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Ring D Modifications of Ellipticine. Part 2.‡ Chlorination of Ellipticine via its N-oxide and Synthesis and Selective Acetylation of 5,6,11-Trimethyl-5*H*-Benzo[*b*]Carbazole.

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Abstract: The N-oxide of ellipticine can be used for the introduction of a chlorine atom at carbon-3 of the ellipticine nucleus. According to modelstudies with 5,8-dimethylisoquinoline-N-oxide the reaction is guided both by steric hindrance and by nitrogen-6 of the ellipticine system. Attempted nucleophilic substitution reactions of 3-chloro-ellipticines failed. The high cytostatic activity observed for 9-acetylellipticine stimulated us to prepare the corresponding deaza analogue. This compound was synthesized in 2 steps starting from 1-methylindole. Regioselective acetylation at C-2 was accomplished using acetic anhydride and $ZnCl_2$ as a catalyst. Under a variety of other conditions the 2,9-diacetylproduct was formed and no 9-monoacetylated compound could be isolated. Just as the parent compound, the acetylated deazaellipticines showed only very low cytostatic activity.

INTRODUCTION

The alkaloid ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, **1**) is well known for its cytostatic activity which was discovered in 1967 (Figure 1).[1,2] This has led to numerous syntheses which have been reviewed in several papers.[3-7] From these it is obvious that direct introduction of substituents is restricted to C-1, N-2, C-9 and C-11.[8-13]

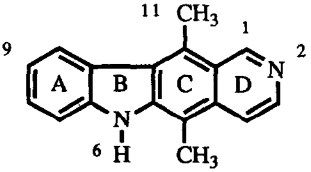

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Figure 1

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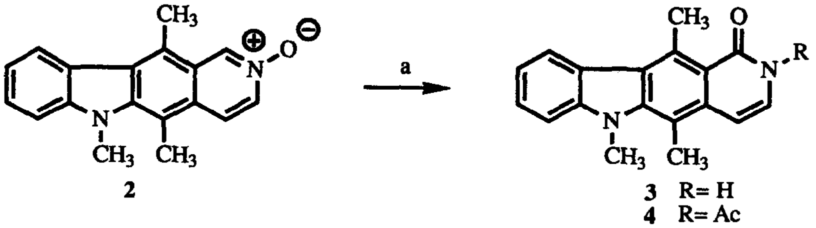
‡ Part 1 published previously in this journal.

In order to functionalize the 11-methylgroup an attempt by our group was made to apply well known pyridine-N-oxide chemistry to the pyridocarbazole system since the 11-methylgroup is conjugatively analogous to the methylgroup in 2-methylpyridine.[10] Upon reacting 6-methylellipticine-N-oxide (**2**) with Ac_2O the carbazolone derivatives **3** and **4** were isolated instead of the desired 11-functionalized ellipticines (Scheme 1).

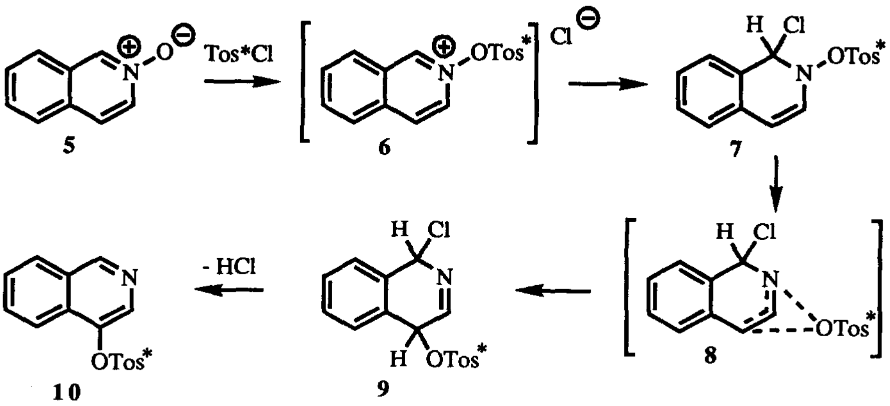


a) Ac_2O, NaOAc.

Scheme 1

Extending this idea of making the oxygen part of a leaving group, other reactants such as p-TosCl or MsCl can replace Ac_2O for the synthesis of 1-functionalized ellipticines. Our interest was stimulated further by papers which dealt with the reactions of heterocyclic N-oxides with Ac_2O and p-TosCl. Reaction of quinoline-N-oxide with Ac_2O or p-TosCl gave quinolin-2-(1*H*)-one.[14] Isoquinoline-N-oxide reacted in a similar manner with Ac_2O but upon treatment with p-TosCl 4-tosylisoquinoline was isolated instead. Since the ellipticineskeleton contains an isoquinoline structure, this result could in principle open a way for the synthesis of 4-substituted ellipticines.

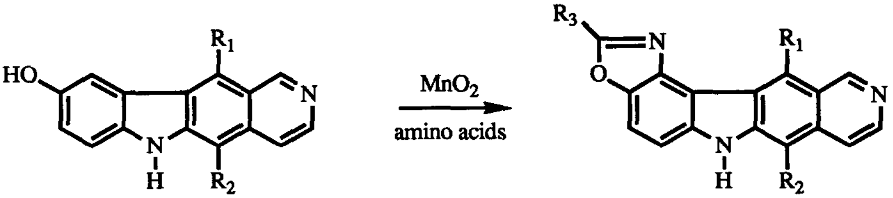
The mechanism of the reaction of isoquinoline-N-oxide (**5**) to **6** with p-TosCl has been extensively investigated using p-TosCl labelled with ^{18}O and it is assumed that the rearrangement proceeds via an intimate ion pair (**8**) since almost no scrambling of the isotopes was observed (Scheme 2).[15,16] After reaction of the tosylgroup with the N-oxide function of **5** to **6** the chloride-ion adds to C-1 (**7**) whereafter the tosyloxygroup shifts to C-4 (**9**) via **8** retaining its stereochemical structure. Finally hydrochloric acid eliminates from **9** to give 4-tosylisoquinoline (**10**).



Scheme 2

It has been established that there are several ways by which ellipticines can express their antitumour activity. After the discovery of its antitumour activity intercalation due to its planar structure, was assumed to be responsible for the activity.[17,18] Since 9-hydroxyellipticine (**11**) also showed high antitumour activity, another possibility of antitumour action was proposed.[19,20] Oxidation of **11** should lead to the formation of a quinonimine which has been shown to react *in vitro* with ribonucleos(t)ides and with amino acids to form oxazolopyridocarbazoles **12** (Scheme 3).[21,22] Recent developments show a third way in which topoisomerase II is playing a central role.[23,24]

Serious doubt was raised by Archer et. al about the quinonimine theory.[25,26] They suggested an alternative in which the 5-methylgroup plays a central role. Reinvestigation of the available literature concerning the biological activity of ellipticines led them to the conclusion that the 5-methylgroup is essential for antitumour action. They therefore synthesized 9-hydroxy-6*H*-pyrido[4,3-*b*]carbazole (**13**) which upon oxidation in the presence of amino acids formed oxazolopyridocarbazoles of type **14** (Scheme 3). Although **13** could be oxidized to a quinonimine, the compound was shown to be devoid of any cytotoxic activity, thus establishing that a 9-hydroxy function is not sufficient for antitumour activity.



11 $R_1 = R_2 = CH_3$
13 $R_1 = R_2 = H$

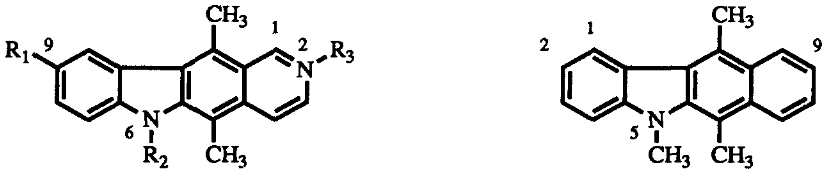
12 $R_1 = R_2 = CH_3$
14 $R_1 = R_2 = H$
R_3= Amino acid residue

Scheme 3

Research performed in our group showed that the 9-hydroxy function is also not a condition for cytostatic activity.[13] We found that 9-acylated ellipticines showed unexpected high antitumour activity. For instance 9-acetyl-6-methylellipticine (**15**) showed an IC_{50} value against B16 melanoma of 44 ng/ml similar to 9-hydroxy-2-methylellipticinium acetate (**16**, elliptinium®), the clinically active drug (Figure 2).[6,27]

This result is remarkable since conversion into a hydroxy group via an enzymatic Baeyer-Villiger oxidation is unlikely. Up till now the only enzyme mediated Baeyer-Villiger oxidation has been found in a bacteria.[28] Therefore the 9-acylellipticines should display their activity via a hitherto unknown mechanism, probably without interference of a quinonimine.

Although the deaza-analogues of ellipticine showed little or no antitumour activity the results mentioned above, stimulated us to synthesize the deaza-analogue of **15**. In this paper we wish to report on the synthesis of 3-chloro-ellipticines, 5,6,11-trimethyl-5*H*-benzo[*b*]carbazole (2-deaza-6-methylellipticine, **17**) and on the selective acetylation of the latter compound (Figure 2).[29]



15 R_1= CH_3CO, R_2= CH_3, R_3= -
16 R_1= OH, R_2= H, R_3= CH_3

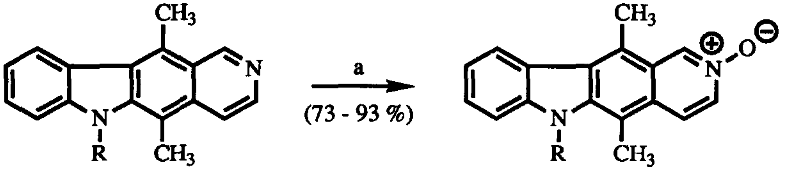
17

Figure 2

RESULTS

SYNTHESIS OF THE CHLORO-ELLIPTICINES

Starting from ellipticine (**1**), 6-methylellipticine (**18**) and 6-benzylellipticine (**19**) were prepared by deprotonation of **1** in THF or DMF with NaH followed by the addition of CH_3I or $PhCH_2Br$. After treatment of the ellipticines **1**, **18** and **19** with m-CPBA, the corresponding N-oxides **20**, **2** and **21** were obtained (Scheme 4).[10]



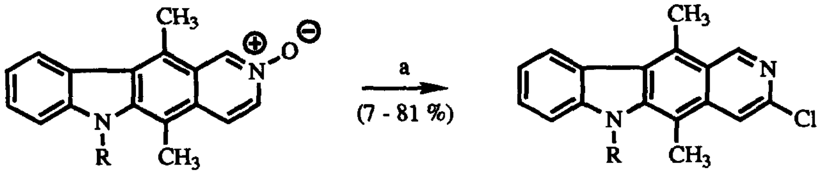
1 R= H
18 R= CH_3
19 R= CH_2Ph

2 R= CH_3
20 R= H
21 R= CH_2Ph

a) m-CPBA, CH_2Cl_2, 0°C.

Scheme 4

Reactions of p-TosCl with **2** in the presence of nucleophiles like KOH or NaOAc did not give unequivocal results and since the chloride ion is a weak nucleophile we investigated if it interfered with the reaction. Thus a series of acid chlorides was reacted with **2** to give the same product which could be identified as 3-chloro-6-methylellipticine (**22**) (Scheme 5). No trace of 4-substituted ellipticines could be detected. The reaction conditions were optimized using p-TosCl and **2** increasing the yield of **22** to 56 %. Under these conditions **20** and **21** were converted in the corresponding 3-chloro-ellipticines **23** and **24**.



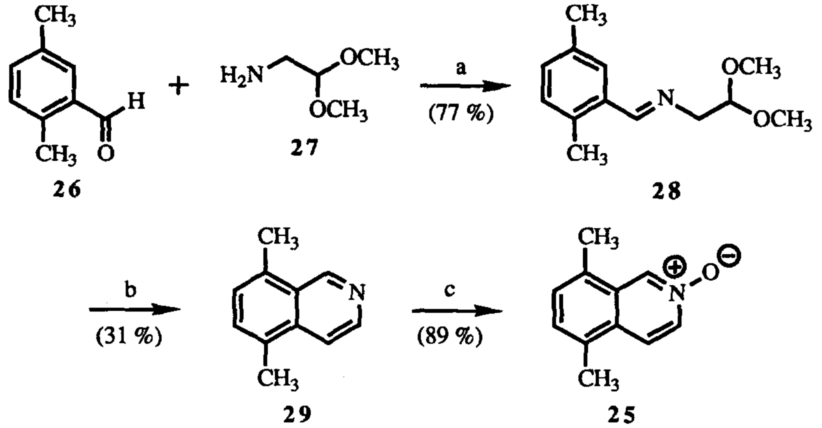
2 R= CH_3
20 R= H
21 R= CH_2Ph

22 R= CH_3
23 R= H
24 R= CH_2Ph

a) Acid chloride (SO_2Cl_2, $SOCl_2$, MsCl or TosCl), DMF.

Scheme 5

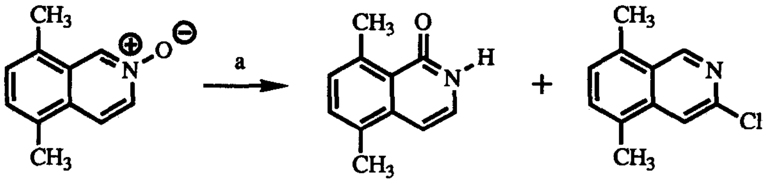
The results mentioned above contradict those obtained by Ochiai and Oae for isoquinoline-N-oxide.[15,16] They isolated 4-tosyloxy- or 4-hydroxy-isoquinolines upon reaction of isoquinoline-N-oxide with p-TosCl. Therefore it was tempting to speculate if this result was influenced by the presence of the methylgroups. To investigate this proposition we synthesized the corresponding substituted isoquinoline-N-oxide (**25**) (Scheme 6). This compound was obtained via condensation of 2,5-dimethyl-benzaldehyde (**26**) and 2-amino-ethanaldimethoxyacetal (**27**) to imine **28**, followed by cyclisization in hot concentrated sulphuric acid to 5,8-dimethylisoquinoline (**29**).[30,31] With m-CPBA **29** was converted to 5,8-dimethylisoquinoline-N-oxide (**25**).[10]



a) Dean-Stark, toluene; b) conc. H_2SO_4, 160 °C; c) m-CPBA, CH_2Cl_2.

Scheme 6

Under the same reaction conditions in which the 3-chloro-ellipticines were obtained, **25** was reacted with p-TosCl (Scheme 7). Two products were formed in this reaction, 5,8-dimethylisoquinolin-1-(2*H*)-one (**30**) as the major product and a small amount of 3-chloro-5,8-dimethylisoquinoline (**31**) (See discussion).



25 **30** **31**

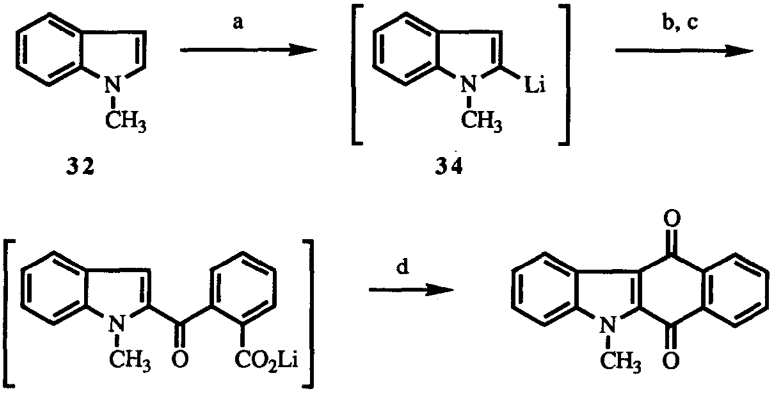
a) TosCl, DMF, 80 °C.

Scheme 7

With several 3-chloro-ellipticines substitution experiments were performed but these resulted only in the formation of tarry substances from which no products could be isolated. This resembles the lack of reactivity observed for 3-chloro-isoquinolines. Here substitution is only accomplished under forcing reaction conditions.[32]

SYNTHESIS AND ACETYLATION OF 5,6,11-TRIMETHYL-5*H*-BENZO[*b*]CARBAZOLE.

Carba analogues of **1** have been synthesized via a variety of methods including Diels-Alder reactions, reaction of 2-alkylindole with cyclic enones and selective lithiation of indole.[33-35] Starting from 1-methylindole (**32**) we obtained via the last method 5-methyl-5*H*-benzo[*b*]carbazole-6,11-quinone (**33**) (Scheme 8, for numbering see Figure 2). Thus **32** was selectively deprotonated with BuLi at C-2 to **34** followed by coupling with phtalic anhydride at low temperatures. The intermediate lithium salt **35** was not isolated but directly cyclized in strong acidic medium to **33** in an overall yield of 44 %.

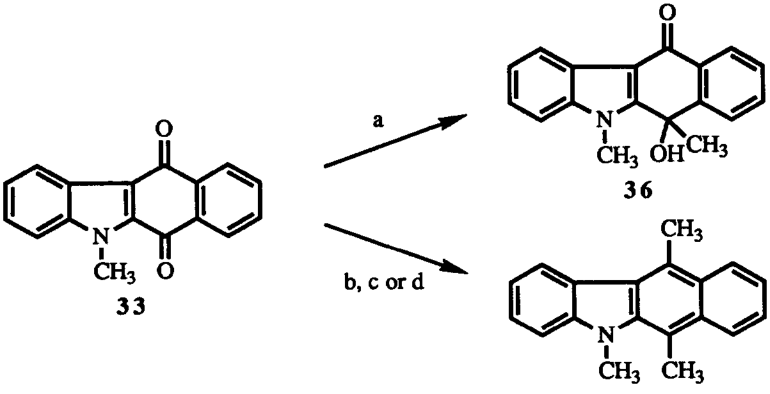


32 **34** **35** **33**

a) BuLi, THF, -15 °C; b) Phtalic anh., THF, -78 °C; c) -78 °C → R.T., 20 h.
d) conc. HCl, reflux (Overall yield: 44 %).

Scheme 8

The quinone **33** was methylated with CH_3Li, CH_3MgI or CH_3MgBr. The carbonylbonds differ in reactivity since C-11 is the carbonylgroup which possesses amidelike properties.[31] This was shown by the synthesis of 5,6-dimethyl-5-hydroxy-5*H*-benzo[*b*]carbazol-11-one (**36**) upon reacting **33** with excess CH_3MgBr followed by quenching the reaction in the cold (-50 °C) with NH_4Cl (Scheme 9). When the reaction was performed at higher temperatures followed by a reduction step with $NaBH_4$ or $SnCl_2/HCl$ the deaza analogue **17** could be isolated.[36-38] Best results were obtained using a combination of CH_3Li and $SnCl_2/HCl$ without a quenching step between methylation and reduction.



33 **36** **17**

a) *i*: CH_3MgBr, THF, -78 °C, *ii*: -78 °C → -50 °C, *iii*: NH_4Cl, 52 %.
b) *i*: CH_3Li, THF, R.T., *ii*: $NaBH_4$, 39 %.
c) *i*: CH_3MgI, THF, -20 °C, *ii*: NH_4Cl, *iii*: $SnCl_2/HCl$, 54 %.
d) *i*: CH_3Li, THF, -100 °C, *ii*: -100 °C → -78 °C, *iii*: $SnCl_2/HCl$, 83 %.

Scheme 9

SELECTIVE ACETYLATION OF 17

In order to obtain selective acetylation at C-2 of **17** a mild acetylating agent must be used since on both C-2 and C-9 the electron density is influenced by the nitrogen atom making both susceptible to electrophilic attack. The only difference between these positions is the length of the mesomeric system. This difference must decide if and where the acetylgroup will be introduced, at C-2 or at C-9.

The acetylgroup can be introduced via a Friedel-Crafts acetylation. The variety of reagents and catalysts aivalable for this reaction offers a good prospect to achieve selective acetylation of **17** although Mabille and Buu-Hoï found that 5*H*-benzo[*b*]carbazole was acetylated on both C-2 and C-9.[39] Also by the presence of the methylgroups high selectivity might be be expected using mild reagents such as Ac_2O and $ZnCl_2$.[40]

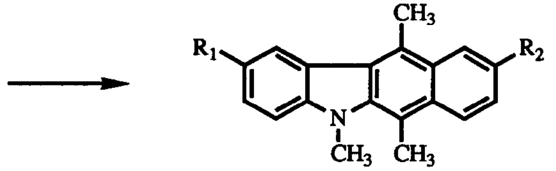
The acetylation reactions of **17** were performed on a small scale using AcCl and Ac_2O as acetylating agents in combination with several catalysts to find the optimal conditions for selective acetylation (Table 1). According to TLC analysis both mono- (**37**) and disubstituted (**38**) products were formed in the reactions. No mono acetylation product at C-9 (**39**) could be identified suggesting that this position reacts only after acetylation at

C-2 has occurred. From table 1 it is clear that selective acetylation is possible using $ZnCl_2$ and Ac_2O in nitrobenzene and diacetylation can be achieved in $CHCl_3$. Furthermore in most of the reactions both products are formed which is indicative for the minor difference in electron density of C-2 and C-9. The formation of a single product in nitrobenzene can be attributed to the formation of a large complex composed of catalyst, solvent and reagent which experiences steric hindrance from the 11-methylgroup when acetylating at C-9.[41]

Table 1

Reaction conditions for the acetylation of **17**

17



37 R_1= Ac, R_2= H
38 R_1= R_2= Ac
39 R_1= H, R_2= Ac

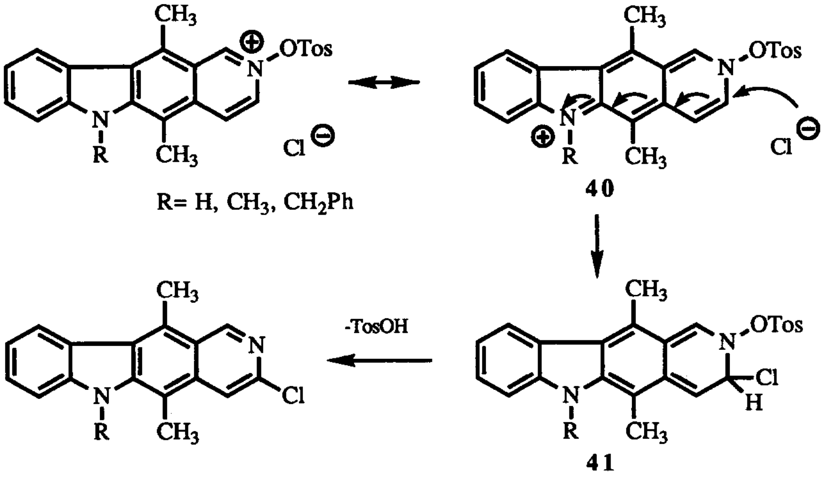
Reagent	Catalyst	Solvent	Temperature and duration	Products according to TLC	Yield [1] (%)
Ac_2O	---	$CHCl_3$	reflux, 5 days	---	---
Ac_2O	---	DMF	70 °C, 2 hour	---	---
Ac_2O	pTosOH	CH_2Cl_2	RT, 5 days	37, 38	---
Ac_2O	AcOH	CH_2Cl_2	0 °C - reflux, 4 days	---	---
Ac_2O	AcOH	AcOH	reflux, 3 days	37, 38	---
Ac_2O	$ZnCl_2$	$CHCl_3$	reflux, 0.5 hour	38	45
Ac_2O	$ZnCl_2$	Ac_2O	70 °C, 4 days	37, 38	---
Ac_2O	$ZnCl_2$	$PhNO_2$	0 °C, 4 hours	37	85
Ac_2O	$ZnCl_2$/AcOH	CH_2Cl_2	reflux, 4 days	37, 38	---
Ac_2O	$ZnCl_2$/AcOH	DMF	140 °C, 3 days	---	---
AcCl	Pyridine	CH_2Cl_2	RT, 5 days	---	---
AcCl	Pyridine	$CHCl_3$	reflux, 5 hours	37, 38	---
AcCl	Pyridine	Pyridine	90 °C, 4 hours	38	---
AcCl	$ZnCl_2$	CH_2Cl_2	RT, 2 days	---	---
AcCl	$AlCl_3$	THF	0 °C, 1 hour	tar	---
AcCl/Ac_2O	$ZnCl_2$	CH_2Cl_2	RT, 27 d	37, 38	---

1. Yield not determined unless given

Several attempts were made to synthesize the 2-hydroxy derivative from **37** via a Baeyer-Villiger rearrangement of the acetyl group but none of them was successful.[31] In all instances tarry residues were formed probably as a result of oxidation of the aromatic system.

DISCUSSION

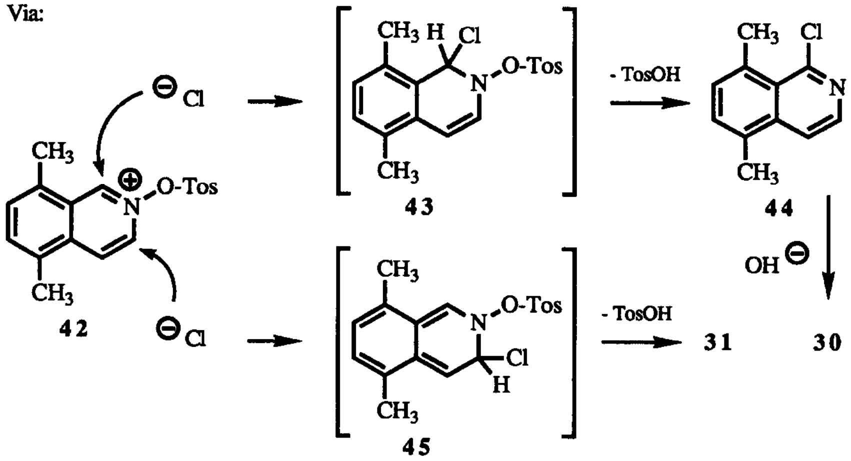
The behaviour of ellipticine-N-oxides towards p-TosCl differs from the modelsystem **25** and both differ from the reaction of isoquinoline-N-oxide with p-TosCl. The positive charge in the ellipticine oxides **2**, **20** and **21** is partially delocalized (**40**) which in combination with steric hindrance by the 11-methylgroup and the 2-tosyloxygroup, are making C-1 unattractive for a reaction by the chloride-ion (Scheme 10). Alternatively the chloride-ion reacts with **40** at C-3 to form the intermediate **41**. Finally TosOH is eliminated from **41** to produce the 3-chloro-ellipticines **22** - **24**.



Scheme 10

In the reaction of **42** with p-TosCl the chloride-ion can add to both C-1 and C-3 since both addition products are isolated (Scheme 11). Here addition to C-1 is preferred since the aromaticity of the benzene ring is not disturbed. Upon elimination of TosOH from **43** the 1-chloro-5,8-dimethylisoquinoline (**44**) is formed which under the conditions of work up with hydroxide is rapidly converted to the isoquinolinone **30**. For addition to C-3 the aromaticity of the benzenering must be strongly disturbed leading to a highly reactive quinodimethanelike intermediate **45**. Subsequent detosylation leads to 3-chloro-5,8-dimethylisoquinoline (**31**) which is further unreactive towards the reaction conditions. Thus for **42** addition to C-1 is preferred over C-3 despite the more crowded surrounding of C-1.

A remarkable aspect of this reaction is that no shift of the tosylgroup is observed in contrast with the mechanistic studies of Ochiai and Oae.[15,16] The difference in observations are probably caused by the different solvents used. Ochiai and Oae performed their reactions in CH_2Cl_2 while DMF is used in this work. DMF has the ability to act as a base by deprotonation of the intermediate adduct immediately after its formation thereby preventing the shift of the tosyloxygroup to C-4.



Scheme 11

ACKNOWLEDGEMENT

The ellipticine used for this research was a generous gift by the Natural Products Branch division of Cancer Treatment, N.C.I., through the courtesy of dr. M. Suffness. We gratefully acknowledge dr. P. Lelieveld and dr. Peters for testing several of the ellipticine derivatives described for their antitumour activity.[42]

ANTITUMOUR ACTIVITY

The compounds **17**, **23** and **37** were tested for their antitumour activity and they showed a comparable rather low activity against an *in vitro* culture of WiDR (IC_{50} for **17**= 3.0 μg/ml and IC_{50} for **37**= 3.2 μg/ml).[43] This result suggests that the pyridine nitrogen atom in ellipticine is a condition for useful antitumour activity. The antitumour activity of **23** was tested against an *in vitro* culture of L1210 cells but it proved to be inactive.

EXPERIMENTAL

General remarks and materials

Infrared spectra (IR) were recorded on a Perkin Elmer 1310 spectrophotometer and the absorptions are given in cm^{-1}. Proton nuclear resonance (^{1}H-N.M.R.) spectra were recorded on Brucker WM 250 and AC 200 instruments. Chemical shifts are given in ppm downfield of tetramethylsilane (TMS). Mass spectra were obtained with a Varian Matt-711 spectrometer and relative intensities are given in percentages. Flash chromatography was performed on silicagel 60 (230 - 390 mesh). Thin layer chromatography was carried out on silica coated plastic sheets (Merck silicagel 60 F_{254}). Melting points are uncorrected. Dry solvents were obtained by distillation from an appropriate drying agent. 6-Methylellipticine (**18**)[10], 6-benzylellipticine (**19**)[8], 6-methylellipticine-N-oxide (**2**)[10], 1-Methylindole (**32**)[44] and 5,8-dimethylisoquinoline (**29**)[45] were synthesized according tot standard procedures.

General procedure for synthesis of ellipticine-N-oxides

To a solution of the appropriate ellipticine in CH_2Cl_2 (25 ml) at 0 °C was added m-CPBA (1.5 eq). The solution was stirred for 6 h then a saturated aqueous solution of $NaHCO_3$ (50 ml) was added and after 0.5 h the organic layer was separated. The waterlayer was extracted with CH_2Cl_2 (3 x 25 ml) and the combined organic fractions were washed with saturated aqueous solution of $NaHCO_3$ (2 x 50 ml), water (2 x 50 ml), brine (2 x 50 ml) and dried ($MgSO_4$). The residue obtained after filtration was subjected to flash chromatography (silica, eluent: $CHCl_3$/MeOH; 100/0, 99/1, 98/2, 95/5, 90/10, v/v).

*Ellipticine-N-oxide (**20**)*

Yield: 237 mg (90 %). M.p. (EtOH): 212-8 °C. Yellow needles. I.R. (KBr): 3500-3100, 2950, 1600, 1575, 1410, 1240, 1180 cm^{-1}. ^{1}H-N.M.R. (DMSO-D_6, 250 MHz): 2.78 (s, 3H, 5-CH_3), 3.07 (s, 3H, 11-CH_3), 7.26 (dt, 1H, J_1= 1.8 Hz, J_2= 7.0 Hz, H-9), 7.55 (m, 2H, H-7 and H-8), 8.03 (d, 1H, J= 7.4 Hz, H-4), 8.10 (dd, 1H, J_1= 1.3 Hz, J_2= 7.4 Hz, H-3), 8.35 (d, 1H, J= 7.9 Hz, H-10), 9.14 (d, 1H, J= 1.1 Hz, H-1), 11.49 (s, 1H, H-6). The signal of H-6 (s, 11.49 ppm) disappeared upon the addition of D_2O.

*6-Benzylellipticine-N-oxide (**21**)*

Yield: 79 mg (73 %). M.p. (EtOH): 200-2 °C. Yellow needles. I.R. ($CHCl_3$): 2960, 1580, 1470, 1445, 1390, 1345, 1180, 1165, 1010 cm^{-1}. ^{1}H-N.M.R. ($CDCl_3$, 200 MHz): 2.73 (s, 3H, 5-CH_3), 3.18 (s, 3H, 11-CH_3), 5.60 (s, 2H, 6-CH_2), 7.16 (dd, 1H, J_1= 2.2 Hz, J_2= 7.8 Hz, H-7), 7.29 (m, 6H, 5 x Ph-H and H-9), 7.54 (dt, 1H, J_1= 1.1 Hz, J_2= 7.7 Hz, H-8), 7.90 (d, 1H, J= 7.6 Hz, H-4), 8.13 (dd, 1H, J_1= 1.8 Hz, J_2= 7.5 Hz, H-3), 8.38 (d, 1H, J= 7.5 Hz, H-10), 9.24 (d, 1H, 1.8 Hz, H-1).

General procedure for synthesis of 3-chloro-ellipticines

A solution of the N-oxide in dry DMF (15 ml) is heated to 80 °C under an atmosphere of dry nitrogen. Then p-TosCl (6 eq) is added and the mixture is stirred for 6 h at 80 °C. The reaction is stopped by carefully pouring the solution into an aqueous saturated solution of $NaHCO_3$ (50 ml) under vigorous stirring. After stirring for 0.5 h the solution is extracted with $CHCl_3$ (3 x25 ml). The combined organic fractions are successively washed with water (2 x 100 ml), brine (2 x 100 ml) and dried ($MgSO_4$). After filtration and evaporation of the solvent the residue was subjected to flash chromatography (silica, eluent; $CHCl_3$/EtOH: 100/0, 99/1, 98/2, 95/5, v/v).

*3-Chloro-6-methylellipticine (**22**)*

Yield: 33 mg (56 %). M.p. (EtOH): 245-7 °C, subl. Yellow needles. I.R. ($CHCl_3$): 2920, 2850, 1585, 1470, 1385, 1315, 1105, 850 cm^{-1}. ^{1}H-N.M.R. (250 MHz, $CDCl_3$): 2.94 (s, 3H, 5-CH_3), 3.13 (s, 3H, 11-CH_3), 4.07 (s, 3H, 6-CH_3), 7.30 (t, 1H, J= 7.3 Hz, H-9), 7.37 (d, 1H, J= 8.2 Hz, H-7), 7.57 (t, 1H, J= 7.5 Hz, H-8), 7.88 (s, 1H, H-4), 8.27 (d, 1H, J= 7.8 Hz, H-10), 9.38 (s, 1H, H-1). NOE: irradiation at the signal of 5-CH_3 (s, 2.94 ppm) showed a nOe-effect on both 6-CH_3 (s, 4.07 ppm) and H-4 (s, 7.88 ppm): irradiation at the signal of 11-CH_3 (s, 3.13 ppm) showed a nOe-effect on both H-1 (s, 9.38 ppm) and H-10 (d, 8.27 ppm). Mass (EI): 296 (12), 294 (32), 279 (15). Acc. mass: Calc. for $C_{18}H_{15}ClN_2$: 294.0924; Observed: 294.0929.

*3-Chloro-ellipticine (**23**)*

Yield: 24 mg (43 %). M.p. (EtOH): 343-5 °C, dec.Yellow needles. I.R. ($CHCl_3$): 3600-3300, 3470, 3000, 2920, 2850, 1590, 1485, 1460, 1370, 1260, 1140, 1110, 855 cm^{-1}. ^{1}H-N.M.R. (250 MHz, DMSO-D_6): 2.72 (s, 3H, 5-CH_3), 3.19 (s, 3H, 11-CH_3), 7.27 (m, 1H, H-9), 7.56 (m, 2H, H-7, H-8), 7.93 (s, 1H, H-4), 8.33 (d, 1H, J= 7.5 Hz, H-10), 9.48 (s, 1H, H-1), 11.45 (s, 1H, H-6). NOE: irradiation at the signal of 5-CH_3 (s, 2.72 ppm) showed a nOe-effect both H-4 (s, 7.93 ppm) and H-6 (s, 11.45 ppm): irradiation at the signal of 11-CH_3 (s, 3.19 ppm) showed a nOe-effect on both H-1 (s, 9.48 ppm) and H-10 (d, 8.33 ppm). Mass (EI): 280 (100), 265 (14), 243 (9), 229 (9). Acc. mass: Calc. for $C_{17}H_{13}ClN_2$: 280.0767; Observed: 280.0761.

*3-Chloro-6-benzylellipticine (**24**)*

Yield: 30 mg (81 %). M.p. (EtOH): 217-21 °C. Yellow needles. I.R. ($CHCl_3$): 3000, 1585, 1465, 1390, 1350, 1190, 1120, 845 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.78 (s, 3H, 5-CH_3), 3.28 (s, 3H, 11-CH_3), 5.75 (s, 2H, 6-CH_2), 7.18 (d, 1H, J= 7.5 Hz, H-7), 7.30 (m, 6H, H-9, 5 x Ph-H), 7.52 (t, 1H, J= 7.7 Hz, H-8), 7.89 (s, 1H, H-4), 8.39 (d, 1H, J= 7.8 Hz, H-10), 9.49 (s, 1H, H-1). Acc. mass: Calc. for $C_{24}H_{19}ClN_2$: 370.1237; Observed: 370.1242.

*Synthesis of imine **28***

To a solution of **26** (4.4 gr, 33 mmol) in toluene (200 ml) at reflux was added during 1 h a solution of **27** (3.6 gr, 35 mmol) in toluene (50 ml). The water was removed via a Dean-Stark trap. After 6 h of reflux extra **27** (1.5 gr, 14 mmol) was added and the solution was stirred at reflux for an additional 3 h. Toluene was removed by distillation at atmospheric pressure and the product was distilled under reduced pressure. B.p. : 118-23 °C (0.4 mm Hg). I.R. ($CHCl_3$): 3000, 2930, 2840, 1635, 1490, 1450, 1375, 1130, 1070 cm^{-1}. ^{1}H-N.M.R. (60 MHz, $CDCl_3$ + TMS): 2.30 (s, 3H, 2-CH_3), 2.45 (s, 3H, 5-CH_3), 3.41 (s, 6H, 2 x OCH_3), 3.78 (d, 2H, J= 5 Hz, CH_2), 4.70 (t, 1H, J= 5 Hz, $C\underline{H}(OCH_3)_2$, 7.70 (s, 1H, H-6), 7.15 (s, 1H, H-4), 7.06 (s, 1H, H-3), 8.51 (s, 1H, -CH=N).

*5,8-dimethylisoquinoline (**29**)*

To concentrated H_2SO_4 (50 ml) at 160 °C under an atmosphere of dry nitrogen was added slowly a solution of **21** (1.13 gr, 5.1 mmol) in dry MeOH (5 ml). The reaction mixture was stirred at 160 °C for 2 h, cooled to R.T. and poured carefully on to crushed ice (250 ml). The resulting mixture cautiously was neutralized with solid NaOH to pH 9. The product was removed from the black solution by steamdestillation. The product was extracted from the distillate with ether (3 x 50 ml) and the combined organic fractions were washed with brine (2 x 50 ml) and dried ($MgSO_4$). Evaporation of the solvent left the isoquinoline as a colourless oil (250 mg, 31 %). I.R. ($CHCl_3$): 3040, 2960, 2860, 1610, 1590, 1580, 1490, 1460, 1440, 1385, 1260, 1030 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.63 (s, 3H, 5-CH_3), 2.76 (s, 3H, 8-CH_3), 7.27 (d, 1H, J= 7.0 Hz, H-7), 7.40 (d, 1H, J= 7.1 Hz, H-6), 7.76 (d, 1H, J= 5.9 Hz, H-4), 8.58 (d, 1H, J= 5.9 Hz, H-3), 9.45 (s, 1H, H-1). Mass (EI): 157 (100), 156 (36), 142 (52). Acc. mass: Calc. for $C_{11}H_{11}N$: 157.0890; Observed: 157.0891.

*5,8-Dimethylisoquinoline-N-oxide (**25**)*

To a solution of **29** (173 mg, 1.1 mmol) in CH_2Cl_2 (25 ml) was added a solution of m-CPBA (250 mg, 85 %, 1.2 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 5 h before extra m-CPBA (100 mg, 85 %, 0.5 mmol) was added. The resulting solution was stirred for an additional 16 h. A saturated aqueous solution of $NaHCO_3$ (25 ml) was added and stirring was continued for 0.5 h. The organic fraction was separated and the remaining fraction washed with CH_2Cl_2 (2 x 25 ml). The combined organic fractions were washed with water (2 x 25 ml), brine (2 x 25 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: $CHCl_3$/MeOH; 95/5, 90/10, 85/15, 80/20, v/v) which gave the N-oxide **25** (170 mg, 89 %). M.p. (EtOH): 146-9 ℃. White needles. I.R. ($CHCl_3$): 3000, 2985, 2925, 1580, 1455, 1375, 1260, 1020, 955, 820 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 2.61 (s, 6H, 5-CH_3 en 8-CH_3), 7,32 (s, 2H, H-6, H-7), 7.82 (d, 1H, J= 7.2 Hz, H-4), 8.24 (dd, 1H, J_1= 1.5 Hz, J_2= 7.2 Hz, H-3), 9.03 (d, 1H, J= 1.3 Hz, H-1).

*Reaction of **25** with p-TosCl*

To a solution of **25** (35 mg, 0.2 mmol) in dry DMF (1.5 ml) at 80 ℃ under an atmosphere of dry nitrogen was added a solution of p-TosCl (100 mg, 0.6 mmol) in dry DMF (1 ml). The solution turned immediately brown and was stirred for 4 h. Then extra p-TosCl (60 mg, 0.6 mmol) was added and the reaction mixture was stirred for an additional 72 h. After cooling to R.T. the solution was poured into a saturated aqueous solution of $NaHCO_3$ (25 ml) and stirred for 0.5 h. The mixture was extracted with ether (3 x 20 ml) and CH_2Cl_2 (3 x 20 ml). The combined organic fractions were washed with water (2 x 50 ml), brine (2 x 50 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: $CHCl_3$/MeOH; 0/100, 5/95, v/v) to give two products 5,8-dimethylisoquinolin-1-(2*H*)-one (**30**, 22 mg, 63 %) and 3-chloro-5,8-dimethylisoquinoline (**31**) both as an oil. The fraction of **31** was partially polluted. I.R. of **30** ($CHCl_3$): 3410, 3050, 2950, 2920, 2850, 1640, 1580, 1455, 1375, 1320, 1260, 1100, 1015, 890, 820, 695 cm^{-1}. ^{1}H-N.M.R. of **30** (200 MHz, $CDCl_3$): 2.47 (s, 3H, 5-CH_3), 2.89 (s, 3H, 8-CH_3), 6.58 (d, 1H, J= 7.3 Hz, H-4), 7.07 (d, 1 H, J= 9.0 Hz, H-6), 7.16 (d, 1H, J= 8.8 Hz, H-7), 7.34 (d, 1H, J= 7.7 Hz, H-3). I.R. of **31** ($CHCl_3$): 3040, 2960, 2920, 2850, 1600, 1570, 1460, 1375, 1255, 1100, 1090, 1010, 860 cm^{-1}. ^{1}H-N.M.R. of **31** (200 MHz, $CDCl_3$): 2.60 (s, 3H, 5-CH_3), 2.74 (s, 3H, 8-CH_3), 7.28 (d, 1H, J= 7.1 Hz, H-6), 7.41 (d, 1H, J= 7.0 Hz, H-7), 7.81 (s, 1H, H-4), 9.23 (s, 1H, H-1).

*5-Methyl-5H-benzo[b]-carbazole-6,11-dione (**33**)*

To a solution of **32** (1.3 gr, 10 mmol) in THF (50 ml) under an atmosphere of dry nitrogen at -15 ℃ was added a solution of BuLi in hexane (8 ml, 1.6 M). The solution was heated to reflux for a period of 5 minutes and cooled to R.T. and a white a precipitate of 2-lithio-1-methylindole (**34**) was formed. A solution of phtalic anhydride (1.8 gr, 12 mmol) in THF (40 ml) was prepared under an atmosphere of dry nitrogen and cooled to -78 ℃. To this solution the suspension of **34** was added via a syringe. During the next 20 h the resulting solution was slowly warmed to R.T. The reaction was stopped by the addition of water (10 ml) and neutralized to pH ~ 7. After concentrating to about 50 ml concentrated HCl (25 ml) was added. The resulting mixture was heated to reflux during 4 h and after cooling to R.T. extracted with CH_2Cl_2 (3 x 50 ml). The combined organic fractions were washed with water (2 x 50 ml) and dried ($MgSO_4$). The residue obtained after evaporation of the solvent was subjected to flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 90/10, 75/25, 60/40, v/v) to give pure **33** (1.7 gr, 44 %). M.p. (EtOH): 206-8 °C (Lit. 213 °C[46]), orange needles. I.R. ($CHCl_3$): 3050, 3000, 2930, 1650, 1590, 1510, 1475, 1390, 1260, 1230, 1055, 950 cm^{-1}. ^1H-N.M.R. ($CDCl_3$, 200 MHz): 4.20 (s, 3H, 5-CH_3), 7.37 (m, 3H, H-2, H-3, H-4), 7.67 (m, 2H, H-8, H-9), 8.15 (m, 2H, H-7, H-10), 8.39 (dd, 1H, J_1= 1.6 Hz, J_2= 7.1 Hz, H-1). Mass (EI): 262 (15), 261 (100), 260 (32), 232 (11), 204 (10). Acc. mass: Calc. for $C_{17}H_{11}NO_2$: 261.0790; observed: 261.0793.

*6-Hydroxy-5,6-dimethyl-5H-benzo[b]-carbazol-11-one (**36**)*
A solution of CH_3MgBr (3 ml, 3 M) in ether was added to a solution of **33** (52 mg, 0.2 mmol) in THF under an atmosphere of dry nitrogen at -78 °C. The reaction mixture was stirred for 2 h at -78 °C during which the colour changed from red to yellow. Then the solution was warmed to -50 °C and the reaction was stopped by the addition of a saturated aqueous solution of NH_4Cl (1 ml) and solid NH_4Cl (0.5 gr). The mixture was warmed to R.T. before THF (15 ml) and enough water were added to obtain two clear layers. The organic layer was separated, washed with brine (2 x 25 ml) and dried ($MgSO_4$). The product was purified by flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 95/5, 90/10, 85/15, 75/25, v/v) giving pure **36** (26 mg, 52 %). M.p. (petroleum ether 60-80): 125-8 °C, dec. White needles. I.R. ($CHCl_3$): 3370, 3050, 2990, 2920, 2840, 1620, 1590, 1475, 1460, 1390, 1230, 1125, 1075, 1035, 890 cm^{-1}. ^1H-N.M.R. ($CDCl_3$, 200 MHz): 1.70 (s, 3H, 6-CH_3), 3.93 (s, 3H, 5-CH_3), 4.23 (bs, 1H, 6-OH), 6.96 (d, 1H, J= 7.9 Hz, H-4), 7.08 (t, 1H, J= 7.7 Hz, H-2), 7.19 (m, 2H, H-8, H-9), 7.40 (t, 1H, J= 7.6 Hz, H-3), 7.53 (d, 1H, J= 7.7 Hz, H-10), 7.74 (d, 1H, J= 7.9 Hz, H-7), 8.08 (d, 1H, J= 7.0 Hz, H-1). Upon the addition of D_2O the singlet at 4.23 ppm (6-OH) collapsed. N.O.E.: Irradiation at the signal of 6-CH_3 (1.70 ppm) showed a nOe-effect on 5-CH_3 (s, 3.93 ppm) and H-7 (d, 7.74 ppm) and a negative effect on 6-OH (s, 4.23 ppm): Irradiation at the signal of 5-CH_3 (3.93 ppm) showed a nOe-effect on both 6-CH_3 (s, 1.70 ppm) and H-4 (d, 6.96 ppm).

*Synthesis of **17** by methylation with CH_3Li followed by reduction with $NaBH_4$*
To a solution of **33** (52 mg, 0.2 mmol) in THF (10 ml) under an atmosphere of dry nitrogen at -20 °C was added a freshly prepared solution of CH_3Li (1 ml, 1 M). The resulting solution was stirred for a period of 2 h at -20 °C and 2 h at R.T. Then the mixture was poured into a suspension of $NaBH_4$ (1 gr, 26 mmol) in EtOH (50 ml) and the resulting mixture was stirred for 1 h before an aqueous solution of HCl (1N, 50 ml), ether (50 ml) and THF (50 ml) were added. The organic layer was separated and washed successively with a saturated aqueous solution of $NaHCO_3$ (50 ml), water (2 x 50 ml) and brine (50 ml) and dried ($MgSO_4$). The product was purified by flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 95/5, 90/10, 85/15, 75/25, v/v) giving **17** (20 mg, 39 %). For spectral data of **17** see below.

*Synthesis of **17** by methylation with CH_3MgI followed by reduction with $SnCl_2$*
To a solution of **33** (53 mg, 0.2 mmol) in THF (10 ml) under an atmosphere of dry nitrogen at -20 °C was added a solution of CH_3MgI in ether (3 ml, 3 M). The reaction mixture was stirred for 2 h at -20 °C followed by 2 h at R.T. The reaction was stopped by the addition of a saturated aqueous solution of NH_4Cl (5 ml) after which the mixture was poured directly into a suspension of $SnCl_2{\cdot}2H_2O$ (8.9 mmol) in ether (25 ml) and concentrated HCl (25 ml). After 1 h of vigorous stirring the product was isolated by extraction with $CHCl_3$ (3 x

50 ml). The combined organic fractions were washed with brine (2 x 50 ml) and dried ($MgSO_4$). The residue obtained after filtration and evaporation was subjected to flash chromatography (silica, eluent: petroleum ether 60-80) to give pure **17** (28 mg, 54 %). For spectral data of **17** see below.

Synthesis of 17 by methylation with CH_3Li followed by reduction with $SnCl_2$

A solution of **33** (520 mg, 2 mmol) in THF (50 ml) under dry nitrogen was cooled to -100 °C before a solution CH_3Li in ether (3 ml, 3M) was added. The reaction mixture was allowed to warm to -78 °C and stirred for 3 h at this temperature. During this period a suspension of $SnCl_2{\bullet}2H_2O$ (4.3 gr, 20 mmol) in ether (50 ml) and concentrated HCl (50 ml) was prepared. Then the reaction mixture was carefully poured into the suspension of $SnCl_2$ and vigorously stirred for 2 h. The product was isolated by extraction with $CHCl_3$ (3 x 100 ml). The combined organic fractions were washed with a saturated solution of $NaHCO_3$ (2 x 100 ml), water (2 x 100 ml) and brine (2 x 100 ml) and dried ($MgSO_4$). The residue obtained after evaporation of the solvent was subjected to flash chromatography (silica, eluent: petroleum ether 60-80) to give **17** (429 mg, 83 %). M.p. (petroleum ether 60-80): 179-81 °C. I.R. ($CHCl_3$): 3070, 3000, 2950, 2920, 1590, 1475, 1380, 1290, 1235, 1145, 1090, 990 cm^{-1}. ^{1}H-N.M.R. (200 MHz, $CDCl_3$): 3.12 (s, 3H, 6-CH_3), 3.21 (s, 3H, 11-CH_3), 4.10 (s, 3H, 5-CH_3), 7.27 (dt, 1H, J_1= 1.1 Hz, J_2= 7.5 Hz, H-2), 7.38 (d, 1H, J= 8.0 Hz, H-4), 7.47 (dt, 1H, J_1= 1.5 Hz, J_2= 8.2 Hz, H-3), (7.56, dt, 1H, J_1= 1.4 Hz, J_2= 6.6 Hz, H-8), 7.56 (dt, 1H, J_1= 1.4 Hz, J_2= 6.6 Hz, H-9), 8.21 (dd, 1H, J_1= 1.6 Hz, J_2= 8.1 Hz, H-7), 8.34 (dd, 1H, J_1= 1.5 Hz, J_2= 7.7 Hz, H-10), 8.38 (d, 1H, J= 7.2 Hz, H-1). N.O.E.: Irradiation at the signal of 5-CH_3 (4.10 ppm) showed a nOe-effect on both 6-CH_3 (s, 3.12 ppm) and H-4 (d, 7.38 ppm): Irradiation at the signal of 6-CH_3 (3.12 ppm) showed a nOe-effect on both 5-CH_3 (s, 4.10 ppm) and on H-7 (d, 8.21 ppm): Irradiation at the signal of 11-CH_3 (3.21 ppm) showed a nOe-effect on both H-10 (d, 8.34 ppm) and on H-1 (d, 8.38 ppm). Mass (EI): 260 (23), 259 (100), 258 (16), 244 (34), 129 (11). Acc. mass: Calc. for $C_{19}H_{17}N$: 259.1361 ; Observed: 259.1373.

Regioselective acetylation of 17

In nitrobenzene (25 ml) **17** (115 mg, 0.6 mmol) was dissolved and the solution was cooled to 0 °C. Then Ac_2O (1 ml) and $ZnCl_2{\bullet}2Et_2O$ (1 ml) were added and the resulting mixture was stirred for 6 h at 0 °C. A saturated aqueous solution of $NaHCO_3$ was added and stirring was continued until the evolution of CO_2 stopped. The product was isolated by extraction with ether (3 x 50 ml). The combined organic fractions were successively washed with saturated aqueous solution of $NaHCO_3$ (2 x 50 ml) and brine (2 x 50 ml) and dried ($MgSO_4$). The ether was removed by evaporation and the nitrobenzene by distillation in vacuo. The residue was dissolved in a suspension of silica (1.5 gr) in $CHCl_3$ (5 ml). Renewed evaporation of the solvent gave a residue which was subjected to flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 98/2, 96/4, 94/6, 92/8, 85/15, v/v) giving pure **37** (154 mg, 85 %). M.p. (EtOAc): 183-5 °C. Brown needles. I.R. ($CHCl_3$): 3070, 2990, 2950, 1660, 1585, 1490, 1455, 1360, 1295, 1255, 1105, 1065, 905, 810 cm^{-1}. ^{1}H-N.M.R. ($CDCl_3$, 200 MHz): 2.68 (s, 3H, 2-$COCH_3$), 2.99 (s, 3H, 6-CH_3), 3.09 (s, 3H, 11-CH_3), 3.97 (s, 3H, 5-CH_3), 7.22 (d, 1H, J= 8.6 Hz, H-4), 7.51 (dt, 1H, J_1= 1.5 Hz, J_2= 6.6 Hz, H-9), 7.56 (dt, 1H, J_1= 1.5 Hz, J_2= 6.6 Hz, H-8), 8.08 (dd, 1H, J_1= 1.7 Hz, J_2= 8.7 Hz, H-3), 8.13 (dd, 1H, J_1= 1.6 Hz, J_2= 7.6 Hz, H-7), 8.27 (dd, 1H, J_1= 1.5 Hz, J_2= 6.7 Hz, H-10), 8.79 (d, 1H, J=1.7 Hz, H-1). Double resonance: upon irradiation at the signal of H-4 the signal of H-3 (8.08 ppm) changed into a doublet; upon irradiation at the signal of H-10 (8.27 ppm) the signal of H-9 (7.51 ppm) changed into a doublet; upon irradiation at the signal of H-7 (8.13 ppm) the signal of H-8 (7.56 ppm) changed into a doublet. N.O.E.: Irradiation at the signal of 2-$COCH_3$ (2.68 ppm) showed a nOe-effect on both H-1 (d, 8.79 ppm) and H-3 (dd, 8.08 ppm); Irradiation at the signal of 6-CH_3 (2.99 ppm) showed a nOe-effect on both 5-CH_3 (s, 3.97 ppm) and H-7 (d, 8.13 ppm); Irradiation at the signal of 5-CH_3 (3.97 ppm) showed a nOe-effect on both 6-CH_3 (s, 2.99 ppm) and on H-4 (d, 7.22 ppm). Mass (EI): 302 (40), 301 (100), 286 (28), 258 (28), 243 (9), 143 (10). Acc. mass: Calc. for $C_{21}H_{19}NO$: 301.1467; Observed: 301.1459.

Diacetylation of ***17***

To a solution of **17** (20 mg, 77 µmol) in $CHCl_3$ (10 ml) was added Ac_2O (1 ml) and $ZnCl_2 \cdot 2Et_2O$ (1 ml). During 0.5 h the reaction mixture was heated to reflux then carefully poured into a saturated aqueous solution of $NaHCO_3$ (50 ml). After the evolution of CO_2 had ceased $CHCl_3$ (50 ml) was added and the organic layer separated. This was successively washed with saturated aqueous solution of $NaHCO_3$ (2 x 50 ml) and brine (2 x 50 ml) and dried ($MgSO_4$). After concentrating to a few millilitres silica (0.5 gr) was added and the remaining solvent was evaporated. The residue was subjected to flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 98/2, 96/4, 94/6, 92/8, 90/10, 85/15, 80/20, 75/25, 50/50, v/v) giving pure **38** (9 mg, 45 %). M.p. (EtOAc): 274-6 ℃. Brown needles. I.R. ($CHCl_3$): 3000, 2920, 1660, 1585, 1355, 1295, 1245, 1105 cm^{-1}. ^{1}H-N.M.R. ($CDCl_3$, 200 MHz): 2.73 (s, 3H, 9-$COCH_3$), 2.78 (s, 3H, 2-$COCH_3$), 3.07 (s, 3H, 6-CH_3), 3.24 (s, 3H, 11-CH_3), 4.12 (s, 3H, 5-CH_3), 7.34 (d, 1H, J= 8.6 Hz, H-4), 8.06 (dd, 1H, J_1= 9.1 Hz, J_2= 1.5 Hz, H-8), 8.17 (dd, 1H, J_1= 8.6 Hz, J_2= 1.5 Hz, H-3), 8.19 (d, 1H, J= 9.1 Hz, H-7), 8.92 (d, 1H, J= 1.4 Hz, H-1), 8.95 (d, 1H, J= 1.5 Hz, H-10). Mass (EI): 344 (25), 343 (100), 328 (28), 315 (73), 301 (25), 300 (23). Acc. mass: Calc. for $C_{23}H_{21}NO_2$: 343.1572; Observed: 343.1579.

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