recrystallized from 95% ethanol; m.p. 135–136° (lit. 132°)[9]; yield 75%.

Anal. Calcd. for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.94; H, 6.93.

β-(p-Methoxyphenyl)-α-phenylacrylic acid, ethyl ester (Id) was prepared in the usual way by refluxing the acid with 5% ethanolic hydrogen chloride; recrystallized from ethanol; m.p. 48–50°; yield 51%.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.79; H, 6.30.

3-(p-Methoxyphenyl)-2-phenylpropionic acid, ethyl ester (Id dihydro) was prepared by hydrogenation of the acrylate (Id), 35 g , ethanol, 120 ml., and nickel-kieselguhr catalyst,[5] 5 g. at 2000 p.s.i. and at 130° for approximately 1 hr.; recrystallized from 95% ethanol; m.p. 57–59°; yield quantitative.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.60; H, 7.29.

3-(o-Methoxyphenyl)-2-phenylpropionic acid, methyl ester (Ic dihydro) was prepared in the same manner as the ethyl ester (described above); b.p. 147–155°/0.5 mm., n_D^{25}° 1.5538; yield quantitative.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 76.01; H, 6.86.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, methyl ester (If dihydro) was prepared as described above; b.p. 162–195°/0.2 mm., n_D^{25}° 1.5636; yield quantitative.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67. Found: C, 71.06; H, 5.94.

3-(3,4-Methylenedioxyphenyl)-2-phenylpropionic acid, ethyl ester (Ia dihydro) was prepared as described above; b.p. 161–190°/0.2 mm., n_D^{25} 1.5552; yield quantitative.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.10; H, 6.41.

2,3-Dipiperonylidenesuccinic acid, dimethyl ester (IV) was prepared by refluxing 2,3-dipiperonylidenesuccinic acid,[6] 83 g., sulfuric acid, 50 g., and methanol, 1 l., for 6 hr. The product was isolated in the usual way; recrystallized from ethanol; m.p. 181–182°; yield quantitative.

Anal. Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 63.83; H, 4.70.

N,N-Diethyl-β-(3,4-methylenedioxyphenyl)-α-phenylacrylamide (Ig) was prepared in the usual way by reacting the acid chloride with diethylamine; recrystallized from 95% ethanol; m.p. 128–129°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{21}NO_3$: N, 4.33. Found: N, 4.07.

N,N-Diethyl-β-(p-methoxyphenyl)-α-phenylacrylamide (Ih) was prepared as described above; recrystallized from ethanol-water (4:1); m.p. 68–70°; crude yield quantitative.

Anal. Calcd. for $C_{20}H_{23}NO_2$: N, 4.53. Found: 4.77.

Acknowledgment. All microanalyses were performed by Kathryn Gerdeman, of the Chemistry Department, University of Maryland.

BELTSVILLE, MD.

(9) M. S. Kharasch and H. G. Clapp, *J. Org. Chem.*, **3**, 355–60 (1938).

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A Preparation and Certain Properties of 2-Carbomethoxy-*N*-methylgranatonine

STEPHEN P. FINDLAY*

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The preparation of racemic 2-carbomethoxy-*N*-methylgranatonine is described, and certain of its physical and chemical properties are compared with those of racemic 2-carbomethoxytropinone.

Succindialdehyde combines with methylamine and the half methyl ester (II) of β-ketoglutaric anhydride (I), the principal product being racemic 2-carbomethoxytropinone (VI and its mirror image).[1] The readiness with which this variation of Robinson's biological synthesis[2,3] occurs made it seem probable that an analogous condensation in which glutaraldehyde, now obtainable commercially,[4] was used in the place of succindialdehyde would give racemic 2-carbomethoxy-*N*-methylgranatonine (3 - keto - 2 - carbomethoxy - 9 - methyl - 9 - azabicyclo[3.3.1]nonane)(III) with comparable ease; and it was thought that this compound, which has not been reported before, would permit some instructive comparisons with racemic 2-carbomethoxytropinone and that it might constitute a valuable intermediate in the synthesis either of analgesics like cocaine and psicaine[5] or of certain derivatives of cyclooctane or of both.

By this procedure 2-carbomethoxy-*N*-methylgranatonine (III) was indeed obtained, but the yield realized (*ca.* 25%) was disappointing, being no greater than half that of 2-carbomethoxytropinone.[1] The large quantities of colored by-products likewise isolated, are, because of their solubility in aqueous alkali, very probably β-keto esters also. It is pertinent here to note that, although *trans* fusion of the rings in the reaction leading to 2-carbomethoxytropinone (VI) is almost certainly

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(1) S. P. Findlay, *J. Org. Chem.*, **22**, 1385 (1957).

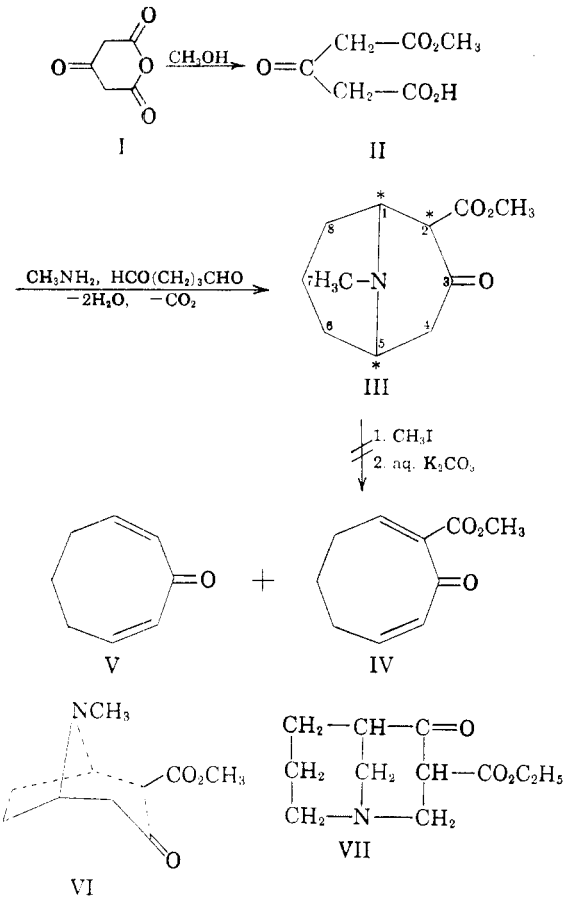
(2) R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

(3) R. Willstätter, H. Wolfes, and R. Mader, *Ann.*, **434**, 111 (1923).

(4) K. Alder and H. A. Dortmann, *Chem. Ber.*, **86**, 1544 (1953).

(5) *The Merck Index*, Sixth Edition, Merck & Co., Inc., Rahway, N. J., 1952, p. 803.

impossible, some *trans* combination of the piperidine rings formed in this reaction is at least conceivable and that in instances in which ring strain is non-existent, as in the synthesis of the analogous 1,2,6-trimethyl-4-piperidone, both the *cis* and *trans* isomers are obtained.[6] However, in this reaction no evidence of the formation of *trans* isomer was found. It is worth noting also that the phenomena observed in connection with the preparation of each of these two compounds resemble those recorded by McElvain and Adams of the amino β-keto ester, ethyl isogranatonine carboxylate (VII).[7]



Certain of the physical properties of racemic 2-carbomethoxy-*N*-methylgranatonine indicate it to be a mixture: in the anhydrous form, obtained by sublimation, it melts over a considerable range (97.3–101.8°), and in chloroform solution this modification has absorption maxima characteristic of both keto and enol structures. Its solubility in both polar and non-polar solvents is considerable, and it readily forms a hydrate when its solution in acetone is diluted with water. In all these respects it resembles 2-carbomethoxytropinone closely.[1] On the other hand, its picrate, prepared in methanol, was not converted to another modification by recrystallization from acetone.[1]

The ultraviolet absorption spectra indicate that in absolute alcoholic solution the proportion of 2-carbomethoxy-*N*-methylgranatonine existing as the enol tautomer is considerably greater than that of 2-carbomethoxytropinone (Table I). It is noteworthy that the location of the absorption maximum and the molar extinction coefficient, both of which are different for the two compounds in absolute alcohol, have both become the same or nearly so in 50% aqueous acetic acid. Presumably in this solvent the two esters are enolized entirely.

TABLE I

	Racemic 2-Carbomethoxytropinone	Racemic 2-Carbomethoxy-*N*-methylgranatonine
Melting points		
Anhydrous form	102–104°[1]	97.3–101.6°[a]
Hydrated form	93–96°[1]	98–100.5°[a]
Picrate salt	168°[1] and 176°[1]	207°[a]
Absorption spectra		
Absolute alcohol	255 mμ (ε = 6190)[1]	253 mμ (ε = 8930)[a]
50% Aq. acetic acid	248 mμ (ε = 9727)[a]	248 mμ (ε = 9420)[a]

[a] This investigation.

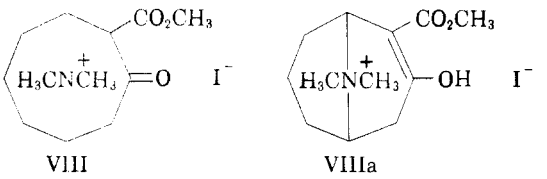
Methyl iodide combines with racemic 2-carbomethoxy-*N*-methylgranatonine in acetone solution to give a derivative having the composition of the methiodide, $C_{12}H_{20}INO_3$. This substance is soluble in cold aqueous potassium carbonate, but the resulting solution does not yield 2-carbomethoxy-2,7-cyclooctadienone (IV) or 2,7-cyclooctadienone (V) either at room temperature or on heating. The apparent pronounced stabilization of an essentially labile compound through combination with methyl iodide arises probably from the formation of an inner salt like that present in phenolbetaines which makes the Hofmann Degradation of phenolic alkaloids difficult also[8] and, together with its tendency to lose hydrogen iodide (see Experimental section), suggests that this substance has structure IX rather than structure VIII or VIIIa. The methiodide has absorption maxima at 221 mμ (ε = 15,600) and at 247 mμ (ε = 8,600) in absolute alcohol, and at 228 mμ (ε = 15,930) and approximately at 250 mμ in aqueous solution. These are due presumably to the iodide ion[9] and to the α,β-unsaturated ester linkage.

(6) C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

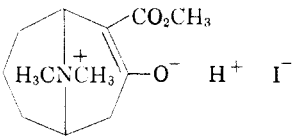
(7) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2738 (1923); see also, R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Vol. I, Academic Press, Inc., New York, 1950, p. 188.

(8) *Cf.*, L. F. Small and R. E. Lutz, *The Chemistry of the Opium Alkaloids*, United States Government Printing Office, Washington, D. C., 1932, pp. 147 and 268.

(9) For iodide in aqueous solution λ_{max} = *ca.* 226.5 mμ (ε = 18,200) [A. D. Awtrey and R. E. Connick, *J. Am. Chem. Soc.*, **73**, 1842 (1951)].



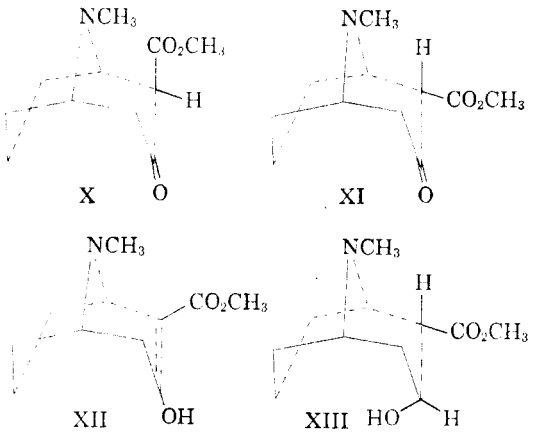
VIII VIIIa



IX

By recrystallizing the L-bitartrate of the racemic base from water a small yield of one antipode of 2-carbomethoxy-*N*-methylgranatonine as the L-bitartrate salt, $C_{15}H_{23}NO_9 \cdot 2H_2O$, was obtained pure or nearly pure: $[\alpha]_D^{20}$ +43.4° in water. In analogy with (+)-(2-carbomethoxytropinone) (VI), the L-bitartrate of which is less soluble in water than that of the (−)-antipode,[1] the basic moiety of this L-bitartrate should have the absolute configuration or three-dimensional structures of formulas, X-XII, representing the enol form and the two possible keto forms of the base.

Catalytic hydrogenation[1] of this antipode in aqueous acetic acid should result in the two optically active 2-carbomethoxy-*N*-methylgranatolines (XIII and its C_2 epimer) having an axial C_3-hydroxyl group (tropine or α configuration),[10-12] whilst hydrogenation with sodium amalgam[3] should afford the two optically active 2-carbomethoxy-*N*-methylgranatolines having an equatorial C_3-hydroxyl group (pseudotropine or β configuration).[10,11,13] Benzoylation of these esters should furnish analogues of the cocaines[3,12,13] and hydrolysis hydroxyamino acids closely related to the ecgonines.[3,12-14]



X XI

XII XIII

This investigation will not be continued.

(10) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).
(11) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).
(12) S. P. Findlay, *J. Org. Chem.*, **21**, 711 (1956).
(13) S. P. Findlay, *J. Am. Chem. Soc.*, **76**, 2855 (1954).
(14) A. Einhorn and A. Marquardt, *Ber.*, **23**, 468 (1890).

EXPERIMENTAL[15]

Materials. Glutaraldehyde, supplied and used as a 25% solution in water, was a gift of the Carbide and Carbon Chemicals Company. Fisher C.P. methylamine hydrochloride and Mallinckrodt A.R. L-tartaric acid (the common or naturally occurring antipode) were employed.

Racemic 2-carbomethoxy-N-methylgranatonine (3-keto-2-carbomethoxy-9-methyl-9-azabicyclo[3.3.1]nonane) (III). β-Ketoglutaric anhydride[1,16] (13.5 g., 0.105 mole) was dissolved in Fisher absolute methanol (100 ml.) at 0°. This mixture was kept one hour at room temperature and poured into another consisting of methylamine hydrochloride (10.0 g., 0.148 mole), 4*N* aqueous sodium hydroxide (25 ml.), and water (850 ml.). To the resulting solution glutaraldehyde (40 g. of a 25% aqueous solution, 0.100 mole) was immediately added. The evolution of carbon dioxide soon became noticeable, and after 2 to 3 hr. the initially rather pale yellow solution had acquired an orange hue.

After 24 hr. at room temperature the orange reaction mixture was filtered from some flocculent matter and the filtrate brought to *p*H *ca.* 4 with 6*N* sulfuric acid, an observable evolution of carbon dioxide being thus brought about. A little potassium bicarbonate, anhydrous sodium sulfate (50 g.), and more potassium bicarbonate (15 g. altogether) were successively dissolved in this mixture, which was then extracted with chloroform (6 × 100 ml.). The dried (sodium sulfate) extracts were concentrated on the steam bath and then *in vacuo* to a thick, orange brown oil (18.5 g.) having a greenish fluorescence. Seeded with material from a previous preparation, long, delicate filaments grew gradually from the upper walls of the flask to the surface of the red liquid which during the course of several weeks was slowly converted thereby to a semi-circle of mounds consisting of slender prisms mixed with reddish-brown liquid impurities.

By leaching with boiling ligroin (b.p. 60–71°) (2 × 100 and 50 ml.) from the reddish-brown by-products and removing the solvent from the yellow leachings *in vacuo*, an oil (8.0 g.) was isolated which, when mixed with absolute methanol (5 ml.) and seeded with anhydrous 2-carbomethoxy-*N*-methylgranatonine, slowly solidified. This material was purified by distillation about 90°/1 mm.: 5.1 g. (24%) of pale yellow solid melting at 98.7–101.6°.

Another preparation conducted essentially as the foregoing except that the temperature was maintained about 0° for 24 hr. gave *ca.* 5.5 g. of the β-keto ester.

The above-mentioned brown, ligroin-insoluble by-products (10.5 g.) were soft at 60° but solid at room temperature. This mixture was dissolved in a solution of potassium hydroxide (2.2 g.) in methanol (25 ml.) and precipitated at 0° therefrom with carbon dioxide. The recovered, brick-red solid could not be sublimed *in vacuo*, and attempted recrystallization from aqueous acetone gave only a small yield of yellow solid. The ligroin-insoluble fraction was not further investigated.

Physical properties of racemic 2-carbomethoxy-N-methylgranatonine. A small amount (*ca.* 0.1 g.) of the filaments (m.p. 102–104°) described above were sublimed about 90°/1 mm. The nearly colorless sublimate adhered tenaciously to the cold finger, readily acquired an electric charge, and melted over a considerable range, 97.3–101.8°.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.28; H, 8.06.

The sublimed base (1.0 g.) was dissolved in hot acetone (5.0 ml.); and, after cooling the solution somewhat, water (1.0 ml.) was added. The crystals which soon began to precipitate were collected after a day and washed with acetone: rosettes of colorless, minute, broken prisms, m.p. 98–100.5°.

(15) The melting points herein recorded are corrected and were observed in Pyrex capillaries.
(16) R. Kaushall, *J. Indian Chem. Soc.*, **17**, 138 (1940).

Anal. Calcd. for $C_{11}H_{17}NO_3 \cdot 1^1/_2H_2O$: C, 55.44; H, 8.46. Found: C, 55.33; H, 8.44.

In chloroform solution the anhydrous base did not absorb near 3.0 μ but did so at 5.76 μ, 5.87 μ, and 6.03 μ, band locations characteristic of unconjugated ester, unconjugated ketone, and conjugated ester groupings, respectively. The band intensities in the 5.5–6.5 μ region were measured about 10 min. after making up the chloroform solution and again about 2 hr. later. No change of intensities was noticed. In Nujol it did not absorb appreciably near 3.0 μ, or 5.75 μ, or 5.85 μ; but it did have a strong band at 6.04 μ. The sesquihydrate absorbed strongly in the 3-μ region and at 6.0 μ in Nujol; but, like the anhydrous modification, it had no bands near 5.75 μ and 5.85 μ.

In absolute alcohol the β-keto ester had an absorption maximum at 253 mμ (ϵ = 8930) and in aqueous acetic acid (50% by weight) at 248 mμ (ϵ = 9420). In the latter solvent a sample of anhydrous racemic 2-carbomethoxytropinone[1] absorbed at 248 mμ (ϵ = 9727).

The anhydrous base dissolved readily in alcohols, acetone, and chloroform, and also in water. It was less soluble in ether and in ligroin.

Racemic 2-carbomethoxy-N-methylgranatonine hydropicrate. Sublimed racemic 2-carbomethoxy-*N*-granatonine (0.42 g.), dissolved in warm methanol (6 ml.), was added to a hot solution of picric acid (0.46 g.) and methanol (5 ml.). Yellowish orange grains of the picrate melting at 204.5–205° precipitated at once. Recrystallized from methanol, it was obtained as stout prisms, m.p. 207° (bubbling), the salt discoloring several degrees below the fusion point. From acetone it separated as minute cubes which melted also at 207° but did not discolor below this temperature. The sample from acetone was dried 18 hr. at room temperature *in vacuo* over potassium hydroxide for analysis.

Anal. Calcd. for $C_{17}H_{20}N_4O_{10}$: C, 46.36; H, 4.58. Found: C, 46.60; H, 4.51.

Racemic 2-carbomethoxy-N-methylgranatonine methiodide. Sublimed racemic 2-carbomethoxy-*N*-methylgranatonine (2.0 g.), dissolved in acetone (25 ml.), was mixed with methyl iodide (2.0 ml.); and the resulting solution was left 1 hr. at room temperature. The crystals which began to precipitate almost immediately were then collected, washed with acetone, and dried overnight *in vacuo* over potassium hydroxide: 3.05 g. (91%) of yellowish white methiodide melting above 300°, which is low in iodine, presumably through loss of hydrogen iodide, as in the case of pseudoecgonine methiodide.[13]

Anal. Calcd. for $C_{12}H_{20}INO_3$: C, 40.80; H, 5.71; I, 35.93. Found: C, 41.06; H, 5.54; I, 35.35. Kept overnight the mother liquors deposited an additional small amount of methiodide.

In absolute alcohol the methiodide had absorption maxima at 221 mμ (ϵ = 15,600) and at 247 mμ (ϵ = 8600) and the indication of a weak maximum at 335 mμ. The proximity of the first two maxima makes the molar extinction coefficients, especially the second, probably not very accurate. In water it absorbed strongly at 228 mμ (ϵ = 15,930), and a shoulder on the longer wave length side of this maximum indicated another, hidden maximum about 250 mμ.

The methiodide (0.73 g.) was suspended in water (10 ml.) in which it did not completely dissolve, and saturated aqueous potassium carbonate (10 ml.) was added. The resulting clear solution was shaken 70 min. with ether (75 ml.). From the dried (sodium sulfate) ethereal phase a negligible residue was obtained. The aqueous phase was heated at 100° 1.5 hr. during which interval a moderate turbidity developed. Kept overnight at 0°, the mixture deposited no crystalline material. It was made mildly acidic with 6*N* aqueous sulfuric acid and extracted with ether (4 × 25 ml.). Evaporation of the dried (sodium sulfate) extracts again resulted in the recovery of a negligible residue. Throughout these operations the color of the aqueous phase changed very little or not at all.

Resolution of racemic 2-carbomethoxy-N-methylgranatonine. Sublimed racemic 2-carbomethoxy-*N*-methylgranatonine (4.84 g.) and L-tartaric acid (3.31 g.) were dissolved in water (12 ml.). Exposed to air the solution became more viscous, but no crystals formed. After a day the evaporated water was replaced, and the solution was left once more exposed to air. During the next day or so crystals slowly separated. These were recrystallized from water (2.0 ml.): 0.95 g., $[\alpha]_D^{20}$ +42.1° (c, 2, water).[17] Recrystallized again from water the L-bitartrate dihydrate as colorless needles was obtained: 0.2 g., $[\alpha]_D^{20}$ +43.4° (c, 2, water).[17]

Anal. Calcd. for $C_{15}H_{23}NO_9 \cdot 2H_2O$: C, 45.33; H, 6.85. Found: C, 45.07; H, 6.92.

Dried to constant weight at 57° *in vacuo alto* the salt underwent a weight loss of 9.53% (theoretical loss for two moles of water: 9.07%), and the residue appeared to be anhydrous.

Anal. Calcd. for $C_{15}H_{23}NO_9$: C, 49.30; H, 6.42. Found: C, 49.71; H, 6.60.

The bitartrate is extremely soluble in water and appears to crystallize much more slowly from solution after seeding than the 2-carbomethoxytropinone bitartrates.[1] From the mother liquors the base slightly enriched in one antipode was recovered by adding excess potassium bicarbonate and extracting with chloroform.

Spectral measurements. The infrared measurements were made with a Perkin-Elmer (Model 21) double beam spectrophotometer having sodium chloride optics. The ultraviolet absorption spectra were determined by a Cary Recording Spectrophotometer (Model 11).

Acknowledgment. The analytical data herein recorded were determined principally by Miss Paula M. Parisius of the Institute's Microanalytical Services Laboratory directed by Dr. William C. Alford. Mr. Harold K. Miller measured the infrared absorption spectra and Mrs. Charles I. Wright the ultraviolet absorption spectra.

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(17) This measurement was by Mrs. Evelyn G. Peake of This Institute.