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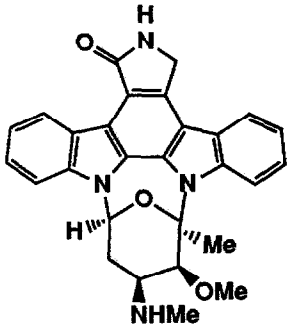
OXIDATION OF METHYL INDOLE-3-ACETATE INDUCED BY $FeCl_3$ AND SECONDARY AMINES.

J. Bergman, S. Bergman and J.-O. Lindström
Department of Organic Chemistry, Royal Institute of Technology
S-100 44 Stockholm, SWEDEN

Abstract: Oxidation of methyl indole-3-acetate with $FeCl_3$ in the presence of dimethylamine gave methyl α-(dimethylamino)-indole-3-acetate, **4d**, which could be quaternized and subsequently coupled with methyl indole-3-acetate in the presence of LDA.

In connection with studies[1,2] of indolocarbazole alkaloids[3,4] such as staurosporin (**1**) and arcyriaflavin (**2**) we have synthesized **3a** by a iodine promoted coupling[1] of the trianion of indole-3-acetic acid. As a complement to this method we now report that **4a** can be oxidized by $FeCl_3$ complexed with secondary amines. The products (e.g. **4b**) can be quaternized and subsequently coupled with **4a** under basic conditions to the methyl ester of **3a**. This approach should be particularly useful for the synthesis of unsymmetrical derivatives of **3a**, such as **3b**.



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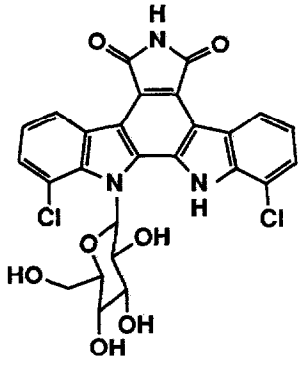

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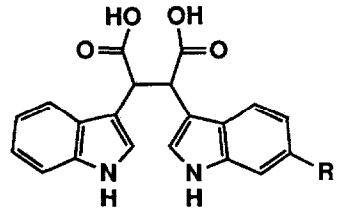


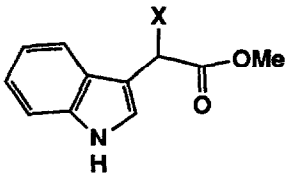
3a R=H
b R=OMe

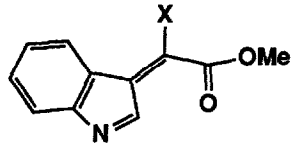
When methyl indole-3-acetate (**4a**) in dry ether was treated with $FeCl_3$ in the presence of $(C_3H_7)_2NH$ an excellent yield (>90%) of **4b** was produced. The yield decreased with smaller dialkylamines, and **4c** and **4d** were formed from $(C_2H_5)_2NH$ and $(CH_3)_2NH$ in 60% and 48% yield, respectively. The reaction pathway is assumed to include the radical cation of **4a** and the conjugated system **5** (X=H). Interestingly the alcohol **4e** can be readily converted to the amine **4b** by interaction with $FeCl_3$-$(C_3H_7)_2NH$ in ether. Similar transformations are also possible with the parent alcohol, indole-3-carbinol.

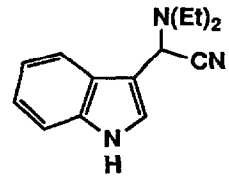
The ester **4e** could also be prepared (40% yield) by electrophilic diethylamination of the dianion of methyl indole-3-acetate with *N,N*-diethyl-*O*-mesitylenesulfonylhydroxylamine, a reagent previously[5] used to diethylaminate the anion of 5,10-dihydroindeno[1,2-b] indole.

Some of the oxidations now investigated have previously been studied by von Dobeneck and Lehnerer[6] who incorrectly, based on certain mechanistic assumptions, assigned the complex structure **6** to the product[7,8] obtained from **4a** and $FeCl_3$-$(C_3H_7)_2NH$ (which is in fact **4b**). The amino esters **4b** and **4c** obtained were further characterized by reduction with $LiAlH_4$ in ether providing the unrearranged (cf ref 9) amino alcohols **7a** and **7b**, which were identical with products prepared from indole, $HOCH_2CHO$ and the appropriate amines as described by Julia.[10] The parent amino alcohol (**7** ,R=H) has recently been described by Katz et al.[11]

Replacement of **4a** with indole-3-acetonitrile in the oxidation reaction similarly gave **8**, which was identical with a sample prepared according to Snyder's method[12] starting from 3-formylindole. Expectedly compound **8** was found to be more sensitive to hydrolysis (yielding 3-formylindole) than the amino esters **4b**, **4c** and **4d.**



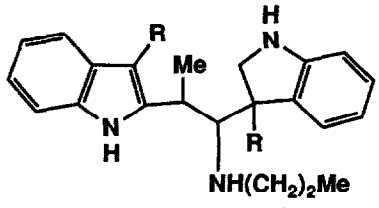


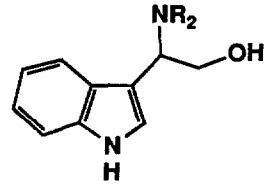


4 **a** X=H
b X=$N(C_3H_7)_2$
c X=$N(C_2H_5)_2$
d X=$N(CH_3)_2$
e X=OH

5

8

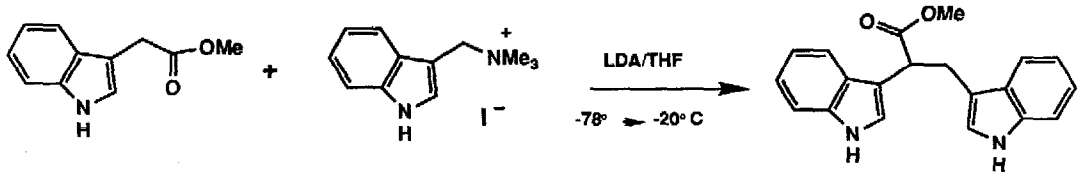




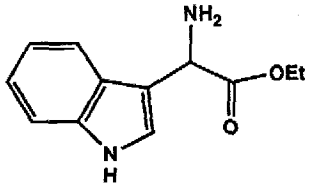
6 R=$CH_2CO_2CH_3$

7 **a** R=C_2H_5
b R=C_3H_7

Winterfeldt and Sarstedt[13,14] have performed the following coupling reaction:



An obvious extension would be to substitute the quaternized gramine with quaternized derivatives of **4b**, **4c** or **4d**. This should allow ready availability of compounds such as **3b**, which is a useful precursor for the synthesis of indolocarbazole alkaloids. Some attempts along this road have already been reported by Steglich and Casser[15], who readily prepared the amino ester (**9**) (cf also ref 11) using the protected amino ester (**10**) as the key reagent. However, attempted[15] methylation of (*9*) gave a complex mixture including dimeric products. As expected **4d** is much more easy to quaternize and subsequent coupling with methyl indole-3-acetate using the conditions given above readily gave the known[2] dimethyl ester of **3a**.



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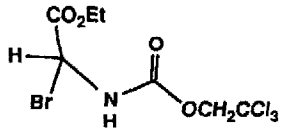

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SPECTRAL DATA

4b: **mp.** 115-116°C., lit.[6] mp. 114°C. **PMR**($CDCl_3$): 0.77(t, 6H), 1.34(m, 4H), 2.5(m, 4H), 3.31(s, 3H), 4.91(s, 1H), 7.1-7-4(m, 4H), 7.78(d, 1H) and 8.3(br s, 1H) ppm.

4c: **mp.** 128-129° C. **^{13}C-NMR**($CDCl_3$): 173.4(s), 136.2(s), 127.1(s),124.3(d),122.1(d), 119.7(d), 119.7(d), 111.3(s), 111.2(d), 61.4(d), 51.6(q), 43.8(t) and 12.2(q) ppm. **PMR**($CDCl_3$) 1.02(t ,6H), 2.73)q, 4H), 4.87(s, 3H), 4.87(s, 1H), 7.2-7.4(m, 4H), 7.80
(d, 1H) and 8.48(br s, 1H) ppm.

4d: **mp.** 96-97°C. **^{13}C-NMR**($CDCl_3$): 172.8(s), 136.2(s), 127.0(s), 124.7(d), 122.1(d), 119.8(d), 111.6(d), 110.5(s), 66.6(d), 51.8(q) and 43.2(q) ppm.

7a: **mp.** 118-119°C.**^{13}C-NMR**($CDCl_3$): 136.0(s), 128.5(s), 123.6(d), 123.2(d), 119.8(d), 119.3(d), 111.5(s), 111.2(d), 61.2(t), 57.5(d), 52.5(t), 22.0(t) and 11.9(q) ppm.

References and Notes

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7. The reported analytical data[6], C=70.51, H =8.31, N=9.72, are in disagreement with those calculated, C=70.41, H=8.31, N=8.80, for **6**, but in reasonable agreement with those calculated for **4b**.

8a. In addition to the basic product the German workers also noted a neutral product (mp. 232° C), which was also given a complex structure. In fact it is the well-known ester methyl indole-3-glyoxylate (lit.[8b] mp. 230-231°C). Its formation is readily explained by a secondary dehydrogenation of **4b**, giving **5** (X=NR_2), followed by hydrolysis during work-up.

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