Tetrahedron. Vol. 30, pp. 3027 to 3030. Pergamon Press 1974. Printed in Great Britain

A NEW SYNTHESIS OF THE ALKALOID (±)-CRYPTOPLEURINE *VIA* ANODIC OXIDATION

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(*Received in Japan* 25 *March* 1974; *Received in UK for publication* 23 *April* 1974)

Abstract—The alkaoid (±)-cryptopleurine **1** was synthesized by anodic oxidation of the quinolizidinone **3** followed by subsequent transformation of **6a** to **1** and **5a** to **6a**.

The vesicant alkaloid cryptopleurine **1**, an alkaloid isolated from *Cryptocarya pleurosperma*,[1] *Boehmeria platyphylla*[2] and *B. cylindrica*,[3] which has the phenanthro-quinolizidine ring system, is known by means of its interesting biological as well as pharmacological properties, namely the mitotic poison,[4] cytotoxic,[3] and antiviral activities.[5] At least two of the biogeneticaly related alkaloids, tylophorine **2a**, and tylocrebrine **2b** which have the phenanthroindolizidine ring system,[6] other than cryptopleurine are known to be powerful vesicants. Although the total syntheses of cryptopleurine have been achieved by three groups,[7] development of additional synthetic methods are also necessary to make accessible a range of related compounds with a view to study of their physiological activities. This paper is concerned with a new synthesis of (±)-cryptopleurine by the oxidation of the quinolizidinone **3** using electrochemical method followed by subsequent transformation in high yield.

Previously, Pauson *et al* [7c] reported the synthesis of (±)-cryptopleurine based on biogenetic consideration from 2-methylpyridine, methyl 3,4-dimethoxybenzoate, and 4-methoxyphenylacetyl chloride. The oxidative coupling reaction by MnO_2 of the phenol **4b**, prepared from the quinolizidinone **3** by demethylation followed by hydrogenation, to give the spirodienone **5b** (15–20% yield) was a key-step reaction for the construction of phenan-

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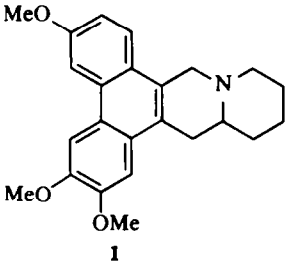
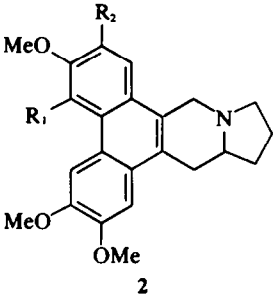
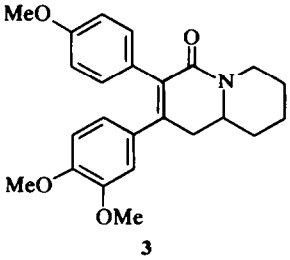


1

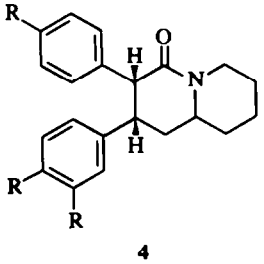


2

a: R_1 = H, R_2 = OMe
b: R_1 = OMe, R_2 = H



3



4

a: R = OMe
b: R = OH

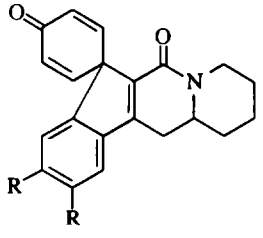
throquinolizidine nucleus in their synthesis. Meanwhile, intramolecular oxidative non-phenol coupling reaction by electrochemical method has been gave to raise attention as a new method and these anodic oxidation reaction afford superior results than chemical phenol coupling reactions in some cases.[8] Thus, we attempted to use these electrochemical methods for the synthesis of the alkaloid cryptopleurine from the quinolizidinone **3** to provide an improved synthesis than previous reports.

Preliminary investigations for the synthesis of phenanthrene ring by anodic oxidation were carried out with the model compounds **7a** and **7b**, though the syntheses of the phenanthrenes from diazonium salts of 2-amino-α-phenylcinnamic acid by electro-Pschorr reaction[9] and from the tetramethoxybibenzyl by anodic oxidation[10] were already reported. The anodic oxidation of the methyl cinnamate **7a**[11] was done by the similar method reported in the previous communications[8] in the presence of Et_4NClO_4 as a electrolyte to afford the phenanthrene carboxylate **8a** in yield 50%, and in the presence of HBF_4 to give **8a** in yield 25%. Similarly, the oxidation of **7b**[11] in the presence of Et_4NClO_4 as a electrolyte gaves **8b** in yield 45%. The phenanthrene carboxylate **8a** has been synthesized by the photolytic reaction for the synthesis of the alkaloid tylophorine[12] and **8b** by Pschorr synthesis.[13] According to the above results, the anodic oxidation of the quinolizidinone **3a**, synthesized in a similar manner as the report of Pauson,[7c] was done in CH_3CN at room temperature in the presence of HBF_4 as a electrolyte. At that time, the current 110 mA maintaining the potential at 1·07 V (SCE) was smoothly down to 20 mA in 30 min and the reaction mixture was consisted with a spirodienone **5a** and an unexpected but favorable coupling product **6a** in yield 60% and 31%, respectively. The oxidation of **4a** does not gave any intramolecular coupling products different from the chemical oxidation experiment by Pauson.[7c]

Subsequently, the spirodienone **5a** was subjected to the dienone-phenol rearrengement reaction with Ac_2O–H_2SO_4 into the acetate **6b**. Resulting **6b** was hydrolysed to give **6c** followed by methylation with diazomethane to afford **6a** in overall yield 80% from **5a**. LAH reduction of the phenanthroquinolizidinone **6a** afforded (±)-cryptopleurine **1** in almost quantitative yield. The synthetic cryptopleurine had the same UV, IR, NMR, and mass spectra as with those of authentic sample of (−)-cryptopleurine.

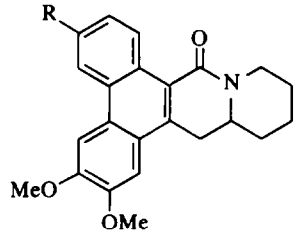
EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded with a Hitachi 215 spectrometer, UV spectra with a Hitachi 124 spectrometer, NMR spectra with a Varian T-60 spectrometer with TMS as internal standard for $CDCl_3$ soln, and mass spectra with a Hitachi RMS-4 spectrometer at 70 eV with direct insertion technique. Elementary analysis were done by Miss K. Sasaki, Kissei Pharmaceutical Company, Matsumoto, Japan. Mallinckrodt silica gel (100 mesh), Merck aluminiumoxid (Act II-III)



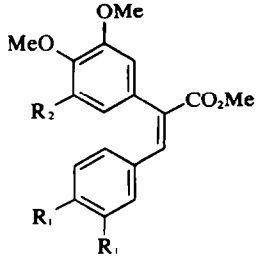
5

a: R = OMe
b: R = OH



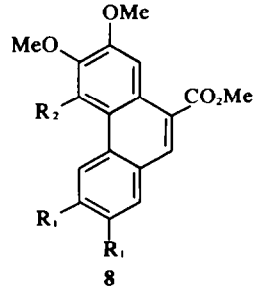
6

a: R = OMe
b: R = OAc
c: R = OH



7

a: R_1 = OMe, R_2 = H
b: R_1 = –OCH_2O–, R_2 = OMe



8

a: R_1 = OMe, R_2 = H
b: R_1 = –OCH_2O–, R_2 = OMe

and Merck Kieselgel G Stahl were used for column chromatography and TLC, respectively.

General electrolysis procedure. Electrolysis was performed in a H-type one compartment glass cell in conjuction with a Yanagimoto V-8 controlled potential electrolyser. All potentials were measured against a saturated calomel reference electrode. The working electrode was used a platinum gauze. Oxidations were carried out in commercial acetonitrile without purification at room temp with stirring at anode site by magnetic stirrer. The concentration of reactants was *ca* 0·01 M and the supporting electrolyte was 0·1 M. Generally, the potential was maintained at *ca* 1·00–1·10 V (SCE) with initial currents 110–120 mA. Electrolysis was usually discontinued when the current dropped to 10–20 mA which generally took 20–45 min. The soln was concentrated under vacuum to near dryness, then taken up in water, and extracted with chloroform. The combined organic layers were dried with anhydrous sodium sulfate, then concentrated.

Methyl 2,3,6,7-*tetramethoxyphenanthrene*-10-*carboxylate* (**8a**)

(a) Compound **7a**[11] (100 mg) and Et_4NClO_4 (800 mg) were dissolved in MeCN (35 ml) and oxidized at 0·97 V for 45 min, in the manner described above to give 50 mg (50%) of **8a** as white needles (ether-hexane), m.p. 203–205°; mass *m/e*: 356 (M^+, $C_{20}H_{20}O_6$), 341 (M^+–CH_3), 325 (M^+–OCH_3), and 313 (M^+–$COCH_3$); IR (nujol) cm^{-1}: 1718, 1621 and 1519; UV (EtOH) mμ (log ϵ): 263 (4·94), 287 (4·70), and 325 (4·25); NMR ($CDCl_3$) δ: 8·68 (1H, s), 8·40 (1H, s), 7·77 (1H, s), 7·71 (1H, s), 7·22 (1H, s), 4·20 (9H, s, 3 × OCH_3), and 4·10 (6H, s, 2 × OCH_3).

(b) Electrolysis of **7a** (100 mg) and 42% HBF_4 (1 ml) in MeCN (35 ml) in the described fashion at 1·01 V gives 25 mg (25%) of **8a**. Spectroscopic data were identical with those of the above specimen.

Methyl 2,3,4 - *trimethoxy* - 6,7 - *methylenedioxyphenanthrene* - 10 - *carboxylate* (**8b**)

Compound **7b**[11] (100 mg) and Et_4NClO_4 (800 mg) in MeCN (35 ml) at 1·08 V for 20 min in the same fashion described above gave 45 mg (45%) of **8b** as white needles (ether-hexane), m.p. 156–157°; mass *m/e*: 370 (M^+, $C_{20}H_{18}O_7$), 355 (M^+–CH_3), 327 (M^+–$COCH_3$); IR (nujol) cm^{-1}: 1704; NMR ($CDCl_3$) δ: 9·02 (1H, s), 8·48 (1H, s), 8·35 (1H, s), 7·22 (1H, s), 6·15 (2H, s, –OCH_2O–), 4·10 (6H, s, 2 × OCH_3), 4·05 (3H, s, OCH_3), 4·01 (3H, s, OCH_3).

Hydrolysis of **8b** with 15% KOH gave an acid as white needles (acetone), m.p. 272–274°.

2 - (3,4 - *Dimethoxyphenyl*) - 1,6,7,8,9,9a - *hexahydro* - 3 - (4 - *methoxyphenyl*) - *quinolizin* - 4 - *one* (**3**)

A soln of 2 - (3,4 - dimethoxyphenacyl) - N - (4 - methoxyphenylacetyl) - piperidine[7c] (500 mg) and 5% NaOH (30 ml) in EtOH was refluxed on water bath for 2 hr. The soln was concentrated under vacuum, taken up in $CHCl_3$ and then washed with 10% HCl. The organic layers were concentrated, then the residue was subjected to alumina chromatography. The first benzene elution provides 400 mg (80% yield) of **3** as white needles (ether-hexane), m.p. 141–142°. These synthesis described above afforded a better result than the previous report.[7c]

Electrolysis of **3**

The quinolizidinone **3** (150 mg) and 42% HBF_4 (1 ml) were dissolved in MeCN (35 ml) and oxidized at 1·07 V for 30 min. Resulting residue was subjected to chromatography on 10 g Al_2O_3. From the first benzene elution, 45 mg (31%) of **6a**, m.p. 194–195°, straw colored needles; mass *m/e*: 391 (M^+, $C_{24}H_{25}NO_4$), 308 (M^+–C_5H_9N), 280 (M^+–C_5H_9N–CO), and 265 (M^+–C_5H_9N–CO–CH_3); IR (KBr) cm^{-1}: 1635, 1619, and 1512; UV (EtOH) mμ (log ϵ): 253 (4·68), 259 (4·68), 283 (4·42), and 336 (3·97); NMR ($CDCl_3$) δ: 9·60 (1H, d, J = 10 Hz, Ar–H), 7·70 (1H, s, Ar–H), 7·72 (1H, d, J = 10 Hz, Ar–H), 7·70 (1H, s, Ar–H), 7·72 (1H, d, J = 2 Hz, Ar–H), 7·17 (1H, dd, J = 10 Hz, J = 2 Hz, Ar–H), 7·09 (1H, s, Ar–H), 4·08 (3H, s, OCH_3), and 4·0 (6H, s, 2 × OCH_3) was obtained. From the second elution by benzene-chloroform (1 : 1), 90 mg (60%) of **5a**, m.p. 220–222°, pale yellow crystalline; mass *m/e*: 377 (M^+, $C_{23}H_{23}NO_4$), 349 (M^+–CO), 334 (M^+–CO–CH_3), 294 (M^+–C_5H_9N), 266 (M^+–C_5H_9N–CO), and 251 (M^+–C_5H_9N–CO–CH_3); IR (KBr) cm^{-1}: 1666, 1651 (sh), 1643 (sh), 1621, 1577, and 1501; UV (EtOH) mμ (log ϵ): 247 (4·57), 297 (3·72), and 340 (4·12); NMR ($CDCl_3$) δ: 6·98 (1H, s, Ar–H), 6·63 (1H, s, Ar–H), 6·57 (2H, d, J = 10 Hz, olefinic H), 6·33 (2H, d, J = 10 Hz, olefinic H), 3·98 (3H, s, OCH_3), and 3·88 (3H, s, OCH_3) was isolated. Both compound **6a** and **5a** were recrystallised from MeOH.

2,3 - *Dimethoxy* - 6 - *acetoxyphenanthro* [9, 10 - *b*] - 11,12,13,14,14*a*,15 - *hexahydroquinolizin* - 9 - *one* (**6b**)

To a soln of **5a** (200 mg) in Ac_2O (7 ml), a soln of conc H_2SO_4 2·5 ml in 6·5 ml Ac_2O was added, and left for 4 hr at room temp. The resulting green soln was poured into ice water and the ppt which separated was collected. The ppt was recrystallised from MeOH to yield 215 mg (98%) of **6b** as white needles, m.p. 241–243°; mass *m/e*: 419 (M^+, $C_{25}H_{25}O_5N$), 377 (M^+–C_2H_2O), 294 ($M^+C_2H_2O$–C_5H_9N), and 266 M^+–C_2H_2O–C_5H_9N–CO); Ir (nujol) cm^{-1}: 1760, 1640, and 1619; NMR ($CDCl_3$) δ: 9·78 (1H, d, J = 10 Hz, Ar–H), 8·18 (1H, d, J = 2 Hz, Ar–H), 7·80 (1H, s), s), 7·36 (1H, dd, J = 10 Hz, J = 2 Hz, Ar-H), 7·30 (1H, s, Ar–H), 4·17 (3H, s, OCH_3), 4·10 (3H, s, OCH_3), and 2·43 (3H, s, $OCOCH_3$).

2,3 - *Dimethoxy* - 6 - *hydroxyphenanthro* [9,10 - *b*] - 11,12,13,14,14*a*,15 - *hexahydroquinolizin* - 9 - *one* (**6c**)

Hydrolysis of **6b** (200 mg) with 5% methanolic KOH gave 170 mg (94%) of **6c**, white needles, crystallised from methylene chloride-ether, m.p. 245–246°; mass *m/e*: 377 (M^+, $C_{23}H_{23}NO_4$), 294 (M^+–C_5H_9N), 266 (M^+–C_5H_9N–CO), and 251 (M^+–C_5H_9N–CO–CH_3); IR (nujol) cm^{-1}: 3300, 1610.

Methylation of **6c** with diazomethane in MeOH in the presence of glass boiling chips afforded **6a** in almost quantitative yield.

2,3,6 - *Trimethoxyphenanthro* [9,10 - *b*] - 11,12,13,14, 14b,15 - *hexahydro* - 9H - *quinolizine* (1, (±) - *crytopleurine*)

To a soln of **6a** (100 mg) in dry THF (50 ml) a soln of LAH (250 mg) in dry THF (125 ml) was added dropwise in ice cooled bath with stirring, then refluxed for 5 hr. Resulting soln was concentrated under vaccum, decomposed the excess hydride with ice water, and added ammonium chloride and few drops of ammonia, then extracted with CH_2Cl_2. Organic layers were concentrated and recrystallised from acetone to give 94 mg (98%) of **1** as white fine needles, m.p. 199–200°; (Found: C, 76·25; H, 7·18; N, 3·60. $C_{24}H_{27}NO_3$ requires: C, 76·36; H, 7·21; N, 3·71) mass *m/e*: 377 (M^+, 21·5%), 294 (M^+–C_5H_9N, 100%), and 279 (M^+–C_5H_9N–CH_3, 5·4%); IR (KBr) cm^{-1}: 1612, 1530, 1512,

1471, 1452, 1422, 1259, 1232, 1209, 1171, 1126, 1039, 849, 831, 811 and 782; UV (EtOH) mμ (log ε): 258 (4·60), 286 (4·34), 343 (2·90), and 359 (2·60); NMR ($CDCl_3$) δ: 7·80 (1H, s, Ar–H), 7·83 (1H, d, J = 2 Hz, Ar–H), 7·75 (1H, d, J = 10 Hz, Ar–H), 7·17 (1H, s, Ar–H), 7·12 (1H, dd, J = 10 Hz, J = 2 Hz, Ar–H), 4·04 (3H, s, OCH_3), 4·0 (3H, s, OCH_3), and 3·97 (3H, s, OCH_3).

Acknowledgements—We thank Dr. J. A. Lamberton, Division of Applied Chemistry, CSIRO, Australia, and Prof. E. Gellert, Wollongong University College, Australia, for the comparison and identification of the synthetic and authentic sample of cryptopleurine.

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