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Ring D Modifications of Ellipticine. Part 2.‡


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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 model studies 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-acetyllellipticine stimulated us to prepare the corresponding deaza analogue. This compound was synthesised in 2 steps starting from 1-methylindole. Regioselective acetylation at C-2 was accomplished using acetic anhydride and ZnCl₂ as a catalyst. Under a variety of other conditions the 2,9-diacetyl product 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-6H-pyrrolo[4,3-b]carbazole, 1) is well known for its cytostatic activity which was discovered in 1967 (Figure 1). This has led to numerous syntheses which have been reviewed in several papers. From these it is obvious that direct introduction of substituents is restricted to C-1, N-2, C-9 and C-11.

Figure 1

‡ Part 1 published previously in this journal.
In order to functionalize the 11-methyl group an attempt by our group was made to apply well known pyridine-N-oxide chemistry to the pyridocarbazole system since the 11-methyl group is conjugatively analogous to the methyl group in 2-methylpyridine. Upon reacting 6-methylellipticine-N-oxide (2) with Ac₂O the carbazolone derivatives 3 and 4 were isolated instead of the desired 11-functionalized ellipticines (Scheme 1).

```
CH₃
\[\text{N}\]
\[\text{N}\]
\[\text{O}\]
\[\text{+}\]
\[\text{O}^–\]
\[\text{CH₃}\]
\[\text{CH₃}\]
\[\text{2}\]
\[\text{a}\]
\[\text{Ac}_2\text{O}, \text{NaOAc}\]
\[\text{3 R=H}\]
\[\text{4 R=Ac}\]
```

**Scheme 1**

Extending this idea of making the oxygen part of a leaving group, other reactants such as p-TosCl or MsCl can replace Ac₂O for the synthesis of 1-functionalized ellipticines. Our interest was stimulated further by papers which dealt with the reactions of heterocyclic N-oxides with Ac₂O and p-TosCl. Reaction of quinoline-N-oxide with Ac₂O or p-TosCl gave quinolin-2-(H)-one. Isoquinoline-N-oxide reacted in a similar manner with Ac₂O but upon treatment with p-TosCl 4-tosylisoquinoline was isolated instead. Since the ellipticines skeleton 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 ¹⁸O 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). After reaction of the tosyl group with the N-oxide function of 5 to 6 the chloride-ion adds to C-1 (7) whereafter the tosyl group shifts to C-4 (9) via 8 retaining its stereochemical structure. Finally hydrochloric acid eliminates from 9 to give 4-tosylisoquinoline (10).

```
\[\text{5}\]
\[\text{5}\text{Cl}\text{O}\text{Tos}^*\]
\[\text{6}\]
\[\text{6}\text{Cl}\text{O}\text{Tos}^*\]
\[\text{7}\]
\[\text{7}\text{Cl}\text{O}\text{Tos}^*\]
\[\text{8}\text{Cl}\text{O}\text{Tos}^*\]
\[\text{9}\text{Cl}\text{O}\text{Tos}^*\]
\[\text{10}\text{Cl}\text{O}\text{Tos}^*\]
```

**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. Since 9-hydroxyellipticine (11) also showed high antitumour activity, another possibility of antitumour action was proposed. Oxidation of 11 should lead to the formation of a quinonimine which has been shown to react in vitro with ribonucleosides and with amino acids to form oxazolopyridocarbazoles 12 (Scheme 3). Recent developments show a third way in which topoisomerase II is playing a central role.

Serious doubt was raised by Archer et al about the quinonimine theory. They suggested an alternative in which the 5-methyl group plays a central role. Reinvestigation of the available literature concerning the biological activity of ellipticines led them to the conclusion that the 5-methyl group is essential for antitumour action. They therefore synthesized 9-hydroxy-6H-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.

Research performed in our group showed that the 9-hydroxy function is also not a condition for cytostatic activity. We found that 9-acylated ellipticines showed unexpected high antitumour activity. For instance 9-acetyl-6methylellipticine (15) showed an IC50 value against B16 melanoma of 44 ng/ml similar to 9-hydroxy-2-methylellipticinium acetate (16, elliptinium®), the clinically active drug (Figure 2). 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. Therefore the 9-acyllellipticines 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-5H-benzol[b]carbazole (2-deaza-6-methylellipticine, 17) and on the selective acetylation of the latter compound (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$_3$I or PhCH$_2$Br. After treatment of the ellipticines 1, 18 and 19 with m-CPBA, the corresponding N-oxides 20, 2 and 21 were obtained (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.
The results mentioned above contradict those obtained by Ochiai and Oae for isoquinoline-N-oxide.\textsuperscript{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 methyl groups. 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-aminoethanaldimethoxyacetal (27) to imine 28, followed by cyclization in hot concentrated sulphuric acid to 5,8-dimethylisoquinoline (29).\textsuperscript{30,31} With m-CPBA 29 was converted to 5,8-dimethylisoquinoline-N-oxide (25).\textsuperscript{10}

a) Dean-Stark, toluene; b) conc. H\textsubscript{2}SO\textsubscript{4}, 160 °C; c) m-CPBA, CH\textsubscript{2}Cl\textsubscript{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-(2H)-one (30) as the major product and a small amount of 3-chloro-5,8-dimethylisoquinoline (31) (See discussion).
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-5H-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-5H-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 %.

Scheme 7

Scheme 8
The quinone 33 was methylated with CH$_3$Li, CH$_3$MgI or CH$_3$MgBr. The carbonyl bonds differ in reactivity since C-11 is the carbonyl group which possesses amidelike properties.$^{31}$ This was shown by the synthesis of 5,6-dimethyl-5-hydroxy-5H-benzo[b]carbazol-11-one (36) upon reacting 33 with excess CH$_3$MgBr followed by quenching the reaction in the cold (-50 °C) with NH$_4$Cl (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$_3$Li and SnCl$_2$/HCl without a quenching step between methylation and reduction.

![Scheme 9](image)

**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 acetyl group will be introduced, at C-2 or at C-9.

The acetyl group can be introduced via a Friedel-Crafts acetylation. The variety of reagents and catalysts available for this reaction offers a good prospect to achieve selective acetylation of 17 although Mabille and Buu-Hoi found that 5H-benzo[b]carbazole was acetylated on both C-2 and C-9.$^{39}$ Also by the presence of the methyl groups high selectivity might be expected using mild reagents such as Ac$_2$O and ZnCl$_2$.$^{40}$

The acetylation reactions of 17 were performed on a small scale using AcCl and Ac$_2$O 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$_2$O 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 acetyling at C-9.$^{41}$

**Table 1**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature and duration</th>
<th>Products according to TLC</th>
<th>Yield(^1) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac$_2$O</td>
<td>---</td>
<td>CHCl$_3$</td>
<td>reflux, 5 days</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>---</td>
<td>DMF</td>
<td>70 °C, 2 hour</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>pTosOH</td>
<td>CH$_2$Cl$_2$</td>
<td>RT, 5 days</td>
<td>37, 38</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>AcOH</td>
<td>CH$_2$Cl$_2$</td>
<td>0 °C - reflux, 4 days</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>AcOH</td>
<td>AcOH</td>
<td>reflux, 3 days</td>
<td>37, 38</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>ZnCl$_2$</td>
<td>CHCl$_3$</td>
<td>reflux, 0.5 hour</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>ZnCl$_2$</td>
<td>Ac$_2$O</td>
<td>70 °C, 4 days</td>
<td>37, 38</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>ZnCl$_2$</td>
<td>PhNO$_2$</td>
<td>0 °C, 4 hours</td>
<td>37</td>
<td>85</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>ZnCl$_2$/AcOH</td>
<td>CH$_2$Cl$_2$</td>
<td>reflux, 4 days</td>
<td>37, 38</td>
<td>---</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>ZnCl$_2$/AcOH</td>
<td>DMF</td>
<td>140 °C, 3 days</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>AcCl</td>
<td>Pyridine</td>
<td>CH$_2$Cl$_2$</td>
<td>RT, 5 days</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>AcCl</td>
<td>Pyridine</td>
<td>CHCl$_3$</td>
<td>reflux, 5 hours</td>
<td>37, 38</td>
<td>---</td>
</tr>
<tr>
<td>AcCl</td>
<td>Pyridine</td>
<td>Pyridine</td>
<td>90 °C, 4 hours</td>
<td>38</td>
<td>---</td>
</tr>
<tr>
<td>AcCl</td>
<td>ZnCl$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>RT, 2 days</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
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<td>AlCl$_3$</td>
<td>THF</td>
<td>0 °C, 1 hour</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>AcCl/Ac$_2$O</td>
<td>ZnCl$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>RT, 27 d</td>
<td>37, 38</td>
<td>---</td>
</tr>
</tbody>
</table>

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 model system 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-methyl group and the 2-tosyloxy group, 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.

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 benzene ring must be strongly disturbed leading to a highly reactive quinodimethanellike 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 tosyl group 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 CH₂Cl₂ 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 tosyl group to C-4.
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 (IC₅₀ for 17 = 3.0 µg/ml and IC₅₀ 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 (¹H-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 F₂₅₄). Melting points are uncorrected. Dry solvents were obtained by distillation from an appropriate drying agent. 6-Methylellipticine (18) ⁴⁰, 6-benzy llellipticine (19) ⁹, 6-methylellipticine-N-oxide (2) ⁴⁰, 1-Methylindole (32) ⁴⁴ and 5,8-dimethylisoquinoline (29) ⁴⁵ were synthesized according to standard procedures.
General procedure for synthesis of ellipticine-N-oxides
To a solution of the appropriate ellipticine in CH₂Cl₂ (2.5 ml) at 0 °C was added m-CPBA (1.5 eq). The solution was stirred for 6 h then a saturated aqueous solution of NaHCO₃ (50 ml) was added and after 0.5 h the organic layer was separated. The water layer was extracted with CH₂Cl₂ (3 x 25 ml) and the combined organic fractions were washed with saturated aqueous solution of NaHCO₃ (2 x 50 ml), water (2 x 50 ml), brine (2 x 50 ml) and dried (MgSO₄). The residue obtained after filtration was subjected to flash chromatography (silica, eluent: CHCl₃/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. ¹H-N.M.R. (DMSO-D₆, 250 MHz): 2.78 (s, 3H, 5-CH₃), 3.07 (s, 3H, 11-CH₃), 7.26 (dt, 1H, J₁ = 1.8 Hz, J₂ = 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, J₁ = 1.3 Hz, J₂ = 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 D₂O.

6-Benzylellipticine-N-oxide (21)
Yield: 79 mg (73 %). M.p. (EtOH): 200-2 °C. Yellow needles. I.R. (CHCl₃): 2960, 1580, 1470, 1385, 1165, 1010 cm⁻¹. ¹H-N.M.R. (CDCl₃, 200 MHz): 2.73 (s, 3H, 5-CH₃), 3.18 (s, 3H, 11-CH₃), 5.60 (s, 2H, 6-CH₂), 7.16 (dd, 1H, J₁= 2.2 Hz, J₂= 7.8 Hz, H-7), 7.29 (m, 6H, 5 x Ph-H and H-9), 7.54 (dt, 1H, J₁ = 1.1 Hz, J₂ = 7.7 Hz, H-8), 7.90 (d, 1H, J = 7.6 Hz, H-4), 8.13 (dd, 1H, J₁ = 1.8 Hz, J₂ = 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 NaHCO₃ (50 ml) under vigorous stirring. After stirring for 0.5 h the solution is extracted with CHCl₃ (3 x 25 ml). The combined organic fractions are successively washed with water (2 x 100 ml), brine (2 x 100 ml) and dried (MgSO₄). After filtration and evaporation of the solvent the residue was subjected to flash chromatography (silica, eluent; CHCl₃/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. (CHCl₃): 2920, 2850, 1585, 1470, 1385, 1315, 1105, 850 cm⁻¹. ¹H-N.M.R. (250 MHz, CDCl₃): 2.94 (s, 3H, 5-CH₃), 3.13 (s, 3H, 11-CH₃), 4.07 (s, 3H, 6-CH₃), 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-CH₃ (s, 2.94 ppm) showed a nOe-effect on both 6-CH₃ (s, 4.07 ppm) and H-4 (s, 7.88 ppm); irradiation at the signal of 11-CH₃ (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 C₁₈H₁₄ClN₂: 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$_3$ (2.72 ppm) showed a NOe-effect on both H-4 (7.93 ppm) and H-6 (11.45 ppm): irradiation at the signal of 11-CH$_3$ (3.19 ppm) showed a NOe-effect on both H-1 (9.48 ppm) and H-10 (8.33 ppm). Mass (EI): 280 (100), 265 (14), 243 (9), 229 (9). Acc. mass: Calc. for C$_{17}$H$_{11}$N$_2$: 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, 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, 14 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, CH(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$_2$SO$_4$ (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 steam distillation. 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 CH₂Cl₂ (25 ml) was added a solution of m-CPBA (250 mg, 85 %, 1.2 mmol) in CH₂Cl₂ (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 NaHCO₃ (25 ml) was added and stirring was continued for 0.5 h. The organic fraction was separated and the remaining fraction washed with CH₂Cl₂ (2 x 25 ml). The combined organic fractions were washed with water (2 x 25 ml), brine (2 x 25 ml) and dried (MgSO₄). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: CHCl₃/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 °C. White needles. I.R. (CHCl₃): 3000, 2985, 2925, 1580, 1455, 1375, 1260, 1020, 955, 820 cm⁻¹. ¹H-N.M.R. (200 MHz, CDCl₃): 2.61 (s, 6H, 5-CH₃ en 8-CH₃), 7.32 (s, 2H, H-6, H-7), 7.82 (d, 1H, J = 7.2 Hz, H-4), 8.24 (dd, 1H, J₁ = 1.5 Hz, J₂ = 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 °C 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 NaHCO₃ (25 ml) and stirred for 0.5 h. The mixture was extracted with ether (3 x 20 ml) and CH₂Cl₂ (3 x 20 ml). The combined organic fractions were washed with water (2 x 50 ml), brine (2 x 50 ml) and dried (MgSO₄). The residue obtained after filtration and evaporation of the solvent was subjected to flash chromatography (silica, eluent: CHCl₃/MeOH; 0/100, 5/95, v/v) to give two products 5,8-dimethylisoquinolin-1-(2H)-one (30, 22 mg, 63 %) and 3-chloro-5,8-dimethylisoquinoline (31) both as an oil. The I.R. of 31 was partially polluted. I.R. of 30 (CHCl₃): 3400, 3050, 2950, 2920, 2850, 1640, 1580, 1455, 1375, 1320, 1260, 1100, 1015, 890, 820, 695 cm⁻¹. ¹H-N.M.R. of 30 (200 MHz, CDCl₃): 2.47 (s, 3H, 5-CH₃), 2.89 (s, 3H, 8-CH₃), 6.58 (d, 1H, J = 7.3 Hz, H-4), 7.07 (d, 1H, 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 (CHCl₃): 3400, 2960, 2920, 2850, 1600, 1570, 1460, 1375, 1255, 1100, 1090, 1010, 860 cm⁻¹. ¹H-N.M.R. of 31 (200 MHz, CDCl₃): 2.60 (s, 3H, 5-CH₃), 2.74 (s, 3H, 8-CH₃), 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).

**S-Methyl-SH-benzo[b]-carbazole-4,1-dione (32)**

To a solution of 32 (1.3 gr, 10 mmol) in THF (50 ml) under an atmosphere of dry nitrogen at -15 °C 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 °C. 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 CH₂Cl₂ (3 x 50 ml). The combined organic fractions were washed with water (2 x 50 ml) and dried (MgSO₄). The residue obtained after evaporation of the solvent was subjected to flash chromatography (silica, eluent: petroleum ether 60-80/EtOAc; 100/0, 90/10, 80/20, v/v) which gave the N-oxide 25 (170 mg, 89 %). M.p. (EtOH): 146-9 °C. White needles. I.R. (CHCl₃): 3000, 2985, 2925, 1580, 1455, 1375, 1260, 1020, 955, 820 cm⁻¹. ¹H-N.M.R. (200 MHz, CDCl₃): 2.61 (s, 6H, 5-CH₃ en 8-CH₃), 7.32 (s, 2H, H-6, H-7), 7.82 (d, 1H, J = 7.2 Hz, H-4), 8.24 (dd, 1H, J₁ = 1.5 Hz, J₂ = 7.2 Hz, H-3), 9.03 (d, 1H, J = 1.3 Hz, H-1).
75/25, 60/40, v/v) to give pure 33 (1.7 gr, 44%). M.p. (EtOH): 206-8 °C (Lit. 213 °C), orange needles. I.R. (CHCl₃): 3050, 3000, 2930, 1590, 1510, 1475, 1390, 1260, 1230, 1055, 950 cm⁻¹. ¹H-N.M.R. (CDCl₃, 200 MHz): 4.20 (s, 3H, 5-CH₃), 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, J₁= 1.6 Hz, J₂= 7.1 Hz, H-1). Mass (EI): 262 (15), 261 (100), 260 (32), 232 (11), 204 (10). Acc. mass: Calc. for C₁₁H₁₁N₂O₂: 261.0790; observed: 261.0793.

6-Hydroxy-5,6-dimethyl-5H-benzo[b]-carbazol-11-one (36)

A solution of CH₃MgBr (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 NH₄Cl (1 ml) and solid NH₂Cl (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 (MgSO₄). 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. (CHCl₃): 3370, 3050, 2990, 2840, 1620, 1590, 1475, 1460, 1390, 1230, 1125, 1075, 1035, 890 cm⁻¹. ¹H-N.M.R. (CDCl₃, 200 MHz): 1.70 (s, 3H, 6-CH₃), 3.93 (s, 3H, 5-CH₃), 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 D₂O the singlet at 4.23 ppm (6-OH) collapsed N.O.E.: Irradiation at the signal of 6-CH₃ (1.70 ppm) showed a nOe-effect on 5-CH₃ (3.93 ppm) and H-7 (7.74 ppm) and a negative effect on 6-OH (s, 4.23 ppm): Irradiation at the signal of 5-CH₃ (3.93 ppm) showed a nOe-effect on both 6-CH₃ (s, 1.70 ppm) and H-4 (d, 6.96 ppm).

Synthesis of 17 by methylation with CH₃Li followed by reduction with NaBH₄

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 CH₃Li (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 NaBH₄ (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 NaHCO₃ (50 ml), water (2 x 50 ml) and brine (50 ml) and dried (MgSO₄). 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 CH₃MgI followed by reduction with SnCl₂

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 CH₃MgI 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 NH₄Cl (5 ml) after which the mixture was poured directly into a suspension of SnCl₂·2H₂O (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 CHCl₃ (3 x
50 ml). The combined organic fractions were washed with brine (2 x 50 ml) and dried (MgSO₄). 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 CH₃Li followed by reduction with SnCl₂**

A solution of 33 (520 mg, 2 mmol) in THF (50 ml) under dry nitrogen was cooled to -100 °C before a solution of CH₃Li 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 SnCl₂·2H₂O (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 SnCl₂ and vigorously stirred for 2 h. The product was isolated by extraction with CHCl₃ (3 x 100 ml). The combined organic fractions were washed with a saturated solution of NaHCO₃ (2 x 100 ml), water (2 x 100 ml) and brine (2 x 100 ml) and dried (MgSO₄). 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): 179-181 °C. I.R. (CHCl₃): 3070, 3000, 2950, 2920, 1590, 1475, 1380, 1295, 1235, 1145, 1090, 990 cm⁻¹. ¹H-N.M.R. (200 MHz, CDCl₃): 3.12 (s, 3H, 6-CH₃), 3.21 (s, 3H, 11-CH₃), 4.10 (s, 3H, 5-CH₃), 7.27 (dt, 1H, J₁ = 1.1 Hz, J₂ = 7.5 Hz, H-2), 7.38 (d, 1H, J₁ = 8.0 Hz, H-4), 7.47 (dt, 1H, J₁ = 1.5 Hz, J₂ = 8.2 Hz, H-3), 7.56 (dt, 1H, J₁ = 1.4 Hz, J₂ = 6.6 Hz, H-8), 7.56 (dt, 1H, J₁ = 1.4 Hz, J₂ = 6.6 Hz, H-9), 8.21 (dd, 1H, J₁ = 1.6 Hz, J₂ = 8.1 Hz, H-7), 8.34 (dd, 1H, J₁ = 1.5 Hz, J₂ = 7.7 Hz, H-10), 8.38 (d, 1H, J₁ = 7.2 Hz, H-1). N.O.E.: Irradiation at the signal of 5-CH₃ (4.10 ppm) showed a nOe-effect on both 6-CH₃ (s, 3.12 ppm) and H-4 (d, 7.38 ppm). Irradiation at the signal of 6-CH₃ (3.12 ppm) showed a nOe-effect on both 5-CH₃ (s, 4.10 ppm) and on both H-10 and H-1 (d, 8.38 ppm). Mass (EI): 260 (23), 259 (100), 258 (16), 244 (34), 129 (11). Acc. mass: Calc. for C₁₉H₁₇N: 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 Ac₂O (1 ml) and ZnCl₂·2Et₂O (1 ml) were added and the resulting mixture was stirred for 6 h at 0 °C. A saturated aqueous solution of NaHCO₃ was added and stirring was continued until the evolution of CO₂ 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 NaHCO₃ (2 x 50 ml) and brine (2 x 50 ml) and dried (MgSO₄). 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 CHCl₃ (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. (CHCl₃): 3070, 2990, 2950, 1660, 1585, 1490, 1455, 1360, 1295, 1255, 1105, 1065, 905, 810 cm⁻¹. ¹H-N.M.R. (CDCl₃, 200 MHz): 2.68 (s, 3H, 2-COCH₃), 2.99 (s, 3H, 6-CH₃), 3.09 (s, 3H, 11-CH₃), 2.97 (s, 3H, 5-CH₃), 7.22 (d, 1H, J₁ = 8.6 Hz, H-4), 7.51 (dt, 1H, J₁ = 1.5 Hz, J₂ = 6.6 Hz, H-9), 7.56 (dt, 1H, J₁ = 1.5 Hz, J₂ = 6.6 Hz, H-8), 8.08 (dd, 1H, J₁ = 1.7 Hz, J₂ = 8.7 Hz, H-3), 8.13 (dd, 1H, J₁ = 1.6 Hz, J₂ = 7.6 Hz, H-7), 8.27 (dd, 1H, J₁ = 1.5 Hz, J₂ = 6.7 Hz, H-10), 8.79 (d, 1H, J₁ = 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-COCH₃ (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-CH₃
(2.99 ppm) showed a nOe-effect on both 5-CH₃ (s, 3.97 ppm) and H-7 (d, 8.13 ppm); Irradiation at the signal
of 5-CH₃ (3.97 ppm) showed a nOe-effect on both 6-CH₃ (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 C₂₁H₁₈NO: 301.1467;
Observed: 301.1459.

Diacetylation of 17
To a solution of 17 (20 mg, 77 μmol) in CHCl₃ (10 ml) was added Ac₂O (1 ml) and ZnCl₂+2Et₂O (1 ml).
During 0.5 h the reaction mixture was heated to reflux then carefully poured into a saturated aqueous solution of
NaHCO₃ (50 ml). After the evolution of CO₂ had ceased CHCl₃ (50 ml) was added and the organic layer
separated. This was successively washed with saturated aqueous solution of NaHCO₃ (2 x 50 ml) and brine (2
x 50 ml) and dried (MgSO₄). 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 °C. Brown needles. I.R. (CHCl₃): 3000, 2920, 1660, 1585, 1355, 1295, 1245,
1105 cm⁻¹. ¹H-N.M.R. (CDCl₃, 200 MHz): 2.73 (s, 3H, 9-COCH₃), 2.78 (s, 3H, 2-COCH₃), 3.07 (s, 3H,
6-CH₃), 3.24 (s, 3H, 11-CH₃), 4.12 (s, 3H, 5-CH₃), 7.34 (d, 1H, J = 8.6 Hz, H-4), 8.06 (dd, 1H, J₁ = 9.1
Hz, J₂ = 1.5 Hz, H-8), 8.17 (dd, 1H, J₁ = 8.6 Hz, J₂ = 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 C₂₂H₂₁NO₂: 343.1572; Observed: 343.1579.
REFERENCES AND NOTES

42. The antitumour activities were determined at TNO, Rijswijk, The Netherlands (P. Lelieveld) and at the VU Academic Hospital, Amsterdam, The Netherlands (G.J. Peters).
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