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Syntheses and Transformations of Novel Nitrogen and Sulfur Containing Morphinanedienes

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Summary. The synthesis of 6-azido-6-demethoxythebaine (**10**) has been performed starting from thebaine (**1**). Compound **10** undergoes a cycloaddition reaction with the azadienophile *PTAD* to form bridgehead azide **14**. The acid catalyzed rearrangement of isothiocyanato diene **11** obtained from azido diene **10** and thiocyanato dienes **8** and **9** leads to sulfur containing derivatives of apocodeine (**17–20**).

Keywords. 6-Azido-6-demethoxythebaine; *Diels-Alder* reaction; 6-Izothiocyanato-6-demethoxythebaine; 3-Mercaptoapocodeine.

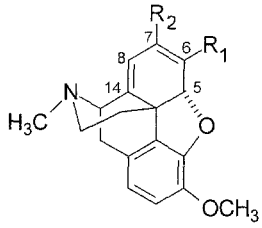
Darstellung und Reaktionen stickstoff- und schwefelhaltiger Morphinandiene

Zusammenfassung. 6-Azido-6-demethoxythebain (**10**) wurde ausgehend von Thebain (**1**) hergestellt. Verbindung **10** wurde in einer Cycloadditionsreaktion mit dem Azadienophil *PTAD* zum Brückenkopfazid **14** umgesetzt. Das aus dem Azidodien **10** erhältliche Isothiocyanatodien **11** und die bereits früher gewonnenen Thiocyanatodiene **8** und **9** liefern bei säurekatalysierter Umlagerung die Apokodeinderivate **17–20**.

Introduction

In recent years, increasing attention has been devoted to the alkaloids of poppy since they serve as an unexhaustable source with respect to the preparation of numerous semisynthetic derivatives of great biological relevance [1]. In this field, thebaine (**1**) with its dienoid structure is regarded as a classical starting material, since it can be transformed in various ways due to its considerable reactivity. The synthesis of several highly efficient opiate receptor agonists and antagonists might be launched by employing either addition reaction (*e.g.* naloxone, naltrexone) [2] or cycloaddition reaction (*e.g.* etorphine, buprenorphine) [3] of thebaine. Yet, the acid catalyzed rearrangement reactions of thebaine make it possible to attain the semisynthesis of various effective and selective 2-substituted apomorphine derivatives [4].

In previous years, we have produced 6-demethoxythebaine (**2**) [5] as well as some of its halogene substituted (**3–7**) [6–8] and thiocyanato substituted (**8, 9**) [9]



	R_1	R_2	Ref.
1	OCH_3	H	
2	H	H	[5]
3	F	H	[8,11]
4	Cl	H	[6]
5	Br	H	[6]
6	H	Cl	[7]
7	H	Br	[7]
8	SCN	H	[9]
9	H	SCN	[9]
10	N_3	H	
11	NCS	H	

Fig. 1

derivatives, respectively. The major characteristics of the dienes mentioned above involve the feasibility of *Diels-Alder* reactions producing novel and effective bridged compounds [10]. By investigation of their acid catalyzed rearrangement reaction, new synthetic methods might be elaborated to prepare 2-halogene substituted apomorphines [8, 11].

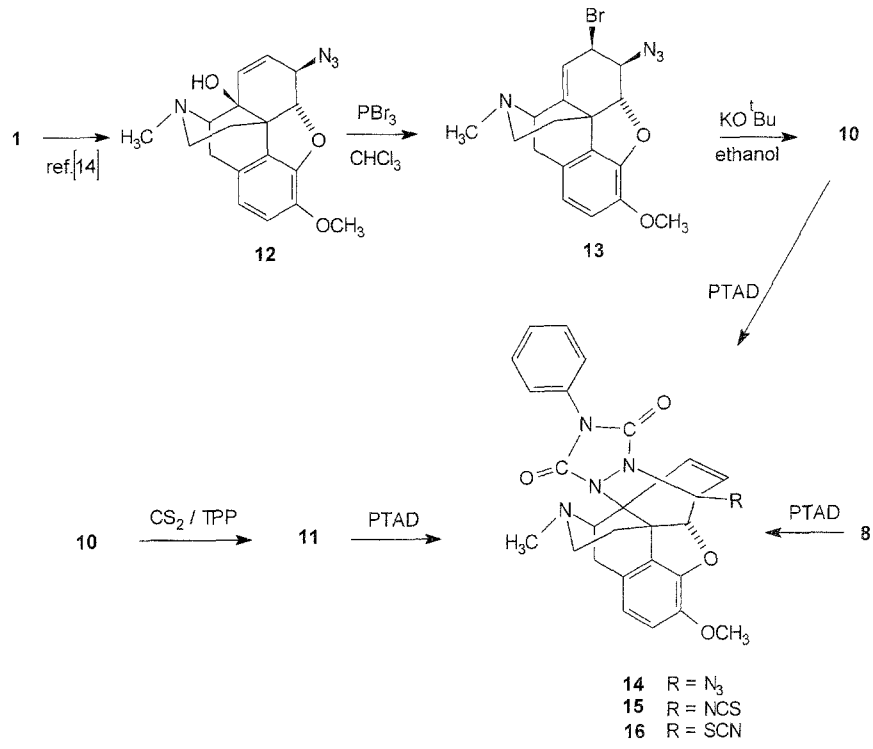
We have reported on the preparation of azidomorphines, as they are called, for nearly 25 years [12], and observed that in case of morphine derivatives azidolysis of the C-6 hydroxy group resulted in a definite alteration of the biological action. Throughout the last decades, the pharmacophoric features of the azido group have been confirmed by applying various other therapeutic agents as well [13].

For these reasons, we set out for the production of novel azido derivatives among the ring C bridged compounds with morphine and aporphine skeletone, respectively. In this paper we report on the synthesis of 6-azido-6-demethoxy-thebaine (**10**) as well as on the cycloaddition and acid catalyzed rearrangement reaction of some nitrogen and sulfur containing morphinanedienes.

Results and Discussion

For the preparation of the diene **10**, we used 6β-azido-14β-hydroxydeoxycodeine (**12**) prepared from thebaine (**1**) [14] as starting material. Compound **12** has been converted at the first stage into 6β-azido-7β-bromodeoxyneopine (**13**) with phosphorus tribromide. In this compound, the 7β-bromo and 6α-hydrogen moities are situated *trans*-diaxial to one another; therefore, the elimination of hydrogene bromide is so favourable that it occurs even upon storage at room temperature. The elimination proceeds to completion in ethanol with potassium *tert*-butoxide upon stirring at room temperature for 30 minutes, and 6-azido-6-demethoxythebaine (**10**) could be isolated in crystalline form.

Diene **10** (as characteristic for vinylazides [15]) is unstable; within some days at room temperature, it decomposes virtually entirely. It may be stored, however, at $-20°C$ without danger of disintegration. The structure of the compound was evidenced by its ^1H NMR (signals between 5.4 and 6.7 ppm characteristic for 6-substituted dienes) and IR spectra (sharp, intense peak at 2096 cm^{-1}). **10** decomposes in concentrated acidic medium under vigorous evolution of N_2. Both thermal (boiling in benzene) and acidic (adding methanesulfonic acid at room temperature) decomposition gave rise to multicomponent reaction mixtures



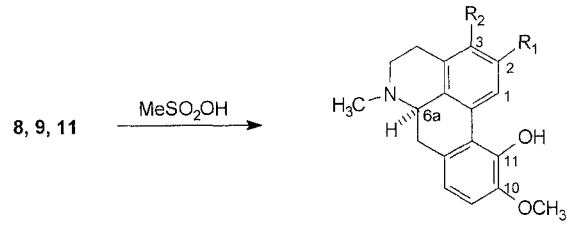
Scheme 1

consisting of not isolable products. In the course of acidic decomposition, not even traces of compounds with an aporphine skeletone could be observed.

The cycloaddition reaction of diene **10** with methyl vinyl ketone did not lead to isolable addition compounds at 80°C due to thermolability. Thus, a highly reactive aza dienophile was selected as a reactant: 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (*PTAD*). *PTAD* affords a *Diels-Alder* adduct with thebaine (**1**) even at low temperature [16]. In our case, *PTAD* reacted readily with **10**, and at 0°C the bridgehead azide **14** was produced in excellent yield.

The structure of diene **10** was supported by distinctive chemical transformation. In carbon disulfide in the presence of triphenylphosphine it produced 6-isothiocyanato-6-demethoxythebaine (**11**) whose IR spectrum shows a broad, intense peak at 2016 cm^{-1}. A further support for the structure of the new diene **11** was provided by the comparison of the IR spectra of the *PTAD* adduct **15** prepared from **11** and the *PTAD* adduct **16** of the already known 6-thiocyanato-6-demethoxythebaine (**8**) [9].

Investigation of the methanesulfonic acid induced rearrangement of the sulfur containing dienes **8**, **9**, and **11** showed that their conversion to the 2- and 3-substituted apocodeine derivatives **17**, **18** and **19** was completed in 20 min at 0°C. The acid catalyzed rearrangement of **8** and **11** under the usual reaction conditions [17] (90°C, 30 min) gave rise to a non-separable multicomponent mixture. On the other hand, 3-mercaptoapocodeine (**20**) was produced from 7-thiocianato diene **9**, indicating that the rearrangement at elevated temperature is accompanied by hydrolysis of the thiocyanato group.



	R_1	R_2
17	NCS	H
18	SCN	H
19	H	SCN
20	H	SH

Scheme 2

Experimental

Commercially available reagents and compounds were purchased from Aldrich. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. All reactions were monitored by TLC on precoated Merck 5554 Kieselgel $40\,F_{254}$ foils using chloroform : methanol (9:1, v/v) as eluent. The spots were visualized with *Dragendorff*'s reagent. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba 1106 analyser. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer; chemical shifts are reported in ppm (δ) from internal *TMS*, coupling constants (J) in Hz. Mass spectra were measured with a VG-7035 (GC-MS-DS) instrument. IR spectra were recorded on a Perkin-Elmer 283B spectrometer. Optical rotations were determined with a Perkin Elmer 311 polarimeter.

7β-Bromo-6β-azidodeoxyneopine (**13**)

To a solution of 6β-azido-14-hydroxydeoxycodeine (**12**, 1 g, 2.9 mmol) in dry chloroform (10 cm^3), phosphorus tribromide (0.6 cm^3, 5.8 mmol) was added dropwise at 0°C with stirring. After completion of the addition the mixture was warmed to 50°C, stirred for 2 h at this temperature, and then cooled to room temperature. Water (10 cm^3) was added dropwise with external cooling, and the mixture was adjusted to *pH* 8 by addition of ammonium hydroxide with continuous stirring and cooling. The organic layer was separated, and the aqueous phase was extracted with chloroform (3×10 cm^3). The combined organic extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. Crystallization of the residue from ethanol afforded *compound* **13**.

Yield: 0.91 g (77.8%); m.p.: > 160°C (decomp.); $C_{18}H_{19}O_2N_4Br$; (found: C 53.73, H 4.68, N, 13.92, Br 20.10; calc.: C 53.61, H 4.75, N 13.89, Br 19.82; ^{1}H NMR (200 MHz, $CDCl_3$): 1.82 (1H, m, C-H), 2.18–2.9 (4H, m, C-H), 2.49 (3H, s, N-Me), 3.3 (1H, d, $J = 18$, 10β-H), 3.47 (1H, dd, 6-H), 3.6 (1H, d, $J = 6$, 9-H), 3.9 (3H, s, O-Me), 4.53 (1H, m, 7-H), 5.0 (1H, d, $J = 8$, 5-H), 5.9 (1H, d, $J = 6$, 8-H), 6.7 (2H, dd, Ar-H).

6-Azido-6-demethoxythebaine (**10**)

A mixture of compound **13** (1 g, 2.5 mmol) and potassium *tert*-butoxid (1 g, 8.9 mmol) in absolute ethanol (50 cm^3) was stirred at room temperature for 0.5 h. The reaction mixture was filtered, concentrated, and the residue was crystallized from diethyl ether to give **10**.

Yield: 0.61 g (75.7%); $C_{18}H_{18}O_2N_4$; found: C 66.8, H 5.55, N 17.53; calc.: C 67.06, H 5.03, N 17.38; $[\alpha]_D^{22} = -434.9$ ($c = 0.2$, $CHCl_3$); IR (KBr): $\nu = 2096$ cm^{-1} (N_3); ^{1}H NMR (200 MHz, $CDCl_3$): 1.78 (1H, m, C-H), 2.15–2.35 (1H, m, C-H), 2.5 (3H, s, N-Me), 2.55–2.9 (3H, m, C-H), 3.35

(1H, d, $J = 18, 10\beta$-H), 3.63 (1H, d, $J = 6$, 9-H), 3.9 (3H, s, O-Me), 5.35 (1H, s, 5-H), 5.6 (2H, s, 7-H and 8-H), 6.65 (2H, dd, Ar-H).

6-Isothiocyanato-6-demethoxythebaine (**11**)

6-Azido-6-demethoxythebaine (**10**; 1 g, 3.1 mmol) was dissolved in carbon disulfide (15 cm^3), and triphenylphosphine (0.81 g, 3.1 mmol) was added. The solution was refluxed for 2 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in chloroform : methanol = 9 : 1 (30 cm^3). The non-dissolved triphenylphosphine sulfide was removed by filtration. The filtrate was evaporated to dryness. The product was still contaminated with triphenylphosphine sulfide which was removed by means of column chromatography (Kieselgel 40, chloroform : methanol = 9 : 1). The product was crystallized from diethyl ether to give **11**.

Yield: 0.54 g (51.5%); m.p.: 146–149°C; $C_{19}H_{18}O_2N_2S$; found: C 67.25, H 5.25, N 8.37, S 9.58; calc.: C 67.43, H 5.36, N 8.28, S 9.47; $[\alpha]_D^{22} = -772$ ($c = 0.2$, $CHCl_3$); IR (KBr): $\nu = 2016$ cm^{-1} (NCS); ^{1}H NMR (200 MHz, $CDCl_3$): 1.8 (1H, m, C-H), 2.15–2.35 (1H, m, C-H), 2.45 (3H, s, N-Me), 2.58–3.0 (3H, m, C-H), 3.35 (1H, d, $J = 18, 10\beta$-H), 3.65 (1H, d, $J = 6$, 9-H), 3.95 (3H, s, O-Me), 5.35 (1H, s, 5-H), 5.6 (1H, d, $J = 8$, 8-H), 5.9 (1H, d, $J = 8$, 7-H), 6.65 (2 H, dd, Ar-H); MS: m/z= 338 (M^+, 70%).

Preparation of PTAD adducts **14–16** (*general procedure*)

A mixture of the diene (1.55 mmol) and *PTAD* (0.33 g, 1.86 mmol) was stirred in acetone (20 cm^3) at room temperature for 20 minutes. The reaction mixture was evaporated, then dissolved in acetone ether (1:1) and filtered. The filtrate was evaporated to dryness, and the residue was crystallized from diethyl ether.

PTAD adduct of 6-azido-6-demethoxythebaine (**15**)

From **10**; yellow solid; yield: 0.55 g (71.3%); m.p.: > 210°C (decomp.); $C_{26}H_{23}O_4N_7$; found: C 62.5, H 4.58, N 19.85; calc.: C 62.77, H 4.66, N 19.71; $[\alpha]_D^{22} = -50.5$ ($c = 0.2$, acetone): IR (KBr): $\nu = 2124$ cm^{-1} (N_3); ^{1}H NMR (200 MHz, $CDCl_3$): 2.05 (1H, m, C-H), 2.3–3.0 (4H, m, C-H), 2.55 (3H, s, N-Me), 3.4 (1H, d, $J = 18, 10\beta$-H), 3.88 (3H, s, O-Me), 4.58 (1H, d, $J = 7, 9\alpha$-H), 4.75 (1H, s, 5-H), 5.88 (2H, dd, 18 and 19-H), 6.7 (2H, dd, Ar-H), 7.3–7.6 (5H, m, AR-H); MS: $m/z = 497$ (M^+, 25%).

PTAD adduct of 6-isothiocyanato-6-demethoxythebaine (**15**)

In the case of **11**, the crystalline product was filtered off after 20 min of stirring and washed with acetone to give **15**. Yield: 0.64 g (80.4%); m.p.: 204–206°C; $C_{27}H_{23}O_4N_5S$; found: C 62.88, H 4.41, N 13.81, S 6.38; calc.: C 63.14, H 4.51, N 13.64, S 6.25; $[\alpha]_D^{22} = -86.5$ ($c = 0.2$, $CHCl_3$); IR (KBr): $\nu = 2016$ cm^{-1} (NCS); ^{1}H NMR (200 MHz, $CDCl_3$): 2.05 (1H, m, C-H), 2.3–2.85 (4H, m, C-H), 2.55 (3H, s, N-Me), 3.45 (1H, d, $J = 18, 10\beta$-H), 3.9 (3H, s, O-Me), 4.6 (1H, d, $J = 6, 9\alpha$-H), 4.8 (1H, s, 5-H), 5.85 (1H, d, $J = 8$, 19-H), 6.05 (1H, d, $J = 8$, 18-H), 6.7 (2H, dd, Ar-H), 7.3–7.5 (5H, m, Ar-H).

PTAD adduct of 6-thiocyanato-6-demethoxythebaine (**16**)

From **8**; yellow solid; yield: 0.58 g (72.8%); m.p.: 168–173°C; $C_{27}H_{23}O_4N_5S$; found: C 62.98, H 4.58, N 13.71, S 6.34; calc.: C 63.14, H 4.51, N 13.64, S 6.25; $[\alpha]_D^{22} = -45.9$($c = 0.16$, acetone); IR (KBr): $\nu = 2160$ cm^{-1} (SCN); ^{1}H NMR (200 MHz, $CDCl_3$): 1.9 (1H, m, C-H), 2.2 (3H, s, N-Me),

2.4–3.0 (4H, m, C-H), 3.5 (1H, m, C-H), 3.9 (3H, s, O-Me), 4.7 (1H, d, 9α-H), 4.8 (1H, d, 5-H), 6.05 (2H, dd, 18 and 19-H), 6.7 (2H, dd, Ar-H), 7.3–7.6 (5H, m, Ar-H).

Rearrangement of morphinanedienes **8**, **9**, and **11** in methanesulfonic acid (general procedure)

A mixture of the diene (1.48 mmol) and methanesulfonic acid (5 cm^3) was stirred for 20 min at 0°C. Then the reaction mixture was added dropwise, with stirring and external ice-cooling, to a solution of potassium hydrogen carbonate (10 g) in water (50 cm^3). After extraction with chloroform (3 × 15 cm^3), the combined extracts were washed with a saturated brine, dried ($MgSO_4$), and concentrated. The residue was submitted to purification by means of column chromatography (Kieselgel 40, hexane : dichloromethane : methanol = 8:2:1)

2-Thiocyanatoapocodeine (**17**)

From diene **8**; crystalline product; yield: 0.18 g (36%); m.p.: 86–88°C; $C_{19}H_{18}O_2N_2S$; found: C 66.98, H 5.54, N 7.82, S 10.05; calc.: C 67.43, H 5.36, N 8.28, S 9.47; $[\alpha]_D^{22} = -152$ ($c = 0.12$, $CHCl_3$); IR (KBr): $\nu = 2154\,cm^{-1}$ (SCN); ^1H NMR (200 MHz, $CDCl_3$): 2.55 (3H, s, N-Me), 2.7–3.4 (6H, m, C-H), 3.9 (3H, s, O-Me), 6.4 (1H, s, OH), 6.8 (2H, s, 8-H and 9-H), 7.4 (1H, s, 3-H), 8.4 (1H, s, 1-H); MS: $m/z = 338$ (M^+, 80%).

3-Thiocyanatoapocodeine (**18**)

From diene **9**; syrupy product; yield: 0.3 g (60%). **18** was transformed to the hydrochloride salt of the title compound by treatment with HCl in abs. ethanol. M.p.: 229–233°C; $C_{19}H_{18}O_2N_2S{\cdot}HCl$; found: C 60.23, H 4.58, N 7.22, S 8.64; calc.: C 60.86, H 4.83, N 7.47, S 8.55. Base: $[\alpha]_D^{20} = -34$ ($c = 0.1$, $CHCl_3$); IR (KBr): $\nu = 2151\,cm^{-1}$ (SCN); ^1H NMR (200 MHz, $CDCl_3$): 2.5 (3H, s, N-Me), 2.4–2.6 (2H, m, CH), 2.8–3.2 (5H, m, CH), 3.95 (3H, s, O-Me), 6.3 (1H, s, OH), 6.8 (2H, s, 8-H and 9-H), 7.6 (1H, d, $J = 8$, 3-H), 8.4 (1H, d, $J = 8$, 1-H,); MS: $m/z = 338$ (M^+, 80%).

2-Isothiocyanatoapocodeine (**19**)

From diene **11**; syrupy product; yield: 0.18 g (35.9%); **11** was then transformed to the hydrochloride salt of the title compound by treatment with HCl in abs. ethanol. M.p.: 227–230°C; $C_{19}H_{18}O_2N_2S{\cdot}HCl$; found: C 60.53, H 4.92, N 7.55, S 8.71; calc.: C 60.87, H 5.11, N 7.47, S 8.55; $[\alpha]_D^{22} = -179.6$($c = 0.2$, methanol). Base: IR (KBr): $\nu = 2118\,cm^{-1}$ (NCS); ^1H NMR (200 MHz, $CDCl_3$): 2.4–2.8 (3H, m, C-H), 2.55 (3H, s, N-Me), 2.95–3.25 (4H, m, C-H), 3.9 (3H, s, O-Me), 6.5 (1H, s, O-H), 6.8 (2H, s, 8-H and 9-H), 6.9 (1H, d, $J = 1$, 3-H), 8.15 (1H, d, $J = 1$, 1-H); MS: $m/z = 338$ (M^+, 25%).

3-Mercaptoapocodeine (**20**)

7-Thiocyanato-6-demethoxythebaine (**9**, 0.5 g, 1.48 mmol) is dissolved in methanesulfonic acid (5 cm^3) at room temperature, and the solution is kept at 90°C for 30 min. Working up of the reaction mixture, as described above, following chromatographic purification gives 250 mg of a syrupy product which is dissolved in dichloromethane (1 cm^3). The HCl salt of **20** is precipitated by the addition of ethanolic HCl.

Yield: 170 mg (32%); m.p.: 217–222°C; $C_{18}H_{19}O_2NS{\cdot}HCl$; found: C 61.22, H 6.55, N 3.87, S 8.96; calc.: C 61.78, H 5.47, N 4.00, S 9.16. Base: $[\alpha]_D^{20} = 187$ ($c = 0.1$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): 2.5 (3H, s, N-Me), 2.4–2.6 (2H, m, CH), 2.8–3.4 (5H, m, CH), 3.9 (s, 3H, O-Me), 6.4 (1H, s, OH), 6.7 (2H, s, 8-H and 9-H), 7.5 (1H, d, $J = 8$, 3-H), 8.2 (1H, d, $J = 8$, 1-H); MS: $m/z = 313$ (M^+, 80%).

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