Reprint

Synthesis of the Dicarboxylic Acid $C_{12}H_{14}O_4$ - Degradation Product of Picrotoxin. (J. Org. Chem., 1958, 23, 584.)
Synthesis of the Dicarboxylic Acid C_{12}H_{14}O_{4}—Degradation Product of Picrotoxin

MONOJIT GHOSAL, BISWAJIT SINHA, and P. BAGCHI

Received September 9, 1957

7-(2-Carboxy-6-methylphenyl)butyric acid, a degradation product of picrotoxin, has been synthesized following an unambiguous procedure. The synthetic compound possesses properties similar to those described for the product from natural sources.

Picrotoxin is a molecular compound of picrotin and picrotoxinine. Each of these compounds when boiled with phosphorus and hydriodic acid produces picrotic acid.\(^1\) The latter, on hydrolytic fission produces acetone and a dibasic acid, C_{12}H_{14}O_{4}.\(^2\) Out of the two possible structures for this dibasic acid,

\(^{(1)}\) F. Angelico, \textit{Gazz. chim. ital.} 42, ii, 337 (1911).

\(^{(2)}\) F. Angelico and F. Monforte, \textit{Gazz. chim. ital.}, 53, 800 (1923).
Robertson has chosen structure (V) on the basis of its transformation to 5-methyltetralone. The acid (V) has been synthesized by an unambiguous method shown in the flow sheet.

\[\gamma-(2\text{-Methylbenzoyl})\text{butyric acid (I, } R = \text{H)} \]
was prepared following two different routes. In the first method o-tolycadmium bromide was made to react with \(\gamma\text{-carboxybutryloyl chloride resulting in the formation of ethyl } \gamma-(2\text{-methylbenzoyl})\text{butyrate (I, } R = \text{Et})\) which gave acid (I, \(R = \text{H})\) on hydrolysis with alkali. In the second method the Grignard complex of o-bromotoluene was reacted with cyclopentanone and the resulting mixture of tertiary alcohol (VII) and the corresponding dehydrated product was oxidized with chromic acid to acid I (\(R = \text{H})\).

Huang-Minlon reduction of compound I (\(R = \text{Et}\)) gave \(5\text{-o-tolylic acid (II)}\) in satisfactory yield. Cyclization of acid II with polyphosphoric acid gave \(1\text{-methylbenzoxytolyloxybutyroyl chloride}\) (III) in almost quantitative yield. Compound III was converted into the formyl derivative (IV) which on oxidation with potassium permanganate or on ozonolysis furnished a dibasic acid which gave analytical figures agreeing with the molecular formula \(C_{18}H_{18}O_4\) and melted at 136–136.5° (uncorrected). Robertson et al. report melting point 135–136° for the degradation product of picrotoxin. A direct comparison of the synthetic specimen was not possible owing to unavailability of a sample from natural sources. The synthetic acid, however, could be converted to 5-methyltetralone according to the method of Robertson et al. This definitely shows that the synthetic acid is identical with the acid from natural sources.

**EXPERIMENTAL**

Melting and boiling points are uncorrected. Ethyl \(\gamma-(2\text{-methylbenzoyl})\text{butyrate (I, } R = \text{Et})\) was obtained from natural sources. The synthetic acid, however, could be converted to 5-methyltetralone according to the method of Robertson et al. This definitely shows that the synthetic acid is identical with the acid from natural sources.

...more experimental details...
bicarbonate solution and the alkaline layer acidified. The precipitated acid was purified by sublimation under low pressure. When the product (1.6 g.), m.p. 72-73°, was crystallized from water containing a few drops of acetic acid the melting point rose to 80°. Mixed m.p. with the acid previously described was undepressed.

5-(o-tolyl)valeric acid (II). To a solution of sodium hydroxide (4 g.) in diethylene glycol (42 ml.) was added ethyl 2-methylbenzoyl butyrate (5.9 g.) followed by hydrazine hydrate (50%, 8.5 ml.). The mixture was refluxed on an oil bath kept at 140° for 1 hr. The system was then connected to a distilling arrangement and the temperature was raised to 200°. Brisk evolution of nitrogen set in, and a few milliliters of water distilled out. After 3 hr. the reaction mixture was cooled, diluted with water, and acidified with hydrochloric acid (1:1) in the cold. The precipitated white solid (3.9 g.) had m.p. 57-58° which rose to 58.5-59° on crystallization from petroleum ether (b.p. 40-60°).

Anal. Calcd. for C12H14O: C, 82.76; H, 8.05. Found: C, 82.52; H, 8.11.

1-Methylbenzoxyl-5-one. (III). To a mixture of phosphorus pentoxide (153 g.) and phosphoric acid (89%, 97.5 ml.), maintained at 100°, o-(o-tolyl)valeric acid (3 g.) was gradually added with stirring. In 7 min., the reaction mixture turned an amber color which gradually deepened. The temperature was maintained at 100° for 2 hr. Then the reaction mixture was decomposed with ice water, and allowed to stand for 15 min. The separated solid was filtered, washed with dilute ammonia; yield, 4.9 g., m.p. 62-63°, which rose to 65° on sublimation in high vacuum and crystallization from methanol.

Anal. Calcd. for C12H14O: C, 82.76; H, 8.05. Found: C, 82.52; H, 8.11.

The 5,6-dinitrophenylhydrazone crystallized from benzene-ethanol acetate mixture, m.p. 240°.

6-Formyl-1-methylbenzoxyl-5-one (IV). To an ice-cold suspension of sodium ethoxide from sodium (0.65 g.) and ethanol (1.4 ml.) in thionyl-free benzene (26 ml.) was added a mixture of compound III (2.1 g.) and ethyl formate (1.8 g.) in benzene (15 ml.) under nitrogen. After keeping overnight in a nitrogen atmosphere, the reaction mixture was decomposed with ice water. The benzene layer was separated and washed twice with 3% alkali, and mixed with the water layer. The combined aqueous solution was extracted once with ether, and then acidified with 80% acetic acid. The formyl derivative was extracted with ether and distilled to yield 1.8 g., b.p. 133°/0.4 mm. With ferric chloride it gave a reddish violet color turning greenish violet.


γ-(2-Carboxy-6-methylphenyl)butyric acid (V). (a) By ozonolysis: Sufficient ozonized oxygen was passed through a solution of the formyl derivative (IV, 0.2 g.) in a mixture of ethyl acetate (5 ml.) and glacial acetic acid (5 ml.) chilled in an ice-salt bath. Three such lots were combined and treated with water (4.5 ml.) and hydrogen peroxide (30%, 1.5 ml.). The mixture was then kept overnight. Ethyl acetate and acetic acid were removed under reduced pressure and the residue was treated with water and then taken up in ether. The ether solution was thoroughly extracted with saturated sodium bicarbonate solution. The combined bicarbonate solutions were acidified and extracted with ether. Removal of ether and trituration of the residue with petroleum ether (b.p. 40-60°) gave a solid having an indefinite melting point. Evaporative distillation followed by two crystallizations from benzene gave colorless crystals having m.p. 136-136.5° which was not depressed on admixture with the product prepared according to the method (a).


Calcutta, India