

water-methanol, yielded 0.5–1.0 g. of 7-hydroxy-3-methylphthalide as the monohydrate,  $C_9H_8O_3 \cdot H_2O$ , m.p. 109–110°.<sup>3</sup>

**Carbon Dioxide and Acetic Acid.**—Ten grams of terramycin dihydrate (0.0202 mole) was dissolved in 100 ml. of 25% sodium hydroxide, free of carbonate, and heated under reflux in a nitrogen atmosphere with 30 g. of acid washed granulated zinc for 22 hours.

The solution was decanted from the zinc, acidified to pH 1 with sulfuric acid, and again heated under reflux in a stream of nitrogen for 2 hours. Carbon dioxide was collected as barium carbonate (2.80 g., 0.0142 mole).

The acid solution was distilled to small volume, diluted with water and redistilled to yield 0.0078 mole of acetic acid, which was identified microscopically<sup>7</sup> as its sodium uranyl salt, and as its silver salt.

**Alkali Fusion of Terramycin.**—Terramycin base (25 g., 0.05 mole) was added portionwise over one hour to a melt of 120 g. of potassium hydroxide and 60 g. of sodium hydroxide at 200–210°. After 2 hours further heating, the melt was cooled, dissolved in water, acidified, and extracted with three 100-ml. portions of ethyl acetate. The ethyl acetate extract was evaporated to dryness and the tarry product sublimed at 200° (0.1 mm.) to yield 3.6 g. of oily crystals. Direct crystallization from water, followed by recrystallization,

yielded 0.66 g. of salicylic acid, m.p. 158–159°, mixed melting point with an authentic sample not depressed. The identification was confirmed by the preparation of the acetyl derivative, m.p. 134–135°.

The aqueous mother liquors from the crystallization of the salicylic acid were subjected to a 12-plate countercurrent extraction vs. 1:1 ethyl acetate-benzene. Tubes 1 to 5 were fractionally recrystallized from water to yield a further 0.10 g. of salicylic acid (total yield, 0.76 g., 11%) and 0.35 g. (5%) of *m*-hydroxybenzoic acid, m.p. 199.5–201°, mixed m.p. with an authentic sample not depressed.

*Anal.* Calcd. for  $C_7H_6O_3$ : C, 60.90; H, 4.47; mol. wt., 138. Found: C, 60.81; H, 4.71; mol. wt. (Rast), 135.

Tubes 8 to 12 yielded on sublimation, 1.0 g. (17%) of succinic acid and succinic anhydride, which was dissolved in water, and resublimed at 0.05 mm. to yield succinic acid, m.p. 186–187°, mixed m.p. with an authentic sample not depressed.

*Anal.* Calcd. for  $C_4H_6O_4$ : C, 40.65; H, 5.13; mol. wt., 118. Found: C, 40.84; H, 5.38; mol. wt. (Rast), 123.

The succinic acid was further characterized by conversion to succinic anhydride, m.p. 118–119°, mixed m.p. with an authentic sample of m.p. 119–120°, not depressed.

**Acknowledgment.**—We are indebted to Dr. J. Means for the microanalyses.

BROOKLYN, NEW YORK RECEIVED NOVEMBER 15, 1951

(7) E. M. Chamot and C. M. Mason, "Handbook of Chemical Microscopy," John Wiley and Sons, Inc., New York, N. Y., 1939, p. 389.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

## Terramycin. III. Structure of Terracinoic Acid, an Alkaline Degradation Product<sup>1</sup>

By R. PASTERNAK, L. H. CONOVER, A. BAVLEY, F. A. HOCHSTEIN, G. B. HESS AND K. J. BRUNINGS

Terracinoic acid,  $C_{13}H_{12}O_6$ , a product of the alkaline degradation of the antibiotic terramycin, is shown to have the structure 4-carboxy-5-hydroxy-3-methylindanone-2-acetic acid. The principal features of the proof of structure are: (1) determination of the carbon skeleton by caustic fusion and hydrogenation, (2) proof of the presence of a  $\gamma$ -keto acid system by pyridazine formation and decarboxylation of 2-bromoterracinoic acid by dehydrobromination, and (3) determination of the orientation of the functional groups by comparative studies of acid strengths and of ultraviolet and infrared spectra of terracinoic acid and its derivatives. The basic structure was checked by showing that the ultraviolet spectrum of 5-hydroxyindanone is practically identical with that of decarboxyterracinoic acid.

Terracinoic acid,<sup>2,3</sup>  $C_{13}H_{12}O_6$ , is the principal nitrogen-free product formed by the aqueous alkali degradation of the antibiotic terramycin. In this paper, experimental evidence is presented for assigning to terracinoic acid the structural formula 4-carboxy-5-hydroxy-3-methylindanone-2-acetic acid (I).

Terracinoic acid is an optically inactive, colorless, tribasic acid melting at 233–234°. It gives a magenta color with ferric chloride, and a positive Millon test. Fehling and Tollens tests are negative. The presence of a benzene ring in the structure of terracinoic acid is suggested by the isolation of *m*-ethylphenol and of related carboxylic acids from the products of alkali fusion. Confirmation that the benzene ring is present as such in terracinoic acid is provided by nitration to yield a mononitro derivative, m.p. 201–202°, which can be reduced to an aromatic amine.

The hydrogenation of terracinoic acid over palladium and glacial acetic acid results in the absorption of 5.6 to 5.9 moles of hydrogen to yield a saturated dicarboxylic acid,  $C_{13}H_{20}O_4$ , m.p. 149.5–150.5°. The formula of this saturated compound

is consistent with a bicyclic system and thus it may be concluded that terracinoic acid contains a benzene ring fused to a carbocyclic system.

The presence of an ethylenic double bond in terracinoic acid is not indicated by its behavior toward permanganate oxidation and bromination. Terracinoic acid reacts slowly with alkaline permanganate at room temperature to yield 2-hydroxyterracinoic acid (VII),  $C_{13}H_{12}O_7$ , m.p. 244–245°. On warming, a more vigorous reaction takes place resulting in drastic degradation of the molecule. Acetic acid (0.6 mole) has been isolated from this reaction, establishing the presence of a C-methyl group.

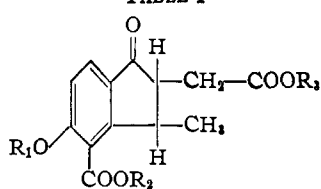
Terracinoic acid reacts readily with bromine in cold glacial acetic acid by substitution to form 2-bromoterracinoic acid (VI),  $C_{13}H_{11}BrO_6$ , m.p. 280–281° (dec.). The bromine in this compound is labile and may be replaced with a hydroxyl group by reaction in aqueous sodium acetate to yield the above-mentioned 2-hydroxyterracinoic acid. The 2-bromoterracinoic acid undergoes dehydrobromination and loss of a carboxyl group by the action of aqueous alkali to form compound VIII,  $C_{12}H_{10}O_4$ , m.p. 230.5–231°. In warm aqueous solution, the bromination of terracinoic acid results in decarboxylation and the formation of 4,6-dibromodecarboxyterracinoic acid, m.p. 169–170°. The bromine in this compound is not labile

(1) Presented before the 12th International Congress of Pure and Applied Chemistry, September, 1951, in New York, N. Y.

(2) R. Pasternack and collaborators, *THIS JOURNAL*, **73**, 2400 (1951).

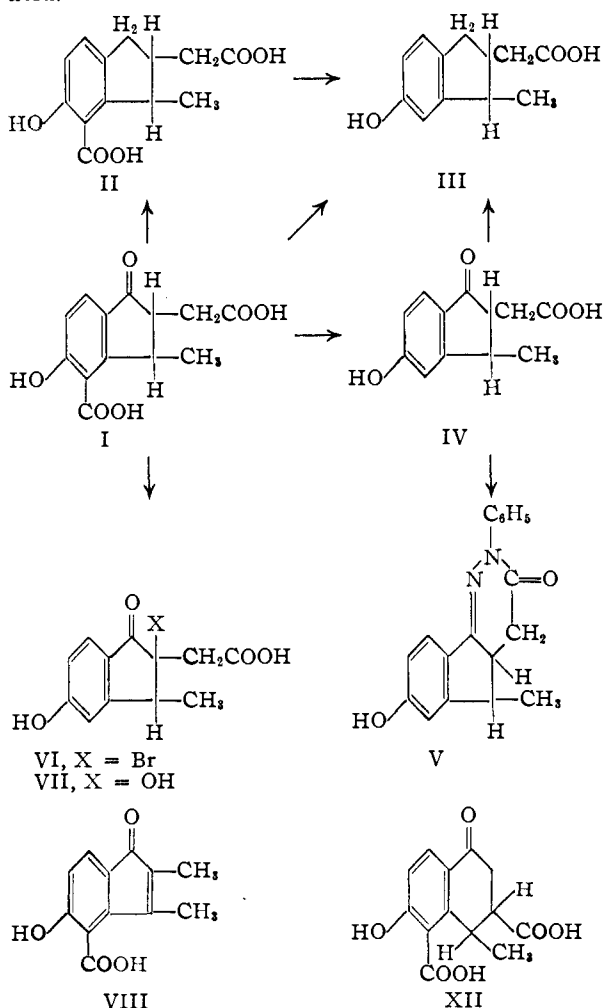
(3) R. Pasternack, A. Bavley, R. L. Wagner, F. A. Hochstein, P. P. Regna and K. J. Brunings, *ibid.*, **74**, 1926 (1952).

TABLE I



No.	Name	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	<i>pK<sub>a</sub></i>	I.R. Carbonyl absorption bands dioxane solution		
I	Terracinoic acid	H	H	H	2.6, 4.7, 9.5	5.77	5.86	6.02
Ia	Monoethyl ester	H	H	CH <sub>3</sub>	3.1, >10	5.77	5.88	6.03
Ib	Monoethyl ester	H	CH <sub>3</sub>	H	5.4, 7.8	5.75	5.85	6.01
Ic	Dimethyl ester	H	CH <sub>3</sub>	CH <sub>3</sub>	8.0	5.75	5.85	6.01
Id	Dimethyl ester methyl ether	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	...	5.77	5.86	
Ie	Methyl ether	CH <sub>3</sub>	H	H	3.1, 4.9	5.78	5.85	
IV	Decarboxyterracinoic acid	H	..	H	4.8, 8.0	5.75	5.87	
IVa	Methyl ester	H	..	CH <sub>3</sub>	8.1	5.74	5.86	
IVb	Methyl ester methyl ether	CH <sub>3</sub>	..	CH <sub>3</sub>	...	5.73	5.85	

and the reaction is indicative of a phenolic system. It is seen that bromination always occurs by substitution and hence there is no indication by this criterion of an ethylenic double bond in terracinoic acid.



A Zerewitinoff determination shows three active hydrogens for terracinoic acid and titration data give *pK<sub>a</sub>* values 2.6, 4.7 and 9.5. The strongest acid function is a carboxyl group which can be

removed readily by heating in strong mineral acid whereby decarboxyterracinoic acid (IV) C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>, m.p. 169–170° with *pK<sub>a</sub>* values 4.8 and 8.0 is formed. This strongest carboxyl group may be esterified by treating terracinoic acid with 1 mole of diazomethane to yield a monomethyl ester with *pK<sub>a</sub>* values 5.4 and 7.8 (Ib, Table I).

Treatment with methanolic hydrogen chloride yields a different monomethyl ester, Ia, with *pK<sub>a</sub>* values of 3.1 and > 10. Further esterification does not take place in methanol even under forcing conditions, thus indicating that the stronger carboxylic acid is sterically hindered.

The infrared spectrum of terracinoic acid in dioxane has three distinct carbonyl bands at 5.77, 5.86 and 6.02 m $\mu$  (Fig. 3). A study of the infrared spectra of terracinoic acid, decarboxyterracinoic acid and of their esters indicates that the band at 6.02 m $\mu$  should be assigned to the *pK<sub>a</sub>* 2.6 carboxyl group. The high wave length of this band suggests that this is an aromatic carboxylic group strongly influenced by hydrogen bonding from a neighboring hydroxyl.

The identification of the *pK<sub>a</sub>* 4.7 function as an aliphatic carboxyl group is supported by a very difficult decarboxylation of decarboxyterracinoic acid in hot quinoline containing copper chromite. As already described, this weaker carboxylic group is smoothly cleaved by the action of alkali in the dehydrobromination of 2-bromoterracinoic acid. The resulting product (VIII) has *pK<sub>a</sub>* values 3.1 and > 10.0 and the infrared spectrum shows that the aromatic carboxyl group is still present.

Treatment of terracinoic acid with 2 moles of diazomethane yields a dimethyl ester, Ic, and exhaustive treatment with this reagent provides a trimethyl compound, Id. The monomethyl and dimethyl esters are readily saponified to terracinoic acid while alkaline hydrolysis of the trimethyl compound yields a stable monomethyl ether of terracinoic acid (Ie) which is in agreement with the presence of a phenolic system in the latter.

Evidence for the presence of a phenol has already been found in the formation of *m*-ethylphenol by caustic fusion and the reaction of terracinoic acid to form a dibromo derivative by decarboxylation. Further evidence for the presence of a phenolic

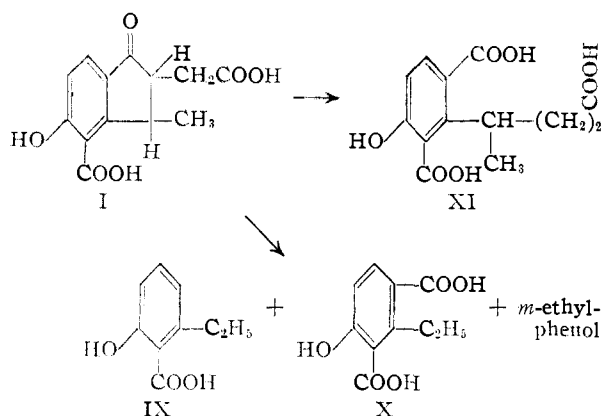
hydroxyl is found in the observation that the acetyl number of terracinoic acid, determined in pyridine, corresponds to one acetyl group. The formation of a crystalline diacetyl derivative in acetic anhydride-sulfuric acid is the result of acetylation of the phenol group and the formation of a lactol or enol acetate from a carbonyl function in terracinoic acid. A clear-cut phenolic hydroxyl band is not observed in the infrared spectrum of terracinoic acid but a well-defined band at 3.1  $\mu$  is observed for decarboxyterracinoic acid, indicating that the strong carboxylic acid group is involved in hydrogen bonding with the phenolic hydroxyl in terracinoic acid. The magenta ferric chloride test indicative of a salicylic acid group in terracinoic acid is not given by decarboxyterracinoic acid.

The presence of a carbonyl group is demonstrated by monoxime formation, and by a conjugated ketone carbonyl band at 5.86  $\mu$  in the infrared spectrum of terracinoic acid in dioxane. Decarboxyterracinoic acid reacts with phenylhydrazine with the loss of two moles of water to yield a compound with a molecular formula and chemical and physical properties consistent with the dihydropyridazone structure, V. The formation of this derivative points to a  $\gamma$ -keto acid system. This interpretation is confirmed by the smooth decarboxylation which occurs in the course of alkaline dehydrobromination of bromoterracinoic acid (VI).

The carbonyl must be conjugated to the benzene ring since it is reduced to a methylene group by palladium catalyzed hydrogenation. The resulting desoxy compound, II, readily loses its most strongly acidic carboxyl group by heating in mineral acid, to yield III,  $C_{12}H_{14}O_3$ , m.p. 146°, which can also be produced by the hydrogenation of decarboxyterracinoic acid (IV) over palladium, or rather less satisfactorily, by direct decarboxylation and reduction of terracinoic acid in hot hydriodic acid.

The nature of the non-aromatic ring is developed from information provided by the caustic fusion of terracinoic acid, which, in addition to the already-mentioned *m*-ethylphenol, yields 6-ethylsalicylic acid (IX), a dicarboxylic acid  $C_{10}H_{10}O_5$ , X, and a tricarboxylic acid,  $C_{13}H_{14}O_7$ , XI. The 6-ethylsalicylic acid was identified as a salicylic acid by its purple ferric chloride test, by the position of its carbonyl absorption at 6.09  $\mu$  in the infrared spectrum, and by the observed  $pK_a$  value of 3.7. Decarboxylation to *m*-ethylphenol fixes the relative positions of the hydroxyl and ethyl groups and, therefore, the compound is either 4- or 6-ethylsalicylic acid. Direct comparison with 4-ethylsalicylic eliminates this isomer, and establishes the structure as 6-ethylsalicylic acid. The structure X for the dicarboxylic acid is consistent with its salicylic acid type properties and its ready decarboxylation to *m*-ethylphenol. The tricarboxylic acid,  $C_{13}H_{14}O_7$ , XI, loses carbon dioxide readily, but does not yield *m*-ethylphenol. Its infrared absorption spectrum indicates two aromatic carboxylic acid groups. The precise structures of these two acids have not been rigorously established, but follow from structure I for terracinoic acid.

The isolation of *m*-ethylphenol and 6-ethylsalicylic acid establishes the relationship between the



phenol group and one point of attachment of the carbocyclic system. Since acetic acid and no propionic acid is produced by the vigorous permanganate oxidation of terracinoic acid, the ethyl group cannot be present as such and it also follows that the  $\alpha$ -carbon of the ethyl group must be in the carbocyclic ring. The salicylic acid moiety, the  $\gamma$ -keto acid chain and the ethyl group account for all of the carbon atoms in the formula of terracinoic acid and, therefore, the other point of attachment of the carbocyclic ring must involve one of the two methylene groups in the  $\gamma$ -keto acid chain. Thus, we arrive at either an indanone or a tetralone structure (*e.g.*, XII). The tetralone structure XII is excluded since it would be sterically incapable of forming a dihydropyridazone derivative as is observed for decarboxyterracinoic acid. The tetralone formula is also inconsistent with the already-mentioned behavior of 2-bromoterracinoic acid with alkali. Dehydrobromination and decarboxylation of a tetralone should yield a 1,6-dihydroxynaphthalene, with loss of the ketone function. The properties of the product VIII are not in agreement with this interpretation. Although the structure of VIII has not been determined with absolute certainty, the presence of two carbonyl bands in its infrared absorption spectrum at 5.91 and 6.03  $\mu$ , the observed  $pK_a$  values of 3.1 and  $> 10$ , and the tendency to polymerize in acids are to be expected of the indenone structure.

There remain two possible expressions for decarboxyterracinoic acid, namely, 7- or 5-hydroxy-3-methylindanone-2-acetic acid. A comparison of the ultraviolet absorption spectra of decarboxyterracinoic acid (IV) with that of 5-hydroxy- and 7-hydroxyindanones (Fig. 2) shows the near identity of the 5-hydroxy isomer with decarboxyterracinoic acid, and effectively excludes the 7-hydroxy isomer from further consideration.

The structure of terracinoic acid is thus derived as 4-carboxy-5-hydroxy-3-methylindanone-2-acetic acid. The position of the carboxyl group in the 4-position is the only one consistent with the isolation of 6-ethylsalicylic acid from the caustic fusion. This position is also in agreement with the steric hindrance observed for the aromatic carboxyl group.

Terracinoic acid is optically inactive and since carbon atoms 2 and 3 in the substituted indanone structure are asymmetric, it must be assumed either that terracinoic acid is racemized in the course of

alkaline degradation or that the terracinoic acid structure does not exist as such in terramycin. While carbon atom 2 would racemize readily, it is doubtful that carbon atom 3 would racemize to the extent that no optical activity would be found even when the degradation is carried out in 4% sodium hydroxide.<sup>3</sup> Consequently, it is very unlikely that carbon atom 3 exists as such in terramycin itself. This conclusion is supported by the fact that none of the three products of the alkali fusion of terramycin (salicylic, *m*-hydroxybenzoic and succinic acids) is found in the alkali fusion products of terracinoic acid.

### Experimental<sup>4</sup>

**Terracinoic Acid (I).**—Terracinoic acid was isolated by a previously described procedure.<sup>3</sup> The ultraviolet absorption spectrum of terracinoic acid in methanol (Fig. 1) shows peaks at 218  $\mu$ ,  $\log \epsilon$  4.194; 241  $\mu$ ,  $\log \epsilon$  4.226; and 282  $\mu$ ,  $\log \epsilon$  4.109.

**Monomethylterracoate (Ia).**—This compound, m.p. 217–218°, is formed by esterification of terracinoic acid in methanol–hydrochloric acid.<sup>3</sup> The titration curve shows two breaks, corresponding to  $pK_a$  3.1 and  $> 10$ . This ester sublimes at 180° (0.01 mm.). Hydrolysis in hot alcoholic sodium hydroxide regenerates terracinoic acid.

**Monomethylterracoate (Ib).**—An ether solution of 0.84 g. (0.02 mole) of diazomethane was added to 5.3 g. (0.02 mole) of terracinoic acid in 125 ml. of dioxane at 10°. After 15 minutes, the solution was evaporated *in vacuo*, and the viscous residue crystallized from ether–ligroin to yield 3.8 g. (68%) of colorless crystals, m.p. 122–124°. A titration curve shows breaks corresponding to  $pK_a$  5.4 and 7.8.

*Anal.* Calcd. methoxyl, 11.12. Found: methoxyl, 11.27.

**Dimethylterracoate (Ic).**—Monomethylterracoate, (Ia, m.p. 217–218°) 5.6 g., (0.02 mole) was dissolved in 110 ml. of cold dioxane. Diazomethane, 0.85 g. (0.02 mole), in ether solution was added over 50 minutes. Solvent was removed *in vacuo*, and the ether solution of the viscous residue was washed with three 100-ml. portions of 2% sodium bicarbonate solution. Evaporation to dryness yielded a crude dimethyl ester, which crystallized slowly. Trituration with ether, and washing with ligroin–ether yielded 2.0 g. of crystalline product, m.p. 64–66°. The titration curve shows a single break corresponding to  $pK_a$  8.

*Anal.* Calcd.: methoxyl, 21.24. Found: methoxyl, 20.9.

**Dimethylterracoate Methyl Ether (Id).**—An ether solution of 6.3 g., 0.15 mole, of diazomethane was added slowly to 11.7 g., 0.044 mole, of terracinoic acid dissolved in 235 ml. of dry dioxane at 5°. Twelve hours later, solvent was removed *in vacuo*, and the crude crystalline product recrystallized from ether–ligroin to yield 8.8 g. of product, m.p. 89–90°. This product gives no color with ferric chloride.

*Anal.* Calcd. for  $C_{16}H_{18}O_6$ : C, 62.75; H, 5.88; methoxyl, 30.4. Found: C, 62.29; H, 6.02; methoxyl, 30.92.

**Terracinoic Acid Methyl Ether (Ie).**—Dimethylterracoate methyl ether, Id (3.06 g., 0.01 mole) was heated under reflux in 40 ml. of 1 *N* sodium hydroxide for one hour. The cooled solution was acidified, and the crystalline product recrystallized from hot water to yield 2.3 g. (77%) of terracinoic acid methyl ether as a hydrate. This product was dried at 100°, 0.01 mm. for 6 hours and then melted at 180° with decomposition.

*Anal.* Calcd. for  $C_{14}H_{14}O_6$ : C, 60.43; H, 5.07; methoxyl, 11.12. Found: C, 60.23, 60.12; H, 5.15, 4.92; methoxyl, 11.10.

This compound gives no color with ferric chloride. The titration curve shows two breaks corresponding to  $pK_a$  3.1 and 4.9.

**Terracinoic Acid Oxime.**—Two grams each of terracinoic acid and hydroxylamine hydrochloride were dissolved in 10 ml. of pyridine and 10 ml. of anhydrous ethanol and heated under reflux for two hours. The solvent was removed *in vacuo*, and the pyridine salt of terracinoic acid oxime dis-

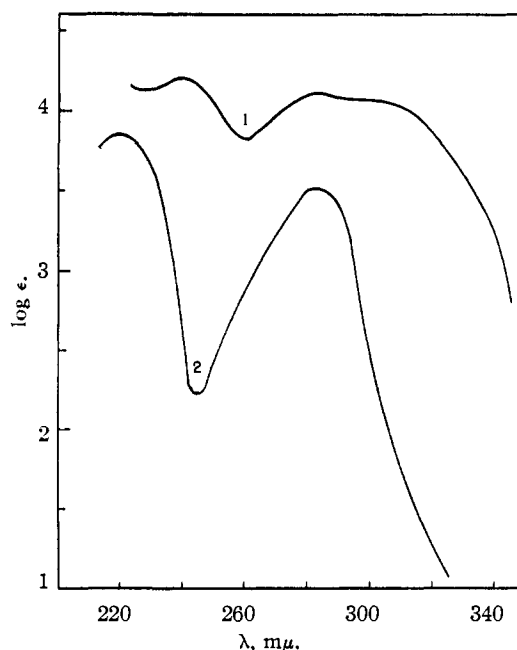


Fig. 1.—Ultraviolet absorption spectra in methanol solution: 1, terracoic acid (I); 2, 5-hydroxy-3-methylindane-2-acetic acid (III).

solved in 5% sodium carbonate, and cautiously acidified. The crystalline precipitate was washed thoroughly with water. After two recrystallizations from aqueous ethanol, and drying at 100° *in vacuo* for 2 hours, the oxime decomposed over a 20–30° range starting at 225°.

*Anal.* Calcd. for  $C_{13}H_{13}NO_6$ : C, 55.89; H, 4.66; N, 5.02. Found: C, 56.09; H, 5.00; N, 5.00.

When 0.5 g. of terracoic acid oxime was hydrolyzed in 50 ml. of 2 *N* hydrochloric acid at 90° for six hours, 0.4 g. of terracoic acid, m.p. 232–234°, was recovered. The identity of this product was confirmed by mixed melting point determination, and by comparison of the infrared absorption spectrum with that of an authentic sample of terracoic acid.

**Terracoic Acid Diacetate.**—One gram of terracoic acid was dissolved in 10 ml. of acetic anhydride and 0.1 ml. of concentrated sulfuric acid, and left at room temperature for 48 hours. The reaction mixture was poured into 100 ml. of water, extracted with ether, concentrated to dryness, and the oily crystals, which separated overnight, were recrystallized twice from benzene. The product appeared to contain benzene of crystallization. After drying at 100° for four hours, it melted at 168–169°. The infrared absorption spectrum in dioxane shows carbonyl peaks at 5.55, 5.67, 5.72 and 5.83  $\mu$ . This would appear to exclude a mixed anhydride and favor a lactol acetate formula rather than the enol acetate.

*Anal.* Calcd. for  $C_{17}H_{18}O_8$ : C, 58.60; H, 4.63; acetyl, 24.15. Found: C, 58.45, 58.51; H, 4.77, 4.76; acetyl, 23.20, 23.49.

Following the procedure of Siggia,<sup>5</sup> terracoic acid reacts with 0.95 mole of acetic anhydride in pyridine solution. The monoacetyl derivative, isolated from an acetylation in pyridine, was not obtained in crystalline form.

**Nitration of Terracoic Acid.**—Two and six-tenths grams of terracoic acid (0.01 mole) was dissolved in 10 ml. of concentrated sulfuric acid at 0°. Nitric acid, 0.65 g. (0.01 mole) was added, and the solution left at 25° for 30 minutes. The reaction mixture was quenched on cracked ice, and the pale yellow product recrystallized from ethyl acetate. After drying at 100° (0.05 mm.) for 2 hours, it melted at 201–202°. The titration curve showed three breaks corresponding to  $pK_a$  values of 2.0, 5.6 and 8.6. This derivative is presumably 4-carboxy-5-hydroxy-3-methyl-6-nitroindanone-2-acetic acid.

(4) All melting points are corrected.

(5) S. Siggia, "Quantitative Organic Analysis via Functional Groups," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 4.

*Anal.* Calcd. for  $C_{13}H_{11}NO_3$ : N, 4.53. Found: N, 4.39, 4.46.

An alcoholic solution was reduced with tin-hydrochloric acid, after which it gave the red-orange color with pyridylpyridinium chloride characteristic of aromatic amines. A portion of the amine diazotized on a qualitative scale yielded a deep red coupling product with  $\alpha$ -naphthol.

**4,6-Dibromo-5-hydroxy-3-methylindanone-2-acetic Acid.**—Tetracinoic acid, 0.8 g., was dissolved in 100 ml. of hot water. An aqueous solution containing 10% bromine and 15% potassium bromide was added to the warm tetracinoic acid until a yellow color persisted. Carbon dioxide was evolved. The precipitate, which formed on cooling, was recrystallized from ethanol to yield 0.5 g. of a dibrominated product, m.p. 169–170°.

*Anal.* Calcd. for  $C_{12}H_{10}O_4Br_2$ : C, 38.13; H, 2.65; Br, 42.28. Found: C, 38.01; H, 2.90; Br, 42.11.

The titration curve showed two breaks corresponding to  $pK_a$  values of 4.4 and 5.3, equivalent wt. 376 (calcd. 378). An identical product was obtained by a similar bromination of decarboxytetracinoic acid. This product gives no precipitate with hot alcoholic silver nitrate.

**2-Bromotetracinoic Acid (VI).**—Ten grams of finely ground tetracinoic acid was added to 200 ml. of glacial acetic acid and 8 g. of bromine, and the mixture stirred for 6 hours. The crystalline product was filtered, washed with acetic acid, then by ligroin, and dried at 25° for 24 hours in a slow stream of nitrogen, finally at 0.05 mm. for 5 minutes. 2-Bromo-4-carboxy-5-hydroxy-3-methylindanone-2-acetic acid (VI) containing acetic acid of crystallization, was obtained in 11.5 g. yield, m.p. 280–281° (dec.).

*Anal.* Calcd. for  $C_{13}H_{11}O_5Br \cdot C_2H_4O_2$ : volatile, 14.89; Br, 19.82. Found: volatile (100°, 0.01 mm.), 14.92; Br, 19.72, 19.95.

The dried sample, which also melted at 280–281° (decomp.), shows some loss of bromine.

*Anal.* Calcd. for  $C_{13}H_{11}O_5Br$ : C, 45.50; H, 3.23; Br, 23.29. Found: C, 45.86; H, 3.55; Br, 22.22.

This compound gives an instant precipitate with hot alcoholic silver nitrate.

**4-Carboxy-2,3-dimethyl-5-hydroxyindenone (VIII).**—A solution of 28 g. of 2-bromotetracinoic acid (VI) in 250 ml. of 1 *N* sodium hydroxide was heated under reflux for 1 hour, cooled and carefully acidified with 6 *N* sulfuric acid. Copious evolution of carbon dioxide accompanied the precipitation of 10.2 g. of white crystalline solid, m.p. 220–225°. After recrystallization from aqueous ethanol, pure 4-carboxy-2,3-dimethyl-5-hydroxyindenone was obtained, m.p. 230.5–231° (dec.).

*Anal.* Calcd. for  $C_{12}H_{10}O_4$ : C, 66.05; H, 4.62; active hydrogens, 2. Found: C, 66.15; H, 4.69; active hydrogens, 1.9.<sup>6</sup>

This bromine-free product sublimes at 160° (0.01 mm.). The infrared absorption spectrum in dioxane solution shows carbonyl peaks at 5.91 and 6.03  $\mu$ . The titration curve indicated  $pK_a$  values of 3.1 and > 10, equivalent wt. 218 (calcd. 224). An attempt to decarboxylate this substance in hot 60% phosphoric acid yielded a product predominantly polymeric, and only traces of a colorless crystalline bicarbonate insoluble solid, m.p. 155–157°, which was not investigated. Hydrogenation of VIII over palladium-charcoal catalyst in ethanol resulted in the rapid absorption of one mole of hydrogen.

**4-Carboxy-2,5-dihydroxy-3-methylindanone-2-acetic Acid (VII).** a.—A solution of 4 g. of 2-bromotetracinoic acid (VI) in 50 ml. of 2% aqueous sodium acetate was heated on the steam-bath for 15 minutes, cooled, and acidified with dilute sulfuric acid. The product was extracted with ether, and crystallized on concentration to 10 ml.; yield 1.0 g., m.p. 245° (dec.). The melting point was not raised by redissolving in 0.1 *N* alkali, and precipitation with acid. A sample was dried at 100° (0.01 mm.) for analysis.

*Anal.* Calcd. for  $C_{13}H_{12}O_7$ : C, 55.71; H, 4.32. Found: C, 55.82; H, 4.48.

The infrared absorption curve of this substance shows a sharp hydroxyl peak at 3.28  $\mu$ . A titration curve shows two breaks corresponding to  $pK_a$  values 3.0 and 4.8, equivalent wt. 279 (calcd. 280). An active hydrogen determination by Zerewitinoff's method showed 3.9 active hydrogens.

b.—VII may also be prepared by the oxidation of tetracinoic acid. Two hundred and fifty ml. of 1% potassium permanganate was added in 50-ml. portions to a solution of 2.5 g. of tetracinoic acid in 200 ml. of 3% potassium hydroxide. After decolorization of the last portion of oxidant was complete (2 hours), manganese dioxide was removed by filtration, the solution was acidified with sulfuric acid and extracted with five 100-ml. portions of ether to yield, on concentration to 20 ml., 0.8 g. of product, m.p. 245°, identical with that described above.

**Decarboxytetracinoic Acid (IV).** a.—The preparation of this compound, 5-hydroxy-3-methylindanone-2-acetic acid, by decarboxylation of tetracinoic acid in hot phosphoric acid has been described.<sup>3</sup> Hot 40% hydrobromic acid may be used in place of the phosphoric acid.

b.—Decarboxytetracinoic acid has also been prepared in about 40% yield by the thermal decarboxylation of tetracinoic acid at 230°.

c.—Tetracinoic acid, 1.17 g. (0.0044 mole) was dissolved in 100 ml. of distilled quinoline, and heated to 210° for 3 hours with 0.25 g. of copper chromite catalyst in a slow stream of nitrogen. The carbon dioxide recovery was 0.0048 mole, 110% of theory. Crude decarboxytetracinoic acid was recovered from the quinoline in 78% yield by extraction with 5% sodium hydroxide. After two recrystallizations from water, it melted at 167–168°. The titration curve shows two breaks corresponding to  $pK_a$  values of 4.8 and 8.0, equivalent wt. 218 (calcd. 220). This compound gives no color with ferric chloride. The aminoantipyrine test for phenols<sup>7</sup> is negative. The infrared absorption spectrum in dioxane solution is shown in Fig. 3. The ultraviolet absorption spectrum in methanol (Fig. 2) shows peaks at 226  $\mu$ ,  $\log \epsilon$  4.143; 270  $\mu$ ,  $\log \epsilon$  4.142; 292  $\mu$ ,  $\log \epsilon$  4.078. When decarboxytetracinoic acid was heated to 240° in quinoline-copper chromite for 24 hours, 79% of one mole of carbon dioxide was obtained. No crystalline product could be isolated.

**Decarboxytetracinoic Acid Methyl Ester (IVa).**—A solution of 2.0 g. of decarboxytetracinoic acid in 30 ml. of methanol saturated with hydrogen chloride was left at room temperature for 4 days, evaporated to 15 ml. *in vacuo*, and diluted to 60 ml. with water. Sodium bicarbonate was added until the solution was alkaline, and the product was extracted with ether. Following a recrystallization from water, the colorless needles were sublimed at 120° (0.05 mm.) and recrystallized from ether-ligroin to yield about 1.0 g. of pure 5-hydroxy-3-methylindanone-2-acetic acid methyl ester, m.p. 105–106°.

*Anal.* Calcd. for  $C_{13}H_{14}O_4$ : C, 66.65; H, 6.02; methoxyl, 13.25; mol. wt., 234. Found: C, 66.94, 66.87; H, 6.23, 6.31; methoxyl, 13.10; equiv. wt., by titration, 234 ( $pK_a$  8.1).

This ester can also be prepared by the reaction of one equivalent of diazomethane with decarboxytetracinoic acid in cold ether, or by the dry thermal decarboxylation of tetracinoic acid monomethyl ester Ia, m.p. 218°, with copper powder catalyst.

**Decarboxytetracinoic Acid Methyl Ester Methyl Ether (IVb).**—Decarboxytetracinoic acid, 2.0 g., was dissolved in 40 ml. of dry dioxane, and an ether solution of 1.25 g. of diazomethane added in 30 minutes. Solvent was removed *in vacuo* and the viscous oil crystallized from ether to yield 2.2 g. of 5-methoxy-3-methylindanone-2-acetic acid methyl ester, m.p. 74–75°.

*Anal.* Calcd. for  $C_{14}H_{16}O_4$ : C, 67.73; H, 6.46; methoxyl, 25.00. Found: C, 67.57, 67.83; H, 6.53, 6.60; methoxyl, 25.2.

**2,3,4,4a-Tetrahydro-7-hydroxy-5-methyl-2-phenyl-5H-indeno[1,2-c]pyridazine-3-one (V).**—Decarboxytetracinoic acid, 0.7 g. (0.0032 mole) and phenylhydrazine, 1.5 g. (0.014 mole) were dissolved in 7 ml. of 40% acetic acid and heated on the steam-bath for 2 hours. One gram of tau solid was filtered from the cold reaction mixture. After three recrystallizations from ethanol, the product, V, was dried at 80° (0.02 mm.) for 4 hours, m.p. 273–279° (decomp.).

*Anal.* Calcd. for  $C_{18}H_{16}N_2O_2$ : C, 73.95; H, 5.52; N, 9.59. Found: C, 73.74, 73.55; H, 5.64, 5.62; N, 9.48, 9.54.

This substance does not liberate carbon dioxide from

(6) F. A. Hochstein, *This Journal*, **71**, 305 (1949).

(7) E. Emerson, *J. Org. Chem.*, **8**, 417 (1943).

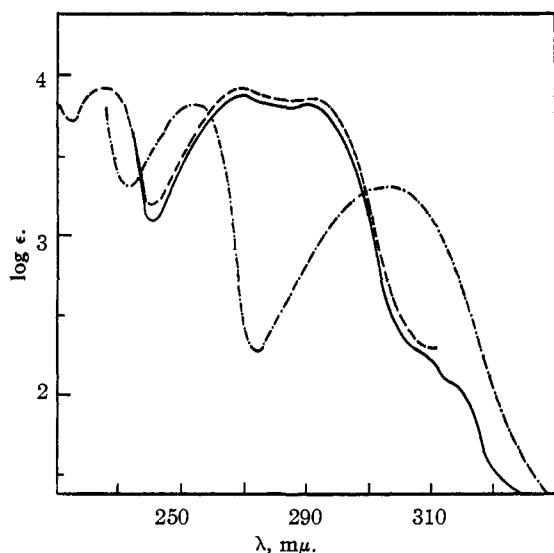


Fig. 2.—Ultraviolet absorption spectra in ethanol solution: decarboxytetracinoic acid (IV), - - - -; 5-hydroxyindanone, —; 7-hydroxyindanone, - · - · - ·.

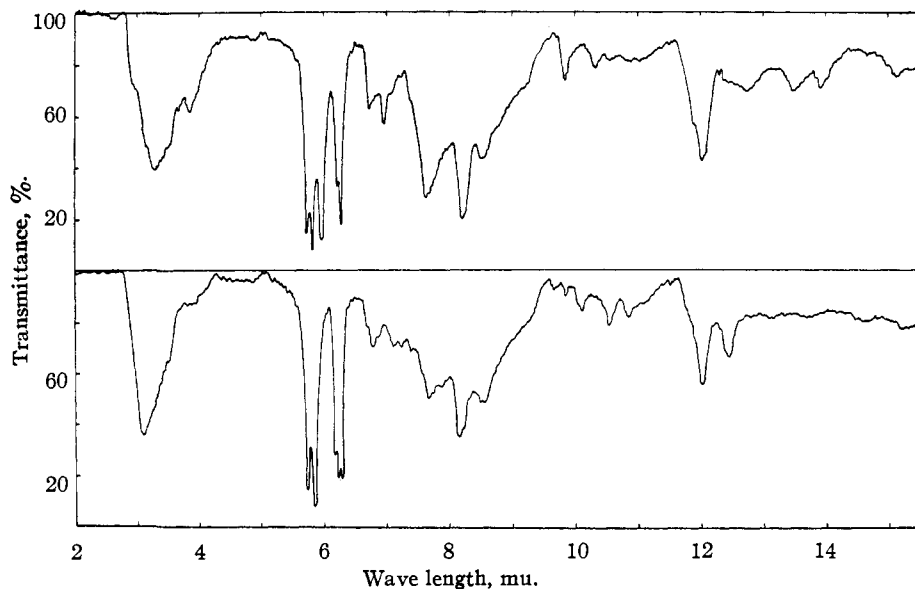


Fig. 3.—Infrared absorption spectrum of tetracinoic acid, I, above, and of decarboxytetracinoic acid, IV, below; five per cent. solutions in dioxane, 0.10 mm. cells.

aqueous bicarbonate. An attempt at titration in aqueous alcohol showed no strong acid function. It gives a positive Knorr<sup>8</sup> pyrazoline test.

**4-Carboxy-5-hydroxy-3-methylindane-2-acetic Acid (II).**—A solution of 5.0 g. of tetracinoic acid in 25 ml. of absolute ethanol was shaken under 25 lb. (initial) hydrogen pressure with 0.75 g. of 5% palladium-charcoal for 16 hours. The pressure drop observed in this time corresponded to the uptake of 1.9 moles of hydrogen. The catalyst was removed by filtration and the solvent distilled from the light purple solution *in vacuo*. The glassy solid product crystallized from water-acetone and melted at 195–197°; yield 4.0 g., 85%. Further recrystallizations from water-acetone and benzene-acetone raised the melting point to 200–201°. This material gave a transient red aminoantipyrine test,<sup>7</sup> a deep blue ferric chloride test in aqueous solution, and failed to react with 2,4-dinitrophenylhydrazine when subjected to the conventional reaction conditions for derivative formation.

*Anal.* Calcd. for  $C_{13}H_{14}O_5$ : C, 62.39; H, 5.64; mol. wt., 250. Found: C, 62.53; H, 5.71; mol. wt. (titration),

(8) L. Knorr, *Ber.*, **26**, 100 (1893).

248, 252;  $pK_a$ , 4.0, 5.6 in methanol-water; lithium aluminum hydride revealed 2.90 active hydrogens per mole.<sup>6</sup>

**5-Hydroxy-3-methylindane-2-acetic Acid (III).** a.—A solution of 1.1 g. II in 70 ml. of 40% hydrobromic acid was heated under reflux in a slow nitrogen stream for 8 hours. Carbon dioxide corresponding to 0.9 mole was collected as barium carbonate. The cooled reaction mixture was diluted with an equal volume of water, and extracted with five 100-ml. portions of ether. The dried ether extracts were evaporated to yield 0.80 g. of crude material which was crystallized from water to give 0.55 g. (61%) of white crystals, m.p. 139–143°. Recrystallization from toluene-ethyl acetate followed by sublimation at 150° (0.05 mm.) raised the melting point to 145.5–146.5°.

*Anal.* Calcd. for  $C_{12}H_{14}O_3$ : C, 69.87; H, 6.84. Found: C, 69.93; H, 6.96.

The titration curve showed an equivalent weight of 205 (calcd. 206),  $pK_a$ , 5.3. This compound gives a negative ferric chloride test, and a fleeting magenta color with aminoantipyrine. The infrared absorption spectrum in dioxane reveals a single carbonyl band at 5.77  $\mu$ , and hydroxyl absorption at 3.03  $\mu$ . The ultraviolet absorption spectrum is shown in Fig. 1.

b.—A solution of 3.3 g. of decarboxytetracinoic acid (IV) in 15 ml. of absolute ethanol was hydrogenated over 0.35 g. of 5% palladium-charcoal catalyst at an initial hydrogen pressure of 30 lb. After 26 hours the pressure drop corresponded to a hydrogen uptake of 2.0 moles. Catalyst was

removed, solvent distilled off *in vacuo*, and the crude product was sublimed to yield 0.95 g. of crystalline material, which was recrystallized from water. The melting point, 144–146°, was not depressed by admixture with material prepared by method a. The infrared absorption spectra of the two preparations are identical.

c.—III can also be prepared by heating a solution of tetracinoic acid (I) or of decarboxytetracinoic acid (IV) in hydriodic acid under reflux for 12 hours. The yields are erratic, and appear to depend in part on the source of hydriodic acid. When red phosphorus was added to the reaction mixture, III was obtained fairly consistently in 20% yield.

**6-(or 4)-Bromo-5-hydroxy-3-methylindanone-2-acetic Acid.**—A solution of 14.5 mg. (0.071 mmole) of III in 1 ml. of glacial acetic acid readily absorbed 11 mg. (0.067 mmole) of bromine. Hydrogen bromide was evolved. The solution was evaporated to 0.10 ml., and 0.15 ml. of water added. A colorless crystalline monobromo derivative, m.p. 120–121° separated. This substance yielded no silver bromide with boiling alcoholic silver nitrate. From steric considerations only, this compound is more probably the 6-bromo derivative than the 4-bromo derivative.

*Anal.* Calcd. for  $C_{12}H_{13}BrO_3$ : C, 50.55; H, 4.60. Found: C, 50.31; H, 5.01.

**4-Carboxyhexahydroindane-2-acetic Acid.**—The hydrogenation of 1 g. of terracinoic acid in 20 ml. of glacial acetic acid with 0.20 g. of Adams platinum catalyst proceeded slowly at atmospheric pressure. Hydrogen absorption ceased after 10 hours, when 5.9 moles (in another experiment, 5.6 moles) of hydrogen had been absorbed. Solvent was evaporated *in vacuo*, the crude product dissolved in ethanol, and a crystalline compound precipitated by the addition of water to turbidity. This crude product was twice recrystallized from 1:1 benzene-hexane, to yield 0.25 g. of 4-carboxyhexahydroindane-2-acetic acid, m.p. 149.5–150.5°.

*Anal.* Calcd. for  $C_{13}H_{20}O_4$ : C, 64.95; H, 8.37; mol. wt., 240.3. Found: C, 64.65; H, 8.04.

A titration curve in aqueous ethanol showed a single break corresponding to an equivalent weight of 118,  $pK_a$  6.0. This acid does not add bromine in glacial acetic acid, nor does a neutral aqueous solution decolorize potassium permanganate. The infrared absorption spectrum in nujol mull shows carbonyl absorption at 5.82 and 5.91  $\mu$ , and no evidence of ethylenic double bonds.

**5- and 7-Hydroxyindanones.**—These two compounds were prepared and separated by the method of von Auwers and Hilliger.<sup>9</sup> It was noted that 5-hydroxyindane obtained by the palladium-charcoal-catalyzed hydrogenation of 5-hydroxyindanone in ethanol, gives, like III, a positive, though somewhat fleeting magenta aminoantipyrine test.<sup>7</sup> This test is normally given only by phenols having hydrogen, or an easily displaced group in the para position.

**Alkali Fusion of Terracinoic Acid.**—Three grams of terracinoic acid and 30 g. of powdered potassium hydroxide were placed in a nickel crucible, and heated for 15 minutes in a Wood's metal bath preheated to 300°. The fused product was cooled, dissolved in 150 ml. of water, and made strongly acid with 40% sulfuric acid. The aqueous solution was extracted repeatedly with ether, the ether extract evaporated to a sirupy consistency, and digested with 100 ml. of chloroform. The dark semi-solid residue was digested with a further 50 ml. of chloroform; the chloroform insoluble product was dissolved in 100 ml. of ether, and treated with 0.5 g. of charcoal, filtered and concentrated to 10 ml. The crystals, which separated overnight, were purified by solution in a minimum of boiling ether, and addition of an equal volume of benzene. The product, 4-(2,6-dicarboxy-3-hydroxyphenyl)-pentanoic acid (XI) melted at 190–191° (dec.). The titration curve shows breaks corresponding to  $pK_a$  4.0, 5.5 and 7.5, equivalent weight 280. The infrared absorption spectrum in Nujol mull shows peaks at 5.85, 5.90 and 6.09  $\mu$ .

*Anal.* Calcd. for  $C_{13}H_{14}O_7$ : C, 55.32; H, 5.00; mol. wt., 282.2. Found: C, 55.37; H, 5.01.

Decarboxylation in hot 85% phosphoric acid proceeded readily. The oily product was not *m*-ethylphenol.

The combined chloroform extracts were extracted with three 20-ml. portions of water and the combined water ex-

tracts were then extracted exhaustively with ether. The dried ether solution was concentrated to 3 ml. and diluted with benzene to turbidity. The crystalline precipitate which separated overnight was recrystallized from ether-benzene, and sublimed at 0.01 mm. to yield 0.15 g. of 2-ethyl-4-hydroxyisophthalic acid (X), m.p. 209–210° (decomp.).

*Anal.* Calcd. for  $C_{10}H_{10}O_5$ : C, 57.14; H, 4.80; mol. wt., 210.2. Found: C, 57.12, 57.20; H, 5.10, 4.90.

The titration curve showed two breaks corresponding to  $pK_a$  2.4 and 4.1, equivalent wt. 208. The infrared absorption curve in nujol mull showed carbonyl peaks at 5.96 and 6.09  $\mu$ . This acid gives a red ferric chloride test. Decarboxylation in hot 80% phosphoric acid yielded *m*-ethylphenol.

The chloroform solution remaining after the water extraction was washed repeatedly with 2% sodium bicarbonate, the bicarbonate extract acidified with dilute sulfuric acid and back extracted with ether. The combined ether extracts were evaporated to dryness, sublimed at 100° (0.01 mm.) and recrystallized twice from water to yield 0.20 g. of pure 6-ethylsalicylic acid (IX), m.p. 136.5–137.5°.

*Anal.* Calcd. for  $C_9H_{10}O_3$ : C, 65.07; H, 6.03; mol. wt., 166.2. Found: C, 65.04, 64.90; H, 6.21, 6.16; mol. wt. (Rast), 161.

The titration curve shows a break corresponding to  $pK_a$  3.7. The infrared absorption spectrum in nujol mull shows carbonyl absorption at 6.09  $\mu$ . The ferric chloride test is purple in aqueous or alcoholic solution. A mixed melting point with 4-ethylsalicylic acid,<sup>10</sup> m.p. 125–126°, was depressed to 100–110°. The infrared absorption spectrum of the 4-ethylsalicylic acid is markedly different from that of IX in the 7–16  $\mu$  region, and it is extremely similar to that of 4-methylsalicylic acid.<sup>11</sup> Decarboxylation of IX in hot 80% phosphoric acid yielded *m*-ethylphenol.

The chloroform solution remaining after the bicarbonate extraction was extracted with 1 *N* sodium hydroxide. The sodium hydroxide extract was acidified, and extracted with carbon disulfide to yield, after distillation, 50 mg. of *m*-ethylphenol, which was identified through its benzoate, m.p. 59°, not depressed by admixture with an authentic sample. Comparison of the infrared absorption spectrum of this phenol with authentic *m*-ethylphenol confirmed this identity.

In a separate experiment, the crude total alkali fusion product of terracinoic acid was decarboxylated directly in hot 85% phosphoric acid. Steam distillation yielded 20% of the theoretical amount of *m*-ethylphenol.

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