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THE SYNTHESIS OF SYRINGALDEHYDE FROM VANILLIN[1]

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ABSTRACT

Syringaldehyde has been synthesized in high yields from vanillin. The process consists of the iodination of vanillin, followed by the interaction of the resultant 5-iodovanillin with sodium methoxide in anhydrous methanol at temperatures of 130 ± 4° C. for one hour in the presence of a copper catalyst. Along with the syringaldehyde, small amounts of unchanged 5-iodovanillin and vanillin were always found in the reaction mixture. Analysis of the final product was made by an initial separation of the components by downward paper chromatography using a mixture of petroleum ether (b.p. 100–120° C.), di-*n*-butyl ether, and water (10: 1: 1) as the developing agent for a period of 10 hr. The separated compounds were extracted from the paper and their concentrations in alcoholic alkaline solutions determined spectrophotometrically.

Under conditions by which 5-iodovanillin was converted to syringaldehyde in better than a 95% yield, 5-bromovanillin gave only a 61% yield and 5-chlorovanillin gave no detectable amounts of syringaldehyde.

In connection with an investigation into the fundamental nature of isolated lignins and their degradation products from angiosperms (poplar wood and cereal straws), it was important to have available many reference compounds of known structure. For such work the compounds required are, for the most part, of two types: those containing the guaiacyl (4-hydroxy-3-methoxyphenyl) nucleus and those containing the syringyl (4-hydroxy-3,5-dimethoxyphenyl) nucleus. Many derivatives having the former structure have been synthesized from vanillin (4-hydroxy-3-methoxybenzaldehyde) which is readily available as an oxidation product of gymnosperm lignin or its derivatives. Much less work has been reported on the chemistry of compounds having the syringyl nucleus. A logical starting material for their syntheses would be the corresponding aldehyde, syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde). Even though the oxidation of lignified angiosperm material gives rise to a mixture of both vanillin and syringaldehyde, the separation and recovery of each is not readily accomplished, so another source of this latter aldehyde is preferred.

Many syntheses, as outlined by Pearl (9), have been reported, and a laboratory procedure has appeared in Organic Syntheses (1). The main starting material in these procedures is either 1,3-dimethylpyrogallol or gallic acid, the conversion of either of which to the aldehyde involves many separate steps and therefore low over-all yields. A recent publication (10) describes a new synthesis involving the conversion of vanillin to 5-hydroxyvanillin, complete methylation followed by selective demethylation of the 4-methoxy group to give syringaldehyde in good yield. These authors also report that their attempts at the conversion of 5-halovanillin to syringaldehyde were universally unsuccessful. Some time ago an investigation was begun in these laboratories to study this same synthesis of syringaldehyde from vanillin by the introduction

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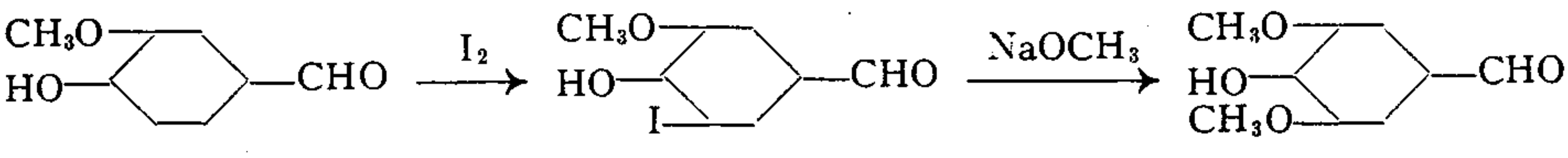
of a methoxy grouping. One value of such a method would be the possibility of thereby converting a mixture of the aldehydes obtained by the oxidation of hardwoods into pure syringaldehyde should a valuable use be found for this chemical.

In a previous communication (8) it was reported that preliminary experiments on the two-step synthesis: vanillin → 5-bromovanillin → syringaldehyde, appeared promising. By treatment of the 5-bromovanillin with sodium methoxide in anhydrous methanol in the presence of copper turnings at temperatures of 160–200° C., small yields of syringaldehyde were obtained along with other reaction products. Because of the well known reactivity of halogen substituted aromatic compounds increasing from chloro- through bromo- to iodo-derivatives in nucleophilic substitution reactions (3), it was thought that the use of 5-iodovanillin in a similar synthesis would be more suitable. Excellent yields of syringaldehyde (II) have now been obtained from vanillin (I) by this method according to the following equations:



I II

Preliminary runs were carried out in which 5-iodovanillin, anhydrous methanol, sodium methoxide, and a copper catalyst were heated together in a rocking autoclave at temperatures ranging from 72° C. to 180° C. and for reaction times of from one to eight hours. After dilution of the orange to dark red reaction mixture with water and filtration to remove the copper, the products were extracted into chloroform and then treated as follows. First they were separated into bicarbonate-soluble and bicarbonate-insoluble fractions, and then each of these was subdivided into sodium bisulphite-soluble and sodium bisulphite-insoluble portions. It was often noticed that complete acidification of the original alkaline reaction mixture caused any unchanged 5-iodovanillin to precipitate. This insolubility of 5-iodovanillin in acidic aqueous methanol permitted its ready separation from the other components of the reaction mixture. Support was found in these experiments for an observation reported earlier (11) that, from "neutral" lignin fractions, compounds having a syringyl nucleus were isolated. In this case the incomplete liberation of phenolic compounds by the exhaustive carbonation of a strongly alkaline solution was borne out by finding phenolic aldehydic products in both the bicarbonate-soluble and bicarbonate-insoluble portions.

The aqueous residues from the various runs were analyzed for iodide ion by a standard method (12). These results along with the amount of unchanged 5-iodovanillin recovered are given in Table I, where iodide ion is expressed as the corresponding weight of 5-iodovanillin. The values reported for the iodide ion determinations are averages of duplicate analyses which agreed within one per cent and are minimum values since, prior to the analyses, the aqueous solutions had been acidified and extracted several times with chloroform. It

TABLE I

PRELIMINARY EXPERIMENTS USING 5-IODOVANILLIN[a]

Run No.	Average temp., ° C.	Reaction time, hr.	Nonaldehydic fraction[b], gm.	Syringaldehyde containing fraction[c], gm.	Percentage of original 5-iodovanillin		
					Recovered unchanged	Converted to iodide	Total accounted for
1	179	1.0	8.8	2.0	Nil	—	—
2	154	5.0	7.1	0.8	Nil	96.0	96.0
3[d]	72	7.5	0.3	0.6	82.4	7.8	90.2
4	137	1.25	3.9	3.9	Nil	93.4	93.4
5	110	1.0	—	4.8	36.9	48.3	85.2
6	123	1.2	0.3	6.2	19.2	77.6	96.8
7	118	1.0	1.0	4.9	25.4	68.0	93.4
8	118	6.25	—	7.2	Nil	92.8	92.8
9	123	8.5	3.0	6.0	Nil	93.4	93.4
10	116	8.0	0.4	4.3	13.0	81.0	94.0

[a] *For each run, 5-iodovanillin (13.0 gm.), anhydrous methanol (250 ml.), sodium (10.0 gm.) (with the exception of Run 1 in which 5.0 gm. were used), and copper catalyst A (12.8 gm.) were reacted.*

[b] *Bicarbonate-insoluble, sodium bisulphite-insoluble.*

[c] *Combined bicarbonate-insoluble, sodium bisulphite-soluble, and bicarbonate-soluble fractions.*

[d] *Run carried out at atmospheric pressure under reflux.*

seems reasonable to conclude that, under the conditions employed, all or nearly all of the 5-iodovanillin which reacts loses iodine.

Varying small amounts of syringaldehyde were isolated by crystallization and sublimation from many of the fractions obtained in these preliminary experiments, but the amounts given in Table I represent only the weight of the crude products shown to contain syringaldehyde. It appears that, with such a reaction mixture, increasing temperatures lead to an increase in the syringaldehyde-containing fractions until a temperature of 135° C. is reached and that above this temperature the yield of the nonaldehydic fraction becomes more and more appreciable. The chemical nature of this derivative, referred to as the "Unknown" in Fig. 1, has not as yet been determined but qualitative tests show that it is phenolic and contains no iodine.

In an analysis of the reaction product of Run 10 by a chromatographic method, an appreciable quantity of vanillin (28%, based on 5-iodovanillin) along with syringaldehyde was detected. The presence of vanillin, characterized by the comparison of its ultraviolet absorption spectrum and chromatographic behavior with an authentic sample, is not surprising. The reductive cleavage of aryl halides is not uncommon under similar alkaline conditions (3, 10).

The lack of a single fraction containing all of the syringaldehyde, and the detection of vanillin in the reaction product, indicated that a new method of determining yields was required. A method of analysis similar to that used by Stone and Blundell (13) proved satisfactory. The use of a 10: 1: 1 mixture of petroleum ether (b.p. 100–120° C.), di-*n*-butyl ether, and water as the developing solvent gave an adequate separation of syringaldehyde, vanillin, 5-iodovanillin, and the unidentified reaction product on a paper strip (Fig. 1).

The positions of the various phenolic compounds were determined by

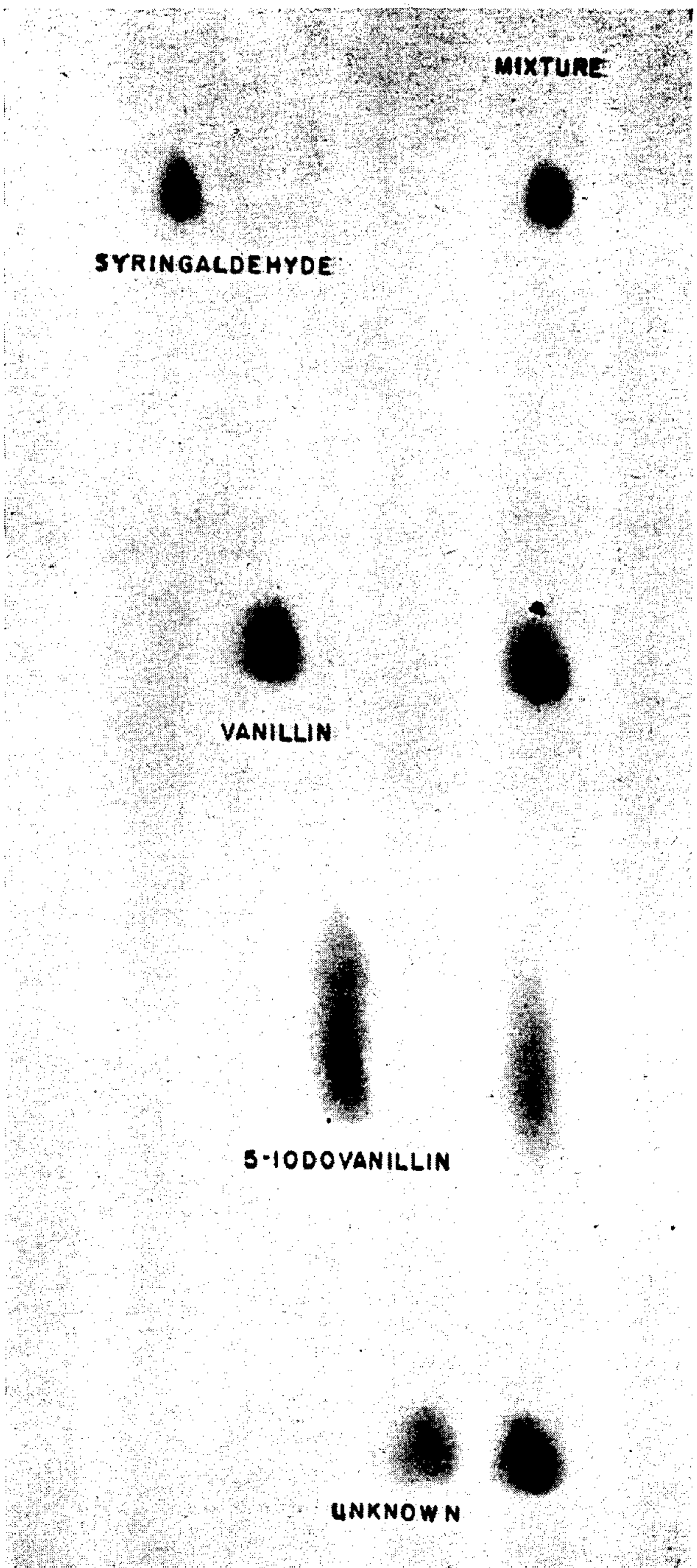


FIG. 1. Chromatographic separation of syringaldehyde, vanillin, 5-iodovanillin, and an unidentified phenolic reaction product. Chromatogram developed for 10 hr. using petroleum ether (b.p. 100–120° C.), butyl ether, and water (10.1.1).

spraying test strips of the chromatogram with a ferric chloride – potassium ferricyanide mixture (2). The separated bands were then extracted with ethanol and the concentrations of the extracts determined spectrophotometrically. Such analyses of known mixtures showed that an average of 7.6% of the syringaldehyde, 18.0% of the vanillin, and a negligible amount of 5-iodovanillin were lost during the analysis. The results of subsequent analyses were corrected for these losses.

A second series of experiments was then carried out and the products analyzed by this preferred method. The results are given in Table II. The results of Runs 11 and 12 indicate that a copper catalyst is necessary in this reaction. It was thought that the extreme variations in yields of products of Runs 11, 13, 14, and 15 were not due primarily to the slight temperature differences recorded but rather to differences in the catalyst, a fresh batch of which had

TABLE II

CONVERSION OF 5-IODOVANILLIN TO SYRINGALDEHYDE[a]

Run No.	Copper catalyst[b]	Average temp., °C.[c]	Analysis of reaction mixture			Total yield, %
			Component[d]	Duplicate analyses, gm.	Mean yield, %	
11	A	122	SA	5.39 5.38	63.2	
			V	1.30 1.26	18.0	
			5IV	2.35 2.40	18.3	99.5
12	—	122	SA	0.52 0.52	6.1	
			5IV	12.7 12.3	96.3	102.4
13	A	128	SA	7.50 7.32	87.0	
			V	0.28 0.25	3.7	
			5IV	1.61 1.64	12.5	103.2
14	A	133	SA	6.38 6.59	76.2	
			V	0.88 0.92	12.7	
			5IV	1.39 1.30	10.4	99.3
15	A	128	SA	7.10 7.02	83.0	
			V	0.92 0.98	13.4	
			5IV	0.18 0.12	1.5	97.9
16	B	126	SA	8.42 8.44	98.9	
			V	0.14 0.18	2.2	
			5IV	0.31 0.33	2.5	103.5
17	B	129	SA	8.41 8.26	97.9	
			V	0.20 0.20	2.8	
			5IV	0.25 0.25	1.9	102.6

[a] *For each run 5-iodovanillin (13.0 gm.), sodium (10 gm.), anhydrous methanol (250 ml.), and copper catalyst (12.8 gm.*) were used; reaction time one hour at elevated temperature.*

[b] *Catalyst A prepared by precipitating copper from copper sulphate solution with zinc; catalyst B was British Drug Houses' precipitated copper powder, reagent grade.*

[c] *Maximum temperature variation, ±4° C.*

[d] *Abbreviations: SA for syringaldehyde, V for vanillin, and 5IV for 5-iodovanillin.*

* *Some later work has indicated that under similar conditions this amount of copper may be reduced to 2.0 gm. without serious decrease in percentage conversions and also that yields of around 50% of syringaldehyde may be obtained if 0.5 gm. iodine are used in place of the metallic copper catalyst.*

been prepared for each run. Using catalyst portions taken from the same source (Catalyst B), reproducible results were obtained (Runs 16 and 17). Furthermore, the high yields of syringaldehyde obtained indicated that the British Drug Houses precipitated copper powder was the preferred catalyst for this reaction. Subsequently, many runs similar to Runs 16 have been made and pure syringaldehyde readily recovered and recrystallized as light yellow needles from Skellysolve "C", m.p. 109–110° C. in yields of 85% or better.

The possibility of converting either of the cheaper 5-chloro- or 5-bromovanillin to syringaldehyde under similar conditions was investigated. Both these 5-halovanillins moved further than vanillin or syringaldehyde under the previously used chromatographic conditions and hence did not interfere with the analyses. Using 5-bromovanillin, runs carried out at 130° C. and 140° C. gave rise in each case to products representing a 61% conversion to syringaldehyde. Under similar conditions using 5-chlorovanillin at any of 130° C., 140° C., or 175° C., no syringaldehyde was detected. This decreased conversion of the 5-halovanillins to syringaldehyde from 5-iodo- through 5-bromo- to 5-chloro- is in agreement with the known reactivities of halogen substituted aromatic compounds.

This method for the preparation of large amounts of syringaldehyde has since been used very successfully in our laboratories.

EXPERIMENTAL*

Reagents.—The 5-halovanillins were prepared according to the following previously reported procedures: 5-iodovanillin (m.p. 178.5–179.5° C.) by the method of Erdtman (6)**; 5-bromovanillin (m.p. 164° C.) by McIvor and Pepper (8), and 5-chlorovanillin (m.p. 160.5–162° C.) according to Hopkins and Chisholm (7).

Copper Catalyst A.—The early experiments were carried out using a copper preparation prepared by the addition of zinc to copper sulphate solution according to the method of Brewster and Groening (4). The catalyst was prepared immediately prior to each run and washed with 10 portions of absolute methanol before use.

Copper Catalyst B.—British Drug Houses' precipitated copper powder, Reagent Grade, was used in the later experiments.

Apparatus.—All the reactions were carried out in a stainless steel liner, capacity 1080 ml., of an Aminco high pressure hydrogenator, Model No. 406-01 DA. This apparatus served as a rocking autoclave. A Brown Indicating Controller (0–600° C.) coupled with an Aminco variable voltage transformer inserted into the automatic heating circuit permitted temperature control to within ±4° C. A Beckmann Model DU spectrophotometer was used to obtain the ultraviolet absorption data.

Procedure Employed in Runs 11–17

These runs (Table II) were maintained at the stated reaction temperatures for one hour, after which the bomb was cooled slowly. In each case the product

* *All melting points are corrected.*

** *It appears that the 0.2 N sodium hydroxide reported should read 2.0 N sodium hydroxide.*

was diluted with water (500 ml.) and filtered to remove the copper. The filtrate, which varied in color from yellow to orange red, was analyzed by the chromatographic–spectrophotometric method.

The chromatography was carried out according to the method of Stone and Blundell (13). Strips of Whatman No. 1 filter paper, 22 in. × 6 in., were spotted along a base line with the alkaline reaction mixture. The volumes of the drops were measured by a 1 ml. capacity Emil Greiner ultramicroburette which was graduated in 0.001 ml. divisions. After acidification of the material on the paper using acetic acid vapor, the development was conducted in a descending manner in an apparatus similar to that described by Consden *et al.* (5). Water was placed in the bottom of a tall glass cylinder and the organic phase from a 10: 1: 1 mixture of petroleum ether (b.p. 100–120° C.), di-*n*-butyl ether, and water was placed in the small trough near the top and also in a small beaker placed on the bottom of the tightly closed vessel which was allowed to stand for one-half hour prior to putting the paper in place. After development for 10 hr., the paper strips were removed, and the test strip cut off and sprayed with a 1% solution of ferric chloride followed by a 1% solution of potassium ferricyanide, which indicated, by pronounced blue spots, the position of the phenolic compounds (2). The main chromatogram was then cut into horizontal strips, each of which contained only one compound which was separately extracted with ethanol in Soxhlet extractors for two hours. Each extract was transferred to a 50 ml. volumetric flask containing 4 ml. of 0.2 *N* potassium hydroxide in ethanol, and made up to 50 ml. with ethanol.

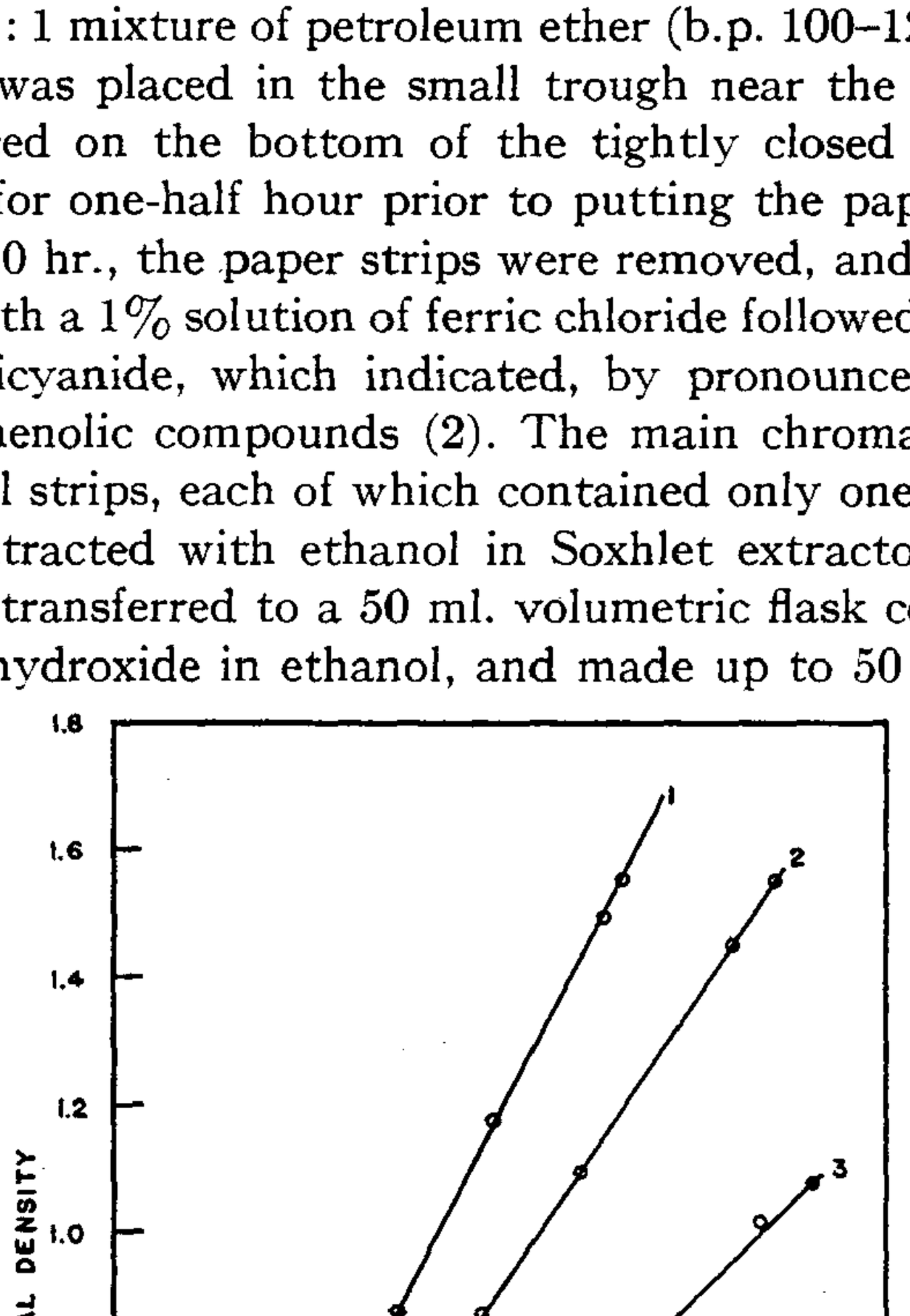


FIG. 2. Concentration vs. optical density curves in alkali-ethanol for (1) vanillin, (2) syringaldehyde, and (3) 5-iodovanillin.

The concentration of the extract was then determined by the measurement of its optical density and by making use of previously determined optical density versus concentration curves (Fig. 2). The wave lengths used were those determined by an examination of the ultraviolet absorption spectra of the compounds in alcoholic potassium hydroxide and were 368, 352, and 356 mμ for syringaldehyde, vanillin, and 5-iodovanillin, respectively.

Syringaldehyde.—Run 16 serves to illustrate a typical preparation of syringaldehyde by this method. Sodium (10.0 gm.) was dissolved in anhydrous methanol (250 ml.). This solution together with 5-iodovanillin (13.0 gm.) and British Drug Houses' precipitated copper powder catalyst (12.8 gm.) was heated in the rocking autoclave at 124–128° C. for one hour. After cooling, the reaction product was diluted with water (500 ml.), filtered to remove the copper, and acidified with hydrochloric acid. A small amount of unchanged 5-iodovanillin precipitated and was removed by filtration. The filtrate was extracted with chloroform (5 × 200 ml.) and the chloroform extract back extracted first with a few milliliters of sodium thiosulphate, to remove any free iodine, and then with water (2 × 10 ml.). After drying over anhydrous sodium sulphate the chloroform solution was concentrated to a small volume by distillation. The residue was crystallized from Skellysolve "C", yielding light yellow needles (7.28 gm.) (85.5%), m.p. 109–110° C. A mixed melting point with authentic syringaldehyde prepared according to Pearl (9) showed no depression. A similarly obtained product, recrystallized several times from Skellysolve "C" and twice from water, melted at 109.8–110.2° C.

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