Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part XXIV.[1] 15,16-Didehydro-6,14-*endo*-etheno-6,7,8,14-tetrahydro-thebaines and -oripavines

By **D. I. Haddlesey, J. W. Lewis,* P. A. Mayor,** and **G. R. Young,** Reckitt and Colman, Pharmaceutical Division, Hull

A series of 15,16-didehydro-compounds has been prepared by mercury(II) acetate dehydrogenation of 6,14-*endo*-ethenotetrahydro-thebaines and -oripavines. The reaction has also been applied to certain other morphine derivatives. Reduction of the didehydro-compounds with sodium borohydride in the presence of tritiated water gave the [15-^{3}H]-derivatives.

THE nitrogen atom is believed to play an important role in the biological action of morphine-like analgesics.[2] It may be expected therefore that modification of the piperidine ring of the morphine molecule would have a profound effect on the biological activity. To test this idea we have selected for study some of the potent analgesics found amongst the 6,14-*endo*-ethenotetrahydrothebaines described earlier,[3,4] and in this and the following paper we describe the synthesis of some derivatives modified at C-15 and C-16.

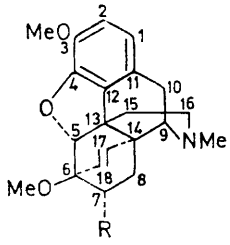
Dehydrogenation of cyclic amines with mercury(II) acetate gives the corresponding enamines.[5] This reaction has been applied to pethidine[6] and certain alkaloids[7] but until now not successfully[8] in the morphine series. Dehydrogenation generally proceeded smoothly with 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (1a) and the carbinols (2) to give the corresponding 15,16-didehydro-compounds (3a) and (4), respectively. In the *N*-methyl series (2; R^2 = Me) only one product was observed. There was no evidence for the formation of an intermediate exocyclic iminium ion, which would be readily hydrolysed under the reaction conditions to a nor-compound. The production of an iminium ion by loss of the C-9 proton would contravene Bredt's rule. In those derivatives that contain an unsaturated *N*-substituent (2; R^2 = allyl or cyclopropylmethyl), where production of an exocyclic intermediate iminium ion seems more probable, the final product was still the 15,16-didehydro-compound. Dehydrogenation of the primary carbinol (1b) with mercury(II) acetate was not achieved satisfactorily, and the didehydro-derivative (3b) was best prepared by

[1] Part XXIII, K. W. Bentley, J. W. Lewis, and A. C. B. Smith, preceding paper.
[2] A. H. Beckett, *Progr. Drug Res.*, 1959, **1**, 527.
[3] K. W. Bentley, D. G. Hardy, and B. Meek, *J. Amer. Chem. Soc.*, 1967, **89**, 3273.
[4] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3281.
[5] N. J. Leonard, A. S. Hay, R. W. Fulmor, and D. W. Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[6] J. W. Lewis and P. A. Mayor, *J. Chem. Soc.* (*C*), 1970, 1074.
[7] O. Cervinka in 'Enamines: Synthesis, Structure and Reactions,' ed. A. G. Cook, Marcel Dekker, New York, 1969, p. 253.
[8] H. Dieterle and P. Dickens, *Arch. Pharm.*, 1926, **264**, 257.

reduction of the didehydro-ester (3c) with lithium aluminium hydride. Dehydrogenations were also successful with the oripavines (2; $R^1 = H$).

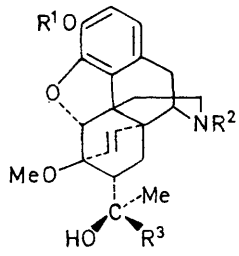
Other morphine derivatives may also be dehydrogenated with mercury(II) acetate provided that they do not contain a reactive olefinic bond; in the latter case the double bond is also attacked [9] and the products are intractable. [The etheno-bridge in the 6,14-*endo*-ethenotetrahydrothebaines is inert [3] and does not react with mercury(II) acetate.] Thus, didehydro-compounds were prepared from dihydrocodeine and its methyl ether, dihydrocodeinone, and 4-hydroxy-1,13-dimethyl-10-phenethyl-10-azatricyclo[7,3,1,0 ^{2,7}]trideca-2,4,6-triene-(phenazocine), but no identifiable product was obtained from codeine or morphine. Dieterle and Dickens [8] have also oxidised dihydrocodeine and its acetate and codeine with mercury(II) acetate but failed to obtain crystalline products.

The 15,16-didehydro-compounds were readily reduced with sodium borohydride or hydrogen in the presence of



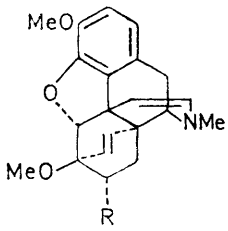
(1)

a; R = Ac
b; R = CH_2·OH



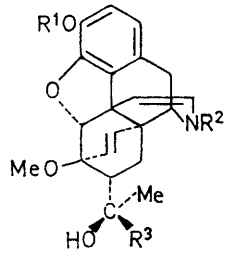
(2)

a; R^1 = H, R^2 = Me, R^3 = Pr^n
b; R^1 = R^2 = Me, R^3 = cyclohexyl



(3)

a; R = Ac
b; R = CH_2·OH
c; R = CO_2Et



(4)

a; R^1 = R^2 = Me, R^3 = cyclohexyl

palladium–charcoal to regenerate the starting alkaloid. This process of dehydrogenation followed by reduction offers a convenient and rapid way of introducing tritium specifically into the 15-position. Thus 7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydro-oripavine (etorphine) (2a), a potent analgesic used for the immobilisation of wild game,[4,10] was labelled with tritium at C-15 by equilibrating the 15,16-didehydro-compound with tritiated water and reducing the labelled didehydro-compound with sodium borohydride. Since the tritium is introduced in the final stage, high specific activities may be obtained. Etorphine labelled with tritium at C-8 has been previously prepared by a rather tedious process.[11]

The 15,16-didehydro-carbinols (4) were all less potent analgesics than the parent carbinols (2) when tested in rats by the tail pressure method.[12] For example the didehydro-carbinol (4a) (ED_{50} 17 mg per kg) was much weaker than its parent compound (2b) (ED_{50} 56 μg per kg). The former carbinol was a potent antitussive (ED_{50} 0·44 mg per kg) when tested in guinea pigs by the method of Winter and Flataker.[13]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. The n.m.r. spectrum was measured with a Varian T60 instrument, with tetramethylsilane as internal standard.

7α-Acetyl-15,16-didehydro-6,14-endo-ethenotetrahydrothebaine (3a).—A solution of 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine [14] (21·6 g) and yellow mercury(II) oxide (66 g) in 1·5N-acetic acid (1200 ml) was boiled for 0·5 h, cooled, saturated with hydrogen sulphide, and filtered. Neutralisation of the filtrate with potassium carbonate gave gave the *didehydro-compound* (3a) (17 g), m.p. 104—109° (from ethanol) (Found: C, 72·7; H, 6·8. $C_{23}H_{25}NO_4$ requires C, 72·8; H, 6·6%), $\nu_{max.}$ (KBr) 1625 (enamine) and 1715 cm^{-1} (COMe), τ ($CDCl_3$) 3·45 (s, H-1 and H-2), 4·10 and 4·47 (ABq, H-18 and H-17, *J* 9 Hz), 4·21 and 5·48 (ABq, H-16 and H-15, *J* 8 Hz), 5·17 (d, H-5β, coupled to H-18, *J ca.* 0·7 Hz), 6·20 (s, 3-OMe), 6·39 (s, 6-OMe), 7·16 (s, NMe), and 7·89 (s, COMe).

The *perchlorate*, prepared by dissolving the base in dilute acetic acid and adding sodium perchlorate solution, crystallised from methanol as needles, m.p. 189—191° (Found: C, 57·8; H, 5·7; Cl, 7·65; N, 3·25. $C_{23}H_{25}NO_4$,$HClO_4$ requires C, 57·6; H, 5·5; Cl, 7·4; N, 2·9%), $\nu_{max.}$ (KBr) 1690 (C=N^+) and 1710 cm^{-1} (COMe).

Other 15,16-didehydro-compounds prepared in this way are listed in Tables 1 and 2.

15,16-Didehydro-6,14-endo-etheno-7α-hydroxymethyltetrahydrothebaine (3b).—Ethyl 15,16-didehydro-6,14-*endo*-ethenotetrahydrothebaine-7α-carboxylate (1 g) in tetrahydrofuran (10 ml) was added to a slurry of aluminium lithium hydride (0·2 g) in tetrahydrofuran (10 ml), and the mixture was refluxed for 3 h. The complex was decomposed with water (0·5 ml) and the solution was filtered and evaporated to yield the *didehydro-carbinol* (3b) (0·9 g), m.p. 124—126° (from ethanol) (Found: C, 71·2; H, 7·1. $C_{22}H_{25}NO_4$ requires C, 71·9; H, 6·9%).

Hydrogenation of 7α-Acetyl-15,16-didehydro-6,14-endo-ethenotetrahydrothebaine.—The base (0·1 g) and 10% palladised charcoal (0·05 g) in ethanol (10 ml) were shaken in hydrogen at atmospheric temperature and pressure. The reduction was complete after 20 min. The solution

[9] See for example J. Chatt, *Chem. Rev.*, 1951, **48**, 7.
[10] J. M. King and B. H. Carter, *East African Wild Life J.*, 1965, **3**, 19; A. M. Harthoorn and J. Bligh, *Res. Vet. Sci.*, 1965, **6**, 290.
[11] A. C. Lane, A. McCoubrey, and R. Peaker, *J. Labelled Compounds*, 1966, **2**, 284.
[12] A. F. Green and P. A. Young, *Brit. J. Pharmacol.*, 1951, **6**, 572.
[13] C. A. Winter and L. Flataker, *J. Pharmacol.*, 1954, **112**, 99.
[14] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3267.

was filtered and evaporated to give 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine, identified by m.p., mixed m.p., and i.r. spectrum.

15,16-*Didehydrodihydrocodein* A solution of dihydrocodeine (3 g) and mercury(II) oxide (11 g) in 1·5N-acetic acid (200 ml) was boiled for 8 h, cooled, saturated with hydrogen sulphide, and filtered. Neutralisation of the filtrate with potassium carbonate gave **15,16-*didehydrodihydrocodeine*** (1·5 g), which crystallised from ethanol as prisms, m.p. 134—136° (Found: C, 69·8; H, 7·2; N, 4·6. $C_{18}H_{21}NO_3,0{\cdot}5H_2O$ requires C, 70·1; H, 7·2; N, 4·6%).

Similarly were prepared **15,16-*didehydrodihydrocodeine methyl ether***, m.p. 193—195° (from ethanol) (Found: C, 72·5; H, 7·3; N, 4·5. $C_{19}H_{23}NO_3$ requires C, 72·8; H, 7·4; N, 4·5%); **15,16-*didehydrodihydrocodeinone***, m.p. 191—193° (Found: C, 69·8; H, 6·3; N, 4·5. $3C_{18}H_{19}NO_3,2H_2O$ requires C, 69·8; H, 6·6; N, 4·5%); **4-*hydroxy*-1,13-*dimethyl*-10-*phenethyl*-10-*azatricyclo*[7,3,1,0 ^{2,7}]*trideca*-2,4,6,11-*tetraene***, m.p. 108—110° (from ethanol) (Found: C, 82·7; H, 8·2; N, 4·0. $C_{22}H_{25}NO$ requires C, 82·7; H, 7·9; N, 4·4%).

6,14-endo-*Etheno*-7α-(1-*hydroxy*-1-*methylbutyl*)*tetrahydro*-[15-^{3}H]*oripavine*.—15,16-Didehydro-6,14-*endo*-etheno-7α-(1-hydroxy-1-methylbutyl)tetrahydro-oripavine (0·64 g) (prepared by the general method already described) in anhydrous dioxan (2 ml) was placed in a vessel attached to a vacuum bridge. Tritiated water (*ca.* 20 Ci in 80 μl) was frozen in liquid nitrogen, dioxan (0·5 ml) was added, and the mixture was vacuum-transferred into the flask. The vacuum was released for the addition of sodium borohydride (0·6 g). The bridge was evacuated, sealed, and kept at ambient temperature. After 24 h the solvent was vacuum-transferred to an ampoule which was sealed for re-use. Potassium carbonate (0·5 g) in water (5 ml) and dioxan (5 ml) was added to the flask and the mixture was heated to 90° for 10 min to decompose the complex. The solvent was again removed under vacuum. Water (5 ml) was added and the mixture was extracted with chloroform. The crude product obtained by evaporation of the chloroform was chromatographed on silica (20 g; Merck GF 254). Elution with ether gave the tritiated base (148 mg), specific activity 100 mCi mmol^{-1}. T.l.c. [Antec silica; n-butanol–acetic acid–water (20 : 5 : 8)] showed only one radioactive spot, with the expected R_F value.

We thank Dr. I. A. Selby for the n.m.r. spectrum and Mrs. P. A. Southwell for experimental assistance.

[1/1091 *Received*, 29*th June*, 1971]

TABLE 1

15,16-Didehydro-carbinols of structure (4)

R^1	R^2	R^3	Reaction time (h)	M.p. (°C)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
Me	Me	Me	1·5	151—153	72·8	6·9	$C_{24}H_{29}NO_4$	72·9	7·4
Me	Me	Me	1·5	117—118	72·5	7·7	$C_{24}H_{31}NO_4$ *	72·5	7·9
Me	Me	Et	1·0	72—75	73·7	7·9	$C_{25}H_{31}NO_4$	73·3	7·6
Me	Me	Pr^n	1·0	192—194	73·6	8·0	$C_{26}H_{33}NO_4$	73·7	7·9
Me	Me	Bu^n	2·5	168—170	74·2	8·1	$C_{27}H_{35}NO_4$	74·1	8·1
Me	Me	n-Pentyl	1·2	99—102	74·5	8·3	$C_{28}H_{37}NO_4$	74·5	8·3
Me	Me	Cyclohexyl	0·5	119—120	73·7	8·0	$C_{29}H_{37}NO_4,0{\cdot}5H_2O$	73·7	8·1
Me	Me	Cyclohexyl	1·5	164—165	74·5	8·8	$C_{29}H_{39}NO_4$ *	74·8	8·4
Me	Me	CH_2Ph	1·0	195—197	76·3	7·1	$C_{30}H_{33}NO_4$	76·4	7·1
Me	Me	$[CH_2]_2Ph$	1·25	159—160	76·1	7·3	$C_{31}H_{35}NO_4$	76·7	7·3
Me	Et	Me	0·5	170—171	72·9	7·6	$C_{25}H_{31}NO_4$	73·3	7·6
Me	$CH_2{\cdot}CH{\cdot}CH_2{\cdot}CH_2$	Me	1·25	136—137	74·2	8·0	$C_{27}H_{35}NO_4$ *	74·1	8·1
Me	$CH_2{\cdot}CH{\cdot}CH_2{\cdot}CH_2$	Et	0·25	123—124	74·1	8·1	$C_{28}H_{35}NO_4$	74·8	7·85
Me	$CH_2{\cdot}CH{\cdot}CH_2{\cdot}CH_2$	Bu^n	1·0	96—98	75·1	8·2	$C_{30}H_{39}NO_4$	75·4	8·2
H	Me	Cyclohexyl	0·5	142—145	72·1	8·0	$C_{28}H_{35}NO_4,H_2O$	71·9	8·0
H	$CH_2CH{=}CH_2$	Pr^n	0·75	236—238	73·4	7·7	$C_{27}H_{33}NO_4,0{\cdot}5C_2H_5OH$	73·3	7·9
H	$CH_2{\cdot}CH{\cdot}CH_2{\cdot}CH_2$	Me	0·75	239—240	73·9	7·4	$C_{26}H_{31}NO_4$	74·1	7·4

* 6,14-*endo*-Ethano-compounds.

TABLE 2

Didehydro-compounds of structure (3)

R	Reaction time (h)	M.p. (°C)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
CO_2Et	0·75	91—93	70·0	6·6	$C_{24}H_{27}NO_5$	70·4	6·7
β-CN	0·75	223—225	72·5	6·2	$C_{22}H_{24}N_2O_3$	72·5	6·6