Photochemical Substitution of Methoxyanthraquinones with Amines and Other Nucleophiles

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1-Methoxyanthraquinone undergoes photochemical nucleophilic substitution with ammonia and primary aliphatic amines to give good yields of the 1-amino- or 1-alkylamino-anthraquinone. The reaction does not occur with secondary amines and primary arylamines. Photosubstitution is also observed with certain inorganic nucleophiles. 2-Methoxyanthraquinone is less reactive, but undergoes photochemical substitution with ammonia to give 2-amino- and 1-amino-2-methoxy-anthraquinone, the relative proportions depending on the availability of oxygen during the reaction. Less efficient photoreactions occur with primary aliphatic amines and inorganic nucleophiles. The synthetic implications of these reactions are discussed.

PHOTOCHEMICAL substitutions with nucleophilic species have been investigated for many aromatic compounds: there is often a marked difference between corresponding photochemical and thermal substitution reactions; *e.g.*, photochemical displacement of methoxide ion from the nitroanisoles by ammonia occurs most readily when the nitro-group is in the *meta* position, whereas the thermal process is activated by *ortho*- and *para*-nitro groups.[1] In general, photochemical nucleophilic substitution requires the presence of a strong electron withdrawing group attached to the aromatic ring (*e.g.* NO_2 or CN), or a ring heteroatom as in pyridine derivatives. The leaving group may be methoxide, halide, hydride, or even the electronegative group itself, but the reactions appear to be most specific and efficient when an electron donor and acceptor are both present in the molecule, as in the nitroanisoles.

These photosubstitution reactions follow complex pathways which depend on the nucleophile and the solvent used, and no satisfactory theoretical interpretation has yet been achieved, although qualitative valence bond arguments can account for many of the results.[2] A further complicating factor is the multiplicity of the excited state involved in photosubstitution, as this also appears to vary with the nature of the nucleophile.[3]

Photochemical nucleophilic substitution of quinones provides an interesting extension of these reactions, as the quinone carbonyl groups behave as electron acceptors, and consequently many substituted quinones show an appreciable reactivity towards thermal nucleophilic substitution. In the 9,10-anthraquinone series, substituents in positions 1—8 are *meta* to one of the carbonyl groups, and thus by analogy with benzene derivatives, photochemical nucleophilic displacement reactions might also be observable. Anthraquinonesulphonic acids react photochemcially with aqueous alkali,[4,5] water,[6] chloride ions,[7] and ammonia,[8] but in view of the complexity of the products often formed, the inhibiting effect of radical scavengers, or the detection of radical intermediates, these cannot be regarded as simple nucleophilic displacements. Formin *et al.* have shown that radical anion intermediates are involved in the photodesulphonation of anthraquinone-1-sulphonates in the presence of alcohols and amines.[9] The displacement of bromine ion from 1-amino-4-bromoanthraquinone-2-sulphonic acid by amines has been reported, but as oxygen appears to be essential for reaction, this may not be a true nucleophilic substitution.[10]

In a preliminary report,[11] photosubstitution of 1- and 2-methoxyanthraquinones with ammonia was described, and because of the insensitivity of these reactions to radical scavengers it appeared that these were the first examples of direct nucleophilic substitution from the excited state of an anthraquinone. These reactions have

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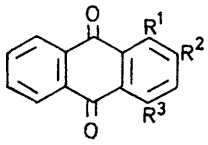
now been extended to include a wide range of amines and inorganic nucleophiles, and the synthetic applications are examined.

RESULTS AND DISCUSSION

Reactions of 1-Methoxyanthraquinone with Ammonia and Amines.—When solutions of 1-methoxyanthraquinone (Ia) (2×10^{-3}M) in 1 : 1 acetonitrile–water containing ammonia (7M) were exposed to Pyrex-filtered u.v. light, a rapid reaction ensued, accompanied by the conversion of the initially pale yellow solutions to a deep red. The



(I)

	R^1	R^2	R^3
a	MeO	H	H
b	H	MeO	H
c	NH_2	H	H
d	MeO	H	NH_2
e	NHMe	H	H
f	MeO	H	NHMe
g	NHEt	H	H
h	$NHPr^n$	H	H
i	$NHBu^i$	H	H
j	NHC_6H_{11}	H	H
k	$NHCH_2Ph$	H	H
l	$NH[CH_2]_2OH$	H	H
m	OH	H	H
n	MeO	H	Cl
o	H	NH_2	H
p	NH_2	MeO	H
q	H	NHMe	H
r	NHMe	MeO	H
s	H	OH	H

reaction proceeded equally well under air or nitrogen, to give the same two products (t.l.c.). The major red product, isolated in 96% yield, was identified as 1-aminoanthraquinone (Ic).* The second, violet component, formed in trace amounts only, was 1-amino-4-methoxyanthraquinone (Id). The rate of photosubstitution was unaffected by 2,6-di-t-butylphenol, an efficient radical scavenger.

As the thermal displacement of groups such as alkoxy and halogeno from 1-substituted anthraquinones by ammonia or amines generally requires severe reaction conditions, photochemical substitution appeared a promising route to 1-alkylamino- or 1-arylamino-anthraquinones, which are valuable as dyes or dye intermediates. To examine this possibility further, photosubstitution of (Ia) was attempted with several primary aliphatic amines. Although the reaction with ammonia was most conveniently carried out in aqueous acetonitrile, for other amines methylene chloride was more suitable. Liquid (at room temperature) amines were added directly to solutions of 1-methoxyanthraquinone in methylene chloride, while for gaseous amines the commercially available solutions in water or ethanol were used, adding sufficient methanol where necessary to give a homogeneous solution. In general the photosubstitution reactions gave identical results whether carried out under air or with nitrogen-saturated solutions.

With methylamine the reaction was rapid, and 1-methylaminoanthraquinone (Ie) was isolated in 81% yield. A violet crystalline compound was also obtained (7% yield) and shown to be 1-methylamino-4-methoxyanthraquinone (If). Thus substitution of (Ia) in the 4-position occurs rather more readily when methylamine is the nucleophile.

Increasing the size of the alkyl residue in the amine steadily decreased the efficiency of displacement of methoxide ion from (Ia) (Table 1) and the yield of the 1-alkylamino-derivative decreased from 96 to 59% in the series

TABLE 1

Photosubstitution of 1-methoxyanthraquinone (Ia) with amines and inorganic ions

Nucleophile	Substitution product [a]	Yield [b] (%)
NH_3	(Ic)	96
	(Id)	*ca.* 0·5
$MeNH_2$	(Ie)	81
	(If)	7
$EtNH_2$	(Ig)	69
Pr^nNH_2	(Ih)	73
Bu^iNH_2	(Ii)	67
Cyclo-$C_6H_{11}NH_2$	(Ij)	59
$PhCH_2NH_2$	(Ik)	52
$HOCH_2CH_2NH_2$	(Il)	36
HO^-	(Im)	84
NCO^-	(Ic)	87
Cl^-	(In)	7

[a] Authentic samples for comparison were either purified commercial samples, or were prepared by standard thermal substitution routes. Products were identified by comparison of i.r. spectra and mixed m.p. [b] Yields are quoted for isolated pure material.

NH_3, $MeNH_2$, $EtNH_2$, Pr^nNH_2, Bu^iNH_2, cyclo-$C_6H_{11}NH_2$. Since there is no great difference in nucleophilicity in this series, this is most probably a steric effect. Attack at position 1 in (Ia) by the amine would give a σ-complex with considerable steric crowding, and the size of the amine may significantly influence the rate of the first addition step: with bulkier amines, competing reactions may become important. In all cases, the substitutions provided small amounts of the corresponding 1-alkylamino-4-methoxyanthraquinone. Ethanolamine behaved normally, and afforded 1-(2-hydroxyethylamino)-anthraquinone (Il) in 36% yield, and no trace of the isomeric 1-(2-aminoethoxy)anthraquinone could be detected. This compound could arise by displacement of methoxide from (Ia) by the hydroxy-group of ethanolamine.

Diethylamine was used to examine the effect of increasing the nucleophilicity of the amine. Surprisingly, photosubstitution with this amine was very slow, and after prolonged reaction 1-dimethylaminoanthraquinone was the only tractable product (4% yield). A steric effect alone could not account for this dramatic decrease in reaction efficiency, and a competing reaction is probably inhibiting normal photosubstitution. A simi-

* Photoproducts were identified by i.r., m.p., and mixed m.p. comparison with authentic samples prepared by standard thermal routes.

lar decrease in reaction efficiency has been observed in the photoreaction of anthraquinonesulphonic acids with diethylamine.[8] Any such competing process must be reversible, as the consumption of (Ia) approximately corresponds to the amount of substitution product formed even after long reaction times. Other secondary amines, *e.g.* piperidine and pyrrolidine, showed the same apparent lack of reactivity.

Photosubstitution of (Ia) with primary arylamines was also unsuccessful, and steric inhibition was precluded as an explanation by the observation that benzylamine and cyclohexylamine, which have similar steric requirements to aniline, reacted normally (Table 1). The lower nucleophilicity of arylamines compared to the alkylamines may account for the difference in reactivity, but *p*-anisidine, which is appreciably more nucleophilic than aniline, also gave no detectable substitution products: a competing reaction, analogous to that suggested for secondary alkylamines, may also be occurring with arylamines. The mechanistic aspects of these substitution reactions and the anomalous behaviour of secondary alkylamines and primary arylamines will be discussed elsewhere. Inoue *et al.* found a similar lack of reactivity with arylamines in the photosubstitutions of 1-amino-4-bromoanthraquinone-2-sulphonic acid.[10] As a means of obtaining 1-arylaminoanthraquinones, the photochemical route is thus unsuccessful. However, these compounds can be prepared by a thermal reaction between the amine and the 1-alkoxy- or 1-halogeno-anthraquinone in the presence of a copper catalyst at *ca.* 200°.[12]

Reactions of 1-*Methoxyanthraquinone with Other Nucleophiles.*—In view of the efficiency of the photoreaction of (Ia) with primary aliphatic amines, other nucleophiles were examined to test the generality of the reaction (Table 1). In the presence of sodium hydroxide (0·6M), aqueous acetonitrile solutions of (Ia) reacted rapidly under air when irradiated to give 1-hydroxyanthraquinone (Im) (84%) yield. Whilst this work was in progress, Ahmed *et al.*[5] reported a similar photochemical reaction of (Ia) in oxygen-saturated aqueous propan-2-ol at high pH to give 1-hydroxyanthraquinone. Their mechanistic evidence suggested that the reaction did not proceed by direct substitution of an excited state of the quinone, but rather that the anthrasemiquinone radical anion, formed by hydrogen abstraction from propan-2-ol and subsequent deprotonation or by direct electron transfer from hydroxide ion, was involved in nucleophilic substitution. Presumably a similar mechanism could occur in aqueous acetonitrile.

The nitrite ion with (Ia) failed to give any trace of 1-nitroanthraquinone. This lack of reactivity is probably due to the filtering action of the nitrite ion towards u.v. light, as this ion absorbs strongly in the same region (300—400 nm) as the long wavelength absorption band of 1-methoxyanthraquinone. Reaction of (Ia) with chloride ions was also very slow, and surprisingly no 1-chloroanthraquinone was formed, the only tractable product being 1-methoxy-4-chloroanthraquinone (In), isolated in 7% yield.

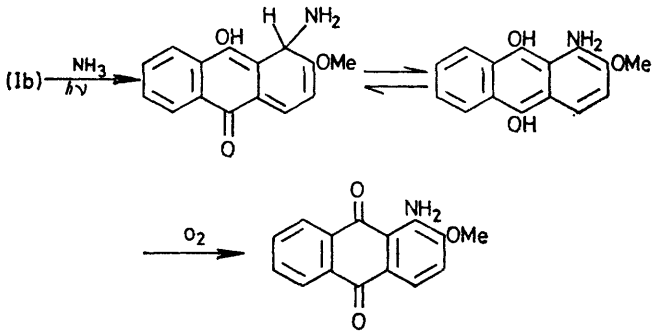
Photosubstitution with potassium cyanate was more efficient, proceeding rapidly to give an 87% yield of 1-aminoanthraquinone (Ic). This is presumably formed by hydrolysis of the intermediate 1-isocyanatoanthraquinone. Attempts to trap the isocyanate as a urethane by carrying out the photosubstitution in anhydrous methanol were unsuccessful, and again 1-aminoanthraquinone was the sole product. The isocyanate, or, more likely, the urethane, possibly suffers secondary photolysis during the reaction. With the more nucleophilic azide ion, which does not absorb in the region 300—400 nm, no substitution reactions with (Ia) could be detected, suggesting that, as with secondary alkylamines, a competing reversible photoreaction could be occurring. It may be significant that secondary amines and the azide ion readily take part in electron abstraction reactions.

Photochemical Substitution Reactions of 2-*Methoxyanthraquinone.*—Unlike the corresponding reaction of 1-methoxyanthraquinone, the photosubstitution of 2-methoxyanthraquinone (Ib) with ammonia was affected by the presence of oxygen. Solutions (2×10^{-3}M) of 2-methoxyanthraquinone in 1 : 1 acetonitrile–water reacted readily with dissolved ammonia (7M) when irradiated, as indicated by a deep red colouration. When solutions were degassed with nitrogen the rate of reaction was reduced, and after 30 min exposure, g.l.c. showed 35% unchanged starting material. A similar reaction under oxygen showed complete reaction after this time. Even in the latter case, however, the overall rate of reaction was considerably slower than for 1-methoxyanthraquinone. Column chromatography of the reaction mixture separated orange 2-aminoanthraquinone (Io), and red 1-amino-2-methoxyanthraquinone (Ip). For reactions carried out under air, g.l.c. showed that the mono- and di-substituted products were formed in 25 and 70% yields respectively. Under nitrogen the two components were formed in approximately equal amounts, whereas under oxygen there was a fourfold excess of the disubstituted derivative over 2-aminoanthraquinone. This involvement of oxygen suggests that either the reactions do not involve direct nucleophilic substitution of an excited state of the quinone, or that there is one or more competing reversible reaction which inhibits the direct substitution and which is affected by the presence of oxygen. A radical mechanism seems unlikely as the rate of reaction under air showed no retardation in the presence of 2,6-di-t-butylphenol, and in fact this additive led to higher overall yields of substitution products.

Formation of 1-amino-2-methoxyanthraquinone (Ip) parallels the formation of 1-amino-4-methoxyanthraquinone (Id) from (Ia), although the former is much more efficient. Both involve formal replacement of hydride by amide ion and a possible mechanism is shown in the Scheme. The *leuco*-compound formed according to this route would be oxidised to the observed 1,2-disubstituted anthraquinone by dissolved oxygen, in agreement with the observation that oxygen favours formation of the di-substituted product.

[12] *E.g.*, F. Ullmann and O. Fodor, *Annalen*, 1911, **380**, 317.

Reactions with primary aliphatic amines were less efficient than with ammonia (Table 2), and again oxygen



SCHEME

exerted an accelerating effect. The u.v. spectrum of the solution obtained by irradiating (Ib) under nitrogen in the presence of methylamine showed the rapid build-up of a colourless intermediate which absorbed strongly in the same region as the long wavelength absorption band of (Ib). At this stage the reaction virtually stopped. Reaction under oxygen showed very little of this colourless intermediate to be formed, and photosubstitution occurred more readily. The nature and role of the intermediate will be discussed elsewhere. In a typical reaction, irradiation of (Ib) in the presence of methylamine for 25 min under air gave 2-methylaminoanthraquinone (Iq) (4%) and 1-methylamino-2-methoxyanthraquinone (Ir) (34%), together with unchanged starting material (58%). Longer reaction times gave higher conversions of starting material but lower yields of the substitution products, presumably owing to intervention of secondary reactions. Analogous products were formed with benzylamine and cyclohexylamine, but again much less efficiently than with ammonia. As expected, photosubstitution of (Ib) with dimethylamine and aniline was unsuccessful.

TABLE 2

Photosubstitution of 2-methoxyanthraquinone (Ib) with amines and inorganic ions

Nucleophile	Product [a]	Yield (%)
NH_3	(Io)	25,[b] 22,[c] 12 [d]
	(Ip)	70,[b] 18,[c] 45 [d]
$MeNH_2$	(Iq)	4 [b]
	(Ir)	34 [b]
HO^-	(Is)	7 [e]
NCO^-	(Ip)	10 [e]

[a] See note *a*, Table 1. [b] Reaction under air; yields calculated from g.l.c. analysis. [c] Reaction under nitrogen; yields calculated from g.l.c. analysis. [d] Reaction under oxygen; yields calculated from g.l.c. analysis. [e] Reaction under air; isolated material.

2-Methoxyanthraquinone was relatively unreactive towards the various inorganic nucleophiles (Table 2). With hydroxide ion, 2-hydroxyanthraquinone (Is) was isolated in 7% yield, but no reaction occurred with chloride or azide ions. Cyanate ions gave 1-amino-2-methoxyanthraquinone (Ip) in low yield, but no trace of 2-aminoanthraquinone could be detected.

Synthetic Implications.—Photosubstitution of 1-methoxyanthraquinone to give 1-amino-derivatives is only applicable to primary aliphatic or alicyclic amines, and fails with secondary amines or primary arylamines. Thermal substitution of anthraquinones with good leaving groups in the 1-position is well known, but for displacement by amines, temperatures in excess of 150° are required, which causes difficulties with lower boiling and thermally sensitive amines: in these cases the photochemical method may be advantageous, as it proceeds efficiently at room temperature. Photosubstitution of (Ia) with inorganic nucleophiles, however, appears to offer no particular synthetic advantages.

In the 2-methoxy-series the photosubstitution reactions with amines are less efficient and two products are obtained. The 2-aminoanthraquinone is usually the minor component, and this approach is thus of little value for these derivatives, particularly as the thermal substitutions are more specific. However, the major component can be formed in reasonable yields, particularly under oxygen, and this might be a useful route to 1-alkylamino-2-methoxyanthraquinones since these derivatives are not easily accessible by conventional thermal reactions.

EXPERIMENTAL

G.l.c. analyses were carried out on a 5 ft column of 10% E30 on siliconised Diatomite C at 242°. Peak areas were related to absolute concentrations by calibration with standard solutions of the pure compounds.

In the photochemical reactions, solutions were sealed in Pyrex tubes under air, oxygen, or nitrogen, and were placed *ca.* 10 cm from a 500 W medium-pressure mercury lamp. The solutions were maintained at *ca.* 15 °C by water cooling.

Photoreaction of 1-Methoxyanthraquinone with Ammonia.—1-Methoxyanthraquinone (0·100 g, 0·42 mmol) in acetonitrile (100 ml) was treated with aqueous ammonia (*d* 0·880; 100 ml) and the mixture irradiated under air in the usual way. After 1 h g.l.c. analysis showed complete disappearance of starting material and the formation of 1-aminoanthraquinone. Ammonia and acetonitrile were removed under reduced pressure and the aqueous solution was extracted with methylene chloride. The dried and concentrated extracts were chromatographed over silica gel in benzene–methylene chloride, giving a deep yellow eluate, which on evaporation afforded 1-aminoanthraquinone (96%) as red crystals, m.p. 246—247°, identical by i.r., m.p., and mixed m.p. with an authentic sample. The column was eluted with methanol–methylene chloride to remove a purple fraction, which on evaporation gave a small amount of 1-amino-4-methoxyanthraquinone, identified by comparison with an authentic specimen.

Photosubstitution of 1-Methoxyanthraquinone with Amines.—Solutions of 1-methoxyanthraquinone (0·100 g, 0·42 mmol) in redistilled methylene chloride (100 ml) were treated with the appropriate amine (1·9 mmol). In the case of methylamine and dimethylamine, 25% solutions of the amines in water were used, and sufficient methanol was added to give a clear solution. With ethylamine a 25% ethanolic solution was used. All other amines were added as neat liquids. The solutions were sealed under air in Pyrex tubes and irradiated in the usual way for 40 min. The

solvent and excess of amine were removed under reduced pressure, and the residues chromatographed over silica gel in methylene chloride. The yields of the crystalline 1-alkylaminoanthraquinones are summarised in Table 1. Small amounts of the 1-alkylamino-4-methoxyanthraquinone were also obtained by elution of the column with methanol.

Photosubstitution of 1-*Methoxyanthraquinone with Inorganic Nucleophiles*.—Solutions of (Ia) (0·100 g, 0·42 mmol) in acetonitrile (50 ml) were treated with the appropriate inorganic salt (NaOH, 0·20 g; KOCN, 0·50 g; $NaNO_2$, 0·50 g; NaN_3, 0·50 g; NaCl, 0·50 g) and the minimum amount of water was added to give a clear solution. The solutions were irradiated in the usual way under air for periods of 1—2 h, and the course of the reaction was followed by t.l.c. or g.l.c. The acetonitrile was removed under reduced pressure and the residues extracted into methylene chloride. The concentrated extracts were examined by t.l.c. for the presence of substitution products. Where these were present, the mixture was separated by column chromatography over silica gel, using benzene–methylene chloride as eluant. The yields of products are given in Table 1.

Photoreaction of 2-*Methoxyanthraquinone with Ammonia*.—A solution of 2-methoxyanthraquinone (0·05 g) in acetonitrile (45 ml) was treated with aqueous ammonia (*d* 0·880; 45 ml) and sealed in a Pyrex tube under air. The solution was irradiated for 1 h, when g.l.c. showed that no starting material remained and that two main products were present, corresponding to 2-aminoanthraquinone (25%) and 1-amino-2-methoxyanthraquinone (70%). The acetonitrile and excess of ammonia were removed under reduced pressure, and the aqueous solution was extracted with methylene chloride. The dried, concentrated extracts were chromatographed over silica gel in methylene chloride, when two coloured bands were observed. The first, orange band eluted was 1-amino-2-methoxyanthraquinone, which formed red crystals, m.p. 221—222°, identical by i.r, m.p., and mixed m.p. with an authentic sample. The second, yellow band was eluted with methanol, to give 2-aminoanthraquinone.

Similar reactions were carried out with oxygen- or nitrogen-saturated solutions, and the relative yields of substitution products were determined by g.l.c.

Photoreactions of 2-*Methoxyanthraquinone with Amines and Inorganic Nucleophiles*.—Solutions of 2-methoxyanthraquinone (0·100 g, 0·42 mmol) in acetonitrile (100 ml) were treated with the appropriate amine or inorganic salt as described for 1-methoxyanthraquinone. The solutions were saturated with oxygen and sealed in Pyrex tubes. In the case of reactions with amines, irradiation was carried out for 25 min, as longer times did not give higher yields of tractable products, but increased the complexity of the reaction mixtures. Longer periods of irradiation were used for the inorganic salts. Products were separated by preparative t.l.c. on neutral alumina, using benzene as solvent. The products (Table 2) were identified by i.r. and m.p. comparison with authentic samples.

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