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N^α,*N*^α-Dimethylhistamine, a Hypotensive Principle in *Casimiroa edulis* Llave et Lex^{*}

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The seeds of *Casimiroa edulis* Llave et Lex., a tree growing in Mexico and Central America, have been used in native medicine as a hypnotic and sedative.^{1,2} Ramirez and Rivero³ have reported that an extract of the seeds is used clinically in insomnia in hypertension; deLille⁴ found that intravenous administration of such extracts produced a marked decrease of blood pressure in dogs, and that the material was toxic in higher doses.

A number of chemical investigations of the seeds of *Casimiroa edulis* have been reported.^{2,5,6} About a dozen compounds have been isolated, including known coumarins, furanoquinoline alkaloids, and flavones, and some of as yet unknown structure. It was suggested that *N*-benzoyltyramine might be responsible for the pharmacological activity of the plant⁶ but no details were given.

The hypotensive action of an extract of *Casimiroa edulis* seeds prepared in this laboratory has been confirmed by Dr. C. A. Stone, of the Merck Institute for Therapeutic Research, West Point, Pa. He found, also, that this effect was not obtained if an antihistamine was also administered, indicating that the hypotensive agent was histamine or a histamine-like compound.

Paper chromatographic analysis of a crude extract of *Casimiroa edulis* seeds by the method of

Ames and Mitchell⁷ showed that histamine itself was absent. However, at least two other compounds were found which gave positive reactions to the Pauly reagent (diazobenzenesulfonic acid), an agent which gives fairly characteristic reactions with imidazoles. Separation of the imidazoles from the crude extract was then effected by the method of Koessler and Hanke.⁸ Eventually, a pure compound was isolated as its hydrochloride and its picrate; it was identical with *N*^α,*N*^α-dimethylhistamine which had been produced synthetically;⁹ yield of pure compound from seeds was 0.05%. The search for the second compound which gave a positive reaction to Pauly's reagent is being continued.

According to Huebner, Turner, and Scholz, *N*^α,*N*^α-dimethylhistamine acts pharmacologically much like histamine,^{9,10} in causing a marked lowering of the blood pressure of animals. Apparently, at least part of the pharmacological activity of *Casimiroa edulis* seeds may be attributed to the presence of *N*^α,*N*^α-dimethylhistamine. As far as we know, previously this compound has been found in nature only in the sponge *Geodia gigas*, and in this case it was not fully characterized.¹¹

EXPERIMENTAL¹²

Seven hundred grams of finely powdered air-dried *Casimiroa edulis* seeds (S. B. Penick, New York) were triturated with five 2500-cc. portions of boiling methanol. The filtered extracts were combined, 250 cc. of water was added and the methanol was removed by distillation. The dark brown residue was extracted thrice with 100-cc. portions of petroleum ether in order to eliminate fats. The petroleum ether extract was discarded since it was negative to Pauly's reagent. The aqueous phase was filtered, alkalized with cooling to pH 11 with sodium hydroxide, and saturated with sodium sulfate. The resulting dark brown liquid was extracted 12 times with 100 cc. of 1-butanol each. The remaining aqueous layer gave no color reaction with Pauly's reagent and was discarded.

The combined butanol extracts were shaken with small portions of diluted hydrochloric acid until all imidazole derivatives, according to Pauly's test, were removed. The acidic aqueous layer was evaporated to dryness in a vacuum desiccator over potassium hydroxide pellets. The black, semisolid residue was dissolved in 50 cc. of absolute ethanol, filtered from sodium chloride, and evaporated again to dryness; yield crude hydrochloride 7.8 g. as a black resin.

By paper chromatography (descending on Whatman No. 1, system 1-propanol/0.2*N* ammonia 2:1, developed with

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(12) All melting points are uncorrected.

* It has come to our attention that Hochstein, Ling, and P'an have also noted the presence of dimethylhistamine in *C. edulis* and have observed its marked hypotensive activity. [J. S. L. Ling, S. Y. P'an, and F. A. Hochstein, *J. Pharmacol. Exptl. Therap.*, **122**, 44A (1958)]. No details of the isolation have appeared in print. Dr. Hochstein informs us that the yields they obtained were comparable to those reported here.

(1) M. Martinez, *Plantas Medicinales de México*, 3rd ed., Ediciones Botas, Mexico, 1944, p. 326.

(2) A. Aebi, *Helv. Chim. Acta*, **39**, 1495 (1956).

(3) E. Ramirez and M. Rivero, *Rev. mensual méd. México*, **9**, I, No. 3 (1936); *Chem. Abstr.*, **32**, 5924 (1938).

(4) J. deLille, *Anales inst. biol. (Mex.)*, **5**, 45 (1934); *Chem. Abstr.*, **31**, 3570 (1937).

(5) F. B. Power and Th. Callan, *J. Chem. Soc.*, **99**, 1993 (1911).

(6) F. A. Kincl, J. Romo, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 4163 (1956); A. Meisels and F. Sondheimer, *J. Am. Chem. Soc.*, **79**, 6328 (1957).

Pauly's reagent) the crude hydrochloride gave three red spots with R_f 0.74 (strong), R_f 0.83 (strong) and R_f 0.95 (weak). By comparison, histamine under the same conditions gave a spot at R_f 0.65, as reported by Ames and Mitchell.⁷

The crude hydrochloride described above was dissolved in 300 cc. of water. To this solution was added a hot solution of 20 g. of picric acid in 250 cc. of water. A black oil separated immediately. The mixture was refluxed for a short time, decanted from an insoluble precipitate which was again extracted with 250 cc. of boiling water. Upon conversion to the hydrochloride the residue gave only a slight pink color with Pauly's reagent and was discarded. Upon cooling the combined aqueous layers, yellow crystals separated, which were filtered and washed with water and ether in order to remove picric acid; yield nearly pure picrate, 1.7 g., m.p. 223–226° (dec.); this corresponds to 0.4 g. of dimethylhistamine or about 0.06% of the original weight of the seeds used. Four recrystallizations from water with very little loss of material raised the m.p. to 229–230°, either alone or in mixture with an authentic sample of synthetic $N\alpha, N\alpha$ -dimethylhistamine dipicrate.⁹

Anal. Calcd. for $C_7H_{13}N_3 \cdot 2C_6H_2N_2O_7$: C, 38.20; H, 3.21; N, 21.10. Found: C, 38.12; H, 3.03; N, 20.86.

A sample of the picrate was dissolved in a small amount of 50% ethanol and shaken with sufficient anion exchange resin Dowex 1-X4 in the chloride form to decolorize the solution. Upon evaporation the dihydrochloride was obtained, m.p. 182–184°, either alone or in mixture with an authentic sample of synthetic $N\alpha, N\alpha$ -dimethylhistamine dihydrochloride.⁹

Anal. Calcd. for $C_7H_{13}N_3 + 2HCl$: C, 39.63; H, 7.13; N, 19.81; Cl, 33.43. Found: C, 39.50; H, 7.14; N, 19.40; Cl, 33.31.

The infrared spectra of both salts and of the corresponding authentic synthetic salts were superimposable. With paper chromatography both the isolated material and the synthetic sample gave a single spot at R_f 0.81 under the conditions described above.

The mother liquor from the crude picrate, above, was evaporated to dryness, washed with ether to remove excess picric acid and the amorphous picrate which remained was converted into the hydrochloride, yield 5.0 g. of black resin. On paper chromatography a sample showed a single spot at R_f 0.73. This product is now being investigated.

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Addition of Dibutyltin Hydride to Tetrafluoroethylene

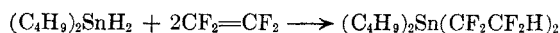
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Silanes have been reported to add to fluoroolefins *via* the inorganic free radicals, and the pos-

sibility of extending this type of reaction to various metal hydrides has been considered.¹ However, no such addition of a metal hydride to a fluoro-olefin to form a fluoro-organometallic compound has been reported up to this time.

Tin hydrides have previously been added to a number of olefins such as styrene and acrylonitrile to form new organotin compounds.² This reaction evidently does not involve free radicals since it occurs in the presence of radical inhibitors. Extension of the reaction to include tetrafluoroethylene as the olefin has now been accomplished with di-*n*-butyltin hydride at 90°. Like the other adducts from tin hydrides, this fluoroalkyltin compound is readily formed without the aid of a free radical initiator.



EXPERIMENTAL

Di-*n*-butyltin hydride, b.p. 56–59° (5 mm.), was prepared by reduction of di-*n*-butyltin dichloride with lithium aluminum hydride.³ A mixture of 4.0 g. (0.017 mole) of di-*n*-butyltin hydride and 10 g. (0.10 mole) of tetrafluoroethylene was heated in an 80-ml. shaker tube at 90° under autogenous pressure for 4 hr. Distillation of the liquid product gave 2.1 g. (28% conversion based on the hydride) of di-*n*-butylbis(1,1,2,2-tetrafluoroethyl)tin, b.p. 46–47° (0.2 mm.).

Anal. Calcd. for $C_{12}H_{20}F_8Sn$: C, 33.13; H, 4.64; F, 34.94; Sn, 27.29. Found: C, 33.14; H, 4.39; F, 34.52; Sn, 27.88. The structure was confirmed by determination of the F^{19} and H^1 spectra by nuclear magnetic resonance. The expected doublet for fluorine and triplet for hydrogen, characteristic of the CF_2H group, were found. The presence of the Sn— CF_2 group was established by the observation that this fluorine peak had satellites attributable to splitting by tin isotopes.

There was no evidence that the product, a clear colorless oil, decomposed to tin fluorides and trifluoroethylene under the conditions of the reaction.

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Formation of an *N*-Acylamide in Peptide Synthesis

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The reaction between mixed carbonic-carboxylic anhydrides and amines has by now been successfully applied to the synthesis of a large number of

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