

SYNTHESIS OF LEONURINE

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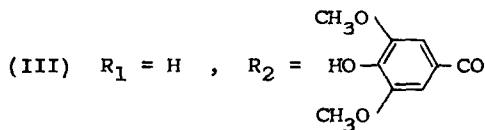
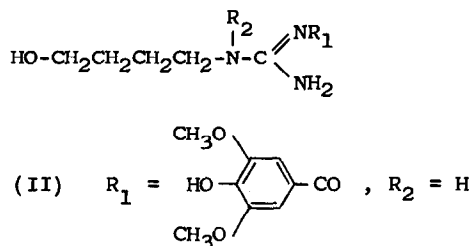
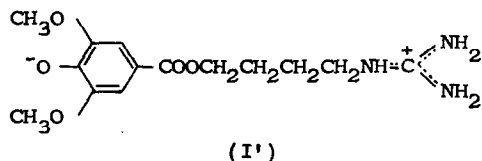
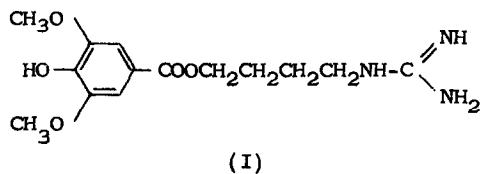
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In the previous communication (1) it was reported that leonurine, an alkaloid isolated from Leonurus sibiricus L., was composed of the two moieties, i.e. syringic acid part and δ -hydroxybutyl-guanidine part. There remained three possible combinations of these two moieties as I, II, and III; one of which is acyl ester (I) and two are acylguanidine derivatives (II, III).

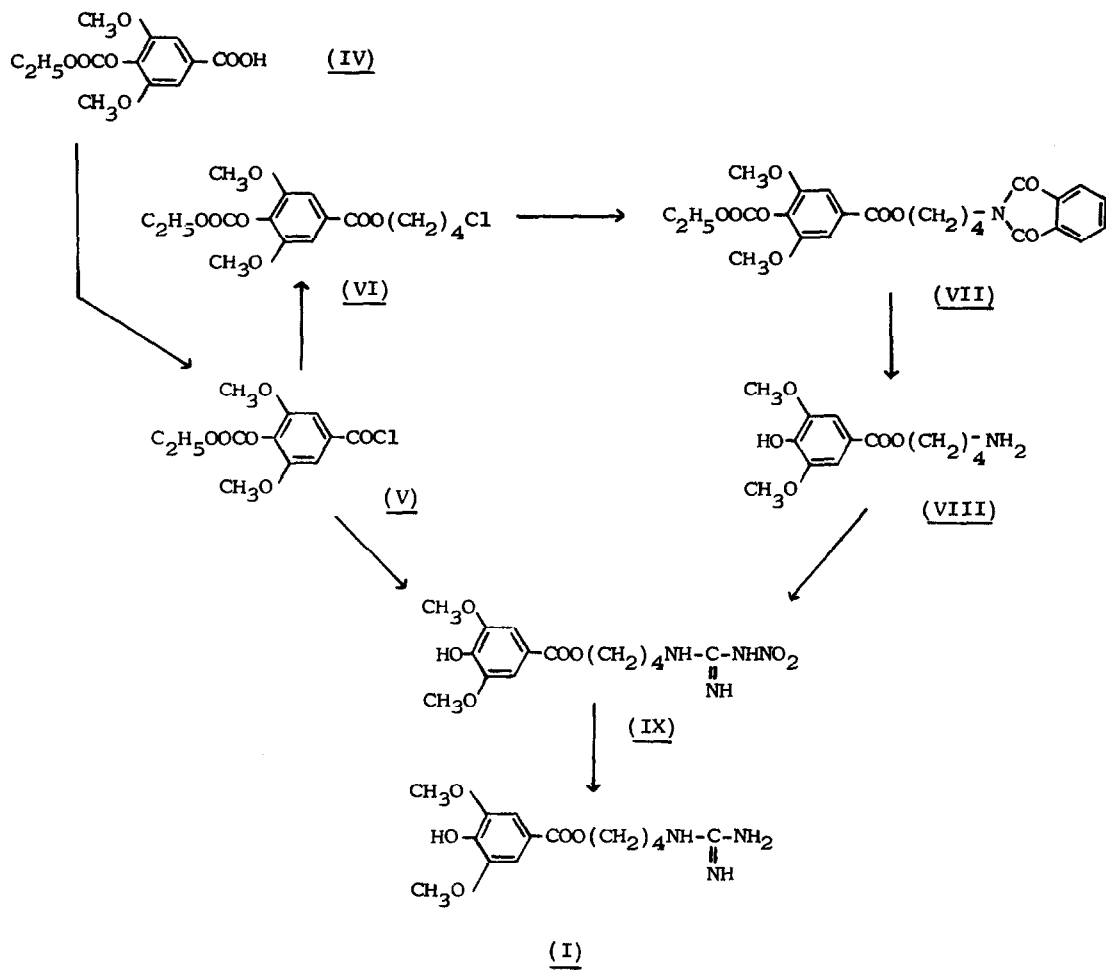


One of the acylguanidines (II) was synthesized, but it was not identical with the natural product (1). Since the alkaloid shows a basic pK_a' at 7.9, the acylguanidine (III) rather than the ester (I) was suggested to be the preferred structure (1). The ester (I) can not be excluded, however, because the phenol group might show an apparently basic pK_a' at a smaller pK_a' value than that expected from a normal phenol (2), if it exists in a zwitterionic form (I'). This is indeed the case. This communication described synthesis of the ester (I), which was proved to be identical with natural leonurine.

Carbomethoxylation of syringic acid gave 4-carbomethoxysyringic acid (IV), m.p. 179-181^o (3), which was converted by refluxing with thionyl chloride to its acid chloride (V), m.p. 74.5^o (3). Reaction of the acid chloride with tetrahydrofuran in the presence of zinc chloride at 70^o (4) afforded the δ -chlorobutyl-ester (VI), which was treated without purification, with potassium phthalimide in dimethylformamide on a water bath. The resulting phthalimide derivative (VII), m.p. 125-126^o, was dissolved in ethanol and the solution was refluxed with hydrazine hydrate in the presence of sodium acetate or triethylamine to give, on cooling, crystalline precipitates, which were then dissolved in aqueous potassium hydroxide and the resulting solution was immediately acidified with hydrochloric acid. The product precipitated was obtained by filtration and treated with 10 % sodium bicarbonate to give the corresponding amine (VIII), m.p. 214-215^o (decomp.), which was again converted to its hydrochloride, m.p. 195-196^o. During these reactions two protecting groups, phthaloyl and carbomethoxyl groups, were removed, whereas the syringic ester linkage remained unhydrolyzed.

The amine (VIII) is a zwitterionic compound having pK_a 's of phenolic hydroxyl and amino groups at 8.12 and 10.43 in water and 8.77 and 10.18 in 50 % ethanol, respectively (5). Addition of formalin lowers the pK_a' of amino group from 10.43 to ca. 6.5, whereas pK_a' of phenol becomes 10.0, since the condensation product of the amine and formaldehyde is not zwitterionic (6).

Attempts to condense the amine (VIII) with S-methylisothiourea or cyanamide failed, but condensation with N-nitro-S-methylisothiourea was effected in pyridine



under cooling and the resulting nitroguanidine (IX), m.p. 128.5-129.5^o, was then reduced catalytically in acetic acid containing hydrochloric acid in the presence of palladium on charcoal to hydrochloride of δ-guanidinobutyl-syringate (I), m.p. 191-194^o, which was proved to be identical with leonurine hydrochloride, m.p. 193-194^o, by comparison of ultraviolet and infrared spectra (Fig.1) and by mixed m.p. determination.

Alternatively, leonurine was also synthesized from 4-carbomethoxy-syringic acid chloride (V) by condensation with N-nitro-N'-(δ-hydroxybutyl)guanidine, m.p. 115^o, prepared from 4-aminobutanol and N-nitro-S-methylisothiourea, and then by catalytic reduction.

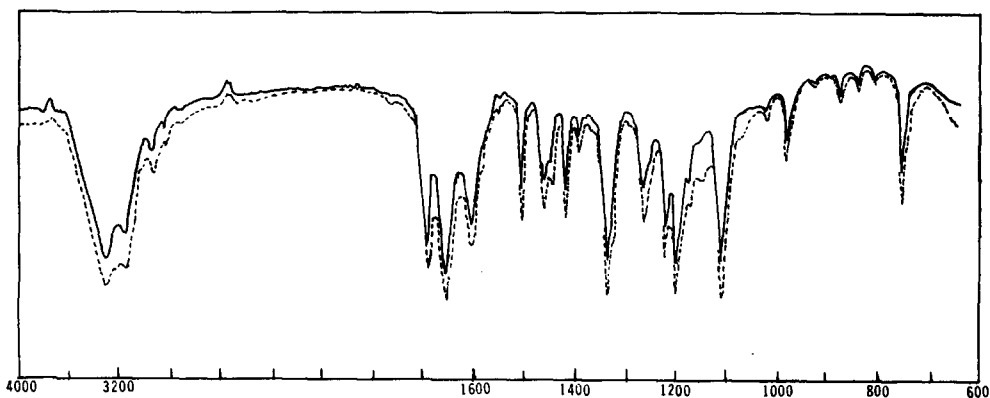


Fig.1 Infrared spectra of natural leonurine hydrochloride (-----) and synthetic leonurine (——) in KBr

Satisfactory elemental analyses were obtained for all new compounds whose m.p.s are given.

REFERENCES

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