Preparation of 7-(1,3,4-Oxadiazolyl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines and Related Compounds as Potential Analgesics

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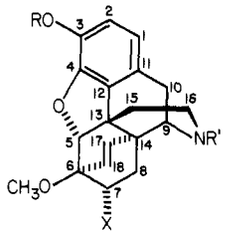
General procedures for the preparation of 7α-(2-substituted-1,3,4-oxadiazol-5-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines are described. Substituents include alkyl, aryl, amino, cycloamino, and alkylthio functions. Many of these and related compounds show analgesic activity intermediate between codeine and morphine in the Hendershot and Forsaith writhing test. An unsuccessful attempt was made to synthesize 7β-(1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine.

Many compounds containing the bridged thebaine (**1**, R = CH_3) or bridged oripavine (**1**, R = H) skeleton are potent analgesics, and the nature of the C-7 substituent has an important bearing on this activity.[1] Recently, we reported the synthesis of 7α-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (**2a**, X = O) and the related thione **2b** (X = S).[2]



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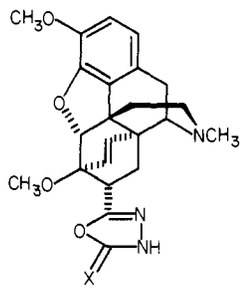
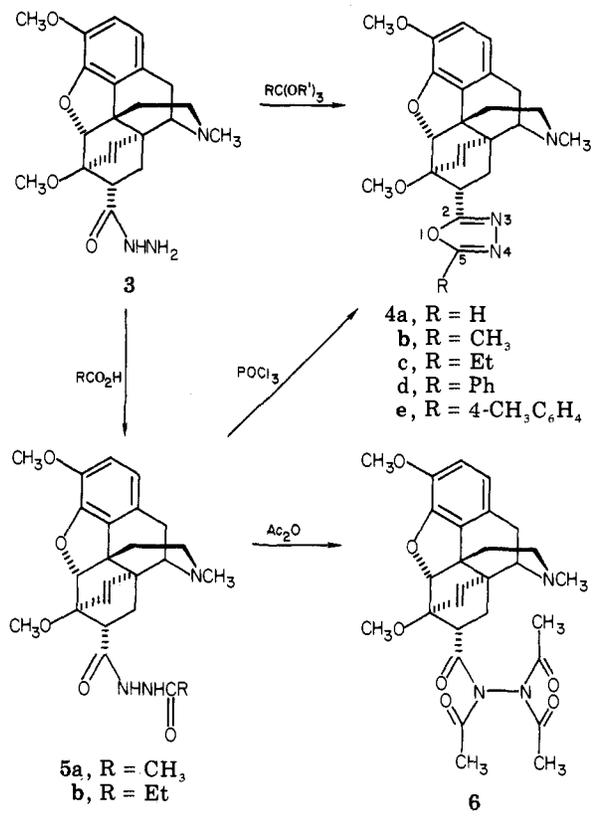


2a, X = O
b, X = S

Prior to our work, one report had appeared in the literature describing bridged thebaines and oripavines with other heterocyclic rings attached at C-7, viz., 5-pyrazolyl, 5-isoxazolyl, and 2- or 4-pyrimidyl, which showed analgesic activity.[3] We therefore wished to develop syntheses of 7-(1,3,4-oxadiazolyl)-6,14-*endo*-ethenotetrahydrothebaines by mild routes that would avoid ring-opening complications, which are the principle problems associated with the chemistry of the bridged thebaine unit,[4] and to study their pharmacology.

Chemistry. (a) 7α Series. The condensation between hydrazides and ortho esters is a relatively mild method for alkyl- or aryl-1,3,4-oxadiazole synthesis.[5] The starting 7α-hydrazide **3** was prepared by a modification of the known procedure[6] using the 7α-methyl ester[7] instead of the 7α-ethyl ester. Heating **3** under reflux in the appropriate ortho ester resulted in the smooth formation of the corresponding oxiadizole **4a–e**. This method is limited by the availability of a series of ortho esters. We therefore examined an alternative approach, namely, the dehydration of *N,N'*-diacylhydrazines[8] for which a variety of reagents, including acetic anhydride,[9] have been used.



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The required starting materials **5a** and **5b** were obtained by refluxing **3** with the relevant carboxylic acid. Subsequently, heating **5a** in acetic anhydride for 4.5 h did not furnish the expected oxadiazole **4b** (mp 204–205 °C). Instead, a crystalline compound (mp 186–187 °C) showing strong carbonyl absorption in the IR (ν_{max} 1725 cm^{-1} with shoulder at 1740 cm^{-1}), but no NH, was isolated. The ^1H NMR showed four methyl resonances (δ 2.37, 6 H; δ 2.41, 3 H; δ 2.48, 3 H) in addition to those of the two methoxy groups; on this evidence we propose the tetraacylhydrazine structure **6**, which is also in accord with the microanalysis and accurate measured mass. Few examples of the conversion of diacylhydrazines into tetraacylhydrazines by this procedure are known.[10] A sample of **4b** from the ortho

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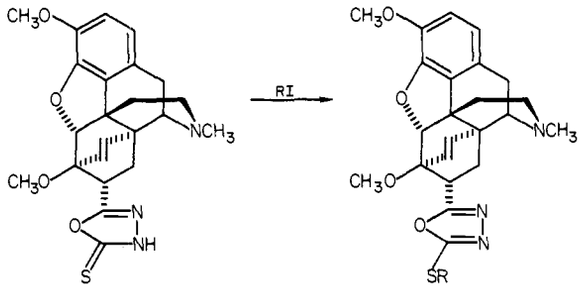
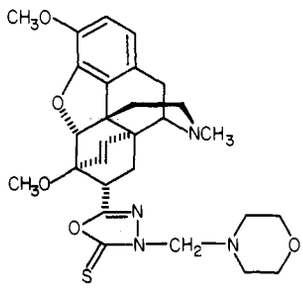
ester route was recovered unchanged after heating under reflux for 48 h in acetic anhydride, thus precluding the possibility of attack on the preformed oxadiazole ring. However, cyclization of **5a** to **4b** was accomplished by the use of phosphorus oxychloride but in only moderate yield (35%).

We also wished to develop routes to oxadiazoles with relatively polar substituents, to permit comparison of analgesic activity with that shown by the alkyl and aryl derivatives 4a–e. The thione **2b**[2] provided a convenient starting point. Three alkylthiooxadiazoles (**7a–c**) were produced smoothly by treatment of **2b** with the appropriate alkyl halide. No products of oxadiazole ring opening were observed, in contrast to the reaction between **2b** and benzyl bromide, which gives[2] the open-chain thiocarbazate 1 (R = R′ = Me, X = $CONHNHCOSCH_2Ph$). Heating **2b** with 1-bromooctane in ethanol for 18 h did not lead to any isolatable products.



2b

7a, R = CH_3
b, R = Et
c, R = $(CH_3)_2CH$



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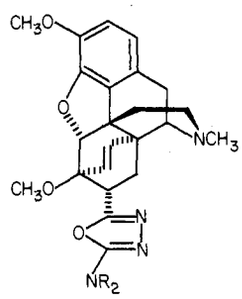
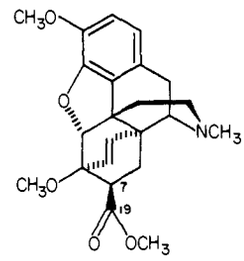


9a, NR_2 = 
b, NR_2 = 
c, NR_2 = 
d, $NR_2 = NH_2$

When **2b** was treated with aqueous formaldehyde and morpholine in ethanol, the Mannich base **8** was formed, though in low yield (20%). Simple oxadiazolones are known to undergo this type of reaction.[11] Assignment of structure **8** and not **7** (R = morpholinomethyl) to this product was supported by the similarity between the UV spectrum in ethanol of **8**, showing λ_{max} 263 nm, and that of starting material **2b**, with λ_{max} 265 nm,[2] which differed significantly from that of **7a**, λ_{max} 286 nm.

The amino derivatives **9a–c** were obtained by displacement of the SCH_3 group in **7a** with the appropriate secondary amine.[12] The parent aminooxadiazole **9d** was formed directly from the hydrazide **3** on treatment with cyanogen bromide.[13]

(b) 7β Series. After isolation of the 7α-methyl ester from the Diels–Alder reaction between thebaine and methyl acrylate, the 7β-methyl ester **10** (8%) was obtained from the mother liquors after column chromatography and fractional crystallization. Treatment of **10** with hydrazine hydrate afforded the 7β-hydrazide **11**.



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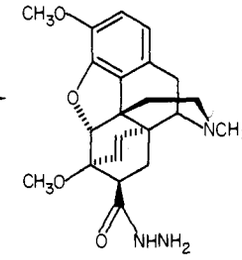

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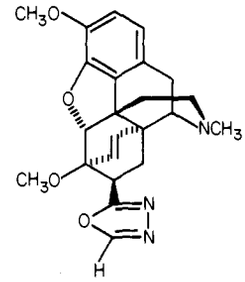

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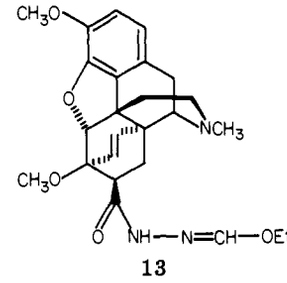

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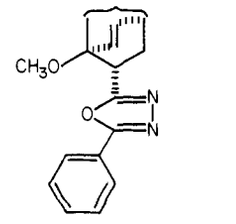

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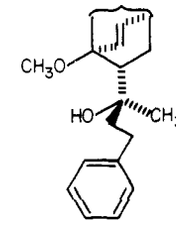

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Use of an excess of triethylorthoformate under the same conditions as already used with the 7α-epimer **3** failed to transform **11** into the desired 7β-oxadiazole **12**. Instead, the hydrazonate derivative **13** was obtained. Derivatives of this type have been isolated from the reaction between hydrazides and ortho esters and can themselves be converted into oxadiazoles.[5,14] However sublimation of **13** gave a complex mixture of compounds from which **12** could be isolated.

Pharmacology. The compounds shown in the Table I were examined for analgesic activity by the Hendershot and Forsaith writhing test (H and F) in mice.[15] Those compounds showing significant activity (ED_{50} < 30 mg/kg)

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(14) Ainsworth, C. *J. Am. Chem. Soc.* **1965**, *87*, 5800.

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Table I. Analgesic Activity of Compounds **2a–11**[a]

compd	ED_{50}, mg/kg H and F[b]	ED_{50}, mg/kg RTP[c]	compd	ED_{50}, mg/kg H and F[b]	ED_{50}, mg/kg RTP[c]
2a[d,e]	>30				
2b[d]	25	>30	**7b**	8.8	>10
4a	10	>30	**7c**	4.3	>10
4b	2.2	>30	**8**	>30	>30
4c	1.6	14.5 (9.86–21.3)	**9a**	4.0	>10
4d	0.175	0.7 (0.4–1.24)	**9b**	3.6	11.5 (6.46–20.5)
4e	3.2	2.05 (1.40–2.99)	**9c**	3.7	>10
5a	>30		**9d**	24.0	>10
5b	7.1	>10	**10**	3.5	>10
6	>30		**11**	2.9	>10
7a	3.0	>30	morphine[f]	0.64	0.49 (0.34–0.69)
			codeine[g]	5.6	13.5 (11.3–16.2)

[a] Compounds were administered by the subcutaneous route as a 0.1-mL solution in saline (free bases being solubilized by addition of dilute hydrochloric acid) for each 10 g of animal, 30 min prior to challenge with the nociceptive stimulus. [b] Mouse writing test;[15] five animals used for each determination. [c] Rat tail pressure test;[16] 10 animals used for each determination; values in parentheses are 95% confidence limits. [d] Reference 2. [e] Hydrochloride. [f] Sulfate. [g] Phosphate.

were further examined by the rat tail pressure (RTP) test.[16] Compounds were administered as a 0.1-mL solution in saline for each 10 g of animal by the subcutaneous route 30 min prior to challenge with the nociceptive stimulus.

The most active compounds were the fully aromatic oxadiazoles with nonpolar alkyl or aryl substituents (**4b–e**). The analgesic potency increases with increasing size of substituent, reaching a peak at phenyl and declining slightly on progression to *p*-tolyl, i.e., *p*-tolyl < Ph > Et > CH_3 > H. The most active compound, **4d**, has similar potency to morphine (RTP test). Previous work has shown one of the most potent analgesics in the bridged thebaine series to be the phenethylcarbinol, with *R* stereochemistry at C-19 (**1**, R = R^1 = CH_3, X = (*R*)-$C(CH_3)(OH)$-CH_2CH_2Ph) (110 times more potent than morphine, RTP test).[17] Data for this and related carbinols[1] suggested there exists a specific site on the opiate receptor for the lipophilic groups incorporated into the C-7 substituent. In comparison of the side chains of **14** and **15** of the phenyloxadiazole **4d** and the phenethylcarbinol, respectively, relative to the bridged thebaine system, the oxygen atoms and the phenyl rings are similarly disposed in space but cannot be entirely superimposed, the greater potency of **15** implying the better receptor fit. The bridged thebaines studied previously[3] carrying different heterocycles at C-7 were less sterically related to **15**: the most active of those reported[3] were 7α-(5-pyrazolyl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine and the 7α-[1-(2-quinolyl)-5-pyrazolyl] analogue. When examined by a phenyl-*p*-quinone-induced writhing test in mice, after oral administration, they showed analgesic activity at a dose of 100 mg/kg of body weight.[3]

Oxadiazoles with polar substituents (thioethers, **7a–c**, or amines, **9a–d**) exhibited ED_{50} values similar to that of codeine in the writhing test, except for the aminooxadiazole **9d**, which was less active; all, however, were inactive in the RTP test situation. Oxadiazoles containing an exocyclic double bond (**2a,b** and **8**) were all less active than those containing the fully aromatic system. Only **5b** of the three 7α-open-chain compounds showed any activity: the two 7β compounds, **10** and **11**, were both slightly more potent than codeine in the writhing test. In this respect it is of interest to note that high analgesic activity has been recently reported for a series of 7β-(arylalkyl)-4,5α-epoxymorphinans.[18]

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(17) Lewis, J. W.; Readhead, M. J. *J. Med. Chem.* **1970**, *13*, 525.
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Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 177 grating spectrometer as Nujol mulls. Proton NMR were recorded on a Varian EM360A spectrometer (60 MHz) and a Perkin-Elmer R32 spectrometer (90 MHz) with Me_4Si as internal standard. Ultraviolet spectra were recorded on a Unicam SP800 spectrophotometer. Mass spectra were obtained on a AEI MS12 instrument and accurate mass measurements were performed by the Physico-Chemical Measurements Unit, Aldermaston, U.K., on an AEI MS50 machine. Elemental analyses were determined by the Microanalytical Laboratory, University of Manchester, U.K., and are within 0.4% of the theoretical values unless otherwise noted.

1-[(6,14-*endo*-Etheno-6,7,8,14-tetrahydrothebain-7α-yl)-carbonyl-]-2-acetylhydrazine (5a). The 7α-hydrazide **3**[6] (4.0 g, 10 mmol) was refluxed in acetic acid (50 mL) for 1 h. The resulting solution was neutralized with aqueous NaOH and extracted with chloroform. After drying (K_2CO_3) and evaporation, the residual gum was triturated with ethyl acetate/diethyl ether and the solid produced was recrystallized from ethyl acetate/methanol to give **5a**: colorless needles, 3.9 g, 88%, mp 153–156 °C; IR (Nujol) ν_{max} 3225, 1605 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (3 H, s, CH_3 adjacent to C=O), 2.38 (3 H, s, NCH_3), 3.68 (3 H, s, C-6 OCH_3), 3.84 (3 H, s, C-3 OCH_3), 4.54 (1 H, s, $H_{5\beta}$), 5.57 (1 H, d, J = 9 Hz, H_{17}), 5.94 (1 H, d, J = 9 Hz, H_{18}), 6.59 (2 H, m, H_1 and H_2), 9.36 (2 H, s, br, 2 NH). Anal. ($C_{24}H_{29}N_3O_5$) C, N; H: calcd, 6.65; found, 7.1.

1-[(6,14-*endo*-Etheno-6,7,8,14-tetrahydrothebain-7α-yl)-carbonyl]-2-propionylhydrazine (5b). Using the 7α-hydrazide **3** (3.0 g, 7.56 mmol) and propionic acid (50 mL) in an analogous procedure to that used for the formation of **5a** gave **5b** as long colorless needles from ethyl acetate (2.44 g, 59%, mp 128–131 °C). Anal. ($C_{25}H_{31}N_3O_5 \cdot 0.5H_2O$), C, H, N.

1-[(6,14-*endo*-Etheno-6,7,8,14-tetrahydrothebain-7α-yl)-carbonyl]-1,2,2-triacetylhydrazine (6). The diacylhydrazine **5a** (0.5 g, 1.14 mmol) was refluxed with acetic anhydride (25 mL) for 4.5 h. The solvent was then taken off in vacuo and the residual oil dissolved in diethyl ether and stored at −20 °C for 2 days. The *tetraacyylhydrazine* **6** was collected as colorless needles: (0.24 g, 39%, mp 186–187 °C; IR (Nujol) ν_{max} 1725 cm^{-1} (sh, 1740 cm^{-1}); NMR ($CDCl_3$) δ 1.35 (1 H, m, $H_{8\alpha}$), 2.37 (6 H, s), 2.41 (3 H, s) and 2.48 (3 H, s) (NCH_3 and 3 CH_3C=O), 3.66 (3 H, s, C-6 OCH_3), 3.85 (3 H, s, C-3 OCH_3), 4.48 (1 H, s, $H_{5\beta}$), 5.60 (1 H, d, J = 9 Hz, H_{17}), 6.10 (1 H, d, J = 9 Hz, H_{18}), 6.60 (2 H, m, H_1 and H_2); measured mass 523.2310 ($C_{28}H_{33}N_3O_7$ requires 523.2319). Anal. ($C_{28}H_{33}N_3O_7$) C, H, N.

7α-(1,3,4-Oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (4a). The 7α-hydrazide **3** (2.0 g, 5.04 mmol) was refluxed with triethylorthoformate (50 mL) for 24 h. The excess ortho ester was removed under vacuum and the residue was crystallized from ethanol to give the *oxadiazole* **4a** as colorless plates: 1.4 g, 70%, mp 201–203 °C. Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

7α-(5-Methyl-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-

6,7,8,14-tetrahydrothebaine (4b) by the Ortho Ester Route. The 7α-hydrazide **3** (5.0 g, 12.6 mmol) was refluxed in triethylorthoacetate (50 mL, 378 mmol) for 24 h. The excess ortho ester was removed in vacuo and the residue recrystallized from absolute ethanol to give the *methyloxadiazole* **4b** as colorless rhombs: 4.54 g, 86%, mp 204–205 °C; IR (Nujol) ν_{max} 1640, 1610, 1598 cm^{-1}. Anal. ($C_{24}H_{27}N_3O_4$) C, H, N.

7α-(5-Ethyl-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (4c). Using the hydrazide **3** (2.0 g, 5.04 mmol) and triethylorthopropionate (50 mL) in the procedure described above for the formation of **4a** afforded the *ethyloxadiazole* **4c** as colorless rhombs from ethanol: 0.92 g, 42%, mp 169–170 °C. Anal. ($C_{25}H_{29}N_3O_4$) C, H, N.

7α-(5-Phenyl-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (4d). The hydrazide **3** (1.0 g, 2.52 mmol) and trimethylorthobenzoate (6.4 g, 35.16 mmol) were heated under reflux in dry *p*-xylene (20 mL) for 24 h. The solvent was removed in vacuo and methanol added. The phenyloxadiazole **4d** crystallized out as colorless rhombs: 1.18 g, 100%, mp 210–212 °C. Anal. ($C_{29}H_{29}N_3O_4$) C, H, N.

7α-(5-*p*-Tolyl-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (4e). The hydrazide **3** (2.0 g, 5.04 mmol) and trimethyl ortho-*p*-toluoate[19] (11.0 g, 56 mmol) were heated under reflux in dry xylene (15 mL) for 24 h. Excess solvent was removed under vacuum on a hot water bath until a solid began to appear. Diethyl ether (100 mL) was then added and more solid precipitated. The solid was filtered off and washed with diethyl ether to give **4e** (0.56 g). The filtrate was allowed to stand for several days and some of the starting material **3** crystallized out (0.5 g collected by filtration). After the filtrate stood for several more days, additional **4e** (0.47 g) crystallized out. This gave a total yield of **4e** of 1.03 g: 55% based on recovered starting material, colorless rhombs, mp 234–236 °C from EtOH. Anal. ($C_{30}H_{31}N_3O_4$) C, H, N.

7α-(5-Methyl-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (4b) from Diacylhydrazine 5a. The diacylhydrazine **5a** (0.4 g, 0.911 mmol) was heated under reflux in phosphorus oxychloride (20 mL) for 1 h. The solution was cooled and added in portions to ice (50 g). This solution was neutralized (aqueous KOH) with cooling and then extracted with chloroform. The chloroform extract was dried (K_2CO_3) and on evaporation gave a foam, which was washed in hot diethyl ether. The ether solution was decanted off from a discolored gum, which remained undissolved. The ether solution was evaporated, and trituration of the residual gum with EtOH afforded the *methyloxadiazole* **4b**: 0.139 g, 35%, colorless rhombs, mp 199–201 °C from EtOH. The sample had an identical IR spectrum with that of **4b** as prepared by the ortho ester route described above, and the melting point was not depressed by admixture with a sample from that route.

7α-[5-(Methylthio)-1,3,4-oxadiazol-2-yl]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (7a). Methyl iodide (5.0 g, 35.2 mmol), the oxidiazolthione **2b**[2] (5.0 g, 11.4 mmol), and MeOH (50 mL) were refluxed for 1 h. The solvent was evaporated in vacuo and the residue was recrystallized from MeOH containing a small amount of water to give **7a** as colorless needles: (4.5 g, 87%, mp 186–187 °C; IR (Nujol) ν_{max} 1632, 1608, 1583 cm^{-1}; UV (EtOH) λ_{max} 286 nm. Anal. ($C_{24}H_{27}N_3O_4S \cdot H_2O$) C, H, N.

7α-[5-(Ethylthio)-1,3,4-oxadiazol-2-yl]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (7b). The oxadiazolthione **2b** (1.0 g, 2.28 mmol) and ethyl idodide (2.2 g, 14.1 mmol) were refluxed in ethanol for 2 h. After evaporation of the solution to dryness, the residue was dissolved in the minimum amount of methanol and purified by application to an alumina column which was eluted with chloroform. The product **7b** crystallized from diethyl ether as colorless rhombs: 0.54 g, 51%, mp 125–126 °C). Anal. ($C_{25}H_{29}N_3O_4S$) C, H, N.

7α-[5-(Isopropylthio)-1,3,4-oxadiazol-2-yl]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (7c). 2-Iodopropane (2.5 g, 14.7 mmol) and the oxadiazolthione **2b** (1.5 g, 3.41 mmol) were refluxed in 2-propanol (50 mL) for 18 h. After evaporation of the solvent, the residue was dissolved in chloroform, placed on an alumina column, and eluted with 20% v/v chloroform/diethyl ether. The *oxadiazole* **7c** was recrystallized from ethanol: 0.62 g, 38%, mp 144–145 °C. Anal. ($C_{26}H_{31}N_3O_4S$) C, H, N.

7α-[2,3-Dihydro-3-(morpholinomethyl)-2-thioxo-1,3,4-oxadiazol-5-yl]-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (8). To a stirred suspension of the oxadiazolethione **2b** (1.0 g, 2.28 mmol) in ethanol (10 mL) were added formaldehyde (0.19 mL of a 40% solution in water, 2.50 mmol) and morpholine (0.199 g, 2.28 mmol). The mixture was stirred for 1 h at ambient temperature and then the solution was refluxed for 1 h. The solvent was removed in vacuo and the residue applied to an alumina column, which was eluted with chloroform until a dark band reached the bottom of the column. (The dark band was not eluted.) Evaporation of the eluate and trituration with diethyl ether afforded the *Mannich base* **8**: 0.28 g, 20%, colorless rhombs, mp 198–200 °C from ethanol; IR (Nujol) ν_{max} 1628 cm^{-1}; UV (EtOH) λ_{max} 263 nm; NMR ($CDCl_3$) δ 2.39 (3 H, s, NCH_3), 2.78 (4 H, t, NCH_2's in morpholine ring), 3.61 (3 H, s, C-6 OCH_3), 3.70 (4 H, t, CH_2OCH_2), 3.86 (3 H, s, C-3 OCH_3), 4.66 (1 H, s, $H_{5\beta}$), 4.95 (2 H, s, NCH_2N), 5.67 (1 H, d, J = 9 Hz, H_{17}), 5.89 (1 H, d, J = 9 Hz, H_{18}), 6.62 (2 H, m, H_1 and H_2). Anal. ($C_{28}H_{34}N_4O_5S$) C, H, N.

7α-(5-Pyrrolidino-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (9a). The (methylthio)oxadiazole **7a** (0.5 g, 1.1 mmol) and pyrrolidine (2.0 g, 28.17 mmol) were heated under reflux in dry *p*-xylene (25 mL) for 12 days. The solution was evaporated in vacuo and the residue was placed on an alumina column and eluted with chloroform/petroleum ether. The *pyrrolidinooxadiazole* **9a** was crystallized from diethyl ether and then recrystallized from ethanol: 0.32 g, 61%, mp 234–235 °C. Anal. ($C_{27}H_{32}N_4O_4$) C, H, N.

7α-(5-Piperidino-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (9b). Refluxing **7a** (1.5 g, 3.31 mmol) and piperidine (7.0 g, 82.35 mmol) in dry *p*-xylene for 6 days, followed by workup as described for **9a**, afforded the *piperidinooxadiazole* **9b**: 0.62 g, 38%, mp 208–209 °C from ethanol. Anal. ($C_{28}H_{34}N_4O_4$) C, H, N.

7α-(5-Morpholino-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (9c). The (methylthio)oxadiazole **7a** (1.5 g, 3.31 mmol) and morpholine (7.0 g, 80.46 mmol) were heated under reflux in dry *p*-xylene for 6 days. Workup as above gave the *morpholinooxadiazole* **9c**, which was recrystallized from ethanol: 0.74 g, 45%, mp 206–208 °C. Anal. ($C_{27}H_{32}N_4O_5$) C, H, N.

7α-(5-Amino-1,3,4-oxadiazol-2-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (9d). The hydrazide **3** (10.0 g, 25.2 mmol) and cyanogen bromide (2.9 g, 27.5 mmol) were heated under reflux in methanol (125 mL) for 2 h, the solvent was evaporated off, and water (125 mL) was added. The solution was basified (concentrated NH_4OH) to pH ~9 and extracted with chloroform. The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to yield a pink oil, which was taken up in the minimum of hot methanol containing a small amount of water. Storing for 1 day at −20 °C gave the *aminooxadiazole* **9d** as colorless needles: 5.27 g, 50%, mp 143–146 °C; IR (Nujol) ν_{max} 3300 and 3150 (NH), 1650 cm^{-1} (C=N). Anal. ($C_{23}H_{26}N_4O_4 \cdot H_2O$) C, H, N.

7β-(Methoxycarbonyl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (10). Thebaine (50 g, 0.16 mol) was heated under reflux with methyl acrylate (100 mL, 1.11 mol) for 10 h. The excess acrylate was removed under reduced pressure until separation of solid matter began. This solid was recrystallized from MeOH to give the 7α-methyl ester as colorless prisms: 54 g, 85%, mp 148–149 °C (lit.[7] mp 148 °C); IR (Nujol) ν_{max} 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (1 H, m, $H_{8\alpha}$), 2.39 (3 H, s, NCH_3), 3.64 (3 H, s, C-6 OCH_3), 3.69 (3 H, s, C-19 OCH_3), 3.84 (3 H, s, C-3 OCH_3), 4.60 (1 H, s, $H_{5\beta}$), 5.57 (1 H, d, J = 9 Hz, H_{17}), 5.89 (1 H, d, J = 9 Hz, H_{18}), 6.60 (2 H, m, H_1 and H_2).

The mother liquors were evaporated to dryness, and the residue was dissolved in chloroform and placed on an alumina column. The column was eluted with chloroform. From the second 50-mL fraction a solid was obtained, which after three recrystallizations from MeOH gave the *7β-methyl ester* **10** (4.0 g, 8%, mp 187–189 °C) as short colorless needles: IR (Nujol) ν_{max} 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (3 H, m, $H_{8\alpha}$ + two other protons), 2.39 (3 H, s, NCH_3), 3.58 (3 H, s, C-6 OCH_3), 3.76 (3 H, s, C-19 OCH_3), 3.84 (3 H, s, C-3 OCH_3), 5.21 (1 H, d, J = 1 Hz, $H_{5\beta}$), 5.49 (1 H, d, J = 9 Hz H_{17}), 6.07 (1 H, dd, J = 9 and ≃1 Hz, H_{18}), 6.60 (2 H, m, H_1 and H_2). Anal. ($C_{23}H_{27}NO_5$) C, H, N.

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7β-(Hydrazinocarbonyl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine (11). The 7β-methyl ester **10** (1.5 g, 3.78 mmol) was heated under reflux with 100% hydrazine hydrate (5 mL ≃ 103 mmol) and 2-ethoxyethanol (3.8 mL) for 8 h. The reaction mixture was cooled and an equal volume of water was added. On scratching, the *7β-hydrazide* **11** crystallized out as colorless needles, which were recrystallized from water containing a small amount of EtOH: 0.54 g, 36%, mp 106 °C; IR (Nujol) ν_{max} 3310 (br, NH and NH_2), 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.97 (1 H, d, J = 1.5 Hz, $H_{5\beta}$). Anal. ($C_{22}H_{27}N_3O_4 \cdot H_2O$) C, H, N.

Ethyl *N*-(6,14-*endo*-Etheno-6,7,8,14-tetrahydrothebain-7β-ylcarbonyl)formohydrazonate (13). The 7β-hydrazide **11** (0.33 g, 0.83 mmol) was heated under reflux with triethylorthoformate (25 mL) for 24 h. The excess ortho ester was removed in vacuo and the oily residue was dissolved in ethanol (15 mL). The ethanol was evaporated and the residue, by now partly solid, was taken up in hot diethyl ether. The hydrazonate **13** precipitated out as an amorphous solid after several days: 0.1424 g, 38%, mp 134–139 °C; IR (Nujol) ν_{max} 3320 (NH), 1693 (C=O), 1638 cm^{-1} (C=N); NMR ($CDCl_3$) δ 1.41 (3 H, t, J = 7 Hz, CH_3CH_2O), 2.38 (3 H, s, NCH_3), 3.57 (3 H, s, C-6 OCH_3), 3.83 (3 H, s, C-3 OCH_3), 4.18 (2 H, q, J = 7 Hz, CH_3CH_2O), 4.87 (1 H, s, $H_{5\beta}$), 6.59 (3 H, m, H_1, H_2, and N=C*H*OEt); measured mass 453.2255 ($C_{25}H_{31}N_3O_5$ requires 453.2264).

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Registry No. **2b**, 83933-13-5; **3**, 24482-20-0; **4a**, 91085-16-4; **4b**, 91085-17-5; **4c**, 91085-18-6; **4d**, 91110-26-8; **4e**, 91085-19-7; **5a**, 91110-54-2; **5b**, 91110-55-3; **6**, 91085-15-3; **7a**, 91085-20-0; **7b**, 91085-21-1; **7c**, 91085-22-2; **8**, 91085-23-3; **9a**, 91085-24-4; **9b**, 91085-25-5; **9c**, 91085-26-6; **9d**, 91085-27-7; 7β-**10**, 91176-83-9; 7α-**10**, 16193-33-2; **11**, 91176-84-0; **13**, 91085-28-8; triethyl orthopropionate, 115-80-0; trimethyl orthobenzoate, 707-07-3; trimethyl ortho-*p*-toluate, 22911-22-4; pyrrolidine, 123-75-1; triethyl orthoformate, 122-51-0; triethyl orthoacetate, 78-39-7; piperidine, 110-89-4; morpholine, 110-91-8; thebaine, 115-37-7; methyl acrylate, 96-33-3.

Dichloro[1,2-bis(4-hydroxyphenyl)ethylenediamine]platinum(II) Complexes: An Approach To Develop Compounds with a Specific Effect on the Hormone-Dependent Mammary Carcinoma

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Stereoisomeric dichloro[1,2-bis(4-hydroxyphenyl)ethylenediamine]platinum(II) complexes (*meso*-**3a**, (±)-**3b**, (+)-**3c**, (−)-**3d**) and their *N,N'*-dibutyl derivatives (*meso*-**4a**, (±)-**4b**, (+)-**4c**, (−)-**4d**) were synthesized and tested on antitumor activity. The most active compound, **3d**, shows a modest inhibition of the [^{3}H]estradiol receptor interaction and causes a marked effect on the growth of the hormone-dependent human MCF 7 breast cancer cell line. It is also active on the hormone-independent human MDA-MB 231 breast cancer cell line, on the ADJ/PC6 plasmacytoma of the Balb/C mouse, and on the L 5222 leukemia of the BD IX rat. Apparently the inhibition of the MCF 7 cell line is not mediated by the estrogen receptor system. Histopathological studies on **3d** revealed very low toxicity.

The resistance of the hormone-dependent mammary carcinoma against cisplatin tempted us to synthesize cytotoxic platinum complexes containing stereoisomeric *N,N'*-dibutyl-1,2-bis(4-hydroxyphenyl)ethylenediamines as ligands, which are able to bind to the estrogen receptor (Scheme I, "estrophilic platinum complexes" **4a–d**).[1] This approach is based on the assumption that these platinum complexes are translocated into the nucleus of the mammary tumor cell by the estrogen receptor system, thereby causing a specific activity against the hormone-dependent breast cancer. Efforts in this direction have also been made by linking cytotoxic agents to estrogens or antiestrogens.[2-8]

Chemistry. The stereoisomeric dichloroplatinum(II) complexes **3a–d** and **4a–d** were synthesized by reacting K_2PtCl_4 with the 1,2-bis(4-hydroxyphenyl)ethylenediamines **1a–d** and the related *N,N'*-dibutyl derivatives **2a–d**. The diamines were applied either as dihydrobromides (method A) or as free bases (method B). The analytical data are listed in Table I. The IR spectra reveal that the N–H stretching vibration has considerably changed upon the formation of the metal–nitrogen bond (free ligand ν(N–H), 3380 cm^{-1}; Pt bond ligand ν(N–H), 3260 cm^{-1}).[9] The weak absorptions in the region of 530 cm^{-1} are characteristic for the metal–nitrogen stretching vibration.[10]

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