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Three New Alkaloids from the Bark of *Erythrophleum guineense* G. Don syn. *E. suaveolens* (Guill. & Perr) Brenan

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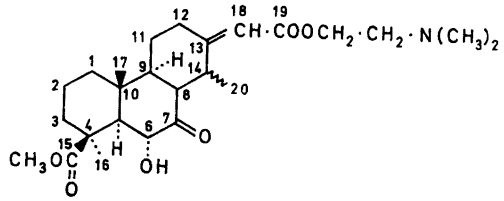
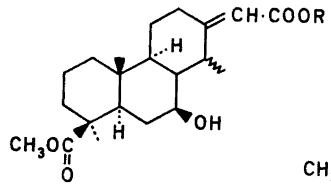
Three new alkaloids have been isolated from the bark of *Erythrophleum guineense* G. Don. syn. *E. suaveolens* (Guill. & Perr) Brenan. Chemical and spectroscopic data provide evidence for the structure of two of them, cassamidine (*IIa*) and coumidine (*IVa*) and strongly indicate that the third alkaloid, erythrosuamine, is represented by (*VIa*).

In a previous paper [1] we described the isolation of a new alkaloid, erythrophleguine (*I*), from the bark of *Erythrophleum guineense* syn. *E. suaveolens*. The presence of several other unknown compounds in the alkaloid fraction was indicated by thin-layer chromatography. In this paper we report the isolation of three new alkaloids. Chemical and spectroscopic evidence for the structures of two of them, cassamidine (*IIa*) and coumidine (*IVa*), is presented. A tentative structure (*VIa*) for the third alkaloid is proposed.

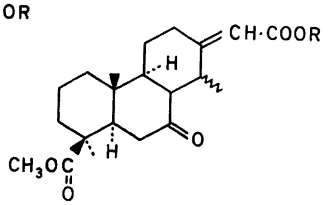
One of the previous fractions (E *II*; Ref. 1, p. 323) from the column chromatography of an alkaloid mixture obtained from *E. guineense* was shown by TLC to contain "coumingine", cassaine, cassaidine, and two unknown compounds (R_F 0.39 and 0.28). Rechromatography (Table 2) of this fraction enabled the isolation of these two unknown constituents below named cassamidine (*IIa*) and coumidine (*IVa*). Furthermore an oily fraction possessing similar TLC properties to that of coumingine was obtained. By changing the TLC conditions this fraction was shown to be homogeneous and different from coumingine. The alkaloid of this fraction will be named erythrosuamine.



I. Erythrophleguine



II a. Cassamidine
R = $\cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$
b. R = H



III a. Cassamine R = $\cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$
b. Cassamic acid R = H

Cassamidine (*IIa*). The oily alkaloid cassamidine (*IIa*; M^+ 435 *) yielded a crystalline hydrochloride ($C_{25}H_{41}NO_5HCl$; m.p. 235—236°; $[\alpha]_D$ —47°, *c* in EtOH 1.0). The alkaloid exhibited similar properties to a product previously prepared [2] by borohydride reduction of cassamine (*IIIa*). The structure of the alkaloid was settled as follows.

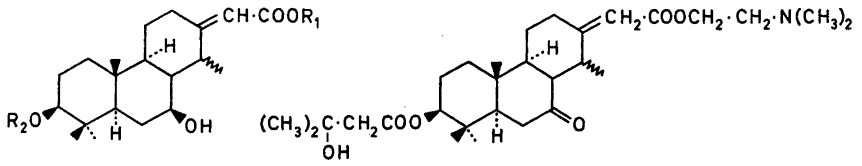
Acid hydrolysis gave dimethylaminoethanol and a crystalline acid. This acid was identical (m.p., mixed m.p., TLC, and IR) with a previously described [2]

* Determined by mass spectrometry

Table 1. NMR data of some *Erythrophleum*

Compound	C(4) $-CH_3$	C(10) $-CH_3$	C(14) $-CH_3$	C(18)—H	$-COOCH_3$
Erythrophleguine(*I*) [1]	1.44	0.88	d 1.13(*J* 7)	5.76	3.70
Cassamidine(*IIa*) hydrochloride	1.17	0.60	d 1.06(*J* 7)	5.80	3.64
Cassamic acid (*IIIb*)	1.15	0.78	d 1.06(*J* 7)	5.70	3.64
Coumidine(*IVa*)	0.89(6H)	0.84	d 1.05(*J* 7)	5.75	
Erythrosuamine(*VIa*)	1.21	0.89	d 1.19(*J* 7)	5.82	3.72
Methyl erythrosuamate(*VIc*)	1.21	0.89	d 1.21(*J* 7)	5.80	3.72(6H)
Erythrosuamic acid acetate (*VId*)	1.23	1.00	d 1.18(*J* 6.5)	5.82	3.72
Diol-ester(*VIIb*)	1.31	0.82	d 1.11(*J* 7)	5.80	3.72; 3.81

[a] Deuterochloroform solutions. Chemical shifts in ppm from tetramethylsilane (internal stand-



IV a. Coumidine $R_1 = \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$

$R_2 = \cdot C(=O) \cdot CH_2 \cdot C(OH)(CH_3)_2$

b. Coumidic acid $R_1 = H$

$R_2 = \cdot C(=O) \cdot CH_2 \cdot C(OH)(CH_3)_2$

c. Cassaidic acid $R_1 = R_2 = H$

d. Cassaidine $R_1 = \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$

$R_2 = H$

V. Coumingine

compound (*IIb*), prepared by acid hydrolysis of the product formed by borohydride reduction of cassamine.*

Coumidine (*IVa*). Coumidine ($C_{29}H_{49}NO_6$, M^+ 507; m.p. 130—132°; $[\alpha]_D$ —58°, *c* in $CHCl_3$ 0.5) gave on acid hydrolysis dimethylaminoethanol and a mixture of two acids which were separated by preparative TLC. One of the acids was found to be identical (m.p., mixed m.p., TLC, and IR) with cassaidic

* Since the configurations at C-14 and of the 13 (18)-double bond in cassaine recently has been assigned (for references see Morin, R. B. in "*The Alkaloids*", Vol. X, (Ed. Manske, R. H. F.), Academic, New York 1968, p. 287) the configurations at these centra in cassamidine (IIa) and coumidine (IVa) follow from known chemical interrelations.

alkaloids and related compounds.[a]

$-O-CH_2-$	$-CH_2-N<$	$-N(CH_3)_2$	Other protons
t 4.18(*J* 7) t 4.54(*J* 6)	t 2.56(*J* 7) t 3.53(*J* 6)	2.28 2.98	C(6α)—H, d 4.79(*J* 12.5)
t 4.20(*J* 6.5) t 4.21(*J* 6.5)	t 2.59(*J* 6.5) t 2.59(*J* 6.5)	2.28 2.28	$-C(OH)(CH_3)_2$, 1.28 (6H); $-CO-CH_2-$, 2.49 C(7α)—H, d 3.93(*J* 8) C(7α)—H, d 3.95(*J* 8); C(5α)—H, 2.28
			C(7α)—H, d 5.19(*J* 10); C(5α)—H, 2.28 C(6α)—H, q 4.47(J_1 4; J_2 4); C(7α)—H, q 4.20(J_1 4; J_2 8)

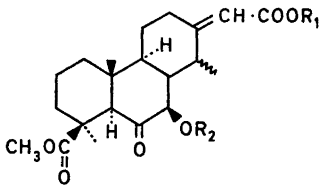
ard), singlets unless otherwise stated (abbreviations: d, doublet; t, triplet; q, quartet).

acid (*IVc*), which also could be obtained upon further hydrolysis of the second acid.

The NMR spectrum of coumidine exhibited signals which were assigned to the protons of a β-hydroxyisovaleriate grouping (Table 1). The presence of such a substituent was further confirmed by an alkaline hydrolysis of coumidine to yield β-hydroxyisovaleric acid identified by GLC of its methyl ester.

The structure of coumidine (*IVa*) follows from its chromic acid oxidation to yield coumingine (*V*). Furthermore a borohydride reduction of coumingine was found to yield coumidine which thus also settles the configuration of the 7β-hydroxy group (a stereospecific reduction from the less hindered α-side).

Erythrosuamine. Erythrosuamine could not be induced to crystallize but the alkaloid was characterized by its crystalline hydrochloride (m.p. 139—141°;

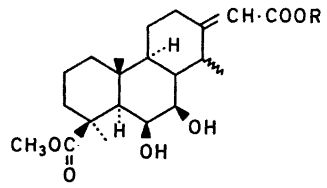


VI (tentative) a. Erythrosuamine $R_1 = \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$; $R_2 = H$

b. $R_1 = R_2 = H$

c. $R_1 = \cdot CH_3$; $R_2 = H$

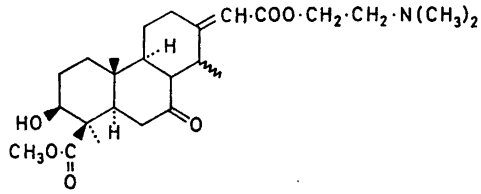
d. $R_1 = H$; $R_2 = \cdot COCH_3$



VII (tentative) a. R = H

b. R = ·CH3

$[\alpha]_D$ −67°, *c* in EtOH 0.9) or by hydrolysis to yield dimethylaminoethanol and an acid ($C_{21}H_{30}O_6$, M^+ 378; m.p. 195—196°; $[\alpha]_D$ −75°, *c* in EtOH 1.0). The alkaloid exhibited a mass-spectrum (M^+ 449) which was similar to that of erythrophleguine (*I*). Furthermore it gave on chromic acid oxidation a product



VIII. Erythrophlamine

mixture which according to TLC was almost identical to that obtained by a similar oxidation of erythrophleguine. Due to a shortage of material, none of the oxidation products could be isolated. Both erythrophleguine (*I*) and erythrosuamine could be oxidized with periodic acid whereas erythrophlamine (*VIII*) was almost stable to such an oxidation. The above results indicate that

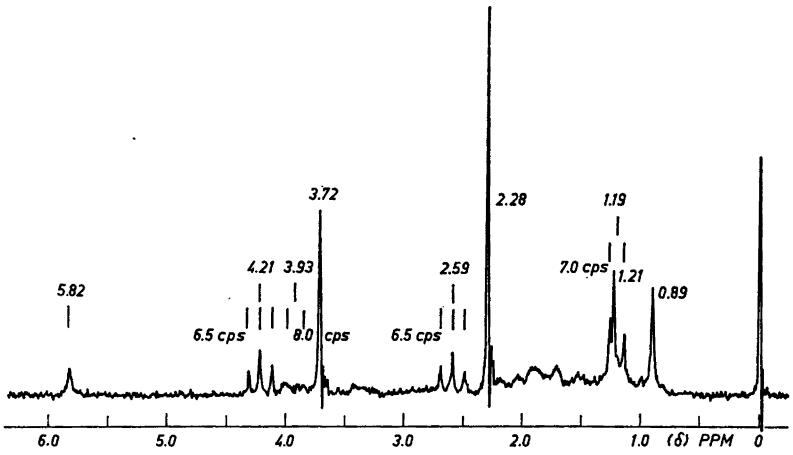


Fig. 1. Nuclear magnetic resonance spectrum of erythrosuamine in deuterochloroform solution.

erythrosuamine is isomeric to erythrophleguine (*I*) possessing an α-hydroxyketo grouping in the 6,7-position.

Erythrophleguine (*I*) upon acid hydrolysis gave dehydrocassamic acid as the sole acid-product. However, this acid could not be detected in the hydrolysis product of erythrosuamine. Instead the above acid ($C_{21}H_{30}O_6$) was formed in a high yield.

The NMR spectra of erythrosuamine (Fig. 1) and of some of its derivatives (Table 1) provide strong indications for structure (*VIa*) of the alkaloid. The signals due to the dimethylaminoethanol grouping of erythrosuamine appear as sharp singlets at 2.28 ppm * [$-N(CH_3)_2$] and two triplets at 2.59 ppm (*J* 6.5 cps, $-CH_2-N<$) and 4.21 ppm (*J* 6.5 cps, $-O-CH_2-$). The signal at 5.82 ppm in the spectrum of erythrosuamine (Fig. 1) is assigned to the olefinic proton of the α,β-unsaturated ester grouping characteristic of *Erythrophleum* alkaloids. The sharp singlet at 3.72 ppm is attributed to the protons of the carbomethoxy grouping (*cf.* the corresponding signal at 3.70 ppm in the spectrum of erythrophleguine, *I*).

Erythrosuamine exhibits methyl singlets at 0.89 and 1.21 ppm assigned to the C_{17}- and C_{16}-methyl groups, respectively, and a doublet at 1.19 ppm (*J* 7.0 cps) due to the secondary C(20)-methyl group. A comparison of chemical shift data of the C(20)-methyl protons has indicated that changes in substitution pattern of the C(7)-position causes significant shift of this methyl signal.[1] However, it should be noted that the doublets assigned to the C(20)-methyl protons in the spectra of erythrosuamine and its derivatives are shifted only slightly downfield compared to those in the spectra of erythrophleguine (*I*) and cassamic acid (*IIIb*) (*cf.* Ref. 1), possessing a 7-keto group, and of cassa-

* The chemical shifts are given in ppm from tetramethylsilane (internal standard).

midine (*IIa*), coumidine (*IVa*), and cassaidine (*IVd*), possessing a 7β-hydroxy group.

In the spectrum of erythrosuamine there is a slightly broadened doublet at 3.93 ppm (J 8 cps) which is attributed to the 7α-proton. The corresponding signal in the spectrum of the acetate (*VId*) prepared in the usual manner from erythrosuamic acid (*VIb*) appears at 5.19 ppm (J 10 cps).

In the spectrum of methyl erythrosuamate (*VIc*) and erythrosuamic acid acetate (*VId*) there is a slightly broadened singlet at 2.28 ppm which is assigned to the C(5)-proton. In the spectrum of erythrosuamine (*VIa*) this signal is overlapped by the singlet due to the $N(CH_3)_2$-protons. However, the observed integrated area corresponds to seven protons.

The observed coupling constants of the signals assigned to the 7α-protons in the spectra of erythrosuamine (*VIa*; $\delta_{7\alpha}$ 3.93 ppm, $J_{7\alpha,8\beta}$ 8 cps), the dimethyl ester (*VIc*; $\delta_{7\alpha}$ 3.95, $J_{7\alpha,8\beta}$ 8 cps), and the acid acetate (*VId*; $\delta_{7\alpha}$ 5.19 ppm, $J_{7\alpha,8\beta}$ 10 cps) indicate that the parent alkaloid, erythrosuamine, possesses a 6-keto-7β-hydroxy grouping and "normal" configuration in the BC-ring junction as indicated in structure (*VIa*).

A small amount of erythrosuamic acid was treated with sodium borohydride in methanol. The product thus obtained was methylated and the main constituent, the diol-ester (*VIIb*), was separated by preparative TLC. The NMR spectrum of this diol-ester was recorded using a microcell technique. Characteristic signals in the spectrum are given in Table 1. A significant downfield shift is observed for a signal due to protons of one of the carbomethoxy groups. This must be interpreted as being due to a deshielding effect of a 6β-hydroxy group (formed by a stereospecific reduction from the less hindered α-side) upon the protons of the 4β-carbomethoxy group. The signals assigned to the protons of the C(16)- and C(17)-methyl groups are also significantly shifted due to the interaction of the neighbouring carbomethoxy and hydroxy groups. The observed coupling constants of the signals assigned to the 6α- and 7α-protons ($\delta_{6\alpha}$ 4.47 ppm, $J_{6\alpha,5\alpha}$ 4 cps, $J_{6\alpha,7\alpha}$ 4 cps; $\delta_{7\alpha}$ 4.20 ppm, $J_{7\alpha,6\alpha}$ 4 cps, $J_{7\alpha,8\alpha}$ 8 cps) in the spectrum of the diol-ester (*VIIb*) provide strong indications for the configuration of the diol grouping and of a normal trans AB-ring junction as shown in the structure (*VIIb*). Thus the AB-*trans* configuration should be stable also in the parent alkaloid (*VIa*).

Pharmacological test. The inhibiting effect of these alkaloids on the ATP-ase system earlier identified with a Digitalis receptor system was tested by Prof. K. Repke. Coumidine showed a remarkable high activity using the testing method earlier described.[3] The results will be published elsehwere.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage or in closed capillaries *in vacuo*. Infrared spectra were recorded with a Perkin-Elmer 237 spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Varian A-60 A instrument (60 Mc/s) using deuterochloroform solutions. The chemical shifts are given in ppm from tetramethylsilane (internal standard). Light petroleum refers to a fraction b.p. 40–60°.

The following conditions were used for TLC: 1. Silica Gel G, cyclohexane-chloroform-diethylamine (5:4:1) (for bases). 2. Silica Gel G, chloroform-acetic acid (9:1) (for acids). 3. Aluminium oxide G, ether-ethanol-diethylamine (98.5:1.5:0.25) (for bases).

Table 2. Chromatography of fraction EII (Ref. 1).

Tube No.[a]	Solvents: Light petroleum/benzene/ chloroform	Fraction	Tube No.	Weight, g	Major alkaloid
1	350:75:50	1	1— 62	1.25	Erythrosuamine
↓		2	63— 78	0.68	
↓		3	79—110	1.38	
↓		4	111—139	0.46	
181	325:75:75	5	140—320	1.28	Cassamidine
↓					
321	315:75:85	6	321—345	0.18	
↓					
391	300:75:100	7	346—435	0.73	
↓					
425	290:75:110	8	436—484	0.52	
↓		9	485—495	0.10	
↓		10	496—539	0.60	
681	275:75:125	11	540—740	1.40	Coumidine
↓					
800	275:75:600	12	741—809	0.52	
↓		13	810—839	1.00	Cassaidine
			Total weight	10.1	

[a] Tube volume 50 ml.

Spray reagent for alkaloids, iodoplatinate reagent.[1] Acids were located after spraying with a vanilline-sulfuric acid reagent (0.5 ml conc. H_2SO_4 is added to a solution of 3 g vanilline in 100 ml abs. ethanol) followed by heating to 120°. Some acids were better located after spraying with 50 % H_2SO_4 followed by heating.

R_F values (system 2) and spot colours (vanilline reagent) for the acids of the *Erythrophleum* alkaloids are: Cassamic acid 0.68, light brown; 8,9-dehydrocassamic acid 0.64, red-brown; erythrosuamic acid 0.53, red-violet changing into yellow-green; erythrophlamic acid 0.52, light-brown; cassamidic acid 0.42, green; cassaic acid 0.38, green-brown; coumidic acid 0.31, blue; cassaidic acid 0.20, blue.

Chromatography of the alkaloid fractions designated EII.[1] Aluminium oxide (900 g active neutral, Merck) was deactivated with 100 ml water and packed in a column 3.6 × 91

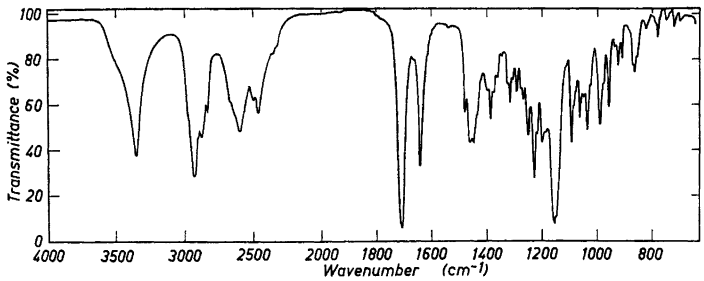


Fig. 2. Infrared spectrum of cassamidine HCl (KBr disc).

cm. A part (12 g) of fraction EII [1] was chromatographed using the solvents indicated in Table 2. Fractions of 50 ml were collected.

Cassamidine (IIa). Cassamidine was obtained as a non-crystalline base (M^+ 435) from fraction 5 (Table 2) and gave a crystalline hydrochloride: m.p. 235—236°, $[\alpha]_D$ −47° (c in ethanol 1.0). IR spectrum Fig. 2, NMR data Table 1. (Found: C 63.9; H 9.0; N 3.1. Calc. for $C_{25}H_{41}NO_5 \cdot HCl$: C 63.6; H 8.9; N 3.0).

Acid hydrolysis of cassamidine. Cassamidine HCl (70 mg) in hydrochloric acid (1 ml, 2 M) was refluxed for 3 h.[1] The acidic product (*IIb*) was crystallized from acetone/hexane: m.p. 235—237°. Dimethylaminoethanol was identified as described previously.[1]

Reduction of cassamine (III).[2] Cassamine (50 mg), dissolved in methanol (2 ml), was treated overnight at room temperature with sodium borohydride (10 mg) yielding an oily product with similar properties (TLC, IR) to those of cassamidine (*IIa*); hydrochloride, m.p. 235—236°, recrystallized from ethanol/ether (lit.[2] m.p. 234—235°).

Acid hydrolysis of reduced cassamine. Compound (*IIa*) was hydrolyzed as described above for cassamidine to yield the crystalline acid (*IIb*), m.p. 235—237° (lit.[2] m.p. 234—235°) identical in all respects (m.p., mixed m.p., TLC, IR) with the acid obtained by hydrolysis of cassamidine.

Coumidine (IVa). Coumidine (M^+ 507) was obtained from fraction 11 (Table 2) by recrystallization from ether: m.p. 130—132°, $[\alpha]_D$ −58° (c in chloroform 5). IR spectrum Fig. 3, NMR data Table 1). (Found: C 69.1; H 9.9; N 2.8. Calc. for $C_{29}H_{49}NO_6$: C 68.6; H 9.7; N 2.8).

Acid hydrolysis of coumidine. Coumidine (80 mg) was refluxed in hydrochloric acid (2 N, 4 ml) for 0.5 h when an oily phase had formed which was separated by extraction with ether. The aqueous solution was refluxed for another hour and after cooling a crystalline precipitate was recovered by filtration. This crystalline precipitate was identical (m.p. 275—277°, mixed m.p., TLC, IR) to cassaidic acid (*IVc*). Dimethylaminoethanol was identified as described previously.[1]

Basic compounds of the oily phase were removed by extraction with ether from an alkaline aqueous solution. After acidification acids were extracted with ether. TLC of the acidic fraction showed the presence of two main components which were separated by preparative TLC (system 2). One of the acids (R_F 0.20) was identified (m.p., mixed m.p., IR) as cassaidic acid (*IVc*). The other acidic component (R_F 0.38) was recrystallized from acetone/water and acetone/hexane: m.p. 240—242°. Upon further hydrolysis with hydrochloric acid, this acid (R_F 0.38) was converted to cassaidic acid (*IVc*). Therefore the acid should be the β-hydroxyisovalerate ester (*IVb*) of cassaidic acid.

Oxidation of coumidine. Coumidine (10 mg) was dissolved in glacial acetic acid (0.5 ml) and a solution of chromium trioxide (5 mg) in water (0.05 ml) and acetic acid (0.5 ml) was added. After standing overnight at room temperature, the resulting product was worked up according to the usual procedure, precipitated from ether as a hydrochloride which was crystallized from ethanol/ether: m.p. 194—195°; identical (m.p., mixed m.p., IR) with coumingine HCl.

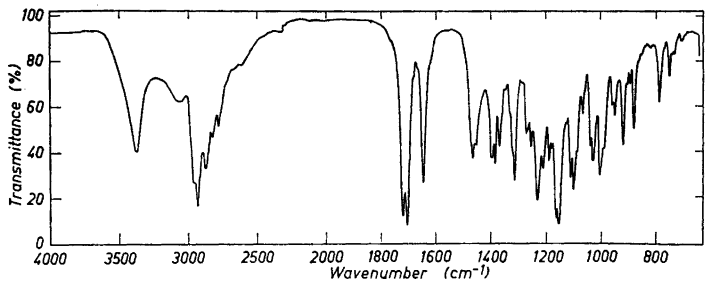


Fig. 3. Infrared spectrum of coumidine (KBr disc).

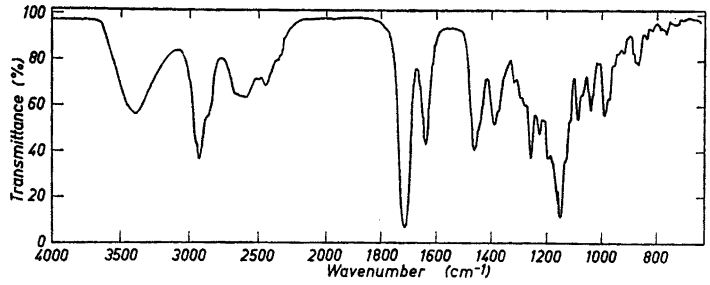


Fig. 4. Infrared spectrum of erythrosuamine HCl (KBr disc).

Reduction of coumingine (V). A few mg of coumingine HCl was reduced with sodium borohydride as described previously. The product, isolated by preparative TLC, was identical with coumidine (m.p., mixed m.p., TLC).

β-Hydroxyisovaleric acid from coumidine (cf. Refs. 4, 5). Coumidine (24 mg) was refluxed for 1.5 h in ethanol (2 ml) and aqueous potassium hydroxide (1 N, 0.35 ml). The solution was evaporated *in vacuo* to 1 ml after addition of water and was acidified. The precipitate which crystallized during standing at 7° was removed by filtration. The residual aqueous solution was extracted repeatedly with ether. The dried ether solution was concentrated to 1 ml and treated with an ethereal solution of diazomethane. This methylated extract was found by GLC (10 % Carbowax 20 M on Chromosorb W, temp. 95°) to contain a single compound with identical retention time as that of synthetic [6] methyl β-hydroxyisovalerate.

Erythrosuamine (VIa). This alkaloid (M^+ 449, NMR spectrum Fig. 1) was obtained from fraction 1 (Table 2) and further amounts also by rechromatography of the fraction designated BE IV in the previous publication.[1] Mixtures of erythrosuamine and erythrophlamine could also be separated by fractional crystallization whereby the former remained in the mother liquors. Erythrosuamine is a non-crystalline alkaloid which yields a crystalline hydrochloride which was recrystallized from ethanol/ether: m.p. 139–141°, $[\alpha]_D$ −67° (c in ethanol 0.9); IR spectrum, Fig. 4.

Acid hydrolysis of erythrosuamine (VIa). Erythrosuamine HCl (70 mg) was hydrolyzed with hydrochloric acid to yield an acid (*VIb*) M^+ 378, m.p. 195–196°, $[\alpha]_D$ −75° (c in ethanol 1.0). Dimethylaminoethanol was identified as described earlier.[1]

A small part of the acid (*VIb*) was esterified with diazomethane. The product was purified by preparative TLC on Silica Gel GF with ether-light petroleum (6:4). The NMR spectrum of the dimethylester (*VIc*) was recorded (Table 1). A further portion of the acid (*VIb*) was acetylated with acetic anhydride in pyridine overnight at room temperature. The acetylated product was purified by preparative TLC (system 2). The NMR spectrum of the acid acetate (*VId*) was recorded (Table 1).

Reduction of the acid (VIb). A small amount (10 mg) of the acid (*VIb*) was reduced with sodium borohydride according to the usual procedure to yield the diol-acid (*VIIa*): m.p. 220–221°. A portion of the reduced acid was treated with ethereal diazomethane. The oily methyl ester (*VIIb*) was purified by preparative TLC (solvent: ether). For characteristic peaks in the NMR spectrum of this methyl ester, see Table 1.

Oxidation of erythrosuamine (VIa) with chromic acid. Erythrosuamine HCl (50 mg) in acetic acid (1.25 ml) was oxidized overnight at room temperature with chromium trioxide (15 mg) dissolved in water (0.12 ml) and acetic acid (1.13 ml). The basic fraction obtained consisted of two major components. (TLC, system 1; R_F 0.61 and 0.54).

Oxidation of erythrophleguine (I) with chromic acid. Erythrophleguine was oxidized with CrO_3 as described for erythrosuamine (*VIa*). The product exhibited similar TLC properties to that of erythrosuamine (TLC, system 1; R_F main products 0.61 and 0.54).

Periodate oxidation of erythrophleguine (I), erythrosuamine (VIa), and erythrophlamine (VIII). The procedure described by Pohle *et al.*[7] was followed (reaction time, 17 h).

Alkaloid	Percentage of oxidized alkaloid
Erythrophlamine (*VIII*)	5
Erythrophleguine (*I*)	112
Erythrosuamine (*VIa*)	109

Erythrophlamine (*VIII*). This alkaloid was obtained by rechromatography of fraction BE IV [1] using the conditions given in Table 2. The properties of the isolated alkaloid were identical with those of an authentic sample. Erythrophlamine HCl: m.p. 196—197°. Erythrophlamine has a similar R_F value as erythrosuamine in system 1. In system 3, these two alkaloids are well separated.

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REFERENCES

1. Lindvall, O., Norin, T., Sandberg, F. and Thorsén, R. *Acta Pharm. Suecica* **2** (1965) 313.
2. Arya, V. P. and Engel, B. G. *Helv. Chim. Acta* **44** (1961) 1650.
3. Portius, H. J. and Repke, K. *Arzneimittelforschung* **14** (1964) 1073.
4. Ruzicka, L., Dalma, G. and Scott, W. E. *Helv. Chim. Acta* **24** (1941) 63.
5. Ruzicka, L., Dalma, G., Engel, B. G. and Scott, W. E. *Helv. Chim. Acta* **24** (1941) 1449.
6. Kohn, M. *Monatsh.* **24** (1903) 765.
7. Pohle, W. D., Mehlenbacher, V. C. and Cook, J. H. *Oil and Soap* **22** (1945) 115.

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