4,5,6,6a-Tetradehydro-*N*-methyl-7-oxoaporphinium Salts

By HELENE GUINAUDEAU and MAURICE SHAMMA*

(*Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania* 16802 and *U.E.R. Chimie Thérapeutique, E.R.A.* 317, 92290 *Chatenay-Malabry, France*)

and BAMRUNG TANTISEWIE* and KALAYA PHARADAI

(*Department of Pharmacognosy, Chulalonghorn University, Bangkok* 5, *Thailand*)

Summary *Stephania venosa* Spreng. (Menispermaceae) has yielded the first two 4,5,6,6a-tetradehydro-*N*-methyl-7-oxoaporphinium salts known, namely uthongine (**4**) and thailandine (**5**), which are partially decomposed by chromatography on silica gel to 7-oxocrebanine (**6**) and 7-oxostephanine (**7**), respectively.

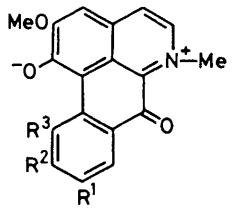
AMONG the oxoaporphine alkaloids so far recorded in the literature, there are no known examples of *N*-methyloxoaporphinium salts which incorporate an *N*-methyloxoaporphinium cation carrying a net positive charge. Three naturally occurring tetradehydro-*N*-methyl-7-oxoaporphines are known, corunnine (**1**), alkaloid PO-3 (**2**), and nandazurine (**3**). However, in each case the C-1 substituent is an oxide anion, so that these alkaloids are betaines rather than salts.[1]

We now describe the isolation and characterization of the first two true 4,5,6,6a-tetrahydro-*N*-methyl-7-oxoaporphinium salts, namely uthongine (**4**) and thailandine (**5**).

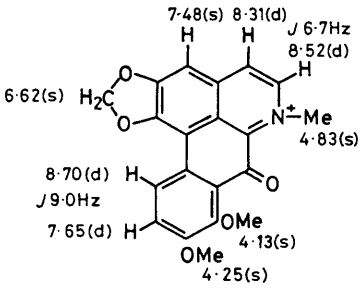
Silica-gel column chromatography of the fraction containing polar alkaloids, obtained from the extraction of dried tuberous roots (2·9 kg) of *Stephania venosa* Spreng. (= *S. rotunda* Lour.) (Menispermaceae), native to Thailand, gave, upon elution with 10% methanol in chloroform, the yellow oxocrebanine (**6**) (6 mg), m.p. 260—265 °C (MeOH). This compound was previously known only from the *in vitro* oxidation of the aporphine (−)-crebanine (**8**).[2] Further elution using 15% methanol in chloroform furnished the known oxoaporphine, oxostephanine (**7**) (5 mg), m.p. 170—172 °C (EtOH).

When the polarity of the eluant was appreciably increased through the use of 25% methanol in chloroform, a red band (7 mg), followed by an orange band (3 mg), were collected.

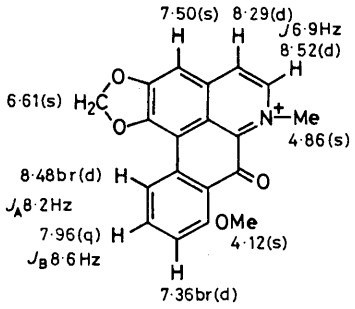
The red band proved to be uthongine (**4**), the Fourier-transform (FT) n.m.r. spectrum (360 MHz, CF_3CO_2D) of which is summarized in structure (**4**). Of particular importance in this spectrum is the downfield *N*-methyl singlet at δ 4·83. Most significantly, thin layer chromatography (t.l.c.) or column chromatography of this material over



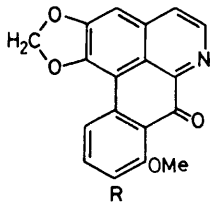
(1) $R^1 = R^2 = OMe$, $R^3 = H$
(2) $R^1 = R^2 = H$, $R^3 = OMe$
(3) $R^1, R^2 = OCH_2O$, $R^3 = H$



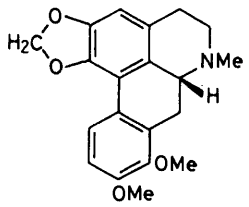
(4)



(5)



(6) R = OMe
(7) R = H



(8)

silica gel inevitably gave a relatively fast moving band identified as 7-oxocrebanine (**6**), together with a much slower band consisting of uthongine (**4**). Uthongine thus suffers facile *N*-demethylation upon chromatography, with formation of the corresponding free-base oxocrebanine.† To prove the structure of uthongine conclusively, *N*-methylation of oxocrebanine with methyl iodide in refluxing acetonitrile yielded (80%) amorphous uthongine iodide; λ_{max}^{EtOH} 217, 229, 263, 284, 385, and 500 nm (log ϵ 4·04, 4·01, 3·96, 3·87, 3·12, and 2·94, respectively);‡ *m/e* 351 $(M + 1)^+$, 350 (M^+, $C_{20}H_{16}NO_5$), and 335 $(M - Me)^+$. The ^1H n.m.r. spectrum of the semi-synthetic uthongine iodide in CF_3CO_2D was identical with that of the natural product in the same solvent.

The orange band, thailandine (**5**), has an FT n.m.r. spectrum (CF_3CO_2D) which again shows a characteristic downfield *N*-methyl singlet at δ 4·86. As with uthongine (**4**), chromatography of thailandine (**5**) resulted in some *N*-demethylation to furnish 7-oxostephanine (**7**) together with undemethylated starting material.† Additionally, *N*-methylation of compound (**7**) with methyl iodide in acetonitrile gave amorphous thailandine iodide in 75% yield; λ_{max}^{MeOH} 216, 257, 288, 325sh, 376, and 464 nm (log ϵ 4·34, 4·35, 4·18, 3·63, 3·83, and 3·73, respectively),‡ *m/e* 321 $(M + 1)^+$, 320 (M^+, $C_{19}H_{14}NO_4$), 306 $(M + 1 - Me)^+$, and 305 $(M - Me)^+$. As expected, the n.m.r. spectrum of semi-synthetic thailandine iodide in CF_3CO_2D was identical with that of the natural product.

An interesting conclusion is that some or part of the oxoaporphines isolated from plant sources may exist in nature as the corresponding *N*-metho-salts. Such salts would then undergo easy *N*-demethylation upon chromatographic purification. A possible route to the oxoaporphines in nature would thus involve the sequence aporphine → dehydroaporphine → *N*-methyloxoaporphinium cation → oxoaporphine,§ while another would consist of the progression noraporphine → dehydronoraporphine → oxoaporphine.

This research was supported by the National Cancer Institute, National Institutes of Health, USDHHS. H. G. is the recipient of a N.A.T.O. fellowship.

(*Received*, 6*th July* 1981; *Com.* 780.)

† Solutions of compounds (**4**) and (**5**) as the iodide salts are stable in methanol. When methanolic solutions of these iodides were allowed to stand overnight and were monitored by u.v. spectroscopy, none of the corresponding oxoaporphines was detected the next day.

‡ Significantly, the positions of the maxima in the u.v. spectrum of uthongine iodide correspond to those for oxocrebanine in acid solution. It follows that protonation of oxoaporphines takes place on the nitrogen atom, rather than on the carbonyl oxygen. The same spectral phenomenon is observed in the case of thailandine and oxostephanine.

§ This sequence would particularly apply to *S. venosa* where we have also found crebanine and dehydrocrebanine, as well as a 7-hydroxylated crebanine, while no norcrebanine could be detected. Likewise, no norstephanine was found.

[1] For a listing of the aporphinoids, see H. Guinaudeau, M. Leboeuf, and A. Cavé, *Lloydia*, 1975, **38**, 275; *ibid.*, 1979, **42**, 325; as well as the annual chapters on the aporphinoids in 'Specialist Periodical Reports, The Alkaloids,' ed. M. F. Grundon, The Royal Society of Chemistry, London.
[2] J.-I. Kunitomo, Y. Murakami, M. Oshikata, T. Shingu, M. Akasu, S.-T. Lu, and I.-S. Chen, *Phytochem.*, 1980, **19**, 2735.