

THE STRUCTURE OF CASTORAMINE

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THE scent glands of the beaver, known commercially under the name castoreum, contain a veritable treasure of organic substances, presumed to be derived mainly from barks and buds of trees, the beaver's principal food. One of the interesting castoreum constituents isolated and investigated by Lederer^{1,2} is the base castoramine, $C_{15}H_{23}O_2N$. According to Lederer, castoramine is a strong base which is relatively unstable to light and oxygen. It can be purified by recrystallization of the corresponding sulphate, m.p. 212-216^o, from which the free base can be liberated in crystalline form, m.p. 65-66^o.² The French author further reported that castoramine contains no methoxyl or N-methyl groups and shows no active hydrogen in the Zerewitinoff determination. The base did not react with 2,4-dinitrophenylhydrazine and was found to be resistant to acid or alkaline hydrolysis and to a catalytic hydrogenation with palladium on charcoal.

We became interested in castoramine since it appeared that it should

¹ E. Lederer, Perfumery Essent. Oil Rec. 40, 353 (1949).

² E. Lederer, Bull. Soc. Chem. Biol. 25, 1381 (1943).

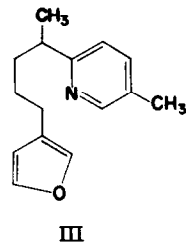
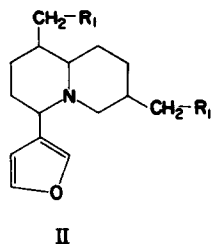
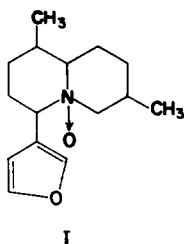
be either a sesquiterpene base or a compound biologically formed by a multiple acetate and/or propionate condensation. The extraction of the basic material from the air-dried glands of the Canadian beaver followed by a distillation, yielded an oily fraction (125-135°/0.08 mm Hg) which according to its infrared spectrum was almost pure castoramine (yield = 0.4 per cent of partially dried glands). The analysis of the crystalline sulphate and the sublimed free base confirmed Lederer's $C_{15}H_{23}O_2N$ formula. Castoramine was found to contain one C-methyl group (50 per cent), no methoxyl and no N-alkyl. In contrast to Lederer's report, however, our analytical results indicated one active hydrogen in the molecule. The infrared spectrum of castoramine showed a band at 3250 cm^{-1} (CHCl_3) and acetylation of the base with acetic anhydride-pyridine yielded an oily basic acetate (Found: C, 70.14; H, 8.49; O, 16.32; N, 4.62. $C_{17}H_{25}O_3N$ requires: C, 70.16; H, 8.66; O, 16.49; N, 4.82) (I.R. max. = 1725 cm^{-1} in CHCl_3), showing the presence of a hydroxyl group in castoramine.

The nature of the second oxygen became clear when it was realized that castoramine contains a furan ring. While the ultraviolet spectrum of the base showed only end-absorption, the presence of an aromatic system was indicated by the uptake of 2-3 moles of hydrogen on reduction of the sulphate with an active platinum catalyst and by sharp I.R. peaks at 1505 and 872 cm^{-1} . The NMR spectrum of castoramine³ with peaks at -104 counts/sec (double intensity) and -70 counts/sec (single intensity) quite clearly

³ The spectrum was determined with a 60 mc/sec instrument in chloroform solution. The values have been converted to c.p.s. relative to water at 40 mc/sec for easier reference with the literature values (See ref. 4). We thank Dr. R. R. Fraser, University Ottawa, for doing this determination for us.

established the presence of a β -monosubstituted furan ring⁴. A C-methyl peak at +162 counts/sec (triple intensity) confirmed our analytical value mentioned earlier.

At this point it became attractive to speculate that castoramine is in fact a sesquiterpene containing one oxygen ring and one or more likely two nitrogen rings. Now such a compound has already been found in Nature by two Japanese groups.^{5,6} In an excellent degradative study, they found that the alkaloid nupharidine, obtained from the water-lily Nupher japonicum was the N-oxide (I). Since the Canadian beaver is known to feed on stems and roots of water-plants, a relationship between the two bases became very likely.



The reaction of castoramine with phosphorus oxychloride gave a

⁴ E. J. Corey, G. Slomp, S. Dev, S. Tobinaga and E. R. Glasier, J. Amer. Chem. Soc., **80**, 1204 (1958).

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

⁶ Y. Arata and T. Ohashi, J. Pharm. Soc. Japan **77**, 236 (1957).

chloro-compound $C_{15}H_{22}ONCl$, m.p. 68° , which could also be obtained by a treatment of the base with tosyl chloride in pyridine. Reduction of the chloro-compound in boiling glacial acetic acid with zinc dust in the presence of sodium iodide gave an oily base which could be purified through its crystalline hydrochloride, m.p. $215-220^\circ$. This base was found to be identical by infrared spectra with desoxynupharidine (II) ($R_1 = R_2 = H$) obtained by the Japanese workers by the reduction of (I)^{7,8}.

It follows that the structure of castoramine is (II) ($R_1 = H, R_2 = OH$) or (II) ($R_1 = OH, R_2 = H$). Selenium dehydrogenation of castoramine gave an oily base, which was purified through the crystalline picrate, m.p. $69-71^\circ$ (!) and sublimed for analysis. (Found: C, 78.59; H, 8.32; O, 7.29; N, 6.32. $C_{15}H_{19}NO$ requires: C, 78.67; H, 8.36; O, 6.99; N, 6.12). Its ultraviolet spectrum ($\lambda_{max} = 268 \text{ m}\mu$, $\epsilon = 7400$ with inflections at 262 and 275 $\text{m}\mu$) indicated a disubstituted pyridine derivative. We believe that the dehydrogenation product is in fact (III), also obtained by the Japanese workers from desoxynupharidine⁵. For this reason, we prefer structure (II) ($R_1 = H, R_2 = OH$) for castoramine.

Two further observations deserve comment. Unlike simple furans, castoramine is very stable to aqueous acid. Prolonged boiling with sulphuric acid in ethanol destroyed only a small part of the material. Obviously, the charged nitrogen makes a further attack of a positive ion

⁷ S. Kusumoto, *J. Japan Chem. Soc.*, 78, 488 (1956).

⁸ We thank Dr. Kusumoto, Osaka University, Japan, for making this article available to us. We are also grateful to him for supplying us with a generous sample of desoxynupharidine hydrochloride.

very difficult. Secondly, castoramine acetate (see above) shows an I.R. maximum at 1725 cm^{-1} (CHCl_3), while the corresponding hydrochloride has the acetate peak in the usual position (1740 cm^{-1} in CHCl_3). It appears that the tertiary nitrogen of the free base can interact with the acetate carbonyl group (1,6 relationship).

Additional reactions of castoramine together with stereochemical considerations will be published at a later date. We are at the present time investigating the alkaloid content of New Brunswick water-lilies.

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