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ALKALOIDS OF NUPHAR LUTEUM (L) SM. ISOLATION OF ALKALOIDS CONTAINING SULPHUR

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SYSTEMATIC chemical studies have only recently been extended to plants of the genus *Nuphar* (*Nymphaeceae*), and in only two of the species - *Nuphar japonicum* D.C. (Kawahone) and *N. luteum* (L) Sm. (yellow water-lily) - has the content and structure of alkaloids been investigated in any detail.

The rhizome of *N. japonicum*, which was investigated first, yielded nupharidine[1], desoxynupharidine[2] and nupharamine[3], and the rhizome of *N. luteum* gave desoxynupharadine and beta-desoxynupharidine[4].

Thanks to the Japanese chemists Kotake *et al.*[5] and Arata *et al.*[6], the structure of nupharidine and desoxynupharidine as well as nupharamine is elucidated. On evidence obtained from degradation experiments these authors accepted for nupharadine, desoxynupharadine and nupharamine the formulae (I), (II) and (III) respectively. The first two formulae have

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[1] J. Arima and T. Takahashi, *J. Chem. Soc., Japan* **52** 815.

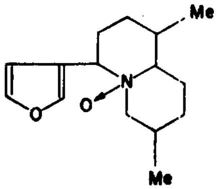
[2] Y. Arata, T. T. Ohashi and T. Ukai, *Ann. Rept. Fac. Pharm. Univ. Kanazawa* **1**, 75 (1951).

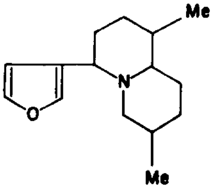
[3] Y. Arata and T. Ohashi, *C.A.* **51**, 17 (1957).

[4] O. Achmatowicz and M. Mollowna, *R. Chemii* **19**, 493 (1939).

[5] M. Kotake, S. Kusumoto and T. Ohara, *Ann.* **606**, 148 (1957).

[6] Y. Arata, T. Ohashi and T. Ukai, *Ann. Rept. Fac. Pharm. Univ. Kanazawa* **1**, 75 (1951).


I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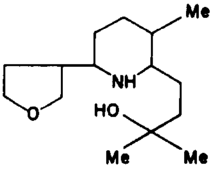
III

recently been confirmed by Kaneko, Kawasaki and Okamoto[7] by total synthesis of dl-desoxynupharidine.

Desoxynupharidine and beta-desoxynupharidine constitute together about 12 per cent of the alkaloid content of N. luteum rhizome. It may be presumed that nupharidine, desoxynupharidine and nupharamine make up a similarly small percentage in N. japonicum. Hence, far the greatest part of the alkaloids of the genus Nuphar remains yet to be investigated, and this has led us to resume studies on N. luteum alkaloids.

Our most important result has been isolation from the rhizome of N. luteum of alkaloids containing sulphur, never yet recorded in this class of natural products. In all, we have isolated four thioalkaloids, and their chemical composition suggests close relationship to desoxynupharidine.

The main alkaloid (prismatic needles, m.p. 129°-130°), designated "thiobinupharidine", has the empirical formula $C_{30}H_{40}O_2N_2S$ (Calc.: C,73.17; H,8.13; N,5.69; S,6.50; M W, 492. Found: C,73.01; H,8.42; N,5.81; S,5.89; M W, 508) or $C_{30}H_{42}O_2N_2S$ (Calc.: C,72.84; H,8.50; N,5.63; S,6.38: M W, 494), which, if sulphur is ignored, is almost precisely double the empirical formula of desoxynupharidine ($C_{15}H_{23}O\ N$). Thiobinupharidine

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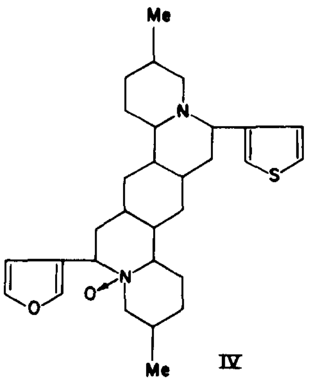
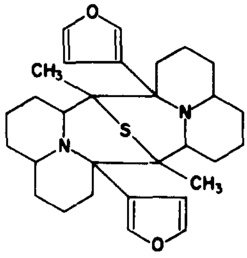
[7] T. Kaneko, I. Kawasaki and T. Okamoto, Chemistry and Industry **38**, 1191 (1959).

is a dextrorotatory (diperchlorate $[\alpha]_D^{H_2O}$ + 49.8) diacidic base (diperchlorate $C_{30}H_{40}O_2N_2S.2HClO_4$, prisms m.p. 282-284°. Calc.: C,51.94; H,6.11; N,4.08; S,4.61; 2CCH$_3$,4.31. Found: C,52.03; H,6.39; N,4.04; S,4.61; CCH$_3$,4.06,. Does not add hydrogen (Pd), and groups OH, SH, and NH, as well as OCH$_3$ and NCH$_3$ could be demonstrated neither chemically nor spectroscopically. The alkaloid did not react with reagents for CO group (hydroxylamine, 2,4-dinitrophenylhydrazine), but has two groups CCH$_3$ (Kuhn-Roth). IR spectrum, main maxima: 1660cm^{-1}, 1425cm^{-1} and 878cm^{-1} (furan ring), 2750cm^{-1} (CH-N), 3419cm^{-1} (CH). UV spectrum for thiobinupharidine diperchlorate λ_{max}^{EtOH} 298 mμ and ε 1115. On this evidence, thiobinupharidine was initially thought to be built of two parts: desoxynupharidine and a hypothetical thionupharidine, united at the price of four hydrogen atoms and with two methyl groups used to build the bridge-ring. Of a number of formulae satisfying these requirements, preference was given to formula (IV)



IV



V

Further investigations, however, called formula (IV) in question. We found that on either treatment with sulphur dioxide or reduction with hydrogen in presence of palladium, thiobinupharidine - unlike nupharidine (I) - does not lose oxygen and, consequently, cannot contain the group

N ⟶ O required by formula (IV). The formula is also undermined by the NMR spectrum. The spectrum shows three main groups of signals and the ratio of the areas is 3.6 to 2.0 to 36.8. This is in agreement with formula (IV), which requires 4:2,36. However, absence of fine structure near the peaks 2.7 τ and 3.6 τ makes beta-substituted thiopene grouping rather unlikely, but suggests two furan rings rather. The spectrum contains a band at 9.1 τ, which corresponds to two methyl groups attached to saturated carbon atom. However, this band is a singlet which would indicate that the methyl groups are attached to quaternary carbon atoms. In the light of these data, a formula of type (V) may be derived for thiobinupharidine.

The remaining three thioalkaloids were isolated as diperchlorates: (i) Allo-thiobinupharidine diperchlorate ($C_{30}H_{42}O_2N_2S.2HClO_4$ requires: C,51.94; H,6.11; S,4.61. Found: C,52.03; H,6.32; S,4.70), plates m.p. 320-325°,; (ii) Pseudothiobinupharidine diperchlorate forms prisms m.p. 173-175°, $[\alpha]^{EtOH}_{D}$ +186.2 ($C_{30}H_{40}O_2N_2S.2HClO_4.2H_2O$ requires: C,49.44; H,6.42; N,3.8; S,4.4; $2CCH_3$,4.1. Found: C,49.69; H,6.38; N,4.10; S,4.71; CCH_3,4.04); (iii) Thiobidesoxynupharidine diperchlorate crystallizes as clusters of prisms m.p. 225-226°, $[\alpha]^{EtOH}_{D}$ +26.6 ($C_{30}H_{40}ON_2S.2HClO_4$ requires: C,53.2; H,6.3; N,4.1; S,4.7; $2CCH_3$,4.4. Found: C,53.5; H,6.91; N,4.10; S,5.02; CCH_3,3.9).

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