A Reinvestigation of the Synthesis of Hantzsch's Acid: Comparison of Derivatives of Hantzsch's Acid with a Product from the Reaction of 2,4,6-Trichlorophenol and Hypochlorite Ion in Methanol

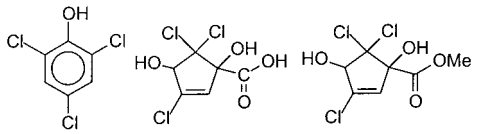
Victor L. Heasley,* Brian D. Wadley, Matthew D. Alexander, James D. Anderson, Jennifer H. Anderson, R. Todd Allen, Mark L. Hernandez, Michael L. Ismail, Geoff A. Sigmund, and Dale F. Shellhamer

Department of Chemistry, Point Loma Nazarene University, San Diego, California 92106

vheasley@ptloma.edu.

Received July 3, 2000

During our continuing investigation of the degradation[1,2] of phenols with hypochlorite ion (OCl^-) and monochloramine (NH_2Cl), we observed that 2,4,6-trichlorophenol (**1**) reacted with calcium hypochlorite ($Ca(OCl)_2$) in methanol (MeOH) to form a product[3] whose infrared (GC FT-IR) and mass (GC-MS) spectra suggested the presence of an alcohol, methyl ester, and three chlorine atoms.[4] Since the analogous reaction of OCl^- with **1** in water and base has been shown to yield Hantzsch's acid (**2**),[5,6] we suspected that the observed compound in the solvent MeOH might be the methyl ester of Hantzsch's acid (**3**). Therefore, we proposed to synthesize Hantzsch's acid (**2**) and convert it to its ester (**3**) for comparison purposes. From the outset, the synthesis of **2** looked challenging since the procedure is lengthy and messy,[5,6] and the results are reported to be highly erratic.[6] It seemed to us that a simplified synthesis of Hantzsch's acid **(2)** could prove to be valuable as a major source of cyclopentanyl and cyclopentenyl compounds since **2** has been reported as the starting material in the synthesis of more than 15 derivatives.[5,6]



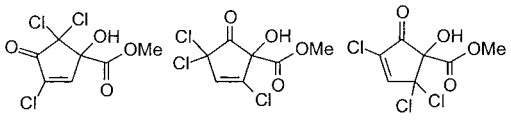
1 **2** **3**

Results and Discussion

Our experience with the literature[5,6] syntheses of **2** was completely unsatisfactory. The procedure was difficult and lengthy (the synthesis involves formation of crude **2**; precipitation, isolation, and recrystallization of the ammonium salt of **2**, formed with NH_3 gas; regeneration of purer **2** from the ammonium salt with H_2SO_4/Ba^{2+}; isolation and recrystallization of **2**), frequently no product was obtained at all, and we never approached the reported high yield.[5] On the basis of our investigation, we wish to report a simplified, one-step synthesis of **2** in a modest, recrystallized yield (40%). Our procedure depends on the following criteria: rapid addition of Cl_2, control of the pH and temperature, and a new, simple isolation procedure.

With easy access to an ample supply of Hantzsch's acid (**2**), we attempted the synthesis of the methyl ester (**3**) using diazomethane, CH_2N_2, as described in the literature,[5] so that a comparison could be made to the unknown compound. We found that the reported synthesis procedure was unsatisfactory because the product always consisted of a mixture of **3** and the methoxy methyl ester, resulting from methylation of one of the alcohol groups in addition to carboxyl group. However, ester **3** was obtained in high yield by refluxing **2** in MeOH and BF_3. The structure of ester **3** was confirmed by comparison to the literature[5] melting point and by its IR, ^{1}H NMR, and mass spectra. Unfortunately, gas chromatography−mass spectrometry (GC-MS) showed that **3** and the unknown compound were not the same. It occurred to us that the unknown compound might be an ester-ketone **4**, resulting from the oxidation of the secondary alcohol in **3**, where the carbonyl absorptions for the ester and the ketone groups fortuitously appeared as one peak in the IR spectrum. The oxidation of **3** to **4** was now undertaken.

Ester-ketone **4**, which had not been reported previously, was synthesized by oxidation of ester **3** with $Na_2Cr_2O_7/H_2SO_4$ in glyme/H_2O. The standard oxidation procedure for the oxidation of α,β-unsaturated alcohols involving pyridinium dichromate and pyridinium chlorochromate in CH_2Cl_2 or DMF failed because the reaction stopped after only about 10% oxidation and could not be forced to go further. The presence of ester and ketone carbonyl groups in **4** was confirmed by the ^{13}C NMR spectrum which showed peaks for both groups: ester (168.7 ppm) and ketone (184.5 ppm). Additional structure proofs include ^{1}H and ^{13}C NMR, IR, and mass spectra and an exact mass determination.



4 **5** **6**

The IR spectrum of **4** was almost identical to the unknown compound, showing only minor differences in the fingerprint region; the ^{1}H and ^{13}C NMR spectra showed some significant differences in chemical shifts, indicating that **4** and the unknown compound were not the same, but were probably closely related isomers. (The NMR spectra of the unknown product showed minor impurity peaks, even though the GC analysis indicated that the purity of the GC-collected product was approximately 90%. Apparently some high-boiling materials

(1) Heasley, V. L.; Anderson, M. E.; Combes, D. S.; Elias, D. S.; Gardner, J. T.; Hernandez, M. L.; Moreland, R. J.; Shellhamer, D. F. *Environ. Toxicol. Chem.* **1993**, *12*, 1653.

(2) Heasley, V. L.; Alexander, M. B.; DeBoard, R. H.; Hanley, Jr. J. C.; McKee, T. C.; Wadly, B. D.; Shellhamer, D. F. *Environ. Toxicol. Chem.* **1999**, *18*, 2406−2409.

(3) The unknown compound is a minor product (ca. 5%). The major product, which will be reported elsewhere and does not result from ring-contraction or ring-opening, is a trichlorophenoxy dichloroquinone.

(4) A third chlorine is obvious in the mass spectrum in the peaks at 199, 201, and 203 amu. These fragments result from the loss of MeOCO and show a 3-chlorine isotope pattern.

(5) Burgstahler, A. W.; Lewis, T. B.; Rahman-Abdel, M. O. *J. Org. Chem.* **1966**, *31*, 3516; other references included therein.

(6) Moye, C. J.; Sternhell, S. *Aust. J. Chem.* **1966**, *19*, 2107; other references included therein.

10.1021/jo0010025 CCC: $19.00
Published on Web 10/26/2000

eluted from the column, were collected, but did not appear in the GC analysis). The mass spectra of **4** and the unknown compound were essentially identical except for shifts in the intensities of the base peaks. The base peak for **4**, resulting from loss of MeOCO, occurred at $m/z = 199$ (and isotopes) with a lesser loss of Cl (55% of base peak) at $m/z = 223$ (and isotopes). The base peak for the unknown compound, resulting from loss of Cl, occurred at $m/z = 223$ (and isotopes), with a minor loss of MeOCO (13% of base peak) at $m/z = 199$ (and isotopes).

Two isomers[7] of **4** are shown in structures **5** and **6**. Both isomers **5** and **6** should lose Cl more readily than **4** in the mass spectrometer since they can form allylic cations. The cation resulting from loss of Cl in isomer **4**, should be less stable because it would not be allylic and would be situated between a carbonyl and a carbon with a carbonyl and an oxygen. Loss of the MeOCO radical (59) from **4** occurs to a significant extent because of the formation of an allylic cation which is stabilized by resonance interaction with the adjacent oxygen.

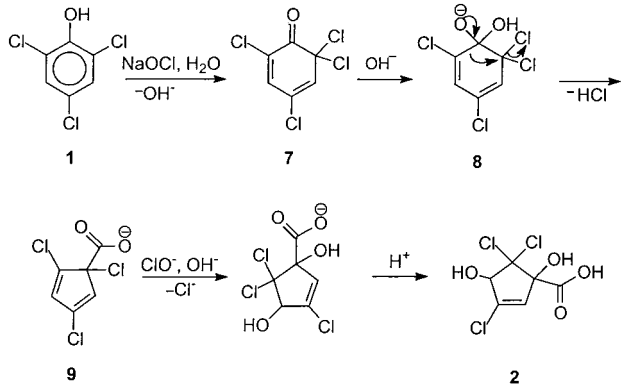
On the basis of the following observations, we suspect that the unknown compound, formed in the reaction of **1** with OCl^- in MeOH, is **6** rather than **5**: the peak at 1597 cm^{-1} in the IR spectrum of the unknown compound suggests that the C=C bond is conjugated with the carbonyl group; the similarities of the ketone carbonyl carbons frequencies in the ^{13}C NMR spectra at 184.5 and 186.2 ppm for **4** and the unknown compound, respectively, support **6** since the ketone carbonyl carbon in **5** is not conjugated and should be downfield by approximately 10 ppm; the mechanistic reactions presented below show how **6** could be formed, but we have been unable to develop a mechanism for **5**; conjugation of the α,β-unsaturated ketone exists for **4** and **6** but not **5**.

These data show that the reactions of **1** with OCl^- are very different in MeOH and H_2O. Hantzsch's acid (**2**) is the major product in H_2O; its methyl ester (**3**), the anticipated product in MeOH, was not detected. We also established that the presence of sodium methoxide, NaOMe, in the MeOH had no affect on the products. Chlorine (Cl_2) and NaOMe in MeOH did not produce **4** or **6**.

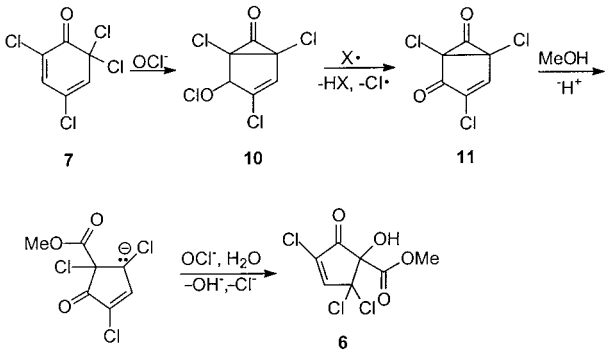
We assume, as have the previous authors,[5,6] that the mechanism in the synthesis of Hantzsch's acid involves attack of OH^- on the carbonyl carbon in the intermediate dienone **7**, ring contraction in **8**, and solvolysis/electrophilic addition of Cl (from OCl^-), OH^- (from H_2O) in diene **9** (Scheme 1). Compound **6** may be formed as shown in Scheme 2.[8]

We also considered the possibility that hypochlorite **10** could exchange chlorine with MeOH to give **12** as shown in Scheme 3. Intermediate **12**, after subsequent reactions as shown for the reaction of cyclopropanone **11** with MeOH, would yield **13** which could be oxidized to **6**. We concluded that the oxidation of **13** to **6** was unlikely since we established that **3** is not oxidized to **4** by $Ca(OCl)_2$ in MeOH.

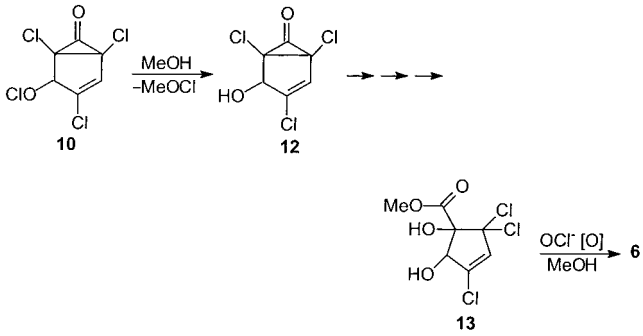
Scheme 1



Scheme 2



Scheme 3



Experimental Section

Materials. 2,4,6-Trichlorophenol (**1**), $Ca(OCl)_2$, and MeOH (anhydrous) were obtained from Aldrich.

Instrumentation. ^{13}C NMR spectra were obtained at 75.4 MHz. Mass spectral data are expressed as m/z and as relative intensity (%). GC and GC-MS analyses were done with a 25 m ultraperformance column of internal diameter 0.20 mm with a methyl silicone stationary phase of 0.33 mm film thickness.

1,4-Dihydroxy-3,5,5-trichloro-2-cyclopentene-1-carboxylic Acid (Hantzsch's Acid) (2). To a 500-mL, three-neck flask equipped with a stirring bar, pH electrode, thermometer, and gas dispersion tube was added 18.0 g (0.091 mol) of 2,4,6-trichlorophenol (**1**) dissolved in 250 mL of 2.5 M NaOH. Chlorine (Cl_2) was bubbled rapidly into the solution while maintaining the temperature in a 0 to −4 °C range with an acetone−dry ice bath. (The acetone−dry ice bath was saturated with dry ice. The temperature was prevented from dropping below the range by the rapid addition of Cl_2. Occasionally, it was necessary to lower the cooling bath to maintain the temperature or to melt ice that formed in the flask.) When the pH reached 10, it dropped rapidly

(7) Another isomer is possible in which the vinyl chlorine and proton in **6** are transposed. We did not include this isomer since the exchange of chlorine and proton are highly unlikely and because we could not develop a mechanistic pathway leading to this isomer.

(8) We are unaware of any report in the literature of hypochlorite ion reacting as a nucleophile, as shown in the conversion of **7** to **10**. The basis for the radical transformation of hypochlorite **10** to ketone **11** has been suggested by McDonald et al. (McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741). It is conceivable that dienone **7** is attacked by a trace of H_2O at the β-carbon leading to a secondary alcohol which, in turn, reacts with hypochlorous acid to give hypochlorite **10**.

to 8 (approximately 6 min from the start of Cl_2 addition) and the temperature rose. Addition of Cl_2 was stopped. When the temperature again reached 0 to −4 °C, 50 mL of 5.0 M NaOH was added, and Cl_2 was passed into the solution until the pH again reached 5 (approximately 15 min from the start of the second chlorination). At this point, chlorination was stopped, and 12 M HCl was added dropwise until the pH reached 2. The solution was filtered to remove polymeric byproducts and extracted three times with 80 mL portions of ether, and the combined extracts were dried over $MgSO_4$. The temperature was maintained at approximately 0 °C throughout the acidification and filtration process.

Hantzsch's acid (**2**) was isolated by removing the ether under vacuum with a rotary evaporator, cooling the yellow liquid in the freezer (−10 °C) overnight, and adding 10−20 mL of ice-cold pentane/ether (80:20) with stirring to the viscous syrup/crystals. The white or pale yellow crystals were isolated by filtration. If crystallization does not occur, seeding is effective. Crystals of **2** can always be obtained by adding a few drops of the syrup to ice-cold $CHCl_3$.

An alternate isolation procedure, which did not require waiting overnight, was to place the flask containing the crude, syrupy **2** in the freezer for 3 h. Then the flask was placed in an ice bath, and 75 mL of ice-cold $CHCl_3$ was added with stirring. After a short time, a gelatinous precipitate began to form. At this point, the flask was placed in a warm water bath on the rotary evaporator, and the solvent was removed under vacuum. Crystals of **2** formed immediately. Precipitation was completed in an ice bath.

Acid **2** was recrystallized from $CHCl_3$/ethyl acetate as follows: **2** was suspended in $CHCl_3$ and heated to the boiling point. Ethyl acetate was added dropwise until the solid dissolved. Cooling with stirring in an ice bath gave white crystals: mp 177 °C; reported[5,6] mp 176−177 °C. Average yield, 40%. The $CHCl_3$/ethyl acetate recrystallization system was far superior to the previously reported petroleum ether/ether system[5] because the crystals were less clumpy and the return was much greater. ^{1}H NMR (60 MHz, acetone-d_6):δ 5.16 (d, 1H, J = 1.7 Hz), 6.02 (d, 1H, J = 1.7 Hz), 6.70 (s, 3H).

Methyl 1,4-Dihydroxy-3,5,5-trichloro-2-cyclopentene-1-carboxylate (3). An amount of 12.4 g (50 mmol) of **2**, 30 mL of MeOH, and 2.0 mL of BF_3 etherate were refluxed for 2 h. A volume of 30 mL of H_2O was added, the solution was saturated with NaCl, extracted with ether, and dried over $MgSO_4$. Removal of the ether gave a waxy material which was recrystallized from $CHCl_3$ to give **3** in 70% yield by GC: mp 126 °C; reported[5,6] mp 126 °C. ^{1}H NMR (60 MHz): δ 5.92 (s, 1H), 4.94 (s, 1H), 3.88 (s, 3H). IR (cm^{-1}): HO, 3515, 3427; MeO, 2860; CO, 1747. GC analysis conditions: programmed from 120 to 220 °C at 10 °C/min; retention time (min), 8.5. Synthesis of **3** from diazomethane, CH_2N_2, as described by Burgstahler et al.[5] did not work well for us since extensive methylation of one of the alcohols occurred. Apparently, the previous group[5] removed the methylated impurity by extensive recrystallization.

Methyl 1-Hydroxy-3,5,5-trichloro-4-keto-2-cyclopentene-1-carboxylate (4). To 200 mg (0.77 mmol) of **3** dissolved in 0.3 mL of glyme and 0.3 mL of H_2O in 10 mL flask in an ice bath equipped with stirrer was added dropwise 70 drops of an ice-cooled solution of 0.5 mL of H_2O, 1.5 g (5.0 mmol) of $Na_2Cr_2O_7 \cdot 2H_2O$, and 2 mL of concentrated H_2SO_4. The reaction was worked up by adding 3 mL of H_2O, saturating with salt, and extracting with two 3 mL portions of ether. The ether extracts were washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was decanted and removed under vacuum to yield 150 mg (0.58 mmol; 80% yield by GC) of **4**. Compound **4**, a liquid which solidified in the refrigerator, was purified over TLC grade silica gel (Aldrich: 28,851-9) using hexane/ether; **4** eluted in 50% ether. A purity of 90% or greater was established by HPLC with a RP column, using acetonitrile/H_2O as the solvent. ^{1}H NMR (60 MHz): δ 3.88 (s, 3H), 4.5 (s,1H) 7.20 (s, 1H). ^{13}C NMR: δ 54.8, 83.4, 102.5, 136.4, 148.5, 168.7, 184.5. GC-MS m/z (EI): 227, 225, 223 (M − Cl, 6, 36, 55), 205, 203, 201, 199 (M − $MeOCO_2$, 3, 32, 93, 100), 183, 181, 179 (M − Cl − CO_2, 5, 29, 48), 168, 166, 164 (M − $MeOCO_2$ − Cl, 5, 27, 40), 139, 137, 135 (5, 17, 30), 111, 109, 107 (8, 37, 64), 91, 89 (7, 25), 72 (41), 59 ($MeOCO_2$, 90). HRMS (CI): MNH_4^+, calculated for $C_7H_5O_4Cl_3$, 275.9585, found: 275.9597. IR (cm^{-1}): OH, 3528; C−H, 2969; MeO, 2860; CO, 1776; C=C, 1622; 1449; 1281; 1208; 1127; 987; 876; 799. GC analysis conditions: programmed from 120 to 220 °C at 10 °C/min; retention time (min), 7.8.

Both pyridinium chlorochromate and pyridinium dichromate failed in the oxidation of **3** to **4** because they gave only a 10% yield of ketone, and the reaction could not be forced to proceed further.

Methyl 1-Hydroxy-2,2,4-trichloro-5-keto-3-cyclopentene-1-carboxylate (6). To 150 mg (0.76 mmol) of **1** in 5 mL of MeOH in a 25 mL flask with stirrer was added 80 mg (0.56 mmol) of $Ca(OCl)_2$. After 10 min of rapid stirring, 10 mL of H_2O and 5 mL of CH_2Cl_2 were added. The organic layer was removed and dried over $MgSO_4$. GC and GC-MS analyses were performed on this solution under the following conditions: programming from 120 to 220 °C at 10 °C/min; retention time (min) of **6**, 7.8. Product **6** was one of several compounds[3] in the chromatogram, formed in ca. 5% yield by GC. Isolation of **6** involved preparative GC using a 2.6 m × 1 cm glass column packed with DC 550 on Chromosorb W at 150 °C with a He flow rate of 100 mL/min. Capillary GC analysis, under the conditions described above, showed that the preparative GC-collected **6** had a purity of greater than 90%. ^{1}H NMR (60 MHz): δ 3.85 (s, 3H), 4.69 (s, 1H), 6.61 (s, 1H). ^{13}C NMR: δ 55.1, 86.7, 107.7, 129.5,134.0, 162.7, 167.8, 186.2. The two peaks at 162.7 and 167.8 ppm may represent conformers of **6** where the hydroxy group and carbonyl group are anti and syn, with hydrogen bonding. A small peak at 85.9 ppm, and not listed, probably results from an impurity). GC-MS m/z (EI): 227, 225, 223 (M − Cl, 11, 62, 100), 205, 203, 201, 199 (M − $MeOCO_2$, 0.4, 4, 12, 13), 183, 181, 179 (M − Cl − CO_2, 0.9, 5, 7), 168, 166, 164 (M − $MeOCO_2$ − Cl, 1, 6, 11), 139, 137, 135 (2, 8, 9), 111, 109, 107 (2, 10, 16), 91, 89 (0.7, 4), 72 (14), 59 ($MeOCO_2$, 7). IR (cm^{-1})(vapor phase): HO, 3520; C−H, 2988; CH_3O, 2850; CO, 1788; 1597; 1442; 1273; 1240; 1189; 1083; 989; 840; 788.

Acknowledgment. We recognize, with pleasure, support from the following sources: NIH (1-R15ES05671-01); NSF-RUI (CHE-9528446); NSF-RUI (CHE-9902718); Howard Hughes Medical Institute Award, 71196-552001 (Geoff A. Sigmund); Research Associates of Point Loma Nazarene University; the Mass Spectroscopy Facility, University of California, Riverside.

Supporting Information Available: NMR, IR, and mass spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0010025