SYNTHESIS AND REACTIVITY OF 6,7,8,9-TETRAHYDROPYRIDO[1,2-a] BENZIMIDAZOL-9-ONE.

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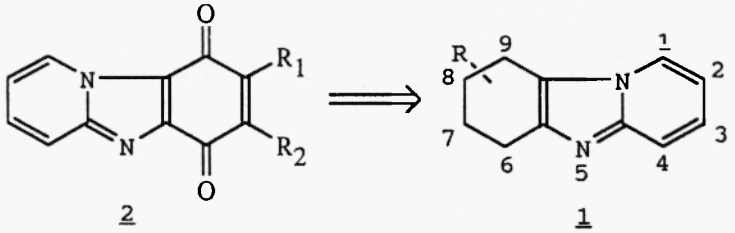
Abstract- Synthesis of a tricyclic imidazo[1,2-a]pyridine system (**1**), and reactivity of the cyclohexyl moiety are described.

Tetrahydrocarbazoles are of great interest for the construction of many complex alkaloids belonging to the *Murrayaquinones* families (1). As a part of our program on azaindolic structures, we have recently described the photochemistry of azineenaminones with a view to construct azacarbazole skeleton (2). In continuation of our studies, we now develop a program concerning the synthesis and antitumoral potentiality of modified murrayaquinone ring system 2. In this context, the synthesis of the tricyclic bridgehead heterocyclic system 1, and our preliminary investigations on the reactivity of the cyclohexyl moiety are reported (scheme 1).

Scheme 1

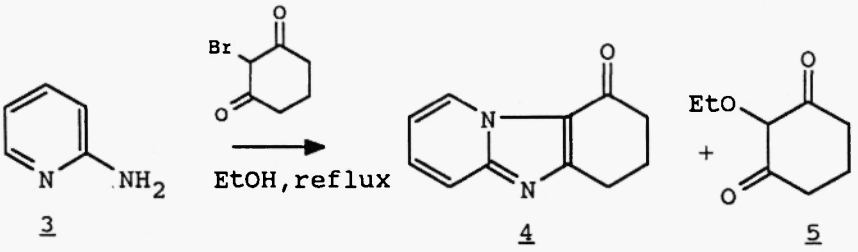


2 1

Condensation of 2-aminopyridine 3 with 2-bromo-1,3-cyclohexanedione (3) using reported methods (4) led to 6,7,8,9-tetrahydropyrido[1,2-a] benzimidazol-9-one 4 admixed with 2-ethoxy-1,3-cyclohexanedione 5 (scheme

2). Structural determination of 4 was made on the basis of ^{1}H and ^{13}C-nmr spectra. From the COSY ^{1}H-^{1}H spectrum, the signals of H-6,7,8 could be discriminated and attributed as follow: δ 2.26 for H-7 (pseudoquintuplet, J_{6-7} = 6.15 and J_{7-8} = 5.93), δ 2.67 for H-8 (triplet) and d 3.08 for H-6 (triplet): complete attribution is reported in experimental part, and is in good agreement with the values obtained for imidazo[1,2-a]pyridine (5) and tetrahydrocarbazole system (1,6).

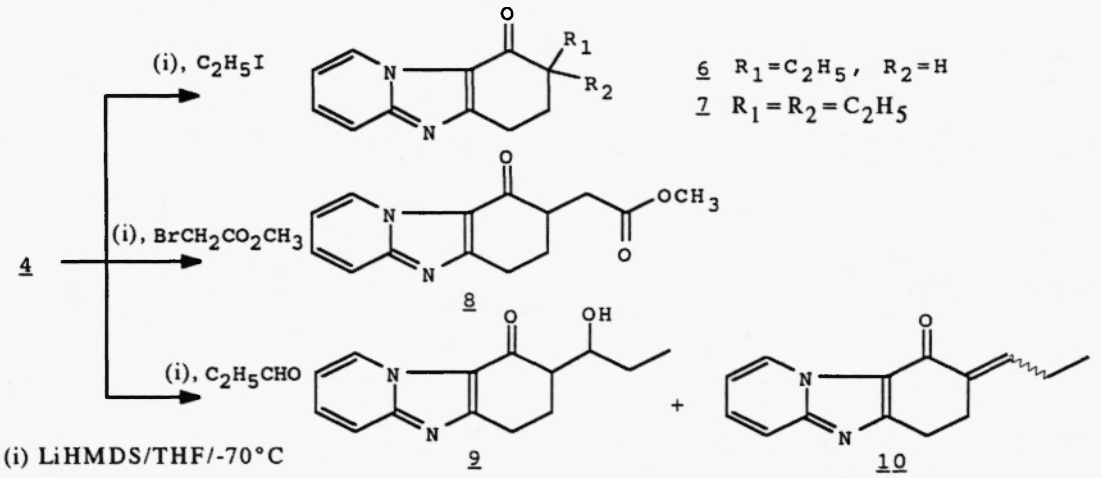
Scheme 2



3 4 5

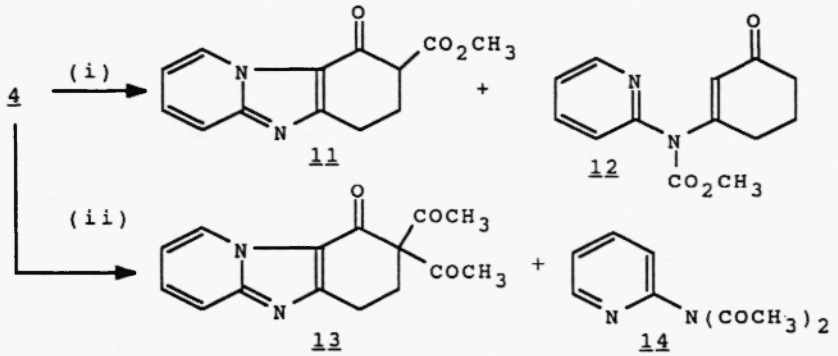
In view of elaboration of structures such as 2, we then turned our interest on the functionalization of the C-8 position. For this, we have investigated the reactivity of the enolate salt of 4 toward various electrophiles. Reaction of 4 with lithium bistrimethylsilylamide (1 eq.) at -70°C followed by treatment with ethyl iodide led to the formation of the expected 8-ethyl derivative 6, admixed with the dialkylated compound 7 in 69% and 10% yield respectively. Structural determination of 6 was achieved by ^{1}H and ^{13}C-nmr, ^{1}H-^{1}H and ^{1}H-^{13}C correlations, and by comparison with the tetrahydrocarbazole serie[1]. From these experiments, complete assignment of 6 was given (see experimental part) and served as a reference for further structural elucidations. Using methyl bromoacetate instead of ethyl iodide, we were able to isolate only one compound. Identification to the mono substituted derivative 8 was unambiguously made by analysis of ^{1}H and ^{13}C-nmr spectra. ^{1}H-nmr spectrum showed only one methyl signal as a singlet at δ 3.69 and ^{13}C-nmr showed three CH_2 signals at δ 24.0, 29.8, and 34.1 respectively attributed to C-6, C-7 and $\underline{CH_2}CO_2CH_3$. When propionaldehyde was used as electrophile, the expected alcohol 9 was obtained admixed with the unsaturated derivative 10 which structure was made evident by ^{1}H-nmr with a triplet at δ 6.79 (J = 7.33 Hz) corresponding to the vinylic proton and by ^{13}C-nmr with a quaternary carbon at δ 134.4 for C-8 and a tertiary one at δ 139.3 for $\underline{CH}CH_2$ (scheme 3)

Scheme 3



In addition to these results, we have investigated the reactivity of 4 toward methyl chloroformate and acetyl chloride. When 4 was treated with methyl chloroformate in the conditions noted above, the expected ester 11 was obtained admixed with the N-protected enaminone 12. Structure of 12 was easily determined by ^{1}H-nmr which showed a singlet at δ 5.22 for H-2 and by ^{13}C-nmr which showed the characteristic signals of a 2-substituted pyridine nucleus and a signal at δ 116.8 for C-2 which is in good agreement with the values obtained previously for the unprotected derivative (2). Using acetyl chloride, two compounds were also isolated: the disubstituted tricycle 13 admixed with 2-diacetylaminopyridine 14.

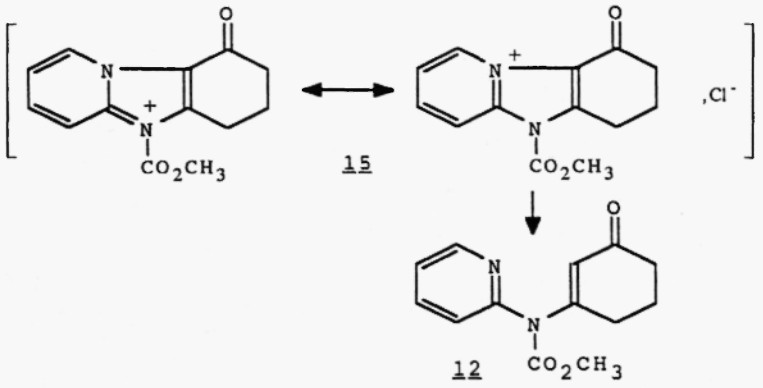
Scheme 4



(i) a: LiHMDS/THF/-70°C, b: $ClCO_2CH_3$ (ii) a: LiHMDS/THF/-70°C, b: $ClCOCH_3$

Formation of 12 is probably due to an N-addition of the electrophile on the N-5 position to give **15** followed by a C_{9a}-N_{10} bond reductive cleavage. This mechanism does not involve the enolate salt of 4, but only the strenght of the electrophile. This could explain that this reaction did not occur in

the cases described above.



In conclusion, we have described an efficient synthesis of 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazole ring systems such as 4. Functionalization of cyclohexyl moiety via the enolate salt is shown to be dependent on the nature of the electrophilic species. Studies are now in progress for the construction of the heterocyclic quinones such as 2.

Experimental

general. Mp were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis was performed by the Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-Nmr spectra were recorded on a Varian EM 360 (60 MHz) or a Brüker AC 100; ^{13}C-Nmr spectra were obtained at 26°C with proton noise decoupling at 25 MHz with a Brüker AC 100 instrument. Chemical shifts are expressed in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a LKB 2091 spectrometer at 70eV [$\theta_{(source)}$=180°C]. Compounds were purified by high performance liquid chromatography (hplc), Waters M 590, on a preparative alumina or silica gel column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatographies (Tlc) were performed on 0.25 mm E. Merck precoated neutral alumina plates.

6,7,8,9-Tetrahydropyrido[1,2-a]benzimidazol-9-one 4 and 2-ethoxy-1,3-cyclohexanedione 5. 2-aminopyridine 3, (2 g, 21.3 mmol.) and 2-bromo-1,3-cyclohexadione[3] (5 g, 26.1 mmol) were refluxed in dry ethanol for 6 hours. After evaporation of the solvent, the residual oil was diluted in water and basified with sodium carbonate. The mixture was extracted three times with dichloromethane, the organic layers dried and evaporated under *vacuo*. Chromatography on silica gel eluted with ethyl acetate gave 5 (70 mg) as an

oil[7]. Further elution with ethyl acetate/methanol (90/10) gave 4 (2.14 g, 54 %); mp 131-133°C; ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 2.26 ($q_{obs.}$, J_{6-7} =6.15 Hz, J_{7-8} = 5.93 Hz, 2H, H-7), 2.67 (t, 2H, H-8), 3.08 (t, 2H, H-6), 7.06 (dt, 1H, J_{1-2} = J_{2-3} = 6.7 Hz, J_{2-4} = 1.09 Hz, H-2), 7.38 (dt, 1H, J_{1-3} = 1.3 Hz, J_{3-4} = 6.7 Hz, H-3), 7.70 (d, 1H, H-4), 9.30 (d, 1H, H-1); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ: 24.0 (C-6), 25.6 (C-7), 38.6 (C-8), 114.9 (C-2), 117.0 (C-4), 120.6 (C-9a), 128.7 (C-1), 129.9 (C-3), 147.9 (C-5a), 160.2 (C-4a), 188.5 (CO); *Anal.* calc. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.89; H, 5.50; N, 14.98.

General method for alkylation of 4. 3 ml of a 1M solution of LiHMDS in hexane/THF was added in 10 ml of cooled THF (-70°C). Compound 4 (500 mg, 2.68 mmol) dissolved in 10 ml of THF, was added dropwise. After 15 mn, 1 equivalent of the desired electrophile was quickly added, and the mixture stirred at -70°C for 2 hours, and then two more hours at 0°C. The solution was treated with a saturated solution of ammonium chloride and extracted three times with methylene chloride. The organic layers were drierd over anhydrous sodium sulfate, concentrated *in vacuo* and the residu submitted to a chromatography on silica gel eluted with a solution of ether/methanol (90/10).

8-Ethyl-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 6 and 8,8-diethylthyl-6,7,8,9-tetrahydro pyrido[1,2-a]benzimidazol-9-one 7. Purification of the crude mixture in the conditions cited above gave first 6 as an oil (69 % yield); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 0.96 (t, J = 7.6 Hz, CH_3), 1.54 (m, 1H, CH_2CH_3), 1.92 (m, 1H, CH_2CH_3), 1.97 (m, H-7_{ax}), 2.25 (m, H-7_{eq}), 2.42 (m, H-8), 2.94 (m, H-6_{ax}), 3.05 (m, H-6_{eq}), 6.94 (td, J_{1-2} = 6.8 Hz, J_{2-3} =1.2 Hz, H-2), 7.38 (ddd, J_{1-3} = 1.4 Hz, J_{3-4} = 8.9 Hz, H-3), 7.57 (ddd, J_{1-4} = 1.12 Hz, H-4), 9.22 (ddd, H-1); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ: 11.65 (CH_3), 22.24 (CH_2CH_3), 24.1 (C-6), 28.2 (C-7), 48.4 (C-8), 114.1 (C-2), 116.7 (C-4), 119.3 (C-9a), 128.1 (C-1), 129.1 (C-3), 147.9 (C-4a), 159.5 (C-5a), 190.5 (CO); *Anal.* calc. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.98, H, 6.48; N, 13.13. Further elution gave 7 (oil, 10%); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 0.92 (t, J =7.47 Hz, 6H, CH_3), 1.66 (m, 4H, CH_2CH_3), 1.73(m, 4H, CH_2CH_3), 2.15 (m, 2H, H-7), 3.08 (m, 2H,H-6), 7.03 (t, J = 6.2 Hz, H-2), 7.48 (t, H-3), 7.69 (d, J = 8.7 Hz, H-4), 9.39 (d, H-1); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ: 8.6 (CH_3), 22.2 (CH_2CH_3), 27.0 (C-6), 31.33 (C-7), 49.3 (C-8), 114.39 (C-2), 116.8 (C-4), 119.4 (C-9a), 128.5 (C-1), 129.35 (C-3), 148.3 (C-4a), 158.81 (C-5a), 193.4 (CO); *Anal.* calc. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.19; H, 7.53; N, 11.49.

8-Acetoxymethyl-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 8. 61%; brown oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.05-2.55 (m, 3H, H-7, H-8), 2.86-3.13 (m, 3H, H-6, $CH_2CO_2CH_3$), 3.69 (s, CH_3), 6.97 (t, $J_{2-3} = J_{1-2}$ =6.6 Hz, H-2), 7.50 (t, J_{3-4} = 6.6 Hz, H-3), 7.61 (d, H-4), 9.20 (d, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 24.0 (C-6), 29.8 (C-7), 34.1 ($CH_2CO_2CH_3$), 43.7 (C-8), 51.6 (CH_3), 114.3 (C-2), 118.9 (C-9a), 116.7 (C-4), 128.4 (C-1), 129.0 (C-3), 148.0 (C-4a), 159.8 (C-5a), 172.78 (CO_2CH_3), 187.9 (CO); *Anal.* calc. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.22; H, 5.35; N, 10.87.

8-(1-Hydroxypropyl)-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 9 and 8-(1-propenyl)-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 10. By chromatography, 10 was first obtained in 19 % as an oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.07 (t, J = 7.44 Hz, CH_3), 2.26 (m, CH_2CH_3), 2.89 (m, 2H, H-7), 3.03 (m, 2H, H-8), 6.79 (t, J = 7.33 Hz, $CHCH_2$), 6.93 (t, J =6.7 Hz, H-2), 7.44 (t, J = 6.7 Hz, H-3), 7.64 (d, H-4), 9.35 (d, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 13.4 (CH_3), 21.4 (CH_2CH_3), 24.9 (C-6, C-7), 114.2 (C-2), 116.9 (C-4), 120.0 (C-9a), 128.3 (C-1), 129.2 (C-3), 134.4 (C-8), 139.3 ($CHCH_2$), 148.3 (C-4a), 159.3 (C-5a), 178.3 (CO); *Anal.* calc. for $C_{14}H_{13}N_2O$: C, 74.65; H, 5.82; N, 12.44. Found: C, 74.72; H, 5.71; N, 12.51. Further elution gave **9** as an brown oil (48 %); ^{1}H-nmr (CDCl3, 100 MHz) δ: 1.02 (t, J = 7.3 Hz, CH_3), 1.54 (m, 2H, CH_2CH_3), 2.02 (m, 2H, H-8), 2.25 (m, H-7), 2.51 (m, H-7'), 3.06 (m, 2H, H-6), 4.00 (m, CH(OH)), 7.01 (t, J_{1-2} = 6.6 Hz, H-2), 7.48 (m, H-3,4), 9.21 (d, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 9.2 (CH3), 24.9 (C-6), 25.8 (C-7), 26.8 (CH_2CH_3), 51.1 (C-8), 72.7 (CHOH), 114.21, C-2), 116.4 (C-4), 119.11 (C-9a), 127.9 (C-1), 129.4 (C-4),147.9 (C-4a), 160.1 (C-5a), 190.8 (CO); *Anal.* calc. for $C_{14}H_{15}N_2O_2$: C, 69.12; H, 6.21; N, 11.51. Found: C, 68.99; H, 6.29; N, 11.62.

8-Acetoxy-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 11 and enaminone 12. Compound 11 was first obtained, 51 % as an oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.40 (m, 2H, H-7), 3.01 (m, 2H, H-6), 3.58 (m; 2H, H-8), 3.66 (s, CH_3), 6.94 (t, $J_{1-2} = J_{2-3}$ =6.6 Hz, H-2), 7.40 (t, J_{3-4} =6.6 Hz, H-3), 7.55 (d, H-4), 9.09 (d, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 23.5 (C-6), 26.9 (C-7), 52.22 (C-8*), 53.43 (CH_3*), 114.6 (C-2), 116.7 (C-4), 118.6 (C-9a), 128.1 (C-1), 129.9 (C-3), 148.1 (C-4a), 159.9 (C-5a), 170.3 ($COCH_3$), 182.0 (CO); *Anal.* calc. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N,

11.47. Found: C, 63.81; H, 5.07; N, 11.39. Further elution gave 12 in 15 % as an oil; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.99 (m, 2H, H-5), 2.33 (t, J = 6.39 Hz, 2H, H-6), 2.69 (t, J = 5.64 Hz, 2H, H-4), 3.67 (s, CH_3), 5.44 (s, H-2), 7.24 (m, 2H, H-11, H-13), 7.74 (dt, J_{11-12} = 6.27 Hz, J_{12-13} = 1.9 Hz, H-12), 8.45 (d, J_{10-11} = 3.7 Hz, H-10); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 22.3 (C-5), 28.6 (C-6), 36.4 (C-4), 53.5 (CH_3), 116.6 (C-2), 122.3 (C-11*), 122.8 (C-13*), 149.3 (C-10,), 152.6 (C-3*), 153.3 (C-8*), 160.9 (CO_2CH_3), 199.12 (CO); *Anal.* calc. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63,51; H, 5.67; N, 11.39.

8,8-diacetyl-6,7,8,9-tetrahydropyrido[1,2-a]benzimidazol-9-one 13 and 2-diacetylaminopyridine 14. Chromatography gave 13 as an oil (61%); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.23 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.85 (m, 2H, H-7), 3.03 (m, 2H, H-8), 7.04 (dt, J_{2-3} =J_{1-2} = 6.95 Hz, J_{2-4} = 1.6 Hz, H-2), 7.48 (t, J_{3-4} = 6.95 Hz, J_{1-3} = 1.37 Hz, H-3), 7.67 (dd, H-4), 9.41 (dd, H-1); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ_{CH}: 18.01 (CH_3), 20.1 (CH_3), 25.1 (C-6), 26.0 (C-7), 114.4 (C-2), 116.9 (C-4), 128.3 (C-1), 129.5 (C-4); *Anal.* calc. for $C_{15}H_{14}N_2O_3$: C, 66.64; H, 5.22; N, 10.37. Found: C, 66.51; H, 5.37; N, 10.39. Further elution gave 14 (oil) in 8 % yield; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 2.29 (s, 6H, CH_3), 7.22-7.45 (m, 2H, H-5,3), 7.75 (dt, J_{3-4} = J_{4-5} = 7.68 Hz, J_{4-6} =1.9 Hz, H-4), 8.61 (dd, J_{5-6} = 4.8 Hz, H-6).

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