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Otto Nitz

State University of Iowa

L. Chas. Raiford

State University of Iowa

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THE EFFECTS OF SUBSTITUENTS ON THE REACTIONS OF CERTAIN VANILLIN DERIVATIVES

OTTO NITZ AND L. CHAS. RAIFORD

As far back as 1894 Victor Meyer (1) reported research on the effect of an ortho substituent influencing the reactivity of an active group. He observed among other things that methyl, chloride, bromide, or iodide substituents produced a steric hindrance effect roughly proportional to the molecular weight of the substituent. He also observed that the nitro group had an effect out of proportion to its weight, which indicated that its chemical nature also had a bearing. Cases have been reported in which the nitro group had an accelerating effect rather than a hindering one (2).

In view of the above facts it was interesting to prepare the oxime of 2-nitro and 6-nitrovanillin, and study their behavior. Vanillin was first acetylated by the use of acetic anhydride in ether and was then nitrated by the use of a large excess of fuming nitric acid with the temperature kept below six degrees (3). This produced a mixture of the acetates of 2-nitro and 6-nitrovanillin. This was hydrolyzed and the isomers were separated by making use of their differing solubilities in cold alcohol. The 6-nitrovanillin was present to the extent of about four per cent. This was the only satisfactory source we had for 6-nitrovanillin.

The oximes of both 2-nitro and 6-nitrovanillin were prepared by refluxing the aldehyde with hydroxylamine hydrochloride in carbonate solution. A yield of 95 per cent was obtained in the case of the 2-nitro isomer.

On treatment of 2-nitrovanillin oxime under varying conditions with acetic anhydride a monoacetate and a diacetate were obtained. These were hydrolyzed with the greatest ease to the original oxime, and the monoacetate could be converted to the diacetate. Because of the instability of the compounds analytical data was not particularly good.

2-nitrovanillin oxime was converted to 2-nitro-3-methoxy-4-acetoxybenzotrile by more drastic treatment with acetic anhydride. The yield was practically quantitative. The acetyl group was removed by hydrolysis in acetic acid solution.

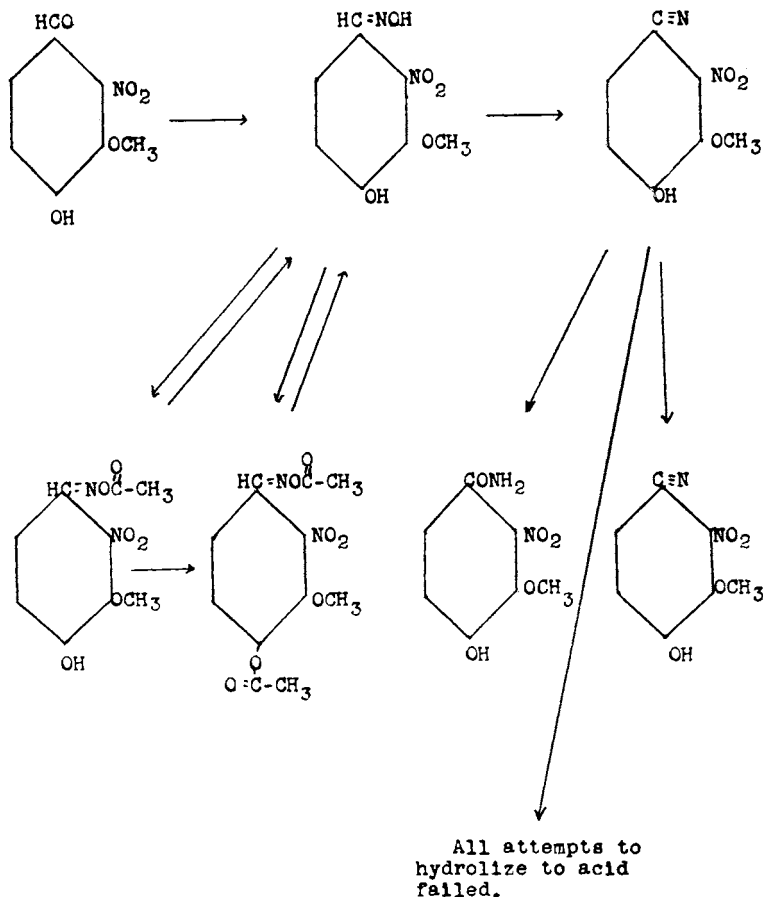
When 2-nitro-3-methoxy-4-acetoxybenzotrile was hydrolyzed

in dilute sodium hydroxide solution about a 50 per cent yield of the corresponding amide was obtained. The yield here was much smaller than in the previous reactions.

Many attempts were made under differing conditions to hydrolyze the nitrile to the acid stage, but all failed. It was shown that ammonia was always evolved, but each attempt yielded only an oil which was evidently a decomposition product.

All compounds containing the 2-nitro group darken in a few days on exposure to daylight. In certain of the compounds this was accompanied by a slow drop in the melting point.

TABLE 1
2-NITROVANILLIN SERIES

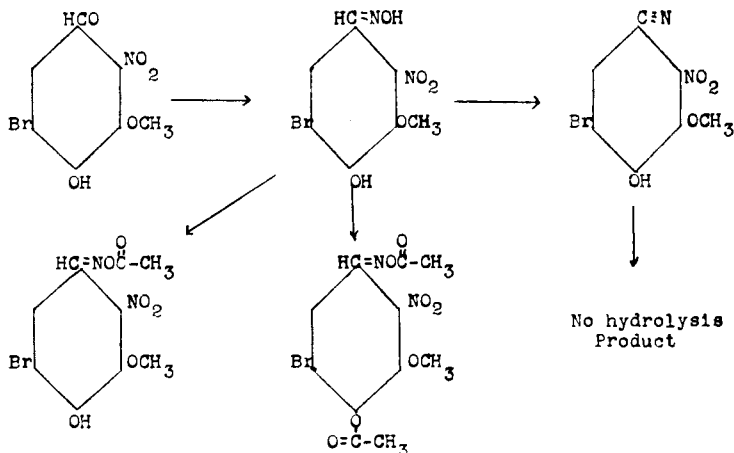


These results indicate that the ortho nitro group exerts no appreciable hindering influence to any reaction of the active groups thus far studied other than hydrolysis. Formation of decomposition products points to the conclusion that the chemical nature of the nitro group, decreasing the general stability of the molecule, has a bearing as well as its mechanical interference with the active group. Table 1 outlines the reactions.

On the theory that the presence of a halogen atom in the ring might stabilize the molecule sufficiently to permit hydrolysis of the nitrile, 2-nitrovanillin was brominated directly. The product was 2-nitro-5-bromovanillin. It was subjected to the same series of reactions as 2-nitrovanillin, with exactly analogous results. The oxime, mono and diacetate and nitrile were easily obtained. All attempts to hydrolyze the nitrile to the acid resulted in decomposition. See Table 2. Evidently then the presence of the halogen in the ring has little or no bearing on the effect of the nitro group.

TABLE 2

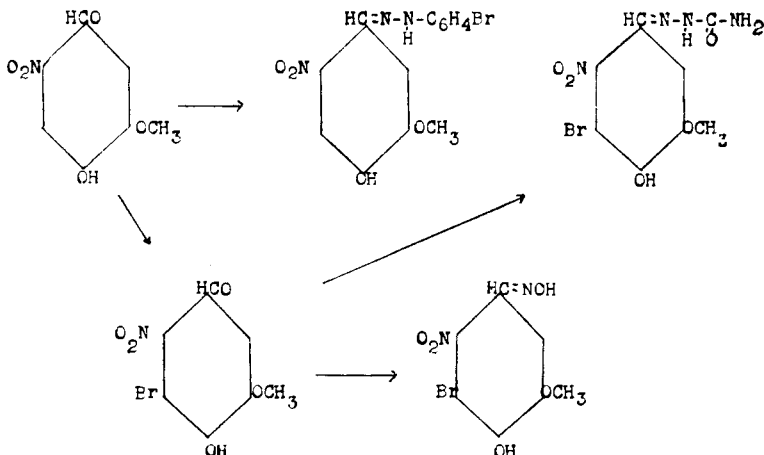
2-NITRO-5-BROMOVANILLIN SERIES-



A study was now made of the effect of the nitro group in the other ortho position to the aldehyde group; in other words, 6-nitrovanillin. Our only source of this material was the three or four per cent formed in the preparation of 2-nitrovanillin. With this very small supply the investigations were necessarily limited. The *p*-bromophenylhydrazone of 6-nitrovanillin was prepared without difficulty. 6-nitrovanillin was brominated directly by the use of iron and iodine as a catalyst. The product was 6-nitro-5-bromovanillin. The oxime and semicarbozone of 6-nitro-5-bromovanillin

were readily obtained in practically quantitative yields. See Table 3. The investigation ended here. It would be of interest to know if the nitro group in the 6 position exerts the same hindering influence to the hydrolysis of the nitrile as it does in the 2 position. See Table 5 for comparison of yields.

TABLE 3
6-NITROVANILLIN SERIES



A second portion of this investigation deals with the possibility of obtaining isomeric oximes of substituted vanillins. Brady and Dunn (4) state that "certain negative substituents in the benzene ring seem to favor the existence of isomeric oximes." They also claim that "no evidence of the existence of a second isomeride has been obtained in the case of any of the hydroxybenzaloximes." Raiford and Oberst prepared a series of oximes of nitrovanillins and halogenated nitrovanillins but were not able to obtain a second isomeride. They conclude that "introduction of more negative substituents into the phenyl nucleus of vanillin does not aid in the formation of stereoisomeric oximes." They further conclude that "when in certain hydroxybenzaloximes the hydrogen of the hydroxyl group is replaced by a negative radical, it is possible to isolate two isomerides, provided a negative group is not ortho to the aldehyde radical." In this work it was desired to test further the effect of negative substituents on transmutation, and to determine what effect the methoxy group replacing the hydroxyl group in the ring might have.

To effect these conversions the oxime was in all cases dissolved in ether dried over sodium, and dry hydrogen chloride gas was

passed in. The precipitate was treated with a sodium carbonate solution to decompose the salt in the cases in which it was formed. Table 4 lists the negatively substituted vanillins and summarizes the results. In no case was it possible to transmute the halogenated vanillin oxime. However when the hydroxy group was converted to a methoxy group transmutation was possible in every case except that of 2-nitromethylvanillin oxime. The original form of the oxime is probably the anti form, and this is transmuted to the syn

TABLE 4
EFFECT OF METHYLATING VANILLIN

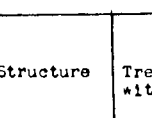
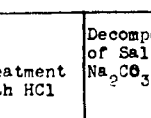
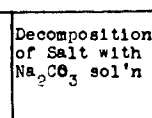
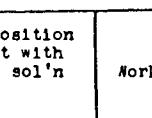
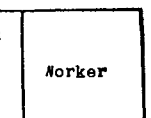
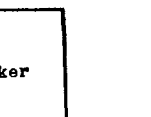


Name	Structure	Treatment with HCl	Decomposition of Salt with Na_2CO_3 sol'n	Worker
5-Bromovanillin oxime		Salt formed	No transmutation	Brady
5-Bromomethylvanillin oxime M.P. 83		Salt formed M.P. 120-125	Transmutation M.P. 108	Brady
5-Chlorovanillin oxime M.P. 170-172		Salt formed M.P. 172-174	No transmutation	Nitz
5-Chloromethylvanillin oxime M.P. 90		Salt formed M.P. 117	Transmutation M.P. 114	Hann
5-Iodovanillin oxime M.P. 177-178		Salt formed M.P. 172-174	No transmutation	Nitz
5-Iodomethylvanillin oxime M.P. 107-109		Salt formed M.P. 139-142	Transmutation M.P. 117-119	Nitz
2-Nitrovanillin oxime M.P. 131-133		Salt formed M.P. 117-120	No transmutation	Oberst
2-Nitromethylvanillin oxime M.P. 145-147		No salt formed		Nitz

TABLE 5

Name	Formula	Yield	Yield Corresponding 2-nitro-5-bromo-vanillin derivative	Yield Corresponding 6-nitro-5-bromo-vanillin der
2-nitrovanillin oxime		95.3 %	82.5 %	98.2 %
Acetate of 2-nitrovanillin oxime		86.4 %	49.5 %	
Acetate of acetyl-2-nitrovanillin oxime		94.5 %	90.5 %	
2-nitro-3-methoxy-4-acetoxybenzotrile		100 %	100 %	
2-nitro-3-methoxy-4-hydroxybenzotrile		94.5 %		
2-nitro-3-methoxy-4-hydroxybenzamide		50 %	None	
2-nitrovanillic acid		None	None	

form when transmutation occurs. Efforts to definitely establish the configuration have been made but the work is not complete.

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ORGANIC LABORATORIES,
STATE UNIVERSITY OF IOWA,
IOWA CITY, IOWA.