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One of the most effective methods for obtaining 3,4,5-trimethoxybenzaldehyde — an essential intermediate in the preparation of 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine (trimethoprim) — is a three-stage synthesis based on vanillin (I), which includes bromination of I in glacial acetic acid to 5-bromovanillin (II), replacement of bromine by a methoxy group, and methylation of the syringaldehyde formed [8]. This method for brominating I, as well as the bromination of I in 48% HBr [7] or chlorinated hydrocarbons [4], has a number of disadvantages due to the necessity for using an excess of difficultly available bromine (5–15 mole %), the large quantity of acidic aqueous mother liquors, and also the difficulty in isolating the required product. Moreover, in all of these methods 5-bromovanillin (II) is usually contaminated with vanillin (3% or more) and requires additional purification. Attempts to obtain bromo-substituted hydroxybenzaldehydes in aqueous medium in a similar manner to iodination of I in an I_2 -KI-water system did not give the desired results, as in this case the process was accompanied by separation of carbon monoxide and formation of a mixture of di- and tribromophenol [2].

A method for the bromination of vanillin in a two-phase $CHCl_3$ -mineral acid solution system using different oxidizing agents for converting the HBr formed into bromine has recently been reported [5]. This method can be used to obtain II in good yield and substantially reduce the consumption of bromine. There is no other information in the literature about the oxidative bromination of vanillin, in particular concerning the nature of the impurities formed.

In this connection the present work attempts a detailed investigation of this reaction with identification of the impurities formed in order to determine the mechanism of this process and the nature of the side reactions that occur.

EXPERIMENTAL

GLC analysis was carried out on a Tsvet-100 instrument with flame ionization detector and operating with temperature programming on packed steel columns using 3% OB-17 on Chromatone N-AW-DCMS. As an example, Fig. 1 depicts the chromatogram obtained when analyzing the dichloroethane mother liquor after fivefold utilization of the reaction solutions.

TLC was carried out on Silufol UV-254 plates using a hexane-ether (7:3) solvent system. The by-products were separated on a glass column of length 700 mm and diameter 30 mm filled with L 100/250 silica gel using a hexane-ether (1:1) solvent mixture.

Mass spectra were recorded on a MAT-112 (Varian, FRG) instrument with direct introduction of the sample into the ionization chamber and also by chromatography-mass spectrometry.

5-Bromovanillin (II). To a solution of 15.2 g (0.1 mole) of I in 120 ml of dichloroethane was added 25 ml of 55% H_2SO_4 and the mixture was heated with agitation to 45°C. Over a period of 40–60 min 8.79 g (0.055 mole) of Br_2 was added and the mixture was kept at the same temperature for 30 min and then 5.5 ml (0.055 mole) of a 30% solution of H_2O_2 was added over a period of 1 h. On completion of this the mixture was kept for 2 h at 45°C. As the reaction proceeded II was precipitated. After cooling the mixture to 20°C the product was filtered off, washed with water, and dried. Yield of II was 91–92% of theoretical based on I. The product was a fine crystalline powder with a pale cream color, mp 163–164°C (164° according to [6]). The content of the main product was not less than 99% and that of vanillin was not more than 0.5%.

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TABLE 1. Mass Spectra of Compounds III-VII

Compound	Fragment*									Empirical formula
	M ⁺	[M-CO] ⁺	[M-2H-CO] ⁺	[M-Br] ⁺	[M-Br-CO] ⁺	[M-Br-2H-CO] ⁺	[M-CH ₃] ⁺	[M-CH ₃ -CO] ⁺	[C ₂ OBr] ⁺	
3-Bromo-4,5- dihydroxy- benzaldehyde (III)	216 (1Br)	188	186							C ₇ H ₅ BrO ₃
2,3-Dibromo-4,5-dihy- droxybenzaldehyde (IV)	294 [*] (2Br)	266	264	215	187				131	C ₇ H ₄ Br ₂ O ₃
2-Methoxy-4,5,6-tribromo- phenol (V)	358 (3Br)						343			C ₇ H ₃ Br ₃ O ₂
2-Methoxy-4,6-dibromo- phenol (VI)	280 (2Br)						265	237		C ₇ H ₃ Br ₂ O ₂
3,4-Dihydroxy-2,5,6-tri- bromobenzaldehyde (VII)	372 (3Br)	344		293	265	263			131	C ₇ H ₃ Br ₃ O ₃

*Mass numbers are indicated for ions containing ⁷⁹Br.

TABLE 2. Results of Three Series of Experiments on Oxidative Bromination of I

Experi- ment No.	Tempera- ture, °C	Concentra- tion of H ₂ SO ₄ solu- tion, %	Yield of crude II, %	Content according to GLC, %			Yield of II, %
				I	II	total of III-V	
1	45	0 (water)	88,3	1,3	98,3	0,4	86,8
2	45	5	88,4	1,5	98,1	0,4	86,7
3	45	15	88,6	0,8	98,8	0,4	87,5
4	45	25	86,7	0,8	98,7	0,5	85,6
5	45	35	89,5	0,7	98,7	0,6	88,3
6	45	45	90,0	0,9	98,9	0,2	89,0
7	45	55	91,3	0,4	99,4	0,2	90,8
8	0	55	86,9	6,5	93,3	0,2	81,1
9	23	55	88,9	3,4	96,0	0,6	85,3
10	35	55	90,3	2,4	96,9	0,7	87,5
11	45	55	91,3	0,4	99,4	0,2	90,8
12	55	55	89,2	0,3	99,1	0,6	88,4
13	60	55	91,4	none	98,3	1,7	89,8
14	70	55	90,5	none	97,8	2,2	88,5
15	45	55	92,4	0,3	99,5	0,2	91,9
16	45	55	100	0,4	99,4	0,2	99,4
17	45	55	100	0,3	99,5	0,2	99,5
18	45	55	100	0,4	99,4	0,2	99,4
19	45	55	100	0,2	99,5	0,3	99,5

DISCUSSION OF RESULTS

The oxidative bromination of I in a two-phase system (organic solvent immiscible with water and solution of H₂SO₄) includes two successive stages: a) bromination of I in the organic phase with a lesser quantity of bromine according to the reaction

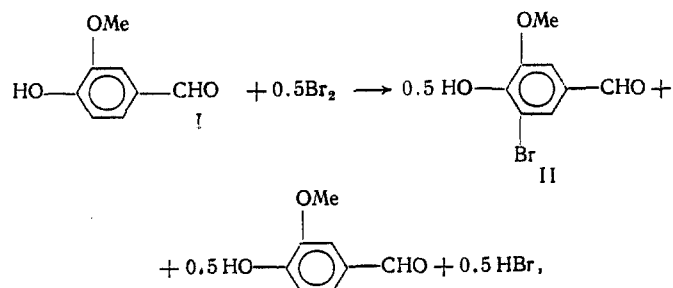


TABLE 3. Results of GLC Analysis of Dry Residues after Evaporation of Dichloroethane Mother Liquors

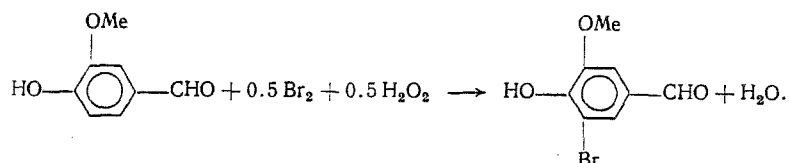
No. of combined mother liquor	Dry residue of experiments given in Table 2	Content, %				
		I	III	II	IV	V
1	2-6*	20,9	1,0	74,4	3,5	0,2
2	10-14**	2,7	16,0	69,7	8,5	3,1
3	19	13,0	8,9	40,9	36,5	0,7

*Experiments 1 and 7 excluded.

**Experiments 8 and 9 excluded.

the HBr formed in the process is absorbed by the aqueous phase and II is precipitated out; b) treatment of the reaction mass formed with a concentrated solution of H_2O_2 resulting in oxidation of HBr in the aqueous phase to free bromine. The latter is extracted into the organic phase and reacts with I.

The overall reaction for oxidative bromination of vanillin is given by the equation



This method of conducting the process makes it possible for virtually all of the Br_2 introduced into the reaction to be used, and to a considerable extent it avoids the formation of by-products obtained by further bromination of the benzene ring.

We have investigated the possibility of using different solvents in this process. Vanillin (I) is readily soluble in CH_2Cl_2 , CHCl_3 , and dichloroethane (3-5 parts by volume of these solvents are consumed per 1 part by weight of product). From our point of view the most convenient is dichloroethane, as using CHCl_3 in conjunction with H_2O_2 may lead to the formation of phosgene [3], while CH_2Cl_2 has a low boiling point. Moreover, II has limited solubility in dichloroethane, which simplifies its isolation from the reaction mass. It is best to use 7-8 parts by volume of solvent per one part by weight of I. The most convenient volumetric ratio of solvent to H_2SO_4 solution is 1.0:0.2.

TLC and GLC analysis of the dichloroethane mother liquor, in which the by-products of the reaction were dissolved, showed the presence in addition to I and II of three major (III-V) and two minor (VI, VII) by-products, the structure of which has been determined from their mass spectra and chromatography-mass spectra (Table 1).

We can assume from the structure of the products isolated that the side reactions which occur during oxidative bromination of vanillin in a two-phase system are: a greater degree of bromination of the benzene ring accompanied by hydrolysis of the methoxy group to give 2,3-dibromo-4,5-dihydroxybenzaldehyde (IV) and 3,4-dihydroxy-2,5,6-tribromobenzaldehyde (VII); hydrolysis of the methoxy group of II to give 3-bromo-4,5-dihydroxybenzaldehyde (I₁); replacement of the aldehyde group by Br to give di- and tribromo derivatives of 2-methoxyphenol (V, VI). Hydrolysis of the methoxy group does not occur for the latter compounds.

It should be noted that during the experiment Baeyer-Villiger oxidation [1] of the aldehyde group by H_2O_2 does not occur, as substituted benzoic acids or their esters were not detected.

Table 2 presents the results of two series of experiments on the oxidative bromination of vanillin, from which it is possible to determine the effect of the concentration of the H_2SO_4 solution (experiments 1-7) and also the experimental temperature (experiments 8-14) on the yield and quality of 5-bromovanillin. In all the experiments an $\text{I}-\text{Br}_2-\text{H}_2\text{O}_2$ molar ratio of 1:0.55:0.55 was used. A ratio of 1:0.5:0.5 leads to a decrease in yield of II and a ratio of 1:0.6:0.6 does not improve the yield of product but increases the quantity of by-products derived from further bromination of the benzene ring.

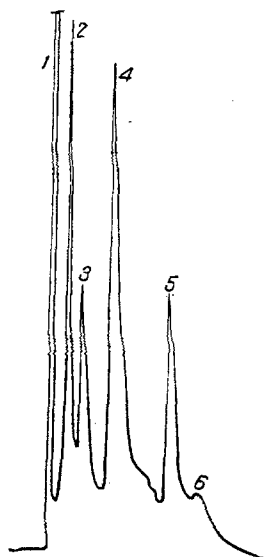


Fig. 1. Chromatogram of dichloroethane mother liquor after fivefold utilization of the reaction solutions: 1) dichloroethane; 2) I; 3) III; 4) II; 5) IV; 6) V.

In the first series of experiments (1-7) the concentration of H_2SO_4 was varied (0-55%) at a constant temperature ($45^\circ C$). As can be seen from Table 2, in these experiments there is a slight dependence of the yield and quality of II on the concentration of the H_2SO_4 solution. However, the color of the organic layer is intensified by changing from pale brown to black when used with dilute solutions of H_2SO_4 (less than 55%), which indicates that tar is formed. In the same way the external appearance of the isolated product deteriorates from pale cream (55% H_2SO_4) to brown (water).

In the second series of experiments (8-14) the temperature was varied from 0 to $70^\circ C$ at a constant concentration of H_2SO_4 (55%). The results indicate that at temperatures below $45^\circ C$ the yield of II decreases and the content of I in the product increases. At temperatures above $45^\circ C$ the yield of II is constant and it contains very little I, but there is a noticeable increase in the content of by-products (III-V). It can be seen from Table 2 that the best results are obtained in the temperature range $45-55^\circ C$ and when 55% H_2SO_4 is used.

Since I and II are partly lost during isolation of the product in both the organic and aqueous phases, it was of interest to study the possibility of repeated utilization of these solutions in order to increase the yield of II and reduce the consumption of solvent as well as H_2SO_4 . After each cycle the dichloroethane solution was washed three times with water (1:1) and the spent H_2SO_4 solution (45-47%) was strengthened to 55% again. It can be seen from Table 2 (experiments 15-19) that repeated utilization of the reaction solutions leads to an increase in yield of II. Thus, the average yield of II when there is a fivefold recycling of solvent and H_2SO_4 solution (experiments 15-19) is 97.9% based on a fivefold batch of I, and the content of primary substance in the isolated products of the third series was not less than 99.4%.

Table 3 presents the results of gas chromatographic analysis of the dry residues obtained after evaporation of the dichloroethane mother liquors combined within each series. It can be seen from Table 3 that an increase in the H_2SO_4 concentration and raising the temperature of the reaction facilitate a higher conversion of I to II (cf. dry residues of 1 and 2), while fivefold utilization of the reaction solutions leads to conversion of II dissolved in dichloroethane to 2,3-dibromo-4,5-dihydroxybenzaldehyde (cf. dry residues of 2 and 3).

Thus, it is shown that when the reaction is carried out in a two-phase system with fivefold utilization of the reaction solutions it is possible to conduct the oxidative bromination of I to II in high yield with complete utilization of bromine and also to reduce the consumption of dichloroethane and H_2SO_4 by a factor of 3-4.

By using GLC and mass spectrometry we have identified the main by-products formed during the reaction: 3-bromo-4,5-dihydroxybenzaldehyde derived from the acidic hydrolysis of the methoxy group of II; 2,3-dibromo-4,5-dihydroxybenzaldehyde and 3,4-dihydroxy-2,5,6-tribromobenzaldehyde derived from further bromination of II and concurrent hydrolysis of the methoxy group; 2-methoxy-4,6-dibromophenol and 2-methoxy-4,5,6-tribromophenol obtained by replacement of the aldehyde group by Br in II and 2,3-dibromo-5-methoxy-4-hydroxybenzaldehyde respectively.

Under the conditions determined by us the quantity of initial I and by-products in II did not exceed 1%.

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