ALKYLATION OF METHYL 3-HYDROXYINDOLE-2-CARBOXYLATE USE IN PYRIMIDINE SYNTHESIS

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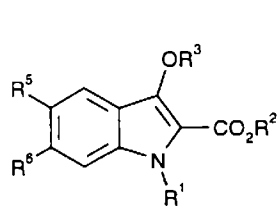
Abstract : Three alkylation sites (O,C-2 or N atoms) are present on methyl 3-hydroxyindole-2-carboxylate **4a**. Functionalized halides were used to study the regioselectivity of these alkylations. In order to illustrate this work, the pyrimidine **17** has been synthesized from the *O*-alkylated compound **13a**.

Introduction : 3-Hydroxyindole-2-carboxylic acid derivatives **1** represent well-known and readily available compounds (1). Compounds **1** are used as synthons for the preparation of indole-fused heterocycles, incorporating the 3-hydroxy group in ring formation to give compounds of potential medicinal interest, e.g. **2** (anti-allergy and/or CNS activities) (2,3). Recently, Hirota *et al.* reported that some 4-alkylamino-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepines **3a** or 5,6-dihydro[1]benzoxepino[5,4-*d*]pyrimidin-4(3*H*)-one **3b** (6) show stronger inhibitory activity against collagen-induced aggregation of rabbit blood platelets than aspirin, which is an anti-platelet agent (6,7). Our goal was to replace the benzo part of compound **3b** by an indole moiety.



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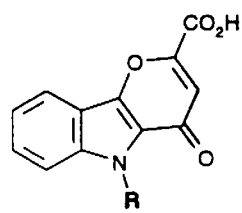

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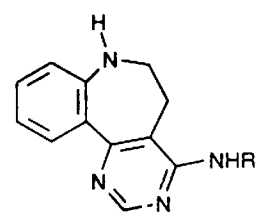
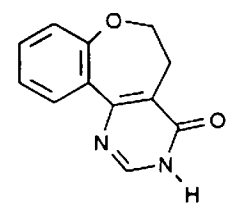
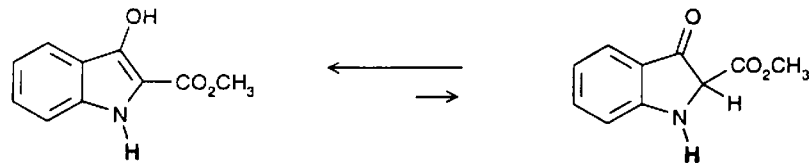


3a



3b

Methyl 3-hydroxyindole-2-carboxylate may exist in two tautomeric forms, **4a** and **4b** :



4a **4b**

The reactivity of the ketoester is mainly governed by the enolic form **4a**; **4a** is soluble in aqueous sodium hydroxide and precipitated with acid. In $CDCl_3$ solution, **4a** is the only present tautomeric form. Such a behaviour has also been reported for the corresponding 3-hydroxy-1*H*-indol-2-yl ethanone (4).

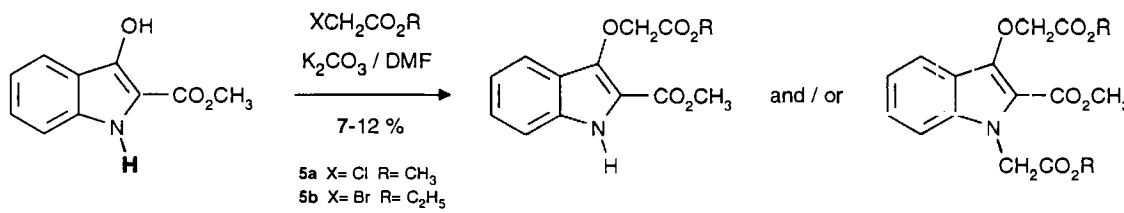
Three alkylation sites are present in compound **4a**, so *O*, *C* or *N*-alkylation can occur. Polar aprotic solvents and large cations favour *O*-alkylation; according to the HSAB theory, iodo compounds give mainly *C*-alkylation while sulfonates give *O*-alkylation (8). For compound **4a**, the possibility of *N*-alkylation also exists.

We have recently revisited the alkylation of methyl indole-2-carboxylate with the functionalized halides **5** and **8**. In all cases the *N*-alkylation was observed (9).

Compound **4a** has been previously *C*- and/or *O*-alkylated using allylic bromides (10,11) and exclusively *O*-alkylated with methyl or allylic tosylates (10), with compound **5b** (15) or with 2-bromopropane (12). These *O*-alkylated compounds have been *N*-phenylated (Ullmann-type reaction) (12). The methoxycarbonyl group of compound **4a** has been transformed into a β-keto sulfone group (4). Ethyl 3-hydroxy-1-methylindole-2-carboxylate **22** was not obtained by *N*-methylation of ethyl 3-hydroxyindole-2-carboxylate, but only by reacting *N*-methylaniline with diethyl bromomalonate (5).

The present investigation was undertaken to examine the regioselectivity of the alkylation of **4a** with functionalized halides like **5**, **8**, **12** in order to obtain diesters or cyanoesters, which could be submitted to a Dieckmann condensation; the products obtained are potential anti-platelet agents (13,14). (The experimental conditions were K_2CO_3 as base, with 1 equivalent of halide, in DMF at 90°C).

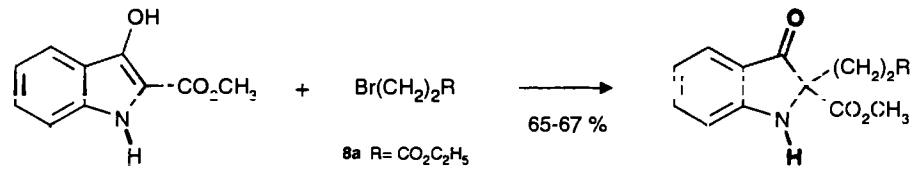
Results :



4a **6a** R= CH_3 **7a** R= CH_3 **7b** R=C_2H_5

Compound **4a**, treated with 1 equivalent of methyl chloroacetate **5a**, led to a mixture of *O*-alkylated compound **6a** and *N,O*-disubstituted compound **7a**. The treatment of **4a** with 1 equivalent of ethyl bromoacetate **5b** gave only the *N,O*-disubstituted product **7b**. The same disubstituted compound **7b** was obtained if only 0.5 equivalent of **5b** was used.

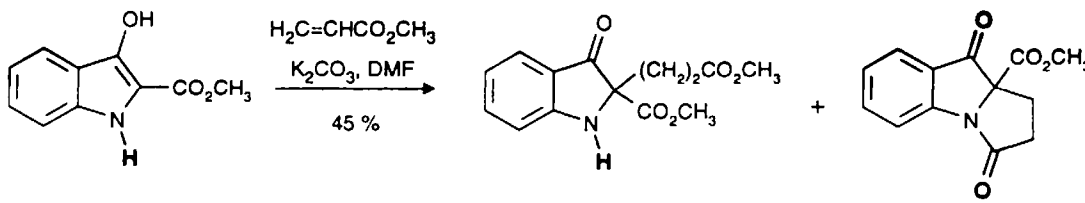
The reaction of **4a** with the halides **5** allowed us to obtain only the *O*- and/or *N,O*-dialkylated compounds; meanwhile the yields are low in isolated products after purification on silica gel chromatography (< 20%). It has been reported that much higher yields result using acetone instead of DMF as solvent, in the *O*-alkylation of ethyl 3-hydroxyindole-2-carboxylate with **5b** (15). 1-Chloro-2-propanone in refluxing acetone led also in good yield (74%) to the *O*-alkylated compound (16). Hirota *et al.* also reported the *O*-alkylation of 3-hydroxybenzo[*b*]thiophene-2-carbonitrile, using K_2CO_3 and chloroacetonitrile, in acetone in 70% yield (17).



4a

9a R= $CO_2C_2H_5$
9b R= CN

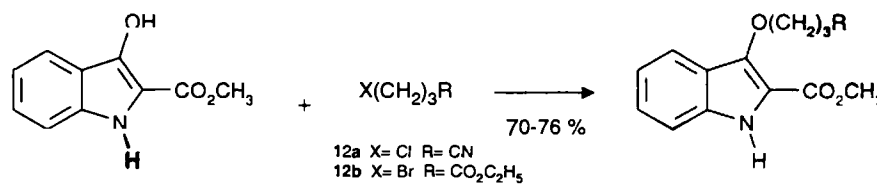
The incorporation of one more methylene unit in the halides **8** resulted in a selective *C*-alkylation of compound **4a** with much higher yield : indeed, reaction of compound **4a** with ethyl 3-bromopropanoate **8a** gave the product **9a** in 65% yield, and reaction with 3-bromopropanenitrile **8b** led to the product **9b** in 67% yield.



4a **10** **11**

The Michael addition of compound **4a** on methyl acrylate led to a mixture of the *C*-alkylated product **10** in 20% yield, and of the tricyclic compound **11** in 25% yield. Compound **11** was the result of the intramolecular acylation of **10**. Its structure has been elucidated using 2D NMR and by an independent synthesis (16)).

We switched from *C*-alkylation to *O*-alkylation by using the halides **12** with one additional methylene unit.



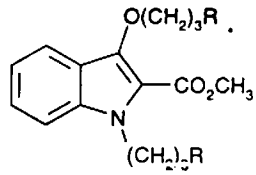
4a

13a R= CN
13b R= $CO_2C_2H_5$

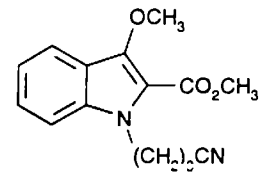
Action of 4-chlorobutanenitrile **12a** with compound **4a** gave the *O*-alkylated product **13a** in 76% yield, and action of ethyl 4-bromobutanoate **12b** led similarly to the *O*-alkylated compound **13b** in 70% yield. We have observed in both

cases a trace of the *N,O*-disubstituted compounds **14**. The use of refluxing acetone, instead of DMF, gave much lower yields of *O*-alkylated products **13a,b**.

Using 5 eq. of 4-chlorobutanenitrile **12a** with compound **4a**, in refluxing acetonitrile (48 h), led to the *N,O*-dialkylated product **14a** in 50% yield. Compound **14a** was also obtained by *N*-alkylation of **13a** with 4-chlorobutanenitrile. Compound **14b** was similarly obtained from **4a** using an excess of **12b** (4 eq.), in 60% yield (18).



14a R= CN
14b R=$CO_2C_2H_5$



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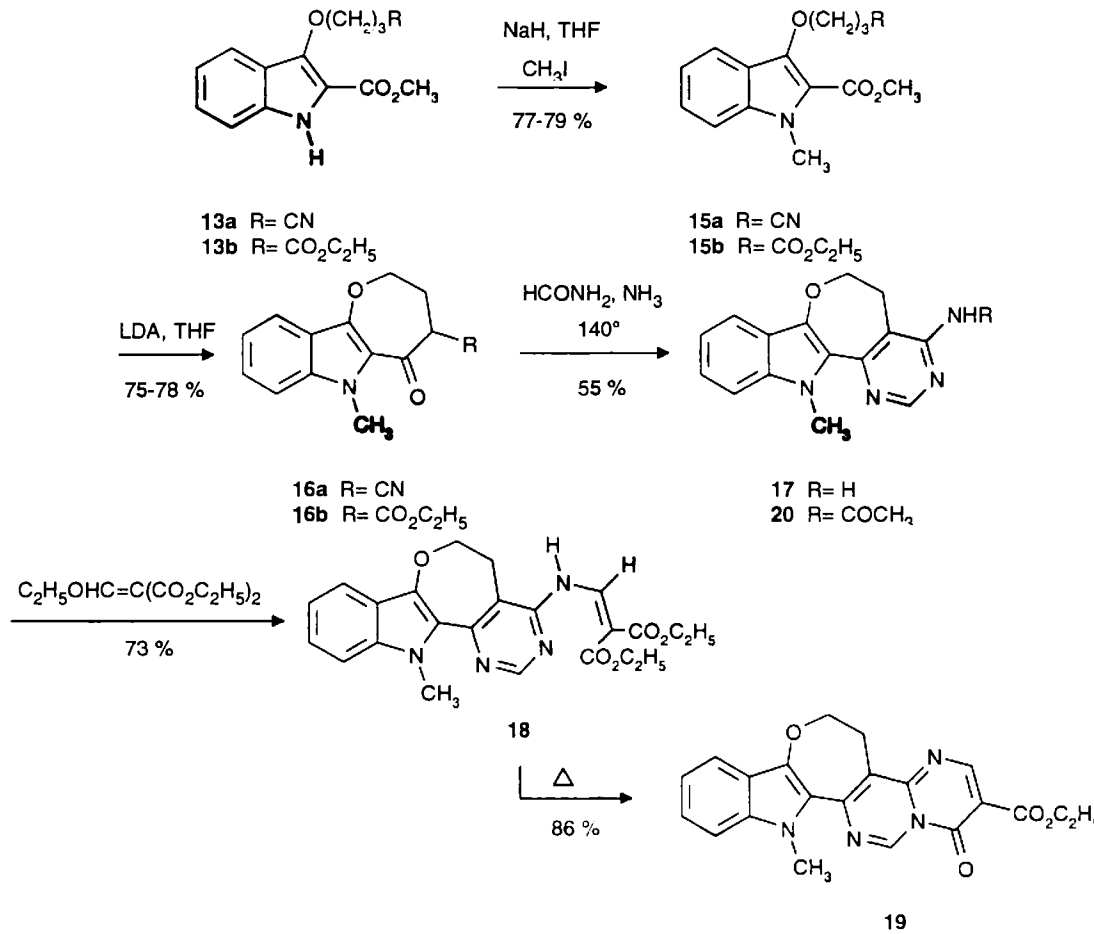
In connection with molecules which might have potential biological activities (6,7,19), we describe here the use of compound **13a** in the synthesis of pyrimidine derivative **17** (Scheme 1) :



13a R= CN
13b R= $CO_2C_2H_5$

15a R= CN
15b R= $CO_2C_2H_5$

16a R= CN
16b R= $CO_2C_2H_5$

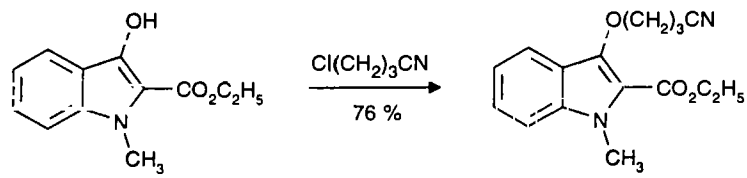
17 R= H
20 R= $COCH_3$

18

19

SCHEME 1

Methylation of compounds **13a,b** with iodomethane gave the *N*-methyl compounds **15a,b**. Structure of compound **15a** has been confirmed by treating ethyl 3-hydroxy-1-methylindole-2-carboxylate **22** with 4-chlorobutanenitrile **12a** under the same conditions of alkylation as for **4a** : compound **23** was isolated in 76% yield and its NMR data were in agreement with those of compound **15a**. Similarly, alkylation of methyl 3-methoxyindole-2-carboxylate with the halide **12a** afforded the *N*-alkylated compound **24** (δ_{NCH_2}= 4.55 ppm) (16).



22 **23**

After unsuccessful attempts (Na/xylene, tBuOK, NaH/THF), the Dieckmann-type cyclization of compounds **15a,b** was performed using LDA/THF at low temperature to give **16a,b** in good yields. This cyclization can also be directly performed on compound **13a** in 72% yield. The ketonitrile **16a** was either *O*-alkylated with methyl tosylate, or *C*-alkylated with methyl iodide. Reactivity of the ketoester **16b** (*C*-alkylation, decarboxylation) will be presented later. The β-oxo nitrile **16a** was then cyclized by the reaction with formamide under ammonia stream at 140-150°C to give the compound **17** with a pyrimidine ring in 55% yield.

In order to study the reactivity of pyrimidine derivative **17**, diethyl ethoxymethylenemalonate was reacted with compound **17** (14) to give the compound **18** in 73% yield, which was cyclized in diphenyl ether at 250°C to afford compound **19** , as shown in Scheme 1. The pyrimidine derivative **17** treated with acetyl chloride led to the compound **20** in 78% yield.

Conclusions : We have described a number of examples in which methyl 3-hydroxyindole-2-carboxylate **4a** shows specific alkylation sites depending of the number of methylene units of the halide used. Further comprehensive studies of the alkylation of compound **4a** are currently under investigation and will be reported in due course. Additionaly, these results allowed us to obtain the pharmacological interesting pyrimidine derivative **17**.

Experimental :

Melting points were measured using a Kofler apparatus and are uncorrected. IR Spectra were recorded on a Perkin-Elmer 257 spectrometer, ^1H and ^{13}C-NMR spectra were recorded on a Bruker AM 300 spectrometer using TMS as internal reference and mass spectra were recorded on a Nermag R-10-10C spectrometer. Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh).

Alkylation of methyl 3-hydroxyindole-2-carboxylate; Typical procedure :

Methyl 3-methoxycarbonylmethoxyindole-2-carboxylate **6a** :

Ketoester **4a** (0.250 g, 1.90 mmol) and K_2CO_3 (0.450 g, 5.13 mmol) were added to dry DMF (12 mL). Ethyl bromoacetate (0.2 mL, 1.90 mmol) was then added dropwise, and the reaction mixture was stirred for 90 mn at 90°C. The solvent was evaporated under reduced pressure and the residue was quenched with H_2O (15 mL). The aq. layer was neutralized with a solution of 10% HCl and extracted with CH_2Cl_2 (2x10 mL). The organic extracts were washed with H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed over silica gel using CH_2Cl_2 as eluent to give **6a**; yield : 0.035 g (10%) ; oil. IR (film) ν= 3380 (br NH), 1760, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 3.71 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.87 (s, 2H, OCH_2), 7.05-7.36 (m, 3H, H_{arom}), 7.81 (d, 1H, J=7.8, H-4).

Methyl 3-methoxycarbonylmethoxy-1-methoxycarbonylmethylindole-2-carboxylate **7a** :
Yield : 0.030 g (7%); oil. IR (film) ν= 1760, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 3.69 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3) 4.75 (s, 2H, OCH_2), 5.16 (s, 2H, NCH_2), 7.10 (dd, 1H, J=7.5,7.9, H-5), 7.19 (d, 1H, J=8.3, H-7), 7.30 (dd, 1H, J=7.5,8.2, H-6), 7.80 (d, 1H, J=7.9, H-4).

Methyl 3-ethoxycarbonylmethoxy-1-ethoxycarbonylmethylindole-2-carboxylate **7b** :
Yield : 0.057 g (12%); oil. IR (film) ν= 1740, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.25 (t, 3H, J=7.2, OCH_2CH_3), 1.31 (t, 3H, J=7.2, OCH_2CH_3), 3.92 (s, 3H, OCH_3), 4.19 (q, 2H, J=6.6, OCH_2), 4.28 (q, 2H, J=6.3, OCH_2), 4.78 (s, 2H, OCH_2), 5.20 (s, 2H, NCH_2), 7.13-7.39 (m, 3H, H_{arom}), 7.85 (d, 1H, J=8.3, H-7).

2-(2-Ethoxycarbonylethyl)-2-methoxycarbonyl-3-oxo-2,3-dihydroindole **9a** :
Yield : 0.247 g (65%); oil. IR (film) ν= 3380 (br NH), 1750, 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.18 (t, 3H, J=6.9, OCH_2CH_3), 2.26-2.56 (m, 4H, $CH_2CO_2C_2H_5$ + $CH_2CH_2CO_2C_2H_5$), 3.72 (s, 3H, OCH_3), 4.08 (quint., 2H, J=7.1, OCH_2CH_3), 5.40 (br s, 1H, NH), 6.89 (t, 1H, J=7.4, H-5), 6.97 (d, 1H, J=7.7, H-7), 7.48 (t, 1H, J=7.6, H-6), 7.58 (d, 1H, J=7.5, H-4).

2-(2-Cyanoethyl)-2-methoxycarbonyl-3-oxo-2,3-dihydroindole **9b** :
Yield : 0.214 g (67%); oil. IR (film) ν= 3380 (br NH), 2220 (C≡N), 1730, 1670 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.28-2.43 (m, 4H, CH_2CN + CH_2CH_2CN), 3.72 (s, 3H, OCH_3), 5.34 (br s, 1H, NH), 6.87 (dd, 1H, J=7.8,7.3, H-5), 6.97 (d, 1H, J=7.9, H-7), 7.46 (dd, 1H, J=7.3,7.9, H-6), 7.53 (d, 1H, J=7.9, H-4).

2-(2-Methoxycarbonylethyl)-2-methoxycarbonyl-3-oxo-2,3-dihydroindole **10** :
Yield : 0.047 g (20%); oil. IR (film) ν= 3380 (br NH), 1750, 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.28-2.37 (m, 2H, $CH_2CH_2CO_2$), 2.41-2.55 (m, 2H, $CH_2CO_2CH_3$), 3.64 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.90 (dd, 1H, J=7.2,7.7, H-5), 6.97 (d, 1H, J=8.6, H-7), 7.49 (dd, 1H, J=7.1,8.6, H-6), 7.59 (d, 1H, J=7.9, H-4). MS (NH_3) *m/z*= 278 (M^++1).

Methyl 3,9-dioxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9a-carboxylate **11** :
Yield : 0.038 g (25%); oil. IR (film) ν= 3380 (br NH), 1750, 1730, 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.17-2.29 (m, 1H, NCCH), 2.56-2.65 (m, 1H, NCOCH), 2.98-3.11 (m, 2H, NCCH+NCOCH), 3.77 (s, 3H, OCH_3), 7.23-7.31 (m, 1H, H-4), 7.69-7.74 (m, 2H, H-5, H-6), 7.92 (d, 1H, J=7.9, H-7). ^{13}C-NMR ($CDCl_3$) δ= 26.61 ($C\underline{C}H_2$), 34.66 ($NCO\underline{C}H_2$), 53.73 (OCH_3), 76.51 (NCCO), 117.07 (CH_{arom}), 125.06 (CH_{arom}), 125.09 (C_{arom}), 125.28 (CH_{arom}), 137.47 (CH_{arom}), 151.13 (C_{arom}), 167.54 ($\underline{C}O_2CH_3$), 173.07 (NCO), 194.08 (CO). MS (NH_3) *m/z*= 246 (M^++1).

Methyl 3-(3-cyanopropoxy)indole-2-carboxylate **13a** :

Yield : 0.257 g (76%); mp 124-126°C (EtOH). IR (KBr) ν= 3300 (br NH), 2200 (C≡N), 1680 (C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.25 (quint., 2H, J=6.3, OCH_2CH_2), 2.82 (t, 2H, J=6.7, CH_2CH_2CN), 3.96 (s, 3H, OCH_3), 4.23 (t, 2H, J=5.5, OCH_2), 7.07-7.14 (m, 2H, H_{arom}), 7.36-7.38 (m, 1H, H_{arom}), 7.76 (d, 1H, J=8.2, H-7), 8.36 (br s, 1H, NH).

Methyl 3-(3-ethoxycarbonylpropoxy)indole-2-carboxylate **13b** :

Yield : 0.280 g (70%); mp 62-64°C (EtOH). IR (KBr) ν= 3300 (br NH), 1720 (ν br C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.25 (t, 3H, J=7.4, OCH_2CH_3), 2.14 (quint., 2H, J=6.8, OCH_2CH_2), 2.64 (t, 2H, J=8.0, CH_2CO), 3.97 (s, 3H, OCH_3), 4.14 (q, 2H, J=6.9, OCH_2CH_3), 4.32 (t, 2H, J=6.9, OCH_2), 7.06-7.13 (m, 4H, H_{arom}).

Methyl [3-(3-cyanopropoxy)-1-(3-cyanopropyl)]indole-2-carboxylate **14a** :

Yield : 0.213 g (50%); mp 86-88°C (EtOH). IR (KBr) ν= 2220 (C≡N), 1675 (C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.15 (m, 4H, OCH_2CH_2 + NCH_2CH_2), 2.30 (t, 2H, J=7.0, CH_2CN), 2.70 (t, 2H, J=7.0, CH_2CN), 3.92 (s, 3H, OCH_3), 4.25 (t, 2H, J=6.0, OCH_2), 4.56 (t, 2H, J=7.0, NCH_2), 7.08-7.15 (m, 2H, H_{arom}), 7.36-7.37 (m, 1H, H_{arom}), 7.63 (d, 1H, J=8.0, H-7).

Methyl [3-(3-ethoxycarbonylpropoxy)-1-(3-ethoxycarbonylpropyl)]indole-2-carboxylate **14b** :

Yield : 0.329 g (60%); oil. IR (film) ν= 1725, 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.20 (t, 3H, J=7.0, OCH_2CH_3), 1.23 (t, 3H, J=7.0, OCH_2CH_3), 2.00-2.16 (m, 4H, 2x $CH_2CH_2CH_2$), 2.59 (t, 2H, J=7.0, CH_2CO_2), 2.27 (t, 2H, J=7.0, CH_2CO_2), 3.90 (s, 3H, OCH_3), 4.05-4.19 (m, 4H, 2xOCH_2CH_3), 4.49 (t, 2H, J=7.0, NCH_2), 7.06 (dd, 1H, J=7.0,7.9, H-5), 7.29 (dd, 1H, J=8.4,7.1, H-6), 7.36 (d, 1H, J=8.5, H-7), 7.66 (d, 1H, J=8.0, H-4).

Methyl 3-(3-cyanopropoxy)-1-methylindole-2-carboxylate **15a**; **Typical Procedure** :

A solution of compound **13a** (5 g, 19.4 mmol) in dry THF (15 mL) was added slowly to a supension of sodium hydride (0.698 g, 23.3 mmol) in dry THF (5 mL) at 0°C. The mixture was stirred at this temperature for 1h, then iodomethane (5.43 mL, 87.3 mmol) was added. The reaction mixture was allowed to warm up to r.t. for 6 h. The solvent was evaporated in vacuo, the mixture quenched with H_2O, neutralized with a solution of 10% HCl. The solution was extracted with CH_2Cl_2 (3x15 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. Column chromatography on silica gel using CH_2Cl_2 as eluent afforded **15a**, yield : 4.08 g (77%); mp 70-72°C (EtOH). IR (KBr) ν= 2220 (C≡N), 1680 (C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.17 (quint., 2H, J=6.2, OCH_2CH_2), 2.74 (t, 2H, J=6.7, CH_2CN), 3.96 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 4.29 (t, 2H, J=5.5, OCH_2), 7.10-7.16 (m, 2H, H_{arom}), 7.35-7.37 (m, 1H, H_{arom}), 7.67 (d, 1H, J=8.5, H-7).

Methyl 3-(3-ethoxycarbonylpropoxy)-1-methylindole-2-carboxylate **15b** :

Yield : 4.13 g (79%); oil. IR (film) ν= 1720, 1680 (C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.27 (t, 3H, J=7.9, OCH_2CH_3), 2.14 (quint., 2H, J=7.1, OCH_2CH_2), 2.63 (t, 2H, J=7.9, CH_2CO), 3.94 (s, 3H, NCH_3), 3.97 (s, 3H, OCH_3), 4.12-4.23 (m, 4H, OCH_2 + OCH_2CH_3), 7.06-7.12 (m, 2H, H_{arom}), 7.30-7.36 (m, 1H, H_{arom}),7.70 (d, 1H, J=8.1, H-7).

4-Cyano-6-methyl-5-oxo-2,3,4,5-tetrahydrooxepino[3,2-*b*]indole **16a**; **Typical Procedure :**

To a stirred solution of diisopropylamine (0.77 mL, 5.5 mmol) in dry THF (10 mL) was added dropwise butyllithium (1.6 M in hexane, 3.44 mL, 5.5 mmol) at -78°C under nitrogen atmosphere and the mixture was stirred for 30 min. A solution of

the compound **15a** (1.5 g, 5.5 mmol) in dry THF (10 mL) was added dropwise and the mixture was stirred at this temperature for 45 min. The solution was allowed to warm up to r.t. for 3 h. The solvent was evaporated in vacuo, the mixture quenched with H_2O, neutralized with a solution of 10% HCl. The solution was extracted with CH_2Cl_2 (2x15 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. Column chromatography on silica gel eluting with CH_2Cl_2 afforded **16a**, yield : 1.03 g (78%); mp 120-122°C (EtOH). IR (KBr) v= 2200 (C≡N), 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.44-2.71 (m, 2H, OCH_2CH_2), 3.91 (s, 3H, NCH_3), 4.88 (q, 1H, J=4.5, CHCN), 4.40-4.57 (m, 2H, OCH_2), 7.10 (t, 1H, J=7.6, H-5), 7.25-7.30 (m, 2H, H_{arom}), 7.40-7.46 (m, 1H, H_{arom}), 7.70 (d, 1H, J=8.2, H-7). MS (NH_3) *m/z*= 241 (M^++1).

4-Ethoxycarbonyl-12-methyl-5-oxo-2,3,4,5-tetrahydrooxepino[3,2-*b*]indole **16b** :

Yield : 1.00 g (75%); oil. IR (film) v= 1730 (C=O ester), 1640 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.26 (t, 3H, J=6.2, OCH_2CH_3), 2.36-2.63 (m, 2H, OCH_2CH_2), 2.87 (t, 1H, J=3.8, $CHCO_2$), 3.90 (s, 3H, NCH_3), 4.24 (quint., 2H, J=6.9, OCH_2), 4.37-4.51 (m, 2H, OCH_2), 7.06 (t, 1H, J=7.1, H-5), 7.24 (d, 1H, J=8.5, H-7), 7.38 (t, 1H, J=8.5, H-6), 7.67 (d, 1H, J=7.8, H-4). MS (NH_3) *m/z*= 288 (M^++1).

4-Amino-12-methyl-5,6-dihydroindolo[3,2-*b*]oxepino[5,4-*d*]pyrimidine **17** :

A mixture of **16a** (0.200 g, 0.83 mmol) and formamide (10 mL) was heated at 140-150°C with stirring under NH_3 stream for 36 h until the substrate **16a** has disappeared. The mixture was cooled and quenched with H_2O. It was extracted with CH_2Cl_2 (3x10 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuo. Column chromatography on silica gel (CH_2Cl_2 / MeOH, 99:1) gave **17**, yield : 0.121 g (55%); mp 166-168°C (EtOH). IR (KBr) v= 3400 (br NH_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 2.94 (t, 2H, J=5.9, OCH_2CH_2), 4.03 (s, 3H, NCH_3), 4.54 (t, 2H, J=5.9, OCH_2), 5.00 (br s, 2H, NH_2), 7.05-7.10 (m, 2H, H_{arom}), 7.32 (d, 1H, J=8.3, H-7), 7.65 (d, 1H, J=7.9, H-4), 8.54 (s, 1H, N=CH). MS (NH_3) *m/z*= 267 (M^++1).

Diethyl N-(5,6-dihydro-12-methylindolo[3,2-*b*]oxepino[5,4-*d*]pyrimidin-4-yl)aminomethylene malonate **18** :

A mixture of compound 17 (0.050 g, 0.19 mmol) and diethyl ethoxymethylenemalonate (0.1 mL, 0.38 mmol) in xylene (5 mL) was refluxed for 18 h. After evaporation of the reaction mixture, the residue was chromatographed on silica gel using petroleum ether/ethyle acetate 9:1 as eluent to give **18**, yield : 0.060 g (73%); mp 180-182°C (EtOH). IR (KBr) v= 3180 (br NH), 1720 (C=O), 1650 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.30 (t, 3H, J=7.3, OCH_2CH_3), 1.35 (t, 3H, J=7.3, OCH_2CH_3), 3.04-3.11 (m, 2H, OCH_2CH_2), 3.97 (s, 3H, NCH_3), 4.24 (q, 2H, J=7.3, OCH_2), 4.30 (q, 2H, J=7.3, OCH_2), 4.48-4.55 (m, 2H, OCH_2), 7.00-7.35 (m, 3H, H_{arom}), 7.62 (d, 1H, J=8.1, H-7), 8.76 (s, 1H, N=CH), 9.24 (d, 1H, J=11.7, =CH), 11.62 (br d,1H, NH). MS (NH_3) *m/z*= 437 (M^++1).

Ethyl 1-oxo-5,6-dihydro-12-methylindolo[3,2-*b*]oxepino[4,5-*e*]pyrimido[1,2-*c*]pyrimidin-2-yl carboxylate 19 :

Compound **18** (0.040 g, 0.09 mmol) in diphenyl ether (5 mL) was heated at 250-260°C with a metallic bath for 90 mn. After cooling of the reaction mixture, petroleum ether was added to the mixture. The precipitated solid was collected by filtration, washed with petroleum ether and dried in vacuo to afford **19**, yield : 0.031 g (86%); mp 220-222°C (EtOH). IR (KBr) v= 1710 (C=O ester),1680 (C=O), 1610 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.37 (t, 3H, J=7.5, OCH_2CH_3), 3.58-3.67 (m, 2H, OCH_2CH_2), 3.98 (s, 3H, NCH_3), 4.37 (q, 2H, J=7.5, OCH_2), 4.47-4.58 (m, 2H, OCH_2), 6.99-7.40 (m, 3H, H_{arom}), 7.62 (d, 1H, J=8.1, H-7), 8.95 (s, 1H, =CH), 9.78 (s, 1H, N=CH). MS (NH_3) *m/z*= 391 (M^++1).

4-Acetamido-5,6-dihydro-12-methylindolo[3,2-*b*]oxepino[5,4-*d*]pyrimidine **20** :

The pyrimidine **17** (0.040 g, 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C with an ice-bath, under argon atmosphere. Acetyl chloride (0.01 mL, 0.16 mmol) and triethylamine (0.02 mL, 0.16 mmol) were added slowly. The mixture was stirred at r.t. for 18 h, hydrolyzed and extracted with CH_2Cl_2 (2x5 mL). The organic extracts were washed with H_2O, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed over silica gel using CH_2Cl_2 to give **20**, yield : 0.036 g (78%); mp 188-190°C (EtOH). IR (KBr) ν= 3400 (br NH), 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ = 2.31 (s, 3H, $COCH_3$), 2.91 (t, 2H, J=4.4, OCH_2CH_2), 4.02 (s, 3H, NCH_3), 4.40 (t, 2H, J=4.4, OCH_2), 6.99-7.38 (m, 3H, H_{arom}), 7.62 (d, 1H, J=8.1, H-7), 8.99 (s, 1H, N=CH). MS (NH_3) *m/z*= 309 (M^++1).

Ethyl 3-(3-cyanopropoxy)-1-methylindole-2-carboxylate **23** :

Yield : 0.248 g (76%); oil. IR (film) ν= 2200 (C≡N), 1680 (C=O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.43 (t, 3H, J=7.1, OCH_2CH_3), 2.15 (quint., 2H, J=6.3, OCH_2CH_2), 2.74 (t, 2H, J=6.7, CH_2CN), 3.96 (s, 3H, NCH_3), 4.29 (t, 2H, J=5.5, OCH_2), 4.43 (q, 2H, J=7.1, OCH_2), 7.10-7.16 (m, 2H, H_{arom}), 7.35-7.37 (m, 1H, H_{arom}), 7.67 (d, 1H, J=8.5, H-7).

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