

92. *Azlactones and Phenylacetic Acids derived from the 2-Nitro-derivatives of Vanillin, isoVanillin, and Veratraldehyde.*

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2-Nitro-3-hydroxy-4-methoxyphenylacetic acid, which should be a useful intermediate for the synthesis of such aporphine alkaloids as bulbocapnine, has been prepared from 2-nitroisovanillin *via* an intermediate azlactone. An improved method for preparing such azlactones also made 2-nitro-3-methoxy-4-hydroxyphenylacetic acid more readily available, and provided an alternative route to 2-nitro-3:4-dimethoxyphenylacetic acid.

Of the methods which might be applied to the preparation of 2-nitro-3-hydroxy-4-methoxyphenylacetic acid from 2-nitroisovanillin, that used in preparing 2-nitrohomoveratric acid *via* its nitrile (Kay and Pictet, *J.*, 1913, **103**, 947) involves the low yield of a Cannizzaro reaction, and an excellent modification (Slotta and Lauersen, *J. pr. Chem.*, 1934, **139**, 220) appears to be applicable only to the fully methylated derivatives, for we could not reduce 2-nitrovanillin acetate by the aluminium *isopropoxide* method. A second possibility was to proceed through the azlactone obtained by condensing the aldehyde with hippuric acid. This has been done with 2-nitrovanillin (Gulland, Ross, and Smellie, *J.*, 1931, 2885) and, as far as the phenylpyruvic acid, with 2-nitroveratraldehyde (Avenarius and Pschorr, *Ber.*, 1929, **62**, 321; Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924). The yields of the azlactones were variable, and their hydrolysis to the phenylpyruvic acids difficult.

It was found that the aldehydes mentioned above may be condensed with aceturic or hippuric acid in the presence of acetic anhydride to give azlactones if the usual catalyst, sodium acetate, is replaced by triethylamine, and long reaction times at relatively low temperatures are employed. In this way pure products were obtained directly, and in good yield, regardless of the size of the run.

When aceturic acid was used, the *azlactones* obtained were easily hydrolysed to the pyruvic acids, from which the phenylacetic acids were obtained by oxidation in the usual manner. The preparation of 2-nitrohomovanillic acid from vanillin acetate proceeded very smoothly in 40% over-all yield, compared with a maximum of 15% by the earlier method (Gulland, Ross, and Smellie, *loc. cit.*). That of 2-nitro-3-hydroxy-4-methoxy- and of 2-nitro-3:4-dimethoxyphenylacetic acid went less smoothly. In the latter case, the yield was good, but the m. p. of the product could not be brought to the value recorded in the literature.

It was not found possible to replace aceturic acid by formylglycine, in the preparation of the azlactones, to facilitate further their hydrolysis.

It was observed by Gulland, Ross, and Smellie (*loc. cit.*) that crystallisation of azlactones from alcohol might result in rupture of the azlactone ring with the formation of acylamido-cinnamic esters. In this connection, we have observed that the azlactones obtained by condensing benzaldehyde or veratraldehyde with aceturic or hippuric acid were quantitatively converted into the acylamido-cinnamic esters by refluxing for about one hour with methyl or ethyl alcohol in the presence of (neutral) sodium acetate; without the acetate they were unchanged, and its catalytic action was inhibited by a little acetic acid.

The preparation of 2-nitroveratraldehyde was improved by methylating 2-nitrovanillin acetate directly, a method which was also applied to the benzylation of the latter.

EXPERIMENTAL.

2-Nitrovanillin Acetate.—Vanillin acetate was nitrated at -5° to 0° (Pschorr and Somuleanu, *Ber.*, 1899, **32**, 3405) by fresh fuming nitric acid (*d* 1.59–1.60) with vigorous stirring. The crude product, after being washed with much cold water, was crystallised from acetic acid (2 parts)–water (0.5 part). In runs of 50–250 g., yields of 75–85% were obtained; m. p. 85° . The use of older acid decreased the yield to as low as 50%; weaker acids (*d* 1.50) resulted in oily products (cf. Gulland, Ross, and Smellie, *loc. cit.*).

The mother-liquors from the crystallisation sometimes deposited pale yellow plates, m. p. 121.5° ,

identified as 6-nitrovanillin acetate by conversion into 6-nitrovanillin (Raiford and Stoesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2556).

Azlactone of 2-Nitro- α -benzamido-3-methoxy-4-acetoxycinnamic Acid.—2-Nitrovanillin acetate (23.9 g.), hippuric acid (20 g.), acetic anhydride (30 c.c.), and triethylamine (10 c.c.) were mixed and kept in a stoppered flask at 25° for some hours, at 40° for 1 day, at 50° for 2 days, and at 0° for 1 day. The azlactone was then filtered off, washed with alcohol and with water, and crystallised from acetic acid containing acetic anhydride, giving yellow plates (21.7 g., 61%), m. p. 171.5—172.5° (Gulland, Ross, and Smellie, *loc. cit.*, found m. p. 171—172°).

Azlactone of 2-Nitro- α -acetamido-3-methoxy-4-acetoxycinnamic Acid.—2-Nitrovanillin acetate (47.8 g.), aceturic acid (25 g.), and acetic anhydride (50 c.c.) were mixed, and triethylamine (20 c.c.) added, a rise in temperature being avoided. The mixture was kept in a stoppered flask at 20° for 1 day, at 40° for 6 days, at 55° for 1 day, then at 0° for 2 days. The azlactone was then filtered off and washed with cold 75% alcohol (200 c.c.) and with hot water, giving yellow needles (39.5 g., 62%), m. p. 130°. Crystallised from acetic acid containing acetic anhydride, it had m. p. 131° (Found: N, 8.25. $C_{14}H_{12}O_7N_2$ requires N, 8.75%).

2-Nitro-4-hydroxy-3-methoxyphenylpyruvic Acid.—The crude azlactone of 2-nitro- α -acetamido-4-hydroxy-3-methoxycinnamic acid (10 g.) was refluxed with water (90 c.c.) and hydrochloric acid (10 c.c.) for 2½ hours; during the first ½ hour the mixture was frequently shaken, and the lumps broken up to bring about rapid solution. The solution was then cooled, water (50 c.c.) and 40% aqueous sodium hydrogen sulphite (45 c.c.) added, and the solution saturated with sulphur dioxide and extracted three times with ether. The aqueous layer, containing some crystalline solid matter, was treated with hydrochloric acid (20 c.c.) and evaporated in a vacuum nearly to dryness. Extraction of the residue with ethyl acetate, distillation of the solvent from the extract, and washing of the product on to the filter with benzene gave 7.08 g. (88%), m. p. 180—181° (Gulland, Ross, and Smellie, *loc. cit.*, found 182°).

2-Nitro-4-hydroxy-3-methoxyphenylacetic Acid.—The above phenylpyruvic acid was dissolved in cold *N*-sodium hydroxide (100 c.c.), and 30% hydrogen peroxide (3.6 c.c.) added at 0—10°. After the mixture had been left overnight at 0°, saturation with sulphur dioxide gave the product as yellow plates (5.57 g.), m. p. 159.5—160.5°. The mother-liquors gave 0.17 g., m. p. 158—159°, by extraction with ethyl acetate and crystallisation of the residue, left on removing the solvent, from water (8 c.c.) (charcoal); total yield, 91%. For analysis it was crystallised from 10 parts of water, giving thick, pale yellow, hexagonal plates, m. p. 159.5—160.5° (Gulland, Ross, and Smellie, *loc. cit.*, gave 161°) (Found: N, 6.1. Calc. for $C_9H_9O_6N$: N, 6.2%).

Benzyl Ether of 2-Nitrovanillin.—A mixture of 2-nitrovanillin acetate (12 g.), powdered sodium hydrogen carbonate (8.5 g.), benzyl chloride (6 c.c.), and methanol (60 c.c.) was refluxed for 5 hours, then most of the methanol was distilled off. Water (100 c.c.) and 50% aqueous sodium hydroxide (15 c.c.) were added, the mixture was shaken at 80°, cooled, shaken with light petroleum, and the benzyl ether filtered off. After being washed with water and light petroleum, and crystallised from acetic acid-water, it was obtained as colourless plates (7 g.), m. p. 111—112°. For analysis it was recrystallised from acetic acid; m. p. 111.5—112.5° (Found: C, 62.8; H, 4.3. $C_{15}H_{13}O_5N$ requires C, 62.7; H, 4.6%).

Azlactone of 2-Nitro- α -acetamido-4-benzoyloxy-3-methoxycinnamic Acid.—The benzyl ether of 2-nitrovanillin (5 g.), aceturic acid (2.5 g.), acetic anhydride (7 c.c.), and triethylamine (2 c.c.) were mixed and kept in a stoppered flask for 1 day at 25°, for 2 days at 40°, and for successive one-day periods at 50°, 60°, 70°, 80°, and 0°. The azlactone was then filtered off and washed with 95% alcohol, giving 4.5 g. (70%), m. p. 163—164°. Recrystallisation from acetic acid containing acetic anhydride gave thick yellow needles, m. p. 163.5—164.5° (Found: N, 7.3. $C_{18}H_{16}O_8N_2$ requires N, 7.6%).

isoVanillin.—The following method is an improvement upon recorded methods. Protocatechuic aldehyde (*Org. Synth.*, **18**, 75) (100 g. of the crude product) was stirred in water (2 l.) held at 80° in a 4-l. beaker. Sodium hydrogen carbonate (70 g.) was then added, followed by methyl sulphate (60 c.c.) in four portions. The alternate addition of sodium hydrogen carbonate (63 g.) and of methyl sulphate (60 c.c.) was then repeated three times, each pair of additions requiring about 6 minutes; the pH fluctuated between 7 and 8. The mixture was then cooled, and the product filtered off. The mother-liquor was then methylated at 80° as above with three lots of the bicarbonate and of methyl sulphate, and cooled, salt (400 g.) added, and the mixture extracted with ether (500 c.c.). The ether and the product previously filtered off were shaken together with 10% aqueous sodium hydroxide (450 c.c.). Addition of salt (100 g.) to the aqueous layer, cooling, and adjustment of the pH to 6, precipitated *isovanillin* (46 g.) which, after 2 crystallisations from water (charcoal), gave 35 g., m. p. 114—115°.

The ethereal layer gave veratraldehyde (43 g.) from which more *isovanillin* was obtained by demethylation (Robinson and Sugawara, *J.*, 1931, 3167).

2-Nitroisovanillin.—This was prepared by Pschorr and Stohrer's method (*Ber.*, 1902, **35**, 4393). No better results were obtained by nitrating *isovanillin* in various solvents with acetyl nitrate, benzoyl nitrate, or anhydrous nitric acid.

Azlactone of 2-Nitro- α -acetamido-3-acetoxy-4-methoxycinnamic Acid.—2-Nitroisovanillin (20 g.), acetic anhydride (40 c.c.), and powdered aceturic acid (14 g.) were mixed, and triethylamine (10 c.c.) added, the temperature being held below 30°. The flask containing the mixture was stoppered and heated for 2 days at 37°, then for five days at 50°, then kept at 0° for two days. The azlactone was filtered off, slurried, and washed with cold 50% alcohol (110 c.c.), giving 19.7 g. (61%) as a light orange powder, m. p. 198°. Recrystallised twice from five parts of acetic acid-acetic anhydride (4:1), it formed orange prisms, m. p. 199.5—200.5° (Found: C, 52.5; H, 3.8; N, 8.6. $C_{14}H_{12}O_7N_2$ requires C, 52.5; H, 3.8; N, 8.75%).

2-Nitro-3-hydroxy-4-methoxyphenylpyruvic Acid.—The foregoing crude azlactone (5 g.) was refluxed for 2½ hours with water (45 c.c.) and hydrochloric acid (5 c.c.), the mixture being shaken and the lumps broken up occasionally during the first ½ hour until the solid had dissolved. Sodium hydrogen sulphite (25 c.c. of a 40% solution) was added, and the solution cooled and extracted three times with ether.

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The aqueous layer was treated with hydrochloric acid (12 c.c.), shaken under vacuum until frothing ceased, boiled in a current of carbon dioxide, then distilled in a vacuum to dryness. The solid was extracted with ethyl acetate, which on evaporation left the required acid (3.8 g.). Crystallisation from acetic acid gave plates, m. p. 168.5—169° (Found: N, 5.5. $C_{10}H_9O_7N$ requires N, 5.5%).

2-Nitro-3-hydroxy-4-methoxyphenylacetic Acid.—The crude pyruvic acid (above) was dissolved in 6.6% sodium hydroxide (33 c.c.), and hydrogen peroxide (2 c.c. of 30%) added at 0°. After standing for a day at 0°, the product (2.4 g.) was precipitated by sulphuric acid. After four recrystallisations from water (25 c.c.) (charcoal), it was obtained as yellow plates (1.15 g., 33%), m. p. 166—167° (Found: C, 47.6; H, 4.1; N, 6.2. $C_9H_9O_6N$ requires C, 47.6; H, 4.0; N, 6.2%).

2-Nitroveratraldehyde.—2-Nitrovanillin acetate (150 g.), water (600 c.c.), and methyl sulphate (250 c.c.) were mixed and stirred vigorously while 50% aqueous sodium hydroxide (100 c.c.) was added dropwise during one hour, the pH being kept at about 8 and the temperature at 35—40° throughout. Methyl sulphate (125 c.c.) was then added, and more alkali (100 c.c.) as before, but the last 50 c.c. were added to keep the pH at about 11. After 20 minutes' more stirring, the mixture was made alkaline, cooled, ice and ammonia added, and the whole left at 0°. The product was filtered off, washed with water (3 l.), and crystallised from acetic acid (385 c.c.)—water (250 c.c.); more was obtained by recrystallising a second crop obtained by diluting the mother-liquors; yield, 114 g. (86%), m. p. 63.5—64°.

Azlactone of 2-Nitro- α -acetamido-3:4-dimethoxycinnamic Acid.—2-Nitroveratraldehyde (84.4 g.), acetic acid (50 g.), and acetic anhydride (100 c.c.) were mixed, and triethylamine (40 c.c.) added, a rise in temperature being avoided. The flask was stoppered, and the mixture kept for successive one-day periods at 25°, 40°, 60°, 80°, and 0°. The azlactone was then filtered off and washed with cold 50% alcohol (250 c.c.) then with water, giving 87.5 g. (75%), m. p. 199°. Recrystallisation from acetic acid containing acetic anhydride gave yellow needles, m. p. 201° (Found: C, 53.6; H, 4.0; N, 9.5. $C_{13}H_{12}O_6N_2$ requires C, 53.4; H, 4.1; N, 9.6%).

2-Nitro-3:4-dimethoxyphenylpyruvic Acid.—To the foregoing crude azlactone (12 g.) and dioxan (50 c.c.), water (500 c.c.) was added, and the mixture refluxed for 1 hour. Hydrochloric acid (50 c.c.) was then added, and refluxing continued for 2½ hours. The mixture was frequently shaken throughout. It was then filtered hot (charcoal). Cooling precipitated most of the crude product; the remainder was extracted with ether after saturation of the mother-liquor with salt. The ether and then the solid were extracted with 2N-sodium hydroxide (130 c.c.), and the alkaline solution treated with 40% sodium hydrogen sulphite (15 c.c.), saturated with sulphur dioxide, extracted three times with ether, hydrochloric acid (35 c.c.) added, and sulphur dioxide removed in a vacuum on the water-bath. After cooling, the pale yellow plates (8 g., 72%) were filtered off, m. p. 177° (Avenarius and Pschorr, *loc. cit.*, gave 172°) (Found: N, 4.9. Calc. for $C_{11}H_{11}O_7N$: N, 5.2%).

2-Nitro-3:4-dimethoxyphenylacetic Acid.—The foregoing crude acid (8 g.) in *n*-sodium hydroxide (110 c.c.) was oxidised with 30% hydrogen peroxide (4 c.c.) below 10°. Sulphur dioxide precipitated colourless plates (6.8 g., 95%), m. p. 143°. Repeated crystallisation from water, attended by considerable losses, did not raise the m. p. above 145° (Slotta and Lauenstein, *loc. cit.*, give 146°) (Found: C, 49.8; H, 4.4. Calc. for $C_{10}H_{11}O_6N$: C, 49.8; H, 4.6%).

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