

formation of this substance into salicylic acid was 70% efficient.

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### Preparation of Tetramethylene Bromide

By SHERMAN FRIED AND RICHARD D. KLEENE

Tetramethylene bromide has previously been available by the reaction between N-benzoylpyrrolidine and phosphorus pentabromide.<sup>1</sup> We have now found that the cleavage of tetrahydrofuran by hydrogen bromide, which is analogous to the reaction previously applied by Starr and Hixon,<sup>2</sup> for the preparation of the corresponding chlorohydrin, is much simpler and gives a comparable yield from more readily available starting materials.

Furan was prepared by the decarboxylation of furoic acid in the presence of copper oxide and quinoline,<sup>3</sup> using, however, a Dewar jacketed trap cooled with dry-ice to prevent entrainment of the furan by escaping carbon dioxide. The furan was readily hydrogenated in 95% yield to tetrahydrofuran using palladium-palladium oxide as a catalyst.<sup>4</sup>

Dry hydrogen bromide was passed into the tetrahydrofuran in a flask fitted with a side-tube, reflux condenser and thermometer, until the temperature reached 150°, when the theoretical quantity of hydrogen bromide had been added. The resulting black tarry product was washed thoroughly with water and then with sodium bicarbonate solution until it was free of hydrobromic acid. It was then taken up with ether and dried over anhydrous copper sulfate. The product was fractionated under diminished pressure and 134 g. (yield, 70%) of tetramethylene bromide (b. p. 198° at normal pressure) was collected.

The authors gratefully acknowledge the assistance of Professor W. G. Brown, who designed the apparatus used in the preparation of the furan.

- (1) Von Braun and Müller, *Ber.*, **39**, 4124 (1906).
- (2) Starr and Hixon, *THIS JOURNAL*, **56**, 1595 (1934).
- (3) Wagner and Simmons, *J. Chem. Ed.*, **13**, 270 (1936).
- (4) Shriner and Adams, *THIS JOURNAL*, **46**, 1683 (1924).

DEPARTMENT OF CHEMISTRY  
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### The Isolation of Eriodictyol and Homoeriodictyol. An Improved Procedure

By T. A. GEISSMAN

The question of the existence of a substance having vitamin-like properties in its effect upon capillary permeability, and called "Vitamin P" by Szent-Györgyi<sup>1</sup> remains unanswered. So far

(1) Szent-Györgyi, *et al.*, *Nature*, **138**, 27, 798 (1936); *Z. physiol. Chem.*, **255**, 216 (1938).

practically all the studies that have been made upon the putative vitamin have been made upon "citricin," a crude flavanone fraction isolated from lemon peel. Reports of experiments in which this material has been used in clinical studies and in animal (guinea pig) tests are conflicting<sup>2</sup> and allow no definite conclusion to be drawn as to the physiological action of "citricin," although the balance of the evidence seems to support the belief that it does contain some substance which exerts a vitamin-like action, when acting in conjunction with vitamin C, in certain types of hemorrhagic diathesis.

Szent-Györgyi has attributed the vitamin activity of "citricin" to the presence of an eriodictyol glycoside<sup>3</sup> although definite experimental proof of its presence in "citricin" is lacking. It is probable, however, that "citricin" does contain eriodictyol (as a glycoside?) since certain color tests (ferric chloride, hot aqueous alkali) shown by "citricin" are also given by pure eriodictyol. It is clear that even if it can be shown that "citricin" contains eriodictyol this will not constitute proof that eriodictyol is "vitamin P." Indeed, Scarborough's results<sup>2c</sup> indicate that hesperidin (also a constituent of "citricin") has "citricin" activity in certain types of purpura.

In an approach to the problem through studies on pure flavanones which are known to be or suspected of being present in "citricin" the preparation of pure eriodictyol has been undertaken.

Eriodictyol (5,7,3',4'-tetrahydroxyflavanone) has been isolated from *Eriodictyon californicum* by Power and Tutin<sup>4</sup> and from *Lespedeza cyrtobotrya* by Ohira.<sup>5</sup> It has been isolated, along with homoeriodictyol, for the present study from *Eriodictyon californicum* by a procedure which combines the best features of the method of Power and Tutin with those of the method used by Mossler<sup>6</sup> in isolating homoeriodictyol from the same plant. The yields of both eriodictyol and homoeriodictyol were about double those obtained by Power and Tutin but this improvement may not be inherent in the present method since studies now in progress in this Laboratory have indicated that considerable variation can occur

(2) (a) Szent-Györgyi, *et al.*, *Nature*, **139**, 326 (1937); **140**, 426 (1938); (b) Zilva, *Biochem. J.*, **31**, 915, 1488 (1937); (c) Scarborough, *ibid.*, **33**, 1400 (1939).

- (3) Bruckner and Szent-Györgyi, *Nature*, **138**, 1057 (1936).
- (4) Power and Tutin, *Pharm. Rev.*, **24**, 301 (1907); *Pharm. J.*, **77**, 381 (1906); Tutin and Clewer, *J. Chem. Soc.*, **95**, 81 (1909).
- (5) T. Ohira, *J. Agr. Chem. Soc. Japan*, **9**, 448 (1933).
- (6) Mossler, *Ann.*, **351**, 223 (1907).

in the flavanone content of samples of *Eriodictyon* collected in various parts of this state. The material used in the procedure described was a commercially available product collected near Colusa, California, and marketed as "yerba santa."

The flavanones are being tested for "vitamin P" activity.

### Experimental

**Eriodictyol.**—A total of 700 g. of powdered *Eriodictyon californicum* was extracted in about 70-g. portions with 500 ml. of ether in a Soxhlet extractor. The deep brown-green ether solution was filtered and shaken with successive portions of ammonium carbonate solution to remove acidic tarry material and then with 400 ml. of cold 10% sodium carbonate solution. A thick yellow precipitate of the sodium salt of homoeriodictyol formed and was collected by filtration on a large Büchner funnel, the filtrate being allowed to drop directly into dilute hydrochloric acid. The tarry precipitate from the filtrate was taken up in ether and again shaken with cold 10% sodium carbonate solution and the precipitate of sodium homoeriodictate collected by filtration. The filtrate, again dropping directly into dilute acid, deposited a tarry mass which was removed, transferred to a 2-liter round-bottomed flask and boiled with several 1.5-liter portions of water. The aqueous extracts were decanted from the tar and, after cooling, extracted with ether. The combined ether extracts were shaken with 300 ml. of ice-cold 10% sodium carbonate and the aqueous layer kept in an ice-bath for thirty minutes and then filtered from a rather small amount of precipitated sodium homoeriodictate. The filtrate was acidified with dilute hydrochloric acid, yielding a yellowish-brown tar. The tar was separated from the aqueous layer, transferred to a small beaker and rubbed with ether until the crystalline powder (A) which formed was no longer sticky. The product (about 8 g., moist) was collected and the filtrate allowed to evaporate slowly. A further amount (1 g.) of solid separated (B).

The first crop of material (A) was recrystallized from dilute alcohol, yielding 2.85 g. of colorless needles, m. p. 262–265°, dec. Dilution of the mother liquor yielded an additional 0.84 g. of product, m. p. 261–264° dec. Recrystallization of crop (B) yielded 0.78 g., m. p. 260–263° dec. The total yield was thus 4.47 g. of crude eriodictyol (0.64%). Recrystallized from dilute alcohol the substance formed tiny colorless needles, m. p. 265–266° dec. Descriptions of eriodictyol in the literature fail to record the fact that the m. p. of the compound depends upon the heating rate. Taken in the usual way, the m. p. may vary between 262 and 266°, with decomposition to a red liquid. If a sample is plunged into a preheated bath it melts at 267° (the usually recorded m. p.) to a pale yellow liquid.

Since the most probable impurity in the eriodictyol was homoeriodictyol a methoxyl determination was carried out but no methoxyl was found. The acetate, prepared with acetic anhydride–sodium acetate, formed colorless needles, m. p. 136–137° (literature<sup>7</sup> 137°).

The purified material dissolves in cold 10% sodium hydroxide solution to give a colorless solution which upon

standing rapidly darkens. A solution of eriodictyol in 10% sodium hydroxide develops an intense blood-red color upon heating. Ferric chloride in methanol causes a transient green color which is immediately succeeded by brown-red.

**Homoeriodictyol.**—The various fractions of sodium salt collected as described above were combined and recrystallized from water. The moist salt (nearly colorless needles) was dissolved in about 400 ml. of boiling glacial acetic acid. Upon cooling there was obtained 40.5 g. of pale buff homoeriodictyol, m. p. 220°. Recrystallization raises the m. p. to the reported<sup>7</sup> value, 224°.

The acetate, prepared with sodium acetate–acetic anhydride, melted at 161–162° (reported<sup>7</sup> 163°).

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### Isotopic Composition of Cuprite Oxygen

BY W. HEINLEN HALL AND CLARENCE HOCHANADEL

The isotopic composition of oxygen in carbonate rocks and iron oxide ores recently has been determined by Dole and Slobod.<sup>1</sup> We wish to report similar data for cuprite (Dana 224), one of the naturally occurring oxides of copper. The sample used by us was obtained from Ward's Natural Science Establishment and came from Bisbee, Arizona.

The technique which we used consisted in the reduction<sup>2</sup> of the oxide with commercial electrolytic hydrogen followed by a comparison of the density of the resulting water with that of water formed with the same hydrogen and atmospheric oxygen. The procedure used in purifying the water and determining the densities was the same as that used in earlier work.<sup>3</sup>

Densities were determined to within 1 p. p. m. by the buoyancy balance method in which temperature (measured with two Bureau of Standards calibrated Beckmann thermometers) was the observed variable. A completely submerged Pyrex float was used.<sup>4</sup>

After repeated purification of both samples, we observed that the floating temperature for water prepared from cuprite oxygen and commercial hydrogen was 0.021° lower than the floating temperature for water prepared by burning the same hydrogen in atmospheric oxygen under con-

(1) Malcolm Dole and R. L. Slobod, *THIS JOURNAL*, **62**, 471–479 (1940).

(2) Reduction was carried out in such a way that the sample of hydrogen reacted completely, thus avoiding any fractionation.

(3) Hall and Johnston, *THIS JOURNAL*, **57**, 1515–1517 (1935).

(4) In this and other work extending over a period of five years, we have found variations in the floating temperature for any given float using ordinary water. We have attributed this to the dissolving of the float and/or to changes in the thermometers. It would appear from the observation made by Dole and Slobod that the thermometers may be responsible for the change since they found no appreciable effect when using a platinum resistance thermometer.

(7) Shinoda and Sato, *J. Pharm. Soc. Japan*, **49**, 71 (1929).