The Reaction of Mesembrine and Mesembrenone with Diethyl Azodicarboxylate

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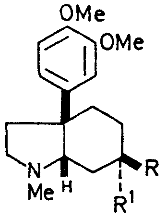
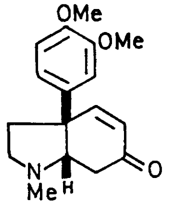
Summary The alkaloids mesembrine (1; $R^1 = R^2 = O$) and mesembrenone (2) undergo a novel oxidation with diethyl azodicarboxylate to afford the β-enaminoketones (4) and (6), respectively.

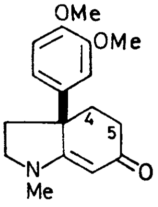
WE report on the characterization of the products obtained from an attempted *N*-demethylation of mesembrine (1; $R^1 = R^2 = O$)[1] and mesembrenone (2) with diethyl azodicarboxylate (DAD). The early work of Diels and his co-workers[2] showed that tertiary amines containing an *N*-methyl group react with DAD to afford adducts of the type represented by structure (3).† These adducts were shown to undergo hydrolysis with 2N-sulphuric acid to formaldehyde, diethyl hydrazine-1,2-dicarboxylate (DHD), and the corresponding secondary amine (see Scheme).



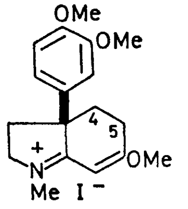
(1)



(2)



(4)



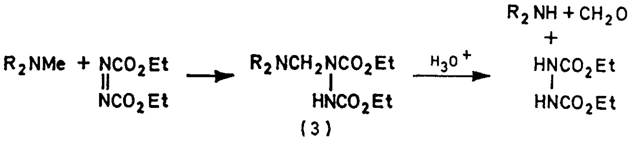
(5)

(6) $\Delta^{4(5)}$

(7) $\Delta^{4(5)}$

Treatment of mesembrine with DAD under reflux in acetone for 2 h afforded DHD on concentration of the solution, together with an optically active non-crystalline product whose spectral properties {^{1}H n.m.r. ($CHCl_3$) δ 2·98 (s, 3H, *N*-methyl) 3·86 (s, 6H, aromatic methoxyls), and 5·19 (s, 1H, 7-H); i.r. (neat), 1595 cm^{-1} (N·CH=CH·CO); u.v. (95% EtOH), λ_{max} 292 nm (ϵ 20,000); o.r.d. (*c* 0·0733, 95% EtOH at 25°), $[\phi]_{312}$ −19,970} were in accord[4] with its formulation as the β-enamino-ketone (4). It was found that (4) reacted slowly with methyl iodide to afford a crystalline product, m.p. 146—147°, which is formulated as the *O*-alkylated compound (5) on the basis of its u.v. spectrum [λ_{max} 218 (ϵ 22,200) and 278 nm (ϵ 25,400)] and by its ready re-conversion into (4) on treatment with a saturated sodium carbonate solution. The formation of the *O*-alkylated product is consistent with the known behaviour of β-enamino-ketones with methyl iodide.[5]

Reduction of (4) proceeded smoothly with sodium in refluxing 2-methylbutanol–toluene (1 : 1) to give a 70 : 30 mixture of mesembranol (1; $R^1 = H$, $R^2 = OH$) and its 6-epimer (1; $R^1 = OH$, $R^2 = H$). Catalytic reduction of (4) over Pd/C proceeded readily and gave a single product identified as mesembrane (1; $R^1 = R^2 = H$). The results of these reductions parallel those reported by Grob and Wilkens[6] for some analogous cyclic β-enamino-ketones, and, taken together with the above mentioned spectral and chemical results, constitute firm evidence for the correctness of structure (4).



SCHEME

Similarly, it was found that (±)-mesembrenone (2) reacts rapidly with DAD in refluxing acetone to form the analogous product (6), m.p. 132—133°, which was characterized by its spectral properties [^{1}H n.m.r. ($CHCl_3$), δ 2·96 (s, 3H, *N*-methyl), 3·83 (s, 6H, aromatic methoxyls), 5·40 (doublet, 1H, $J_{5,7}$ 1·5 Hz, 7-H), 5·99 (1H, doublet of doublets, $J_{5,7}$ 1·5 Hz, $J_{4,5}$ 10·0 Hz, 5-H), and 6·83 (1H, doublet, $J_{4,5}$ 10·0 Hz, 4-H)] and by conversion into the *O*-methyl derivative (7), m.p. 155—156°, [u.v. (95% EtOH), 220 (ϵ 42,000), 275 (ϵ 8800), and 336 nm (ϵ, 6000)] with methyl iodide.

Some insight into the reaction of (1) and (2) with DAD is provided by the results of a recent study of the behaviour of certain tertiary amines with this reagent. It was shown[7] that the reaction proceeds in two steps: the first involves dehydrogenation of the amine to an enamine which reacts in a second step with DAD to form an adduct. The reaction of mesembrine and mesembrenone with DAD probably proceeds in an analogous fashion except since the dehydrogenation leads to a β-enamino-ketone rather than an enamine, then there is no tendency for it to react further with DAD. The factors which influence the course of the reaction of tertiary amines with DAD in terms of those involving products derived from enamine intermediates and those corresponding to products of the type represented by (3) in the Scheme are not clear.

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†Other possible structures considered by Diels and Paquin have been excluded by more recent work.[3]

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