Synthesis of Heterocyclic Quinones

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For the purposes of this Review, the term 'heterocyclic quinone' is taken to mean a quinone in which a heterocyclic ring (or rings) is fused directly onto the quinone moiety and it excludes those which contain a heterocyclic ring insulated from the quinone nucleus and those which possess a heterocyclic system as a substituent.

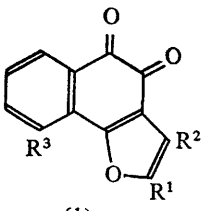
In the past, heterocyclic quinones have found application as dyes, catalysts, and drugs and recently renewed interest in their use as drugs has been stimulated by the discovery of a number of antibiotics containing such systems, *e.g.* streptonigrin and the mitomycins.

It is the aim of this Review to discuss the synthesis of heterocyclic quinones, but reference to their reactions and uses will be made where appropriate.[1]

1 Furan

Quinones containing a furan nucleus, many examples of which occur in nature, are, in general, stable compounds and methods for their synthesis are well developed.

Oxidation of 4-hydroxy-7-aminobenzofurans with chromic acid,[2] 4-methoxy-7-aminobenzofurans with nitric acid,[3] and 4-hydroxybenzofurans with Fremy's

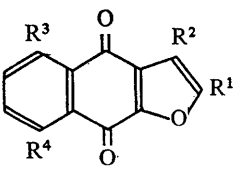


(1)

a; $R^1 = Me$, $R^2 = R^3 = H$

b; $R^1 = CHMe_2$, $R^2 = R^3 = H$

c; $R^1 = H$, $R^2 = R^3 = Me$



(2)

a; $R^1 = Me$, $R^2 = CO_2Et$, $R^3 = R^4 = H$

b; $R^1 = CHMe_2$, $R^2 = R^3 = R^4 = H$

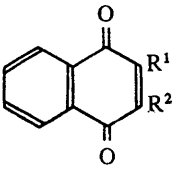
c; $R^1 = R^4 = H$, $R^2 = R^3 = Me$

d; $R^1 = R^3 = H$, $R^2 = R^4 = Me$

[1] (*a*) The synthesis of heterocyclic quinones from 2,3-dichloro-1,4-naphthoquinone has been reviewed by M. F. Sartori, *Chem. Rev.*, 1963, **63**, 279; (*b*) The synthesis and thermal reactions of *ortho*-quinones has been reviewed by W. M. Horspool, *Quart. Rev.*, 1969, **23**, 204.

[2] C. J. P. Spruit, *Rec. Trav. chim.*, 1962, **81**, 810.

[3] G. Rodighiero and U. Fornasiero, *Gazzetta*, 1961, **91**, 90.



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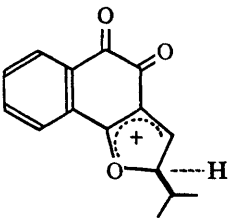

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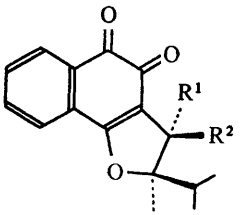
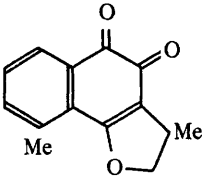


(5) H

a; R^1 = H, R^2 = AcO

b; R^1 = AcO, R^2 = H



(6)

salt[4] have all been found to give reasonable yields of benzofuran-4,7-diones.

Quinones derived from naphtho[1,2-*b*]furan and naphtho[2,3-*b*]furan may also be obtained by oxidation of suitably substituted derivatives of the parent systems. Thus, oxidation of 5-hydroxy-2-methylnaphtho[1,2-*b*]furan with Fremy's salt yields quinone (1a).[5] An alternative approach to the synthesis of these quinones involves intramolecular cyclisation of suitably substituted 1,4-naphthoquinones. This versatile method may be illustrated by the following examples. In the presence of base, ethyl acetoacetate displaces a chloride ion from 2,3-dichloro-1,4-naphthoquinone (DCNQ) and the enolate anion of the product so formed undergoes cyclisation with displacement of a second chloride ion to yield furan (2a).[1a,6] Other β-dicarbonyl compounds may replace ethyl acetoacetate in the above reaction.

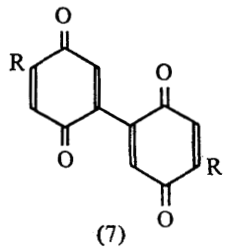
Isolapachol (3; R^1 = CH=CH·CHMe$_2$, R^2 = OH) undergoes oxidative cyclisation in the presence of mercuric acetate and acetic acid to form the *ortho*-quinone (1b). It seems likely that the stabilised carbonium ion (4), formed either by substrate–metal electron transfer or oxymercuration, is an intermediate in the reaction since the two stereoisomeric acetates (5a) and (5b) are also obtained in low yield.[7] On treatment with hydrochloric acid *ortho*-quinone (1b) undergoes

[4] (*a*) H. Kakisawa and Y. Inouye, *Chem. Comm.*, 1968, 1327; (*b*) B. D. Cavell and J. MacMillan, *J. Chem. Soc.* (*C*), 1967, 310.
[5] D. W. Cameron and E. M. Hildyard, *J. Chem. Soc.* (*C*), 1967, 2126.
[6] G. A. Reynolds, J. A. Van Allan, and R. E. Adel, *J. Org. Chem.*, 1965, **30**, 3819.
[7] K. H. Dudley and H. W. Miller, *J. Org. Chem.*, 1967, **32**, 2341.

ortho–para rearrangement of the type characterised by Hooker[8] to yield the quinone (2b).

Free-radical alkylation of 2-hydroxy-5-methyl-1,4-naphthoquinone with β-chloro-α-methylpropionyl peroxide gives the dihydrofuranoquinone (6) which may be dehydrogenated to the *ortho*-quinone (1c). Alternatively, treatment of (6) with concentrated hydrochloric acid followed by pyridine causes rearrangement to the dihydrofurano-*p*-quinone which, on dehydrogenation, yields maturinone (2c).[9]

A third general approach to the synthesis of naphthofuranoquinones utilises the reactivity of benzofuran-4,7-diones in the Diels–Alder reaction. Penta-1,3-diene reacts with 3-methylbenzofuran-4,7-dione at room temperature to give a good yield of a mixture of the two possible adducts which, after aerial oxidation in alkaline solution, furnishes maturinone (2c) and its 8-methyl isomer (2d). The latter is the major product (74%) and can be isolated by crystallisation.[10] Other examples of the Diels–Alder reaction with 3-methylbenzofuran-4,7-dione have been reported.[4a]



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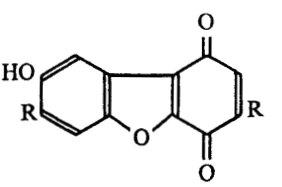

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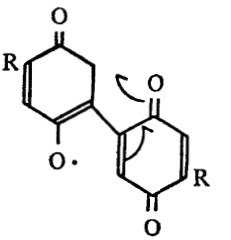
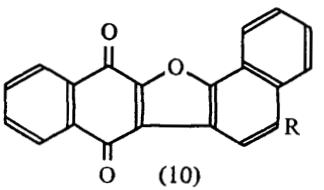


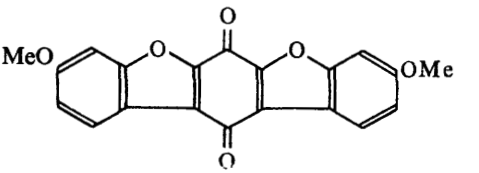
(9)

R = OMe, Me



(10)

a; R = OH
b; R = H



(11)

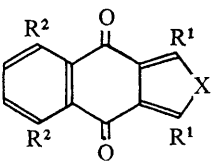
Cyclisation of diphenyldiquinones of type (7) leads to the formation of dibenzofuran derivatives (8). Originally the cyclisation was performed thermally[11] but subsequent investigations have shown that better yields may be obtained by

[8] S. C. Hooker and A. Steyermark, *J. Amer. Chem. Soc.*, 1936, **58**, 1202.
[9] P. M. Brown and R. H. Thomson, *J. Chem. Soc.* (*C*), 1969, 1184.
[10] H. Kakisawa, Y. Inouye, and J. Romo, *Tetrahedron Letters*, 1969, 1929.
[11] H. G. H. Erdtmann, *Proc. Roy. Soc.*, 1933, **A143**, 223.

photolysis. The latter reaction probably involves $n \rightarrow \pi^*$ excitation to form the diradical (9), followed by formation of the oxygen bridge, electron demotion, and rearrangement.[12a]

Extension of this photochemical reaction to 2,2′-binaphthoquinones has led to formation of dinaphthofuranoquinones (10a)[12] possessing a hydroxy-group at C-5. The formation of quinones of this series possessing other substituents at this position and elsewhere may be achieved by direct oxidation of the parent heterocycles.[13] Oxidation in a ring remote from the heterocyclic nucleus has not been observed and diquinone formation rarely takes place. An alternative approach, which is attractive because of the large variation in substituents permissible, is the base-catalysed reaction of DCNQ with a phenol, *e.g.* quinone (10b) from 1-naphthol. The scope of this reaction has been reviewed.[1a,14] Extensions of this method to the formation of benzodifuran derivatives from one molecule of chloranil and two molecules of a phenol is possible, but in this instance the reaction suffers from the disadvantage that mixtures of isomers may result. Thus *m*-methoxyphenol reacts with chloranil to give a mixture (8:1) of dione (11) and its isomer 3,9-dimethoxybenzo[1,2-*b*; 4,5-*b*′]bisbenzofuran-6,12-dione.[15]

Dinaphtho- and benzonaphtho-furanoquinones may also be obtained by a reaction resembling a standard anthraquinone synthesis. In this approach the



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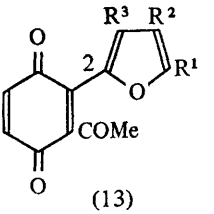

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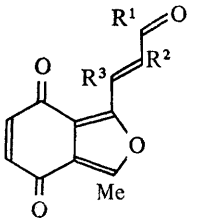

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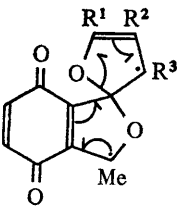


(15)

[12] (*a*) A. J. Shand and R. H. Thomson, *Tetrahedron*, 1963, **19**, 1919; (*b*) R. G. Cooke and L. G. Sparrow, *Austral. J. Chem.*, 1965, **18**, 218; (*c*) D. Schulte-Frohlinde and V. Werner, *Chem. Ber.*, 1961, **94**, 2726.

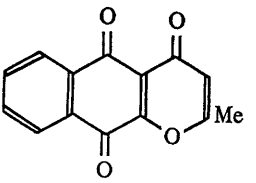
[13] G. R. Clemo and R. Spence, *J. Chem. Soc.*, 1928, 2811.

[14] R. V. Acharya, B. D. Tilak, and M. R. Venkiteswaren, *J. Sci. Ind. Res., India*, 1957, **16B**, 400.

[15] J. Gripenberg and M. Lounasmaa, *Acta Chem. Scand.*, 1965, **19**, 1063.

naphthoquinone moiety is built onto a benzo- or naphtho-furan nucleus by a Friedel–Crafts reaction on the acid chloride of 2-benzoylbenzo- or naphtho-furan-3-carboxylic acids. The latter acids are conveniently prepared by the condensation of 2,3-dihydrobenzo- or naphtho-furan-2,3-diones with ω-brom-acetophenones in the presence of base.[16]

The synthesis of quinones of type (12; X = O) in which the furan oxygen atom is β to the quinone nucleus has been described. Various toluenes and xylenes can be diacylated with 2,5-dimethyl- and 2,5-diphenyl-furan-3,4-di-carboxylic acid in the presence of aluminium chloride to give good yields of the diones (12; X = O, R^1 = R^2 = alkyl or phenyl).[17] High yields of these quinones are also obtained from a reaction resembling the standard furan synthesis from 1,4-dicarbonyl compounds, namely acid-catalysed cyclodehydration of 2,3-diacyl-1,4-dihydroxy-benzenes or -naphthalenes.[18] An interesting photochemical synthesis of this type of quinone has been reported by Weisgerber and Eugster.[19] 2-Acetyl-3-(2-furyl)-1,4-benzoquinones (13) when irradiated in aprotic solvents rearrange to give quinones (14) in 50—90% yield. It has been suggested that $n \rightarrow \pi^*$ excitation of the acetyl group occurs followed by attack at the 2-position of the furan to give diradical (15), which rearranges to form the quinone (14). Similar reactions occur with 2-acetyl-3-(2-furyl)-1,4-naphthoquinones.



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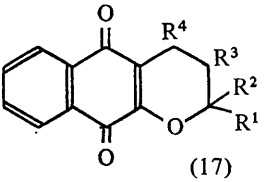
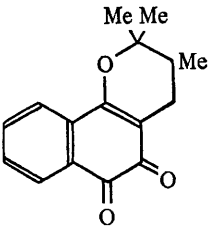


(17)

a; $R^1 = R^2 = R^3 = Me$, $R^4 = H$

b; $R^1 = OMe$, $R^2 = Me$, $R^3 = H$, $R^4 = Ph$



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[16] J. N. Chatterjea, S. N. P. Gupta, and V. N. Mehrotra, *J. Indian Chem. Soc.*, 1965, **42**, 205; J. N. Chatterjea, R. F. Curtis, and S. P. Dhoubhadel, *J. Chem. Soc.*, 1961, 765.

[17] D. V. Nightingale and B. Sukornick, *J. Org. Chem.*, 1959, **24**, 497; D. V. Nightingale and H. L. Needles, *J. Heterocyclic Chem.*, 1964, **1**, 74.

[18] (*a*) L. A. Cort and P. A. B. Rodriguez, *J. Chem. Soc.*, (*C*), 1967, 949; (*b*) O. Dischendorfer, K. Lercher, and J. Marek, *Monatsh.*, 1949, **80**, 333; (*c*) R. Pummerer and G. Marondel, *Chem. Ber.*, 1956, **89**, 1454.

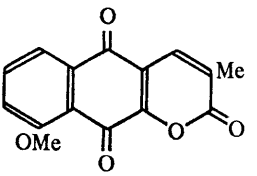
[19] G. Weisgerber and C. H. Eugster, *Helv. Chim. Acta*, 1966, **49**, 1806.

2 Pyran

None of the parent benzopyran quinones are known, but a number of their derivatives occur naturally and their chemistry has been reviewed.[20] Like the furan quinones, those of the pyran series may be divided into two groups in which the heterocyclic oxygen atom is located either α or β to the quinone nucleus. The bulk of the synthetic studies has been aimed at the *ortho*- and *para*-quinones of the α-series.

Oxidation of the appropriate hydroxy-, hydroxyamino-, and dimethoxy-derivatives of the parent ring system has been employed in the synthesis of both *ortho*- and *para*-α-pyranquinones.[21] Thus, 2-methyl-5-hydroxy- and 2-methyl-5-amino-10-hydroxynaphtho[2,3-*b*]-γ-pyrone are oxidised by potassium persulphate and nitrous acid respectively to quinone (16) in low yield.[21a,b]

Intramolecular cyclisation reactions of 2-hydroxy-1,4-naphthoquinones substituted at C-3 with a side-chain possessing a reaction site in the γ-position is a versatile method of synthesis of both linear *para*- and angular *ortho*-naphthopyran quinones, types (17) and (18) respectively. Hooker[22] has demonstrated that the *para*-quinones rearrange to the *ortho* in conc. sulphuric acid while the reverse process may be effected by conc. hydrochloric acid. Ettlinger,[23] using good model compounds, has shown that the *ortho*-quinones of this type are several hundred times more basic than the corresponding *para*-compounds. Qualitatively, the *ortho*-quinone cation is the more stable of the two cations while the *para*-quinone



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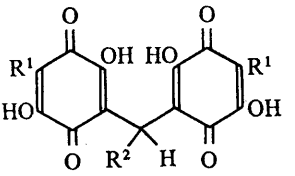

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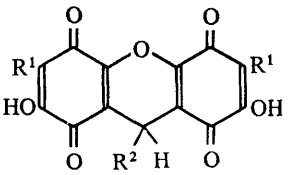


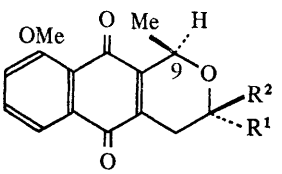
(21)

[20] F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds', Butterworths, London, 1963; R. H. Thomson, 'Naturally Occurring Quinones', Butterworths, London, 1957.
[21] (*a*) A. Ueno, *Chem. Pharm. Bull.*, 1966, **14**, 121; (*b*) S. Fukushima, A. Ueno, and Y. Akahori, *Chem. Pharm. Bull.*, 1964, **12**, 307; (*c*) L. Farkas, M. Nogradi, and B. Vermes, *Chem. Ber.* 1967, **100**, 2296; (*d*) H. N. Grant, V. Prelog, and R. P. A. Sneeden, *Helv. Chim. Acta*, 1963, **46**, 415; (*e*) L. Horner and W. Dürckheimer, *Z. Naturforsch.*, 1959, **14b**, 741.
[22] S. C. Hooker, *J. Amer. Chem. Soc.*, 1936, **58**, 1168.
[23] M. G. Ettlinger, *J. Amer. Chem. Soc.*, 1950, **72**, 3090.

is the more stable of the free quinones. In conc. sulphuric acid (18 mol % of water) both quinones are protonated and the *ortho*-quinone cation predominates. On quenching with water the *ortho*-quinone is isolated. In conc. hydrochloric acid (containing 77 mol % of water) ionisation of the *ortho*-quinone is diminished and the equilibrium remains on the side of the *para*-quinone. Treatment of the hydroxynaphthoquinone (3; R^1 = $CH_2CMe{=}CMe_2$, R^2 = OH) with hydrochloric acid forms the *para*-quinone (17a) which rearranges to the *ortho*-quinone (18) in sulphuric acid.[24]

Alkylation of 2-hydroxy-1,4-naphthoquinone with benzal–acetone *via* a Michael reaction yields quinone (3; R^1 = $CHPhCH_2COMe$, R^2 = OH) which cyclises in methanolic hydrogen chloride to the acetal (17b).[25] Hooker[26] has shown that 2-hydroxy-1,4-naphthoquinone condenses readily with aldehydes (RCH_2CHO) in the presence of acid to form the 3-alkenyl derivatives (3; R^1 = $CH{=}CHR$, R^2 = OH) and it has recently been shown that a similar reaction occurs under mild basic conditions. When 8-methoxy-2-hydroxy-1,4-naphthoquinone reacts with ethyl α-formylpropionate $MeCH(CHO)CO_2Et$, in the presence of pyridine and piperidine, an aldol condensation occurs to give the anion (3; R^1 = $CHOH{\cdot}CHMe{\cdot}CO_2Et$, R^2 = O^-) which cyclises with displacement of ethoxide to form, after dehydration, lambertellin methyl ether (19) in fair yield.[27]

Murty and co-workers[28] have extended Hooker's hydroxynaphthoquinone–aldehyde condensation to the synthesis of dibenzopyran diquinones. When two molecules of a 3-alkyl-2,5-dihydroxy-*p*-benzoquinone react with one of an aldehyde (R^2CHO) in the presence of acid, methylene bis-benzoquinones (20) are formed which may undergo dehydration to form the bicyclic quinones (21).



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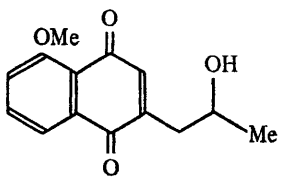

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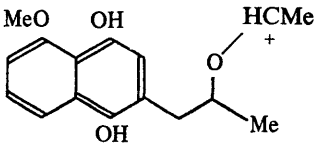

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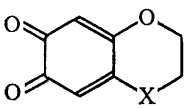
[24] R. G. Cooke and T. C. Somers, *Austral. J. Sci. Res.*, 1950, **3A**, 466.
[25] H. E. Zaugg, *J. Amer. Chem. Soc.*, 1949, **71**, 1890.
[26] S. C. Hooker, *J. Amer. Chem. Soc.*, 1936, **58**, 1163.
[27] P. Brown and R. H. Thomson, *J. Chem. Soc.* (*C*), 1970, 109.
[28] V. K. Murty, T. V. P. Rao, and V. Venkateswarlu, *Tetrahedron*, 1967, **23**, 817.

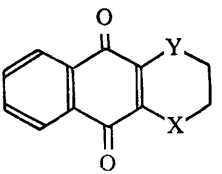
The racemic forms of the naturally occurring naphtho-β-pyran quinones, eleutherin (+ form 22; R^1 = H, R^2 = Me) and isoeleutherin (− form 22; R^1 = Me, R^2 = H) have been synthesised[29] by an acid-catalysed reaction between acetaldehyde and quinone (23). In phosphoric acid a 34% yield of a mixture of racemic eleutherin and isoeleutherin (1:4·6) is obtained. It is suggested that reduction of quinone (23) occurs in the reaction mixture and that the quinol so formed reacts with acetaldehyde to give carbonium ion (24), which then cyclises. Oxidation to the quinone level completes the synthesis. It is known that phosphoric acid causes partial epimerisation at C-9 in eleutherin, isoeleutherin, and their dihydro-derivatives and hence formation of the more stable (*trans*) isoeleutherin is to be expected. On the other hand, a mixture of phosphoric and formic acids causes negligible epimerisation at C-9 and, when this mixture is used in the cyclisation reaction, the major product (15:1) is the *cis*-compound ±eleutherin; thus, the reaction is under kinetic control.

3 1,4-Dioxan

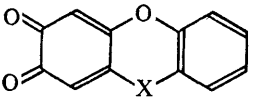
Few quinones containing the 1,4-dioxan system have been described. Oxidation of 6-hydroxybenzodioxan with Fremy's salt has been reported to give the quinone (25; X = O) in high yield.[30] Nitrous acid has been reported to convert 5,10-diaminonaphthodioxan into the quinone (26; X = Y = O) in good yield.[31] The oxidation of catechol with sodium iodate leads to the formation of the dibenzodioxin *o*-quinone (27; X = O), presumably *via* 2,3′,4′-trihydroxydiphenyl ether. The latter would result from the addition of catechol to *o*-benzoquinone and is known to form quinone (27; X = O) under oxidising conditions.[32]



(25)



(26)



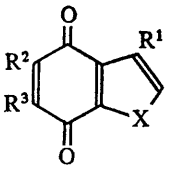
(27)

4 Thiophen and Selenophen

There has been considerable interest in quinones containing a thiophen nucleus because of their possible value as dye-stuff intermediates and vitamin K antagonists. In general, the methods employed in their synthesis have been similar to those of naphtho- and anthra-quinone chemistry, namely either oxidation of the

[29] W. Eisenhuth and H. Schmid, *Helv. Chim. Acta*, 1958, **41**, 2021.
[30] A. V. El'tsov, *Zhur. obshchei. Khim.*, 1963, **33**, 2006 (*Chem. Abs.*, 1963, **59**, 11463e).
[31] P. M. Heertjes, A. M. ter Horst, and J. M. Persijn, *Rec. Trav. chim.*, 1955, **74**, 31.
[32] W. G. C. Forsyth, V. C. Quesnel, and J. B. Roberts, *Biochim. Biophys. Acta*, 1960, **37**, 322.

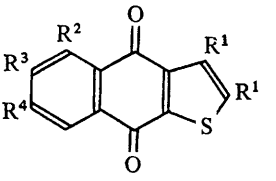
heterocycle and its derivatives or intramolecular acylation. The synthesis and reactions of thiophen quinones has been reviewed.[33]



(28)

a; X = S, $R^1 = R^3 = H$, R^2 = Me

b; X = Se, $R^1 = R^3$ = Me, $R^2 = H$



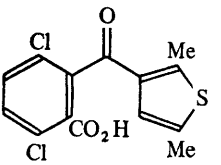
(29)

a; $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$

b; $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$

c; $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$

d; R^1 = CN, $R^2 = R^3 = R^4 = H$



(30)

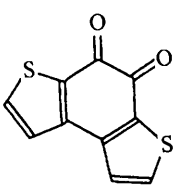
5-Methylbenzothiophen-4,7-dione (28a) has been obtained from the reaction of methylsuccinic acid with thiophen in the presence of aluminium chloride and by the oxidation of 5-methylbenzothiophen and its 4-hydroxy-7-amino-derivative, but the yields in all of these reactions are low.[34] The vitamin K activity of this quinone has been shown to be only 3% of that of 2-methyl-1,4-naphthoquinone.

Several attempts have been made to prepare the *ortho*-quinone benzothiophen-4,5-dione but it appears to be too unstable for isolation, although some of its derivatives possessing a C-7 substituent, *e.g.* SO_3K, Cl, $CH(CN)CO_2Et$, have been isolated.[35]

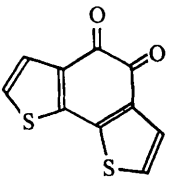
Most of the higher polycyclic thiophen quinones have been synthesised by cyclisation of derivatives of either *o*-(2-thenoyl)benzoic acid or 2-benzoylthio-

[33] H. D. Hartough and S. L. Meisel, 'Condensed Thiophenes', Interscience, New York, 1954.
[34] R. Kitchen and R. B. Sandin, *J. Amer. Chem. Soc.*, 1945, **67**, 1645; D. S. Tarbell, D. K. Fukushima, and H. Dam, *J. Amer. Chem. Soc.*, 1945, **67**, 1643.
[35] L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.*, 1935, **57**, 1611; M. Martin-Smith and M. Gates, *J. Amer. Chem. Soc.*, 1956, **78**, 5351; K. Fries, H. Heering, E. Hemmecke, and G. Siebert, *Annalen*, 1936, **527**, 83.

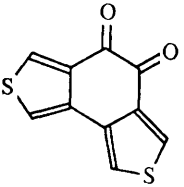
phen-3-carboxylic acid.[36] Care must be exercised in the assignment of structures to the quinones obtained by the first route because rearrangements are known to occur under the conditions of cyclisation. Thus, for example, 3- and 6-nitro-2-(2-thenoyl)benzoic acids are cyclised in sulphuric acid to the 5-nitro-compound (29a). It has been demonstrated by using milder conditions that the 3-nitro-acid rearranges to the 6-nitro-compound prior to cyclisation (a Hayashi rearrangement). It has also been shown that the 4- and 5-nitro-2-(2-thenoyl)benzoic acids cyclise to form a mixture of the two quinones (29b) and (29c). The rearrangement of the 4-nitro- into the 5-nitro-compound could not be demonstrated because it occurs only under conditions drastic enough to effect ring closure.[36d] Reasonably, rearrangement does not occur if the ketone function of the thenoylbenzoic acid is reduced to a methylene group prior to cyclisation. Quinones containing a thiophen ring in which the sulphur atom is β to the quinone nucleus have also been obtained by cyclisation of 2-(3-thenoyl)benzoic acids possessing substituents at positions 2 and 5 of the thiophen nucleus, *e.g.* quinone (12; X = S, R^1 = Me, R^2 = Cl) from acid (30).[37]



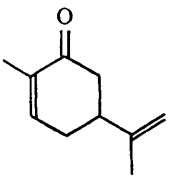
(31)



(32)



(33)



(34)

Wynberg and Sinnige[38] have developed a useful method for the synthesis of benzodithiophen quinones. Intramolecular benzoin condensation, followed by aerial oxidation, converts 2,2′-diformyl-3,3′-dithienyl, 3,3′-diformyl-2,2′-dithienyl, and 3,3′-diformyl-4,4′-dithienyl into quinones (31), (32), and (33) respectively.

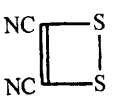
The synthesis of quinones containing a selenophen ring has been virtually unexplored, but it seems reasonable to suggest that some of the methods employed for the formation of thiophen quinones could be applied to the synthesis of the selenium analogues. A novel synthesis of 3,6-dimethylbenzoselenophen-4,7-dione (28b) has been described.[39] When carvone (34) is warmed with selenium dioxide, the product isolated in low yield after distillation (190 °C) is quinone (28b). It is not known if this quinone is formed prior to or during distillation. The mechanism of this reaction is not clear but it may involve oxidation of carvone to 2-methyl-5-isopropenyl-1,4-benzoquinone, a process for

[36] (*a*) H. E. Schroeder and V. Weinmayr, *J. Amer. Chem. Soc.*, 1952, **74**, 4357; (*b*) F. Mayer, *Annalen*, 1931, **488**, 259; (*c*) V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res., India*, 1953, **14B**, 11; (*d*) M. S. Newman and K. G. Ihrman, *J. Amer. Chem. Soc.*, 1958, **80**, 3652.
[37] A. T. Peters and D. Walker, *J. Chem. Soc.*, 1957, 1525.
[38] H. Wynberg and H. J. M. Sinnige, *Rec. Trav. chim.*, 1969, **88**, 1244.
[39] J. Schmitt and J. Seilert, *Annalen*, 1949, **562**, 15.

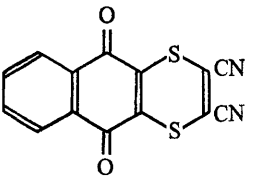
which there is some analogy,[40] followed by a 1,4-addition of selenium to the conjugated diene system and oxidation. In this connection it is worth noting that the formation of selenophen from butadiene and selenium at high temperatures has been observed.[41]

5 1,4-Dithiin and 1,4-Dithian

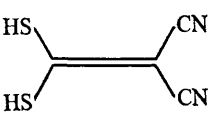
Naphtho[2,3-*b*]-1,4-dithian-5,11-dione (26; X = Y = S) is a stable compound prepared by either a double nucleophilic displacement of chloride from DCNQ by enthanedithiol[42] or, better, acylation of benzene with 1,4-dithian-2,3-dicarboxylic acid anhydride to give 2-benzoyldithian-3-carboxylic acid, followed by cyclisation in polyphosphoric acid.[43]



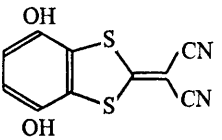
(35)



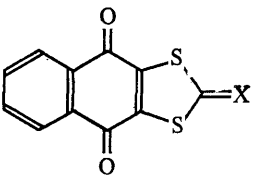
(36)



(37)



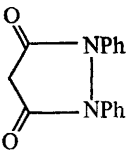
(38)



(39)

a; X = $C(CN)_2$

b; X =



1,2-Dicyanoethylene-1,2-dithiol is oxidised by 1,4-naphthoquinone to dicyano-1,2-dithietene (35), which is not isolated, but which behaves rather like a con-

[40] E. Dane and J. Schmitt, *Annalen*, 1938, **536**, 196.
[41] B. A. Arbuzov and E. G. Kataev, *Doklady. Akad. Nauk. S.S.S.R.*, 1954, **96**, 983 (*Chem. Abs.*, 1955, **49**, 8907); Y. K. Yur'ev and L. I. Khmel'nitskii, *ibid.*, 1954, **94**, 265 (*Chem. Abs.*, 1955, **49**, 3121).
[42] W. E. Hahn and L. Wojciechowski, *Roczniki. Chem.*, 1967, **41**, 1067 (*Chem. Abs.*, 1968, **68**, 59510y).
[43] W. E. Hahn and L. Wojciechowski, Polish patent 49,894 (*Chem. Abs.*, 1966, **65**, 17096e).

jugated diene[44] and adds to a second molecule of naphthoquinone to give, after oxidation, dithiin (36). Similar reactions occur with other quinones.[45] On heating alone or with peracetic acid, quinone (36) undergoes ring contraction with loss of sulphur and sulphur dioxide respectively, to yield the thiophen (29d)[45]—behaviour characteristic of substituted 1,4-dithiins.[46]

6 1,3-Dithioles

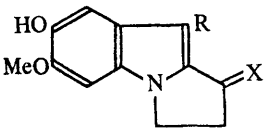
The formation of naphtho[2,3-*b*]-1,3-dithiole-4,9-diones has been reviewed.[1a] Two recent syntheses of quinones containing a dithiole ring involve the addition of dithioacetic acid derivatives to 1,4-quinones. Klemm and Geiger[47] have shown that when dimercaptomethylenedinitrile (37) reacts at 0 °C with an equimolar quantity of 1,4-benzoquinone, then by a series of addition–oxidation reactions the quinol (38) may be obtained; on oxidation with silver oxide the latter forms the corresponding quinone in good yield. Likewise, compound (39a) is obtained from dinitrile (37) and either 1,4-naphthoquinone or DCNQ. In a closely related reaction 1,3-diphenyl-3,5-dioxopyrazolidine-4-dithiocarboxylic acid and DCNQ in the presence of base form the quinone (39b) by a double nucleophilic displacement of chloride ion.[48]

7 Pyrrole

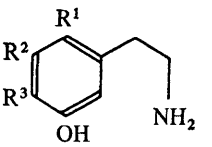
Examples of all four quinones based upon the indole nucleus are known. It has been demonstrated that, providing the appropriate position is unsubstituted, 5- and 6-hydroxyindoles are oxidised in good yield by Fremy's salt to 4,5- and 6,7-indoloquinones respectively, while 4-amino-, as well as 4- and 7-hydroxyindoles are converted into the 4,7-quinones. In the latter cases, if *para*-quinone formation is prevented by the presence of a substituent at the normal site of oxidation, then *ortho*-quinones may be produced.[49] Fremy's salt has been employed in the preparation of compounds related to the antibiotic mitomycin, which contains an indoloquinone moiety. Thus, oxidation of the condensed systems (40; R = H, X = O) and (40; R = CHO, X = H_2) with this reagent yields the corresponding 4,5-quinones.[50] Good yields of 4,7-indoloquinone may also be obtained by oxidation of the appropriate 4,7-diamino- and dihydroxy-

[44] C. G. Krespan and B. C. McKusick, *J. Amer. Chem. Soc.*, 1961, **83**, 3438.
[45] K. Fickentscher, *Arch. Pharm.*, 1969, **302**, 285; K. Fickentscher, R. Wittmann, and H. J. Roth, *Arch. Pharm.*, 1969. **302**, 53.
[46] For a discussion of this reaction see D. S. Breslow and H. Skolnik, 'Multi-Sulphur and Sulphur-Oxygen Five- and Six-membered Heterocycles', Interscience, New York, 1966.
[47] K. Klemm and B. Geiger, *Annalen*, 1969, **726**, 103.
[48] K. Swincicki, E. Degener, and F. Grewe, Belg. patent 623,104 (*Chem. Abs.*, 1964, **60**, 1759c).
[49] H. J. Teuber and G. Thaler, *Chem. Ber.*, 1958, **91**, 2253; H. J. Teuber and G. Staiger, *ibid.*, 1954, **87**, 1251; H. J. Teuber and G. Staiger, *ibid.*, 1959, **92**, 2385; B. Clifford, P. Nixon, C. Salt, and M. Tomlinson, *J. Chem. Soc.*, 1961, 3516; G. R. Allen, J. F. Poletto, and M. J. Weiss, *J. Amer. Chem. Soc.*, 1964, **86**, 3878.
[50] W. A. Remers, P. N. Jones, and M. J. Weiss, *J. Org. Chem.*, 1963, **28**, 1169; G. R. Allen, J. F. Poletto, and M. J. Weiss, *J. Amer. Chem. Soc.*, 1964, **86**, 3877.

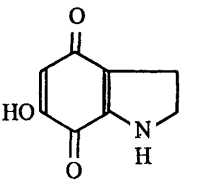
indoles, the latter being available from 2,5-dimethoxyanilines and α-haloketones *via* the Bischler synthesis.[51]



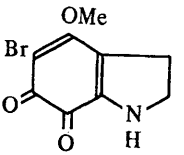
(40)



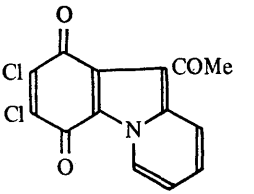
(41)



(42)



(43)



(44)

Oxidative cyclisation of hydroxy-β-phenethylamines and their derivatives often leads to the formation of 2,3-dihydroindoloquinones. Thus, oxidation of 3,4-dihydroxyphenethylamine, 3,4-dihydroxyphenylalanine,[52] and adrenaline[53] produces 2,3-dihydro-5,6-indoloquinones by initial formation of an *ortho*-benzoquinone followed by intramolecular amination (1,4-addition) and oxidation. Phenethylamines (41; $R^1 = R^3 = OH$, $R^2 = H$) and (41; $R^1 = OMe$, $R^2 = Br$, $R^3 = OH$) yield the quinones (42) and (43) respectively.[54]

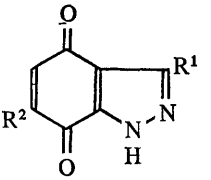
Treatment of chloranil with acetylacetone in the presence of pyridine gives rise to the tricyclic system (44) from the stepwise displacement of two adjacent chloro-substituents by one molecule each of pyridine and acetylacetone followed by cyclisation and deacylation.[55] Several β-dicarbonyl compounds may be used in place of acetylacetone, and DCNQ can replace chloranil.[1a]

8 Pyrazole

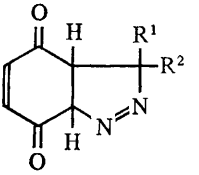
In the indazole series all possible quinones, except the 5,6-dione, have been reported and their chemistry reviewed.[56] Oxidation of hydroxyindazoles with

[51] (*a*) A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 1954, 3916; (*b*) K. Sugimoto, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1950, **71**, 524 (*Chem. Abs.*, 1951, **45**, 6383).
[52] See W. I. Taylor and A. R. Battersby, 'Oxidative Coupling of Phenols', Arnold, London p. 182.
[53] J. Harley-Mason and A. H. Laird, *Tetrahedron*, 1959, **7**, 70.
[54] S. Senoh and B. Witkop, *J. Amer. Chem. Soc.*, 1959, **81**, 6231.
[55] A. M. Islam and M. I. Selim, *J. Org. Chem.*, 1957, **22**, 1641.
[56] L. C. Behr, R. Fusco, and C. H. Jarboe, 'Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings', Interscience, New York, 1967.

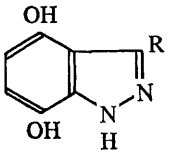
Fremy's salt has received scant attention, although it has been used to advantage in the preparation of 6-methylindazole-4,7-dione (45; R^1 = H, R^2 = Me) from 7-hydroxy-6-methylindazole. Other oxidants lead to dimerisation of 7-hydroxy-6-methylindazole through positions 8.[57]



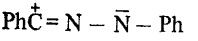
(45)



(46)



(47)



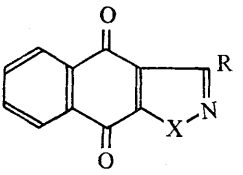
(48)

1,3-Dipolar addition reactions involving 1,4-quinones and diazoalkanes, nitrilimines, or sydnones provide a convenient entry into this series of quinones. In the case of diazoalkanes ($R^1R^2\bar{C}-N=\overset{+}{N}$) the initial product must be of type (46) which, provided that either R^1 or R^2 is a hydrogen atom, rearranges to the more stable tautomer (47). This on either aerial or chemical oxidation forms the quinone (45).[58] The reaction is of greatest value with either a symmetrical 2,3-disubstituted-1,4-benzoquinone or 1,4-naphthoquinone itself because only a single addition product is possible. In the case of the reaction with diazomethane, several intermediates and methylation products have been isolated.[59] Monosubstituted and unsymmetrical 2,3-disubstituted 1,4-benzoquinones may give rise to two isomeric products, *e.g. p*-toluquinone yields a mixture of 5- and 6-methylindazole-4,7-diones with diazomethane.[58b]

Thermolysis of 2,5-diphenyltetrazole at 160—170 °C leads to the nitrilimine (48) which may be trapped by 1,4-naphthoquinone to yield naphthopyrazole (49; R = Ph, X = NPh) in high yield. The mechanism, like that for the addition of diazoalkanes, involves addition, isomerisation, and oxidation.[60] 3-Alkyl-

[57] H. Budzikiewicz and O. S. Ibrahim, *Monatsh.*, 1960, **91**, 1052.
[58] (*a*) H. von Pechmann, *Chem. Ber.*, 1895, **28**, 855; (*b*) I. Awad, A. R. A. Raouf, and A. Boulos, *J. Chem. U.A.R.*, 1966, **9**, 267 (*Chem. Abs.*, 1967, **67**, 100,072); (*c*) L. F. Fieser and M. A. Peters, *J. Amer. Chem. Soc.*, 1931, **53**, 4080.
[59] F. M. Dean and P. G. Jones, *J. Chem. Soc.*, 1963, 5342; W. I. Awad and A. Boulos, *Canad. J. Chem.*, 1964, **42**, 2665.
[60] R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, 1962, **17**, 3.

sydnones (50) also behave as 1,3-dipoles and add through positions 2 and 4 to 1,4-naphthoquinones to yield, presumably, adducts of type (51) which undergo oxidative decarboxylation to form the *N*-alkyl naphthopyrazoles (52; X = CH) and carbon dioxide.[61]



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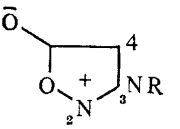

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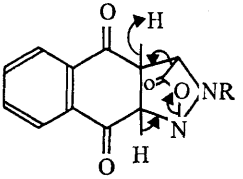

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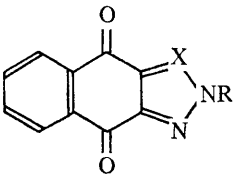

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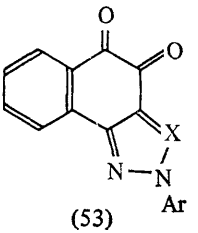
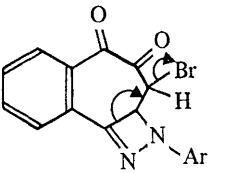


(53)



(54)

Angular fused naphthopyrazolediones (53; X = CH) are reported to be obtained when certain aryl diazonium chlorides react with 7-bromo-3,4-benzotropolone in pyridine solution. The initial product is presumably the 5-arylazo-7-bromo-3,4-benzotropolone which may rearrange through an intermediate such as (54) to form the quinone.[62]

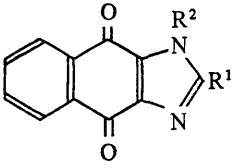
9 Imidazole

Examples of all possible types of quinones in the benzimidazole series have been obtained by oxidation of the appropriate dihydroxybenzimidazoles. The yields are, in general, quite good.[63,64]

Linear naphthimidazole-4,9-diones (55) may be prepared by dichromate oxidation of the parent base[65] but this method is of limited application because 2,3-diaminonaphthalenes necessary for the preparation of the parent bases are not easily available and the vigorous conditions employed during oxidation limit variation in substituents. Hoover and Day[66] have developed a versatile

[61] H. Brockmann and T. Reschke, *Tetrahedron Letters*, 1965, 4593.
[62] S. Ebine, *Bull. Chem. Soc. Japan*, 1965, **38**, 2029.
[63] L. Weinberger and A. R. Day, *J. Org. Chem.*, 1959, **24**, 1451; L. C. March and M. M. Jouillié, *J. Heterocyclic Chem.*, 1970, **7**, 249.
[64] E. R. Zakhs and L. S. Efros, *Zhur. obshchei Khim.*, 1964, **34**, 956 (*Chem. Abs.*, 1964, **60**, 15857); E. R. Zakhs, V. I. Minikin, and L. S. Efros, *Zhur. org. Khim.*, 1965, **1**, 1466 (*Chem. Abs.*, 1966, **64**, 1726); E. R. Zakhs and L. S. Efros, *Zhur. obshchei Khim.*, 1964, **34**, 1633 (*Chem. Abs.*, 1964, **61**, 5636).
[65] K. Fries, R. Walter, and K. Schilling, *Annalen*, 1935, **516**, 248.
[66] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1954, **76**, 4148.

synthesis in which the key step is a base-catalysed cyclisation of naphthoquinones (3; R^1 = NHCOR, R^2 = NH_2). It has been demonstrated that the electron-acceptor ability of the group R does not effect qualitatively the tendency to cyclise and the yields are generally good.[67] The cyclisation of naphthoquinones (3; R^1 = NHCOR, R^2 = NH_2) can also be effected satisfactorily by acid treatment, under reducing conditions, followed by aerial oxidation of the hydroquinone form of the quinone (55; R^1 = R, R^2 = H).



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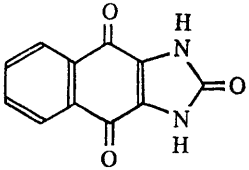

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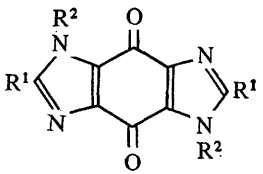

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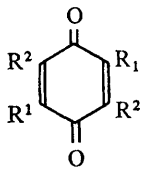


(58)

Base treatment of the naphthoquinone (3; R^1 = $NHCO_2Me$, R^2 = NH_2) leads to the formation of imidazolone (56) which, in the normal way, may be converted into the 2-chloro-derivative (55; R^1 = Cl, R^2 = H) and hence into a number of 2-substituted derivatives.[68] Nucleophilic substitution reactions show that because of the electron-withdrawing effect of the quinone ring, the chloro-substituent in (55; R^1 = Cl, R^2 = Me) is more labile than that in 2-chloro-benzimidazole itself.[69]

The imidazole ring in quinones of type (55; R^1 = R, R^2 = H) is stable to both acid and base, and is not opened under Schotten–Baumann conditions,[66] a fact which may be attributed to the electron-withdrawing effect of the quinone moiety. Ring opening to yield bis-aminated naphthoquinones may be achieved by quaternisation followed by treatment with base.[70] A methyl group in the

[67] V. S. Kuznetsov and L. S. Efros, *Zhur. org. Khim.*, 1965, **1**, 1458 (*Chem. Abs.*, 1966, **64**, 727a).
[68] V. S. Kuznetsov and L. S. Efros, *Zhur. org. Khim.*, 1967, **3**, 393 (*Chem. Abs.*, 1967, **67**, 3069).
[69] G. N. Kulbitskii and L. S. Efros, *Zhur. org. Khim.*, 1967, **3**, 575 (*Chem. Abs.*, 1967, **67**, 11456).
[70] P. Truitt, D. Hayes, and L. T. Creagh, *J. Medicin. Chem.*, 1964, **7**, 362.

2-position of the imidazole ring is sufficiently acidic to condense with aromatic aldehydes.[70]

A large number of derivatives of benzodi-imidazole-4,8-dione (57) have been prepared and some have been found to possess sedative and vasodilatory effects.[71] Fries and Reitz[72] found that on treatment with alcoholic alkali at 260 °C, the benzoquinone (58; R^1 = NHCOMe, R^2 = NHPh) was converted into the tricyclic quinone (57; R^1 = Me, R^2 = Ph), in low yield. It has also been shown that chromic acid oxidation of benzodi-imidazoles possessing no substituents at positions 4 and 8 produces quinones of type (57).[73] Both of these methods are unsuitable for general synthetic work because the former is restricted to the formation of 1-aryl derivatives and the latter to 2,6-disubstituted compounds. Marxer[71] has shown that the quinols derived from benzoquinones of type (58; R^1 = NHCOMe, R^2 = NHAlkyl) may be converted smoothly into the diones (57; R^1 = Me, R^2 = Alkyl) by mild acid treatment followed by oxidation. This method resembles that of Hoover and Day for the synthesis of naphth-imidazole-diones discussed above and is probably the most attractive route to benzodi-imidazole-4,8-diones in view of the mild conditions employed and the variation in substituents allowed.

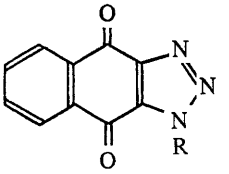
10 1,2,3-Triazole

1,3-Dipolar addition reactions involving 1,4-quinones and azides lead to the formation of *para*-quinones containing a triazole ring. Thus, methyl azide reacts with 1,4-naphthoquinone in benzene to form triazole (59; R = Me).[74] Similar reactions occur with benzo- and *p*-toluquinones but mixtures of isomers result.[75,58b]

Oxidation of hydroxyamino- and dihydroxy-benzotriazoles may also be used in the synthesis of benzotriazole quinones and an interesting example has been reported recently by Rees and West.[76] Oxidation of 4,7-dihydroxy-1-amino-benzotriazole with silver oxide in tetrahydrofuran yields quinone (60) as an unstable oil, which on oxidation with lead tetra-acetate forms benzynequinone (cyclohex-1-en-4-yn-3,6-dione). Although it could not be isolated, benzotriazole-4,5-dione has been obtained in solution by oxidation of 4-amino-5-hydroxy-benzotriazole. Its existence was confined by reaction with sulphur dioxide in solution to yield 4,5-dihydroxybenzotriazole-7-sulphinic acid.[77]

In an extension of his polyhydroxyquinone synthesis, Weygand has shown that triazole-4,5-dialdehydes undergo a double benzoin condensation with glyoxal in the presence of air to form 5,6-dihydroxybenzotriazole-4,7-diones (64; R = alkyl or aryl).[78] The yields are, in general, low.

[71] A. Marxer, *Helv. Chim. Acta*, 1961, **44**, 762.
[72] K. Fries and H. Reitz, *Annalen*, 1936, **527**, 38.
[73] L. S. Efros, *Zhur. obshchei Khim.*, 1952, **22**, 1015 (*Chem. Abs.*, 1953, **47**, 12366g).
[74] L. F. Fieser and J. L. Hartwell, *J. Amer. Chem. Soc.*, 1935, **57**, 1479.
[75] L. Wolff and G. K. Gran, *Annalen*, 1912, **394**, 68.
[76] C. W. Rees and D. E. West, *J. Chem. Soc.* (*C*), 1970, 583.
[77] L. F. Fieser and E. L. Martin, *J. Amer. Chem. Soc.*, 1935, **57**, 1835.
[78] F. Weygand and K. Henkel, *Chem. Ber.*, 1943, **76**, 818.



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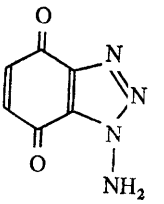

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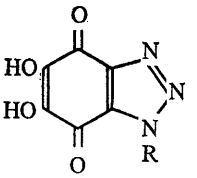

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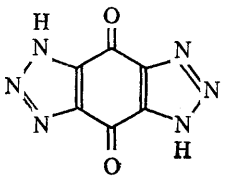

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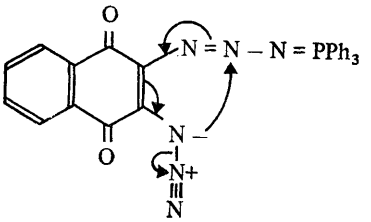


(63)

The standard synthesis of benzotriazoles from *ortho*-diamines and nitrous acid has been applied successfully to the formation of quinones containing a triazole ring. 2,5-Diamino-3,6-diacetamido-1,4-benzoquinone on treatment with nitrous acid undergoes diazotisation, followed by cyclisation to yield the benzobistriazole derivative (62). A similar reaction with 2-amino-3-acetamido-1,4-naphthoquinone failed because of the insolubility of the quinone in the reaction medium. However, when the quinone was reduced to the quinol prior to treatment with nitrous acid, the quinone (59; R = H) was formed in 46% yield. The loss of the acyl group occurs either during the reaction or on work up.[79]

A number of 2-aminonaphthotriazole-4,9-diones, which are useful pigments for plastics, have been prepared. 2,3-Diazidonaphthoquinone (3; $R^1 = R^2 = N_3$) reacts with one mole of triphenylphosphine to yield the triazole (52; R = N=PPh_3, X = N) which may be hydrolysed by acid to 2-aminotriazole (52; R = NH_2, X = N). It has been suggested that quinone (63) is the key intermediate which on cyclisation and elimination of nitrogen (see arrows) forms the triazole (52; R = N=PPh_3, X = N). Reaction of 2,3-diazido-1,4-naphthoquinone with two moles of triphenylphosphine leads to a mixture of triazole (52; R = N=PPh_3, X = N) and quinone (3; $R^1 = R^2$ = N=PPh_3) in yields dependent upon the solvent employed.[80]

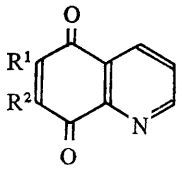
11 Pyridine

Representatives of all four possible *ortho*- and *para*-quinones based upon the

[79] L. F. Fieser and E. L. Martin, *J. Amer. Chem. Soc.*, 1935, **57**, 1844.
[80] W. L. Mosby and M. L. Silva, *J. Chem. Soc.*, 1965, 1003.

quinoline nucleus have been prepared. However, the majority of the synthetic work has been concerned with the 5,8-diones which are of interest because of possible involvement in the antimalarial activity of certain quinolines and because of their relationship to the biologically active 1,4-naphthoquinones.[81]

Quinoline-5,8-diones are normally obtained by the oxidation of 5,8-diamino-, 5(8)-amino-8(5)-hydroxy-, and 5,8-dihydroxy-quinolines.[81a] The 5,8-diamino-quinolines are usually obtained by a coupling reaction between diazotised sulphanilic acid and a 5- or 8-aminoquinoline, followed by reduction. 5-Amino-quinoline is known to couple at both the 6- and 8-positions and, consequently, this method works best if there is a substituent adjacent to the amino-group to prevent coupling in the *ortho*-position. Thus, 6-alkyl-5- and 7-alkyl-8-amino-quinolines form a single coupled product in almost quantitative yield. 5- and 8-Hydroxyquinolines also couple with diazotised sulphanilic acid and the product can be reduced to a hydroxyaminoquinoline, but this method suffers from the disadvantage that homologues of 5- and 8-hydroxyquinolines are not easily available. The quinones from oxidation of the diamino- and hydroxyamino-quinolines are obtained in 20—70% yield.



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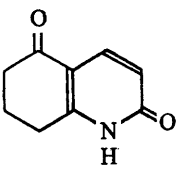

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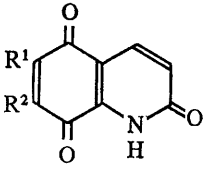


(66)

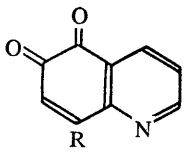
The addition reactions of quinoline-5,8-diones resemble closely those of the corresponding naphthoquinones although small differences arise owing to the presence of the hetero-atom. The addition of an aromatic amine to the quinone (64; $R^1 = R^2 = H$) leads to a mixture of the 6- and 7-amino-compounds (64; $R^1 = NHAr$, $R^2 = H$) and (64; $R^1 = H$, $R^2 = NHAr$) respectively, with the former in excess. In the presence of cerium ion, the 6-amino-compound is the sole product. Likewise, amination of the 6- and 7-chloroquinones (64; $R^1 = Cl$, $R^2 = H$) and (64; $R^1 = H$, $R^2 = Cl$) yields the aminated products (64; $R^1 = Cl$, $R^2 = NHAr$) and (64; $R^1 = NHAr$, $R^2 = Cl$) respectively, but in the presence of cerium ion, attack by amine occurs solely at position 6. The preference for attack at position 6 has been explained in terms of electron withdrawal owing to the ring nitrogen atom. This effect will be greatest at position 8 (*cf.* α-position of pyridine) and will tend to decrease the electron density at position 6, making it more susceptible to nucleophilic attack. It has been argued that cerium ions co-ordinate with the carbonyl group at position 8 and this emphasises the

[81] (*a*) R. Long and K. Schofield, *J. Chem. Soc.*, 1953, 3161; (*b*) N. L. Drake and Y. T. Pratt, *J. Amer. Chem. Soc.*, 1951, **73**, 544; (*c*) L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Medicin. Chem.*, 1967, **10**, 513.

electron deficiency at position 6.[82] The decreased electron density in the 6,7-double bond owing to the presence of the hetero-atom is further illustrated by the observation that quinone (64; $R^1 = R^2 = H$) undergoes the Diels–Alder reaction with a variety of dienes more readily than does naphthoquinone.[83]

Pettit and co-workers[84] have developed routes to carbostyril-5,8-diones in a search for effective anti-malarials. When the ketone (65), prepared from 3-amino-cyclohex-2-enone and methyl propiolate, is oxidised by air, in the presence of potassium t-butoxide, the quinone (66; $R^1 = OH$, $R^2 = H$) is obtained in 70% yield. The latter may be converted by standard reactions into the carbostyril [66; $R^1 = OH$, $R^2 = (n\text{-}C_5H_{11})_2C(OH)(CH_2)_8$], an analogue of the antimalarial lapinone.

Quinoline-5,6-diones (67) have been obtained in good yields by the action of Fremy's salt on 8-substituted-5-hydroxyquinolines. In cases where the 8-substituent is chlorine, the nature of the product depends upon the pH of the reaction mixture. Under acidic conditions the 8-chloro-5,6-dione (67; R = Cl) is obtained, but in neutral solution a dimeric product (68) is formed by displacement of chloride from quinone (67; R = Cl) by the phenolic hydroxyl of a molecule of unoxidised starting material.[85] Phenols are known to undergo *ortho*-hydroxylation on aerial oxidation in the presence of cupric ion–amine mixtures[86] and this reaction has been employed in the formation of a large number of 8-aminoquinoline-5,6-diones (67; R = NX_2). Thus, oxidation of 6-hydroxyquinoline in the presence of piperidine and cupric acetate yields quinone (67; R = N⟨⟩) by hydroxylation followed by oxidation to the *ortho*-quinone, 1,4-addition of amine, and further oxidation.[87]



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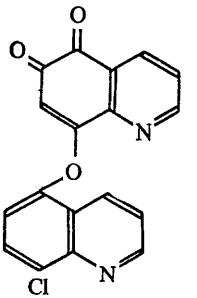

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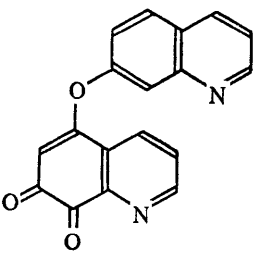
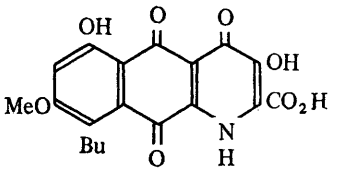


(69)

[82] Y. T. Pratt, *J. Org. Chem.*, 1962, **27**, 3905.
[83] (*a*) J. F. Munshi and M. M. Jouillié, *J. Heterocyclic Chem.*, 1967, **4**, 133; (*b*) A. J. Birch, D. N. Butler, and J. B. Siddall, *J. Chem. Soc.*, 1964, 2941.
[84] G. R. Pettit and L. E. Houghton, *J. Medicin. Chem.*, 1968, **11**, 1080; G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, 1968, **33**, 1089.
[85] H. J. Teuber and S. Benz, *Chem. Ber.*, 1967, **100**, 2918.
[86] W. Brackmann and E. Havinga, *Rec. Trav. chim.*, 1955, **74**, 1107.
[87] Y. S. Tsizin and M. V. Rubstov, *Khim. geterotsikl. Soedinenii*, 1967, 291; *ibid.*, 1969, 682, 687.

5-Substituted-7-hydroxyquinolines possessing an unsubstituted 8-position are oxidised by Fremy's salt to the rather unstable quinoline-7,8-diones. The rate of formation of these quinones is slow and in the absence of a substituent at position 5 the products are dimeric. In acid solution formation of a carbon–carbon bond occurs between position 5 of the quinone and position 8 of the starting phenol and in neutral solution a carbon–oxygen linkage is formed to yield (69).[88]



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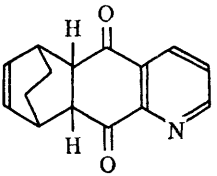

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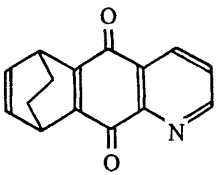

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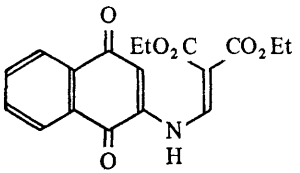

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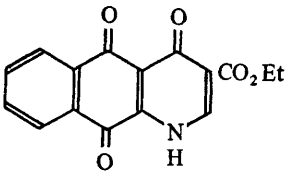

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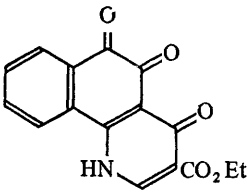

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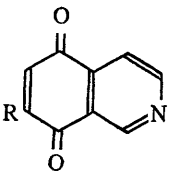


(76)

The characterisation of a naturally occurring 1-aza-anthraquinone phomazarin (70)[89] has stimulated the synthesis of these compounds. Two methods which have found general application in the synthesis of anthraquinones have been extended to simple aza-analogues. Cyclisation of 3-benzoylpyridine-2-carboxylic acids[90] and chromic acid oxidation of benzo[*g*]quinolines[91] leads to the forma-

[88] H. J. Teuber and S. Benz, *Chem. Ber.*, 1967, **100**, 2077.
[89] A. J. Birch, D. N. Butler, and R. W. Rickards, *Tetrahedron Letters*, 1964, 1853.
[90] H. Raudnitz, *Chem. Ber.*, 1929, **62**, 509.
[91] K. Schofield and D. E. Wright, *J. Chem. Soc.*, 1965, 6074.

tion of 1-aza-anthraquinones in fair yields. Birch[83b] has shown that the Diels–Alder adduct (71) formed from quinoline-5,8-dione and 1,3-cyclohexadiene may be converted into quinone (72) by enolisation followed by oxidation with silver oxide. The latter quinone on vacuum sublimation undergoes loss of the two-carbon bridge *via* an Alder–Rickert reaction to form 1-aza-anthraquinone.[83b] The overall yield is about 50% and since a number of conjugated cyclohexadienes are readily available this method offers an attractive approach to the synthesis of 1-aza-anthraquinones. One disadvantage of this route is that the use of an unsymmetrical diene may result in a mixture of adducts.

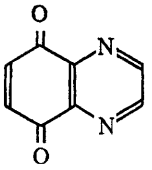
An extension of the Conrad–Limpach synthesis of 4-quinolines has been employed in the formation of a 4-hydroxy-1-aza-anthraquinone. Diethyl ethoxymethylenemalonate reacts with 2-amino-1,4-dihydroxynaphthalene to give, after oxidation, the quinone (73) which, on refluxing in a high boiling inert solvent, undergoes cyclisation with loss of ethanol to form (74) in reasonable yield. A similar reaction sequence using 4-amino-1,2-dihydroxynaphthalene leads to the formation of the 4-azaphenanthraquinone (75).[92]

In comparisons with the quinoline diones the isoquinoline derivatives have received scant attention and the *para*-quinones form the only well-characterised group. Oxidation of 5,8-diamino-, 5-amino-8-hydroxy-, and 5,8-dihydroxyisoquinolines may be employed in their synthesis.[93] The electron-withdrawing effect of the ring nitrogen atom in quinone (76; R = H) would be expected to have most effect on the carbonyl at position 5 (*cf.* γ-position of pyridine), thus making nucleophilic attack at position 7 more favourable, and it has been demonstrated that 7-morpholinoisoquinoline-5,8-dione (76; R = morpholino) is the sole product from the reaction of quinone (76; R = H) with morpholine.[94]

12 Diazines

Interest in the quinoxalines has centred around the 5,8-diones (77) because of their potential as vitamin K antagonists. Oxidation of the appropriate quinoxaline-5,8-diol with silver oxide is a commonly used method of preparation and the yields are usually good.[95] Oxidative demethylation of 5,8-dimethoxyquinoxalines with nitric acid may also be used, although oxidation at a nitrogen atom has been observed.[95] The presence of two nitrogen atoms in these quinones greatly increases the electrophilicity of the 6,7-double bond so that Diels–Alder adducts are readily formed with a number of dienes of varying reactivity and geometry.[96] 1,4-Addition of amines and acids in aprotic solvents also occurs more readily than in the naphthoquinone series.[97]

[92] K. H. Dudley and R. L. McKee, *J. Org. Chem.*, 1967, **32**, 3210.
[93] (*a*) P. K. Joseph and M. M. Jouillié, *J. Medicin. Chem.*, 1964, **7**, 801; (*b*) L. F. Fieser and E. L. Martin, *J. Amer. Chem. Soc.*, 1935, **57**, 1840; (*c*) M. Lora-Tamayo, R. Madronero, and M. Stud, *Chem. Ber.*, 1962, **95**, 2176.
[94] M. M. Jouillié and J. K. Puthenpurayil, *J. Heterocyclic Chem.*, 1969, **6**, 697.
[95] (*a*) J. Adachi, *J. Chem. Soc. Japan*, 1955, **76**, 311 (*Chem. Abs.*, 1957, **51**, 17936); (*b*) M. R. W. Levy and M. M. Jouillié, *J. Heterocyclic Chem.*, 1964, **1**, 171.
[96] W. F. Gum and M. M. Jouillié, *J. Org. Chem.*, 1965, **30**, 2583.
[97] W. F. Gum and M. M. Jouillié, *J. Org. Chem.*, 1967, **32**, 53.



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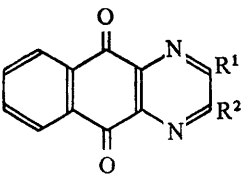

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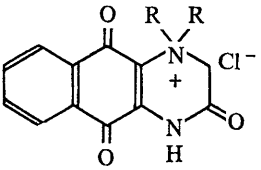

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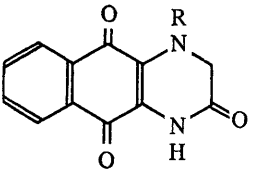

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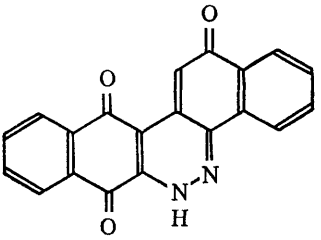

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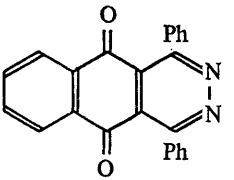


(82)

1,4-Diaza-anthraquinones of the general form (78; R^1 or R^2 = Me or OH) have been synthesised from 2,3-diamino-1,4-naphthoquinone by condensation with a variety of α-dicarbonyl compounds. The methyl groups in these molecules are sufficiently reactive to condense with aromatic aldehydes in the presence of piperidine.[98] On heating in ethyleneglycol, the quinones (3; R^1 = *NN*-dialkylamino, R^2 = $NHCOCH_2Cl$) cyclise to form quaternary salts (79; R = alkyl) which undergo loss of alkyl chloride to yield 1,4-diaza-anthraquinones of type (80).[99]

Quinones derived from cinnoline, phthalazine, and quinazoline have not been studied to any great extent and only isolated references to their preparations are available. Hydrazine hydrate reacts with 1,4-naphthoquinone to yield the pentacyclic trione (81). It has been suggested that the first stage of this reaction in-

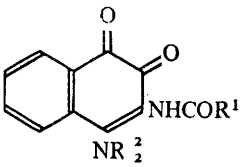
[98] G. A. Efimova and L. S. Efros, *Zhur. org. Khim.*, 1967, **3**, 388 (*Chem. Abs.*, 1967, **67**, 3068).
[99] J. R. E. Hoover and A. R. Day, *J. Amer. Chem. Soc.*, 1955, **77**, 35.

volves dimerisation of naphthoquinone to 2,2′-bisnaphthoquinone, a reaction known to occur under basic conditions. Subsequent attack by hydrazine at position 3 of one quinone nucleus followed by condensation with the carbonyl group at position 1 in the other would lead to quinone (81).[100] Condensation of hydrazine hydrate with 2,3-dibenzoyl-1,4-dihydroxynaphthalene leads to the formation of the expected azine, but this is readily oxidised by air to form the quinone (82).[18b] The preparation of quinazoline-5,8-dione by oxidative demethylation of 5,8-dimethoxyquinazoline has been reported recently.[101]

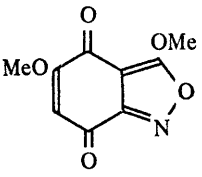
13 Oxazoles

para-Quinones containing a 1,3-benzoxazole nucleus form a well-characterised group and may be prepared by the cyclisation of either 2-halogeno- or 2-hydroxy-3-acylamino-1,4-quinones.[1,102] Carroll and Blackwell[103] have recently reported that certain 2-alkylnaphtho[2,1-*d*]oxazole-4,5-diones (83; R = alkyl) may be prepared by passing 3-acylamino-4-*NN*-dialkylamino-1,2-naphthoquinones (84; $R^1 = R^2$ = alkyl) through a neutral alumina column. A mechanism involving internal addition of the amide carbonyl to the 3,4-double bond followed by elimination of amine has been proposed.

(83)



(84)



(85)

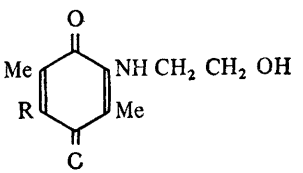
The 1,3-dipolar addition of benzonitrile oxide to 1,4-quinones leads, after oxidation of the initial adduct, to quinones containing a 1,2-benzoxazole ring, *i.e.* (49; R = Ph, X = O) from 1,4-naphthoquinone.[104]

An interesting example of a 2,1-benzoxazole-4,7-dione (85) has been isolated from the reaction of 2-chloro-5-methoxy-3-methoxycarbonyl-1,4-benzoquinone with sodium azide.[105] This reaction can reasonably be supposed to occur by displacement of chloride by azide ion, followed by loss of nitrogen to form a nitrene which then attacks the ester carbonyl group.

[100] E. S. Hand and T. Cohen, *Tetrahedron*, 1967, **23**, 2911.
[101] G. Malesarv, F. Marcolini, and G. Rodighiero, *J. Medicin. Chem.*, 1970, **13**, 161.
[102] A. N. Makarova and A. Y. Berlin, *Zhur. obshchei Khim.*, 1964, **34**, 3037 (*Chem. Abs.* 1964, **61**, 14574e).
[103] F. I. Carroll and J. T. Blackwell, *Chem. Comm.*, 1969, 923.
[104] S. Morrocchi, A. Quilico, A. Ricca, and A. Selva, *Gazzetta*, 1968, **98**, 891.
[105] W. Schäfer and H. Schulde, *Tetrahedron Letters*, 1967, 4313.

14 1,4-Oxazine

Several different types of quinones containing a 1,4-oxazine system have been described. Treatment of either 2-hydroxy-5-(β-hydroxyethylamino)- or 2,5-bis-(β-hydroxyethylamino)-1,4-xyloquinones, (86; R^1 = OH) or (86; R^1 = $NHCH_2CH_2OH$) respectively, with sulphuric acid and quenching with water gives quinone (87), by protonation of the quinone carbonyl group, followed by cyclisation of the side-chain and dehydration. Other β-hydroxyethylaminoxyloquinones behave similarly.[106] It has been demonstrated that, in chloroform solution, quinone (87) exists almost exclusively as its hydroxyquinone imine tautomer (88).[106]



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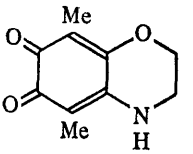
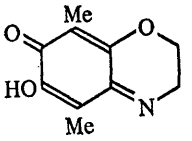


(87)



(88)

A higher homologue, quinone (27; X = NMe), arises from the ferricyanide oxidation of 2-hydroxy-*N*-methylaniline.[107] The mechanism of formation must be similar to that of quinone (27; X = O), namely oxidation of the aminophenol to the *o*-quinoneimine followed by a series of addition–oxidation steps and finally hydrolysis of the imine.

Mild alkaline treatment of 2-amino-3-(1-aziridinyl)-1,4-naphthoquinone (3; $R^1 = NH_2$, R^2 = N⟨⟩) followed by neutralisation with hydrochloric acid yields the naphtho-oxazine system (26; X = O, Y = NH). A mechanism has been proposed which involves hydrolysis of the amino-group followed by iodide ion catalysed opening of the aziridine ring to give quinone (3; $R^1 = O^-$, R^2 = $NHCH_2CH_2I$). Subsequent intramolecular cyclisation with loss of iodide ion gives the quinone (26; X = O, Y = NH).[108]

[106] I. Baxter, D. W. Cameron, and R. G. F. Giles, *J. Chem. Soc.* (*C*), 1969, 1325; I. Baxter and R. B. Titman, *ibid.*, 1970, 2078.
[107] E. Diepolder, *Chem. Ber.*, 1899, **32**, 3514.
[108] G. Casini, F. Claudi, M. Felici, M. Ferrappi, and M. Griafantini, *Farmaco*, 1969, **24**, 732.