tected on the chromatogram (solvent b). It moved at the rate of 2,3,4,6-tetra-*O*-methyl-D-glucose, and gave a yellow-orange color with the *p*-anisidine hydrochloride spray. The sirup, $[\alpha]_D$ +30° (*c* 9.6, in methanol), was boiled with methanolic hydrogen chloride in order to convert VIII to the ester of 2-*O*-methyl-D-glyceronic acid plus the dimethyl acetal of glycolaldehyde. It was anticipated that the latter compound would be unaffected by alcoholic ammonia whereas the glyceronic acid derivative would yield an amide. Accordingly the solution from the methanolysis was neutralized (Ag_2CO_3), saturated with ammonia and after 24 hr. at 0°, it was evaporated to dryness.[2,3] Crystalline 2-*O*-methyl-D-glyceronamide separated, m.p. and mixed m.p. with an authentic specimen,[6] m.p. 88°, $[\alpha]_D$ +78 ± 6° (*c* 0.3 in methanol) remained after recrystallization from acetone–ether mixture.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8. Found: C, 40.4; H, 7.2; N, 11.9.

Conversion of D-*arabo*-Ascorbic Acid to a 3-Hexulose Derivative.—The iso-di-*O*-methyl derivative[10] (5 g.) was reduced by adding its solution in methylal (25 ml.) to a solution of lithium aluminum hydride (5 g.) in methylal (20 ml.). After 3 hr. excess of lithium aluminum hydride was destroyed by addition of ethyl acetate followed by water and the solution was filtered. The filtrate was deionized (Amberlite resins IR-120 and IR4B) and concentrated to a sirup (3.6 g.). Chromatographic examination of this sirup (solvent b) indicated the presence of four substances with R_{Rh} 1.08, 1.6, 1.65 and 1.85.

The sirup was dissolved in *N* formic acid and the solution was heated at 80°. After 3 hr. chromatographic examination of the solution indicated the presence of two major components with R_{Rh} 1.08 and 1.43 (solvent b). The sirup (3.4 g.) remaining after evaporation of the solvents was fractionated on a column of cellulose using 1-butanol:light petroleum (b.p. 100–120°) as solvent, and the following fractions were obtained: fraction I (0.2 g.), $[\alpha]_D$ −16° (*c* 0.2 in methanol); fraction II (2.5 g.), $[\alpha]_D$ −12° (*c* 2.5 in methanol); fraction III (0.6 g.), $[\alpha]_D$ −5° (*c* 0.6 in methanol). Fractions I and III were mixtures, fraction II consisted mainly of the compound with R_{Rh} 1.08 (solvent b).

A sample of this fraction was heated with an equivalent of 2,5-dichlorophenylhydrazine in methanol. Concentration of the solution yielded a crystalline hydrazone derivative, m.p. 134°, $[\alpha]_D$ +12 ± 2° (*c* 0.2 in acetone).

Anal. Calcd. for $C_{13}H_{18}N_2O_5Cl_2$: N, 7.9; OMe, 8.8; Cl, 20.0. Found: N, 8.0; OMe, 8.8; Cl, 19.4.

Conversion of D-Glucoascorbic Acid to a 3-Heptulose Derivative.—2,3-Di-*O*-methyl-D-glucoascorbic acid[11] (2.73 g.) was converted to the isomeric lactone of methyl 2-*O*-methyl-3-heptulonoside and thence by reduction with lithium aluminum hydride to methyl 2-*O*-methyl-3-heptuloside (2.24 g.). Chromatographic examination of the sirup, after its solution had been deionized on Amberlite resins IR-120 and IR-4B, indicated the presence of five components, the major ones having R_{Rh} 1.42 and 0.75 (solvent b). The sirup was dissolved in 0.1 *N* sulfuric acid (50 ml.) and the solution heated on the steam-bath. The observed rotation changed from +1.06 to −2.8° (constant value) in 4 hours. Chromatographic examination of the solution now showed the presence of two materials with R_{Rh} 0.86 and 0.72, the former predominating (solvent b). In solvent a the rates of movement were R_{Rh} 0.95 and 1.04, the slower moving component predominating. The solution was neutralized ($BaCO_3$), filtered and concentrated to a sirup (2.0 g.). A portion of the material when heated with an alcoholic solution of 2,5-dichlorophenylhydrazine until the sugar could no longer be detected chromatographically gave a derivative, m.p. 154°, after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{20}N_2O_5Cl_2$: C, 44.0; H, 5.26; Cl, 18.4; OMe, 8.1. Found: C, 44.1; H, 5.7; Cl, 18.2; OMe, 8.5.

A sample of the sirupy mixture of sugars when oxidized with sodium metaperiodate consumed 3.5 moles of periodate and produced 2.2 moles of formic acid per mole of heptulose derivative.

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(10) E. G. E. Hawkins, E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 246 (1939).

(11) W. N. Haworth, E. L. Hirst and J. K. N. Jones, *ibid.*, 549 (1937).

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[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Formation of Symmetric Azo-compounds from Primary Aromatic Amines by Lead Tetraacetate

BY ERICH BAER AND ANTHONY L. TOSONI

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It is shown that oxidation of primary aromatic amines with lead tetraacetate provides a simple method for the preparation of symmetrically substituted azo compounds.

Several years ago while carrying out an oxidation with lead tetraacetate (LTA) in the presence of an aromatic amine, the writers observed the unexpected development of an intense color. This was soon traced to the oxidative effect of the reagent on the amine. A cursory investigation of this reaction with 2,4-dichloroaniline, 2,4,6-tribromoaniline and 4-bromoaniline as substrates disclosed that the oxidation of substituted primary aromatic amines with LTA gives complex mixtures of colored oxidation products that contain fair amounts of symmetric azo compounds. In the case of the three anilines under investigation, the azobenzenes were isolated in yields ranging from 27–36% of the theory. LTA thus becomes another member of a group of oxidizing agents (potassium permanganate,[1,2] potassium ferricyanide,[3] sodium hypobromide,[4] chromic acid anhydride,[5,6] manganese dioxide[7] and lead peroxide[7]) which are capable of converting primary aromatic amines to azo compounds with varying degrees of efficiency. The oxidation of the aromatic amines by LTA to symmetric azo compounds most likely involves the formation of free radicals. This assumption finds strong support in Goldschmidt and Wurzschmitt's

(1) C. Glaser, *Z. Chem.*, **9**, 308 (1866).
(2) C. Glaser, *Ann.*, **142**, 364 (1867).
(3) E. Bamberger and F. Meimberg, *Ber. deut. chem. Ges.*, **26**, 497, ref. 1 (1893).
(4) W. Meigen and E. Nottebohm, *ibid.*, **39**, 744 (1906).
(5) E. Börnstein, *ibid.*, **34**, 1271 (1901).
(6) F. Meyer and K. Dahlem, *Ann.*, **326**, 338 (1903).
(7) E. Börnstein, *Ber. deut. chem. Ges.*, **34**, 1269 (1901).

unequivocal demonstration of the occurrence of free radicals in the oxidation of aniline by means of lead peroxide.[8]

The intention of making a more thorough investigation of the reaction of primary aromatic amines with LTA has been repeatedly postponed due to the over-riding interest in other investigations. However, it seemed advisable to record briefly our results since they offer the promise of a simple procedure for the synthesis of symmetrically substituted azo compounds.[9]

Experimental Part

4,4'-Dibromoazobenzene.—To a solution of 5.0 g. (29.0 mmoles) of *p*-bromoaniline in 1.2 l. of anhydrous benzene was added with stirring 25.8 g. (58.2 mmoles) of finely powdered lead tetraacetate in the course of 1 hr. At the end of this period the lead diacetate was filtered off and the filtrate was washed thoroughly with 300 ml. of water. After separating the benzene and aqueous layers, the benzene solution was concentrated to a volume of 15 ml. The concentrate on cooling in ice yielded 3.1 g. of a solid material that on sublimation[10] *in vacuo* (0.001 mm.) within the temperature range of 200–250° (air-bath) gave 1.8 g. (36% of the theory) of 4,4'-dibromoazobenzene. After recrystallization from chloroform, its m.p. was 206.5–207.5°; reported m.p. for 4,4'-dibromoazobenzene 205°.[11] Its absorption spectrum in toluene from 400–680 mμ was found to be identical with that of an authentic sample of 4,4'-dibromoazobenzene.

Anal. Calcd. for $C_{12}H_8N_2Br_2$ (340.0): C, 42.38; H, 2.37; Br, 47.0. Found: C, 42.58; H, 2.46; Br, 47.2.

2,2',4,4',6,6'-Hexabromoazobenzene.—To a solution of 5.0 g. (15.1 mmoles) of pure 2,4,6-tribromoaniline[12] in 150 ml. of anhydrous benzene was added with stirring 7.0 g. (15.8 mmoles) of lead tetraacetate. After 90 minutes the benzene solution was washed with water, and brought to dryness under reduced pressure. The residue was taken up in cold ethyl acetate and filtered. The solid material on recrystallization from 200 ml. of ethyl acetate yielded 1.55 g. (31% of the theory) of 2,2',4,4',6,6'-hexabromoazobenzene, m.p. 217–218°, reported[13,14] m.p. 213°.

Anal. Calcd. for $C_{12}H_4N_2Br_6$ (655.7): C, 21.95; H, 0.61. Found: C, 21.95; H, 0.62.

2,2',4,4'-Tetrachloroazobenzene.—To a solution of 4.86 g. (30 mmoles) of 2,4-dichloroaniline in 250 ml. of anhydrous benzene were added 3 g. of magnesium oxide, 10 g. of anhydrous sodium sulfate and 13.3 g. (30 mmoles) of finely powdered lead tetraacetate, and the mixture was shaken for two hours. After removal of the solid material, the solution was washed with water and brought to dryness under reduced pressure. The residue, weighing 1.65 g., on recrystallization from chloroform or 96% ethanol yielded 1.3 g. (27% of theory) of 2,2',4,4'-tetrachloroazobenzene, m.p. 164–166°, reported[15,16] m.p. 161–162°.

Anal. Calcd. for $C_{12}H_6N_2Cl_4$ (320.0): C, 45.04; H, 1.89. Found: C, 45.01; H, 2.09.

(8) St. Goldschmidt and B. Wurzschmitt, *Ber. deut. chem. Ges.*, **55**, 3216 (1922).

(9) After this paper was accepted the authors became aware of a publication by K. H. Pausacker and J. G. Scroggie (*J. Chem. Soc.*, 4003 (1954)) describing the oxidation of primary aromatic amines by lead tetraacetate. These authors used substituted amines which differed from ours. The results of both investigations are in agreement.

(10) To obtain all 4,4'-dibromoazobenzene it was found necessary to interrupt the sublimation occasionally and to pulverize the residue.

(11) A. Werigo, *Ann.*, **165**, 189 (1873).

(12) H. Silberstein, *J. prakt. Chem.*, **27**, 98 (1883).

(13) H. v. Pechmann and A. Nold, *Ber.*, **31**, 557 (1898).

(14) F. D. Chattaway and K. J. P. Orton, *J. Chem. Soc.*, **79**, 467 (1901).

(15) Th. Zinke and A. Kuchenbecker, *Ann.*, **330**, 9, 53 (1904).

(16) Th. Zinke, *Ber. deut. chem. Ges.*, **34**, 2853 (1901).

TORONTO 5, CANADA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XVI. Purines and Thiazolo[5,4-d]pyrimidines from 4-Amino-5-formamido-6-mercaptopyrimidines

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When 4,5-diamino-6-mercaptopyrimidines are treated with aqueous formic acid at room temperature the 5-formamido derivatives can be isolated. The sodium salts of these, on heating, yield 6-mercaptopurines. With stronger formic acid and higher temperatures thiazolo[5,4-d]pyrimidines are produced. This method has been employed for the synthesis of thiazolo[5,4-d]pyrimidine analogs of adenine, hypoxanthine, 2,6-diaminopurine and 6-mercaptopurine.

The present studies originated in an investigation of the synthesis of 6-mercaptopurine[1,2] (VII) from 4,5-diamino-6-mercaptopyrimidine (I) *via* 4-amino-5-formamido-6-mercaptopyrimidine (V). In early work this synthesis was complicated by erratic yields and the presence in the product of an alkali-insoluble fraction. The identification of the latter as 7-aminothiazolo[5,4-d]pyrimidine (VIII) revealed the source of these difficulties. Further investigation has allowed the definition of the conditions conducive to the isolation of the formamido derivative V and the thiazolopyrimidine (VIII), respectively, both in these and in the related reactions leading to thioguanine (XIX) and 5,7-diaminothiazolo[5,4-d]pyrimidine (XVIII).

Several thiazolo[5,4-d]pyrimidines have been synthesized by treatment of mercaptoaminopyrimidines with formic acid.[3–5] However, in none of these instances was an alternative ring closure possible.

The facile cyclization of 4-amino-5-formamido-6-mercaptopyrimidine to 7-aminothiazolo[5,4-d]pyrimidine provided a route to an adenine analog which had been sought unsuccessfully in earlier studies. Previously, as part of a broad program dealing with condensed pyrimidine systems as antagonists of nucleic acid derivatives[6–9] some thi-

(1) G. B. Elion, E. Burgi and G. H. Hitchings, THIS JOURNAL, **74**, 411 (1952).

(2) G. B. Elion and G. H. Hitchings, *ibid.*, **76**, 4027 (1954).

(3) S. J. Childress and R. L. McKee, *ibid.*, **73**, 3862 (1951).

(4) F. L. Rose, *J. Chem. Soc.*, 3448 (1952).

(5) G. P. Hager and C. Kaiser, *J. Amer. Pharm. Assn.*, **44**, 193 (1955).

(6) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(7) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell and H. VanderWerff, *Ann. N. Y. Acad. Sci.*, **52**, 1318 (1950).

(8) G. H. Hitchings and G. B. Elion, *ibid.*, **60**, 195 (1954).

(9) G. H. Hitchings and G. B. Elion, 3^eme Congres International de Biochimie, *Rapports*, 185 (1955).