Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part XXVII.[1] 7-Alkylidene- and 7α-Vinyl-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines

By **J. W. Lewis** * and **M. J. Readhead**, Reckitt and Colman, Pharmaceutical Division, Hull

Detosylation of diastereoisomeric C-19 secondary tosylates in the 6,14-*endo*-ethenotetrahydrothebaine series has been investigated. The products, 7-alkylidene- and 7α-vinyl-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaines. are rearranged by concentrated hydrochloric acid to bridged thebainones.

DEHYDRATION with formic acid of the tertiary alcohol (1a) in the 6,14-*endo*-ethenotetrahydrothebaine series gives the olefin (2a).[2] The acid-catalysed rearrangements of compound (2a) and its analogues have been studied in detail.[2,3] In the present work the action of hydrochloric acid on some simpler olefins related to (2a)

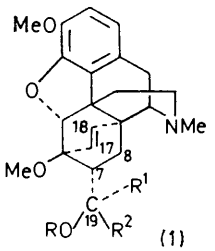
[1] Part XXVI, J. W. Lewis, M. J. Readhead, and A. C. B. Smith, preceding paper.

[2] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3293.

[3] K. W. Bentley, D. G. Hardy, C. F. Howell, W. Fulmor, J. E. Lancaster, J. J. Brown, G. O. Morton, and R. A. Hardy, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 3303.

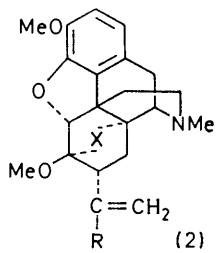
has been investigated. These olefins are the C-7 methylene and ethylidene derivatives (3) and the vinyl compound (2b). The preparation of the alkylidene derivatives from the primary and secondary tosylates (1b and c),[4] and that of the vinyl compound by the Wittig reaction,[2] have been previously described. The detosylation of the diastereoisomeric secondary tosylates (1c and d) has now been investigated in detail.

Both (1c) and (1d) were converted into the ethylidene derivative (3b) when heated under reflux in xylene. When the tosylates were treated with potassium t-butoxide in boiling t-butyl alcohol (1d) gave the ethylidene derivative (3b) but (1c) reacted much more slowly and gave the 7α-vinyl derivative (2b).



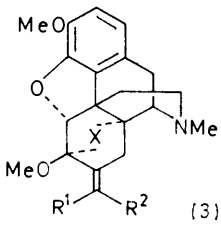
(1)

a; R = H, R^1 = R^2 = Me
b; R = Ts, R^1 = R^2 = H
c; R = Ts, R^1 = H, R^2 = Me
d; R = Ts, R^1 = Me, R^2 = H



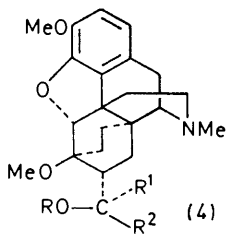
(2)

a; R = Me, X = C_2H_2
b; R = H, X = C_2H_2
c; R = H, X = C_2H_4



(3)

a; R^1 = Me, R^2 = H, X = C_2H_2
b; R^1 = H, R^2 = Me, X = C_2H_2
c; R^1 = H, R^2 = Me, X = C_2H_4
d; R^1 = Me, R^2 = H, X = C_2H_4
e; R^1 = R^2 = H, X = C_2H_2



(4)

a; R = R^2 = H, R^1 = Me
b; R = Ts, R^1 = H, R^2 = Me
c; R = Ts, R^1 = Me, R^2 = H

In order to determine the influence of the nature of the 17,18-bridge on the elimination reactions, the ethano-tosylates (4b and c) were prepared. The (*S*)-C-19 tosylate (4c) in boiling xylene and with potassium t-butoxide in t-butyl alcohol gave the ethano-ethylidene derivative (3c) which was also prepared by atmospheric pressure hydrogenation of the corresponding etheno-derivative. The (*R*)-C-19 tosylate (4b), however, did not behave like the corresponding etheno-compound (1c). In boiling xylene it gave an olefin having the same R_F value (t.l.c.) and i.r. spectrum as 6,14-*endo*-ethano-7-ethylidenetetrahydrothebaine (3c), but which melted at an appreciably lower temperature; the m.p. was not raised by recrystallisation. The n.m.r. spectrum showed a small signal at τ 6·71 in addition to the normal C-6 methoxy-signal at τ 6·60; the combined integral of the two signals was equivalent to three protons. It appeared that the product was largely (3c) but was contaminated with a small amount of (3d), its geometrical isomer. Of the two isomers, (3d) would be expected to show the C-6 methoxy-signal at higher field, owing to increased shielding by the C-19 methyl group. The C-19 methyl group of (3d) should be deshielded by the methoxy-group; in fact a small doublet (*J* 7, Hz) was found at τ 8·15, downfield of the main C-19 doublet (*J* 7 Hz) at τ 8·35.

Detosylation of the toluene-*p*-sulphonate (4b) with potassium t-butoxide was much faster than the similar reaction of the corresponding etheno-compound (1c) and resulted in the formation of two olefins, which were separated by preparative t.l.c. The minor component was the vinyl derivative (2c), and the major product had the same R_F value as (3c) but a lower m.p. Comparison of the n.m.r. spectrum with that of the mixture of olefins from the detosylation of (4b) in xylene led to the conclusion that this product was a mixture of olefins (3c) and (3d) but that, in this case, (3d) predominated.

The manner in which the detosylations were carried out does not permit a rigorous mechanistic interpretation of the reactions. However, the results for the etheno-tosylates are in accord with expectation for a thermal '*cis*'-elimination in boiling xylene and an *E*2 mechanism for the butoxide reaction, if it is accepted that isomerisation of the less stable geometrical isomer [(3a) ⟶ (3b)] can occur under the former conditions. The lower stereospecificity in the eliminations from the ethano-tosylates and the difference in behaviour of the (*R*)-diastereoisomer (4b) compared with the etheno-analogue (1c) suggests that more than one mechanism is operating in these cases.

Before the investigation of the action of acid on the 7-methylene base (3e) was undertaken, we had examined the effect of perchloric acid on the C-7 tertiary alcohol (5).[5] * The product was a saturated ketone (6a), the product of migration of the etheno-bridge from C-6 to C-7. An analogous bridge migration was observed in the reaction of 7α-amino-1-chloro-6,14-*endo*-etheno-tetrahydrothebaine (7) with nitrous acid, which gave (6b);[6] in the latter case, the C-7 carbonium ion must be involved, since the geometry of the bridge ring system is favourable for a concerted migration only when the leaving group at C-7 is β-oriented, as in the tertiary alcohol (5).

The carbonium ion (8) corresponding to (5) should be generated by protonation of the 7-methylene compound (3e). When the latter was treated with per-

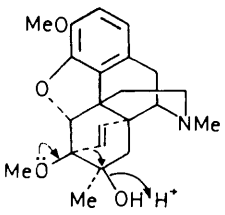
* We thank Dr. A. C. B. Smith for this experiment.

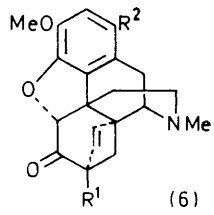
[4] K. W. Bentley, D. G. Hardy, J. W. Lewis, M. J. Readhead, and W. I. Rushworth, *J. Chem. Soc.* (*C*), 1969, 826.

[5] J. W. Lewis, M. J. Readhead, and A. C. B. Smith, to be published in *J. Medicin. Chem.*

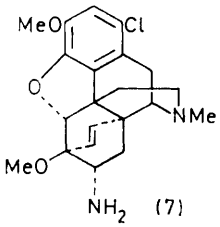
[6] K. W. Bentley, D. G. Hardy, and A. C. B. Smith, *J. Chem. Soc.* (*C*), 1969, 2235.

chloric acid at 100°, the isolated material was a C-4 phenolic αβ-unsaturated ketone, to which was assigned


(5)


(6)

a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Cl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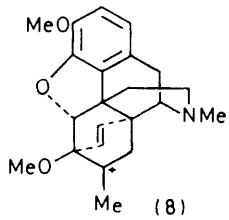
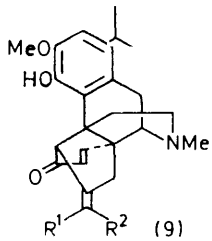
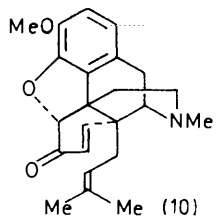

(8)

structure (9a); the formation of this product could not have involved carbonium ion (8). The structure (9a) is directly analogous to that of the compound (9b) obtained from similar treatment of the olefin (2a).[2]


(9)

a; R^1 = R^2 = H
b; R^1 = R^2 = Me
c; R^1 = H, R^2 = Me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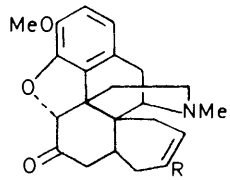
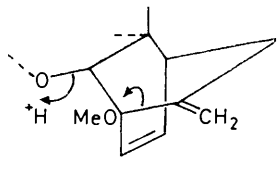

(11)

a; R = Me b; R = H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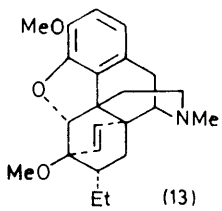
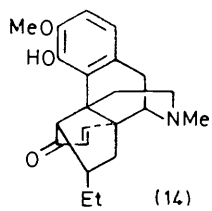

(13)


(14)

The 14-alkenylcodeinone (10) is an intermediate in the formation of (9b),[2] and the reaction also gives cyclohexenodihydrocodeinone (11a),[3] the product of an alternative transformation of the alkenylcodeinone. An equivalent sequence for the 7-methylene compound (3e) requires anti-Markownikov protonation of the exocyclic double bond to give the primary carbonium ion before ring opening to the alkenylcodeinone. A more satisfactory mechanism is initiated by protonation of the cyclic oxygen atom leading to fission of the oxide bridge and a concerted migration as shown in part structure (12).

The 7-ethylidene base (3b) behaved like the methylene compound and was rearranged within 30 min in hot concentrated hydrochloric acid to the unsaturated ketone (9c). The 7α-vinyl derivative (2b) also gave (9c) under these conditions, but the reaction was appreciably slower. Since there was no evidence that any cyclohexenodihydrocodeinone (11b) was present in the product it seems unlikely that an alkenylcodeinone intermediate is involved in the rearrangement, which probably owes its relative slowness to the lower migratory aptitude of the allylic C-7 compared with the vinylic C-7 in the rearrangement of the alkylidene compounds. Even slower was the rearrangement of 7α-ethyl compound (13),[4] which gave only a low yield of the C-4 phenol (14) on prolonged heating with concentrated hydrochloric acid.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal standard at 60 MHz or 100 MHz (instrument indicated in individual cases). I.r. absorption spectra were determined for potassium bromide pellets with a Perkin-Elmer 237 spectrometer.

6,14-endo-*Ethano*-7α-[(1S)-1-*hydroxyethyl*]*tetrahydrothebaine* (4a).—This was prepared by hydrogenation of the corresponding etheno-alcohol[7] at 2·5 atm and room temperatute for 16 h over 10% palladised charcoal. The *hydrochloride* had m.p. 252—257° (decomp.) (Found: C, 63·1; H, 8·1; Cl, 8·3; N, 3·2. $C_{23}H_{32}ClNO_4,H_2O$ requires C, 62·8; H, 7·8; Cl, 8·1; N, 3·2%).

The following toluene-*p*-sulphonates were prepared by the method previously described for 6,14-*endo*-etheno-7α-[(1*R*)-1-*p*-tolylsulphonyloxyethyl]tetrahydrothebaine[4] but with a reaction time of 24 h: 6,14-endo-*etheno*-7α-[(1S)-1-p-*tolylsulphonyloxyethyl*]*tetrahydrothebaine* (1d), m.p. 174—176° (from ethanol) (Found: C, 66·8; H, 6·8; N, 2·7. $C_{30}H_{35}NO_6S$ requires C, 67·0; H, 6·7; N, 2·6%); 6,14-endo-*ethano*-7α-[(1R)-1-p-*tolylsulphonyloxyethyl*]*tetrahydrothebaine* (4b), m.p. 156—157° (from ethanol) (Found: C, 66·9; H, 7·7; N, 2·5. $C_{30}H_{37}NO_6S$ requires C, 66·8; H, 7·8; N, 2·6%); 6,14-endo-*ethano*-7α-[(1S)-1-p-*tolylsulphonyloxyethyl*]*tetrahydrothebaine* (4c), m.p. 149—150° (from ethanol) (Found: C, 65·8; H, 6·9; N, 2·6; S, 5·9. $C_{30}H_{37}NO_6S,0·5H_2O$ requires C, 65·7; H, 7·0; N, 2·5; S, 5·8%).

6,14-endo-*Etheno*-7-*ethylidenetetrahydrothebaine* (3a).—In boiling xylene, under the conditions previously described[4] for 6,14-*endo*-etheno-7α-[(1*R*)-1-*p*-tolylsulphonyloxyethyl]-tetrahydrothebaine, the (*S*)-diastereoisomer (2 g) gave

[7] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3273.

the ethylidene compound (1·1 g), m.p. 205—207°, identical with authentic material.[4] The ethylidene compound (0·3 g) (from ethanol) was also obtained when the (*S*)-tosylate (0·5 g) was boiled under reflux in t-butyl alcohol with potassium t-butoxide (0·5 g) for 4 h.

6,14-endo-*Etheno*-7α-*vinyltetrahydrothebaine* (2b).—6,14-*endo*-Etheno-7α-[(1*R*)-1-*p*-tolylsulphonyloxyethyl]tetrahydrothebaine (0·5 g) and potassium t-butoxide (0·5 g) were heated together in boiling t-butyl alcohol under reflux for 18 h. The cooled mixture was poured into water and the precipitated solid was collected and recrystallised from ethanol to give the vinyl compound (0·25 g), m.p. 128—130°, identical with authentic material.[2]

6,14-endo-*Ethano*-7-*ethylidenetetrahydrothebaine* (3c).—(*a*) 6,14-*endo*-Etheno-7-ethylidenetetrahydrothebaine (4·0 g) was hydrogenated at atmospheric pressure over 10% palladised charcoal (0·4 g) in glacial acetic acid. After uptake of 1 mol. equiv. of hydrogen (35 min) the catalyst was removed, and the solution was diluted with water and basified. Crystallisation from ethanol of the precipitated material gave the *ethano-ethylidene compound* (3c) (3·5 g), m.p. 233—235° (Found: C, 75·2; H, 7·9; N, 3·6. $C_{23}H_{29}NO_3$ requires C, 75·2; H, 7·9; N, 3·8%), τ (Varian T60) 3·25 and 3·45 (2H, ABq, H-2 and H-1, *J* 8 Hz), 6·0—6·4 (1H, multiplet, H-19), 5·65 (1H, s, H-5), 6·15 (3H, s, 3-OMe), 6·65 (3H, s, 6-OMe), 7·75 (3H, s, NMe), and 8·35 (1H, d, 19-Me).

(*b*) 6,14-*endo*-Ethano-7α-[(1*S*)-1-*p*-tolylsulphonyloxyethyl]tetrahydrothebaine (4c) (1·5 g) gave (3c) as its toluene-*p*-sulphonate salt (1·3 g) when it was heated under reflux in boiling xylene for 3 h. The ethano-ethylidene compound (0·8 g) (from ethanol) was also obtained from (4c) (1·5 g) by treatment with potassium t-butoxide (1·5 g) in boiling t-butyl alcohol [procedure analogous to that for the etheno-(*R*)-diastereoisomer].

Detosylation of 6,14-endo-*Ethano*-7α-[(1R)-1-p-*tolylsulphonyloxyethyl]tetrahydrothebaine* (4b).—(*a*) The toluene-*p*-sulphonate (4b) (5 g) in boiling xylene for 4 h gave a toluene-*p*-sulphonate salt (4 g), which was treated with ammonia (*d* 0·880) to give a mixture, m.p. 217—222° (from 2-ethoxyethanol), of the ethano-ethylidene compound (3c) and its geometrical isomer (3d). Two recrystallisations from ethanol did not change the m.p.; τ (Varian T60) 3·25 and 3·45 (2H, ABq, H-2 and H-1, *J* 8 Hz), 6·0—6·45 (1H, multiplet, H-19), 5·65 (1H, s, H-5), 6·18 (3H, s, 3-OMe), 6·65 and 6·75 (3H, pair of singlets in ratio 4 : 1, 6-OMe), 7·75 (3H, s, NMe), and 8·15 and 8·35 (pair of doublets, 19-Me, *J* 7 Hz).

(*b*) The toluene-*p*-sulphonate (4b) (2 g) was treated with potassium t-butoxide (2 g) in boiling t-butyl alcohol (30 ml) for 4 h. The mixture was cooled and diluted with water (400 ml). The precipitated solid was collected and subjected to preparative t.l.c. (silica : ether). The minor component was recrystallised from ethanol to give 6,14-endo-*ethano*-7α-*vinyltetrahydrothebaine* (2b), m.p. 128—131° (Found: C, 75·0; H, 8·0; N, 4·0. $C_{23}H_{29}NO_3$ requires C, 75·2; H, 7·9; N, 3·8%), τ (Jeol 100 MHz) 3·22 and 3·40 (2H, ABq, H-2 and H-1, *J* 7·5 Hz), 3·7—4·15 (1H, m, H-19), 4·7 and 4·92 (2H, H-20), 5·4 (1H, s, H-5), 6·10 (3H, s, 3-OMe), 6·62 (3H, s, 6-OMe), and 7·65 (3H, s, NMe).

The major component was recrystallised from ethanol to give a mixture of the geometrical isomers of the ethano-ethylidene compound, m.p. 182—186°, τ (Varian T60) 3·15 and 3·25 (2H, ABq, H-2 and H-1, *J* 8 Hz), 4·0—4·4 (1H, m, H-19), 5·60 (1H, s, H-5), 6·15 (3H, s, 3-OMe), 6·0 and 6·70 [3H, s (pair, ratio 2 : 3), 6-OMe], 7·65 (3H, s, NMe), and 8·15 and 8·35 [3H, d (pair), 19-Me].

7,14-endo-*Etheno*-7-*methyldihydrocodeinone* (6a) (by A. C. B. Smith).—A solution of the tertiary alcohol (5) [5] (1·0 g) in aqueous perchloric acid (36% w/w; 4 ml) was kept at 90° for 30 min, then poured into water, and the precipitated perchloric salt (1·2 g) was recrystallised from methanol. The *dihydrocodeinone* (6a) base was an amorphous solid, m.p. *ca.* 95°, $\nu_{max.}$ 1712 cm^{-1} (CCl_4) (Found: C, 74·6; H, 7·0; N, 4·0. $C_{21}H_{23}NO_3$ requires C, 74·7; H, 6·9; N, 4·2%), τ (Jeol 100 MHz) 3·25 and 3·35 (2H, ABq, H-2 and H-1, *J* 8 Hz), 4·65 (1H, d, H-18, *J* 5·5, Hz), 4·95 (1H, d, H-17, *J* 5·5 Hz), 5·45 (1H, s, H-5), 6·16 (3H, s, 3-OMe), 6·61 (3H, s, NMe), and 8·68 (3H, s, 7-Me).

5,14-*Ethano*-18-*methylenethebainone* (9a).—6,14-*endo*-Etheno-7-methylenetetrahydrothebaine (3a) [4] (0·5 g) in perchloric acid (36% w/w; 4 ml) was immersed in a boiling water-bath for 30 min. The solution was cooled to give (9a) as its *perchlorate salt* (0·7 g), m.p. 280—285° (from ethanol) (Found: C, 57·6; H, 5·7; Cl, 8·2; N, 3·2. $C_{21}H_{23}NO_3,HClO_4$ requires C, 57·6; H, 5·5; Cl, 8·1; N, 3·2%), τ (free base) (Varian T60) 3·15 (1H, d, H-7, *J* 10 Hz), 3·40 (2H, s, H-1 and H-2), 4·30 (1H, s, 4-OH), 4·29 (1H, dd, H-8, *J* 10 and 2 Hz), 5·2 and 4·83 (2H, 2m, $=CH_2$), 5·78 (1H, m, 5-H), 6·22 (3H, s, 6-OMe), and 7·66 (3H, s, NMe).

5,14-*Ethano*-18-*ethylidenethebainone* (9c).—(*a*) 6,14-*endo*-Etheno-7-ethylidenetetrahydrothebaine (1 g) was dissolved in concentrated hydrochloric acid (3 ml) and the solution was immersed in a boiling water-bath for 30 min; a precipitate slowly formed. The mixture was diluted with water (3 ml) and the hydrochloride was filtered off; it was dissolved in water and the free base was liberated with ammonia. Crystallisation from aqueous ethanol afforded the *thebainone* (9c) (0·5 g), m.p. 145—148° (Found: C, 75·0; H, 7·3; N, 3·9. $C_{22}H_{25}NO_3$ requires C, 75·2; H, 7·2; N, 4·0%), τ (Varian T60) 3·15 (1H, d, H-7, *J* 10 Hz), 3·42 (2H, s, H-1 and H-2), 4·15 (1H, H-19), 4·25 (1H, s, 4-OH), 4·32 (1H, d, H-8, *J* 10 Hz), 5·8 (1H, s, H-5), 6·4 (3H, s, 6-OMe), 7·65 (3H, s, NMe), and 8·35 (1H, d, 19-Me, *J* 5 Hz).

(*b*) 6,14-*endo*-Etheno-7α-vinyltetrahydrothebaine (1 g) in concentrated hydrochloric acid (3 ml) was immersed in boiling water for 2·5 h. The solution was cooled, diluted with water, and made alkaline with ammonia (*d* 0·880). The precipitated base (0·7 g) was identified as the thebainone derivative (9c).

5,14-*Ethano*-18-*ethylthebainone* (14).—A solution of 6,14-*endo*-etheno-7α-ethyltetrahydrothebaine (2·5 g) [4] in concentrated hydrochloric acid (13 ml) was boiled under reflux for 7 h, cooled, and made alkaline with ammonia (*d* 0·880). The dried base (1·6 g) was dissolved in benzene and chromatographed on alumina (neutral, grade 1); elution with 20% ethyl acetate–benzene gave the *thebainone* (14), m.p. 200—203°. $\nu_{max.}$ 1675 (C=C–C=O) and 1487 (C-4 phenol) [8] cm^{-1} (Found: C, 74·8; H, 7·9; N, 3·7. $C_{22}H_{27}NO_3$ requires C, 74·8; H, 7·7; N, 4·0%).

We thank Mr. C. A. Young for preparative t.l.c., Dr. I. A. Selby for n.m.r. spectra, and Dr. S. Turner for discussions.

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[8] J. W. Lewis and M. J. Readhead, *J. Chem. Soc.* (*C*), 1971, 1161.