Pergamon

Tetrahedron, Vol. 52, No. 7, pp. 2449-2464, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01066-1

Reaction of Morphinan-6,8-dienes with Azadienophiles+**

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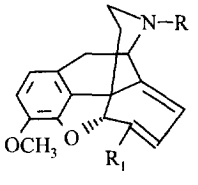
Abstract: Reaction of various morphinan dienes, i.e. thebaine (**1a**), *N*-demethyl-*N*-formylthebaine (**1b**), 6-demethoxythebaine (**1c**), β-dihydrothebaine (**2a**), 4-acetoxy-β-dihydrothebaine (**2b**), 7-chloro-6-demethoxythebaine (**3a**) and 7-bromo-6-demethoxythebaine (**3b**) with 4-phenyl-*4H*-1,2,4-triazoline-3,5-dione (PTAD) gave rise to new Diels-Alder (DA) adducts. DA-reaction of **1a**, **1b** and **1c** with PTAD led to the products of the β-face attack of the dienophile at the diene unit. The W coupling ($^4J_{5\beta,18}$) in the ^{1}H-NMR spectra was indicative of these structures. α-Face addition took place in the case of morphinan dienes with opened ring E, and a by-product was formed due to the S_E reaction of PTAD with the adducts. The structure of these derivatives was confirmed by means of NMR spectroscopic methods. The retro Diels-Alder (rDA) reaction of the adducts **4a** and **4b** readily took place in polar-aprotic solvents in the presence of bases with low nucleophilic character.

Althoug *Bentley* and his co-workers examined[1,2] the DA-reactions of thebaine with a large variety of dienophiles, *Merz* and *Pook*[3] were the first to report on the detailed investigation of such reactions carried out with azadienophiles, most of all with azodicarboxylates. In the field of the morphine alkaloids azodicarboxylates have been shown useful in *N*-demethylation reactions[4]. With one equivalent of the reagent thebaine (**1a**) gives *N*-demethyl-17-(*N,N'*-dialkoxycarbonyl-hydrazinomethyl)-thebaine, but when two equivalents of azodicarboxylate is used formation of the product of the DA-reaction is also expectable[3].

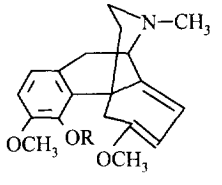
** Dedicated to *Prof. Dr. W. Fleischhacker* on the occasion of his 65th birthday.

Bentley et al. described[2,5] that the reaction of thebaine with dimethyl azodicarboxylate did not give the normal DA-adduct, but from *N*-demethyl-*N*-trifluoroacetylthebaine the expected DA-product was produced[3]. *Hromataka* et al. reported[6,7] on the cycloaddition reactions of thebaine with various cyclic azadienophiles (4,4-diethylpyrazolin-3,5-dione, 3-indazolone, PTAD).



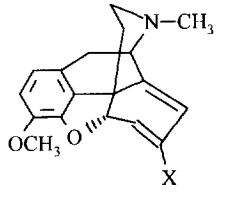
1

1	R	R_1
a	CH_3	OCH_3
b	CHO	OCH_3
c	CH_3	H



2

2	R
a	H
b	Ac



3

3	X
a	Cl
b	Br

The present paper deals with the DA-reactions of morphinan dienes, i.e. thebaine (**1a**), *N*-demethyl-*N*-formylthebaine (**1b**), 6-demethoxythebaine (**1c**), β-dihydrothebaine (**2a**), 4-acetoxy-β-dihydrothebaine (**2b**), 7-chloro-6-demethoxythebaine (**3a**) and 7-bromo-6-demethoxythebaine (**3b**) with PTAD as the dienophile. In the case of **1b** diethyl azodicarboxylate (DEAD) was also employed.

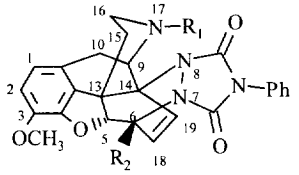
The starting morphinan dienes were prepared according to literature procedures[8-12]. As no data for the rDA-reactions of the DA-adducts of morphinan-6,8-dienes have been found, related recations were also investigated with the goal of examining PTAD as a possible protecting group for morphinan dienes.

DA and rDA-reactions are extensively employed[13] for the protection of the cojugated diene function. Thus, PTAD (*Cookson* reagent[19]) have been reported[14-18] as a suitable reagent for the protection of steroid compounds (e.g. colesterol and ergosterol-5,7-dienes). PTAD is a highly reactive dienophile, reacting quickly with numerous dienes at room temperature[16], but cycloadditions performed at - 70 °C have also been reported[20]. Removal of the protecting group can be readily accomplished with strong organic bases (*sym.*-collidine, tetramethylguanidine)[14], with KOH in methanol[15], by refluxing with K_2CO_3 in DMSO[16], as well as by treatment with KOH in 95% ethanol[15], with NaOMe/MeOH[18] or with $LiAlH_4$[13].

From the calculated molecular orbital energy values[21] and the energy-separations *normal* $HOMO_{diene}$ - *controlled* DA-reactions are expected. Based on the results of *Linders* and *Maat*[22] and additional literature data[23] an α-face addition was expected in the case of **2a** and **2b** due to steric reasons and the change of the conformation of ring C.

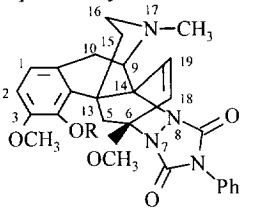
The reaction of **1b** with PTAD (room temperature, 1 h) gave the product **4b** in high yield, as a result of a β-face attack. The DA-reaction of 6-demethoxythebaine with PTAD was complete in 1h at room temperature and adduct **4c** was isolated with good yield. Structures **4a-c** could be readily confirmed by the long-range $^4J_{5\beta,18}$ W coupling (1.3-1.5 Hz) in the NMR spectra.

The reaction of β-dihydrothebaine (**2a**) or 4-acetoxy-β-dihydrothebaine (**2b**) with PTAD led to the formation of two products, which were separated by means of column chromatography.



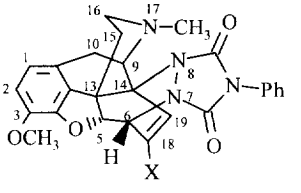
4

4	R_1	R_2
a	CH_3	OCH_3
b	CHO	OCH_3
c	CH_3	H



5

5	R
a	H
b	Ac

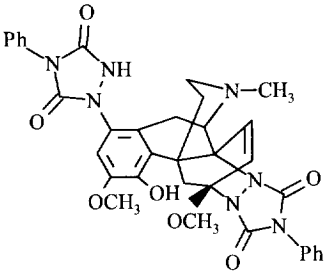


6

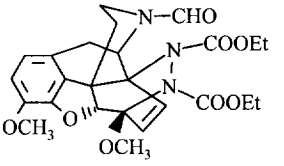
6	X
a	Cl
b	Br

Due to the differences between the two structures in the case of a β-face adduct saturation of the 19-H would cause an NOE effect at the 10α-H, whereas a similar effect for the α-face adduct would appear at the 15β-H. As the latter effect was observed for the major products isolated from the DA-reaction of both **2a** and **2b** with PTAD an α-face addition, resulting in the adducts **5a** and **5b**, respectively, could be unequivocally established.

Both of the above two reactions also gave a by-product, compound **7**, as a result of an electrophile substitution reaction of PTAD with the major, α-face addition products. Similar reactions of PTAD have been reported[24], but in the case of **2b** and PTAD the cleavage of the 4-OAc group is also carried out. The structure of **7** was confirmed by NMR measurements; the α-face addition was justified by the observed change in the intensity for the 19-H when saturated the protons at C-15. The NOE data for compounds **7** and **6a** are summarized in **Table I**.



7



8

Table I. NOE data for compounds **6a-b** and 7

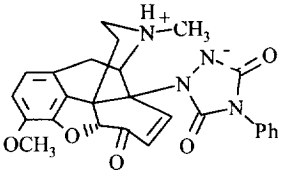
Compound	NOE[a] data
6a	$f_{19\text{-H}}$ (10α-H) = 3.0; $f_{19\text{-H}}$ (9-H) = 3.9;
6b	$f_{19\text{-H}}$ (10α-H) = 2.0; $f_{19\text{-H}}$ (9-H) = 3.8;
7	$f_{2\text{-H}}$ (3-OMe) = 17.3; $f_{3\text{-OMe}}$ (2-H) = 8.8; $f_{18\text{-H}}$ (19-H) = 10.3; $f_{19\text{-H}}$ (18-H) = 16.8; $f_{19\text{-H}}$ (9-H) = 5.7; $f_{10\beta\text{-H}}$ (10α-H) = 18.8; $f_{10\beta\text{-H}}$ (9-H) = 3.5; $f_{10\beta\text{-H}}$ (NCH_3) = 6.8

a: The irradiated proton is indicated in the subscript and the protons whose signals suffered intensity change are in brackets

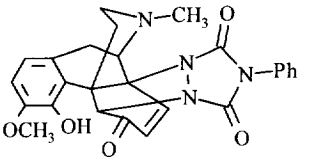
In the reactions of **3a-b** with PTAD the β-face adducts **6a-b** were obtained after a 70% conversion.

The DA-reaction of **1b** with diethyl azodicarboxylate afforded the adduct **8**, as a rusult of a β-face attack, in good yield. For completing the reaction a longer reation time and higher temperature (toluene, reflux for 5h) was required.

Ginsburg et al.[25] have reported that the most intensive peak in the mass spectrum of **4a** was observed at m/z = 311, which is due to an rDA-reaction carried out in the spectrometer. The structure of **4b** could only be assigned by NMR and IR measurements, since both of the EI (70 eV or 30 eV) and the "thermospray" (TSP) techniques allowed the exclusive detection of an m/z = 326 ion formed in the rDA-reaction. For compounds **4c** and **5a** the EI method gave molecular ions with 30 % and 3 % intensity. In the case of the adduct (**5b**) of 4-acetoxy-β-dihydrothebaine the m/z = 531 $[M+1]^+$ ion (4 %) could only be detected by means of the TSP technique. For **4c**, **5a** and **5b** the most intense ion was that of the fragment produced in the rDA-reaction. In the mass spectrum of **8** the ion characteristic of the rDA-reaction could also be detected, but – contrary to the mass spectra of the PTDA adducts – it was not the most intensive. In the case of **7** the $[M+1]^+$ ion could only be obtained by means of the ESI technique.



9

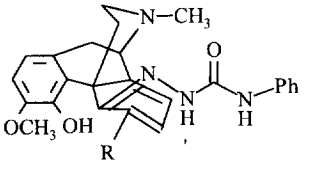


10

Studies on the synthesis of the retrodiene **4a** showed that the rDA-reaction could be triggered only by a thermal effect but the conversion was still very low; refluxing in toluene for 3 days the reaction proceeded as low as up to 30 %. In 95 % ethanol and in the presence of diethyl amine **10** was produced *via* **9** in 69 % yield after refluxing for 5 hrs. For elucidation of the structure of **10** an authentic sample was synthesized by using the procedure of *Ginsburg* et al.[25], and the physical and spectral data were found completely identical.

When refluxing **4a** in collidine the complete conversion required 7 hours, and the major product was, again, compound **10** (46 %), accompanied by thebaine (**1a**, 30 %) – arising from the rDA-reaction. When **4a** was treated with 2N KOH in 95% ethanol at 60 °C the starting adduct decomposed in 10 min. and the product **11a** could be isolated in good yield (60 %) after chromatographic purification. A similar reaction of **4c** afforded **11b**.

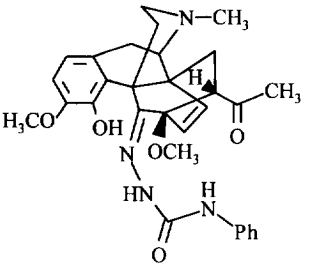
Elucidation of the structure of **11a** was carried out by means of NMR and mass spectrometric measurements. The m/z = 461 {$[M+1]^+$} ion could only be deteceted with the TSP method. When employing the EI technique (70 eV) the fragment appearing at the highest m/z value was that produced upon loss of C_6H_5NCO. The mechanism of the formation of compounds with structure **11** could not be explained as yet.



11

11	R
a	OCH_3
b	H

The reaction of **11a** and methyl vinyl ketone resulted in the adduct **12**, thus supporting the presence of the 6,8-diene system in **11a**. The formation of the β-face adduct was proved by homonuclear NOE difference measurements: by saturating the 19-H an intensity-change was observed for the signal of 10α-H. The additional NMR data are summarized in **Table II.**



12

Table II. NOE data for compound **12.**

Compound	NOE[a] data	r_{19}- [nm]
12	$f_{19\text{-H}}$ (18-H) = 9.5; $f_{19\text{-H}}$ (9-H) = 3.3; $f_{19\text{-H}}$ (10α-H) = 4.9;	9-H = 0.273 10α-H = 0.229

a: The irradiated proton is indicated in the subscript and the protons whose signals suffered intensity change are in brackets.

When **4a** was treated with anhydrous potassium carbonate in hot *N,N*-dimethyl formamide (100 °C) thebaine (**1a**) as the product of the retrodiene synthesis was isolated with good yield. Thebaine was obtained, again, when compound **4a** was reacted with 7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene (MTBD) in acetonitrile. At 60 °C the conversion was only ca. 10 % even after 3 days, but by refluxing for 8 hours the reaction was complete, as shown by monitoring the transformation by means of thin layer chromatography.

When **4b** was refluxed in collidine compound **1b** also appeared in the reaction mixture. By freezing the reaction after 0.5 hour **1b** was separated by column chromatography and its structure was identified (m.p., TLC and ^{1}H-NMR measurements). By continuing the reaction at reflux temperature the uncontrolable decomposition processes dominated after a reaction time of 1 hour. For the synthesis of the retrodiene **4b**, again the application of K_2CO_3 proved to be the most efficient. In each reaction where an rDA-process had occurred PTAD was also produced, which could not be isolated, but the products of its extensive decomposition could be detected by thin layer chromatography.

The above results clearly demonstrate that the rDA-reactions of the investigated DA-adducts **4a** and **4b** can be readily accomplished and the compounds carrying the diene system can be obtained with excellent yields. Although the rDA-reaction proceeds on a thermal effect, sufficient rate can be ensured in polar-aprotic solvents in the presence of bases with slight nucleophilic character.

Experimental

Melting points (uncorrected) were measured with a Büchi-apparatus in open capillary tubes. Thin layer chromatography was carried out on precoated Kieselgel 60 F_{254} plates (Merck 5719), by applying 10µl of the 10 mg/ml chloroform solutions on the plates. Preceeding chromatography the chambers were saturated with the solvent systems for 30 min at 25 °C. The front height was 8 cm with the developing systems (v/v): 8:2 benzene-methanol [A]; 9:1 chloroform-methanol [B] and 5:4:1 chloroform-acetone-diethyl amine [C]. The chromatograms were visualized with a 254 nm UV lamp or with the Dragendorff reagent.

For column chromatography Kieselgel 60 (particle size 0.063-0.2 mm) was employed with the eluent systems mentiond above, and also with 8:2:0.1 ethyl acetate-methanol-ammonia (v/v) [D].

The optical rotation values were measured with a Polmat-A (Zeiss, Jena) polarimeter. The IR spectra were obtained in KBr pellets with a Digilab FTS-40 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian-Gemini-200 instrument at 20 °C in $CDCl_3$ (or in the case of **7** in polysol). For the ^{1}H-NMR examinations TMS (δ=0.00 ppm) was used as the internal standard and the ^{13}C-NMR signals were related to the signal of $CDCl_3$ (δ=77.0 ppm). The assignments were carried out with the aid of APT experiments. Abbreviations: Ph: protons of the phenyl group; [a]: deuterable.

Mass spectra were obtained with a VG Trio-2 instrument by using the EI method (70 eV), or occasionally by means of the "thermospray technique" (TSP) and in the case of compound **7** with the "electrospray" (ESI) method.

The elemental analyses were carried out at the Department of Organic Chemistry, Lajos Kossuth University with a Carlo Erba automatic analyser.

4-Phenyl-1,2,4-triazolidine-3,5-dione was synthesized according to a literature procedure[26] from which PTAD was obtained by treatment[27] with fuming nitric acid.

The PTAD adduct (**4a**) *of thebaine:* To a solution of thebaine (**1a**) (4.3 g; 13.8 mmol) in acetone (200 ml) a solution of PTAD (2.9 g; 16.5 mmol) in acetone (20 ml) was added and the resulting red reaction mixture was stirred at room temperature for 20 minutes. The solvent was evaporated under diminished pressure below 40 °C to obtain 5.4 g (80%) of the product. Mp. 207-208 °C [acetone]. Lit.[7]: 210-212 °C [EtOH], Lit[25]: 200-204 °C [acetone]. – R_{fA} = 0.77; R_{fB} = 0.92; R_{fC} = 0.91. – ^{1}H-NMR($CDCl_3$): δ = 2.03 (m, 1H, 15α-H); 2.35-2.85 (m, 4H, 15β-H, 16β-H, 16α-H, 10α-H); 2.53 (s, 3H, NCH_3); 3.42 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 3.84 (s, 3H, 6-OCH_3); 3.92 (s, 3H, 3-OCH_3); 4.58 (d, $J_{9\alpha,10\alpha}$ = 6.74 Hz, 1H, 9α-H);

5.03 (d, $J_{5\beta,18}$ = 1.47 Hz, 1H, 5β-H); 5.77 (d, $J_{19,18}$ = 8.55 Hz, 1H, 19-H); 6.01 (dd, $J_{18,19}$ = 8.55 Hz, $J_{18,5\beta}$ = 1.5 Hz, 1H, 18-H); 6.63 (d, J = 8 Hz, 1H, 1-H); 6.72 (d, 1H, 2-H); 7.30-7.50 (m, 5H, N-Ph). – ^{13}C-NMR: δ = 23.18 (C-10); 32.26 (C-15); 42.64 (NCH_3); 44.84 (C-16); 47.36 (C-13); 53.96 (6-OCH_3); 56.49 (3-OCH_3); 57.25 (C-9); 62.76 (C-14); 85.11 (C-5); 96.44 (C-6); 114.43 (C-2); 120.51 (C-1); 126.91 (C-18); 127.01 (C-11); 130.71 (C-12); 132.68 (C-19); 142.47 (C-3); 145.50 (C-4); others: aromatic: 125.73 (2); 128.87 (2); 128.16 (1); 131.13 (q); C=O: 154.34; 155.65. – MS (EI - 70 eV) m/z: 486 (3) [M^+], 311 (100) – $[\alpha]_D^{25}$ = - 13.4 (c = 1, $CHCl_3$) – IR (KBr) [cm^{-1}]: ν_{CO} 1771, 1718 – $C_{27}H_{26}N_4O_5$ (486.5). – Calcd.: C: 66.66; H: 5.39; N: 11.52; Found: C: 66.61; H: 5,48; N: 11,42.

The PTAD adduct (**4b**) *of N-demethyl-N-formylthebaine*: To a suspension of *N*-demethyl-*N*-formylthebaine[8] (**1b**) (1.9 g; 5.8 mmol) in acetone (22 ml) a solution of PTAD (1.1 g; 6.2 mmol) in acetone (14 ml) was dropwise added at room temperature over a period of 15 min. The suspension turned to a clear solution and then precipitatation of the product begun. After stirring for additional 1 h the product was filtered off and washed with a small volume of cold acetone to obtain 2.30 g (79%) of colourless crystalline **4b**, mp. 212-213 °C – R_{fA} = 0.71; R_{fB} = 0.91; R_{fC} = 0.88. – ^{1}H-NMR($CDCl_3$): δ = 2.07 (dd, 1H, 15α-H); 2.35 (ddd, 1H, 15β-H); 2.97 (ddd, 1H, 16β-H); 3.18 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 3.32 (dd, 1H, 10α-H); 3.86 (s, 3H, 6-OCH_3), 3.91 (s, 3H, 3-OCH_3); 4.53 (dd, 1H, 16α-H); 5.02 (d, $J_{5\beta,18}$ = 1.46 Hz, 1H, 5β-H); 5.42 (d, $J_{9,10\alpha}$ = 6.91 Hz, 1H, 9α-H); 5.82 (d, $J_{19,18}$ = 7.8 Hz, 1H, 19-H); 6.09 (dd, $J_{18,19}$ = 7.8 Hz, $J_{18,5\beta}$ = 1.46 Hz 1H, 18-H); 6.67 (d, 1H, 1-H); 6.78 (d, 1H, 2-H); 7.30-7.50 (m, 5H, N-Ph); 8.41 (s, 1H, N-CHO). – ^{13}C-NMR: δ = 31.69 (C-15); 33.49 (C-10); 32.27 (C-16); 48.83 (C-13); 54.11 (6-OCH_3); 56.53 (3-OCH_3); 51.88 (C-9); 61.79 (C-14); 85.28 (C-5); 96.62 (C-6); 115.12 (C-2); 120.98 (C-1); 124.81 (C-11); 128.21 (C-18); 129.39 (C-12); 131.18 (C-19); 142.95 (C-3); 147.91 (C-4); others: aromatic: 125.72 (2); 129.07 (2); 128.56 (1); 130.70 (q); C=O: 153.91; 156.30; 161.86. – MS (EI - 70 eV, TSP): [M^+] could not be detected; 325(45), 267(100) – $[\alpha]_D^{25}$ = - 134.9 (c =1, $CHCl_3$) – IR (KBr) [cm^{-1}]: ν_{CO} 1175, 1718, 1675 – $C_{27}H_{24}N_4O_6$ (500.5). – Calcd.: C: 64.79; H: 4.83; N:11.19; Found: C: 64.75 H: 4.88; N:11.10.

The PTDA adduct (**4c**) *of 6-demethoxythebaine*: The reaction of 6-demethoxythebaine[9] (**1c**) (2.00 g; 7.1 mmol) and PTAD (1.5 g; 8.5 mmol) in acetone (70 ml) for 1 h was accomplished as described above for **4b** to obtain 2.99 g (92%) of **4c**, mp. 179-180 °C [acetone]. – R_{fA} = 0.80; R_{fB} = 0.93; R_{fC} = 0.91. – ^{1}H-NMR ($CDCl_3$): δ = 1.98 (m, 1H, 15α-H); 2.30-2.85 (m, 4H, 15β-H, 16β-H, 16α-H, 10α-H); 2.53 (s, 3H,

NCH_3); 3.42 (d, $J_{10\beta,10\alpha}$ = 17.8 Hz, 1H, 10β-H); 3.82 (s, 3H, 3-OCH_3); 4.48 (d, $J_{9,10\alpha}$ = 6.72 Hz, 1H, 9α-H); 4.88 (d, $J_{5\beta,6}$ = 4.39 Hz, 1H, 5β-H); 5.18 (dd, 1H, 6-H); 5.82 (d, $J_{19,18}$ = 8.42 Hz, 1H, 19-H); 6.08 (dd, 1H, 18-H); 6.62 (d, 1H, 1-H); 6.72 (d, 1H, 2-H); 7.25-7.50 (m, 5H, NPh). – ^{13}C-NMR: δ = 23.22 (C-10); 32.62 (C-15); 42.57 (NCH_3); 44.84 (C-13); 46.05 (C-16); 54.64 (C-6); 54.64 (6-OCH_3); 56.44 (3-OCH_3); 57.07 (C-9); 63.43 (C-14); 86.55 (C-5); 114.27 (C-2); 120.33 (C-1); 123.24 (C-18); 126.71 (C-11); 131.08 (C-12); 134.61 (C-19); 142.30 (C-3); 147.81 (C-4); others: aromatic: 125.49 (2); 128.86 (2); 128.13 (1); 131.27 (q); C=O: 155.15; 156.39. – MS (EI-70 eV) m/z: 456 (30) [M^+], 280(100) – $[\alpha]_D^{25}$ = - 71.8 (c =1, $CHCl_3$). – IR (KBr) [cm^{-1}]: ν_{CO} 1771, 1716. – $C_{26}H_{24}N_4O_4$ (456.5). – Calcd.: C: 68.41; H: 5.30; N: 12.27; Found: C: 68.41; H: 5.22; N: 12.18.

The reaction of β*-dihydrothebaine with PTAD. Preparation of* **5a** *and* 7: To a stirred solution of of β-dihydrothebaine[10] (**2a**; 2 g; 6.4 mmol) in acetone (120 ml) a solution of PTAD (1.4 g; 8 mmol) in acetone (12 ml) was dropwise added at room temperature over a period of 20 minutes. The resulting dark solution was stirred at room temperature for 1.5 hours, when TLC showed that all of the starting material had reacted. The solvent was distilled off at diminished pressure, the residue was subjected to column chromatography ([D]) and the separated products were triturated with ether. *Fraction 1* (**5a**): 1.36 g (43%) – Mp. 150-151 °C. – R_{fA} = 0.88; R_{fB} = 0.76; R_{fC} = 0.88; R_{fD} = 0.85. – ^{1}H-NMR ($CDCl_3$): δ = 1.65-1.90 (m, 3H, 5β-H, 15α-H, 15β-H); 2.08 (m, 1H, 16β-H); 2.35 (m, 1H, 16α-H); 2.42 (s, 3H, NCH_3); 3.08 (d, $J_{10\beta,10\alpha}$ = 18.5 Hz, 1H, 10β-H); 3.50 (d, 1H, 5α-H); 3.56 (dd, 1H, 10α-H); 3.70 (s, 3H, 6-OCH_3); 3.87 (s, 3H, 3-OCH_3); 4.15 (d, $J_{9,10\alpha}$ = 4.9 Hz, 1H, 9α-H); 6.07 (s[a], 1H, 4-OH); 6.33 (d, $J_{18,19}$ = 8.35 Hz, 1H, 18-H); 6.70 (d, $J_{19,18}$ = 8.35 Hz, 1H, 19-H); 6.72 (d, 1H, 1-H); 6.78 (d, 1H, 2-H); 7.25-7.50 (m, 5H, N-Ph). – ^{13}C-NMR: δ = 23.42 (C-10); 36.32 (C-15); 39.09 (C-13); 39.60 (C-5); 42.91 (NCH_3); 46.70 (C-16); 52.76 (6-OCH_3); 55.75 (C-9); 56.15 (3-OCH_3); 64.44 (C-14); 93.89 (C-6); 109.33 (C-2); 118.12 (C-1); 125.23 (C-12); 129.61 (C-18); 130.94 (C-11); 132.27 (C-19); 143.24 (C-3); 144.73 (C-4); others: aromatic: 125.84 (2); 128.79 (2); 128.04 (1); 131.32 (q); C=O: 154.06; 156.01. – $[\alpha]_D^{25}$ = + 62.7 (c = 1, $CHCl_3$) – IR (KBr) [cm^{-1}]: ν_{CO} 1767, 1713. – MS (EI - 70 eV) m/z : 488 (3) [M^+], 312 (100). – $C_{27}H_{28}N_4O_5$ (488.5). – Calcd.: C: 66.38; H: 5.78; N: 11.47; Found: C: 66.28; H: 5.75; N: 11.38.

Fraction 2 (7): 0.74 g (23 %) – Mp. 216-217 °C. – R_{fA} = 0.46; R_{fB} = 0.55; R_{fC} = 0.06; R_{fD} = 0.14. – ^{1}H-NMR (polysol): δ = 1.60-1.95 (m, 3H, 5α-H, 15α-H, 15β-H); 2.09 (m, 1H, 16β-H); 2.40 (m, 1H, 16α-H); 2.43 (s, 3H, NCH_3); 3.12 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 3.40 (m, 2H, 5β-H, 10α-H); 3.63 (s, 3H, 6-

OCH_3); 3.88 (s, 3H, 3-OCH_3); 4.18 (d, $J_{9,10\alpha}$ = 4.5 Hz, 1H, 9α-H); 6.33 (d, $J_{18,19}$ = 8.34 Hz, 1H, 18-H); 6.73 (d, $J_{19,18}$ = 6.38 Hz, 1H, 19-H); 7.02 (s, 1H, 2-H); 7.20-7.60 (m, 10H, 2xN-Ph); 9.02 (s[a], 1H, NH). – ^{13}C-NMR: δ = 19.32 (C-10); 35.53 (C-15); 39.02 (C-13); 39.79 (C-5); 42.71 (NCH_3); 46.40 (C-16); 52.41 (6-OCH_3); 54.90 (C-9); 56.16 (3-OCH_3); 63.96 (C-14); 93.76 (C-6); 109.28 (C-2); 126.38 (C-1); 123.42 (C-12); 129.49 (C-11); 129.56 (C-18); 132.99 (C-19); 145.01 (C-3); 146.14 (C-4); others: aromatic: 125.92 (2); 128.99 (2); 128.83 (4); 127.89 (1); 128.26 (1); 131.03 (q); 131.72 (q); C=O: 150.41; 152.40; 153.64; 155.41. – $[\alpha]_D^{25}$ = - 35.2 (c = 1, $CHCl_3$) – IR (KBr) [cm^{-1}]: ν_{CO} 1771, 1715. – MS (TSP) m/z: 487 (100), [M^+] could not be detected; MS (ESI) m/z: 664 $[M+1]^+$. – $C_{35}H_{33}N_7O_7$ (663.6). – Calcd.: C: 63.34; H: 5.01; N: 14.77; Found: C: 63.26; H: 4.93; N: 14.50.

The reaction of 4-acetoxy-β-dihydrothebaine (**2b**) *with PTAD. Preparation of* **5b** *and* **7**: To a stirred solution of 4-acetoxy-β-dihydrothebaine[11] (**2b**; 4.0 g; 11.2 mmol) in acetone (220 ml) a solution of PTAD (2.2 g; 12.5 mmol) in acetone (20 ml) was dropwise added over a period of 20 minutes. The reaction mixture was stirred at room temperature for 1.5 hours, the solvent was distilled off under reduced pressure and the residue was crystallized from ethanol. The crystalline product was filtered off and washed with a small volume of cold ethanol and ether to obtain 4.0 g (67%) of pale yellow **5b**, mp. 194-196 °C. – R_{fA} = 0.82; R_{fB} = 0.91; R_{fC} = 0.88. – ^{1}H-NMR ($CDCl_3$): δ = 1.58 (m, 1H, 15α-H); 1.72 (d, 1H, 5β-H); 1.82 (ddd, 1H, 15β-H); 2.10 (ddd, 1H, 16β-H); 2.33 (s, 3H, 4-$OCOCH_3$); 2.42 (s, 3H, NCH_3); 3.10 (d, $J_{10\beta,10\alpha}$ = 18.6 Hz, 1H, 10β-H); 3.20 (m, 1H, 5α-H); 3.58 (dd, 1H, 10α-H); 3.68 (s, 3H, 6-OCH_3); 3.81 (s, 3H, 3-OCH_3); 4.16 (d, $J_{9,10\alpha}$ = 5.1 Hz, 1H, 9α-H); 6.33 (d, $J_{18,19}$ = 8.4 Hz, 1H, 18-H); 6.70 (d, $J_{19,18}$ = 8.4 Hz, 1H, 19-H); 6.88 (d, $J_{1,2}$ = 8.46 Hz, 1H, 1-H); 7.07 (d, 1H, 2-H); 7.25-7.50 (m, 5H, N-Ph). – ^{13}C-NMR: δ = 23.49 (C-10); 37.39 (C-15); 39.36 (C-13); 40.23 (C-5); 42.86 (NCH_3); 46.41 (C-16); 52.81 (6-OCH_3); 55.57 (C-9); 56.12 (3-OCH_3); 64.15 (C-14); 93.15 (C-6); 111.13 (C-2); 125.25 (C-1); 129.47 (C-18); 130.52 (C-12); 132.77 (C-11); 133.39 (C-19); 138.21 (C-3); 149.54 (C-4); others: aromatic: 125.91 (2); 128.86 (2); 128.16 (1); 131.14 (q); C=O: 153.88; 155.90; 168.71. – $[\alpha]_D^{25}$ = + 86.7 (c = 1, $CHCl_3$). – IR (KBr) [cm^{-1}]: ν_{CO} 1768, 1716 – MS (TSP) m/z : 531 (4) $[M+1]^+$, 372 (25), 354 (100). – $C_{29}H_{30}N_4O_6$ (530.5). – Calcd.: C: 65.65; H: 5.70; N: 10.56; Found: C: 65.60; H: 5.71; N:10.48.

The produced by-product remained in the mother liquor, and after column chromatography ([D]) 0.2 g (3%) of **5b** and 0.4 g (7%) of **7** were isolated.

The PTAD adduct (**6a**) *of 7-chloro-6-demethoxythebaine*: The reaction of 7-chloro-6--demethoxythebaine[12] (**3a**, 2.50 g; 7.9 mmol) and PTAD (1.5 g; 8.5 mmol) in acetone (40 ml) for 20 min was carried out as described above for **5b** to obtain 2.47 g (64%) of **6a**, mp., 245-249 °C [acetone]. – R_{fA} = 0.86; R_{fB} = 0.96; R_{fC} = 0.91. – ^{1}H-NMR ($CDCl_3$): δ = 2.02 (m, 1H, 15α-H); 2.30-2.85 (m, 4H, 15β-H, 16β-H, 16α-H, 10α-H); 2.53 (s, 3H, NCH_3); 3.42 (d, $J_{10\beta,10\alpha}$ = 18.86 Hz, 1H, 10β-H); 3.83 (s, 3H, 3-OCH_3); 4.47 (d, $J_{9,10\alpha}$ = 6.77 Hz, 1H, 9α-H); 4.92 (d, $J_{5\beta,6}$ = 4.21 Hz, 1H, 5β-H); 5.25 (dd, 1H, 6-H); 5.75 (d, 1H, 19-H); 6.65 (d, 1H, 1-H); 6.76 (d, 1H, 2-H); 7.28-7.52 (m, 5H, NPh). – MS (EI-70 eV) m/z: 490 (30) [M^+], 314 (45). – $C_{26}H_{23}N_4O_4Cl$ (490.9). – Calcd.: C 63.61; H: 4.72; N: 11.41; Found: C: 63.54; H: 4.68; N: 11.45.

The PTAD adduct (**6b**) *of 7-bromo-6-demethoxythebaine*: The reaction of 7-bromo-6--demethoxythebaine[12] (**3b**, 2.10 g; 5.8 mmol) and PTAD (1.5 g; 8.5 mmol) in acetone (70 ml) for 20 min was carried out as described above for **5b** to obtain 1.39 g (45 %) of **6b**, mp., 259-261°C [acetone]. – R_{fA} = 0.86; R_{fB} = 0.96; R_{fC} = 0.91. – ^{1}H-NMR ($CDCl_3$): δ = 2.02 (m, 1H, 15α-H); 2.30-2.85 (m, 4H, 15β-H, 16β-H, 16α-H, 10α-H); 2.52 (s, 3H, NCH_3); 3.43 (d, $J_{10\beta,10\alpha}$ = 19.8 Hz, 1H, 10β-H); 3.87 (s, 3H, 3-OCH_3); 4.47 (d, $J_{9,10\alpha}$ = 5.41 Hz, 1H, 9α-H); 4.93 (d, $J_{5\beta,6}$ = 4 Hz, 1H, 5β-H); 5.34 (dd, 1H, 6-H); 5.97 (d, 1H, 19-H); 6.63 (d, 1H, 1-H); 6.77 (d, 1H, 2-H); 7.30-7.50 (m, 5H, NPh). – MS (EI-70 eV) m/z: 534 (34) [M^+], 360 (95), 119 (100). – $C_{26}H_{23}N_4O_4Br$ (534.1). – Calcd.: C: 58.42; H: 4.34; N: 10.49; Found: C: 58.35; H: 4.36; N: 10.53.

The reaction of N-demethyl-N-formylthebaine with DEAD. Preparation of **8**: A mixture of *N*-demethyl-*N*-formylthebaine[8] (**1b**, 5.4 g; 16.5 mmol) and DEAD (5.4 ml; 34.7 mmol) in toluene (52 ml) was boiled under reflux for 5 hours. The solvent was distilled off under diminished pressure and the resulting syrupy residue was triturated with ether to yield 7.8 g (94%) of pale yellow, crystalline **8**, mp. 203-204 °C. – R_{fA} = 0.71; R_{fB} = 0.82; R_{fC} = 0.91. – ^{1}H-NMR ($CDCl_3$): 1.22 (m, 6H, 2xOCH$_2$<u>CH$_3$</u>); 3.50 (s, 3H, 6-OCH_3); 3.82 (s, 3H, 3-OCH_3); 4.14 (m, 4H, 2xO<u>CH$_2$</u>CH$_3$); 4.92 (d, J = 1.2 Hz, 5β-H); 5.63 (d, J = 5.3 Hz, 1H, 9α-H); 6.05 (m, 2H, 19-H, 18-H); 6.60 (d, J = 8 Hz, 1H, 1-H); 6.73 (d, 1H, 2-H); 8.27 (s, 1H, CHO). – MS (EI - 70 eV) m/z: 499 (12) [M^+], 325 (35), 267 (100). – $[\alpha]_D^{25}$ = - 177.6 (c = 1, $CHCl_3$) – IR (KBr) [cm^{-1}]: ν 1746, 1711, 1657. – $C_{25}H_{29}N_3O_8$ (499.5). – Calcd.: C: 60.11; H: 5.85; N: 8.41; Found: C: 60.03; H: 5.84; N: 8.59.

The retro Diels-Alder reactions and rearrangements of 4a and 4b

A: A mixture of **4a** (4 g; 8.2 mmol) and collidine (40 ml) was refluxed for 7 hour: during this time all of the starting compound had reacted. Collidine was removed by distillation under diminsihed pressure and the resulting two-component product mixture was separated by column chromatography ([D]).

Fraction 1 (**10**): 1.8 g (46 %) – Mp.: 282-283 °C [EtOH] (Lit.[25] mp.: 275-279 °C [CH_2Cl_2-hexane]) – R_{fD} = 0.72. – ^{1}H-NMR ($CDCl_3$): 2.55 (s, 3H, NCH_3); 3.34 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 3.82 (s, 3H, 3-OCH_3); 4.05 (d, $J_{9,10\alpha}$ = 6 Hz, 1H, 9α-H); 5.35 (d, $J_{5,7}$ = 1.5 Hz, 1H, 5β-H); 5.78 (s[a], 1H, 4-OH); 6.12 (dd, $J_{7,8}$ = 9.6 Hz, $J_{7,5}$ = 1.5 Hz, 1H, 7-H); 6.64 (d, 1H, 1-H); 6.72 (d, 1H, 2-H); 6.87 (d, $J_{8,7}$ = 9.6 Hz); 7.31-7.45 (m, 5H, N-Ph). – IR (KBr) [cm^{-1}]: ν 1775, 1724, 1689. – MS (EI-70 eV) m/z: 472 (45) [M^+], 230(100) – $C_{26}H_{24}N_4O_5$ (472.5).

Fraction 2 (**1a**): 0.75 g (30%) – Mp. 190-191 °C [EtOH], (lit. 193-194 °C [EtOH], R_{fD} = 0.24 – on the basis of ^{1}H-NMR is thebaine.

B: A mixture of **4a** (9 g; 18.5 mmol), fused K_2CO_3 (4.5 g) and abs. *N,N*-dimethyl formamide (50 ml) was stirred on a 100 °C oil bath for 6 hours. The inorganic salts were filtered off, the solvent was distilled off under diminished pressure, the residue was suspended in water, alkalized with a small volume of aqueous ammonia and extracted with a 8:2 (v/v) mixture of chloroform and ethanol. After drying (Na_2SO_4) the solvents were evaporated and the residue was crystallized from ethanol to obtain 1.9 g of **1a**. Column chromatography of the mother liquor gave a second corp of thebaine (1.7 g). Yield: 3.6 g (63 %).

C: A mixture of **4a** (2 g; 4.1 mmol), diethyl amine (5 ml) and ethanol (100 ml) was refluxed for 6 hours. The solvent was then distilled off *in vacuo* and the residue was crystallized from ethanol to give pure **10** (1.35 g; 69 %) as the product.

D: To a solution of **4a** (1.94 g; 4 mmol) in acetonitrile (30 ml) 0.57 ml of MTBD was added at room temperature and the mixture was boiled under reflux for 8 hours. The solvent was removed under diminished pressure, the residue was dissolved in chloroform (50 ml) and the solution was washed with 5% aqueous NH_4Cl and then with saturated NaCl. The organic layer was dried over Na_2SO_4, concentrated, and the residue was purified by means of column chromatography ([D]) to obtain 0.8 g (64%) of thebaine (**1a**).

E: A solution of **4a** (2.0 g; 4.1 mmol) in 2N KOH in 95% ethanol (187 ml) was stirred in a stream of N_2 at 60 °C. After 10 min all of the starting material had reacted and the solvent was removed under diminished pressure. A small volume of water was added to the residue and then extracted with chloroform, the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by means of column chromatography ([D]) to furnish 1.15 g (60%) of **11a** as a pale yellow syrup, which was triturated with ether, mp. 148-150 °C – R_{fA} = 0.33; R_{fB} = 0.37; R_{fC} = 0.61. – ^{1}H-NMR($CDCl_3$): δ = 2.32-2.78 (m, 4H, 16α-H, 16β-H, 15α-H, 15β-H); 2.46 (s, 3H, N-CH_3); 2.95 (dd, $J_{10\alpha,10\beta}$ = 18 Hz, $J_{10\alpha,9}$ = 6 Hz, 1H, 10α-H); 3.34 (d, $J_{10\beta,10\alpha}$ = 18 Hz, 1H, 10β-H); 3.58 (d, $J_{9,10\alpha}$ = 6 Hz, 1H, 9H); 3.67 (s, 3H, 6-OCH_3); 3.80 (s, 3H, 3-OCH_3); 5.33 (d, $J_{7,8}$ = 6.6 Hz, 1H, 7-H); 5.77 (d, 1H, 8-H); 6.25 (s[a], 1H, 4-OH); 6.57 (d, $J_{1,2}$ = 8.4 Hz, 1H, 1-H); 6.71 (d, 1H, 2-H); 6.98-7.56 (m, 5H, NPh); 8.30 (s[a], 1H, NH); 9.85 (s[a], 1H, NH). – ^{13}C-NMR: δ = 31.09 (C-10); 34.44 (C-15); 41.55 (NCH_3); 45.68 (C-16); 47.26 (C-13); 55.06 (6-OCH_3); 56.00 (3-OCH_3); 60.36 (C-9); 101.92 (C-7); 109.35 (C-2); 114.12 (C-8); 118.26 (C-1); 125.28 (C-12); 130.55 (C-11); 137.95 (C-14); 143.70 (C-5); 144.35 (C-4); 144.83 (C-3); 149.63 (C-6); others: aromatic: 119.21 (2); 122.89 (1); 128.78 (2); 138.14 (q): C=O: 152.86. – MS (TSP) m/z: 461 (70) $[M+1]^+$; EI (70 eV) m/z: 341 (22), 326 (8), 301 (100). – IR (KBr) [cm^{-1}]: ν 1698, 1602, 1590. – $C_{26}H_{28}N_4O_4$ (460.5). – Calcd.: C: 67.81; H: 6.13; N: 12.17; Found: C: 67.64; H: 6.11; N: 11.97.

Similar treatment (**E**) of **4c** (0.6 g; 1.3 mmol) gave 0.35 g (61%) of **11b**, mp. 233-235 °C [ether] – R_{fA} = 0.32; R_{fB} = 0.41; R_{fC} = 0.37. – ^{1}H-NMR($CDCl_3$): δ = 2.25-2.80 (m, 4H, 16α-H, 16β-H, 15α-H, 15β-H); 2.46 (s, 3H, N-CH_3); 3.00 (dd, $J_{10\alpha,10\beta}$ = 18.4 Hz, $J_{10\alpha,9}$ = 6.5 Hz, 1H, 10α-H); 3.35 (d, $J_{10\beta,10\alpha}$ = 18.4 Hz, 1H, 10β-H); 3.60 (d, $J_{9,10\alpha}$ = 6 Hz, 1H, 9H); 3.81 (s, 3H, 3-OCH_3); 5.95 (d, $J_{6,7}$ = 5.64 Hz, 1H, 6-H); 6.26 (m, 1H, 7-H); 6.51 (d, $J_{8,7}$ = 9.7 Hz, 1H, 8-H); 6.64 (s[a], 1H, 4-OH); 6.58 (d, $J_{1,2}$ = 8.24 Hz, 1H, 1-H); 6.71 (d, 1H, 2-H); 6.97-7.58 (m, 5H, NPh); 8.28 (s[a], 1H, NH); 8.92 (s[a], 1H, NH). – ^{13}C-NMR: δ = 32.79 (C-10); 34.34 (C-15); 41.92 (NCH_3); 45.94 (C-13); 46.17 (C-16); 56.13 (3-OCH_3); 60.91 (C-9); 101.70 (C-2); 114.53 (C-8); 115.63 (C-7); 118.54 (C-1); 124.99 (C-12); 130.53 (C-11); 131.72 (C-6); 144.81 (C-4); 145.27 (C-3); 151.27 (C-6); others: aromatic: 119.40 (2); 123.12 (1); 128.86 (2); 138.19 (q): C=O: 153.57. – MS (TSP) m/z: 431 (100) $[M+1]^+$ – $C_{25}H_{26}N_4O_3$ (430.5). – Calcd.: C: 69.75; H: 6.09; N: 13.01; Found: C: 69.67; H: 6.12; N: 12.95.

The reaction of **11a** *with methyl vinyl ketone:* A mixture of **11a** (0.4 g; 0.86 mmol) and methyl vinyl ketone (4 ml) was boiled under reflux for 1 hour. The excess of the reagent was distilled off under diminished pressure and the residue was purified by means of column chromatography ([B]). The resulting syrup was triturated with hexane to afford pure crystalline **12** (0.28 g; 60%). – Mp. 99-101 °C – R_{fA} = 0.73; R_{fB} = 0.74; R_{fC} = 0.87. – ^{1}H-NMR ($CDCl_3$): δ = 1.65 (dd, $J_{8\alpha,8\beta}$ = 12.6 Hz, $J_{8\alpha,7\beta}$ = 3.6 Hz, 8α-H); 2.24 (s, 3H, NCH_3); 2.36 (s, 3H, 7α-Ac); 2.68 (m, 1H, 8β-H); 2.98 (dd, $J_{10\alpha,10\beta}$ = 17.3 Hz, $J_{10\alpha,9}$ = 6 Hz, 1H, 10α-H); 3.08 (d, $J_{9,10\alpha}$ = 6 Hz, 1H, 9α-H); 3.22 (d, $J_{10\beta,10\alpha}$ = 17.3 Hz, 1H, 10β-H); 3.36 (m, 1H, 7β-H); 3.46 (s, 3H, 6-OCH_3); 3.81 (s, 3H, 3-OCH_3); 5.90 (d, $J_{18,19}$ = 8.2 Hz, 1H, 18-H); 6.23 (d, 1H, 19-H); 6.53 (s[a], 1H, 4-OH); 6.63 (d, 1H, 1-H); 6.73 (d, 1H, 2-H); 7.00-7.57 (m, 5H, N-Ph); 8.25 (s[a], 1H, NH); 10.30 (s[a], 1H, NH). – MS (TSP) m/z: 531 (100) $[M+1]^+$ – $C_{30}H_{34}N_4O_5$ (530.6). – Calcd.: C: 67.91; H: 6.46; N: 10.56; Found: C: 67.83; H: 6.42; N: 10.51.

Retro Diels-Alder reaction of **4b**: A mixture of **4b** (1 g; 2 mmol), fused K_2CO_3 (0.5 g) and abs. *N,N*-dimethyl formamide (20 ml) was reacted as described above in method **B**. The crude product was crystallized from ethanol to give 0.4 g (61%) of pure **1b**.

Acknowledgements:

This work was supported, in part, by grants (*OTKA I/3 reg. No.: 1722 and T 013991*) obtained from the National Science Foundation (Budapest, Hungary).

The authors thank *Mrs. Julianna Nagy* and *Mrs. Julianna Kabai* for their technical assistance and *Dr. JózsefJekő* for measuring the mass spectra.

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data for **3b** E_{HOMO} = - 8.7005 E_{LUMO} = - 0.3615 C-6: - 0.141 C-7: - 0.140 C-8: - 0.118 C-14: - 0.100; data for PTAD E_{HOMO} = -9.5252 E_{LUMO} = -1.838

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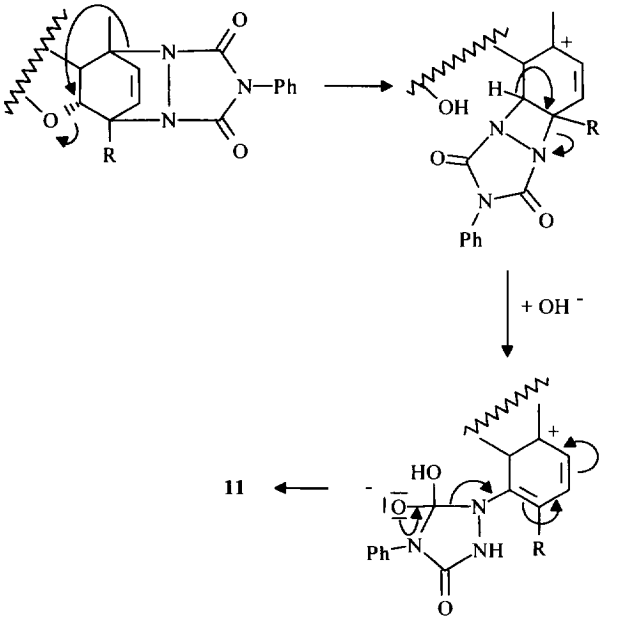
The authors are grateful to a referee for the reaction mechanism proposed for the formation of **11**.



(*Received in UK* 25 *September* 1995; *revised* 4 *December* 1995; *accepted* 7 *December* 1995)