benzoylurea. Side reactions yield benzoic acid, aniline, and aminotetrazoles. The latter are not the product of consecutive reactions. The Schmidt reaction does not involve the Beckmann rearrangement or imino diradicals.

MADISON, WISCONSIN RECEIVED OCTOBER 30, 1937

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, THE CITY COLLEGE, COLLEGE OF CITY OF NEW YORK]

Alkanolamines. III. Reactions of Chloronitrobenzenes with Ethanolamines

BY M. MELTSNER, L. GREENSTEIN, G. GROSS AND M. COHEN

In a previous communication from this Laboratory, Kremer[1] confirmed the reduction action of monoethanolamine as first reported by Meltsner,[2] *et al.* In addition to reduction products of nitrochlorobenzenes, Kremer also obtained condensation products, *e. g.*, 2-(*o*-nitroanilino)-ethanol from *o*-nitrochlorobenzene and monoethanolamine in the presence of sodium carbonate.

The present paper reports the results of additional experiments on the nitrohalides with mono-, di- and triethanolamines. The ethanolamines may bring about reduction to the azoxy, azo or amino compound, condensation, hydrolysis or combinations of these reactions. Condensations do not require the use of sodium carbonate as previously reported, although the yield may be greater in presence of the alkali carbonate. The addition of sodium hydroxide increases the yield of azo compounds.

Diethanolamine leads to the formation of a compound which is believed to be 2-aminophenylmorpholine, $NH_2C_6H_4N\langle^{CH_2CH_2}_{CH_2CH_2}\rangle O$ by condensation with *o*-nitrochlorobenzene and the reduction of the condensation product. Further identification of this compound is being undertaken. The presence of water and excess ethanolamine favor condensation. Triethanolamine produces no condensation product.

Experimental

Reaction of *o*-Nitrochlorobenzene with Diethanolamine.—Thirty grams of *o*-nitrochlorobenzene was placed in a 3-necked flask fitted with a reflux condenser and a dropping funnel. The temperature was raised to 175–180° in an oil-bath and then 126 g. of diethanolamine was added dropwise. The heating was continued for a total of three hours. The reaction mixture was treated with ice to complete precipitation and filtered. The insoluble residue, after further washing with cold water, was recrystallized from alcohol and yielded orange crystals, m. p. 134°, which proved to be 2,2′-dichloroazobenzene.

The filtrate was steam distilled. The distillate after extraction with ether and acidification of the extract yielded *o*-chloroaniline hydrochloride. The residue from the steam distillation was acidified and steam distilled. The ether extract of the distillate yielded yellow crystals, m. p. 44° and identified as *o*-nitrophenol.

The residue was made alkaline, evaporated as much as possible on a water-bath and then distilled under vacuum. The fraction collected at 155–175° (20 mm.), which contained some diethanolamine, on standing deposited white crystals. These crystals were recrystallized several times from benzene and then gave a melting point of 133–134°. They were soluble in water, almost insoluble in ether. A fusion test for elements showed the presence of nitrogen but no chlorine. It reduces ammoniacal silver nitrate at 100°. Evaporation of the crystals with hydrochloric acid leaves a white solid which contains chlorine and melts at 200°. The compound is probably *o*-aminophenylmorpholine, $o\text{-}NH_2C_6H_4N\langle^{CH_2CH_2}_{CH_2CH_2}\rangle O$. Calcd. N, 15.73. Found, N, 15.51.

Reaction with Diethanolamine and Water.—Sixty-three grams of water was added to the diethanolamine and the solution added as in the previous experiment. After heating for three hours at 175–180° the mixture was treated with ice water and filtered. The filtrate was steam distilled and further treated as in the previous experiment.

The residue, insoluble in the ice water, was steam distilled to separate any unreduced nitrochlorobenzene.

Reaction with Monoethanolamine and Water.—Twenty-four grams of water was added to 48 g. of monoethanolamine and the solution added dropwise to 30 g. of *o*-nitrochlorobenzene. The temperature was kept at 175° for three hours. Ice water was added and the mixture filtered. The filtrate was steam distilled and yielded *o*-chloroaniline. The residue insoluble in ice water was dissolved in boiling benzene, cooled, and petroleum ether added. On standing crystals separated out. The crystals were identified as 2-(*o*-nitroanilino)-ethanol.

Summary

Mononitrohalides of benzene yield reduction, hydrolytic and condensation products when treated with ethanolamines, except that *m*-nitro-

(1) C. B. Kremer, THIS JOURNAL, **59**, 1681 (1937).

(2) M. Meltsner, C. Wohlberg and M. J. Kleiner, *ibid.*, **57**, 2554 (1935).

chlorobenzene does not give a condensation product, nor does triethanolamine condense with the nitro halides.

The presence of water or alkali determines the yield of each type of product.

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[CONTRIBUTION FROM THE LABORATORIES OF THE WM. S. MERRELL CO.]

A Further Note on the Purification of Piperidine

BY E. S. COOK[1]

In previous papers have been described in detail the purification of piperidine by a distillation process[2] and the effect of this purification upon the activity of derived local anesthetics,[3] especially Diothane (piperidinopropanediol diphenylurethan hydrochloride).[4] In these papers it was shown that piperidine fractions boiling both higher and lower than pure piperidine gave less active anesthetics and that this depression in activity is at least partially accounted for by a physiological antagonism between the individual compounds present in the anesthetics prepared from the impure fractions.

The piperidine used for the earlier studies was obtained by the electrolytic reduction of pyridine. There has now become available commercially a piperidine prepared by catalytic reduction[5] and it became desirable to repeat a part of our studies using the catalytically prepared piperidine.

Experimental Part

The piperidine prepared by electrolytic and catalytic reduction of pyridine had a reboiling range,[6] uncorrected, of 103–111° and 104.6–106°, respectively. These two varieties of piperidine were then purified by a single distillation through the 9-foot (2-meter) column previously described.[2] The low fraction of the electrolytic and catalytic varieties (15 and 12%) had a reboiling range of 96–106° and 97.6–105.8°, respectively. The middle fraction (50 and 85%) had a reboiling range of 105.4–106.2° and 105.4–106.1°, respectively. Of the catalytic variety only a 3% residue remained, which was not examined; the corresponding residue from the electrolytic variety (35%) had a reboiling range of 106–116°. Extensive drying removed some water from both low fractions, but in no case was the boiling point raised to that of pure piperidine, which was found to be 106.3° (corr.) at 751 mm.

Piperidinopropanediol diphenylurethan hydrochloride (diothane) was prepared from all piperidine fractions (except the residual high fraction from the catalytic piperidine) by a procedure essentially similar to that previously reported.[7] The various samples all melted within a few degrees of each other (between 199 and 205°, corr.) as would be expected from the previous work.

These samples in 0.125% solution were tested for local anesthetic activity on the rabbit cornea. The duration of anesthesia for the diothane prepared from the electrolytic and catalytic varieties of piperidine was as follows: the low fractions, 21 and 22 min., the middle fractions, thirty-six and one-half and thirty-four min., respectively; that of the high fraction of the electrolytic, 26 min.

Summary

Piperidine prepared by the catalytic reduction of pyridine is of higher purity than that prepared by electrolytic reduction. Both, however, contain impurities which lower the local anesthetic activity of piperidinopropanediol diphenylurethan hydrochloride and which can be removed by distillation through a proper column. The piperidine prepared by catalytic reduction is particularly free from high boiling impurities.

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(1) Present address: Institutum Divi Thomae, Cincinnati, Ohio.

(2) E. S. Cook and T. H. Rider, THIS JOURNAL, **59**, 1739 (1937).

(3) T. H. Rider and E. S. Cook, *ibid.*, **59**, 1741 (1937).

(4) T. H. Rider and E. S. Cook, *J. Pharmacol.*, in press.

(5) Piperidine prepared by both processes was furnished by the Monsanto Chemical Co.

(6) For determination of reboiling range, see ref. 2.

(7) T. H. Rider, THIS JOURNAL, **52**, 2115 (1930).