added. The temperature was slowly raised and kept at 65° until no more nitrogen was evolved. Then the reaction mixture was steam distilled. The solid distillate collected was recrystallized from 70% alcohol giving colorless needles, m.p. 58–59°.

Anal. Calcd. for $C_8H_7O_2I$: C, 36.67; H, 2.69; I, 48.4. Found: C, 36.22; H, 2.91; I, 48.2.

2′-Hydroxy-3′-iodochalcone, 8-iodoflavone, -flavanone, -flavonol and the 4′-methoxy compounds were prepared as described earlier,[7] and the melting points and analytical data are shown in Table II.

(C) *Synthesis of 8-bromoflavone by Ruhemann method. Ethyl β-(o-bromophenoxy)cinnamate.* To a solution of metallic sodium (1.2 g.) in absolute ethanol (30 ml.), *o*-bromophenol (8.8 g.) was added. The solution was evaporated, then heated at 140°. To this dry solid, *o*-bromophenol (11 g.) and ethyl phenyl propiolate (8.7 g.) were promptly added, and the mixture was kept at 165–175° for 3 hr. The reaction mixture was cooled and decomposed with 2*N* sulfuric acid. The mixture was extracted with ether, and the ether solution washed successively with 2*N* aqueous potassium hydroxide and water. The ether solution was dried over calcium chloride, evaporated, and the remaining yellow oil was distilled to yield a light yellowish liquid, b.p. 226–228° at 17 mm., which solidified soon, and recrystallized from alcohol yielding colorless leaflets (7.2 g.), m.p. 76–77°.

Anal. Calcd. for $C_{17}H_{15}O_3Br$: C, 58.80 H, 4.36; Br, 23.02. Found: C, 58.6; H, 4.5; Br, 23.0.

β-(o-Bromophenoxy)cinnamic acid. The above ester (7.2 g.) was refluxed with 2% alcoholic potassium hydroxide (55 ml.) for 1 hr. The solution was evaporated, then water was added and the solution neutralized with 2*N* hydrochloric acid. The precipitate was collected and recrystallized from 50% alcohol, yielding colorless prisms (6 g.), m.p. 148° (shrinking at 132°).

Anal. Calcd. for $C_{15}H_{11}O_3Br$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.2; H, 3.6; Br, 25.1.

8-Bromoflavone. To a suspension of the above acid (5 g.) in absolute benzene (50 ml.), phosphorus pentachloride (3.5 g.) was added. After standing at room temperature for awhile, the mixture became clear, then anhydrous aluminum chloride (10 g.) was added. The mixture was poured over ice and extracted with ether. The ether-benzene layer was separated and washed with dilute potassium hydroxide. The ether-benzene was removed, and the remaining yellowish material was recrystallized from ethanol to produce colorless needles (4 g.), m.p. 178.5–179°.

Anal. Calcd. for $C_{15}H_9O_2Br$: C, 59.84; H, 2.99; Br, 26.53. Found: C, 59.9; H, 3.1; Br, 26.3.

(D) *Synthesis of 8-chloroflavone.* Reaction similar to the one above gave *ethyl β-(o-chlorophenoxy)cinnamate*, b.p. 218–220° at 17 mm.; *β-(o-chloro-phenoxy)cinnamic acid*, colorless cubes from 50% alcohol and *8-chloroflavone*, colorless needles from ethanol, m.p. 167–168° (recorded,[4] 169–170°).

Acknowledgment. The authors wish to express their sincere thanks to Professor Simon H. Wender of the University of Oklahoma for kindly reading this manuscript, to President S. L. Chien of this University, and Professor Y. Sebe of Japan for encouragement and microanalyses, to Mr. T. Ueng for technical assistance. Financial support by the Asia Foundation and the National Council on Science Development is also gratefully acknowledged.

Department of Chemistry
National Taiwan University
Taipei, Taiwan (Formosa)

Reduction of Substituted Nitrobenzenes. I. Reduction of Monohalogenated Nitrobenzenes with Reducing Sugars in Alkaline Medium

Brian T. Newbold and Raymond P. Le Blanc[1]

Received June 9, 1961

A survey of the chemical literature shows that nitrobenzenes have been reduced to a variety of products by means of different reducing agents. One of the reducing agents used on nitrobenzene itself was glucose in alkaline medium.[2a] In later work, Opolonick[2b] studied the reduction of nitrobenzene with the same reducing agent and found that the main product was azoxybenzene with some azobenzene and aniline being formed as well. When a great excess of glucose was used the principal product was azobenzene. Bigelow and Palmer[3] have also reduced nitrobenzene with glucose in

TABLE I

Reductions of Nitrobenzene

Sugar	Time, Min.	Temp.	Products, % Recovered Nitro.	Azoxy.	Amine
[a] Galactose	60	88	8.2	66.1	Nil
	120	98			
[a] Fructose	60	60–90	12.2	67.3	Nil
	120	95			
[b] Lactose	45	83	10.0	19.5	Nil
[b] Maltose	45	85–90	5.0	19.5	Nil

[a] Nitrobenzene, 0.166 mole; sugar, 0.117 mole; sodium hydroxide, 0.738 mole; and water, 100 ml. [b] Half quantities of the materials shown in footnote *a* were used, except for water, 100 ml.

TABLE II

Reductions of Chloronitrobenzenes[a]

Compound	Sugar	Products, % Recovered Nitro.	Azoxy.	Amine
3-Chloronitro-benzene	Glucose	0.04	87.0	Nil
	Galactose	0.10	91.6	Nil
	Fructose	0.74	86.3	Nil
	Lactose	Nil	81.4	Nil
	Maltose	Nil	69.9	Nil
4-Chloronitro-benzene	Glucose	15.4	67.3	0.5
	Galactose	13.1	70.8	0.5
	Fructose	14.2	73.5	0.5
	Lactose	0.01	55.3	13.9
	Maltose	1.80	65.5	10.2

[a] Substituted nitrobenzene, 0.17 mole; sugar, 0.13 mole; sodium hydroxide, 0.75 mole; water, 285 ml.; reaction time, 40–45 min.; and reaction temperatures, 70–85°C.

(1) Graduate research assistant.

(2)(a) E. Noetling, *Ber.*, **37**, 1019 (1904). (b) N. Opolonick, *Ind. Eng. Chem.*, **27**, 1045 (1935).

(3) H. E. Bigelow and A. Palmer, *Org. Syntheses*, Coll. Vol. II, 59 (1943).

TABLE III

REDUCTIONS OF BROMO- AND IODONITROBENZENES

Compound	Sugar	Products, % Recovered Nitro.	Azoxy.	Amine.
[a] 2-Bromonitrobenzene	Glucose	24.0	40.9	Nil
[a]	Galactose	9.2	50.0	Nil[g]
[a]	Fructose	32.0	34.1	Nil[g]
[a]	Mannose	2.2	32.1	Nil[g]
[a]	Lactose	4.0	47.7	Nil
[a]	Maltose	6.0	34.1	Nil
[a] 3-Bromonitrobenzene	Glucose	10.0	73.7	Nil
[a]	Galactose	6.0	68.2	Nil[g]
[a]	Fructose	8.4	77.3	Nil[g]
[a]	Mannose	4.0	75.0	Nil[g]
[a]	Lactose	16.0	34.1	25.6
[a]	Maltose	2.4	56.8	20.9
[b] 4-Bromonitrobenzene	Glucose	27.9	46.2	1.0
[a]	Galactose	16.0	56.8	Nil[g]
[c]	Fructose	11.4	34.4	1.2
[a]	Mannose	22.4	38.6	Nil[g]
[b]	Lactose	18.0	24.4	0.5
[b]	Maltose	20.3	28.4	6.7
[d] 2-Iodonitrobenzene	Glucose	1.2	5.5	Nil[g]
[d]	Galactose	Nil	Nil	Nil[g]
[e]	Mannose	12.7	Nil	Nil[g]
[d]	Lactose	Nil	Nil	Nil[g]
[d]	Maltose	3.2	0.8	Nil[g]
[d] 3-Iodonitrobenzene	Glucose	17.8	28.8	Nil[g]
[d]	Galactose	18.0	53.1	Nil[g]
[d]	Fructose	48.0	28.8	Nil[g]
[f]	Mannose	Nil	24.3	Nil[g]
[d]	Lactose	Nil	53.1	Nil[g]
[d]	Maltose	9.8	42.0	Nil[g]
[d] 4-Iodonitrobenzene	Glucose	8.0	73.0	Nil
[d]	Galactose	35.0	64.2	Nil
[d]	Fructose	72.0	4.4	Nil[g]
[d]	Mannose	70.0	9.7	Nil[g]
[d]	Lactose	28.0	26.5	Nil
[d]	Maltose	24.0	26.5	Nil

[a] Substituted nitrobenzene, 0.025 mole; sugar, 0.020 mole; sodium hydroxide, 0.111 mole; water, 50 ml.; reaction time, 45–50 min.; and reaction temperatures, 75–88°. [b] 3.4 × the quantities of materials used in footnote *a*, except for water, 143 ml., and time, 40 min. [c] Twice the quantities of materials used in footnote *a*, except for water, 85 ml. [d] 0.8 of the quantities of materials used in footnote *a*. [e] One quarter of the materials used in footnote *a*, except for water, 20 ml. [f] One half of the quantities of the materials used in footnote *d*. [g] In these reductions the sugar was added in one portion only.

alkaline medium, and Galbraith *et al.*[4] more recently used this means to reduce a variety of aromatic compounds.

Halogenated nitrobenzenes have been reduced by many different reducing agents, for instance chloronitrobenzenes have been reduced with: stannous oxide and sodium hydroxide,[5] sodium alcoholates,[6,7] alcoholic potassium hydroxide,[8–12] magnesium and methanol,[13,14] magnesium and ammonium chloride,[15] and sodium arsenite in sodium hydroxide.[16,17] Some reductions have also been carried out using glucose, for example, 2-chloronitrobenzene was reduced to the azoxy compound by Lacy and Brouillard,[18] and other chloronitrobenzenes were reduced with the same reagent.[16,17] Much less work has been done on the reduction of bromo- and iodonitrobenzenes, although several reducing agents have been employed.[7,13,14,19–21]

The object of the present work was to study the reduction to the corresponding azoxybenzenes of a

(4) H. W. Galbraith, E. F. Degering, and E. F. Hitch, *J. Am. Chem. Soc.*, **73**, 1323 (1951).
(5) G. Lock and E. Bayer, *Ber.*, 69B, 2666 (1936).
(6) F. B. Dains and W. O. Kenyon, *J. Am. Chem. Soc.*, **53**, 2357 (1931).
(7) K. Brand, *J. prakt. chem.* (2), **67**, 148 (1903).
(8) C. M. Suter and F. B. Dains, *J. Am. Chem. Soc.*, **50**, 2733 (1928).
(9) A. Laubenheimer, *Ber.*, **8**, 1623 (1875).
(10) C. Willgerodt, *Ber.*, **12**, 767 (1879).
(11) D. H. Richardson, *J. Chem. Soc.*, 522 (1926).
(12) K. Heumann, *Ber.*, **5**, 911 (1872).
(13) L. Zechmeister and P. Rom, *Ann.*, **468**, 117 (1928).
(14) K. F. Keirstead, *Can. J. Chem.*, **31**, 1064 (1953).
(15) L. Zechmeister and P. Rom, *Ber.*, **59**, 867 (1926).
(16) R. Gaudry and K. F. Keirstead, *Can. J. Research*, B27, 890 (1949).
(17) P. E. Gagnon, K. F. Keirstead, and B. T. Newbold, *Can. J. Chem.*, **35**, 1304 (1957).
(18) H. T. Lacy and R. E. Brouillard, U. S. Patent **2,383,134** (1945).
(19) S. Gabriel, *Ber.*, 9, 1405 (1876).
(20) A. H. Cook and D. G. Jones, *J. Chem. Soc.*, 1311 (1939).
(21) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **38**, 2363 (1960).

series of monochloro-, bromo-, and iodonitrobenzenes using both reducing monosaccharides and disaccharides in alkaline medium.

Before carrying out reduction studies on halogenated nitrobenzenes, some preliminary reductions were performed on nitrobenzene with the reducing sugars galactose, fructose, lactose, and maltose, in order to compare the effectiveness of these reducing agents. Azoxybenzene was obtained in fair yield using galactose and fructose and no aniline was isolated. With the disaccharides a lower yield of azoxybenzene was obtained, together with some aniline. The results are given in Table I.

In this study, the monosaccharides were employed as mild reducing agents for the preparation of dihalogenated azoxybenzenes. It was expected that the reducing monosaccharides would be equally effective as reducing agents because of their similar reducing powers. The ketose, fructose, should have similar reducing power to that of the aldoses. The disaccharides, lactose and maltose, having less reducing power than the monosaccharides were expected to be milder reducing agents. The results obtained from the reduction of chloro-, bromo-, and iodonitrobenzenes with various sugars are shown in Tables II and III.

CONCLUSIONS

Comparison of the effectiveness of the reducing sugars with regard to the preparation of dihalogenated azoxybenzenes from monohalogenated nitrobenzenes leads to some interesting conclusions. Preliminary experiments on the reduction of nitrobenzene showed that monosaccharides were stronger reducing agents for the preparation of azoxybenzene than the disaccharides.

For the first time, galactose, fructose, and mannose were used as reducing agents for halogenated nitrobenzenes. The main product of these reductions was the dihalogenated azoxybenzene and in some cases the amine was formed. Monosaccharides were found to be the best reducing agents for the preparation of dichloroazoxybenzenes. 3,3′-dichloroazoxybenzene was obtained in higher yield than 4,4′-dichloroazoxybenzene regardless of the sugar employed. Similar results were obtained with the reductions of the bromonitrobenzenes. Reductions of 4-chloro- and 3-bromonitrobenzene with the disaccharides led to substantial yields of the halogenated anilines.

Reduction of 2-iodonitrobenzene to the azoxybenzene was not easy—only glucose and maltose gave any of this substance. For the preparation of 3,3′-diiodoazoxybenzene, lactose and maltose were good reducing agents; on the other hand, 4,4′-diiodoazoxybenzene was obtained in highest yield when using glucose and galactose.

The 2-halogenated nitrobenzenes were the most difficult to reduce. The nitro group in 2-bromo- and 2-iodonitrobenzene is sterically hindered and these compounds are not very stable in the reducing medium, thus reduction is rendered difficult as shown by the low yields of the azoxybenzenes, the lower recovery of unreacted starting material, and the increased appearance of tars.

Monosaccharides, especially glucose and galactose, are good reducing agents for the preparation of dichloro- and dibromoazoxybenzenes, whereas the milder reducing disaccharides are more suitable for the preparation of diiodoazoxybenzenes.

EXPERIMENTAL[22]

Materials. The chloro-, bromo-, and iodonitrobenzenes used in this work were commercially available reagent grade samples.

Reduction of monohalogenated nitrobenzenes. As a similar procedure was employed for all compounds, only one reduction will be described as an example of the method employed.

Reduction of 4-chloronitrobenzene with galactose. 4-chloronitrobenzene (26.7 g., 0.17 mole) and sodium hydroxide (30.0 g., 0.75 mole) in water (260 ml.) were heated to 60° whereupon galactose (23.0 g., 0.13 mole) as a paste in water (25 ml.) was added in small portions. The mixture was heated at 70–72°, for 40 min. with stirring. Steam distillation produced a distillate, which on being acidified with hydrochloric acid and standing overnight gave recovered 4-chloronitrobenzene, m.p. 84–85°, (lit. m.p. 83.5°),[23] yield 3.5 g. (13.1%). The acid filtrate was made alkaline with sodium hydroxide and allowed to stand overnight. 4-chloroaniline separated out, yield 0.1 g., (0.5%) and was recrystallized from aqueous ethanol, m.p. 70–72°, (lit. m.p. 70–71°).[23] Acetylation gave 4-chloroacetanilide (from aqueous ethanol), m.p. 178–179°, (lit. m.p. 178.4°).[23]

The granular orange-yellow residue left in the reaction flask after steam distillation was 4,4′-dichloroazoxybenzene, m.p. 149–151°, yield, 16.0 g. (70.8%), which recrystallized from ethanol as pale yellow needles, m.p. 154.5–155.5°, alone or with an authentic sample (lit. m.p. 154–155°).[12]

In reductions of bromo- and iodonitrobenzenes, the azoxybenzenes were extracted from the reaction residues with ethanol and the extracts given several charcoal treatments, before evaporation and dilution with water to isolate the products.

Acknowledgment. The authors wish to express their appreciation to the National Research Council of Canada for financial assistance during part of this work.

DEPARTMENT OF CHEMISTRY
ST. JOSEPH'S UNIVERSITY
MONCTON, NEW BRUNSWICK, CANADA

(22) All melting points are uncorrected.

(23) *Handbook of Chemistry & Physics*, 42nd ed., Chemical Rubber Co., Hodgman, Weast, and Selby, Cleveland, Ohio (1960–1961).

Synthesis of Aldosterone-1α,2α-H[3][1]

K. R. LAUMAS AND MARCEL GUT

Received June 12, 1961

The need for radioactive aldosterone of high specific activity for use as an indicator in analysis

(1) This study was supported by U. S. Atomic Energy Commission Contract AT(30-1)-918 and by National Institutes of Health grants A-3419 and A-3179.