Notes

Synthesis of Shihunine and Dihydroshihunine[1]

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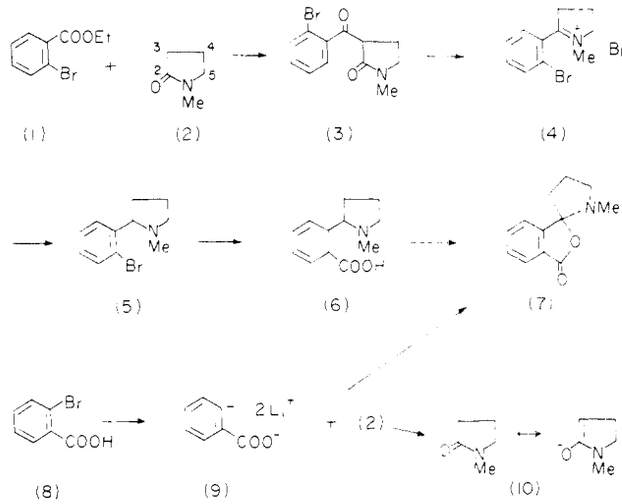
Shihunine (**7**) is the major alkaloid found in several species of *Dendrobium*, and we have established that it is formed in nature from *o*-succinylbenzoic acid.[3] In connection with this investigation a sample of this alkaloid was required for carrying out dilutions of labeled shihunine, and for practicing degradations to determine the location of labeled atoms. Previous syntheses[4,5] afforded quite low yields of shihunine.

In the present work dihydroshihunine [1-methyl-2-(*o*-carboxyphenyl)pyrrolidine (**6**)] was obtained by a sequence of reactions analogous to Späth's synthesis of nicotine,[6] and is illustrated in Scheme I. Condensation of ethyl *o*-bromobenzoate (**1**) with 1-methyl-2-pyrrolidone (**2**) in the presence of sodium hydride in boiling benzene afforded 1-methyl-3-(*o*-bromobenzoyl)-2-pyrrolidone (**3**). Refluxing this compound with hydrobromic acid yielded the pyrrolinium salt (**4**), which was reduced with sodium borohydride to 1-methyl-2-(*o*-bromophenyl)pyrrolidine (**5**). This bromo compound was metalated with *n*-butyllithium and treated with carbon dioxide to yield dihydroshihunine. Attempts to convert this compound to shihunine using a variety of oxidizing agents[7] gave very poor or negligible yields of the alkaloid (see Experimental Section).

Shihunine was successfully obtained by adding the dilithio anion (**9**), prepared from *o*-bromobenzoic acid (**8**) by Parham's method,[8] to **2**. Using an equivalent amount of the two reactants the maximum yield of shihunine was 23%. Large amounts of benzoic acid and **2** were recovered from the reaction mixture. Since great care was taken to exclude water from the reaction it seemed probable that the proton source for the production of benzoic acid was **2**. The formation of the anion **10** would thus be the major competing and unavoidable reaction. This was confirmed by quenching the reaction mixture (after 2 h) with D_2O. The recovered benzoic acid was a mixture of undeuterated (87%) and monodeuterated (13%), indicating that only a small quantity of the dianion (**9**) remained unreacted after 2 h. The recovered 1-methyl-2-pyrrolidone contained 74% of a monodeuterated species. The location of the deuterium was determined by examination of its ^1H noise-decoupled ^{13}C NMR spectrum, which showed C-3 as a triplet and all the other carbons being singlets, thus indicating that all the deuterium was at C-3. The ^{13}C NMR spectrum of unenriched **2** was assigned by off-resonance decoupling and by comparison with the spectrum of 2-pyrrolidone.[9] The yield of shihunine produced in this one-step reaction is only moderate; however, it is far superior to the previous syntheses, and it is readily adaptable for the production of isotopically labeled alkaloid, which will be used in metabolism studies.

Scheme I. Synthesis of Shihunine and Dihydroshihunine



Experimental Section[10]

1-Methyl-3-(*o*-bromobenzoyl)-2-pyrrolidone (3). A 57% suspension of NaH in mineral oil (14 g) was washed with benzene (3 × 50 mL) in a N_2 atmosphere, and then suspended in boiling benzene (200 mL) while a solution of ethyl *o*-bromobenzoate (16 g) and 1-methyl-2-pyrrolidone (14 g, dried over 4A molecular sieves) in benzene (50 mL) was added during 2 h. After refluxing for an additional 20 h, the cooled reaction mixture was added to ice (400 g) and acetic acid (35 g). The ether (2 × 200 mL) extract of this mixture was washed with water, 5% Na_2CO_3, and brine, and then dried ($MgSO_4$). The oil (14 g, 71%) obtained on evaporation of the ether was used without further purification in the next step. A small sample was distilled [135–140 °C (10^{-3} mm)] affording **3** as a pale yellow liquid: IR ($CHCl_3$) ν_{max} 1680 (ketone C=O), 1642 (amide C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73–7.13 (m, 4 H, aromatic), 4.60–4.05 (m, 1 H, 3), 3.73–3.13 (m, 2 H), 2.88, 2.83 (d, 3 H, NMe), 2.67–1.92 (m, 2 H); MS *m/e* (rel intensity) 283, 281 (M^+, 4), 203 (15), 202 (100), 185 (29), 183 (31), 157 (10), 155 (10), 98 (13), 42 (13).

1-Methyl-2-(*o*-bromophenyl)pyrrolidine (5). The amide **3** (17 g) was refluxed in 47% HBr (100 mL) for 8 h. The dark residue obtained on evaporation was dissolved in MeOH (100 mL), the pH was adjusted to 8 with 10% KOH in MeOH, and the

(1) This investigation was supported by Research Grant GM-13246 from the National Institutes of Health, U.S. Public Health Service.
(2) Contribution No. 168 from this laboratory.
(3) E. Leete and G. B. Bodem, *J. Am. Chem. Soc.*, **98**, 6321 (1976).
(4) T. Onaka, *Yakugaku Zasshi*, **85**, 839 (1965). We have modified this synthesis, condensing diethyl phthalate with **2** in boiling benzene using NaH as the basic catalyst (instead of sodium methoxide), yielding 1-methyl-3-(*o*-carboxybenzoyl)-2-pyrrolidone, which on refluxing with 48% HBr afforded shihunine (8% yield from diethyl phthalate).
(5) E. Breuer and S. Zbaida, *Synth. Commun.*, **4**, 21 (1974); *Tetrahedron*, **31**, 499 (1975).
(6) E. Späth and H. Bretschneider, *Ber. Dtsch. Chem. Ges.*, **61**, 327 (1928).
(7) A. Picot and X. Lusinchi, *Synthesis*, 109 (1975).
(8) W. E. Parham and Y. A. Sayed, *J. Org. Chem.*, **3**, 2051, 2053 (1974).
(9) Spectrum No. 67, J. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, 1972.
(10) All melting points are corrected. ^1H NMR spectra were determined on a Varian T-60 spectrometer. ^{13}C NMR spectra were determined by Dr. Richard A. Newmark, 3M Company, St. Paul, on a Varian XL-100-15 instrument operated at 25.16 MHz and interfaced with a 620i/Mark I Fourier transform system. Mass spectra were determined by Dr. Roger Upham and his associates at the University of Minnesota using an AEI MS-30 double beam, double focusing spectrometer. Elemental analyses were determined at M-H-W Laboratories, Garden City, Michigan.

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solution was treated with sodium borohydride (12 g) added in small portions with cooling. After stirring for 18 h at room temperature, the reaction mixture was acidified with HCl and evaporated to dryness. The residue was made strongly basic with KOH and extracted with ether. Distillation [51–53 °C (0.15 mm)] of the residue obtained on evaporation of the dried (K_2CO_3) extract afforded the pyrrolidine **5** as a colorless oil (8.2 g, 59%): n^{25}_D 1.5551; IR (neat) ν_{max} 2760 (NMe), 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–6.87 (m, 4 H, aromatic), 3.70–3.10 (m, 2 H), 2.73–1.30 (complex multiplet, 8 H), with overlapping at δ 2.23 (NMe). It afforded a picrate, yellow needles from ethanol, mp 129.5–131 °C.

Anal. Calcd for $C_{17}H_{17}BrN_4O_7$: C, 43.51; H, 3.65; Br, 17.03; N, 11.94. Found: C, 43.77; H, 3.76; Br, 16.91; N, 12.17.

Dihydroshihunine (6). A solution of **5** (2.22 g) in dry THF (40 mL) was treated at −78 °C in a N_2 atmosphere over 30 min with 9 mL of *n*-butyllithium (2.3 M solution in hexane). After stirring for an additional 30 min the solution was saturated with dry CO_2 gas and allowed to warm to room temperature. The reaction mixture was then added to 5% HCl, concentrated, washed with ether, made strongly basic with KOH, and again extracted with ether. The aqueous solution was then acidified with HCl and chromatographed on a column of ion-exchange resin (BioRad, AG-50 W-X4, H^+ form). The column was washed with water, and then dihydroshihunine (1.38 g, 67%) eluted with 3 N ammonium hydroxide. Sublimation [130 °C (10^{-4} mm)] and crystallization from ethanol–ethyl acetate afforded colorless prisms, mp 184–194 °C (lit.[11] mp 190–201 °C) identical (mixed melting point, IR, NMR, MS) with an authentic specimen obtained by the hydrogenation of shihunine.

Oxidation of Dihydroshihunine to Shihunine. (a) With *N*-Bromosuccinimide. Dihydroshihunine (221 mg) was stirred for 18 h with *N*-bromosuccinimide (237 mg) in 5% aqueous $NaHCO_3$ (10 mL). Continuous extraction of the reaction mixture with CH_2Cl_2 afforded a brown gum (144 mg) which was subject to preparative TLC on alumina PF 254 (Merck) developing with a mixture of chloroform, methanol, and concentrated NH_3 (50:5:1). Shihunine (11 mg, 5%), R_f 0.43, and dihydroshihunine (62 mg, 28%), R_f 0.67, were obtained.

(b) With Mercuric Acetate. A solution of dihydroshihunine (158 mg) in 5% acetic acid (5 mL) containing mercuric acetate (1.0 g) was heated in a N_2 atmosphere for 2.5 h at 90–95 °C. The precipitated mercurous acetate (290 mg, 75%) which began to form almost immediately was removed by centrifuging. The supernatant solution was saturated with H_2S, again centrifuged, and then evaporated to dryness. The residue after TLC, as before, yielded shihunine (9 mg, 6%) and dihydroshihunine (33 mg, 21%).

Attempted oxidation of dihydroshihunine with bromine in CH_2Cl_2[7] failed to yield any shihunine.

One-Step Synthesis of Shihunine. A solution of *o*-bromobenzoic acid (2.50 g) in 50 mL of dry THF (distilled from $LiAlH_4$) was cooled to −100 °C using a bath of liquid N_2 and ethanol. The reaction mixture was maintained at −100 °C in a N_2 atmosphere while 12.5 mL of *n*-butyllithium (2 M in hexane) was added over 45 min. The reaction mixture was allowed to warm to −78 °C for 2 h, and a solution of 1-methyl-2-pyrrolidone (1.28 g) in THF (10 mL) was added during 15 min. The reaction mixture was stirred for 2 h at −78 °C, allowed to warm to −20 °C, and poured into 5% HCl (100 mL). This solution was extracted with ether (3 × 75 mL), affording after drying ($MgSO_4$) benzoic acid (0.98 g, 65%) uncontaminated with any *o*-bromobenzoic acid.[12] The aqueous phase was then concentrated to 50 mL, brought to pH 10 with NaOH, and then extracted continuously with CH_2Cl_2. Evaporation of the extract yielded a mixture of shihunine (0.58 g, 23%) and 1-methyl-2-pyrrolidone (100 mg), separated by TLC on alumina PF 254. Crystallization of the former from ether–hexane afforded colorless needles, mp 76–78 °C, identical (mixed melting point, IR, NMR) with an authentic specimen of shihunine obtained from *Dendrobium pierardii*.[3]

The reaction was repeated, and after 2 h at −80 °C D_2O (5 mL) was added to the reaction mixture followed by workup as previously described. The benzoic acid, purified by sublimation, had a MS *m/e* (rel intensity) 124 (2.0), 123 (23.3), 122 (82.1) compared with natural abundance benzoic acid, *m/e* 124 (0.9), 123 (7.6), 122 (90.1), indicating a ratio of unlabeled to monodeuteriobenzoic acid of 87:13. The recovered 1-methyl-2-pyrrolidone (0.7 g) had MS *m/e* (rel intensity) 102 (0.7), 101 (83), 100 (100), 99 (97.4), 98 (22.3), compared with unlabeled material of *m/e* 101 (0.7), 100 (76), 99 (100), 98 (68.0), 97 (0.8), indicating a 74% enrichment of the 1-methyl-2-pyrrolidone with a single deuterium. The ^1H noise-decoupled ^{13}C NMR spectrum of unlabeled 1-methyl-2-pyrrolidone (in $CDCl_3$) was (δ_c, ppm from Me_4Si): C-2 (177.1), C-3 (31.1), C-4 (18.1), C-5 (50.0), NMe (29.7). The ^1H noise-decoupled ^{13}C NMR spectrum of the enriched 1-methyl-2-pyrrolidone was identical except that the signal due to C-3 was a triplet.

Registry No. 1, 6091-64-1; **2**, 872-50-4; **3**, 71819-30-2; **5**, 71819-31-3; **5** picrate, 71819-32-4; **6**, 20323-99-3; **7**, 4031-12-3; **8**, 88-65-3.

(11) (a) Y. Inubushi, Y. Tsuda, T. Konita, and S. Matsumoto, *Chem. Pharm. Bull.*, **12**, 749 (1964); (b) *ibid.*, **16**, 1014 (1968).

(12) The benzoic acid was converted to its methyl ester with diazomethane and analyzed by GLC on 10% Carbowax 20 M on Chromosorb W (60–80 mesh) at 185 °C. With a He flow rate of 25 mL/min the retention times of methyl benzoate and methyl *o*-bromobenzoate were 2.7 and 8.7 min, respectively.

Rearrangement of 2-Diazoceph-3-em 1β-Oxides: Migration of Oxygen from Sulfur to Carbon

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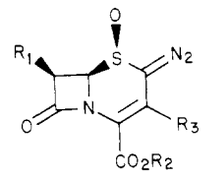
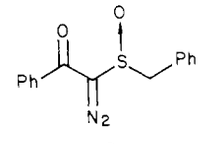
Publications by Bremner and Campbell[1] on the preparation and chemistry of diazosulfoxide **1a** have prompted



1a, R_1 = $C_6H_5OCH_2CONH$; R_2 = CH_2CCl_3; R_3 = CH_3
b, R_1 = $C_6H_5OCH_2CONH$; R_2 = $CH(C_6H_5)_2$; R_3 = CH_2OAc
c, R_1 = H; R_2 = $CH(C_6H_5)_2$; R_3 = CH_3
d, R_1 = H; R_2 = $CH_2OCOC(CH_3)_3$; R_3 = CH_2OAc

us to report our work in this area. We viewed such highly functionalized cephalosporin derivatives as useful for further β-lactam nuclear modification. Specifically, we were interested in examining the behavior of diazosulfoxides such as **1a** in the presence of metal catalysts in order to probe the effect of generating a carbenoid species α to the sulfoxide moiety. Hodson and Holt,[2] in an unsuccessful attempt to prepare a similar but less complex α-diazo-β-ketosulfoxide **2** by diazo transfer, isolated **3** and postulated



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its formation via an intramolecular rearrangement, giving intermediate thiol ester **4** (not isolated or characterized).

(1) (a) Bremner, D. H.; Campbell, M. M. *J. Chem. Soc., Chem. Commun.* **1976**, 538. (b) Bremner, D. H.; Campbell, M. M. *J. Chem. Soc. Perkin Trans. 1* **1977**, 2298.

(2) Hodson, D.; Holt, G. *J. Chem. Soc. C* **1968**, 1602.

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