ΓE ON THE FORMATION OF QUINONES BY XIDATIVE DEMETHYLATION AND THE ːCT OF METHYLATING AGENTS ON THEM

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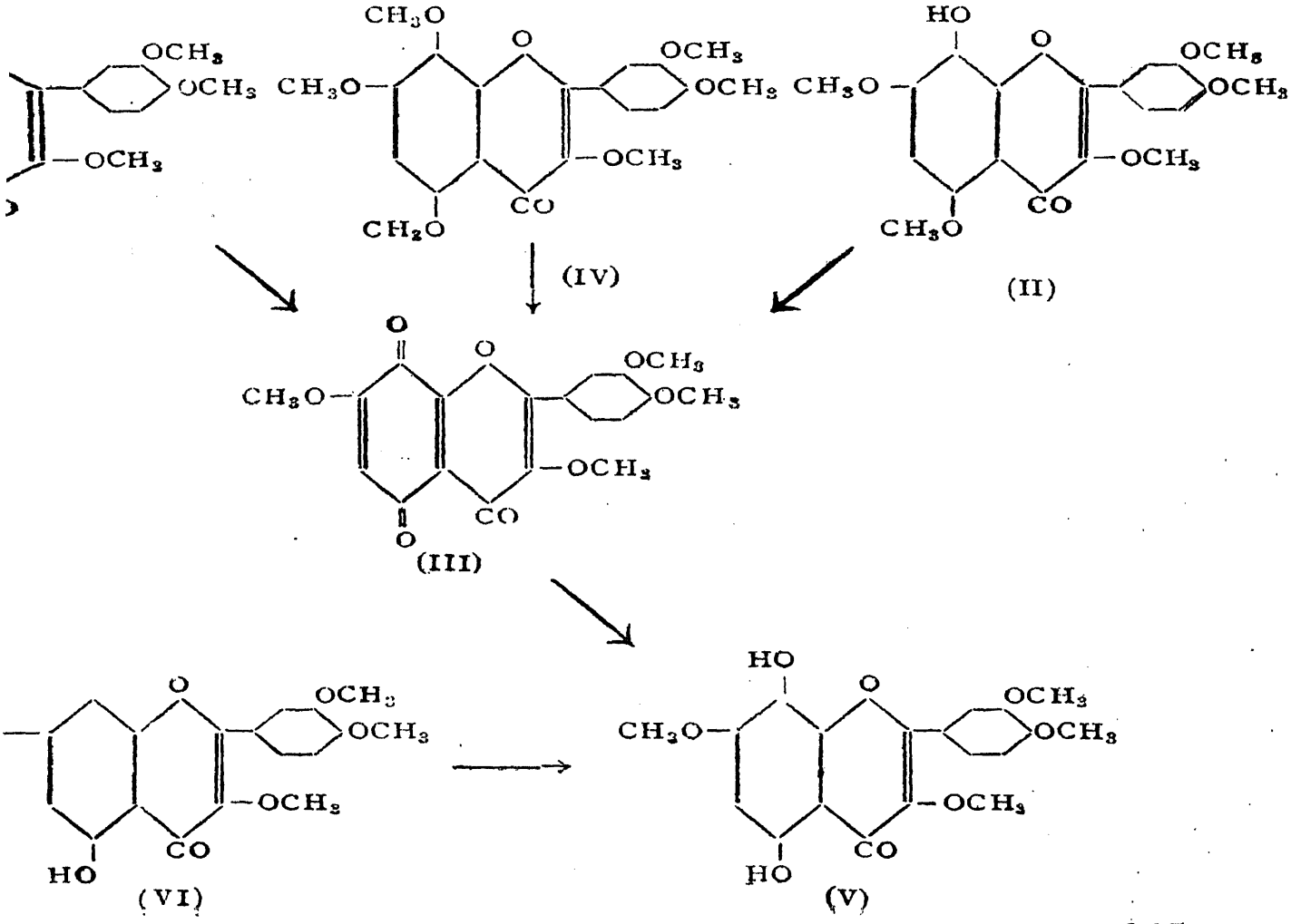
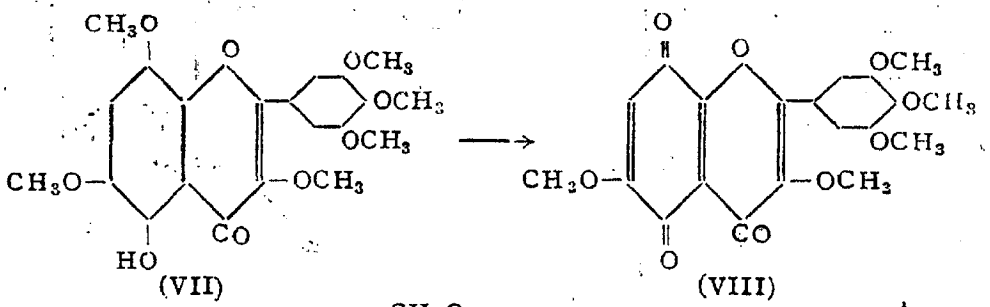
ː demethylation using nitric acid has recently been found to be se in the study of the structure of partial methyl ethers of hydroxy nd also in their synthesis. This reaction was first studied in detail npounds of the gossypetin group.[1] *O*-Pentamethyl gossypetins having a free hydroxyl in the 5- or 8-position readily undergo this o yield tetramethyl-gossypetone (III). This takes place even with ι–hexamethyl ether (IV) with almost equal ease. The nature of



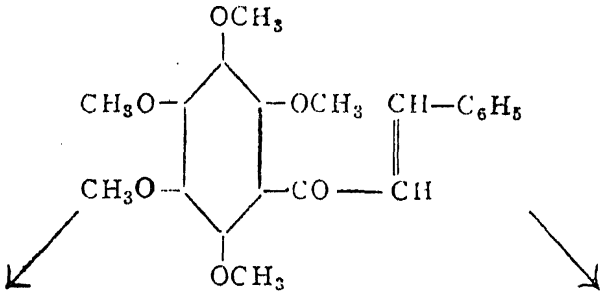
the product has been established by reduction and methylation whereby the original compound (IV) is obtained and also by comparing the quinol (V) with that formed by the nuclear oxidation of quercetin-tetramethyl ether (VI).

The above oxidative demethylation has also been studied using the dimethyl derivative of the flavone, wogonin.[2] Methoxyls para to each other are involved and no further change, either further demethylation or nuclear oxidation is found to take place. An orthodimethyl ether, 7 : 8-dimethoxy-flavone has now been tested and is found to be unaffected. These experiments definitely support the explanation of the behaviour of gardenin (VII) towards nitric acid as given by Bose and Nath.[3] This reaction was originally studied by Stenhouse and Groves[4] who called the product gardenic acid. Bose and Nath showed this to be a quinone (VIII) yielding a quinol on reduction. More recently Balakrishna and Seshadri[5] have found that methyl gardenin (IX) behaves similarly and that the action of nitric acid with this substance runs a course which is quite parallel to that with gossypetin hexamethyl ether. This has therefore been taken as definite proof of the existence of two methoxyl groups in the 5- and 8-positions.

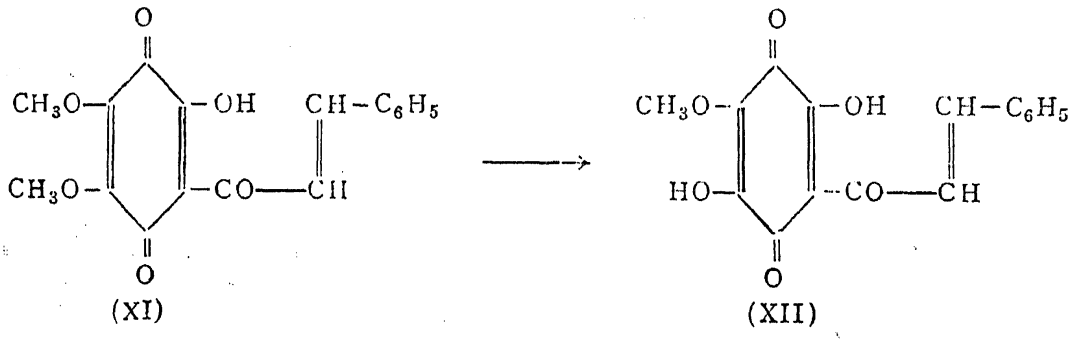


In contrast with the behaviour of the above flavone methyl ethers, pedicellin[6] (X) which is a fully methylated chalkone ether suffers further demethylation also so that the product is a hydroxy quinone. Methyl-pedicinin (XI) is the major first product of the reaction and in its formation three methoxyl groups are involved, two being oxidised to the quinone and the third converted into a hydroxyl group. In the course of this treatment with nitric acid some quantity of pedicinin (XII) is also formed as the result of further demethylation of a fourth methoxyl group, though for effecting

this change and getting a good yield of pedicinin final addition of alkali is better. There seems to be little doubt that the first stage is the formation of a quinone which subsequently undergoes demethylation. The ready demethylation of methoxy quinones under the influence of alkali is already known. The reaction is analogous to ester hydrolysis. From the example of the pedicellin-pedicinin change, this can obviously take place even in acid medium though it was not noted earlier in any other case.



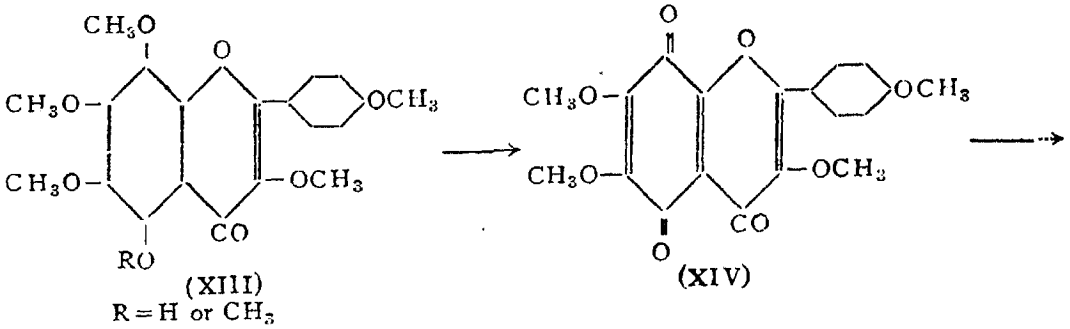
(X)



(XI) (XII)

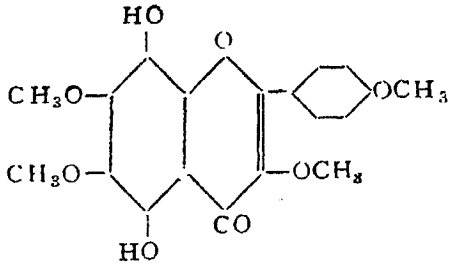
In the course of the work described in this paper certain select cases have been examined anew in order to get more information on this phenomenon and to find out what structural conditions are responsible for the differences existing between methoxy flavones on the one hand and pedicellin on the other. Among methoxy-flavones the 5:7:8-type (gossypetin group) and the 5:6:8-type (gardenin) have already been examined. As examples of the 5:6:7:8-type have now been studied calycopterin-mono and dimethyl-ethers (XIII, R = H or CH_3). These include in their structures both 5:6:8 and 5:7:8-combinations and in conformity with the other flavones they undergo straightforward oxidative-demethylation to form a quinone (XIV) and no further change.

Of the simple methoxy-benzenes having para methoxyl groups the reaction of 1:2:4-trimethoxy benzene with nitric acid has already been studied by Schüler[7] who reported the formation a diphenyl diquinone along with some nitro compound. 1:2:4:5-Tetramethoxy benzene[8] (XV) was found to behave in a simpler manner and form the dimethoxy quinone (XVI) undergoing thus only oxidative demethylation. On the other hand, 1:2:3:5-tetramethoxy benzene (XVII) represents a third type yielding a



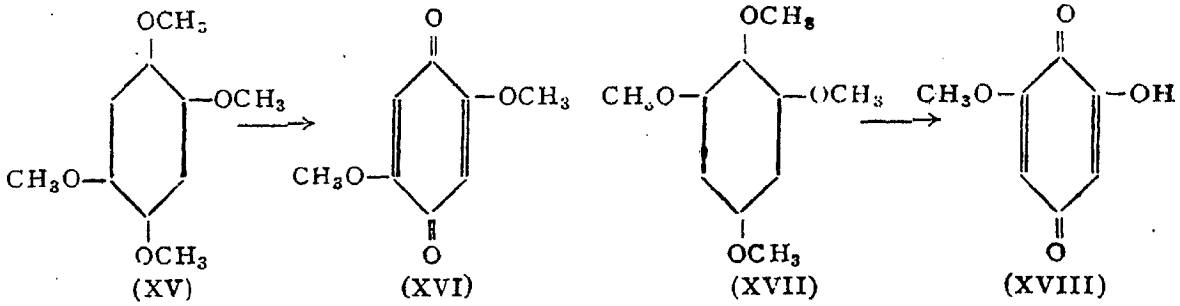
(XIII)
R = H or CH_3

(XIV)



(XIV *a*)

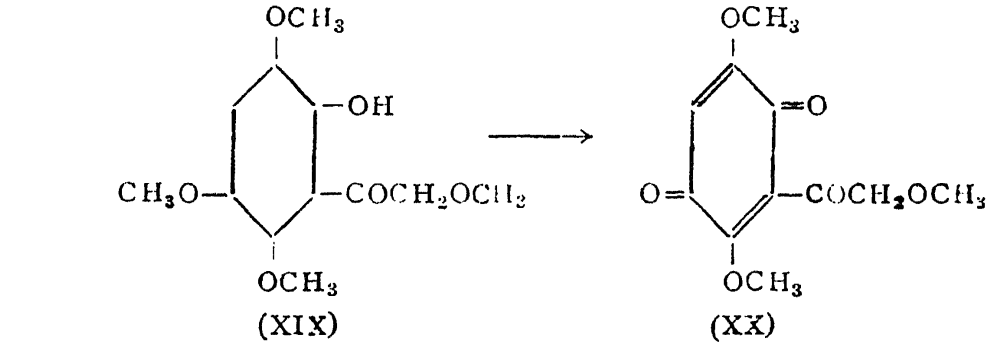
hydroxy-quinone (XVIII) as the product. This involves oxidative demethylation to the methoxy quinone stage and further demethylation to the hydroxy quinone.



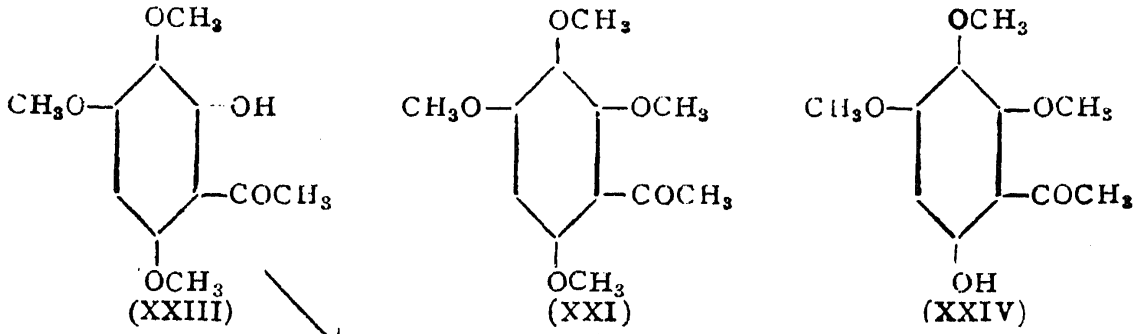
(XV) (XVI) (XVII) (XVIII)

As examples of compounds more closely related to flavones and also to the chalkones, methoxy acetophenones have been chosen for study. Recently 2-hydroxy-ω: 3: 5: 6-tetramethoxy acetophenone (XIX) which is a product of fission of methyl gardenin has been studied by Balakrishna and Seshadri[5] and they have recorded that it forms a trimethoxy quinone (XX) undergoing simple oxidative demethylation just as the related 1: 2: 4: 5-tetramethoxy benzene. On the other hand, 2: 3: 4: 6-tetramethoxy acetophenone (XXI) yields a hydroxy quinone (XXII) under the same conditions. In this reaction three methoxyl groups undergo removal, two of them yielding place to the quinone structure and the third being converted into a hydroxyl The location of the hydroxyl as ortho to the ketonic carbonyl is indicated by the prominent ferric chloride colour. This inference is supported by its independent preparation from 2-hydroxy-3: 4: 6-trimethoxy acetophenone (XXIII). Even the isomeric 2-hydroxy-4: 5: 6-trimethoxy acetophenone (XXIV) yields the same product. All these reactions are correctly explained

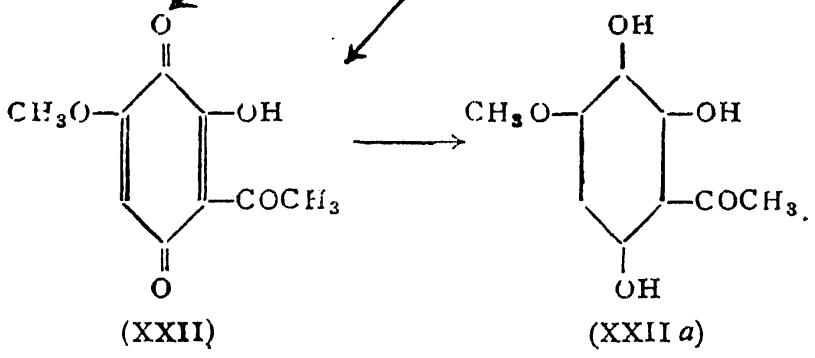
by (1) oxidative demethylation involving the para substituted positions and (2) further demethylation of an ortho methoxyl if it should be present. The following formulæ explain the changes. It should be noted that these three ketones are derivatives of 1 : 2 : 3 : 5-tetramethoxy benzene. Thus there is some correlation between the behaviour of methoxy benzenes and the derived acetophenones. However, explanation of this marked difference in the behaviour of these two types of methoxy-benzene derivatives is not clear.



(XIX) (XX)



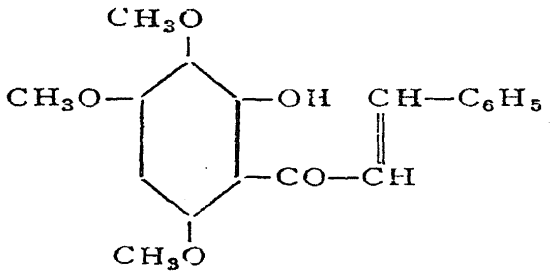
(XXIII) (XXI) (XXIV)



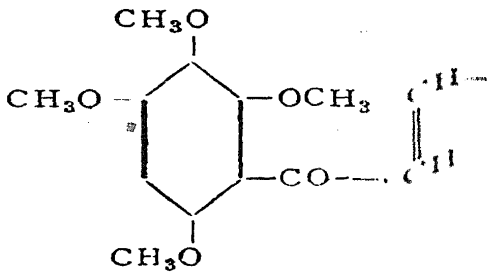
(XXII) (XXII *a*)

The important point to be noted in the above reactions with the ketones is the second stage demethylation taking place in the position ortho to the ketonic carbonyl group, the one in the para position being left out. It is of significance in the interpretation of the conversion of pedicellin into methyl-pedicinin and pedicinin.

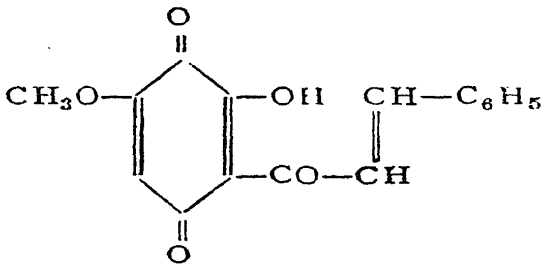
In the next stage of our study 2-hydroxy-3 : 4 : 6-trimethoxy chalkone (XXV) and its fully methylated ether (XXVI) were found to behave very similar to pedicellin, a hydroxy quinone (XXVII) being produced as the product.



(XXV)

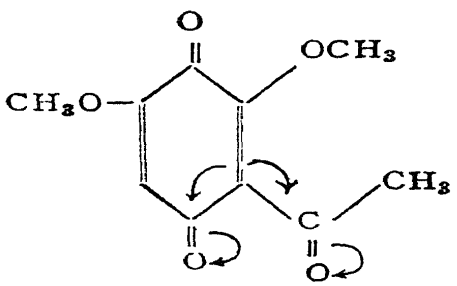


(XXVI)

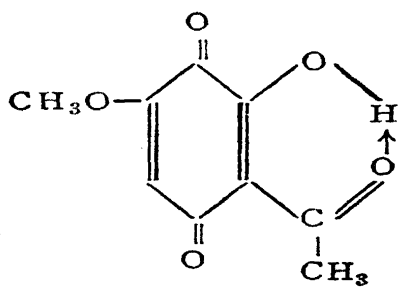


(XXVII)

With regard to the above ketones and chalkones derived from tetramethoxy benzene it is necessary to explain why the particular ortho to the ketonic carbonyl is preferentially demethylated. I formula (XXVIII) it will be clear that this particular position re double effect of the quinone and the ketonic carbonyl groups wh other methoxyl can be affected by the quinone carbonyl only. point that should be noted is that compounds of the type (XX hydroxy quinone ketones, give prominent red ferric chloride colou holic solution and differ markedly from the simpler hydroxy quinones Ferric chloride colour is generally attributed to the presence of between a ketonic carbonyl and a phenolic hydroxyl in the ortho and it is favoured by the existence of the benzene double bond bet concerned groups. In the case of the hydroxy-quinone-ketones thou is no benzenoid structure a double bond is present in the required all the same. But this chelation seems to be rather weak since quinone-ketones are still readily soluble in sodium bicarbonate.



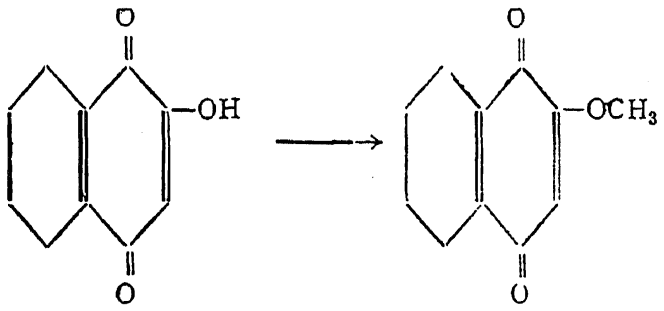
(XXVIII)



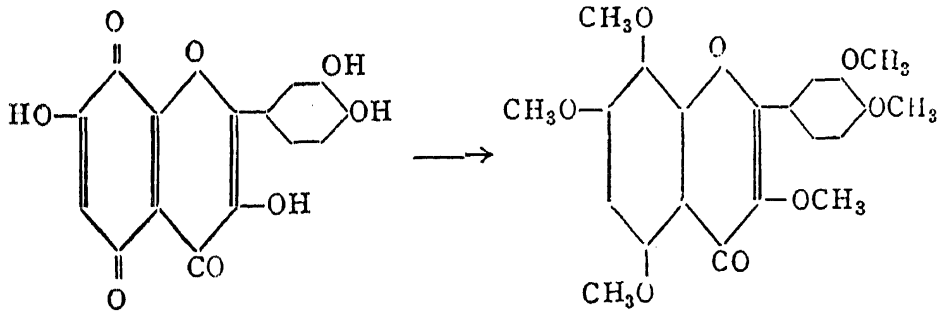
(XXIX)

Methylation of quinones

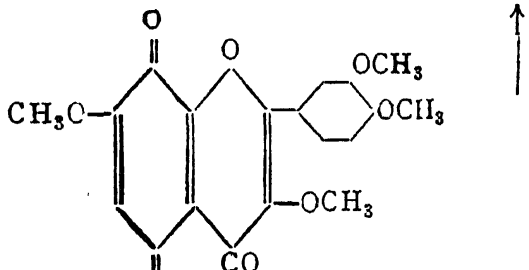
The methylation of hydroxy-quinones is not invariably successful. Only in favourable cases can it be carried out satisfactorily; an example described here is the methylation of lawsone (XXX). It was originally done by means of methyl alcohol and hydrogen chloride. The methyl ether (XXXI) has now been made easily using dimethyl sulphate and potassium carbonate in acetone medium and heating for a restricted period. The cause of failure in other cases and of the general difficulty experienced, is to be attributed to the readiness with which quinones undergo other changes. In a few of the cases studied by us it has been possible to isolate minor quantities of crystalline compounds identified as the methyl ethers of the corresponding quinols. For example from the methylation of gossypetone (XXXII) has been isolated gossypetin hexamethyl ether (IV). In this case after the methylation of the hydroxyl groups further change sets in which results in the formation of the above hexamethyl ether besides amorphous and complex products. This is supported by the fact that tetramethyl gossypetone (III) itself behaves similarly under the above conditions.



(XXX) (XXXI)



(XXXII) (IV)



The explanation of the above reaction requires the dismutation of the methoxy quinone involving self-hydrogenation and dehydrogenation. The former gives rise to the quinol which undergoes further methylation and the latter results in polymerisation and related changes. The simplest example, quinone itself forms quinol dimethyl ether under these conditions.

That benzoquinone forms quinol as one of the products of decomposition in the presence of alkali has been observed by a number of workers in the past (see Erdtman[9]). This change is conveniently shown by the preparation of the benzoate and methyl ether of quinol from the alkaline solution. This reaction seems to be more general since it is found that gossypetone tetramethyl ether (III) yields the corresponding quinol (V) by short treatment with dilute aqueous potash. It could obviously take place even in the presence of potassium carbonate because as mentioned above the quinol methyl ethers are formed when the quinones are subjected to methylation.

Experimental

Oxidation of calycopterin dimethyl ether to 3 : 6 : 7 : 4′*-tetramethoxy-flavoquinone (XIV)*

Nitric acid (d. 1·25; 10 c.c.) was added to finely powdered calycopterin dimethyl ether (XIII, R = CH_3) (0·5 g.) with vigorous stirring. The solid assumed an orange colour and soon changed into a dark red semisolid mass. The temperature was kept at 15–20° for 15 minutes when the product became a definite red solid. It was filtered, washed with a little nitric acid of the same density followed by excess of water. When crystallised twice from benzene it appeared as orange red needles melting at 194–95°. (Found: C, 61·0; H, 4·0; $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%.) Yield, 0·3 g. It dissolved in aqueous sodium hydroxide to a greenish brown solution which changed to yellowish brown.

Oxidation of 4′*-O-methyl-calycopterin (XIII, R = H)*

The oxidation was carried out just as in the case of the dimethyl ether. The reaction was very quick and the product readily separated out as a red solid. It was identical with the quinone described above.

Reduction of the flavoquinone to 5 : 8*-dihydroxy*-3 : 6 : 7 : 4′*-tetramethoxy flavone (XIV a)*

A solution of the above flavoquinone (XIV) (0·3 g.) in glacial acetic acid (2 c.c.) was treated with sodium sulphite (0·5 g.) when the deep red colour immediately changed to bright yellow. After stirring for a minute, water (50 c.c.) was added and the yellow solid filtered and washed with

water. It crystallised from benzene in the form of glistening golden yellow rectangular plates, melting at 210–12°, alone or in admixture with the sample obtained by the oxidation of 5-hydroxy-3 : 6 : 7 : 4′-tetramethoxy flavone[10] with alkaline persulphate. It readily dissolved in aqueous sodium hydroxide to a bright red solution and in alcoholic solution gave a green colour with one drop of ferric chloride and with more of the reagent the colour changed to deep brown.

Oxidation of 1 : 2 : 3 : 5-*tetramethoxy benzene to* 2-*hydroxy*-6-*methoxy-quinone* (*XVIII*)

A solution of 1 : 2 : 3 : 5-tetramethoxy benzene[11] (XVII) (5 g.) in alcohol (20 c.c.) was treated with nitric acid (d. 1 ·25; 20 c.c.). It was cooled so that the temperature did not rise above 50° for 15 minutes and the deep red reaction mixture was diluted with a large volume of water (500 c.c.). On saturating the solution with sodium chloride and cooling, a yellow solid separated out which was filtered and washed with a little water. The filtrate on extraction with chloroform yielded some more of the solid. When crystallised from chloroform it separated in the form of pale yellow narrow rectangular plates melting at 240–45° with decomposition. (Found: C, 54 ·2; H, 4 ·2; $C_7H_6O_4$ requires C, 54 ·6; H, 3 ·9%.) It was easily soluble in alcohol and sparingly in chloroform. In aqueous sodium bicarbonate it readily dissolved to a red solution and with ferric chloride in alcoholic solution it gave a pale brown colour.

2-*Hydroxy*-4-*methoxy*-3 : 6-*quino-acetophenone* (*XXII*)

(*a*) *From* 2-*Hydroxy*-3 : 4 : 6-*trimethoxy acetophenone* (*XXIII*).—A solution of the ketone (XXIII) (1 g.) in anhydrous ether (10 c.c.) was cautiously treated with fuming nitric acid (1 c.c.). After keeping the reaction mixture overnight the ether was removed in the cold, water was added and the mixture extracted with chloroform. The chloroform extract was dried over sodium sulphate and distilled. The orange red solid left behind was crystallised from benzene when it appeared as glistening orange red micacious plates melting at 158–60°. (Found: C, 54 ·8; H, 4 ·4; $C_9H_8O_5$ requires C, 55 ·1; H, 4 ·1%.) It was easily soluble in aqueous sodium bicarbonate giving a red colour. In alcoholic solution it gave a deep red colour with ferric chloride. Yield, 0 ·35 g.

(*b*) *From* 2-*Hydroxy*-4 : 5 : 6-*trimethoxy acetophenone*(*XXIV*).—A solution of the above ketone (XXIV) (0 ·5 g.) in dry ether (5 c.c.) was treated with fuming nitric acid (1 c.c.). After keeping at the laboratory temperature for three hours the bright orange red crystals of the quinone were filtered,

washed with a little ether and distilled water. Yield, 0·35 g. It melted at 158–60° alone or in admixture with the sample obtained from 2-hydroxy-3:4:6-trimethoxy acetophenone and the properties were also identical.

(*c*) *From* 2:3:4:6-*tetramethoxy acetophenone* (*XXI*).—A solution of 2:3:4:6-tetramethoxy acetophenone (2 g.) in anhydrous ether (10 c.c.) was treated with fuming nitric acid (2 g.). On keeping overnight an orange red crystalline solid separated out in good yield. It was filtered, washed with a little ether and recrystallised from benzene when it appeared as micacious plates melting at 158–60° alone or in admixture with the quinone obtained from 2-hydroxy-3:4:6-trimethoxy acetophenone.

2:3:6-*Trihydroxy*-4-*methoxy acetophenone* (*XXII a*)

Into a suspension of the above quinone (XXII) (0·2 g.) in water (5 c.c.) a current of sulphur dioxide was passed. The quinone dissolved and very soon pale yellow crystals separated out. After filtering, washing and recrystallising from benzene the ketone appeared as rectangular plates melting at 170–71°. (Found: C, 54·9; H, 5·4; $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%.) It was easily soluble in alcohol and sparingly in benzene. In aqueous sodium hydroxide it dissolved to a deep brown solution which became colourless on shaking with air. In alcoholic solution it gave with ferric chloride a green colour which changed to brown.

Oxidation of 2-*hydroxy*-3:4:6-*trimethoxy chalkone* (*XXV*) *to* 2-*Hydroxy*-4-*methoxy*-3:6-*quino-chalkone* (*XXVII*)

A solution of 2-hydroxy-3:4:6-trimethoxy chalkone[11] (0·5 g.) in glacial acetic acid (5 c.c.) was treated with concentrated nitric acid (1 c.c.). A deep reddish brown solution resulted. After five minutes the solution was diluted with water and the orange coloured solid filtered and washed with water. Crystallisation from chloroform yielded orange red thin plates melting at 186–87°. (Found: C, 67·5; H, 4·5; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%.) It was sparingly soluble in alcohol, chloroform and benzene, and readily soluble in aqueous sodium bicarbonate to a reddish brown solution. In alcoholic solution it gave a deep red colour with ferric chloride.

2:3:4:6-*Tetramethoxy chalkone* (*XXVI*)

Preparation.—A solution of 2-hydroxy-3:4:6-trimethoxy chalkone (2 g.) in acetone (25 c.c.) was refluxed with dimethyl sulphate (2 c.c.) and potassium carbonate (10 g.) for 12 hours. The solvent was distilled off, the residue treated with water and extracted with ether. On evaporating off the ether a very pale yellow oily liquid was left behind which did not crystallise even on keeping for a long time. It was insoluble in aqueous sodium hydroxide

and gave no colour with ferric chloride. It was therefore directly employed for oxidation.

Oxidation.—A solution of the tetramethoxy chalkone (1 g.) in glacial acetic acid (3 c.c.) was treated with concentrated nitric acid (1 c.c.). On cooling and stirring the dark red solution an orange red crystalline solid separated out. The mixture was then diluted with ether and filtered; the solid residue was washed with ether and crystallised from chloroform. It formed orange red plates melting at 186–87°. Mixed melting point with the quinone prepared from 2-hydroxy-3 : 4 : 6-trimethoxy chalkone was not depressed.

Methylation of lawsone: *2-methoxy-α-naphthoquinone* (*XXXI*)

2-Hydroxy-α-naphthoquinone was prepared from 1-amino-2-naphthol-4-sulphonic acid by the method of Fieser[12] and also by extracting the leaves of *Lawsonia alba*[14]. The two samples were identical in all respects.

A solution of 2-hydroxy-α-naphthoquinone (1 g.) in anhydrous acetone (50 c.c.) was treated with dimethyl sulphate (1 c.c., excess) and potassium carbonate (5 g.). The latter immediately assumed bright red colour due to the formation of a potassium salt. It was refluxed for 3 hours whereby most of the red colour of the solid was lost. Heating was stopped at this stage, the solid filtered and washed with hot acetone and the filtrate distilled. A pale yellow crystalline solid was left behind which was crystallised from benzene when it appeared as pale yellow narrow rectangular plates melting at 183–85°. Mixed melting point with a sample of 2-methoxy-α-naphthoquinone prepared by the method of Fieser, was not depressed. Yield, 0·9 g. It was insoluble in aqueous sodium bicarbonate but slowly dissolved in aqueous sodium hydroxide giving a yellow colour which changed to orange red. When this solution was acidified, 2-hydroxy-α-naphthoquinone was obtained.

Particular care should be taken in the above methylation to watch the course of the reaction and to stop it at the proper stage. Longer heating brings about further changes and the yield suffers. It is a disadvantage to use only one molecule of dimethyl sulphate. The reaction is then slow and due to the long heating dark coloured products are formed.

Methylation of benzoquinone

1*st method.*—A solution of benzoquinone (1 g.) in acetone (25 c.c.) was refluxed with dimethyl sulphate (1 c.c.) and potassium carbonate (5 g.) for 6 hours. The dark coloured reaction mixture was filtered, the solid washed with a little acetone and the filtrate distilled. The residue was extracted with

ether; on evaporating the ether extract a yellowish brown oil remained which crystallised on stirring. It melted at 58° alone or in admixture with an authentic sample of quinol dimethyl ether. Yield, 0·3 g.

2nd method.—Benzoquinone (1 g.) was dissolved in 5% aqueous sodium hydroxide (25 c.c.) and the dark green solution shaken with dimethyl sulphate (5 c.c.). A dark brown solid product separated out. The mixture was extracted with ether and the ether extract evaporated when a crystalline solid was obtained. It melted at 58° and was identical with quinol dimethyl ether. Yield, 0·2 g.

Benzoylation of benzoquinone

Benzoquinone (1 g.) was dissolved in 10% aqueous sodium hydroxide (50 c.c.) and the solution shaken with benzoyl chloride (5 c.c.) until it was all used up. The pale brown solid that separated out was filtered, washed and crystallised twice from benzene when colourless needles separated out melting at 200–02° identical with quinol dibenzoate. Yield, 0·5 g.

Action of alkali on Gossypetone tetramethyl ether (III)

The above flavoquinone was prepared from the hexamethyl ether of gossypetin using nitric acid as already described.[1]

Finely powdered gossypetone tetramethyl ether (0·3 g.) was made into a suspension with water (3 c.c.) and 10% aqueous sodium hydroxide (10 c.c.) added. The dark bluish violet solution was stirred for a minute and acidified with concentrated hydrochloric acid. The mixture was raised to the boil and the yellowish brown precipitate filtered, washed and crystallised from alcohol when it appeared as glistening golden yellow needles melting at 250–52°. It was identical with 5:8-dihydroxy-3:7:3′:4′-tetramethoxy flavone (V) prepared by the reduction of the above quinone with sulphur dioxide. Yield, 0·15 g.

Methylation of gossypetone (XXXII)

Gossypetone (0·2 g.) prepared according to the method of Perkin,[13] was dissolved in acetone (25 c.c.) and refluxed with dimethyl sulphate (1 c.c.) and potassium carbonate (5 g.). The solution first assumed a deep brown colour but it slowly became paler. After 8 hours the solvent was distilled off, water added and the solution extracted with ether. On concentrating the ether extract a small quantity of a white crystalline solid separated. It was filtered, washed with a little ether and recrystallised from alcohol when it separated out as colourless needles melting at 170–72° and identical with the hexamethyl ether of gossypetin (IV).

Methylation of gossypetone tetramethyl ether (III)

A solution of gossypetone tetramethyl ether (0·2 g.) in acetone (25 c.c.) was methylated with dimethyl sulphate (0·5 c.c.) and potassium carbonate (3 g.). After refluxing for 8 hours the product was worked up as in the previous case. It crystallised from alcohol as colourless needles melting at 170–72° and identical with the hexamethyl ether of gossypetin (IV).

Summary

Using typical examples, some of which are new, oxidative demethylation of methoxy benzenes, ketones, chalkones and flavones with nitric acid is discussed. The flavones without exception undergo simple conversion into para quinones. The others fall into two categories: (*a*) 1:2:4:5-Tetramethoxy benzene and its derivatives suffer only oxidative demethylation like the flavones to yield the corresponding para quinones. (*b*) 1:2:3:5-Tetramethoxy benzene and its derivatives, either ketones or chalkones, on the other hand undergo further change involving demethylation of another methoxyl group yielding hydroxy quinones. In the case of ketones and chalkones this second stage demethylation involves the methoxyl which is situated ortho to the ketonic carbonyl and which is subjected to the combined influence of this carbonyl and the one in the quinone group. These results are of importance in the study of pedicellin-pedicinin conversion.

Under favourable conditions hydroxy quinones can be methylated by means of dimethyl sulphate and potassium carbonate to the corresponding methyl ethers, *e.g.* lawsone. In some cases fully methylated ethers of the corresponding quinols could be obtained *e.g.* gossypetone. This is obviously due to the preliminary dismutation of the quinone into the corresponding quinol and complex products. The action of alkali on benzoquinone and tetramethyl gossypetone has been studied using different conditions.

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