290. *A New Sequence for the Conversion of an Aromatic Aldehyde into the Next Higher Acid. A New Synthesis of* m-*Nitrophenylacetic Acid.*

By K. F. JENNINGS.

m-Nitrobenzaldehyde has been converted into 2-methyl-4-*m*-nitrobenzylideneoxazolone, which on mild treatment with hydrazine hydrate gave α-acetamido-*m*-nitrocinnamhydrazide. This, on diazotisation, produced the azide, which in boiling benzene gave 3 : 4-dihydro-6-methyl-4-*m*-nitrobenzylidene-2-oxo-1 : 3 : 5-oxadiazine. Hydrolysis of the last compound gave *m*-nitrophenylacetic acid. The overall yield was 31%. α-Acetamido- and α-benzamido-*m*-nitrocinnamhydrazide, upon digestion with acetic anhydride–acetic acid, gave partly reduced 1 : 2 : 4-triazines, whose structures were not fully established. The latter on alkaline hydrolysis gave α-benzamido-*m*-nitrocinnamic acid quantitatively. Aceturhydrazide yielded *N*-aceturyl-*N*′-acetylhydrazine.

THAT 4-*m*-nitrobenzylideneoxazolones cannot be hydrolysed to α-oxo-acids is well known,[1] and the same is true for the rhodanines. Hence, attention was directed to the possible hydrolysis products of the oxadiazine derivatives (IV) obtained from the azides (III) of α-substituted amino-hydrazides (II), which in turn are derivable from oxazolones (I).[2]

As models, the azlactones obtained from *m*-nitrobenzaldehyde were examined. 2-Methyl-4-*m*-nitrobenzylideneoxazolone (I; R = Me) on treatment with hydrazine hydrate, in ethanol, at room temperature, gave α-acetamido-*m*-nitrocinnamhydrazide (II; R = Me), which with one equivalent of nitrous acid yielded α-acetamido-*m*-nitrocinnamoyl azide (III; R = Me). Azides of this type may undergo various transformations; in cold pyridine or boiling ethanol they are converted into the parent oxazolone, whereas in hot benzene or toluene partly saturated 2-oxo-1 : 3 : 5-oxadiazines result. The azides may be recrystallised (although in this series, badly) from acetone. As expected,

---

[1] Burton, *J.*, 1935, 1265; cf. Jennings, *J.*, 1957, 1172.

[2] Clarke, Johnson, and Robinson, "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 735.

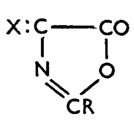
the compound (III; R = Me) in boiling benzene gave 3 : 4-dihydro-6-methyl-4-*m*-nitrobenzylidene-2-oxo-1 : 3 : 5-oxadiazine (IV; R = Me), presumably *via* an *iso*cyanate. On digestion with warm aqueous sodium hydroxide, this gave a very low yield of *m*-nitrophenylacetic acid, but acid hydrolysis gave the same product quantitatively. The overall yield from *m*-nitrobenzaldehyde was 31%.

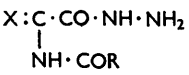
For comparison, the phenyl analogues (I, II, III, and IV; R = Ph) were prepared in a similar manner. In the case of α-benzamido-*m*-nitrocinnamhydrazide (II; R = Ph) *cis*- and *trans*-isomers were isolated, the latter greatly predominating. Presumably, the phenyl analogue (IV; R = Ph) on similar acid hydrolysis gave the desired product and benzoic acid, but as these have the same m. p. and parallel solubilities in water, separation was not accomplished. However, the yield of 3 : 4-dihydro-4-*m*-nitrobenzylidene-2-oxo-6-phenyl-1 : 3 : 5-oxadiazine (IV; R = Ph) from *m*-nitrobenzaldehyde was 42%, which contrasts favourably with the methyl series.

Hence, a new route from an aromatic aldehyde to the arylacetic acid is announced. It offers the advantage over the Erlenmeyer azlactone synthesis in that a nitro-group attached to the aromatic (or principal aromatic) residue in the *meta* position does not prevent it. Although twice as many steps from the oxazolone are needed, they are rapid and easy.

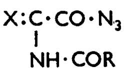
Treatment of α-acetamido-*m*-nitrocinnamhydrazide with hot acetic anhydride–acetic acid gave the triazine derivative (V) or (VI) (R = Me),[3] depending upon the reactivities of the carbonyl group of the acetylhydrazino- or amido-residue. Undoubtedly, acetylation is the first step. *trans*-α-Benzamido-*m*-nitrocinnamhydrazide similarly yielded either (V) or (VI) (R = Ph).

It is yet possible that the acetamidohydrazide (II; R = Me) may have afforded the triazine (V; R = Me), and the benzamidohydrazide (II; R = Ph) the triazine (VI; R = Ph), or *vice versa*. These classes of compounds are new.

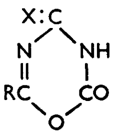

(I)

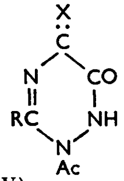

$\underset{\mathrm{NH\cdot COR}}{\underset{|}{\mathrm{X{:}C}}}\mathrm{\cdot CO\cdot NH\cdot NH_2}$

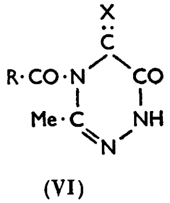
(II)

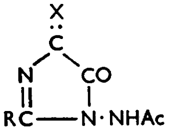

$\underset{\mathrm{NH\cdot COR}}{\underset{|}{\mathrm{X{:}C}}}\mathrm{\cdot CO\cdot N_3}$

(III)


(IV)


(V)


(VI)


(VII)

X = *m*-$NO_2\cdot C_6H_4\cdot CH=$

An alternative possibility of cyclisation to the glyoxaline derivative (VII) is discounted, since the compound (V or VI; R = Ph) on digestion with aqueous alkali gave a quantitative yield of α-benzamido-*m*-nitrocinnamic acid, while (V or VI; R = Me) in similar circumstances produced a tar. The glyoxaline ring would be stable under these conditions.

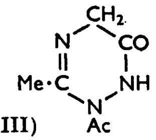
Presumably, another product from the hydrolysis of (V or VI; R = Ph) would be acethydrazide, since α-benzamidocinnamhydrazide with alkali gave 5-benzyl-6-hydroxy-3-phenyl-1 : 2 : 4-triazine.[4] Had α-acetamido- and α-benzamido-*m*-nitrocinnamhydrazide yielded simple acetyl derivatives, these upon digestion with alkali might have been expected

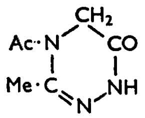
---

[3] Cf. Vanghelovici and Stefanescu, *Soc. Chim. România, Sect. Soc. române Stiinte, Bul. Chim. pură Apl.*, 1941—42, [2], **3**, *A*, 159; *Chem. Abs.*, 1944, **38**, 5501.

[4] Ref. 2, p. 736.

to produce 6-hydroxy-3-methyl-5-nitrobenzyl-1 : 2 : 4-triazine and its 3-phenyl analogue respectively.


(VIII)


(IX)

An attempt to prepare the *pseudo*-parent compound (VIII) or (IX) from aceturhydrazide gave only a low yield of two crystalline forms of *N*-aceturyl-*N'*-acetylhydrazine. This is somewhat surprising in view of the ready cyclisations reported above, and the presumed ring closure of aceturic acid in the Erlenmeyer azlactone synthesis.

EXPERIMENTAL

M. p.s are corrected.

2-*Methyl*-4-m-*nitrobenzylideneoxazolone*.—*m*-Nitrobenzaldehyde (15·1 g.), fused sodium acetate (16·4 g.), aceturic acid (11·1 g.), and acetic anhydride (31 g.) were heated in a boiling-water bath for 3 hr., the mixture setting to a yellow solid. Water (50 ml.) was added and, when cool, the cake was filtered off and washed with hot water and cold ethanol. 2-*Methyl*-4-m-*nitrobenzylideneoxazolone* (18·5 g., 80%) had m. p. 156—157°. Recrystallisation from acetone–ethanol gave bright yellow needles of unchanged m. p. (Found : N, 11·8. $C_{11}H_8O_4N_2$ requires N, 12·1%). In EtOH it has one maximum at 3200 Å (ε 15,400).

α-*Acetamido*-m-*nitrocinnamhydrazide*.—2-Methyl-4-*m*-nitrobenzylideneoxazolone (1·85 g.) was mixed with a solution of 100% hydrazine hydrate (1·0 g.) in ethanol (9 ml.), the deep yellow colour of the oxazolone immediately changing to the light yellow of the product, which was filtered off, washed with ethanol, and dried. α-*Acetamido*-m-*nitrocinnamhydrazide* (1·55 g., 74%), recrystallised from ethanol, gave long needles, m. p. 160—161° (Found: C, 50·2; H, 4·6; N, 21·0. $C_{11}H_{12}O_4N_4$ requires C, 50·0; H, 4·6; N, 21·2%). In EtOH it has one maximum at 2700 Å (ε 17,200).

α-*Acetamido*-m-*nitrocinnamoyl Azide*.—α-Acetamido-*m*-nitrocinnamhydrazide (5·5 g.) was treated in N-hydrochloric acid (60 ml.) with 95% sodium nitrite (2·0 g.) in water (40 ml.), with stirring. The immediate precipitate was filtered off, washed with water, and dried to give α-*acetamido*-m-*nitrocinnamoyl azide* (5·3 g., 93%), m. p. 100—102° (decomp.) (Found : C, 47·3; H, 3·6; N, 24·4. $C_{11}H_9O_4N_5,\frac{1}{4}H_2O$ requires C, 47·2; H, 3·4; N, 25·0%).

3 : 4-*Dihydro*-6-*methyl*-4-m-*nitrobenzylidene*-2-*oxo*-1 : 3 : 5-*oxadiazine*.—α-Acetamido-*m*-nitrocinnamoyl azide (2·0 g.) in benzene (20 ml.) was refluxed for 30 min. The solution was filtered, and on cooling deposited orange needles of the *oxadiazine* (1·0 g., 56%), m. p. 109—110°. Recrystallisation from benzene raised the m. p. to 116—117° (Found : C, 53·9; H, 4·0. $C_{11}H_9O_4N_3$ requires C, 53·4; H, 3·7%). It has, in MeOH, one maximum at 2650 Å (ε 19,600).

m-*Nitrophenylacetic Acid*.—(*a*) The foregoing oxadiazine (1·5 g.) in 10% aqueous sodium hydroxide (30 ml., and kept at 80° for 5 min. When cool, acidification of the solution by hydrochloric acid gave a tar (0·3 g.) which was removed and concentration of the filtrate gave impure *m*-nitrophenylacetic acid (0·2 g.). Recrystallisation of this from water yielded fawn needles (0·1 g., 9%), m. p. 118·5—119·5° (Found : N, 7·6. Calc. for $C_8H_7O_4N$: N, 7·8%). Salkowski [5] reported m. p. 120°.

(*b*) The oxadiazine (1·55 g.) was heated with 5N-hydrochloric acid (40 ml.) at 80° for 30 min. Upon cooling, the solution gave *m*-nitrophenylacetic acid (0·75 g.), m. p. 117—118°, and concentration of the mother-liquor gave a second crop (0·4 g.) of the same m. p. and mixed m. p. The total yield was 100%.

α-*Benzamido*-m-*nitrocinnamhydrazide*.—4-*m*-Nitrobenzylidene-2-phenyloxazolone [6] (11·7 g.) was mixed with ethanol (65 ml.) containing 100% hydrazine hydrate (10·0 g.). After a few minutes, α-*benzamido*-m-*nitrocinnamhydrazide* (10·0 g., 77%) was filtered off, washed with ether, and dried; it had m. p. 190—191° (Found : C, 59·1; H, 4·1; N, 17·0. $C_{16}H_{14}O_4N_4$ requires C, 58·9; H, 4·3; N, 17·2%). In MeOH, this had maxima at 2300 and 2625 Å (ε 17,000

---

[5] Salkowski, *Ber.*, 1884, **17**, 506.

[6] Douglas and Gulland, *J.*, 1931, 2893.

and 16,150 respectively), and is probably the *trans*-isomer.[7] Concentration of the ethanolic mother-liquor gave a second crop (0·5 g., 3·5%), m. p. 208—209°, depressed in m. p. on admixture with the above sample. Recrystallisation from ethanol gave needles, m. p. 208—208·5° (Found : C, 59·05; H, 4·0; N, 16·8%). This had, in MeOH, one maximum at 2600 Å (ε 7600) and is probably the cis-*isomer*. In the infrared absorption spectra, the positions of the bands were similar, but not their intensities. Vanghelovici and Stefanescu[3] gave m. p. 195° and an erroneous constitution of this compound.

*α-Benzamido-*m*-nitrocinnamoyl Azide*.—α-Benzamido-*m*-nitrocinnamhydrazide (3·25 g.; m. p. 190—191°), treated in the same way as the acetamido-analogue, gave *α-benzamido-*m*-nitrocinnamoyl azide* (2·95 g., 88%), m. p. 76—77° (Found : C, 53·8; H, 3·5. $C_{16}H_{11}O_4N_5,H_2O$ requires C, 54·1; H, 3·7%). Vanghelovici *et al.*[3] give m. p. 80° (decomp.) and an erroneous formulation. This compound is white when wet with water, and yellow when a monohydrate.

3 : 4-*Dihydro*-4-m-*nitrobenzylidene*-2-*oxo*-6-*phenyl*-1 : 3 : 5-*oxadiazine*.—α-Benzamido-*m*-nitrocinnamoyl azide (2·8 g.) in benzene (56 ml.) was heated at 85—90° for 20 min. There was brisk evolution of nitrogen with precipitation of the product. When cool, the *oxadiazine* (1·7 g., 66%) was filtered off: it had m. p. 185—186·5° (decomp.) (Found: N, 13·4. $C_{16}H_{11}O_4N_3$ requires N, 13·6%). In MeOH, it has maxima at 2550, 2750, 3550, and 3700 Å (ε 13,200, 12,200, 5100, and 5100 respectively).

*Treatment of α-Acetamido-*m*-nitrocinnamhydrazide with Acetic Anhydride–Acetic Acid.*—A solution of α-acetamido-*m*-nitrocinnamhydrazide (1·0 g.) in acetic anhydride (10 ml.) and acetic acid (10 ml.) was heated at 100° for 30 min., and then cooled. Dilution with water (30 ml.) gave a product (0·5 g., 57%) of m. p. 215—216°. Recrystallisation from ethanol gave light yellow microcrystals of unchanged m. p. (Found : C, 54·0, 53·7; H, 4·4, 4·2; N, 19·8; *C*-Me, 18·6. $C_{13}H_{12}O_4N_4$ requires C, 54·2; H, 4·2; N, 19·45; *C*-Me, 18·7%). In Nujol, the principal bands of this compound are at 2·99 (>NH), 5·79 (cyclic lactam), 5·94 (>NAc), 6·03 (conjugated C:N), and 6·54 μ (bending >NH); and in MeOH, it has maxima at 2450, 2750, and 3400 Å (ε 9500, 12,300, and 16,500 respectively). It is formulated, therefore, as either 2-*acetyl*-1 : 2 : 5 : 6-*tetrahydro*-3-*methyl*-5-m-*nitrobenzylidene*-6-*oxo*-1 : 2 : 4-*triazine* or 4-*acetyl*-1 : 4 : 5 : 6-*tetrahydro*-3-*methyl*-5-m-*nitrobenzylidene*-6-*oxo*-1 : 2 : 4-*triazine*.

*Treatment of α-Benzamido-*m*-nitrocinnamhydrazide with Acetic Anhydride–Acetic Acid.*—A solution of α-benzamido-*m*-nitrocinnamhydrazide (4·8 g; m. p. 190—191°) in acetic anhydride (70 ml.) and acetic acid (70 ml.) was heated at 100° for 40 min. After filtration and dilution with water (100 ml.), the product (3·4 g., 66%) was recrystallised from ethanol–water and gave needles, m. p. 199—201° (Found: C, 59·1; H, 4·6; N, 14·7. $C_{18}H_{14}O_4N_4,H_2O$ requires C, 58·7; H, 4·4; N, 15·2%). The principal infrared absorption bands (in Nujol) are at 3·08 (>NH), 5·75 (weak, undesignated), 5·98 (conjugated >CO), 6·04 (amide), 6·55 μ; (secondary amide); and in MeOH it has maxima at 2300, 2675, and 3600 Å (ε 12,700, 12,200, and 1870 respectively). This product is probably 2-*acetyl*-1 : 2 : 5 : 6-*tetrahydro*-6-*oxo*-5-m-*nitrobenzylidene*-3-*phenyl*-1 : 2 : 4-*triazine* or 4-*benzoyl*-1 : 2 : 5 : 6-*tetrahydro*-3-*methyl*-5-m-*nitrobenzylidene*-6-*oxo*-1 : 2 : 4-*triazine*.

*α-Benzamido-*m*-nitrocinnamic Acid.*—(*a*) The product (0·7 g.) obtained as described immediately above, was heated with 10% aqueous sodium hydroxide (*ca.* 10 ml.) until dissolved (*ca.* 1 min. at 100°). The dark red solution was cooled and acidified to Congo-red by hydrochloric acid, and the pink precipitate was collected, washed, and dried, to give α-benzamido-*m*-nitrocinnamic acid (0·6 g., 100%), m. p. 220—222°. Recrystallisation from acetone–benzene raised the m. p. to 230—231° (Found : C, 61·1; H, 4·1; N, 9·35. Calc. for $C_{16}H_{12}O_5N_2$: C, 61·5; H, 3·85; N, 9·0%). In EtOH, the acid has maxima at 2250 and 2650 Å (ε 30,300 and 23,200 respectively).

(*b*) 4-*m*-Nitrobenzylidene-2-phenyloxazolone[8] (2·0 g.) was heated at 100° with 10% aqueous sodium hydroxide (20 ml.) for 5 min. (*i.e.*, until homogeneous), cooled, and made acid to Congo-red by hydrochloric acid. The precipitate (1·4 g., 66%) had m. p. 222—223°, undepressed on admixture with the above sample. Douglas and Gulland,[8] in a preparation requiring 4 days, obtained a product of m. p. 223—224°.

N-*Aceturyl*-N′-*acetylhydrazine*.—Aceturhydrazide[9] (1·35 g.) was heated in 1 : 1 acetic

---

[7] Cf. Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Arnold, London, 1954, p. 232.

[8] Ref. 6, p. 2902.

[9] Radenhausen, *J. prakt. Chem.*, 1895, **52**, 442.

anhydride–glacial acetic acid (20 ml.) at 100° for 30 min. Removal of the solvents ***in vacuo*** gave a yellow oil, which, from methanol, yielded N-*aceturyl*-N′-*acetylhydrazine* (0·05 g., 3%) as small granules of m. p. 220° (decomp.) (Found: C, 41·4; H, 6·3. $C_6H_{11}O_3N_3$ requires C, 41·6; H, 6·4%). By dilution of the methanolic solution with ether, there was obtained a second crop (0·3 g., 17%), m. p. 181·5—182° (Found: C, 41·6; H, 6·4%). This compound is very water-soluble.

I thank Sir Robert Robinson, O.M., F.R.S., for his interest, and the Rockefeller Fund for financial assistance.

DYSON PERRINS LABORATORY, SOUTH PARKS ROAD, OXFORD.
[Present address: DEFENCE RESEARCH CHEMICAL LABORATORIES,
OTTAWA, CANADA.]

[*Received, August 24th,* 1956.]