PHENOL TAUTOMERISM

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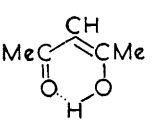
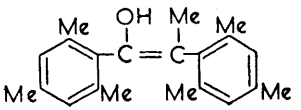
Carbonyl compounds exist almost exclusively in the keto-form unless structural features are present (*e.g.*, hydrogen bonding or steric hindrance) which stabilise the enol form as in the β-diketone (I) or the complex enol [1] (II). On the other hand, simple aromatic enols, *i.e.*, phenols, exist exclusively in the enolic form, but ketonic properties become more pronounced



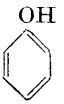
(I)



(II)

in polyhydric phenols and especially in the hydroxyl derivatives of polycyclic aromatic hydrocarbons. This Review deals with the tautomeric behaviour of aromatic enols, particularly those which can be isolated in the ketonic form. The hydroxyl derivatives of thiophen and furan are included, but not heterocyclic compounds which show lactam–lactim tautomerism.

Hydroxybenzenes.—Summation of the bond energies for the system $>CH-\underset{|}{C}=O$ and $>\underset{|}{C}=C-OH$ shows [2] that the keto-structure is more stable than the enol by *ca.* 18 kcal./mole. In phenol (III), however, the energy gained by rearrangement to the hypothetical keto-structures (IV) is offset by the simultaneous large decrease in resonance energy (*ca.* 35 kcal./mole). These figures, although only approximate, indicate that phenol must be



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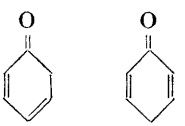
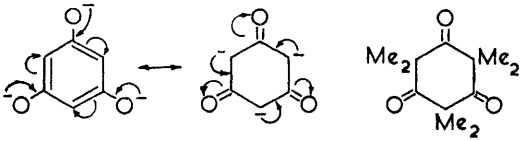


(IV)

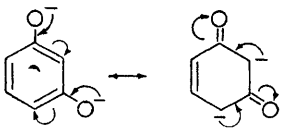
predominantly enolic. [Conant and Kistiakowsky [3] calculated the free energy of enolisation of (IV) to be − 18·6 kcal./mole.] There is in fact no evidence for the existence of the keto-forms although the presence of a minute proportion of them in equilibrium with the "enol" (III) is not ruled out (cf. acetone,[4] at the other extreme, where the enol content is only $2{\cdot}5 \times 10^{-4}\%$).

[1] Fuson, Corse, and McKeever, *J. Amer. Chem. Soc.*, 1940, **62**, 3250.
[2] Branch and Calvin, "The Theory of Organic Chemistry", Prentice-Hall Inc., New York, 1946.
[3] Conant and Kistiakowsky, *Chem. Rev.*, 1937, **20**, 181.
[4] Schwarzenbach and Wittwer, *Helv. Chim. Acta*, 1947, **30**, 669.

The introduction of additional enolic centres should assist the development of ketonic character since the energy which accrues in the formation of multiple keto-groups would compensate for the loss of resonance stabilisation. However a survey of the literature reveals no clear evidence that ketonic forms are present in solution, even in the most favourable case of phloroglucinol. (The infrared spectra [5] establish that the solids are entirely enolic.) Hayashi [6] claimed that carbonyl bands in the Raman spectrum of resorcinol (in methanol solution) confirm the existence of the ketonic form but as the measurements were obtained by irradiating the resorcinol solution for periods of 17 hours upwards, during which it became pale red, this claim is open to doubt. The ultraviolet spectrum of resorcinol is that of a normal phenol.[7] Sonn and Winter [8] concluded from bromination experiments that phloroglucinol existed in alcoholic solution in a tautomeric monoketo-form but evidence based solely on chemical reactions is inconclusive and supporting physical evidence is lacking. As judged by the infrared spectrum, phloroglucinol is entirely enolic in dioxan solution.[9] The classical evidence for the tautomeric nature of phloroglucinol is the



(V) (VI)



(VII)

formation of a trioxime,[10] the structure of which has recently been confirmed,[9] and, if hydroxylamine is replaced by ammonia, reaction under similar conditions (long storage in a closed vessel at room temperature) yields 3 : 5-dihydroxyaniline and 3 : 5-diaminophenol.[11] As these experiments with phloroglucinol were done in a basic medium the presence of the mesomeric anion (V) may be inferred but the free existence of *cyclo*hexanetrione molecules is doubtful. The only true ketones obtained from phloroglucinol are polysubstituted derivatives in which one or more of the

[5] Barnes, Gore, Liddel, and Williams, " Infrared Spectroscopy ", Reinhold, New York, 1944 ; Randall, Fowler, Fuson, and Dangl, " Infrared Determination of Organic Structures ", Van Nostrand, New York, 1949.

[6] Hayashi, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), 1933, **21**, 69.

[7] Friedel and Orchin, " Ultraviolet Spectra of Aromatic Compounds ", Wiley, New York, 1951.

[8] Sonn and Winter, *Ber.*, 1928, **61**, 2303.

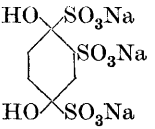
[9] Farmer and Thomson, *Chem. and Ind.*, 1956, 86.

[10] Baeyer, *Ber.*, 1886, **19**, 159.

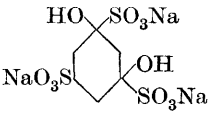
[11] Pollak, *Monatsh.*, 1893, **14**, 419.

labile hydrogen atoms has been replaced. Thus methylation with methyl iodide and aqueous potassium hydroxide gives a mixture of *O*-Me and *C*-Me compounds leading ultimately to the hexamethyl ketone (VI).[12] Chlorination of phloroglucinol also gives a hexachlorinated end-product (VI ; Cl in place of Me).[13] Similar *gem*-substitution occurs in resorcinol, but in phenols which lack a vicinal carbon atom activated by two enolic centres alkylation is restricted to simple *C*-substitution by the Claisen procedure, using reactive allyl or benzyl halides.[14] The mesomeric anion (VII) of resorcinol contains an $\alpha\beta$-unsaturated carbonyl system, the existence of which is neatly demonstrated by reduction with sodium amalgam to *cyclo*hexane-1 : 3-dione (dihydroresorcinol).[15] Hydrogenation over nickel in alkaline solution is more efficient.[16]

In a search for further evidence on the tautomeric nature of polyhydric phenols Fuchs [17] studied the addition of sodium hydrogen sulphite to quinol, resorcinol, and phloroglucinol. After prolonged reaction, adducts were obtained from quinol and resorcinol to which he assigned the structures (VIII) and (IX) respectively.* (An adduct $C_6H_6O_3,3NaHSO_3$ from phloroglucinol was not obtained pure.) These structures imply that



(VIII)



(IX)

addition has occurred at the ethylenic double bond, as well as at the tautomeric carbonyl groups, which is plausible in the case of resorcinol but the structure (VIII) is doubtful. Apart from this work, there are no other indications that quinol can react in a tautomeric form † and the product obtained by Fuchs gave a transient blue ferric chloride colour, suggesting the presence of a quinolsulphonic acid. Similar bisulphite compounds are of course intermediates in the Bucherer reaction which is of great technical importance in the naphthalene series.[18] From a study of the reaction kinetics Cowdrey and Hinshelwood [19] suggest that bisulphite adds to a C=C and not to a C=O linkage. This seems to be a necessary postulate

[12] Herzig and Erthal, *Monatsh.*, 1910, **31,** 827.
[13] Zincke and Kegel, *Ber.*, 1889, **22,** 1467.
[14] Claisen, *Annalen*, 1925, **442,** 210.
[15] Merling, *ibid.*, 1894, **278,** 28. [16] *Org. Synth.*, Coll. Vol. III, p. 278.
[17] Fuchs and Elsner, *Ber.*, 1919, **52,** 2281 ; 1920, **53,** 886 ; Fuchs, *Ber.*, 1921, **54,** 245.
[18] Reviewed by Drake, " Organic Reactions ", Wiley, New York, 1942, Vol. I, Chapt. 5.
[19] Cowdrey and Hinshelwood, *J.*, 1946, 1036 ; Cowdrey, *J.*, 1946, 1041, 1044.

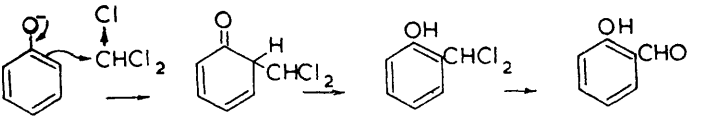
* The compounds were originally written with sulphite ester groups,

$$>C(OH)\cdot O\cdot SO_2Na.$$

† A number of substituted quinols can be obtained in both enol and keto-form by independent methods. Tautomerism is restricted to keto ⟶ enol conversion.
See p. 37.

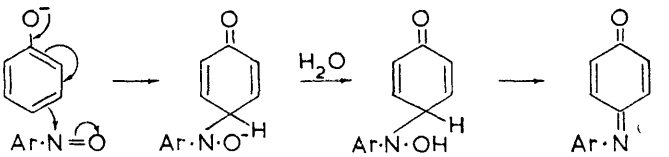
in Bucherer reactions involving secondary amines and may well be true in other cases but, until we know more about the reaction of bisulphite with aromatic compounds in general, addition products, such as those of Fuchs, are of limited value in the study of tautomerism. Bucherer and Schenkel [20] showed long ago that even pyridine forms an adduct with bisulphite, of formula $C_5H_5N,3NaHSO_3,2H_2O$; the nature of this compound is obscure but the pyridine molecule was profoundly modified as the adduct readily liberated ammonia on treatment with alkali.

Tautomerism is by no means confined to the polyhydric phenols. Many reactions of monohydric phenols involve the tautomeric form which becomes obvious if the labile hydrogen is replaced by an entering substituent, thus



(X) (XI) (XII)

enabling a ketonic product to be isolated. A well-known example is the Reimer–Tiemann reaction, the first step of which can be considered a special case of *C*-alkylation. The reaction is not impeded by small alkyl groups in the *o*- and *p*-positions so that, *e.g.*, *o*-cresol yields [21] the ketone (X) as well as the hydroxy-aldehyde (XI). The formation of a " blocked tautomer " in this way has been used by Woodward [22] as a method for the introduction of angular methyl groups. Thus the hydroxy-aldehyde formed in the reaction of 6-hydroxytetralin with chloroform in alkaline solution is accompanied by the dienone (XII) which may then be hydrogenated to a methyldecalol.

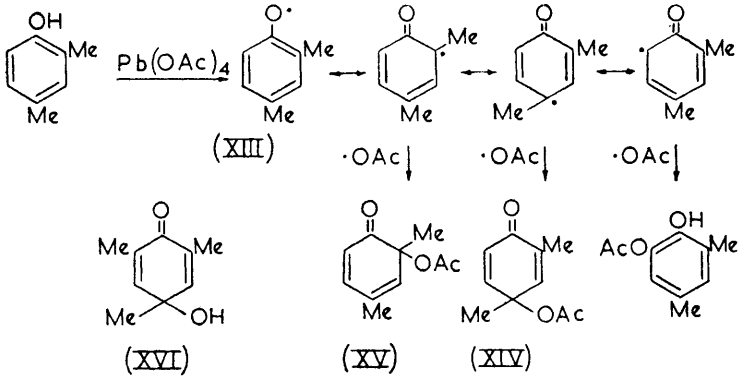


Another old reaction in this category is the formation of indophenols by condensation of arylnitroso-compounds with phenols under basic conditions. This reaction is of practical importance in the preparation of

[20] Bucherer and Schenkel, *Ber.*, 1908, **41**, 1346.
[21] Auwers and Keil, *Ber.*, 1902, **35**, 4201.
[22] Woodward, *J. Amer. Chem. Soc.*, 1940, **62**, 1208.

oxazine dyes from *p*-nitroso-dialkylanilines ; with the latter, basic conditions are obviously unsuitable and usually the phenol is condensed with the hydrochloride of the nitrosoamine in acetic acid.[23]

More recently, it has been shown that ketones may be formed by oxidation of monohydric phenols with lead tetra-acetate.[24] Here the essential intermediate is a mesomeric radical produced by dehydrogenation of a suitably substituted phenol, *e.g.*, (XIII). The final products depend upon the structure of the phenol and also on the solvent ; dimerisation occurs in benzene solution, but in acetic acid, which assists the propagation of acetate radicals, acetoxylation predominates. Phenol itself affords only a



dimeric product (4 : 4′-dihydroxydiphenyl), but with increasing *o* : *p*-substitution this reaction diminishes and with mesitol only acetoxylation occurs, irrespective of solvent. Attack by acetate radicals at substituted *o*- and *p*-positions stabilises the dienone system, 2 : 4-dimethylphenol yielding the ketones (XIV) and (XV). Similar products are obtained by oxidising phenols with organic peroxides.[25] A related reaction is Bamberger's oxidation [26] of *p*-alkylated phenols to ψ-quinols [*e.g.*, (XVI) from mesitol] by using Caro's acid in the presence of magnesium carbonate where the substitution is presumably effected by $\cdot O \cdot SO_3^-$ radical ions.

Hydroxynaphthalenes (excluding 1 : 4-naphthaquinols).—The tautomeric properties of the hydroxynaphthalenes are one of the many indications that naphthalene is less aromatic than benzene. The naphthols are in general much more reactive than phenol and share many reactions in common with resorcinol, which is to be expected in view of the large resonance stabilisation of the ketonic structures (XVII) as compared with (IV). There are, however, a few limitations due to bond fixation as seen

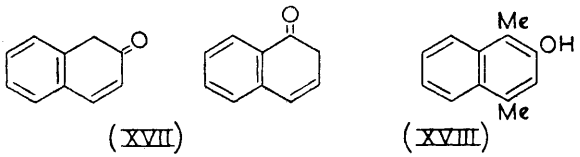
[23] Koechlin and Witt, G. P. 15,915 ; Möhlau, *Ber.*, 1883, **16,** 2843 ; 1892, **25,** 1055.

[24] Wessely *et al.*, *Monatsh.*, 1954, **85,** 69, and previous papers ; Cavill, Cole, Gilham, and McHugh, *J.*, 1954, 2785.

[25] Cosgrove and Waters, *J.*, 1951, 388 ; Campbell and Coppinger, *J. Amer. Chem. Soc.*, 1952, **74,** 1469 ; Wessely and Schinzel, *Monatsh.*, 1953, **84,** 425, 969.

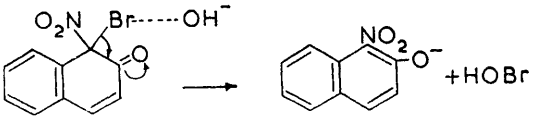
[26] Bamberger, *Ber.*, 1903, **36,** 2028.

in the failure of the naphthol (XVIII) to condense with *p*-nitrosodimethylaniline.[27]



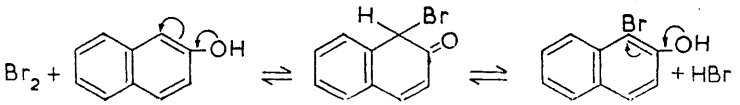
(XVII) (XVIII)

Numerous *gem*-substituted derivatives are known, especially of β-naphthol. A feature of these ketones is the ease with which blocking substituents are eliminated to restore the more stable fully aromatic structure.

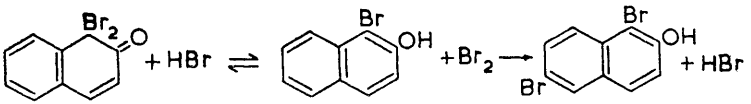


(XIX)

This tendency is demonstrated by the formation of 1-nitro-2-naphthol by reaction of the ketone (XIX) in acetone with aqueous sodium hydroxide.[28] In an extensive investigation of the halogenonaphthols, Fries [29] and his



associates showed that bromination of β-naphthol in acetic acid was a reversible reaction, and for the *gem*-dibromo-ketone (XX) this results in rearrangement to 1 : 6-dibromo-2-naphthol when the ketone is treated with

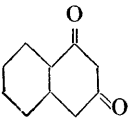


(XX)

hydrogen bromide in acetic acid. Further debromination of the dibromonaphthol (to 6-bromo-2-naphthol) is then possible. The selective removal of *o*-halogen substituents by acid reducing agents (commonly acid stannous chloride) is a useful reaction in the naphthol series. Nicolet [30] showed the reaction to be independent of the stannous chloride concentration and the first step is clearly the acid dehalogenation shown above.

[27] Wedekind, *Ber.*, 1898, **31**, 1675.
[28] Fries, *Annalen*, 1912, **389**, 315.
[29] Fries and Schimmelschmidt, *ibid.*, 1930, **484**, 245.
[30] Nicolet, *J. Amer. Chem. Soc.*, 1927, **49**, 1810.

Ketones can frequently be obtained by reduction of naphthols under basic conditions, the nearest parallel to the sodium amalgam reduction of resorcinol being the formation of the diketone (XXI) by reduction of naphtharesorcinol with Raney nickel alloy and aqueous sodium hydroxide,[31] although unfortunately the compound has not been adequately characterised. Reduction of 1 : 5- and 1 : 6-dihydroxynaphthalenes by the same method gives 5- and 6-hydroxytetralones respectively, but α- and β-naphthol are unaffected. However, reduction of β-naphthol with sodium and liquid ammonia in the presence of pentyl alcohol gives β-tetralone,[32] and the latter can also be obtained by hydrogenation of β-naphthol over palladium–charcoal in the presence of a base.[33]



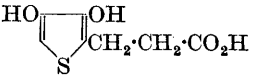
(XXI)

Hydroxythiophens.—Since tautomerisation in phenol is restricted by resonance stabilisation it would be expected that enols which form part of less aromatic systems might in some cases exist in the ketonic form. This is not found in the naphthol series but is exemplified by the hydroxythiophens. 2-Hydroxythiophen [34] (XXII) is a weak acid, it gives a red ferric chloride colour, couples in alkaline solution with diazo-compounds,

(XXII)

or

(XXIII)



(XXIV)

and forms an acetate, benzoate, and methyl ether; on the other hand, in the tautomeric keto-form (XXIII) it yields a benzylidene derivative and readily undergoes hydrolytic fission (the keto-form is of course a thiolactone). Its ultraviolet absorption (in aqueous solution) is in accord with the ketonic structure whilst the infrared spectrum of the liquid itself shows carbonyl and hydroxyl absorption and peaks corresponding to both aliphatic and aromatic C–H bonds. These properties amply demonstrate the existence of a tautomeric equilibrium, in marked contrast to phenol. It is interesting, too, that the enol derivatives (*e.g.*, the acetate and the methyl ether) of 2-hydroxythiophen and of phenol show a close physical resemblance (b.p., odour) typical of thiophen and benzene analogues, but the parent hydroxy-compounds themselves are physically dissimilar. 3-Hydroxythiophen [34] is less stable and has not been isolated in a pure state. 3 : 4-Dihydroxythiophen is known only as its dibenzoate,[35] but the compound (XXIV) has been obtained and is, as expected, entirely enolic.[36] Normally one carbonyl group of a cyclic *o*-diketone is enolised, as in this form the repulsion of the *cis*-carbon–oxygen bonds is reduced [37] and in a thiophan

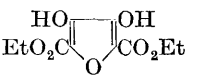
[31] Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366.
[32] Birch, *J.*, 1944, 430.
[33] Stork and Foreman, *J. Amer. Chem. Soc.*, 1946, **68**, 2172.
[34] Hurd and Kreutz, *ibid.*, 1950, **72**, 5543.
[35] Fager, *ibid.*, 1945, **67**, 2217.
[36] Karrer and Kehrer, *Helv. Chim. Acta*, 1944, **27**, 142.
[37] Dewar, " The Electronic Theory of Organic Chemistry ", Oxford, 1949, p. 102.

ring greater stability is achieved by complete enolisation giving a fully conjugated system.

Hydroxyfurans.—Much less is known about the hydroxyl compounds in this series. They appear to be predominantly ketonic, in no way resembling phenols, and with the exception of the 2-hydroxyfurans (XXV) [which exist as but-β-enolides, *e.g.*, (XXVI)] and the 2 : 5-dihydroxyfurans (*i.e.*, succinic anhydrides) the majority are unstable. This agrees with the low resonance stabilisation of the furan ring. It is doubtful if the monohydroxyfurans themselves have ever been obtained as such although both have been claimed.[38] The substances were described as crystalline solids

(XXV)

(XXVI)



(XXVII)

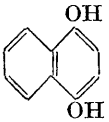
which darken and resinify spontaneously, form dark solutions in aqueous alkali, and do not reduce Tollens' reagent; yet in spite of their instability both can be nitrated, and then reduced, to give seemingly stable aminohydroxy-compounds.[39] 3-Hydroxyfuran forms an adduct with maleic anhydride but there is no real evidence for the structure of the isomeric compound (prepared by fusion of 5-sulphofuran-2-carboxylic acid with sodium hydroxide in the presence of potassium chlorate) which appears to be unlike its homologues. Cleavage of the acetate of 2-hydroxyfuran (XXV) (obtained by pyrolysis of 2 : 5-diacetoxy-2 : 5-dihydrofuran) yields crotonolactone [double-bond isomer of (XXVI)]. This occurs to some extent during the preparation [40] of 2-acetoxyfuran and again, on its treatment with chlorine or bromine (at $-5°$ to $-10°$), halogenocrotonolactones result.[41] The free existence of the enol (XXV) therefore seems very unlikely. Most known 3-hydroxyfurans are highly substituted and appear to have the properties of aliphatic keto–enol systems but physical data are lacking. 3 : 4-Dihydroxyfuran has not been prepared but the compound (XXVII) is known [42] and exists essentially in the enol form. In addition to the normal enolisation of cyclic *o*-diketones this compound, which can be regarded as two linked β-keto-ester systems, is stabilised by chelation.

Hydroxythionaphthens and Hydroxybenzofurans.—As we have seen, fusion of a second benzene ring on to phenol leads to increased ketonic character and the effect on the hydroxythiophens and hydroxyfurans is the same, the benzo-analogues being best described as thionaphthenones and benzofuranones (coumaranones and *iso*coumaranones). Both groups show the characteristic chemical properties of keto- and enol forms with the exception of the *iso*coumaranones which behave as lactones.[43, 44] They

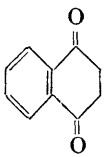
[38] Hodgson and Davies, *J.*, 1939, 806. [39] *Idem*, *J.*, 1939, 1013.
[40] Clauson-Kaas and Elming, *Acta Chem. Scand.*, 1952, **6**, 560.
[41] Elming and Clauson-Kaas, *ibid.*, p. 565.
[42] Hoehn, *Iowa State Coll. J. Sci.*, 1936, **11**, 66.
[43] Hartough and Meisel, "Compounds with Condensed Thiophen Rings", Interscience, New York, 1954.
[44] Elderfield, "Heterocyclic Compounds", Wiley, New York, 1951, Vol. II.

probably all exist in the keto-form in the solid state ; the benzofuranones remain in the keto-form in solution but there is no reliable information concerning the thionaphthenones which may, like the hydroxythiophens, form an equilibrium in solution. Bromine estimations showed coumaranone [45] to be almost entirely ketonic and thionaphthen-3-one [46] to contain 5% of the enol form in solution, but again this is chemical evidence only. Marschalk [47] apparently obtained thionaphthen-2-one in two modifications. Distillation of a sample of m.p. 44—45° gave a product of m.p. 33—34° and in one experiment he was able to convert this back into the higher-melting form by dissolution in aqueous sodium hydroxide and acidification. This suggests that the compound, m.p. 44—45°, is the enol and the compound, m.p. 33—34°, is the keto-form, but apparently it is only the latter which gives a ferric chloride colour (blue). There is evidently some confusion here, but it is just possible that Marschalk did isolate two tautomeric forms, although he did not make this claim himself. If so, this is the simplest aromatic enol known in both forms. *iso*Coumaranone is known in two crystal modifications but these are not tautomeric forms.[48]

1 : 4-Naphthaquinols.—In the naphthalene series, when two hydroxyl groups are present in the same ring it becomes possible to isolate the tautomeric diketo-form, provided that both carbonyl groups are conjugated with the second benzene ring as in (XXIX). [The gain in bond energy as a result of ketonisation (*ca.* 2 × 18 kcal./mole) is approximately equal to the loss of resonance energy of one benzene ring.] Both the dienol (XXVIII) and the diketone (XXIX) are stable compounds under normal



(XXVIII)

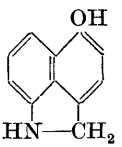


(XXIX)

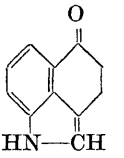
conditions and can be crystallised unchanged. A spectroscopic examination [49] has shown that the diketone exists as such both in the solid state and in solution and there is no indication of the existence of an equilibrium at ordinary temperatures. However, in the estimation of naphthaquinol by ceric sulphate titration, Braude *et al.*[50] found that the titre gradually decreased to about 75% of its original value when the quinol was heated in phenetole at 131° : tautomerisation would account for this but other factors may be concerned as the proportion of the keto-form seems rather high. The diketone * (XXIX) was first obtained by Madinaveitia and

[45] Auwers and Auffenberg, *Ber.*, 1919, **52,** 92.
[46] Auwers and Theis, *Ber.*, 1920, **53,** 2285.
[47] Marschalk, *J. prakt. Chem.*, 1913, **88,** 227.
[48] Stoermer, *Annalen*, 1900, **313,** 79.
[49] Thomson, *J.*, 1950, 1737.
[50] Braude, Jackman, and Linstead, *J.*, 1954, 3548.
* Formulated as a monoketone by Olay, *Rev. Acad. Cienc. Madrid*, 1935, **32,** 384.

Olay [51] by fusion of the dienol (XXVIII) at *ca.* 210° in a vacuum, followed by rapid cooling to " freeze the equilibrium " ; the diketone (2 : 3-dihydronaphthaquinone) was then separated by chloroform extraction. In this way about 10% of the dienol can be isolated in the tautomeric form.[49] All the simple 2 : 3-dihydronaphthaquinones have been obtained by Olay's procedure but the method is limited as some quinols decompose on being heated. A possible alternative is the catalytic method employed by Grob *et al.*[52] in the isomerisation of the enol (XXX) to the ketone (XXXI).



(XXX)



(XXXI)

In this case direct heating (at temperatures below the decomposition point) effected no rearrangement but by heating the phenol with palladium–charcoal in xylene–tetralin the ketone was obtained in 80% yield. Although keto–enol changes (*e.g.*, carvone → carvacrol [53]) and dienone → phenol rearrangements [54] have been brought about by heating with palladium–charcoal this enol → keto conversion appears to be unique. Rearrangement of the naphthalene system (in XXX) to the dihydroindole system (in XXXI) (ΔH *ca.* 4·5 kcal./mole) is possibly more favourable energetically than the conversion of the naphthalene system (in XXVIII) into the benzene system (in XXIX) but nevertheless this technique merits investigation. The reverse keto → enol change (XXIX → XXVIII) is readily effected by dissolution of the diketone in cold alkali and in practice enolisation occurs frequently under reaction conditions.

Certain reactions of naphthaquinols proceed *via* the diketo-forms although this does not establish the existence of a tautomeric equilibrium. A number of substituents, including halogen, NHPh, SR, SO_2R, SO_3H, and (in some cases) OH, can be removed from positions 2 and 3 of 1 : 4-naphthaquinones by reduction with acid stannous chloride, the first step being a rapid reduction of the quinone to the quinol (XXXIII).[55] A few *o*-substituents can also be removed from naphthols of the type (XXXII ; R = halogen, SO_3H, and probably SR *) under the same conditions, but the others are stable unless a second hydroxyl group is present as in (XXXIII). It is likely therefore that the reaction proceeds by tautomerisation to the

[51] Madinaveitia and Olay, *Anal. Fís. Quím.*, 1933, **31,** 134.

[52] Grob and Voltz, *Helv. Chim. Acta,* 1950, **33,** 1796 ; Grob and Hofer, *ibid.*, 1952, **35,** 2095.

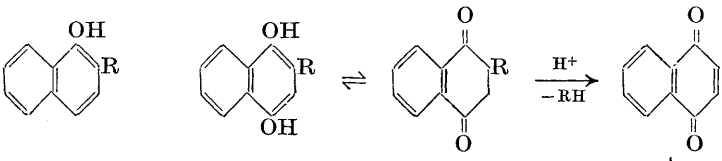
[53] Linstead, Michaelis, and Thomas, *J.*, 1940, 1139.

[54] Horning, *J. Org. Chem.*, 1945, **10,** 263 ; Leonard and Berry, *J. Amer. Chem. Soc.*, 1953, **75,** 4989.

[55] Bruce and Thomson, *J.*, 1954, 1428.

* 1-*p*-Tolylthio-2-naphthol can be reduced to β-naphthol with stannous chloride.

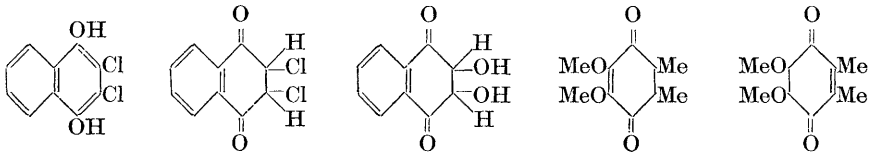
diketone (XXXIV ; R = OH, NHPh, or SO_2R) followed by acid-catalysed elimination of the substituent R as shown.



(XXXII) (XXXIII) (XXXIV) (XXVIII)

Another reaction which involves the ketonic forms of naphthaquinols is the formation of tetralins by Clemmensen reduction. Tetralin can also be obtained, less readily, by Clemmensen reduction of α- and β-naphthol, and Madinaveitia [56] considered the rate of reduction to be proportional to the ease of tautomerisation. The diketone (XXIX) forms a bis-*p*-nitrophenylhydrazone : attempts to obtain this by reaction of the dienol (XXVIII) with *p*-nitrophenylhydrazine produce only 4-*p*-nitrophenylazo-1-naphthol, the initial hydrazone, formed by condensation at one enolic centre, being oxidised in the tautomeric hydrazo-form.

A number of naphthaquinols are known in both keto- and enol forms which are not interconvertible : 2 : 3-dichloronaphthaquinol (XXXV) and 1 : 4-naphthaquinone dichloride (XXXVI) are typical. Enol ⟶ keto conversion cannot be brought about by fusion, as the dienol decomposes at high temperatures, and the reverse change is restricted by the tendency of the diketone to form a quinone by elimination of hydrochloric acid. This is facilitated by both acids and bases, so that in ketones of type

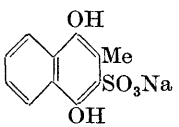


(XXXV) (XXXVI) (XXXVII) (XXXVIII) (XXXIX)

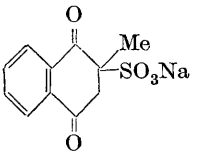
(XXXVI) enolisation and elimination reactions, which proceed *via* similar ionic intermediates, are in competition and the result depends upon the structure of the diketone and sometimes on the catalyst. In naphthalene compounds elimination predominates, but concurrent enolisation and elimination has been observed in a few instances, whereas the corresponding benzenoid compounds show a greater tendency to rearrange to aromatic structures as shown by the natural product, gliorosein (XXXVIII or XXXIX), which rapidly enolises in a basic medium.[57] Benzoquinone dichloride slowly forms the corresponding dienol diacetate when warmed with acetic anhydride in the presence of sulphuric acid, but if the catalyst is changed to toluene-*p*-sulphonic acid the elimination proceeds more

[56] Madinaveitia, *Anal. Fis. Quim.*, 1934, **32**, 1100.
[57] Vischer, *J.*, 1953, 815.

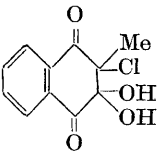
rapidly and the product (after re-addition of the hydrochloric acid) is 2 : 5-dichloroquinol diacetate. Under the same conditions the dichloride (XXXVI) gives only 2-chloro-1 : 4-naphthaquinone. Again, when benzoquinone dichloride is suspended in acid stannous chloride at 0° both elimination and enolisation occur and a mixture of 2-chloro- and 2 : 3-dichloro-quinol is obtained.[58] Amongst related naphthalene compounds Russian workers[59] have shown that 2 : 3-epoxynaphthaquinone in hot aqueous solution gives, *via* the glycol (XXXVII), a mixture of 2-hydroxy-1 : 4-naphthaquinone (by elimination) and 2 : 3-dihydroxy-1 : 4-naphthaquinone (by enolisation and aerial oxidation), and the latter is also obtained by aeration of the diacetate of (XXXVII) in alcoholic potassium hydroxide.[60] Blocked tautomers are also found in this group but, whereas they are obtained from monohydric phenols by substitution reactions, here they are usually formed by quinone addition reactions, *e.g.*, addition of sodium hydrogen sulphite to 2-methyl-1 : 4-naphthaquinone gives both the quinol (XL) and the diketone (XLI).[61] The compound (XLII), obtained by addition of hypochlorous acid to 3-hydroxy-2-methyl-1 : 4-naphthaquinone,



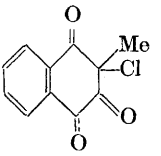
(XL)



(XLI)

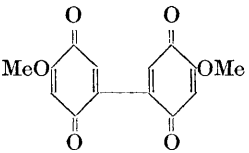


(XLII)

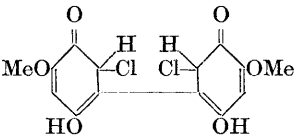


(XLIII)

is remarkable[62] in that it does not revert to a quinone when heated *in vacuo* but loses water to form the triketone (XLIII). In one instance a non-enolisable ketone has been obtained in the diphenyl series by a quinone addition reaction : addition of hydrochloric acid to the diquinone (XLIV)



(XLIV)



(XLV)

gives the adduct (XLV) (and not the isomeric diquinol), which, in spite of the extended conjugated system in the compound, is very unstable and on attempted crystallisation dissociates into the original components.[63]

The introduction of hydroxyl groups at the *peri*-positions of 2 : 3-dihydro-

[58] Dimroth, Eber, and Wehr, *Annalen*, 1925, **446**, 132.

[59] Shchukina, Khokhlov and Shemyakin, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 908.

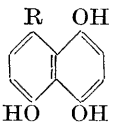
[60] Shchukina, Vinogradova, and Shemyakin, *ibid.*, p. 1661.

[61] Cormack, Moore, and Balis, *J. Amer. Chem. Soc.*, 1950, **72**, 844 ; Moore and Washburn, *ibid.*, 1955, **77**, 6384.

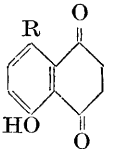
[62] Shvetsov and Shemyakin, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 480.

[63] Lindberg, *Acta Chem. Scand.*, 1951, **5**, 885 ; Erdtman, *Proc. Roy. Soc.*, 1933, *A*, **143**, 191.

naphthaquinone, as in β-hydrojuglone (XLVII ; R = H) and β-hydronaphthazarin (XLVII ; R = OH), stabilises the diketo-system,* in part

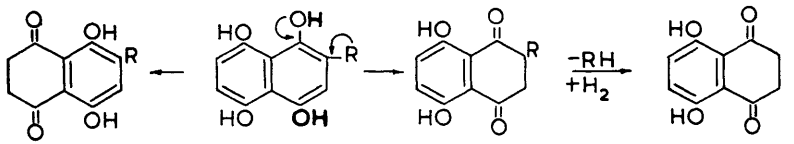


(XLVI)



(XLVII)

by strong hydrogen bonding, and lowers the activation energy for the enol ⟶ keto change so that these ketones can be obtained under much less vigorous conditions. Thus, when a solution of α-hydrojuglone (XLVI ; R = H) in dilute hydrochloric acid (containing a little stannous chloride to prevent oxidation) is warmed it becomes yellow and the keto-form can be isolated by chloroform extraction. If the colourless solution is then set aside it slowly becomes yellow again as the equilibrium is restored.† The tetrahydroxynaphthalene (XLVI ; R = OH) behaves in the same way but, as this compound is very susceptible to oxidation, β-hydronaphthazarin is normally made by reduction of naphthazarin (5 : 8-dihydroxy-1 : 4-naphthaquinone) in hot acid stannous chloride solution from which it crystallises on cooling (90% yield [64]). Elimination of substituents from naphthaquinols proceeds much more readily when a *peri*-hydroxyl group is present and a new feature arises in the case of substituted α-hydronaphthazarins.[65, 66] The compound (XLIX) can tautomerise in two ways, the reaction being controlled by the substituent. It can be seen that tautomerisation at one enolic centre will be opposed by the + *T* effect of the



(XLVIII) (XLIX) (L)

group R, and consequently rearrangement will occur preferentially in the other ring. Hence, in the reduction of naphthazarins, where R = OH or NHPh, ketones of type (XLVIII) are formed, but where R = SO_2R the alternative (L) is produced and the substituent is then eliminated to give

[64] Wheeler and Edwards, *J. Amer. Chem. Soc.*, 1916, **38,** 387.

[65] Bruce and Thomson, *J.*, 1952, 2759.

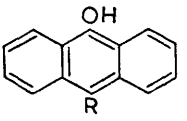
[66] *Idem*, *J.*, 1955, 1089.

* The 7-methyl derivative of (XLVII ; R = H) occurs in Nature (Cooke, Dowd, and Webb, *Nature*, 1952, **169,** 974 ; Cooke and Dowd, *Austral. J. Sci. Res.*, 1952, **5,** *A*, 760 ; *Austral. J. Chem.*, 1953, **6,** 53).

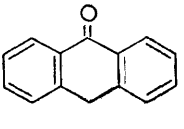
† Olay (*Rev. Acad. Cienc. Madrid*, 1935, **32,** 384) found (by Meyer estimation) that 2-methyl-β-hydrojuglone was 43% ketonic at equilibrium and 1 : 4-naphthaquinol 10% ketonic. Both figures are probably too high but they illustrate the difference between the two compounds.

β-hydronaphthazarin as the final product. Weaker + *T* groups (SR and halogen) are also eliminated but this of course occurs in simple naphthols.

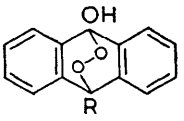
Hydroxyanthracenes.—In the anthracene series the general pattern is very similar to that seen in the naphthalene compounds, the hydroxyl derivatives showing a greater tendency to exist in the tautomeric keto-form. Of the monohydroxy-compounds, α- and β-anthranol are very like α- and β-naphthol, but in 9-anthranol (LI ; R = H) we have the simplest monohydroxy-aromatic compound (excluding 2-hydroxythionaphthen) which is stable in both tautomeric forms. The keto-form (LII) (cf. benzophenone) is the more stable, which implies that the resonance energy associated with the central " benzene " ring is < 18 kcal./mole, in accord with the absence



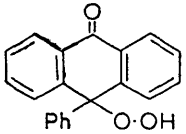
(LI)



(LII)

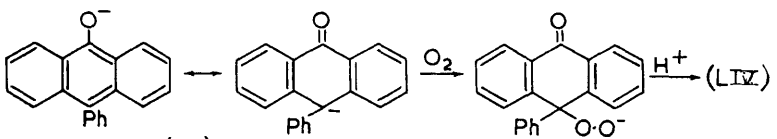


(LIII)



(LIV)

of aromatic properties. In his classical work Meyer [67] showed that both forms tautomerise slowly in solution (in the absence of catalysts), the equilibrium attained being always predominantly ketonic. On slow cooling, a melt crystallises as anthrone, but after rapid cooling some anthranol is also present. The chemical properties of the two forms are quite distinct at ordinary temperatures, the keto-form being comparatively unreactive in the absence of enolising catalysts. It was observed by Julian *et al.*[68] that 10-alkyl(and -aryl)-anthranols (LI) readily took up atmospheric oxygen to form peroxides, considered to have the transannular structure (LIII) as they could be reduced catalytically to the corresponding 10-alkyl-



(LV)

oxanthranols and, on pyrolysis, they yielded anthraquinone and the corresponding alcohol. The transannular structure was disputed by Dufraisse *et al.*,[69] and by a detailed study of the oxidation product of 9-phenylanthranol

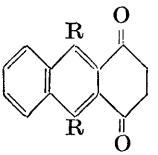
[67] Meyer, *Annalen*, 1911, **379**, 37.

[68] Julian and Cole, *J. Amer. Chem. Soc.*, 1935, **57**, 1607 ; Julian, Cole, and Diemer, *ibid.*, 1945, **67**, 1721.

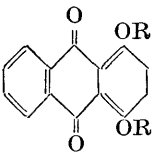
[69] Dufraisse, Etienne, and Rigaudy, *Bull. Soc. chim.* (*France*), 1948, 804.

they established the keto-hydroperoxide structure (LIV). These anthranols therefore fall into line with a number of other aryl-substituted enols which form hydroperoxides.[70] Of particular interest is the formation of the keto-hydroperoxide (LIV) by aeration of an alkaline solution of the anthranol which involves oxidation of the mesomeric anion (LV) as shown.

Relatively little is known of the dihydroxyanthracenes. 1 : 4-Dihydroxyanthracene is converted into the diketo-form (LVI ; R = H) by fusion (50% yield),[65] and the diphenyl derivative (LVI ; R = Ph) is formed merely by treating a solution of 1 : 4-dihydroxy-9 : 10-diphenylanthracene with hydrochloric acid.[71] As in the naphthalene series very stable diketones are formed when *peri*-hydroxyl groups are present. *leuco*Quinizarin (LVI ; R = OH) is easily obtained by reduction of quinizarin in hot acid solution : [72] it enolises in alkaline solution but the tetrahydroxyanthracene obtained on acidification rearranges to the more stable diketone during crystallisation. The structure of the compound (LVI ; R = OH) is established by its synthesis from naphthaquinol and succinic anhydride [73] and by its infrared spectrum,[74] but the structures of the diacetate and dimethyl ether are uncertain. By treatment of *leuco*quinizarin with acetyl chloride in cold pyridine, the diacetate can be formed without enolisation of the carbonyl



(LVI)



(LVII)

groups (this is verified by acetylation of β-hydronaphthazarin and β-hydrojuglone in the same way). The identical diacetate can also be obtained by reduction of quinizarin diacetate in the cold with zinc and acetic acid, followed by warming of the solution of 1 : 4-diacetoxyanthraquinol in an inert atmosphere. Zahn and Ochwat [73] proposed structure (LVII ; R = Ac) for this compound which implies that *leuco*quinizarin reacts in the tautomeric form (LVII ; R = H) in the first method of preparation and a rather improbable tautomerisation occurs in the second. The alternative structure (LVI ; R = OAc) is more plausible. If this is correct, migration of the acetyl groups to *peri*-positions must have occurred in the course of the synthesis from quinizarin diacetate ; there are several precedents for this : similar migration of acyl groups has been observed, under various conditions, in glycerides,[75] *o*-dihydroxyanthraquinones,[76] and,

[70] Criegee in Houben-Weyl, " Methoden der Organischen Chemie ", Georg Thiem Verlag, Stuttgart, 4th Edn., 1952, Vol. 8, p. 25.

[71] Bichet, *Ann. Chim.* (*France*), 1952, **7**, 235.

[72] Meyer and Sander, *Annalen*, 1920, **420**, 113.

[73] Zahn and Ochwat, *ibid.*, 1928, **462**, 72.

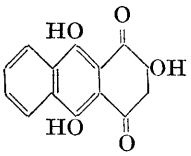
[74] Flett, *J.*, 1948, 1441.

[75] Daubert and King, *J. Amer. Chem. Soc.*, 1938, **60**, 3003.

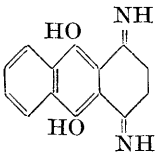
[76] Kubota and Perkin, *J.*, 1925, **127**, 1889 ; Perkin and Storey, *J.*, 1928, 229 ; Perkin and Storey, *J.*, 1929, 1399.

in one instance, in a *peri*-dihydroxynaphthalene.[77] *leuco*Quinizarin dimethyl ether presents a similar problem : it is formulated [73] as (LVII ; R = Me) but it is not clear how this arises by reduction of quinizarin dimethyl ether.

In general, β-substituents (Cl, OH, SO_3H, NHPh) [72, 78] are very readily eliminated on reduction of quinizarins. There is, however, one case (purpurin) in which reduction (in the absence of strong acids) leads to retention of a β-substituent : the product (LVIII), on subsequent treatment with strong acid or alkali, is smoothly converted into quinizarin and no doubt analogues of (LVIII) could be obtained by reduction in the same way.

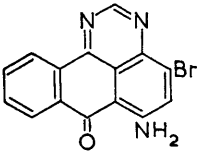


(LVIII)

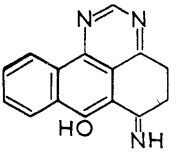


(LIX)

It is relevant here that certain aminoanthracenes have tautomeric properties not shown by the aminobenzenes and aminonaphthalenes. 9-Anthramine [79] is not unlike anthranol although it is known only in the amino-form,[80] but imino-forms can be isolated if *peri*-hydroxyl groups are also present. The simplest example is *leuco*-1 : 4-diaminoanthraquinone (LIX). This can be obtained by hydrogenation of the diaminoquinone in the cold and then heating in an inert atmosphere.[65] It is normally made on the large scale by heating *leuco*quinizarin with ammonia and the ready introduction of basic groups by direct condensation of primary amines with *leuco*quinizarin makes the latter a key intermediate in the manufacture



(LX)



(LXI)

of many aminoanthraquinones. As the imino-groups are rather easily hydrolysed, conversion of the *leuco*-compounds into the quinones by aeration of their alkaline solutions must be avoided and the usual procedure is to heat the *leuco*-compound in nitrobenzene, preferably with an enolising catalyst. Again, elimination of β-substituents can occur during the formation of the *leuco*-amino-compounds, and this extends also to heterocyclic derivatives. Reduction of the bromoanthrapyrimidine (LX) with acid

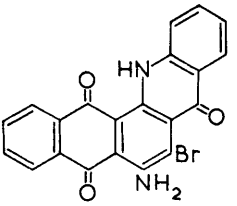
[77] Hayes and Thomson, *J.*, 1955, 904.

[78] Marschalk, *Bull. Soc. chim.* (*France*), 1927, **41**, 943 ; G.P. 95,271.

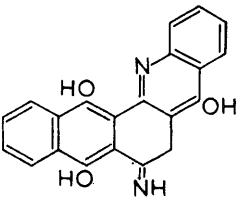
[79] Kauffler and Suchannek, *Ber.*, 1907, **40**, 518 ; Meyer and Schlosser, *Ber.*, 1913, **46**, 29.

[80] Craig and Short, *J.*, 1945, 419.

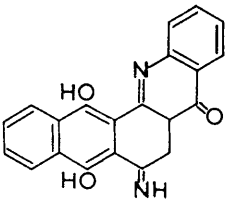
stannous chloride or sodium dithionite gives a bromine-free *leuco*-compound,[81] presumably (LXI), and halogen is similarly lost in the reduction [82] of the



(LXII)



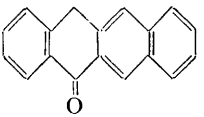
(LXIII)



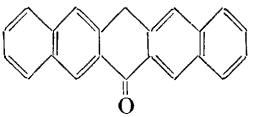
(LXIV)

phthaloylacridone (LXII). In this case the stable *leuco*-compound formed must be (LXIII) or (LXIV).

Hydroxyl Derivatives of More Complex Hydrocarbons.—In the higher polycyclic compounds keto-forms become increasingly stable. Compounds with hydroxyl groups located in a terminal ring are similar to α- and β-anthranol but when an enolic centre occurs at a *meso*-position in a linear hydrocarbon usually only the keto-form is known although tautomerism similar to the anthrone–anthranol system may occur in angular hydrocarbons. This distinction arises because the linear enol structures include more quinonoid rings, and hence are less stable, than the angular enol structures.* The simplest angular enol is 9-phenanthrol, the keto-form of which is unknown (contrast anthranol), whereas the ketones (LXV) and

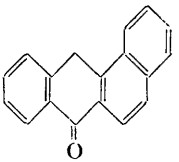


(LXV)



(LXVI)

(LXVI) are insoluble in boiling aqueous sodium hydroxide and their enols have not been isolated. On the other hand, both tautomeric forms of the benzanthrone (LXVII) exist and can be crystallised unchanged from benzene although the enol isomerises fairly rapidly in acetone.[83]



(LXVII)

[81] Reports on Dyestuffs Intermediates, etc. Microfilm P.B. 70,332, Reel 1c, Frames 216–220.

[82] B.P. 587,006.

[83] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 1028.

* The para-localisation energies of a number of polycyclic hydrocarbons have been calculated by Brown (*J.*, 1950, 691) and are in accord with the stability of the keto-forms.