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THE STRUCTURE OF LEONURINE

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AN ALKALOID, leonurine, was first isolated in 1930 from the leaves of Leonurus Sibiricus L. by Kubota and Nakajima[1], who assigned a molecular formula $C_{13}H_{24}O_4N_4$ to it. In this communication we wish to report the complete structure of leonurine.

From the elemental analysis and titration, the molecular formula of leonurine hydrochloride (I), m.p. 193-194°, was revised to $C_{14}H_{21}O_5N_3 \cdot HCl \cdot H_2O$ (Found: C, 45.91, 45.85; H, 6.93, 6.83; N, 11.76, 11.25; Cl, 9.94; mol. wt. 385. Calc.: C, 45.96; H, 6.61; N, 11.49; Cl, 9.69; mol. wt. 365.79); the water of crystallization is easily removed by heating to 70° under vacuum but quickly re-absorbed from atmosphere at room temperature. The alkaloid has following properties: pKa' 7.9 in water; Sakaguchi, Dragendorff, and ferric chloride tests are positive; ν_{KBr} 1709, 1675, 1626 cm^{-1}.

When a solution of leonurine (I) in 6 N hydrochloric acid was heated and then extracted with ether, there was obtained an acid (II) $C_9H_{10}O_5$*,

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* Satisfactory analysis was obtained.

[1] S. Kubota and S. Nakajima, Nippon Yakubutsugaku Zasshi (Japan) 153 (1930).

m.p. 209.5-211.5°, which was identified as syringic acid (3,5-dimethoxy-4-hydroxybenzoic acid) through mixed melting point determination and spectral comparisons with an authentic sample. The residual aqueous solution showed positive Sakaguchi but negative Dragendorff reactions suggesting that it contains a monosubstituted guanidine (III). The solution, when treated with aqueous picric acid, gave a picrate of (III) $C_5H_{13}ON_3 \cdot C_6H_3O_7N_3 \cdot H_2O$ *, m.p. 153°. Hydrolysis of the guanidine (III) with 10 per cent sodium hydroxide afforded 1.7 moles of ammonia (calc. from the alkaloid used) and a ninhydrin-positive substance (IV) that could not be extracted with ether. This substance (IV) was converted by Schotten-Baumann method to a monobenzoate $C_{11}H_{15}O_2N$ *, m.p. 74.5°, and by treatment with p-nitrobenzoyl chloride in pyridine to a di-p-nitrobenzoate $C_{18}H_{17}O_7N_3$ *, m.p. 162-163°. That the infra-red spectrum of the latter shows characteristic bands of an ester (1723 cm^{-1}) and an amide (1641) suggests that the original substance (IV) is a butanolamine. Since NMR spectrum of the benzoate has no indication of $C\text{-}CH_3$ group, possible structure of (IV) is δ-hydroxy-n-butylamine. Synthetic δ-hydroxy-n-butylamine N-benzoate and O,N-di-p-nitrobenzoate were shown to be identical with the benzoate and di-p-nitrobenzoate of (IV), respectively. The guanidine compound (III) must, therefore, be δ-hydroxy-n-butylguanidine.

From the consideration of the molecular formula and the NMR spectrum [two protons at -14 cps (arom.), two at +89 ($O\text{-}CH_2$), six at +106 (OCH_3), two at +126 ($N\text{-}CH_2$), four at +186 ($\text{-}CH_2CH_2\text{-}$), and no other signals were observed],[2] it is evident that leonurine is composed of syringic acid (II) and δ-hydroxy-n-butylguanidine (III). That syringic acid moiety links through its carboxyl group, and not through its phenolic hydroxyl, with the

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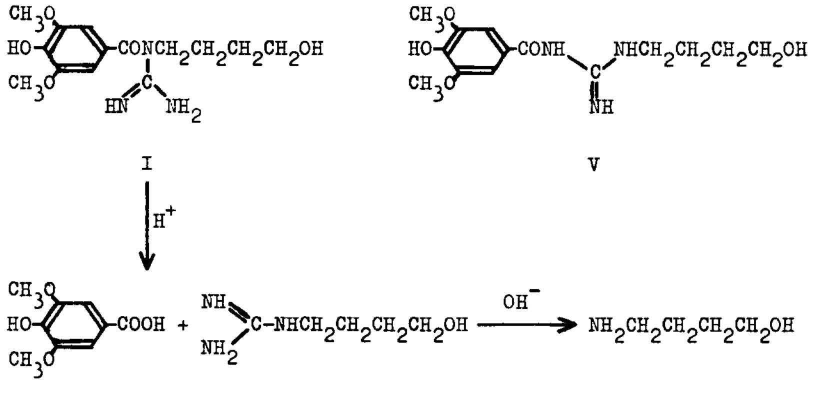
* Satisfactory analyses were obtained.

[2] Spectrum was taken on a Nihondenshi JM (40 Mc) Spectrometer using D_2O as solvent and benzene as an external standard (0 cps).

guanidine (III) is deduced from the facts that the ultra-violet spectrum of leonurine hydrochloride [λ_{max}^{MeOH} 276 mμ (log ε 4.0), λ_{max}^{NaOH} 239, 326 (4.3, 4.7)] is almost superimposable with that of methyl syringate [λ_{max}^{MeOH} 275 (4.0), λ_{max}^{NaOH} 237, 325 (4.2, 4.5)] but not with that of 3,4,5-trimethoxybenzoic acid [λ_{max}^{MeOH} 215, 260, 300 (4.2, 3.7, sh.), λ_{max}^{NaOH} 252, 293 (3.9, sh.)], and that leonurine shows positive reaction with ferric chloride.



I

V

II

III

IV

On the other hand, δ-hydroxy-n-butylguanidine (III) has three possible positions that can link with syringic acid, i.e. two (N and N') in the guanidino group and one in the hydroxyl. Since pKa (7.9) of the alkaloid is close to that of benzoylated guanidines (ca. 7)[3] but not to that of alkylated ones (ca. 13)[4], syringic acid must be attached to the guanidino group (N or N') of (III).

One of the two possible isomers, N'-substituted δ-hydroxy-n-butylguanidine (V), was synthesized. Condensation of 3,5-dimethoxy-4-acetoxybenzoyl chloride and S-methylisothiourea afforded N-(3,5-dimethoxy-4-acetoxybenzoyl)-S-methylisothiourea which was then treated with δ-hydroxy-n-butyl-

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[3] pKa': benzoylguanidine 6.8; 3,4,5-trimethoxybenzoylguanidine 6.8; N-benzoyl-N'-isopropylguanidine 7.1.

[4] S.J. Angyl and W.K. Warburton, J. Chem. Soc. 2492 (1951).

amine to give, with simultaneous deacetylation, N-(3,5-dimethoxy-4-hydroxybenzoyl)-N'-(δ-hydroxy-n-butyl)guanidine (V) isolated as its hydrochloride $C_{14}H_{21}O_5N_3 \cdot HCl$*, m.p. 192°, pKa' 7.0 and 9.0, ν_{KBr} 1685, 1610 cm^{-1}. This compound was, however, not identical with the alkaloid. Therefore leonurine must be the N,N-isomer (I). Incidentally, Dragendorff test of the alkaloid and all benzoylguanidine derivatives synthesized[3] was positive.

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* Satisfactory analysis was obtained.