Contribution to the Synthesis of (±)-Cryptopleurine and Related Phenanthroquinolizidines

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The synthesis of the alkaloid cryptopleurine **7b** has been accomplished by a sequence involving as a key step the selective Borch reduction of an amidoester **1b** to the corresponding aminoester **2b**. This route is applicable to the synthesis of derivatives such as **7a**.

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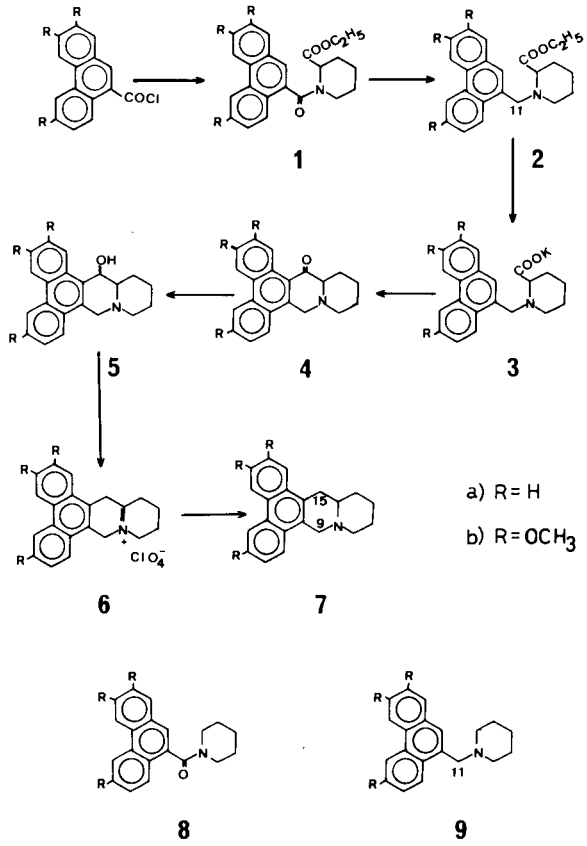
Cryptopleurine **7b**, the phenanthro[9,10-*b*]quinolizidine alkaloid, isolated from *Cryptocarya pleurosperma (Lauraceae)* (1), *Boehmeria platyphylla* (2) and *B. cylindrica (Urticaceae)* (3), is known not only by means of its vesicant properties (1), but also by its various interesting pharmacological properties like its anti-tumor action (4).

Biochemical studies enclose cryptopleurine under translocation phase protein synthesis inhibitors, as are also the ipecacuanha alkaloids emetine, tubulosine, and the Tylophora alkaloids (5,6).

Although the total synthesis of cryptopleurine have been achieved by various groups (7-12), based some of them on biogenetic considerations (10-12), development of additional synthetic routes are necessary to make approachable a range of analogues of this alkaloid, with a view to study their structure-activity relationships. The present work is based mainly on the earlier synthetic routes of Marchini and Belleau (8) and Földeak (9) introducing some modifications by which yields are improved. In particular the selective Borch reduction (13), employed by Herbert and Moody (14) in the tylophorine synthesis, allows us to shorten considerably the general synthetic scheme in the first steps, applied to the synthesis of aminoesters **2a,b** (Scheme I).

Condensation of the suitable 9-phenanthrenecarbonyl chloride with ethyl pipecolate in presence of pyridine gives the amidoester **1** in good yields. The Borch reduction (13) of **1**, consisting by an *O*-alkylation of the tertiary amide with triethyloxonium fluoroborate and later sodium borohydride reduction, leads to the aminoester **2** in a 93% yield. Hydrolysis of **2** to the corresponding potassium salt is achieved in hydro-alcoholic potassium hydroxide in quantitative yields. Friedel-Crafts cyclisation of **3** in polyphosphoric acid under nitrogen, gives the unstable aminoketone in approximately 65-70% yield. The reduction of **4** with lithium aluminium hydride leads to the alcohols **5**, which are dehydrated with 70% perchloric acid, to give the iminium perchlorates **6**. The quaternary compounds are reduced with sodium borohydride to the phenanthro-[9,10-*b*]quinolizidine **7a** and cryptopleurine **7b**. The



SCHEME 1

synthetic cryptopleurine has the same ir, nmr and mass date as are described for the natural alkaloid.

Most of the intermediates and final compounds have been characterized by ir, nmr spectra and mycroanalyses, as well as mass spectra in some cases. Details are reported in the experimental section, but there are some features of the amino-esters **2a,b** of interest.

The C-11 protons in compounds **2a,b** appear as an AB quartet with chemical shifts of δ 3.85 and 4.35 ppm and a coupling constant J = 13 Hz. This proton becomes

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equivalent in the piperidine derivatives **9a,b**, where they resonate as a singlet at 3.8 ppm. Johns, *et al.* (15) observed a non-equivalence of the C-9 axial and equatorial protons in cryptopleurine. This is in accordance with the observations made by Fitzgerald, *et al.*, (16) and Hamlow, *et al.*, (17) that the axial and equatorial protons of methylene groups α to the nitrogen in quinolizidines have a marked difference in chemical shift. So, here we can also suggest, as it is the case in pyrrolidine derivatives (18), that a preferred orientation of the two protons at C-11 concerned relative to the phenanthrene ring and the nitrogen lone pair is due to conformational rigidity in compounds **2a,b**, probably caused by restricted rotation about the phenanthrene C-11 bond.

EXPERIMENTAL

The melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer 577 spectrometer. The nmr spectra were measured using tetramethylsilane as the internal standard, with a Perkin-Elmer mod. R-24A (60 MHz) and a Variant XL 100 spectrometer. Microanalyses were done with a Carlo Erba 1104 analyser. The mass spectra were obtained with a Hitachi Perkin Elmer, RMU-6M spectrometer.

9-Phenanthrenecarbonyl Chloride.

This compound was prepared as described by Goldberg, *et al.*, (19).

2,3,6-Trimethoxy-9-phenanthrenecarbonyl Chloride.

To a suspension of 3 g. of 2,3,6-trimethoxy-9-phenanthrenecarboxylic acid (9) in 30 ml. of dry chloroform was added dropwise 10.5 ml. of thionyl chloride and the mixture was refluxed on a water bath during 30 minutes. The solvent was evaporated *in vacuo* at 40-50° yielding 3.12 g. (98.1%) of the acyl chloride. M.p. 142-144° (from benzene); ir (potassium bromide): 1745.

Anal. Calcd. for $C_{18}H_{15}ClO_4$: C, 65.35; H, 4.54. Found: C, 65.13; H, 4.64.

Preparation of Compounds **1**.

To a solution of 0.015 mole of acyl chloride, 0.015 mole of pyridine and 100 ml. of dry benzene was added 0.015 mole of ethyl pipecolate in 10 ml. of dry benzene, dropwise with stirring. The mixture was set aside 24 hours at room temperature. The pyridine hydrochloride was filtered off and the liquids were washed with diluted hydrochloric acid and water. Evaporation of the dried benzene layer left the product.

Ethyl *N*-(9-Phenanthrylcarbonyl)-2-piperidinecarboxylate **1a**.

The product was purified by chromatography (Kieselgel G column) (ether/benzene eluyent (1:1)), yield, 59.42%, m.p. 91-93° (from ether/light petroleum); ir (potassium bromide): 1735, 1640; nmr (deuteriochloroform): δ 1.3-2.0 (6H, m, $(CH_2)_3$), 1.45 (3H, t, J = 7 Hz, CH_3), 3.2-3.5 (2H, m, N-CH_2), 4.4 (2H, q, J = 7 Hz, CH_2), 5.8 (1H, dbr, N-CH-COO), 7.5-8.5 (7H, m, Ar-H), 8,6-8.9 (2H, m, Ar-H).

Anal. Calcd. for $C_{23}H_{23}NO_3$: C, 76.45; H, 6.31; N, 3.88. Found: C, 76.16; H, 6.55; N, 3.66.

Ethyl *N*-(2,3,6-Trimethoxy-9-phenanthrylcarbonyl)-2-piperidinecarboxylate **1b**.

This compound was obtained in a yield of 80.7%, m.p. 118-120° (from ethanol/water); ir (potassium bromide): 1735, 1635; nmr (deuteriochloroform): δ 1.2-1.7 (6H, m, $(CH_2)_3$), 1.4 (3H, t, J = 7 Hz, CH_3) 3.3 (2H, m, N-CH_2), 4.06 (2H, q, J = 7 Hz, CH_2), 4.02 (6H, s, 2 x OCH_3), 4.1 (3H, s, OCH_3), 5.7 (1H, m, N-CH-COO), 7.2 (2H, m, C-1, C-7, Ar-H), 7.49 (1H, s, C-10, Ar-H), 7.87 (3H, m, C-5, C-4, C-8, Ar-H).

Anal. Calcd. for $C_{26}H_{29}NO_6$: C, 69.18; H, 6.43; N, 3.10. Found: C, 69.14; H, 6.83; N, 2.97.

Preparation of Compounds **2**.

A solution of 0.0067 mole of compound **1** and triethyloxonium fluoroborate (20) (0.0075 mole) in 9 ml. of dry methylene chloride was stirred for 20 hours at room temperature. The solvent was removed in vacuum and the residue was dissolved in 9 ml. of absolute ethanol. Sodium borohydride (0.63 g., 0.0166 mole) was added in small portions to the stirred solution at 0°; when the addition was complete stirring was continued for 18 hours at room temperature. The solution was poured into 100 ml. of water and the solid which formed was filtered.

Ethyl *N*-(9-Phenanthrylmethyl)-2-piperidinecarboxylate **2a**.

This compound was obtained in a yield of 93.7%, m.p. 90° (from ethanol) as described (9); ir (potassium bromide): 1735, nmr (deuteriochloroform): 1.3 (3H, t, J = 7.5 Hz, CH_3), 1.6 (6H, m, $(CH_2)_3$), 2.3 (1H, m, J = 11 Hz, N-C6ax-H), 3.25 (1H, m, J = 11 Hz, N-C6eq-H), 3.05 (1H, m, N-C2′-H), 3.85 (1H, ABq, J = 13 Hz, Ar-CH_2-N), 4.21 (2H, q, J = 7.5 Hz, CH_2), 4.35 (1H, ABq, J = 13 Hz, Ar-CH_2-N), 7.65 (6H, m, Ar-H), 8.65 (3H, m, Ar-H).

Anal. Calcd. for $C_{23}H_{25}NO_2$: C, 79.54; H, 7.20; N, 4.03. Found: C, 79.43; H, 7.43; N, 4.07.

Ethyl *N*-(2,3,6-Trimethoxy-9-phenanthrylmethyl)-2-piperidinecarboxylate **2b**.

This compound was obtained in a yield of 92.9%, m.p. 145° as described (9); ir (potassium bromide): 1725; nmr (deuteriochloroform): 1.3 (3H, t, J = 7.5 Hz, CH_3), 1.4-1.85 (6H, m, $(CH_2)_3$), 2.22 (1H, m, J = 12 Hz, N-C6ax-H), 2.98 (1H, m, N-C2-H), 3.2 (1H, m, J = 12 Hz, N-C6eq-H), 3.68 (1H, ABq, J = 13 Hz, Ar-CH_2-N), 4.01 (6H, s, 2 x OCH_3), 4.09 (3H, s, OCH_3), 4.2 (2H, q, J = 7.5 Hz, CH_2), 4.32 (1H, ABq, J = 13 Hz, Ar-CH_2-N), 7.18 (1H, s, C-1 Ar-H), 7.26 (1H, q, C-7 Ar-H), 7.44 (1H, s, C-10 Ar-H), 7.88 (3H, m, C-4, C-5, C-8 Ar-H).

Preparation of Compounds **3** and **4**.

Compound **2** (0.0056 mole), 28 ml. of ethanol, 3.4 ml. of water and 2.2 g. of potassium hydroxide were kept at reflux for 30 minutes. The precipitate of the cold solution was collected and dried, yields of the potassium salt, quantitative. The potassium salt **3** (0.0056 mole) and 10 g. of polyphosphoric acid were kept under nitrogen, in a parafin bath, with stirring at 110° for 6-7 hours (product **3a**), and at 85-90° for 3.5 hours (product **3b**). After cooling, the dark viscous solution was poured slowly on ice water (100 ml.) and basified, at 20°, with 50% potassium hydroxide, to *p*H 8-9. The mixture was extracted with chloroform the organic layers washed with water, dried and evaporated, *in vacuo* at 35°, to give a solid in a yield of 71.4% (**4a**) and 65.7% (**4b**), which was not further purified.

Preparation of Compounds **5**.

The ketone **4** (0.005 mole), in 30 ml. of dry benzene, was added dropwise with stirring to a suspension of 700 mg. of lithium aluminium hydride in dry ether/benzene (1:1) (40 ml.),

prolonging the reaction for two hours. Destruction of the lithium aluminium hydride with ice, filtration and evaporation of the dried organic layers, led to the compounds **5a** (68% yield) and **5b** (65% yield).

11,12,13,14,14a,15-Hexahydro-9*H*-phenanthro[9,10-*b*]quinolizin-15-ol **5a**.

This compound had m.p. 206-207° (from acetone); lit. (9): 231-232° (isomer A), 208-209° (isomer B); nmr (deuteriochloroform): δ 1.4-2.5 (8H, m, $(CH_2)_3$, C-11ax, C-14a), 2.82 (1H, dbr, J = 11.5 Hz, C-11eq-H), 3.22 (1H, dbr, J = 16 Hz, C-9ax-H), 3.95 (1H, dbr, J = 16 Hz, C-9eq-H), 4.95 (1H, dbr, J = 6 Hz, C-15-H) 7.5 (7H, m, Ar-H), 8.5 (2H, m, Ar-H). The mass spectrum had the molecular ion peak at m/e 303 and abundant fragment peaks at m/e 280, 220 (retro Diels-Alder), 219, 218, 203, 191, 190, 189, 165, 84 (100%).

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.16; H, 6.93; N, 4.62. Found: C, 83.04; H, 7.10; N, 4.28.

11,12,13,14,14a,15-Hexahydro-2,3,6-trimethoxy-9*H*-phenanthro-[9,10-*b*]quinolizin-15-ol **5b**.

This compound had m.p. 203-205° (from acetone); lit. (9): 236-237° (isomer A), 208-209° (isomer B); nmr (deuteriochloroform): δ 1.5-2.5 (8H, m, $(CH_2)_3$, C-11ax, C-14a), 2.65 (1H, dbr, J = 12 Hz, C-11eq-H), 2.75 (1H, sbr, OH), 3 (1H, dbr, J = 15.5 Hz, C-9ax-H), 4 (1H, dbr, J = 15.5 Hz, C-9eq-H), 3.98, 4.02, 4.10 (9H, 3s, 3 x OCH_3), 4.52 (1H, sbr, C-15-H), 6.62 (2H, m, Ar-H), 7.74 (3H, m, Ar-H). The mass spectrum had the molecular ion peak at m/e 393 and abundant fragment peaks at m/e 310 (retro Diels-Alder), 295, 282, 267, 239, 224, 84 (100%).

Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.28; H, 6.87; N, 3.56. Found: C, 73.57; H, 7.07; N, 3.35.

Preparation of Compounds **6** and **7**.

The compounds were prepared as described by Földeak and Hegyes (21).

11,12,13,14,14a,15-Hexahydro-9*H*-phenanthro[9,10-*b*]quinolizine **7a**.

This compound was obtained in a yield of 68%, m.p. 169-170°, lit. 169-170° (8), 174-175° (9).

Anal. Calcd. for $C_{21}H_{21}N$: C, 87.82; H, 7.31; N, 4.87. Found: C, 87.58; H, 7.58; N, 4.68.

Cryptopleurine **7b**.

This compound was obtained in a yield of 65%, m.p. 196.5-198°, lit. 197-198° (corr.) (22); 199-200° (8).

Anal. Calcd. for $C_{24}H_{27}NO_3$: C, 76.39; H, 7.16; N, 3.71. Found: C, 76.14; H, 7.30; N, 3.52.

Preparation of Compounds **8**.

To a solution of 0.03 mole of acyl chloride, in 70 ml. of dry benzene, 1.5 ml. of piperidine was added, and the mixture was set aside overnight. The piperidine hydrochloride was filtered off, and the benzene layer was washed with diluted hydrochloric acid and water. Evaporation of the dried benzene layer left the product, which was purified by recristallisation in ethanol.

N-(Phenanthrene-9-carbonyl)piperidine **8a**.

This compound was obtained in a yield of 57.8%, m.p. 143-145° (from ethanol/water); ir (potassium bromide): 1625; nmr (deuteriochloroform): δ 1.56 (6H, m, $(CH_2)_3$), 3.19 (2H, m, $(CH_2)_2$-N ax), 3.9 (2H, m, $(CH_2)_2$N eq), 7.75 (7H, m, Ar-H), 9.68 (2H, m, C-4,5 Ar-H).

Anal. Calcd. for $C_{20}H_{21}NO$: C, 83.05; H, 6.57; N, 4.84. Found: C, 82.99; H, 6.42; N, 4.68.

N-(2,3,6-Trimethoxyphenanthrene-9-carbonyl)piperidine **8b**.

This compound was obtained in a yield of 73.4%, m.p. 183-184° (from ethanol); ir (potassium bromide): 1615; nmr (deuteriochloroform): δ 1.7 (6H, m, $(CH_2)_3$), 3.25 (2H, m, $(CH_2)_2$N ax), 4.0 (2H, m, $(CH_2)_2$N eq), 4.09 (6H, s, 2 x OCH_3), 4.19 (3H, s, OCH_3), 7.25-7.28 (6H, Ar-H).

Anal. Calcd. for $C_{23}H_{25}NO_4$: C, 72.82; H, 6.59; N, 3.69. Found: C, 72.50; H, 6.57; N, 3.42.

Preparation of Compounds **9**.

To a suspension of 0.5 g. of lithium aluminium hydride in ether was added dropwise, with stirring, a solution of 0.002 mole of the amide **8** in 30 ml. of benzene/ether (2/1). The mixture is refluxed 4 hours and left overnight at room temperature. The excess of lithium aluminium hydride was destroyed with ethanol and water and dried. Evaporation left **9**, which was purified by recristallisation in ethanol/water.

N-(9-Phenanthrylmethyl)piperidine **9a**.

This compound was obtained in a yield of 96.8%, m.p. 110-111.5°, lit. 117°(23); ir (potassium bromide): 2800, 2750, 2720, 2680, 1625, 1600, 1495; nmr (deuteriochloroform): δ 1.55 (6H, m, $(CH_2)_3$), 2.45 (4H, m, $(CH_2)_2$N), 3.8 (2H, s, Ar-CH_2-N), 7.6 (6H, m, Ar-H), 8.4-8.6 (3H, m, Ar-H). The mass spectrum had the molecular ion peak at m/e 275 and abundant fragment peaks at m/e 192, 191, 189, 165, 98, 84 (100%).

Anal. Calcd. for $C_{20}H_{23}N$: C, 87.27; H, 7.64; N, 5.09. Found: C, 87.16; H, 7.67; N, 5.21.

N-(2,3,6-Trimethoxyphenentryl-9-methyl)piperidine **9b**.

This compound was obtained in a yield of 85%, m.p. 167-168°, lit. 167° (23); ir (potassium bromide): 2795, 2758, 2720, 2682, 1629, 1615, 1515; nmr (deuteriochloroform): δ 1.55 (6H, m, $(CH_2)_3$), 2.55 (4H, m, $(CH_2)_2$N), 3.87 (2H, s, Ar-CH_2-N), 4.07, 4.15 (9H, 2s, 3 x OCH_3), 7.29-7.99 (5H, m, Ar-H), 8.45 (1H, d, Ar-H). The mass spectrum had the molecular ion peak at m/e 365 and abundant fragment peaks at m/e 282 (100%), 281, 267, 251, 98, 84.

Anal. Calcd. for $C_{23}H_{27}NO_3$: C, 75.62; H, 7.39; N, 3.83. Found: C, 75.77; H, 7.38; N, 3.95.

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REFERENCES AND NOTES

(1) I. S. de la Lande, *Aust. J. Biol. Med. Sci.*, **26**, 181 (1948).

(2) N. K. Hart, S. R. Johns, J. A. Lamberton, *Aust. J. Chem.*, **21**, 2579 (1968).

(3) N. R. Farnworth, N. K. Hart, S. R. Johns, J. A. Lamberton, W. H. Messner, *ibid.*, **22**, 1805 (1969).

(4) E. Gellert, R. Rudzats, *J. Med. Chem.*, **7**, 361 (1964); G. R. Donaldson, M. R. Atkinson, A. W. Murray, *Biochem. Biophys. Res. Commun.*, **31**, 104 (1968).

(5) L. Sánchez, D. Vázquez, A. Jiménez, *Molec. Gen. Genet.*, **156**, 319 (1977).

(6) S. R. Gupta, L. Siminovitch, *Biochemistry*, **16**, 3209 (1977).

(7) C. K. Bradsher, H. Berger, *J. Am. Chem. Soc.*, **79**, 3287 (1957).

(8) P. Marchini, B. Belleau, *Can. J. Chem.*, **36**, 581 (1958).

(9) S. Földeak, *Tetrahedron*, **27**, 3465 (1971).
(10) J. M. Paton, P. L. Pauson, T. S. Stevens, *J. Chem. Soc. (C)*, 1309 (1969).
(11) E. Kotani, M. Kitazawa, S. Tobinaga, *Tetrahedron*, **30**, 3027 (1974).
(12) R. B. Herbert, *J. Chem. Soc., Chem. Commun.*, 794 (1978).
(13) R. F. Borch, *Tetrahedron Letters*, 61 (1968).
(14) R. B. Herbert, C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 121 (1970).
(15) S. R. Johns, J. A. Lamberton, A. A. Sioumis, R. I. Willing, *Aust. J. Chem.*, **23**, 353 (1970).
(16) J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, A. H. Redcliffe, *ibid.*, **19**, 151 (1966).
(17) H. P. Hamlow, S. Okuda, N. Nakagawa, *Tetrahedron Letters*, 2553 (1964).
(18) B. Chauncy, E. Gellert, *Aust. J. Chem.*, **23**, 2503 (1970).
(19) Goldberg, Ordas, Carsh, *J. Am. Chem. Soc.*, **69**, 260 (1947).
(20) H. Meerwein, *Org. Synth.*, **46**, 113 (1966).
(21) S. Földeak, P. Hegyes, *Acta Phys. Chem.*, **20**, 111 (1974).
(22) E. Gellert, N. V. Riggs, *Aust. J. Chem.*, **7**, 113 (1954).
(23) D. O. Shah, K. N. Trivedi, *Indian J. Chem. (B)*, **15**, 599 (1977).