[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Quassin. III. Picrasmin

BY E. P. CLARK

Picrasma, or *Picraena*, *excelsa* is a simaroubaceous tree closely related to *Quassia amara*. Its wood contains an extremely bitter substance, and because of this it is often chopped or rasped and sold on the market as quassia chips.

The bitter constituent of the wood was first isolated and studied by Massute[1] in 1890. He obtained several preparations by an involved procedure used by earlier investigators to obtain quassin, and as these materials differed somewhat in melting point and elemental analysis, he assumed that he was dealing with a series of homologs, of which he designated the following: $C_{29}H_{34}O_{10}(CH_2)_6$, m. p. 204°; $C_{29}H_{34}O_{10}(CH_2)_7$, m. p. 209–212°; and $C_{29}H_{34}O_{10}$, m. p. 212–216°. The last was assumed to be a break-down product of the others. These materials were called picrasmins. Some reactions similar to those given by quassin were reported, but on the whole the work is not convincing. Because of this and the results recently reported concerning quassin,[2] the problem has been reopened. The purpose of this communication is to show that the bitter substance under consideration is essentially one product, picrasmin, and is an isomer of quassin and neoquassin.

Because of the close physical and chemical relationships between picrasmin and quassin, a comparison of the properties and the reactions of the two materials will be made as the reactions of picrasmin are presented.

The picrasmin employed in thus study was prepared by the method used to obtain quassin from quassia wood.[2] The yield of crude crystalline material was 0.1% of the rasped wood employed. As it consisted essentially of one compound, its purification was not particularly difficult, but the process was tedious because many recrystallizations were necessary to obtain a homogeneous, constant melting product. When thoroughly purified, it consists of long colorless rectangular plates and occasional rods, which melt at 218°. It is dextrorotatory, $[\alpha]^{20}D$ +45.4° when C is 5.04 in chloroform. This value is close to that of quassin (+39.8°). Moreover, its optical crystallographic constants are so much like those of quassin—only η_γ differs by 0.003—that by the use of these values alone it would be very difficult, if not impossible, to distinguish one from the other in a mixture. Picrasmin, like quassin and neoquassin, has two methoxyl groups.

The reactions of picrasmin that have been studied are, with only two exceptions, the same as those of quassin. The action of boiling 3.5% aqueous hydrochloric acid upon picrasmin gives approximately the same yield of semidemethoxyquassin as is obtained from quassin. The action of a mixture of acetic and concentrated hydrochloric acids upon picrasmin gives quassinol, which is obtained from quassin by the same reaction. The yield of quassinol from picrasmin, however, is approximately one-third greater than that obtained from quassin. Chromic acid in an acetic acid solution has the same effect upon picrasmin as it has upon quassin. The product is isoquassin, and the yields from both materials are of the same magnitude. Finally, boiling dilute ethanolic potassium hydroxide solution affects picrasmin as it does quassin, in that the compound is so altered that no definite material has been isolated from the reaction mixture.

The two reagents that gave results different from those obtained with quassin are ethanolic hydrochloric acid and acetic anhydride with sodium acetate. When treated with ethanolic hydrochloric acid, picrasmin did not yield a mixture of ethoxyquassin and isoquassin. All that could be isolated from the reaction mixture was unchanged material. Boiling acetic anhydride and sodium acetate partly converted picrasmin into dehydroquassin. No other reaction was observed. In contrast, quassin gives dehydro- and anhydroquassin, while some is isomerized to picrasmin.

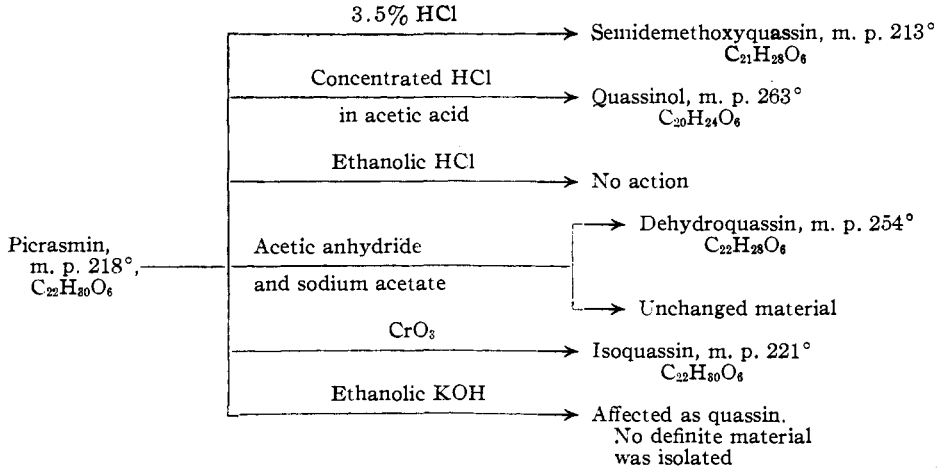
These various reactions are summarized diagrammatically in the accompanying chart. It follows from the results just enumerated that the structures of picrasmin and quassin must be very much alike.

Experimental

Preparation of Picrasmin.—With a few exceptions the method used to prepare picrasmin was the same as that employed to prepare quassin. The exact details are as follows.

(1) F. Massute, *Arch. Pharm.*, **228**, 147 (1890).
(2) E. P. Clark, THIS JOURNAL, **59**, (a) 927; (b) 2511 (1937).

SUMMARY OF THE REACTIONS OF PICRASMIN WHICH SO FAR HAVE BEEN STUDIED



Rasped picraena wood in 20-kg. lots was extracted by covering each lot with hot water for three hours. The decoction was decanted and the process repeated twice. Approximately 75 liters of extract was obtained from each treatment. Each extract was treated with a solution of lead acetate until the precipitation that it caused was complete; then, without removal of the separated material, sufficient activated carbon (Darco G 60) was added to adsorb the bitter material present. The following quantities of lead and carbon were necessary for each extract.

Extract	Carbon, g.	Lead acetate, g.
1	450	175
2	250	100
3	150	75

The carbon was filtered from the liquid and air dried. That obtained from the three extracts was then moistened with 1600 cc. of chloroform, packed in a percolator, and thoroughly exhausted with chloroform. The solvent in the extract was removed by distillation under reduced pressure, and the residue was dissolved in 200 cc. of methanol. This solution was treated with 1200 cc. of water at 60°, and the resulting turbid liquid was filtered through a thin layer of norit and allowed to crystallize. The yield of crude picrasmin was usually 20 g., or 0.1% of the wood used. The melting point of the crude material was usually 202–205°.

The crude picrasmin was purified by dissolving it in hot methanol in the proportion of 1 g. of substance to 10 cc. of solvent and then adding 3 volumes of water. Crystallization began at once and was completed within a few hours. The process was repeated until the crystals had a uniform microscopic appearance and a constant melting point of 218°.

Dilute acetic acid (10%) and a mixture of *n*-butanol and *n*-butyl ether are also good solvents for recrystallization. In both cases the picrasmin is dissolved in hot acetic acid or hot butanol, and the other component of the mixture is then added. Preparations obtained by each method gave, within experimental error, the same analytical results.

Picrasmin obtained from dilute methanol consists of long, thin, colorless, rectangular plates and occasional rods which melt at 218°. In parallel polarized light (crossed nicols) the extinction is straight and the elongation is positive: η_α 1.575 (crosswise), η_γ 1.587 (lengthwise), both ± 0.003.[3] A solution of 115 mg. of picrasmin in 2.28 cc. of chloroform (*c*, 5.04), when placed in a 96-mm. tube at 20°, rotated the plane of polarized light 2.2° to the right. Therefore, $[\alpha]^{20}D$ is +45.4°.

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.75; $(OCH_3)_2$, 15.9; mol. wt., 390.3. Found: C, 67.7, 67.8; H, 7.6, 7.7; OCH_3, 15.6, 15.6; mol. wt. (Rast), 407, 410.

Semidemethoxyquassin.—This compound was obtained from picrasmin just as it was from quassin.[1] The course of the experiments was so much the same that no difference could be detected. The product was identified by its melting point, mixed melting point with an authentic sample from quassin, and optical crystallographic properties.

Quassinol.—Quassinol was obtained by the method recorded for its preparation from quassin. The purified material was identified in the usual manner by comparison with an authentic sample made from quassin. The yield of quassinol from picrasmin, however, was approximately one-third larger than that from quassin.

Isoquassin.—This compound was also obtained from picrasmin in the manner in which it was obtained from quassin. The yields were essentially the same, and the purified product was identified as isoquassin by the procedure used to identify semidemethoxyquassin and quassinol.

Action of Ethanolic Potassium Hydroxide upon Picrasmin.—When picrasmin was treated with 2.5% ethanolic potassium hydroxide solution as described in a similar experiment with neoquassin,[2b] it failed to yield any material that could be identified. In this respect it is like quassin.

Action of Ethanolic Hydrochloric Acid upon Picrasmin.—The method employed to prepare ethoxyquassin from quassin and neoquassin was used with picrasmin. Only unchanged material could be isolated from the reaction

(3) The optical crystallographic data reported here, as well as the comparisons to which reference will be made, were determined by George L. Keenan, of the Food and Drug Administration, U. S. Department of Agriculture.

mixture. In this respect picrasmin differs from the other two isomers.

Action of Acetic Anhydride and Sodium Acetate upon Picrasmin.—A solution of 1 g. of picrasmin in an acetylating mixture of 8 cc. of acetic anhydride and 0.25 g. of anhydrous sodium acetate was boiled for one and one-half hours. Most of the anhydride was then removed by distillation, and the resulting mass was treated with water. The product that separated soon crystallized and yielded 0.8 g. of material with a melting poing of 200–205°.

The crude crystals were dissolved in boiling methanol and allowed to crystallize. They yielded 220 mg. of needles and boat-shaped plates, which melted at 255°. Recrystallization did not alter the melting point. The substance was identified as dehydroquassin by comparison with an authentic sample from quassin as to melting point, mixed melting point, and optical crystallographic properties.

The mother liquors from the first crystallization were diluted with two volumes of water, which caused the crystallization of a quantity of impure starting material. Purification of this from 35% methanol gave unchanged picrasmin and a small quantity of dehydroquassin. The former was identified by its melting point and mixed melting point.

Summary

Evidence has been presented to show that picrasmin, the bitter constituent of the wood of *Picrasma excelsa*, is an isomer of quassin and neoquassin, and hence has the molecular formula $C_{22}H_{30}O_6$. It is optically active and contains two methoxyl groups.

A method for the preparation of this material is described and some of its reactions are compared with those of quassin. The great similarity between the reactions of picrasmin and quassin indicates that the two materials are structurally very much alike. A summary of the reactions recorded for picrasmin is presented diagrammatically.

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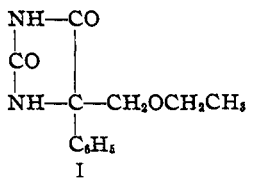
[CONTRIBUTION NO. 131 FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of Compounds with Hypnotic Properties. II. Phenoxymethylhydantoins[1,2]

BY WILLIAM B. WHITNEY[3] WITH HENRY R. HENZE

Research in the field of synthetic drugs possessing potency as hypnotics has demonstrated that the compounds showing most promise are of a type in which fat-soluble alkyl groups are attached to a water-soluble nucleus such as barbituric acid.[4] Since hydantoin is closely related to barbituric acid in structure and solubility in water, and inasmuch as the hydantoin nucleus can be substituted similarly by alkyl groups, the fact that certain alkylated (or arylated) hydantoins produce narcosis is not surprising. However, most of these derivatives are not sufficiently potent and for the remainder the margin of safety between the effective and lethal doses is not sufficient to warrant their use. In hopes of improving this factor of safety, alkoxymethyl groups were used as substituents in a previous investigation.[5] By utilization of this ether linkage, substituted in the methyl group which is attached to the 5-position of the hydantoin nucleus, it was expected that much of the narcotic effect produced when methyl is substituted by a higher alkyl might be retained, but that the toxicity of the compound might be diminished. In at least two instances it was found that compounds with definite narcotic action were thus produced. As all of the hydantoins prepared in this previous investigation were, with the single exception of ethoxymethylphenylhydantoin (I), alkoxymethyl alkylhydantoins, it was of interest to continue the study by synthesizing and testing pharmacologically a series of the aryloxy analogs. Especially should the synthesis of phenoxymethylethylhydantoin (II) be desirable, since from its evaluation might be acquired data relating to the effect of position isomerism upon hypnotic activity.



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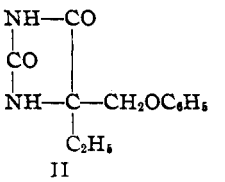

II

It was to be anticipated that the synthesis of 5,5-aryloxymethyl alkyl (or aryl) hydantoins would

(1) From a dissertation presented by Wm. B. Whitney to the Faculty of the Graduate School of the University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1937.

(2) Presented before the Division of Organic Chemistry at the 95th meeting of the American Chemical Society, April 18 to 21, 1938, at Dallas, Texas.

(3) Present address, Department of Chemistry, North Texas Agricultural College, Arlington, Texas.

(4) Tabern and Shelberg, THIS JOURNAL, **55**, 328 (1933).

(5) Rigler with Henze, *ibid.*, **58**, 474 (1936).