A DIRECT CONVERSION OF PHENANTHRENES TO APORPHINOIDS

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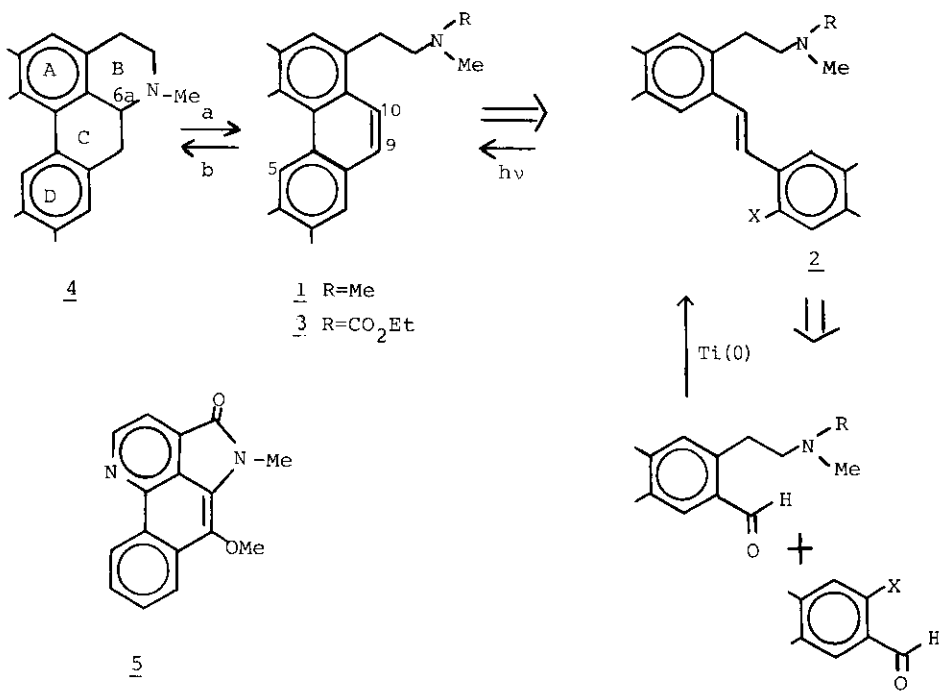
Abstract - *We describe a single-step conversion of phenanthrene alkaloid derivatives into oxoaporphines based on the cyclization of 9,10-phenanthrenediones with ethanamine side-chains under basic conditions.*

We recently reported the synthesis of phenanthrene alkaloids (1)[1] using the low-valent titanium dicarbonyl coupling reaction to produce the stilbene intermediate (2) (SCHEME I). This type of alkaloids (1) had previously been obtained from the parent aporphinoids (4) by degradation procedures (path a) closely resembling biogenetic hypothesis.[2]



4 1 R=Me 3 R=CO_2Et 2 5

SCHEME I

With (3) now readily available, we have turned our attention to the reverse of the degradation reaction, the synthesis of aporphinoids starting from the appropriate phenanthrene derivative (path b). This strategy requires the formation of the N-C_{6a} bond in the final stages, a step as yet unexploited in the field of aporphine alkaloids[3], the sole exception being the construction of the five-membered lactam ring in the pyridinolactam eupolauramine (5)[4].

Attempts at inducing the nucleophilic attack of the nitrogen on the C_{10} position to form ring B of (4) via epoxidation[4] or aminomercuriation[5] of the C_9-C_{10} double bond of phenanthrenes (3a) and (3c) (SCHEME II) resulted in failure. We therefore decided to oxidize phenanthrene (3) to 9,10-phenanthrenedione (6) with HIO_3 in AcOH[4]. As the severe conditions needed to hydrolize the N-carbethoxy group[6] in (6, R=CO_2Et) were thought to be incompatible with the 9,10-dione function, the starting phenanthrenes first used were the free base (3c) and its hydrochloride (3e), which were cleanly oxidized to the corresponding 9,10-phenanthrenedione (6). When treated with a basic methanolic solution, this compound afforded the oxo-aporphine O-methylatheroline (7a) together with a small amount of zwitterionic corunnine (8) (SCHEME II), both of which were identified by comparison with natural specimens[7].

When the N-trifluoroacetamide (3d, easily obtained from the corresponding aporphine[8], path a, SCHEME I) was oxidized as above, phenanthrenedione (6d) was formed, and the deprotection of the attacking N-group with a basic methanolic solution, followed by cyclization and a sequence of oxidation-elimination reactions, afforded 62% of (7a) and 4% of (8).

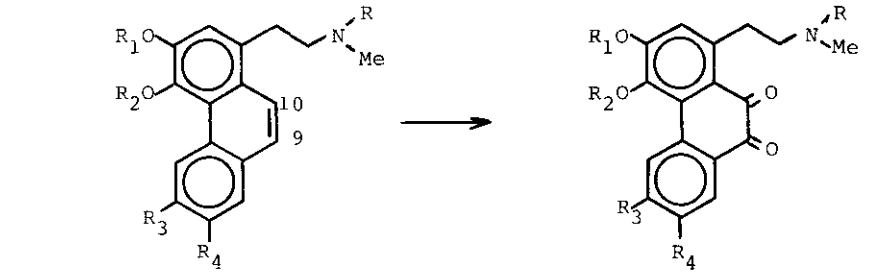
The results obtained using different reaction conditions are given in table I.

TABLE I

Starting Material	Reaction Conditions	7a(%)	8(%)
3c	1) HIO_3/80°C 2) A	60	10
3d	1) HIO_3/80°C 2) A	62	4
3e	1) HIO_3/80°C 2) A	67	5
3e	1) HIO_3/80°C 2) B	57	22

A: sat. Na_2CO_3, MeOH, 80°C, 1 h; B: sat. Na_2CO_3, MeOH, r.t., 1 h.

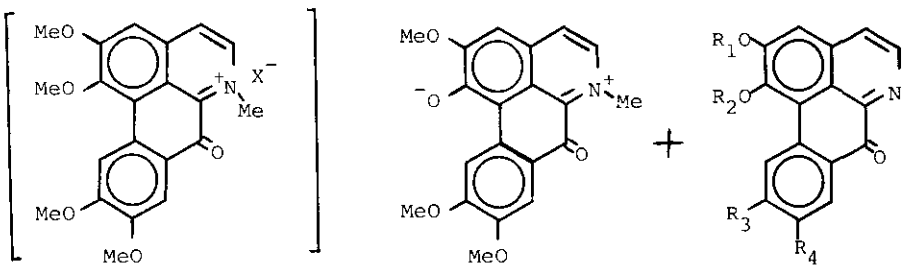
The formation of (8) initially suggested an intermediate like (9) in which competition for the elimination of labile N and O-methyl groups might be expected and would explain (7a) and (8). However, this hypothesis was discarded after subjecting O-methylatheroline methiodide (9, X=I) to basic hydrolysis conditions, which afforded nearly equal yields of the oxoaporphine products (26% and 24% for 7a and 8 respectively). It therefore seems likely that N^+-Me elimination precedes the aromatization step, and that products like (8) are formed by thermal decomposition when, like (7a), the resulting oxoaporphines have OMe at C_9.



3

a: $R_1=R_2=Me$, $R_3=R_4=OMe$, $R=CO_2Et$
b: $R_1+R_2=-CH_2-$, $R_3=R_4=H$, $R=CO_2Et$
c: $R_1=R_2=Me$, $R_3=R_4=OMe$, $R=H$
d: $R_1=R_2=Me$, $R_3=R_4=OMe$, $R=COCF_3$
e: $R_1=R_2=Me$, $R_3=R_4=OMe$, $R=H(HCl)$
f: $R_1+R_2=-CH_2-$, $R_3=R_4=H$, $R=H(HCl)$

6



9 8 7

a: $R_1=R_2=Me$, $R_3=R_4=OMe$
b: $R_1+R_2=-CH_2-$, $R_3=R_4=H$

SCHEME II

Finally, when compound (3f) obtained from (3b) was subjected to the reaction conditions used with (3e), it afforded liriodenine[10] (7b) in 68% yield, further demonstrating the reliability of this short procedure for the total synthesis of oxoaporphine alkaloids described in this article.

EXPERIMENTAL

All melting points are uncorrected. Proton NMR spectra were obtained on a Varian CFT-20 (80 MHz) or a Bruker WM-250 (250 MHz), using $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded with a Kratos MS-25 instrument at a 70 eV ionizing energy. IR spectra were recorded with a PYE UNICAM 1100 spectrometer using KBr pellets unless otherwise stated and UV spectra were recorded with a PYE UNICAM 1700. Thin layer cromatography (TLC) was performed on analytical plates coated with silica gel GF_{254} (type 60) (Merck). All new compounds gave satisfactory elemental analyses.

N-Carbethoxysecoglaucine (3a). To an ice-cooled solution of 0.305 g (0.864 mmol) of glaucine (4a) in 5 ml of dry pyridine, 1 ml of ethyl chloroformate was added and the resulting suspension was heated with stirring for 2 h at 100°C. After adding 30 ml of 10% HCl the solution was extracted with CH_2Cl_2 (3 x 25 ml). The organic layer was washed twice with water (25 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by preparative TLC to afford compound (3a) (0.281 g, 76% yield), mp: 110-111°C (abs. EtOH); PMR (80 MHz, δ): 9.28 (s, 1H, H_5), 7.86 and 7.55 (ABq, 2H, J=9 Hz, H_9 and H_{10}), 7.21 and 7.15 (2 s, 2H, ArH), 4.07, 4.04, 4.02 and 3.92 (4 s, 12H, 4 x OMe), 4.19-3.92 (m, 2H, $O\underline{CH_2}CH_3$), 3.63-3.28 (m, 4H, 2 x $-CH_2-$), 2.89 (broad s, 3H, NMe), 1.25 (t, 3H, J=7.4 Hz, $OCH_2\underline{CH_3}$); m/e (%): 427 (M^+, 35), 311 (100), 116 (28), 44 (93); IR: 1690 cm^{-1}; UV $\lambda_{max.}^{MeOH}$: 284, 310, 322, 348, 364 nm.

N-Carbethoxysecoroemerine (3b). Starting from 0.191 g (0.684 mmol) of roemerine (4b), 0.156 g of (3b) was obtained (65% yield) by the same procedure as used with (4a). An additional 10 ml of dry pyridine were needed to dissolve an initial precipitate, mp: 88-89.5°C (abs. EtOH); PMR (250 MHz, δ): 9.04-9.00 (m, 1H, H_5), 7.93-7.74 (m, 2H, ArH), 7.58-6.96 (m, 4H, ArH), 6.19 (s, 2H, $-OCH_2O-$), 4.17-4.07 (m, 2H, $-O\underline{CH_2}CH_3$), 3.50-3.07 (m, 4H, 2 x $-CH_2-$), 2.86 and 2.74 (2s, 3H, NMe), 1.29-1.21 (m, 3H, $-OCH_2\underline{CH_3}$); m/e (%): 351 (M^+, 21), 248 (13), 235 (64), 116 (51), 44 (100); IR: 1690 cm^{-1}; UV $\lambda_{max.}^{EtOH}$: 214, 248, 258, 284, 322, 352, 370 nm.

Secoglaucine (3c) by Hydrolysis of N-Carbethoxysecoglaucine (3a). Potassium hydroxide (9 g) was dissolved in absolute ethanol (50 ml) by heating under argon. The resulting solution was cooled and added to the carbamate (1.915 mmol) and the solution was then refluxed for 15 h under argon. To the cooled solution was then added dropwise a solution of 9 g of citric acid in distilled water (50 ml). After stirring for 10 min, EtOH was evaporated and the aqueous mixture was extracted with CH_2Cl_2 (3 x 50 ml). The dried (Na_2SO_4) organic extracts were concentrated in vacuo. Spectral and physical data of the residue were those of secoglaucine and identification was completed by comparison with an authentical sample supplied by Bremner[11]. The hydrochloride of (3c) melted at 245-248°C (decomp) (abs. EtOH). Total yield 85%.

Secoroemerine (3f). As above we obtained secoroemerine as an oil in 74% yield; its hydrochloride melted at 224-226°C (decomp) (abs. EtOH); PMR (250 MHz, δ): 9.11-9.07 (m, 1H, H_5), 7.89-7.81 (m, 2H, ArH), 7.62-7.54 (m, 3H, ArH), 7.15 (s, 1H, ArH), 6.23 (s, 2H, $-OCH_2O-$), 3.24 (t, 2H, J=7.1 Hz, $-CH_2N$), 2.92 (t, 2H, J=7.1 Hz, $ArCH_2$), 2.44 (s, 3H, NMe); m/e (%): 279 (M^+, 4), 236 (100); IR (film, NaCl): 3460-3340 cm^{-1}; UV $\lambda_{max.}^{MeOH}$: 216, 240, 250, 284, 322, 354, 362 nm.

N-Trifluoroacetylsecoglaucine (3d). Starting from 0.200 g (0.566 mmol) of glaucine (4a) and 1 ml of trifluoroacetic anhydride instead of ethyl chloroformate, compound (3d) (0.204 g, 80% yield) was obtained by the same procedure used for (3a); mp: 145-146°C (EtOH); PMR (250 MHz, δ): 9.28 (s, 1H, H_5), 7.85 and 7.59 (ABq, 2H, J= 9.1 Hz, H_9 and H_{10}), 7.22 (s, 1H, ArH), 7.14 (s, 1H, ArH), 4.07, 4.05, 4.02 and 3.92 (4 s, 12H, 4 x OMe), 3.76 (t, 2H, J=8 Hz, $-CH_2N$), 3.40 (t, 2H, J=8 Hz, $ArCH_2$); m/e (%): 451 (M^+, 55), 311 (100), 140 (55), 69 (51); IR: 1690 cm^{-1}; UV $\lambda_{max.}^{MeOH}$: 264, 284, 310, 322, 348, 364 nm.

Phenanthrenedione (6d). To a solution of 0.250 g (0.591 mmol) of N-trifluoroacetylsecoglaucine (3d) in 30 ml of acetic acid was added a solution of 0.300 g (1.71 mmol) of iodic acid in 20 ml of water. The reaction mixture was refluxed for 5 h and then was cooled to room temperature. The solvent was removed in vacuo, and the residue was dissolved in methylene chloride (50 ml). The organic solution was washed with aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and concentrated to dryness. The residue was purified by preparative TLC yielding 0.214 g (80%) of (6d); mp: 199-201°C (EtOH); PMR (80 MHz, δ): 8.49 (s, 1H, H_5), 7.56 (s, 1H, ArH), 6.78 (s, 1H, ArH), 4.01 (s, 6H, 2 x OMe), 3.99 and 3.78 (2 s, 6H, 2 x OMe), 3.78 (broad s, 2H, $-CH_2N$), 3.29 (br s, 5H, $ArCH_2$ and NMe); m/e (%): 481 (M^+, 33), 354 (21), 341 (100), 326 (57), 313 (26); IR: 1690, 1660 cm^{-1}; UV $\lambda_{max.}^{MeOH}$: 210, 230, 262, 282, 360, 500 nm.

Cyclization of (6d). A saturated aqueous solution of Na_2CO_3 (20 ml) was added to a solution of 0.100 g (0.208 mmol) of (6d) in 20 ml of MeOH and the mixture was heated to 80°C for 1 h. The alcohol was removed in vacuo, the pH was adjusted to 8 with 10% HCl and the resulting solution was extracted with CH_2Cl_2 (5 x 20 ml). The dried (Na_2SO_4) extracts were concentrated in vacuo and the residue was purified by preparative TLC using CH_2Cl_2-MeOH (10:1) as eluent to afford 48 mg of O-methylatheroline[9] (62% yield) and 3 mg of corunnine[7] (8) (4% yield), both identical with natural specimens.

Syntheses and Cyclization of (6c, 6e and 6f). Starting from (3c, 3e and 3f) and using the same procedure as described for the synthesis of (6d), phenanthrenediones (6c, 6e and 6f) were obtained. The corresponding crude products were heated to 80°C for 1 h with a MeOH/sat. aq. Na_2CO_3 solution and worked up as above.

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