[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

FRIEDEL AND CRAFTS' REACTION IN THE PYRIDINE SERIES

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Engler[1] and Wolffenstein and Hartwich[2] made unsuccessful attempts to condense acid chlorides with pyridine in the presence of aluminum chloride. When phthalic anhydride is used with pyridine in benzene solution and aluminum chloride, only phthalic acid is obtained because an addition compound of phthalic anhydride and pyridine is formed which prevents the reaction and even prevents the formation of *o*-benzoylbenzoic acid. It was thought that if the hydrochloric acid salt of pyridine or the alkyl halide or acyl halide addition compound were used, there would be no addition compound with the acid anhydride. These compounds, however, were found to be very slightly soluble in benzene or carbon disulfide and after the Friedel and Crafts' reaction only *o*-benzoylbenzoic acid was obtained from the benzene solution and phthalic acid from the carbon disulfide solution. When these addition compounds of quinoline were used the results were also unsatisfactory.

Bernthsen and Mettegang,[3] Jeiteles,[4] and Kirpal[5] have studied the reaction of quinolinic anhydride with benzene and aluminum chloride. Just,[6] Fulda[7] and Halla[8] used toluene instead of benzene and Halla also used xylene. In each case only derivatives of picolinic acid were obtained and no derivatives of nicotinic acid. Derivatives of picolinic acid are easily distinguished from derivatives of nicotinic acid by the red color given when they are dissolved in aqueous or alcoholic solution of ferrous sulfate.

In the present research, the work of Just, Fulda and Halla has been extended using naphthalene, acenaphthene and diphenyl, respectively. In each case only derivatives of picolinic acid were obtained and in the case of naphthalene both the α-naphthoyl and β-naphthoyl derivatives were formed. The yield never exceeded 22%. Phenylpyridophthalide has also been used in the Friedel and Crafts' reaction and in each case the product was a derivative of picolinic acid and there was no evidence of the formation of a ketone. This corresponds with the results of King[9] who used phthalides. The yields were about 25–30%.

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[1] Engler, *Ber.*, **24**, 2525 (1891).

[2] Wolffenstein and Hartwich, *Ber.*, **48**, 2043 (1915).

[3] Bernthsen and Mettegang, *Ber.*, **20**, 1208 (1887).

[4] Jeiteles, *Monatsh.*, **17**, 515 (1896).

[5] Kirpal, *ibid.*, **27**, 371 (1906); **31**, 295 (1910).

[6] Just, *ibid.*, **18**, 452 (1897).

[7] Fulda, *ibid.*, **21**, 981 (1900).

[8] Halla, *ibid.*, **32**, 747 (1911).

[9] King, THIS JOURNAL, **49**, 562 (1927).

In studying the Friedel and Crafts' reaction using the acid chlorides of the monomethyl esters of quinolinic acid, it has been shown that the ester of m. p. 108° gave two products and is, therefore, a mixture.

Quinolinic Anhydride with Aluminum Chloride and Naphthalene in Benzene Solution.—Thirty g. of anhydride and 30 g. of naphthalene were partially dissolved in 200 cc. of benzene and 75 g. of aluminum chloride were added. After heating for twenty-four hours on the water-bath, dilute hydrochloric acid was added and the benzene and excess naphthalene were removed by distillation with steam. The remaining tar was boiled several times with hydrochloric acid and the acid solutions were combined. Addition of cupric chloride solution to the combined acid solutions gave a grayish-blue precipitate which was filtered off and the filtrate on standing gave a bright blue precipitate. These precipitates were suspended separately in hot water, decomposed by hydrogen sulfide and filtered. The filtrates were evaporated to dryness and the filtrate from the bright blue precipitate gave only quinolinic acid. The filtrate from the first precipitate gave a residue part of which was soluble in dilute acetic acid, m. p. 145°, and the insoluble part melted at 155°. The total yield was 22% but much the larger part melted at 145° and qualitative tests showed both to be derivatives of picolinic acid. The silver salt of the product melting at 155° was analyzed.

Anal. Calcd. for $C_{17}H_{10}O_3NAg$: Ag, 28.1. Found: 28.1.

The product melting at 145° was fused with sodium hydroxide and gave β-naphthoic acid. The latter is, therefore, β-naphthoylpicolinic acid (1,2) and the former α-naphthoylpicolinic acid (1,2).

Quinoline Anhydride with Aluminum Chloride and Acenaphthene in Benzene Solution.—Ten g. of quinolinic anhydride, 11 g. of acenaphthene, 23 g. of aluminum chloride, and 100 cc. of benzene were used. The product obtained from the decomposition of the cupric chloride precipitate was recrystallized from dilute acetic acid; m. p. 168–169°; yield, 10%. This product was shown to be a derivative of picolinic acid and is believed to be 4-acenaphthoylpicolinic acid, as Lorriman[10] has shown that phthalic anhydride reacts with acenaphthene to give the 4-acenaphthoyl derivative.

Quinolinic Anhydride with Aluminum Chloride and Diphenyl in Benzene Solution.—Three g. of quinolinic anhydride, 5 g. of diphenyl, 10 g. of aluminum chloride and 100 cc. of benzene were used. This yielded a yellow solution and a bright yellow precipitate. The solution after treatment with cupric chloride gave 2.5 g. of benzoylpicolinic acid. The yellow precipitate after solution in sodium hydroxide and acidification was a white, flaky precipitate; m. p. 170–171°; yield, 1 g. On fusion with sodium hydroxide this compound gave *p*-phenylbenzoic acid and is, therefore, *p*-phenylbenzoylpicolinic acid (1,2).

Phenylpyridophthalide with Aluminum Chloride and Benzene.—Three g. of phenylpyridophthalide was partially dissolved in 100 cc. of benzene and 10 g. of aluminum chloride added. After removal of benzene the solution yielded 1.2 g. of white, needle-like crystals. On recrystallization these melted sharply at 155°. This compound is diphenylmethylpicolinic acid (1,2).

Anal. Calcd. for $C_{19}H_{14}O_2NAg$: Ag, 27.2. Found: 27.0.

The Monomethyl Esters of Quinolinic Acid.—Two monomethyl esters of quinolinic acid have been described, m. p. 123° and m. p. 108°, but there has been some confusion about their identification.

These esters were prepared from quinolinic anhydride and after separation of the ester of m. p. 123° a much smaller amount of the ester of m. p. 108° was obtained.

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[10] Lorriman, This Journal, 47, 211 (1925).

The first ester was dissolved in thionyl chloride, the solution evaporated to dryness and toluene and aluminum chloride added. The product from this Friedel and Crafts' reaction was *p*-tolylpicolinic acid (1,2), confirming the view that this ester of m. p. 123° was α-monomethyl quinolinate.

When the second ester was dissolved in thionyl chloride and the resulting acid chloride treated with benzene and aluminum chloride, the product melted at 170°. Kirpal in the same experiment had obtained a product with m. p. 176° which he called α-benzoylnicotinic acid. On treating the product of m. p. 170° with hot water two fractions were obtained. The soluble part was benzoylnicotinic acid (1,2) and the insoluble part melted at about 285°, and as the latter was not a derivative of picolinic acid it was assumed to be benzoylnicotinic acid (1,2). This experiment showed that the substance melting at 108° was a mixture of the two monomethyl quinolinates and that the substance melting at 176° contained considerable amounts of benzoylpicolinic acid (1,2). It also showed that benzoylnicotinic acid melted about 100° higher than had previously been reported by Kirpal.

Various methods were used in an attempt to prepare diphenylpyridophthalide. Quinolinic anhydride, benzene, aluminum chloride and acetic anhydride gave only benzoylpicolinic acid (1,2). The acetyl derivative of benzoylpicolinic acid with benzene and aluminum chloride gave equally unsatisfactory results. Oxidation of diphenylmethylpicolinic acid (1,2) gave a small quantity of a material which may have been the desired substance but there was too little of it for identification.

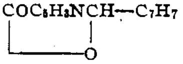
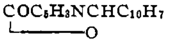
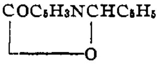
The following table indicates the preparation of the substances obtained in the above experiments and some of their derivatives as well as the preparation of some other pyridine derivatives.

TABLE I

PREPARATION AND PROPERTIES OF COMPOUNDS

Name	Formula	Preparation	Remarks
β-Naphthoylpicolinic acid (1,2)	$C_{10}H_7COC_5H_3NCO_2H$	Quinolinic anhydride, $AlCl_3$ and naphthalene in benzene soln.	M. p. 145°. Chlorohydrate, m. p. 172–173°. Methyl ester, m. p. 80–82°. Hydrate from hot water, m. p. 109°
α-Naphthoylpicolinic acid (1,2)	$C_{10}H_7COC_5H_3NCO_2H$	Quinolinic anhydride, $AlCl_3$ and naphthalene in benzene soln.	M. p. 155°. Chlorohydrate, m. p. 179–180°. Methyl ester, m. p. 100–101°
4-Acenaphthoylpicolinic acid (1,2)	$C_{12}H_9COC_5H_3NCO_2H$	Quinolinic anhydride, $AlCl_3$ and acenaphthene in benzene soln.	M. p. 168–169°. Chlorohydrate, m. p. 175°. Methyl ester, m. p. 113–114°. Hydrate from hot water m. p. 121°
p-Phenylbenzoylpicolinic acid (1,2)	$C_6H_5C_6H_4COC_5H_3NCO_2H$	Quinolinic anhydride, $AlCl_3$ and diphenyl in benzene soln.	M. p. 170–171°
Benzoylnicotinic acid (1,2)	$C_6H_5COC_5H_3NCO_2H$	Monomethyl quinolinate, m. p. 108°, with thionyl chloride and then benzene and $AlCl_3$	M. p. 285°. Methyl ester, m. p. 87°
Dibenzoylpyridine (1,2)	$(C_6H_5CO)_2C_5H_3N$	Benzoylpicolinyl chloride with benzene and $AlCl_3$	M. p. 186–187°
Tolylbenzoylpyridine (1,2)	$C_7H_7COC_5H_3NCOC_6H_5$	Benzoylpicolinyl chloride with toluene and $AlCl_3$	M. p. 190–193°

TABLE I (*Concluded*)

Name	Formula	Preparation	Remarks
p-Tolylpyridophthalide	 $COC_5H_3NCH—C_7H_7$, O	Reduction of *p*-tolylpicolinic acid (1,2) by zinc in ammoniacal soln.	M. p. 144°
β-Naphthoylpyridophthalide	 $COC_5H_3NCHC_{10}H_7$, O	Reduction of β-naphthoylpicolinic acid (1,2)	M. p. 127°
Lactone of β-carbohydroxy-α-pyridylphenyl carbinol	 $COC_5H_3NCHC_6H_5$, O	Reduction of benzoylnicotinic acid (1,2)	M. p. 128°
Diphenylmethylpicolinic acid (1,2)	$(C_6H_5)_2CHC_5H_3NCO_2H$	Phenylpyridophthalide with benzene and AlCl₃	M. p. 153°. Methyl ester, m. p. 109°
Phenyltolylmethylpicolinic acid (1,2)	$C_6H_5C_7H_7CHC_5H_3NCO_2H$	Phenylpyridophthalide with toluene and AlCl₃	M. p. 161°
β-Pyridyldiphenylmethane	$C_5H_4NCH(C_6H_5)_2$	Heating diphenylmethylpicolinic acid (1,2) to 170°	M. p. 78–79°

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Summary

1. Phthalic anhydride with aluminum chloride and various addition compounds of pyridine and of quinoline showed no reaction between the phthalic anhydride and the addition compounds.

2. Quinolinic anhydride with aluminum chloride and naphthalene, acenaphthene and diphenyl, respectively, gave only the corresponding picolinic acid derivatives and no benzoylpicolinic acid except in the case of diphenyl.

3. Various derivatives of picolinic and nicotinic acids have been prepared from the monomethyl quinolinates and it has been shown that the β-monomethyl quinolinate and α-benzoylnicotinic acid, previously described, were mixtures.

4. Phenylpyridophthalide with aluminum chloride and benzene or toluene gave only derivatives of picolinic acid.

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