

THE ALKALOIDS OF *CROTON SALUTARIS*

RODERICK A. BARNES and ORLANDO M. SOEIRO

Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 21941, RJ, Brazil

(Received 24 June 1980)

Key Word Index—*Croton salutaris*; Euphorbiaceae; salutarine; salutaridine; *N*-norsalutaridine.

INTRODUCTION

An earlier investigation [1] led to the isolation of two alkaloids, salutarine and salutaridine, from the leaves and twigs of *Croton salutaris* Casar, a tree which is rather common in the mountains west of Rio de Janeiro at altitudes of about 2000 m. The structure of salutaridine was finally established [2, 3] by comparison with a sample prepared by Barton *et al.* [4] from phenolic dihydrothebaine and confirmed by an X-ray study of its methiodide [5]. The present note deals with the nature of salutarine.

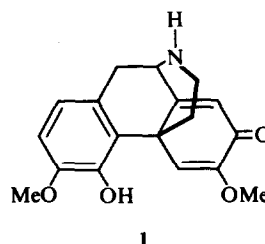
RESULTS AND DISCUSSION

The difference between salutarine and salutaridine was for a time elusive. The complete separation of the two was difficult and initial studies [2] of salutarine were made with a sample which still contained some salutaridine. A purification using initially the difference in the solubility of the picrates furnished pure salutarine which had no measurable optical rotation. However since the infra-red and magnetic resonance spectra were identical with those of salutaridine, salutarine must be the racemic form. The oriental plant *Sinomenium acutum* produces the levorotatory enantiomer [6, 7].

Because the relative amounts of the two alkaloids were different in early collections, a more systematic observation was made during 1978. Plant material collected from the same area every other month was processed to separate the alkaloids and the optical rotation observed. For most of the year the rotation of the alkaloid mixture was $0 \pm 3^\circ$. However the mixture obtained in the colder months, May ($+16^\circ$) and July ($+8^\circ$), was definitely dextrorotatory indicating that salutaridine predominated. Barton *et al.* [8] have observed a somewhat parallel seasonal variation in the incorporation of (+)-reticuline to form sinomenine in *Sinomenium acutum*. A possible explanation is that in *Croton salutaris* the cyclization which establishes the stereochemistry can take place either on an enzyme surface to form the benzyloquinoline precursor to salutaridine or in solution to form a racemic precursor which leads to salutarine.

TLC revealed the presence of small quantities of a third alkaloid. Fractions eluted from an alumina column after removal of most of the salutarine and salutaridine were combined and after prep. TLC the new alkaloid was isolated as an oil, readily oxidized in air. The MS and ^1H NMR spectrum showed that it was an alkaloid without the *N*-methyl group.

The optical rotation of two samples of this alkaloid showed it to be *N*-norsalutaridine (1), containing different amounts of the racemic form.



By analogy with *Croton flavens* and *C. linearis* in which plants *N*-demethylation has been shown [9], our alkaloid could result from demethylation of both salutaridine and salutarine. However, this contrasts with the observation of Chambers *et al.* [10] that *C. balsamifera* produces salutaridine and *N*-norsinoacutine. The difference may be that the demethylating enzyme of *C. salutaris* is non specific while that of *C. balsamifera* effects reaction with only the levorotatory isomer.

EXPERIMENTAL

Salutarine. Leaves and twigs of *Croton salutaris* Casar, identified by Professor Paulo Occhioni by comparison with a sample in the herbarium of the Botanical Garden, Rio de Janeiro, were extracted with alcohol and the bases separated with dil. HCl. The crude alkaloid mixture was treated with an equal weight of picric acid in EtOH. The picrate which separated, mp $222-7^\circ$ after recrystallization proved to be that of salutaridine, mp $229-32^\circ$. Regeneration of the alkaloid from the picrate mother liquors, followed by chromatography on alumina (elution with benzene-EtOAc) and recrystallization from benzene-isopropanol furnished salutarine, mp $222-4^\circ$ [αD^{25} $0 \pm 0.5^\circ$ ($\text{C}_2\text{H}_5\text{OH}$)]. ^1H NMR (100 MHz, CDCl_3): 2.45 (3H, s, NCH_3), 3.75 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.34 (1H, s, C-8), 6.72 (2H, AB pattern, $\text{C}_1 + \text{C}_2$), 7.60 (1H, s, C-5). (Found: C, 69.38; H, 6.52; N, 4.24. $\text{C}_{19}\text{H}_{21}\text{NO}_4$ requires: C, 69.70; H, 6.78; N, 4.18). The picrate of this alkaloid had mp $219-22^\circ$ while a synthetic sample of (\pm)-salutaridine (salutarine) prepared by Kametani and co-workers [1] was obtained as a yellow syrup which formed a picrate, mp $211-5^\circ$.

***N*-norsalutaridine.** The first sample of this base (10 mg) had [αD^{25} $+80 \pm 10^\circ$ ($\text{C}_2\text{H}_5\text{OH}$)] corresponding to about 70% norsalutaridine. A second sample showing a single spot on TLC

and having the correct ^{13}C NMR (being published separately)

had $[\alpha]_{24}^{\lambda} \frac{589 \quad 578 \quad 546 \text{ nm}}{+38.6 \quad +40.8 \quad +48.4} \quad (c = 3.4). \quad ^1\text{H} \quad \text{NMR}$
 (100 MHz, CDCl_3): 3.78 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.32 (1H, s, C-8), 6.72 (2H, AB pattern, C-1 + C-2), 7.58 (1H, s, C-5).
 MS: $\text{M}^+ m/e$ 313.127 (36%) ($\text{C}_{18}\text{H}_{19}\text{NO}_4$ requires 313.131).

Acknowledgements—The authors are indebted to the Ministry of Planning (FINEP), The National Research Council (CNPq) and the Research Council of this University (CEPG) for financial assistance.

REFERENCES

1. Barnes, R. A. and Gilbert, M. E. A. (1959) *Bol. Inst. Quim. Agric.* **58**, 1.
2. Fong, J. W. (1962) Ph.D. Thesis, Rutgers University.
3. Barnes, R. A. (1964). *An. Acad. Bras. Ciênc.* **36**, 238.
4. Barton, D. H. R., Kirby, G. W., Steglich, W. and Thomas, G. M. (1963) *Proc. Chem. Soc.* 203.
5. Collins, D. (1965) Ph.D. Thesis, Rutgers University.
6. Hsu, J. S., Lo, S. Y. and Chu, J. H. (1964) *Sci. Sinica* **13**, 2016.
7. Hsu, J. S., Lo, S. Y. and Chu, J. H. (1965) *Chem Abstr.* **62**, 9183.
8. Barton, D. H. R., Kirby, A. J. and Kirby, G. W. (1968) *J. Chem. Soc. C*, **929**.
9. Stuart, K. L. and Graham, L. (1971) *J. Chem. Soc. D*, 392.
10. Chambers, C., Haynes, L. J. and Stuart, K. L. (1966) *Chem. Commun.* 449.
11. Kametani, T., Ihara, M., Fukumoto, K., and Yagi, H. (1969) *J. Chem. Soc. C* 2030.