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ISOLATION OF NORCASSAMIDIDE AND AUTHENTIC NORCASSAMIDINE FROM *ERYTHROPHLEUM CHLOROSTACHYS*. STRUCTURAL REVISION OF THE ALKALOIDS PREVIOUSLY KNOWN AS NORCASSAMIDINE, NORCASSAMINE, NORETHYTHROSUAMINE AND DEHYDRO-NORERYTHROSUAMINE.

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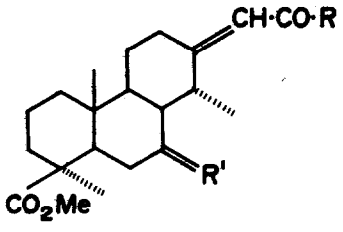
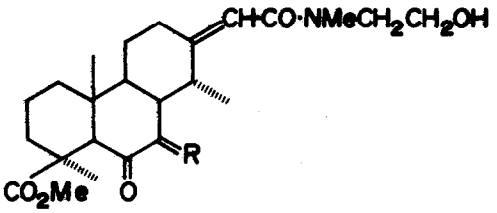
A recent paper by Friedrich-Fiechtl and Spiteller[1] describes four new alkaloids from *Erythrophleum guineense* under the names norcassamine, norcassamidine, norethythrosuamine and dehydro-norethythrosuamine. On hydrolysis these alkaloids gave N-methylethanolamine and different diterpene acids which were either known compounds or were converted into known compounds in such a way that structures could be assigned to the acids without ambiguity. It was assumed by the authors that the alkaloids were esters of these acids and N-methylethanolamine, but no direct supporting evidence was presented. We show here that the compounds described are not esters but the corresponding amides. This is in keeping with our earlier finding[2] that alkaloidal esters of N-methylethanolamine and ethanolamine readily rearrange to amides in alkaline solution or when chromatographed on alumina, the isolation conditions used by Friedrich-Fiechtl and Spiteller.

From the bark of *E. chlorostachys* we have isolated an unstable (non-crystalline) alkaloidal ester (1) and its isomeric amide (2), m.p. 115°, $[\alpha]_D$ -18.5° (EtOH), of which the latter is identical with Friedrich-Fiechtl and Spiteller's compound 7 (m.p. 115°, $[\alpha]_D$ -22.5° (EtOH), identical n.m.r. and mass spectra). The structures of these compounds are based on mass spectra (both give M^+ ions of the appropriate formula $C_{24}H_{39}NO_5$), i.r., u.v., and n.m.r. spectra. We find that the fragmentation patterns of ester and amide are similar, but can readily be distinguished by the intense base peak of ester (1) at m/e 57, whereas the amide (2) has the M^+ ion, m/e 421, as base peak. Further, the ester (1) has ν_{max} ($CHCl_3$): 1715 ester carbonyls, 1640 conj. C=C, 1160 cm^{-1} ester C-O stretch, while the amide (2) has ν_{max} ($CHCl_3$):

1720 C-4 ester carbonyl, 1645 conj. C=C, 1605 amide, and no intense 1160 cm^{-1} band. The u.v. absorption of ester (1) has λ_{max} (EtOH) 224 nm, log ε 4.18 while the amide has λ_{max} (EtOH) 213 nm, log ε 4.12. The chemical shifts of the $N\text{-}CH_3$, $N\text{-}CH_2$ and $O\text{-}CH_2$ hydrogen atoms distinguish very clearly between the ester and amide series of compounds from *Erythrophleum* species and the chemical shift of the olefinic hydrogen at C-18 provides another useful criterion (Table 1). Despite an influence due to the degree of methylation, the $N\text{-}CH_3$ shifts fall within the ranges 2.25-2.47 for esters and 3.05-3.08 for amides. The $N\text{-}CH_2$ and $O\text{-}CH_2$ signals are widely separated and well resolved triplets in esters, with ranges δ 2.55-2.84 and 4.15-4.20 respectively, but slightly overlap in amides forming a broad envelope between δ 3.3 and 4.0 which is poorly resolved and partly obscured by signals from the methoxycarbonyl when present, as well as from hydrogen atoms on C-3 and C-7 when these carry hydroxyl groups. The data for (1) and (2) leave no doubt as to their ester and amide character, respectively. We propose to use the names norcassamidine for (1) and norcassamidide for (2) and Friedrich-Fiechtl and Spiteller's compound 7.





(1) R=OCH_2CH_2NHMe R'=H,OH

(2) R=$NMeCH_2CH_2OH$ R'=H,OH

(3) R=$NMeCH_2CH_2OH$ R'=O

(4) R=H, OH

(5) R=O

The chemical shifts quoted by Friedrich-Fiechtl and Spiteller for the $N\text{-}CH_3$ and C18-H hydrogen atoms of "norcassamine" and "norerythrosuamine" are sufficient evidence of amide structures (Table 1). "Norcassamine" appears in fact to be identical with the amide, cassamide (3), isolated from *E. ivorense* by Crönlund and Sandberg.[3] These authors established the amide character of cassamide by its relative resistance to hydrolysis in alkaline methanol compared to the normal dimethylaminoethyl esters, the presence of amide rather than ester bands in the i.r. spectrum and an assignment of signals in the n.m.r. spectrum corresponding to the data in Table 1. No n.m.r. data were given for "dehydro-norerythrosuamine" but it was structurally related by oxidation to "norerythrosuamine". These compounds are thus very probably (4) and (5).

TABLE 1

N.m.r. data for N-methylated ethanolamine derivatives

measured in $CDCl_3$

Compounds	Range of chemical shifts			
	$N-CH_3$	$N-CH_2$	$O-CH_2$	18-H
Esters of N,N-dimethylethanolamine[a]	2.25-2.32	2.55-2.63	4.15-4.20	5.71-5.82
Esters of N-methylethanolamine[b]	2.46-2.47	2.84	4.19-4.20	5.71-5.72
Amides of N-methylethanolamine[c]	3.05-3.08[d] and 2.98-3.01	3.3-3.9		5.83-5.88[e] and 5.95-5.98
This work: norcassamidine (1)	2.46	2.84	4.20	5.72
norcassamidide (2)	3.08[d] and 3.00	3.3-3.9		5.85[e] and 5.95
Friedrich-Fiechtl and Spiteller's:				
"norcassamidine"	3.06	not quoted		5.83
"norcassamine"	3.07	not quoted		5.87
"norerythrosuamine"	3.06	not quoted		5.88
Crönlund and Sandberg's "cassamide"	3.06	3.4-3.9		5.85

a Values from published data for cassaine[3], erythrophlamine[3], cassamine[3], erythrophleguine[4], coumidine[4], erythrosuamine[4], and our own measurements on cassaidine and cassamidine.

b Values from our own measurements on norcassamidine and other new nor-alkaloids from *E. chlorostachys*.

c Values from published data for (nor)cassaide[3], (nor)erythrophlamide[3], (nor)cassamide[3], and our own measurements on norerythrophlamide, norcassamidide, norcassaidide, and other new amides from *E. chlorostachys*.

d Shift for the stronger downfield signal.

e Shift for the stronger upfield signal.

de Amide spectra were measured on a Varian HA-100 spectrometer at 30°. For double signals, the peak height ratios fell in the range 1 : 2.4-3.2.

We suggest they be renamed norerythrosuamide and dehydro-norerythrosuamide, respectively, leaving the original names for the corresponding amines.

A confusing situation has arisen in the literature from the naming of the first amides isolated from *E. ivorense*. These were called cassamide, erythrophlamide, and cassaide. While not ambiguous, these names are not strictly logical as the amides are not isomers of the related amines cassamine, erythrophlamine and cassaine, but contain one less N-methyl group. As an isomeric pair has now been isolated, norcassamidine (1) and norcassamidide (2), and it is known that other nor-amines are present in *Erythrophleum* species, it seems more appropriate that *E. ivorense* amides should be called norcassamide, norerythrophlamide and norcassaide.

In all *Erythrophleum* amide spectra we have measured in $CDCl_3$ at 30-35° the H-18 and N-methyl signals are doubled although these signals sometimes degenerate into broad singlets when measured on spectrometers operating at slightly higher temperatures. Thus Crönlund and Sandberg[3] noted an occasional doubling of the H-18 signal of (nor)cassaide, (nor)erythrophlamide, and (nor)cassamide and suggested that it may be due to the compound being a mixture of cis and trans isomers, or to configurational isomerism of the amide nitrogen. A study on norcassamidide shows these signals are temperature dependent and the disappearance of double peaks as the temperature is raised supports the presence of rotational species due to restricted movement about the C-N amide linkage. By 50° only single broad peaks were observed at δ 5.82 and 3.02 and these became single sharp peaks by 100° while the 3.3-3.9 multiplet became more clearly resolved.

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