m.p. 208°, $[\alpha]_D^{25}$° −95.5° (c, 4% in methanol), was obtained in 88% yield.

Anal. Calcd. for $C_{16}H_{16}O_4N_2$: C, 64.0; H, 5.4; N, 9.3. Found: C, 63.9; H, 5.4; N, 9.3.

*N-Benzoyl-β-(4-pyridyl-1-oxide)-*L*-alanine ethyl ester.* This ester was prepared as described for the DL-ester. Recrystallization of the crude product from wet ethyl acetate gave 86% of the L-ester, m.p. 181.0–182.5°, $[\alpha]_D^{25}$° −87.3° (c, 1.5% in methanol).

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 65.0; H, 5.8; N, 8.9. Found: C, 64.9; H, 5.9; N, 8.9.

4-(Pyridyl-1-oxide)carbinol. To 23 g. of 4-pyridylcarbinol dissolved in 200 ml. of glacial acetic acid was added 30 ml. of 30% aqueous hydrogen peroxide, the solution held at 70° for three hours, another 30 ml. of hydrogen peroxide added and the solution held at 70° overnight. The solvent was removed *in vacuo* and the residue recrystallized from a mixture of ethanol and ethyl acetate to give 19.6 g. (74%) of fine needles, m.p. 111.5–112.0°.

Anal. Calcd. for $C_6H_7NO_2$ (125): C, 57.6; H, 5.6; N, 11.2. Found: C, 57.6; H, 5.6; N, 11.1.

4-(Pyridyl-1-oxide)methyl bromide hydrobromide. A solution of 10.0 g. of 4-(pyridyl-1-oxide)carbinol in 50 ml. of 48% hydrobromic acid was heated twice to the boiling point and allowed to stand overnight. The acid was removed *in vacuo*, 50 ml. of absolute ethanol added, and the solution cooled to 0° to give a paste, which was recrystallized from absolute ethanol to give 8.2 g. of the hydrobromide of 4-(pyridyl-1-oxide)carbinol, m.p. 93–95°. This material, 6.53 g., was dissolved in 25 ml. of hydrobromic acid and held at reflux for 18 hr. The acid was removed *in vacuo*. The addition of absolute ethanol to the residue caused the formation of a white crystalline solid, which was collected, washed with absolute ethanol, and dried *in vacuo* to give 7.2 g. (88%) of a hygroscopic product, m.p. 170.5–171.8°.

Anal. Calcd. for $C_6H_6ONBr \cdot HBr$: C, 26.8; H, 2.6; N, 5.3; Br, 59.4. Found: C, 26.9; H, 2.6; N, 5,2; Br, 59.4.

4-(Pyridyl-1-oxide)methyl bromide. Five g. of the above bromide hydrobromide was dissolved in the minimum amount of water and solid sodium bicarbonate was added until the solution was adjusted to *p*H 7.0. The solution was saturated with salt and extracted with chloroform. The extracts were dried and the solvent removed to give the theoretical amount of solid, m.p. 138–138.5°. No analysis was obtained as the compound becomes colored and decomposes within several hours.

Thioisonicotinyl morpholine. A suspension of 9.6 g. (0.3 g.-atom) of sulfur in a mixture of 10.9 g. (0.1 mole) of 4-picoline-1-oxide and 13.1 g. (0.15 mole) of morpholine was heated at 170° for 12 hr. The reaction mixture was cooled, diluted with 50 ml. of absolute ethanol, the precipitate collected and recrystallized twice from ethanol to give 11.4 g. (55%) of product, m.p. 150–152° lit.,[56] 150–151°.

Anal. Calcd. for $C_{10}H_{12}N_2OS$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.6; H, 5.8; N, 13.4.

*Catalytic hydrogenation of β-(4-pyridyl)-*DL*-alanine and its N-oxide.* The reductions were conducted in the same manner for both compounds. A weighed sample of each compound was dissolved in 25 ml. of water, the weighed platinum dioxide catalyst added, and the mixture hydrogenated at 40 p.s.i. and 25°. At selected time intervals the hydrogenation was interrupted, a 2.5-ml. aliquot removed, filtered and a 1.0-ml. aliquot of the filtrate diluted 1:10 for β-(4-pyridyl)-DL-alanine and 1:100 to 1:5 for the *N*-oxide. The spectra were taken at 260 and 250 mμ. The data are summarized in Table I. The data for the mole percentage of β-(4-pyridyl)-DL-alanine and β-(4-piperidyl)-DL-alanine in the reduction of β-(4-pyridyl-1-oxide)-DL-alanine have error in them estimated at ± 10 mole percent through the fifth point, and about ± 2 mole percent in the last points. This is due to the fact there is approximately a factor of 10 between the molar extinction coefficients of β-(4-pyridyl-1-oxide)-DL-alanine and β-(4-pyridyl)-DL-alanine and small errors in the concentration of the former component are reflected by *ca.* 10 times that error in the concentration of the latter. β-(4-Piperidyl)-DL-alanine has no absorption in this region.

To a solution of 5.0 g. (.0275 mole) of β-(4-pyridyl-1-oxide)-DL-alanine in 25 ml. of water was added 0.5 g. of platinum dioxide and the mixture hydrogenated at 40 p.s.i. and 25° until 0.069 mole of hydrogen had been absorbed. The catalyst was removed and the solution evaporated in dryness *in vacuo*. The solid was extracted with 25 ml. of dry methanol and the residue, 2.82 g., dried *in vacuo*. An oily solid was isolated from the methanol extract. β-(4-Piperidyl)-DL-alanine is very hygroscopic. A determination of the extinction coefficient at 256 mμ, assuming the absence of β-(4-pyridyl-1-oxide)-DL-alanine, gave a value of 311 ± 16 for the molecular weight of the solid product. After a second extraction with methanol, a value of 380 ± 10 was obtained. The molecular weight of β-(4-piperidinium)-DL-alanine β-(4-pyridyl)-DL-alaninate is 338. The solid decomposed at 250–280° and gave a blue-purple color with ninhydrin. The yield of 2.8 g. compares favorably with the yield of 2.5 g. expected on the basis of hydrogen uptake.

PASADENA, CALIF.

(56) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).

[CONTRIBUTION FROM INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of the Dicarboxylic Acid $C_{12}H_{14}O_4$—Degradation Product of Picrotoxin

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γ-(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, *Gazz. chim. ital.* **42**, ii, 337 (1911).

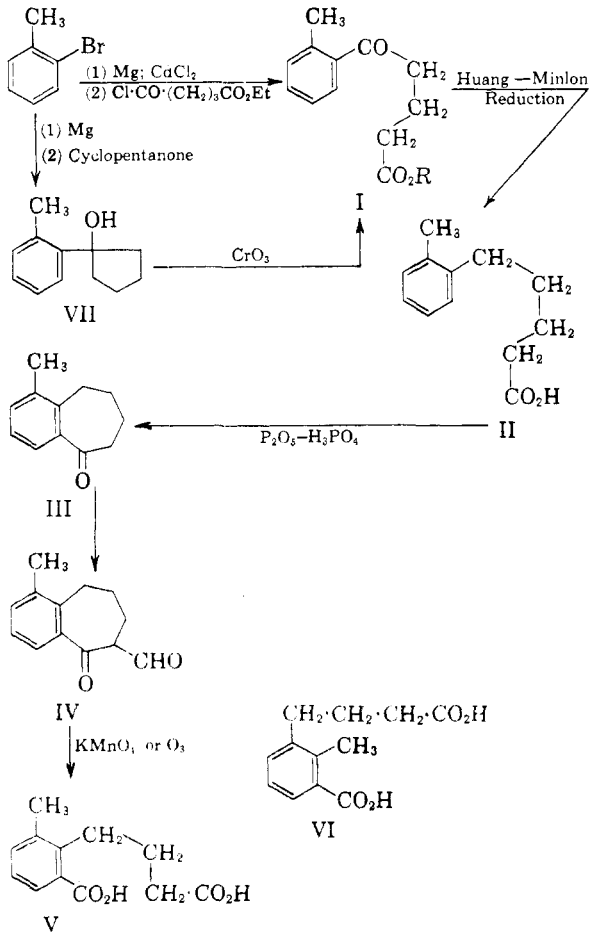
(2) F. Angelico and F. Monforte, *Gazz. chim. ital.*, **53**, 800 (1923).

Robertson has chosen structure (V) on the basis of its transformation to 5-methyltetralone.[3]

The acid (V) has been synthesized by an unambiguous method shown in the flow sheet.

γ-(2-Methylbenzoyl)butyric acid (I, R = H) was prepared following two different routes. In the first method *o*-tolylcadmium bromide was made to react with γ-carbethoxybutyroyl chloride resulting in the formation of ethyl γ-(2-methylbenzoyl)butyrate (I, R = Et)[4] which gave acid (I, R = 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 = H).[5]

Huang-Minlon reduction of compound I (R = Et) gave δ-*o*-tolylvaleric acid (II) in satisfactory yield. Cyclization of acid II with polyphosphoric acid gave 1′-methylbenzocyclohepten-3-one (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 $C_{12}H_{14}O_4$ and melted at 136–136.5° (uncorrected). Robertson *et al.*[3] 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.*[3] This definitely shows that the synthetic acid is identical with the acid from natural sources.



(3) D. Mercer, A. Robertson, and R. S. Cahn, *J. Chem. Soc.*, 997 (1935).

(4) J. Cason and P. Prout, *J. Am. Chem. Soc.*, 66, 46 (1944).

(5) L. F. Fieser and J. Szmuszkovicz, *J. Am. Chem. Soc.*, 70, 3352 (1948).

EXPERIMENTAL

Melting and boiling points are uncorrected.

Ethyl γ-(2-methylbenzoyl)butyrate (I, R = Et). A solution of *o*-bromotoluene (45 g.) in a mixture of dry ether (132 ml.) and thiophene-free benzene (44 ml.) was added with stirring in the course of 1.5 hr. to magnesium turnings (6.5 g.) covered with ether containing a little methyl iodide maintaining gentle reflux of the reaction mixture. The Grignard solution was then cooled in an ice bath and anhydrous cadmium chloride (29 g.) was added. The resulting mixture was heated under reflux with stirring for 45 min. The ether in the mixture was then distilled off until the mixture in the flask became a thin slurry and the distillation became slow. Thiophene-free benzene (176 ml.) was added and 22 ml. of benzene were distilled off.

A solution of γ-carbethoxybutyroyl chloride (47.1 ml.) dissolved in thiophene-free benzene (44 ml.) was added with vigorous stirring to the hot mixture (kept in nitrogen atmosphere) as quickly as possible. An exothermic reaction ensued, and cadmium halide precipitated out. The mixture was then heated under reflux for 1 hr., and processed in the usual manner. Ethyl γ-(2-methylbenzoyl)butyrate (19 g.) b.p. 157.5° (4.0 mm.) was obtained.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.38; H, 7.80.

The *2,4-dinitrophenylhydrazone* crystallized from alcohol, m.p. 100°.

Anal. Calcd. for $C_{20}H_{22}N_4O_6$: N, 13.53. Found: N, 13.41.

The ester (1.3 g) was hydrolyzed with sodium hydroxide (1 g.) in a mixture of ethanol (6 ml.) and water (4 ml.). γ-(2-Methylbenzoyl)butyric acid (I, R = H) was obtained as a white solid which was purified with the help of sodium bicarbonate and then crystallized from water containing a few drops of acetic acid; m.p. 80°, which did not rise on further crystallization. Yield—0.7 g.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.79. Found: C, 69.61; H, 6.93.

1-o-Tolylcyclopentanol. (VII) To a Grignard solution prepared from *o*-bromotoluene (105.5 g.), magnesium (14.5 g.), ether (310 ml.), and methyl iodide (1 ml.) cooled in ice was added cyclopentanone (50.0 g.) in 175 ml. of ether with stirring. A white solid was precipitated. The reaction mixture was left overnight, and then refluxed for 3 hr. It was then cooled in an ice bath and decomposed with saturated ammonium chloride solution and worked up in the usual manner. On distillation a clear liquid (12.5 g.), b.p. 110–115°/6 mm., was obtained.

γ-(2-Methylbenzoyl)butyric acid (I, R = H). The above Grignard product (12.5 g.) was dissolved in acetic acid (375 ml.) and chromic acid solution (7*N*, 165 ml.) was added gradually in the course of 1 hr. The temperature of the reaction mixture was kept below 25°. Excess chromic acid was decomposed with sodium bisulfite. Acetic acid was removed by distillation under reduced pressure below 100°. The residue was treated with 10% sulfuric acid and extracted with ether. The ethereal extract was treated with 5% sodium

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.

δ-(o-tolyl)valeric acid (II). To a solution of sodium hydroxide (4 g.) in diethylene glycol (42 ml.) was added ethyl γ-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 $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.10; H, 8.60.

1-Methylbenzosuber-5-one. (III). To a mixture of phosphorus pentoxide (153 g.) and phosphoric acid (89%, 97.5 ml.), maintained at 100°, δ-(*o*-tolyl)valeric acid (5 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, and 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 $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.52; H, 8.11.

The *2,4-dinitrophenylhydrazone* crystallized from benzene–ethyl acetate mixture, m.p. 240°.

Anal. Calcd. for $C_{18}H_{18}O_4N_4$: C, 61.02; H, 5.08. Found: C, 61.12; H, 5.22.

6-Formyl-1-methylbenzosuber-5-one (IV). To an ice-cold suspension of sodium ethoxide from sodium (0.55 g.) and ethanol (1.4 ml.) in thiophene-free benzene (26 ml.) was added a mixture of compound III (2.1 g.) and ethyl formate (1.8 g.) in benzene (13 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.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.65; H, 7.12.

γ-(2-Carboxy-6-methylphenyl)butyric acid (V). (*a*) *By oxidation with permanganate:* To an ice-cold solution of the formyl derivative (IV, 1.65 g.) in 3% sodium hydroxide, powdered potassium permanganate (3.9 g.) was added slowly with stirring. After 2 hr., the solution was treated with sufficient hydrochloric acid (1:1) and saturated sodium bisulfite solution when a tarry mass separated. This was removed and washed several times by decantation with water and then dissolved in hot sodium bicarbonate solution. The alkaline solution was acidified and left in a refrigerator overnight. Black and white particles of solid separated, the latter melting at 129–130°. This was subjected to evaporative distillation and the distillate crystallized twice from benzene to yield 0.3 g., m.p. 136–136.5°.

(*b*) *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).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.80; H, 6.16.

CALCUTTA, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FRESNO STATE COLLEGE]

A Comparison of Rates of Precipitation of Substituted Hippuric Anilides Formed by Papain-Catalyzed Reactions between Hippuric Acid and Substituted Anilines at Approximately *p*H 4.6

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The rates of precipitation of twelve substituted hippuric anilides have been studied, in papain-catalyzed reactions between hippuric acid and substituted anilines at pH ≅ 4.6. Six of these are new compounds. A comparison of these rates permits a reasonable interpretation of results in terms of steric hindrance, electrostatic effects and resonance. In the absence of steric effects, the reaction of substituted anilines appears to increase with increasing basicity.

Preliminary to a series of enzymatic resolutions being instigated in this laboratory, it was important to study the relative rates of precipitation of a few well-chosen substituted hippuric anilides, formed by papain-catalyzed reactions between hippuric acid and appropriately substituted anilines. The general procedure given by Bergmann and Fraenkel-Conrat,[1] as subsequently adapted by

(1) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, 119, 707 (1937).