69% yield and decomposition of the metal alcoholate by alkaline hydrolysis according to the procedure of Amundsen and Nelson[10] gave a 49% yield. **The 2,4-dinitrophenylhydrazone** was obtained as red needles, m.p. 152–152.5°.

Anal. Calcd. for $C_{13}H_{14}O_7N_4$: C, 53.79; H, 4.86. Found: C, 53.89; H, 4.94.

The semicarbazone melted at 177.5–179° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_8H_{13}ON_3$: C, 57.46; H, 7.83. Found: C, 57.29; H, 7.65.

A solution of 1.1 g. (0.01 mole) of IV in 15 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure with 0.2 g. of 30% palladium-on-charcoal. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and the alcoholic filtrate was used directly for the preparation of the 2,4-dinitrophenylhydrazone. This derivative melted at 161.5–163° after recrystallization from alcohol. The melting point was not depressed on admixture with an authentic sample of 3-methylcyclohexanone-2,4-dinitrophenylhydrazone (m.p. 161.5–163°).

5-Methyl-2-cyclohexenone was also obtained in low yield from 2,4-lutidine by the method of Birch[6]; $n^{25}D$ 1.4743. The 2,4-dinitrophenylhydrazone melted at 149.5–150.5°. The melting point was not depressed on admixture with an authentic sample of 5-methyl-2-cyclohexenone-2,4-dinitrophenylhydrazone.

The material reported by Godchot and Bedos[5] was prepared according to their directions; $n^{25}D$ 1.4456 (reported[5] $n^{26}D$ 1.44635). The semicarbazone melted at 178–179°. When mixed with an authentic sample of the semicarbazone of IV (m.p. 177.5–179°), the melting point was depressed considerably.

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Some Derivatives of 2,5-Dimethoxyacetophenone

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A number of compounds derived from 2,5-dimethoxyacetophenone have been prepared as intermediates in the synthesis of chloramphenicol analogs. 2,5-Dimethoxyacetophenone was brominated to give ω-bromo-3,5-dimethoxyacetophenone, which, on nitration, yielded a mixture of two mononitrated isomers. The lower melting isomer gave an indigo derivative when treated with ammonium sulfide,[2] hence is ω-bromo-3,6-dimethoxy-2-nitroacetophenone. The other isomer gave no indigo derivative, did not yield 2,5-dimethoxy-3-nitrobenzoic acid on oxidation with hypohalite, and hence is ω-bromo-2,5-dimethoxy-4-nitroacetophenone. ω-Bromo-3,6-dimethoxy-2-nitroacetophenone was converted by the method of Delepine to the ω-amino hydrochloride, which was then acetylated and reduced with aluminum isopropoxide to yield 1-(3,6-dimethoxy-2-nitrophenyl)-2-acetamidoethanol. This compound was hydrolyzed to the free amine, which on dichloroacetylation gave 1-(3,6-dimethoxy-2-nitrophenyl)-2-dichloroacetamidoethanol.

The procedures used in converting ω-bromo-3,6-dimethoxy-2-nitroacetophenone to 1-(3,6-dimethoxy-2-nitrophenyl)-2-dichloroacetamidoethanol were patterned after those of Long and co-workers in preparing various chloramphenicol derivatives.[3,4]

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Experimental

ω-Bromo-2,5-dimethoxyacetophenone.—Forty-one ml. of bromine was added dropwise over 45 minutes to a stirred suspension of 2.5 g. of anhydrous aluminum chloride, 147 g. of 2,5-dimethoxyacetophenone[5] and 200 ml. of anhydrous diethyl ether at 0°. The ether and hydrogen bromide were then removed at room temperature under reduced pressure. The crude product was shaken with a 1:1 water–petroleum ether mixture and recrystallized from 1.2 liters of absolute ethanol to give 143 g. (67%) of slightly yellowish needles, m.p. 84–85°. A second recrystallization from ethanol yielded long white needles, m.p. 86° (reported m.p. 91°).[6]

A small portion was converted with hypohalite to 2,5-dimethoxybenzoic acid, m.p. 76–77° (reported m.p. 76°),[7] which, on treatment with thionyl chloride and then ammonium hydroxide, gave 2,5-dimethoxybenzamide, m.p. 138–139° (reported m.p. 140°).[8]

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.74. Found: N, 7.64.

Nitration of ω-Bromo-2,5-dimethoxyacetophenone.—To 135 ml. of stirred nitric acid (sp. gr. 1.42) at 0° was slowly added 25.9 g. of ω-bromo-2,5-dimethoxyacetophenone. After six hours of stirring at 0° the mixture was poured into 1.3 liters of ice-water and the crude product, which weighed 26.1 g., recovered by filtration. This was dissolved in 300 ml. of hot absolute ethanol and 2.7 liters of hot petroleum ether (b.p. 90–100°) was added. This solution on cooling yielded 19.2 g. (63%) of an ω-bromodimethoxynitroacetophenone as long yellow needles, m.p. 103–104°. Recrystallization from ethanol or ethanol–petroleum ether did not raise the melting point.

Anal. Calcd. for $C_{10}H_{10}O_5NBr$: C, 39.5; H, 3.32; N, 4.60; $-OCH_3$, 20.4. Found: C, 39.3; H, 3.52; N, 4.62; $-OCH_3$, 20.1.

The filtrate from the above was concentrated to one-half its volume and on cooling yielded 2.5 g. of ragged crystals, m.p. 107–111°. Recrystallization from absolute ethanol gave 2.0 g. (7%) of a second ω-bromodimethoxynitroacetophenone as fine yellow needles, m.p. 118.5–119.2° (mixed m.p. with the lower melting isomer, 85–90°). Recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{10}H_{10}O_5NBr$: C, 39.5; H, 3.32; N, 4.60; $-OCH_3$, 20.4. Found: C, 39.8; H, 3.54; N, 4.58; $-OCH_3$, 20.3.

A solution of one gram of the lower melting isomer in 25 ml. of ethanol was refluxed for 30 minutes with 7 ml. of yellow ammonium sulfide solution.[2] The crude solid product was filtered, washed successively with hot ethanol and carbon disulfide, and sublimed *in vacuo*. The indigo-colored crystalline product thus obtained exhibited typical indigoid properties: color and solubility in aniline and nitrobenzene; reduction with sodium hydrosulfite to a colorless form, reoxidizable by air. It is undoubtedly 4,4′,7,7′-tetramethoxyindigotin.

Anal. Calcd. for $C_{20}H_{18}O_6N_2$: N, 7.32. Found: N, 6.91.

Identical treatment of the higher melting isomer yielded no indigo-like product.

The lower melting isomer is hence ω-bromo-3,6-dimethoxy-2-nitroacetophenone. On treatment with hypohalite it gave 3,6-dimethoxy-2-nitrobenzoic acid, m.p. 192–193° (reported m.p., 192°).[9]

Anal. Calcd. for $C_9H_9O_6N$: N, 6.17. Found: N, 6.27.

The higher melting isomer on treatment with hypohalite yielded a dimethoxynitrobenzoic acid, m.p. 192–193.5° (mixed m.p. with 3,6-dimethoxy-2-nitrobenzoic acid, 163–173°).

Anal. Calcd. for $C_9H_9O_6N$: N, 6.17. Found: N, 6.28.

Since 2,5-dimethoxy-3-nitrobenzoic acid melts at 181–183°,[9,10] this compound must be the hitherto unreported 2,5-dimethoxy-4-nitrobenzoic acid, and the higher melting isomer from which it is derived is hence ω-bromo-2,5-dimethoxy-4-nitroacetophenone.

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ω-Amino-3,6-dimethoxy-2-nitroacetophenone Hydrochloride.—To a stirred suspension of 21 g. of hexamethylene tetramine in 150 ml. of chlorobenzene at room temperature was added in one portion 45.6 g. of ω-bromo-3,6-dimethoxy-2-nitroacetophenone. The mixture was stirred at 60–70° for 4.5 hours, then chilled in an ice-bath and filtered. The dried, yellow powder, which weighed 62 g., was stirred at room temperature for 18 hours with 140 ml. of 95% ethanol and 70 ml. of concentrated hydrochloric acid. The yellow solid was recovered by filtration and stirred for 20 minutes with 70 ml. of water. The suspension was chilled and filtered. The yellow product weighed 31.5 g. (71%). A small sample was recrystallized with high recovery from 10% hydrochloric acid as long yellow needles, m.p. 222–223° (dec.).

Anal. Calcd. for $C_{10}H_{13}O_6N_2Cl$: C, 43.4; H, 4.71; N, 10.12. Found: C, 43.1; H, 4.73; N, 10.18.

ω-Acetamido-3,6-dimethoxy-2-nitroacetophenone.—Twenty-seven and one-half grams of ω-amino-3,6-dimethoxy-2-nitroacetophenone hydrochloride was acetylated by the procedure of Long and Troutman[3] with 19.2 ml. of acetic anhydride and 27.6 g. of sodium acetate trihydrate, followed by 60 ml. of concentrated hydrochloric acid. The dried product weighed 25 g. (87%). A small portion was recrystallized with high recovery from ethyl acetate. The short, thick yellow needles melted with reddening and partial sublimation at 170–173°.

Anal. Calcd. for $C_{12}H_{14}O_6N_2$: C, 51.1; H, 5.00; N, 9.92; $-OCH_3$, 22.0. Found: C, 51.4; H, 5.24; N, 9.93; $-OCH_3$, 21.9.

1-(3,6-Dimethoxy-2-nitrophenyl)-2-acetamidoethanol.—Twenty-four grams of ω-acetamido-3,6-dimethoxy-2-nitroacetophenone was reduced with a solution of 24.2 g. of aluminum isopropoxide in 205 ml. of isopropyl alcohol by the procedure of Long, *et al.*[3,4] The reaction mixture was hydrolyzed with 25 ml. of water and the product extracted out with hot 80% isopropyl alcohol. Light tan crystals weighing 17.5 g. (73%), m.p. 168° (dec.), were obtained by chilling, then concentrating the extracts. A small sample was recrystallized from hot water as thick, tan crystals, m.p. 169° (dec.).

Anal. Calcd. for $C_{12}H_{16}O_6N_2$: C, 50.7; H, 5.68; N, 9.85; $-OCH_3$, 21.9. Found: C, 50.4; H, 5.88; N, 9.83; $-OCH_3$, 21.7.

1-(3,6-Dimethoxy-2-nitrophenyl)-2-aminoethanol.—A mixture of 17.5 g. of 1-(3,6-dimethoxy-2-nitrophenyl)-2-acetamidoethanol and 200 ml. of 5% hydrochloric acid was stirred at 100° for six hours. The resulting solution was filtered and made basic with 25% sodium hydroxide while still hot. Twelve and one-half grams (84%) of light tan crystals was obtained on cooling. A small sample was recrystallized twice from hot water (Norite). The light tan, shining platelets melted at 171° (dec.) using the technique of Cortese and Bauman.[11]

Anal. Calcd. for $C_{10}H_{14}O_5N_2$: C, 49.6; H, 5.83; N, 11.56. Found: C, 49.4; H, 6.00; N, 11.41.

1-(3,6-Dimethoxy-2-nitrophenyl)-2-dichloroacetamidoethanol.—A mixture of 12.5 g. of 1-(3,6-dimethoxy-2-nitrophenyl)-2-aminoethanol and 75 ml. of methyl dichloroacetate was warmed at 75° for two hours with occasional swirling. The dark solution was filtered and the filtrate evaporated to dryness on a steam-bath under reduced pressure (30 mm.). The residue was washed with two small portions of chloroform. The yellow powder which remained weighed 10.5 g. and was recrystallized from 2.1 liters of 33% ethanol. The long yellow needles weighed 8.1 g. (46%), m.p. 163–165°. A second recrystallization raised the melting point to 164–166°.

Anal. Calcd. for $C_{12}H_{14}O_6N_2Cl_2$: C, 40.8; H, 4.00; N, 7.93; Cl, 20.1. Found: C, 41.1; H, 4.14; N, 7.85; Cl, 19.6.

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Reduction of Organic Azides to Primary Amines with Lithium Aluminum Hydride

BY J. H. BOYER

The reduction of aliphatic and aromatic azides to primary amines with lithium aluminum hydride has been realized (1). The reaction provides a new procedure for the preparation of α-aminocarbinols from α-azidoketones (2). Stoichiometrically the reactions may proceed according to the following equations, although in the preliminary experiments shown here a two- to five-fold excess of lithium aluminum hydride was used to assure a positive reaction.

$$4R{-}N_3 + LiAlH_4 \longrightarrow (R{-}NH{-})_4AlLi + 4N_2 \quad (1)$$

$$2R{-}\underset{\underset{O}{\|}}{C}{-}CH_2N_3 + LiAlH_4 \longrightarrow (R{-}\underset{\underset{O{-}}{|}}{CH}CH_2NH{-})_2AlLi + 2N_2 \quad (2)$$

Experimental[1]

Reduction of the azides was carried out under the general conditions for lithium aluminum hydride reduction described by Nystrom and Brown.[2] In each case a suspension of the hydride in dry ether was treated with an ethereal solution of the azide at such a rate that reflux was maintained. Following addition of the azide the mixture was kept at reflux temperature for two hours. Moist ether was then added to destroy the excess lithium aluminum hydride, followed by distilled water to break up the complex. The inorganic salts were removed by filtration and the amines were isolated from the ethereal layer of the filtrate. Modifications found useful for the isolation of the aminoalcohols from the filtrates obtained at this stage in the reduction of the azidoketones are described below.

α-Naphthylamine.—From 1.7 g. (0.01 mole) of α-naphthyl azide[3] in 100 ml. of anhydrous ether and 0.60 g. (0.015 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether there was obtained 1.13 g. (79% based on the azide) of α-naphthylamine, m.p. 50°, alone and when mixed with an authentic sample of α-naphthylamine. The picrate derivative was prepared in ether and recrystallized from aqueous ethanol, m.p. 183–185°, alone and when mixed with an authentic sample.

β-Phenylethylamine.—From 3.0 g. (0.02 mole) of β-phenylethyl azide[4] in 100 ml. of anhydrous ether and 1.0 g. (0.025 mole) of lithium aluminum hydride in 250 ml. of anhydrous ether there was obtained 2.15 g. (89% based on the azide) of β-phenylethylamine (absorbs carbon dioxide), b.p. 190–192°,[5] carbonate, m.p. 105–106°,[6] picrate m.p. 169–170°,[5] and hydrochloride, m.p. 217°.[5]

α-Phenyl-β-aminoethanol.—From 4.6 g. (0.029 mole of phenacyl azide,[7] m.p. 17°, in 250 ml. of anhydrous ether and 1.5 g. (0.04 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether was obtained 1.94 g. of the light yellow α-phenyl-β-aminoethanol, b.p. 135–137° (1 mm.), m.p. 43–45°[8] (49.5% based on the azide). Appreciable solubility in both water and ether accounted for the isolation of this product in roughly equal quantities from the aqueous and ethereal layers of the filtrate obtained from the filtration of the inorganic salts. A picrate derivative was prepared in benzene and recrystallized from a mixture of chloroform and alcohol, m.p. 154–155°.[9]

(1) Microanalyses by the Clark Microanalytical Laboratory, Urbana, Illinois. Melting and boiling points are uncorrected.

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