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

PARA-CYMENE STUDIES. VII. THE BROMINATION OF PARA-CYMYLENE-2,6-DIAMINE[1]

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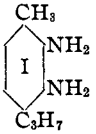
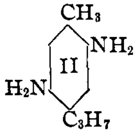
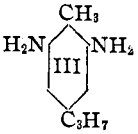
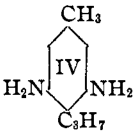
No bromine derivatives of the cymylenediamines have hitherto been described. There are four possible diamines of the *p*-cymene series as indicated in the formulas









Forms I and IV have not yet been prepared, although Lubs and Young[2] have described a chloro-cymylenediamine with the amino groups at Positions 2 and 3 and chlorine at 6. Form II as the hydrochloride only was first obtained by Liebermann and Ilinski[3] through the reduction of polythymoquinone dioxime. The salt was unstable. Kehrmann and Messinger[4] prepared it similarly, obtaining the salt in a pure state. Wallach[5] obtained the salt also, starting with *l*-α-phellandrene, but the product was impure. In this Laboratory we have prepared 2-amino-5-nitrocymene and will reduce this to the corresponding diamine. Form III was isolated by Alfthan[6] in a pure condition. It formed lustrous leaves, m. p. 95–96°, and could be kept a long time in a closed vessel.

This paper deals with Form III and methods of brominating it. Alfthan started with cymene, nitrating it with fuming nitric acid at 0°, and obtained a mixture of nitration products which he separated more or less successfully by fractional distillation. The fraction regarded as 2,6-dinitrocymene was reduced with tin, zinc and hydrochloric acid but the product gave six fractions on distillation, proving the raw material to be very impure. Two compounds were identified as *p*-cymylene-2,6-diamine and 2,4-toluylenediamine. We improved upon this method by starting with a pure 2,6-dinitrocymene and by working up the reduction products by a crystallization method.

The character of the bromine derivatives of the diamine varies according

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[1] This paper is an abstract of a thesis submitted by Earle deW. Jennings in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of North Carolina in June, 1926.

[2] Lubs and Young, *J. Ind. Eng. Chem.*, **11**, 1132 (1919).

[3] Liebermann and Ilinski, *Ber.*, **18**, 3200 (1885).

[4] Kehrmann and Messinger, *Ber.*, **23**, 3562 (1890).

[5] Wallach, *Ann.*, **336**, 22 (1904).

[6] Alfthan, *Ber.*, **53**, 86 (1920).

to whether we use the free base or the acetyl derivative. When the acetyl derivative in carbon tetrachloride solution is brominated at a low temperature, one bromine atom enters the ring, giving a crystalline acetate melting at 261° and a crystalline free base melting at 99–100°. The monohydrochloride and benzoate were also prepared. When the free base in carbon tetrachloride solution was brominated at low temperature, two bromine atoms entered the ring. The product was the dihydrobromide and we did not succeed in getting it in pure condition. Neither could a stable base be obtained. The diacetyl and dibenzoyl derivatives, however, were obtained in a pure state.

Experimental Part

Reduction of 2,6-Dinitro-*p*-cymene.—The method of Alfthan[6] was modified, being carried out as follows.

Fifty g. of dinitrocymene was dissolved in 250 cc. of glacial acetic acid, and 5 g. of tin and 20 g. of zinc were added. Very moderate action took place, but this was increased by adding 50 cc. of hydrochloric acid in 10cc. portions. The temperature was held below 100° by running cold water when needed. When the oily layer disappeared, the acid mixture was extracted with ether to remove important impurities. The mixture was then made alkaline and again extracted with ether to remove the cymylenediamine. Distillation of the ether left a residue which was a fairly pure product; yield, 80%. Purification was effected by dissolving the product in ether and reprecipitating with petroleum ether. We obtained the melting point 99–100°, as given by Alfthan.

THE DIACETATE was prepared by treating 10 g. of the diamine with 7 g. of acetyl chloride, the reaction being rapid with evolution of heat. We recrystallized the product from boiling alcohol, obtaining crystals melting at 254°, as given by Alfthan.

Bromination of the Diacetate

_p_-Cymylene-3-bromo-2,6-diacetyldiamine, $C_6HCH_3C_3H_7Br(NHCOCH_3)_2$.—Ten g. of the diacetate was dissolved in 100 cc. of carbon tetrachloride and cooled with a freezing mixture. Thirteen g. of bromine in 100 cc. of carbon tetrachloride was added drop by drop with stirring. The reaction mixture was kept an hour before being worked up. It contained an excess of bromine and a brown, tarry mass. The latter was separated by filtration, washed with water, dried and recrystallized from ether in extremely fine, white needles; m. p., 261°, with decomposition.

Anal. Subs., 0.1900: AgBr, 0.1082. Calcd. for $C_{14}H_{19}O_2N_2Br$: Br, 24.43. Found: 24.24.

_p_-Cymylene-3-bromo-2,6-diamine, $C_6HCH_3C_3H_7Br(NH_2)_2$.—The hydrolysis of the diacetate could not be accomplished with hot water but was readily effected with boiling dilute hydrochloric acid in an hour. The cooled solution was made alkaline and extracted with ether. Evaporation of the ether left a pinkish sirup which did not crystallize. It was washed with a little cold alcohol, dissolved in hot alcohol, and water added until precipitation began. On being warmed, this precipitate was redissolved. Crystals finally formed on scratching the walls of the vessel; they were short, fine, white needles; m. p., 99–100°, after three recrystallizations.

Anal. Subs., 0.0782: AgBr, 0.0614. Calcd. for $C_{10}H_{15}N_2Br$: Br, 32.89. Found: 33.41.

MONOHYDROCHLORIDE.—The monohydrochloride was prepared by passing hydrogen chloride into an absolute ether solution of the bromodiamine. It precipitated at once as a white solid which melts with decomposition at 162–168°.

Anal. Subs., 0.1168: 5.597 cc. of 0.0741 *N* base. Calcd. for $C_{10}H_{15}N_2Br.HCl$: HCl, 13.43. Found: 12.95.

DIBENZOATE, $C_6HCH_3C_3H_7Br(NHCOC_6H_5)_2$.—The benzoate immediately formed on mixing two moles of benzoyl chloride with one mole of the diamine. The solid product was washed with water, dried and recrystallized from absolute alcohol, giving short, white needles; m. p., 257°.

Anal. Subs., 0.1102: AgBr, 0.0451. Calcd. for $C_{24}H_{23}O_2N_2Br$: Br, 17.74. Found: 17.42.

Bromination of the Free Base

Ten g. of cymylenediamine was dissolved in 100 cc. of carbon tetrachloride and cooled with a freezing mixture. Twenty g. of bromine in 100 cc. of carbon tetrachloride was added dropwise with mechanical stirring. There was no evolution of hydrobromic acid. Stirring was continued for some time after the addition of the bromine. The dark brown semi-solid which formed was filtered off and dissolved in hot alcohol, from which it crystallized on cooling below 0°. Analysis indicated the compound to be the following one.

Dihydrobromide of *p*-Cymylene-3,5-dibromo-2,6-diamine.—The percentage of bromine was found to be 63.70; calculated, 66.12. The low figure was due to the unstable character of the salt. It is not stable in alcohol or other solvents and turns yellow on exposure to the air. The crystals are truncated prisms, darkening at 125° and decomposing completely at 136°. The hydrobromic acid was easily removed with silver nitrate. Analysis by titration could not be employed owing to the strong yellow color of its solutions.

***p*-Cymylene-3,5-dibromo-2,6-diacetyldiamine,** $C_6CH_3C_3H_7Br_2(NHCOCH_3)_2$.—The dihydrobromide was boiled for 30 minutes with acetyl chloride. The excess of acetyl chloride was evaporated off on the steam-bath and the white residue was redissolved in hot alcohol. After several recrystallizations the colorless needles melted at 232°.

Anal. Subs., 0.1617: AgBr, 0.1482. Calcd. for $C_{14}H_{18}O_2N_2Br_2$: Br, 39.38. Found: 39.01.

***p*-Cymylene-3,5-dibromo-2,6-dibenzoyldiamine,** $C_6CH_3C_3H_7Br_2(NHCOC_6H_5)_2$.—The dihydrobromide was boiled with benzoyl chloride, hydrobromic acid being evolved. The white residue left after evaporation of the excess of benzoyl chloride was recrystallized from alcohol, giving fine, white needles; m. p., 215°.

Anal. Subs., 0.1223: AgBr, 0.0855. Calcd. for $C_{24}H_{22}O_2N_2Br_2$: Br, 30.19. Found: 29.75.

Summary

1. An improved method is given for the preparation of *p*-cymylene-2,6-diamine.

2. When this amine is brominated in the cold, two atoms of bromine enter the ring, undoubtedly at Positions 3 and 5.

3. When the diacetyl derivative of the amine is brominated in the cold, one atom of bromine enters the ring. Positions 3 and 5 are identical.

The following new compounds were made: *p*-cymylene-3-bromo-2,6-diamine, its monohydrochloride, its diacetyl and dibenzoyl derivatives;

the dihydrobromide of *p*-cymylene-3,5-dibromo-2,6-diamine and the acetyl and benzoyl derivatives of the free base.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

THE BIOCHEMISTRY OF SULFUR. I. THE IDENTITY OF ERGOTHIONEINE FROM ERGOT OF RYE WITH SYMPECTOTHION AND THIASINE FROM PIGS' BLOOD

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This paper is the first contribution from this Laboratory to a new series of publications dealing with the chemistry of sulfur compounds having biological significance. The work which led to the chemical study discussed in this paper was the independent discoveries by Hunter and Eagles[2,3] and Benedict, Newton and Behre[4,5] of new organic sulfur compounds occurring in the corpuscles of pigs' blood. Hunter and Eagles[6] have assigned to their compound, which was originally called "substance X," the name "sympectothion," having the formula $C_{18}H_{32}N_6S_2O_5$. Benedict and his co-workers[5] assigned to their product the name "thiasine," having the formula $C_{12}H_{20}N_4O_3S$. At the time that this special research was undertaken in this Laboratory, which was on October 1, 1926, we had no positive evidence of the chemical structure of either of these two products. In fact, from what has been learned by experiment since we became interested in this subject we are now able to conclude that the original formulas assigned were incorrect in both cases. Before we began our research we were fortunate in receiving from Dr. George Hunter of Toronto University and Dr. S. R. Benedict of Cornell University small samples of their respective compounds to aid us in the elucidation of their chemical structure. A careful comparison of the solubility of the two products, their behavior towards alkali and the fact that neither compound revealed the presence of amino nitrogen and that both gave the same color reactions with phosphotungstic acid indicated that the same organic structure functioned in both compounds. We are now able to report positively that Hunter and Eagles, and Benedict and his co-workers were dealing with the same compound, but one having a different empirical formula than those reported in their last publications.

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[1] Holder of a Sterling Research Fellowship in Chemistry at Yale University, 1926–1927.

[2] Bulmer, Eagles and Hunter, *J. Biol. Chem.*, **63**, 17 (1925).

[3] Hunter and Eagles, *ibid.*, **65**, 623 (1925).

[4] Benedict, *ibid.*, **64**, 215 (1925).

[5] Benedict, Newton, and Behre, *ibid.*, **67**, 267 (1926).

[6] Hunter and Eagles, *ibid.* (in press).