NOTES

The Synthesis of 3-*t*-Butyl-6-methyl-2-benzofurylacetic Acid

By the late D. S. DEORHA and Padma GUPTA
Chemistry Department, University of Rajasthan, Jaipur, India

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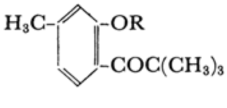
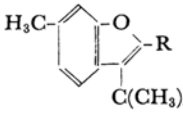
Arylacetic acid is made from an aromatic aldehyde by the hydrolysis of derived azlactone to pyruvic acid and by subsequent oxidation. During the investigation it has been observed that the azlactones of a few 2-formylbenzofurans offer resistance to hydrolysis, which therefore sometimes results only in tars. Moreover, the derived pyruvic acids are so sensitive to oxidation by alkaline hydrogen peroxide that the reaction is hard to control and sometimes furnishes sticky intractable gums. The reaction explored by Jennings[1] for the conversion of *m*-nitrobenzaldehyde to *m*-nitrophenylacetic acid has been successfully used by Dean and coworkers[2]; it has now been extended to the preparation of 3-*t*-butyl-6-methyl-2-benzofurylacetic acid from 2-formyl-3-*t*-butylbenzofuran.

For this purpose 2-hydroxy-4-methylphenyl *t*-butyl ketone (I, $R=H$), and 5-methyl-2-pivaloylphenoxyacetic acid (I, $R=CH_2COOH$) have been prepared and converted into 3-*t*-butyl-6-methylbenzofuran (II, $R=H$), which, when dimethylformamide and phosphorus oxychloride[3] are employed, yields 2-formyl-3-*t*-butyl-6-methylbenzofuran (II, $R=CHO$) in a good yield. The orientation of the formyl group in it has been confirmed by its oxidation to the carboxylic acid (II, $R=COOH$), which is identical with that formed by the cyclisation of the phenoxyester (I, $R=CH_2COOC_2H_5$) and by subsequent hydrolysis (II, $R=COOC_2H_5$). Thus, 4-[(3′-*t*-butyl-6′-methyl-2′-benzofuryl)methylene]-2-phenyloxazolin-5-one (III), obtained from 2-formyl-3-*t*-butyl-6-methylbenzofuran (II, $R=CHO$) by heating it with hippuric acid and sodium acetate in acetic anhydride, reacts with hydrazine hydrate to yield α-benzamido-β-(3-*t*-butyl-6-methyl-2-benzofuryl)acrylohydrazide (IV, $R=NHNH_2$). The latter, with nitrous acid, forms α-benzamido-β-(3-*t*-butyl-6-methyl-2-benzofuryl) acryloazide (IV, $R=N_3$). Upon being refluxed in dry benzene this azide furnishes 4-[(3′-*t*-butyl-6′-methyl-2′-benzofuryl)methyl]-6-phenyl-2*H*-1, 3, 5-oxadiazin-2-one (V), which, with hydrochloric acid, yields 3-*t*-butyl-6-methyl-2-benzofurylacetic acid (II, $R=CH_2COOH$).

Though more steps are involved in this method, it gives purer products and all the reactions proceed quite smoothly.



(I)



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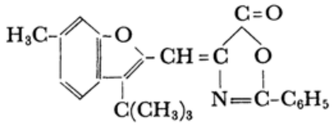

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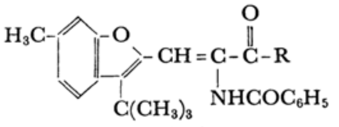

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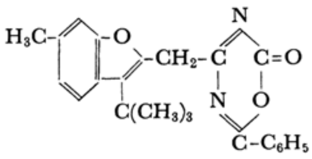

(V)

Experimental

2-Hydroxy-4-methylphenyl *t*-Butyl Ketone.—Pivalyl chloride (13.0 g.) was added gradually to a solution of *m*-cresol (10.8 g.) in dry ether (50 ml.) containing dry pyridine (9 ml.), the temperature maintained below 10°C. After it had been kept for 18 hr. at room temperature, the mixture was treated with water and then extracted with ether. The ether extract was thoroughly washed with aqueous sodium bicarbonate and then with water. The evaporation of the ether left an oil which, on distillation (b. p. 130°C/20 mmHg), furnished 3-methylphenyl pivalate[4] (17 g.) as a colorless oil.

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1) K. F. Jennings, *J. Chem. Soc.*, **1957**, 1512.

2) F. M. Dean, D. S. Deorha, J. C. Knight and T. Francis, ibid., **1961**, 327.

3) M. Bisagni, Ng. Ph. Buu Hoi and R. Royer, ibid., **1955**, 3688.

4) R. Batzly, W. S. Ide and A. P. Phillips, *J. Am. Chem. Soc.*, **77**, 2522 (1955).

To the above ester (5 g.) finely-powdered anhydrous aluminum chloride (5 g.) was added in small quantities at room temperature. The reaction commenced immediately. After the addition, the mixture was heated at 70°C for 12 hr. The complex was decomposed with ice and 10 ml. of concentrated hydrochloric acid. The product, which was isolated with ether in the usual way, was distilled, whereby hydroxy ketone (2 g.) was obtained as a viscous liquid, b. p. 150°C/0.3 mmHg.

Found: C, 74.82; H, 8.46. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33%.

With hydroxylamine the ketone formed an oxime which separated from benzene as colorless crystals, m. p. 164°C.

Found: N, 6.88. Calcd. for $C_{12}H_{17}NO_2$: N, 6.76%.

Ethyl 5-Methyl-2-pivaloylphenoxyacetate. — A mixture of 2-hydroxy-4-methylphenyl *t*-butyl ketone (15.5 g.), anhydrous potassium carbonate (40 g.), ethyl chloroacetate (10.2 g.), potassium iodide (0.1 g.), and dry acetone (150 ml.) was refluxed on a water bath for 18 hr. and then filtered. The residue was washed with hot acetone, and the combined acetone filtrates were distilled. The residue was crystallized from ethanol as colorless plates (21 g., 91%), m. p. 63°C.

Found: C, 69.25; H, 8.10. Calcd. for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97%.

Its 2, 4-dinitrophenylhydrazone separated from ethanol in the form of yellow needles, m. p. 152°C.

Found: N, 12.00. Calcd. for $C_{22}H_{26}N_4O_7$: N, 12.22%.

5-Methyl-2-pivaloylphenoxyacetic Acid. — The foregoing ester (10 g.) was heated with sodium hydroxide (5%, 100 ml.) and ethanol (15 ml.) until it dissolved (2 hr.). The acidification of the cooled and diluted solution furnished the *phenoxyacetic* acid, which crystallized from ethanol as needles (8 g., 90%), m. p. 143°C.

Found: C, 67.34; H, 7.40. Calcd. for $C_{14}H_{18}O_4$: C, 67.17, H, 7.25%.

Its 2, 4-dinitrophenylhydrazone was crystallized from ethanol in the form of orange plates, m. p. 230°C.

Found: N, 13.28. Calcd. for $C_{20}H_{22}N_4O_7$: N, 13.02%.

3-*t*-Butyl-6-methylbenzofuran.—The above phenoxyacetic acid (14.0 g.) was mixed with anhydrous sodium acetate (25 g.) and acetic anhydride (50 ml.), kept at 160°C (oil bath) for 3 hr., and then poured into cold water (200 ml.). After 24 hr. the product was extracted with ether in the usual way. The removal of the ether left an oil which was distilled under reduced pressure as a colorless liquid (7.5 g., 73%, b. p. 100°C/5 mmHg).

Found: C, 83.14; H, 8.70. Calcd. for $C_{13}H_{16}O$: C, 82.93; H, 8.57%.

2-Formyl-3-*t*-butyl-6-methylbenzofuran.—a) An ice-cold mixture of *N, N*-dimethylformamide (3.5 ml.) and freshly-distilled phosphorus oxychloride (3.5 ml.) was added to a solution of 3-*t*-butyl-6-methylbenzofuran (1.0 g.) in *N, N*-dimethylformamide (3.5 ml.). The mixture was then heated on a water bath for 4 hr., cooled, diluted with water, and neutralized with sodium bicarbonate. After 2 hr., the product was extracted with ether in the usual way, and recovered by the evaporation of the solvent. The residue was crystallized from ethanol, furnishing the 2-formylbenzofuran (1.0 g., 89%) in the form of colorless needles, m. p. 60°C.

Found: C, 77.90; H, 7.30. Calcd. for $C_{14}H_{16}O_2$: C, 77.71; H, 7.45%.

b) A solution of 3-*t*-butyl-6-methylbenzofuran (1.0 g.) in ether (10 ml.) containing hydrogen cyanide (0.7 ml.) and aluminum chloride (1.0 g.) was saturated at 0°C with hydrogen chloride, kept for 24 hr., and then evaporated in a current of air. The hydrolysis of the residue with 40 ml. of water at 0°C, and then on a boiling water bath for 1 hr., gave a low-melting solid. The product was isolated by ether in the usual way. The removal of the ether left a residue which, on crystallization from ethanol, furnished 2-formyl-3-*t*-butyl-6-methylbenzofuran (0.35 g., 30%) in the form of colorless needles, m. p. and mixed m. p. with the above sample under a), 60°C.

The 2, 4-dinitrophenylhydrazone separated from ethanol in the form of red crystals, m. p. 261°C.

Found: N, 14.40. Calcd. for $C_{20}H_{20}N_4O_5$: N, 14.14%.

4-[(3′-*t*-Butyl-6′-methyl-2′-benzofuryl)methylene]-2-phenyloxazolin-5-one.— A mixture of the above-mentioned formylbenzofuran (4.65 g.), benzoylglycine (7 g.), anhydrous sodium acetate (4.0 g.), and acetic anhydride (25 ml.) was heated on a water bath for 2 hr., cooled, diluted with ethanol (100 ml.), and kept overnight. The crystalline solid was then filtered and crystallized from ethanol as orange yellow needles (7.7 g., 72%), m. p. 195°C.

Found: N, 4.15. Calcd. for $C_{23}H_{21}NO_3$: N, 3.09%.

α-Benzamido-β-(3-*t*-butyl-6-methyl-2-benzofuryl) Acrylohydrazide. — To a suspension of the finely-powdered oxazolone (5.0 g.) in ethanol (150 ml.), 99% hydrazine hydrate (0.7 g.) was added. This mixture was vigorously stirred until the color had been discharged. The solid was then collected and crystallized from ethanol to furnish acrylohydrazide (5.4 g., 89%) in the form of light yellow needles, m. p. 187°C.

Found: N, 10.59. Calcd. for $C_{23}H_{25}N_3O_3$: N, 10.74%.

4-[3′-*t*-Butyl-6′-methyl-2′-benzofuryl)methyl]-6-phenyl-2*H*-1, 3, 5-oxadiazin-2-one.—An ice-cold solution of sodium nitrite (0.3 g.) in a minimum amount of water was added slowly to a solution of the α-benzamido-β-(3-*t*-butyl-6-methyl-2-benzofuryl) acrylohydrazide (1 g.) in glacial acetic acid (25 ml.), the temperature being kept below 10°C. After 30 min., the yellow crystalline precipitate was filtered, washed with water, and dried in air.

The crude azide (1 g.) (decomp. 136°C) was then extracted from a soxhlet thimble with benzene (50 ml.); when concentrated and cooled, the benzene extracts deposited a product which, on recrystallization from benzene, gave the oxidiazine (0.7 g., 85%) in the form of orange-yellow needles, m. p. 214°C.

Found: N, 7.20. Calcd. for $C_{23}H_{22}N_2O_3$: N, 7.48%.

3-*t*-Butyl-6-methyl-2-benzofurylpyruvic Acid. — A mixture of 4-[(3′-*t*-butyl-6′-methyl-2′-benzofuryl)-methylene]-2-phenyloxazolin-5-one (1.0 g.) and potassium hydroxide (20%, 20 ml.) was boiled under reflux until the oxazolone dissolved completely. The condenser was then removed, and the hydrolysis was completed by gentle boiling until ammonia could no longer be detected in the issuing vapors. During the latter part of the reaction, the volume of the solution was kept at 20ml. by the occassional addition of water.

The solution was then diluted with water (50 ml.) and filtered. The cold filtrate was acidified with concentrated hydrochloric acid, and then warmed on a steam bath to 60°C. In this form, the pyruvic acid separated in a granular form and was easily filtered. The benzoic acid formed in the reaction remained in solution. The pyruvic acid crystallized from benzene as colorless plates (0.25 g., 24%), m. p. 206°C.

Found: C, 70.20; H, 6.40. Calcd. for $C_{16}H_{18}O_4$: C, 70.01; H, 6.61%.

3-*t*-Butyl-6-methyl-2-benzofurylacetic Acid.—a) A suspension of the above-mentioned oxadiazine (3.74 g.) in acetic acid (40 ml.) and 5 N hydrochloric acid (5 ml.) was refluxed until its dissolution was complete and the color of the solution had been completely discharged, whereafter dilution with water precipitated the 2-benzofurylacetic and benzoic acids. The latter was leached out with water at 60°C, leaving the crude 2-benzofurylacetic acid, which was then crystallized from aqueous ethanol (1 : 1) in colorless plates (2.0 g., 85%), m. p. 130°C.

Found: C, 73.00; H, 7.95. Calcd. for $C_{15}H_{18}O_3$: C, 73.13; H, 7.83%.

b) A solution of the crude pyruvic acid (1.0 g.) in aqueous potassium hydroxide (5 ml., 10%) at 0°C was mixed with hydrogen peroxide (20 ml., 100 vol.), warmed until effervescence began, cooled to 0°C, diluted with ice water, and finally acidified with concentrated hydrochloric acid. The 3-*t*-butyl-6-methyl-2-benzofurylacetic acid thus precipitated crystallized from aqueous ethanol (1 : 1) as colorless plates (0.31 g., 35%), m. p. and mixed m. p. with the sample under a), 130°C.

Its methyl ester, prepared by diazomethane, crystallized from benzene in the form of colorless needles, m. p. 52°C.

Found: C, 73.96; H, 7.60. Calcd. for $C_{16}H_{20}O_3$: C, 73.79; H, 7.74%.

3-*t*-Butyl-6-methyl-2-benzofurylcarboxylic Acid.—a) Ethyl 5-methyl-2-pivaloylphenoxyacetate (1.08 g.) was dissolved in ethanol (10 ml.), and a solution of sodium ethoxide (0.2 g. of sodium in 10 ml. of dry ethanol) was added. The solution was heated on a water bath for 15 min. and then diluted with water (20 ml.). The clear solution was acidified with 5 N hydrochloric acid. The product was crystallized from ethanol in the form of colorless prisms (0.4 g., 40%), m. p. 234°C.

Found: C, 73.19; H, 7.18. Calcd. for $C_{14}H_{16}O_3$: C, 73.00; H, 7.00%.

b) 2-Formyl-3-*t*-butyl-6-methylbenzofuran (1.0 g.) was dissolved in purified acetone (50 ml.), and a solution of potassium permanganate (0.6 g.) in water (20 ml.) was added. The solution slowly deposited manganese dioxide; after 18 hr., this was removed by means of sulfur dioxide. The solution was then diluted with water, and the solid that separated was collected, dissolved in ether, and extracted with a sodium bicarbonate solution. The extract was acidified with 5 N hydrochloric acid to give the acid (0.5 g., 46%), which was crystallized from ethanol, m. p. and mixed m. p. with the above sample under a), 234°C.

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