Lewis-acid Promoted Rearrangement of σ-Homo-*o*-benzoquinones to α-Tropolone Derivatives: Application to Regiocontrolled Syntheses of MY3-469 and Isopygmaein

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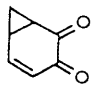
Reaction of various σ-homo-*o*-benzoquinones, *e.g.* **42**, with $BF_3{\cdot}Et_2O$ results in the formation of the tropolonoboron difluoride derivatives, *e.g.* **43**, of the isomeric α-tropolones, *e.g.* isopygmaein **33**.

σ-Homo-*o*-benzoquinone **1**[1] is isomeric with, but presumably less stable than, α-tropolone **2**. Interestingly, it has been proposed (Scheme 1)[2] that formation of the troponoid C-ring of the alkaloid colchicine **5** occurs late in the biosynthetic process and involves rearrangement of the *O*-methylated σ-homo-*o*-benzoquinone **3** to the α-tropolone *O*-methyl ether **4**. Although there have been several reports[3] where derivatives of **1** could be implicated as intermediates in the synthesis of α-tropolones, no direct observation of the conversion of the former compounds into the latter has been made. In part at least, this situation arises because of the lack of useful synthetic routes to σ-homo-*o*-benzoquinones. We now describe two short and convenient routes to this class of compound and provide the first definitive report on their rearrangement to α-tropolone derivatives.

The acetonides **6**[4] and **7**,[5] readily derived from the corresponding commercially available diols, served as convenient starting materials for the synthesis of a variety of σ-homo-*o*-benzoquinones (Scheme 2) including the parent system. Thus, dichlorocarbene addition to **6** provided the adduct **8**[4b] (m.p. = 43–45 °C) (92%) which upon hydrolysis afforded diol **9**† (m.p. = 86–87 °C) (77%). Reductive dechlorination of **9** produced compound **10** (m.p. = 49–51 °C) (80%) which was converted into **1** (m.p. = 53–56 °C; lit.[1] m.p. = 58 °C) (79%) upon oxidation with oxalyl chloride activated dimethyl sulphoxide. The dibromo-analogue of **9**, compound **11**,[6] which has been prepared in an analogous manner from **6**, was reduced with tri-n-butyltin hydride to a 1 : 1 mixture of the epimeric monobromides **12** (m.p. = 123–124 °C) (30%) and **13** (m.p. = 87–88 °C) (30%) which could be separated chromatographically. Independent oxidation of the monobromo-diols then gave the corresponding diketones **14** (m.p. = 129–131 °C) (66%) and **15** (m.p. = 76–78 °C) (66%).



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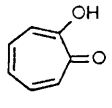

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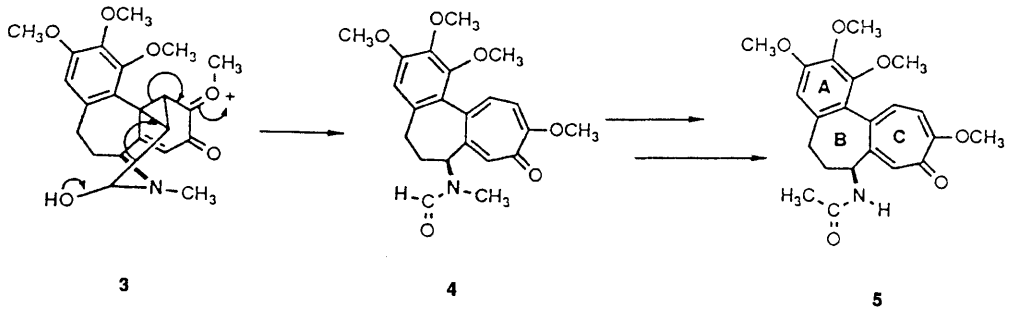
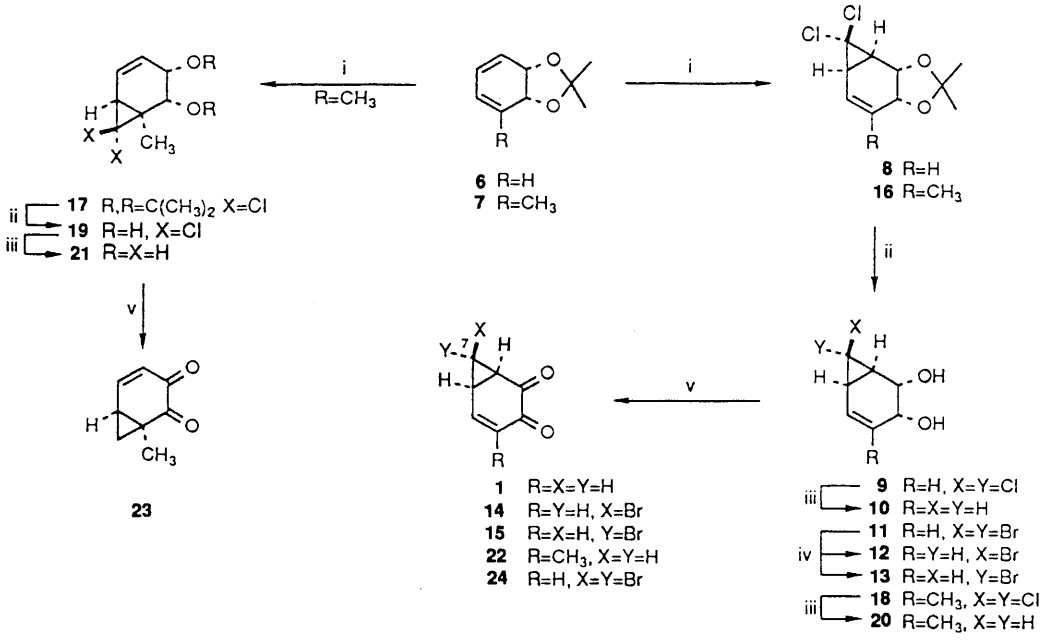
† Unless indicated by the citation of a specific rotation, all new compounds that contain chiral centres are racemic but only one enantiomer is depicted for clarity. All new substances had spectroscopic data [IR, NMR, mass spectrum and UV (where appropriate)] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds. Unless otherwise specified yields refer to isolated compounds.



3 4 5

Scheme 1



Scheme 2 *Reagents and conditions*: i, $CHCl_3$, 50% aq. NaOH, benzyltriethylammonium chloride, 18 °C, 24 h; ii, HCl, tetrahydrofuran–water, 18 °C, 48 h; iii, Na, ethanol, reflux, 3 h; iv, Bu_3SnH (1.5 equiv.), C_6H_6, 18 °C, 6 h; v, for non-halogenated substrates-$(CH_3)_2SO$ (8 equiv.), oxalyl chloride (2.5 eqiv.), −60 °C, 15 min, then $(CH_3CH_2)_3N$ (10 equiv.); for halogenated substrates-$(CH_3)_2SO$ (3.2 equiv.), $(CF_3CO)_2O$ (2.8 equiv.), −60 °C, 2 h, then $(CH_3CH_2)_3N$ (6.6 equiv.)

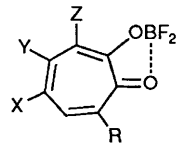
Dichlorocarbene addition to the scalemic diene **7** produced a 1:1.2 mixture of the regioisomeric adducts **16** {m.p. = 24–26 °C, $[\alpha]_D$‡ = −142.3° (*c* 3.1)} and **17** {$[\alpha]_D$ = +193.3° (*c* 7.5)} (82% combined yield) which could only be separated by HPLC. However, hydrolysis of this mixture produced the corresponding diols **18** {m.p. = 94–95 °C; $[\alpha]_D$ = −229.3° (*c* 4.0)} and **19** {m.p. = 116–117 °C; $[\alpha]_D$ = +238.2° (*c* 3.3)} (75% combined yield) which proved separable by MPLC. Reductive dechlorination of compounds **18** and **19** provided diols **20** {m.p. = 82–84 °C; $[\alpha]_D$ = +118.5° (*c* 2.0)} (86%) and **21** {m.p. = 45–47 °C; $[\alpha]_D$ = −89.9° (*c* 0.8)} (88%), respectively which were then oxidised to the corresponding σ-homo-*o*-benzoquinones, **22** {m.p. = 76–77 °C; $[\alpha]_D$ = +340.5° (*c* 2.1)} (71%) and **23** {m.p. = 34–35 °C; $[\alpha]_D$ = −618.5° (*c* 4.1)} (78%), respectively.

The σ-homo-*o*-benzoquinones **1, 14, 15, 22, 23** and **24**[6] were treated with a range of electrophiles including various trimethyloxonium salts and several Brønsted–Lowry or Lewis acids but only $BF_3{\cdot}Et_2O$ was effective in converting these compounds into troponoids. Thus, reaction of a dichloromethane solution of **1** with 10 mol equiv. of $BF_3{\cdot}Et_2O$ for 5 h at ambient temperatures provided tropolonoboron difluoride **25** (m.p. = 152–154 °C; lit.[7] m.p. = 150 °C) (37%) together with trace amounts (as determined by 400 MHz ^1H NMR analysis of the crude reaction mixture) of α-tropolone **2** itself. No other characterisable materials could be isolated from the reaction mixture. The methylated derivatives of **1**, compounds **22** and **23**, reacted analogously (3 mol equiv. $BF_3{\cdot}Et_2O$, 2.5–3 h) and gave **26** (m.p. = 170–172 °C) (50 and 44%, respectively) together with trace amounts of **27**. Treatment of the dibromo-compound **24** with $BF_3{\cdot}Et_2O$ (4 mol equiv., 10 h, refluxing dichloromethane) provided **28** (m.p. = 138–141 °C) (16%) and 4-bromotropolone **29** (21%).[8] The epimeric monobromo compounds **14** and **15** both reacted in the same manner (2.5–4 mol equiv. $BF_3{\cdot}Et_2O$, 17 h, reflux) and gave a mixture of **25** (9 and 19%, respectively) and **2** (40 and 23%, respectively) together with trace amounts of **30** (m.p. = 180–182 °C) and **31** (m.p. > 270 °C) (the identities of products **30** and **31** were established by their independent preparation from 3-§ or 5-[8] bromotropolone and $BF_3{\cdot}Et_2O$).

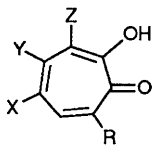
Regardless of the precise mode of formation of troponoids **2, 25, 30** and **31** from compounds **14** and **15**, these results suggest that the configuration of the leaving group (H^+ or

‡ Optical rotations were determined in chloroform solution at 18 °C.

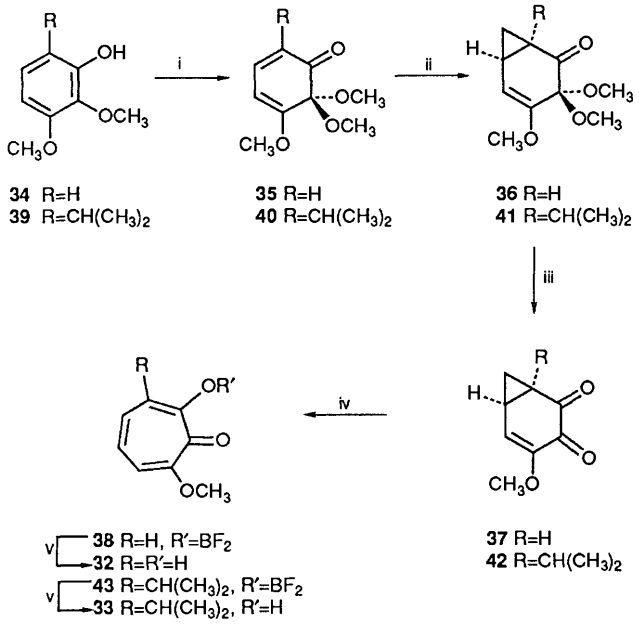
§ 3-Bromotropolone was prepared by demethylation (using 48% HBr in glacial acetic acid) of 3-bromo-2-methoxytropone (H. Takeshita, A. Mori and T. Kusaba, *Synthesis*, 1986, 578).



25 R=X=Y=Z=H
26 R=CH_3, X=Y=Z=H
28 R=X=Z=H, Y=Br
30 R=X=Y=H, Z=Br
31 R=Y=Z=H, X=Br



2 R=X=Y=Z=H
27 R=CH_3, X=Y=Z=H
29 R=X=Z=H, Y=Br



34 R=H
39 R=$CH(CH_3)_2$

35 R=H
40 R=$CH(CH_3)_2$

36 R=H
41 R=$CH(CH_3)_2$

38 R=H, R'=BF_2
32 R=R'=H

43 R=$CH(CH_3)_2$, R'=BF_2
33 R=$CH(CH_3)_2$, R'=H

37 R=H
42 R=$CH(CH_3)_2$

Scheme 3 *Reagents and conditions*: i, $Tl^{III}(NO_3)_3$ (1.1 equiv.), CH_3OH, −40 °C, 15 min; ii, $H_2CS(O)(CH_3)_2$ (1.1 equiv.), $(CH_3)_2SO$, 18 °C, 3 h; iii, HCl, acetone–water, 18 °C, 20 h; iv, $BF_3{\cdot}Et_2O$ (3 equiv.), CH_2Cl_2, 18 °C, 5 h; v, 2 mol dm^{-3} H_2SO_4, ethanol, reflux, 8 h

Br^+) at C-7 in the σ-homo-*o*-benzoquinone is not critical to the success of the rearrangement process.

We have exploited this new method for the synthesis of α-tropolones in the preparation of the natural products MY3-469 **32**[9] and isopygmaein **33**[10] (Scheme 3). These reaction sequences, which provide the first total synthesis of **33**, also demonstrate an alternative method for the preparation of σ-homo-*o*-benzoquinones. Thus, oxidation of commercially available 2,3-dimethoxyphenol **34** with thallium(III) nitrate in methanol provided the acetal **35**,[11] which on subjection to nucleophilic cyclopropanation with dimethyloxosulphonium methylide[12] gave the bicyclic ketone **36** (m.p. = 60–61 °C) (35%). Hydrolysis of compound **36** under standard conditions afforded the σ-homo-*o*-benzoquinone **37** (m.p. = 137–138 °C) (84%) which upon treatment with 6 mol equiv. of $BF_3{\cdot}Et_2O$ at ambient temperatures for 5 h provided a mixture of tropolonoboron difluoride **38** (m.p. = 216–219 °C) (55%) and **32** (2%). Subjection of **38** to reaction with aqueous sulphuric acid then provided **32** [m.p. = 108–110 °C; lit.[9] m.p. = 113–114 °C (decomp.)] (83%) which was identical in all respects with an authentic sample.[13] An exactly analogous reaction sequence starting with the isopropylated phenol **39** (m.p. = 45–46 °C) provided isopygmaein **33**. Thus, thallium(III)-mediated oxidation of **39** in the presence of methanol afforded **40** (m.p. = 44–46 °C) (100%) which upon subjection to nucleophilic cyclopropanation provided **41** (m.p. = 36–38 °C) (57%). Hydrolysis of acetal **41** gave the σ-homo-*o*-benzoquinone **42** (m.p. = 124–125 °C) (80%) which when treated with $BF_3{\cdot}Et_2O$ afforded **43** (66%). Finally, treatment of **43** with aqueous sulphuric acid afforded isopygmaein **33**¶ (m.p. = 109–112 °C; lit.[10] m.p. = 111–112 °C) (90%).

In concluding, it should be noted that the efficiency of the title rearrangement appears to increase with increasing substitution in the σ-homo-*o*-benzoquinone framework. This observation is consistent with the notion that, under the reaction conditions described herein, considerable carbocationic character develops during the conversion of **1** and its derivatives into α-tropolones.

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¶ *Selected spectral data* for **33**: ^1H NMR (400 MHz) δ 7.20 (dd, *J* 10.5 and 1.2 Hz, 1H), 7.08 (dd, *J* 10.5 and 1.2 Hz, 1H), 7.03 (t, *J* 10.5 Hz, 1H), 4.00 (s, 3H), 3.74 (septet, *J* 6.8 Hz, 1H), 1.27 (d, *J* 6.8 Hz, 6H); ^{13}C NMR (100 MHz) δ 169.7, 160.2, 159.1, 140.3, 129.1, 125.1, 117.1, 56.5, 29.8, 22.2; UV (isooctane) λ_{max} 375 (log ε 3.8), 362 (log ε 3.8), 329 (log ε 3.8), 317 infl. (log ε 3.7), 253 (log ε 4.2) nm; IR (KBr), ν_{max} 3410, 3200, 1581, 1547, 1490, 1469, 1454 cm^{-1}; MS, *mz* (70 eV) 194(100%) (M), 179(98) (M − CH_3), 151(33) (M − CH_3−CO).