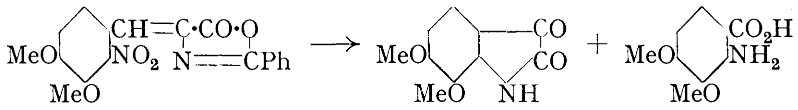
300. *The Alkaline Hydrolysis of the Azlactones derived from Certain* o-*Nitrobenzaldehydes.*

By Harold Burton.

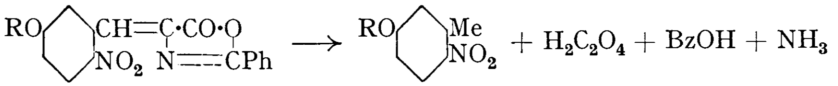
The customary alkaline hydrolysis of 5-keto-2-phenyl-4-benzylidene-4 : 5-dihydro-oxazoles (azlactones) to phenylpyruvic acids fails when the azlactone contains a nitro-group substituted in the benzylidene residue (cf. Douglas and Gulland, J., 1931, 2902). On the other hand, Gulland, Robinson, Scott, and Thornley (J., 1929, 2924) have shown that hydrolysis of 5-keto-2-phenyl-4-(2′-nitro-3′ : 4′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole (I) with aqueous-alcoholic sodium hydroxide involves an intramolecular oxidation–reduction process and gives a mixture of 6 : 7-dimethoxyisatin (II) and 2-aminoveratric acid (III); the reaction is comparable with that of *o*-nitrophenylpyruvic acid with aqueous alkali (Reissert, *Ber.*, 1897, **30**, 1036), whereby isatin, *o*-nitrotoluene, and 2 : 2′-dinitrodibenzyl are produced. Furthermore, hydrolysis of the analogous 5-keto-2-phenyl-4-(2′-nitro-4′-acetoxy-3′-methoxybenzylidene)-4 : 5-dihydro-oxazole with baryta has been shown by Gulland, Ross, and Smellie (J., 1931, 2890) to give non-homogeneous material consisting, in part, of probably an isatin.



(I.) (II.) (III.)

The alkaline hydrolysis of azlactones derived from other *o*-nitrobenzaldehydes has now been studied, but isatin formation has not been found to occur. 2-*Nitro*-5-*benzyloxybenz*-

aldehyde yielded 5-*keto*-2-*phenyl*-4-(2′-*nitro*-5′-*benzyloxybenzylidene*)-4 : 5-*dihydro-oxazole* (IV, R = CH_2Ph) when condensed with hippuric acid in presence of acetic anhydride and sodium acetate. Hydrolysis of this azlactone by boiling 10% sodium hydroxide solution gave an 82% yield of an insoluble compound, m. p. 72—73°, together with oxalic and benzoic acids. The compound was shown by analysis, and by its synthesis from 6-nitro-*m*-cresol and benzyl chloride, to be 2-*nitro*-5-*benzyloxytoluene* (V, R = CH_2Ph). The analogous 5-*keto*-2-*phenyl*-4-(2′-*nitro*-5′-*methoxy*- and -5′-*acetoxy-benzylidene*)-4 : 5-*dihydro-oxazoles* similarly yielded 75·5 and 68% of 2-nitro-5-methoxytoluene and 6-nitro-*m*-cresol, respectively. That the *o*-nitro-group is the controlling factor in the reaction is clearly shown by the behaviour of 5-*keto*-2-*phenyl*-4-o-*nitrobenzylidene*-4 : 5-*dihydro-oxazole* (IV, OR = H), which is similarly converted into *o*-nitrotoluene in 70% yield. This result is in striking contrast to that obtained with either the *m*- or the *p*-nitro-isomeride; in both these cases, the amount of nitrotoluene formed is too small to allow of identification.

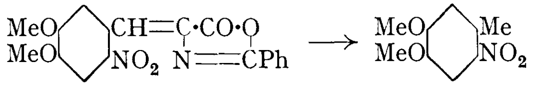


(IV.) (V.)

The results of this investigation suggest that the above-mentioned production of 2-aminoveratric acid from (I) may involve the intermediate 2-nitrohomoveratrole, which, under the influence of the alkali, undergoes intramolecular dismutation.

Whilst this paper was being written, a closely related investigation was published by Oliverio (*Gazzetta*, 1935, **65**, 143), showing that hydrolysis of 5-keto-2-phenyl-4-(6′-nitro-3′ : 4′-dimethoxybenzylidene)-4 : 5-dihydro-oxazole (VI) with 10% potassium hydroxide solution affords, as the initial product, 6-nitrohomoveratrole (VII)—a result in complete accord with the above.

(VI.)



(VII.)

Experimental.

2-*Nitro*-5-*benzyloxybenzaldehyde*.—A mixture of 2-nitro-5-hydroxybenzaldehyde (33·4 g.), benzyl chloride (27·8 g.), sodium hydroxide (8·8 g. in 50 c.c. of water), and alcohol (300 c.c.) was boiled under reflux for 8 hours, the alcohol removed by distillation, and water added to the residue. The *aldehyde* (40 g.), which separated as an oil and gradually solidified, crystallised from benzene–ligroin in almost colourless, prismatic needles, m. p. 75—76° (Found : C, 65·4; H, 4·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%). The *phenylhydrazone* separated from glacial acetic acid in crimson needles, m. p. 180° (Found : C, 69·2; H, 4·95. $C_{20}H_{17}O_3N_3$ requires C, 69·15; H, 4·9%), and the 2 : 4-*dinitrophenylhydrazone* from xylene in small clusters of yellow needles, m. p. 199° after previous shrinking (Found : C, 55·0; H, 3·55. $C_{20}H_{15}O_7N_5$ requires C, 54·9; H, 3·4%).

5-*Keto*-2-*phenyl*-4-(2′-*nitro*-5′-*benzyloxybenzylidene*)-4 : 5-*dihydro-oxazole* (IV, R = CH_2Ph).—A mixture of dry 2-nitro-5-benzyloxybenzaldehyde (26 g.), hippuric acid (20 g.), and acetic anhydride (50 c.c.) was heated on the steam-bath for 30 minutes with fused sodium acetate (25 g.), a crystalline product separating. The acetic anhydride was decomposed with hot water, and the solid washed repeatedly with boiling water and finally with cold acetone. The *azlactone* separated from acetone in yellow felted needles (24 g.), m. p. 157° (Found : C, 68·9; H, 3·75; N, 7·2. $C_{23}H_{16}O_5N_2$ requires C, 69·0; H, 4·0; N, 7·0%).

2-*Nitro*-α-*benzamido*-5-*benzyloxycinnamic acid*, obtained from the above azlactone after 1—2 mins.' boiling with 10% sodium hydroxide solution, crystallised from glacial acetic acid in colourless needles, m. p. 219—220° (decomp.) (Found : C, 66·0; H, 4·3. $C_{23}H_{18}O_6N_2$ requires C, 66·0; H, 4·3%). It was immediately converted into the azlactone on heating with acetic anhydride.

2-*Nitro*-5-*benzyloxytoluene* (V, R = CH_2Ph).—(i) A mixture of 6-nitro-*m*-cresol (15·3 g.), benzyl chloride (14·9 g.), sodium hydroxide (4·4 g. in 25 c.c. of water), and alcohol (100 c.c.) was boiled under reflux for 8 hours. Addition of water to the cooled mixture precipitated an oil, which gradually solidified. Recrystallisation of the solid from alcohol (charcoal) gave 20 g. of 2-*nitro*-5-*benzyloxytoluene* as nearly colourless, prismatic needles, m. p. 73—74° (Found : C, 69·1; H, 5·4; N, 5·9. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·35; N, 5·8%).

(ii) A mixture of 5-keto-2-phenyl-4-(2′-nitro-5′-benzyloxybenzylidene)-4 : 5-dihydro-oxazole (20 g.) and 10% sodium hydroxide solution (200 c.c.) was boiled under reflux for 4½ hours; ammonia was evolved after the first few minutes, and oil separated. The mixture was cooled, the mother-liquor decanted, and the semi-solid residue washed with small amounts of cold water and crystallised from the minimum quantity of alcohol, giving 10 g. (82% yield) of 2-nitro-5-benzyloxytoluene, m. p. 72—73° either alone or mixed with a specimen prepared by method (i). The alkaline mother-liquor contained benzoic acid (precipitated as such) and oxalic acid (precipitated as calcium oxalate).

5-*Keto*-2-*phenyl*-4-(2′-*nitro*-5′-*methoxybenzylidene*)-4 : 5-*dihydro-oxazole* (IV, R = Me).—This *azlactone*, prepared from 2-nitro-5-methoxybenzaldehyde (18 g.) by the method used for the benzyl analogue, separated from ethyl acetate, in which it was only sparingly soluble, in small yellow needles (27 g.), m. p. 218—219° (Found: C, 62·9; H, 3·7; N, 8·6. $C_{17}H_{12}O_5N_2$ requires C, 62·95; H, 3·7; N, 8·6%).

Hydrolysis of the azlactone. (i) Short treatment with boiling 10% sodium hydroxide solution gave 2-*nitro*-α-*benzamido*-5-*methoxycinnamic acid*, which separated from glacial acetic acid in colourless needles, m. p. 222—223° (decomp.) (Found: C, 59·6; H, 4·3. $C_{17}H_{14}O_6N_2$ requires C, 59·65; H, 4·1%).

(ii) The azlactone (16·2 g.) was boiled with 10% sodium hydroxide solution (200 c.c.) for 4½ hours, an oil separating after a few minutes. The mixture was cooled and the solid was collected, dried, and extracted with ligroin. The concentrated extract deposited 6·3 g. (75·5%) of 2-nitro-5-methoxytoluene, colourless needles, m. p. 54° (cf. Blaikie and Perkin, J., 1924, **125**, 308) (Found: C, 57·5; H, 5·3. Calc. for $C_8H_9O_3N$: C, 57·5; H, 5·4%).

5-*Keto*-2-*phenyl*-4-(2′-*nitro*-5′-*acetoxybenzylidene*)-4 : 5-*dihydro-oxazole* (IV, R = Ac).—This *azlactone* was prepared by the above method from 2-nitro-5-hydroxybenzaldehyde (16·7 g.); it separated from acetone in clusters of fine yellow needles (23 g.), m. p. 165—166° (Found: C, 61·4; H, 3·3; N, 8·0. $C_{18}H_{12}O_6N_2$ requires C, 61·4; H, 3·4; N, 7·95%). When a solution in acetone was cooled below 0°, a mixture of needles and prisms, separable by hand-picking, was obtained. Both forms had the same m. p. (165—166°) and gave no depression (Found, for prisms: C, 61·3; H, 3·4; N, 8·2%).

Hydrolysis of the azlactone. The azlactone (17·6 g.) was boiled with 10% sodium hydroxide solution (300 c.c.) under reflux for 4 hours. The dark red solution was cooled, filtered, and acidified (Congo-red) with concentrated hydrochloric acid. The precipitate was dried in a vacuum desiccator, dissolved in the minimum amount of boiling benzene, and cooled; there were obtained 5·2 g. (68% yield) of 6-nitro-*m*-cresol, m. p. 129°, unchanged by recrystallisation from water (Found: C, 55·1; H, 4·65. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6%).

5-*Keto*-2-*phenyl*-4-o-*nitrobenzylidene*-4 : 5-*dihydro-oxazole* (IV, OR = H).—This *azlactone*, prepared by the above general method from *o*-nitrobenzaldehyde (25 g.), separated from ethyl acetate in yellow needles (30 g.), m. p. 167—168° (Found: C, 65·1; H, 3·7; N, 9·2. $C_{16}H_{10}O_4N_2$ requires C, 65·3; H, 3·4; N, 9·5%).

Hydrolysis of the azlactone. (i) Short treatment with boiling 10% sodium hydroxide solution gave o-*nitro*-α-*benzamidocinnamic acid*, which separated from 50% acetic acid in clusters of colourless small needles, m. p. 181—182° (Found: C, 61·4; H, 3·9. $C_{16}H_{12}O_5N_2$ requires C, 61·5; H, 3·85%).

(ii) The azlactone (22 g.) was hydrolysed as for (IV, R = Ac). The dark brown solution was cooled and extracted with ether. The dried extract (sodium sulphate) afforded 6·7 g. (70% yield) of a pale yellow oil, b. p. 218°, characterised as *o*-nitrotoluene by nitration to 2 : 4-dinitrotoluene, m. p. and mixed m. p. 70°.

5-*Keto*-2-*phenyl*-4-m- *and* -p-*nitrobenzylidene*-4 : 5-*dihydro-oxazoles*.—These were prepared by Douglas and Gulland's method (*loc. cit.*). They were best crystallised from acetic anhydride, being obtained with m. p.'s 178° and 239°, respectively (Douglas and Gulland give m. p.'s 174° and 233°). When either azlactone (14·7 g.) was boiled with 10% sodium hydroxide solution (200 c.c.) for 4 hours and the reaction mixture was then steam-distilled, merely a trace of volatile product (nitrotoluene) was obtained. The hydrolysate was not further investigated.

p-*Nitro*-α-*benzamidocinnamic acid*, obtained by short treatment of the azlactone with boiling 10% sodium hydroxide solution, separated from glacial acetic acid in nearly colourless, fine needles, m. p. 243° (decomp.) (Found: C, 61·3; H, 3·8. $C_{16}H_{12}O_5N_2$ requires C, 61·5; H, 3·85%).

The author acknowledges a grant from the Royal Society in aid of the investigation.

THE UNIVERSITY, LEEDS.

[*Received, July 4th,* 1935.]