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BASE-CATALYSED REARRANGEMENT OF THEBAINEHYDROQUINONES

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Abstract—On the basis of spectra and pK_a values structures are assigned to the monomethyl ethers of thebainehydroquinone. Thebainehydroquinone (**1a**) and its 21-methyl ether (**1b**) rearrange under basic conditions to the corresponding flavothebaones (**2a** and **2c**). The 18-methyl ether (**1c**) does not rearrange. A mechanism involving a cyclopropane intermediate is proposed for the rearrangements.

THE structure **2a** for flavothebaone (obtained by acid treatment of thebainehydroquinone **1a**) was established by Bentley,[1] Meinwald,[2] and their co-workers. Bentley reported two monomethyl ethers (A, m.p. 221–222°, and B, m.p. 258°) of **1a**. The former was obtained by heating **1a** with methyl sulphate at 150°; the latter by adding methyl sulphate to a boiling solution of **1a** in alkaline 50% aqueous 2-ethoxyethanol. Examination of the IR, UV and NMR spectra of these ethers indicates that they are, as Bentley thought, unrearranged products with structures **1b** and **1c**. There remains the problem of assigning these structures to the individual ethers.

Meinwald and Wiley[3] used IR and UV spectral measurements to solve the related problem of the monoacetates (**1d** and **1e**). They assumed that hydrogen-bonding between the 21-OH and the nitrogen was stronger than that between the 18-OH and the C_6-OMe groups. On this basis the monoacetate with m.p. 222–222·5° was assigned structure **1d** and that with m.p. 256–257° structure **1e**. They also assigned structure **1b** to a monomethyl ether with m.p. 238–240°. We examined the NMR spectra of **1a**, its monoacetates, monomethyl ethers and diacetate (**1f**). The spectrum of **1a** has peaks due to the phenolic hydrogens at $\delta = 9{\cdot}02$ and 12·21 ppm. The signal at 9·02 does not appear in the spectrum of the acetate, m.p. 255–257°; and that at 12·21 is not present in the acetate 221–222°. These results conform to the earlier assignments.[3] By analogy, we can assign from the NMR spectra of the monomethyl ethers, structure **1b** to A and **1c** to B. The stronger hydrogen-bonding at 21 makes this OH more reactive under nonbasic conditions; under basic conditions, however, the 18-OH ionizes first; and thus reaction occurs at that centre.

As indicated above the deductions of structures **1b**–**1e** from spectral measurements depends on a reasonable assumption concerning relative hydrogen bonding at the C_{18} and C_{21}-OH groups. To confirm these assignments independently the pK_a's of **1a**, **1b** and **1c** were measured in aqueous dioxan. Although it was difficult to obtain good titration curves we feel our values are at least reliable to one decimal place. We expected that methylation at 21 would change the pK_a of **1a** more than methylation at 18. In accord with this we found **1b** (in which the nitrogen is not involved

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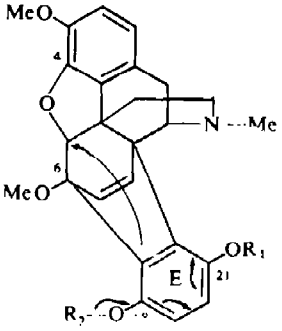
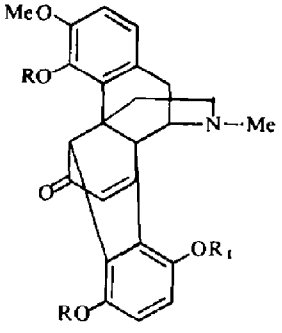
in hydrogen-bonding) is a stronger base (pK_a = 6·5) than **1a** (4·3) and **1c** (4·6). The pK_a value of **1b** is close to that of thebaine (6·7). Thus the studies of pK_a clearly confirm the structures of the methyl ethers.

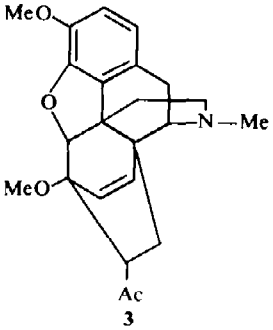
In one attempt to prepare **1c** the methyl sulphate was added more slowly than in Bentley's preparation, and the product had m.p. 252°. Examination of its spectra suggested that a rearrangement had taken place. Comparison with an authentic sample showed that the new product was **2b**, the trimethyl ether of flavothebaone. Following this observation we found that thebainehydroquinone (**1a**) and the 21 methyl ether (**1b**) with base gave flavothebaone (**2a**) and the corresponding methyl ether (**2c**) respectively. However, the 18 methyl ether (**1c**) did not rearrange under similar conditions. This fact and the failure of the 21 OH of **1a** to methylate under basic conditions indicates that **2a** or its 4-methyl ether was an intermediate in the pathway from **1a** to **2b**. The rearrangement was not produced by heat alone; nor did it take place when **1a** was methylated in base in refluxing aqueous acetone. The latter reaction gives **1c** and is probably the best way of making this compound.



1a: $R_1 = R_2 = H$
1b: R_1 = Me; R_2 = H
1c: R_1 = H; R_2 = Me
1d: R_1 = Ac; R_2 = H
1e: R_1 = H; R_2 = Ac
1f: $R_1 = R_2$ = Ac



2a: $R = R_1 = H$
2b: $R = R_1$ = Me
2c: R = H; R_1 = Me



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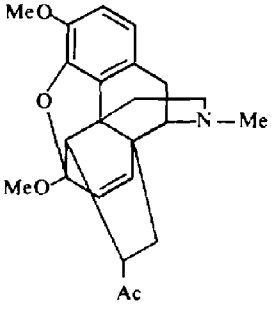

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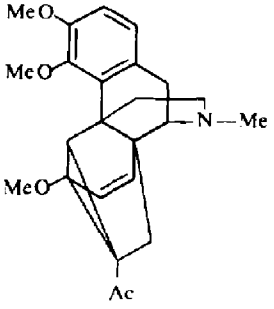

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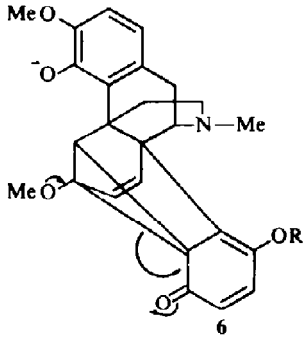
DISCUSSION

Bentley *et al.*[4] reported rearrangements related to that of **1a** to **2a**. Their starting compounds did not have an aromatic ring E. For example, they found that treatment of **3** with base gave the rearranged ketal **4**, which with acid gave a phenolic unsaturated ketone corresponding to **2a**. If **3** was treated with base and then methyl iodide the cyclopropyl compound **5** was isolated. Apparently the free oxygen anion at C_4 which attacked C_6 was necessary to assist the ketone to open the 3-membered ring.



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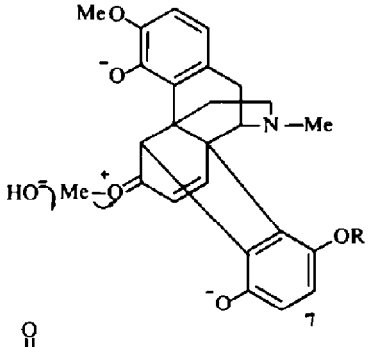

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We propose that our rearrangement is initiated by the process indicated on **1** to give **6**. The cyclopropyl ring then opens to give **7** which is attacked by OH ion to give the product **2**. The stages **6** to **7** to **2** may be concerted. This mechanism explains why **1c** does not rearrange. Further the precipitation of **2b** directly from the reaction mixture shows that our rearrangements (in contrast to Bentley's) go directly to the flavothebaone in base and the opening of the 3-membered ring does not involve the C_4 anion. Presumably the driving force for the ring opening in **6** is the accompanying dienone phenol transformation. Baird and Winstein[5] reported that *p*-cyclopropyl dienones (e.g. **8**) are very labile. Similarly Meinwald and Wiley[6] proposed that a nortricyclodienone was an intermediate (not isolated) in a base catalysed rearrangement of a benzonorbornadiene epoxide.

Kanematsu and Sasaki[7] recently found that photolysis of the adduct of thebaine and the dimethyl ester of acetylene dicarboxylic acid gave a product of type **4** together with a small yield of the corresponding phenolic unsaturated ketone. By contrast, we[8] observed that **1a** on irradiation with ultraviolet light gave an unrearranged dimer.

EXPERIMENTAL*

Thebainehydroquinone. Thebainehydroquinone (**1a**) m.p. 273° had NMR spectrum: δ: 12·21 (1H, s,† disappears on addition of D_2O), 9·02 (1H, s, disappears on addition of D_2O), 6·60–6·80 (4H, complex), 5·60–6·55 (2H, AB qu, J = 8 c/s with minor splitting, J = 1·5 c/s, on pair at lower field), 4·65 (1H, d, J = 1·5 c/s), 3·60–4·15 (7H, complex, with strong s's at 3·92 and 3·83), 3·40 (1H, d, J = 18 c/s), 2·35–2·85 (6H, complex, with a strong s at 2·55), and 1·50–1·85 (2H, complex) ppm.

* Unless otherwise specified UV spectra were taken in EtOH solns, IR spectra in CH_2Cl_2 solns and NMR spectra in $CDCl_3$ solns. M.ps are uncorrected.

† s = singlet; qu = quartet; d = doublet.

Thebainehydroquinone-18-acetate. Compound **1e** m.p. 255–257° (lit.[3] 256–257°) had NMR spectrum: δ: 12·97 (1H, s), 6·60–6·80 (4H, complex), 5·55–6·50 (2H, AB qu, J = 12 c/s with minor splitting, J = 2 c/s on pair at lower field), 4·62 (1H, d, J = 2 c/s), 3·95–4·20 (1H, complex), 3·82 (3H, s), 3·68 (3H, s), 3·25–3·60 (1H, complex), 2·35–2·95 (6H, complex, with a strong s at 2·59), 2·27 (3H, s), and 1·50–1·90 (2H, complex) ppm.

Thebainehydroquinone-21-acetate. Compound **1d** m.p. 221–222° (lit.[3] 222–222·5°) had NMR spectrum: δ: 9·31 (1H, s), 6·55–6·70 (4H, complex), 5·70–6·50 (2H, AB qu, J = 9 c/s with minor splitting, J = 2 c/s on lower field pair), 4·73 (1H, d, J = 2 c/s), 3·80–4·20 (7H, complex with strong s's at 3·92 and 3·81), 3·38 (1H, d, J = 18 c/s), 2·20–2·80 (9H, complex with strong s's at 2·40 and 2·28) and 1·50–1·75 (2H, complex) ppm.

Thebainehydroquinone-18,21-diacetate. Compound **1f** m.p. 186–187° (lit.[3] 187–187·7°) had NMR spectrum: δ: 6·50–7·00 (4H, complex), 5·55–6·45 (2H, AB qu, J = 8 c/s with minor splitting, J = 2 c/s on pair at lower field), 4·75 (1H, d, J = 2 c/s), 3·90–4·25 (1H, complex), 3·82 (3H, s), 3·60 (3H, s), 3·40 (1H, d, J = 18 c/s), 2·20–2·75 (12H, complex with strong s's at 2·45, 2·35, and 2·32), and 1·40–1·80 (2H, complex) ppm.

Thebainehydroquinone-21-methyl ether. Compound **1b**, m.p. 232–233° (lit. 222°[1b] and 238–240°[3]), had NMR spectrum: δ: 9·20 (1H, s), 6·50–6·90 (4H, complex), 5·70–6·50 (2H, AB qu, J = 9 c/s, with minor splitting, J = 1·5 c/s on pair at lower field), 4·72 (1H, d, J = 1·5 c/s), 4·22 (1H, d, J = 6 c/s), 3·90 (3H, s), 3·82 (3H, s), 3·72 (3H, s), 3·10–3·67 (1H, complex), 2·20–2·70 (6H, complex with strong s at 2·47), and 1·50–1·70 (2H, complex) ppm; λ_{max} = 308 mμ (ε 5800).

Thebainehydroquinone-18-methyl ether. Compound **1c**, m.p. 258° (lit.[1b] 258°) had NMR spectrum: δ: 12·80 (1H, s), 6·60–6·90 (4H, complex), 5·50–6·50 (2H, AB, qu, J = 9 c/s with minor splitting, J = 1·5 c/s on pair at lower field), 4·60 (1H, d, J = 2 c/s), 3·20–4·20 (11H, complex with strong s's at 3·87, 3·81 and 3·73), 2·20–3·00 (6H, complex with a strong s at 2·58), and 1·50–2·00 (2H, complex) ppm, λ_{max} = 298 mμ (ε 4200); ν_{max}: 2905, 2790, 1625, 1590, 1500, 1480, 1435, 1350, 1320, 1300, 1245, 1215, 1190, 1170, 1135, 1105, 1075, 1055, 1020, 1005, 975, 965, 940, 915, 875, 865, 825, 800, and 785 cm^{-1}.

Flavothebaone trimethyl ether from thebainehydroquinone. Me_2SO_4 (25 ml) was added over a period of 1½ hr to a refluxing mixture of water (75 ml), 2-ethoxyethanol (75 ml), KOH (35 g) and thebainehydroquinone (5·0 g). The cooled mixture was kept overnight, and the ppt was washed with water, and crystallized from MeOH to give flavothebaone trimethyl ether in pale yellow plates, m.p. 251–252° (1·2 g); ν_{max}: 3000, 2940, 2840, 2775, 1675, 1600, 1495, 1480, 1375, 1345, 1325, 1250, 1215, 1175, 1150, 1105, 1095, 1075, 1055, 995, 980, 970, 925, 905, 850, 835, and 795 cm^{-1}; λ_{max} = 275 mμ (ε 2450), and 335 mμ (ε 3200)); NMR peaks at δ: 6·70–6·90 (4H, complex), 5·20–7·25 (2H, AB qu, J = 9 c/s with minor splitting, J = 1·5 c/s on pair at higher field 4·65–5·20 (15H, complex with a singlet at 4·80 and strong s's at 4·02 and 3·87), and 1·30–3·30 (8H, complex with a strong singlet at 2·43) ppm.

The identity of this compound was established by m.p., mixed m.p., IR, UV and NMR spectral comparison with an authentic specimen of **2b** (m.p. 252°, lit.[9] 252°) prepared by methylation of **2a** under the conditions described above for thebainehydroquinone.

Base-catalysed rearrangement of thebainehydroquinone. A mixture of thebainehydroquinone (1·0 g), KOH (7·0 g) water (15 ml) and 2-ethoxyethanol (15 ml) was refluxed for 1 hr. The pH of the soln was lowered to 6 with conc HCl, and the volume was decreased under reduced press. On saturation of the resulting soln with NaCl, flavothebaone HCl separated out. Addition of conc NH_4OH to an aqueous soln of the hydrochloride precipitated the free base, m.p. 195–205° (dec), identified by m.p., mixed m.p. and IR, UV, and NMR spectral comparison with an authentic specimen.

Base-catalysed rearrangement of thebainehydroquinone-21-methyl ether. Thebainehydroquinone-21-methyl ether (0·7 g) was heated to reflux in a soln of KOH (14 g), water (30 ml), and 2-ethoxyethanol (30 ml). The soln turned dark red-brown and was cooled. The pH of the mixture was lowered to 8 with conc HCl and flavothebaone-21-methyl ether (m.p. 257–259°) (lit.[1b] 272°) (0·3 g) separated. The product was identified as the 21-methyl ether of flavothebaone by mixed m.p. and IR spectral comparison with an authentic sample. The latter, prepared by the acid catalysed rearrangement of **1b**, had m.p. 260–265° (lit.[1b] 272°): ν_{max}^{KBr}: 3570, 3300, 1665, 1495, 1430, 1390, 1320, 1285, 1250, 1220, 1190, 1180, 1145, 1125, 1070, 1045, 1025, 1010, 965, 955, 915, 888, 865, 810, 790, 755, 730, and 695 cm^{-1}; λ_{max} 279 mμ (ε 2600) and 343 mμ (ε 2800), and NMR peaks (in C_5D_5N) at δ: 8·88 (1H, s), 7·70 (1H, s), 6·70–7·20 (4H, complex), 5·40–7·50 (2H, AB qu, J = 10 c/s, with minor splitting, J = 1·5 c/s, on pair at higher field), 5·87 (1H, d, J = 1·5 c/s), 2·80–4·40 (9H, complex with strong s's at 3·88 and 3·67), and 1·20–2·70 (7H, complex with strong s at 2·47) ppm

The 18-methyl ether on similar treatment with base was recovered unchanged.

Methylation of thebainehydroquinone in aqueous acetone. Me_2SO_4 (5·0 ml) was added over 25 min to a refluxing soln of thebainehydroquinone (0·92 g) in KOH aq (14 g in 30 ml of H_2O) and acetone (30 ml). The crude product precipitated from the cooled soln and on crystallization from MeOH separated as plates m.p. 254–256° (0·24 g) identified as **1c** by m.p., mixed m.p., IR and NMR spectral comparisons with authentic material. Further crystallization and drying under vacuum gave m.p. 256–257°.

Determination of pK_a *values.* A weighed amount of base (about 100 mg) in aqueous 75% dioxan (20 ml) was titrated with HCl (0·1886N, standardized against standard Na_2CO_3). The pH values were determined potentiometrically on a pH meter which was buffered at 3·55 with a standard soln of potassium hydrogen tartrate. The following pK_a values were obtained as the midpoint of the respective buffer regions: thebainehydroquinone, 4·3; thebainehydroquinone-18-methyl ether, 4·6; thebainehydroquinone-21-methyl ether, 6·5; thebaine, 6·7; thebainequinone, 5·0; flavothebaone, 5·0; flavothebaone trimethyl ether, 5·9.

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