Notes

Regioselective Synthesis of Islandicin and Digitopurpone

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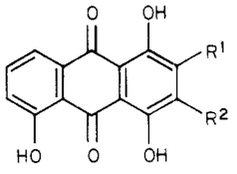
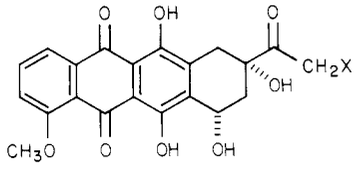
Renewed interest in the synthesis of the anthraquinone pigments islandicin (**1a**)[1] and digitopurpone (**1b**)[2] has been aroused since these substances bear a substitution pattern reminisecnt of the clinically important anthracyclinones daunomycinone (**2a**)[3] and adriamycinone (**2b**).[4]

Recently, total syntheses[5] of these compounds and some



1a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$

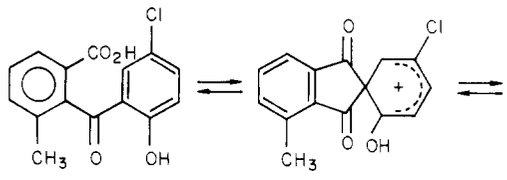


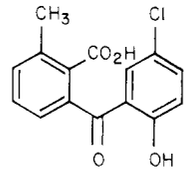
2a, X = H
b, X = OH

analogues[6] have been reported. However, in several of these the general approach involves a Friedel–Crafts cyclization to construct the three-ring system. This method has the disadvantage of the Hayashi rearrangement (Scheme I).[7] Thus, attempted closure of substituted benzoylbenzoic acids can result in scrambling or complete reversal of desired substitution patterns in the products.

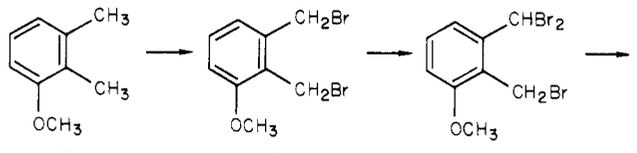
Cava prepared 1,4-anthraquinone (**3**) by reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (**4**) with sodium iodide in the presence of benzoquinone.[8] This reaction proceeds via the intermediate **5** which is trapped in a Diels–Alder reaction with benzoquinone.

Scheme I

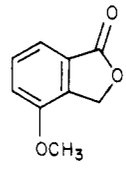




Scheme II



8 9 10



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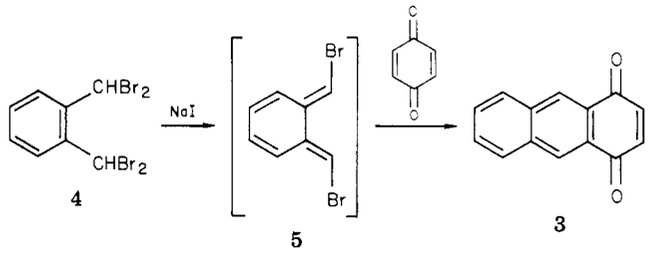

4 5 3

Various studies have shown that *o*-quinodimethan **7** substituents on dienes and dienophiles impart good selectivity to Diels–Alder reactions.[9] We are investigating the cycloaddition reactions between unsymmetrically substituted *o*-quinodimethans and quinones, and in this paper we report the regioselective syntheses of islandicin (**1a**) and digitopurpone (**1b**) via the 1,4-anthraquinones **6a** and **6b**. These 1,4-anthraquinones are prepared in regioselective Diels–Alder reactions between *o*-quinodi-

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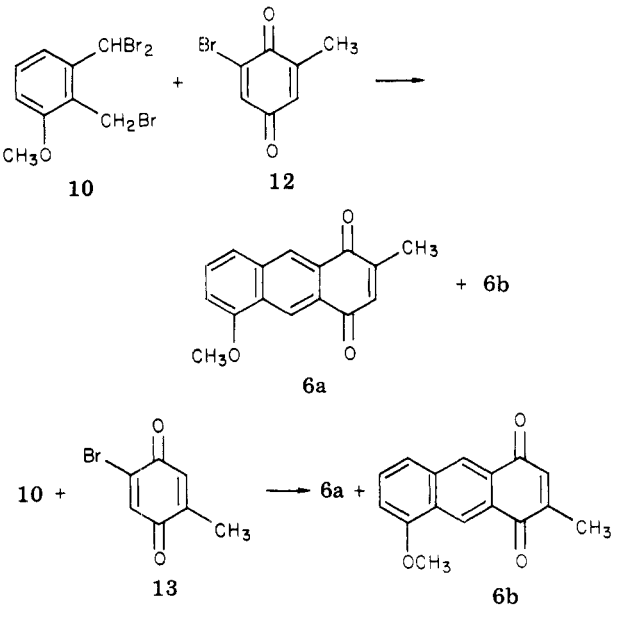
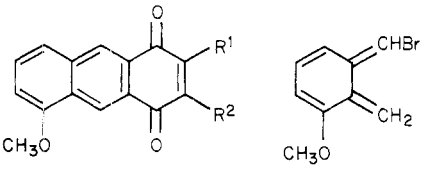
Scheme III



methan **7** and, respectively, 6-bromotoluquinone (**12**) and 5-bromotoluquinone (**13**).



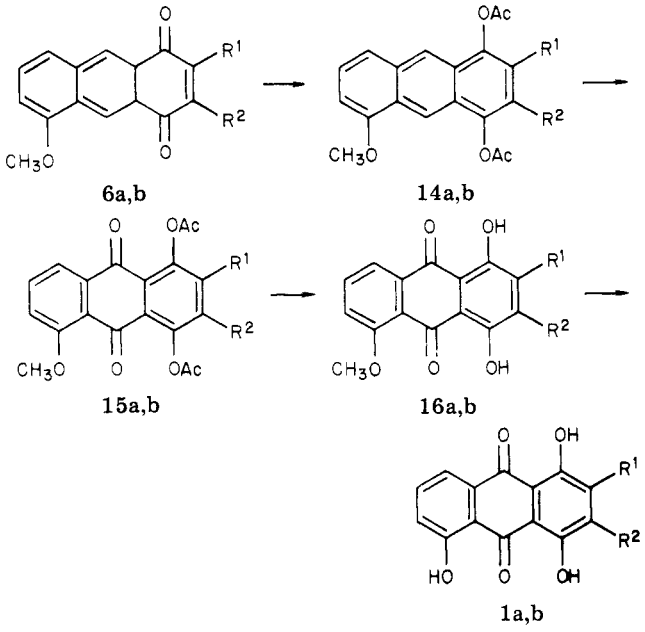
6a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$

7

A suitable precursor for the *o*-quinodimethan **7** was prepared as shown in Scheme II. Bromination of 2,3-dimethylanisole (**8**) with 2 equiv of *N*-bromosuccinimide produced the expected dibromide **9**. Reaction of **9** with an additional equiv of *N*-bromosuccinimide produced the crystalline tribromide **10**. The structural assignment of **10** is based on its transformation into 4-methoxyphthalide (**11**).[10] Hydrolysis of **10** in aqueous tetrahydrofuran containing silver nitrate, followed by oxidation of the intermediate hydroxy aldehyde with silver oxide gave lactone **11** in 91% yield.

Reaction **10** with sodium iodide and 6-bromotoluquinone (**12**)[11] in boiling acetone produced a 92:8 mixture of **6a** and **6b**, from which **6a** could be obtained pure in 46% yield. The relative amounts of **6a** and **6b** were determined by ^1H NMR analysis of the crude reaction products without crystallization and the ratio of **6a** to **6b** reflects the regioselectivity of the Diels–Alder reaction. The resonances of the hydrogens at positions 9 and 10 of anthraquinones **6a** and **6b** are distinctive. In **6a**, these hydrogens resonate at δ 8.53 and 9.01 while in **6b** the two hydrogens resonate at δ 8.48 and 9.03. In each case the lower field resonance is assigned to the hydrogen atom peri to the methoxy group. When dimethylformamide was used as the reaction solvent, the selectivity was about the same, but the yields were lower. When wet acetone was used as the reaction solvent, no regioselectivity was observed; the ratio of **6a** to **6b** was 1:1.

Scheme IV



a, $R^1 = CH_3$; $R^2 = H$ (islandicin series)
b, $R^1 = H$; $R^2 = CH_3$ (digitopurpone series)

The reaction of 5-bromotoluquinone (**13**)[12] with sodium iodide and tribromide **10** proceeded analogously and gave a mixture of **6a** to **6b** in the ratio 8:92. Anthraquinone **6b** was obtained pure in 40% yield. Thus, both reactions are highly regioselective.

Anthraquinones **6a** and **6b** were converted, respectively, into islandicin (**1a**) and digitopurpone (**1b**) in identical fashion. The reaction sequence is shown in Scheme IV and the transformations for only the islandicin series will be described. Reductive acetylation of **6a** with zinc dust and sodium acetate in acetic anhydride at room temperature produced the diacetate **14a** in nearly quantitative yield. Oxidation of the central ring of **14a** was accomplished with Jones reagent to give the quinone diacetate **15a**. Since **15a** was unstable, it was hydrolyzed immediately with 3 N hydrochloric acid in acetic acid to give 5-*O*-methylislandicin (**16a**). The yield of **16a** based on **14a** was 56%. The 5-*O*-methylislandicin was identical in all respects with an authentic sample.[13]

Hydrolysis of islandicin methyl ether **16a** was accomplished by heating **16a** with a mixture of acetic acid and hydrobromic acid. The product had properties identical with those reported for islandicin (**1a**).[1]

The synthesis of digitopurpone from **6b** proceeded similarly to give digitopurpone methyl ether **16b** with properties the same as reported.[5a] Hydrolysis of the methyl ether produced digitopurpone.

This work demonstrates the use of regioselective Diels–Alder reactions between *o*-quinodimethans and quinones for the synthesis of anthracenes and anthraquinones. Strategic placement of bromine substituents on the *o*-quinodimethan and quinone provide excellent orientational control in the cycloaddition reactions.

Experimental Section

General Procedures. Melting points were taken on a Thomas Hoover capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer 457 grating infrared spectropho-

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(13) We are grateful to Professor H. W. Whitlock for a sample of authentic islandicin methyl ether.

tometer from potassium bromide pellets. NMR spectra were measured on a Varian T-60A spectrometer and a JEOL PFT-100 spectrometer and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on AEI-MS-902 and Finnigan 4000 instruments. Ultraviolet spectra were recorded with a Cary 19 spectrophotometer using ethanol solutions. Analyses were performed by Spang Microanalytical Laboratories.

2,3-Bis(bromomethyl)anisole (9). To a solution of 13.6 g (0.1 mol) of **8** in 120 mL of carbon tetrachloride in a 250-mL round-bottomed flask was added 35.6 g (0.2 mol) of recrystallized *N*-bromosuccinimide. The solution was stirred by a magnetic stirrer and irradiated for 10 min with a 275-W Sylvania sunlamp. After 10 min a reflux condenser was placed on the flask and the solution was warmed to boiling. After 6 h, the succinimide was filtered off and washed with three portions of warm carbon tetrachloride. The solvent was removed in vacuo to give an oil which solidified on standing. The gummy solid was triturated with two portions of petroleum ether to give 24 g (82%) of the dibromide **9** as a white powder: mp 80–81 °C (ethanol); IR ($CHCl_3$) 3002, 2842, 1595, 1477, 1273, 1062 cm^{-1}; NMR ($CDCl_3$) 3.90 (s, 3 H), 4.63 (s, 2 H), 4.80 (s, 2 H), 6.92 (dd, 1 H, J = 7.9 Hz, J' = 1.5 Hz), 7.12 (dd, 1 H, J = 7.9 Hz, J' = 1.5 Hz), 7.34 (t, 1 H, J = 7.9 Hz); MS m/e (%) 296 (1.7), 294 (3.6), 292 (1.6), 215 (71.2), 213 (72.5), 104 (100).

Anal. Calcd for $C_9H_{10}Br_2O$: C, 36.77; H, 3.43; Br, 54.37. Found: C, 36.78; H, 3.35; Br, 54.32.

2-(Bromomethyl)-3-(dibromomethyl)anisole (10). To a stirred solution of 5.88 g (0.02 mol) of the dibromide **9** in 20 mL of carbon tetrachloride in a 50-mL round-bottomed flask was added 3.56 g (0.02 mol) of recrystallized *N*-bromosuccinimide. This was irradiated as above and heated to reflux for 5 h. The reaction mixture was worked up in a similar way to give 6.1 g (81%) of **10** as a white powder. Recrystallization of this material from carbon tetrachloride gave the analytical sample: mp 93–94 °C; IR ($CHCl_3$) 3002, 2841, 1600, 1588, 1478, 1227, 1062 cm^{-1}; NMR ($CDCl_3$) 3.92 (s, 3 H), 4.75 (s, 2 H), 6.70 (dd, 1 H, J = 7.5 Hz, J' = 1.5 Hz), 6.92 (s, 1 H), 7.20 (t, 1 H, J = 7.5 Hz), 7.42 (dd, 1 H, J = 7.5 Hz, J' = 1.5 Hz); MS m/e (%) 376 (5.5), 374 (13), 372 (13), 370 (5.5), 295 (51), 293 (100), 291 (53), 214 (38), 212 (38).

Anal. Calcd for $C_9H_9Br_3O$: C, 28.98; H, 2.43; Br, 64.29. Found: C, 28.91; H, 2.53; Br, 64.20.

Hydrolysis of Tribromide 10. In a 50-mL Erlenmeyer flask equipped with a stirring bar, 1.12 g (3.0 mmol) of tribromide **10** was dissolved in 5 mL of freshly distilled tetrahydrofuran. This solution was stirred and a solution of 1.8 g (10.5 mmol, 3.5 equiv) of silver nitrate in 11 mL of water was added dropwise. Addition was complete in 3 min and after 10 min no further precipitation of silver bromide was observed. The precipitated salts were filtered off and washed with tetrahydrofuran and water to give a clear colorless solution. This solution was treated with 770 mg (3.1 mmol) of silver oxide, and 5 mL of a 10% sodium hydroxide solution was added dropwise with stirring. After 1 h, the mixture was filtered and the filter cake washed with water. The filtrate was acidified with concentrated sulfuric acid to pH 2 and extracted four times with 20 mL of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo to give a white solid. Recrystallization from water gave 450 mg (91.5%) of lactone **11**: mp 127.5–129 °C (lit.[10] mp 127 °C); IR ($CHCl_3$) 1790 cm^{-1}; NMR ($CDCl_3$) 3.95 (s, 3 H), 5.27 (s, 2 H), 7.25 (m, 3 H).

2-Methyl-5-methoxy-1,4-anthraquinone (6a). A 50-mL round-bottomed flask equipped with a stirring bar and a reflux condenser, under a nitrogen atmosphere, was charged with a solution of 1.2 g of sodium iodide in 25 mL of dry acetone. After slight cooling 0.93 g (2.5 mmol) of **10** and 0.63 g (3.1 mmol, 1.26 equiv) of **12** were added. This was stirred under gentle reflux for 21 h at which time a second solution of 0.4 g of sodium iodide in 5 mL of acetone was added. The reaction was boiled for 10 h longer and then cooled to room temperature. The sodium bromide produced was filtered off and washed with acetone. The filtrate was cooled in a refrigerator for several hours and **6a** crystallized as a red precipitate. The crystals were collected on a filter and washed with cold ethanol to give 288 mg (46%) of **6a**. Recrystallization from ethanol–water gave an analytical sample, mp 207.5–208 °C. During melting point determinations, a phase transition characterized by a change in color from red to orange was observed at 190 °C: IR (KBr) 1655, 1605, 1587 cm^{-1}; NMR ($CDCl_3$) 2.20 (d, 3 H, J = 1.5 Hz), 4.03 (s, 3 H), 7.23 (m, 4 H), 8.53 (s, 1 H), 9.01 (s, 1 H); MS m/e 252 (M^+, base), 209, 181, 152, 113; UV (EtOH) (log ϵ) 244 (4.78), 287 (3.88), 299 (3.87), 436 (3.71) nm.

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 75.95; H, 4.90.

2-Methyl-8-methoxy-1,4-anthraquinone (6b). A 1.83-g sample of tribromide **10** and 1.25 g of 5-bromotoluquinone were used in the same procedure described above for **6a** to produce 0.51 g (40%) of **6b**: mp 229–230 °C (ethanol–water); IR (KBr) 1655, 1605, 1587 cm^{-1}; NMR ($CDCl_3$) 2.22 (d, 3 H, J = 1.5 Hz), 4.03 (s, 3 H), 7.20 (m, 4 H), 8.48 (s, 1 H), 9.03 (s, 1 H); MS m/e 252 (M^+, base), 209, 181, 152, 141; UV (EtOH) (log ϵ) 246.5 (4.85), 285 (3.98), 298 (3.96), 436 (3.77) nm.

Anal. Calcd for $C_{16}H_{12}O_3$ C, 76.18; H, 4.79. Found: C, 76.24; H, 4.94.

1,4-Diacetoxy-5-methoxy-2-methylanthracene (14a). A 50-mL round-bottomed flask equipped with a stirring bar and under a nitrogen atmosphere was charged with 252 mg (1.0 mmol) of **6a**, 760 mg of zinc dust, 500 mg of anhydrous sodium acetate, and 24 mL of acetic anhydride. This mixture was stirred for 5 h at room temperature. The excess zinc was filtered off and the filter cake washed with methanol. The remaining acetic anhydride was destroyed by adding 11 mL of methanol to the above filtrate and heating slightly to initiate boiling. When the mixture stopped boiling on its own, the solution was heated under reflux for 30 min longer and then cooled. The solution was diluted with 100 mL of water and extracted three times with 20 mL of methylene chloride. The combined extracts were washed four times with 40 mL of water, dried over sodium sulfate, and evaporated in vacuo to give a yellow oil which crystallized on standing. The solid was recrystallized from ethanol to give 322 mg (95%) of yellowish brown hexagonal plates: mp 158–158.5 °C; IR (KBr) 1754 cm^{-1}; NMR ($CDCl_3$) 2.31 (s, 3 H), 2.47 (s, 3 H), 2.48 (s, 3 H), 3.95 (s, 3 H), 6.65 (d, 1 H, J = 7.3 Hz), 7.10 (s, 1 H), 7.32 (dd, 1 H, J = 7.3, 8.5 Hz), 7.52 (d, 1 H, J = 8.5 Hz), 8.20 (s, 1 H), 8.78 (s, 1 H); MS m/e 339 (M^+), 296, 254 (base); UV (log ϵ) 220 (4.20), 259 (5.10), 376 (3.85), 396 (3.75) nm.

Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.83; H, 5.17.

1,4-Diacetoxy-8-methoxy-2-methylanthracene (14b). The procedure described above for **14a** was used to convert **6b** (123 mg) into **14b** (159 mg, 95% yield): mp 174.5–176 °C (ethanol); IR (KBr) 1752 cm^{-1}; MS m/e (%) 338 (26), 296 (22), 255 (28), 254 (100), 253 (28); NMR ($CDCl_3$) 2.32 (s, 3 H), 2.47 (s, 3 H), 2.53 (s, 3 H), 3.99 (s, 3 H), 6.69 (d, 1 H, J = 7.3 Hz), 7.12 (s, 1 H), 7.32 (dd, 1 H, J = 7.3, 9.3 Hz), 7.53 (d, 1 H, J = 9.3 Hz), 8.29 (s, 1 H), 8.70 (s, 1 H); UV (log ϵ) 220 (4.00), 259.5 (5.13), 361 (3.67), 375.5 (3.77), 3.96 (3.66) nm.

Anal. Calcd for $C_{30}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.88; H, 5.21.

1,4-Dihydroxy-5-methoxy-2-methylanthraquinone (16a). A chromic acid solution was prepared from 6.0 g of chromium trioxide and 5.2 mL of concentrated sulfuric acid in enough water to make 100 mL. To a solution of 100 mg (0.26 mmol) of diacetate **14a** in 12 mL of acetone contained in a 50-mL flask was added 3.3 mL (1.98 mmol) of the chromic acid solution. The solution was stirred with a magnetic bar for 18 h at room temperature. The reaction was quenched with isopropyl alcohol and extracted with chloroform (3 × 15 mL). The combined extracts were washed with water (20 mL) and saturated sodium bicarbonate (20 mL), dried over sodium sulfate, and evaporated to give 148 mg of a yellow-orange semisolid. This material was hydrolyzed immediately. A 50-mL round-bottomed flask was charged with the above product, 7 mL of glacial acetic acid, and 7 mL of 6 N hydrochloric acid. The solution was heated at 70 °C for 30 min. The cooled solution was extracted with methylene chloride (2 × 20 mL). The combined extracts were washed with water (3 × 40 mL) and saturated sodium bicarbonate (40 mL) and then dried over sodium sulfate to give 41 mg of a dark red solid. Chromatography on silica gel with chloroform–carbon tetrachloride gave 39.9 mg (56%) of **16a**: mp 193.5–195 °C (lit.[5a] mp 194–195 °C); IR (KBr) 1608, 1588 cm^{-1}; NMR ($CDCl_3$) 2.32 (s, 3 H), 4.05 (s, 3 H), 7.11 (s, 1 H), 7.64 (m, 3 H), 13.26 (s, 1 H), 13.27 (s, 1 H); MS m/e 284 (M^+), 266, 254, 238; UV (log ϵ) 231 (4.55), 249 (4.33),

286.4 (3.96), 469 (sh) (3.99), 480 (4.00), 494.4 (4.01), 512 (inf) (3.85), 529.6 (3.77).

1,4-Dihydroxy-8-methoxy-2-methylanthraquinone (16b). The procedure described above for the preparation of **14a** was used to acetylate reductively 0.252 g of **6b** to **14b**, which crystallized in long needles when the extraction solvent, methylene chloride, was evaporated. The entire product **14b** was oxidized and hydrolyzed by the procedure described for the preparation of **16a**, giving 141 mg of **16b** (50% yield based on **6b**): mp 208–210.5 °C (chloroform–hexane) (lit.[5a] mp 209–211 °C); IR (KBr) 1610 cm^{-1}; MS *m/e* 284 (M^+), 266, 254, 238; NMR ($CDCl_3$) 2.30 (s, 3 H), 4.01 (s, 3 H), 7.03 (s, 1 H), 7.60 (m, 3 H), 12.85 (s, 1 H), 13.60 (s, 1 H); UV (log ε) 231 (4.56), 247.5 (4.31), 285.5 (3.95), 470 (sh) (4.00), 479.5 (4.01), 493 (4.01), 512 (inf) (3.87), 528 (3.77) nm.

Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.58; H, 4.30.

Islandicin (1a). A 50-mL flask was charged with 17.0 mg of methylislandicin (**16a**) and dissolved in 7 mL of glacial acetic acid and 7 mL of 48% hydrobromic acid. This solution was heated under reflux for 5 h under a nitrogen atmosphere. The hot solution was filtered and upon cooling to room temperature islandicin crystallized as dark red lustrous plates (14.1 mg, 87%). Recrystallization from chloroform–ligroin gave pure islandicin, mp 220–221 °C (lit.[1] mp 218 °C).

Digitopurpone (1b). Digitopurpone was prepared as described above for islandicin, starting with 7.0 mg of digitopurpone methyl ether and yielding 3.4 mg (51%) of bright red needles, mp 210.5–212 °C (lit.[2] mp 209–211 °C) from chloroform–ligroin.

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Registry No. 1a, 476-56-2; **1b**, 34425-57-5; **6a**, 71785-94-9; **6b**, 71785-95-0; **8**, 2944-49-2; **9**, 71785-96-1; **10**, 71785-97-2; **11**, 4792-33-0; **12**, 6293-55-6; **13**, 13070-25-2; **14a**, 71785-98-3; **14b**, 71785-99-4; **16a**, 71786-00-0; **16b**, 68047-75-6.

Pyridinium Halides as Reagents: Ring Fission Modes in α-Cyclopropyl Ketones and Oximes

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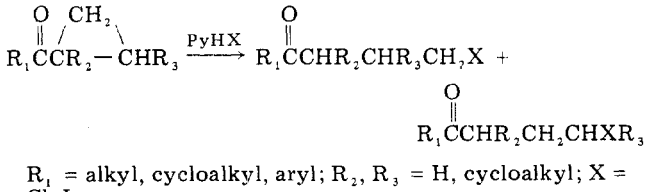
Cyclopropyl ring fission reactions by both nucleophilic and electrophilic reagents are the subject of current interest.[1]

We recently proposed pyridinium chloride in acetonitrile as a mild reagent for cyclopropyl ring fission of α-cyclopropyl ketones.[2,3] The products were γ-chloro ketones.



R_1 = alkyl, cycloalkyl, aryl; R_2, R_3 = H, cycloalkyl; X = Cl, I

Table I. Reaction of α-Cyclopropyl Ketones with Pyridinium Halides[a]

substrate	PyHCl	PyHI
1	2	3
4	5	6
7	8	9
10	11	12
13	14	15
16	17	18
19	20	21
22	23	24
25	26	27

[a] The residue percentage was the starting ketone.

Among the substrates we tested (**1**, **6**, **9**, **19**, and **22**), bicyclo[4.1.0]heptan-2-one (**6**) and 1-acetylbicyclo[4.1.0]-heptane (**19**) gave a selective ring fission reaction, while other substrates (**1** and **9**) gave products coming from the two possible modes of cyclopropyl ring fission (Table I).

Clearly this point is a limiting factor for the synthetic scope of this reaction, although, in most cases, a satisfactory chromatographic separation of the two chloro ketones is possible. In order to gain more information on the factors directing the reaction and to improve the synthetic potential, we enlarged the study to other substrates and conditions. First, we considered the possibility of changing the nucleophilic part of the reagent, and then we tested pyridinium iodide in the hope of gaining a more selective ring opening.

Most of the substrates (**1**, **6**, and **9**) were bicyclic compounds having a five-, six-, or seven-membered ring fused to the cyclopropyl ring. Here the carbonyl group is in a relatively fixed geometry with respect to the three-membered ring. Other substrates (**13** and **19**) contained similar bicyclic systems, but the carbonyl group was held by a free rotating side chain. Cyclopropyl methyl ketone (**22**) and cyclopropyl phenyl ketone (**25**) were also considered as peculiar terms.

The results obtained from the reactions on ketones in the presence of pyridinium chloride or iodide in acetonitrile are reported in Table I.

The following discussion is organized according to cyclopropyl ketone type.

Reaction between α-Cyclopropyl Ketones and Pyridinium Halides. Bicyclo[*n*.1.0]alkan-2-ones. On reaction with pyridinium chloride, bicyclo[3.1.0]hexan-2-one (**1**) gave the two possible products of ring fission, namely, 3-(chloromethyl)cyclopentanone (**2**) and 4-chlorocyclohexanone (**3**) after 28 h of reflux. Bicyclo-[4.1.0]heptan-2-one (**6**) regioselectively afforded a 76% yield of 3-(chloromethyl)cyclohexanone (**7**) in 11 h.[3] Bicyclo[5.1.0]octan-2-one (**9**) gave 3-(chloromethyl)cycloheptanone (**10**) and 4-chlorocyclooctanone (**11**) in 41 and 35% yield, respectively, in 42 h.[4] The product ratio (1.08) is quite close to that obtained from ketone **1** (1.17).

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