THE PREPARATION OF *o*- AND *p*-ACETAMINOBENZALDEHYDES[1]

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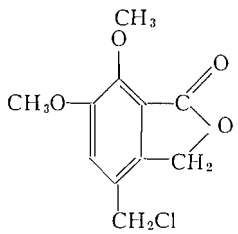
ABSTRACT

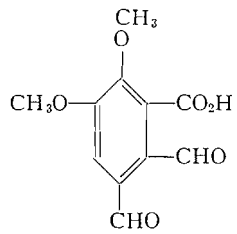
Treatment of N,N-diacetyl-*o*-toluidine with N-bromosuccinimide followed by hydrolysis of the intermediate dibromo compound gave *o*-acetaminobenzaldehyde. The reaction was applied successfully to N,N-diacetyl-*p*-toluidine, N,N-diacetyl-4-chloro-*o*-toluidine, 2,4-bis(diacetamino)toluene, and 4-acetoxy-N,N-diacetyl-*o*-toluidine.

Both *o*- and *p*-acetaminobenzaldehyde were required for synthetic work in this laboratory. These compounds have been prepared in the usual way by the acetylation (6, 7) of *o*- and *p*-aminobenzaldehyde. However, the methods described in the literature for the preparation of *o*-aminobenzaldehyde by the reduction of *o*-nitrobenzaldehyde with ferrous sulphate and ammonia (15) and for *p*-aminobenzaldehyde by the action of sodium polysulphide upon *p*-nitrotoluene (3) are tedious, and the products must be used immediately in order to avoid self-condensation.

A direct preparation of *o*- and *p*-acetaminobenzaldehyde was suggested by the hydrolysis of N,N-diacetyl-*p*-toluidine (16) using aqueous sodium carbonate which gave a quantitative yield of *p*-acetotoluidide, and also by the work of Brown and Newbold (2) who used N-bromosuccinimide to oxidize 4-chloromethylmeconin(I) to 3-formylopianic acid (II).



I



II

We found that treatment of N,N-diacetyl-*p*-toluidine with two moles of N-bromosuccinimide in carbon tetrachloride, followed by aqueous sodium carbonate hydrolysis without isolation of the intermediate bromo compound, gave *p*-acetaminobenzaldehyde in 70% yield. Similarly, N,N-diacetyl-*o*-toluidine (16) gave *o*-acetaminobenzaldehyde in 66% yield.

The reaction was investigated further with respect to certain 4-substituted N,N-diacetyl-*o*-toluidines prepared by prolonged refluxing of the toluidine or its acetyl derivative in acetic anhydride. N,N-Diacetyl-4-chloro-*o*-toluidine, 2,4-bis(diacetamino)toluene, and 4-acetoxy-N,N-diacetyl-*o*-toluidine when

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treated with N-bromosuccinimide as above gave 2-acetamino-4-chlorobenzaldehyde (69%), 2,4-bis(acetamino)benzaldehyde (79%), and 2-acetamino-4-hydroxybenzaldehyde (70%) respectively.

The reaction was also applied to N,N-diacetyl-4-nitro-*o*-toluidine but the acetaminobenzaldehyde could not be isolated from the reaction mixture.

EXPERIMENTAL

Brominations using N-bromosuccinimide were carried out with irradiation from a Westinghouse Sunlamp (type R.S.-275 Watt) placed close to the flask.

p-Acetotoluidide

N,N-Diacetyl-*p*-toluidine (5 gm.) was treated with anhydrous sodium carbonate (10 gm.) and water (100 ml.) on the steam bath for one hour. Partial solution took place, and the solid which separated on cooling was crystallized from benzene to give *p*-acetotoluidide as blades, m.p. and mixed m.p. 149–150°.

p-Acetaminobenzaldehyde

A solution of N,N-diacetyl-*p*-toluidine (5 gm.) in carbon tetrachloride (100 ml.) containing 10.3 gm. of N-bromosuccinimide was heated under reflux on the steam bath for one hour. The filtered solution was evaporated under reduced pressure, and the residual red oil was heated with anhydrous sodium carbonate (10 gm.) in water (100 ml.) for one hour on the steam bath. The solution was decanted from a small amount of tar, extracted with ether (3×100 ml.), and the combined extracts were dried with sodium sulphate. Removal of solvent under reduced pressure gave a yellow solid which was crystallized from benzene – light petroleum (b.p. 30–60°) to give *p*-acetaminobenzaldehyde as needles (3 gm., 70%), m.p. 152–153° (lit.(7) 154.5–155°). Oxime, m.p. 206–207° (lit.(7) 205–206°). Calc. for $C_9H_9O_2N$: C, 66.2; H, 5.6. Found: C, 66.4; 5.5%.

o-Acetaminobenzaldehyde

N,N-Diacetyl-*o*-toluidine (5 gm.) was brominated as above, with the reflux time extended to eight hours. After hydrolysis of the product, the dried (Na_2SO_4) ethereal extract was evaporated to a dark red oil which was extracted thoroughly with boiling light petroleum (b.p. 30–60°). The extract was reduced to a small volume and placed in the refrigerator for one hour when *o*-acetaminobenzaldehyde separated as needles (2.8 gm., 66%), m.p. 68–70°. A specimen recrystallized from light petroleum (b.p. 30–60°) melted at 70–71° (lit. (6) 70–71°). Found: C, 66.6; H, 5.6%. Oxime, m.p. 193–194° (lit.(1) 194°).

N,N-Diacetyl-4-chloro-o-toluidine

4-Chloro-*o*-toluidine was prepared in good yield by the method of Hodgson and Moore (8). Twenty grams of 4-chloro-*o*-toluidine in acetic anhydride (50 ml.) was heated under reflux for 17 hr. The cooled solution was diluted with water (200 ml.) and the brown oil which separated was extracted with ether (3×50 ml.). The combined ethereal extracts were washed with water (2×50 ml.), 10% sodium bicarbonate solution (3×50 ml.), and water (50 ml.) and then dried (Na_2SO_4). The red oil obtained on removal of the solvent under reduced pressure was distilled to give N,N-diacetyl-4-chloro-*o*-toluidine as a

colorless oil which rapidly crystallized as needles (24 gm.), m.p. 40–42°, b.p. 154° at 8.5 mm. Calc. for $C_{11}H_{12}O_2NCl$: C, 58.5; H, 5.4. Found: C, 58.6; H, 5.6%.

2-Acetamino-4-chlorobenzaldehyde

N,N-Diacetyl-4-chloro-*o*-toluidine (5 gm.), N-bromosuccinimide (9 gm.), and carbon tetrachloride (100 ml.) were heated under reflux on the steam bath for three hours. The filtered solution when evaporated gave a yellow solid which was heated under reflux for 30 min. with a solution of anhydrous sodium carbonate (10 gm.) in water (50 ml.). The cooled reaction mixture was extracted with chloroform (3×50 ml.) and the combined chloroform extracts were dried (Na_2SO_4). Evaporation of solvent under reduced pressure, followed by crystallization of the yellow solid from aqueous ethanol, gave 2-acetamino-4-chlorobenzaldehyde as yellow blades (3 gm., 69%), m.p. 124–125°. Calc. for $C_9H_8O_2NCl$: C, 54.7; H, 4.1. Found: C, 54.7; H, 4.1%. The oxime crystallized from aqueous ethanol as needles, m.p. 215–216°. Calc. for $C_9H_9O_2N_2Cl$: C, 50.9; H, 4.3. Found: C, 50.8; H, 4.4%.

2-Acetamino-4-chlorobenzaldehyde was hydrolyzed to 2-amino-4-chlorobenzaldehyde by heating the former compound (1 gm.) with sodium hydroxide solution (40 ml., 2 *N*) and methanol (20 ml.) on the steam bath for 15 min. with occasional shaking. The solution was decanted from a small amount of tar, cooled, and extracted with ether (3×30 ml.). The combined ethereal extracts were washed with water (30 ml.), dried (Na_2SO_4), and evaporated to a yellow oil which soon solidified. Crystallization from aqueous ethanol gave 2-amino-4-chlorobenzaldehyde as needles (550 mgm.), m.p. 86–87°. Calc. for C_7H_6ONCl: C, 54.0; H, 3.9. Found: C, 53.8; H, 3.8%. Sachs and Sichel (14) give a melting point of 86° for the same compound obtained by reduction of 4-chloro-2-nitrobenzaldehyde using titanous chloride.

2,4-Bis(diacetamino)toluene

2,4-Bis(acetamino)toluene was prepared from 2,4-diaminotoluene (11) by the method of Lumière and Barbier (10). The compound melted at 219–223° (lit.(9) 223°). 2,4-Bis(acetamino)toluene (40 gm.) and acetic anhydride (200 ml.) were heated under reflux for 17 hr. The acetic anhydride was removed under reduced pressure and water (50 ml.) was added to the residue which was then extracted with chloroform (3×50 ml.). The combined chloroform extracts were washed with water (50 ml.), 10% sodium bicarbonate solution (50 ml.), and water (50 ml.) and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a dark brown oil which solidified on standing. The solid, which was filtered with the aid of some ether and then washed with a small amount of ether, crystallized from benzene – light petroleum (b.p. 30–60°) to give 2,4-bis(diacetamino)toluene as prisms (20 gm.), m.p. 109–110°. Calc. for $C_{15}H_{18}O_4N_2$: C, 62.0; H, 6.25. Found: C, 62.2; H, 6.4%.

2,4-Bis(acetamino)benzaldehyde

2,4-Bis(diacetamino)toluene (5 gm.), N-bromosuccinimide (6.75 gm.), and carbon tetrachloride (100 ml.) were heated under reflux on the steam bath for

three hours. Evaporation of the solvent after filtration gave a yellow oil which was heated on the steam bath for 15 min. with a solution of anhydrous sodium carbonate (10 gm.) in water (50 ml.). The solid which separated on cooling was collected and crystallized from ethanol to give 2,4-bis(acetamino)benzaldehyde as plates (3 gm., 79%), m.p. 233–235°. Calc. for $C_{11}H_{12}O_3N_2$: C, 60.0; H, 5.5. Found: C, 59.8; H, 5.5%. Sachs and Kempf (13) give m.p. 235.5° for the compound obtained by treating the product of the ammonium sulphide reduction of 2,4-dinitrobenzaldehyde with acetic anhydride. The phenylhydrazone melted at 252–254° (lit.(13) 246–252°).

2-Amino-p-cresol (Me = 1)

2-Nitro-*p*-toluidine, prepared in excellent yield by the method of Cohen and Dakin (4) for 4-nitro-*o*-toluidine, was converted into 2-nitro-*p*-cresol (17). Sodium dithionite (50 gm.) was added in small portions, with stirring, to 2-nitro-*p*-cresol (5 gm.) in a solution of potassium hydroxide (12 gm.) in water (100 ml.). After 15 min. at room temperature, the solution was acidified to Congo red with hydrochloric acid (d., 1.16) and heated on the steam bath to remove sulphur dioxide. The filtered solution was neutralized with 10% sodium bicarbonate, extracted with ether (4×100 ml.), and the combined ethereal extracts were washed with water (100 ml.) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure yielded 2-amino-*p*-cresol as a brown solid (3 gm.), m.p. 147–150°. Copisarow (5) reports a melting point of 157–159° for the compound obtained by sodium sulphide reduction of 2-nitro-*p*-cresol.

4-Acetoxy-N,N-diacetyl-o-toluidine

2-Amino-*p*-cresol (5 gm.) and acetic anhydride (20 ml.) were heated under reflux for 17 hr. The cooled solution was diluted with water (100 ml.) and the product was isolated with ether as before. Removal of solvent gave a red oil which was extracted with boiling light petroleum (b.p. 30–60°). The solvent was reduced in volume and the remaining solution cooled in a refrigerator for one hour. The 4-acetoxy-N,N-diacetyl-*o*-toluidine separated as needles (4 gm.), m.p. 72–73°. Calc. for $C_{13}H_{15}O_4N$: C, 62.6; H, 6.1. Found: C, 62.4; H, 6.2%.

2-Acetamino-4-hydroxybenzaldehyde

4-Acetoxy-N,N-diacetyl-*o*-toluidine (2 gm.) and N-bromosuccinimide (3.15 gm.) in carbon tetrachloride (30 ml.) were heated under reflux for two and one-half hours on the steam bath. The yellow oil, obtained by evaporation of the filtered solvent, was heated on the steam bath for 30 min. with a solution of anhydrous sodium carbonate (4 gm.) in water (25 ml.). The solution was acidified with acetic acid and extracted with ether (5×50 ml.). The dried solution (Na_2SO_4), freed of solvent under reduced pressure, gave 2-acetamino-4-hydroxybenzaldehyde as a light brown solid. Crystallization from aqueous ethanol gave needles (1 gm., 70%) melting at 238–239°. Calc. for $C_9H_9O_3N$: C, 60.3; H, 5.1. Found: C, 60.2; H, 5.4%. The oxime crystallized from water as needles, m.p. 215° (decomp.). Calc. for $C_9H_{10}O_3N_2$: C, 55.7; H, 5.2. Found: C, 55.5; H, 5.5%.

N,N-Diacetyl-4-nitro-o-toluidine

4-Nitro-*o*-toluidine (20 gm.) (prepared according to Cohen and Dakin (4)) in acetic anhydride (50 ml.) was heated under reflux for 17 hr. The cooled solution was diluted with water (200 ml.) and the product, a dark red oil, was isolated with chloroform. The oil was dissolved in a few milliliters of benzene and the 4-nitro-*o*-acetotoluidide (5 gm.) which separated was filtered off, m.p. 151–153° (lit.(12) 150–151°). Evaporation of the filtrate gave a dark oil which soon solidified. Crystallization from benzene – light petroleum (b.p. 30–60°) gave N,N-diacetyl-4-nitro-*o*-toluidine as prisms (16 gm.), m.p. 81–83°. Calc. for $C_{11}H_{12}O_4N_2$: C, 55.9; H, 5.1. Found: C, 56.1; H, 5.2%.

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