esterification, and methyl etherification. Methanolic diazomethane was used to prepare methyl ethers. The scheme allowed identification of a T_3 isomer in plaice, a flatfish (*Pleuronectes platessa*).

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N^{α},N^{α}-Dimethylhistamine, the Hypotensive Principle of the Sponge *Ianthella* sp.

Keyphrases ☐ *Ianthella* sp.—hypotensive constituent ☐ N^{α},N^{α}-Dimethylhistamine—isolation, identification ☐ Hypotensive activity—N^{α},N^{α}-dimethylhistamine

Sir:

The ubiquity of histamine in nature is well known; however, the occurrence of histamine derivatives in biological systems is less well known (1–8). We wish to report the isolation and identification of the potent hypotensive agent 4(or 5)-[2-(dimethylamino)ethyl]-imidazole from the sponge *Ianthella* sp.[1]. A previous report suggested the presence of this compound in the sponge *Geodia gigas*, but insufficient data were presented to afford unambiguous structure assignment (7, 8). Isolation of N^{α},N^{α}-dimethylhistamine from aqueous extracts of the sponge *Ianthella* sp. was effected by a combination of absorption and partition chromatography. Purification was followed by hypotensive activity in the anesthetized dog preparation.

Experimental[2]—Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. IR spectra were determined on a Beckman model IR-8 spectrometer. NMR spectra were determined on a Varian A-60 spectrometer, using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard. Mass spectra were determined on a Hitachi-RMU-6H mass spectrometer.

Isolation of 4(or 5)-[2-(Dimethylamino)ethyl]imidazole—A 100-g. sample of dried pulverized sponge *Ianthella* sp. was shaken with two 600-ml. portions of water for 2 hr. The two fractions were combined, and water was removed under reduced pressure at a temperature less than 50°. The residue was triturated with two 600-ml. portions of absolute ethanol. Combination of the fractions and removal of solvent gave 9 g. of residue, which had appreciable activity as a hypotensive agent.

Chromatography—The residue from initial extractions (9 g.) was dissolved in a minimum of absolute ethanol and placed on a 550-g. Florisil[3] column. The column was developed with increasing concentrations of ammonium hydroxide in absolute ethanol. Column effluence was monitored both by residue weight and hypotensive activity as determined in the anesthetized dog. Material eluted with 1 and 2% ammonium hydroxide in ethanol contained the desired activity. These fractions were combined, and the solvent was removed under reduced pressure to give 1.7 g. of material. TLC (acetonitrile–ammonium hydroxide) analysis of the residue indicated one principal component.

Further purification was effected by partition chromatography in the solvent system 2-butanol–ethyl acetate–triethylamine–water (600:400:10:990) using Celite 545[4] as the column support. Fractions (10 ml.) were collected automatically. Column fractions were monitored by weight and hypotensive activity. The fractions (homogeneous by TLC) were combined, and the solvent was removed under reduced pressure to give 685 mg. of desired material.

Characterization of 4(or 5)-[2-(Dimethylamino)ethyl]-imidazole—An analytical sample prepared by molecular distillation of the active component from column chromatography had an elemental analysis consistent with the formula $C_7H_{13}N_3$. The mass spectrum was characterized by a parent ion peak at *m/e* 139 with additional principal peaks at 124, 95, and 81 mass units. The NMR spectrum (D_2O) exhibited a sharp 6-proton absorption at δ2.19 (CH_3), a 4-proton absorption at δ2.65 (CH_2), and 2 broad singlets (1-proton each) at δ6.83 and δ7.62 (imidazole ring protons). A picrate salt, m.p. 223–226° [lit. (1) 223–226°], and the dihydrochloride salt, m.p. 183.5-184° [lit. (1) 182–184°], were prepared and characterized by elemental analysis. Comparison of the material from the sponge *Ianthella* sp. with a synthetically prepared sample of 4(or 5)-[2-(dimethylamino)-

[1] A voucher specimen of sponge *Ianthella* sp. is maintained at A. H. Robins Co., Richmond, VA 23220

[2] Microanalyses were performed by Mr. Malcolm Stone of the A. H. Robins Co. Hypotensive activity was determined in the anesthetized dog preparation by Dr. Bernard V. Franko of the A. H. Robins Co.
[3] Floridin Co., Pittsburgh, Pa.
[4] The Johns-Manville Co., New York, N. Y.

ethyl]imidazole (10, 11) showed the materials to be identical in all respects.

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Unexpected Variable in the USP–NF Rotating Basket Dissolution Test

Keyphrases ☐ Dissolution test—rotating basket method ☐ Rotating basket dissolution test—vibration effect

Sir:

To increase our capability for dissolution-rate testing by the USP XVIII–NF XIII rotating basket method[1], we recently designed and constructed a mechanized apparatus capable of testing six dosage units simultaneously. To our surprise, this apparatus gave significantly longer dissolution times, especially at rotation speeds of 150 r.p.m. or less, than were obtained previously under the same conditions with a nonmechanized apparatus.

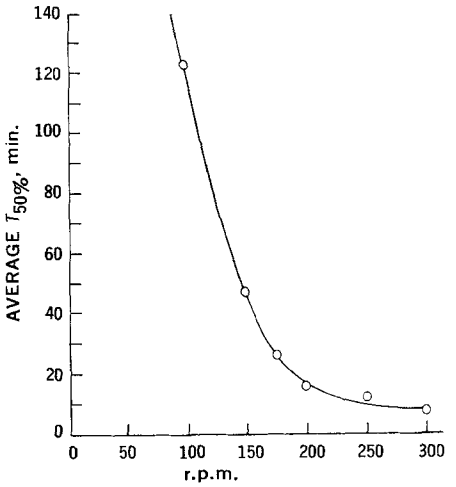

Figure 1—*Effect of rotation speed on dissolution rate of tolbutamide tablets USP, using the USP XVIII procedure with the mechanized apparatus.*

An investigation was undertaken to find the cause of this variation. Both pieces of apparatus conform to the requirements of the compendia (2, 3). By inspection, both permit smooth rotation of the basket assembly without perceptible wobble. The flask and stirrer assembly of the nonmechanized apparatus is mounted with a Fisher frame. The mechanized apparatus is of a unitized design; the six stirrers operate from a single-drive shaft; the flasks, held in place by a common manifold plate, rest on conical springs. The speeds of rotation for both pieces of equipment, as measured by a strobe light (or by counting revolutions at low speed), were well within the ±5% tolerance limits specified in the compendia. Both incorporate the same specified flask, which is sampled by a continuous flow system of the same pumping rate with similarly positioned inlet and outlet tubes of identical hold-up volumes.

Investigation finally revealed that a very subtle difference existed in the vibrational levels of the two pieces of equipment. Vibration was suspected when it was observed that the introduction of vibration by gentle tapping of the dissolution flask caused particles of a disintegrating tablet to spray from the basket; this was accompanied by an abrupt deflection in the dissolution profile toward higher percent dissolution. The vibrational levels associated with the two pieces of equip-

Table I—Effect of Vibration on Dissolution Times of a Single Lot of Tolbutamide Tablets USP by the USP Rotating Basket Method

Apparatus	Vibration[a] Displacement, mils	Vibration[a] Frequency, c.p.m.	Magnitude[b] of Vibration	Minutes for 50% Dissolution[c] 150 r.p.m.	300 r.p.m.
Nonmechanized unit	0.8	3600	Slightly rough	8.2	5.0
Nonmechanized unit, water pump off	0.2	3000	Very good	24	4.7
Mechanized unit	0.05	600	Extremely smooth	48	7.4

[a] Determined with Vibration Analyzer, model 600, International Research and Development Co., Columbus, Ohio. [b] From General Machinery "Vibration Severity Chart," International Research and Development Co., Columbus, Ohio. [c] Average of six tablets.

[1] The USP XVIII and NF XIII Method I dissolution test methods are identical, both being a modification of the method described by Pernarowski *et al.* (1).