Novel Analgesics and Molecular Rearrangements in the Morphine–Thebaine Group. Part XXIII.[1] Adducts of Thebaine with Divinyl Sulphone and with Methyl Vinyl Sulphone

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Adducts of thebaine with divinyl sulphone and with methyl vinyl sulphone are described and some observations relating to their C-7 stereochemistry are reported.

A VARIETY of Diels–Alder condensations with thebaine as diene component have been described.[2] We here report an extension to include αβ-unsaturated sulphones as dienophiles.

Thebaine and divinyl sulphone formed a 1 : 1 adduct (Ia; R = $CH{:}CH_2$). The presence of exocyclic vinyl protons was established by the n.m.r. spectrum; further the material was easily hydrogenated to the 7-ethylsulphonyl compound (Ia; R = Et). The original adduct was initially assigned as the 7α-vinylsulphonyl compound by analogy with previously described[2] Diels–Alder adducts of thebaine with monosubstituted ethylenes.

Treatment of the ethylsulphonyl compound (Ia; R = Et) with hot ethanolic sodium hydroxide caused epimerisation at C-7 to the 7β-product (Ib; R = Et). The n.m.r. spectra of the two epimers differed particularly in the resonance of the C-5 proton [(Ia; R = Et), τ 5·59; (Ib; R = Et), τ 4·47]. This distinction supports the present C-7 assignments provided that a 7β-sulphonyl group has a qualitatively similar effect on the C-5β proton resonance as that previously recorded[3] for other 7β-electron-attracting groups.

Certain other thebaine Diels–Alder adducts having an electron-withdrawing 7α-substituent and a 7β-proton (II; R = COMe, CO_2Et, or CN) are known to rearrange on treatment with alkali.[4] The rearrangement products are themselves labile to acid, giving derivatives of 5,14-ethanothebainone[4] (III). Compound (Ib; R = Et) was unaffected by acid, confirming its dissimilarity to these examples. The failure to rearrange may reflect a weaker nucleophilic character of the sulphonyl carbanion.

The adduct (Ia; R = Me) from thebaine and methyl vinyl sulphone was also epimerised on heating with ethanolic sodium hydroxide. The n.m.r. spectra of this epimeric pair showed a similar relationship to that for the ethyl homologues, *viz.* for 5β-H τ 5·50 (Ia; R = Me); τ 4·46 (Ib; R = Me).

Tertiary amines (Ia; R = 2-morpholinoethyl, 2-piperidinoethyl, 2-dimethylaminoethyl, or 2-diethylaminoethyl) resulted from treatment of the vinylsulphonyl adduct (Ia; R = $CH{:}CH_2$) with the appropriate secondary amines. The n.m.r. spectra of these products indicated stereochemical similarity to the starting material (based on 5β-H resonance).

The compounds were examined for analgesic activity

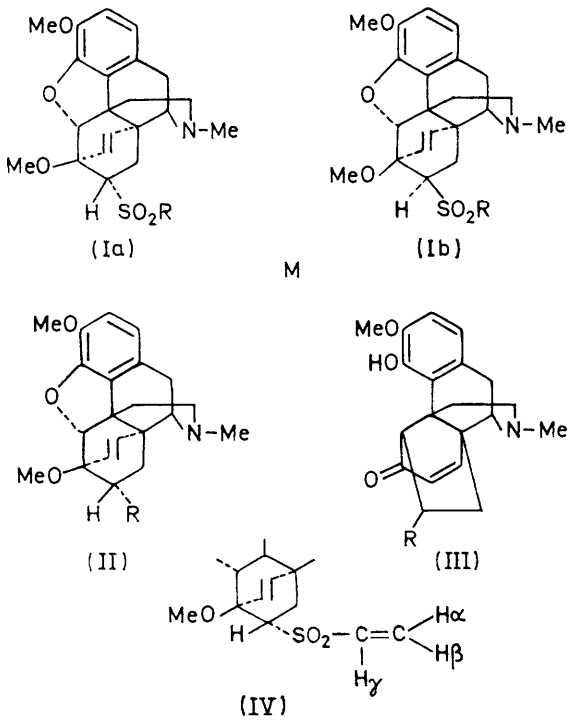
[1] Part XXII, J. W. Lewis and M. J. Readhead, *J. Chem. Soc.* (*C*), 1971, 2298.

[2] K. W. Bentley and D. G. Hardy, *J. Amer. Chem. Soc.*, 1967, **89**, 3267 and references cited therein.

[3] W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. H. Howell, C. T. Nora, and R. A. Hardy, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 3322.

[4] K. W. Bentley, D. G. Hardy, H. P. Crocker, D. I. Haddlesey, and P. A. Mayor, *J. Amer. Chem. Soc.*, 1967, **89**, 3312.

in the rat (tail pressure test, intraperitoneal [5]). The 7α-ethylsulphonyl, 7α-(2-morpholinoethylsulphonyl), 7α-(2-piperidinoethylsulphonyl), and 7β-methylsulphonyl



compounds were the most active, being of similar potency to codeine. No correlation between activity and C-7 stereochemistry was apparent from examination of the two diastereoisomeric pairs.

Analgesic activities

R in (Ia)	ED_{50} (mg per kg)	R in (Ib)	ED_{50}
CH_2:CH	54	Me	10
Me	23	Et	*ca.* 10
Et	14		
2-Morpholinoethyl	13		
2-Piperidinoethyl	10		
2-Dimethylaminoethyl	70		
2-Diethylaminoethyl	40		

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined for potassium bromide pellets with a Perkin-Elmer 137 spectrometer, and n.m.r. spectra for solutions in deuteriochloroform with a Varian T60 or Jeol 100 MHz instrument, with tetramethylsilane as internal standard.

6,14-endo-*Etheno*-7α-*vinylsulphonyltetrahydrothebaine* (Ia; R = CH:CH_2).—A solution of thebaine (55 g) and divinyl sulphone (25 g) in dry toluene (500 ml) was boiled for 46 h. The cooled solution afforded the *adduct* (Ia; R = CH:CH_2) (44·7 g), m.p. 190—192° (from 2-ethoxyethanol) (Found: C, 64·4; H, 6·4; N, 3·1; S, 7·4. $C_{23}H_{27}NO_5S$ requires C, 64·3; H, 6·3; N, 3·3; S, 7·5%), τ (Jeol 100 MHz) 7·66 (s, NMe), 6·30 (s, 6-OMe), 6·19 (s, 3-OMe), 5·52 (d, H-5, *J ca.* 1 Hz), 4·48 (d, H-17, *J ca.* 8·8 Hz), *ca.* 4·0 (2 × d or d and dd, H-18 and SO_2·CH:CH_β, *J ca.* 8·8 and 8·8 Hz), 3·69 (d, SO_2·CH:CH_α, *J* 17·5 Hz), 3·41 (ABq, H-1 and H-2, *J* 7·5 Hz), and 3·17 (dd, SO_2·CH, *J* 8·8 Hz).

6,14-endo-*Etheno*-7α-*ethylsulphonyltetrahydrothebaine* (Ia; R = Et).— 6,14-*endo*-Etheno-7α-vinylsulphonyltetrahydrothebaine (2 g) in glacial acetic acid (22 ml) was hydrogenated over 10% palladium–charcoal (0·2 g) at room temperature and atmospheric pressure for 40 min. The mixture was diluted with water and filtered. The solid (1·8 g) obtained by addition of ammonia (*d* 0·880) to the filtrate gave the *ethyl derivative* (Ia; R = Et) (1·4 g), m.p. 225—226° (from ethanol) (Found: C, 64·0; H, 6·9; N, 3·5; S, 7·4. $C_{23}H_{29}NO_5S$ requires C, 64·0; H, 6·8; N, 3·2; S, 7·4%), τ (Jeol 100 MHz) 8·68 (t, CH_2*Me*), 7·77 (s, NMe), 6·29 (s, 6-OMe), 6·21 (s, 3-OMe), 5·59 (d, H-5, *J* 8·8 Hz), 4·52 (d, H-17, *J* 8·8 Hz), 4·01 (dd, H-18, *J* 8·8 and *ca.* 1 Hz), and 3·47 (ABq, H-1 and H-2, *J* 7·5 Hz).

6,14-endo-*Etheno*-7β-*ethylsulphonyltetrahydrothebaine* (Ib; R = Et).— 6,14-*endo*-Etheno-7α-ethylsulphonyltetrahydrothebaine (0·25 g) was heated in boiling ethanol (5 ml) containing sodium hydroxide (0·1 g) for 4 h. The solid (0·2 g) isolated after pouring the mixture into water (20 ml) had m.p. *ca.* 310° (decomp.). Crystallisation from 2-ethoxyethanol gave the *epimer* (Ib; R = Et) (0·08 g), m.p. *ca.* 315° (decomp.) (Found: C, 64·0; H, 6·6; N, 3·4; S, 7·3. $C_{23}H_{29}NO_5S$ requires C, 64·0; H, 6·8; N, 3·2; S, 7·4%), τ (Jeol 100 MHz) 8·6 (t, CH_2*Me*, *J* 7·5 Hz), 7·66 (s, NMe), 6·68 (q, CH_2Me, *J* 7·5 Hz), 6·30 (s, 6-OMe), 6·19 (s, 3-OMe), 4·47 (d, H-5, *J ca.* 1 Hz), 4·46 (d, H-17, *J* 7·5 Hz), 3·97 (dd, H-18, *J* 7·5 and *ca.* 1 Hz), and 3·43 (ABq, H-1 and H-2, *J* 7·5 Hz).

Stability of 6,14-endo-*Etheno*-7β-*ethylsulphonyltetrahydrothebaine towards Mineral Acid.*—The sulphone (0·3 g) in N-hydrochloric acid (2 ml) was kept at *ca.* 100° for 2 h. After dilution with water, filtration, and basification (ammonia), the precipitated material was collected, washed with water, and dried to give solid (0·2 g) identical with starting material (m.p., i.r., t.l.c.).

6,14-endo-*Etheno*-7α-*methylsulphonyltetrahydrothebaine* (Ia; R = Me).—A solution of thebaine (10 g) and methyl vinyl sulphone (5 g) in dry toluene (100 ml) was boiled for 40 h. T.l.c. indicated that a significant amount of unchanged thebaine was present, so more methyl vinyl sulphone (5 g) was added and boiling was continued for a further 40 h. The solution was then diluted with ether (50 ml) and extracted with aqueous 5% acetic acid (4 × 50 ml). The acetic acid extract was washed with ether (2 × 50 ml) and heated with charcoal; the filtered solution was treated with ammonia (*d* 0·880) and the precipitate (8·15 g) was crystallised from ethanol to give the *adduct* (Ia; R = Me) (6·2 g), m.p. 201—204° (Found: C, 62·8; H, 6·4; N, 3·3; S, 7·7. $C_{22}H_{27}NO_5S$ requires C, 63·3; H, 6·5; N, 3·4; S, 7·7%), τ (Varian T60) 7·66 (s, NMe), 6·97 (s, SO_2Me), 6·25 (s, 6-OMe), 6·17 (s, 3-OMe), 5·50 (d, H-5, *J* 1 Hz), 4·42 (d, H-17, *J* 9 Hz), 3·93br (d, H-18, *J* 9 Hz), and 3·37 (ABq, H-1 and H-2, *J* 8·5 Hz).

6,14-endo-*Etheno*-7β-*methylsulphonyltetrahydrothebaine* (Ib; R = Me).—6,14-*endo*-Etheno-7α-methylsulphonyltetrahydrothebaine (0·25 g) was heated in boiling ethanol (5 ml) containing sodium hydroxide (0·1 g) for 2½ h, during which time solid separated. The mixture was poured into water (*ca.* 30 ml) to give solid (0·18 g), which afforded the *epimer* (Ib; R = Me) (0·07 g), m.p. 304—307° (from ethanol) (Found: C, 63·4; H, 6·9; N, 3·1; S, 7·7.

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

$C_{22}H_{27}NO_5S$ requires C, 63·3; H, 6·5; N, 3·4; S, 7·7%), τ (Varian T60) 7·67 (s, NMe), 6·89 (s, SO_2Me), 6·30 (s, 6-OMe), 6·19 (s, 3-OMe), 4·46 (d, H-17, *J* 9·5 Hz), 4·46 (d, H-5, *J* 1·5 Hz), 3·93 (dd, H-18, *J* 8 and 2 Hz), and 3·42 (ABq, H-1 and H-2 *J* 8 Hz).

6,14-endo-*Etheno*-7α-(2-*morpholinoethylsulphonyl*)*tetrahydrothebaine*.— 6,14-*endo*-Etheno-7α-vinylsulphonyltetrahydrothebaine (2·15 g) was stirred overnight with ethanol (20 ml) containing morpholine (1·3 g). Evaporation of the resulting solution gave a glass which was converted into solid (1·3 g) by dissolving in dilute acetic acid followed by addition of aqueous sodium hydroxide. Crystallisation from ethanol afforded the *morpholine derivative* (0·87 g), m.p. 189—191° (Found: C, 62·6; H, 7·1; N, 5·4; S, 6·2. $C_{27}H_{36}N_2O_6S$ requires C, 62·8; H, 7·0; N, 5·4; S, 6·2%), τ (Varian T60) 7·65 (s, NMe), 6·27 (s, 6-OMe), 6·20 (s, 3-OMe), 5·60 (s, H-5, *J* 1 Hz), 4·47 (d, H-17, *J* 9 Hz), 3·90 (dd, H-18, *J* 9 and 1 Hz), and 3·44 (ABq, H-1 and H-2, *J* 8 Hz).

The following compounds were also obtained from (Ia; R = $CH{:}CH_2$) by treatment with the appropriate amine at room temperature: 6,14-endo-*etheno*-7α-(2-*piperidinoethylsulphonyl*)*tetrahydrothebaine*, m.p. *ca.* 105° (indefinite) (Found: C, 64·5; H, 7·3; N, 5·4; S, 6·1. $C_{28}H_{38}N_2O_5S$ requires C, 65·3; H, 7·4; N, 5·4; S, 6·2%), τ (Varian T60) 7·64 (s, NMe), 6·22 (s, 6-OMe), 6·15 (s, 3-OMe), 5·47br (d, H-5, *J* 1 Hz), 4·41 (d, H-17, *J* 9 Hz), 3·83 (dd, H-18, *J* 9 and 1 Hz), and 3·36 (ABq, H-1 and H-2, *J* 9 Hz); 7α-(2-*dimethylaminoethylsulphonyl*)-6,14-endo-*ethenotetrahydrothebaine*, m.p. 186—188° (from ethanol) (Found: C, 63·3; H, 7·2; N, 5·9; S, 6·7. $C_{25}H_{34}N_2O_5S$ requires C, 63·3; H, 7·2; N, 5·9; S, 6·8%), τ (Varian T60) 7·74br (s, NMe_2), 7·66 (s, NMe), 6·26 (s, 6-OMe), 6·20 (s, 3-OMe), 5·60br (d, H-5, *J* 1 Hz), 4·44 (d, H-17, *J* 9 Hz), 3·90br (d, H-18, *J* 9 Hz), and 3·41 (ABq, H-1 and H-2, *J* 8—9 Hz); 7α-(2-*diethylaminoethylsulphonyl*)-6,14-endo-*ethenotetrahydrothebaine*, m.p. 125—127° (from water–ethanol) (Found: C, 64·7; H, 7·3; N, 5·3; S, 6·5. $C_{27}H_{38}N_2O_5S$ requires C, 64·5; H, 7·6; N, 5·6; S, 6·4%), τ (Varian T60) 8·93 (t, CH_2Me, *J* 7 Hz), 7·66 (s, NMe), 6·25 (s, 6-OMe), 6·19 (s, 3-OMe), 5·55br (d, H-5, *J* 1 Hz), 4·45 (d, H-17, *J* 9 Hz), 3·87br (d, H-18, *J* 9 Hz), and 3·40 (ABq, H-1 and H-2, *J* 8 Hz).

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