A Photochemical Reaction of 2-Acetyl-3-alkylamino-1,4-benzoquinones: Formation of Benzoxazoles [1]

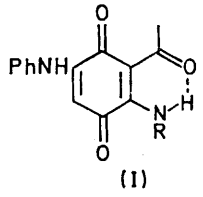
By **Robin G. F. Giles,* Peter R. K. Mitchell,** and **Gregory H. P. Roos,** Department of Chemistry, University of Cape Town, South Africa
Ian Baxter, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

A number of 2-acetyl-3-alkylamino-6-anilino-1,4-benzoquinones have been prepared by the reaction of 2-acetyl-3,6-dianilino-1,4-benzoquinone with alkylamines in chloroform solution. Irradiation of 3-methylamino-, 3-n-propylamino-, and 3-phenethylamino-2-acetyl-6-anilino-1,4-benzoquinones in solution gave benzoxazoles and 2-acetyl-3-amino-6-anilino-1,4-benzoquinone.

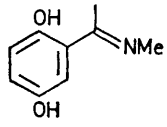
PHOTOISOMERISATION of 3,6-bisdialkylamino-*p*-xyloquinones in benzene solution is known to give rise to benzoxazolines.[2] However, related 3,6-bismonoalkylamino-*p*-xyloquinones fail to undergo photoreaction,[2] presumably because of an unfavourable spatial relationship between the *N*-alkyl group and the quinone carbonyl group preventing abstraction of a hydrogen radical. We now describe the synthesis and photochemistry of quinones of type (I) in which the *N*-alkyl group is held near to the quinone carbonyl group by means of a hydrogen bond between the NH group and the carbonyl of an acetyl group.

Compounds (Ib—j) were conveniently prepared from 2-acetyl-3,6-dianilino-1,4-benzoquinone (Ia) by amine exchange in chloroform solution. The reactions were essentially complete after a few minutes except in the case of t-butylamine which required a long reaction period, presumably because of increased steric hindrance. The synthesis of compounds (Ib and c) by a similar method has since been reported by other workers.[3] Attempts to replace the second anilino-residue by using a large excess of alkylamine and extended reaction times on both the dianilino-compound (Ia) and the monoalkylamino-derivatives failed. Treatment of the methylamino-quinone (Ib) with neat n-butylamine gave the quinone (Ii) by alkylamine exchange. The reaction of 2′,5′-dihydroxyacetophenone with methylamine in the presence of air failed to yield the known bismethylaminoquinone [4] (Ib; MeNH in place of PhNH) but gave instead the imine (II). The structure of this product was supported both by its spectroscopic properties and by its hydrolysis to 2′,5′-dihydroxyacetophenone. We also prepared imines from *o*-hydroxyacetophenone and methylamine and ammonia for comparison purposes. Schiff's bases derived from *o*-hydroxyaromatic ketones are known to possess considerable stability owing to intermolecular hydrogen bonding.[5]

The n.m.r. spectrum of compound (Ib) (detailed in the Experimental section) confirmed the gross structure and indicated the presence of a strongly hydrogen-bonded NH proton (τ −3·42). That it is the alkylamino NH which is so bonded was confirmed by the observation that spin-decoupling of this low-field signal caused the doublet at τ 6·44, assigned to the *N*-methyl group, to collapse to a singlet. Support for the supposition that this hydrogen bond is with the acetyl rather than with the quinone carbonyl group may be inferred from the course of the photoreactions discussed later. The use of

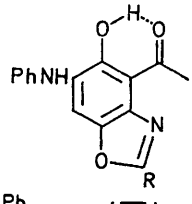


(I)



(II)

a; R = Ph
b; R = Me
c; R = H
d; R = Pr^n
e; R = CH_2CH_2Ph
f; R = cyclohexyl
g; R = CHMeEt
h; R = Bu^t
i; R = Bu^n
j; R = CH_2Ph



a; R = H
b; R = Et
c; R = CH_2Ph

(III)

i.r. spectroscopy to obtain evidence for hydrogen bonding to the acetyl group is limited because of uncertainties concerning the assignment of peaks in the 1650—1600 cm^{-1} region. Compounds of type (I), with the exception of (Ic), show a medium intensity absorption in the 1656—1640 cm^{-1} region which could be assigned to the acetyl carbonyl group, the frequency being lowered by hydrogen bonding and/or conjugation with the amino-substituent. However, it is known that there are considerable contributions by quadrupolar species to the structures of aminated benzoquinones which in this case could involve the acetyl group and thus lead to a lowering of the frequency of the carbonyl absorption.[4,6]

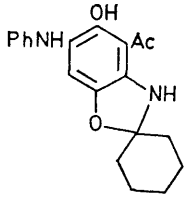
Irradiation of a solution of the quinone (Ib) in benzene gave the quinone (Ic) and the benzoxazole (IIIa) in 20 and 80% yields, respectively. The structure of the quinone (Ic) was deduced from spectral data and confirmed by synthesis from the quinone (Ia) and ammonia.

[1] Preliminary report, R. G. F. Giles, *Tetrahedron Letters*, 1972, 2253.
[2] D. W. Cameron and R. G. F. Giles, *J. Chem. Soc.* (*C*), 1968, 1461.
[3] W. Schäfer and A. Aguado, *Angew. Chem. Internat. Edn.*, 1971, **6**, 405.
[4] W. Schäfer and H. Schulde, *Tetrahedron Letters*, 1967, 4307.
[5] A. F. Al-Sayyab and A. Lawson, *J. Chem. Soc.* (*C*), 1968, 406.
[6] S. Dähne, J. Ranft, and H. Paul, *Tetrahedron Letters*, 1964, 3355; S. Dähne and D. Leupold, *Angew. Chem. Internat. Edn.*, 1966, **5**, 984; D. W. Cameron, R. G. F. Giles, and M. H. Pay, *Tetrahedron Letters*, 1970, 2047.

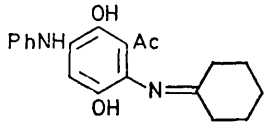
The structure of the oxazole (IIIa) was supported by its i.r. spectrum [$\nu_{max.}$ 3410 (NH), 3115 (oxazole CH), and 1630 cm^{-1} (H-bonded CO)] and its n.m.r. spectrum [τ 2·42 (7-H), 2·06 (2-H), and −3·67 (H-bonded OH)]. Catalytic reduction of the quinone (Ic) to the quinol followed by reaction with formalin yielded the benzoxazole (IIIa), thus confirming its structure. Irradiation of the quinones (Id and e) gave the benzoxazoles (IIIb and c), respectively, as well as the quinone (Ic).

Photolysis of the cyclohexylamino-compound (If) gave a photoproduct which was too unstable for characterisation but which decomposed to yield cyclohexanone and the quinone (Ic). The formation of these two products is consistent with the photoproduct being either the benzoxazoline (IV) (*cf.* ref. 2) or the imine (V). Photolysis of the s-butylamino-quinone (Ig) also gave a similarly unstable photo-product.

The photochemical formation of the benzoxazoles



(IV)



(V)

presumably involves intramolecular hydrogen abstraction by the excited quinone as the first step since if there are no α-hydrogen atoms in the alkylamino side-chain [as in (Ih)] no photoreaction is observed. Subsequently the diradical could lead to the benzoxazole either by hydrogen transfer, ring closure, and aromatisation, or *via* a spiroaziridine species [7] or loss of a hydrogen radical and formation of an imine of type (V), which may cyclise either photochemically [8] or thermally [9] to yield oxazoles.

The formation of the aminoquinone (Ic) may be due to hydrolysis of an intermediate by a trace of water in the organic solvent. Consistent with this view, photolysis of the quinone (Ib), when performed in benzene to which a small quantity of water had been added, gave the quinone (Ic) and the benzoxazole (IIIa). The yield of the former was significantly increased at the expense of that of the latter.

EXPERIMENTAL

Unless otherwise stated i.r. spectra were measured for Nujol mulls and n.m.r. spectra for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference. Chromatography was carried out using Merck Kieselgel (30—70 mesh).

2-Acetyl-3,6-dianilino-1,4-benzoquinone (Ia).—This was prepared by the method of Vorozhtsov and Marmaev [10] and also as follows. A mixture of 2′,5′-dihydroxyacetophenone (50 mg), aniline (130 mg), and silver carbonate (970 mg) in dry benzene (25 ml) was refluxed for 2 min and filtered; the solution was evaporated to dryness under reduced pressure. Recrystallisation from ethanol gave the quinone (60 mg), m.p. 200° (lit.,[10] 189·5—190°) (with darkening), $\nu_{max.}$ 3305, 1652, and 1631 cm^{-1}, τ 7·38 (s, Ac), 3·98 (s, CH=C), 3·0—2·6 (m, ArH), 1·82br (s, NH), and −3·75br (s, NH).

2-Acetyl-3-amino-6-anilino-1,4-benzoquinone (Ic).—To a stirred solution of the foregoing quinone (190 mg) in a mixture of chloroform (15 ml) and ethanol (10 ml) was added aqueous 5N-ammonium hydroxide (0·2 ml). After 30 min the resulting precipitate was collected and recrystallised from benzene to give the quinone (55 mg), m.p. *ca.* 280° (lit.,[3] 282°) (Found: C, 65·8; H, 4·9; N, 10·8. Calc. for $C_{14}H_{12}N_2O_3$: C, 65·6; H, 4·7; N, 10·9%), $\nu_{max.}$ 3300, 3240, 1645w,sh, 1610, and 1590 cm^{-1}; $\lambda_{max.}$ (EtOH) 247, 285, 317, and 437 nm (log ε 3·91, 3·92, 3·98, and 3·10).

Reaction of 2-Acetyl-3,6-dianilino-1,4-benzoquinone with Primary Amines.—(a) *Methylamine.* A mixture of the quinone (0·5 g), aqueous methylamine (33% w/w; 0·2 ml), and chloroform (30 ml) was stirred at room temperature for 5 min, washed with dilute hydrochloric acid, and evaporated to dryness. Recrystallisation of the residue from ethanol gave 2-acetyl-6-anilino-3-methylamino-1,4-benzoquinone (Ib) (0·4 g), m.p. 137° (lit.,[3] 138°) (Found: C, 66·6; H, 5·4; N, 10·3. Calc. for $C_{15}H_{14}N_2O_3$: C, 66·6; H, 5·2; N, 10·4%), $\nu_{max.}$ 3280, 1648, 1630, 1585, and 1510 cm^{-1}, $\lambda_{max.}$ (EtOH) 243, 295, 348, and 487 nm (log ε 3·95, 3·90, 4·01, and 2·96), τ 7·32 (s, Ac), 6·44 (d, *J* 6 Hz, NMe), 3·82 (s, CH=C), 2·7—2·4 (m, ArH), and 1·58br and −3·42br (2s, NH).

(b) *n-Propylamine.* A mixture of the quinone (0·66 g) and amine (0·12 g) in chloroform (20 ml) similarly gave *2-acetyl-6-anilino-3-n-propylamino-1,4-benzoquinone* (Id) (0·52 g), m.p. 145—146° (from ethanol) (Found: C, 68·8; H, 6·2; N, 9·4. $C_{17}H_{18}N_2O_3$ requires C, 68·4; H, 6·0; N, 9·4%), $\nu_{max.}$ 3258, 1643, and 1620 cm^{-1}, τ 8·9 (t, $CH_3{\cdot}CH_2{\cdot}CH_2$), 8·3 (m, $CH_3{\cdot}CH_2{\cdot}CH_2$), 7·38 (s, Ac), 6·08 (m, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}NH$), 3·94 (s, CH=C), 2·9—2·6 (m, ArH), and 1·78br (s, NH).

(c) *Phenethylamine.* A mixture of the quinone (0·45 g) and amine (0·33 g) similarly yielded *2-acetyl-6-anilino-3-phenethylamino-1,4-benzoquinone* (Ie) (0·46 g), m.p. 138° (from ethanol) (Found: C, 73·7; H, 5·2; N, 7·5. $C_{22}H_{20}N_2O_3$ requires C, 73·5; H, 5·6; N, 7·8%), τ 7·40 (s, Ac), 7·02 (t, $PhCH_2{\cdot}CH_2$), 5·8 (m, $CH_2{\cdot}CH_2{\cdot}NH$), 3·96 (s, CH=C), 3·0—2·4 (m, ArH), and 1·78 (s, NH).

(d) *Cyclohexylamine.* A mixture of the quinone (0·2 g) and amine (0·11 g) gave after 5 min *2-acetyl-6-anilino-3-cyclohexylamino-1,4-benzoquinone* (If) (0·16 g), m.p. 137—138° (from ethanol) (Found: C, 70·7; H, 6·5; N, 8·4. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·5; N, 8·3%), $\nu_{max.}$ 3300, 1635, and 1620 cm^{-1}, τ 8·8—8·0 (m, cyclohexyl CH_2), 7·38 (s, Ac), 6·20 (m, CH·N), 3·96 (s, CH=C), 2·9—2·5 (m, ArH), and 1·74br (s, NH).

(e) *2-Aminobutane.* A mixture of the quinone (0·75 g) and amine (0·2 g) gave *2-acetyl-6-anilino-3-(2-methylpropylamino)-1,4-benzoquinone* (Ig) (0·64 g), m.p. 120—121° (from ethanol) (Found: C, 69·4; H, 6·6; N, 9·0. $C_{18}H_{20}N_2O_3$ requires C, 69·3; H, 6·4; N, 9·0%).

[7] C. M. Orlando, H. Mark, A. K. Bose, and M. S. Manhas, *J. Org. Chem.*, 1968, **33**, 3512.
[8] K. H. Grellmann and E. Tauer, *Tetrahedron Letters*, 1967, 1909.
[9] *Cf.* I. Baxter and W. R. Phillips, *J.C.S. Chem. Comm.*, 1972, 78.
[10] N. N. Vorozhtsov and V. P. Marmaev, *Sbornik. Statei obshchei Khim., Akad. Nauk. S.S.S.R.*, 1953, **1**, 533 (*Chem. Abs.*, 1955, **49**, 925e).

(f) *t-Butylamine*. A mixture of the quinone (0·72 g) and amine (0·2 g) in chloroform (30 ml) was kept for 1 week and worked up as before to give 2-*acetyl*-6-*anilino*-3-*t-butylamino*-1,4-*benzoquinone* (Ih) (0·51 g), m.p. 151—152° (from ethanol) (Found: C, 69·2; H, 6·1; N, 9·1. $C_{18}H_{20}N_2O_3$ requires C, 69·3; H, 6·4; N, 9·0%), $\nu_{max.}$ 3310, 1656, and 1621 cm^{-1}, τ 8·44 (s, Bu^t), 7·37 (s, Ac), 3·92 (s, CH=C), 2·9—2·5 (m, ArH), 1·8br (s, NH), and —3·75br (s, NH).

(g) *n-Butylamine*. (i) A mixture of the quinone (0·6 g) and amine (0·135 g) gave 2-*acetyl*-6-*anilino*-3-*n-butylamino*-1,4-*benzoquinone* (Ii) (0·48 g), m.p. 113—114° (from ethanol) (Found: C, 69·4; H, 6·5; N, 8·9. $C_{18}H_{20}N_2O_3$ requires C, 69·3; H, 6·4; N, 9·0%), $\nu_{max.}$ 3287, 1643, and 1622 cm^{-1}.

(ii) A solution of the quinone (Ib) (40 mg) in freshly distilled n-butylamine (0·5 ml) was kept for 1 h and evaporated to dryness. Crystallisation of the residue gave the quinone (Ii) (30 mg), m.p. 113—114° (from ethanol).

(h) *Benzylamine*. A mixture of the quinone (0·4 g) and amine (0·25 g) yielded after 7 min 2-*acetyl*-6-*anilino*-3-*benzylamino*-1,4-*benzoquinone* (Ij) (0·39 g), m.p. 136—137° (from ethanol) (Found: C, 72·5; H, 5·5; N, 8·3. $C_{21}H_{18}N_2O_3$ requires C, 72·7; H, 5·2; N, 8·1%), $\nu_{max.}$ 3285, 1642, and 1616 cm^{-1}, τ 7·40 (s, Ac), 4·86 (d, J 6 Hz, CH_2·NH), 3·93 (s, CH=C), 2·9—2·6 (m, ArH), and 1·76br (s, NH).

Reaction between 2′,5′-Dihydroxyacetophenone and Methylamine.—Air was passed through a mixture of the acetophenone (2·00 g), 33% aqueous methylamine (5 ml), and ethanol (200 ml) for 5 h. The resulting precipitate was collected and recrystallised from ethanol to give 2-(1-*methyliminoethyl*)*hydroquinone* (II) (2·00 g), m.p. 273° (decomp.) (Found: C, 65·5; H, 6·8; N, 8·5. $C_9H_{11}NO_2$ requires C, 65·5; H, 6·6; N, 8·5%), $\nu_{max.}$ 2500—2400, 1647, and 1545 cm^{-1}, τ (CF_3·CO_2H) 7·06 (s, MeC=N), 6·24 (d, J 5 Hz, MeN$^+$), 2·70 (d, J 9 Hz, H-6), 2·47 (dd, J 9 and 3 Hz, H-5), and 2·28 (d, J 3 Hz, H-3).

The same product was obtained when air was not passed through the solution.

A solution of the foregoing imine (40 mg) in dilute hydrochloric acid (15 ml) was kept at 50° for 1 h and cooled. The resulting precipitate was collected and shown to be 2′,5′-dihydroxyacetophenone (30 mg), m.p. 202—203°, i.r. spectrum identical with that of an authentic sample.

Reaction between 2′-Hydroxyacetophenone and Methylamine.—A mixture of the acetophenone (2·83 g), aqueous methylamine (33% w/w; 7·5 ml), and ethanol (100 ml) was stirred at room temperature for 17 h and evaporated to dryness. The residue was sublimed at 0·01 mmHg to yield 2-(1-*methyliminoethyl*)*phenol* (2·75 g), m.p. 62—64° (Found: C, 72·3; H, 7·4; N, 8·9. $C_9H_{11}NO$ requires C, 72·5; H, 7·4; N, 9·4%), $\nu_{max.}$ 1620 and 1600 cm^{-1}, τ (CF_3·CO_2H) 6·94 (s, MeC=N), 6·14 (d, J 6 Hz, MeN$^+$), and 2·5—1·6 (m, ArH).

Reaction between 2′-Hydroxyacetophenone and Ammonia.—The reaction was carried out as in the preceding experiment, with aqueous 5N-ammonium hydroxide in place of aqueous methylamine, and gave 2-(1-*iminoethyl*)*phenol*, m.p. 139—140° (Found: C, 71·1; H, 6·7; N, 10·4. C_8H_9NO requires C, 71·1; H, 6·7; N, 10·2%), $\nu_{max.}$ 2700—2100, 1620, and 1600 cm^{-1}.

Photolysis of the Quinones (Ib and d—j).—All photolyses were carried out under nitrogen with a 450 W high-pressure Hanovia mercury vapour photoreactor and a Pyrex filter.

(a) *Quinone* (Ib). A solution of the quinone (0·120 g) in benzene (800 ml) was irradiated for 1 h, and evaporated under reduced pressure. The residue was chromatographed. Elution with benzene gave 4-*acetyl*-6-*anilinobenzoxazol*-5-*ol* (IIIa) (0·096 g), m.p. 132—133° (from ethanol) (Found: C, 66·9; H, 4·5; N, 10·1. $C_{15}H_{12}N_2O_3$ requires C, 67·2; H, 4·5; N, 10·4%), $\nu_{max.}$ 3410, 3115, and 1630 cm^{-1}, $\lambda_{max.}$ (EtOH) 276 and 410 nm (log ε 4·14 and 2·61), τ 6·92 (s, Ac), 3·5br (s, NH), 3·1—2·5 (m, PhN), 2·42 (s, ArH), 2·06 (s, CH=N), and —3·67 (s, OH). Elution with chloroform gave 2-acetyl-3-amino-6-anilino-1,4-benzoquinone (0·022 g), m.p. 284—286°, identical with product obtained earlier.

Repetition of this reaction with the quinone (0·083 g) in benzene (800 ml) containing water (0·5 ml) and 2 drops of hydrochloric acid gave, as before, the benzoxazole (IIIa) (0·018 g) and the quinone (Ic) (0·061 g).

(b) *Quinone* (Id). A suspension of the quinone (0·43 g) in cyclohexane (800 ml) was irradiated for 45 min, then evaporated to dryness. The residue was chromatographed. Elution with benzene gave 4-*acetyl*-6-*anilino*-2-*ethylbenzoxazol*-5-*ol* (IIIb) (0·19 g), m.p. 143—144° (from ethanol) (Found: C, 68·8; H, 5·7; N, 9·4. $C_{17}H_{16}N_2O_3$ requires C, 68·9; H, 5·4; N, 9·4%), $\nu_{max.}$ 3420, 1628, and 1603 cm^{-1}, τ 8·57 (t, J 7 Hz, CH_3·CH_2), 7·06 (q, J 7 Hz, CH_3·CH_2), 6·92 (s, Ac), 3·75br (s, NH), 3·0—2·6 (m, PhN), 2·44 (s, ArH), and —3·45 (s, OH). Further elution with chloroform gave a coloured fraction which was rechromatographed to yield the starting quinone (0·04 g), and 2-acetyl-3-amino-6-anilino-1,4-benzoquinone (Ic) (0·07 g), m.p. *ca.* 280°.

(c) *Quinone* (Ie). A solution of the quinone (0·35 g) in benzene (800 ml) was similarly irradiated for 45 min and evaporated to dryness. The residue was chromatographed. Elution with benzene gave 4-*acetyl*-6-*anilino*-2-*benzylbenzoxazol*-5-*ol* (IIIc) (0·13 g), m.p. 131—132° (from ethanol) (Found: C, 73·6; H, 5·1; N, 8·1. $C_{22}H_{18}N_2O_3$ requires C, 73·8; H, 5·0; N, 7·8%), $\nu_{max.}$ 3405, 1630, and 1604 cm^{-1}, τ 6·95 (s, Ac), 4·78 (s, CH_2Ph), 3·68br (s, NH), 3·1—2·6 (m, ArH), 2·49 (s, ArH), and —3·50 (s, OH). Further elution with chloroform gave 2-acetyl-3-amino-6-anilino-1,4-benzoquinone (0·07 g).

Quinone (If). A solution of the quinone (0·35 g) in dry ether (800 ml) was irradiated for 35 min. The photoproduct was too unstable for isolation. The solution was concentrated under reduced pressure and the last traces of solvent were removed in a stream of nitrogen. Aqueous 10% sulphuric acid (140 ml) was added and resulting solution distilled at constant volume into a saturated solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid. When 80 ml of distillate had been collected, the precipitate (0·15 g) was removed and recrystallised from ethanol to give cyclohexanone 2,4-dinitrophenylhydrazone (0·115 g), m.p. 157—158°, identical with an authentic sample. No product was isolated from the aqueous residue of the distillation.

From another reaction in which the irradiated solution was kept in the air for several days, 2-acetyl-3-amino-6-anilino-1,4-benzoquinone (0·09 g) was obtained by filtration.

4-*Acetyl*-6-*anilinobenzoxazol*-5-*ol* (IIIa).—A solution of 2-acetyl-3-amino-6-anilino-1,4-benzoquinone (0·424 g) in benzene (70 ml) was stirred with pre-reduced Adams catalyst in hydrogen until 1 equiv. of hydrogen had been absorbed. A solution of aqueous formaldehyde (40%; 4 ml) in ethanol (10 ml) was added and the mixture was stirred overnight, filtered, and evaporated to dryness. Chromatography of the residue and elution with benzene

gave the benzoxazole (0·165 g), m.p. 128—129°, identical with material obtained earlier.

Financial support from the Council of the University of Cape Town and the South African Council for Scientific and Industrial Research is acknowledged. One of us (G. H. P. R.) thanks the C.S.I.R. for a Student Bursary. We are indebted to Mr. I. B. Finter for determination of the n.m.r. spectra.

[2/2124 *Received*, 11*th September*, 1972]