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The Importance of Preliminary Orientation in [4+2]-Cycloadditions of Dienes and Dienophiles with Complex Structures

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The [4+2]-cycloaddition reaction of quinopimaric acid with thebaine or β-dihydrothebaine has been performed in order to illustrate the importance of preliminary orientation of the diene and dienophile in the reaction complex stabilized due to different factors: salification was shown to be the principal factor in the orientation of the diene and dienophile in aqueous media, and steric factors were found to dominate in hydrocarbon solvents.

Diels–Alder reactions with morphinan-6,8-dienes were studied to show that with respect to the direction of dienophile attack, 6α,14α-ethenoisomorphinanes (α-face approach) or 6β,14β-ethenomorphinanes (β-face approach) were the reaction products.[1,2] To proceed with our research into methods of controlling the cycloaddition of polyfunctional dienes and dienophiles,[3,4] we demonstrated the structural dependence of the adducts on the solution polarity during reactions of quinopimaric acid **1**, derived from levopimaric acid and benzoquinone,[5] with thebaine **2** and its dihydro derivatives **3a,c**. In a polar solvent (aqueous dioxane, 100 °C, 10 h) favourable for ionization, the orientation of the diene and dienophile in a transition state is determined by salification due to the carboxy group in **1** and the amine function of **2**. As a result, **4** is preferentially formed (**4**:**5** = 8:1; 88%). When the same reaction is carried out in hydrocarbon solvents (benzene or toluene) in the presence of 4 Å molecular sieves, the isomer **5** prevails (**5**:**4** = 10–12:1; 56–78%). It is obvious that in hydrocarbon solvents the carboxy group in **1** is bound to the carbonyl quinone fragment by an intramolecular hydrogen bond. A molecular mechanics method was used to determine the distance COO···O=C = 2.05 Å, appropriate for a sufficiently strong hydrogen bond. The structure of the pre-reaction complex leading to **5** is fixed by the fact that the dienophile approaches it from the lowest shielded side of the diene and also by the growing interaction between the carboxy group and the oxygen of the methoxy group. It is important to state that both adducts **4** and **5** possess hydroquinone fragments, due to the spontaneous isomerization of enediones resulting from the Diels–Alder reaction.

Thebaine reacts with hydroquinone **6** in the presence of Ag_2O in an alcohol–benzene solution (1:5, v/v) to give a mixture of **4** and **5** in a 4:5 ratio (72%). Conducting the same reaction in alcohol gives **4** and **5** in a 6:1 ratio (60%).

The structures of the compounds **4** and **5** were assigned after pure **4** and **5** had been thermolized into 7,9- or 6,8-disubstituted naphthoquinone derivatives of tetrahydrothebaine.[6]

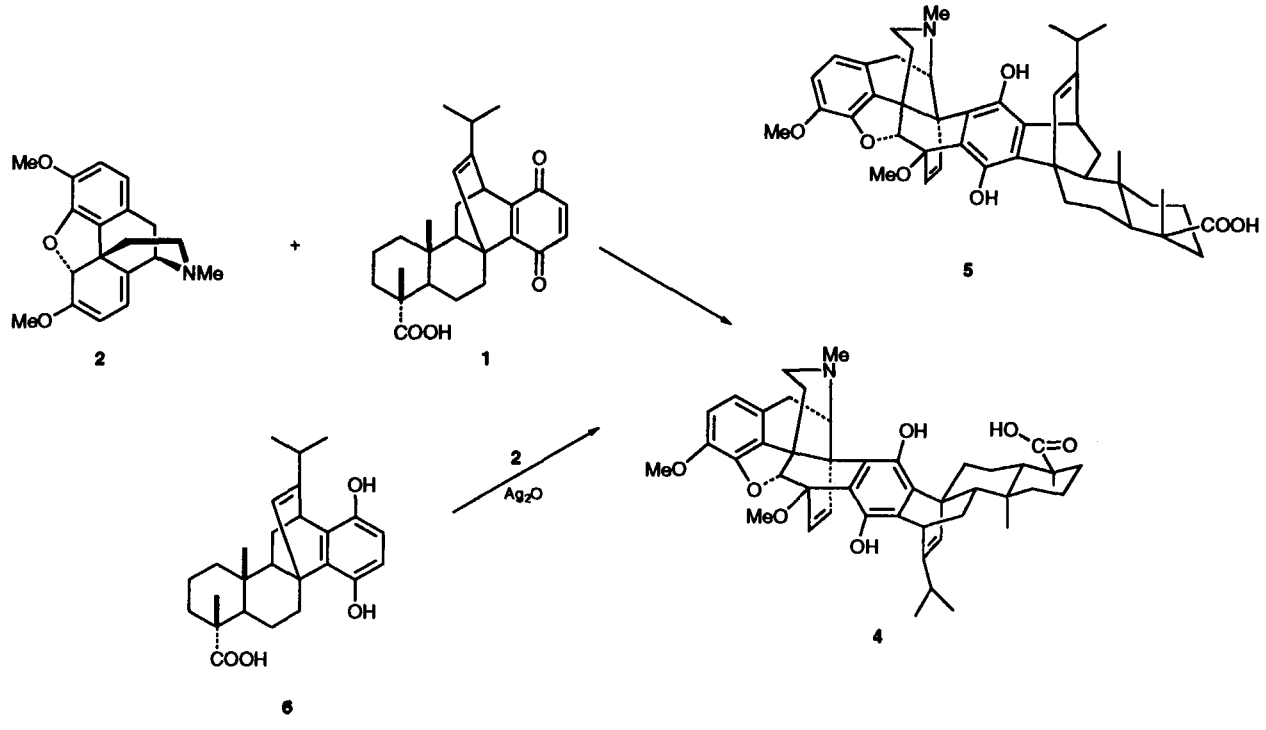
The ^{1}H NMR spectra recorded for the adducts **4** and **5** were reported in our earlier publication.[6] The principal differences between the ^{1}H NMR spectra of **4** and **5** lie in the downfield shifts of the C5-proton and the protons in NCH_3, and also in the higher diastereotopicity of the isopropyl group protons in the spectrum of **5**. For **4**, a concentration dependence of the chemical shift of the hydroxy group was found (δ 9.6–9.4 ppm). The chemical shifts of the carbons C5, 6, 9, 17, 18, 13, 14 differ within the range 0.2–0.8 ppm, and those of C 1a, 4a, 7a differ within 1.0–2.0 ppm.

During the reaction of dihydrothebaine derivatives **3a,b** with **1**, the oxygen substituents in the aromatic fragment produce a powerful orientating effect. Cycloaddition in boiling benzene yields individual adducts **7a,b**.† The rate of formation of **7a** was sharply increased (5–5.5 times) by adsorbing the diene **3a** and dienophile **1** in dichloromethane on Florisil. The direction of cycloaddition could not be changed even using aqueous dioxane. Thus, it is evident that no isomerization into a hydroquinone such as **4** or **5** occurs in this case as opposed to reactions with thebaine. This is ascertained by the fact that compound **7a** can be transformed into a cage diketone **8** *via* photocyclization conducted under irradiation in a $CHCl_3$ solution according to Cookson.[7]

†7β,8β-[2′,3′-(1,4-Dioxo-7,10a-dimethyl-13-isopropyl-7-carboxy-1, 1a,2,3,4,4a-hexadehydro-4b,12-*exo*-etheno)]-3,6-dimethoxy-*N*-methyl-4-hydroxy-6β,14β-*exo*-ethenomorphinane **7a** (70%), m.p. 197–198 °C (from ethyl acetate); $[\alpha]_D^{25}$ + 75.7° (*c* 1.1, $CHCl_3$); IR (ν/cm^{-1}) 725, 750, 780, 1010, 1040, 1090, 1135, 1190, 1230, 1305, 1500, 1610, 1675, 1715. ^{1}H NMR (δ, ppm): 0.7s (Me), 1.02d, 1.04d (Me, *J* 6.4 Hz), 1.25s (Me), 1.30m (7H), 1.50m (4H), 1.80m (7H), 2.38s (Me), 2.82m (6H), 3.60m (3H, $H_{2,3,12}$), 3.45s (MeO), 3.88s (MeO), 5.58s (H_{14}), 5.80d (1H, H_{18}, *J* 8.5 Hz), 6.10d (1H, H_{17}, *J* 8.5 Hz), 6.68d (1H, H_2, *J* 8.2 Hz), 6.72d (1H, H_1); ^{13}C NMR (δ, ppm): 118.44d (C_1), 109.02d (C_2), 151.80s (C_3), 143.56s (C_4), 46.77t (C_5), 80.74s (C_6), 50.85d (C_7), 51.03d (C_8), 57.62d (C_9), 22.42t (C_{10}), 129.22s (C_{11}), 126.73s (C_{12}), 42.17s (C_{13}), 47.35s (C_{14}), 38.57t (C_{15}), 47.69t (C_{16}), 134.61d (C_{17}), 131.32d (C_{18}), 193.38s ($C_{1'}$), 159.89s ($C_{1'a}$), 196.86s ($C_{4'}$), 159.07s ($C_{4'a}$), 36.75t ($C_{5'}$), 21.56t ($C_{6'}$), 47.35s ($C_{7'}$), 45.69s ($C_{4'a}$), 51.00d ($C_{6'a}$), 39.65t ($C_{8'}$), 17.29t ($C_{9'}$); 39.43t ($C_{10'}$), 38.32s ($C_{10'a}$), 54.82d ($C_{10'b}$), 28.15t ($C_{11'}$), 38.16d ($C_{12'}$), 145.06s ($C_{13'}$), 127.10d ($C_{14'}$), 32.15d ($C_{15'}$), 43.12q (Me), 55.59q (Me), 56.18q (Me), 20.92q, 20.49q (Me), 16.79q (Me), 16.47q (Me), 184.15s (CO).

7β,8β-[2′,3′-(1,4-Dioxo-7,10a-dimethyl-13-isopropyl-7-carboxy-1, 1a,2,3,4,4a-hexadehydro-4b,12-*exo*-etheno)]-3,6-dimethoxy-*N*-methyl-4-phenoxy-6β, 14β-*exo*-ethenomorphinane **7b** (73%), m.p. 188–190 °C (from ether), $[\alpha]_D^{25}$ + 38.65° (*c* 2.1, $CHCl_3$); IR (ν/cm^{-1}): 720, 780, 1000, 1090, 1130, 1190, 1230, 1300, 1610, 1680, 1710; ^{1}H NMR (δ, ppm): 0.77s (Me), 1.02d, 1.05d (Me, 6H), 1.25s (Me), 1.35m (11H), 1.80m (7H), 2.39s (Me), 2.90m (6H), 3.65m (3H), 3.48s (MeO), 3.88s (MeO), 5.56s ($H_{14'}$), 5.82d (H_{18}), 6.12d (H_{17}, *J* 8.6 Hz), 6.48m (2H, Ph), 6.68d (1H, H_2), 6.72d (1H, H_1), 6.80m (3H, Ph).

Compound **8** (48%), m.p. 218–220 °C (from ether); $[\alpha]_D^{25}$ + 38.2° (*c* 0.9, $CHCl_3$); IR (ν/cm^{-1}): 1710, 1730, 1750 (C=O); ^{1}H NMR (δ, ppm): 0.6s (Me), 1.02d, 1.12d (6H, Me, *J* 6.7Hz), 1.30s (Me), 1.50m (13H), 1.80m (7H), 2.27s (Me), 2.30m (4H), 2.80m (2H, $H_{8,10}$), 2.90m (2H), 3.40dd (1H, H_7, *J* 8.8 and 1.8 Hz), 3.20s (MeO), 3.88s (MeO). 5.60s ($H_{14'}$), 6.58d (1H, H_2, *J* 8.5Hz), 6.72d (1H H_1).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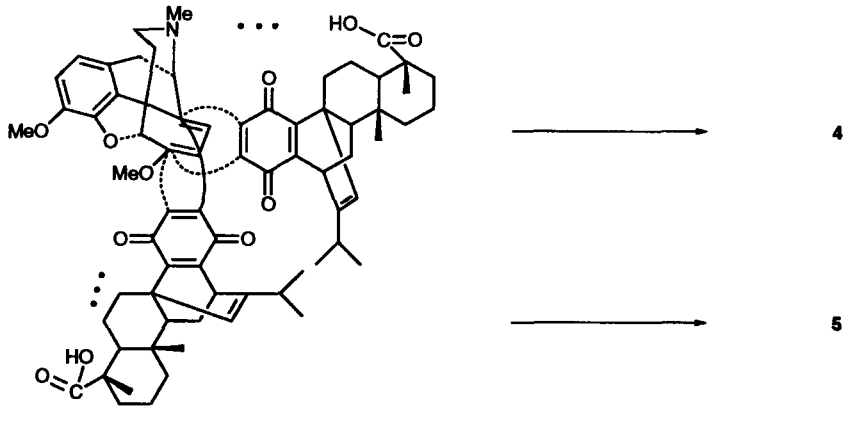
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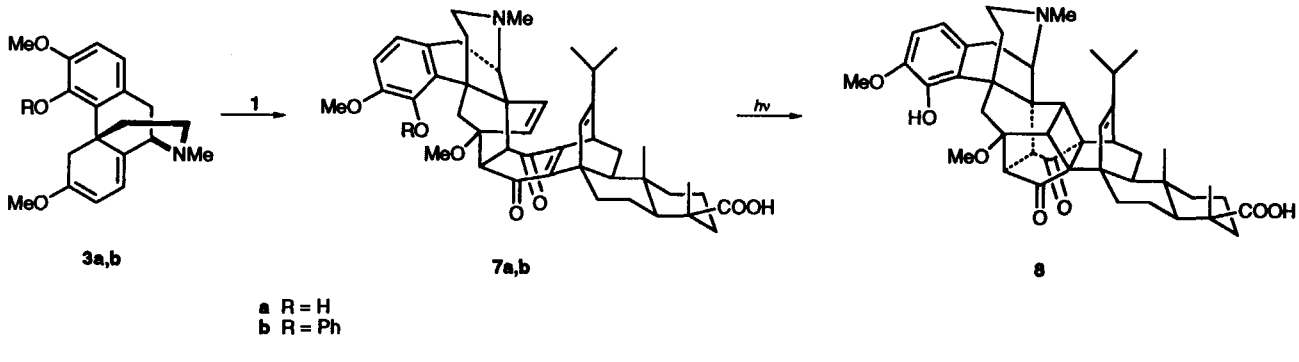
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HO
MeO
COOH
8

a R = H
b R = Ph

Mendeleev Commun., 1994, 4(2), 60–62

There are many publications concerning facial diastereoselection in Diels–Alder cycloadditions with planar non-symmetric dienes bearing a heteroatom.[8] In our case, the presence of a nitrogen atom placed several atoms away from the bond-forming site is predominant in improving the facial selectivity in the absence of a 4,5-epoxy bond, due to its ability to bring about an effective influence on the double bonds in ring C to a much greater extent than on intramolecular interaction.

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