[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

4-AMINO-5-BROMO-1,3-DIMETHYLBENZENE

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5-Bromo-*m*-xylidine (old nomenclature) has been prepared by bromination of *m*-4-xylidine in hydrochloric acid solution[2] and also in glacial acetic acid,[3] the latter method being adopted in this investigation. Bromination of the free base produces the 5-bromo isomer, while the acetate gives the 6-bromo with a small amount of the 2-bromo form. The hydrochloride, benzoate, xylenol,[4] methyl and ethyl ethers and two dyes were also prepared.

Experimental Part

4-Amino-5-bromo-1,3-dimethylbenzene.—The method of preparation given by Noelting, Braun and Thesmar[3] was followed. However, in order to avoid the formation of an oil, the bromination product, instead of being poured into water, was filtered off, washed with glacial acetic acid and dried. The base was set free with sodium carbonate solution and recrystallized from dilute methyl alcohol; m. p. 46°.

Hydrochloride.—The hydrochloride consists of white crystals which are quite stable, not changing in a year. It readily sublimes without decomposition.

Anal. Calcd. for $C_8H_{10}NBr \cdot HCl$: HCl, 15.25. Found: 15.28.

Benzoate.—The benzoate was prepared by the Schotten-Baumann reaction. The product, obtained in nearly quantitative yield, was recrystallized from dilute alcohol. It forms prismatic needles melting at 186°.

Anal. Calcd. for $C_{15}H_{14}ONBr$: Br, 26.29. Found: 26.20.

Methyl Ether of 4-Hydroxy-5-bromo-1,3-dimethylbenzene, $C_6H_2(CH_3)_2BrOCH_3$.—The bromoxylidine was diazotized in the presence of sulfuric acid and converted into the xylenol (b. p. 228–230°) by boiling the solution; 3.1 g. of the xylenol was mixed with 1.2 cc. of methyl iodide and 0.36 g. of sodium in 10 cc. of methanol. After heating for two hours over steam, the volatile portion was boiled off, water added to the residue and the mixture extracted with ether. The oil obtained boiled chiefly at 232°; sp. gr. 1.362 (25°/25°); yield, high.

Anal. Calcd. for $C_9H_{11}OBr$: Br, 37.1. Found: 37.7.

Ethyl Ether.–Yield, high; boils chiefly at 246°; sp. gr. 1.290 (25°/25°).

Anal. Calcd. for $C_{10}H_{13}OBr$: Br, 34.9. Found: 34.9.

4-Chloro-5-bromo-1,3-dimethylbenzene, $C_6H_2(CH_3)_2ClBr$.—The bromoxylidine was diazotized in the presence of hydrochloric acid and copper paste was added. The product from the distillation with steam was extracted with ether. The oil recovered from the ether boiled over a wide range. The portion boiling a little below to a little above 250° was analyzed.

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[1] This paper is an abstract of a Master's Thesis presented to the Faculty of the University of North Carolina by R. E. Thomas in June, 1928.

[2] Fischer and Windaus, *Ber.*, **33**, 1971 (1900).

[3] Noelting, Braun and Thesmar, *Ber.*, **34**, 2255 (1901).

[4] Stoermer and Göhl, *Ber.*, **36**, 2875 (1903).

Anal. Calcd. for C_8H_8ClBr: Cl, 16.16. Found: 16.00.

1,3-Xylyl-5-bromo-4-nitrile, $C_6H_2(CH_3)_2BrCN$.—The bromoxylidine was converted into the nitrile by the Gattermann-Sandmeyer reaction. In the distillation with steam the nitrile crystallized in the condenser, from which it was removed with hot alcohol. It crystallized in needles which melted at 86–87°. A by-product appeared in the receiver. It boiled at 205° and was therefore regarded as 5-bromo-1,3-dimethylbenzene.

Anal. Calcd. for C_9H_8BrN: Br, 38.05. Found: 38.00.

1-(5-Bromo-1,3-xylyl-4-azo)-2-naphthol, $C_6H_2(CH_3)_2BrN_2C_{12}H_6OH$.—The bromoxylidine was diazotized and coupled with 2-naphthol in the presence of sodium hydroxide. The crude red precipitate melted at 132°. Recrystallization from a mixture of alcohol and petroleum ether gave rich red needles melting at 136°.

Anal. Calcd. for $C_{18}H_{15}ON_2Br$: Br, 23.50. Found: 23.15.

1-(5-Bromo-1,3-xylyl-4-azo)-4-phenol, $C_6H_2(CH_3)_2BrN_2C_6H_4OH$.—On coupling phenol with diazotized bromoxylidine a dark yellow precipitate formed; weight 3 g. from 2 g. of the xylidine. It was recrystallized from 90% acetic acid, or from a mixture of 3 parts of benzene and 7 parts of alcohol, to give small orange-colored crystals which melt at 166°.

Anal. Calcd. for $C_{14}H_{13}ON_2Br$: Br, 26.20. Found: 26.14.

Summary

1. The preparation of 4-amino-5-bromo-1,3-dimethylbenzene was improved upon.
2. Its hydrochloride and benzoate are described.
3. The methyl and ethyl ethers of the bromoxylenol were prepared.
4. The amino group was replaced by Cl and by CN.
5. Two azo dyes were made by coupling the diazotized bromoxylidine with phenol and with 2-naphthol.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYNTHETIC HOMOLOGS OF *d,l*-EPHEDRINE

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The interesting and important drug, ephedrine (I) has in recent years been brought to the attention of the medical profession and has become widely used chiefly through the brilliant investigations of Dr. K. K. Chen.[2] Although a careful comparison of the pharmacological action of *l*-ephedrine with *d,l*-ephedrine and pseudo-ephedrine has been completed, no study has as yet been made of the comparative values of *l*-ephedrine or *d,l*-ephedrine with a series of homologs, particularly those in which an

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[1] Portions of theses of J. F. Hyde and E. Browning submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] Chen and Kao, *J. Am. Pharm. Assocn.*, **15**, 625 (1926). At the end of this article is given a bibliography of chemical, pharmacological and medical articles on ephedrine.