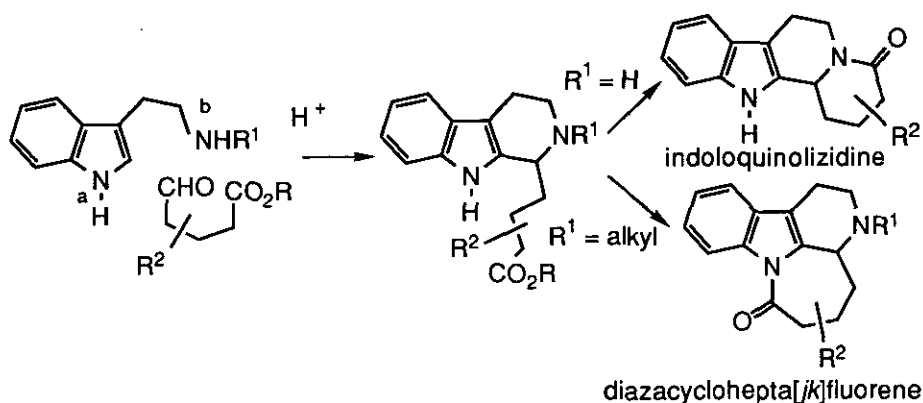


TETRACYCLIC INDOLE DERIVATIVES FROM THE REACTION OF METHYL 2,4-DIOXO-6,6-DIMETHOXYHEXANOATE WITH TRYPTAMINE: INDOLO [2,3-*a*] – QUINOLIZIDINE VS 3,7a-DIAZACYCLOHEPTA[*jk*]FLUORENE

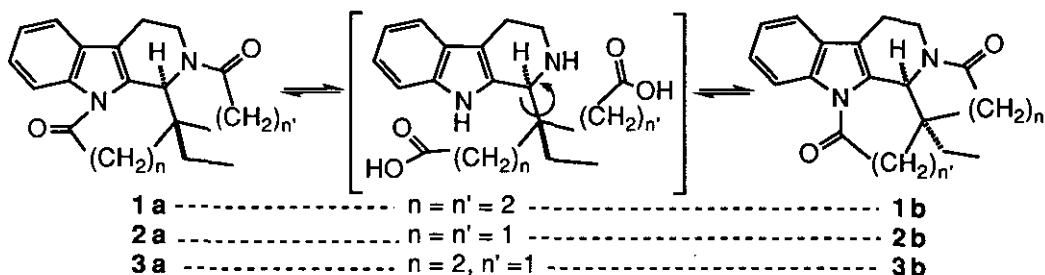
Jean-Yves Laronze*, Jacqueline Laronze, F. Wemba-Lenga, and Jean Lévy
 Laboratoire de Transformations et Synthèse de Substances Naturelles,
 associé au CNRS, Université de Reims, Faculté de Pharmacie,
 51 rue Cognacq-Jay, 51096 Reims-France

Abstract ---- Depending on the acid used for cyclization, reaction of methyl 6,6-dimethoxy-2,4-dioxohexanoate (**4**) with tryptamine yielded indoloquinolizidine (**8**) (AcOH) or diazacycloheptafluorene (**10**) (TFA). Treatment of **8** with TFA gave **10**.

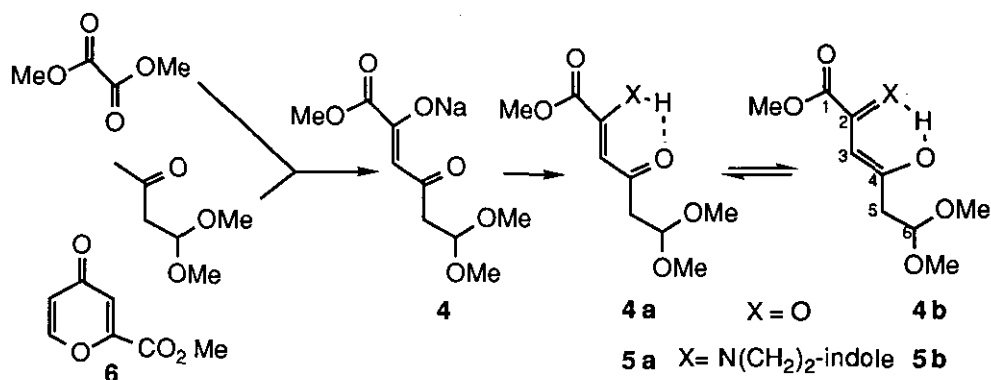
The acid-catalyzed reaction of 4-formylhexanoic acids or esters with tryptamine has been widely used for constructing the indolo [2,3-*a*] quinolizidine ring system upon Pictet-Spengler cyclization to a tetrahydro- β -carboline and concomitant lactamization onto N_b.¹ With N_b-monoalkyltryptamines, the cyclization of the isolated tetrahydro- β -carboline may be forced under strongly basic (^tBuOK)² or acidic (PPA)³ conditions onto the less basic N_a, leading to the diazacyclohepta[*jk*]fluorene ring system.



The possibility of interconverting the two ring systems is illustrated by "epimerization" of **1a** to **1b** (PPA)³ and of **2a** to **2b** (TFA),⁴ and by rearrangement of **3a** to **3b** (PPA).⁵



The present work deals with similar reactions using an 1,5-dicarbonyl synthon instead of an 1,5-aldehydo-ester; in contrast with the above reported results, experimental conditions could be found allowing the direct construction of any of the two ring systems from an *unsubstituted* tryptamine. Moreover, whereas basicity of N_b and easier formation of a six- over a seven-membered ring would apparently favor the indoloquinolizidine, a smooth rearrangement of the latter skeleton to the isomeric diazacycloheptafluorene (with a free N_b -H) was performed.

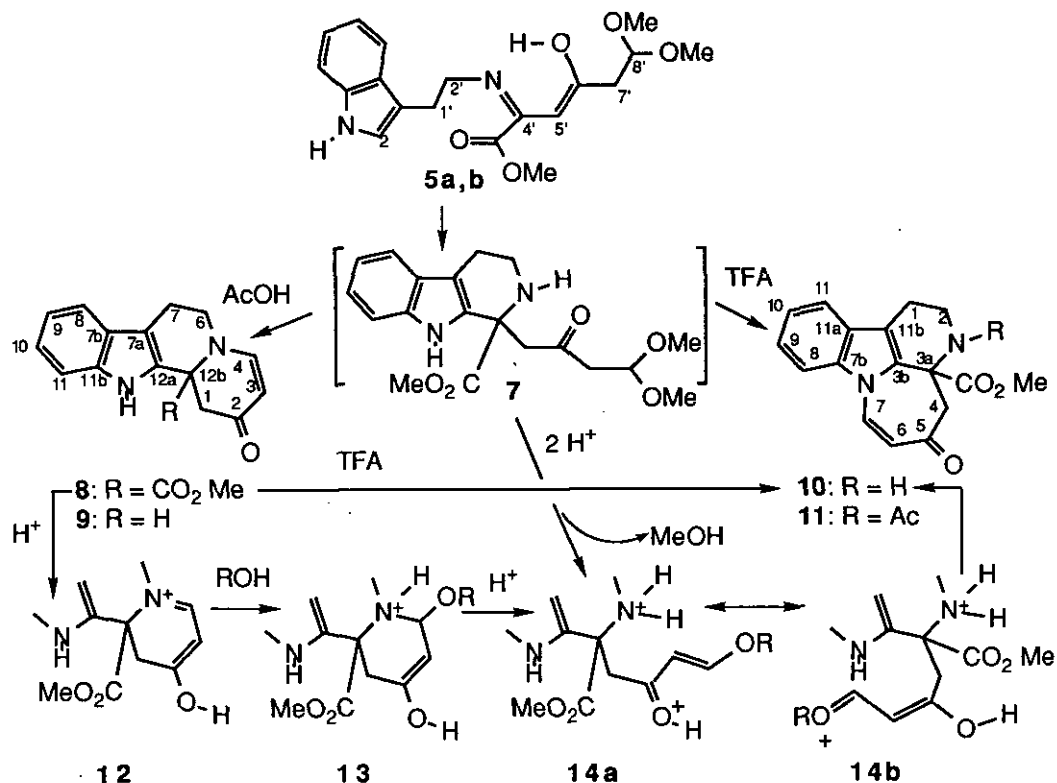


In analogy with the synthesis of oxalylacetone from diethyl oxalate and acetone⁶ reaction of dimethyl oxalate with 1,1-dimethoxybutan-3-one in the presence of sodium methoxide yielded the red sodium enolate (**4**), which was transformed by careful acidification into the unstable enol (**4a,b**) without deprotection of the aldehyde group (ms, ¹H nmr). Slow hydrolysis

occurred however upon standing, resulting in formation of methyl comanate (**6**). Freshly prepared **4a,b** was reacted with tryptamine in refluxing benzene under water abstraction to yield a microcrystalline colored compound upon evaporation of the solvent. Although being not completely homogeneous (tlc), the mixture mainly contained the uncyclized imine-enamine (**5a,b**) as indicated by ms (M^+ = 360; abundant indole ions at m/z 130, 143, 144; ions at m/z 271 = M^+ - $CH_2CH(OMe)_2$, m/z 328 = M^+ - MeOH; no detectable ion at m/z 301 = M^+ - COOMe) and 1H nmr (three methoxy groups; indole-2-H at 7.20 ppm; acetal proton at 4.85 ppm, t and neighbouring methylene at 2.70 ppm, d).

When heated for 30 min in acetic acid, the crude product (**5a,b**) cyclized (52 %) to the indoloquinolizidine derivative (**8**). On its 1H nmr spectrum, the two protons of the enaminone gave doublets at 5.03 and 7.52 ppm respectively (J = 8 Hz) while the isolated methylene was assigned as an AB-system (2.72 and 3.37 ppm, J = 17 Hz) due to the unsymmetrically substituted neighbouring sp^3 carbon atom. The uv spectrum revealed a superimposition of the enaminone chromophor (315 nm) to that of the indole (215, 280, 288 nm). The mass spectrum (M^+ = 296) was dominated by the easy loss of COOMe (m/z 237, 95 %), accompanied by hydrogen rearrangement (m/z 238, 100 %). Cleavage of the ester group could also be chemically performed upon heating of **8** with barium hydroxide in dioxane, followed by acidification with CO_2 . Isolation (97 %) of the known⁷ enaminone (**9**) then left no doubt about the structure of **8**.

Otherwise, reaction of **4a,b** with tryptamine (equimolar) in trifluoroacetic acid at room temperature for 70 h gave (58 %) the diazacycloheptafluorene derivative (**10**). Reaction of methyl comanate (**6**) with tryptamine under identical conditions failed, which indicated **10** to result from an initial Pictet-Spengler cyclization, prior to the reaction of the masked aldehyde group. Conjugation of the enone with the indole chromophore now gave rise to a long wave uv maximum at 340 nm. The mass spectrum (M^+ = 296) had its base peak at m/z 237 (loss of COOMe) and a significant fragment (40 %) at m/z 197 ($C_{12}H_9N_2O$, postulated as a CO-bearing tetrahydro- β -carboline ion) indicated the position of the ester group. The 1H nmr spectrum disclosed the two enamine protons as doublets at 5.58 and 7.58 ppm, respectively (J = 11 Hz) and the isolated methylene as an AB-system (3.05, 3.18 ppm, J = 16 Hz). The free N_b -H appeared as a broad signal at 2.2 ppm (disappearing upon exchange with D_2O) and was further confirmed by acetylation to the amide (**11**).



Formation of **10** in trifluoroacetic acid, compared with that of **8** from **5a,b** in acetic acid most probably results from di-protonation of the primarily formed tetrahydro- β -carboline (**7**) to a dication which slowly eliminates methanol to form a reactive oxonium such as **14a** \leftrightarrow **14b** ($\text{R} = \text{Me}$). Dipolar interaction then takes the oxonium in **14b** away from the protonated N_b , and addition of the unprotonated N_a followed by extrusion of methanol finally accounts for the formation of **10**.

In the course of the synthesis of **10**, a small amount of **8** was detected (tlc) after 2 days, which progressively vanished for longer reaction times. This observation prompted us to react **8** with trifluoroacetic acid, which promoted its quantitative rearrangement to **10** within 40-80 h. It is thought that **8** protonates to **12**, whose opening to the reactive dication (**14a,b**) via the protonated carbinolamine (**13**) is catalyzed by traces of water ($\text{R} = \text{H}$) or methanol ($\text{R} = \text{Me}$), which are themselves regenerated after cyclization onto N_a .

EXPERIMENTAL

Melting points are uncorrected. Uv spectra were measured in MeOH on a Varian 634 apparatus. Ir spectra were recorded on a Beckman Acculab 4 spectrometer after evaporation of a concentrated chloroform soln of the product. Nmr chemical shifts are given in ppm relative to TMS as internal standard; they are followed (brackets) with the multiplicity, the coupling constant (Hz), the integral, and the attribution (interchangeable marked with *); ^1H nmr spectra were recorded either on a Varian A 60 (60 MHz), or on a IEF 400 (400 MHz) spectrometer; ^{13}C nmr were measured on a Bruker AC 300 (75 MHz) spectrometer. Eims spectra were measured with a JEOL JMS D300 high-resolution spectrometer; m/z values are followed (brackets) with the % relative intensities, and eventually with the elemental composition.

Reaction of dimethyl oxalate with 1,1-dimethoxybutan-3-one: methyl 6,6-dimethoxy-2,4-dioxohexanoate **4a,b**: To a solution of 1,1-dimethoxybutan-3-one (2.64 g, 20 mmol) and dimethyl oxalate (2.37 g, 20 mmol) in 50 ml of absolute methanol 0.5 g of Na (22 mmol) was portionwise added. The solution turned red. After 1 h at room temperature, it was cooled at 0°C for 1 day. The precipitate (2.65 g) was collected by centrifugation, then poured into 20 ml of water. Aqueous HCl (10 %) was quickly added to the solution which turned yellow (pH = 1). Extraction with CHCl_3 gave after evaporation 2.24 g (53%) of crude **4a,b** (oil): uv 260, 315 nm; ir 1745, 1640, 1600, 1270 cm^{-1} ; ^1H (60 MHz) 6.55 (s, 1H, $\text{C}_3\text{-H}$), 4.90 (t, $J=7$, 1H, $\text{C}_6\text{-H}$), 3.95 (s, 3H, $\text{C}_1\text{-OCH}_3$), 3.45 (s, 6H, $\text{C}_6\text{-OCH}_3$), 2.85 (d, $J=7$, 2H, $\text{C}_5\text{-H}_2$); ms 69 (100), 70 (80), 97 (85), 127 (50), 154 (70), 155 (35), 156 (85), 219 ($[\text{M} + \text{H}]^+$, 10). Upon standing, **4a,b** rapidly cyclized into methyl comanate **6**, mp 88°C (ether), (lit.,⁸ mp 90°C).

Reaction of **4a,b** with tryptamine: compound **5a,b**: A solution of **4a,b** (350 mg, 1.6 mmol) and tryptamine (256 mg, 1.6 mmol) in benzene (50 ml) was refluxed for 1.5 h in a water-separating apparatus. The solution was filtered on silica (2g); evaporation of the solvent gave a red-brown gum: **5a,b** (crude product): uv 218, 275, 288, 315 nm; ir 3300 br, 1730, 1650, 1610, 1580 cm^{-1} ; ^1H nmr (60 MHz) 7.2 (s, 1H, $\text{C}_2\text{-H}$), 5.45 (s, 1H, $\text{C}_5\text{-H}$), 4.85 (t, $J=7$, 1H, $\text{C}_8\text{-H}$), 3.65 (s, 3H, $\text{CH}_3\text{-ester}$), 3.35 (s, 6H, $\text{C}_8\text{-OCH}_3$), 2.70 (d, $J=7$, 2H, $\text{C}_7\text{-H}_2$); ms 130 (100), 143 (100), 144 (100), 271 (30), 328 (5), 360 (M^+ , 5).

Cyclization of **5a,b** in acetic acid: enaminone **8**: A solution of **5a,b** (crude product from the above reaction) in acetic acid (10 ml) was heated at 100°C for 30 min, under Ar atmosphere. The acetic acid was then evaporated, and the residue was dissolved into CH_2Cl_2 (100 ml). The solution was washed with 10 % aqueous Na_2CO_3 and the solvent was evaporated. Compound (**8**) slowly crystallized from MeOH (119 mg); a second crop (182 mg) was obtained from the mother-liquors, by tlc (eluent $\text{CHCl}_3\text{-MeOH}$ 97:3) (301 mg, 52 % from **4a,b**). **8**: mp $209\text{-}10^\circ\text{C}$; uv 215, 280, 290, 315 nm; ir 3300 br, 1740, 1635, 1580 cm^{-1} ; ms 167 (30), 237 (95), 238 (100), 296.1145 (M^+ , 10, $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$); ^1H nmr (400 MHz) 9.2 (m, 1H, $\text{N}_{12}\text{-H}$), 7.52 (d, $J=8$, 1H, $\text{C}_4\text{-H}$), 7.36 (d, $J=7$, 1H, $\text{C}_{11}\text{-H}$), 7.25 (d, $J=7$, 1H, $\text{C}_8\text{-H}$), 7.14 (t, $J=7$, 1H, $\text{C}_{10}\text{-H}$), 7.06 (t, $J=7$, 1H, $\text{C}_9\text{-H}$), 5.03 (d, $J=8$, 1H, $\text{C}_8\text{-H}$), 3.85 (dt, $J=5$ and 14, 1H, $\text{C}_6\text{-H}$), 3.80 (m, 1H, $\text{C}_6\text{-H}'$), 3.80 (s, 3H, $\text{CH}_3\text{-ester}$), 3.37 (d, $J=17$, 1H, $\text{C}_1\text{-H}$), 2.72 (d, $J=17$, 1H, $\text{C}_1\text{-H}'$); ^{13}C nmr 189.5 (C_5), 170.4 (CO_2CH_3), 154.2 (C_4), 136.6 (C_{11b}), 129.2 (C_{12a}), 125.9 (C_{7b}), 123.1 (C_{10}), 120.0 (C_9), 118.6 (C_8), 111.7 (C_{11}), 109.5 (C_{7a}), 98.9 (C_3), 64.2 (C_{12b}), 50.0 (C_6), 46.0 (C_1), 21.8 (C_7).

Saponification-decarboxylation of **8**: enaminone **9**: A solution of **8** (40 mg, 0.14 mmol) in dioxane (2 ml) was mixed with a saturated soln of aqueous $\text{Ba}(\text{OH})_2$ (10 ml), then refluxed for 2 h, bubbled with CO_2 and filtered off. The filtrate was evaporated and purification by tlc (eluent: $\text{CHCl}_3\text{-MeOH}$ 98:2) gave **9** (31 mg, 97 %), mp 229°C (ether) (lit.,⁷ mp $232\text{-}233^\circ\text{C}$); other spectral data in accordance with those reported.⁷

Condensation of 4a,b with tryptamine in trifluoroacetic acid: enamionone 10: A solution of tryptamine (160 mg, 1 mmol) and crude 4a,b (260 mg ~ 1 eq.) in trifluoroacetic acid (5 ml) was left at room temperature for 1 day. Two new products were detected by tlc; the faster moving one which was identical with 8 slowly disappeared from the reaction mixture and the reaction was completed within 70-80 h. Saturated aqueous Na₂CO₃ (5 ml) was then added and the mixture was extracted with CH₂Cl₂ (50 ml). The organic layer was dried (MgSO₄), filtered off, evaporated and purified by tlc (eluent CHCl₃-MeOH 97:3) yielding 10 (171 mg, 58%); uv 210, 270, 280, 340 nm; ir 3310 br, 2850, 1730, 1625 cm⁻¹; ¹H nmr (400 MHz) 7.58 (d, J = 11, 1H, C₇-H), 7.54* (d, J = 7, 1H, C₁₁-H), 7.48* (d, J = 7, 1H, C₈-H), 7.35 (t, J = 7, 1H, C₉-H), 7.29 (t, J = 7, 1H, C₁₀-H), 5.58 (d, J = 11, 1H, C₆-H), 3.72 (s, 3H, CH₃-ester), 3.35 (m, 1H, C₂-H), 3.18 (d, J = 16, 1H, C₄-H), 3.03 (d, J = 16, 1H, C₄-H'), 3.02 (m, 1H, C₂-H'), 2.90 (m, 1H, C₁-H), 2.76 (dd, J = 5 and 16, 1H, C₁-H'), 2.2 (m, 1H, exchangeable for deuterium, N₃-H); ¹³C nmr (75 MHz) 193.5 (C₅), 172.3 (CO₂CH₃), 136.6 (C₇), 133.2 (C₇), 132.0 (C_{3b}), 127.6 (C_{11a}), 124.3 (C₉), 123.0 (C₁₁), 119.3 (C₁₀), 116.6 (C_{11b}), 109.6* (C₆), 109.1* (C₈), 59.4 (C_{3a}), 52.9 (C₄), 52.6 (-OCH₃), 41.0 (C₂), 21.7 (C₁); ms 197 (100), 237 (100), 270 (4), 296 (M⁺, 1).

Acetylation of 10: amide 11: A solution of 10 (60 mg, 0.2 mmol), acetic anhydride (0.1 ml), and triethylamine (20 μl) in CH₂Cl₂ (20 ml) was refluxed for 10 h. The cooled solution was washed with water (5 ml), then dried (MgSO₄), filtered off and evaporated. Purification by tlc (eluent CHCl₃-MeOH 98:2) yielded 11 (52 mg, 77%); mp 234-235°C (MeOH); uv 220, 272, 280 sh, 342 nm; ir 2840, 1740, 1665, 1640, 1633 cm⁻¹; ¹H nmr (400 MHz) 7.58* (d, J = 7, 1H, C₁₁-H), 7.48* (d, J = 7, 1H, C₈-H), 7.42 (d, J = 11, 1H, C₇-H), 7.38 (t, J = 7, 1H, C₉-H), 7.29 (t, J = 7, 1H, C₁₀-H), 5.70 (d, J = 11, 1H, C₆-H), 4.22 (m, 1H, C₂-H), 3.64 (d, J = 17, 1H, C₄-H), 3.58 (s, 3H, OCH₃), 3.38 (m, 1H, C₂-H'), 3.0 (m, 2H, C₁-H₂), 2.98 (d, J = 17, 1H, C₄-H'); ¹³C nmr: 194.0 (C₅), 169.8* (CO₂CH₃), 169.0* (N-COCH₃), 137.2 (C_{7b}), 131.1 (C_{3b}), 128.8 (C₇), 126.5 (C_{11a}), 124.8 (C₁₁), 122.9 (C₁₀), 119.2 (C₉), 118.9 (C_{11b}), 110.9** (C₆), 109.9** (C₆), 60.9 (C_{3a}), 52.8 (CO₂CH₃), 46.7 (C₄), 42.9 (C₂), 23.0 (N-COCH₃), 21.9 (C₁); ms 93 (15), 196 (20), 237 (100), 279 (45), 338.1260 (M⁺, 15, C₁₉H₁₈N₂O₄).

ACKNOWLEDGEMENTS

The authors are grateful to Dr. G. Massiot and Dr. S. Kan for ¹H nmr experiments.

REFERENCES

1. M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 5941; M.E. Kuehne, *J. Amer. Chem. Soc.*, 1964, **86**, 2946; J. E. D. Barton and J. Harley-Mason, *J. Chem. Soc., Chem. Comm.*, 1965, 197; J.-Y. Laronze, J. Laronze, D. Royer, J. Lévy, and J. Le Men, *Bull. Soc. Chim. Fr.*, 1977, 1215.
2. J.-Y. Laronze, J. Laronze, B. Caron, J. Lévy, and J. Le Men, *Bull. Soc. Chim. Fr.*, 1977, 1207.
3. J. Laronze, J.-Y. Laronze, J. Lévy, and J. Le Men, *Bull. Soc. Chim. Fr.*, 1977, 1195.
4. M. Mailand and E. Winterfeldt, *Chem. Ber.*, 1981, **114**, 1926.
5. D. Cartier, Thèse de Doctorat ès Sciences Physiques, Université de Reims (France), 1983.
6. F. C. Whitmore and G. E. Woodward, *Org. Synth., Coll. Vol.*, III, ed. by H. Gilman, John Wiley and Sons, New-York, 1932, pp. 238-240.
7. J.-P. Vacca, *Tetrahedron Lett.*, 1985, **26**, 1277.
8. J.-A. Elvidge and R. Stevens, *J. Chem. Soc.*, 1965, 2257.

Received, 18th December, 1991