New Diels-Alder Reactions of (-)-Thebaine and First X-Ray Crystallographic Structure Analyses of the Cycloadducts

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Diels-Alder reactions of (-)-thebaine (1) as an electron-rich diene system with acceptor-substituted ethenes gave rise to the cycloadducts 2, 3, and 4 in high regio- and stereoselectivities. Structural analyses were performed by high resolution NMR spectroscopy and, for the first time in the thebaine cycloadduct series, by X-ray crystallographic structural analyses of the compounds 2, 3a, and 3b. In the reaction of (-)-thebaine (1) with an in situ generated aryne, the annelated azocene derivative 5 was formed.

In this paper, we describe some further Diels-Alder reactions of the opium alkaloid (-)-thebaine (1) as an electron-rich diene have been the subject of several investigations, in particular in the field of medicinal chemistry for the development of drugs with analgesic activities [1–5]. Recently, we have fulfilled the demand for more precise information on the stereochemistries of some reinvestigated and newly synthesized cycloadducts of thebaine by means of high resolution 1H-NMR spectroscopy [6]. It was concluded that the β-face endo approach [6] of the dienophile to the cyclohexadiene ring C in 1 is unambiguously favoured on steric and electronic grounds; moreover, in the latter case, the experimental results are fully compatible with frontier molecular orbital considerations [6]. In the context of our current investigations on the cycloaddition reactions of various electron-rich heterocycles [7], we are also continuing our studies of these special Diels-Alder reactions with (-)-thebaine (1), because the results will be of general interest for the future development of drugs.

In this paper, we describe some further Diels-Alder reactions of (-)-thebaine (1) with selected carbodienophiles and report the first X-ray crystallographic structural analyses of Diels-Alder adducts of thebaine. These structural investigations will most certainly shed new light on the some times rather unclear and less convincing configurational data given in the earlier reports [1–4] and, last but not least, also provide incontrovertible sustenance for our recent, more detailed report [6].

Results and Discussion

Synthetic aspects

(-)-Thebaine (1) reacts with divinylsulfone regio- and stereoselectively to furnish the Diels-Alder product 2 (63% yield). No other isomeric cycloadducts were detected by TLC. However, this product was previously described in ref. [8], but no fully convincing data for the (absolute) stereochemistry of the newly formed stereocentres were given. The structure of 2 has now been unambiguously elucidated by NMR spectroscopy and X-ray crystallography (see below and Fig. 2). According to semiempirical quantum mechanical AM1 calculations [9] (for details see [6]), the dienophile attacks the β side of the diene system and the thus resulting endo-transition state is energetically favoured by HOMO(diene)–LUMO(dienophile) interactions involving secondary orbital overlap [10]. In further experiments, we examined the Diels-Alder reactivity of 1 towards some (E)- and (Z)-1,2-ethenedicarboxylates and found that 1 reacts with dimethyl and diethyl fumarate to give the cycloadducts 3a and 3b stereoselectively (by TLC) in 48 and 52% yields, respectively. In these cases also, the stereochemistries were clarified by NMR spectroscopy and X-ray crystallography (see Fig. 3). In summary, the three

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performed X-ray structural analyses of products 2, 3a, and 3b are unique in the Diels-Alder chemistry of thebaine and further substantiate the structural investigations on the previous Diels-Alder adducts prepared from 1 [6].

It is known that (Z)-dialkyl 1,2-ethenedicarboxylates are, in general, less reactive than their (E)-counterparts [12]. Thus, in our hands, dimethyl maleate reacted with 1 to give a lower yield (28%) of the cycloadduct 4 [11], albeit stereoselectively. The stereoselective Diels-Alder reactions of (−)-thebaine (1) with these dialkyl 1,2-ethenedicarboxylates suggest the exclusive participation of a concerted mechanism.

Acetylenic dienophiles react, in some cases, with (−)-thebaine (1) via a one-bond addition and subsequent piperidine ring enlargement reaction to yield polycyclic azocine derivatives [13−15]. We have now found that an in situ generated aryne is also able to effect a ring enlargement reaction in 1. Thus, (−)-thebaine (1) reacted with benzyne, readily generated from diazotized anthranilic acid [16], to give rise to the hexacyclic benzof[b]naphtho[2,1-e]azocine 5, albeit only in 6% yield together with several other, less stable products. However, no normal Diels-Alder product could be isolated from crude reaction mixture. As a mechanistic rationale for this reaction, we propose a primary nucleophilic attack of the piperidine nitrogen atom at one aryne sp-centre [17]. The thus formed intermediate is then stabilized by heterolytic C9−N σ-bond cleavage which initiates the piperidine ring enlargement reaction (for an analogous mechanistic explanation, see ref. [14]).

**NMR spectroscopic investigations**

The 1H and 13C NMR spectroscopic data of the new Diels-Alder adducts are fully compatible with the recently reported data [6]. Typical for the stereochemistry of the Diels-Alder products is, for example, the W-coupling of H5 with H17 (approx. 1.20 Hz). Additionally, 1H,1H NOE measurements are frequently useful to obtain more configur-
<table>
<thead>
<tr>
<th>Crystal data</th>
<th><strong>2</strong> (KE 27)</th>
<th><strong>3a</strong> (KE 14)</th>
<th><strong>3b</strong> (KE 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula, M_r</td>
<td>C_{27}H_{32}NO_5</td>
<td>C_{25}H_{32}NO_3</td>
<td>C_{29}H_{32}NO_3</td>
</tr>
<tr>
<td>Crystal size (mm³)</td>
<td>0.21×0.42×0.13</td>
<td>0.35×0.06×0.1</td>
<td>0.3×1.0×0.6</td>
</tr>
<tr>
<td>Crystal system</td>
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<td>orthorhombic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁</td>
<td>P2₂2₁2₁</td>
<td>P2₁</td>
</tr>
<tr>
<td>Unit cell</td>
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<td>9.6374(2)</td>
<td>10.639(1)</td>
</tr>
<tr>
<td></td>
<td>( b (\text{Å}) )</td>
<td>7.0729(2)</td>
<td>11.017(1)</td>
</tr>
<tr>
<td></td>
<td>( c (\text{Å}) )</td>
<td>15.5698(4)</td>
<td>18.784(1)</td>
</tr>
<tr>
<td>Determined from</td>
<td>75 refl.</td>
<td>31 refl.</td>
<td>75 refl.</td>
</tr>
<tr>
<td>Packing: ( V(\text{Å}^3) ), F(000)</td>
<td>( \theta = 65° )</td>
<td>( \theta = 63° )</td>
<td>( \theta = 65° )</td>
</tr>
<tr>
<td>( Z ), ( d_{\text{calc}}(\text{g/cm}^{-3}) )</td>
<td>2, 1.416</td>
<td>4, 1.374</td>
<td>2, 1.246</td>
</tr>
<tr>
<td>( \mu(\text{cm}^{-1}) )</td>
<td>11.39</td>
<td>8.3</td>
<td>6.53</td>
</tr>
</tbody>
</table>

**Data Collection**

| Radiation, diffractometer, scan type, temperature | Cu–Kα graphite monochromator Enraf-Nonius CAD 4, Ω/2θ, 298 K |
| θ Range | 1.5° ≤ θ ≤ 70.0° |
| Range of hkl | 0 ≤ h ≤ 11, 0 ≤ k ≤ 13, 0 ≤ l ≤ 22 |
| Reflections: meas., Indep., \( R_{\text{int}} \) | 4386, 3796, 0.02 |
| Friedel-pairs used, limit (F/σ(F)> | 4710, 4107, 0.03 |
| Refinement | 3614, 4 |
| Friedel-pairs | 4707, 4 |

Choice of displ. parameters:

- non-Hydrogen hydrogen anisotropic, riding, isotropic anisotropic, riding, isotropic anisotropic, riding, isotropic
- Variables | 286 | 327 | 334 |
- Last shift (σesd) | 0.001 | 0.001 | 0.01 |
- Final \( R, R_w \) | 0.038 (0.054) | 0.114, 0.042 | 0.050, 0.062 |
- Flack-Parameter | \( -0.2(2) \) |
- Weighting scheme | unit |
- \( P \) | \( 1/[(\sigma^2(F_o^2)+0.26\times P)^{3/2}] \) |
- Goodness of fit | \( 0.0072(2) \) |
- Extinction parameter | \( 0.035(2) \) |
- Fourier maxima (eÅ⁻³) | \( 0.42, -0.57 \) | \( 0.18, -0.14 \) | \( 0.51, -0.49 \) |

**Used programs:**

- Solution | SHELXS-86 [20] | SHELXS-86 | SHELXS-86 |
- Method | Direct Methods | Direct Methods | Direct Methods |
- Scattering factors | SHELXL-93 | SHELX-76 | SHELX-76 |
- from geometrical calculations | GEOM [24] | GEOM | GEOM |

1 Substance code in supplemental material.
tional details about the newly formed stereo-centres. In the case of compound 3a, interatomic distances were exemplarily analyzed by NOE experiments (steady state NOE) and proton T1 measurements [18]. On the basis of a calculated (fixed) H–H reference distance (averaged distance H5–H,H15a,b by MMX molecular mechanics method = 2.58 Å [19]), the configurations at C7 and C8 were established. In summary, the relevance of more sophisticated NMR spectroscopic configuration analysis in the thebaine cycloadduct series is nicely illustrated by these studies in combination with the X-ray crystallographic results.

In the case of the hexacyclic product 5, firstly the diagnostically relevant ¹H,¹H NOE’s from H17 to N5–CH, and vice versa (averaged H–H distance of approx. 3.2 Å according to MMX force field calculations [19], see also Fig. 1), in addition, a paramagnetic shift of the signal for H17 of approx 0.5 ppm in comparison to the analogous shift in the thebaine cycloadducts and an H,H–COSY spectrum are highly indicative for the structure of 5 given.

X-ray crystallographic structural analyses of 2, 3a, and 3b

Experimental details for the structural analyses of compounds 2, 3a, and 3b are listed in Table I. The investigated compounds all crystallized in non-centrosymmetric space groups, thus only one enantiomer is present in each case. As shown in Table II, the most important geometrical parameters for the compounds are all equal within the limits of accuracy and lie in the normal range. The phenyl ring is approximately planar, the five-membered ring C4, C12, C13, C5, O1 is twisted with C5 being above and C13 being below the least squares plane. As shown in Fig. 2, it can be concluded from the least squares calculations and from the values of the torsional angles that the cyclohexane ring has the boat conformation, while the piperidine ring takes up the chair conformation. The etheno bridge C6–C17–C18–C14 is nearly perpendicular to the least squares plane of the cyclohexane ring.

Further details of X-ray structural analyses can be obtained on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eg-
Fig. 3. X-ray structures of 3a (above) and 3b (below), SCHAKAL plot [23]. A disorder was found at C27. One of the possible orders was chosen.
Experimental

$^1$H NMR spectra were recorded at 200 and 400 MHz with Bruker AC 200 and AMX 400 spectrometers. $^{13}$C NMR spectra were measured at 50.3 MHz with a Bruker AC 200 instrument; J-modulated spin echo spectra were obtained in all cases ($C_p$ = primary, $C_s$ = secondary, $C_t$ = tertiary, and $C_q$ = quaternary carbon atoms). The EI (70 eV) mass spectra were recorded on a Varian MAT 7 spectrometer. Elemental analyses were performed by using a Carlo Erba Strumentazione 1106 apparatus. Melting points were measured with an Electrothermal 8200 instrument. Flash chromatography was performed on Merck 60 silica gel (particle size: 0.040-0.063 mm). The petroleum ether used had the boiling range 40–60°C.

All reactions were performed in highly pure, anhydrous solvents. The yields given refer to analytically pure compounds, some product loss occurred during chromatographic work-up.

4,5a-Epoxy-3,6-dimethoxy-N-methyl-7a-vinylsulfonyl-6a, 14a-endo-etheno-isomorphinane (2)

(-)-Thebaine (1) (200 mg, 0.64 mmol) was dissolved in 20 ml toluene. After addition of divinylsulfone (75.6 mg, 0.64 mmol), the mixture was stirred for 24 h at 20°C. The formed precipitate was recrystallized four times from ethyl acetate/petroleum ether. Yield 170 mg (63%), m.p. 188–190°C (ethyl acetate, petroleum ether).

EI-MS: m/z (% ) = 429 (16) [M]+, 338 (43).

C_{25}H_{29}NOSO_{2} (455.52)
Calcd C 65.92 H 6.42 N 3.07%,
Found C 65.96 H 6.37 N 3.16%.

4,5a-Epoxy-7β,8a-bis(methoxycarbonyl)-3,6-dimethoxy-N-methyl-6a, 14a-endo-etheno-isomorphinane (3a)

(-)-Thebaine (1) (200 mg, 0.64 mmol) and diethyl fumarate (365 mg, 3.2 mmol) were heated under reflux in 30 ml toluene for 4 d. The mixture was then concentrated to 1 ml and the residue obtained was purified by flash chromatography (ethyl acetate/petroleum ether, 3:1). Yield 140 mg (48%), m.p. 159–162°C (ethyl acetate).

EI-MS: m/z (% ) = 455 (69) [M]+, 311 (13).

C_{25}H_{29}NOSO_{2} (455.52)
Calcd C 65.92 H 6.42 N 3.07%,
Found C 65.96 H 6.37 N 3.16%.

From (-)-thebaine (1) (200 mg, 0.64 mmol) and diethyl fumarate (551 mg, 3.2 mmol) following the procedure described above for compound 3a. Yield 160 mg (52%), m.p. 108–110°C (ethyl acetate).

EI-MS: m/z (% ) = 455 (69) [M]+
8,17a-Epoxy-9,16-dimethoxy-5-methyl-
5,6,7,9a,12,14β-hexahydro-7-oxa,14α-[1]-
propenobenz[b]naphtho[2,1-e]azocine (5)

Anthraniolic acid (950 mg, 6.92 mmol) and tri-
chloroacetic acid (8.4 mg, 0.05 mmol) were suspended
in 20 ml tetrahydrofuran and cooled to 0 °C. To this mixture in over a period of 2 min was added isomyl nitrite (1.6 ml, 11.8 mmol) at same
temperature. After the mixture had been stirred at
20 °C for 1.5 h the precipitate was separated and
purified by washing with tetrahydrofuran. The thus obtained o-benzene-diazonium carboxylate was suspended in dichloromethane. The resultant suspension was added in small portions to a refluxing solution of (-)-thebaine (I) (388.75 mg, 1.25 mmol) in 25 ml dichloromethane over a period of 30 min. After being heated under reflux for 30 min, the mixture was concentrated carefully under reduced pressure and the residue obtained purified by flash chromatography (ethyl acetate/petroleum ether, 3:1). Yield 30 mg (6%), m.p. 186 °C (ethyl acetate). - 1H NMR (400 MHz, CDCl3); δ = 1.59 [dd, 1H, J(H7, H6) 13.91 Hz, J(H7, H6) 4.38 Hz, H7], 2.33 (m, 1H, H6), 2.75 (s, 3H, NCH3), 2.94 (m, 2H, H6, H7), 3.22 (m, 2H, 2×H12), 3.45 (s, 3H, OCH3), 3.84 (s, 3H, OCH3), 4.21 [d, 1H, J(H14, H15) 6.07 Hz, H14], 4.74 [d, 1H, J(H15, H14) 6.14 Hz, H15], 5.43 (s, 1H, H17), 6.14 [dd, 1H, J(H13, H12) = 5.73, J(H13, H14) 2.59 Hz, H13], 6.66 [d, 1H, J(H11, H10) 8.02 Hz, H10], 6.69 [d, 1H, J(H10, H11) 8.10 Hz, H10], 6.98 (m, 1H, aromatic), 7.19 (m, 3H, aromatic). - 13C NMR (50.3 MHz, CDCl3); δ(Cp) = 39.24, 49.87, 54.87 (1×NCH3, 2×OCH3); δ(Cp) = 29.78, 37.23, 60.71 (C6, C7, C12); δ(Cp) = 56.87, 88.75 (C14, C17), 100.64, 112.41 (C13, C15), 119.15, 119.88, 123.65, 125.91, 127.79, 131.43 (C1, C2, C3, C4, C10, C11); δ(Cp) = 51.33 (C7a), 128.79, 136.13 (C13a, C16), 139.89, 143.03, 143.31, 145.03, 152.70, 154.76 (C4a, C7b, C8, C9, C11a, C14a). - EI-MS: m/z (%) = 387 (100) [M]+.

Analysis C25H23NO3 (387.49)
Calcd C 77.49, H 6.50 N 3.61%,
Found C 76.69 H 6.98 N 3.84%.

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schaft (Bonn) for financial support of this work and are also grateful to H. Kolshorn, Institute of Organic Chemistry, University of Mainz, for the special NMR spectroscopic measurements.
[19] MMX force field calculations (a variant of MM2 method) see: J. J. Gajewski, K. E. Gilbert, J. McKelvey, Adv. Molec. Mod. 2, 65 (1990); the program packet PCMODEL 3.2 from Serena Software, Bloomington, IN, was used.