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Synthesis of a 1,3,4,5-Tetrahydropyrrolo[4,3,2-*de*]quinoline from a Quinoline

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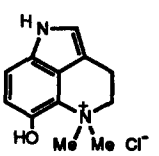
Key Words: Damirones; batzellines; isobatzellines; dehydrobufotenine; 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline.

Abstract: 6-Methoxy-4-methylquinoline has been converted into 8-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline.

	R^1	R^2
damirone B	H	H
batzelline C	Cl	Me

isobatzelline C



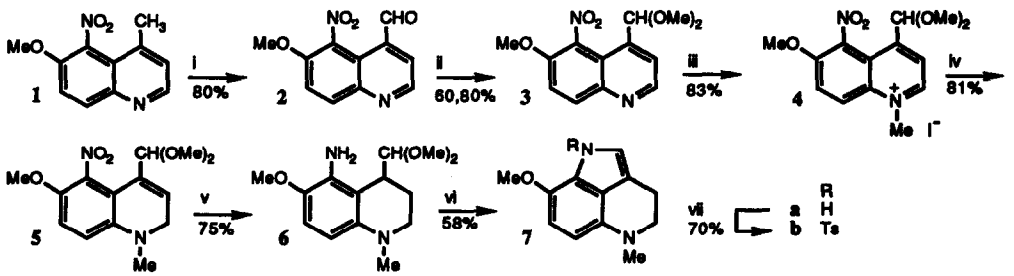
dehydrobufotenine chloride

The 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system was first recognised as a component of a natural product when the structure of the toad poison, dehydrobufotenine was elucidated.[1] Much more recently, several marine alkaloids[2] such as the tricyclic batzellines,[3] isobatzellines,[4] and damirones,[5] (the simplest example from each of these groups is shown above) and more complex molecules such as the discorhabdines,[6] and prianosines[7] have been described which are also based on a 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline nucleus.

In *all* synthetic work so far described, relating to these natural products, including preparations of the unsubstituted-[8,9] and 1-methyl-[10] tricyclic system, of *O*-methylnordehydrobufotenine,[11] of dehydrobufotenine itself[12], and then later of batzelline C and isobatzelline C,[13] discorhabdin C,[14] and damirones A and B,[15] the tricyclic heterocycle has been constructed *from an indole, i.e.* by forming the six-membered nitrogen-containing ring as a late step, by cyclisation either of a 4-aminoindole carrying a two-carbon chain at its C-3,[8-14] or of a tryptamine quinone.[15]

We have taken a different approach to the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline system and describe here how a quinoline can be utilised as starting point. 6-Methoxy-4-methyl-5-nitroquinoline,[16] **1**, was oxidised to the 4-aldehyde, **2** using Vismara's method.[17] Although the aldehyde could be converted into an acetal with ethane-1,2-diol, problems arose at a later stage when too vigorous conditions were required for its removal, so the dimethyl acetal, **3**, was prepared and carried forward. Quaternisation (→ **4**) then borohydride reduction produced the 1,2-dihydroquinoline, **5** which on subjection to catalytic hydrogenation was reduced at the C-C double bond *and* the nitro group, producing acetal-amine, **6**.

The completion of the synthesis required removal of the acetal protection – it was at this stage that acid hydrolysis of the ethane-1,2-diol acetal proved to require too vigorous conditions – however the dimethyl acetal



Reagents: i, I_2, *t*-BuI, $FeCl_2$, TFA, DMSO, 80°C; ii, $HC(OMe)_3$/MeOH/reflux or dry HCl/MeOH/reflux; iii, MeI/MeCN/50°C; iv, $NaBH_4$/MeOH/20°C; v, H_2/Pt-C/20°C; vi, aq. 1N HCl/THF/40°C/24 h or *p*-TsOH/THF/reflux/3 h; vii, $TsCl/CH_2Cl_2/Bu_4N^+ HO^-$.

could be hydrolysed, with ring closure to indole **7a** under mild conditions. Characterisation of 'purified' **7a** proved difficult, for although a perfectly satisfactory ^1H NMR spectrum[18] could be obtained on the 'crude' product, after chromatography, material was obtained which though homogenous by the usual criteria, and giving a mass spectrum consistent with structure **7a**, yet would give no ^1H NMR signals; this observation was reproducible. Conversion to the *N*-tosyl derivative, **7b**, gave material which gave entirely consistent spectroscopic data.[19]

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18 Amorphous gum, δ_H ($CDCl_3$) 2.96 (3H, s), 3.09 (2H, t, J 5.5 Hz), 3.27 (2H, t, J 5.5 Hz), 3.93 (3H, s), 6.14 (1H, d, J 8.0 Hz), 6.75 (1H, d, J 8.0 Hz), 6.77 (1H, s), and 8.05 (1H, bs).
19 Amorphous solid, δ_H ($CDCl_3$) 2.37 (3H, s), 2.88 (3H, s), 3.00 (2H, t, J 6.0 Hz), 3.20 (2H, t, J 6.0 Hz), 3.71 (3H, s), 6.28 (1H, d, J 8.3 Hz), 6.62 (1H, d, J. 8.3 Hz), 7.23 (2H, d, J 8.3 Hz), 7.34 (1H, s), 7.79 (2H, d, J 8.3 Hz).

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