SYNTHETIC POTENTIAL OF PAPAVERINE DERIVATIVES VIA BENZYNES

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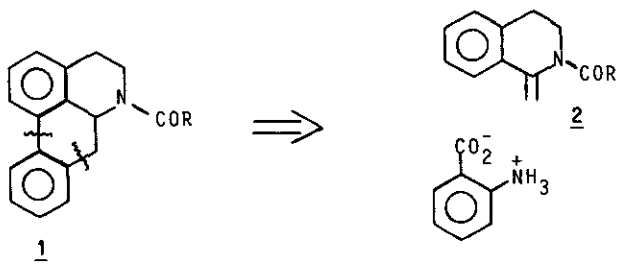
Abstract - When 6'-bromoderivatives of papaverine and papaveraldine were treated with dimsyl sodium, products which incorporate the reagent are obtained. Under similar conditions 6'-bromopapaverine methiodide afforded the expected aporphine skeleton.

Since the discovery of the utility of benzynes (dehydrobenzenes) as intermediates in certain organic reactions, this kind of mediation has received a great deal of attention, and many synthetic approaches to natural products have been based on their generation.[2]

Among the natural products containing an isoquinoline ring[3] that can be synthesized by generating a benzyne intermediate are the *dibenzopyrrocolines*[4], the phenanthridines[5], the dehydroaporphines[6] and the cularines[7], in whose synthesis the dehydrohalogenation of an appropriate bromobenzene generates a benzyne which then suffers attack by the nucleophile. A somewhat different approach to aporphinoids 1 termed Intermolecular Benzyne Cyclization (inter-BC), which has recently been introduced by our laboratory[8], is based on a formal Diels-Alder type cycloaddition between a suitable protected alkylidene-isoquinoline 2 and the appropriate aryne, which is generated by thermal decomposition of the diazonium salt of 3 (Figure I). This approach afforded regiospecific syntheses of dehydroaprophines, 4,5-dioxoaporphines, aristolactams, aporphines[8] (schematically represented by structure 1), protoberberines[9] and other isoquinoline-containing compounds[7,8].



1 2 3

Figure I

In our approach to the synthesis of cularine alkaloids[7] using an aromatic isoquinoline nucleus, we were unable to avoid the formation of an indole ring by N-attack (which competed with O-attack). We therefore decided to investigate the reactivity *of isoquinoline-containing products towards benzyne.* For this purpose, we selected

the benzylisoquinoline derivatives 5-9 which resulted from simple structural modifications including benzylic oxidation and quaternizations of readily available 6'-bromopapaverine 5[10].As a base to bring about dehydrohalogenation we selected dimsylsodium (sodium methylsulfinylmethylide, $Na^+ \ ^-CH_2SOCH_3$), which has been used in all the abovementioned syntheses[4-7] and can easily be prepared by the procedure of Corey and Chaykovsky[11].

When 6'-bromopapaverine 5[10] was allowed to react with excess dimsylsodium for 6 h at 40ºC we obtained, after column chromatography, three products which were identified mainly by interpretration of their PMR spectra. All of them maintained the isoquinoline nucleus ($J_{3,4}$= 5.9 Hz) along with 4 aromatic protons and 4 -OMe singlets, which immediately suggested that they were ipso-substitution products of bromine at position C-6'. Product A (27% yield) crystallized from EtOH-CH_2Cl_2, mp 158-160ºC and was identified as styrene 10 by the characteristic signals of its ABX (styrene) system in the PMR spectrum (δ_A= 5.17, δ_B=5.56 and δ_X= 7.13 ppm; J_{AB}= 1.6Hz, J_{AX}= 10.9 Hz, J_{BX}= 17.3 Hz). Product B (22% yield) was a syrup, identified as arylmethylsulfoxide 11 by the characteristic $-SOCH_3$ signal (δ=2.73 ppm) in its PMR spectrum. Finally, product C (32% yield) crystallized from EtOAc, mp 194-195ºC. Its structure was deduced to be the phenethylmethylsufoxide 12 on the basis of the presence of an $-SOCH_3$ signal (δ= 2.47 ppm) along with those of the $Ar-CH_2-CH_2-SO-$ group (δ=2.77 and δ=3.08 ppm; both m) in its PMR spectrum.

The formation of these products can be envisaged as beginning with dimsyl sodium attack on benzyne 13 followed by a nitrogen-mediated elimination (benzylic proton mediation cannot be excluded) of the methylsulfenate anion (CH_3SO^-)[12,13] to give intermediate 14. Attact by $^-SOCH_3$ on benzyne 13 would give 11, while dimsyl sodium attack on 14 would generate product 12. Finally, β-elimination in 12 would afford styrene 10. The suggested relationship of 12 and 10 was demonstrated by further treatment of 12 with additional dimsyl sodium, which cleanly afforded 10 (Figure II).

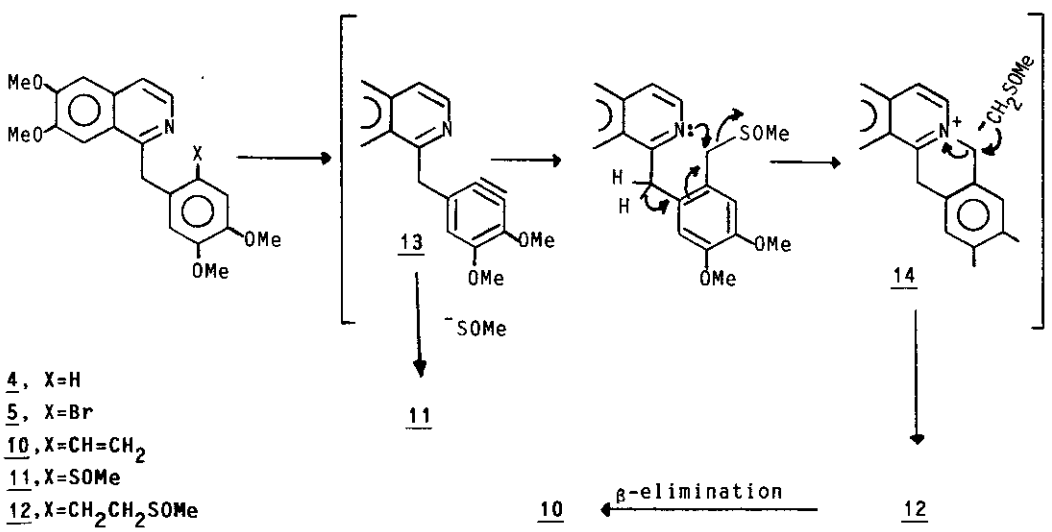


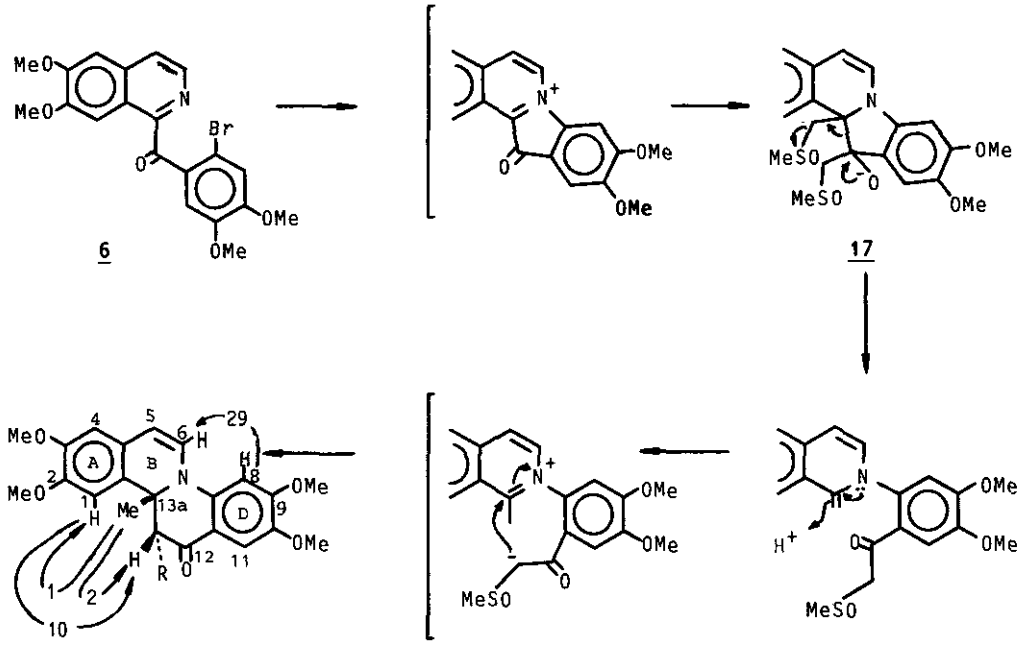
Figure II

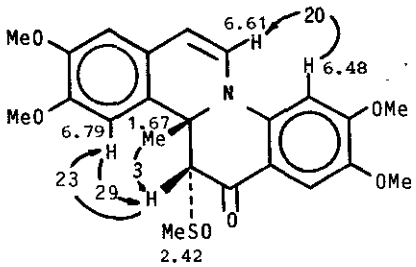
We next subjected 6'-bromopapaveraldine 6 to dimsyl sodium treatment as with 5. After purification, we obtained 50% yield of an intense red-coloured solid ,15, structural elucidation of which proved to be not so easy as in the case of the products described above. The PMR of 15 showed it to be a mixture of two products in a 2:1 ratio, the presence of well-separated double signals suggesting that they were diastereomers. Worthy of note are singlet signals for an aliphatic methyl group (δ=1.75 and 1.67 ppm), for a -CH-$SOCH_3$ unit (δ=3.66, 1H; δ=2.66, 3H and δ=4.26, 1H; δ=2.42, 3H, for each diastereomer) and for an aromatic ABq group (δ_A= 5.53, δ_B= 6.70, J= 8.0 Hz, and δ_A= 5.65, δ_B= 6.61, J_{AB}= 7.9 Hz, respectively) with a coupling constant attributed to protons H-4 and H-3 of a 1,2-dihydroisoquinoline structure. The mass spectrum (M^+= 443) showed the incorporation of the dimsyl sodium components plus additional aliphatic methyl group, as seen in the PMR spectrum. Elemental analysis confirmed the formula $C_{23}H_{25}NO_6S$ for this mixture.

Assuming product 15 to be a mixture of -$SOCH_3$ diastereomers, we desulfurized the mixture by catalytic hydrogenation to obtain a single product whose PMR spectrum showed 4 singlet aromatic protons, an olefinic ABq (J= 7.8 Hz), four -OMe groups, an aliphatic methyl group (δ= 1.37 ppm) and an ABq system (δ_A= 3.22, δ_B= 3.35, J_{AB}= 15.7 Hz) in a downfield methylene group. Further insight into its structure came from a set of NOE experiments[14], which established the close proximity of one aromatic proton (δ= 6.48 ppm) to the downfield olefinic AB proton (δ= 6.71 ppm) and also the aromatic proton at 6.68 ppm to the aliphatic methyl group and one of the methylene protons (δ_A= 3.22 ppm). These data suggested structure 16 (Figure III), that is, a quinolizin-12-one with a trans B,C-junction. This structure, besides explaining the above PMR experiments, also explains the IR spectrum of these compounds, because the 4-quinolinone (or 4-pyridone) system is unique[15] in failing to show distinctive carbonyl bands (except very weak bands at 1500-1600 cm^{-1}). As others have pointed out[15], a general technique for the identification of quinolinone is still very much needed.

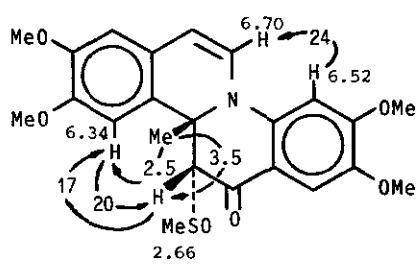
Turning to the diastereomeric mixture obtained in the dimsyl sodium reaction, we carried out an exhaustive NOE study in order to determine whether they were diastereoisomers at the carbon or the sulfoxide centre of the -CHSOCH_3 unit. The results are shown in Figure III. Worthy of note is the strong NOE between H-13 and H-1 (see numbering) in both compounds, which indicates a similar configuration at C-13, as can be easily seen with the help of Dreiding models. Futhermore, when methyl signals at 1.75 and 1.67 ppm were irradiated, a small NOE was observed in H-13, which would be improbable with the inverse configuration at C-13. As can be seen , strong NOE was again observed between H-8 and H-6, which established that both compounds had the same trans-B,C-junction and ruled out conformational differences. Finally, further treatment of the mixture with basic ($Et_3N/CHCl_3$ or additional dimsyl sodium/DMSO, 80ºC, 6h) or acidic (TFA) medium failed to change the initial 2:1 ratio, showing that the more stable compound had been obtained.

The formation of 15 can be explained by assuming an initial attack on benzyne by the nitrogen atom followed by nucleophilic addition of dimsyl sodium to both imminium and carbonyl functions to give intermediate 17, which could rearrange with the indoline ring opening to 18. Imine-enamine equilibration and dimsyl sodium generated carbanion attack on the imminium would give compound 15 (Figure III).





15 (minor diastereomer)



15 (major diastereomer)

Figure III

Next, we subjected 6'-bromopapaveraldine methiodide 7 to dimsyl sodium treatment, trying to avoid the N-attack on benzyne. The main product, after purification, was easily identified as isoquinolone 19[16] (32% yield). Cyclization by carbon would have given the aporphinoid compound. Formation of 19 may involve the formation of an epoxide ring, which on opening lose the benzylic portion (Figure IV).

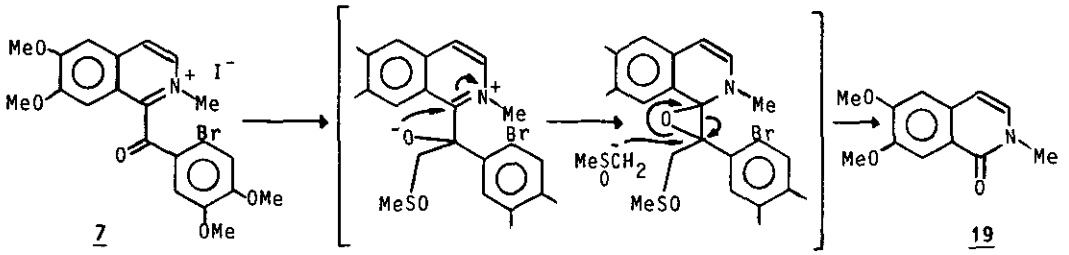


Figure IV

Continuing with quaternization modifications, we tried the N-protected 6'-bromopapaverine compounds 8 and 9[17](Figure V). In the former case, we thought of the N-oxide function as a possible precursor of 6'-hydroxypapaverine: the N-oxide group would act as a nucleophile on the benzyne derived from 8, as in the reaction of acridine N-oxides with benzyne[18]. C-attack would give aporphinoids. However, the reaction produced a complex mixture of products.

In the case of 9, no other nucleophile being present, we expected the formation of an aporphinoid by C-attack, in spite of the lower activation when compared with systems with a phenolic group at C-7[6]. This was, in fact, what happened. When 6'-bromopapaverine methiodide 9 [17] was subjected to dimsyl sodium treatment for 2 h at 40ºC, we obtained, after careful work-up, the expected tetradehydroglaucine 20[19] in 56% yield. This method parallels the electrochemical cathodic cyclization reported by Neumeyer and Gottlieb[20] starting from iodobenzylisoquinolinium salts.

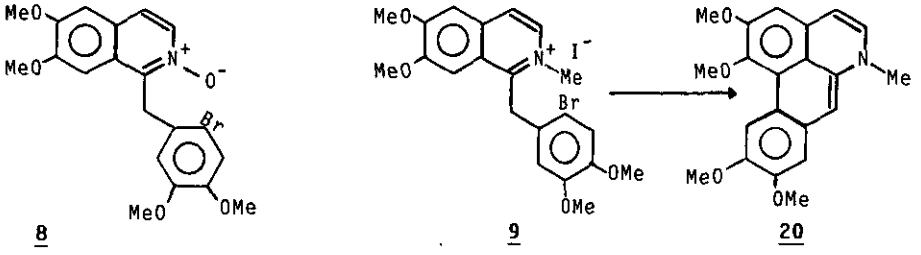


Figure V

EXPERIMENTAL

Materials and techniques

Melting points were determined with a Büchi apparatus and are uncorrected. Infrared spectra were taken in KBr pellets with a PYe Unicam spectrometer. Ultraviolet-visible spectra were determined in ethanol solution on a PYe Unicam SP-1700 spectrophotometer. NMR spectra were recorded on either a Varian CFT-20 or a Bruker WM-250 spectrometer; chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent for NMR spectra was deuteriochloroform unless otherwise stated. NMR multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; J=coupling constant (Hertz). ^{13}C-NMR multiplicities were assigned using INEPT techniques.[21] Routine mass spectra were obtained using a Kratos MS-25 instrument operating at 70 eV. Combustion analyses were performed with a Perkin-Elmer model 240 B at the Inorganic Chemistry Department.

All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2-mm silica gel 60 GF-254 (Merck) plates using UV light and iodine vapour as the developing agent. Preparative layer chromatography was performed on 0.5 mm x 20 mm silica gel 60 GF-254 (Merck) plates. Column chromatography was conducted with silica gel 60 (Merck).

Dimethyl sulfoxide was dried from calcium hydride, distilled under reduced pressure and stored over 4A molecular sieves.

6'-Bromopapaverine 5.

13.6 g (0.04 mol) of commercially available papaverine were dissolved in the minimum amount of 35% HCl and water was added as needed to ensure the formation of a suspension. To this mechanically stirred suspension a solution of 7 ml of bromine in water (30 ml) was added dropwise, and stirring was continued for a further 2.5 h. The precipitate was filtered and washed thoroughly with water and 5% $NaHCO_3$. The white solid so obtained crystallized from EtOH-CH_2Cl_2 (3:2), mp 142-144ºC (Lit[10]: 142-144ºC). Yield 97%

6'-Bromopapaveraldine 6.

A mixture of 0.5 g (1.2 mmol) of 6'-bromopapaverine 5, 0.6 g (2.04 mmol) of $K_2Cr_2O_7$ and 3 ml of 70% AcOH was refluxed with stirring for 1.5 h. After basification with 24% NH_4OH, the solution was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and concentrated to dryness. The crude product crystallized from EtOH, mp 194-196ºC; 90% yield. IR: 1665 (C=O) cm^{-1}. UV λ_{max}^{EtOH}: 237 and 338 nm. PMR: 3.91, 3.92, 4.05 and 4.05 (4 x 3H, each s, 4 x OMe), 7.03, 7.13, 7.25 and 8.03 (4H, each s, ArH), 7.65 and 8.42 (2H, AB_q, J=5.5 Hz, H-4 and H-3). MS m/z (%): 433 and 431 (M^+, 1), 351 (100), 337 and 335 (35), 323 and 321 (18). *Anal. Calcd for* $C_{20}H_{18}BrNO_5$: C, 55.55; H, 4.16; N, 3.24. Found: C, 55.62; H, 4.10; N, 3.02.

6'-Bromopapaverine N-Oxide 8.

1.224 g (6 mmol) of 85% metachloroperbenzoic acid were added in small portions to a solution of 1.2 g (2.9 mmol) of 6'-bromopapaverine 5 in 18 ml of CH_2Cl_2. The

solid obtained was filtered and washed with CH_2Cl_2. The organic extracts were washed with 5% NaOH and 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated to dryness. Crystallization from hexane-CH_2Cl_2 (3:1) gave a white solid, mp 180-182ºC; 85% yield. IR: 1520 ($-\overset{+}{N}-O^-$) cm^{-1}. UV: λ_{max}^{EtOH} 212, 260, 296 and 352 nm. PMR: 3.65, 3.83, 3.92 and 3.92 (4 x 3H, each s, 4 x OMe), 4.92 (2H, s, Ar-CH_2-), 6.91, 7.02, 7.02 and 7.19 (4 x 1H, each s, ArH), 7.43 and 8.21 (2H, AB_q, J=7.0 Hz, H-4 and H-3). MS m/z (%): 435 and 433 (M^+, 1), 368 (7), 354 (52), 338 (100) and 322 (38). Anal. Calcd for $C_{20}H_{20}BrNO_5$: C, 55.29; H, 4.60; N, 3.22. Found: C, 54.87; H, 4.36; N, 3.01.

6'-Bromopapaverine Methiodide 9.

10 ml (0.16 mol) of MeI were added to a solution of 0.8 g (1.9 mmol) of 6'-bromopapaverine in 20 ml of acetone. The solution was left at room temperature for 24 h. The yellow precipitate was filtered to give a quantitative yield of the methiodide 9, mp 224-226ºC (Lit.[17]: 224-225°C).

6'-Bromopapaveraldine Methiodide 7.

The same procedure as used for the synthesis of 9 was employed, with a reaction time of 3 days. The yellow crystals were filtered, giving a 90% yield of 7, mp 205-207ºC. IR: 1660 (C=O) cm^{-1}. UV λ_{max}^{EtOH}: 233, 258 and 330 nm. PMR: 3.81, 4.00, 4.00 and 4.22 (4 x 3H, each s, 4 x OMe), 4.43 (3H, s, -$\overset{+}{N}$Me), 6.79, 7.10, 7.75 and 8.00(4H, each s, ArH), 8.76 and 9.26 (2H, AB_q, J= 6.3Hz, H_4 and H_3). MS m/z (%): 446 (1), 366 (16), 352 (100), 338 (90), 336 (48), 324 (48). Anal. Calcd for $C_{21}H_{21}BrINO_5$: C, 43.90; H, 3.65; N, 2.44. Found: C, 43.77; H, 3.49; N, 2.20.

Dimsyl Sodium Treatment of 6'-Bromopapaverine 5.

A solution of 1.0 g (2.39 mmol) of 6'-bromopapaverine 5 in 7.5 ml of anhydrous DMSO was added through a septum to a stirred suspension of dimsyl sodium[11] (prepared from 0.35 g of 80% NaH and 7.5 ml of anhydrous DMSO). After 6 h stirring at 40ºC, the resulting solution was poured into ice-water. After adding solid NH_4Cl, the solution was extracted with CH_2Cl_2 (5 x 50 ml). The organic extracts were washed with water, brine and water again, dried (Na_2SO_4) and concentrated in vacuo. The crude product was chromatographed on a silica gel column using CH_2Cl_2 and variable amounts of EtOH (up to 5%). The three main products, in order of elution, presented the following physical and spectroscopic data:

Product 10; 0.23 g (27% yield); mp 158-160ºC (CH_2Cl_2-EtOH 2:3 v/v). UV λ_{max}^{EtOH}: 242, 266, 318 and 330 nm. PMR (CD_3COCD_3): 3.62, 3.80, 3.86 and 3.94 (4x3H, each s, 4 x OMe), 4.59 (2H, s, $ArCH_2$-), 5.17, 5.56 and 7.13 (3H, ABX, J_{AB}=1.6Hz, J_{AX}= 10.9Hz, J_{BX}= 17.3Hz, C-CH=CH_2), 6.78, 7.13, 7.25 and 7.40 (4H, each s, ArH), 7.47 and 8.24 (2H, AB_q, J=5.9Hz, H-4 and H-3). MS m/z (%): 365 (M^+, 36), 350 (100), 334 (10), 306(5). Anal. Calcd for $C_{22}H_{23}NO_4.1/2\ H_2O$: C, 70.59; H, 6.42; N, 3.74. Found: C, 70.44; H, 6.29; N, 3.40.

Product 11, 0.21g (22% yield); mp 80-91ºC (non crystaline solid). IR (CCl_4): 1050 (S-O) cm^{-1}. UV λ_{max}^{EtOH}: 218, 242, 286 and 330 nm. PMR: 2.73 (3H,s, -$SOCH_3$), 3.71, 3.95, 3.98 and 4.00 (4x3H,each s,4xOMe), 4.60(2H,s,$ArCH_2$-), 6.70, 7.06, 7.34 and 7.51, (4H, each s, ArH), 7.42 and 8.30 (2H, AB_q. J=5.7Hz, H-4 and H-3). MS m/z (%):

401 (M^+, 18), 385 (6), 370 (3), 353 (45), 337 (100) and 321 (70). Anal. Calcd for $C_{21}H_{23}NO_5S.H_2O$: C, 60.14; H, 5.97; N, 3.34. Found: C, 60.37; H, 5.89; N, 3.40. Product 12, 0.33g (32% yield); mp 194-195ºC (AcOEt). IR: 1030 (S-O) cm^{-1}. UV λ_{max}^{EtOH}: 210, 240, 284 and 330 nm. PMR: 2.47 (3H, s, -SOMe), 2.77 (2H, m, $ArCH_2CH_2$-, 3.08 (2H, m, $-CH_2CH_2$-SO-), 3.69, 3.85, 3.90 and 4.01 (4 x 3H, each s, 4 x OMe), 4.57 (2H, s, $ArCH_2$-), 6.66, 6.76, 7.06 and 7.30 (4H, each s, ArH), 7.41 and 8.31 (2H, AB_q, J=5.7Hz, H-4 and H-3). MS m/z (%): 365 (33), 350 (100), 338 (15), 334 (13), 322(7) and 306 (8). Anal. Calcd for $C_{23}H_{27}NO_5S.1/2\ H_2O$: C, 63.01; H, 6.39; N, 3.19. Found: C, 63.03; H, 6.27; N, 3.19.

Dimsyl Sodium Treatment of 6'-Bromopapaveraldine 6.

Treatment of compound 6 with dimsyl sodium as above afforded after column chromatography a 50% of product 15, mp 217-219ºC (EtOH). IR: 1050 and 1635 cm^{-1}. UV λ_{max}^{EtOH} (log ε): 224 (4.54), 258 (4.43), 292 (4.41), 330(4.31), 344 (4.26), 362 (4.12) and 400-500(3.42). Anal.Calcd for $C_{23}H_{25}NO_6S$:C,62.30;H,5.64;N,3.16.Found:C,62.62;H,5.68;N,3.18. PMR (major component): 1.75 (3H, s, -Me), 2.66 (3H, s, -SOMe),3.66 (1H,s, -CHSOMe), 3.81 (3H, s, C_2-OMe), 3.88 (6H,s, C_3-OMe and C_{10}-OMe), 3.94 (3H, s, C_9-OMe), 5.53 and 6.70 (2H, AB_q, J=8.0Hz, H-5 and H-6), 6.34 (1H, s, H-1), 6.50 (1H, s, H-4), 6.52 (1H, s, H-8), and 7.40 (1H, s, H-11). ^{13}C-NMR:26.00 (q), 38.00(q), 55.92 (q), 56.04 (q), 56.11 (q), 56.58 (q), 63.00 (s), 74.00 (d), 98.35 (d), 102.29 (d), 107.71 (d), 108.07 (d), 108.35 (d), 115.90 (s), 124.36 (s), 124.73 (s), 125.82 (d), 142.57 (s), 144.63 (s), 148 (s), 149.41 (s), 156.81 (s) and 184.07 (s).
PMR (minor component): 1.67 (3H, s, -Me), 2.42 (3H, s, -SOMe), 3.88 (6H, s, C_3-OMe and C_{10}-OMe), 3.89 (3H, s, C_2-OMe), 3.97 (3H, s, C_9-OMe), 4.26 (1H, s, -CHSOMe), 5.65 and 6.61 (2H, AB_q, J=7.9 Hz, H-5 and H-6), 6.48 (1H, s, H-8), 6.50 (1H, s, H-4), 6.79 (1H, s, H-1), 7.39 (1H, s, H-11).
MS m/z (%) of product 15: 443 (M^+, 6), 427 (37), 412 (9), 381 (25), 366 (100) and 350 (21).

Hydrogenolysis of 15. Synthesis of 16.

A suspension of 0.1 g (0.22 mmol) of the above mixture 15 in 30 ml of EtOH containing 0.1 g of 10% Pd/C was hydrogenated at atmospheric pressure until uptake of H_2 ceased. The catalyst was filtered and the yellow solution was concentrated in vacuo without heating to obtain 0.7 g (85% yield) of compound 16, which crystallized from EtOH giving yellow crystals, mp 175-177ºC. UV λ_{max}^{EtOH}(log ε): 223 (4.28), 258 (4.41), 278 (4.38), 3.45 (4.04) and 404 br (3.42). PMR: 1.37 (3H, s, -Me), 3.22 and 3.35 (2H, AB_q, J=15.7Hz, $-CH_2$-CO-), 3.88 (3H, s, C_{10}-OMe), 3.89 (6H, s, C_2-OMe and C_3-OMe), 3.97 (3H,s, C_9-OMe), 5.84 and 6.71 (2H, AB_q, J=7.8Hz, H-5 and H-6), 6.48 (1H, s, H-8), 6.58 (1H, s, H-4), 6.68 (1H, s, H-1) and 7.39 (1H, s, H-11). ^{13}C-NMR: 22.05 (q), 47.62 (t), 55.97 (q), 56.06 (q), 56.11 (q), 56.25 (q), 59.81 (s), 96.40 (d), 106.05 (d), 107.17 (d), 108.15 (d), 112.77 (d), 112.77 (s), 123.62 (s), 124.68 (d), 128.88 (s), 141.80 (s), 143.51 (s), 148.22 (s), 148.66 (d), 156.37 (s) and 190.61 (s). MS m/z (%): 381 (M^+, 17), 366 (100), 350 (15), 338 (5), 322 (6), 183 (10). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.29; H, 6.03; N, 3.67. Found: C, 68.87; H, 6.20; N, 3.41.

Dimsyl Sodium Treatment of 6'-Bromopapaveraldine Methiodide 7.

Starting from 0.3 g (0.52 mmol) of 7 and with 15 h stirring at 40-45ºC, 0.038 g (32% yield) of isoquinolone 19 were obtained. It crystallized from MeOH-$CHCl_3$, mp 124-126ºC (Lit.[16]: 124-126 ºC).

Dimsyl Sodium Treatment of 6'-Bromopapaverine Methiodide 9. Synthesis of Tetradehydroglaucine 20.

From 0.5 g (0.9 mmol) of 9 and with 2 h stirring at 40ºC. The reaction mixture was poured into ice-water, solid NH_4Cl added, and the mixture extracted with ether-hexane (2:3). The organic extracts were dried (Na_2SO_4) and evaporated in vacuo to give 0.173 g (58% yield) of pure tetradehydroglaucine 20. Physical and spectroscopic data for 20 coincided with those published[19].

ACKNOWLEDGEMENT

We thank the Comisión Asesora (Spain) for its financial support.

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Received, 25th September, 1986