Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part XXV.[1] Substitution of the Piperidine Ring in Derivatives of 6,14-*endo*-Ethenotetrahydrothebaine

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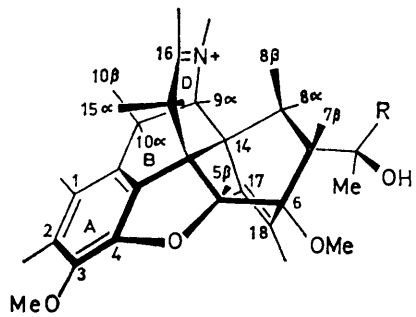
Various 6,14-*endo*-ethenotetrahydrothebaines substituted at positions 15 and 16 have been prepared by electrophilic attack on the corresponding 15,16-didehydro-compounds or nucleophilic attack on the iminium salts derived from these bases. The less hindered approach to C-15 or C-16 is from the α-side (*i.e.* aromatic ring A side) of the molecule.

THE 15,16-didehydro-6,14-*endo*-ethenotetrahydrothebaines described in the preceding paper offer a way of introducing substituents into the morphine nucleus at C-15 and C-16. The iminium perchlorate (2a) reacted with sodium cyanide to give the 16α-nitrile (3a) contaminated with about 5% of the 16β-epimer (3b). A model (Figure) indicates that the less hindered approach



FIGURE

to the iminium ion is from the α-face (*i.e.* the ring A side), the 8β-hydrogen atom effectively shielding the β-face. The configuration of the nitrile group in the major product was confirmed by n.m.r. In deuteriochloroform the 16β-proton resonance at τ 6·11 was partly obscured by the C-3 methoxy-signal at τ 6·18, but in pyridine the signal appeared at τ 5·75 as a triplet (J 5 Hz), due to approximately equal coupling with the two C-15 protons (one *eq–eq* and one *eq–ax* coupling). The 10β-proton lies in the deshielding zone of the axial 16α-nitrile group and the signal for this proton was shifted downfield from its normal position (*ca.* τ 6·9) to τ 6·4.

The axial nitrile group in structure (3a) lies very close to the aromatic ring and thus this structure is clearly thermodynamically unfavoured. In boiling methanol it epimerised to the 16β-nitrile (3b), in which the nitrile group is equatorial and disposed away from the ring system. In the n.m.r. spectrum of compound (3b) the 16α-proton signal appeared as a double doublet (J 7 and 10 Hz) at τ 6·57, typical of an axial proton coupled with vicinal axial and equatorial protons. The 10β-proton resonated at its normal position (τ 6·81). Reduction of the 16β-nitrile with lithium aluminium hydride gave the 16β-aminomethyl compound (3c).

Cyanogen bromide added to the enamine (1a) to give a mixture of two 15-bromo-16-cyano-compounds, readily separated by crystallisation. Both isomers lost hydrogen bromide when treated with alkali, affording the 15,16-didehydro-16-nitrile (1b). The structures of the adducts follow from the work of Fusco *et al.*[2] and the stereochemistry was assigned by n.m.r. The spectrum of the lower melting isomer showed two coupled doublets at τ 4·30 and 6·40 assigned to the C-15 and C-16 protons, respectively. The coupling constant (11 Hz) was typical for 1,2-diaxial protons and this adduct is considered to be the 15α-bromo-16β-nitrile (4a). The 10β-proton resonance was normal (τ 6·76), as expected for a 16β-nitrile. The C-15 and C-16 protons in the higher melting isomer resonated at τ 5·72 and 5·83, respectively. The coupling constant (6·5 Hz) was satisfactory for a 1,2-axial–equatorial proton coupling and this isomer must be the 15α-bromo-16α-nitrile (4b). As before the 16α-cyano-group deshielded the 10β-proton, which resonated at τ 6·28. The production of the two isomers may be rationalised as in Scheme 1. The first step is the attack of a bromonium ion at the less hindered α-face of the enamine to give a bromo-iminium ion. The 15α-bromine atom counterbalances the steric effect of the 8β-proton on C-16 and in the second step the cyanide ion may attack equally well from either side.

The n.m.r. evidence does not exclude the possibility that the lower melting isomer is the 15β-bromo-16α-nitrile, in which the piperidine ring assumes a boat configuration (the ring-D chair configuration of this isomer possesses an axial bromine atom and an axial nitrile group and is very unlikely). In the boat form the C-15 and C-16 protons are *trans*-diaxial and may be expected to show a coupling constant of about 11 Hz. However the formation of such an adduct would involve an initial attack of bromonium ion from the β-side, which seems unlikely on steric grounds.

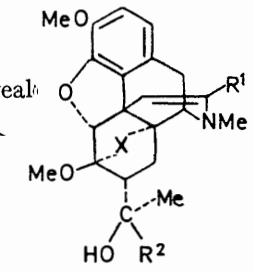
Hydroboration of an enamine followed by peroxidation of the organoborane normally leads to a β-hydroxy-amine.[3] The 15,16-didehydro-compound (1c) reacted vigorously with diborane. Oxidation of the product with hydrogen peroxide gave the 15α-alcohol (4c). In the n.m.r. spectrum of the product the signal for the C-15 proton was superimposed on the C-3 methoxy-signal (τ 6·14) and the splitting pattern could not be

[1] Part XXIV, D. I. Haddlesey, J. W. Lewis, P. A. Mayor, and G. R. Young, preceding paper.

[2] R. Fusco, S. Rossi, and G. Bianchetti, *Gazzetta*, 1961, **91**, 841.

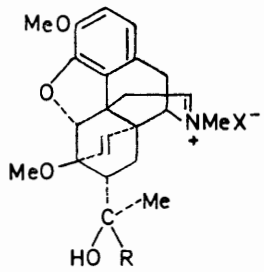
[3] I. J. Borowitz and G. J. Williams, *J. Org. Chem.*, 1967, **32**, 4157.

observed. Acetylation of the 15-hydroxy-group shifted the signal for the C-15 proton downfield to τ 4·81, where it was revealed as a double doublet (J 6 and 10 Hz)



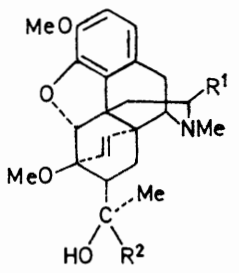
(1)

	R^1	R^2	X
a;	H	Bu^n	CH=CH
b;	CN	Bu^n	CH=CH
c;	H	Me	$CH_2 \cdot CH_2$



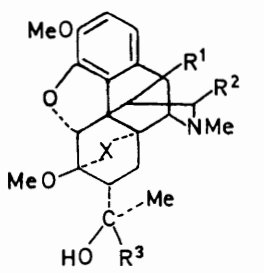
(2)

	R	X
a;	Bu^n	ClO_4
b;	cyclohexyl	Cl



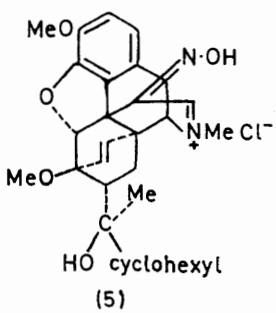
(3)

	R^1	R^2
a;	α-CN	Bu^n
b;	β-CN	Bu^n
c;	β-$CH_2 \cdot NH_2$	Bu^n
d;	H	Me



(4)

	R^1	R^2	R^3	X
a;	α-Br	β-CN	Bu^n	CH=CH
b;	α-Br	α-CN	Bu^n	CH=CH
c;	α-OH	H	Me	$CH_2 \cdot CH_2$



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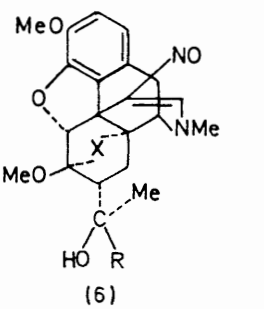
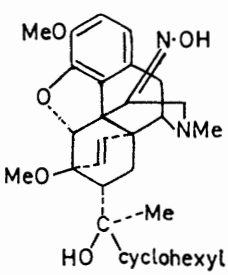


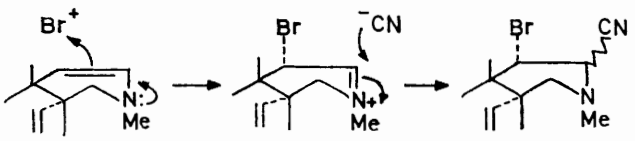
(6)

	R	X
a;	cyclohexyl	CH=CH
b;	Me	$CH_2 \cdot CH_2$



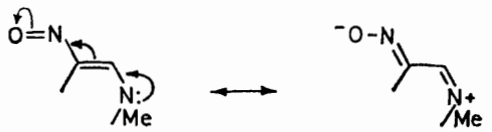
(7)

typical of an axial proton. The 15-hydroxy-group is therefore α-oriented, an assignment in keeping with the general finding that approach to the enamine or iminium salt is less hindered from the α-face. A secondary reaction was the reduction of the enamine to give compound (3d). Protonolysis of an organoborane under oxidising conditions is unusual.



SCHEME 1

The iminium chloride (2b) reacted readily with pentyl nitrite, affording the pale yellow 15-hydroxyimino-iminium chloride (5). Basification of this salt gave the purple 15-nitroso-enamine (6a), from which the salt could be regenerated with dilute hydrochloric acid. The colour of the base may be explained in terms of resonance with a charged structure (Scheme 2). The



SCHEME 2

base was reduced with sodium borohydride to a colourless oxime (7), which proved resistant to further reduction and to acetylation. In ethereal hydrogen chloride solution the oxime isomerised to a second oxime which was readily acetylated. Resonance of the nitroso-enamine according to Scheme 2 will be favoured when the resonating system is planar. The most likely borohydride reduction product would be therefore the *anti*-oxime, in which the hydroxy-group of the oxime is directed away from the piperidine nitrogen atom. The hydroxy-group of the *anti*-oxime is held close to the 5β-proton and understandably acetylation is hindered. In the *syn*-oxime the hydroxy-group projects away from the 5β-proton.

Attempts to alkylate the enamines with alkyl halides and with methyl vinyl ketone failed.

All the tetrahydrothebaines bearing substituents at C-15 or C-16 were considerably less active as analgesics than the unsubstituted compounds when tested in rats by the tail pressure method.[4] The pharmacology of a series of 16-alkyl-6,14-*endo*-ethenotetrahydrothebaines will be discussed elsewhere.

EXPERIMENTAL

N.m.r. spectra were determined for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard at 60 MHz with a Varian T60 spectrometer. The principal bands only are quoted.

The perchlorates of the 15,16-didehydro-compounds were prepared by the method described in the preceding paper. Hydrochlorides were prepared by adding an ethereal solution of hydrogen chloride to the base in ether and

[4] A. F. Green and P. A. Young, *Brit. J. Pharmacol.*, 1951, **6**, 572.

collecting the solid. In general the crude salts were used for subsequent reactions without characterisation.

Reaction of 16,N-*Didehydro*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebainium Perchlorate with Sodium Cyanide.*—A solution of the perchlorate (4 g) and sodium cyanide (2 g) in water (100 ml) was stirred at 24° for 3 h. Ether (50 ml) was added and the stirring was continued for a further 2 h. Evaporation of the ether left 16α-*cyano*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)-*tetrahydrothebaine* (3a) (3·3 g), m.p. 145—150°. T.l.c. indicated that it contained about 5% of the 16β-epimer (Found: C, 72·1; H, 7·5; N, 6·3. $C_{28}H_{36}N_2O_4$ requires C, 72·4; H, 7·8; N, 6·0%), $\nu_{max.}$ 2220 cm^{-1} (CN), τ 3·29 and 3·48 (ABq, H-2 and H-1, *J* 8 Hz), 3·95 and 4·55 (ABq, H-18 and H-17, *J* 9 Hz), 5·22 (s, exchanged with D_2O, OH), 5·48 (s, H-5β), 6·10 (shifted to 5·75 in pyridine) (t, H-16β, *J* 5 Hz), 6·18 (s, 3-OMe), 6·23 (s, 6-OMe), 6·40 (d, H-10β, *J* 19 Hz), 6·79 (d, H-9α, *J* 6 Hz), and 7·38 (s, NMe). When this compound was crystallised once from methanol and twice from ethanol it epimerised to the 16β-*nitrile* (3b), m.p. 166—168° (Found: C, 72·1; H, 7·9; N, 6·1%), $\nu_{max.}$ 2250 cm^{-1} (CN), τ 3·27 and 3·48 (ABq, H-2 and H-1, *J* 8 Hz), 3·95 and 4·58 (ABq, H-18 and H-17, *J* 9 Hz), 5·26 (s, exchanged with D_2O, OH), 5·45 (s, H-5β), 6·18 (s, 3-OMe), 6·23 (s, 6-OMe), 3·43 (dd, H-16α, *J* 7 and 10 Hz), 6·81 (d, H-10β, *J* 19 Hz), 6·75 (d, H-9α, *J* 7 Hz), and 7·40 (s, NMe).

16β-*Aminomethyl*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebaine* (3c).—The 16β-nitrile (3b) (2 g) and lithium aluminium hydride (2 g) in ether (100 ml) were boiled for 18 h. Water (4 ml) was added and the solution was filtered and evaporated to give the 16β-*aminomethyl compound* (1·9 g) (from aqueous ethanol), m.p. 130—132° (Found: C, 71·6; H, 8·7; N, 5·7. $C_{28}H_{40}N_2O_4$ requires C, 71·8; H, 8·7; N, 5·6%).

Addition of Cyanogen Bromide to 15,16-*Didehydro*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebaine.*—A solution of the dehydro-compound (3 g) and cyanogen bromide (3 g) in methylene chloride (40 ml) was kept at 24° for 1 h, filtered, and evaporated to give a froth (4·2 g) which was taken up in methanol (10 ml). After 18 h the crystals (1 g) were collected and recrystallised from ethanol to give 15α-*bromo*-16α-*cyano*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebaine* (4b) (0·6 g), m.p. 188—192° (decomp.) (Found: C, 62·3; H, 6·3; Br, 14·9; N, 5·1. $C_{28}H_{35}BrN_2O_4$ requires C, 61·9; H, 6·5; Br, 14·7; N, 5·2%), τ 5·13 (s, H-5β), 5·27 (s, exchanged with D_2O, OH), 5·72 and 5·83 (ABq, H-15β and H-16β, *J* 6·5 Hz), 6·22 (s, 3-OMe), 6·26 (s, 6-OMe), *ca.* 6·28 (partly obscured by the 6-OMe, H-10β), 6·77 (d, H-9α, *J* 7 Hz), and 7·37 (s, NMe) The CN stretching band was too weak to be observed in the i.r. spectrum. A second crop of crystals harvested from the methanol solution after a further 18 h afforded 15α-*bromo*-16β-*cyano*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebaine* (4a) (0·65 g), m.p. 181—183° (from ethanol) (Found: C, 62·1; H, 6·3; Br, 15·4; N, 5·2%), $\nu_{max.}$ 2250vw cm^{-1} (CN), τ 5·15 (s, H-5β), 5·28 (s, exchanged with D_2O, OH), 5·70 (d, H-15β, *J* 11 Hz), 6·18 (s, 3-OMe), 6·24 (s, 6-OMe), 6·40 (d, H-16α, *J* 11 Hz), 6·71 (d, H-9α, *J* 8 Hz), 6·76 (d, H-10β, *J* 19 Hz), and 7·35 (s, NMe). The two isomers showed different characteristics on t.l.c. (alumina; ether), the 15α-bromo-16β-cyano-compound having the greater R_F value.

16-*Cyano*-15,16-*didehydro*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylpentyl*)*tetrahydrothebaine* (1b).—A solution of either of the cyanogen bromide adducts or a mixture of the two (0·6 g) and potassium hydroxide (0·3 g) in ethanol (30 ml) was boiled for 30 min, filtered, partially evaporated, and diluted with water. The precipitate was collected and crystallised from ethanol to give the *didehydro-nitrile* (0·5 g), m.p. 146—149° (Found: C, 72·9; H, 7·7; N, 5·7. $C_{28}H_{34}N_2O_4$ requires C, 72·7; H, 7·4; N, 6·1%), $\nu_{max.}$ 2230 (CN) and 1605 (enamine) cm^{-1}, τ 3·95 and 4·63 (ABq, H-18 and H-17, *J* 8 Hz), 4·58 (s, H-15), 5·16 (s, H-5β), 5·30 (s, OH), 6·20 (s, 3-OMe), 6·24 (s, 6-OMe), and 6·92 (s, NMe).

Reduction of 15,16-*Didehydro*-6,14-endo-*ethano*-7α-(1-*hydroxy*-1-*methylethyl*)*tetrahydrothebaine with Diborane.*—The didehydro-compound (10 g) in tetrahydrofuran (50 ml) was treated with an excess of diborane in tetrahydrofuran (2%; 40 ml). Vigorous effervescence ensued. After 24 h the solution was warmed gently with 10N-sodium hydroxide (40 ml) and hydrogen peroxide (100 vol; 20 ml). Extraction with ether afforded a white solid (9·6 g), a portion (2·5 g) of which was split into two fractions by preparative t.l.c. [silica; ethyl acetate–propan-2-ol–water (7 : 4 : 3)]. Repeated t.l.c. of the faster running material gave pure 6,14-endo-*ethano*-15α-*hydroxy*-7α-(1-*hydroxy*-1-*methylethyl*)-*tetrahydrothebaine* (1·5 g), m.p. 197—198° (Found: C, 69·7; H, 7·6; N, 3·3. $C_{24}H_{32}NO_5$ requires C, 69·7; H, 8·0; N, 3·3%), τ 4·99 (s, OH), 5·14 (s, H-5β), *ca.* 6·2 (H-15β), 6·14 (s, 3-OMe), 6·45 (s, 6-OMe), 6·88 (d, H-10β, *J* 18 Hz), and 7·48 (s, NMe). Acetylation with pyridine–acetic anhydride mixture gave the 15α-*acetoxy-compound*, m.p. 174—176° (Found: C, 67·6; H, 7·7; N, 2·9. $C_{26}H_{35}NO_6$ requires C, 68·2; H, 7·7; N, 3·1%), τ 5·15 (dd, H-15β, *J* 5 and 10 Hz), 5·05 (s, OH), 5·43 (s, H-5β), 6·12 (s, 3-OMe), 6·45 (s, 6-OMe), 6·85 (d, H-10β, *J* 18 Hz), 7·66 (s, NMe), and 8·02 (s, COMe).

The second component (0·5 g) from the first preparative t.l.c. was identical with an authentic sample of 6,14-*endo*-ethano-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine, m.p. and mixed m.p. 140—142°.

Reaction of Pentyl Nitrite with 7α-(1-*Cyclohexyl*-1-*hydroxyethyl*)-16,N-*didehydro*-6,14-endo-*ethenotetrahydrothebainium Chloride* (2b).—Pentyl nitrite (25 ml) was added to the iminium chloride (30 g) in ethanol (220 ml) and the clear solution was kept at room temperature. After 48 h 7α-(1-*cyclohexyl*-1-*hydroxyethyl*)-16,N-*didehydro*-6,14-endo-*etheno*-15-*hydroxyiminotetrahydrothebainium chloride* (5) was collected as a pale yellow solid (26·5 g), m.p. 290° (decomp.) (Found: C, 64·8; H, 7·3; Cl, 6·5; N, 4·9. $C_{29}H_{36}N_2O_5HCl,0·5H_2O$ requires C, 64·7; H, 7·1; Cl, 6·6; N, 5·2%). The salt in water was basified with ammonia and extracted with chloroform to give 7α-(1-*cyclohexyl*-1-*hydroxyethyl*)-15,16-*didehydro*-6,14-endo-*etheno*-15-*nitroso*-*tetrahydrothebaine* (6a) as a purple solid (24 g), m.p. 245° (decomp.) (Found: C, 70·4; H, 7·4; N, 5·7. $C_{29}H_{36}N_2O_5$ requires C, 70·7; H, 7·4; N, 5·7%). Treatment of the base with dilute hydrochloric acid regenerated the iminium chloride (5).

In the same way was prepared 15,16-*didehydro*-6,14-endo-*ethano*-7α-(1-*hydroxy*-1-*methylethyl*)-15-*nitrosotetrahydro*-*thebaine* (6b), m.p. 265° (decomp.) (Found: C, 67·6; H, 7·1; N, 6·6. $C_{24}H_{30}N_2O_5$ requires C, 67·6; H, 7·1; N, 6·6%).

Sodium Borohydride Reduction of the 15-*Nitroso-enamine* (6a).—Sodium borohydride (10 g) was added in portions to a stirred solution of the nitroso-enamine (20 g) in ethanol (900 ml), and stirring was continued for a further 18 h. The solid was collected and dried to give 7α-(1-*cyclohexyl*-1-*hydroxyethyl*)-6,14-endo-*etheno*-15-anti-*hydroxyiminotetra*-*hydrothebaine* (18·8 g) containing ethanol of crystallisation,

m.p. 279—280° (Found: C, 68·9; H, 8·5; N, 5·2. $C_{29}H_{38}N_2O_5,C_2H_6O$ requires C, 68·9; H, 8·2; N, 5·2%). Attempts to acetylate the oxime gave only starting material. The *anti*-oxime (10 g) in ether was treated with an excess of dry hydrogen chloride. The solid was collected, suspended in water, and neutralised with potassium carbonate. Extraction with chloroform gave the syn-*oxime* (9·2 g), m.p. 285—288° (Found: C, 70·5; H, 7·8; N, 5·3. $C_{29}H_{38}N_2O_5$ requires C, 70·4; H, 7·7; N, 5·7%). Acetylation of the *syn*-oxime with acetic anhydride and pyridine at room temperature gave the *acetate*, m.p. 240—241° (Found: C, 69·4; H, 7·4; N, 5·2. $C_{31}H_{40}N_2O_6$ requires C, 69·4; H, 7·5; N, 5·2%).

Similarly were prepared 6,14-endo-*ethano*-7α-(1-*hydroxy*-1-*methylethyl*)-15-anti-*hydroxyiminotetrahydrothebaine*, m.p. 263—265° (Found: C, 67·3; H, 7·3; N, 6·4. $C_{24}H_{32}N_2O_5$ requires C, 67·3; H, 7·5; N, 6·6%), the syn-*oxime*, m.p. 297—299° (Found: C, 67·4; H, 7·7; N, 6·5%), and the syn-*oxime acetate*, m.p. 222—223° (Found: C, 66·9; H, 7·4; N, 5·8. $C_{26}H_{34}N_2O_6$ requires C, 66·4; H, 7·3; N, 6·0%).

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