The Cerium(IV) Ammonium Nitrate Oxidation of 5-Hydroxy-2-methoxytropone to Bitropolonyl Derivatives and One-Step Synthesis of 3-Methoxy-*p*-tropoquinone

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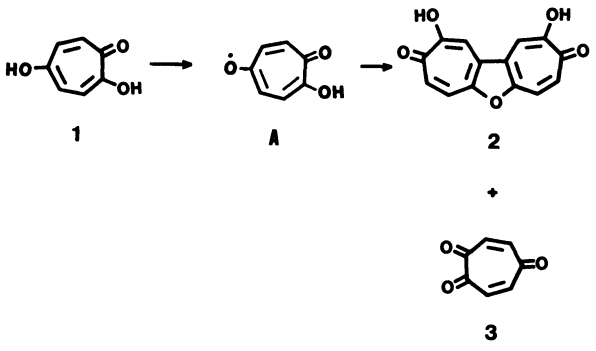
Unlike the benzenoid equivalent, *p*-methoxyphenol, the cerium(IV) ammonium nitrate (CAN)-oxidation of 5-hydroxy-2-methoxytropone gave C–C coupling products. On the other hand, either by thallium(III) nitrate (TTN) or CAN at 50 °C, 5-hydroxytropolone, a free tropolone, gave 3-methoxy-*p*-tropoquinone together with *p*-tropoquinone and 8-oxabicyclo[3.2.1]octenone derivatives, but no dimeric product.

We have recently developed a practical method for preparing *p*-tropoquinone mono- and diacetals by thallium(III) nitrate (TTN) oxidation of 2-alkoxy-5-hydroxytropones,[1] useful intermediates for various functionalized troponoids. This one-pot type preparation of acetals from 2-alkoxy-5-hydroxytropones was favored since it takes advantage of a two-electron oxidation (type I) path. According to the path of a one-electron oxidation (type II), the different behaviors were considered regarding the oxidation of 5-hydroxytropolone (**1**). With a stoichiometric amount of silver acetate,[2] it yielded 2,10-dihydroxydicyclohepta[*b*,*d*]furan-3,9-dione (**2**) through a coupling of the semiquinone radical intermediate (**A**). However, with two moles of the agent, it afforded *p*-tropoquinone (**3**). Indeed, the yields of the tropoquinones were generally better than those produced through a reaction with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ).[3]



Scheme 1.

Accordingly, the oxidation of 2-alkoxy-5-hydroxytropones by a type-II agent, such as cerium(IV) ammonium nitrate (CAN),[4] should be worthwhile. Moreover, although it has already been noticed that the metal salt-induced oxidation of free tropolone derivatives at 0 °C is ineffective due to the formation of insoluble metal salts,[1] the reaction has been produced by heating at 50 °C in methanol. The results are described on the following pages.

Results and Discussion

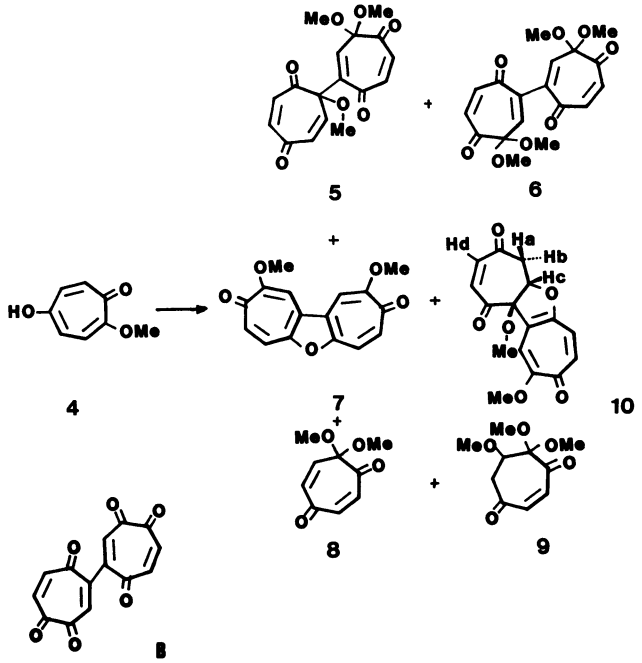
During the oxidation of 5-hydroxy-2-methoxytropone (**4**) with two equivalents of CAN in anhydrous methanol, an instantaneous oxidation occurred to give two crystalline dimeric condensates (**5** and **6**) along with 2,10-dimethoxydicyclohepta[*b*,*d*]furan-3,9-dione (**7**),[5] *p*-tropoquinone dimethyl acetal (**8**)[1,6] and its methanol adduct (**9**).[1]

The dimer (**5**) showed three methoxyl groups on the sp^3-carbons and seven olefinic protons in the ^1H NMR spectrum. Also there were four carbonyl signals in the ^{13}C NMR. All these factors are consistent with our formulation.

The other dimer, **6**, yellow needles, exhibited only eight signals in the ^{13}C NMR, indicating a symmetrical structure. In the ^1H NMR, there were overlapping signals for four methoxyl groups on the sp^3-carbons and six olefinic protons. Therefore, a newly formed C–C bond must be at C-4 and C-4′. Also, **6** was bi(3,3-dimethoxy-4,7-dioxo-1,5-cycloheptadienyl). This corresponds to the bis-monoacetal of hitherto unknown biquinone, bi(*p*-tropoquinonyl) (**B**).

Particularly, this oxidation was sensitive to water. When the CAN-oxidation of **4** was carried out in methanol containing a trace amount of water, a new dimeric product (**10**) was obtained together with **5**, **7**, **8**, and **9**. The ^1H NMR spectrum of **10** revealed signals due to two methoxyl groups, five olefinic protons, and three protons on the sp^3-carbons. The coupling parameters observed in the signals [3.09 (Ha, dd, J=15, 2.5 Hz), 3.42 (Hb, ddd, J=15, 7.5, 1 Hz), 5.06 (Hc, dd, J=7.5, 2.5 Hz), and 6.73 (Hd, dd, J=12.5, 1 Hz)] indicated an arrangement of these four protons as shown in the scheme. Other than **7**, **10** was the only fully-conjugated tropone derivative among the oxidation products. The seven-membered rings of all other products contained a sp^3-carbon, such as an acetal group or a tertiary ether. The formation of **10** under moistened conditions illustrates the important role of a proton in the following step of the reaction; e.g., a coupling of the intermediate, **C** (an analog of **A**) to **D** at C-2 and C-4 via the type II-process, can be readily aromatized to a 5-hydroxy-2-methoxytropone (**E**). The subsequent CAN-oxidation of **E** should give the dimethyl acetal, **5**. However, in the presence of water, **E** was intramolecularly cyclized to **10**. Therefore, a further oxidation of **10** (as well as **7**), having no free hydroxyl group, was slow under these conditions.

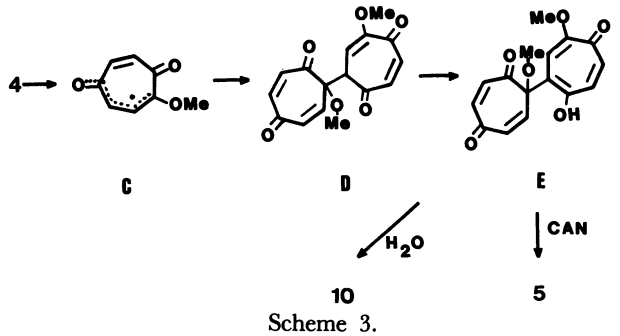
Also, CAN was preferentially co-ordinated with water to prevent the further oxidation.



Scheme 2.

It is possible to classify the products into three categories, i.e., i) monomeric products (**8** and **9**), ii) C-2–C-4′ condensates (**5** and **10**), and iii) C-4–C-4′ condensates (**6** and **7**). The relative yields of these products showed a dependence on several conditions. Under anhydrous conditions, they were 22% for i), 9% for ii), and 48% for iii). In the presence of water, they were 19% for i), 44% for ii), and 20% for iii). Thus, there was a predominance of iii) in an anhydrous media and ii) in the presence of water.

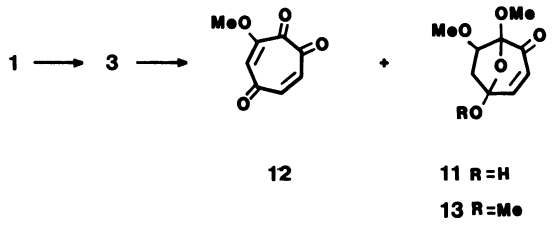
In order to obtain **B**, a hydrolysis of **6** under various conditions has been attempted, but none of the products have been identified. Presumably, **B** is too reactive under the reaction conditions to form complex mixtures. Other transformations attempted so far with these dimeric products were unsatisfactory; i.e., a Thiele reaction in a mixture of acetic anhydride and acetic acid, a zinc reduction in acetic acid, and hydrolysis with perchloric acid in aqueous acetone all gave intractable mixtures.



Scheme 3.

Next, a CAN oxidation of **1** was carried out at room temperature in methanol. A new product (**11**) was identified along with **3**. The ^{1}H NMR spectrum of **11** showed signals attributable to a methylene group, two methoxyl groups, two vicinal vinylic protons on the six-membered ring, and a proton on the sp^3-carbon bearing an oxygen function. Therefore, **11** should be an 8-oxabicyclo[3.2.1]octenone derivative.

For a comparison, the TTN-oxidation of **1** was also carried out in methanol at 50°C to obtain two new products (**12** and **13**). According to spectral evidence, the former, **12**, was 3-methoxy-*p*-tropoquinone. Although its yield was not very high, a one-step preparation should be useful from a practical point of view.[1] The structure of **13** was identified to be a methylated derivative of **11** from NMR spectral evidence; the ^{1}H NMR spectrum of **13** showed a close resemblance to that of **11** except for the presence of an additional methoxyl methyl singlet. Also, a comparison of the ^{13}C NMR chemical shifts led to the same conclusion (see Experimental). Interestingly, a TTN-oxidation of **3** in methanol gave **11** together with **13**. Thus, it is clear that **3** is a precursor of these oxidation products.



Scheme 4.

It should be mentioned that, unlike **4**, the TTN-oxidation of **1** formed no dimers. In other words, for the oxidation of **1**, there is no difference between the oxidizing agents (TTN and CAN) in this respect. This means that the transformations of an intermediate (**A**) to **3** by a one-electron oxidation process is rather easier than the C–C coupling process. This is parallel to the previous results regarding silver salt-oxidation, another one-electron oxidizing process of **1**.[2] With a stoichiometric amount of the reagent, it gave **3** in good yield; but, with a smaller amount, it also gave the C-4–C-4′ coupling product, **2** (Scheme 1).

In conclusion, the major products formed in the CAN-oxidation of **4** were the C–C coupling products. These differed remarkably to those formed in a TTN oxidation. This difference results from the nature of the oxidizing agent, as has been mentioned. It is noteworthy that, as has been reported, the CAN-oxidation of 4-methoxyphenol in methanol gave 4,4-dimethoxy-2,5-cyclohexadienone in 65% yield.[7] No other paper has described any accompanied C–C coupling product until a recent study by Maruyama

et al. They reported such a C-C coupling which gave a benzoquinonoid crown ether derivative.[8] In a contrast a facile C-C bond formation in the troponoids may be attributable to the presence of an adjacent carbonyl group which helps to delocalize an unpaired electron. Accordingly, the semiquinone radicals of tropoquinones would be more stable than those of benzoquinones to enable the intermolecular reaction. Otherwise, quinone acetals, e.g., **8**, should be formed by a reaction with CAN and the solvent-caged methanol. It would be interesting to investigate the electrochemical behaviors by the cyclic voltammetry of the tropoquinones. This would determine whether this is reflected to it or not. Such research will be published in due course.

Experimental

All the mps were measured by means of a Yanagimoto Micro-mp Apparatus and are uncorrected. Elemental analyses were performed by Miss S. Hirashima of the Research Institute of Industrial Science, Kyushu University. The NMR spectra were measured by means of a JEOL FX 100 Spectrometer in $CDCl_3$ solutions and the chemical shifts measured were expressed in δ units from the internal Me_4Si. The mass spectra were measured by means of a JEOL OlSG-2 Spectrometer. The UV spectra were measured by means of a Hitachi 124 Spectro photometer in MeOH. The IR spectra were taken in either as KBr disks or as an inserted liquid film between NaCl plates using a Jasco IR-A 102 Spectrometer.

CAN-Oxidation of 4. a) To an anhydrous MeOH solution (6 cm^3) of **4** (100 mg), carefully desiccated CAN (721 mg) was added at 0 °C. After 1 h, the mixture was warmed to 20—25 °C and stirred for another 30 min. The mixture was then diluted with water, extracted with $CHCl_3$, and chromatographed on a silica-gel column with AcOEt-hexane (1:4) to give **5** [a yellow oil, 9.6 mg; 9%. Found: M.W., 332.0901 (M^+). Calcd for $C_{17}H_{16}O_7$: 332.0895. ^1H NMR δ=3.16 (3H, s), 3.28 (3H, s), 3.30 (3H, s), 6.40 (1H, d, J=12 Hz), 6.43 (2H, d, J=1.5 Hz), 6.44 (1H, s), and 6.74 (1H, d, J=12 Hz). ^{13}C NMR δ=50.7, 50.9, 53.7, 88.8, 103.0, 132.6, 133.5, 134.7, 135.6, 135.8, 137.8, 138.2, 144.1, 189.5, 191.5, 192.1, and 192.4, IR ν: 2950, 1710, 1660, 1620, and 1450 cm^{-1}], **8** (15.5 mg; 13%), and **9** (12.6 mg; 9%), which were identical with authentic samples,[1] together with **6** [yellow needles, mp 100 °C (decomp), 12.0 mg; 10%. Found: C, 59.71; H, 5.09%. Calcd for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01%. ^1H NMR δ= 3.28 (12H, s), 6.40 (2H, d, J=13 Hz), 6.43 (2H. s). and 6.58 (2H, d, J=13 Hz). ^{13}C NMR δ=50.8 (4C), 103.0 (2C), 132.3 (2C), 135.8 (2C), 138.2 (2C), 143.8 (2C), 191.4 (2C), and 191.6 (2C). IR ν: 1710, 1660, 1450, 1160, and 1050 cm^{-1}. UV λ_{max}^{MeOH}: 229 nm(ε=17800) and 380 (900)].

On the other hand, the aqueous washings were acidified with dil HCl, and extracted with 1-butanol; the solvent was evaporated in vacuo to leave **7** (colorless crystals, mp 226—228 °C (lit,[5] mp 227—230 °C), 35.5 mg; 38%.).

b) To an MeOH solution (3 cm^3) of **4** (80 mg), CAN (577 mg), fresh but not further purified, was added all at once at 0 °C. After 1 h, the mixture was warmed to 20—25 °C and stirred for an additional 30 min. The mixture was diluted with water, extracted with $CHCl_3$, washed with $NaHCO_3$, and chromatographed on a silica-gel column to give **8** (9.6 mg; 10%), **9** (9.1 mg; 8%), **5** (5.2 mg; 6%), and **10** [pale yellow needles, mp 150—150.5 °C. 30.2 mg; 38%. Found: M. W., 302.0786 (M^+). Calcd for $C_{16}H_{14}O_6$: 302.0789. ^1H NMR δ=3.09 (1H, dd, J=15, 2.5 Hz), 3.35 (3H, s), 3.42 (1H, ddd, J=15, 7.5, 1 Hz), 3.85 (3H, s), 5.06 (1H, dd. J=7.5, 2.5 Hz), 6.31 (1H, s), 6.37 (1H, dd, J=12.5, 1 Hz), 6.74 (1H, d. J=12.5 Hz), 7.02 (1H, d, J=13 Hz), and 7.26 (1H, d, J=13 Hz). ^{13}C NMR δ=44.8. 52.0, 56.5, 78.8, 97.4, 107.2, 118.4, 125.2, 135.4, 139.8, 140.2, 158.9, 161.0, 178.9, 193.7, and 194.1. IR ν: 1710, 1670, 1560, 1510, 1450, 1320, 1240, and 1070 cm^{-1}. UV λ_{max}^{MeOH}: 234 nm (ε=22700), 336 (8700), 359 (7600), 377 (7950), and 395 (6900)].

From the aqueous washings, **7** (14.9 mg; 20%) was obtained by extraction with 1-butanol.

CAN-Oxidation of 1. To an MeOH solution (2 cm^3) of **1** (70 mg), CAN (280 mg) was added, and stirred at 20—25 °C for 15 min. The mixture was then diluted with water, extracted with $CHCl_3$, and chromatographed on a silica-gel column with AcOEt-hexane (1:4) to give **3** (15.3 mg; 22%) and **11** [a colorless oil, 10.2 mg; 10%. Found: M. W., 200.0696 (M^+). Calcd for $C_9H_{12}O_5$: 200.0686. ^1H NMR δ=2.20 (1H, dd, J=13.5, 2.5 Hz), 2.53 (1H, dd, J=13.5, 10 Hz), 3.26 (3H, s), 3.45 (3H, s), 4.07 (1H, dd, J=10, 2.5 Hz), 6.28 (1H, d, J=9 Hz), and 7.26 (1H, d, J=9 Hz). ^{13}C NMR δ=39.6, 52.5, 58.8, 83.3, 104.2, 104.8, 128.4, 155.0, and 194.4. IR ν: 3400, 1703, and 1610 cm^{-1}].

TTN-Oxidation of 1. To an MeOH solution (5 cm^3) of **1** (200 mg), TTN (950 mg) was added. After 20 min, the reaction mixture was warmed at 50 °C and stirred for 2 h. The mixture was then diluted with water, extracted with $CHCl_3$, and chromatographed on a silica-gel column with AcOEt-hexane (1:3) to give **12** [colorless crystals, mp 121—123 °C, 43.5 mg; 18%. Found: m/z, 138.0310 (M^+—28). Calcd for $C_7H_6O_3$: 138.0315. ^1H NMR δ=3.80 (3H, s), 5.93 (1H, s), 6.61 (1H, d, J=13.5 Hz), and 6.79 (1H, d, J=13.5 Hz). ^{13}C NMR δ=56.2, 107.7, 134.4, 137.2, 158.6, 181.6, and 187.3 (2C). IR ν: 1680, 1640, and 1590 cm^{-1}. UV $\lambda_{max}^{CHCl_3}$: 255 nm (ε=14000), 286 (550), 356 (1100)], and **13** [a colorless oil, 18.6 mg; 6%. Found: M. W., 214.0836 (M^+). Calcd for $C_{10}H_{14}O_5$: 214.0840. ^1H NMR δ=1.97 (1H, dd, J=13.5, 2.5 Hz), 2.53 (1H, dd, J=13.5, 10 Hz), 3.26 (3H, s), 3.47 (3H, s), 3.50 (3H, s), 3.98 (1H, dd, J=10, 2.5 Hz), 6.22 (1H, d, J=10 Hz), and 7.22 (1H, d, J=10 Hz). ^{13}C NMR δ=40.2, 52.3, 53.7, 58.6, 82.9, 105.3, 109.0, 131.2, 153.0, and 192.1. IR ν: 1740, 1710, 1610, 1560, and 1450 cm^{-1}. UV λ_{max}^{MeOH}: 219 nm (ε=6050)].

TTN-Oxidation of 3. To an MeOH solution (2 cm^3) of **3** (178 mg), TTN (575 mg) was added and stirred at 20—25 °C for 10 min. After stirring at 50 °C for 1 h, the mixture was diluted with water and extracted with $CHCl_3$. Silica-gel column chromatography with AcOEt-hexane (2:3) yielded **12** (28.2 mg; 13%) and **11** (42 mg; 16%).

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