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NILGIRINE, A NEW *CROTALARIA* ALKALOID OF SENECIONINE TYPE LACKING THE 1'-CARBON ATOM

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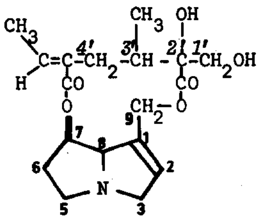
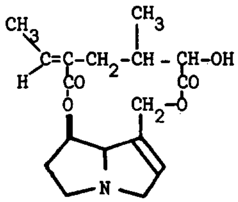
We have previously reported that the major alkaloidal constituent in seeds of *Crotalaria mucronata* (Desv.) is the typical macrocyclic pyrrolizidine diester, usaramine (I)[1]. Although this was true of seed from several different countries, including Angola, Tanganyika, South Africa and Puerto Rico, we now find that seed of this species collected from the Nilgiris (South India) contains a new major alkaloid (II), differing from usaramine by the absence of the 1'-hydroxymethyl group. The 1'-hydroxymethyl or -methyl group is present in the many known alkaloids of senecionine type of which usaramine is a representative and the occurrence of (II) is of special interest in connection with studies on the pathway of biosynthesis of the C$_{10}$ esterifying acids present in these alkaloids. Crout *et al.*[2] and Crout[3] have shown that the five carbons to the left of C-*3'* in diagram (I) are derived from isoleucine and have further proposed that C-*3'* and the attached methyl are derived from pyruvate, C-*2'* and the attached carbonyl from threonine and C-*1'* from a one-carbon source such as methionine or formate. On this basis, variation of an alkaloid structure by the omission of C-*1'* is to be expected and the isolation of (II) from a biochemical variant of a species normally containing usaramine lends support to the scheme proposed.



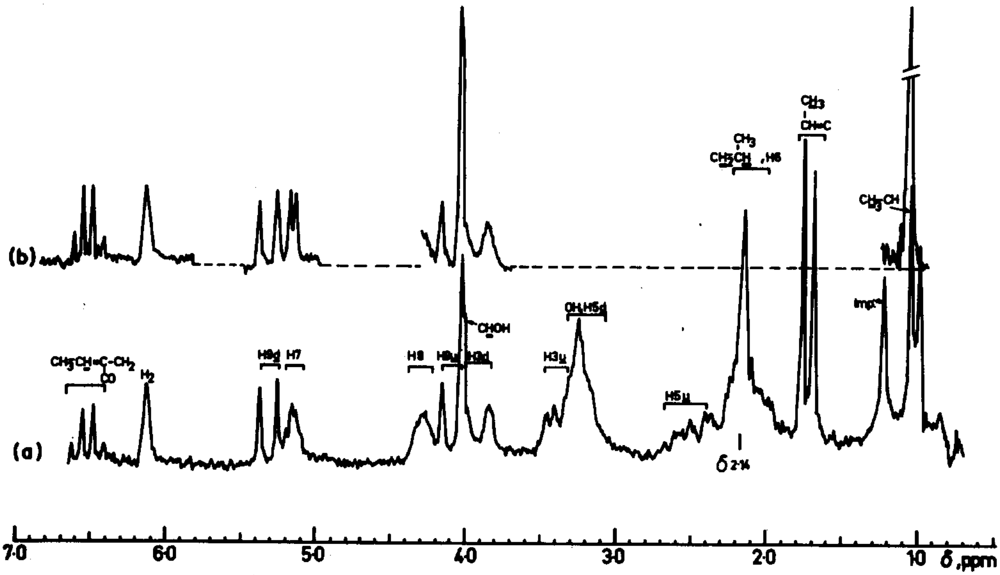
(I)



(II)

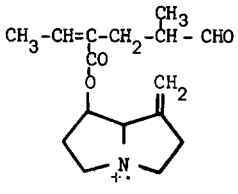
FIGURE

Nuclear magnetic resonance spectrum of nilgirine measured in $CDCl_3$ at 100 Mc/s: (a) under standard conditions, (b) during irradiation at the frequency δ 2.14.

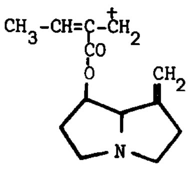


The new alkaloid, nilgirine, has m.p. 127-128°, $[\alpha]_D^{18}$ + 31.5° (ethanol) and the empirical formula, $C_{17}H_{23}O_5N$ (parent ion in the mass spectrum, m/e 321). The structure has been derived mainly from nuclear magnetic resonance spectra measured at 100 Mc/s (Figure). The peaks assigned to protons of the pyrrolizidine system (numbered H2-H9) are typical of macrocyclic diesters of retronecine[4,5], the assignments for H8 and H3u, H3d being confirmed by spin-decoupling (u, d denote the upfield and downfield members, respectively, of a geminal pair). Thus irradiation at δ 2.14 (approximate chemical shift of the H6 protons) collapses the H7 multiplet to a doublet (J 3.8 c/s (c.f. Figure) and double irradiation at δ 2.14 and δ 4.28 reduces H7 to a singlet, showing that the multiplet δ 4.3 is due to H8. Irradiation at δ 3.36, brings the δ 3.84 peak and signals overlapping the doublet, δ 4.02, together at δ 3.96, and irradiation at δ 3.96 enhances the peak height of the signals visible near δ 3.4 and moves them upfield by c. 6 c/s. The main part of the peak centred near δ 3.1 disappears if the solution is shaken with D_2O and is thus due to hydroxyl.

Of the esterifying acid protons, signals due to $C\underline{H}_3$-CH (doublet, δ 1.01) and to $C\underline{H}_3$-C$\underline{H}$=C(CO) with the CH_3 *trans* to the carbonyl (doublet δ 1.73 and quartet δ 6.52, J 7.5 c/s) are readily assigned. The narrow peak, δ 4.02, contains some lines due to other protons but its major part can be assigned to a C$\underline{H}$OH proton adjacent to another deshielding influence such as carbonyl. A CH_2 group makes up the rest of the molecule and is considered to give rise to the tall peak, δ 2.14. Irradiation at this frequency noticeably sharpens the quartet, δ 6.52, but also collapses the doublet, δ 1.01, to a singlet and increases the height of the narrow multiplet, δ 4.02 (Figure). The groupings responsible for the affected multiplets cannot all be linked appropriately to the CH_2 group and the decoupling results are partly due to the CH_3-C$\underline{H}$ proton having approximately the same shift as, and being vicinal to, the $C\underline{H}_2$ protons. This is evident from the second-order character of the $C\underline{H}_3$-CH multiplet, strongly marked in a spectrum measured at 60 Mc/s. A consequence is that decoupling cannot be used to decide whether the CH_2 or CH_3-CH is adjacent to the C=C, nor are the multiplets for the $C\underline{H}_3$-C=C and C$\underline{H}$OH protons sufficiently resolved for this to be determined from the splitting patterns. The sequence shown in diagram (II) is the one commonly found in acids of this type. A downfield shift of the $C\underline{H}_3$-CH protons to δ 1.40 in acetylnilgirine (parent ion m/e 363 in the mass spectrum, doublet δ 4.02 replaced by similar peak at δ 5.02, singlet for $C\underline{H}_3$CO at δ 2.09) favours this arrangement with CH(CH_3) adjacent to CHOH. Definite evidence for this sequence and for the mode of combination of the ester linkages is available from the mass spectrum. This shows minor peaks m/e 277, 220, which are ascribed to the ions (III) and (IV), respectively analogous to and identical with the ions m/e 291, 220 formed in the fragmentation of senecionine[6]. At mass numbers lower than 220, the spectra of nilgirine and senecionine are closely similar. Thus the structure of nilgirine is fully established as (II).



(III)



(IV)

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