Ring Opening of Aziridin-1-yl-quinones

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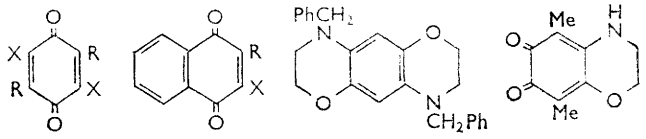
Certain aziridin-1-yl-quinones are converted by the action of sodium iodide and aluminium halides into 2-halogenoethylamino-quinones. The behaviour of the latter on catalytic reduction has been studied. The reaction of 3,6-diaziridin-1-yl-*p*-xyloquinone with concentrated sulphuric acid is reported.

ISOMERISATION of aziridine derivatives has found application in the synthesis of a number of heterocyclic systems.[1] Catalysts which have been employed include mineral acid, sodium iodide, and aluminium halides. In view of the recently reported isomerisation of *N*-(3-oxo-2-phenylcyclohexenyl)aziridine to a hexahydroindole [2] we have investigated the isomerisation of several aziridin-1-yl-quinones in an attempt to prepare benzodipyrrole derivatives.

Treatment of the quinone (I; R = H, X = aziridin-1-yl) with sodium iodide in acetone gave an iodine-containing quinone formulated as (I; R = H, X = $NH{\cdot}CH_2{\cdot}CH_2I$). Its i.r. spectrum indicated the presence of both an NH group and a quinonoid nucleus. The n.m.r. spectrum (trifluoroacetic acid) showed, in addition to a singlet at τ 3·82 assigned to the quinonoid protons, two triplets at τ 5·93 and 6·51 associated with

[1] H. W. Heine, *Angew. Chem. Internat. Edn.*, 1962, **1**, 528.
[2] H. W. Whitlock and G. L. Smith, *J. Amer. Chem. Soc.*, 1967, **89**, 3600.

two adjacent methylene groups. Moreover on catalytic reduction the compound was converted into 2,5-bisethylamino-1,4-benzoquinone. No indolic material could be detected even when the reaction was performed in acetone under reflux or in diethylene glycol dimethyl



(I) (II) (III) (IV)

ether at 140°. Similarly, treatment of the naphthoquinone (II; R = H, X = aziridin-1-yl) with sodium iodide in 1,2-dimethoxyethane at room temperature gave the iodo-quinone (II; R = H, X = NH·CH_2·CH_2I) in 83% yield. Catalytic reduction of the latter gave, after aerial reoxidation of the intermediate quinol, 2-ethylamino-1,4-naphthoquinone, identical with samples obtained by catalytic reduction of quinone (II; R = H, X = aziridin-1-yl) and by amination of 1,4-naphthoquinone.

Aluminium chloride in chloroform (*cf.* ref. 3) converted quinone (I; R = H, X = aziridin-1-yl) into the dichloro-compound (I; R = H, X = NH·CH_2·CH_2Cl) and likewise the dibromo-compound (I; R = H, X = NH·CH_2·CH_2Br) was obtained by the action of aluminium tribromide. The dichloro-compound (I; R = H, X = NH·CH_2·CH_2Cl) has been obtained previously by reaction of quinone (I; R = H, X = aziridin-1-yl) with hydrogen chloride in dimethylformamide.[4] Catalytic reduction of the chloro- and bromo-compounds (I; R = H, X = NH·CH_2·CH_2Cl or NH·CH_2·CH_2Br) under neutral conditions did not cause cleavage of the carbon–halogen bond but simply produced the hydroquinones, which on exposure to air were reoxidised to the quinones. Treatment of the hydroquinone derived from compound (I; R = H, X = NH·CH_2·CH_2Cl) with benzyl bromide and aqueous potassium hydroxide *in situ* led to a halogen-free compound, formulated as the bisoxazine (III). Its i.r. spectrum showed no NH or OH absorption while its n.m.r. spectrum exhibited resonances assignable to aromatic protons and methylene groups only. The formation of compound (III) must involve displacement of chloride ion from the side-chain by phenoxide ion followed by benzylation.

Attempted isomerisation of the *p*-xyloquinone derivative (I; R = Me, X = aziridin-1-yl) with aluminium chloride resulted in a high yield of the dichloro-compound (I; R = Me, X = NH·CH_2·CH_2Cl). However, sodium iodide under a variety of conditions converted quinone (I; R = Me, X = aziridin-1-yl) into a complex mixture from which no pure material could be obtained. The naphthoquinone (II; R = Ph, X = aziridin-1-yl), prepared by amination of 2-phenyl-1,4-naphthoquinone, also yielded an inseparable mixture of materials with sodium iodide.

Treatment of the quinone (I; R = Me, X = aziridin-1-yl) with cold concentrated sulphuric acid (*cf.* ref. 5) led to the formation of some 2,5-dihydroxy-3,6-dimethyl-1,4-benzoquinone and the quinone (IV). The i.r. spectrum of the latter confirmed the presence of either an NH or OH group as well as a quinonoid nucleus, while the n.m.r. ($CDCl_3$) showed two three-proton singlets assigned to methyl groups in slightly different environments and a four-proton multiplet at τ 5·9 assigned to two adjacent methylene groups. The latter signal was resolved into two triplets when the spectrum was recorded for a solution in trifluoroacetic acid. Compound (IV) was also synthesised by treatment of 2-hydroxy-5-(2-hydroxyethylamino)-3,6-dimethyl-1,4-benzoquinone with sulphuric acid. It was also obtained by acid treatment of the quinone (I; R = Me, X = NH·CH_2·CH_2OH).

The quinone (I; R = Me, X = aziridin-1-yl) was readily converted by piperidine into the dipiperidino-compound (I; R = Me, X = NH·CH_2·CH_2·N[CH_2]$_5$).

EXPERIMENTAL

I.r. spectra were measured for Nujol mulls and u.v. and visible spectra for solutions in 95% ethanol. N.m.r. spectra were recorded at either 60 or 100 Mc./sec. All integrations were consistent with structural assignments.

2,5-*Bis*-(2-*iodoethylamino*)-1,4-*benzoquinone* (I; R = H, X = NH·CH_2·CH_2I).—To a solution of 2,5-diaziridin-1-yl-*p*-benzoquinone [6] (113 mg.) in dry acetone (35 ml.) was added sodium iodide (640 mg.) in acetone (35 ml.), and the mixture was kept at room temperature for 2 hr. It developed a mauve colour ($\lambda_{max.}$ 520 mμ) which slowly changed to pink ($\lambda_{max.}$ 495 mμ). The solvent was evaporated off and the residue was thoroughly extracted with hot chloroform. Concentration of the extract gave the *iodo-quinone* (61 mg.), m.p. 186° (decomp.) (from chloroform) (Found: C, 27·2; H, 2·8; N, 6·2. $C_{10}H_{12}I_2N_2O_2$ requires C, 26·9; H, 2·7; N, 6·3%; M^+ at *m/e* 446), $\lambda_{max.}$ 342 and 495 mμ (log ε 4·48 and 2·49), $\nu_{max.}$ 3285, 1635, and 1577 cm.$^{-1}$, τ (CF_3CO_2H) 3·82 (s, quinone H), 5·93 (t, *J* 6 c./sec., N·CH_2), and 6·51 (t, *J* 6 c./sec., CH_2I).

2-(2-*Iodoethylamino*)-1,4-*naphthoquinone* (II; R = H, X = NH·CH_2·CH_2I).—A mixture of 2-aziridin-1-yl-1,4-naphthoquinone [6] (25 mg.) and sodium iodide (38 mg.) in dry 1,2-dimethoxyethane (40 ml.) was kept at room temperature under nitrogen for 30 min. Evaporation of the solvent left a mauve residue which was washed with a little water, dried, and chromatographed on silicic acid. Elution with benzene gave the *iodo-quinone* (34 mg.), m.p. 189—190° (from benzene) (Found: C, 44·5; H, 3·5; N, 4·0. $C_{12}H_{10}INO_2$ requires C, 44·1, H, 3·1, N, 4·3%; M^+ at *m/e* 327), $\lambda_{max.}$ 218, 269, 330, and 447 mμ (log ε 4·23, 4·40, 3·42, and 3·57), λ_{infl} 232 mμ (log ε 4·18), $\nu_{max.}$ 3255, 1683, 1636, 1618, and 1602 cm.$^{-1}$, τ (CF_3CO_2H) 1·8–2·4 (complex, ArH), 3·8br (NH), 4·22 (s, quinone H), and 6·4 and 6·66 (triplets CH_2·CH_2).

2,5-*Bisethylamino*-1,4-*benzoquinone*.—The quinone (I;

[3] H. W. Heine and Z. Procter, *J. Org. Chem.*, 1958, **23**, 1554.
[4] W. Gauss, S. Petersen, and G. Domagk, G.P. 1,030,838 (*Chem. Abs.*, 1960, **54**, 22,498).
[5] H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Amer. Chem. Soc.*, 1959, **81**, 2202.
[6] A. Marxer, *Helv. Chim. Acta*, 1955, **38**, 1473.

R = H, X = NH·CH_2·CH_2I) (60 mg.) was shaken under hydrogen with Adams catalyst in methanol (50 ml.) containing potassium hydroxide (50 mg.). The catalyst was removed, the mixture was diluted with water, and the methanol was removed under reduced pressure. The aqueous solution was extracted with dichloromethane; evaporation of the extract left a residue which gave the bisethylaminoquinone (18 mg.), m.p. and mixed m.p.[7] 208° (from ethanol), τ ($CDCl_3$) 4·66 (s, quinone H), 6·77 (m, N·CH_2), and 8·70 (t, *J* 7 c./sec., Me).

2-*Ethylamino*-1,4-*naphthoquinone*.—(*a*) The iodo-quinone (II; R = H, X = NH·CH_2·CH_2I) (25 mg.) was hydrogenated over Adams catalyst (10 mg.) in methanol (40 ml.) containing potassium hydroxide (40 mg.) as already described. The product (8 mg.) had m.p. and mixed m.p.[8] 139°, $\lambda_{max.}$ 232, 271, 330, and 454 mμ (log ε 4·20, 4·37, 3·42, and 3·56), $\nu_{max.}$ 3320, 1670, 1640, and 1605 cm.$^{-1}$.

(*b*) The quinone (II; R = H, X = aziridin-1-yl) (25 mg.) was hydrogenated over Adams catalyst (10 mg.) as already described and gave the product (16 mg.), m.p. and mixed m.p. 139° (from ethanol).

2,5-*Bis*-(2-*chloroethylamino*)-1,4-*benzoquinone* (I; R = H, X = NH·CH_2·CH_2Cl).—A mixture of the quinone (1; R = H, X = aziridin-1-yl) (200 mg.) and powdered aluminium chloride (800 mg.) in chloroform (45 ml.) was stirred at 30—40° for 1 hr. The excess of aluminium chloride was hydrolysed with dilute hydrochloric acid. Sufficient dimethylformamide was added to dissolve the product and the organic phase was collected and evaporated to dryness. The residue gave the *chloro-compound* (242 mg.), m.p. 227—228° (from ethanol) (lit.,[4] 212°) (Found: C, 45·9; H, 4·8; N, 10·3. $C_{10}H_{12}Cl_2N_2O_2$ requires C, 45·6; H, 4·6; N, 10·6%), $\lambda_{max.}$ 338 and 490 mμ (log ε 4·47 and 2·51), $\nu_{max.}$ 3270, 1641, and 1550 cm.$^{-1}$, τ (CF_3CO_2H) 3·76 (s, quinone H) and 6·01 (m, N·CH_2·CH_2Cl).

2,5-*Bis*-(2-*bromoethylamino*)-1,4-*benzoquinone* (I; R = H, X = NH·CH_2CH_2Br).—Prepared as already described by use of aluminium bromide instead of aluminium chloride. The *bromo-quinone* (65%) had m.p. 198° (decomp.) (Found: N, 7·7. $C_{10}H_{12}Br_2N_2O_2$ requires N, 7·9%), $\nu_{max.}$ 3342, 1640, 1620, and 1563 cm.$^{-1}$, τ (CF_3CO_2H) 3·77 (s, quinone H), 5·88 (t, *J* 6 c/sec., N·CH_2), and 6·27 (t, *J* 6 c/sec., CH_2Br).

4,9-*Dibenzyl*-2,3,7,8-*tetrahydro*-4H,9H-*benzo*[1,2-b : 4,5b']-*bis*[1,4]*oxazine* (III).—2,5-Bis-(2-chloroethylamino)-1,4-benzoquinone (225 mg.) was reduced over Adams catalyst (40 mg.) in dimethylformamide (20 ml.) in the usual way. A solution of potassium hydroxide (175 mg.) in water (25 ml.), previously flushed with hydrogen, was added, followed by benzyl bromide (0·24 ml.) and the whole was stirred for 1 hr. The white crystals which were deposited were collected, dissolved in ether and filtered through Hyflosupercel. Evaporation of the ether gave the *bis-oxazine* (155 mg.), m.p. 159—160° (from propan-2-ol) (Found: C, 77·0; H, 6·5; N, 7·7. $C_{24}H_{24}N_2O_2$ requires C, 77·4; H, 6·5, N, 7·5%; M^+ at *m/e* 372), $\lambda_{max.}$ 260 and 333 mμ (log ε 3·89 and 3·84), τ ($CDCl_3$) 2·72 (s, ArH), 3·72 (s, PhCH_2N), and 5·82 (m, O·CH_2·CH_2·N).

2,5-*Bis*-(2-*chloroethylamino*)-3,6-*dimethyl*-1,4-*benzoquinone* (I; R = Me, X = NH·CH_2·CH_2Cl).—A mixture of 2,5-diaziridin-1-yl-3,6-dimethyl-1,4-benzoquinone [9] (200 mg.) and aluminium chloride (800 mg.) in chloroform was stirred for 1 hr. at room temperature. Dilute hydrochloric acid was added and the organic phase was collected, dried (Na_2SO_4), and evaporated to dryness. Crystallisation of the residue from benzene gave the *chloro-compound* (210 mg.), m.p. 189—190° (Found: C, 49·6; H, 5·5; N, 9·5. $C_{12}H_{16}Cl_2N_2O_2$ requires C, 49·5; H, 5·6; N, 9·6%, $\lambda_{max.}$ 347 and 520 mμ (log ε 4·13 and 2·16), $\nu_{max.}$ 3250, 1640, and 1590 cm.$^{-1}$, τ (CF_3CO_2H) 5·85 and 6·22 (2 triplets, N·CH_2·CH_2Cl) and 7·83 (s, Me).

2-*Aziridin*-1-*yl*-3-*phenyl*-1,4-*naphthoquinone* (II; R = Ph, X = aziridin-1-yl).—Aziridine (1·0 ml.) was added to a solution of 2-phenyl-1,4-naphthoquinone [10] (0·85 g.) in ethanol (200 ml.) and the mixture was kept overnight. Evaporation of the solvent and recrystallisation of the residue from ethanol (×3) gave the *quinone* (0·4 g.), m.p. 170—171° (Found: C, 78·1; H, 5·0; N, 5·4. $C_{18}H_{13}NO_2$ requires C, 78·5; H, 4·8; N, 5·1%), $\lambda_{max.}$ 261 and 420 mμ (log ε 4·28 and 3·34), λ_{infl} 366 mμ (log ε 3·56), τ ($CDCl_3$ 1·8—2·2 (m, ArH), 2·55 (s, Ph), and 7·94 (s, N·CH_2).

Action of Concentrated Sulphuric Acid on Quinone (I; R = Me, X = aziridin-1-yl).—A solution of quinone (120 mg.) in sulphuric acid (3 ml.) was stirred at room temperature for 30 min. and then poured on to ice–water. The product was extracted with dichloromethane; the extract was dried (Na_2SO_4) and gave 2,5-dihydroxy-3,6-dimethylbenzoquinone (15 mg.), m.p. and mixed m.p. 245° (lit.,[11] 245°), $\nu_{max.}$ 3300 and 1615 cm.$^{-1}$. The aqueous solution was neutralised with ammonium hydroxide and extracted with a large volume of dichloromethane. The dried extract (Na_2SO_4) was evaporated to dryness under reduced pressure (no heat) to give a purple coloured solid which was immediately disssolved in a small volume of benzene and chromatographed on SilicAR CC-7. Elution with chloroform gave a purple solid, which (from benzene) gave 2,3-*dihydro*-5,8-*dimethyl*-1,4-*benzoxazine*-6,7-*quinone* (IV) (60 mg.), m.p. 173—174° (Found: C, 61·7; H, 5·6; N, 7·4. $C_{10}H_{11}NO_3$ requires C, 62·1; H, 5·7; N, 7·2%; M^+ at *m/e* 193), $\lambda_{max.}$ 302 and 560 mμ (log ε 4·11 and 3·07), $\nu_{max.}$ 3150, 1655, and 1635 cm.$^{-1}$, τ ($CDCl_3$) 5·9 (m, CH_2·CH_2) and 8·0 and 8·15 (each s, Me), τ (CF_3CO_2H) 5·41 and 5·86 (2 triplets, *J* 5 c/sec., CH_2·CH_2) and 7·86 and 7·94 (each s, Me).

If the crude purple solid was kept at room temperature or heated in dichloromethane solution, it decomposed into a number of compounds (t.l.c). This instability may be due to the presence of base, because, although pure compound (IV) is stable both in the solid phase and in solution, it decomposes in the presence of aqueous ammonium hydroxide.

Compound (IV) (15 mg.) was also obtained from the quinone (I; R = Me, X = NH·CH_2·CH_2·OH) (50 mg.) and sulphuric acid (1 ml.) by the procedure just outlined.

2,5-*Bis*-(2-*hydroxyethylamino*)-3,6-*dimethyl*-1,4-*benzoquinone* (I; R = Me, X = NH·CH_2·CH_2·OH).—A mixture of *p*-xyloquinone (100 mg.) and 2-aminoethanol (0·25 ml.) in ethanol (30 ml.) was kept in the dark for 3 hr. Evaporation left a residue which gave the *quinone* (80 mg.), m.p. 212—213° (from ethanol) (Found: C, 56·5; H, 7·1; N, 10·8. $C_{12}H_{18}N_2O_4$ requires C, 56·7; H, 7·1; N, 11·0%), $\lambda_{max.}$ 222, 350, and 535 mμ (log ε 4·06, 4·11, and 2·70), $\lambda_{max.}$ 3400, 3250, and 1635 cm.$^{-1}$, τ (CD_3·SO·CD_3) 6·43 (s, CH_2·CH_2) and 8·03 (s, Me).

2-*Hydroxy*-5-(2-*hydroxyethylamino*)-3,6-*dimethyl*-1,4-*benzoquinone*.—To a solution of 2-aminoethanol (0·3 g.) in ether

[7] R. N. Harger, *J. Amer. Chem. Soc.*, 1924, **46**, 2540.
[8] T. Zincke, *Ber.*, 1879, **12**, 1641.
[9] D. W. Cameron and R. G. F. Giles, *J. Chem. Soc.* (*C*), 1968, 1461.
[10] T. Zincke and A. Breuer, *Annalen*, 1884, **226**, 23.
[11] F. Fichter and A. Willmann, *Ber.*, 1904, **37**, 2384.

(30 ml.) was added during 5 min. a solution of 3-hydroxy-2,5-dimethyl-1,4-benzoquinone [12] (0·3 g.) in ether (30 ml.). The solution turned purple and a sticky solid was deposited. The ether was decanted after 2 hr. and the residue gave the 2-*aminoethanol salt* of the quinone (0·3 g.), m.p. 161—162° (from methanol) (Found: C, 52·5; H, 7·4; N, 10·5. $C_{12}H_{20}N_2O_5$ requires C, 52·9; H, 7·4; N, 10·3%), $\nu_{max.}$ 3320 and 3240 cm.$^{-1}$.

The salt (0·11 g.) was dissolved in water (2 ml.) and the solution was acidified with dilute hydrochloric acid. The precipitate so formed was recrystallised from a large volume of methanol to give the *quinone* (0·06 g.), m.p. 167—168° (Found: C, 56·5; H, 6·1; N, 6·9. $C_{10}H_{13}NO_4$ requires C, 56·8; H, 6·2; N, 6·6%), $\lambda_{max.}$ 314 and 530 mμ (log ε 4·26 and 3·15), $\nu_{max.}$ 3420, 3260, 1642, and 1605 cm.$^{-1}$.

The quinone (50 mg.) was dissolved in concentrated sulphuric acid (1 ml.). The solution was kept at room temperature for 30 min. then poured into water, neutralised with ammonium hydroxide, and extracted with dichloromethane. The dried extract (Na_2SO_4) was evaporated to dryness (no heat) and the residue was chromatographed on SilicARCC-7 in chloroform to give compound (IV) (30 mg.), m.p. and mixed m.p. 173—174°.

2,5-*Dimethyl*-3,6-*bis*-(2-*piperidinoethylamino*)-1,4-*benzoquinone* (I; R = Me, X = NH·CH_2·CH_2·N[CH_2]$_5$).—A solution of 2,5-diaziridin-1-yl-3,6-dimethyl-1,4-benzoquinone (100 mg.) in piperidine (2 ml.) was heated on a steam-bath for 2 hr. and evaporated to dryness. The residue gave the *quinone* (120 mg.), m.p. 149—150° (from methanol) (Found: C, 67·8; H, 9·6; N, 14·4. $C_{22}H_{36}N_4O_2$ requires C, 68·0; H, 9·4; N, 14·4%), $\lambda_{max.}$ 221, 353, and 535 mμ (log ε 4·41, 4·39, and 2·12), $\nu_{max.}$ 3230 and 1635 cm.$^{-1}$, τ ($CDCl_3$) 2·8br (NH), 6·38 (m, N·CH_2), 7·45 (t, J 6 c/sec., CH_2·CH_2·N), 7·59 (m, piperidino CH_2·N), 7·94 (s, Me), and 8·5br (m, piperidino CH_2).

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[12] R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 1951, 2029.