[CONTRIBUTION FROM THE CHEMICAL LABORATORY, CASE SCHOOL OF APPLIED SCIENCE AND THE PHARMACOLOGIC LABORATORY OF WESTERN RESERVE UNIVERSITY]

CONDENSATION OF AROMATIC ALDEHYDES WITH NITROMETHANE IN THE PRESENCE OF ALCOHOLIC SODIUM HYDROXIDE

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A considerable quantity of the benzyl ether of vanillylidene nitromethane was desired as the starting material for the preparation of vanillylethylamine and its benzyl ether[1] to be used for a pharmacologic study, the results of which will be published elsewhere.[2] Unsuccessful attempts were made to repeat the procedure given by Kobayashi for the condensation of vanillin benzyl ether with nitromethane using methylamine as the condensing agent[3] and in which yields of 89% were reported to have been obtained; the experiment was repeated ten times but the product described by Kobayashi was never obtained; instead an unknown, brown amorphous substance, melting above 260°, was obtained in each case and in yields corresponding to the theoretical yield for a product formed by the condensation which was desired. Thinking that this substance might be the polymer of the desired product, attempts were made at depolymerization with acid and heat but without success. A 32% yield of the product described by Kobayashi was obtained when the method of Rosenmund[4] was used; this method employs the slow addition of alcoholic potassium hydroxide to an alcoholic solution of vanillin benzyl ether and nitromethane after which the mixture is made acid with an excess of 10% hydrochloric acid, precipitating the nitrostyrene derivative mixed with unreacted aldehyde. It was found that cooling the solution prior to acidification did not improve the yield. Worrall[5] has described a method for condensing benzaldehyde with nitromethane in methyl alcoholic solution using aqueous sodium hydroxide at a temperature from 10–15°; the pasty reaction mixture which results is converted to a clear solution by the addition of water and the product is precipitated by slowly pouring the alkaline solution into a large excess of dilute hydrochloric acid, a procedure which is stated to reduce the formation of saturated nitro alcohols, which probably occurs when the acid is added to the alkaline

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[1] Kobayashi, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **6**, 149 (1927).

[2] The writers wish to acknowledge the kindly interest and valuable assistance of Dr. Torald Sollmann of the Department of Pharmacology in the Medical School of Western Reserve University.

[3] Knoevenagel and Walter, *Ber.*, **37**, 4502 (1904).

[4] Rosenmund, *ibid.*, **43**, 3414 (1910).

[5] Worrall, "Organic Syntheses," John Wiley and Sons, Inc., New York, **1929**, Vol. IX, p. 66.

solution as in Rosenmund's procedure. The method of Worrall was not suitable for the condensation of nitromethane and vanillin benzyl ether because the latter unlike benzaldehyde is only slightly soluble in cold alcohol and shows a marked tendency to precipitate unchanged when the aqueous alkaline solution is added.

A modification and combination of the methods of Worrall and Rosenmund was devised giving excellent yields and which was not adversely affected by the low solubility of the aromatic aldehyde in cold alcohol. The method thus far has been used only with vanillin benzyl ether and piperonal but it would seem likely that it would also be successful with other aromatic aldehydes. The general reactions are probably the same as those given by Worrall, *viz.*

$$\mathrm{RCHO + CH_3NO_2 + NaOH \longrightarrow RCHOHCH{=}NO_2Na}$$
$$\mathrm{RCHOHCH{=}NO_2Na + HCl \longrightarrow RCH{=}CHNO_2 + NaCl}$$

Experimental Part

Preparation of ω-3-Methoxy-4-benzyloxynitrostyrene, $(\mathrm{C_6H_5CH_2O})(\mathrm{CH_3O})\mathrm{C_6H_3}$-$\mathrm{CH{=}CHNO_2}$.—Twelve grams of vanillin benzyl ether was dissolved in 400 cc. of 95% ethyl alcohol at room temperature and the solution then cooled to 5–10°, after which 6 g. of nitromethane was added. Then 100 cc. of a solution of 5 g. of sodium hydroxide in 100 cc. of ethyl alcohol, cooled to 5–10°, was added from a dropping funnel at a rate of 5 cc. per minute; the solution of the nitromethane and vanillin benzyl ether in alcohol was vigorously stirred and kept below 15° during the addition of the alcoholic sodium hydroxide. As the reaction proceeded, the insoluble sodium salt of the condensation product precipitated. After all of the alkali had been added and with the temperature kept below 15°, ice water was slowly added until the precipitate just dissolved (about 200 cc.). This clear, cold solution was added in a fine stream (by pouring through a funnel with a constricted stem containing a tuft of glass wool to remove the small amount of undissolved material) to a solution of 60 cc. of concentrated hydrochloric acid in 90 cc. of water with no attempt made to control the temperature but with stirring during the addition. A fine, yellow precipitate was immediately formed and after standing for half an hour was filtered with suction. A 97% yield of the product described by Kobayashi was obtained, m. p. 122–123° (uncorr.). The product thus formed was quite pure and was found to be satisfactory as a starting product for succeeding preparations without further purification by recrystallization. Equally good yields were obtained with larger quantities of reactants.

Preparation of ω-3,4-Methylenedioxynitrostyrene, $\mathrm{CH_2O_2{=}C_6H_3CH{=}CHNO_2}$.—By following the procedure as given above, a 74% yield of this compound was obtained from 7.5 g. of piperonal and 6 g. of nitromethane in 200 cc. of 95% ethyl alcohol. The crude product melted at 158°; one crystallization from alcohol gave a product melting at 161.5° (corr.). The melting point previously reported for this compound was 159°.[6]

Summary

A method is given for the preparation of ω-3-methoxy-4-benzyloxy- and ω-3,4-methylenedioxynitrostyrene by condensation of vanillin benzyl

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[6] Bouveault and Wahl, *Compt. rend.*, **135**, 41–43 (1902); Medinger, *Monatsh.*, **27**, 239 (1906).

ether and of piperonal with nitromethane in alcoholic sodium hydroxide solution.

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QUINAZOLINES. II. THE INTERACTION OF 2,4-DICHLOROQUINAZOLINE IN ALCOHOL WITH SALTS AND BASES

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In a previous communication[1] it was shown that when 2,4-dichloroquinazoline was treated with sodium alcoholates in the presence of phenols only the chlorine atom on position 4 was replaced yielding 2-chloro-4-alkoxyquinazolines, the chlorine atom on position 2 remaining unaffected. In attempting to prepare the nitrile of the as yet unknown quinazoline-2,4-dicarboxylic acid by treatment of dichloroquinazoline with potassium cyanide in alcoholic solution, the same reaction occurred with the formation of 2-chloro-4-ethoxyquinazoline; a similar treatment of dichloroquinzaoline in methyl alcoholic solution gave the corresponding 2-chloro-4-methoxyquinazoline. From this it appears that such chloromono ethers are formed by the splitting out of hydrogen chloride as a result of the interaction of the alcohol and the chlorine atom on position 4; the sodium ethylate (or the potassium cyanide) acting as the salt of a weak acid subsequently removes the hydrogen chloride as it is formed and permits the reaction to proceed to completion; thus

$$C_8H_4N_2Cl_2 + C_2H_5OH \longrightarrow C_8H_4N_2(OC_2H_5)Cl + HCl \tag{1}$$

$$HCl + C_2H_5ONa \longrightarrow NaCl + C_2H_5OH \quad \text{or} \tag{2}$$
$$HCl + KCN \longrightarrow KCl + HCN$$

In the work previously reported, it was found more or less empirically that the best yields of the chloro-alkoxy derivatives were obtained by using dichloroquinazoline, sodium and phenol in the molar proportions of 1:2:1 in the presence of a large excess of alcohol; but when the proportion of phenol was increased, chlorophenoxyquinazoline was formed with a corresponding decrease in the yields of the chloroalkoxy compound. The reason for this is that when two molecular proportions of sodium are treated with an excess of alcohol and one molecular proportion of phenol is added, one-half of the sodium ethylate reacts to form sodium phenolate; greater proportions of phenol will reduce the amount of sodium ethylate available as an acid remover resulting in the formation of a correspondingly smaller amount of chloroalkoxyquinazoline; the increasing yields of the chlorophenoxy derivative with increasing amounts of sodium phenolate

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[1] Lange, Roush and Asbeck, THIS JOURNAL, 52, 3696 (1930).