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Atovaquone: An Antipneumocystic Agent

Atovaquone is a pharmaceutical compound marketed in the United States under different combinations to prevent and treat pneumocystosis and malaria. In a report from 2012, a team of researchers described a novel synthetic process scalable to 200 kg, starting from isochromandione **1** and aldehyde **2** (Scheme 1.1) [1, 2].

The route to **1** is described in Scheme 1.2. A mixture of phthalic anhydride **3** and Et_3N (1.07 equiv.) heated at 80 °C is treated over 4 h by portions of malonic acid (1.2 equiv.) and maintained at 80 °C for 10 h. Gas evolution was observed all along that period.[1] After adding an excess of aq. HCl solution and cooling the mixture to 25 °C, the solid is filtered off and dried to afford acid **5** in 67% yield. This transformation presumably occurs through intermediate **4**, having the molecular formula $C_{10}H_8O_5$ and containing two carboxylic acid groups [3, 4].

Question 1.1: Write the structure of **4** and suggest a plausible mechanism for its formation.

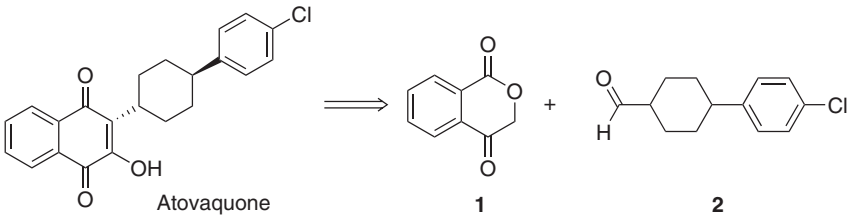
Question 1.2: Suggest a plausible mechanism for the formation of **5** from **4**.

A solution of **5** in chlorobenzene is reacted for 3 h at 30 °C in the presence of HBr (0.05 equiv.) and Br_2 (1 equiv.) in acetic acid. This reaction leads to the formation of intermediate **6** (molecular formula $C_9H_8O_3$) undergoing loss of a molecule of water to give intermediate **7**, transformed into lactones **8** and **9** under reaction conditions. Water is then added, and the mixture is refluxed for 3 h and cooled to 60 °C. The organic layer is removed, the aqueous layer is extracted with chlorobenzene, and the combined organic layers are concentrated under reduced pressure. Addition of *i*-PrOH followed by cooling to 0 °C results in the formation of a solid, which is filtered, washed with *i*-PrOH, and dried to afford **1** in 75% yield.

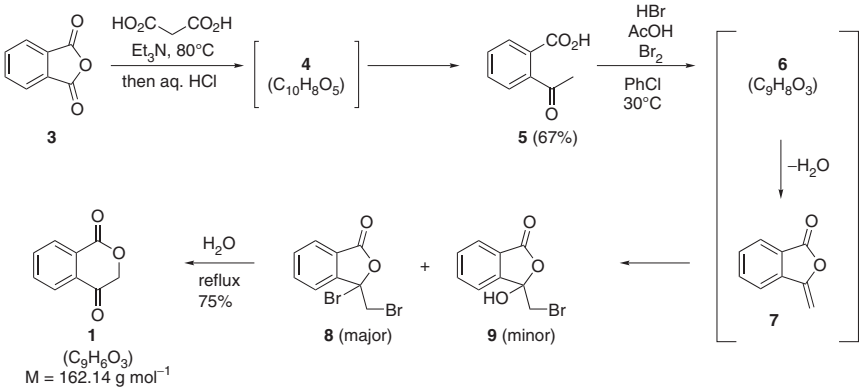
Question 1.3: Write the structure of **6** and suggest a plausible mechanism for its formation from **5** and its transformation into **7**.

1 This phenomenon was not reported in the original article, but was clearly observed under similar reaction conditions [3].

Multi-Step Organic Synthesis: A Guide Through Experiments, First Edition. Nicolas Bogliotti and Roba Moumné.



Scheme 1.1



Scheme 1.2

Question 1.4: Suggest a plausible mechanism for the formation of **1** from **8** and **9**.

Question 1.5: The ^{1}H-NMR spectra reported for compounds **1**, **3**, and **6** are described in the following table.[2] Assign characteristic signals for each compound and identify the corresponding spectrum (**A**, **B**, or **C**).

Spectrum	Description
A	**^{1}H-NMR** (400 MHz, $CDCl_3$): 8.30–8.28 (m, 1H), 8.10–8.08 (m, 1H), 7.91–7.82 (m, 2H), 5.14 (s, 2H) [2]
B	**^{1}H-NMR** (500 MHz, $CDCl_3$): 8.05–8.01 (m, 1H), 7.93–7.90 (m, 1H) [5]
C	**^{1}H-NMR** (400 MHz, $CDCl_3$): 7.86–7.84 (d, 1H), 7.73–7.69 (t, 1H), 7.63-7.52 (m, 2H), 4.13 (br. s, 1H), 1.97 (s, 3H) [2]

Compound **1** was found to be sensitive to basic conditions, undergoing unexpected transformation into a new product **10**. While HRMS analysis reveals a signal at $m/z = 161$ for **1** (negative mode chemical ionization), a signal at $m/z = 325$ (positive mode chemical ionization) was observed for **10**. ^{13}C-NMR spectra

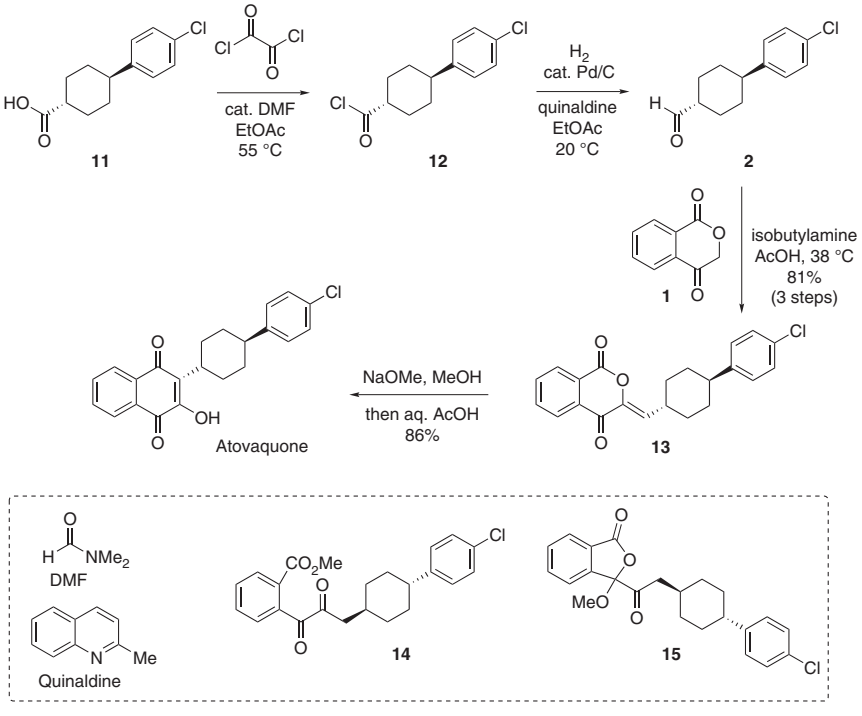
2 In $CDCl_3$ solution, compound **5** was found to spontaneously convert to **6**.

show peaks at 161.3 and 189.5 ppm for **1**, and at 161.5, 163.4 and 190.0 ppm for **10**. This latter compound also exhibits by ^{1}H-NMR spectroscopy (in DMSO-d_6) a broad signal at 6.57 ppm, exchangeable with D_2O.

Question 1.6: Suggest a plausible structure for the ion derived from **1** corresponding to signal at $m/z = 161$.

Question 1.7: Suggest a plausible structure for **10**, based on HRMS, ^{13}C-NMR, and ^{1}H-NMR analysis.

The end of synthesis is described in Scheme 1.3. A suspension of carboxylic acid **11** in ethyl acetate, in the presence of a catalytic amount of dimethylformamide (DMF), is warmed to 55 °C and treated with oxalyl chloride (1.1 equiv.) by slow addition over 30 min, to give acyl chloride **12**. The crude solution is concentrated, cooled to 20 °C, and quinaldine (1.4 equiv.) is added. The mixture is transferred into a hydrogenation vessel loaded with a catalytic amount of Pd/C, and stirred under hydrogen atmosphere until conversion to aldehyde **2** is complete. After removing the catalyst by filtration, **1**, acetic acid, and isobutylamine are successively added to the mixture; then, stirring at 38 °C until complete reaction results in the formation of **13**, isolated in 81% yield after filtration.



Scheme 1.3

Question 1.8: Suggest a plausible reaction mechanism for the formation of **12** from **11**. Clearly evidence the role played by DMF.

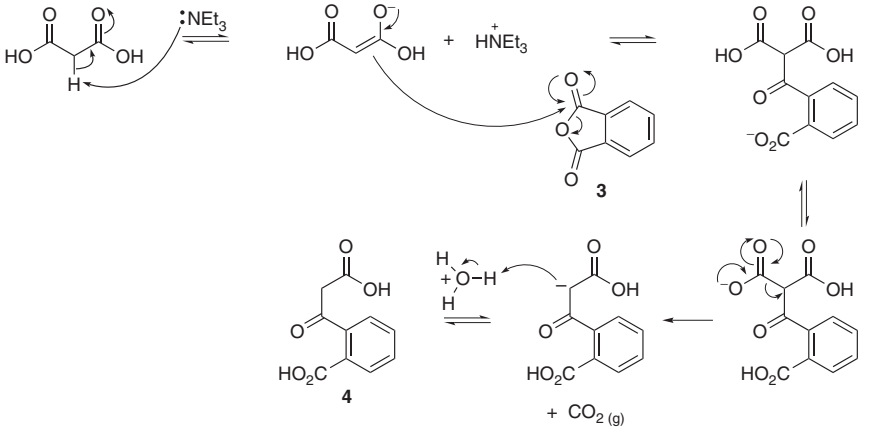
Question 1.9: What is the role of quinaldine during the hydrogenation step? Which other reagent is commonly used to perform such a transformation?

Finally, addition of a solution of sodium methoxide (1.2 equiv.) in methanol to a suspension of **13** in methanol at 20 °C followed by stirring for 18 h leads to the formation of a dark-red solution. Careful monitoring of the reaction reveals the rapid formation of methyl ester **14**, as well as lactone **15**. Treatment with aqueous acetic acid results in the precipitation of atovaquone as a bright-yellow solid collected by filtration in 86% yield.

Question 1.10: Suggest a plausible mechanism for the transformation of **13** into **14** and **15**, and their conversion into atovaquone.

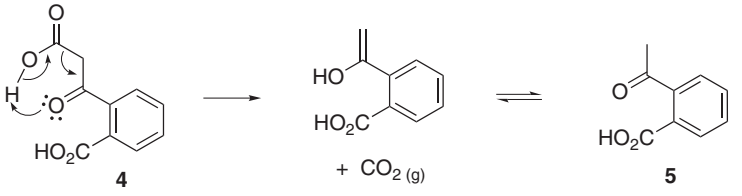
Answers

Question 1.1:

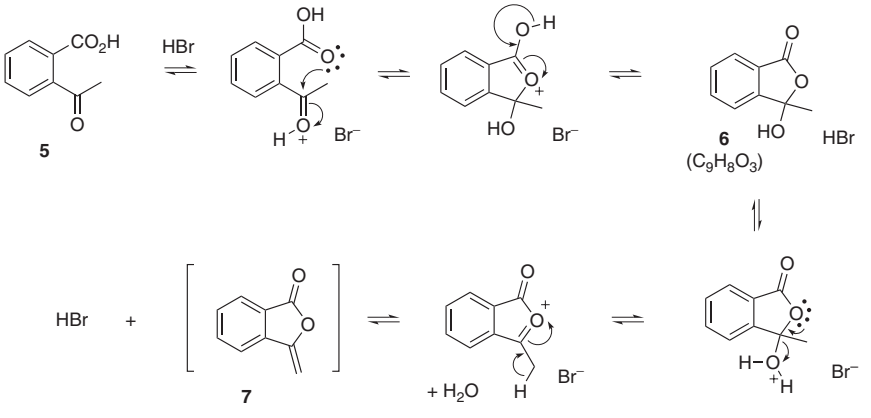


Remark: Hydrogen atoms in the malonic position are less acidic than those of the carboxylic acids and many acid/base exchanges can take place during the reaction. However, only deprotonation at this position allows C–C bond formation, finally leading to **4**, thus shifting all acid/base equilibria toward the desired compound.

Question 1.2:

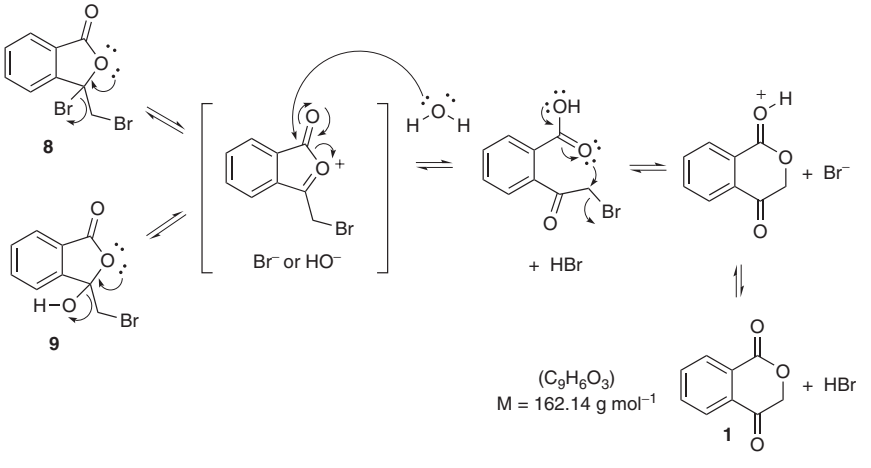


Question 1.3:



Question 1.4:

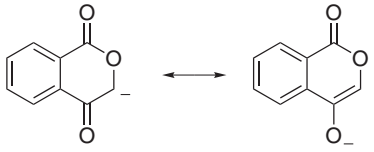
A common mechanism can be suggested for the formation of **1** from **8** or **9**:



Question 1.5:

Spectrum **A** corresponds to compound **1**: 4 aromatic CH, aliphatic CH_2 significantly up-fielded (α to both an oxygen atom and a carbonyl group).
Spectrum **B** corresponds to compound **3**: 4 aromatic CH.
Spectrum **C** corresponds to compound **6**: 4 aromatic CH, 1 exchangeable H (broad, typically OH), aliphatic CH_3.[3]

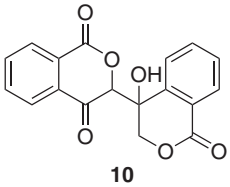
Question 1.6:



Ion derived from **1**: $[M–H]^-$

Question 1.7:

The mass spectrometry (MS) analysis of **10** in positive mode shows a signal at $m/z = 325$, likely corresponding to $[M + H]^+$ ion and thereby suggesting that **10** (M = 324) is a dimer of **1**. While the ^{13}C-NMR spectrum of **1** shows characteristic signals for ester (161.3 ppm) and ketone (189.5 ppm), **10** presumably contains two esters (161.5 and 163.4 ppm) and a ketone (190.0 ppm). The presence of a broad signal at 6.57 ppm (exchangeable with D_2O) in the ^{1}H-NMR spectrum of **10** reveals the presence of a hydroxyl group. Finally, since **1** contains both an enolizable H atom that could be easily deprotonated under basic conditions and an electrophilic ketone moiety, it could self-dimerize to the following compound **10**.



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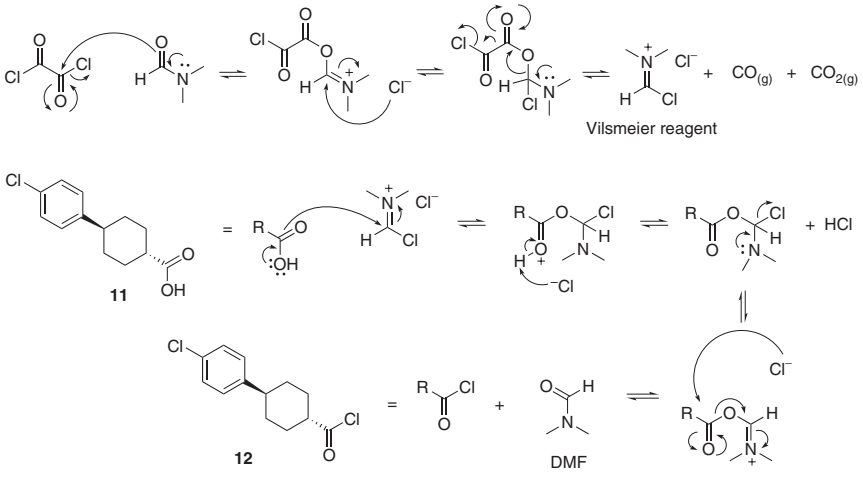
3 Although this spectrum was initially assigned to **5** [2], several studies evidenced an equilibrium in $CDCl_3$ solution favoring its existence as **6** [6, 7].

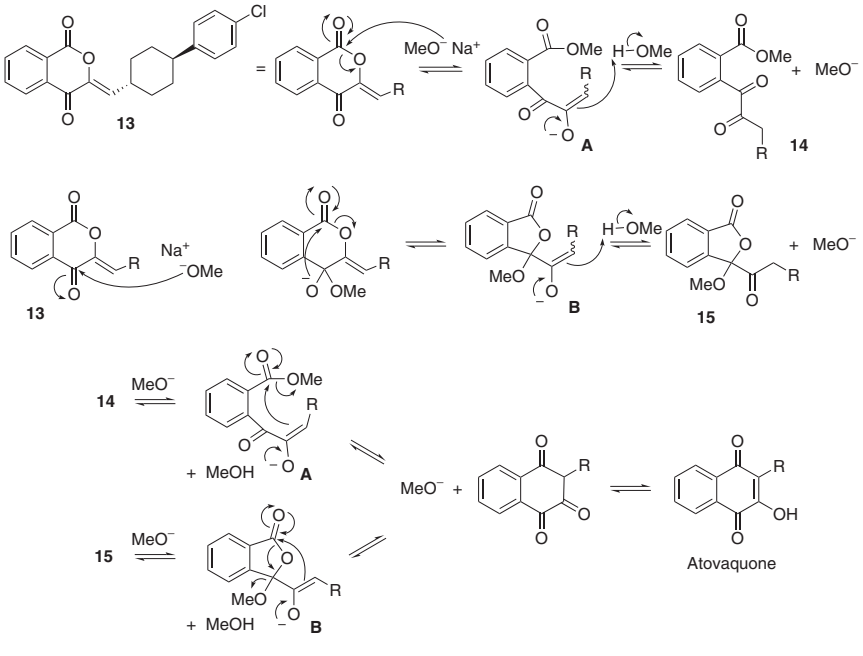
Question 1.8:



Question 1.9:

Quinaldine, like the commonly used quinoline (lacking the methyl substituent), adsorbs at the surface of palladium thus reducing catalyst activity ("poisoning" the catalyst) and avoiding further reduction of aldehyde function into alcohol.

Question 1.10:



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