Anal. Calcd. for $C_{10}H_{20}O_4$: C_2H_5O, 88.2; C, 58.8; H. 9.87. Found: C_2H_5O, 85.8; C, 58.0; H, 9.70.

The petroleum ether insoluble portion of the reaction mixture was covered with toluene and treated with water to liberate ethyl alcohol from the sodium ethoxide produced in the reaction. The water layer was saturated with potassium carbonate and the organic layer was separated. The mixture of organic compounds was distilled and everything collected until pure toluene started to distil. The distillate, when treated with 3,5-dinitrobenzoyl chloride, yielded 10.7 g. of ethyl 3,5-dinitrobenzoate. This corresponds to a 235% yield of alcohol from the reaction between pentaethoxyethane and sodium ethyl to produce ethane, sodium ethoxide and VI.

Tetraethoxyethylene absorbs bromine rapidly with the formation of diethyl oxalate and, presumably, ethyl bromide. No attempt was made to isolate the latter compound. Treatment of the diethyl oxalate so produced with concentrated ammonia gave oxamide, a solid which decomposed without melting when heated to 340° for one minute in a sealed tube and melted with decomposition at 350° when placed in a copper block at that temperature. An authentic sample of oxamide, as well as a mixture of this sample with the amide derived from VI, showed the same behavior, which is in marked contrast to the melting point of 417–419° dec. reported[15] for oxamide in the literature. The diethyl oxalate from VI also was converted to oxalhydrazide by the procedure of Sah[16]; the m. p. of this product was 239–240° dec., as was that of a mixture of this product with an authentic sample of oxalhydrazide.

Summary

Diethoxyacetonitrile has been converted to pentaethoxyethane (ethyl diethoxyorthoacetate). This orthoester reacts with sodium ethyl to give tetraethoxyethylene (diethoxyketene diethylacetal), a colorless liquid, b. p. 195–196°, that shows no tendency to dissociate into carbon monoxide diethylacetal as has been reported by Scheibler and co-workers.

[15] Michael, *Ber.*, **28**, 1632 (1895).

[16] Sah, *Rec. trav. chim.*, **59**, 1036 (1940).

MADISON, WISCONSIN RECEIVED MARCH 22, 1947

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

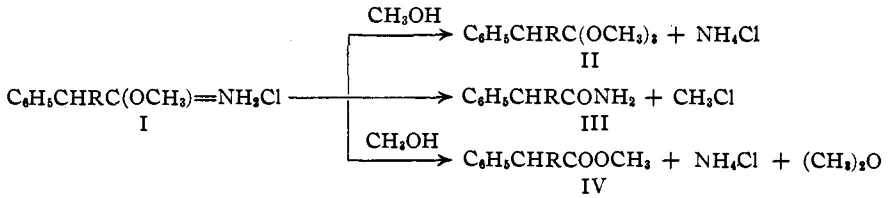
Ester and Orthoester Formation in the Alcoholysis of Iminoester Hydrochlorides. A Proposed Mechanism

BY S. M. MCELVAIN AND CALVIN L. STEVENS[1]

Orthoesters have been used extensively in this Laboratory as intermediates in the preparation of ketene acetals, $RCH{=}C(OR')_2$. When R is alkyl, these acetals are prepared by the action of sodium on the corresponding α-bromoorthoesters[2]; when R is phenyl, the ketene acetals result simply from the pyrolysis of the orthoesters.[3] Consequently, a further extension of the study of ketene acetals, particularly in the direction of the disubstituted compounds $R_2C{=}C(OR')_2$, necessitated the preparation of the corresponding orthoesters.

As previously indicated.[4] the concurrent formation of an amide and an alkyl chloride during the alcoholysis of an iminoester hydrochloride is the chief difficulty that has been encountered in the preparation of orthoesters by the Pinner procedure.[5] Attempts to eliminate or to minimize this undesired side reaction have been reasonably successful when the orthoester has a single α-substituent, but much less so if the orthoester has two α-substituents.[4]

The present paper reports a new complication that has been observed in the attempted preparation of certain α,α-disubstituted orthoesters: the reaction of the iminoester hydrochloride with alcohol to produce the ester, $R_2CHCOOR'$, and an ether, R'_2O. In an attempt to prepare methyl α-phenylorthobutyrate (II, R is C_2H_5) by the alcoholysis of the iminoester hydrochloride (I) derived from α-phenylbutyronitrile, none of the orthoester could be isolated, although the methoxyl content of the products indicated a small amount had been formed; the main products were the amide III together with the ester IV and dimethyl ether.



$$\begin{array}{ll} & \xrightarrow{CH_3OH} \underset{II}{C_6H_5CHRC(OCH_3)_3} + NH_4Cl \\ \underset{I}{C_6H_5CHRC(OCH_3){=}NH_2Cl} & \longrightarrow \underset{III}{C_6H_5CHRCONH_2} + CH_3Cl \\ & \xrightarrow{CH_3OH} \underset{IV}{C_6H_5CHRCOOCH_3} + NH_4Cl + (CH_3)_2O \end{array}$$

However, the methanolysis of the iminoester hydrochloride (I, R is CH_3) derived from α-phenylpropionitrile gave the corresponding orthoester II in 21% yield; accompanying this product was 25% of the amide (III) and 28% of methyl α-phenylpropionate (IV). An intermediate fraction, consisting of approximately equal parts of II and IV, accounted for the remainder of the reaction products.

In the hope that the formation of amide could be prevented, and hence the yield of orthoester increased, the boron trifluoride coördination compound of methyl α-phenyliminopropionate (V)

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[1] Wisconsin Alumni Research Foundation Research Assistant, 1944–1947.

[2] McElvain, *et al.*, THIS JOURNAL, **62**, 1482 (1940); **64**, 1966 (1942).

[3] McElvain and Stevens, *ibid.*, **68**, 1917 (1946).

[4] McElvain and Fajardo-Pinzon, *ibid.*, **67**, 690 (1945).

[5] Pinner, *Ber.*, **16**, 356, 1644 (1883).

was prepared and subjected to alcoholysis. This compound obviously cannot undergo pyrolysis to the amide as does the hydrochloride salt (I). No amide was produced in the methanolysis of V; the reaction products were the ester IV, dimethyl ether and boron fluoride–ammonia

$$\underset{\text{V}}{C_6H_5CH(CH_3)C(OCH_3){=}NHBF_3} \xrightarrow{CH_3OH} \text{IV (R is } CH_3) + H_3N{-}BF_3 + (CH_3)_2O$$

These products formed so readily it appeared that the boron fluoride–ammonia had catalyzed the decomposition of the orthoester as rapidly as it was formed. This seems likely from the fact that an otherwise stable orthoester, methyl orthobutyrate, was smoothly converted to methyl butyrate and dimethyl ether when heated in methanol solution with a catalytic amount of boron fluoride–ammonia.

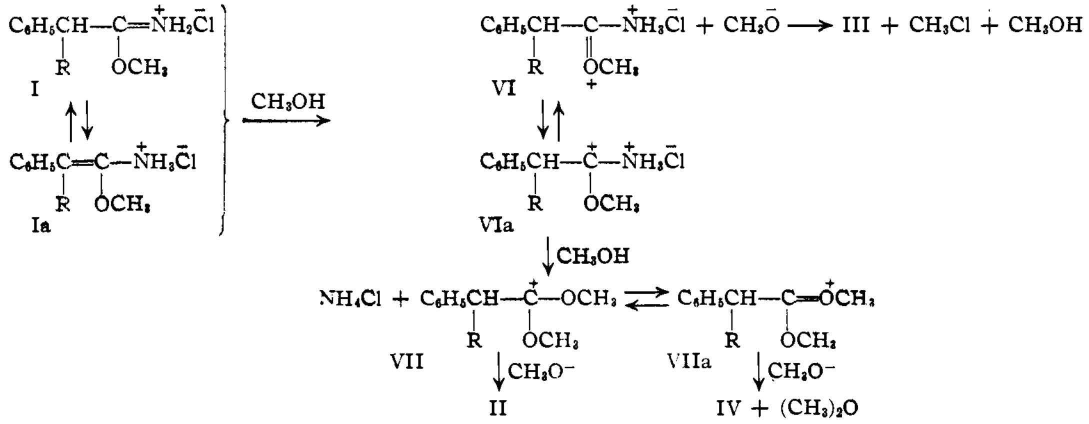
The isolation of some of the ester, ethyl phenylacetate, has been reported[6] in the preparation of phenylketene diethylacetal by the pyrolysis of the alcoholysis product from ethyl phenyliminoacetate hydrochloride. This ester was shown[3] to be produced by the thermal decomposition of the ketene acetal with the concurrent formation of ethylene. This type of ester formation was prevented when the corresponding methyl iminoester hydrochloride was subjected to methanolysis.[3]

Another case of simple ester formation during the alcoholysis of an iminoester hydrochloride recently was noted[7] in this Laboratory in connection with the preparation of pentaethoxyethane. In this case it appeared that the ester (ethyl diethoxyacetate) and diethyl ether resulted from the decomposition of preformed orthoester. This decomposition was shown to be catalyzed by the iminoester hydrochloride and it could be controlled sufficiently to permit the isolation of some orthoester by making the reaction mixture basic with sodium ethoxide at an appropriate stage in the alcoholysis.

The formation of the esters (IV) during the alcoholysis of the salts (I) in the work now described appear to be unrelated to any of the previously observed reactions by which such esters are produced. The formation of the esters (IV) and ether occurs during the alcoholysis of the iminoester hydrochloride and is not the result of decomposition, either thermal or catalyzed, of the orthoesters. The orthoester (II, R is CH_3) is quite thermostable during fractional distillation and the fact that the yields of II are not noticeably affected by making the alcoholysis mixture basic with sodium methoxide before distillation, indicates that the orthoester is not catalytically decomposed by an acidic salt in the reaction mixture as was the case with pentaethoxyethane.[7] Also, dimethyl ether can be isolated from the alcoholysis mixture after it had stood at room temperature for one day. These facts indicate that the formation of the ester (IV) and ether is independent of and takes place concurrently with the production of the orthoester (II).

A factor which appears to have a significant effect on the amount of orthoester produced in the alcoholysis of I is the size of the substituent R. When R is H, only the orthoester, methyl orthophenylacetate, is formed (67%) together with a small amount (8%) of the amide (III)[3]; when R is CH_3 the ester IV is isolated in 28% yield and only a 21% yield of the orthoester II is obtained. When the size of R is increased to C_2H_5, the ester IV is practically the sole alcoholysis product.

These facts are accommodated by the following mechanism, the proposed intermediates of which seem necessary to account for the products (amide, ester and orthoester) that may be obtained from the alcoholysis of such an iminoester hydrochloride as I.



Regardless of the structure (I or Ia) of the iminoester salt, its acquisition of a proton from the alcohol produces the intermediate (VI and VIa). The postulation of an intermediate resulting from the interaction of I with the alcohol seems necessary to account for the fact that a considerable amount of the amide (III) generally is formed during alcoholysis under conditions (in alcohol solution at room temperature) that are consider-

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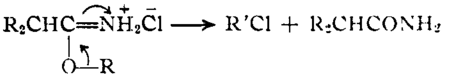
[6] Staudinger, and Rathsam, *Helv. Chim. Acta*, **5**, 645 (1922).

[7] McElvain and Clarke, This Journal, **69**, 2657 (1947).

ably milder than those necessary for the decomposition of the solid iminoester hydrochloride into the amide and alkyl chloride. This latter reaction occurs at the melting point of the salt



$$R_2CHC{=}\overset{+}{N}H_2\overset{-}{Cl} \longrightarrow R'Cl + R_2CHCONH_2$$

The oxonium and carbonium structures (VI and VIa) seem preferable to the intermediate ($C_6H_5CHRC(OCH_3)_2HN_3Cl$) resulting from the direct addition of the alcohol to I, because the coördination of the cation VIa with the methoxyl anion should be conditioned by the steric effect of R as is the coördination of VII, which is discussed below.

The methoxyl anion, resulting from the initial reaction, converts one of the mesomeric forms (presumably VI) into the amide, regenerating the alcohol involved in the first step. Competitive with this reaction is the alcoholysis of VI or VIa to ammonium chloride and the carbonium ion VII, which is stabilized by two mesomeric oxonium structures, VIIa. Which one of these cations reacts with the methoxyl anion produced in the initial step of the alcoholysis appears to be dependent upon the steric effect of the substituent R. If R is H the cation VII coördinates with the methoxyl anion to form the orthoester II exclusively; but when R is the larger ethyl group this type of reaction is prevented and the methoxyl anion abstracts the methyl group from the oxonium cation VII to form IV and the dimethyl ether. However, when R is methyl, the carbonium ion (VII) competes successfully with the VIIa for the methoxyl anion and both II and IV are produced.

Experimental

α-Phenylbutyramide.—A mixture of 82 g. (0.5 mole) of α-phenylbutyric acid[8] and 120 g. (1 mole) of thionyl chloride was heated at reflux for two hours, after which time the hydrogen chloride ceased to be evolved. The excess thionyl chloride was removed under reduced pressure and the resultant crude acid chloride was added slowly and with stirring to 400 ml. of concentrated ammonium hydroxide cooled in an ice-bath. The temperature of the reaction was not allowed to rise above 15°. After all the acid chloride had been added the amide was filtered from the cold solution and dried. The crude amide was dissolved in ethyl acetate and filtered. After removal of the solvent from the filtrate, 80 g. (97%) of α-phenylbutyramide,[9] m. p. 81-85°, crystallized on cooling.

α-Phenylbutyronitrile.—A mixture of 52 g. (0.32 mole) of α-phenylbutyramide and 48 g. (0.4 mole) of thionyl chloride was gently refluxed until gas evolution ceased. After the excess thionyl chloride had been removed under reduced pressure, the crude nitrile was dissolved in an equal volume of ether and washed successively with water, 5% sodium hydroxide solution, and water. The ether solution then was heated to boiling, treated with Norit,[10] filtered, and dried over sodium sulfate. The ether was evaporated and the α-phenylbutyronitrile[11] distilled at reduced pressure. The yield was 41 g. (78%), b. p. 110-112° (9 mm.); $n^{25}D$ 1.5075; $d^{25}{}_4$ 0.9742; M_D 44.4 (calcd. 44.5).

α-Phenylpropionitrile.—This nitrile was prepared by the methylation of benzyl cyanide according to the procedure of Baldinger and Nieuwland.[12] The product so obtained contained some unchanged benzyl cyanide since 0.2 g. of phenylacetamide could be isolated from the hydrolysis of 5 g. of the methylated product. This unchanged benzyl cyanide was removed from the α-phenylpropionitrile by the following procedure.[13] A mixture of 106 g. of the nitrile from the methylation reaction, 30 g. of benzaldehyde and 3 g. of sodium methoxide was stirred for two hours, after which time it was heated for fifteen minutes on a steam-bath. Then an equal volume of benzene was added, the mixture washed with water and finally stirred with a saturated sodium bisulfite solution to remove excess benzaldehyde. The benzene layer was evaporated and the nitrile distilled under reduced pressure. The yield of α-phenylpropionitrile, b. p. 92-94° (6 mm.); $n^{25}D$ 1.5084, amounted to 86 g. A residue of 22 g. of α-phenylcinnamonitrile, m. p. 85-87°,[14] remained from the distillation. A second treatment of the α-phenylpropionitrile so obtained with benzaldehyde produced no additional α-phenylcinnamonitrile.

Methyl α-Phenyliminopropionate Hydrochloride.—Dry hydrogen chloride was bubbled through an ice-cold mixture of 20 g. (0.15 mole) of α-phenylpropionitrile and 5.5 g. (0.17 mole) of absolute methyl alcohol until 6.2 g. (0.17 mole) of the gas was absorbed. After standing in the refrigerator for two days the resulting solution began to crystallize. An equal volume of dry ether then was added and the precipitated salt filtered off. This salt was dried in a desiccator over phosphorus pentoxide and sodium hydroxide for six hours. After triturating with ether and drying in a desiccator, the salt weighed 27 g. (91%).

Anal. Calcd. for $C_{10}H_{14}ClNO$: Cl, 17.8. Found: Cl, 17.7.

Methyl α-Phenylorthopropionate.—A mixture of 136 g. (0.69 mole) of methyl α-phenyliminopropionate hydrochloride and 400 ml. of absolute methyl alcohol was shaken until the salt dissolved. After two hours at room temperature ammonium chloride began to precipitate. At the end of forty-six hours 200 ml. of ether was added, and after another twenty hours 16.3 g. (45%) of precipitated ammonium chloride was filtered off. The filtrate required 0.18 mole of sodium methoxide (equivalent to 26% of the theoretical amount of ammonium chloride) in absolute methanol for neutralization of the ammonium chloride remaining in solution; the total yield of this salt amounted to 71%. The solvents were evaporated under diminished pressure at room temperature, the precipitate of sodium chloride filtered off and washed with ether. The filtrate was distilled and the material (87 g.) boiling at 69-73° (0.5 mm.) collected. A residue of 26 g. (25%) of α-phenylpropionamide, m. p. 88-91°, remained from the distillation.

The 87-g. fraction, b. p. 69-73° (0.5 mm.), was fractionated through a 20-plate Fenske column and separated into three fractions. The first fraction was 32 g. (28%) of pure methyl α-phenylpropionate,[3] b. p. 62-65° (0.5 mm.); $n^{25}D$ 1.5027; which contained 18.7% methoxyl (calcd. 18.9%). Hydrolysis of 10 g. of this ester gave 7.3 g. of α-phenylpropionic acid, b. p. 133-134° (6 mm.); $n^{23}D$ 1.5200; neut. equiv. 151 (calcd. 150). The intermediate fraction (22 g.), b. p. 65-70° (0.5 mm.), was a mixture of approximately equal parts of the ester and the orthoester as determined by methoxyl content and refractive index. The higher boiling orthoester, methyl α-phenylorthopropionate, was the third fraction and

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[8] From the saponification of ethyl α-phenylbutyrate, which was kindly furnished by Dr. V. H. Wallingford, Mallinckrodt Chemical Works, St. Louis, Mo.

[9] Ramart-Lucas and Amagat, *Compt. rend.*, **184**, 30 (1927).

[10] Treatment with charcoal is necessary if a water-white product is to be obtained.

[11] Bodroux and Taboury, *Bull. soc. chim.*, [4] **7**, 666 (1910).

[12] Baldinger and Nieuwland, THIS JOURNAL, **55**, 2851 (1933).

[13] *Cf.* Meyer, *Ann.*, **250**, 118 (1889).

[14] Frost, *Ann.*, **250**, 156 (1889).

amounted to 30 g. (21%): b. p. 70–71.5° (0.5 mm.): n^{25}_D 1.4928: d^{25}_4 1.0334.

Anal. Calcd. for $C_9H_9(OCH_3)_3$: CH_3O, 44.3. Found: CH_3O, 44.3.

Methyl α-Phenyliminopropionate.—A solution of 40 g. of potassium carbonate in 50 ml. of water was mixed with 50 ml. of ether and the mixture stirred and cooled in an ice-bath: then 28 g. of methyl α-phenyliminopropionate hydrochloride was added rapidly. After all of the solid material had disappeared, the layers were separated and the aqueous layer was extracted with ether. The combined ether solutions were dried and distilled. The yield of methyl α-phenyliminopropionate. b. p. 72–73° (1 mm.): n^{25}_D 1.5185: d^{25}_4 1.0216. was 18.5 g. (80%).

Anal. Calcd. for $C_{10}H_{13}NO$: N, 8.6. Found: N, 8.7.

Alcoholysis of Boron Trifluoride–Methyl α-Phenyliminopropionate.—A solution of 12 g. of methyl α-phenyliminopropionate in 10 ml. of benzene was cooled in an ice-bath and treated with boron trifluoride until fuming indicated that the gas was no longer being absorbed. Evaporation of the benzene left a liquid residue that contained 14.4% methoxyl (calcd. for $C_6H_5CH(CH_3)C(OCH_3)$-$=NH—BF_3$: 13.4%).

This material was dissolved in 20 ml. of absolute methanol and the solution refluxed so long as dimethyl ether collected in a cold trap. which was connected to the top of the reflux condenser. A total of 2 ml. of liquid collected in this trap. The liquid was separated from a small amount of methyl alcohol by allowing it to distil into another cold trap. The liquid was shown to be dimethyl ether by conversion to its boron fluoride derivative.[15] b. p. 125–127°.

The precipitated boron trifluoride–ammonia. which amounted to 3.6 g. (80%). was separated from the reaction mixture by filtration. Distillation of the filtrate gave 7.4 g. (85%) of methyl α-phenylpropionate. b. p. 72–74° (1 mm.): n^{20}_D 1.5020. This ester had a methoxyl content of 19.3% (calcd. 18.9%).

To determine if boron trifluoride–ammonia catalyzed the decomposition of the orthoester into dimethyl ether and the ester, a solution of 15 g. of methyl orthobutyrate[16] in 25 ml. of absolute methyl alcohol was treated with 5 g. of boron fluoride–ammonia and refluxed for six hours. During this time 7.5 ml. of liquid collected in the cold trap: from this liquid 10 g. (88%) of the boron fluoride–dimethyl ether, b. p. 127–128°. was obtained. After cooling and filtering, 4.8 g. (96%) of the boron fluoride–ammonia was recovered: distillation of the filtrate yielded 6.5 g. (65%) of methyl butyrate, b. p. 100–103°. No residue remained.

Alcoholysis of Methyl α-Phenyliminobutyrate Hydrochloride.[17]—This salt was prepared by the procedure described above for methyl α-phenyliminopropionate hydrochloride. A mixture of 19 g. (0.09 mole) of the iminobutyrate salt and 50 ml. of alcohol was shaken until the salt went into solution. After twelve hours at room temperature. the ammonium chloride began to precipitate. After twenty-four hours. 50 ml. of ether was added and after an additional twelve hours. the ammonium chloride was removed by filtration. It amounted to 1.5 g. (31%).

The filtrate required 0.023 mole of sodium methoxide in methyl alcohol solution for neutralization of dissolved ammonium chloride; thus the total of ammonium chloride formed in the reaction amounted to 57%. The neutralized solution was filtered and the filtrate distilled; 11.2 g. of a water-white liquid, b. p. 73–75° (0.4 mm.), was collected. This liquid contained 22% methoxyl (calcd. for the ester. 17.4%: for the orthoester. 41.5%). The reaction product, therefore, is mainly methyl α-phenylbutyrate containing a small amount of the corresponding orthoester. The distilled reaction product did not contain any methyl α-phenyliminobutyrate since an ether solution remained clear when treated with hydrogen chloride. Hydrolysis of 6.6 g. of this product with aqueous sodium hydroxide yielded 4.6 g. of α-phenylbutyric acid. b. p. 142–144° (6 mm.): m. p. 41–43°.

The residue remaining in the flask after the distillation of the ester solidified on cooling: it was practically pure α-phenylbutyramide. m. p. 81–85°. and weighed 4.2 g. (29%).

Evidence that dimethyl ether was formed along with the methyl α-phenylbutyrate was obtained in the following experiment: In a flask connected in series to a Dry Ice trap 30 g. of the iminoester hydrochloride was dissolved in 75 ml. of absolute methyl alcohol. This solution was allowed to stand at room temperature for eighteen hours. After this time the ammonium chloride that had precipitated was filtered. The yield was 0.5 g. (15%).

The filtrate was placed in a flask fitted with a coil condenser which was in turn attached to the Dry Ice trap. The liquid was refluxed for four hours. during which time about 4 g. of material collected in the cold trap. This material consisted of methyl chloride. b. p. −24°. dimethyl ether, b. p. −24°. and a small amount of methyl alcohol that was carried through the condenser with these gases. The methyl alcohol was separated from the other constituents by allowing the low boiling material to collect in another cold-trap as the mixture came to room temperature. The dimethyl ether and methyl chloride were separated by means of their different basicities relative to boron trifluoride. The mixture was treated with gaseous boron trifluoride until the appearance of fumes indicated the absorption was complete. It appeared that the methyl chloride as well as the dimethyl ether absorbed an equivalent of boron trifluoride at −80°, but as the temperature was allowed to rise. boron trifluoride fumes appeared and methyl chloride distilled. There remained 0.5 g. of the stable boron trifluoride–dimethyl ether complex. b. p. 125–127°.

From the alcoholic solution 4 g. (16%) of methyl α-phenylbutyrate. b. p. 120–121° (20 mm.) and 17 g. (74%) of α-phenylbutyramide. m. p. 82–85°. was isolated.

Summary

The alcoholysis of an iminoester hydrochloride of the type, $C_6H_5CHRC(OCH_3)=NH_2Cl$. is shown to yield either the ester. $C_6H_5CHRCOOCH_3$, the orthoester, $C_6H_5CHRC(OCH_3)_3$. or both. depending upon the size of the substituent R.

A mechanism for the alcoholysis that accounts for these results is proposed.

Alcoholysis of an iminoester–boron fluoride coordination complex proceeds without the formation of the amide, but yields the ester and an ether. This appears to be due to the catalytic decomposition of the orthoester as it is formed by the other alcoholysis product, boron fluoride–ammonia.

Madison, Wisconsin Received March 22, 1947

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[15] Laubengayer and Finlay, This Journal, **65**, 884 (1943).

[16] This orthoester was prepared in 13% yield by Brooker and White, This Journal, **57**, 2480 (1936), who reported the boiling point as 145–147°. In the present work it was obtained in 68% yield by the procedure used in ref. 3. The product boiled at 83–87° (104 mm.): d^{25}_4 0.9242; n^{25}_D 1.4018; M_D 39.0 (calcd. 39.4).

[17] *Cf.* Rising and Zee, This Journal, **50**, 1208 (1928).