Tetrahedron Letters No.47, pp. 4203–4208, 1965. Pergamon Press Ltd.
Printed in Great Britain.

ERYTHROPHLEGUINE, A NEW ALKALOID FROM THE BARK OF ERYTHROPHLEUM GUINEENSE (G.DON.)

Olle Lindwall, Finn Sandberg, Rune Thorsén

Department of Pharmacognosy, Royal Pharmaceutical Institute, Stockholm, Sweden, and

Torbjörn Norin

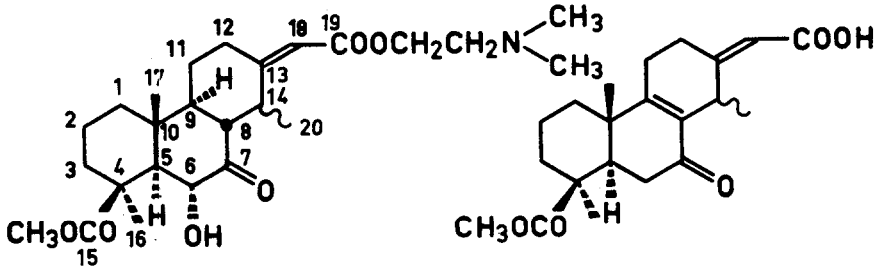
Department of Organic Chemistry, Royal Institute of Technology, Stockholm, Sweden

(Received 2 October 1965)

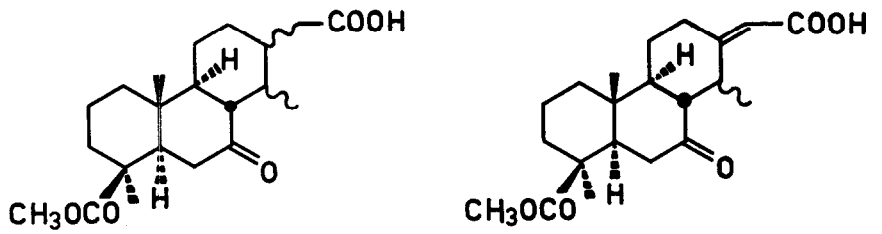
A chromatographic study of extracts of the bark of Erythrophleum guineense (G.Don.) has revealed the presence of several new alkaloids. One of these, erythrophleguine, is described in this paper.

Erythrophleguine (I), $C_{25}H_{39}O_6N$ (M.W. 449[x]), m.p. 77-78° and $[\alpha]_D$ -38° (c in ethanol 1.6) gave, on acidic hydrolysis, dimethylaminoethanol and an acid (II), $C_{21}H_{28}O_5$ (M.W. 360[x]), m.p. 194-196°, $[\alpha]_D$ +54° (c in ethanol 2.2). Spectral properties of erythrophleguine indicate the presence of an αβ-unsaturated ester grouping of the type characteristic of other Erythrophleum alkaloids (λ_{max}^{EtOH} 221 mμ, ε 30 100; ν_{max}^{KBr} 1 720, 1 645 and 860 cm^{-1}). Other characteristic infrared bands show the presence of two additional carbonyl functions

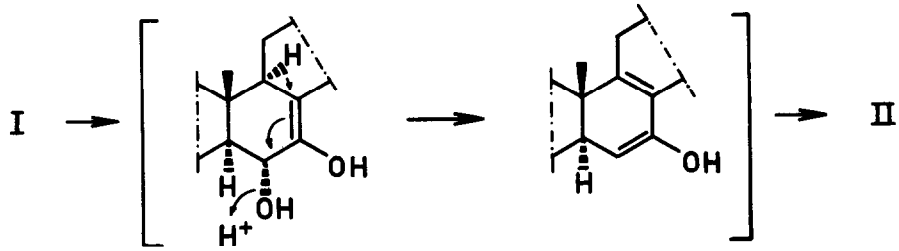
x Determined by mass spectrometry.



I II



III IV



(ν_{max}^{KBr} 1 710 and 1 690 cm^{-1}) and of a hydroxyl group (ν_{max}^{KBr} 3 500 cm^{-1}). Erythrophleguine readily forms a mono-p-nitrobenzoate, $C_{32}H_{42}O_9N_2$, m.p. 171.5-172.5°, $[\alpha]_D$-23° (c 2.2 in $CHCl_3$), the IR spectrum of which does not exhibit any hydroxyl absorption.

On catalytic hydrogenation (Pt/HOAc) acid (II) furnished a tetrahydro product which was identified as dihydrocassamic acid (III)[1] by comparison with an authentic sample. Apart from the positions of the two double bonds this finalizes the structure (II) of the acid. The UV spectrum of the acid has a maximum at 223 mμ (ε 16 200). This shows the presence of a 13,18-double bond which is characteristic of various Erythrophleum acids. The NMR spectrum[x] exhibits a broad singlet at 5.88 ppm, assigned to the C(18)-proton. The corresponding signal for cassamic acid (IV) appears at 5.70 ppm. The second double bond is conjugated to the 7-keto group ($\lambda_{infl.}^{EtOH}$ 243 mμ, ε 12 800; ν_{max}^{KBr} 1 665 cm^{-1}). The lack of any other olefinic proton signal apart from that of the C(18)-proton in the NMR spectrum of acid (II) shows that this second double bond is tetrasubstituted and thus must be in the 8,9-position as shown in formula II.

The formation of 8,9-dehydrocassamic acid on acidic hydrolysis of erythrophleguine involves a dehydration with loss of one mole of water. This transformation confirms the structure (I) of erythrophleguine apart from the positions of the hydroxyl and the keto groups.

---

[x] The NMR spectra are recorded on a Varian A-60 instrument (60 Mc/s) using deuterochloroform solutions. Chemical shifts are given in ppm from tetramethylsilane (internal standard).

Evidence for a 6α-hydroxy-7-keto grouping in erythrophleguine (I) follows from NMR data. The signal resulting from the 6β-proton appears as a doublet centered at 4.75 ppm ($J_{6\beta,5\alpha}$ 12.5 cps). The low field resonance position of this proton is explained by the influence of the neighbouring keto group. The corresponding signal of the mono-p-nitrobenzoate appears at 6.12 ppm (J 12.5 cps).

A 7β-hydroxy-6-keto grouping would also fit the above NMR data. However, the resonance positions of the C(20)-methyl groups of erythrophleguine (I) and cassamic acid (IV) are very similar (1.15 and 1.08 ppm, respectively). Since changes in the substitution pattern of the C(7)-position cause significant shifts of this methyl signal (cf. Ref. 2), erythrophleguine has a 7-keto group like cassamic acid. Furthermore, the 4α-methyl group of erythrophleguine (I) has its resonance position at a lower field (1.44 ppm) than the corresponding group of cassamic acid (IV)/1.16 ppm/. This must be due to the characteristic deshielding effect of a 6α-hydroxyl group. A similar characteristic shift has been observed in the manool series (the resonance position of the 4α-methyl group of 6α-hydroxy-13-epi-manool, "larixol", is at 1.08 ppm and that of 13-epimanool 0.86 ppm)[3].

In accordance with structure (I) the hydroxyl group of erythrophleguine is strongly intramolecularly hydrogen bonded ($\nu_{max}^{CCl_4}$ 3 460 cm^{-1}, c 0.001 M).

The formation of 8,9-dehydrocassamic acid (II) on acidic hydrolysis of erythrophleguine (I) may be explained as the result of a 1,4-elimination of water from the enol (V) to yield the enol

(VI) of 8,9-dehydrocassamic acid (cf. the proposed[4] conversion of 3α-acetoxycholestan-4-one to cholest-5-ene-4-one in the acetolysis of 2α-bromocholestan-3-one).

The configuration (IV) of cassamic acid has previously been proved[5]. The transformation of erythrophleguine to 8,9-dehydrocassamic acid (II) thus settles the configuration (I) of the alkaloid apart from the stereochemistry of the 8- and 9-positions. The optical rotatory dispersion curves of erythrophleguine (I) and cassamic acid (IV) are very similar exhibiting small negative Cotton effects (erythrophleguine, a = -2; cassamic acid, a = -7)[6]. The intramolecular hydrogen bonding between the 7-keto group and the 6α-hydroxyl group in erythrophleguine may strongly affect the optical properties of the carbonyl function. However, the curves of the two compounds have been recorded using methanolic solutions in which the contribution from intramolecular hydrogen bonding is of less importance. Thus the similarities of the two curves strongly suggest that the C(8)- and C(9)-configurations of the two compounds are the same. This is further supported by the fact that the resonance positions of the C(17)- and C(20)-methyl groups of the alkaloid (0.88 and 1.13 ppm, respectively) do not differ very much from those of the corresponding groups of cassamic acid (IV) (0.80 and 1.08 ppm, respectively). Inspection of models reveals that configurational changes at these two positions should affect the resonance positions of the two methyl groups, particularly that of the C(14)-methyl which is close to the anisotropic keto group.

Chapman et al.[5] have previously reported the isolation of a dehydrocassamic acid, m.p. 191-192°, $[\alpha]_D$+40° (c 1.0 in EtOH), from a mixture of diterpene acids obtained by acidic hydrolysis of a crude alkaloid mixture of E. guineense. During the course of our work they determined the structure of this dehydrocassamic acid.[2] The acid was shown to be 8,9-dehydrocassamic acid (II) by methods partly different from those used by us. Most probably the 8,9-dehydrocassamic acid isolated by Chapman et al. was derived mainly from erythrophleguine.

Full details regarding the isolation and structural elucidation of erythrophleguine (I) will be published in Acta Pharmaceutica Suecica.

Acknowledgements. We thank Professor W. Klyne for he optical rotatory dispersion measurements and Docent R. Ryhage for the mass spectra. Financial support from A.B. Hässle, Gothenburg, is gratefully acknowledged.

References

1. D.W. Mathieson, B. Jacques, G.T. Chapman, V.P. Arya, and B.G. Engel, Experientia 16, 404 (1960).
2. G.T. Chapman, J.N.T. Gilberg, B. Jacques, and D.W. Mathieson, J.Chem.Soc. 1965, 403.
3. T. Norin, unpublished results.
4. L.F. Fieser and M. Comero, J.Am.Chem.Soc. 75, 4716 (1953).
5. G.T. Chapman, B. Jacques, D.W. Mathieson, and V.P. Arya, J.Chem.Soc. 1963, 4010.
6. W. Klyne, Tetrahedron 13, 29 (1961).