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

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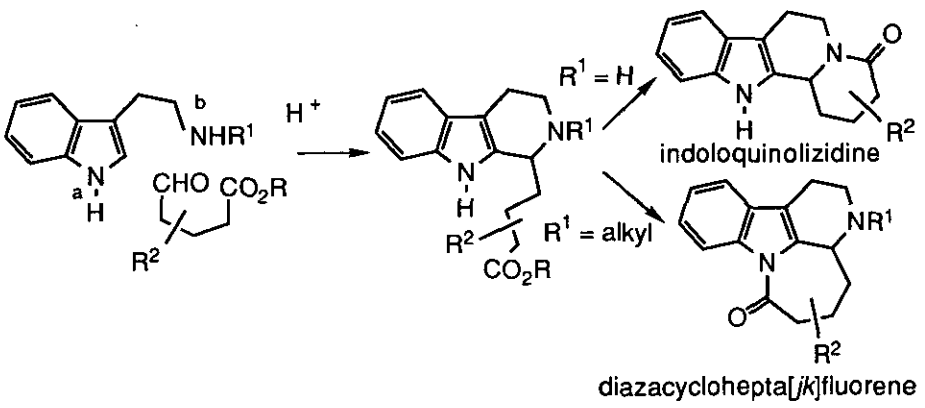
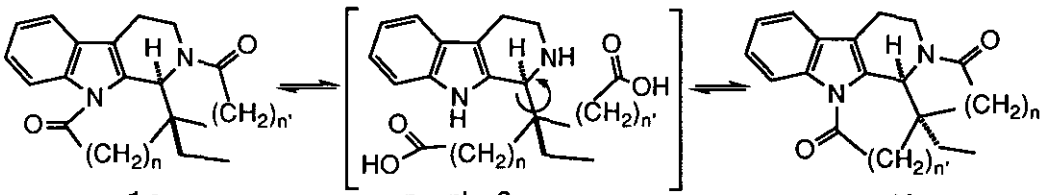
Abstract ---- Depending on the acid used for cyclization, reaction of methyl 6,6-dimethoxy-2,4-dioxohexanoate (**4**) with tryptamine yielded indoloquinolizidine (**8**) (AcOH) or diazacycloheptafluorene (**10**) (TFA). Treatment of **8** with TFA gave **10**.

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-ß-carboline and concomitant lactamization onto N_b.[1] With N_b-monoalkyltryptamines, the cyclization of the isolated tetrahydro-ß-carboline may be forced under strongly basic (^{t}BuOK)[2] or acidic (PPA)[3] conditions onto the less basic N_a, leading to the diazacyclohepta[*jk*]fluorene ring system .

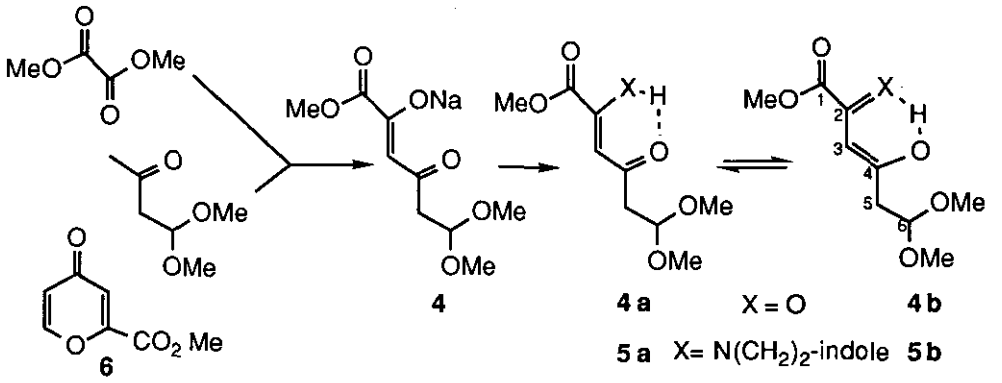


The possibility of interconverting the two ring systems is illustrated by "epimerization" of **1a** to **1b** (PPA)[3] and of **2a** to **2b** (TFA),[4] and by rearrangement of **3a** to **3b** (PPA).[5]



1a ---------- n = n' = 2 ---------- **1b**
2a ---------- n = n' = 1 ---------- **2b**
3a ---------- n = 2, n' =1 ---------- **3b**

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.



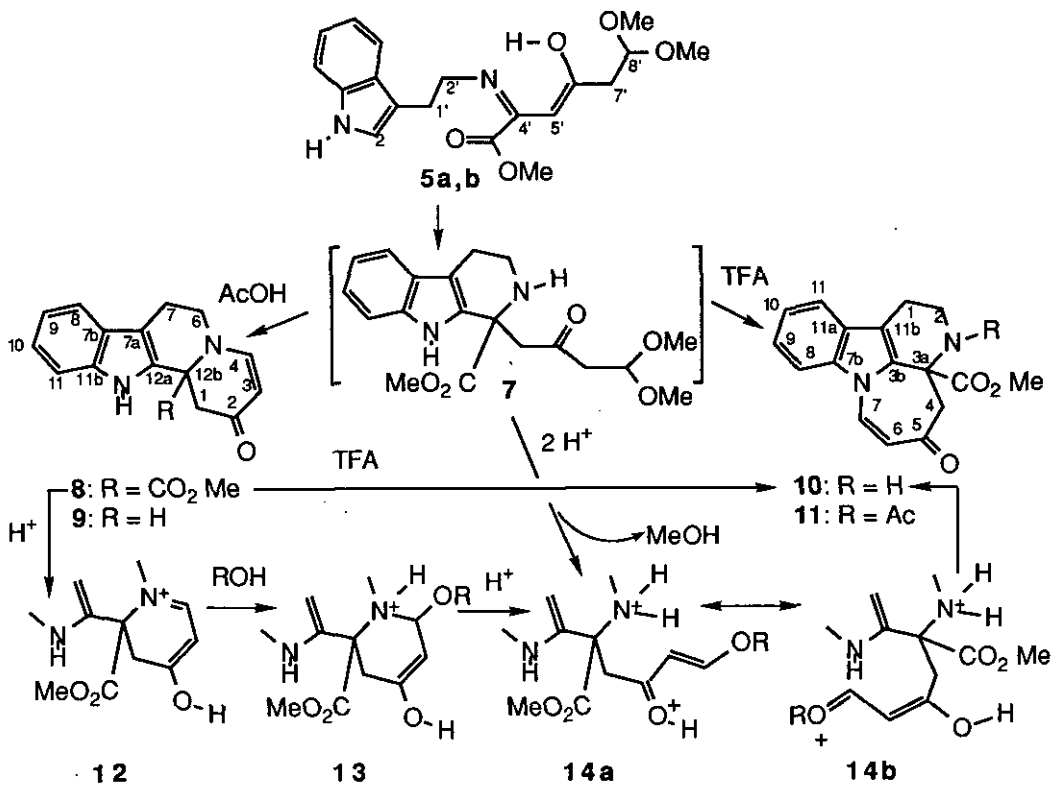
4 **4a** X = O **4b**
5a X= $N(CH_2)_2$-indole **5b**
6

In analogy with the synthesis of oxalylacetone from diethyl oxalate and acetone[6] 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 ($M^{\cdot+}$ = 360; abundant indole ions at m/z 130, 143, 144; ions at m/z 271 = $M^{\cdot+}$ - $CH_2CH(OMe)_2$, m/z 328 = $M^{\cdot+}$ - MeOH; no detectable ion at m/z 301 = $M^{\cdot+}$ - 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 ($M^{\cdot+}$ = 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 known[7] 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 ($M^{\cdot+}$ = 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-ß-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-ß-carboline (**7**) to a dication which slowly eliminates methanol to form a reactive oxonium such as **14a** <-> **14b** (R=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 (R=H) or methanol (R=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, C_3-H), 4.90 (t, J= 7, 1H, C_6-H), 3.95 (s, 3H, C_1-OCH_3), 3.45 (s, 6H, C_6-OCH_3), 2.85 (d, J= 7, 2H, C_5-H_2) ; ms 69 (100), 70 (80), 97 (85), 127 (50), 154 (70), 155 (35), 156 (85), 219 ($[M + H]^+$, 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, C_2-H), 5.45 (s, 1H, C_5-H), 4.85 (t, J= 7, 1H, C_8-H), 3.65 (s, 3H, CH_3-ester), 3.35 (s, 6H, C_8-OCH_3), 2.70 (d, J= 7, 2H, C_7-H_2); ms 130 (100), 143 (100), 144 (100), 271 (30), 328 (5), 360 ($M^{+\cdot}$, 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 $CHCl_3$-MeOH 97:3) (301 mg, 52 % from **4a,b**). **8** : mp 209-10°C; uv 215, 280, 290, 315 nm; ir 3300 br, 1740, 1635, 1580 cm^{-1}; ms 167 (30), 237 (95), 238 (100), 296.1145 ($M^{+\cdot}$, 10,$C_{17}H_{16}N_2O_3$); ^1H nmr (400 MHz) 9.2 (m, 1H, N_{12}-H), 7.52 (d, J=8, 1H, C_4-H), 7.36 (d, J= 7, 1H, C_{11}-H), 7.25 (d, J=7, 1H, C_8-H), 7.14 (t, J=7, 1H, C_{10}-H), 7.06 (t, J=7, 1H, C_9-H), 5.03 (d, J= 8, 1H, C_8-H), 3.85 (dt, J= 5 and 14, 1H, C_6-H), 3.80 (m, 1H, C_6-H'), 3.80 (s, 3H, CH_3-ester), 3.37 (d, J= 17, 1H, C_1-H), 2.72 (d, J= 17, 1H, C_1-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 $Ba(OH)_2$ (10 ml), then refluxed for 2 h, bubbled with CO_2 and filtered off. The filtrate was evaporated and purication by tlc (eluent: $CHCl_3$-MeOH 98:2) gave **9** (31 mg, 97 %), mp 229°C (ether) (lit.,[7] mp 232-233°C); other spectral data in accordance with those reported.[7]

Condensation of **4a,b** with tryptamine in trifluoroacetic acid; enaminone **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 Na_2CO_3 (5 ml) was then added and the mixture was extracted with CH_2Cl_2 (50 ml). The organic layer was dried ($MgSO_4$), filtered off, evaporated and purified by tlc (eluent $CHCl_3$-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, C_{11}-H), 7.48* (d, J= 7, 1H, C_8-H), 7.35 (t, J= 7, 1H, C_9-H), 7.29 (t, J= 7, 1H, C_{10}-H), 5.58 (d, J= 11, 1H, C_6-H), 3.72 (s, 3H, CH_3-ester), 3.35 (m, 1H, C_2-H), 3.18 (d, J= 16, 1H, C_4-H), 3.03 (d, J= 16, 1H, C_4-H'), 3.02 (m, 1H, C_2-H'), 2.90 (m, 1H, C_1-H), 2.76 (dd, J= 5 and 16, 1H, C_1-H'), 2.2 (m, 1H, exchangeable for deuterium, N_3-H) ; ^{13}C nmr (75 MHz) 193.5 (C_5), 172.3 (CO_2CH_3), 136.6 (C_7), 133.2 (C_7), 132.0 (C_{3b}), 127.6 (C_{11a}), 124.3 (C_9), 123.0 (C_{11}), 119.3 (C_{10}), 116.6 (C_{11b}), 109.6* (C_6), 109.1* (C_8), 59.4 (C_{3a}), 52.9 (C_4), 52.6 (-OCH_3), 41.0 (C_2), 21.7 (C_1); ms 197 (100), 237 (100), 270 (4), 296 ($M^{+\cdot}$, 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 CH_2Cl_2 (20 ml) was refluxed for 10 h. The cooled solution was washed with water (5 ml), then dried ($MgSO_4$), filtered off and evaporated. Purification by tlc (eluent $CHCl_3$-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, C_{11}-H)), 7.48* (d, J= 7, 1H, C_8-H)), 7.42 (d, J= 11, 1H, C_7-H), 7.38 (t, J= 7, 1H, C_9-H), 7.29 (t, J= 7, 1H, C_{10}-H), 5.70 (d, J= 11, 1H, C_6-H), 4.22 (m, 1H, C_2-H), 3.64 (d, J= 17, 1H, C_4-H), 3.58 (s, 3H, OCH_3), 3.38 (m, 1H, C_2-H'), 3.0 (m, 2H, C_1-H_2), 2.98 (d, J= 17, 1H, C_4-H') ; ^{13}C nmr : 194.0 (C_5), 169.8* (CO_2CH_3), 169.0* (N-$COCH_3$), 137.2 (C_{7b}), 131.1 (C_{3b}), 128.8 (C_7), 126.5 (C_{11a}), 124.8 (C_{11}), 122.9 (C_{10}), 119.2 (C_9), 118.9 (C_{11b}), 110.9** (C_6), 109.9** (C_6), 60.9 (C_{3a}), 52.8 (CO_2CH_3), 46.7 (C_4), 42.9 (C_2), 23.0 (N-$COCH_3$), 21.9 (C_1); ms 93 (15), 196 (20), 237 (100), 279 (45), 338.1260 ($M^{+\cdot}$, 15, $C_{19}H_{18}N_2O_4$).

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