USE OF THE PUMMERER REACTION IN THE SYNTHESIS OF EBURNA AND ASPIDOSPERMA DERIVATIVES

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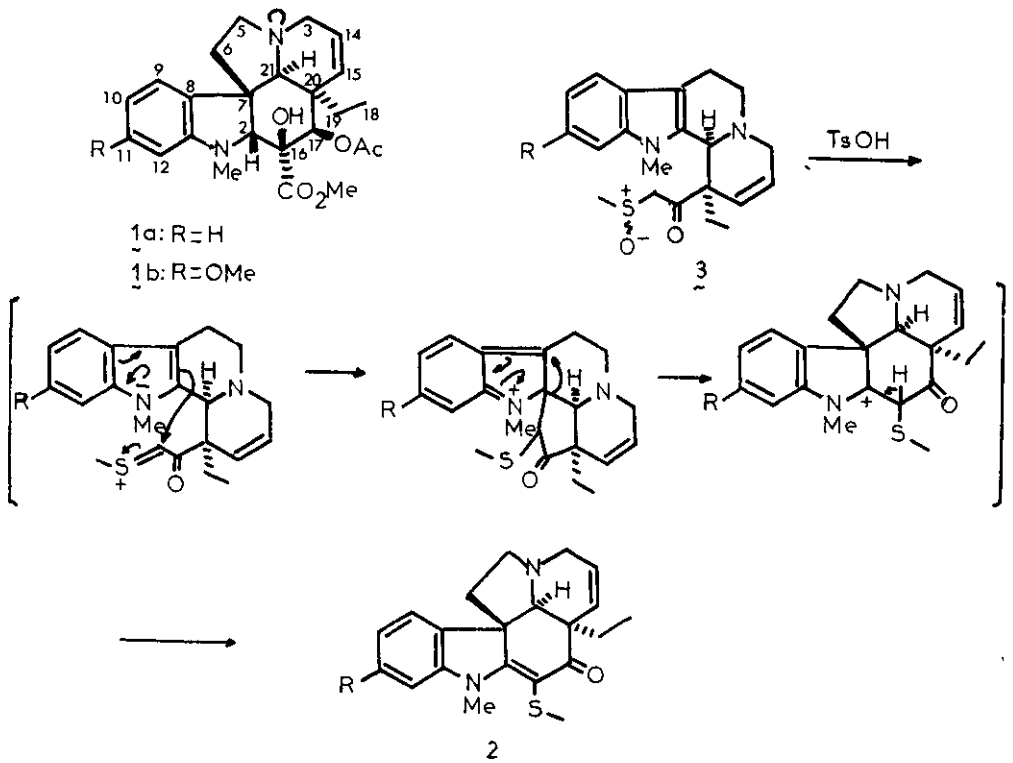
Abstract - The Pummerer reaction applied to indoloquinolizidine derivatives (7) led to compounds (9), (10) and (11) which are precursors of Eburna and Aspidosperma derivatives.

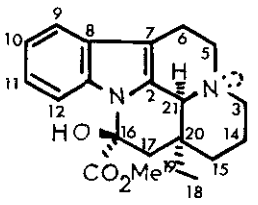
In the course of our total synthesis of Aspidosperma alkaloids vindorosine (1a) and vindoline (1b)[1] the Pummerer reaction was used to induce a rearrangement leading to the pentacyclic ketone (2) from the indoloquinolizidine (3) according to Scheme I.



Scheme I

This "retrobiomimetic" rearrangement followed the reverse pathway affording vincamine (4) from vincadifformine (5)[2].

Over the past twenty years, vincamine (4) and related alkaloids such as eburnamonine (6) have been the subject of intense synthetic interest[3] because of their therapeutic potential as cerebrovasodilators. In this context, we considered that indolo [2,3-a] quinolizidine (7), unsubstituted on the indolic nitrogen could be a synthetic precursor of several analogues of vincamine (4) and eburnamonine (6) after cyclisation induced by the Pummerer reaction and our study of this reaction is reported in the present paper.



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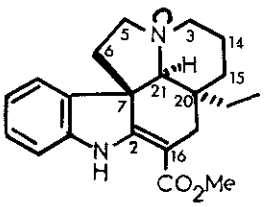

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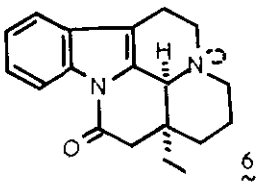

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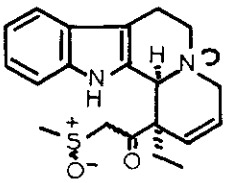

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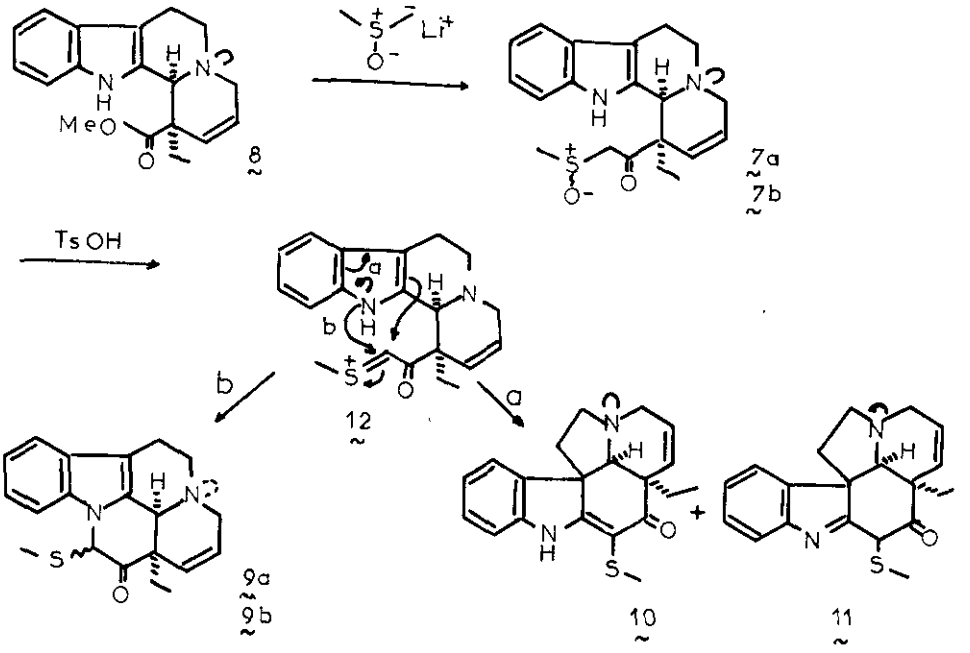
When treated with dimsyllithium[4] in THF-Me_2SO, the indoloquinolizidine derivative (8)[5] led to the expected β-ketosulfoxides (7a) and (7b) as a mixture of diastereomers[6] (96%). Refluxing a solution of (7a) and (7b) in tetrahydrofuran for five minutes in the presence of an excess (6 equiv.) of p-toluenesulfonic acid furnished two epimeric Eburna derivatives (9a) (17%) and (9b) (8%) as well as two isomeric Aspidosperma derivatives (10) (14%) and (11) (17%) (total yield : 56%) (Scheme II).

Compounds (9a) and (9b)[7] which exhibited in their uv spectra an indolic chromophore were characterized peculiarly by the presence of a low field C_{21}-H nmr signal at 4.62 and 4.29 ppm respectively, which are in accord with a cis quinolizidine conformation for the C-D ring junction.[8] These two compounds (9a) and (9b) have been correlated during the following steps of the synthesis.

The uv spectra of Aspidosperma derivatives (10) and (11)[7] were typical of a methylene indoline and an indolenine chromophore, respectively. In the nmr spectra of compounds (10) and (11) one-proton singlets at 2.99 and 2.94 ppm respectively were characteristic of a trans relationship between C_{21}-H and the lone pair of the adjacent nitrogen.[9]

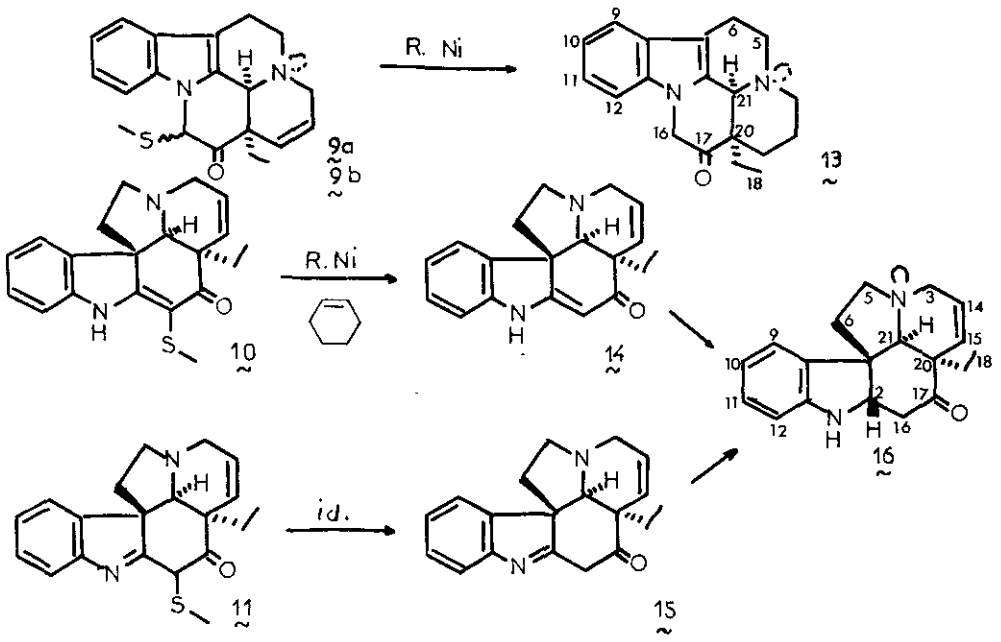
It is noteworthy that the Pummerer reaction, applied to indoloquinolizidines (7a) and (7b) induced, via the cationic intermediate (12), two types of competitive alkylations (Scheme II).



Scheme II

The C-alkylation leading, after rearrangement, to Aspidosperma derivatives (10) and (11) remained the major pathway (path a) compared with the direct N-alkylation (path b). Acetic anhydride, acetyl chloride and trifluoroacetic anhydride which are commonly used in the Pummerer reaction did not afford significant change in the ratio of the products. The orientation of the reaction is probably controlled at least partially by steric factors. As a matter of fact, N-alkylation (path b) implies the switching of trans quinolizidine into cis quinolizidine conformation during the cyclisation. This conformational change is not involved in path a leading to the Aspidosperma framework.[10]

The Eburna derivatives (9a) and (9b) were cleanly reduced and hydrogenolized with Raney-Ni in refluxing acetone and afforded a single compound (13) (93%) identified as 15-oxo-14,15-dihydroeburnamenine[11] (Scheme III) thereby indicating

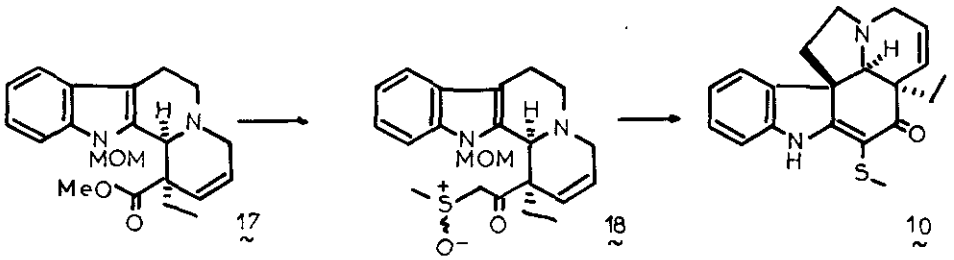


Scheme III

that (9a) and (9b) were diastereomeric at C_{16}.

Careful hydrogenolysis of the Aspidosperma derivatives (10) and (11) (Raney-Ni, cyclohexene, acetone) afforded compounds (14) and (15)[7] (90% and 83%) whose reduction with sodium cyanoborohydride in acidic medium[12] gave rise to a single Aspidosperma derivative (16)[13] (70%) (Scheme III).

The pentacyclic ketone (14) has also been prepared by an unambiguous route starting with N-protected indoloquinolizidine (17)[14] which afforded as previously the β-keto sulfoxide (18). This compound submitted to a sequential treatment with p-toluenesulfonic acid and aqueous hydrochloric acid, gave rise to the Aspidosperma derivative (10) (overall yield from (17) : 69%) (Scheme IV).



Scheme IV

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3. For a review concerning the synthesis of vincamine and related alkaloids see : A.U. Rahman and M. Sultana, Heterocycles, 1984, 22, 841.

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5. Prepared by the sequential treatment : 3,4-dihydro-β-carboline methyl pentadienoate, chlorobenzene, 110°C ; LDA (2.2 equiv.), THF-HMPA, -78°C, then EtI, -40°C (overall yield : 49%).

6. Compounds (7a) and (7b) have not been separated.

7. (7a) + (7b) : nmr (400 MHz, $CDCl_3$, TMS : 0 ppm) : 7.87 (s) and 7.84 (s) N_a-H ; 6.18 (m, 1H) C_{14}-H ; 5.39 (m, 1H) C_{15}-H ; 4.44 (d, J = 15 Hz, 1H) and 4.17 (d, J = 15 Hz, 1H) CH_2 SO ; 2.45 (s) and 1.95 (s) CH_3SO ; 1.05 (t, J = 7 Hz) and 1.03 (t, J = 7 Hz) C_{18}-H_3. ir (ν, cm^{-1}) ; 1690.
(9a) : nmr : 5.53 (s, 1H) C_{16}-H ; 4.62 (s, 1H) C_{21}-H ; 2.14 (s, 3H) S-CH_3 ; ir : 1700 ; uv : λ max (EtOH) : 227, 280, 293.
(9b) : nmr : 5.41 (s, 1H) C_{16}-H ; 4.29 (s, 1H) C_{21}-H ; 2.16 (s, 3H) S-CH_3.
(10) : nmr : 7.48 (s, 1H) N_a-H ; 7.28 (dd, J = 6.6 Hz, 1H) and 6.92 (dd, J = 6.6 Hz, 1H) C_9-H and C_{12}-H ; 7.18 (dd, J = 6.6 Hz, 1H) and 6.97 (dd, J = 6.6 Hz, 1H) C_{10}-H and C_{11}-H ; 6.05 (d, J_{14-15} = 9.6 Hz, 1H) C_{15}-H ; 5.91 (dd, J_{14-15} = 9.6 Hz, J_{14-3} = 4.5 Hz, 1H) C_{14}-H ; 3.49 (dd, $J_{3-3'}$ = 16.5 Hz, J_{14-3} = 4.5 Hz, 1H) C_3-H ; 3.13 (d, $J_{3-3'}$ = 16.5 Hz, 1H) $C_{3'}$-H ; 3.07 (dd, J_{5-6} = 7.5 Hz, $J_{5-5'}$ = 4.5 Hz, 1H) C_5-H ; 2.99 (s, 1H) C_{21}-H ; 2.66 (ddd, $J_{6-5'}$ = 9 Hz, J_{6-5} = 7.5 Hz, $J_{6-6'}$ = 4.5 Hz, 1H) C_6-H ; 2.22 (s, 3H) S-CH_3 ; 2.22 (ddd, $J_{5'-6'}$ = 12 Hz, $J_{5'-6}$ = 9 Hz, $J_{5'-5}$ = 4.5 Hz, 1H) $C_{5'}$-H ; 1.90 (dd, $J_{6'-6}$ = 4.5 Hz, $J_{5'-6'}$ = 12 Hz, 1H) $C_{6'}$-H ; 1.24 (m, 2H) C_{19}-H_2 ; 0.71 (t, J_{19-18} = 7.5 Hz, 3H) C_{18}-H_3. ir : 3380, 1600. uv : 244, 299, 357. ms : 338, 291, 135, 134, 122.
(11) : nmr : 7.82 (dd, J = 7 Hz, 1H) and 7.66 (dd, J = 7 Hz, 1H) C_9-H and C_{12}-H ; 7.37 (dd, J = 7 Hz, 1H) and 7.23 (dd, J = 7 Hz, 1H) C_{10}-H and C_{11}-H ; 6.10 (dd, J_{15-14} = 10.5 Hz, J_{15-3} = 3 Hz, 1H) C_{15}-H ; 5.85 (dd, J_{14-15} = 10.5 Hz, J_{14-3} = 5.2 Hz) C_{14}-H ; 4.19 (s, 1H) C_{16}-H ; 3.69 (d,

$J_{3-3'}$ = 18 Hz, 1H) $C_{3'}$-H ; 3.17 (dd, J_{3-14} = 5.2 Hz, $J_{3-3'}$ = 18 Hz, 1H) C_3-H ; 2.94 (s, 1H) C_{21}-H ; 2.88 (m, 1H) C_5-H ; 2.65 (m, 1H) and 2.59 (m, 1H) C_6-H and $C_{6'}$-H ; 2.22 (s, 3H) S CH_3 ; 1.52 (q, J = 7.5 Hz, 2H) C_{19}-H_2; 1.43 (m, 1H) $C_{5'}$-H ; 0.88 (t, J_{18-19} = 7.5 Hz, 3H) C_{18}-H_3. ir : 2925, 2850. 1700, 1615, 1600. uv : 265. ms : 338, 291.

(13) : nmr : 7.48 (d, J = 8 Hz, 1H) and 7.10 (d, J = 8 Hz, 1H) C_9-H and C_{12}-H ; 7.06 (dd, J = 8 Hz, 1H) and 7.06 (dd, J = 8 Hz, 1H) C_{10}-H and C_{11}-H; 4.78 (d, J = 18 Hz, 1H) and 4.43 (d, J = 18 Hz, 1H) C_{16}-H_2 ; 4.35 (s, 1H) C_{21}-H ; 1.01 (t, J = 7.5 Hz, 3H) C_{18}-H_3. ir : 2950, 1710. uv : 230, 285, 294, 265.

(14) : nmr : 7.54 (d, J = 8 Hz, 1H) et 7.40 (d, J = 8 Hz, 1H) C_9-H and C_{12}-H ; 7.32 (dd, J = 8 Hz, 1H) and 7.21 (dd, J = 8 Hz, 1H) C_{10}-H and C_{11}-H; 6.05 (bs, 1H) N_a-H ; 5.87 (m, 1H) C_{14}-H ; 5.76 (d, J = 10 Hz, 1H) C_{15}-H ; 5.37 (s, 1H) C_{16}-H ; 3.33 (dd, J = 7.5 Hz, 1H) C_5-H ; 2.97 (d, J = 16.5 Hz, 1H) $C_{3'}$-H ; 2.86 (s, 1H) C_{21}-H ; 2.69 (m, 1H) C_6-H ; 2.28 (m, 1H) $C_{5'}$-H ; 1.90 (d, J = 12.6 Hz, J = 5.4 Hz, 1H) $C_{6'}$-H ; 0.97 (m, 2H) C_{19}-H_2 ; 0.54 (t, J = 7.5 Hz, 3H) C_{18}-H_3. ir : 1705, 1800, uv : 238, 296, 345. ms : 292, 277, 135, 122, 121.

(16) : nmr : 7.13 (d, J = 7.5 Hz, 1H) and 6.56 (d, J = 7.5 Hz, 1H) C_9-H and C_{12}-H ; 7.02 (dd, J = 7.5 Hz, 1H) and 6.73 (dd, J = 7.5 Hz, 1H) C_{10}-H and C_{11}-H ; 5.78 (dd, J = 9.6 Hz, J = 4.5 Hz, 1H) C_{14}-H ; 5.53 (d, J = 9.6 Hz 1H) C_{15}-H ; 3.95 (bs, 1H) N_a-H ; 1.48 (m, 2H) C_{19}-H_2 ; 0.42 (t, J = 7.5 Hz, 3H) C_{18}-H_3. ir : 3400, 1700. uv : 243, 305. ms : 294, 122, 121.

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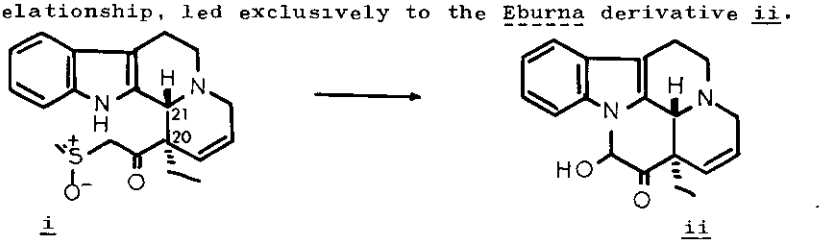

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14. Prepared by the following steps : 3,4 dihydro-β-carboline, NaH methoxymethyl chloride, THF ; methyl pentadienoate, chlorobenzene, 110°C ; LDA (1.1 equiv.) THF-HMPA, -78°C, then EtI, -40°C (overall yield : 35%).

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