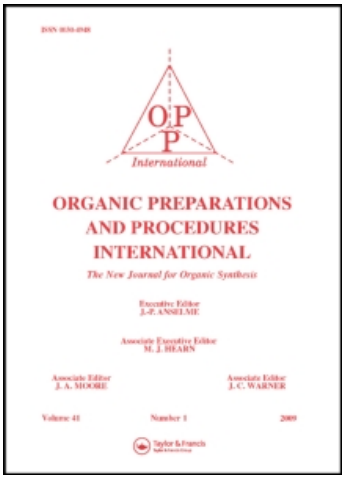

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OPPI BRIEFS

SYNTHESIS OF A NEW AZATETRACYCLODECANE RING SYSTEM via INTRAMOLECULAR ADDITION OF AZIDE ON DOUBLE BOND†

Submitted by (02/08/90)

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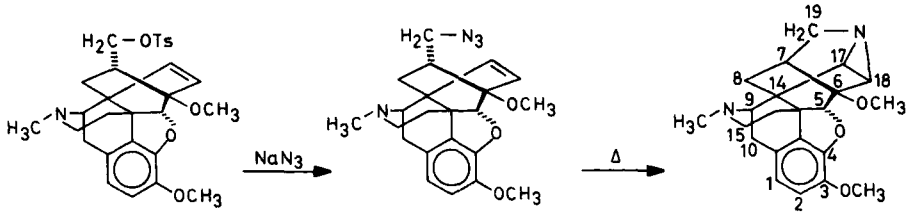
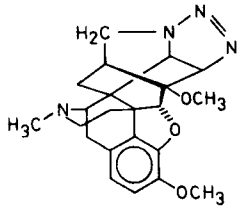
Modified derivatives of Diels-Alder adducts obtained from thebaine have proved to be highly effective analgesics.[1] Pharmacological activity is determined by the chemical surroundings of the C-19 atom and the most efficient compounds are tertiary alcohols. Since the replacement of the C-6 hydroxyl group of morphine by an azido group resulted in favorable pharmacological properties,[2] it seemed useful to prepare the new C-19 azido derivative of substances possessing bridged ring C. Azidolysis of 7α-tosyloxymethyl-6,14-endo-ethenotetrahydrothebaine (1)[3] with NaN_3 in aqueous dimethylformamide for 1 hr at 100° gave azido derivative 2, while prolonged reaction time (24 hrs) resulted in the formation of compound 3 in 57% yield.



1 2 3

Compound 3 was also prepared by heating 2 for 24 hrs in dimethylformamide. In compound 3, ring C of morphine is replaced by a hitherto unknown 4-azatetracyclo-[4.4.0.$0^{3,8}$.$0^{2,4}$]-decane ring-system. The formation of 3 from 2 by intramolecular cyclization



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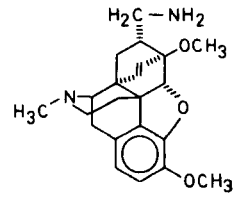

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can be assumed to proceed via intermediate triazoline 4. Mixtures of aziridines and imines[5] or imines[6] have been obtained from similar intramolecular cyclizations. The aziridine nature of 3 was unequivocally established by ^1H and ^{13}C NMR spectra. Azide 2 was reduced in 69% yield to the corresponding amine 5 with hydrazine hydrate in refluxing ethanol in the presence of Raney nickel.

EXPERIMENTAL SECTION

Melting points were obtained on a Kofler hot stage apparatus and are uncorrected. Thin layer chromatography was performed on Merck 5554 silica gel F_{254} foils using benzene:methanol (8:2) developing mixtures. The detecting agent was Dragendorff reagent. The ^1H NMR spectra were obtained with Bruker WP 2000 SY spectrometer, chemical shifts are reported in ppm (δ) from internal TMS. Infrared spectra were recorded on a Perkin-Elmer 283 B spectrometer. Mass spectra were measured with a VG-7035 (GC-MS-DS) instrument. Microanalyses were carried out in the microanalytical laboratory of our Department, using Coleman apparatus.

7α-(Azidomethyl)-6,14-endo-ethenotetrahydrothebaine (2).- To a solution of 1 (4.00 g, 7.64 mmol)[3] in dimethylformamide (120 ml), an aqueous solution (10 ml) of NaN_3 (2.86 g, 38.2 mmol) was added. The mixture was heated at 100° for 1.5 hr, then poured into ice-water and extracted with ether (3 x 100 ml). The organic layers were combined, washed several times with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a viscous oil (3.5 g) which showed two products by TLC: R_f 0.6 and 0.28. The two products were separated by chromatography (Kieselgel 60H, 200 g) and eluted with benzene:methanol (9:1). The NMR of the less mobile product was identical with 3. The faster moving product was the 7α-azidomethyl compound 2 (unstable oil). The ratio of the two products 2 and 3 was 9/1. IR (KBr): 2100, N_3; ^1H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, NMe), 3.59 (s, 6-OMe), 3.82 (s, 3-OMe), 4.59 (s, H-5), 5.49 (d, H-17), 5.74 (d, H-18).

17,18-Aziridino-7α,20-methano-6,14-endo-ethanotetrahydrothebaine (3).- a) A solution of the crude azide 2 (2.0 g, 5.0 mmol) in dimethylformamide (30.0 ml) was heated at 100° for 24 hrs. The solvent was evaporated under reduced pressure and the residual oil was diluted with water (100 ml) and extracted with chloroform (3 x 50 ml). The organic layers were combined, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield an oil. The oil was dissolved in ether (20 ml) and the pH of the solution was adjusted to 5.5 with alcoholic hydrochloric acid. The resultant pink precipitate was collected, washed with ether and air dried to yield 1.2 g of the hydrochloride salt (59%). The salt was dissolved in water (15 ml) and basified with NH_4OH solution and the precipitate filtered. The free base was recrystallized from ether, mp. 159-161°, $[\alpha]_D^{22}$ = -11 (c = 0.1 chloroform); MS (EI, 70 eV): m/z (%) 366 (M^+, 100); ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (d, H-8), 1.25 (dd, H-17, $J_{17\text{-}18}$ = 6.3 Hz), 2.1 (d, H-18), 2.13 (m, H-7), 2.32 (s, N-Me), 3.51 (s, 6-OMe), 3.88 (s, 3-OMe), 4.99 (s, H-5), 6.61 (d, H-1), 6.72 (d, H-2); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 145.99 (C-4), 142.32 (C-3), 133.71 (C-12),

127.31 (C-11), 119.34 (C-1), 114.19 (C-2), 90.77 (C-5), 87.48 (C-6), 62.11 (C-9), 58.85 (C-19), 56.59 (3-OMe), 52.42 (6-OMe), 47.27 (C-13), 44.92(C-16), 43.73 (N-Me), 38.53 (C-17), 38.0 (C-18), 38.02 (C-14), 36.19 (C-7), 31.96 (C-15), 30.93 (C-8), 21.45 (C-10). The structure was unambiguously verified by homo- and heteronuclear correlation spectroscopy.

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.10; H, 7.15; N, 7.65. Found: C, 72.05; H, 7.18; N, 7.64

b) To a solution of 1 (2.0 g, 3.82 mmol) in dimethylformamide (60 ml), was added an aqueous solution (5 ml) of NaN_3 (1.43 g, 19.1 mmol). The mixture was heated at 100° for 24 hrs and worked up as described above to yield 0.79 g (57%) of crystalline product, mp. 158-160°; undepressed upon admixture with above sample.

7α-(Aminomethyl)-6,14-endo-ethenotetrahydrothebaine (5).- A mixture of the crude azide 2 (1.0 g, 2.5 mmol), Raney nickel (Fluka, 1 g, 50% slurry in water), hydrazine hydrate (98%, 1.0 ml, 20.0 mmol) and ethanol (20.0 ml) was heated under reflux for 30 min. The mixture was cooled to room temperature and diluted with ethanol (20.0 ml), and filtered through a pad of Celite. The solvent was removed under reduced pressure to yield an oil. The oil was dissolved in ethanol (10.0 ml) and the pH of the solution was adjusted to 5.5 with alcoholic hydrochloric acid. The acidic solution was diluted with ether and the resultant white solid was collected, washed with ether and air dried to yield 1.9 g of hydrochloride salt. The salt was dissolved in water (20.0 ml) and the pH of the solvent was adjusted to 8.0 with NH_4OH solution and the precipitate (by-product was identical with 3) filtered. Then a 25% NH_4OH solution (5.0 ml) was added to the filtrate and the white precipitate which was formed was collected to yield 1.3 g (69%) mp. 103-105°, $[\alpha]_D^{22}$ = -195 (c = 0.2 chloroform). ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, N-Me), 3.68 (s, 6-OMe), 3.82 (s, 3-OMe), 4.60 (s, H-5), 5.51 (d, H-17), 5.83 (d, H-18), 6.5 (d, H-1), 6.62 (d, H-2). MS (EI, 70 eV): m/z (%) 368 (M^+, 30).

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