dd	26
133.222	dd	18
133.938	dd	10
136.612	st	23
137.216	d	15
159.547	sm	13
181.531	s	22
182.192	s	14
195.565	s	6

[a] Numbering as in adjacent diagram. [b] Multiplicities are indicated by letters in the order of the major and the chief minor interaction.



(**31a**)

A colourless fraction contained benzoic acid (0.3 g) (identified in the usual way), and then another colourless fraction was obtained containing an unidentified *substance* which separated from ethyl acetate as opaque prisms, m.p. 248–249 °C, ν_{max} 1 684, 1 594, 1 448, 1 298, 1 268, 1 219, 1 182, 733, 720, and 688 cm^{-1}, $\delta(CD_2Cl_2)$ 8.16 (1 H, m), 7.97 (1 H, m), *ca.* 7.82 (2 H, mm), *ca.* 7.70 (3 H, mm), *ca.* 7.53 (4 H, mm), 7.37 (2 H, t, *J* 7 Hz), 7.28 (1 H, s), 3.85 (1 H, d, *J* 16.5 Hz), 2.81 (1 H, d, *J* 16.5 Hz), *ca.* 3.6 (2 H, m) (Found: C, 78.4; H, 4.1%; *M*, 576.11).

A solution of the naphthofuranone (0.3 g) in dichloromethane was passed down a column of alumina (Fluka 507, type C, Brockman activity 1). At first a large red band formed but the colour faded in a few minutes and elution provided only a single product (as indicated by TLC) from a faintly yellow band. Elution gave a gum which crystallised from ethanol giving 2-*benzoyl*-3-*phenyl*-9,10-*anthraquinone* (**22a**) as sheaves of fine prisms (0.21 g), m.p. *ca.* 160 °C (fast heating), or 179–180 °C

(slow heating; phase change to fat prisms occurs first); ν_{max} 1 681, 1 654, 1 590, 1 335, 1 309, 1 261, 950, 745, 709, and 687 cm^{-1} (Found: C, 83.6; H, 4.1%; *M*, 388. $C_{27}H_{16}O_3$ requires C, 83.5; H, 4.2%; *M*, 388).

2-(4-*Bromobenzoyl*)-3-(4-*bromobenzoylmethylene*)-2,3-*dihydronaphtho*[1,2-b]*furan*-5(4H)-*one* (**31b**).—2-Bromo-3-methyl-1,4-naphthoquinone (4.22 g, 16.8 mmol) was dissolved in the minimum acetonitrile and powdered (4-bromophenacyl)-pyridinium bromide (12.0 g, 33.6 mmol) was stirred in under argon at room temperature followed by triethylamine (7 ml) in acetonitrile (10 ml). The initial green colour faded rapidly and was replaced by brown and then red, and a red precipitate was formed. In some runs the solid was removed by filtration; this description refers to those where it was not. After 8 h volatile materials were removed under reduced pressure from a bath at 40 °C and the residue was extracted with warm benzene. Insoluble material was purified from ethanol and identified as 4-bromobenzoic acid, m.p. 256–258 °C (3 g). The benzene solution was concentrated until it deposited a red solid which was recrystallised from benzene to give the *naphthofuranone* as fine red needles (5.0 g, 53%), m.p. 211–213 °C, λ_{max}(EtOH) 264, 318, and 494 nm (log ε 4.14, 4.21, and 3.86), ν_{max}(KBr) 1 677, 1 665, 1 650br, 1 625, 1 580, 1 562, 1 550, 1 480, 1 400, 1 392, 1 380, 1 360, 1 330, 1 305, 1 260, 1 066, 1 005, 976, 860, 817, 795, 716, and 610 cm^{-1} [Found (sample dried at 80 °C *in vacuo*): C, 57.2; H, 2.8; Br, 28.4. $C_{27}H_{16}Br_2O_4$ requires C, 57.5; H, 2.9; Br, 28.3%]. The benzene solutions were then combined and the solvent removed; the red residue was chromatographed on silica from dichloromethane–petroleum mixtures but the red colour faded during the operation leaving only pale yellow bands. The fastest moving fractions contained material that separated from tetrachloromethane to furnish 1-(4-*bromobenzoyl*)-2-(4-*bromophenyl*)-9,10-*anthraquinone* (**20b**) as faintly orange thin rods (600 mg, 6%), m.p. 206–210 °C (subl. begins at 190 °C); ν_{max}($CHCl_3$) 1 672, 1 582, 1 325, and 992 cm^{-1} [Found (sample dried for 7 h at 80 °C *in vacuo*): C, 59.5; H, 2.6; Br, 29.4%; *M*, 544, 546, 548. $C_{27}H_{14}Br_2O_3$ requires C, 59.4; H, 2.6; Br, 29.3%; *M*, 544, 546, 548]. The next fractions were darker and contained both the foregoing anthraquinone derivative and 2-(bromophenyl)-9,10-anthraquinone (**21b**) which after fractional crystallisation separated from ethyl acetate–petroleum as feathery orange rosettes (0.3 g), m.p. 224–225 °C (subl. around 200 °C), ν_{max}($CHCl_3$) 1 670, 1 586, and 1 320 cm^{-1} (Found: C, 65.9; H, 3.1; Br, 22.3%; *M*, 363, 361. $C_{20}H_{10}BrO_2$ requires C, 66.1; H, 3.1; Br, 22.0%; *M*, 363, 361).

The slowest fractions were lighter yellow and contained a little of the 1-bromobenzoylanthraquinone derivative which was removed by dissolving it in ethyl acetate–petroleum (1:1) leaving an almost insoluble residue that separated from ethanol to supply 2-(4-*bromo-benzoyl*)-3-(4-*bromophenyl*)-9,10-*anthraquinone* (**22b**) as faintly yellow, irregular rhombs (20 mg), m.p. 237–239 °C, ν_{max}(KBr) 1 662, 1 578, 1 325, 1 250, 992, 710, and 530 cm^{-1} (Found: C, 59.5; H, 2.8; Br, 29.1. $C_{27}H_{14}Br_2O_3$ requires C, 59.4; H, 2.6; Br, 29.3%).

The naphthofuran was sensitive to alkali, less so to acid. It decomposed slowly in contact with silica, and rapidly in contact with alumina. A brief examination showed that whereas the other conditions led to complex mixtures, the reaction on alumina gave a single product. For preparative work, the naphthofuran (200 mg) in dichloromethane was passed down a column of alumina deactivated by water (5 ml kg^{-1}) to give the 2-(4-bromobenzoyl)-3-(4-bromophenyl)anthraquinone (190 mg) in a spectroscopically pure condition.

Obtained as described above, this naphthofuranone gave no ^1H NMR spectrum at normal concentrations and only a very poor one at very high concentrations. A sample (0.11 g) in dichloromethane was washed four times with caesium fluoride in water (1.3 g CsF ml^{-1}) and then continuously overnight with a similar solution. The pigment was recovered in the usual way and was not distinguishable from the original material except that it now gave an NMR spectrum (Table 5) in the normal manner. A solution of the iron-free material in dichloromethane washed once with dilute aqueous iron(III) chloride gave a pigment which again failed to furnish an NMR spectrum.

2-*Furoyl*-4-(2-*furoylmethylene*)-2,3-*dihydronaphtho*[1,2-b]-*furan*-5-*one* (**37a**).—2-Bromo-3-methyl-1,4-naphthoquinone (2.51 g) and (2-furoylmethyl)pyridinium bromide (6.7 g) in acetonitrile (150 ml) were treated with triethylamine (4.33 ml) while under nitrogen and at room temperature. Next day the volatile materials were removed under reduced pressure (bath at 20 °C) and the red residue was extracted with dichloromethane leaving 2-(2-*furyl*)-1-(2-*furoyl*)-9,10-*anthraquinone* (**35a**) which separated from ethanol–chloroform as irregular yellow (sometimes greenish) plates (2.0 g, 54%), m.p. 276–278 °C, λ_{max}(EtOH) 256, 286, 303sh, 325sh, and 397 nm (log ε 5.97, 5.32, 5.23, 4.93, and 4.55); ν_{max}(KBr) 1 672, 1 655, 1 582, 1 565, 1 490, 1 465, 1 330, 1 312, 1 290, 1 262, 1 020, 890, 882, 775, 740, and 712 cm^{-1} [Found (sample dried for 8 h at 80 °C *in vacuo*): C, 74.7; H, 3.4%; *M*, 368. $C_{23}H_{12}O_5$ requires C, 75.0; H, 3.3%; *M*, 368].

The contents of the dichloromethane extract were subjected to rapid chromatography (preferably by HPLC) on silica columns with ethyl acetate–dichloromethane (1:99, v/v) as eluant. The earlier fractions contained the foregoing anthraquinone derivative (0.5 g) and were followed by red fractions from which a gummy red solid was obtained; when crystallised from chloroform–hexane much amorphous material remained in solution and the *naphthofuranone* separated as deep red needles (1.1 g, 28%), m.p. 110–115 °C (rapid heating); λ_{max}(EtOH) 276, 305sh, 319sh, and 502 nm (log ε 4.37, 4.27, 4.26, and 3.84), ν_{max}(KBr) 1 732w, 1 660vs, 1 620, 1 585, 1 566, 1 532, 1 465, 1 395, 1 340, 1 285, 1 275, 1 076, 1 054, 1 015, 983, 746, 720, 605, and 595 cm^{-1} [Found (sample dried at 80 °C for 8 h *in vacuo*): C, 71.0; H, 3.7%; *M*, 386. $C_{23}H_{14}O_6$ requires C, 71.5; H, 3.65%, *M*, 386].

The next fractions were faintly coloured and supplied mainly 2-furoic acid, m.p. 130 °C, identified in the usual way. Further fractions were yellow and gave mass spectroscopic evidence for the presence of 2-(2-furyl)-9,10-anthraquinone but this was not identified by isolation. Further fractions supplied 2-(2-*furyl*)-3-(2-*furoyl*)-9,10-*anthraquinone* (**38a**) which separated from ethanol as orange needles (or sometimes brownish plates) (200 mg), m.p. 207–209 °C (subl. above 199 °C); λ_{max}(EtOH) 253, 294, and 395 nm (log ε 4.36, 4.39, and 3.72), ν_{max}(KBr) 1 670, 1 650, 1 585, 1 458, 1 326, 1 280br, 1 015, 1 000, 960, 755, 712, 590, and 512 cm^{-1} [Found (sample dried at 80 °C *in vacuo*: C, 75.2; H, 3.3%; *M*, 368. $C_{23}H_{12}O_5$ requires C, 75.0; H, 3.3%; *M* 368].

This anthraquinone derivative was also isolated quantitatively from the naphthofuranone (100 mg) after treatment of a solution in dichloromethane with deactivated alumina (5 ml water per kg) for 15 min.

2,3-*Dihydro*-2-(2-*thienyl*)-3-(2-*thenoyl*)*naphtho*[1,2-b]*furan*-5-*one* (**37b**).—The requisite thienylpyridinium bromide (2.84 g) and 2-bromo-3-methyl-1,4-naphthoquinone (1.26 g) were pulverised and shaken with acetonitrile (40 ml) while being cooled in ice and then treated with triethylamine (distilled from KOH, 2 ml). After 10 min the deep red solution deposited a deep green solid that was collected by filtration after another 24 h. This solid was soluble only with difficulty in many organic solvents; when purified from ethanol–chloroform it provided 2-(2-*thienyl*)-1-(2-*thienoyl*)-9,10-*anthraquinone* (**35b**) as yellow prisms (1.5 g, 75%), m.p. 285–286 °C; λ_{max}(EtOH) 255, 271, 290, and 380 nm (log ε 4.56, 4.47, 4.49, and 3.66 subl.); ν_{max}(KBr)

1 647, 1 656, 1 640, 1 580, 1 570, 1 614, 1 412, 1 350, 1 325, 1 312, 1 282, 1 262, 1 156, 1 044, 984, 860, 804, 732, 710, and 644 cm^{-1} (Found: C, 69.1; H, 3.2%; *M*, 400. $C_{23}H_{12}O_3S_2$ requires C, 69.0; H, 3.0%; *M*, 400).

All solvent was removed under reduced pressure from the filtrate at 40 °C and the residue subjected to flash chromatography on silica (Stahl Kieselgel G) from dichloromethane–petroleum mixtures ranging from 30% (v/v) to 50% of the former as development proceeded. The first band was orange and supplied greenish brown crystals (85 mg, 4%), m.p. 175–180 °C (subl.), identified by mass spectrometry as 2-(2-*thienyl*)-9,10-*anthraquinone* (**36**); ν_{max}(KBr) 1 676, 1 590, 1 427, 1 326, 1 290, 940, 728, 712, and 705 cm^{-1} (Found: *M*, 290.0432. $C_{18}H_{10}O_2S$ requires *M*, 290.0399). The mass spectrum was characterised by the losses from the parent ion of CHO, CO, and S fragments in various sequences. The compound differs from 1-(2-thienyl)-9,10-anthraquinone made by a definitive method.[17]

The next fractions were pale and contained 3-(2-*thenoyl*)-*indolizine*-1-*carbonitrile* (**39**) which separated from benzene–petroleum as yellow needles (190 mg), m.p. 165–166 °C; λ_{max}(EtOH) 235, 274, 296sh, 343sh, and 376 nm (log ε 4.41, 4.20, 4.06, 3.91, and 4.24); ν_{max} 2 200, 1 590, 1 510, 1 482, 1 412, 1 350, 1 222, 1 063, 816, 745, and 716 cm^{-1} (Found: N, 11.0%; *M*, 252.0361. $C_{14}H_8N_2OS$ requires N, 11.1%; *M*, 252.0357).

This band was followed immediately by an orange band which furnished material crystallising as orange rods (80 mg), m.p. 198–203 °C, after softening at *ca.* 170 °C. Mass spectrometry showed this substance to consist of 2-(2-thienyl)-3-(2-thenoyl)-9,10-anthraquinone (**38b**) (see below) contaminated by the foregoing indolizine. Attempts failed to obtain this quinone sample free from the indolizine.

The last band to leave the column was deep purple-red and removal of the solvent under reduced pressure at 40 °C and purification of the residue from dichloromethane–petroleum gave the *naphthofuranone* as permanganate-coloured bundles of needles (275 mg, 13%), m.p. 170 °C (decomp.) (rapid heating); λ_{max}(EtOH) 256, 296, 325, and 520 nm (log ε 4.18, 4.24, 4.17, and 3.80); ν_{max}(KBr) 1 655br, 1 628, 1 580br, 1 525, 1 505, 1 412, 1 386, 1 358, 1 260, 1 212, 796, 738, and 714 cm^{-1} (Found: *M*, 418.0290. $C_{23}H_{14}O_4S_2$ requires *M*, 418.0329).

This naphthofuranone (50 mg) in dichloromethane was passed down a column of alumina (as for earlier examples) giving an intensely yellow band that supplied 2-(2-*thienyl*)-3-(2-*thenoyl*)-9,10-*anthraquinone* (**38b**) as orange rods (48 mg, 92%), m.p. 200–204 °C (Found: *M*, 400.0212. $C_{23}H_{12}O_3S_2$ requires *M*, 400.0224). The impure material mentioned above was substantially identical with this compound.

Acknowledgements

We thank Dr B. E. Mann for the ^{13}C spectrum and for the ^1H spectra obtained at 400 MHz and for assistance with the interpretation of them. We thank Mr Kevin Murphy for the atomic absorption measurements.

References

1 Some of the material in this paper was outlined at the First Princess Science Congress, Bangkok, December, 1987.
2 W. Eisenmuth and H. Schmid, *Helv. Chim. Acta*, 1958, **41**, 2021; H. W. Ruelius and A. Gauhe, *Liebigs Ann. Chem.*, 1951, **570**, 121; Tsung-tee Li and R. H. Ellison, *J. Am. Chem. Soc.*, 1978, **100**, 6263; M. F. Semmelhack and A. Zask, *ibid.*, 1983, **105**, 2037; T. Kometani and E. Yoshi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1197.
3 M. F. Aldersley, F. M. Dean, and R. Nayyir-Mashir, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1753; M. F. Aldersley, F. M. Dean, and A. S. Hamzah, *Tetrahedron Lett.*, 1986, **27**, 255.
4 H. Maehr, C. M. Liu, M. Liu, A. Perrotta, J. M. Smallheer, T. H. Williams, and J. F. Blount, *J. Antibiot.*, 1982, **35**, 1627; M. Gordon, A. Stoessl, and J. B. Stothers, *Can. J. Chem.*, 1972, **50**, 122.
5 H. S. El Khadem (ed.), 'Anthracycline Antibiotics,' Academic Press, New York, 1982.
6 W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, 1970, **35**, 3144.
7 N. Jacobsen and K. Torsell, *Liebigs Ann. Chem.*, 1972, **763**, 135; N. Torsell, R. J. DeFranco, and R. E. Benson, *Org. Synth.*, 1977 **56**, 68.
8 P. H. Groggins, *Ind. Eng. Chem.*, 1930, **22**, 620; B. Bolus, *Synth. Commun.*, 1984, **14**, 391; V. Ya. Fain, *Reakts. Sposnobn. Org. Soedin.*, 1973, **10**, 945.
9 D. W. Cameron and P. M. Scott, *J. Chem. Soc.*, 1964, 5369; D. W. Cameron, P. J. Chalmers, and G. I. Feutrill, *Tetrahedron Lett.*, 1984, **25**, 6031; K. T. Finlay, in 'The Chemistry of the Quinonoid Compounds,' ed. S. Patai, Wiley, New York, 1974, ch. 17.
10 F. Kroehnke and W. Heffer, *Ber. Dtsch. Chem. Ges.*, 1937, **70**, 864, 937; V. S. Garkushg-Bozhko, R. O. Kochkanyan, O. P. Shvaika, and S. N. Baranov, *Khim. Geterotsikl. Soedin.*, 1976, 372.
11 R. H. Thomson, 'Naturally Occurring Quinones,' Academic Press, London, 1971.
12 T. Otohito, S. Kanemasa, and S. Takenata, *Heterocycles*, 1983, **20**, 1907.
13 C. Casegrande, A. Invernizzi, R. Ferrini, and G. Miragoli, *Farmaco. Ed. Sci.*, 1971, **26**, 1059.
14 J. K. M. Sanders and B. K. Hunter, 'Modern NMR Spectroscopy,' OUP, Oxford, 1987.
15 W. R. Roth and J. D. Meier, *Tetrahedron Lett.*, 1987, 2053; N. Morita, M. Oda, and T. Aso, *ibid.*, 1984, **25**, 5419; C. G. Pierpont and R. M. Buchanan, *Coord. Chem. Rev.*, 1981, **38**, 45; M. C. Depew and J. K. Wan, in 'The Chemistry of the Quinonoid Compounds,' ed. S. Patai and Z. Rappoport, Wiley, Chichester, 1988, vol. 2, ch. 16.
16 H. H. Inhoffen, K. Bruckner, G. F. Danagk, and H. M. Erdmann, *Chem. Ber.*, 1955, **88**, 1415.
17 G. T. Gmitter and F. L. Benton, *J. Am. Chem. Soc.*, 1950, **72**, 4586.

Paper 9/04753K
Received 6th *November* 1989
Accepted 11th *December* 1989