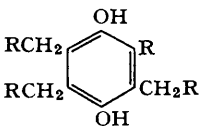
1066. *Facile Loss of C-Methyl Groups during the Amination of Quinones.*

By D. W. Cameron and P. M. Scott.

Methyl-substituted quinones can react with amines at room temperature with the apparent displacement of a methyl by an amino-group. *o*-Xyloquinone, for example, with methylamine gives 2-methyl-3,6-bismethylamino-1,4-benzoquinone in 39% yield. A number of related reactions are described and their possible course discussed. The process is probably general with respect to amine but for practical reasons is more likely to be observed with methylamine than, *e.g.*, with piperidine.

Quinones readily undergo nucleophilic attack by primary or secondary aliphatic amines to yield amino-derivatives. Reaction may proceed by direct 1,4-addition of amine to the quinone followed by oxidation of the intermediate amino-quinol as in the conversion of 1,4-benzoquinone into 2,5-diaminated derivatives, or it may involve nucleophilic displacement of substituents (*e.g.*, halogen, alkoxyl) attached to the quinone nucleus. When, however, the quinone is substituted by alkyl groups, a different mode of reaction may ensue, with amination occurring on the side-chain[1] to yield aminomethylquinols.

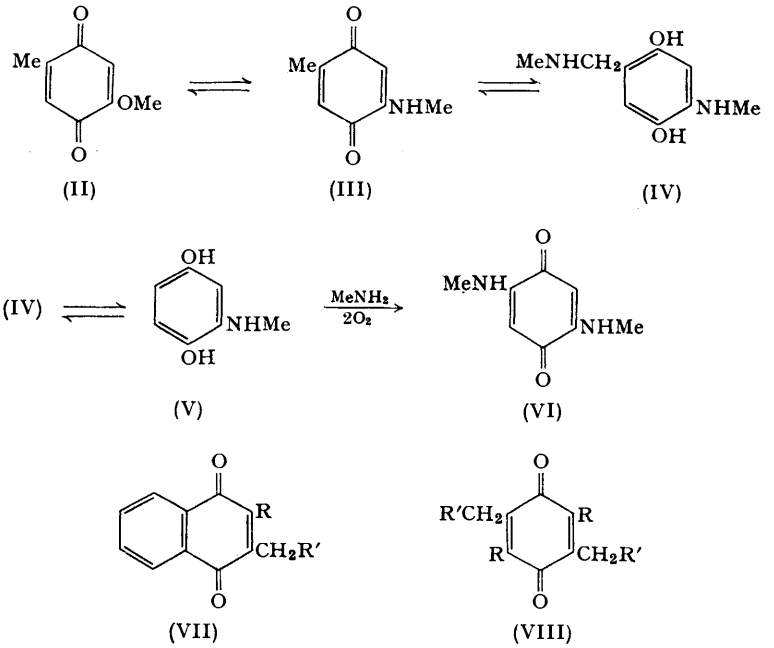


(I)

For 1,4-benzoquinones partly substituted by alkyl groups, nuclear and side-chain amination are competing processes and in some cases the product corresponds to the occurrence of both during the reaction, *e.g.* trimethyl-1,4-benzoquinone is readily converted into compound (I; R = piperidino).[1] However, toluquinone and *p*-xyloquinone react with ethanolic methylamine to yield the corresponding products of nuclear amination only, *viz.* the 3,6-diaminated quinones. The structures of these substances follow from hydrolysis to their respective hydroxy-compounds.[2,3] Similarly *p*-xyloquinone gives with piperidine an analogous product whose nuclear magnetic resonance (n.m.r.) spectrum leaves no doubt that side-chain amination has not occurred. It appears that nuclear rather than side-chain amination of alkylated benzoquinones will occur to a substantial degree provided that two amino-groups can be introduced directly into the system *para* to one another. When this is not the case, an alternative reaction is observed, *e.g.* *o*-xyloquinone on treatment with ethanolic methylamine at room temperature is converted into 2-methyl-3,6-bismethylamino-1,4-benzoquinone in 39% yield. This compound is identical with the direct-amination product of toluquinone mentioned above and indeed is obtained in higher yield from the former reaction. The process evidently involves initial addition of amine to the unsubstituted 6-position of *o*-xyloquinone followed effectively by displacement of the 3-methyl group by a further mole of amine. The same compound is also obtained though in lower yield by similar treatment of *m*-xyloquinone. Likewise, trimethyl-1,4-benzoquinone is converted into 2,5-dimethyl-3,6-bismethylamino-1,4-benzoquinone (40%). In this case the product is identical with that obtained on direct nuclear amination of *p*-xyloquinone and presumably the loss of a methyl group is analogous to the cases mentioned above. The same

[1] D. W. Cameron, P. M. Scott, and Lord Todd, *J.*, 1964, 42.
[2] W. K. Anslow and H. Raistrick, *J.*, 1939, 1446.
[3] F. Fichter and A. Willmann, *Ber.*, 1904, **37**, 2384.

compound is also obtained in low yield when duroquinone is similarly treated; here, apparently, two methyl groups have been lost. Such a reaction probably accounts at least partly for the red colours produced when duroquinone and other alkylated quinones are treated with amines.[1] Finally, all these examples parallel the observation made by Anslow and Raistrick[2] that the quinone (II) undergoes ready conversion into 2,5-bismethylamino-1,4-benzoquinone under equally mild conditions. This process differs from those above only in that an early stage must involve the displacement of methoxyl rather than direct addition of amine. It is accompanied by an overall uptake of oxygen (1·4 mole; this is inconsistent with a previously suggested mechanism[2] involving the evolution of 1 mole of methane), and also by the production of formaldehyde (0·3 mole). Attempts to obtain intermediates either by carrying out the reaction under nitrogen or for limited periods of time were unsuccessful. To account for these observations we suggest the most likely course of the reaction to be as follows. Displacement of the methoxyl group in compound (II) by



amine is followed by side-chain amination to yield the intermediate quinol (IV). Once the methoxyl has been displaced nuclear amination cannot take place because the preferred position of attack is substituted by the methyl group. The intermediate (IV) in the presence of base then undergoes a reverse Mannich reaction with the production of formaldehyde and the quinol (V). A reaction of this kind has been implicated in the long-known conversion of phenolic Mannich bases into diarylmethanes,[4] a process that is generally base-catalysed but which sometimes can be brought about under much milder conditions[5] *e.g.*, refluxing in ethanol. Finally the quinol (V) undergoes irreversible oxidative amination to yield the end-product (VI). However unfavourable the equilibria (III)⇌(IV)⇌(V) may be, the final step (V)→(VI) would tend to drive the reaction forward in the desired direction. An overall uptake of 2 moles of oxygen would be required per mole of starting quinone (II) and in view of the fact that the reaction is non-quantitative the observed uptake (1·4 moles) is in accordance with theory.

All the examples given above in which methyl groups were lost during amination employed ethanolic methylamine as the nucleophile. This is chiefly a matter of convenience since

[4] See, *e.g.*, J. H. Brewster and E. L. Eliel, *Org. Reactions*, 1953, **7**, 132.
[5] W. J. Burke, W. A. Nasutavicus, and C. Weatherbee, *J. Org. Chem.*, 1964, **29**, 407.

generally the bismethylaminobenzoquinones produced in these reactions are considerably less soluble than, *e.g.*, the corresponding bispiperidino-derivatives and their isolation is therefore much easier. Similar reactions have indeed been observed with other bases, *e.g.* the quinone (II) with piperidine or with cyclohexylamine is readily converted into the respective diaminated quinones corresponding to (VI) in yields (16 and 22%), a little lower than that of the bismethylamino-derivative. Smaller amounts of formaldehyde (0·08, 0·13 mole) are also produced in these reactions. There seems therefore little reason to doubt that the process is general with respect to amine and, although we have not examined quinones substituted by alkyl groups higher than methyl, probably with respect to the alkyl group as well.

One way in which ethanolic methylamine differs from piperidine in these reactions is that it is evidently a much weaker nucleophile with respect to side-chain amination, *i.e.* the equilibrium (III)⇌(IV) lies further to the left, and methylaminomethylquinols are not usually isolable as reaction products. Treatment of duroquinone for example leads only to considerable recovery of starting material together with the small amounts of 2,5-dimethyl-3,6-bismethylamino-1,4-benzoquinone mentioned previously. Similarly, whereas piperidine reacts with 1-methyl-1,4-naphthaquinone with both nuclear and side-chain amination[1] leading to (VII; R, R′ = piperidino), ethanolic methylamine gives only the nuclear-aminated product (VII; R = NMHe, R′ = H) whose structure follows from acid hydrolysis[6] and from its n.m.r. spectrum. When compound (VII; R, R′ = piperidino) is treated with methylamine as above, only the nuclear piperidino-group is displaced and the product (VII; R = NHMe, R′ = piperidino) is obtained. (Under the conditions used, 2,5-bispiperidino-1,4-benzoquinone is converted quantitatively into its bismethylamino-analogue.)

Finally, it is interesting to contrast the action of piperidine on 2-methyl-1,4-naphthaquinone with that on *p*-xyloquinone. The former case leads to both nuclear and side-chain amination, the latter to nuclear amination only, and no product corresponding to (VIII; R, R′ = piperidino) is observed. However, such a system is probably obtained indirectly by the prolonged action of methylamine on compound (I; R = piperidino).[1] The structure of the product (VIII; R=NHMe, R′ = piperidino) is suggested by its n.m.r. spectrum and its formation is envisaged as involving loss of a piperidino-methyl group and subsequent amination as in the examples discussed above, followed by displacement of the nuclear piperidino-group in the resulting quinonoid intermediate. Once again displacement of the side-chain piperidino-groups does not occur.

Experimental

Unless otherwise stated, infrared spectra were measured in Nujol mulls and ultraviolet and visible spectra in ethanol. N.m.r. spectra were obtained at 60 Mc./s. Points of reference are quoted as chemical shifts on the τ scale and have been measured against tetramethylsilane as internal reference. Integrated intensities of peaks in the various spectra are consistent with the structural assignments. The oxygen uptake was measured in a microhydrogenator filled with carbon dioxide-free air.

Aminations of Quinones.—Unless otherwise stated quinones were aminated as follows. A solution of the quinone (50 mg.) in ethanol (1 ml.) was treated at room temperature with ethanolic methylamine (2·5 ml. of 33% w/v) or ethanolic piperidine (2·5 ml. of 40% v/v) left overnight in the dark, refrigerated, and the product filtered off and recrystallised from ethanol.

2-Methyl-3,6-bismethylamino-1,4-benzoquinone.—(a) *From o-xyloquinone.* The product from *o*-xyloquinone (50 mg.) was sublimed at 140°/1 mm. to yield 2-methyl-3,6-bismethylamino-1,4-benzoquinone (25 mg.; 39%) as violet crystals m. p. 232° undepressed by authentic material[2] and having an identical infrared spectrum: $\lambda_{max.}$ 217, 343, 524 mμ (log ε 4·36, 4·39, 2·52), $\nu_{max.}$ 3300, 1641, 1600br, 1565 cm.$^{-1}$.

(b) *From m-xyloquinone.* *m*-Xyloquinone (50 mg.) gave the same product (4 mg.; 7%), m. p. 232—233° identified as in (*a*) above.

[6] M. Asano and Z. Hase, *J. Pharm. Soc. Japan*, 1941, **61**, 55.

2,5-*Dimethyl*-3,6-*bismethylamino*-1,4-*benzoquinone*.—(a) *From* p-*xyloquinone*. *p*-Xyloquinone (50 mg.) gave 2,5-*dimethyl*-3,6-*bismethylamino*-1,4-*benzoquinone* (31 mg.; 44%) as pale purple-brown needles, m. p. 269° (at which temperature it sublimes rapidly) (Found: C, 61·7; H, 7·6; N, 14·6. $C_{10}H_{14}N_2O_2$ requires C, 61·8; H, 7·3; N, 14·4%), $\lambda_{max.}$ 224, 348, 545 mμ (log ε 4·31, 4·34, 2·26), $\nu_{max.}$ 3300, 1639, 1575 cm.$^{-1}$. This compound was previously reported[3] as having m. p. 227° but was not analysed.

(b) *From trimethyl*-1,4-*benzoquinone*. Trimethyl-1,4-benzoquinone (50 mg.) gave the same product (24 mg.; 40%), m. p. 267—269°, undepressed in admixture with authentic material and having identical infrared spectrum.

(c) *From duroquinone*. Duroquinone (100 mg.) was treated with methylamine on twice the usual scale and the product (3 mg., 2·5%) purified and identified as in (*b*) above, m. p. 267°. The ethanolic filtrate was evaporated to dryness and extracted with hot light petroleum (b. p. 40—60°). The extracts, on concentration, yielded unchanged duroquinone (infrared spectrum) and an unidentified basic fraction (4 mg.) was extracted from the petroleum-insoluble portion (61 mg.).

2,5-*Dimethyl*-3,6-*bispiperidino*-1,4-*benzoquinone*.—*p*-Xyloquinone (50 mg.) yielded 2,5-*dimethyl*-3,6-*bispiperidino*-1,4-*benzoquinone* (34 mg., 30%) as iodine-like plates having a pronounced green sheen, m. p. 116·5—117·5° (Found: C, 71·3; H, 8·5; N, 9·0. $C_{18}H_{26}N_2O_2$ requires C, 71·5; H, 8·7; N, 9·3%), $\lambda_{max.}$ 235, 300, 443 mμ (log ε 4·16, 3·44, 3·56), $\nu_{max.}$ 1632, 1581 cm.$^{-1}$; n.m.r. (in $CDCl_3$) 6·73 (piperidino-CH_2·N), 8·06 (quinone-Me), 8·34 τ (piperidino-CH_2).

2,5-*Bismethylamino*-1,4-*benzoquinone*.—(a) *From* 2-*methoxy*-5-*methyl*-1,4-*benzoquinone* (II). The quinone (II) (50 mg.) yielded 2,5-bismethylamino-1,4-benzoquinone (16 mg., 30%), reddish crystals, m. p. 283—286° (subliming rapidly), undepressed by authentic material[2] and having identical infrared spectrum. $\lambda_{max.}$ 337, 490 mμ (log ε 4·47, 2·42), $\lambda_{infl.}$ 240 mμ (log ε 3·82), $\nu_{max.}$ 3325, 1644, 1560br cm.$^{-1}$.

(b) *From* 2,5-*bispiperidino*-1,4-*benzoquinone*. This quinone (50 mg.) yielded the same product (29 mg., 96%) purified and identified as in (*a*).

2,5-*Bispiperidino*-1,4-*benzoquinone*.—2-Methoxy-5-methyl-1,4-benzoquinone (50 mg.) yielded 2,5-bispiperidino-1,4-benzoquinone (15 mg.; 16%), violet needles, m. p. 177—179°, undepressed in admixture with authentic material and having identical infrared spectrum, $\lambda_{max.}$ 229, 380 mμ (log ε 4·38, 4·29), $\nu_{max.}$ 1620, 1545br cm.$^{-1}$.

2,5-*Biscyclohexylamino*-1,4-*benzoquinone*.—2-Methoxy-5-methyl-1,4-benzoquinone (50 mg.) in ethanol (26 ml.) was treated with cyclohexylamine (270 mg.) and reacted as for piperidine. The product was recrystallised from ethanol to yield 2,5-biscyclohexylamino-1,4-benzoquinone (22·5 mg., 22%) orange plates, m. p. 242—244° undepressed by authentic material and having identical infrared spectrum, $\lambda_{max.}$ 344, 500 mμ (log ε 4·48, 2·50), $\lambda_{infl.}$ 244 mμ (log ε 3·85), $\nu_{max.}$ 3320, 1637, 1592, 1567 cm.$^{-1}$.

Formaldehyde Estimation.—A solution of 2-methoxy-5-methyl-1,4-benzoquinone (30 mg.) in ethanol (1·5 ml.) was treated with ethanolic methylamine (0·15 ml. of 33%) and left for 24 hr. in the dark. Sulphuric acid (1 ml. of 3N) and water (10 ml.) were added and the mixture steam-distilled at constant volume till a total distillate of 100 ml. has been collected. To an aliquot (1 ml.) was added aqueous chromotropic acid (0·5 ml. of 20%) followed carefully by concentrated sulphuric acid (5 ml.), the mixture heated at 70° for 30 min. and the volume made up to 25 ml. The formaldehyde content was then estimated[7] by measuring its optical density at 570 mμ against a blank in the solvent cell. Yield 0·3 mole.

In a control experiment, using 1,4-benzoquinone (23 mg.), no formaldehyde was produced.

2-*Methyl*-3-*methylamino*-1,4-*naphthaquinone*.—2-Methyl-1,4-naphthaquinone (50 mg.) gave 2-methyl-3-methylamino-1,4-naphthaquinone (36 mg.; 62%), as orange crystals, m. p. 132—133° (lit.,[6] 127—129°), $\lambda_{max.}$ 236, 276, 477 mμ (log ε 4·16, 4·39, 3·51), $\lambda_{infl.}$ 241, 330 mμ (log ε 4·14, 3·26), $\nu_{max.}$ 3400, 1670, 1603, 1566, 1523 cm.$^{-1}$; n.m.r. (in $CHCl_3$) 6·81 (doublet, J = 5·4 c./sec.; MeN), 7·75 τ (quinone-Me).

2-*Methylamino*-3-*piperidinomethyl*-1,4-*naphthaquinone*.—2-Piperidino-3-piperidinomethyl-1,4-naphthaquinone[1] (50 mg.) gave 2-*methylamino*-3-*piperidinomethyl*-1,4-*naphthaquinone* (35 mg; 80%) as glistening orange plates, m. p. 140—141·5° (Found: C, 71·7; H, 6·9; N, 9·4. $C_{17}H_{20}N_2O_2$ requires C, 71·8; H, 7·1; N, 9·8%), $\lambda_{max.}$ 236, 277, 470 mμ (log ε 4·14, 4·33, 3·47), $\lambda_{infl.}$ 330 mμ (log ε 3·37), $\nu_{max.}$ 3300br, 1678, 1600, 1562, 1528 cm.$^{-1}$; n.m.r. (in $CDCl_3$) 1·5—2·5 (multiplet, Ar–H), 6·34 (quinone-CH_2·N), 6·64 (MeN), 7·54 (piperidino-CH_2·N), 8·49 τ (piperidino-CH_2).

[7] C. E. Bricker and H. R. Johnson, *Ind. Eng. Chem. Analyt.*, 1945, **17**, 400.

2,5-*Bismethylamino*-3,6-*bispiperidinomethyl*-1,4-*benzoquinone*.—The tetrapiperidino-compound (III; R = piperidino; 35 mg.) was dissolved in hot ethanol (4 ml.), ethanolic methylamine (2 ml. of 33%) added and the mixture set aside at room temperature for 3 hr. by which time colourless crystals (presumably starting material) had formed accompanied by a small quantity of brick-red crystals of the product. It was then warmed and further methylamine added; this was repeated from time to time during the following three days until the crystals which formed on cooling consisted almost entirely of product. This was filtered off and recrystallised from ethanol (*ca.* 50 ml.) to yield 2,5-*bismethylamino*-3,6-*bispiperidinomethyl*-1,4-*benzoquinone* (11 mg., 42%) as shining brick-red plates, m. p. 240° (decomp.) (Found: C, 66·6; H, 9·1. $C_{20}H_{32}N_4O_2$ requires C, 66·6; H, 8·9%), $\lambda_{max.}$ 343 mμ (log ε 4·30), $\lambda_{infl.}$ 240 mμ (log ε 3·96); n.m.r. (in $CDCl_3$) 6·50 (composite peak MeN, quinone CH_2·N), 7·59 (piperidino-CH_2·N), 8·50 τ (piperidino-CH_2).

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