when the experiment was carried out in a 25° bath with constant agitation. The experiment was repeated with different quantities of benzene and "neutral" solutions of ferrous sulfate and hydrogen peroxide. For a fixed volume and composition of the aqueous phase the reaction time increased markedly with the volume of benzene. For a given volume of benzene and the aqueous phase the time decreased with increasing concentrations of hydrogen peroxide and ferrous sulfate. The violent oxidation did not occur in the presence of 0.1 *N* sulfuric acid. When the first experiment was repeated with a 0.15% solution of phenol in benzene the fast oxidation took place in two minutes.

TABLE I

YIELD OF PHENOL AS A FUNCTION OF REACTION CONDITIONS[a]

The time was measured from the addition of ferrous sulfate to the addition of the 1 *N* sulfuric acid. In experiments 3 and 6 the rapid final oxidation, and the accompanying temperature rise, commenced after 50 min. In the third experiment, the temperature was kept below 26° by the addition of ice to the mixture during the final stage of the reaction.

H_2O_2, ml.	$FeSO_4$, ml.	Reacn. time, min.	Wt. of phenol, g.
100	20	10	0.05
100	20	30	0.36
100	20	55	1.13
50	10	60	0.09
50	10	30	.03
50[b]	10	55	.46
50[b]	10	30	.07
200[c]	20	240	.76
200[d]	20	1800	.17

[a] Temperature 23° (water bath), *p*H 3, volume of benzene 500 ml. except as otherwise noted. [b] 250 ml. of benzene. [c] Temperature in this experiment maintained at 6°. [d] *p*H 1.

The following method was used to study the formation of phenol: A 2.0% solution of ferrous sulfate was added to a mixture of benzene and 3.0% hydrogen peroxide, which was vigorously stirred in a Morton flask, immersed in a bath at a suitable temperature. Before the mixture was allowed to separate at the end of the experiment, it was acidified with 10 ml. of 1 *N* sulfuric acid. In a few runs it was necessary to break up the emulsion by centrifuging. The aqueous layer was discarded and the phenol was isolated from the organic phase by a method described earlier.[3] The phenol, m.p. 38° (uncor.), crystallized in long needles and was in most cases colorless or pale yellow. The yield was calculated from the weight of tribromophenol, m.p. 93° (uncor.), obtained by treating the product with bromine water.

Table I summarizes a number of experiments. The *p*H of the systems obtained by mixing "neutral" solutions of ferrous sulfate and hydrogen peroxide was approximately 3. In one experiment the solution was adjusted to *p*H 1 with sulfuric acid.

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Piscidic Acid from *Narcissus poeticus*[1]

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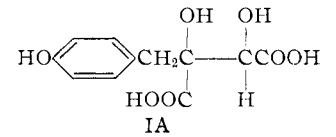
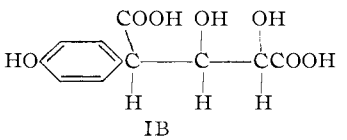
RECEIVED JUNE 4, 1955

The isolation and partial characterization of several apparently new acids from *Narcissus poeticus* bulbs has recently been reported.[2] The most stable acid, $C_{11}H_{12}O_7$ (I), obtained in relatively large amounts, was found to contain one phenolic hydroxyl, two alcoholic hydroxyl and two carboxyl groups.[3]

In further work it has been established that alkali fusion of I results in the formation of *p*-hydroxybenzoic and *p*-hydroxyphenylacetic acids, and that periodate oxidation yields formic and oxalic acids. In the light of these findings it was tentatively concluded that I has either the structure IA or IB



IA



IB

At this point in the study the similarity of I to piscidic acid, obtained by A. Robertson and coworkers from *Piscidia erythrina*,[4] was noted. A comparison of some of the properties of the two substances and their derivatives is given in Table I.[5] At first only free piscidic acid and its dimethyl ester were available for comparison, and it will be seen from Table I that appreciable differences were observed, particularly in the properties of the two free acids. Infrared spectra of the acids were determined as micromulls in mineral oil, and, although the tracings were generally very similar, distinct differences were again apparent. Another point of disagreement noted at first was a 12° difference in the m.p. of the two dimethyl esters. However, it was found that this discrepancy was due to the existence of two polymorphic forms of this ester, one melting at 115° and the other at 127°. Neither gave any m.p. depression with dimethyl piscidate.

TABLE I

COMPARISON OF PISCIDIC ACID AND AN ORGANIC ACID OBTAINED FROM *Narcissus Poeticus* BULBS

Property	Piscidic acid		Compound I
	Lit.[4]	Obsd.	Obsd.
M.p., °C.[a]	186–187	183–184 dec.	184–184.5 dec.
$[\alpha]_D$ (*c* 2.6, water)	+41.02° (20°)	...	+48.88° (28°)
Dimethyl ester, m.p., °C.	127	127	115, 127[b,c]
Dimethyl ester triacetate, m.p.,[d] °C.	84	81–82	82–83
R_f value[e] of free acid	...	0.56	0.42
dimethyl ester	...	0.72	0.72

[a] Mixed m.p. 166–170°. [b] Apparently polymorphic forms, see text. [c] Mixed m.p. with either form, 126–127°. [d] Mixed m.p. 81–82°. [e] Paper chromatograms carried out as previously described.[2]

When the triacetate was prepared from the dimethyl ester of piscidic acid, the m.p. was found to be very nearly the same as that of the corresponding

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Research Foundation.

(2) R. R. Smeby, V. Zbinovsky, R. H. Burris and F. M. Strong, THIS JOURNAL, **76**, 6127 (1954).

(3) This acid was designated compound III in the previous paper.[2] It was obtained only after alkali treatment of extracts of narcissus bulbs and probably does not exist as such in the plant.

(4) W. Bridge, F. Coleman and A. Robertson *J. Chem. Soc.*, 257 (1948).

(5) Samples of piscidic acid and its dimethyl ester were kindly provided by Dr. A. McGookin, University of Liverpool.

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).

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(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

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(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).