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NEW USES OF WESTPHAL CONDENSATION: SYNTHESIS OF FLAVOCORYLENE AND RELATED INDOLO[2,3-a]QUINOLIZINIUM SALTS.

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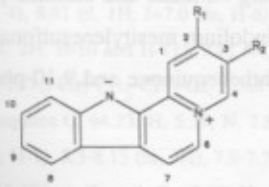
Abstract: Using the Westphal condensation, flavocorylene and related Indolo[2,3-a]-quinolizinium salts have been prepared in two steps, starting from commercially available ß-carboline derivatives.

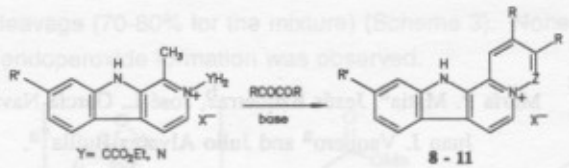
The small group of biogenetically-interesting[1] indole alkaloids that incorporate the zwitterionic indolo[2,3-a]quinolizinium ring system **I** has received limited attention in the synthesis field.[2] Some of its representatives such as flavopereirine (**1**) and sempervirine (**2**) have been described to possess antitumour activity,[3] but the relatively complex preparation methods has reduced the availability of analogs.



R_1=Et R_2=H
R_1-R_2=-$(CH_2)_4$-

Our interest in the Westphal condensation[4] as an easy way to prepare quinolizinium salts[5] led us to exploit the reactivity of 9H-2-ethoxycarbonylmethyl-1-methylpyrido[3,4-b]indolium bromides **4** and **5**, which were prepared in high yields from commercially available ß-carbolines harmane and harmine.[6]

Basic condensation of both salts with symmetric 1,2-diketones, such as 3,4-hexanedione and 1,2-acenaphthenequinone, provided the 12H-indolo[2,3-a]quinolizinium bromides[7] **8a,b** and **9a,b**. Anion exchange of bromide (**8a**, X=Br) produced the already described Flavocorylene hydrochloride[8].



Compound	R'	Z	X	R	R	Yield(%)
8a	H	CH	Br	CH_3CH_2	CH_3CH_2	60
8b	H	CCO_2Et	Br	1,8-Naphthalenediyl		94
9a	OCH_3	CH	Br	CH_3CH_2	CH_3CH_2	50
9b	OCH_3	CCO_2Et	Br	1,8-Naphthalenediyl		70
10b	H	N	MSTS*	1,8-Naphthalenediyl		73
10c	H	N	MSTS	Diphen-*o,o'*-diyl		84
11b	OCH_3	N	MSTS	1,8-Naphthalenediyl		75
11c	H	N	MSTS	Diphen-*o,o'*-diyl		70

* Mesitylensulfonate

Our methodology is equally applicable to the synthesis of the new 12H-pyridazino[2':3',1,2]pyrido-[3,4-b]indolium mesitylenesulfonates **10b,c** and **11b,c** isoelectronic with the bromides **8** and **9**, by a modified Westphal condensation, recently developed by us.[9] Thus, amination with O-mesitylenesulfonyl-hydroxylamine (MSH)[10] of the starting harmane and harmine precursors yielded the corresponding 2-amino-1-methyl-9H-pyrido[3,4-b]-indolium mesitylenesulfonates **6** and **7** (X=MSTS) which, in basic conditions[8], reacted with 1,2-acenaphthenequinone and 9,10-phenanthrenequinone yielding the new salts **10** and **11** (X=MSTS).

Further experiments are in progress to extend this methodology to other 1,2-dicarbonyl compounds as asymmetric diketones and 1,2-ketoaldehydes.

In summary, the new approach represents a straightforward preparation of 12H-indolo[2,3-a]-quinolizinium derivatives which can be easily extended to new biologically interesting compounds.

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6. ^{1}H NMR spectra were recorded on a Varian Unity 300 instrument. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The proton resonances for the mesitylenesulfonate anion in **6, 7, 10b,c** and **11b,c** have not been listed as they are independent of the heterocyclic cation, signals appearing in all cases at 6.62 ppm for the aromatic protons and 2.44 and 2.15 ppm for the ortho and para methyl groups, respectively. Satisfactory microanalyses were obtained for all new compounds described, within 0.4% error.

   Typical procedure: Equivalent amounts (10 mmol) of the corresponding heterocyclic precursor and ethyl bromoacetate in dry acetone (30 ml) were refluxed for 4 hours. The precipitate was collected and recrystallized from ethanol.

   Compound **4**. (250-252°C, 90%) ^{1}H NMR(DMSO-d_6) δ 13.00 (s, 1H, NH), 8.75 (d, 1H, J=6.6 Hz, H-3), 8.60 (d, 1H, J=6.6 Hz, H-4), 8.45 (d, 1H, J=8.0 Hz, H-5), 7.85-7.75 (m, 2H, H-7 and H-8), 7.5-7.4 (m, 1H, H-6), 5.81 (s, 2H, CH_2CO), 4.25 (q, 2H, J=7.1 Hz, -$CH_2$$CH_3$), 3.04 (s, 3H, CH_3-C1), 1.25 (t, 3H, J=7.1 Hz, $CH_2$$CH_3$). (Found: C, 55.10; H, 5.15; N, 7.95. $C_{16}H_{17}BrN_2O_2$ requires C, 55.02; H, 4.91; N, 8.02).

   Compound **5**. (223-225°C, 80%) ^{1}H NMR(DMSO-d_6) δ 12.82 (s, 1H, NH), 8.6-8.5 (m, 2H, H-3 and H-4), 8.31 (d, 1H, J=8.7 Hz, H-5), 7.13 (d, 1H, J=1.9 Hz, H-8), 7.06 (dd, 1H, J=8.8 and 1.9 Hz, H-6), 5.72 (s, 2H, -CH_2CO-), 4.24 (q, 2H, J=7.1 Hz, -$CH_2$$CH_3$), 3.94 (s, 3H, -$OCH_3$), 2.98 (s, 3H, CH_3-C1), 1.26 (t, 3H, J=7.1 Hz, $CH_2$$CH_3$). (Found: C, 53.70; H, 5.20; N, 7.55. $C_{17}H_{19}BrN_2O_3$ requires C, 53.83; H, 5.05; N, 7.39).
7. General Procedure: Equivalent amounts (10 mmol) of the azinium salts **4-7**, the dicarbonyl derivative, and anhydrous sodium acetate (0.82 g, 10 mmol) were suspended in dry acetone (10 ml). The mixture was refluxed for 2 h. The precipitate was filtered. Crystallization from the acetic acid/acetone yielded the compounds **8-11** in analytical grade. All melted above 260°C.

   8a. ^{1}H NMR(CD_3OD) δ 9.05 (s, 1H, H-4), 8.81 (d, 1H, J=7.0 Hz, H-6), 8.63 (s, 1H, H-1), 8.55 (d, 1H, J=7.0 Hz, H-7), 8.32 (d, 1H, J=8.0 Hz, H-8), 7.8-7.65 (m, 2H, H-10 and H-11), 7.45 (bt, 1H, H-9), 3.09 (q, 2H, J=7.3 Hz, CH_2-C2), 2.99 (q, 2H, J=7.3 Hz, CH_2-C3), 1.55 (t, 3H, J=7.3 Hz, CH_3-CH_2-C2), 1.46 (t, 3H, J=7.3 Hz, CH_3-CH_2-C3). (Found: C, 64.13; H, 5.49; N, 7.65. $C_{19}H_{19}BrN_2$ requires C, 64.23; H, 5.39; N, 7.89).

   8b. ^{1}H NMR(CF_3COOD) δ 8.91 (s, 1H, H-1), 8.3-8.15 (m, 3H), 7.9-7.75 (m, 6H), 7.5-7.3 (m, 3H), 5.20 (q, 2H, J=7.1 Hz, -CH_2CO), 1.92 (t, 3H, J=7.0 Hz, CH_3CH_2-). (Found: C, 68.00; H, 3.85; N, 5.70. $C_{28}H_{19}BrN_2O_2$ requires C, 67.89; H, 3.87; N, 5.66).

   9a. ^{1}H NMR(CD_3OD) δ 8.95 (s, 1H, H-4), 8.76 (d, 1H, J=6.9 Hz, H-6), 8.52 (s, 1H, H-1), 8.43 (d, 1H, J=6.9 Hz, H-7), 8.16 (d, 1H, J=8.8 Hz, H-8), 7.20 (d, 1H, J=2.2 Hz, H-11), 7.06 (dd, 1H, J= 8.7 and 2.2 Hz, H-9), 3.97 (s, 3H, OCH_3), 3.06 (q, 2H, J=7.3 Hz, CH_2-C2), 2.98 (q, 2H, J=7.3 Hz, CH_2-C3), 1.54 (t, 3H, J=7.3 Hz, CH_3-CH_2-C2), 1.44 (t, 3H, J=7.3 Hz, CH_3-CH_2-C3). (Found: C, 62.15; H, 5.30; N, 7.45. $C_{20}H_{21}BrN_2O$ requires C, 62.34; H, 5.49; N, 7.27).

9b. ^{1}H NMR(CF_3COOD) δ 9.12 (s, 1H, H-1), 8.6-8.5 (m, 2H), 8.29 (d, 1H, J=7.1 Hz, H-7), 8.2-8.1 (m, 2H), 8.01 (d, 1H, J=6.9 Hz), 7.9-7.7 (m, 4H), 6.95 (bd, 1H, H-9), 5.28 (q, 2H, J=7.1 Hz, -CH_2CO), 3.94 (s, 3H, OCH_3), 1.94 (t, 3H, J=7.0 Hz, CH_3CH_2-). (Found: C, 66.15; H, 4.10; N, 5.25. $C_{29}H_{21}BrN_2O_3$ requires C, 66.29; H, 4.03; N, 5.33).

10b. ^{1}H NMR(CF_3COOD) δ 9.12(s, 1H, H-1), 8.97 (d, 1H, J=7.1 Hz, H-6), 8.42 (d, 1H, J=7.1 Hz), 8.37 (d, 1H, J= 7.1 Hz, H-7), 8.30 (d, 1H, J=6.8 Hz), 8.15-8.05 (m, 3H, H-8 and 2H from the acenaphthene moiety), 7.90 (t, 1H, J=7.5 Hz), 7.83 (t, 1H, J=7.3 Hz), 7.7-7.65 (m, 2H, H-10 and H-11), 7.39 (t, 1H, J= 6.8 Hz, H-9). (Found: C, 72.70; H, 4.50; N, 7.55. $C_{33}H_{25}N_3O_3S$ requires C, 72.91; H, 4.64; N, 7.73).

10c. ^{1}H NMR(CF_3COOD) δ 9.67 (s, 1H, H-1), 8.97 (d, 1H, J=7.0 Hz, H-6), 8.93 (d, 1H, J=7.1 Hz), 8.54 (d, 1H, J=7.1 Hz), 8.46 (d, 1H, J=7.0 Hz, H-7), 8.29 (d, 2H, J=7.1 Hz), 8.14 (d, 1H, J=7.2 Hz, H-8), 7.81 (t, 1H, J=7.2 Hz), 7.75-7.6 (m, 5H, H-10, H-11 and 3H from the phenanthrene moiety), 7.44 (t, 1H, J= 6.8 Hz, H-9). (Found: C, 73.50; H, 4.65; N, 7.20. $C_{35}H_{27}N_3O_3S$ requires C, 73.79; H, 4.78; N, 7.38).

11b. ^{1}H NMR(CF_3COOD) δ 9.13 (s, 1H, H-1), 9.03 (d, 1H, J=7.1 Hz, H-6), 8.49 (d, 1H, J=7.1 Hz, H-7), 8.37 (d, 1H, J=6.8 Hz, 2H), 8.24 (d, 1H, J=8.3 Hz), 8.19 (d, 1H, J=8.5 Hz), 8.09 (d, 1H, J=9.0 Hz, H-8), 8.0-7.9 (m, 2H), 7.23 (s, 1H, H-11), 7.09 (d, 1H, J=8.9 Hz, H-9), 3.99 (s, 3H, OCH_3). (Found: C, 71.20; H, 4.50; N, 7.60 $C_{34}H_{27}N_3O_4S$ requires C, 71.18; H, 4.74; N, 7.33).

11c. ^{1}H NMR(CF_3COOD) δ 9.42 (s, 1H, H-1), 8.9-8.8 (m, 2H), 8.47 (d, 1H, J=7.5 Hz), 8.3-8.2 (m, 3H), 7.9-7.7 (m, 5H), 7.0-6.9 (m, 2H, H-9 and H-11), 3.85 (s, 3H, OCH_3). (Found: C, 71.95; H, 4.90; N, 6.85 $C_{36}H_{29}N_3O_4S$ requires C, 72.10; H, 4.87; N, 7.01).

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10. Standard procedure: To a stirred solution of O-mesitylenesulfonylhydroxylamine (MSH) (2.15 g, 10 mmol) in dichloromethane (20 ml), the corresponding azine (10 mmol) in the same solvent (20 ml) was dropwise added. The mixture was stirred at room temperature for 10 min. Diethyl ether (30 ml) was then added to precipitate the N-aminoazinium salts **6** and **7** which were triturated with ether (3x5 ml) and recrystallized from ethanol.

6. (217-219°C, 92%) ^{1}H NMR(CD_3OD) δ 8.44 (d, 1H, J=6.7 Hz, H-3), 8.37 (d, 1H, J=6.8 Hz, H-4), 8.30 (d, 1H, J=8.1 Hz, H-5), 7.8-7.7 (m, 2H, H-7 and H-8), 7.5-7.4 (m, 1H, H-6), 3.09 (s, 3H, CH_3-C1). (Found: C, 63.25; H, 5.90; N, 10.77. $C_{21}H_{23}N_3O_3S$ requires C, 63.45; H, 5.83; N, 10.57).

7. (234-236°C, 87%) ^{1}H NMR(DMSO-d_6) δ 12.60 (s, 1H, NH), 8.46 (d, 1H, J=6.9 Hz, H-3), 8.36 (d, 1H, J=6.9 Hz, H-4), 8.26 (d, 1H, J=8.5 Hz, H-5), 7.65 (s, 2H, NH_2), 7.10 (d, 1H, J=2.0 Hz, H-8), 7.01 (dd, 1H, J=8.4 and 1.9 Hz, H-6), 3.91 (s, 3H, OCH_3), 2.97 (s, 3H, CH_3-C1). (Found: C, 62.00; H, 5.70; N, 9.80. $C_{22}H_{25}N_3O_4S$ requires C, 61.80; H, 5.89; N, 9.83).

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