Notes

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Tetsuji Kametani, Keiichiro Fukumoto, and Yukio Nomura : Studies on the Syntheses of Heterocyclic Compounds. LIII.[*1] The Formation of Vanillide and Polyvanillide.[*2]

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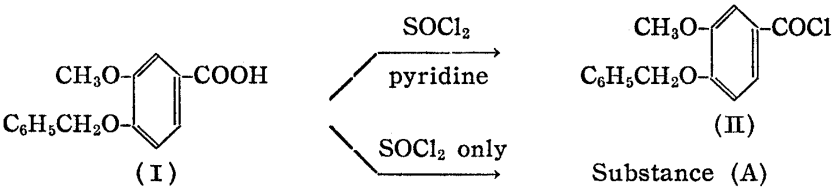
In order to obtain 3-methoxy-4-benzyloxybenzoyl chloride (II), which was required as starting material for water-soluble papaverine derivatives,[1] etc.,[2] 4-benzylvanillic acid (I) was treated with thionyl chloride, using pyridine as a catalyst. When pyridine was not used as catalyst, a great deal of insoluble matter (A) was obtained on heating the reaction mixture for more than 30 minutes and only a scarce amount of acid chloride (II) was obtained. Even when heated for a prolonged period, no chloride was formed. The thionyl chloride used in this study had been stored, sealed in a transparent test tube and allowed to stand for several months after distillation. Although the thionyl chloride used was no different from freshly distilled substance, its properties were examined.



Freshly distilled thionyl chloride also produced a large amount of substance insoluble in ether. This phenomenon has been observed in the synthesis of acyl chloride (II). It was found, as explained later, that the polymer, which should be termed a cyclic lactone or polyester, was formed by way of the removal of benzyl chloride. In the chlorination of acylated hydroxycarboxylic acid by thionyl chloride, pyridine was found to be necessary not only in order to increase the reaction velocity, but also to prevent formation of the polymer.

This substance (A) was collected either by filtration after removal of excess of thionyl chloride by distillation or by filtraton, followed by washing with dehyd. ether without removal of thionyl chloride, As substance (A) was insoluble in ether, it was washed with ether and purified. Benzyl chloride was obtained from the ethereal extracts and ether washing. Substance (A) obtained is considered to be formed via acid chloride (II). 4-Benzylvanillic acid was first chlorinated with an excess of thionyl chloride in the presence of a few drops of pyridine. The acid chloride obtained above was again heated with excess of thionyl chloride, obtaining the same insoluble substance (A).

Substance (A) is insoluble in most organic solvents, but is slightly soluble in dioxane. As it was difficult to purify it by recrystallization, it was sublimed at reduced pressure. White, yellowish needles of m.p. 199~201° were obtained in a yield of about 30%. This sublimate was very readily soluble in most organic solvents and the melting

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[*1] Part LII : This Bulletin, **7**, 567(1959).

[*2] This study was reported at the monthly meeting of the Kinki Local held on December 20, 1958.

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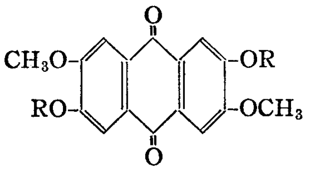
1) T. Kametani : Yakugaku Zasshi, **71**, 323(1951).

2) T. Kametani, Y. Itoh, S. Aonuma : *Ibid.*, **74**, 1303(1954).

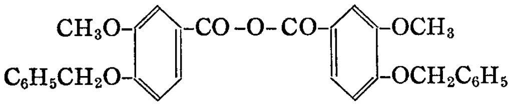
point was lower than the melting point of substance (A). The sublimate was similar to vanillic acid with respect to its melting point. The formation of vanillic acid from the decomposition of (A) was considered. This was, however, disproved by a mixed melting point test. Furthermore, the sublimate was insoluble in sodium bicarbonate solution, but was readily soluble in sodium hydroxide solution and gradually dissolved in sodium carbonate solution.



(III) R= $CH_2C_6H_5$

(IV) R= H

Substance (A) was first considered to be the anthraquinone derivatives, (III) or (IV). From the result of an elementary analysis, the calculated value of (A) agreed with the substance (IV), but, when it was heated with 10% NaOH solution over a free flame for some time, it was very easily saponified, giving vanillic acid. In addition, the result of ultraviolet absorption spectra did not agree with 2,6-dihydroxyanthraquinone by Ikeda, *et al.*[3] Although anthraquinone gives benzoic acid by alkali fusion, the decomposition is not considered to be as simple under such mild conditions. Consequently, anthraquinone derivatives could not have been formed. 4-Benzylvanillic anhydride (V) was then considered to have been formed. Synthesis of the anhydride, m.p. 131~132°, was performed by adding the sodium salt of 4-benzylvanillic acid to the acyl chloride (II) prepared from acid (I) in the presence of pyridine catalyst, and refluxing in toluene. When ether was used as a solvent, the anhydride could not be obtained. Substance (A) of course is different from the anhydride, in view of the elementary analysis and melting point results.



(V)

The infrared absorption band of this compound, that is the polymer, was at 5.73 μ (1745 cm^{-1}). Dioxane-insoluble and -soluble parts of substance (A) were used as samples, and were found to be identical. Phenyl esters usually show absorption bands between 5.70 and 5.92 μ.

Consequently substance (A) was considered to be a polymer, which consists of many molecules of vanillic acid and ester linkages because (1) infrared absorption spectrum showed the band of ester at 5.73 μ; (2) the calculated value of the polymer, $(C_8H_6O_3)_n$, was in agreement with analytical data; (3) it was quickly saponified by 10% NaOH aqueous solution, giving vanillic acid; (4) it did not change when heated with water or with mineral acid such as dilute hydrochloric acid or sulfuric acid; (5) the melting point was higher than 300°; (6) it did not dissolve in most organic solvents; (7) benzyl chloride was obtained as a by-product in the chlorination of 4-benzylvanillic acid; and (8) it was not in agreement with anthraquinone or the anhydride. Accordingly the insoluble substance (A) was considered to be a polyester, but the structure of sublimate (B) could not be explained. In order to clarify the relation between the compounds which gave the same analytical value, the molecular weight of both compounds (A) and (B) were determined by Rast's procedure. From the results the former was found to be a tetramer and the latter a dimer.

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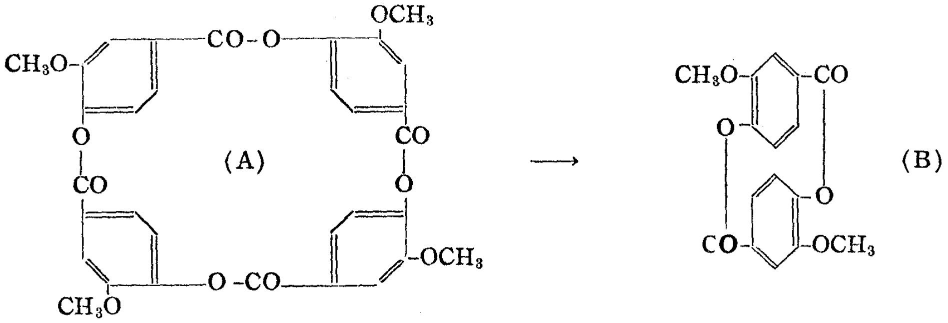
[3] T. Ikeda, Y. Yamamoto, K. Tsukida, S. Kanatomo: Yakugaku Zasshi, **76**, 217(1956).



The existence of a report concerning formation of polyesters, accompanied by the removal of benzyl chloride during chlorination, is yet not known. In general, carboxylic acids containing alcoholic hydroxyl groups respond differently to the action of heat or to dehydrating agents depending upon the relative position of the two functional groups. Glycolic acid contains both types of groups required for esterification and opportunity therefore exists either for formation of an internal ester linkage, or for production of a polyester under the influence of an acid esterification catalyst or of heat. The polyglycolide is obtained from glycolic acid and gives glycolide which is formed by the condensation between two molecules in vacuum distillation. In the present case of 4-benzylvanillic acid, however, the dehydration in a molecule is difficult due to steric hindrance, and the sublimate, that is, dimer formed between two molecules, is considered to exist. Consequently, the polymer (A) was named polyvanillide, substance (A), tetravanillide, and sublimate (B), divanillide.

In addition, the same reaction was examined in the case of vanillic acid in place of 4-benzylvanillic acid. The same insoluble substance (A) was formed. According to infrared absorption spectrum and determination of molecular weight, both compounds were found to be identical, but the yield in case of vanillic acid was less than that from 4-benzylvanillic acid. Furthermore, while substance (A) was heated with pyridine for a prolonged time for purification purposes, the compound of m.p. 272~273° was obtained by leaving the soluble part in pyridine for a long time[*4] and by recystallization from pyridine several times. According to elementary analysis, it agreed with the calculated value of polyvanillide. Although this compound may be considered to be a trimer, the substance could not be obtained a second time by heating the substance (A) with pyridine. As regards the properties of thionyl chloride used further studies will be conducted and reported at a later date.

Experimental[*5]

Reaction between 3-Methoxy-4-benzyloxybenzoic Acid and Thionyl Chloride; Formation of Substance (A) (Polyvanillide)—On mixing 3.5 g. of 4-benzylvanillic acid to 6.3 g. of $SOCl_2$, the heat of formation was immediately recognized, and the mixture was heated for 1 hr. on a water bath at 95~100°. In this case the acid dissolved almost completely in $SOCl_2$ after about 8 min. and the solution colored yellowish. Reddish black crystalline substances began to separate after 15 min. and the reaction mixture nearly solidified after 20 min. After cool, dehyd. ether was added to the reaction mixture and grayish white substance was collected by filtration. This amorphous powder was washed with Et_2O and Me_2CO until it was decolorized, 1.8 g. of grayish white powder being obtained. Its yield was 88.5% of the theoretical amount as a tetramer. m.p. >300°. This hardly dissolved in most organic solvents and was slightly soluble in dioxane or AcOH. The qualitative test for Cl, S, and P was negative. The infrared spectra of portions soluble and insoluble

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[*4] A soluble part dissolved in pyridine while warming was allowed to stand for more than 2 months.

[*5] All m.p.s are not corrected. Analysis was carried out by Mr. Y. Fukuda of Osaka University and infrared spectra were determined by Miss Suzuki.

in dioxane were the same, both having the same absorption band at 5.73 μ. *Anal.* Calcd. for $(C_8H_6O_3)_4$: C, 64.00; H, 4.03; mol. wt., 600. Found : C, 64.37; H, 5.11; mol., wt. 612.

When the ether washings were washed with $NaHCO_3$ solution and dried over Na_2SO_4, 0.3 g. of benzyl chloride, b.p. 180~181°, was obtained by distillation.

Sublimation of Substance (A)—When 0.1 g. of substance (A) was sublimed at 250° in an oil bath under a reduced pressure of 3 mm. Hg, 0.03 g. (30%) of divanillide was obtained as yellowish needles, m.p. 199~201°. This substance was readily soluble in EtOH, Et_2O, and benzene, soluble in hot water and 10% NaOH solution, but insoluble in $NaHCO_3$ solution. When this substance was admixed with vanillic acid, they melted over a range of 177~188°. This was considered to be divanillide according to the result of molecular weight measurement. *Anal.* Calcd. for $(C_8H_6O_3)_2 \cdot 1/3 H_2O$: C, 63.75; H, 4.13; mol. wt., 306. Found : C, 63.54; 5.09; mol. wt., 296.

Reaction of 3-Methoxy-4-benzyloxybenzoyl Chloride and Thionyl Chloride—A mixture of 1 g. of 4-benzylvanillic acid and 1.8 g. of $SOCl_2$, after addition of a few drops of pyridine, was heated on a water bath for about 15 min. and excess of $SOCl_2$ was removed by distillation under a reduced pressure. Afterwards the residue was extracted with dehyd. Et_2O, filtered, and evaporated, 1 g. of 4-benzylvanilloyl chloride, m.p. ca. 80°, being obtained.

To the above-obtained acid chloride, 1.8 g. of $SOCl_2$ was again added and the mixture was heated on a water bath. The mixture gradually began to solidify and the whole mixture solidified after 30 min. The solid was collected and washed with a large quantity of dehyd. Et_2O, 0.6 g. of yellowish powder being obtained. This was found to be identical with the substance (A).

Hydrolysis of Substance (A) with 10% NaOH—i) A mixture of 19 g. of substance (A) and 25 cc. of 10% NaOH solution was heated on a water bath for 1 hr. giving a clear, reddish brown solution. After filtration, the filtrate was decolorized with activated charcoal and acidified with 10% HCl. The turbid mixture was allowed to stand overnight and 0.25 g. of needles of m.p. 200~205° was obtained. It melted at 206~207° after several recrystallizations from water and it agreed with an authentic sample of vanillic acid.

ii) A mixture of 0.5 g. of substance (A) and 5 cc. of 10% NaOH solution was heated over a free flame for 1 hr. After the reaction, 0.4 g. (83.5%) of m.p. 192° was obtained by the usual treatment. This was recrystallized from water and vanillic acid of yellowish white crystals, m.p. 207~209°, was obtained. It dissolved in 5% $NaHCO_3$ solution.

3-Methoxy-4-benzyloxybenzoic Anhydride (V)—A solution of 0.5 g. of 4-benzylvanillic acid dissolved in a hot solution of 0.2 g. of $NaHCO_3$ in 10 cc. of water was concentrated under a reduced pressure after filtration and 0.5 g. of Na salt was obtained as a white powder. To this Na salt, 0.5 g. of 4-benzylvanilloyl chloride, prepared from a mixture of 0.5 g. of 4-benzylvanillic acid, 0.9 g. of $SOCl_2$, and a few drops of pyridine, was added and the mixture was refluxed in an oil bath for 2.5 hr. in the presence of 10 cc. of dehyd. toluene. The crystals were separated at once while cooling. The anhydride was recrystallized from toluene to 0.9 g. of colorless scaly crystals, m.p. 134~134.5°. *Anal.* Calcd. for $C_{30}H_{26}O_7$: C, 72.28; H, 5.26. Found : C, 72.43; H, 5.24.

Preparation of Tetravanillide from Vanillic Acid—A mixture of 0.3 g. of vanillic acid and 0.5 cc. of $SOCl_2$, in which heat formation was immediately recognized, was refluxed on a water bath. Vanillic acid disappeared immediately and yellowish white crystals began to separate after about 10 min., the mixture being almost solidified after 1 hr. After cool, the solid reaction mixture was washed on a filter with dehyd. Et_2O and Me_2CO until it was colorless and 0.2 g. (74.6%) of tetramer was obtained. This was identified with the tetravanillide prepared from 4-benzylvanillic acid by infrared spectrum. Molecular weight measured by the Rast method was 606.06 and this value agreed with the value of 600 calculated for $(C_8H_6O_3)_4$.

Treatment of Substance (A) with Pyridine—The substance (A) prepared from 2 g. of 4-benzylvanillic acid and 4 g. of $SOCl_2$ was extracted with pyridine with heating and a soluble portion dissolved in pyridine with warming was allowed to stand for more than two months. A white amorphous powder of m.p. 272~273°(decomp.) was obtained after recrystallization from pyridine. *Anal.* Calcd. for $(C_8H_6O_3)_n$: C, 64.00; H, 4.03. Found : C, 64.64, 64.63; H, 4.69, 4.69.

Summary

Treatment of 4-benzylvanillic acid with thionyl chloride, without use of a catalyst, afforded a polymer and sublimation of this polymer *in vacuo* gave a dimer of vanillide. According to the molecular weight determination and infrared absorption spectra, this polymer was recognized to be a tetramer and to have an ester, so that the polymer must have been formed from four molecules of the acid by removal of benzyl chloride during the reaction. Therefore, it is thought to be a polyester. The sublimate on the other hand was found to be a dimer formed from the tetramer by thermal decomposition.

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