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THE PREPARATION OF SOME IODINATED PHENYLALKANOIC ACIDS

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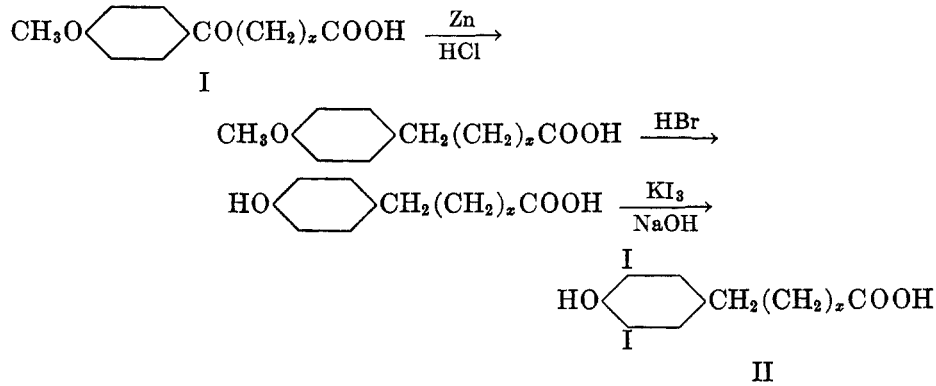
Some years ago we were interested in preparing a series of ω-diiodohydroxyphenylalkanoic acids for testing as radiopaques in cholecystography. This report is prompted by the appearance of a patent by Natelson (1) and a paper by Papa, Schwenk, and Hankin (2).

Natelson outlined the method of synthesis we employed but failed to indicate yields or physical properties of his products. Papa *et al.*, on the other hand, described excellent procedures for the intermediate steps and we wish to supplement some of their observations. The iodinated acids were prepared according to the following equations:



The preparation of δ-anisoylvaleric acid (I, x = 4) was studied in some detail. In agreement with Papa it was found that the condensation between anisole and δ-carbomethoxyvaleroyl chloride in carbon disulfide gave impure keto acid. We were able to isolate δ-(*p*-hydroxybenzoyl)valeric acid by alkali extraction of the crude reaction product, an indication that considerable ether cleavage had occurred. The major product, which melted over a wide range at about 70°, was probably a mixture of the desired methoxy acid and the cleavage product. The hydroxy keto acid was prepared from phenol and carbomethoxyvaleroyl chloride by a procedure similar to that used by Ralston for the reaction between phenol and higher fatty acid chlorides (3). Mixed melting point determinations showed the substances to be identical.

The condensation between anisole and polyadipic anhydride was carried out according to Plant and Tomlinson (4). We were able to isolate δ-anisoylvaleric acid and 1,4-dianisoylbutane in 33 and 47% yields, respectively, based on the anisole.

Although Papa and co-workers found that no cleavage occurred in their

condensation between anisole and δ-carboethoxyvaleroyl chloride at low temperature in tetrachloroethane, under our conditions, which were very similar, we had evidence that this side reaction did occur to some extent. Thus in a typical run in a mixed solvent (20% nitrobenzene, 80% tetrachloroethane) there was obtained a crude acid which melted below 90°. Several recrystallizations were required to raise the melting point above 120°. However, when the material was dissolved in dilute sodium hydroxide and treated with methyl sulfate the substance obtained by acidification melted at 118–120° and needed only one crystallization to reach analytical purity. In every case methylation raised the melting point of the crude acid.

β-Anisoylpropionic and γ-anisoylbutyric acids were prepared from succinic and glutaric anhydrides, respectively, by the excellent procedure of Fieser (5). It is doubtful whether the method of the Schering workers (2) offers any advantage here since two additional steps are required for the preparation of the acid chlorides.

The ω-anisoylalkanoic acids were reduced by the Clemmensen method and then demethylated in hydrobromic acid-acetic acid solution (2).

In pilot experiments on the iodination of ω-(*p*-hydroxyphenyl)caproic acid by the potassium triiodide-sodium hydroxide method it was found advisable to avoid using even a slight excess of reagent. After completion of the iodination the diiodo acid was precipitated as an almost white powder by passing sulfur dioxide *slowly* through the solution to *p*H 2. Rapid acidification usually resulted in the separation of an almost intractable gum.

The direct iodination of δ-anisylvaleric acid in acetic acid solution with iodine monochloride yielded only the monoiodo acid despite the large excess of halogenating agent. Similarly γ-anisylbutyric acid gave γ-(3-iodo-4-methoxyphenyl)butyric acid.

Pharmacology. In experimental animals visualization of the gall bladder was achieved by oral administration of the three 3,5-diiodo-4-hydroxyphenylalkanoic acids (II, x = 2, 3, 4). In agreement with Epstein, *et al.* (6) it was found that the caproic acid gave more intense shadows than the lower homologs. However, the substance did not seem to offer any advantages over iodoalphionic acid [α-phenyl-β-(3,5-diiodo-4-hydroxyphenyl)propionic acid]. Preliminary toxicity data indicate the oral $L.D._{50}$ in mice of the three substances lie within the range 2–4 g./kg.

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EXPERIMENTAL

δ-(p-Hydroxybenzoyl) valeric acid. To a solution of 28 g. (0.3 mole) of phenol in 60 ml. of dry chlorobenzene cooled to 10° was added 40 g. of aluminum chloride, keeping the temperature below 15°. Then 35.6 g. of δ-carbomethoxyvaleroyl chloride was added dropwise over a period of one hour. The mixture was heated at 60° for six hours and then hydrolyzed by pouring onto iced hydrochloric acid. The layers were separated and the water washed with benzene. The combined oil layers were subjected to steam distillation. The residual oil was separated from the water and then washed with a solution of dilute alcoholic sodium

hydroxide (3.0 g. of sodium hydroxide in 160 ml. of water and 40 ml. of ethanol). The basic extract was acidified to precipitate an oil, which upon saponification and subsequent acidification gave the hydroxy keto acid; wt. 17 g. After recrystallization from methanol it melted at 149–150°.

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35.
Found: C, 64.14; H, 6.12.

δ-Anisoylvaleric acid: From δ-carbomethoxyvaleroyl chloride. To a mixture of 43.2 g. of anisole and 71 g. of δ-carbomethoxyvaleroyl chloride in 400 ml. of tetrachloroethane and 100 ml. of nitrobenzene cooled to 0–5° was added 167 g. of aluminum chloride over a period of ninety minutes. The whole was stirred at this temperature for three hours and left overnight. The mixture was poured onto dilute hydrochloric acid and ice and subjected to steam distillation. The residue was separated from the water and saponified with dilute sodium hydroxide. On acidification there was precipitated 85 g. of crude keto acid (90%). It melted at 87–107°. The whole was taken up in dilute sodium hydroxide and treated with 30 ml. of methyl sulfate at 60°. The acid which separated on acidification now melted at 118–122°. After recrystallization from methanol the acid weighed 75 g. (79%); m.p. 122–124°; [lit. value (2) 128°].

From polyadipic anhydride. A solution of 73 g. of adipic acid in 300 ml. of acetic anhydride was refluxed for six hours, and concentrated to dryness *in vacuo*. The polyanhydride was treated with a mixture of 52.5 ml. of anisole, 120 ml. of nitrobenzene and 480 ml. of tetrachloroethane and cooled to 0°. Aluminum chloride (135 g.) was added portionwise to the stirred, cooled solution over a period of two hours. The mixture was left at 5° for two days before being hydrolyzed with ice and hydrochloric acid. After steam distillation the residue was separated from the water, and thoroughly extracted with 10% sodium carbonate solution. The basic extracts were acidified and the solid that separated was methylated and reprecipitated to give 34 g. (33%) of the methoxy acid, m.p. 118–121°. The neutral fraction, which was 1,4-dianisoylbutane, amounted to 37 g. (47%), and melted at 140–142° after recrystallization from alcohol. Plant and Tomlinson (4) who carried out the reaction in carbon disulfide reported m.p. 144° for dianisoylbutane.

γ-Anisoylbutyric acid. The procedure described by Fieser was used for the next higher homolog. From 43.2 g. of anisole was obtained 73 g. of methoxyketo acid (82%). After three recrystallizations from methanol the acid melted at 138–140°; [Papa (2) reported 138–139°].

Anal. Calc'd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35.
Found: C, 64.82; H, 6.43.

δ-(p-Hydroxyphenyl)valeric acid. A solution of 38.6 g. of δ-anisylvaleric acid (2), 485 ml. of 48% hydrobromic acid, and 100 ml. of acetic acid was refluxed for fifteen hours, boiled with charcoal, filtered, and cooled. The solid that separated was crystallized twice from dilute ethanol to yield 24 g. (67%), m.p. 117–119°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26.
Found: C, 68.07; H, 7.06.

δ-(3,5-Diiodo-4-hydroxyphenyl)valeric aicd. A solution of 19.4 g. of δ-(*p*-hydroxyphenyl)-valeric acid in 400 cc. of 1 *N* sodium hydroxide was stirred at room temperature, and a solution of 565 ml. of potassium triiodide which contained 51 g. of iodine was added dropwise over a period of 45 minutes. After one-half hour sulfur dioxide was bubbled through slowly to *p*H 2. The granular solid, which weighed 41 g. and melted at 117–122°, was filtered and washed with water. After two crystallizations from acetic acid and one from toluene there was obtained 24 g. (63%) of pure acid, m.p. 124–126°.

Anal. Calc'd for $C_{11}H_{12}I_2O_3$: C, 29.62; H, 2.71.
Found: C, 29.88; H, 2.62.

The iodination of the corresponding butyric and caproic acids was carried out similarly.

ω-(3,5-Diiodo-4-hydroxyphenyl)caproic acid. Obtained in 58% yield after recrystallization from methanol; m.p. 117–119°.

Anal. Calc'd for $C_{12}H_{14}I_2O_3$: C, 31.33; H, 3.07.
Found: C, 31.40; H, 3.14.

γ-(3,5-Diiodo-4-hydroxyphenyl)butyric acid. Obtained in 72% yield after recrystallization from dilute acetic acid; m.p. 105–107°.

Anal. Calc'd for $C_{10}H_{10}I_2O_3$: C, 27.80; H, 2.33.
Found: C, 27.90; H, 2.33.

δ-(3-Iodo-4-methoxyphenyl)valeric acid. Thirty grams of δ-anisylvaleric acid was dissolved in 100 ml. of acetic acid and warmed to 80°. A solution of 10.5 ml. of iodine monochloride in 25 ml. of acetic acid was added in one portion to the hot solution and the whole stirred for 30 minutes as 100 ml. of water was added dropwise. At the end of the time the hot solution, from which the iodo acid started to separate, was cooled to 10° and sulfur dioxide was bubbled in to discharge the color. The acid was filtered and recrystallized from ethanol to give long needles, m.p. 143–145°, wt. 40 g. (83%). One more crystallization raised the m.p. to 146–148°.

Anal. Calc'd for $C_{12}H_{15}IO_3$: I, 37.98. Found: I, 38.18.

Similarly *γ-(3-iodo-4-methoxyphenyl)butyric acid* was obtained in 77% yield, m.p. 105–107° after crystallization from benzene-ligroin.

Anal. Calc'd for $C_{11}H_{13}IO_3$: I, 39.7. Found: I, 40.6.

SUMMARY

1. ω-(3,5-Diiodo-4-hydroxyphenyl) butyric, valeric, and caproic acids have been prepared by the iodination of the corresponding hydroxy acids.

2. Iodination of two of the corresponding methoxy acids gave only the monoiodo derivatives.

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