Thallium in Organic Synthesis. XLII. Direct Oxidation of 4-Substituted Phenols to 4,4-Disubstituted Cyclohexa-2,5-dienones Using Thallium(III) Nitrate[1]

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Received July 25, 1975

Oxidation of hydroquinones with 1 equiv, and 2,6-disubstituted phenols with 2 equiv, of thallium(III) nitrate (TTN) in methanol gives the corresponding *p*-benzoquinones in high yield. Oxidation of a variety of 4-alkyl- and 4-alkoxyphenols with 1 equiv of TTN in either methanol or trimethyl orthoformate (TMOF), on the other hand, gives 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones in moderate to excellent yield. Formation of cyclohexadienones under these conditions is postulated to proceed via ipso thallation.

There have been a number of reports during the last few years on the oxidations of phenols with thallium(III) salts, and examination of the results indicates that the type of product which is formed depends both on the nature of the thallium reagent employed and on the structure of the phenol. Mel'nikov and Gracheva found that thallium(III) chloride oxidized hydroquinone to a mixture of *p*-benzoquinone and quinhydrone,[2] while Kabbe claimed that conversion of hydroquinone into *p*-benzoquinone was complete within 3 min when thallium(III) acetate was used.[3] This claim has since been shown to be specious,[4] but it has been established that hydroquinones are oxidized to *p*-benzoquinones almost instantaneously and in excellent yield when the more powerful oxidant thallium(III) trifluoroacetate (TTFA) is used.[5] The same reagent has been shown to oxidize a wide variety of 4-substituted phenols HOArX (X = *t*-C_4H_9, Cl, Br, I, CH_3COO) to the corresponding *p*-benzoquinones, and the synthetic utility, scope, and limitations of these processes have been defined.[5] The use of thallium(III) oxide in ethanol for the conversion of certain types of hydroquinone monesters into *p*-benzoquinones has also been described.[6]

Oxidation of 4-substituted phenols to 4,4-disubstituted cyclohexa-2,5-dienones by thallium(III) was first reported by Hecker and Lattrell, who succeeded in isolating quinol ethers and acetates in low yields from the boron trifluoride catalyzed reactions of a number of 4-alkylphenols with thallium(III) acetate in methanol and acetic acid, respectively.[7] Coombs and Jones subsequently showed that oxidation of estrone with TTFA gave 10β-trifluoroacetoxy-19-norandrost-1,4-diene-3,17-dione in high yield,[8] while, more recently, Yamada et al. have converted 5-hydroxyindan and 6-hydroxytetralin into the corresponding *p*-quinols in good yield by use of thallium(III) perchlorate in aqueous acid.[9] Analogous reactions have been reported by Schwartz et al.[10,11] and by Kupchan and Liepa,[12] who have utilized TTFA as a reagent for intramolecular oxidative phenol coupling.

With the exception of the one detailed investigation noted[5] above, no serious attempt has been made either to study the scope and limitations of these oxidations or to postulate reasonable mechanisms for the various conversions. Few of the phenols which have been oxidized are structurally simple, and the range of substrates which has been examined is very restricted; consequently, it is impossible to assess the synthetic utility of these oxidations as applied to simple monocyclic phenols.

The efficacy of thallium(III) salts TlX_3 as oxidants is known to be directly related to the nature of the anionic group X, and it has been adequately demonstrated for a wide range of reactions that the oxidizing power of the commonly available and easily handled thallium(III) salts is in the order nitrate > trifluoroacetate > acetate > chloride.[13] We now report the results of a detailed investigation of the reactions of a wide range of phenols with thallium(III) nitrate (TTN). These show that, as expected, oxidation of hydroquinones to *p*-benzoquinones by TTN in methanol takes place rapidly and proceeds in excellent yield. Of greater interest are the observations that 2,6-disubstituted phenols are also smoothly oxidized to *p*-benzoquinones, while many 4-alkyl- and 4-alkoxyphenols can readily be converted in excellent yield into 4-alkyl-4-methoxy- and 4,4-dimethoxycyclohexa-2,5-dienones, respectively.

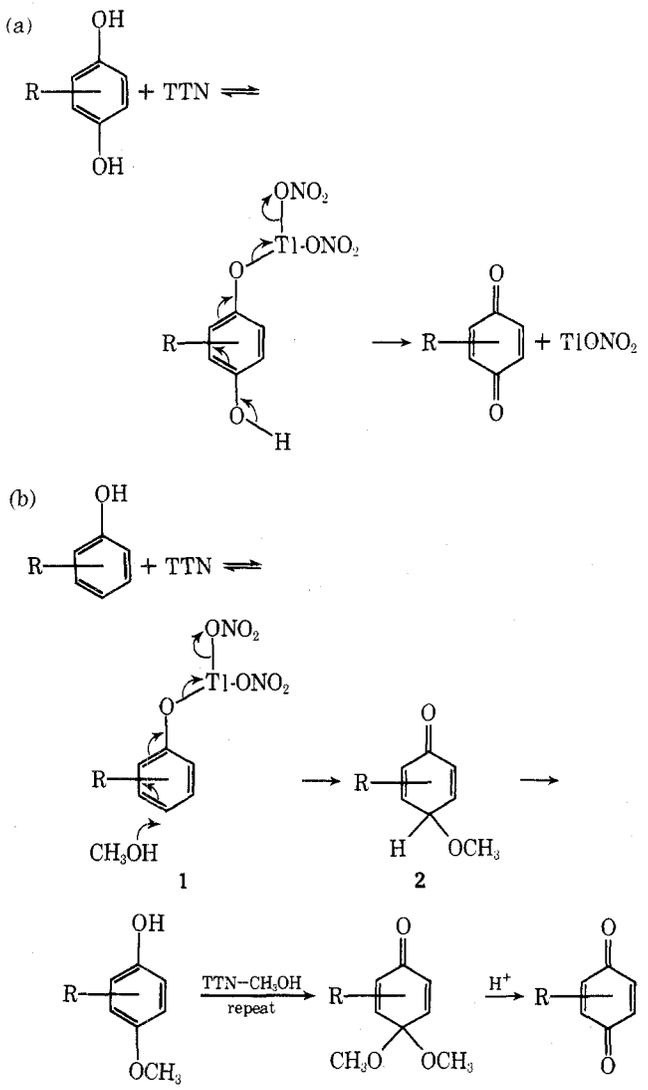
Discussion

Treatment of hydroquinone with 1 equiv of TTN in methanol resulted in almost instantaneous oxidation to give *p*-benzoquinone in 78% yield. 2-*tert*-Butyl-, 2,5-di-*tert*-butyl-, 2-methyl-, and 2,3,5-trimethylhydroquinone reacted analogously and the corresponding *p*-benzoquinones were isolated in 88, 96, 89, and 98% yield, respectively. Oxidation of a number of 2,6-disubstituted phenols with 2 equiv of TTN in methanol also proceeded smoothly, and again the corresponding *p*-benzoquinones were formed. Thus, 2,6-di-*tert*-butylphenol was converted into 2,6-di-*tert*-butyl-*p*-benzoquinone in 83% yield, 2,6-diisopropylphenol was smoothly oxidized to 2,6-diisopropyl-*p*-benzoquinone in 77% yield, 2,6-dimethylphenol gave a mixture of 2,6-dimethyl-*p*-benzoquinone (72%) and 3,3′,5,5′-tetramethyldiphenoquinone (6%), and 2,6-dimethoxyphenol gave 2,6-dimethoxy-*p*-benzoquinone in 80% yield.

In mechanistic terms these oxidations are, at first sight, apparently straightforward. A plausible mechanism for the oxidation of hydroquinones is outlined in Scheme I (a) which involves (1) ligand exchange between one of the phenolic hydroxyl groups and TTN to give an aryloxythallium(III) intermediate, and (2) oxidation of the aromatic ring as shown, with concomitant reduction of thallium(III) to thallium(I). A related mechanism can be postulated for the oxi-

dation of 2,6-disubstituted phenols [Scheme I (b)]. We now believe, however, that these mechanisms, together with

Scheme I

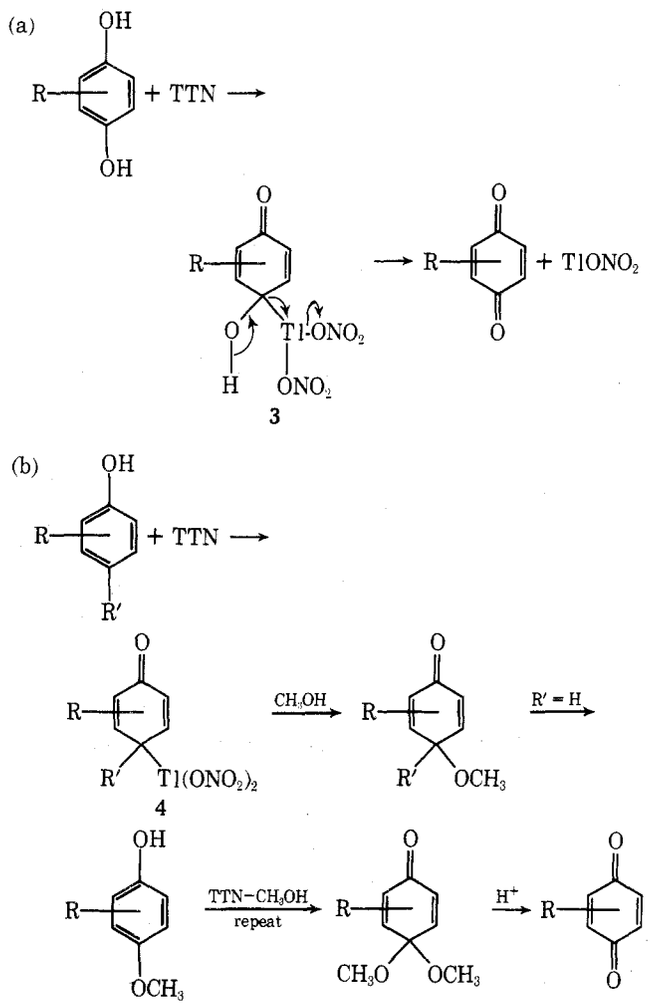


that postulated previously for the oxidation of 4-*tert*-butylphenols with TTFA,[5] are incorrect.

There are three major objections which can be raised with respect to the reactions postulated in Scheme I. (1) There is no precedent for ligand exchange between phenols and TTN and all attempts to prepare $ArOTl(ONO_2)_2$ compounds either by ligand exchange processes or by metathetical reactions have proved totally unsuccessful.[14] On the contrary, it can readily be demonstrated that phenol reacts smoothly with TTN at low temperature to give the expected product of electrophilic aromatic thallation, 4-hydroxyphenylthallium dinitrate. This compound can be isolated and characterized spectroscopically, and readily gives 4-iodophenol on treatment with aqueous potassium iodide.[15] (2) Ligand exchange between 2,6-disubstituted phenols, particularly 2,6-di-*tert*-butylphenol, and a bulky thallium(III) salt is highly unlikely on steric grounds; yet these phenols are smoothly and rapidly oxidized by both TTN and TTFA. (3) The reaction 1 → 2 in Scheme I (b) is *nucleophilic* attack on a phenol derivative, for which again there is no sound precedent. Schwartz et al. tentatively suggested in 1973 that reaction of phenols with TTFA might involve generation of a phenoxonium ion ArO^+,[10] but there is no evidence to substantiate facile formation of these high-energy intermediates under such mild reaction conditions.

Simple alternative mechanisms for the oxidations of hydroquinones and phenols with TTN are outlined in Scheme II. That is, the initial step is ipso thallation; decomposition

Scheme II

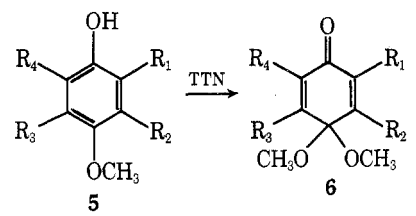


of intermediates of the type **3** in the manner shown is unexceptional (path a), while nucleophilic displacement of the thallium substituent from the intermediate cycloalkylthallium dinitrate **4** by methanol (path b) is a type of reaction for which there is abundant precedent in organothallium chemistry.[13] Ipso substitution is now a well-recognized phenomenon,[16] and 4,4-disubstituted cyclohexa-2,5-dienones have frequently been obtained as the products of electrophilic aromatic substitution reactions (especially nitration and halogenation) of phenols and their derivatives. The major difference between ipso thallation and ipso nitration or halogenation is that in the former case the initially formed organometallic compounds would be expected to be highly unstable, and hence the products which are isolated are those derived from a secondary reaction, namely attack of a nucleophilic species at the developing electrophilic center created by heterolysis of the very weak C–Tl bond. Hence treatment of 4-unsubstituted phenols with TTN would not normally be expected to give stable arylthallium derivatives but, provided sufficient oxidant were used, should lead to quinones, i.e., the situation generally found in practice.

A further logical consequence of the ipso-thallation mechanism is that oxidation of 4-substituted phenols with

1 equiv of TTN in methanol should, depending on the electronic nature of the 4-substituent group, lead directly to 4-methoxy 4-substituted cyclohexa-2,5-dienones. This proved to be the case, and from examination of the reactions of a wide range of substituted phenols we have been able to define the scope and limitations of this synthetic method. Moreover, the results obtained provide indirect evidence that the reaction proceeds via an electrophilic substitution process.

Thus, the 4-methoxyphenols **5a–h** were smoothly converted into the 4,4-dimethoxycyclohexa-2,5-dienones **6a–h** on treatment with TTN in either methanol or a mixture of methanol and trimethyl orthoformate (TMOF).[17] All of

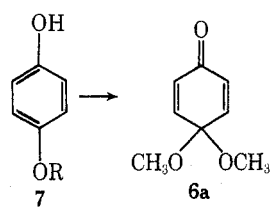


5 **6**

a, $R_1 = R_2 = R_3 = R_4 = H$, 97%
b, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$, 89%
c, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$, 87%
d, $R_1 = R_4 = t\text{-}C_4H_9$; $R_2 = R_3 = H$, 96%
e, $R_1 = R_4 = H$; $R_2 = R_3 = OCH_3$, 95%
f, $R_1 = H$; $R_2 = R_3 = OCH_3$; $R_4 = COCH_3$, 92%
g, $R_1 = Cl$; $R_2 = R_3 = R_4 = H$, 97%
h, $R_1 = Br$; $R_2 = R_3 = R_4 = H$, 91%

these oxidations proceeded rapidly at temperatures in the range −20 to 0°, and the chromatographically pure cyclohexadienone products were readily isolated from the reaction mixtures.

Attempts were then made to extend this type of oxidation to the preparation of unsymmetrical monoketals of *p*-benzoquinones. Thus, the simple hydroquinone monoethers **7a–f** were treated with TTN under conditions identical with those used for the oxidation of **5a–h;** compounds **7a–d** reacted smoothly, but the product formed in each case was 4,4-dimethoxycyclohexa-2,5-dienone (**6a**). Oxidation of the

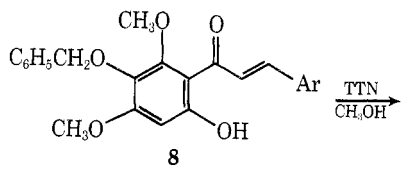


7 **6a**

a, $R = C_2H_5$, 94%
b, $R = CH(CH_3)_2$, 78%
c, $R = (CH_2)_3CH_3$, 91%
d, $R = (CH_2)_6CH_3$, 89%
e, $R = CH_2C_6H_5$, 19%
f, $R = C_6H_5$, 26%

benzyl and phenyl ethers, **7e** and **7f,** gave complex mixtures of products in each case, and again **6a** was formed, albeit in rather low yield. We assume that formation of **6a** in these reactions takes place in two discrete steps, namely initial production of the unsymmetrical ketal followed by rapid thallium(III) induced transketalization,[18] and standard control experiments provided supporting evidence for this hypothesis. Thus, freshly prepared **6a** was recovered unchanged if (1) dissolved in ethanol and the solution allowed to stand overnight at room temperature; (2) dissolved in ethanol containing thallium(I) nitrate and the mixture allowed to stand overnight at room temperature; and (3) dissolved in ethanol and the solution chromatographed on basic alumina (compounds **6a–h** were isolated and purified by chromatography). When, on the other hand, 1.5 mmol of TTN was added to a solution of 10 mmol of **6a** in 5 ml of ethanol and the mixture allowed to stand at room temperature for 10 min, examination of the NMR spectrum of the products obtained after chromatography of the reaction mixture on basic alumina clearly revealed that transketalization had occurred and that some 65–70% of 4,4-diethoxycyclohexa-2,5-dienone had been produced under these conditions.

In contrast to the above results obtained with the simple monoethers of hydroquinone, formation of mixed monoketals of *p*-benzoquinones was observed when 4-alkoxy 3,5-disubstituted phenols were oxidized with TTN. Thus, treatment of the chalcone **8** with TTN at 65° for 30 min gave the mixed ketal **9a** in 36% yield as a stable, yellow, crystalline solid.[19] When the oxidation was allowed to pro-



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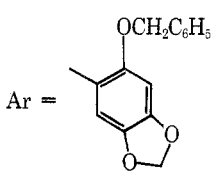
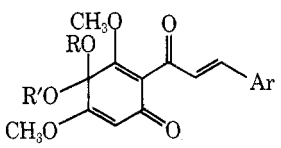
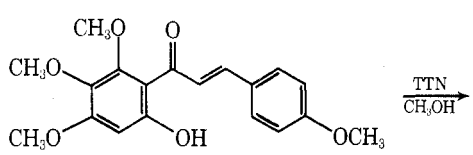




9

a, $R = CH_2C_6H_5$; $R' = CH_3$
b, $R = CH_2C_6H_5$; $R' = H$
c, $R = H$; $R' = CH_3$

ceed for a longer time, however, the initially formed mixed ketal **9a** underwent gradual acid-catalyzed hydrolysis to the hemiketal **9b,** and this compound was isolated in 21% yield after a reaction time of 1 hr. The alternative hemiketal **9c** was prepared in 58% yield by treatment of **9b** with a mixture of methanol and hydrochloric acid. Oxidation of the chalcone **10** with TTN in methanol at 65° also proceeded smoothly to give the hemiketal **11** in 70% yield.



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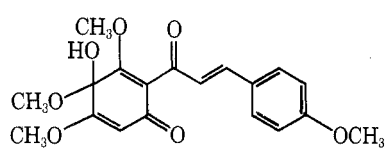

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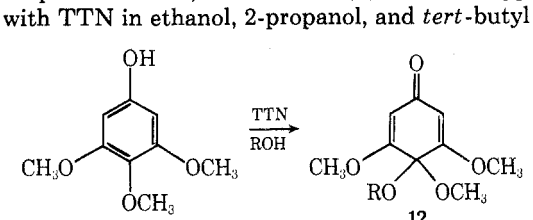
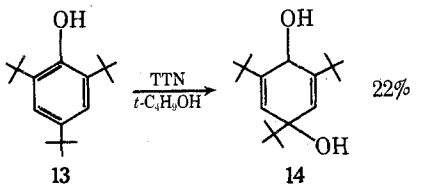
Formation of mixed monoketals and hemiketals in the above chalcone cases is presumably a consequence of steric hindrance both to ketalization and transketalization, and similar results were obtained with a variety of structurally simpler phenols. Thus, oxidation of 3,4,5-trimethoxyphenol (**5e**) with TTN in ethanol, 2-propanol, and *tert*-butyl alco-



5e **12**

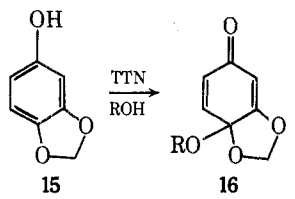
a, $R = C_2H_5$, 30%
b, $R = CH(CH_3)_2$, 29%
c, $R = C(CH_3)_3$, 29%

hol gave the mixed monoketals **12a–c**, respectively. Reaction of 2,4,6-tri-*tert*-butylphenol (**13**) with *tert*-butyl alcohol under the same conditions, on the other hand, gave only the quinol **14**; in this case it is unlikely on steric



13 14

grounds that *tert*-butyl alcohol would readily substitute into the 4 position, and hence water assumes the role of nucleophile (TTN is a trihydrate, and participation of the water of crystallization as a nucleophile has been noted in other reactions involving TTN[20]). Oxidation of 3,4-methylenedioxyphenol (**15**) with TTN in methanol or ethanol gave the mixed monoketals **16a** and **16b**, respectively, pro-

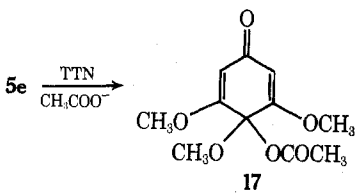


15 16

a, R = CH_3, 45%
b, R = C_2H_5, 59%

vided that the reaction mixtures were worked up immediately after oxidation was complete. These 3-substituted monoketals are considerably less stable than the 3,5-disubstituted compounds **9a** and **12a–c**; if they are allowed to stand in the reaction mixture, which contains nitric acid, or if they are treated with solutions of nitric acid in methanol or ethanol, they are rapidly converted into 2-methoxy- and 2-ethoxy-*p*-benzoquinone, respectively.[21]

We have examined briefly the possibility of utilizing nucleophiles other than alcohols in these oxidations. Treatment of **5e** with TTN and sodium acetate in a mixture of acetic acid and ethyl acetate, for example, gave 3,4,5-trimethoxy-4-acetoxycyclohexa-2,5-dienone (**17**) in poor (19%) yield, while reaction of **13** under the same conditions gave a mixture of the quinol **14** (25%) and the acetate **18** (10%). In



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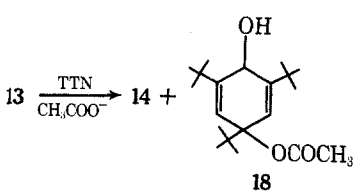

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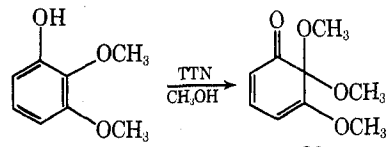
view of the low yields encountered in these reactions, and the few nucleophiles other than carboxylate anions which are compatible with TTN, no further effort was expended on these transformations.

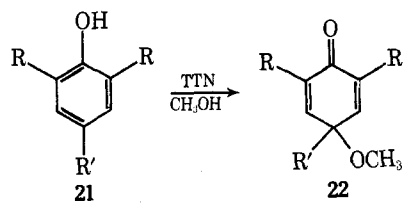
A number of attempts were also made to oxidize 2-methoxyphenols, as there is no simple procedure available for the preparation of 6,6-dimethoxycyclohexa-2,4-dienones. Treatment of 2-methoxyphenol with TTN in methanol gave a complex mixture of products from which no pure materials could be isolated, but oxidation of 2,3-dimethoxyphenol (**19**) under the same conditions gave the expected product **20** in 25% yield. Vanillin, isovanillin, and *o*-vanillin



19 20

were also smoothly oxidized to cyclohexadienones under the same conditions; these initially formed products could not be isolated in a pure state, however, as they rapidly underwent Diels–Alder cycloaddition reactions to give crystalline dimers.[22]

Following from the above results with methoxyphenols, the reactions of TTN with phenols carrying a substituent group other than an oxygen-containing group in the 4 position were investigated. 4-Alkylphenols reacted markedly more slowly than the corresponding 4-methoxy compounds and, except in cases where there were also substituent groups in the 2 and 6 positions, gave complex mixtures of products which proved impossible to separate. The 2,4,6-trialkylphenols **21a–c**, on the other hand, were smoothly converted into the cyclohexadienones **22a–c**. Phenols con-



21 22

a, R = R′ = CH_3, 72%
b, R = t-C_4H_9; R′ = CH_3, 90%
c, R = R′ = t-C_4H_9, 87%

taining an electron-withdrawing substituent in the 4 position (Cl, COOH, $COOCH_3$, NO_2) reacted very slowly with TTN; little of the reagent has been consumed even after reaction for 4 days at room temperature, while attempts to effect oxidation at 65° resulted in extensive decomposition of the phenols and production of tars.

In a qualitative sense, all of the above results are fully consistent with a mechanism for oxidation which involves electrophilic substitution of the aromatic ring, and the ipso thallation processes outlined in Scheme II satisfactorily account for the experimental observations. Unfortunately, all attempts to isolate organothallium intermediates of the type **4** proved totally unsuccessful. As mentioned earlier, however, ipso substitution has frequently been observed in the nitration and halogenation of phenols, and while most of the well-documented examples involve the use of polysubstituted phenols, the results of a recent study by Nilsson, Ronlán, and Parker on the chlorination of *p*-cresol are complementary to those of the present investigation and illustrate how the mechanism of substitution of simple phenols can vary dramatically with the reaction conditions.[23] Thus, treatment of *p*-cresol with $SbCl_5$ at room temperature gave a mixture of chlorinated phenols, but if the reaction was carried out at −50° under carefully controlled conditions 4-chloro-4-methylcyclohexa-2,5-dienone was obtained in 92% yield.

From a synthetic point of view it is obvious from the above results that oxidation of 4-methoxyphenols with TTN in methanol constitutes a convenient and manipulatively simple procedure for the direct preparation of a wide variety of 4,4-dimethoxycyclohexa-2,5-dienones. As far as we are aware there is no general procedure available for the synthesis of these interesting and highly reactive polyfunctional dienones. The parent compound **6a** has been pre-

pared previously by oxidation of 4-methoxyphenol in methanol either by cerium(IV)[24] or electrolytically,[23] and by controlled hydrolysis of *p*-benzoquinone bis(dimethyl ketal).[25] The 2,6-di-*tert*-butyl derivative **6d** has been obtained in excellent yield by treatment of 2,6-di-*tert*-butyl-4-methoxyphenol with copper(I) chloride in a methanol–pyridine mixture,[26] while the 2,3,5,6-tetramethyl[27] and 2,6-dichloro-3,5-dimethyl[28] analogues have been prepared by indirect methods.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope melting point apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders and Mr. J. Robinson of the University of East Anglia and by Mrs. I. Balogh-Batta of the Technical University, Budapest. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer and on a Spectromom Model 2000 spectrophotometer using the standard Nujol mull, potassium bromide disk, and liquid film techniques. Nuclear magnetic resonance spectra were determined as solutions in either $CDCl_3$ or CCl_4 on Perkin-Elmer R12 60-MHz and Varian XL100 100-MHz spectrometers using tetramethylsilane as internal standard.

Starting Materials. All of the phenols used in this study were either commercially available or were prepared by standard literature procedures. All were purified by either distillation or crystallization prior to use.

General Method for the Preparation of 4,4-Dialkoxy- and 4-Alkyl-4-alkoxycyclohexa-2,5-dienones. A. Using TTN in Alcohols. A solution of TTN (5 mmol) in the appropriate alcohol (15 ml) was added to a stirred, cooled (−20°) solution of the phenol (5 mmol) in the same alcohol (15 ml) and the reaction mixture allowed to warm to room temperature. Petroleum ether (60 ml, bp 60–80°) was then added, the thallium(I) nitrate which precipitated was removed by filtration, and the filtrate was passed down a short column of basic alumina (8 × 1 in.) using either petroleum ether or dichloromethane as eluent. Evaporation of the eluate gave the product which, in almost all cases, was chromatographically and spectroscopically pure as isolated. Most of the compounds could be crystallized from either methanol or petroleum ether, preferably at −70°, but only with attendant losses in material of up to 75%.

B. Using TTN in Methanol–Trimethyl Orthoformate (TMOF). The phenol (5 mmol) was added to a stirred solution of TTN (5 mmol) in a mixture of methanol (15 ml) and TMOF (15 ml) cooled to −70°, the cooling bath was removed, and the mixture was allowed to warm to room temperature. Petroleum ether (50 ml) was then added, and the products were isolated in exactly the same way as described in A above.

Yield and physical data for the cyclohexadienones prepared in this way are listed in Table I (see paragraph at end of paper regarding supplementary material).

General Procedure for the Oxidation of Hydroquinones and 2,6-Dialkylphenols with TTN. A solution of the hydroquinone (5 mmol) in methanol (10 ml) was added dropwise to an ice-cold solution of TTN (5 mmol) in methanol (15 ml). After addition had been completed the reaction mixture was stirred for a further 10 min, the thallium(I) nitrate which had precipitated was removed by filtration, and the filtrate was partitioned between dichloromethane and saturated aqueous sodium chloride solution. The organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The crude *p*-benzoquinone thus obtained was purified by chromatography on silica gel or neutral alumina using benzene or benzene–dichloromethane as eluent.

Oxidation of 2,6-dialkylphenols to *p*-benzoquinones was carried out in exactly the same manner except that the reaction was performed at room temperature and 10 mmol of TTN was used.

4-Benzyloxy-2-[3-(2-benzyloxy-4,5-methylenedioxyphenyl)acryloyl]-4-hydroxy-3,5-dimethoxycyclohexa-2,5-dienone (9b). 2,5′-Dibenzyloxy-2′-hydroxy-4′,6′-dimethoxy-4,5-methylenedioxychalcone (**8**,[19] 1 mmol) was oxidized by the general method A but at 65° and for 1 hr; during this time the initially formed ketal **9a**[19] was slowly hydrolyzed to **9b**. The reaction mixture was neutralized with sodium methoxide and evaporated to dryness and the residue chromatographed on silica gel using benzene–acetone (4:1) as eluent. This gave 110 mg (21%) of pure **9b** as red prisms: mp 128–130°; NMR ($CDCl_3$) δ 3.46 (s, 3, 5-OCH_3), 3.84 (s, 3, 3-OCH_3), 4.68 and 4.71 (inner lines of an AB quartet, 4-$OCH_2C_6H_5$), 5.13 (s, 2, 2′-$OCH_2C_6H_5$), 5.60 (s, 1, 6-H), 5.98 (s, 2, $-OCH_2O-$), 6.57 and 7.26 (s, 1 each, 3′,6′-H), 7.43 and 7.41 (s, 10, 2′,4-$OCH_2C_6H_5$), 8.04 (d, 1, J = 16 Hz, COCH=CH), 8.50 (d, 1, J = 16 Hz, COCH=CH).

Anal. Calcd for $C_{32}H_{28}O_9$: C, 69.06; H, 5.07. Found: C, 68.91; H, 5.07.

2-[3-(2-Benzyloxy-4,5-methylenedioxyphenyl)acryloyl]-4-hydroxy-3,4,5-trimethoxycyclohexa-2,5-dienone (9c). A solution of **9b** (100 mg) in a mixture of methanol (30 ml) and 10% hydrochloric acid (0.5 ml) was heated under reflux for 2 hr. The solution was then concentrated to ca. 15 ml by distillation under reduced pressure, when the crude product crystallized. This was collected by filtration, and recrystallization from methanol gave 50 mg (58%) of pure product as brick red needles, mp 168–170°, NMR ($CDCl_3$) δ 3.40 (s, 6, 3,5-OCH_3); the remainder of the signals corresponded to those for **9b**.

Anal. Calcd for $C_{26}H_{24}O_9$: C, 64.99; H, 5.04. Found: C, 64.92; H, 5.64.

3,4,5-Trimethoxy-4-hydroxy-2-[3-(4-methoxyphenyl)acryloyl]cyclohexa-2,5-dienone (11). 2′-Hydroxy-4,4′,5′,6′-tetramethoxychalcone (**10**,[29] 1.5 g) was oxidized at 65° as described for **8** above. Recrystallization of the crude product from methanol gave 1.1 g (70%) of pure **11** as yellow needles: mp 139–140°; NMR ($CDCl_3$) δ 3.42 (s, 3, 4-OCH_3), 3.85 and 3.87 (s, each 3, 3,5-OCH_3), 5.62 (s, 1, 6-H), 6.90 (d, 2, J = 8 Hz, 3′,5′-H), 7.60 (d, 2, J = 8 Hz, 2′,6′-H), 7.94 (d, 1, J = 16 Hz, COCH=CH), 8.21 (d, 1, J = 16 Hz, COCH=CH).

Anal. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 63.37; H, 5.70.

4-Methoxy-3,4-methylenedioxycyclohexa-2,5-dienone (16a). Oxidation of **15** (1.38 g) with TTN in methanol according to the general procedure A gave, after recrystallization of the crude product from petroleum ether (bp 35–40°), 0.75 g (45%) of pure product: mp 56–57°; ir (KBr) 1680 (C=O), 1650 (C=C), and 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.46 (s, 3, 4-OCH_3), 5.62 (d, 1, ^4J = 2 Hz), 5.70 (d, 2, $-OCH_2O-$) 6.40 (q, 1, ^3J = 10, ^4J = 2 Hz, 6-H), 6.95 (d, 1, ^3J = 10 Hz, 5-H).

Anal. Calcd for $C_8H_8O_4$: C, 58.55, H. 2.46. Found: C, 58.62; H, 2.38

4-Ethoxy-3,4-methylenedioxycyclohexa-2,5-dienone (16b). Oxidation of **15** with ethanol according to the general procedure A gave, after recrystallization of the crude product from petroleum ether (bp 35–40°), a 59% yield of **16b** as colorless needles: mp 57–59°; NMR ($CDCl_3$) δ 1.20 (t, 3, J = 7 Hz, OCH_2CH_3), 3.40–4.10 (ABX_3 m, 2, OCH_2CH_3); the other signals were similar to those of **16a**.

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.53; H, 5.41.

4-Acetoxy-3,4,5-trimethoxycyclohexa-2,5-dienone (17). TTN (500 mg) was added to a solution of **5e** (184 mg, 1 mmol) in anhydrous ethyl acetate (10 ml) containing acetic acid (3 ml) and anhydrous sodium acetate (0.5 g) cooled to −20°. The reaction mixture was stirred for 30 min, the thallium(I) nitrate which had precipitated was removed by filtration, and the filtrate was poured into water. The resulting mixture was extracted with chloroform and the extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give 45 mg (19%) of **17** as pale yellow prisms: mp 153–155°; ir (KBr) 1750 (CH_3CO), 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.17 (s, 3, CH_3COO), 2.45 (s, 3, 4-OCH_3), 3.80 (s, 6, 3,5-OCH_3), 5.59 (s, 2, 2,6-H).

Anal. Calcd for $C_{11}H_{14}O_6$; c, 54.54; H, 5.83. Found: C, 54.32; H, 5.97.

4-Acetoxy-2,4,6-tri-*tert*-butylcyclohexa-2,5-dienone (18). Oxidation of **13** as described for **5e** above gave, after fractional crystallization of the crude product from methanol, 25% of **14** and 10% of **18**.[30] The latter compound was characterized spectroscopically: ir (KBr) 1735 (CH_3COO), 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.99 (s, 9, 4-*t*-C_4H_9), 1.50 (s, 18, 2,6-*t*-C_4H_9), 2.08 (s, 3, CH_3COO), 6.50 (s, 2, 3,5-H).

5,6,6-Trimethoxycyclohexa-2,5-dienone (20). Oxidation of **19** (0.77 g) by the general procedure A gave, after chromatography of the crude product on silica gel, 0.22 g (25%) of **20** as pale yellow needles, mp 76–78°, after recrystallization from petroleum ether (bp 35–40°): ir (KBr) 1670 (C=O), 1630 and 1560 cm^{-1} (C=C); NMR ($CDCl_3$) δ 3.36 (s, 6, 6,6-OCH_3), 3.83 (s, 3, 5-OCH_3), 5.42 (d, 1, J_{BX} = 8 Hz, 2-H), 5.85 (d, 1, J_{AX} = 10 Hz, 4-H), 7.08 (q, 1, J_{BX} = 8, J_{AX} = 10 Hz, 5-H).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.79; H, 6.51.

Acknowledgment. One of us (D.H.P.) acknowledges the receipt of an I. C. I. Fellowship.

Registry No.—**5a**, 150-76-5; **5b**, 5307-05-1; **5c**, 2431-91-6; **5d**, 489-01-0; **5e**, 642-71-7; **5f**, 22248-14-2; **5g**, 18113-03-6; **5h**, 17332-11-5; **6a**, 935-50-2; **6b**, 57197-11-2; **6c**, 57197-12-3; **6d**, 33974-39-9; **6e**, 57197-13-4; **6f**, 57197-14-5; **6g**, 57197-15-6; **6h**, 57197-16-7; **7a**, 94-71-3; **7b**, 7495-77-4; **7c**, 122-94-1; **7d**, 13037-86-0; **7e**, 103-16-2; **7f**, 831-82-3; **8**, 52366-32-2; **9a**, 52250-33-6; **9b**, 57197-17-8; **9c**, 57197-18-9; **10**, 3877-67-6; **11**, 57197-19-0; **12a**, 57197-20-3; **12b**, 57197-21-4; **12c**, 57197-22-5; **13**, 732-26-3; **14**, 4971-61-3; **15**, 533-31-3; **16a**, 57197-23-6; **16b**, 57197-24-7; **17**, 57197-25-8; **18**, 20778-61-4; **19**, 5150-42-5; **20**, 57197-26-9; **21a**, 527-60-6; **21b**, 128-37-0; **22a**, 38876-36-7; **22b**, 2411-18-9; **22c**, 15910-49-3; TTN, 13746-98-0.

Supplementary Material Available. Full yield, melting point, analytical, and spectroscopic data (NMR, ir) for compounds **6a–h**, **12a–c**, **14**, and **22a–c** (3 pages) will appear following these pages in the microfilm edition of this volume of the journal.

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A Synthesis of the Pyrazomycins[15]

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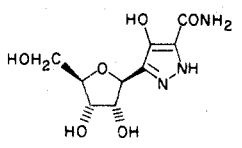
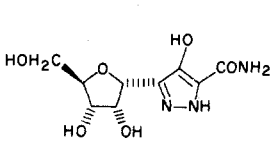
Received August 7, 1975

Pyrazomycin (**1**), an antiviral metabolite of *Streptomyces candidus*, and its congener pyrazomycin B (**2**) were synthesized. Reaction of 2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-β-D-ribosyl bromide (**6**) with diethyl 1,3-acetonedicarboxylate afforded 3-oxo-2-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)glutaric acid diethyl ester (**7**). Diazotization of **7** with *p*-toluenesulfonyl azide gave 5-(2,3-*O*-isopropylidene-5-*O*-*p*-nitrobenzoyl-α-D-ribosyl)-4-oxo-2-pyrazoline-3,5-dicarboxylic acid diethyl ester (**11**). Treatment of **11** with sodium ethoxide accomplished removal of the *p*-nitrobenzoyl group and of the quaternary ethoxycarbonyl function to produce 3-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-4-hydroxypyrazole-5-carboxylic acid ethyl ester (**12**). Ammonolysis of **12** afforded the corresponding amide **13**, and under slightly different conditions, the epimeric amide **14**. Removal of the isopropylidene group from **13** and **14** completed the synthesis of **1** and **2**, respectively.

In recent years considerable interest has been accorded to *C*-nucleoside antibiotics.[1] In this new class of natural products, pyrazomycin[2] deserves particular attention, owing to reports of its antitumor[3] and broad spectrum antiviral[4] activity. Pyrazomycin, 3-(1′-β-D-ribofuranosyl)-4-hydroxypyrazole 5-carboxamide (**1**), was first isolated from fermentations of a strain of *Streptomyces candidus*.[2,5] This organism has recently yielded a second factor, which was characterized as the 1′-α epimer, pyrazomycin B (**2**).[6] A synthesis of **1** has previously been reported.[7] We now wish to describe a new and shorter synthetic route which allowed the preparation of both **1** and **2**.

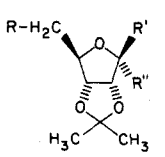


1



2

Our starting material was 2,3-*O*-isopropylidene-D-ribofuranose (**3**),[8] containing both anomers, α and β, in a ratio of 1:9. Reaction of **3** with *p*-nitrobenzoyl chloride in pyridine afforded the two di-*p*-nitrobenzoates **4** and **5** (8:1),



3: R = –OH; R′, R″ = –H, –OH
4: R = R′ = *p*-$NO_2C_6H_4CO_2$–; R″ = –H
5: R = R″ = *p*-$NO_2C_6H_4CO_2$–; R′ = –H
6: R = *p*-$NO_2C_6H_4CO_2$–; R′ = –Br; R″ = –H

which could be separated by fractional crystallization. The configurations at the anomeric carbon atoms (C-1) in **4** and **5** were assigned with the help of NMR spectral data.