derivative of I, the mixed m.p. was not depressed, and the infrared tracings of the two samples, secured on carbon tetrachloride solutions, were identical. Also the dimethyl esters gave identical R_f values in a paper chromatogram (Table I). It is concluded, therefore, that I is identical with natural piscidic acid, and that the differences noted in the properties of the two substances were most probably caused by the presence in I of small amounts of related acids derived from the source material. Several other, closely similar acids are present in *Narcissus poeticus* bulbs, and their separation and purification have been found to be quite difficult.[2]

The structure of piscidic acid was suggested to be IA on the basis of degradation studies.[4] This structure has recently been verified by synthesis and resolution of the synthetic product, which gave piscidic acid identical with the natural occurring substance.[6] The evidence, therefore, seems conclusive that I is a *p*-hydroxybenzyltartaric acid (structure IA).

Acknowledgments.—The authors are indebted to S. M. Aronovic for determination of infrared spectra.

Experimental

Alkali Degradation of Compound I.—About 100 mg. of I was added in small portions to a mixture of 0.5 g. of potassium hydroxide and 0.5 g. of sodium hydroxide preheated to 255–265° and kept under nitrogen. The addition required 10 minutes, and heating was then continued 10 minutes longer. The yellow-colored mixture was allowed to cool to room temperature, taken up in a minimum volume of water, acidified with sulfuric acid, and a heavy inorganic precipitate, presumably silica, filtered off. The aqueous filtrate was extracted with ether, the extract evaporated, and the yellow residue dissolved in 0.5 ml. of 0.1 *N* sodium hydroxide. The solution was then acidified with 1–2 drops of 7 *N* sulfuric acid, and stored at 4° for two days. At the end of this time a few colorless needle crystals had formed in the solution. This product II after being washed with water and air-dried, gave a yellow color with *p*-diazobenzenesulfonic acid[7] and melted at 201–203° (microblock). Mixed with *p*-hydroxybenzoic acid, m.p. 205–206°, the m.p. was 202–204°. On paper chromatograms[8] II migrated in three solvent systems with the same R_f value as known *p*-hydroxybenzoic acid.

The aqueous filtrate remaining after removal of the II crystals gave a pink color with *p*-diazobenzenesulfonic acid. This solution was extracted several times with ether, and the extract on evaporation yielded a pinkish, semi-crystalline solid, m.p. 143–146° (microblock). Mixed with known *p*-hydroxyphenylacetic acid,[9] m.p. 147–148°, the m.p. was 144–146°. When subjected to paper chromatography in three different solvent systems,[8] this degradation product migrated with the same R_f values as *p*-hydroxyphenylacetic acid.

Periodate Oxidation of Compound I.—A mixture of 49.4 mg. of I, 20 ml. of 0.5 *M* phosphate buffer, *p*H 6.5, and 10 ml. of approximately 0.5 *N* aqueous sodium periodate at 4° was diluted to 50 ml. with water and held at 4° for 2.5 hr. The periodate consumed at the end of this time amounted to 2.3 moles per mole of I used. Excess potassium iodide was then added, the solution acidified with sulfuric acid, and the liberated iodine removed by repeated extraction with carbon tetrachloride. The aqueous solution was exhaustively extracted with ether in a continuous, liquid–liquid extractor for 24 hr., the extract evaporated to dryness, and the residue chromatographed on a silicic acid column using 35% *n*-butanol in chloroform as previously described.[2]

Three peaks were eluted from the column, the first two to appear being about equal in size and the last very much smaller. The material comprising the first peak was an unknown phenol which could not be identified. The second and third peaks came off the column in the positions that would be expected for formic and oxalic acids, respectively, and the acids were identified by comparative paper chromatography in four different solvent systems.[8]

Polymorphic Forms of Piscidic Acid Dimethyl Ester.—The dimethyl ester of the acid I from narcissus, which melted at 115° after several recrystallizations, was dissolved in the minimum amount of boiling thiophene-free benzene, and the solution seeded with a trace of piscidic acid dimethyl ester,[5] m.p. 127°. The crystalline precipitate which separated on cooling melted at 127° and gave no melting point depression with piscidic acid dimethyl ester.

Piscidic Acid Dimethyl Ester Triacetate.—To a solution of 20 mg. of piscidic acid dimethyl ester in 0.2 ml. of acetic anhydride was added one drop of concentrated sulfuric acid. The mixture was allowed to stand 30 minutes at room temperature, then chilled in an ice-bath and 1 ml. of water added slowly with shaking. The white crystalline precipitate, after being twice recrystallized from petroleum ether, b.p. 60–80°, melted at 81–82°.

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(6) A. L. J. Buckle, A. McGookin and A. Robertson, *J. Chem. Soc.*, 3981 (1954).

(7) M. T. Hanke and K. K. Koessler, *J. Biol. Chem.*, **50**, 235 (1922).

(8) Details of the paper chromatography of the phenolic degradation products and the acids obtained by periodate oxidation are given in the Ph.D. thesis of R. R. Smeby, University of Wisconsin, 1954.

(9) Kindly provided by O. K. Behrens, Lilly Research Laboratories.

Synthesis of β-(4-Hydroxy-2-methylphenoxy)-lactic Acid, a Metabolite of Mephenesin

BY B. J. LUDWIG, H. LUTS AND W. A. WEST

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The fate of mephenesin (VI) (3-*o*-toloxy-1,2-propanediol) in the animal body was investigated by several workers soon after the introduction of this drug as a muscle relaxing agent. Berger and Schwartz[1] first called attention to a mephenesin metabolic product present in urines of humans receiving this drug which produced a positive Ehrlich[2] reaction. The isolation and identity of a second more abundant metabolic product, β-*o*-toloxylactic acid, was described a short time later by Graves, Elliott and Bradley[3] and by Riley and Berger.[4] The chromogenic metabolite was subsequently isolated and characterized by Riley,[5] on the basis of its composition, physical properties and degradation to toluhydroquinone, as β-(4-hydroxy-2-methylphenoxy)-lactic acid (IV). This Note describes the synthesis of this chromogenic metabolic product and confirms Riley's identification of this compound.

Condensation of toluhydroquinone with one mole of β-chlorolactic acid can result in the formation of β-(4-hydroxy-3-methylphenoxy)- and β-(4-hydroxy-2-methylphenoxy)-lactic acid (III and IV). Several attempts to carry out this condensation resulted in the isolation of low yields of a methyl-4-hydroxyphenoxylactic acid whose melting point differed materially from that of the natural product described by Riley. Apparently the product

(1) F. M. Berger and R. P. Schwartz, *J. Am. Med. Assoc.*, **137**, 772 (1948).

(2) P. B. Hawk and O. Bergeim, "Practical Physiological Chemistry," 11th ed., P. Blakiston's Son and Co., Inc., Philadelphia, Pa., 1937, p. 669.

(3) E. L. Graves, T. J. Elliott and W. Bradley, *Nature*, **162**, 257 (1948).

(4) R. F. Riley and F. M. Berger, *Arch. Biochem.*, **20**, 159 (1949).

(5) R. F. Riley, THIS JOURNAL, **72**, 5712 (1950).

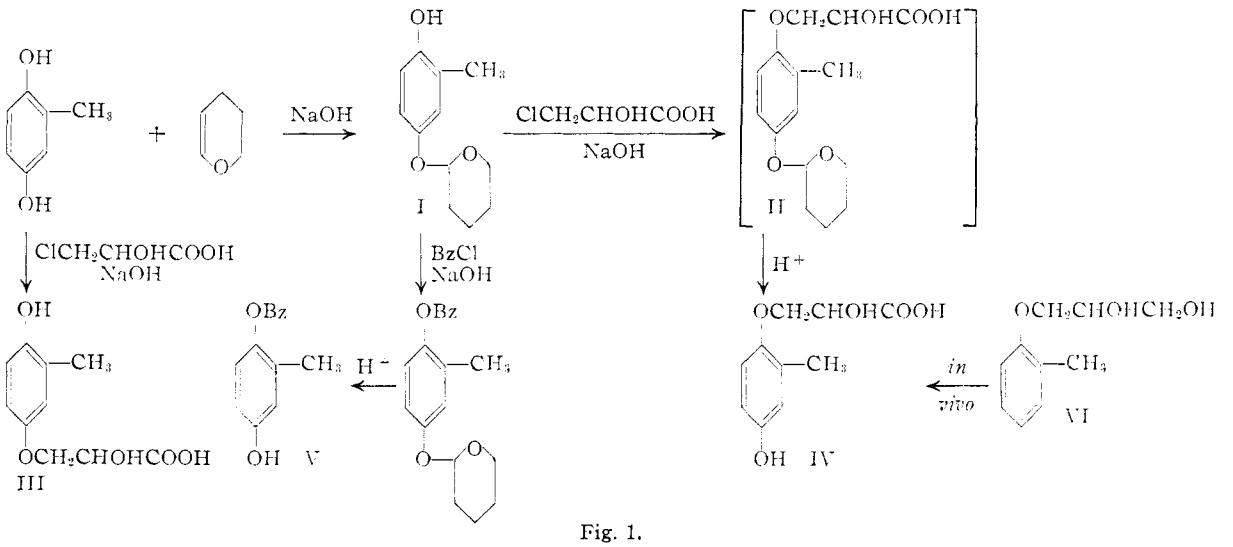

Fig. 1.

obtained by direct reaction was III or a mixture of isomers in which III predominated, indicating a preference for condensation to occur with the hydroxyl group *meta* to the methyl group of toluhydroquinone.

Condensation of β-chlorolactic acid with the *o*-hydroxyl group to give the desired condensation product in low yield was accomplished by monopyranylation of toluhydroquinone to protect the more reactive *m*-hydroxyl group.[6] 4-Hydroxy-3-methylphenyl-2-tetrahydropyranyl ether (I) was converted to the β-lactyl ether (II). The latter compound was hydrolyzed without isolation to yield the desired toluhydroquinone lactyl ether (IV). This compound proved to be identical in every respect with a sample of the natural chromogenic product isolated from human urine.[7]

Further confirmation of the position of the free hydroxyl group in I (and of the position of the lactyl group in IV) was afforded by converting I to the benzyl tetrahydropyranyl diether followed by acid hydrolysis to give 2-benzyloxy-5-hydroxytoluene (V), previously described.[8]

The isomeric compounds III and IV, which differ substantially in their melting points, possess the same ultraviolet absorption maximum and minimum; they are indistinguishable in their behavior on paper partition chromatography and in their production of the Ehrlich diazo color reaction.

Experimental[9]

β-(4-Hydroxy-3-methylphenoxy)-lactic Acid (III).—Toluhydroquinone (24.8 g., 0.2 mole) was dissolved in a solution of 8.0 g. (0.2 mole) of sodium hydroxide in 100 ml. of water. 12.5 g. (0.1 mole) of β-chlorolactic acid was added and the reaction mixture refluxed two hours. After cooling, the mixture was saturated with CO_2 and washed with ether. 19.5 g. of unreacted toluhydroquinone was recovered. The aqueous layer was concentrated under reduced pressure, acidified with hydrochloric acid and extracted with ether. The ether solution on removal of solvent yielded 2.6 g. of a mixture of toluhydroquinone and the desired condensation product. The former was removed by vacuum sublimation, leaving 1.5 g. (20% based on toluhydroquinone consumed) of a tan colored solid, m.p. 116–120°. Repeated recrystallization from hot nitropropane gave slightly colored crystals of β-(4-hydroxy-3-methylphenoxy)-lactic acid, m.p. 121–122°.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.39; H, 5.68.

This compound differs substantially from the natural chromogenic lactic acid derivative in melting point. It exhibits the same ultraviolet maximum and minimum, gives an Ehrlich reaction of similar intensity and is chromatographically indistinguishable from the natural isomer.[10]

Preparation of β-(4-Hydroxy-2-methylphenoxy)-lactic Acid (IV). 4-Hydroxy-3-methylphenyl-2-tetrahydropyranyl ether (I).—Dihydropyran (16.8 g., 0.2 mole) was added to a well-stirred mixture of 12.4 g. (0.1 mole) of toluhydroquinone in 100 ml. of dioxane, containing 2 drops of concentrated hydrochloric acid. External cooling was used to maintain the reaction mixture at 25–30°. The mixture was then allowed to react without cooling for three hours during which period the temperature rose to about 60°. Ether was added and the alkali-soluble portion extracted with 10% sodium hydroxide solution. The alkaline solution was neutralized with carbon dioxide and after diluting with water was extracted with carbon tetrachloride. Concentration of this solution under reduced pressure gave a deposit of 5.3 g. of colored product (26%), m.p. 62–65°. Recrystallization from ether–ligroin mixture containing a drop of dihydropyran gave white crystals, m.p. 90–91.5°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.61; H, 8.15.

Variations in the ratio of reactants, rate and order of addition and extent of temperature control usually gave lower recoveries (5–25%) of usable product. Attempts to purify the crude ether by distillation under diminished pressure resulted in excessive decomposition.

β-(4-Hydroxy-2-methylphenoxy)-lactic Acid (IV).—4-Hydroxy-3-methylphenyl-2-tetrahydropyranyl ether (4.16 g., 0.02 mole) was dissolved in 12 g. of 10% sodium hydroxide solution. 1.25 g. of β-chlorolactic acid (0.01 mole) was added and the mixture refluxed for three hours. The solution was cooled, saturated with CO_2 and the ether soluble fraction removed by extraction. The aqueous portion containing the mixed diether was acidified with hydrochloric acid, saturated with sodium sulfate and extracted with ether. The solution was dried and the ether removed leaving 0.8 g. of colored solid residue. After twice recrystallizing from benzene–ether and once from nitropropane, 410 mg. (11%) of purified product was obtained, m.p. 168–169°.

(6) W. Parham and D. DeLaitsch, THIS JOURNAL, **76**, 4962 (1954).

(7) We are grateful to Dr. Richard F. Riley for supplying us with a sample of this compound isolated by him from human urine.

(8) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).

(9) All melting points reported are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

(10) Riley, in a private communication, reports that he obtained a product, using essentially the same procedure, which melted at 134.5–136°. Mixed melting point studies with III, IV and Riley's compound were inconclusive. Until compound III is prepared by an unambiguous method, its correct melting point will remain in doubt.

Its melting point was unchanged after subjecting it to a nine-tube countercurrent distribution using *p*H 3.5 phosphate buffer–isopropyl ether as the distribution phases.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.81; H, 6.07.

Comparison of Natural and Synthetic Product.—The synthetic product was identical to a sample of natural β-(4-hydroxy-2-methylphenoxy)-lactic acid. A mixed melting point with the natural product, m.p. 168–169°[11] gave no depression. Both compounds exhibited an ultraviolet absorption maximum at 290 mμ and a minimum at 251 mμ and both gave a similar intensity of red color when their solutions were treated with Ehrlich reagent as described by Riley. When subjected to paper chromatography no difference could be detected between the natural product and the two synthetic isomers. In this study butanol saturated with 1.5 *M* ammonium hydroxide was used as the solvent. The location of the spots on the chromatogram was determined by spraying with brom thymol blue solution, and also by using a modification of Ehrlich reagent. The paper was sprayed with a freshly prepared mixture of one part of 0.5% $NaNO_2$ and 25 parts of solution containing 5 g. of sulfanilic acid and 50 ml. of hydrochloric acid per liter. Exposure of the sprayed paper to ammonia vapors located the positions of the compounds as well-defined intense red spots.

2-Benzyloxy-5-hydroxytoluene.—To confirm the location of the tetrahydropyranyl group in I (and the position of the hydroxyl group in IV) compound I was converted to the known toluhydroquinone monobenzyl ether (V). 1.04 g. (0.005 mole) of the monopyranylated ether was treated in the usual manner with one equivalent of benzyl chloride in an aqueous solution of one equivalent of sodium hydroxide. Hydrolysis of the intermediate mixed diether and subsequent workup of the hydrolysis mixture yielded a small quantity of white crystals which on recrystallization from ligroin melted at 69.5–70.5°. Baker and Brown[8] report a melting point of 69–70° for this compound.

(11) Riley (ref. 5, p. 5713) reports m.p. 165–166°.

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The Action of Peracids on the Desoxycodeines[1]

BY HENRY RAPOPORT AND ETHAN C. GALLOWAY

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The fact that a number of various desoxycodeines are now easily available led us to examine their reaction with peracids with the objective of preparing the corresponding epoxides. These in turn might be convertible to codeine isomers with an oxygen function at some position other than 6.

For the three possible sites of oxidation, *viz.*, the tertiary amine, the alicyclic double bond, and the aromatic ring,[2] the expectation was that the rates of oxidation would be appreciably different and would decrease in the above order.[3] Initial experiments with perbenzoic acid and Δ^7-desoxycodeine in chloroform at 0° did show an almost instantaneous consumption of one mole of peracid. That this was due to amine oxide formation was established by hydrogenation of the product to dihydrodesoxycodeine. However, after this very rapid one-mole uptake (less than 15 minutes) consumption of perbenzoic acid continued at a markedly decreased rate and did not reach two moles until after about forty hours.

(1) Supported by a grant from the National Institutes of Health, Bethesda, Md.

(2) (a) H. Fernholz, *Ber.*, **84**, 110 (1951); (b) S. L. Friess, A. H. Soloway, B. K. Morse and W. C. Ingersoll, THIS JOURNAL, **74**, 1305 (1952).

(3) D. Swern, *Chem. Revs.*, **45**, 1 (1949).

To gain insight as to whether the alicyclic double bond or the aromatic nucleus (or both) was being attacked, the rates of peracid consumption by Δ^7-desoxycodeine and dihydrodesoxycodeine were compared and found to be identical. From this it may be concluded that the aromatic nucleus was being oxidized at least as rapidly as the alicyclic double bond, if the latter were being attacked at all.[4] Δ^6-Desoxycodeine, Δ^8-desoxycodeine and 6-methyl-Δ^6-desoxycodeine were also subjected to perbenzoic acid under the same conditions to ascertain whether the position or degree of substitution of the alicyclic double bond might substantially affect its rate of oxidation. Oxidations were also conducted in benzene at 8 and 23°. In every case, irrespective of compound or conditions, the rate of perbenzoic acid consumption was identical with that found for dihydrodesoxycodeine.

In a number of examples, a deactivation of the aromatic nucleus to peracid oxidation has been effected by substitution of bromine into the ring.[5] This possibility was explored through the preparation of 1-bromodihydrodesoxycodeine, but again its rate of oxidation was identical with that of the unbrominated compound.

As a final alternative, oxidation with monoperphthalic acid was examined, since the aromatic ring is relatively unreactive toward this oxidant.[2a] Dihydrodesoxycodeine, Δ^6-, Δ^7-, Δ^8- and 6-methyl-Δ^6-desoxycodeine were subjected to the action of monoperphthalic acid in acetone at 0°. In every case, there was a one-mole consumption of peracid requiring about thirty minutes, and beyond that no further oxidation occurred. Although the alicyclic double bond again was inert, the clean-cut one-mole consumption and no further oxidation at any other site in the molecule indicated that this might be a useful method for preparing amine oxides.

When the oxidations with monoperphthalic acid were conducted with the objective of preparing amine oxides, a good yield of the desired product was obtained with facility in each instance, as shown in Table I. Considering the vigor of the alkaline hydrogen peroxide usually used for this purpose,[6] and the selectivity of monoperphthalic acid in acetone at 0°, the latter reagent appears to be advantageous for amine oxide formation.

Experimental

Δ^6-Desoxycodeine was prepared by dehydrochlorination of dihydrochlorocodide using a 20-hour reflux period in a solution of sodium cyclohexylate in cyclohexanol instead of sodium methylate in methanol at 140°.[7]

Δ^7- and Δ^8-desoxycodeine were prepared by lithium aluminum hydride reduction of *p*-toluenesulfonylcodeine and *p*-toluenesulfonylneopine, respectively.[8] Hydrogenation of Δ^7-desoxycodeine gave **dihydrodesoxycodeine.**[8]

(4) This oxidation of the aromatic ring most probably occurs at C_3–C_4, since this is the position most susceptible to ozonolysis [E. Speyer and A. Popp, *Ber.*, **59**, 390 (1926); E. Speyer, *ibid.*, **62**, 209 (1929); H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950)] even when an alicyclic double bond is present [E. Speyer and L. F. Roell, *Ber.*, **63**, 539 (1930)].

(5) J. Böeseken and C. F. Metz, *Rec. trav. chim.*, **54**, 345 (1935); W. F. Short and H. Wang, *J. Chem. Soc.*, 2979 (1951).

(6) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, England, 1954.

(7) L. F. Small and F. L. Cohen, THIS JOURNAL, **53**, 2214 (1931).

(8) H. Rapoport and R. M. Bonner, *ibid.*, **73**, 2872 (1951).