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Isomerization Reactions of 7-Substituted 6,14-Bridged Thebaine Derivatives (Bentley Compounds)†,‡

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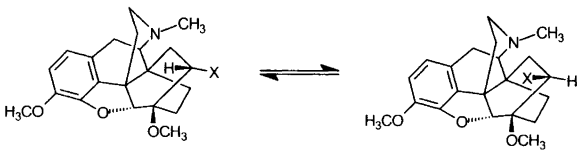
Equilibration of the 7α→7β isomers of 7-substituted 6,14-ethenomorphinanes has been accomplished, for the first time, in dipolar aprotic solvents by the application of bases with weak nucleophilic character. Transformation of the 7β-nitrile with phenylmagnesium bromide led to a new type of 6,6′-dimeric compound.

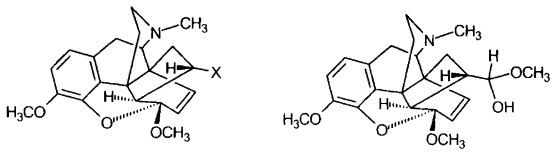
In the regio- and diastereo-selective Diels–Alder reactions[1] of thebaine (**1**) and the related monosubstituted ethylene analogues the major products are the 7α-substituted derivatives (**2**) (Scheme 1). The reaction of **1** with methyl vinyl ketone, executed on a large scale,[2] afforded the 7α-derivative (**2**: X = $COCH_3$, thevinone), and the 7β-isomer (**3**: X = $COCH_3$, β-thevinone) (0.49%) was isolated by fractional crystallization. When phenyl vinyl ketone was the reagent the exclusive formation of the 7α-isomer (**2**: X = COPh, nepenthone) was observed.[3] On the other hand, in the reaction[2] of thebaine (**1**) with acrylonitrile the α/β product ratio is ca. 1:1 and the β-nitrile (**3**: X = CN) was isolated by means of fractional crystallization.

During the large-scale synthesis of buprenorphine, from the α/β-dihydrothevinone mixture (**4** and **5**: X = $COCH_3$), produced upon hydrogenation of α/β-thevinone, 1.3% of β-dihydrothevinone was obtained by fractional crystallization of the bitartrates and several *N*-demethyl-*N*-substituted β-diprenorphine derivatives were synthesized.[4]

For the preparation of additional, novel 7β-analogues of the pharmacologically active semisynthetic 6,14-ethenomorphinane derivatives (buprenorphine,[5,6] diprenorphine,[7,8] etorphine[8,9]), elaboration of a more simple and more effective procedure was necessitated to obtain the 7β-acyl (acetyl, benzoyl) compounds. Apart from the 7β-derivatives synthesized in our laboratory, only a very few related alkaloids have been reported.[10,11]



4 **5**



6 **7**

The 7α→7β isomerization of thevinone (**2**: X = $COCH_3$) and nepenthone (**2**: X = COPh) has been thoroughly investigated by Bentley and his associates,[12,13] whose intention was to establish the 7α/7β equilibrium mixtures by reversible enolisation of 7α-ketones. Sodium hydroxide was employed as the base in methanol but instead of the expected β-derivatives the rearranged so-called iso-derivatives (**6**: X = $COCH_3$; COPh) were obtained and the mechanism of the rearrangement reaction was explained.

In our studies, the 7α→7β isomerization was investigated in dipolar aprotic solvents, by the application of bases[14] with weak nucleophilic character. Thus, upon

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‡ Dedicated to Professor Dr. Gottfried Heinisch on the occasion of his 60th birthday.
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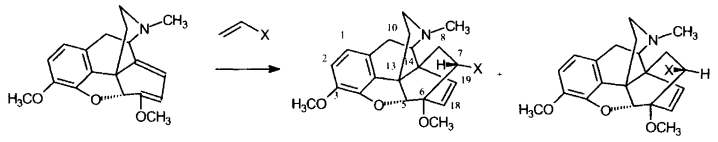


1 2 3

Scheme 1.

treatment of thevinone with 1 equivalent of DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) in acetonitrile at reflux temperature for 7 h, 19% of β-thevinone was obtained. Starting from β-thevinone, 65% of thevinone could be prepared under similar conditions (0.1 equiv. of DBU, acetonitrile, reflux for 24 h).

The α/β isomerization could also be readily executed with the 18,19-dihydro derivatives: dihydrothevinone gave 18% of β-dihydrothevinone (0.1 equiv. of DBU, acetonitrile, reflux for 24 h) and 52% of dihydrothevinone was isolated when β-dihydrothevinone was submitted to analogous reaction conditions. These findings support the equilibrium character of the mechanism proposed by Bentley *et al.*, and also indicate the different stability of the C-7 epimeric ketones. In addition, the isomerization reaction offers a convenient new route for the preparation of β-thevinone and β-dihydrothevinone.[10] The experimental conditions and results of the isomerisation are listed in Table 1.

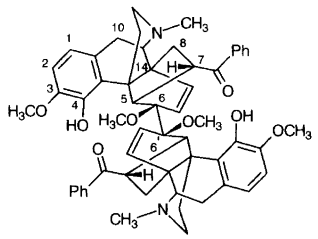
The structures of the products were substantiated[4,11,15] by ^{1}H NMR spectroscopic measurements. The iso-derivatives were prepared as described previously by Bentley *et al.*[12,13] The hitherto unpublished isomerization of the 7α-formyl derivative (**2**: X=CHO) was also studied following the literature procedure,[12,13] however the structure of the product obtained differed from that described for the iso-compounds (**6**: X=$COCH_3$; X=COC_6H_5) and corresponded to **7**. The iso-derivative **6** (X=CHO) was obtained through the procedure developed in our laboratory. Formation of this compound (**7**) can be explained by the addition of methanol to the formyl group.[16] Isomerization of nepenthone into β-nepenthone could not be achieved under the conditions applied. The absence of scalar coupling between H-20 and H-7 in the proton spectrum of compound **7** indicates an approximately 90° dihedral angle between them, which is in accordance with the observed NOE results (saturation of H-20 resulted NOE on H-8α, H-7 and 20-OCH_3 protons) and indicates the *S* configuration for C-20.

Attempts were made to prepare β-thevinone and β-nepenthone from the 7β-nitriles with the appropriate Grignard reagent. Reaction of the 7β-nitrile (**3**: X=CN) with methylmagnesium iodide led to the same rearranged product obtained by Bentley *et al.*[12] from a 7α/7β nitrile mixture. According to TLC, treatment of the 7β-nitrile (**3**: X=CN) with phenylmagnesium bromide resulted in two products of which only the new dimeric compound **8** could be isolated and characterized by means of NMR and mass spectrometric measurements. The stereostructure of this compound was confirmed by the following observation: (i) H-7 proton gave intensive cross peaks with H-15α and H-8β protons in the 2D NOESY spectrum, which proves its β position; (ii) the observed 6.2 Hz coupling and the NOE cross peak between H-5 and H-7 protons indicates their steric proximity; (iii) the presence of 4-OH proton and its long-range hetero-

Table 1. Experimental details and results of the isomerisation of the Bentley compounds.

Starting material	Base (equiv.)	Solvent	τ/h	Product ratio (%)[a]		
				7α	7β	Iso
Thevinone	DBU (1)[d]	Acetonitrile	7	81.5	18.5	[b]
	K_2CO_3 (2)	DMF	14	12.1	9.0	78.9
	DBU (1)	DMF	12	17	5	78
	DBU (2)	Acetonitrile	20	62.5	12.5	25
	DBU (0.1)	Acetonitrile	33	86.6	13.4	[b]
	DBN (0.1)	Acetonitrile	24	88.0	12.0	[b]
	MTBD (0.1)	Acetonitrile	40	69.2	7.7	23.1
β-Thevinone[c]	DBU (0.1)	Acetonitrile	24	65.5	12.5	22.0
Dihydrothevinone	DBU (0.1)	Acetonitrile	24	82.3	17.7	—
β-Dihydrothevinone[c]	DBU (0.1)	Acetonitrile	24	52	48	—
Nepenthone	DBU (0.1)	Acetonitrile	24	90	—	10
Dihydronepenthone	DBU (0.1)	Acetonitrile	24	88.3	11.7	—
7α-CN	DBU (0.1)	Acetonitrile	24	100	—	—
7α-CHO	DBU (0.1)	Acetonitrile	24	16.7	—	83.3
7α-COEt	DBU (1)	Acetonitrile	24	83.4	16.6	—
7β-COEt	DBU (0.1)	Acetonitrile	24	55.1	44.9	—

[a]Based on the ^{1}H NMR spectrum. [b]In traces. [c]Starting from 1 g substrate. [d]Separation of the product mixture was carried out on the basis of a literature procedure.[4]



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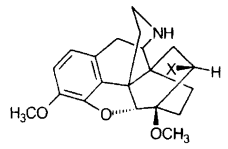
nuclear coupling with C-12, C-3 and C-4; (iv) C-6 proved to be a quaternary carbon and it is long-range coupled with H-5, H-7, H-18 and 6-OCH_3 protons.

N-Demethylation of β-thevinone with diethyl azodicarboxylate was also carried out to obtain *N*-demethyl-β-thevinone (**9**: X = $COCH_3$) with good yield. The present convenient route to the latter compound allows the preparation of novel *N*-demethyl-*N*-substituted β-thevinone analogues.



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Experimental

Melting points (uncorrected): Büchi-535 instrument. TLC: DC-Fertigplatten, Kieselgel 60 F_{254} (Merck-5719), eluent systems (each v/v): 8:2 benzene–methanol [A], 9:1 chloroform–methanol [B], 5:4:1 chloroform–acetone–diethylamine [C]. The spots were visualized with UV light or with the Dragendorff reagent. IR spectra: Digilab FTS-40 spectrometer.

Most of the ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer at 20 °C for samples in $CDCl_3$ [the methyl signal of internal Me_4Si (0.00 ppm) and the carbon signal of $CDCl_3$ (77.0 ppm) were used as references for ^1H and ^{13}C spectra, respectively], however the structural assignments of **7** and **8** are based on their two-dimensional homo- and hetero-nuclear correlation spectra measured by gradient pulse sequences, as well as phase-sensitive NOESY spectra measured on a Bruker DMX500 instrument using an inverse broad-band probe. MS: VG TRIO-2 spectrometer in EI mode at 70 eV, direct insertion technique, and VG-7070 HS FAB technique.

General procedure for the isomerization reaction. A solution of thevinone (40 g, 104 mmol) and the non-nucleophilic base (10.4 mmol) in acetonitrile (110 ml) was heated under reflux. The mixture was then concentrated, the residue was dissolved in chloroform and this solution was washed with aqueous ammonium chloride and water, dried (Na_2SO_4), and concentrated. Separation of the product mixture according to our previously reported method[4] gave 3.4 g (8.5%) of β-thevinone.

Reaction of the thebaine–acrylonitrile adduct (7β) (**3**: X = CN) *with phenylmagnesium bromide.* To the Grignard reagent prepared from magnesium shavings (1.78 g) and bromobenzene (7.7 ml) in abs. toluene (12 ml) and abs. ether (39 ml) a solution of the 7β-nitrile (**3**: X = CN; 4.4 g, 12 mmol) in abs. toluene (77 ml) was added dropwise over a period of 1 h. Then the solution was stirred under gentle reflux for 1.5 h, allowed to cool to room temperature, and poured into 150 ml of saturated aqueous ammonium chloride solution. The mixture was extracted with toluene (3 × 50 ml), the combined organic phase was washed with a saturated aqueous sodium chloride solution, dried (Na_2SO_4) and concentrated to obtain a two-component product (TLC) which was treated with cold ethanol to induce crystallization of **8** (1 g, 21%). M.p. 292–293 °C. ^1H NMR ($CDCl_3$): δ 1.30 (dd, 1 H, 8α-H), 1.60 (dd, 1 H, 15α-H), 1.93 (ddd, 1 H, 15β-H), 2.11 (ddd, 1 H, 16β-H), 2.37 (s, 3 H, NCH_3), 2.42 (m, 1 H, 16α-H), 2.87 (dd, 1 H, 10α-H), 2.98–3.07 (m, 2 H, 8β-H, 9α-H), 3.09 (d, $J_{10\beta,10\alpha}$ = 18.1 Hz, 1 H, 10β-H), 3.49 (s, 3 H, 6-OCH_3), 3.84 (s, 3 H, 3-OCH_3), 3.88 (m, 1 H, 7-H), 4.11 (d, 1 H, 5-H), 5.68 (d, $J_{19,18}$ = 9.7 Hz, 19-H), 5.81 (dd, $J_{18,19}$ = 9.72 Hz, $J_{18,5}$ = 1.6 Hz, 1 H, 18-H), 5.92 (s, 1 H, 4-OH), 6.59 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1-H), 6.64 (d, 1 H, 2-H), 7.35–7.47 [m, 3 H, 20-Ph(*o,p*)], 7.85–7.95 [m, 2 H, 20-Ph(*m*)]. ^{13}C NMR: δ 24.73 (C-10), 26.99 (C-8), 31.74 (C-15), 43.11 (NCH_3), 45.80 (C-13), 46.20 (C-16), 47.67 (C-14), 49.07 (C-7), 50.61 (6-OCH_3), 54.35 (C-5), 55.73 (3-OCH_3), 57.49 (C-9), 104.10 (C-6), 108.27 (C-2), 117.95 (C-1), 127.78 (Ar), 128.44 (Ar), 130.81 (Ar), 130.86 (C-19), 133.68 (Ar), 135.66 (C-18), 143.20 (C-4), 145.33 (C-3), 173.92 (20-CO). IR (KBr): ν_{CO} = 1687 cm^{-1}. FABMS. *m/z* 886. $C_{56}H_{56}N_2O_8$ (885.07).

Reaction of thebaine with ethyl vinyl ketone. Thebaine (25 g, 80 mmol) was boiled in toluene (100 ml) with ethyl vinyl ketone (29.5 ml) in the presence of a small amount of hydroquinone for 6 h. The excess of ethyl vinyl ketone and the solvent were evaporated off under diminished pressure and the residue was crystallized from methanol. Recrystallization from methanol (80 ml) gave 0.5 g (1.6%) of the 7β-propionyl derivative (**3**: X = COEt) as white needles. M.p. 196–197 °C. ^1H NMR ($CDCl_3$): δ 1.04 (t, 3 H, CH_3CH_2CO), 1.42 (dd, 1 H, 8α-H), 2.37 (s, 3 H, NCH_3), 3.36 (d, $J_{10\beta,10\alpha}$ = 18.7 Hz, 1 H, 10β-H), 3.58 (s, 3 H, 6-OCH_3), 3.82 (s, 3 H, 3-OCH_3), 5.12 (d, $J_{5\beta,18}$ = 1.2 Hz, 1 H, 5β-H), 5.47 (d, $J_{19,18}$ = 9 Hz, 1 H, 19-H), 6.05 (dd, $J_{18,19}$ = 9 Hz, $J_{18,5\beta}$ = 1.2 Hz, 1 H, 18-H), 6.51 (d, 1 H, 1-H), 6.63 (d, 1 H, 2-H). MS (EI 70 eV): *m/z* (%) 395 (100) [M^+]. $C_{24}H_{29}NO_4$ (395.5).

The methanolic mother liquor was evaporated to give 28.6 g (90%) of the 7α-propionyl compound (**2**: X = COEt) as a yellow syrup (Lit.[2] m.p. 40–45 °C). ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3 H, CH_3CH_2CO), 1.35 (dd, 1 H, 8α-H), 2.37 (s, 3 H, NCH_3), 3.23 (d, $J_{10\beta,10\alpha}$ = 18.7 Hz, 1 H, 10β-H), 3.58 (s, 3 H, 6-OCH_3), 3.83 (s, 3 H, 3-OCH_3), 4.57 (d, $J_{5\beta,18}$ = 1 Hz, 1 H, 5β-H), 5.57 (d, $J_{19,18}$ = 9 Hz, 1 H, 19-H), 5.93 (dd, $J_{18,19}$ = 9 Hz, $J_{18,5\beta}$ = 1 Hz, 1 H, 18-H), 6.54 (d, 1 H, 1-H), 6.64 (d, 1 H, 2-H). MS (EI 70 eV): *m/z* (%) 395 (95) [M^+], 320 (100). $C_{24}H_{29}NO_4$ (395.5).

The standards of the iso-derivatives were prepared according to literature procedures.[12,13]

6 (X = $COCH_3$, isothevinone): m.p. 165–167 °C (Lit.[12] m.p. 168 °C). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3 H, N-CH_3), 3.36 (d, $J_{10\beta,10\alpha}$ = 18.6 Hz, 10β-H), 3.57 (s, 3 H, 6-OCH_3), 3.83 (s, 3 H, 3-OCH_3), 5.12 (dd, $J_{18,19}$ = 9.5 Hz, $J_{18,5}$ = 2.5 Hz, 1 H, 18-H), 5.95 (d, $J_{18,19}$ = 9.5 Hz, 1 H, 19-H), 6.58 (d, 1 H, 1-H), 6.24 (d, $J_{2,1}$ = 8.3 Hz, 1 H, 2-H). ^{13}C NMR: δ 24.91, 28.63, 30.09, 31.24, 43.28, 44.32, 45.27, 47.04, 50.42, 51.41, 53.21, 56.34, 57.55, 107.65, 109.98, 118.65, 124.14, 129.28, 132.71, 142.42, 143.79, 146.74, 209.30. MS (EI 70 eV): *m/z* (%) 381 (100) [M^+]. $C_{23}H_{27}NO_4$ (381.4).

6 (X = PhCO, isonepenthone): m.p. 173–175 °C (Lit.[13] m.p. 174 °C). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3 H, NCH_3), 3.39 (d, $J_{10\beta,10\alpha}$ = 18.4 Hz, 1 H, 10β-H), 3.56 (s, 3 H, 6-OCH_3), 3.87 (s, 3 H, 3-OCH_3), 5.21 (dd, $J_{18,19}$ = 9.5 Hz, $J_{18,5}$ = 2.4 Hz, 1 H, 18-H), 6.03 (d, $J_{19,18}$ = 9.5 Hz, 1 H, 19-H), 6.12 (d, 1 H, 1-H), 6.18 (d, 1 H, 2-H), 7.53 [m, 3 H, Ph(*o,p*)], 8.50 [m, 2 H, Ph(*m*)]. ^{13}C NMR: δ 25.02, 29.97, 34.00, 43.26, 44.70, 45.35, 46.44, 47.02, 50.52, 53.87, 56.31, 57.60, 108.07, 109.85, 116.65, 118.68, 124.74, 128.60, 128.93, 129.30, 133.12, 136.76, 142.60, 143.81, 146.76, 201.57. MS (EI 70 eV): *m/z* (%) 443 (53) [M^+]; 105 (100). $C_{28}H_{29}NO_4$ (443.5).

Treatment of the thebaine–acroleine adduct (**2**: X = CHO) under similar conditions afforded compound **7**. M.p. 230–231 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (dd, $J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\alpha,7\beta}$ = 2.4 Hz, 1 H, 8α-H), 1.54 (dd, 1 H, 15α-H), 1.80 (ddd, 1 H, 15β-H), 1.99 (ddd, 1 H, 16β-H), 2.34 (s, 3 H, NCH_3), 2.35 (m, 1 H, 16α-H), 2.76 (dd, $J_{10\alpha,10\beta}$ = 18.4 Hz, $J_{10\alpha,9\alpha}$ = 5.7 Hz, 1 H, 10α-H), 2.90 (m, 1 H, 8β-H), 2.95 (m, 2 H, 7β-H, 9α-H), 3.06 (d, $J_{10\beta,10\alpha}$ = 18.4 Hz, 1 H, 10β-H), 3.45 (s, 3 H, 20-OCH_3), 3.49 (s, 3 H, 6-OCH_3), 3.83 (s, 3 H, 3-OCH_3), 3.96 (d, 1 H, 5-H), 4.70 (s, 1 H, 20-H), 5.51 (dd, 1 H, 19-H), 5.75 (s, 1 H, 20-OH), 5.83 (d, $J_{18,19}$ = 9.7 Hz, 1 H, 18-H), 6.55 (d, $J_{1,2}$ = 8.3 Hz, 1 H, 1-H), 6.60 (d, 1 H, 2-H). ^{13}C NMR ($CDCl_3$): δ 24.84 (C-10), 32.25 (C-15), 33.79 (C-8), 43.15 (NCH_3), 46.08 (C-16), 46.53 (C-14), 46.96 (C-13), 47.76 (C-5), 48.43 (C-7), 49.36 (6-OCH_3), 55.00 (20-OCH_3), 55.69 (3-OCH_3), 57.06 (C-9), 106.96 (C-20), 107.98 (C-2), 109.19 (C-6), 117.58 (C-1), 126.73 (C-11), 129.41 (C-19), 131.61 (C-12), 136.72 (C-18), 143.14 (C-3), 144.30 (C-4). MS (EI 70 eV): *m/z* (%) 399 (35) [M^+]; 336 (100). $C_{23}H_{29}NO_5$ (399.5).

Treatment of the thebaine–acroleine adduct (**2**: X = CHO) under the conditions applied by us for the isomerization resulted in the iso-derivative **6** (X = CHO): oil (83%). ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3 H, N-CH_3), 3.38 (d, $J_{10\beta,10\alpha}$ = 17.2 Hz, 1 H, 10β-H), 3.63 (s, 3 H, 6-OCH_3), 3.84 (s, 3 H, 3-OCH_3), 5.11 (dd, $J_{18,19}$ = 10 Hz, $J_{18,5}$ = 1.2 Hz, 1 H, 18-H), 5.94 (d, $J_{19,18}$ = 10 Hz, 1 H, 19-H), 6.57 (d, 1 H, 1-H), 6.65 (d, 1 H, 2-H), 10.00 (s, 1 H, CHO).

N-*Demethylation of β-thevinone.* To a solution of β-thevinone (1 g, 2.6 mmol) in abs. benzene (15 ml) diethyl azodicarboxylate (0.8 ml) was added and the mixture was kept under reflux for 16 h. Following evaporation of the solvent, the residue was taken up in ethanol (20 ml), pyridine hydrochloride (1 g) was added and the mixture was stirred for 24 h at room temperature. The hydrochloride salt of the product was then filtered and converted into the free base; yield: 0.68 g (70%). M.p. 179–181 °C. ^{1}H NMR ($CDCl_3$): δ 1.39 (dd, 1 H, 8α-H), 2.33 (s, 3 H, 7β-Ac), 3.63 (s, 3 H, 6-OCH_3), 3.82 (s, 3 H, 3-OCH_3), 4.84 (d, 1 H, 5β-H), 5.47 (d, $J_{19,18}$ = 9 Hz, 19-H), 6.10 (dd, $J_{18,19}$ = 9 Hz, $J_{18,5}$ = 1.5 Hz, 1 H, 18-H), 6.52 (d, $J_{1,2}$ = 8 Hz, 1 H, 1-H), 6.64 (d, 1 H, 2-H). MS (EI 70 eV): *m/z* (%) 367 [M^+] (42), 104 (100). $C_{22}H_{25}NO_4$ (367.40).

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