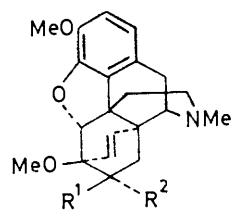
Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part XXVI.[1] Some Reactions of the Thebaine–2-Chloroacrylonitrile Adduct

By **J. W. Lewis,* M. J. Readhead** and **A. C. B. Smith,** Reckitt and Colman, Pharmaceutical Division, Hull

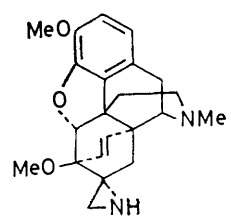
Catalytic hydrogenation and treatment with nucleophiles (Grignard reagent, alkoxide ions, morpholine) results in loss of chlorine from the thebaine–2-chloroacrylonitrile adduct. The products of the latter reactions are derived from the C-7 carbanion (5) and the 7,8-unsaturated 7-carbonitrile (9), in most cases by processes involving rearrangements.

THEBAINE reacts with 2-chloroacrylonitrile to give a 4 : 1 mixture of epimers (1a and b); stereochemistry at C-7 was assigned following conversion of the epimers into spiro-aziridines [*e.g.* (2)] with lithium aluminium hydride.[2] Further reactions of the adducts have now been studied.

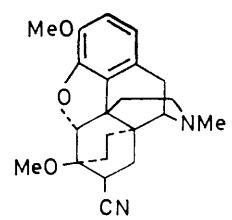


(1)

a; R^1 = CN, R^2 = Cl
b; R^1 = Cl, R^2 = CN
c; R^1 = CN, R^2 = H
d; R^1 = H, R^2 = CN
e; R^1 = H, R^2 = Bz

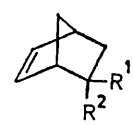


(2)



(3)

a; R^1 = Cl, R^2 = CN
b; R^1 = CN, R^2 = Cl
c; R^1 = H, R^2 = CN
d; R^1 = CN, R^2 = H



(4)

7β-Cyano-6,14-*endo*-ethanotetrahydrothebaine (3) was formed from both epimers (1a and b) by hydrogenation at atmospheric pressure over palladised charcoal. In neither case was there evidence for the formation of the 7α-cyano-compound. Over Raney nickel hydrogenation was slower and stopped with the uptake of 1 mol. equiv. of hydrogen. Both chloronitrile epimers gave 7β-cyano-6,14-*endo*-ethenotetrahydrothebaine (1c); the latter was also formed from (1a) by hydrogenation over 5% platinum on carbon. The stereospecificity of these reactions contrasts with the dehalogenation of the mixed epimers of the cyclopentadiene–2-chloroacrylonitrile adduct (4a and b) with the zinc–copper couple, which gave a 63 : 37 mixture of *endo*- and *exo*-2-cyanobicyclo-[2,2,1]hept-5-ene (4c and d), and hydrogenation over Raney nickel, which gave a similar mixture of the saturated cyano-derivatives.[3]

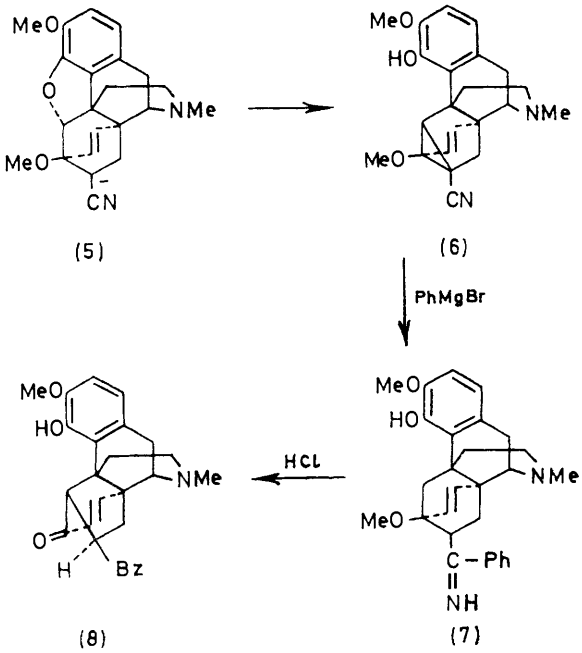
When the thebaine–chloroacrylonitrile adduct (1a) (TCAN) was treated with 4 mol. equiv. of phenyl-

[1] Part XXV, D. I. Haddlesey, J. W. Lewis, and P. A. Mayor, preceding paper.

[2] J. W. Lewis, M. J. Readhead, I. A. Selby, A. C. B. Smith, and C. A. Young, *J. Chem. Soc.* (*C*), 1971, 1158.

[3] H. Krieger, *Suomen Kem.*, 1963, **36***B*, 68.

magnesium bromide in benzene–ether and the Grignard complex was decomposed by cold hydrochloric acid, the product was an imine which was converted to ψ-nepenthone hydrochloride [4] (8) by dilution of a concentrated hydrochloric acid solution with water. Decomposition of the Grignard complex with boiling dilute hydrochloric acid gave a mixture of ψ-nepenthone and a very closely related compound. Extraction of the separate zones of a thin-layer plate resulted in a mixture of composition similar to the original, suggesting that the components were epimers in equilibrium and that re-equilibration occurred during extraction; this was confirmed by demonstration of the same behaviour for ψ-nepenthone. The epimeric chloronitrile (1b) (*epi*-TCAN) also gave ψ-nepenthone in an analogous reaction with phenylmagnesium bromide. The cyclopropanonitrile derivative (6) was shown to be an intermediate in the sequence by its isolation from the reaction of TCAN with 1 mol. equiv. of phenylmagnesium bromide.



These reactions of the chloro-nitriles (1a and b) must be initiated by removal of a chlorine atom by the Grignard reagent leaving the C-7 carbanion (5), which displaces the oxide bridge to give compound (6).[5] Further reaction with the Grignard reagent gives the ketimine (7) which is hydrolysed to ψ-nepenthone.

The Grignard reagent might be expected also to convert the thebaine–acrylonitrile adduct (1d) into the carbanion (5) and thence into ψ-nepenthone (8). From the reaction of a 1 : 1 mixture of epimers (1c and d) with phenylmagnesium bromide, Bentley and Hardy [6] isolated only the unrearranged 7α-ketone (1e) (nepenthone) in low yield. The reaction of the individual epimers with the Grignard reagent was re-investigated: both (1c) and (1d) with 4 mol. equiv. of phenylmagnesium bromide gave, as major product, ψ-nepenthone. The product from the α-epimer also contained nepenthone but no unrearranged ketone was detected in the product from the β-epimer.

With sodium ethoxide in boiling ethanol, TCAN (1a) was converted into a C-4 phenol, the i.r. spectrum of which showed nitrile absorption and also a signal (3080 cm^{-1}) which suggested [7] a cyclopropane structure analogous to that in (6). Then n.m.r. spectrum showed the presence of an ethoxy-group, and the absence of a high-field signal characteristic of the C-8α proton [8] suggested that the ethoxy-group could be occupying this position. Structure (11) satisfies these requirements; dehydrochlorination of the chloro-nitrile to (9) followed by attack of ethoxide ion at C-8 from the less hindered α-face would give the C-7 carbanion (10), which would displace the oxide bridge to give structure (11). The easy hydrolysis of the rearrangement product to an αβ-unsaturated ketone (12) was analogous to similar transformation of compound (6).[5]

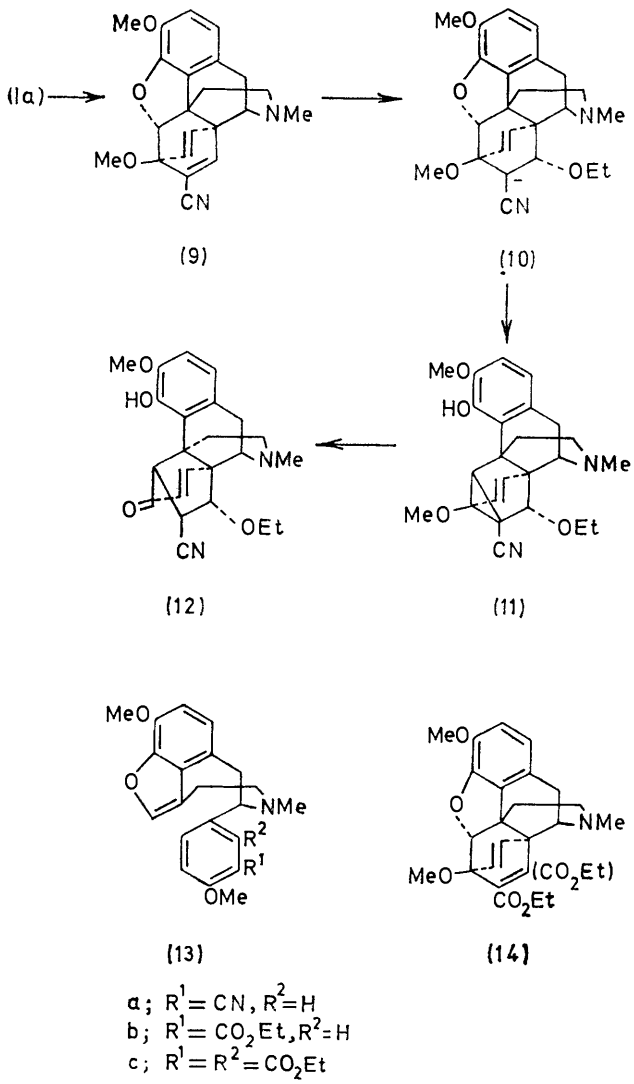
In contrast to the reaction with sodium ethoxide in ethanol, compounds (1a) and (1b) with the same base (or with potassium t-butoxide) in boiling 2-ethoxyethanol gave a non-phenolic product to which was assigned structure (13a). Analogous products (13b and c) have been reported [9] from rearrangement at 130—140° of adducts (14) derived from thebaine and acetylenic dienophiles, which are directly analogous to dehydrochlorination product (9).

When both TCAN (1a) and its epimer (1b) were heated under reflux in morpholine, the major products were the benzofuran derivative (13a) and the dechloro-derivative (1c). The former is formed by the dehydrochlorination–thermal rearrangement sequence as in the sodium ethoxide–2-ethoxyethanol reaction. The hydrogenolysis reaction leading to (1c) must involve attack by morpholine at the chlorine atom rather than at the hindered C-7. The possibility that some of compound (1d) was initially formed in these reactions but underwent epimerisation was ruled out by recovery of unchanged (1d) from treatment with boiling morpholine. The predominance of the 7β-cyano-epimer in the products from both chloronitrile epimers points to the participation of carbanion (5), which undergoes kinetically controlled protonation.

It was surprising that very little of compound (6) was detected in the foregoing reaction, in view of the ease of rearrangement of carbanion (5) when it is generated in Grignard reactions. It appears likely that solvation of the carbanion in the morpholine reaction accounts for lack of rearrangement in this case.

[4] K. W. Bentley and J. C. Ball, *J. Org. Chem.*, 1958, **23**, 1275.
[5] K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Amer. Chem. Soc.*, 1967, **89**, 3312.
[6] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3267.
[7] L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules,' 2nd edn., Methuen, London, 1958, p. 17.
[8] W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 3322.
[9] H. Rapoport and P. Sheldrick, *J. Amer. Chem. Soc.*, 1963, **85**, 1636.

None of the new compounds described in this paper has significant analgesic activity.



a; $R^1 = CN, R^2 = H$
b; $R^1 = CO_2Et, R^2 = H$
c; $R^1 = R^2 = CO_2Et$

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were determined for potassium bromide pellets with a Perkin-Elmer 237 spectrometer and n.m.r. spectra determined for solutions in deuteriochloroform with tetramethylsilane as internal standard (instrument indicated).

Catalytic Hydrogenation of TCAN and epi-*TCAN.*—(*a*) *TCAN* (1a) (2·0 g) was hydrogenated in glacial acetic acid at atmospheric pressure and temperature over palladised charcoal (10%; 0·2 g). After 3½ h 2 mol. equiv. of hydrogen had been absorbed and uptake ceased. The mixture was filtered, diluted with water, and basified with ammonia (*d* 0·880). The precipitated base was recrystallised from ethanol to give 7β-cyano-6,14-*endo*-ethanotetrahydrothebaine (3) (1·5 g), m.p. 218—220°, identical with material obtained by hydrogenation of 7β-cyano-6,14-*endo*-ethenotetrahydrothebaine (Found: C, 72·2; H, 7·0; N, 7·5. $C_{22}H_{26}N_2O_3$ requires C, 72·1; H, 7·2; N, 7·6%). A similar hydrogenation of *epi*-TCAN (1b) (2·0 g) also gave (3) (1·5 g), m.p. 218—220°.

(*b*) TCAN (2 g) in ethanol (50 ml) and glacial acetic acid (10 ml) was hydrogenated at atmospheric pressure and temperature over Raney Nickel-W2. After 1 mol. equiv. of hydrogen had been absorbed (3 h) the catalyst was filtered off. The solution was evaporated *in vacuo* and the residue, dissolved in water, was treated with ammonia (*d* 0·880). The precipitated material afforded 7β-cyano-6,14-*endo*-ethenotetrahydrothebaine (1c) (1·0 g), m.p. 195—197° (from ethanol), identical (m.p., i.r. spectrum, R_F value) with authentic material.[6] In a similar experiment epi-TCAN (1b) (2 g) afforded the same product (1·5 g), m.p. 196—198°. In a similar experiment with 5% platinum–carbon catalyst, TCAN (1 g) afforded the same product (0·7 g), m.p. 195—198°.

Reaction of TCAN *with Phenylmagnesium Bromide.*—(*a*) TCAN (1·0 g, 0·0025 mol.) dissolved in benzene (30 ml) was added dropwise to a stirred boiling solution of phenylmagnesium bromide (0·01 mol) [from bromobenzene (1·57 g) and magnesium (0·24 g)] in ether. The mixture was boiled under reflux for 18 h after which it was cooled and poured with vigorous stirring into 6N-hydrochloric acid (200 ml). The aqueous layer was separated and was heated under reflux for 45 min. After extraction with ether the aqueous layer was basified [NH_4OH (*d* 0·880)]. The free base was filtered off and well washed with water. It was redissolved in aqueous hydrochloric acid and the solution was boiled with animal charcoal for 5 min. The re-isolated base (0·7 g) was compared (t.l.c. on silica) with the material obtained by boiling ψ-nepenthone [4] with 5N-hydrochloric acid for 5 min and was shown to be an identical mixture of epimers; $\nu_{max.}$ 1680 cm^{-1}. When the separate bands from thin-layer plates were extracted with methanol or chloroform only mixtures of the epimers were obtained.

In an analogous reaction, the base was isolated immediately after treatment with 6N-hydrochloric acid in the cold; it showed no carbonyl absorption in the i.r. This product was redissolved in concentrated hydrochloric acid and the solution was heated on a steam-bath; ψ-nepenthone hydrochloride [4] (8) crystallised after 10 min. The free base had m.p. and mixed m.p. 200—202° (from ethanol).

(*b*) The reaction was repeated with 0·05 mol. each of TCAN and the Grignard reagent. The cooled mixture was poured into saturated ammonium chloride solution; after extraction of the mixture with benzene the combined organic solutions were dried and evaporated. T.l.c. showed that the product was a mixture of starting material and 7-cyano-5,7-cyclo-6,14-*endo*-etheno-6-*O*-methyldihydrothebainol (6), and a specimen, m.p. 232—234°, isolated by preparative t.l.c. (alumina; di-isopropyl ether), was identical (m.p., mixed m.p., t.l.c., i.r., n.m.r.) with, authentic material.[5]

The same products were obtained from similar reactions with *epi*-TCAN.

Reaction of 7β-*Cyano*-6,14-endo-*ethenotetrahydrothebaine* (1c) *with Phenylmagnesium Bromide.*—The nitrile (5·4 g) in benzene was slowly added to a stirred ether solution of phenylmagnesium bromide (4 mol. equiv.) [from bromobenzene (9·3 g) and magnesium (0·96 g)]. The stirred mixture was boiled under reflux for 18 h, cooled, and then poured into aqueous saturated ammonium chloride. The organic layer was removed and the aqueous solution was

washed with benzene. The combined organic solutions were dried (Na_2SO_4) and evaporated. The residual oil was treated with dilute acetic acid, quickly extracted with ether and immediately made alkaline with ammonia (*d* 0·880). Extraction with ether then afforded a non-crystalline solid (4·0 g), which was dissolved in 2N-hydrochloric acid and heated on a steam-bath for 30 min. The solution was cooled and made alkaline with ammonia (*d* 0·880). The precipitated solid (2·7 g.) was shown by t.l.c. to be a mixture of *ψ*-nepenthone and its epimer; $\nu_{max.}$ 1680 cm^{-1}. No unrearranged material was detected.

In a similar experiment 7α-cyano-6,14-*endo*-ethenotetrahydrothebaine gave the same mixture of epimers, together with the unrearranged ketone nepenthone (1e) (*ca.* 15%).

7-*Cyano*-5,7-*cyclo*-6,14-endo-*etheno*-8-*ethoxy*-6-O-*methyldihydrothebainol* (11).—TCAN (3 g) was added to a solution of sodium (1 g) in anhydrous ethanol (70 ml). The mixture was boiled under reflux for 18 h, poured into saturated ammonium chloride solution, and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated; the residue afforded the *thebainol* (11) (0·6 g), m.p. 250—252° (from methanol) (Found: C, 70·4; H, 6·8; N, 7·0. $C_{24}H_{28}N_2O_4$ requires C, 70·5; H, 6·9; N, 6·9%), τ (Jeol 100 MHz) 3·4 (2H, s, H-2 and H-1), 3·7 and 4·35 (2H, ABq, H-18 and H-17, *J* 9 Hz), 4·2 (1H, s, H-5), 5·02 (1H, s, OH), 6·2 (s, 3-OMe), 6·4 (s, 6-OMe), 7·65 (s, NMe), and 8·8 (t, 8-OEt).

5,4-(1-*Cyano*-2-*ethoxyethano*)*thebainone* (12).—A suspension of 7-cyano-5,7-cyclo-6,14-*endo*-ethano-8-ethoxy-6-*O*-methyldihydrothebainol (1 g) in 5N-hydrochloric acid (15 ml) was heated on a boiling water-bath for 45 min. The mixture was diluted with water and treated with ammonia (*d* 0·880). The resulting precipitate gave the *thebainone* (12) (0·5 g), m.p. 233—235° (from methanol) (Found: C, 70·2; H, 6·6; N, 7·0. $C_{23}H_{26}N_2O_4$ requires C, 70·0; H, 6·6; N, 7·1%).

6-(3-*Cyano*-4-*methoxyphenyl*)-3,4,6,7-*tetrahydro*-10-*methoxy*-5-*methyl*-5H-*furo*[4,3,2-fg][3]*benzazocine* (13a).—(*a*) TCAN (3 g) and potassium t-butoxide (M.S.A. Research Corporation, Gallery, Pennsylvania, U.S.A.) (1·5 g) were heated together in boiling Cellosolve for 18 h. The mixture was cooled and poured into water, and made acid with 5N-hydrochloric acid. The solution was treated with ammonia (*d* 0·880) and filtered. The dried base (1·5 g) was purified by dissolving in benzene and passing down an alumina (neutral, grade I) column. The eluate gave compound (13a), which was converted into the *hydrochloride*, m.p. 252—255° (Found: C, 64·9; H, 6·1; N, 7·0. $C_{22}H_{22}N_2O_3$-HCl,0·5H_2O requires C, 64·8; H, 5·9; N, 6·9%), τ (Varian A60) 2·6 (1H, s, H-2), 2·7 (2H, m, H-2′ and H-6′), 3·1 (1H, d, H-5′, *J* 8 Hz), 3·37 (2H, s, H-8 and H-9), 6·02 (s, 10-OMe), 4·1 (s, 4′-OMe), and 7·9 (s, NMe).

(*b*) The same material was isolated from a similar reaction with sodium ethoxide in boiling Cellosolve.

Reaction of TCAN with Morpholine.—A mixture of TCAN (2 g) and morpholine (25 ml) was heated at reflux for 6 h. The morpholine was then removed under reduced pressure, leaving a gum. Addition of water (50 ml) gave a solid, which was collected, washed with water, and dried (1·5 g.). This crude product (400 mg) was subjected to preparative t.l.c. Elution with ether–light petroleum (9 : 1) afforded (in order of elution) the compounds shown in the Table. These assessments were in reasonable agreement with those deduced from u.v. intensity measurements on the separated fractions.

Wt. (mg)	(%)	Compound
24	6	(1a), m.p. 170—172° (ref. 2)
143	36	(13a) (hydrochloride, m.p. 250—255°)
156	39	(1c), m.p. 192—195°
5	1	(1d), m.p. 180—182° (ref. 10)
47	11	Unidentified
26	7	Unidentified

In a similar preliminary experiment (but worked up by treatment with water and ether extraction rather than by evaporation), crystallisation of the crude product from ethanol afforded a low recovery (15% of crude material) of 7β-cyano-6,14-*endo*-ethenotetrahydrothebaine, m.p. 189—191°, identical with authentic material (i.r., n.m.r.).

In a similar experiment *epi*-TCAN afforded the same products in essentially the same proportions.

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[10] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3267.