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

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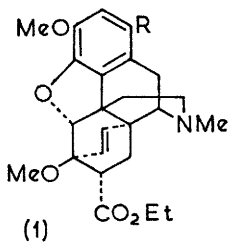
The tetrahydrothebaine ester (1; R = H) has been acetylated with acetic acid and trifluoroacetic anhydride. The product (1; R = Ac) has been reduced to the secondary alcohol and converted by the Schmidt reaction into the acetyl derivative of the amine (1; R = NH_2), which is the product of reduction of the 1-nitro-compound obtainable by nitration of the ester (1; R = H). Chlorination of the tetrahydrothebaine alcohol (2; R = Me) affords the 1-chloro-compound, which has been demethylated to the related phenol. By the Mannich reaction the phenol (2; R = H) has been converted into 2-amino-compounds.

AMINO-GROUPS have been introduced into the aromatic nucleus of compounds in the 6,14-*endo*-ethenotetrahydrothebaine series, which furnishes many analgesics of high potency.[2,3] The ester (1; R = H) is readily acetylated by acetic acid and trifluoroacetic anhydride and the product (1; R = Ac), on reduction with sodium borohydride, gives a mixture of diastereoisomeric secondary alcohols (1; R = CHOH·Me) dehydrated by trifluoroacetic acid to a dimeric anhydro-compound. Treatment of the ketone (1; R = Ac) with sodium azide and hydrochloric acid gave the 1-acetamido-compound (1; R = NHAc), which can be prepared by acetylation of the 1-amino-base (1; R = NH_2), itself obtained by reduction of the nitro-compound (1; R = NO_2), which results from direct nitration of the ester (1; R = H). None of these compounds shows analgesic activity.

The aromatic nucleus in this series can be chlorinated without attack on the 6,14-etheno-bridge, and the alcohol



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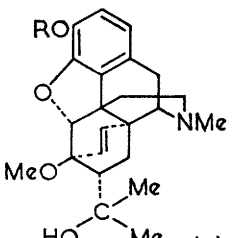

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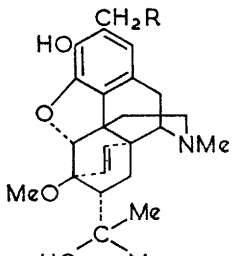

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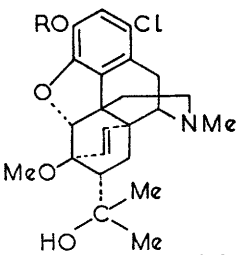

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(2) in this way affords the 1-chloro-compound (4; R = Me), which on demethylation with potassium hydroxide gives the phenol (4; R = H). Both of these bases show markedly less analgesic activity than do the corresponding unsubstituted compounds.

Phenolic bases in this series readily undergo the Mannich reaction with formaldehyde and secondary amines and in this way the phenol (2; R = H) has been converted into the amines (3; R = NMe_2, morpholino, piperidino, or pyrrolidin-1-yl). The presence of the second basic centre in these amines greatly reduces the analgesic potency of the phenol, possibly by alteration of transport mechanisms in the body.

EXPERIMENTAL

Ethyl 1-Acetyl-6,14-endo-ethenotetrahydrothebaine-7α-carboxylate (1; R = Ac).—Ethyl 6,14-*endo*-ethenotetrahydrothebaine-7α-carboxylate (1; R = H) (40 g.) was treated at 90—100° for 6 hr. with acetic acid–trifluoroacetic anhydride [prepared by dilution of trifluoroacetic anhydride (67 ml.) to 98 ml. with glacial acetic acid]. The red solution was cooled and poured with stirring into cold water (1 l.). The solution was filtered and basified with 20% aqueous sodium hydroxide (300 ml.). The precipitated base was washed with water and crystallised twice from ethanol to give the *acetyl derivative* (30·5 g.), m.p. 187—188° (Found: C, 68·8; H, 7·0; N, 3·2. $C_{26}H_{31}NO_6$ requires C, 68·9; H, 6·9; N, 3·1%), $\nu_{max.}$ 1690 cm.$^{-1}$.

Ethyl 6,14-endo-*Etheno*-1-(1-*hydroxyethyl*)*tetrahydrothebaine-7α-carboxylate* (1; R = CHOH·Me).—Ethyl 1-acetyl-6,14-*endo*-ethenotetrahydrothebaine-7α-carboxylate (15·6 g.) in ethanol (150 ml.) was boiled under reflux with sodium borohydride (1·8 g.) and more ethanol (25 ml.) for 15 min. The solvent was evaporated off and the residue was dissolved in N-hydrochloric acid (75 ml.). The solution was diluted with water (50 ml.) and basified with aqueous sodium hydroxide. The precipitated solid (12·7 g.) was crystallised from benzene–light petroleum (b.p. 60—80°) to give a product (7·7 g., 49%), m.p. 145—148°.

Further recrystallisation from light petroleum (b.p. 100—120°) gave the *hydroxyethyl derivative* as prisms m.p. 148—150° (Found: C, 69·0; H, 7·3; N, 3·1. $C_{26}H_{33}NO_6$ requires C, 68·6; H, 7·3; N, 3·1%).

Ethyl 6,14-endo-*Etheno*-1-*vinyltetrahydrothebaine-7α-carboxylate* (*dimer*).—Treatment of the 1-(1-hydroxyethyl) compound (1 g.) with boiling trifluoroacetic acid (4·5 ml.) for 30 min., followed by cooling and dilution with water (100 ml.), heating and basification of the solution with 20% aqueous sodium hydroxide (15 ml.), followed by extraction with ether, gave a solid which gave the 1-vinyl dimer (0·23

[1] Part XIII, K. W. Bentley, J. D. Bower, J. W. Lewis, M. J. Readhead, A. C. B. Smith, and G. R. Young, preceding paper.

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

[3] K. W Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3281.

g.) as prisms, m.p. 239—241° (from ethanol) (Found: C, 70·9; H, 7·1; N, 3·2. $C_{26}H_{31}NO_5$ requires C, 71·4; H, 7·1; N, 3·2%).

Ethyl 1-*Acetamido*-6,14-endo-*ethenotetrahydrothebaine*-7α-*carboxylate* (1; R = NHAc).—The acetyl derivative (1; R = Ac) (1·1 g.) dissolved in concentrated hydrochloric acid (5 ml.) was treated with sodium azide (0·2 g.). The mixture was stirred at room temperature overnight, diluted with water (30 ml.), and basified with 20% aqueous sodium hydroxide (15 ml.). The precipitated solid (0·3 g.), m.p. 204—208° with preliminary softening, gave the 1-*acetamido compound* (0·4 g.)., m.p. 129—133° with reforming of crystals at 150° and final melting at 210—211° (from ethyl acetate).

Ethyl 6,14-endo-*Etheno*-1-*nitrotetrahydrothebaine*-7α-*carboxylate* (1; R = NO_2).—A solution of ethyl 6,14-*endo*-ethenotetrahydrothebaine-7α-carboxylate (1; R = H) (40 g.) in acetic acid (160 ml.) was added slowly to stirred concentrated nitric acid (70% w/w; 80 ml.) during *ca.* 30 min., with the temperature kept below 15°. The mixture was stirred for 1 hr. without cooling, during which time the temperature rose to 20—25°, and then poured into ice–water. The solid was recovered and dissolved in dilute acetic acid. The solution was treated with charcoal, filtered, and basified with ammonia, and the precipitated solid was dissolved in the minimum amount of hot ethanol. Ethanolic hydrogen chloride was added in excess and the solution was allowed to cool to give the hydrochloride, which was dissolved in hot water. This solution was basified with ammonia to give the 1-*nitro-compound* (19 g.) as yellow prisms, m.p. 79—82° (from aqueous methanol) (Found: C, 63·2; H, 6·4; N, 6·0. $C_{24}H_{28}N_2O_7$ requires C, 63·1; H, 6·2; N, 6·1%). The *hydrochloride* was obtained from methanol as yellow prisms, m.p. 205—210° (Found: C, 58·2; H, 5·8; Cl, 7·2; N, 5·5. $C_{24}H_{28}N_2O_7$,HCl requires C, 58·5; H, 5·9; Cl, 7·2; N, 5·7%).

Ethyl 1-*Amino*-6,14-endo-*ethenotetrahydrothebaine*-7α-*carboxylate* (1; R = NH_2).—Ethyl 6,14-*endo*-etheno-1-nitrotetrahydrothebaine-7α-carboxylate (13·3 g.) was hydrogenated in acetic acid (110 ml.) over palladium–charcoal (10%; 0·5 g.) at 23°/760 mm. Absorption of hydrogen ceased after the uptake of 2,128 ml. The catalyst was filtered off and the filtrate was diluted with an equal volume of water, evaporated to *ca.* 75 ml., diluted again with water, and basified with ammonia. The solid was crystallised twice from ethanol to give the 1-*amino-compound* (10·5 g.), m.p. 208—210° (Found: C, 67·3; H, 7·2; N, 6·7. $C_{24}H_{30}N_2O_5$ requires C, 67·6; H, 7·1; N, 6·6%). On diazotisation and coupling with 2-naphthol a crimson dye was formed.

The N-*acetyl derivative*, prepared with acetyl chloride in benzene, had a double m.p., 130—135° and 211—212° (from ethyl acetate) (Found: C, 67·3; H, 7·0; N, 6·0. $C_{26}H_{32}N_2O_6$ requires C, 66·7; H, 6·9; N, 6·0%). Its i.r. spectrum was identical with that of the 1-acetamido-compound prepared before.

The N-*benzoyl derivative*, prepared from benzoyl chloride in benzene solution, was obtained as an amorphous powder, m.p. 135—137° (Found: C, 68·6; H, 6·4; N, 5·0. $C_{31}H_{34}N_2O_6,H_2O$ requires C, 67·8; H, 6·6; N, 5·1%).

1-*Chloro*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylethyl*)-*tetrahydrothebaine* (4; R = Me).—Chlorine (0·8 g.) dissolved in dichloromethane (43 ml.) was added during 20 min. to a solution of 6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)-tetrahydrothebaine (3·97 g.) in dichloromethane (60 ml.). After a further 30 min. the solution was washed with aqueous sodium hydrogen carbonate and then with water; it was dried (Na_2SO_4) and evaporated and the residual gum gave the *chloro-compound* (2·47 g., 57%), m.p. 224—225° (from ethanol) (Found: C, 66·6; H, 7·0; Cl, 8·4; N, 3·0. $C_{24}H_{30}ClNO_4$ requires C, 66·7; H, 7·0; Cl, 8·2; N, 3·2%).

1-*Chloro*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylethyl*)-*tetrahydro-oripavine* (4; R = H).—1-Chloro-6,14-*endo*-etheno-7α-(1-hydroxy-1-methylethyl)tetrahydrothebaine (2 g.) was heated to 120° in diethylene glycol (20 ml.) containing hydrazine hydrate (1 ml.); sodium hydroxide (6 g.) was then added in portions with shaking (frothing occurs). The mixture was further heated and kept at 210° for 30 min. with occasional shaking, and poured into water (200 ml.) to give a gum, which was dissolved on stirring. Addition of warm saturated aqueous ammonium chloride (100 ml.) followed by extraction with ether afforded a gum, which gave the *phenol* (0·63 g., 33%), m.p. 252—255° (from aqueous methanol) (Found: C, 66·2; H, 6·7; Cl, 8·5; N, 3·0. $C_{23}H_{28}ClNO_4$ requires C, 66·1; H, 6·8; Cl, 8·5; N, 3·4%).

6,14-endo-*Etheno*-7α-(1-*hydroxy*-1-*methylethyl*)-2-*pyrrolidinomethyltetrahydro-oripavine* (3; R = pyrrolidino).—6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylethyl)tetrahydro-oripavine (3·5 g.), pyrrolidine (5 g.), and aqueous formaldehyde (36% w/v; 4 ml.) were heated together in boiling ethanol (80 ml.) for 5 hr. The solvent was removed and the residue was dissolved in aqueous hydrochloric acid. The precipitate obtained on basification with aqueous ammonia was crystallised three times from ethanol to give the *pyrrolidino-compound* (0·6 g.) as prisms, m.p. 183—186° (Found: C, 72·6; H, 8·3; N, 5·9%. $C_{28}H_{38}N_2O_4$ requires C, 72·1; H, 8·2; N, 6·0%).

The following analogous compounds were similarly prepared: (i) 2-*Dimethylaminomethyl*-6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylethyl*)*tetrahydro-oripavine*, m.p. 220° (Found: C, 70·5; H, 8·3; N, 6·3. $C_{26}H_{36}N_2O_4$ requires C, 70·9; H, 8·2; N, 6·4%); (ii) 6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylethyl*)-2-*piperidin*-1-*ylmethyltetrahydro-oripavine*, m.p. 199—209° (Found: C, 72·9; H, 8·4; N, 5·8. $C_{29}H_{40}N_2O_4$ requires C, 72·5; H, 8·4; N, 5·8%); and (iii) 6,14-endo-*etheno*-7α-(1-*hydroxy*-1-*methylethyl*)-2-*morpholino-methyltetrahydro-oripavine*, m.p. 198—200° (Found: C, 69·1; H, 7·9; N, 6·1. $C_{28}H_{38}N_2O_5$ requires C, 69·7; H, 7·9; N, 5·8%).

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