ties akin to cod liver oil that tended to cure the rachitic rats. From an examination of the data it is found in the first series that the shrimp oil was as potent as the cod liver oil. The second series showed some cure but less than the cod liver oil, probably due to the increasing rancidity of the shrimp oil.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

PSEUDO BASES IN THE ISOXAZOLE SERIES. THIRD PAPER

BY E. P. KOHLER AND C. L. BICKEL

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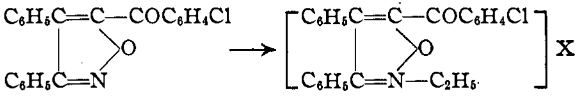
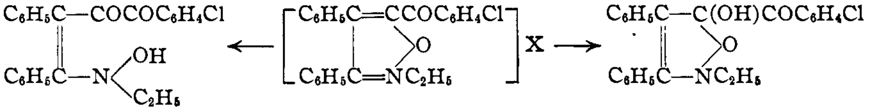
The pseudo bases that have been described in earlier papers of this series are derived from isoxazoles in which all available positions are filled with hydrocarbon residues. In all these cases the rearrangement of the true base results in a pseudo base in which the hydroxyl group occupies the 5-position. In order to determine whether this mode of rearrangement is altered by an acidic group in this position, we have alkylated a ketonic isoxazole and studied the behavior of the resulting salts toward bases



I II

The ethylation presented no difficulties and the salts could be manipulated in the same manner as those described heretofore. When they were shaken at a low temperature with aqueous sodium bicarbonate or sodium hydroxide and ether, the organic material immediately passed from the aqueous to the ethereal layer and when the ethereal solution was acidified the salts were regenerated. The alkylated ketonic isoxazole, therefore, forms a pseudo base in the usual manner.

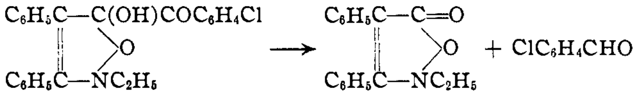
By cautious manipulation of its ethereal solution it was possible to isolate the pseudo base as a colorless crystalline compound. Ozonization of this compound yielded equivalent quantities of benzoic and *p*-chlorobenzoic acids, and a halogen-free substance which has not been identified. This result shows that the rearrangement, as usual in this series, leads to a 5-hydroxy compound, and it leaves but two possible formulas for the pseudo base



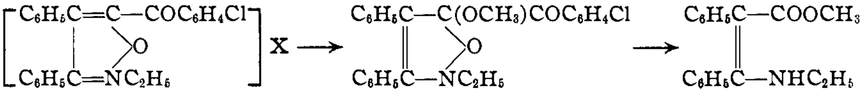
III IV

The lack of color in our pseudo base definitely excludes formula III which represents an α-diketone that would be intensely yellow. The pseudo base, therefore, is constituted precisely like all the others that we have described. It presents, however, certain peculiarities which are due to the substitution of the ketonic group for a hydrocarbon residue. It is not possible, for example, to transform the base into its ether by treatment with alcoholic potassium hydroxide. It is also impossible to secure such an ether directly from the salts. That this difference between the new pseudo base and nearly all others that are known is due to the ketonic group, is shown by the fact that it is equally impossible to methylate the ketonic hydroxy isoxazolines in which the relation between the hydroxyl and ketonic groups is the same.

Another peculiarity of the new pseudo base shows itself in the ease and in the manner in which it alters with time. Other pseudo bases of this series, in solution, and especially in the presence of alkalies, lose water more or less rapidly and pass into open-chained anhydro compounds. The ketonic compound changes spontaneously even in the solid condition and the principal product is ethyl diphenyl isoxazolone

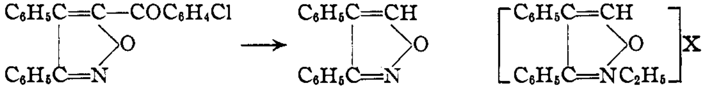


A similar cleavage accounts for some of the difficulties encountered in attempts to prepare the methyl ether directly from the salts. The ether may be formed in the operation but, if so, then it is immediately cleaved and the process goes further than in the spontaneous decomposition, ending in the open-chained compound VI



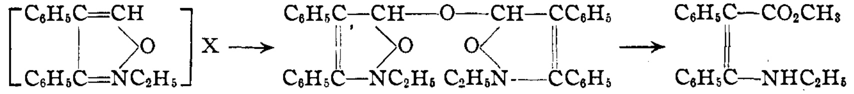
V VI

The open-chained cleavage product may, as has been stated, originate in the methyl ether V, but it is possible also that cleavage precedes methylation. In order to explore this possibility we have also examined the behavior of the salts that are obtained by ethylating 3,4-diphenyl isoxazole. These can be obtained without difficulty by means of a series of reactions which may be represented as follows



VII VIII

In this case neither the pseudo base nor its methyl ether could be isolated. When the salts VIII were treated with aqueous alkalies they immediately yielded a dimolecular anhydride, and when either this anhydride or the salts were acted on by methyl alcoholic sodium hydroxide, the product was the open-chained ester VI



VIII IX VI

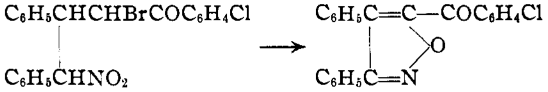
It is evident that the open-chained ester may originate either from the methyl ether V or from an antecedent cleavage product akin to VIII. Its structure is certain because it gives benzoic acid and ethyl benzamide when ozonized, therefore, has a double linkage in the α,β-position, and hydrochloric acid converts it into benzoyl phenyl acetic ester—a characteristic transformation of β-amino unsaturated esters

$$\underset{\text{VI}}{C_6H_5C(NHC_2H_5){=}C(C_6H_5)COOCH_3} \longrightarrow \underset{\text{X}}{C_6H_5COCH(C_6H_5)COOCH_3}$$

The formation of the open-chained ester represents a novel transformation of pseudo bases in the isoxazole series, a transformation which can occur only when the 5-position is unoccupied or is occupied by a group that is easily removed by bases. Since the pseudo bases derived from isoxazoles, in which both the 3- and 5-positions are unoccupied, undergo an entirely different type of rearrangement, this transformation into an open-chained ester may be regarded as a characteristic reaction of pseudo bases derived from 3,4-disubstituted isoxazoles.

Experimental Part

The isozazole that served as a starting point has been described heretofore because it turns up in small quantities whenever the corresponding bromo compound reacts with bases[1]



For preparing it in quantity we devised a method which gives a yield that is almost quantitative. The procedure was as follows.

A suspension of 100 g. of the bromo compound and an equal weight of potassium acetate in 500 cc. of methyl alcohol was boiled until bumping became serious. The mixture was then cooled and filtered. After washing the solid isoxazole with methyl alcohol until it was colorless, the filtrate and washings were boiled again and this operation of boiling and filtering was repeated as often as was necessary until no more solid separated. The filtrate was then concentrated in steps, finally evaporated almost to dryness, and set aside. It deposited a solid cake of isoxazole, bromide and acetate. The salts were removed with water, and the isoxazole washed with ether, which dissolved a green impurity along with a small quantity of the isoxazole. All fractions of the isoxazole were combined and recrystallized from glacial acetic acid. The yield was 77.5 g. or 98%; m. p. 165–166°.

Ethylation.—A suspension of 15 g. of the isoxazole in 50 g. of diethyl sulfate was heated in an oil-bath for two and one half hours at 125–130°. The isoxazole gradually

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[1] Kohler and Addinall, This Journal, **52**, 1597 (1930).

dissolved during the heating, and the solution became quite brown. This solution was used for preparing the salts represented by II.

The Acid Sulfate.—The ethylation mixture was heated on a steam-bath with 25 cc. of concentrated hydrochloric acid and an equal volume of water until the two layers disappeared. The solution was then extracted with ether, which removed unchanged isoxazole and other impurities and evaporated. It finally deposited colorless plates, which were washed with ether, and with a little water, then recrystallized from methyl alcohol. The salt separated in colorless plates melting at 192–193°.

Anal. Calcd. for $C_{24}H_{20}O_6NClS$: C, 59.3; H, 4.2. Found: C, 59.3; H, 4.6.

The Ferric Chloride Double Salts.—The ethylation mixture was hydrolyzed as before, diluted with 20 cc. of water and thoroughly extracted with ether. The aqueous solution was then heated to expel dissolved ether, cooled and treated with a saturated solution of ferric chloride which was added drop by drop as long as a precipitate formed. The precipitate was washed with ether and a little water, dried and recrystallized from glacial acetic acid, from which it separated in yellow plates. The yield was 18.2 g.

The earlier preparations yielded a salt that melted at 130.5°. Later a new salt melting at 139.5° made its appearance, and after that only the higher-melting salt could be obtained. The composition of the two salts was the same.

Anal. Calcd. for $C_{24}H_{19}O_2NCl_5Fe$: Cl, 24.1. Found: (130°) Cl, 23.1; (139°) 23.4.

The Pseudo Base IV.—Inasmuch as the pseudo base decomposes spontaneously it was made only in small quantities as needed. For this purpose 2.25 g. of either of the ferric chloride double salts was suspended in alcohol-free ether and treated with a water solution of 5 g. of sodium bicarbonate. A vigorous reaction occurred and the ether layer immediately became yellow. After removing the ferric hydroxide by filtration the ethereal layer was separated and the aqueous solution extracted with fresh ether. The ethereal solution was dried with sodium sulfate and allowed to evaporate. It deposited a slightly yellow product which became colorless when recrystallized from ether–petroleum ether; yield, 1.3 g., equal to 85%.

Anal. Calcd. for $C_{24}H_{20}O_3NCl$: C, 70.9; H, 5.0. Found: C, 70.5; H, 5.1.

The pseudo base is insoluble in water, soluble in all organic solvents except petroleum ether. It crystallizes in colorless prisms and melts with decomposition at about 128°. When its solution in alcohol-free ether is shaken with 1:1 hydrochloric acid and a saturated solution of ferric chloride, it deposits in nearly the calculated quantity the ferric chloride double salt which melts at 139°.

Spontaneous Decomposition.—A 0.5-g. sample of the pseudo base which had been kept in a glass-stoppered bottle for several months and had become dark in color, was dissolved in ether. From the resulting ethereal solution sodium bicarbonate extracted an acid which was identified as 4-chlorobenzoic acid by its melting point and by comparison with a sample on hand. After removing the chloro acid, the ethereal solution was dried, concentrated and diluted with petroleum ether. It thereupon deposited a solid which crystallized in diamond-shaped prisms and melted at 145–146°.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 77.0; H, 5.7. Found: C, 77.0; H, 5.7.

The composition, solubility, crystalline form and melting point agree with those of ethyl diphenyl isoxazolone. This substance was, therefore, synthesized by the method of Kohler and Blatt.[2] A comparison of the two products proved their identity.

Ozonization of the Pseudo Base.—A current of ozonized oxygen containing about 6% ozone was passed through a suspension of the pseudo base for one and one-half hours. At the outset the ozone was absorbed freely and the base dissolved. The ethyl bromide

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[2] Kohler and Blatt, This Journal, 50, 514 (1928).

was evaporated in a current of dry air, the residual oil shaken with water and the resulting emulsion extracted with ether. From the ethereal solution sodium bicarbonate extracted both benzoic and *p*-chlorobenzoic acids. The ethereal solution from which these acids had been removed was dried, concentrated and diluted with petroleum ether. It deposited a pale yellow solid melting at 120–130°. As no method was found for purifying the substance it could not be identified.

Attempts to Make a Methyl Ether.—Methyl alcohol containing a trace of potassium hydroxide had no action on the pseudo base and sodium methylate was found to be too destructive. The ferric chloride double salt was, therefore, treated with sodium bicarbonate in the following manner. One gram of the finely powdered double salt was suspended in 25 cc. of methyl alcohol. To this suspension were added 25 g. of ice, 40 cc. of alcohol-free ether and 0.6 g. of sodium bicarbonate dissolved in water. The mixture was shaken until the yellow salt had disappeared. The ethereal layer was then decanted and filtered, and the aqueous layer thrice extracted with ether. The ethereal solutions were dried, concentrated to small volume and diluted with petroleum ether. On cooling and rubbing they deposited 0.4 g. of a colorless solid which melted when crude at 102°. Addition of acid to the aqueous solution precipitated *p*-chlorobenzoic acid.

These same products—*p*-chlorobenzoic acid and a substance melting at 101–102°—were obtained when 2 g. of the ferric chloride double salt was shaken with 50 cc. of methyl alcohol, 50 g. of ice, 75 cc. of alcohol-free ether, and 2 g. of sodium hydroxide dissolved in water. The yield of the product melting at 101–102° was 0.9 g. or 90%. The product was recrystallized both from ether–petroleum ether and from acetone–methyl alcohol, but the melting point remained the same.

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.9; H, 6.8; OCH_3, 11.05. Found: C, 76.8; H, 6.8; OCH_3, 10.6.

The ester is readily soluble in acetone, moderately soluble in ether and methyl alcohol. It crystallizes in plates.

Methyl α,β-Diphenyl-β-ethylaminocinnamate

Ozonization of the Ester.—Through a solution of 4 g. of the ester in 35 cc. of carbon tetrachloride a rapid current of ozonized oxygen was passed for one and one-half hours—half an hour after ozone appeared in the effluent gas. The solvent was pumped off and the residual oil shaken with ice water. The resulting emulsion was heated gently, the temperature being kept below 50°, then cooled and extracted with ether. The ethereal solution contained benzoic acid, which was removed with bicarbonate and identified.

After removal of the benzoic acid, the ethereal solution was dried with sodium sulfate and evaporated. It left an oil which solidified after vigorous rubbing. By recrystallization from ether–petroleum ether the solid was obtained in diamond-shaped plates which melted at 68–69°.

Anal. Calcd. for $C_9H_{11}ON$: C, 72.4; H, 7.5. Found: C, 72.5; H, 7.6.

The composition of the substance corresponds to that of ethyl benzamide, and it gave benzoic acid when it was boiled with concentrated hydrochloric acid, but owing to the small quantity available ethylamine could not be identified with certainty. Ethyl benzamide was therefore prepared from benzoyl chloride and ethylamine. It melted at 68–69° and a mixture of the preparation and the ozonization product melted at the same temperature.

Hydrolysis of the Ester.—A solution of 0.55 g. of the ester in concentrated hydrochloric acid was set aside for a day. On dilution with an equal volume of water it deposited a solid which was identified as desoxybenzoin. The diluted solution on standing deposited more solid, which proved to be a mixture. It was separated by fractional crystallization from ether–petroleum ether into desoxybenzoin and a substance which melted at 72–73°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6; Found: C, 75.3; H, 5.7.

This substance was identified as the methyl ester of benzoyl phenyl acetic acid by comparison with a sample on hand.[3] Concentrated hydrochloric acid gradually transformed it into desoxybenzoin.

Preparation of 3,4-Diphenyl Isoxazole (VII).—The preparation of this isoxazole from anisoyl diphenyl isoxazole was described in an earlier paper.[4] We obtained it in a much better yield from *p*-chloro-benzoyl diphenyl isoxazole. Since it is readily cleaved, it is necessary to operate as rapidly as possible and it is advantageous to operate with small quantities. Our procedure was as follows. A suspension of 2 g. of 3,4-diphenyl-5-(*p*-chloro-benzoyl)-isoxazole in 20 cc. of ethyl alcohol, and a solution of 0.5 g. of sodium hydroxide in 10 cc. of ethyl alcohol, were mixed at the boiling point. The mixture was boiled for one and one-half minutes, during which the isoxazole dissolved, then immediately cooled under the tap and filtered, to remove a small quantity of unchanged material. The filtrate was diluted with 150 cc. of water and set aside for thirty minutes, during which it deposited the diphenyl isoxazole. The yield of product was 1.15 g. or 98%, and approximately 0.1 g. of starting material was recovered.

Ethylation.—A suspension of 3.45 g. of diphenyl isoxazole in 5.0 g. of ethyl sulfate was heated in an oil-bath to 110° for four hours. The resulting light brown solution was heated on a steam-bath with 3 cc. of concentrated hydrochloric acid and 3 cc. of water until the mixture became homogeneous. The solution was then diluted with 3 cc. of water, cooled and extracted with ether. The aqueous layer was heated to expel all of the ether, cooled and treated very gradually with excess of saturated ferric chloride solution.

The ferric chloride double salt is uncommonly low-melting, and when it is precipitated rapidly or in the presence of ether it tends to separate as an oil exceedingly difficult to solidify. When no crystals are available for inoculation the ferric chloride should be added a few drops at a time until vigorous scratching of the walls of the vessel starts crystallization. The salt was recrystallized from glacial acetic acid and petroleum ether. It is readily soluble in glacial acetic acid and in methyl alcohol, sparingly soluble in water, almost insoluble in ether and petroleum ether. It crystallizes in pale yellow plates and melts at 75–76°. The yield was 97%.

Anal. Calcd. for $C_{17}H_{16}ONCl_4Fe$: C, 45.5; H, 3.6. Found: C, 45.2; H, 3.9.

Action of Bases on the Salt: The Dimolecular Anhydride (IX).—The usual method of obtaining pseudo bases by shaking the salts with sodium hydroxide in the presence of ether was inapplicable in this case because extraction is too slow and the product is rapidly decomposed by the hydroxide. When benzene was substituted for the ether the result was more satisfactory. Thus one gram of the salt was shaken with 10 cc. of benzene and one gram of sodium hydroxide in 20 g. of ice and water until all of the salt was decomposed. The benzene layer was then decanted, dried and evaporated. It left a solid which was recrystallized from benzene and ether. It separated in colorless prisms melting at 148°.

Anal. Calcd. for $C_{34}H_{32}O_3N$: C, 79.0; H, 6.2; mol. wt., 516. Found: C, 79.0; H, 6.2; mol. wt., 488.

Ozonization.—A solution of 0.7 g. of the substance in 10 cc. of carbon tetrachloride was ozonized for forty-five minutes. The solvent was pumped off and the residual oil shaken with ice water in the usual manner, but the water solution was treated directly

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[3] Kohler, This Journal, **46**, 1742 (1924).

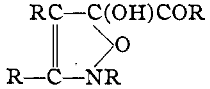
[4] Kohler and Davis, *ibid.*, **52**, 4527 (1930).

with phenylhydrazine hydrochloride. A yellow precipitate formed which was identified as the phenylhydrazone of phenyl glyoxylic acid by comparison with an authentic sample.

Cleavage of Bases.—A solution of a small quantity of the dimolecular compound in methyl alcohol containing a trace of sodium hydroxide was boiled down, cooled and diluted with water. It deposited the unsaturated amino ester VI. The filtrates from the ester later also deposited a small quantity of desoxybenzoin. This unsaturated amino ester was obtained also when the ferric chloride double salt was shaken with ice and methyl alcoholic sodium hydroxide. In this case the yield of ester was 82%.

Summary

1. In the pseudo bases which are formed from isoxazolinium salts that are completely substituted and have an acidic group in the 5-position, the hydroxyl group occupies the 5-position:



Owing to the ease with which they are cleaved, their behavior is quite different from that of the pseudo bases derived from other tri-substituted isoxazoles.

2. The pseudo bases derived from β,γ-diphenyl isoxazole likewise have an hydroxyl group in the 5-position. They undergo a characteristic rearrangement into open-chained compounds.

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[Contribution from the Chemical Laboratory of Iowa State College]

THE INFLUENCE OF ACID CHLORIDES AND OF PYRROLE ON THE COLOR TEST FOR REACTIVE ORGANOMETALLIC COMPOUNDS. THE CONSTITUTION OF PYRRYLMAGNESIUM HALIDES

By Henry Gilman and Lloyd L. Heck

Received August 16, 1930 Published December 18, 1930

Introduction

In continuation of studies[1] on the reaction between acid halides and the Grignard reagent, it was noted that some acid chlorides appeared to interfere with the sensitive color test[2] for reactive organometallic compounds. This prompted an investigation of the effect of several typical acid halides on the color test. It has been found that such interference is not general.

Fortunately, the occasional interference of acid halides need not be of serious consequence for several reasons. First, the reaction between RMgX

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[1] Gilman, Fothergill and Parker, *Rec. trav. chim.*, **48**, 748 (1929); Gilman and Fothergill, This Journal, **51**, 3501 (1929).

[2] (a) Gilman and Schulze, *ibid.*, **47**, 2002 (1925); (b) Gilman and Schulze, *Bull. soc. chim.*, [4] **41**, 1479 (1927); (c) Gilman and Heck, *Rec. trav. chim.*, **48**, 193 (1929); (d) Gilman and Heck, *Ber.*, **62**, 1379 (1929); (e) Gilman, Sweeney and Heck, This Journal, **52**, 1604 (1930); and (f) Gilman and Heck, *Rec. trav. chim.*, **49**, 218 (1930).