The Grignard reagent, phenylmagnesium bromide, reacts with *o*-benzoylbenzoic acid in the proportion of two molecules to one, with the formation of phthalophenone and not dibenzoylbenzene.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

PSEUDO BASES AND THEIR SALTS IN THE ISOXAZOLE SERIES. SECOND PAPER[1]

BY E. P. KOHLER AND N. K. RICHTMYER

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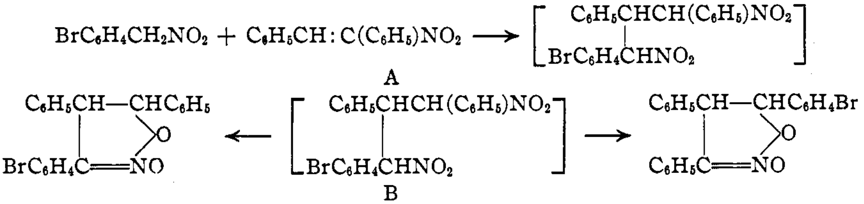
In the first paper[2] it was shown that when the salts that are obtained by methylating triphenyl isoxazole are treated with bases they undergo a series of transformations which can be represented by the sequence

$$\text{Salt} \rightleftarrows \text{base} \rightleftarrows \text{pseudo base} \longrightarrow \text{anhydro compound}$$

Owing to the instability of the base and the pseudo base it was possible to isolate only the first and last members of this series, and it was impossible to establish the structure of the pseudo base, the anhydro compound and their derivatives because all of these substances contain three groups which are the same. We have now found that some of these difficulties can be avoided by alkylating with ethyl instead of with methyl sulfate and that most of the others can be overcome by substituting bromophenyl for one of the phenyl groups.

The change from methylation to ethylation presented no complications but the preparation of a substance which differs from triphenyl isoxazole only in having a substituent in one of the phenyl groups proved to be exceedingly troublesome. No isoxazoles of this type are known and no intermediates are available for making them by any of the methods employed in the preparation of triphenyl isoxazole. Since all methods which hold any promise of success are equally likely to give a mixture of isomers we decided to undertake the preparation of the *p*-bromo compounds by way of the isoxazoline oxides.[3] To this end we condensed *p*-bromophenyl nitromethane with nitrostilbene. It was to be expected that this condensation would give a mixture of two isoxazoline oxides



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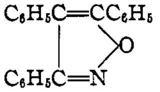
[1] In memory of Ira Remsen.

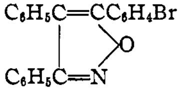
[2] Kohler and Blatt, THIS JOURNAL, **50**, 1217 (1928).

[3] Kohler and Barrett, *ibid.*, **46**, 2105 (1924).

Instead of the two oxides expected we actually obtained three, because some of the nitrostilbene is hydrolyzed and the resulting phenylnitromethane leads to the formation of a small quantity of the unbrominated triphenyl isoxazoline oxide. The separation of this mixture is not feasible; the oxides crystallize indistinctly and since they decompose below the melting point, it is impossible to ascertain whether or not any method of crystallization really results in separation. The mixture of oxides was therefore boiled with alcoholic sodium methylate and thus transformed into a mixture of the corresponding isoxazoles:



I



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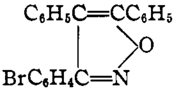
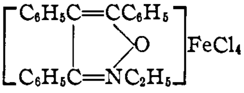
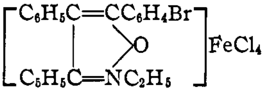


III

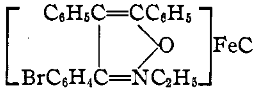
These isoxazoles crystallize fairly well, and they have definite melting points but apparently they are capable of forming mixed crystals in all proportions. The attempt to separate at this stage was, therefore, abandoned. The isoxazoles were ethylated and then transformed into a mixture of ferric chloride salts containing



IV

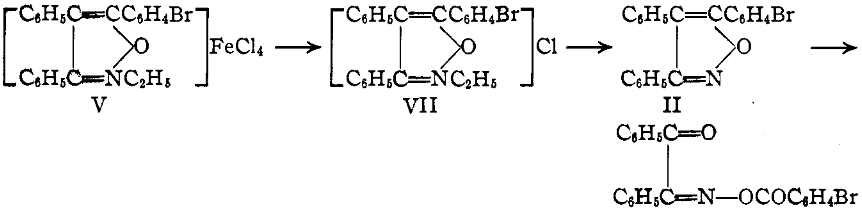


V



VI

By systematic fractional crystallization of this mixture it was possible to isolate one salt which crystallized well from a number of solvents, had a sharp melting point and appeared to be a pure substance. This contained bromine and therefore was either V or VI but inasmuch as the salts are not attacked by ozone it was necessary to convert it into the corresponding isoxazole in order to establish its structure. The isoxazole proved to be 3,4-diphenyl-5-*p*-bromophenyl isoxazole (II) because it formed an ozonide that on hydrolysis gave the *p*-bromobenzoate of *β*-benzilmonoxime.



VIII

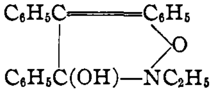
As a result of these operations we now had available for investigation the salt IV, which was easily obtained in a pure condition by ethylation of triphenyl isoxazole, and the salt V which was free from its isomer but—to judge from the analytical results—generally contained a small quantity of the unbrominated compound. We also had a supply of the salt VI which was sufficiently pure for most purposes but always contained appreciable quantities of the unbrominated compound and was not entirely free from its isomer.

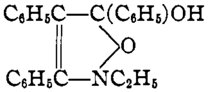
These salts are not attacked by ozone, either in water or in organic solvents—a property which serves to distinguish them as well as the corresponding salts with other acids from all the substances into which they can be transformed. They are readily oxidized by permanganate, both when suspended in water and when dissolved in acetone. Since the salt which has the bromophenyl group in the 5-position gives *p*-bromobenzil and benzoic acid, while that in which the same group occupies the 3-position is oxidized to benzil and *p*-bromobenzoic acid, this reaction with permanganate supplies a reliable means for determining the structure of salts of this type.

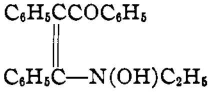
When any one of these salts is added to caustic alkalies in the presence of ether, ferric hydroxide is precipitated and all of the organic matter is immediately found in the ether. Under these conditions, therefore, the change from salt to pseudo base appears to be direct and instantaneous. But when a salt is treated with barely enough cold, saturated sodium bicarbonate to precipitate all of the iron, it yields a clear, colorless, strongly basic solution which contains nothing that can be extracted with ether. This strongly alkaline solution must contain the true base in equilibrium with its carbonates. At low temperatures such solutions remain clear for days but all ultimately become cloudy and deposit the pseudo base and all attempts to concentrate such solutions by evaporation or freezing invariably end in pseudo base. It is not possible, therefore, to isolate any substances corresponding to quaternary ammonium bases; increase in concentration of the hydroxyl ions more than compensates for the effect of lowering the temperature in decreasing the rate of formation of the pseudo bases.

While these pseudo bases are readily formed by the action of alkalies on the salts, they are not easily isolated. It was possible, however, to obtain in pure crystalline form those corresponding to salts IV and V. They are quite insoluble in water, readily soluble in organic solvents. Acids dissolve them slowly but even very dilute acids extract them rapidly and completely from their solutions in organic solvents. Like the pseudo bases derived from unsaturated cyclic amines, they readily form ethers which behave toward acids exactly like the bases themselves.

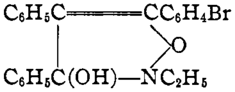
The pseudo bases and their ethers also behave alike toward oxidizing agents. Aqueous permanganate does not attack them but they are rapidly oxidized in acetone, and unlike the salts they are also easily ozonized. All methods of oxidation yield essentially the same products. Thus the pseudo base corresponding to the unbrominated salt IV invariably gives benzoic and acetic acids and benzil; but permanganate also forms variable quantities of acetaldehyde, while ozone gives some nitrogenous compound. The oxidation products, unfortunately, do not distinguish between all possible formulas of the substance. These are

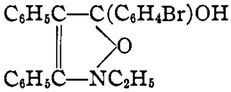

IX

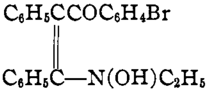

X


XI

Each of these formulas represents a substance which by a combination of oxidation and hydrolysis could give benzil and benzoic acid. In the case of the pseudo base from the brominated salt V the results are somewhat more helpful. Here the oxidation products are bromobenzil, benzoic and acetic acids, and the possible formulas


XII


XIII


XIV

Since the first of these formulas cannot be reconciled with the formation of bromobenzil, this type of formula is definitely excluded for the pseudo bases of the triphenyl isoxazole series.

Between the remaining formulas it is probably impossible to distinguish by chemical methods. Indeed it is not at all improbable that they represent two phases of the same substance which can coexist in solution. Either formula is satisfactory for interpreting the reactions of the pseudo bases but in order to gain an insight into the mechanism by which these substances are formed it is desirable to secure some compound which is formed in a similar manner but has a group less mobile than hydroxyl or methoxyl. With this end in view we treated the chloride with a sulfinate and later with a sulfocyanide but in each case obtained only the corresponding salt. Soluble cyanides formed a cyanogen compound that is not a salt but this proved useless for our purpose because it behaved exactly like the pseudo base and its ether, the cyanogen group disappearing in every reaction.

Since the experiments involving the interaction of soluble salts showed fairly conclusively that it would not be possible to secure the desired type of compound in this manner, it became necessary to resort to metallic derivatives. In a well-conceived series of investigations, Freund[4] showed that the salts of unsaturated cyclic ammonium bases differ much in their behavior toward organic magnesium compounds. Some react very readily, others not at all; but whenever a reaction does occur, the product is always a substance that is constituted like the corresponding pseudo base, the hydrocarbon residue occupying the position of the hydroxyl group.

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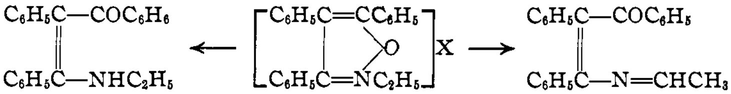
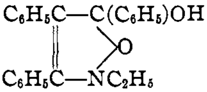
[4] Freund, *Ber.*, **37**, 4666 (1904); Freund and Beck, *Ber.*, **37**, 4673, 4679 (1904); Freund and Richard, *Ber.*, **42**, 1101 (1909); Freund and Bode, *Ber.*, **42**, 1746 (1909).

We found that our chloride reacts slowly with methyl magnesium iodide and that the ferric chloride double salt reacts very smoothly both with methyl magnesium iodide and with phenyl magnesium bromide. In each case, however, the reaction is quite different from that described by Freund: chlorine is removed, hydrogen is introduced, and the product is an open chained amine—XV. Still another type of reaction occurs between the chloride and sodium malonic ester in benzene, but here again the product (XVI) does not meet our needs because it is not constituted like the pseudo bases.

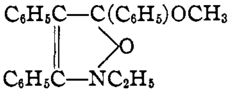


XV XVI

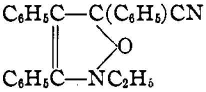
In the absence of definite proof it is necessary to base a choice between the two possible types of formulas for the pseudo bases and the substances constituted like them on circumstantial evidence. Even this is slight. The open chained amine XV, the analogous methyl, and *iso*propyl compounds, the corresponding unsubstituted amine as well as its more complicated substitution products are all yellow in color while the pseudo base, its ethers and the corresponding cyanogen compound are colorless. This invariable difference would hardly be expected if the difference in structure were not greater than that represented by the possible open chained formula of the pseudo base (XI) and the established formula of the amine (XV). Although this evidence is not conclusive—and could not be tested because we were unable to replace the remaining amino hydrogen in the yellow compounds with anything else—we nevertheless deem it sufficiently significant to make us prefer the cyclic formula for the colorless compounds. We shall therefore represent these substances with the formulas.



X

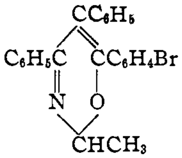


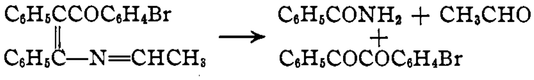
XVII



XVIII

All of these colorless compounds differ notably from the corresponding derivatives of pyridine and other similar unsaturated cyclic nitrogen compounds in stability. Above the melting point and in solutions containing traces of a base they lose water, alcohol or hydrocyanic acid and pass into an "anhydro compound." In the earlier paper the structure of these anhydro compounds was left in doubt. It has now been established with certainty by ozonizing the substance that is formed when the brominated pseudo base loses water. The ozonization products—*p*-bromobenzil, acetaldehyde and benzamide—definitely exclude the cyclic formula XIX and prove that the substance must be constituted like a Schiff base XX.

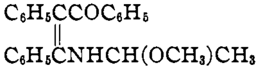




$$\begin{array}{l} C_6H_5CCOC_6H_4Br \\ \quad \| \\ C_6H_5C{-}N{=}CHCH_3 \end{array} \longrightarrow \begin{array}{l} C_6H_5CONH_2 + CH_3CHO \\ \qquad + \\ C_6H_5COCOC_6H_4Br \end{array}$$

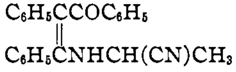
XIX XX XXI

These anhydro compounds are, as would be expected, very actively unsaturated. They combine with alcohols to form alkoxyl compounds that are isomeric with the ethers of the pseudo bases, with hydrocyanic acid to form cyanogen compounds isomeric with those formed from the salts, and with Grignard reagents to form unsaturated secondary amines.



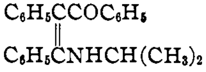
$$\begin{array}{l} C_6H_5CCOC_6H_5 \\ \quad \| \\ C_6H_5CNHCH(OCH_3)CH_3 \end{array}$$

XXII



$$\begin{array}{l} C_6H_5CCOC_6H_5 \\ \quad \| \\ C_6H_5CNHCH(CN)CH_3 \end{array}$$

XXIII

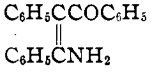


$$\begin{array}{l} C_6H_5CCOC_6H_5 \\ \quad \| \\ C_6H_5CNHCH(CH_3)_2 \end{array}$$

XXIV

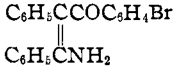
These addition reactions are promoted by bases. Since the ethers and cyanides are sensitive even to traces of base, they show a marked tendency to undergo a rearrangement that ends in yellow amines which constitute the final products of the action of basic reagents on the salts. These amines are always due to secondary reactions but, inasmuch as the changes follow each other in rapid succession, they are easily mistaken for primary products. Thus only the colorless methyl ether (XVII) is formed when slightly less than the equivalent quantity of sodium methylate is added to the chloride in methyl alcohol, but when slightly more than one equivalent is added the sole product is the yellow amino compound XXV.

Another manner in which the active unsaturation of the anhydro compounds manifests itself is in the ease with which they are hydrolyzed. In the presence of traces of acid all of them rapidly pass into the corresponding amines



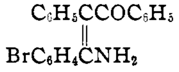
$$\begin{array}{l} C_6H_5CCOC_6H_5 \\ \quad \| \\ C_6H_5CNH_2 \end{array}$$

XXV



$$\begin{array}{l} C_6H_5CCOC_6H_4Br \\ \quad \| \\ C_6H_5CNH_2 \end{array}$$

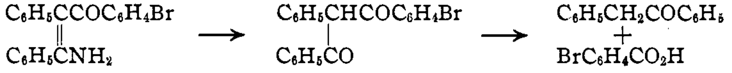
XXVI



$$\begin{array}{l} C_6H_5CCOC_6H_5 \\ \qquad \| \\ BrC_6H_4CNH_2 \end{array}$$

XXVII

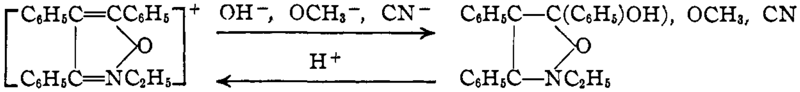
In the presence of more concentrated acid the process does not stop even here but gives first a β-diketone and finally a monoketone and an acid



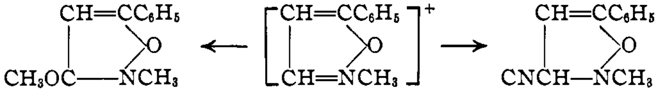
$$\begin{array}{l} C_6H_5CCOC_6H_4Br \\ \quad \| \\ C_6H_5CNH_2 \end{array} \longrightarrow \begin{array}{l} C_6H_5CHCOC_6H_4Br \\ \quad | \\ C_6H_5CO \end{array} \longrightarrow \begin{array}{l} C_6H_5CH_2COC_6H_5 \\ \qquad + \\ BrC_6H_4CO_2H \end{array}$$

A survey of these transformations explains the precautions that are necessary for securing the pseudo bases of the isoxazole series. If the ether that is used is not entirely free from alcohol, the base becomes contaminated with its ethyl ether or the corresponding isomeric amino compound. These prevent it from crystallizing promptly. As it tarries in the solution it begins to lose water and form the anhydro compound. If the ethereal solution is carefully protected this may ultimately crystallize, but the solution generally catches a trace of acid from the air, turns yellow and finally ends by depositing an equivalent quantity of the amine, which is stable under these conditions and crystallizes well.

It is difficult to compare our results with those of earlier investigators who have studied other isoxazoles because since no pseudo bases have heretofore been isolated, it is frequently impossible to distinguish between primary and secondary products. In the triphenyl isoxazole series the first step is probably a direct union of ions to form the undissociated pseudo bases, their ethers or cyanides and the process can easily be reversed.



The same process seems to occur in the case of the salts formed from 3-methyl isoxazole,[5] and 3-phenyl isoxazole,[5] for, although owing to the difference in the number of substituents, the final products obtained from these substances are quite different from ours they appear to be formed from the same type of pseudo base. The salts from 5-methyl isoxazole[6] and from 5-phenyl isoxazole,[7] however, must form a different pseudo base, because such final products as $CH_3COCH_2C(CN)=NCH_3$, $C_6H_5COCH_2C(OCH_3)=NCH_3$ and $C_6H_5COCH_2C(CN)=NCH_3$ can come only from substances that are formed by adding the negative ion in the 3-position



The factors that determine the mode of addition of these ions, therefore, appear to be the same as those which determine the mode of addition in reactions that are not usually supposed to involve ions.

Experimental Part

I. Results Obtained with Triphenyl Isoxazole. A. Cyclic Compounds

Three classes of cyclic compounds were investigated: salts, the pseudo base, and substances which are formed by metathetical reactions of the salts but are constituted like the pseudo base. The distinction between these metathetical products and the salts which are isomeric with them was, in all cases, based on the behavior toward ozone. The salts are not attacked by ozone, while all these other cyclic compounds are readily ozonized.

Ethylation, the Ferric Chloride Double Salt, IV.—Ethyl sulfate was added to triphenyl isoxazole by heating a mixture containing 100 g. of the former and 25 g. of the latter at 120° for five hours. In order to decompose the excess of reagent and

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[5] Mumm, "Dissertation," Kiel, 1902.

[6] Claisen, *Ber.*, **42**, 67 (1909); Mumm and Bergell, *Ber.*, **45**, 3040 (1912).

[7] Mumm and Münchmeyer, *Ber.*, **43**, 3355 (1910).

convert the addition product into a simple salt, the solution was digested on a steam-bath for an hour with 50 cc. of concd. hydrochloric acid diluted with an equal volume of water. The resulting clear solution was cooled, thoroughly extracted with ether and then treated with excess of 1:1 aqueous ferric chloride. This precipitated a pale yellow salt which was washed—first with 1:1 concd. hydrochloric acid and then with ether—and dried to constant weight on a steam-bath; yield 42.0 g. instead of 44.1 g. calculated.

Although the salt was practically pure, it was recrystallized from ethyl bromide, from which it separates in pale yellow plates melting at 165–167°.

Anal. Calcd. for $C_{23}H_{20}ONCl_4Fe$: C, 52.7; H, 3.8; Fe, 10.7. Found: C, 51.9; H, 3.7; Fe, 10.9.

The salt is very soluble in acetone, moderately soluble in ethyl bromide and in glacial acetic acid, sparingly soluble in water and alcohol, insoluble in ether.

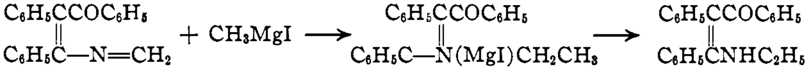
Oxidation.—A current of ozone was passed for six hours through solutions of 2 g. of the salt in water and in ethyl bromide but in each case all of the salt was recovered. A solution of potassium permanganate was then added gradually and in excess to one gram of the salt which was partially dissolved and partially suspended in 50 cc. of water. Each addition of reagent produced a violet colored precipitate—the permanganate—which rapidly turned brown and the odor of acetaldehyde soon became perceptible. On completion of the oxidation the mixture was decolorized with bisulfite and extracted with ether. From the ethereal solution sodium carbonate extracted 0.2 g. of benzoic acid and a trace of acetic acid. The solution was then dried and evaporated. It left 0.31 g. of benzil.

Reaction with Grignard Reagents.—Two g. of the salt was added to a solution of methyl magnesium iodide made from 1 g. of magnesium. The salt reacted at once and the solution became black. It was immediately poured into cracked ice, the ethereal layer separated and the mixed hydroxides extracted with ether until they were free from organic material. The combined ethereal solutions on drying and evaporation deposited a single substance which crystallized in yellow prisms and melted at 118–119°.

Anal. Calcd. for $C_{28}H_{21}ON$: C, 84.4; H, 6.4. Found: C, 84.5; H, 6.5.

The composition of the product corresponds to that of a substance which has hydrogen in place of the $FeCl_4$ group and the color indicated that it was an open chained compound. It was therefore hydrolyzed. This was accomplished by dissolving 1 g. in 10 cc. of boiling methyl alcohol, adding a few drops of concd. hydrochloric acid to the solution, then diluting it with hot water to incipient cloudiness and setting it aside until it became colorless. The colorless crystalline compound which separated was collected on a filter and identified as phenyl dibenzoyl methane by comparison with a sample on hand. The filtrate was thoroughly extracted with ether and then evaporated to dryness. It left a colorless, hygroscopic hydrochloride that crystallized in needles and melted at 78–79°, the melting point of ethylamine hydrochloride.

Synthesis.—In an earlier paper,[2] it was shown that organic magnesium compounds combine with anhydro compounds to form the magnesium derivatives of unsaturated secondary amines. If, as seemed probable from its hydrolysis products, our yellow compound is a secondary amine of this type, then it should be possible to synthesize it from the anhydro compound described in the earlier paper


XV

$$\begin{matrix}C_6H_5CCOC_6H_5\\ \|\\ C_6H_5C{-}N{=}CH_2\end{matrix} + CH_3MgI \longrightarrow \begin{matrix}C_6H_5CCOC_6H_5\\ \|\\ C_6H_5C{-}N(MgI)CH_2CH_3\end{matrix} \longrightarrow \begin{matrix}C_6H_5CCOC_6H_5\\ \|\\ C_6H_5CNHC_2H_5\end{matrix}$$

Six-tenths of a gram of the methylene compound was added to a solution of methyl magnesium iodide containing 0.5 g. of magnesium. The mixture was stirred for fifteen minutes and then decomposed with ice. The ethereal layer gave a product which crystallized in yellow prisms, melted at 117–119° and caused no depression of the melting point of the product from the salt.

Ethyl-1,2-diphenyl-2-benzoyl-vinylamine, XV, is formed with equal ease by the action of methyl magnesium iodide and phenyl magnesium bromide on the ferric chloride double salt. The chloride does not react with phenyl magnesium bromide and it reacts only very slowly with methyl magnesium iodide but it forms the same product as the more soluble ferric chloride double salt.

The Pseudo Base, 2-Ethyl-3,4,5-triphenyl-5-hydroxy Isoxazoline, X.—The pseudo base was obtained in various ways of which the most convenient was as follows. To a solution of 8 g. of sodium hydroxide in 40 cc. of water were added in succession 25 cc. of alcohol-free ether, 50 g. of ice and 8 g. of finely ground ferric chloride double salt. The mixture was shaken for ten minutes, after which the ethereal layer was removed and the aqueous layer extracted a few more times with ether. All ethereal solutions were then combined, dried with sodium sulfate and concentrated under diminished pressure. The result was an oil which solidified when diluted with petroleum ether and rubbed. The yield was 4.5 g. of pseudo base and a residue of base mixed with a small quantity of anhydro compound.

Anal. Calcd. for $C_{23}H_{21}O_2N$: C, 80.5; H, 6.1. Found: C, 80.6; H, 6.4.

The substance is readily soluble in all organic solvents except low-boiling petroleum ether; it is insoluble in water. Unless solid is available for inoculation, it tends to separate from solution as an oil and when this is allowed to remain in contact with the solution it slowly loses water. It is most readily purified by dissolving it in benzene and diluting this solution with petroleum ether. It then crystallizes in colorless prisms. When heated rapidly in a capillary tube it melts with effervescence at about 120°.

Oxidation.—The pseudo base does not reduce cold aqueous permanganate. In acetone the permanganate is reduced, slowly at first, then as rapidly as added; the products are the same as those obtained from the salts. A current of ozonized oxygen was passed for two hours through a cold concentrated solution of 2 g. of the pseudo base. It precipitated a pasty ozonide which was decomposed with water. The resulting oily emulsion, on distillation with steam, yielded 0.5 g. of benzoic acid and 1.1 g. of benzil, and it left a small quantity of a red nitrogenous residue.

Salt Formation.—By shaking an ethereal solution of the pseudo base with an inadequate amount of an acid it is possible to get an aqueous solution of the corresponding salt. From such a solution of the chloride, ferric chloride regenerates the double compound, while potassium chlorate precipitates a moderately soluble salt, potassium bromide, and bromine a very sparingly soluble perbromide and potassium permanganate a violet colored permanganate. At low temperatures and in the presence of acid the permanganate persists for a time but ultimately it turns brown and passes into benzil, acetaldehyde, ammonia and potassium benzoate. Its formation accounts for the fact that the salts are oxidized by permanganate while they are not attacked by ozone or chromic acid.

Metallic Derivatives.—Although the pseudo base is insoluble in aqueous alkalies, it is capable of forming easily hydrolyzable metallic derivatives. Thus when a solution of a salt is added to cold concd. sodium hydroxide it first imparts a yellow color to the solution and then, as the quantity is increased, produces an oily yellow precipitate. The color of both oil and solution fades on dilution with water and when the suspension is shaken with ether the oil disappears and both the ethereal and the water layers become colorless. The ether contains only pseudo base, the water only inorganic compounds.

Slightly less than the calculated quantity of powdered sodium was added to a solution of 2 g. of the pseudo base in absolute ether. Hydrogen was evolved and the sodium slowly changed to a lemon yellow, crystalline powder. This was thoroughly washed with ether, dried and analyzed.

Anal. Calcd. for $C_{23}H_{20}O_2NNa$: Na, 6.3. Found: Na, 6.2, 6.4.

Reaction with Methyl Magnesium Iodide.—A quantitative determination showed that one mole of the pseudo base reacts with 3 moles of methyl magnesium iodide and liberates 2 moles of gas. In accordance with this it was found that the product of the reaction is the same as that formed from the anhydro compound.

The Methyl Ether, 2-Ethyl-3,4,5-triphenyl-5-methoxy Isoxazoline, XVII.—The ethers are easily made by dissolving the pseudo base in alcohols but it is more convenient to prepare them directly from the ferric chloride double salt. Thus the methyl ether was obtained by exactly the same procedure that was employed for making the pseudo base, except that methyl alcohol was substituted for most of the water. Much of the ether crystallized during the operation. This was redissolved by repeated extraction with ether. In order to prevent premature crystallization, a little acetone was added to the ethereal solution, which was then distilled to a small volume. The product was purified by recrystallization from acetone and methyl alcohol; yield 17 g. instead of a possible 18.4 g. from 27 g. of the double salt.

Anal. Calcd. for $C_{24}H_{23}O_2N$: C, 80.7; H, 6.4. Found: C, 80.7; H, 6.5.

The methyl ether crystallizes in small prisms and melts at 100°. It is readily soluble in acetone, moderately soluble in methyl alcohol and in ether. As would be expected, the ether is more stable than the pseudo base but above 150° it effervesces freely as it loses methyl alcohol and passes into the anhydro compound. It is oxidized by permanganate under the same conditions and in the same manner as the pseudo base and it also gives the same products when it is ozonized. Concentrated aqueous sodium hydroxide does not attack the ether but methyl alcoholic solutions that contain the merest trace of base soon become yellow and ultimately all of the ether is changed into the same yellow methoxyl compound that is formed by adding methyl alcohol to the anhydro compound. Since the ether behaves toward acids exactly like the pseudo base, is stable and is easily made and purified, it constitutes the most convenient intermediate for the preparation of soluble salts.

The Cyanide, 2-Ethyl-3,4,5-triphenyl-5-cyano Isoxazoline, XVIII.—Dry hydrogen chloride was passed into a cooled solution of 5 g. of the methyl ether in absolute ethyl ether until the precipitation of the crystalline chloride was complete. The chloride was collected on a filter, washed with dry ether and dissolved in water. The slightly acid solution was neutralized and then treated with a solution of 3 g. of sodium cyanide in 10 cc. of water. The resulting paste was extracted with ether, the ethereal solution dried with sodium sulfate, concentrated under diminished pressure and diluted with low-boiling petroleum ether. It deposited the cyanogen compound in colorless prisms which after recrystallization melted at 89°; yield, 4.1 g.

Anal. Calcd. for $C_{24}H_{20}ON_2$: C, 81.8; H, 5.7. Found: C, 81.5; H, 5.9.

The cyanogen compound behaves toward permanganate, ozone and acids exactly like the methyl ether. At the melting point it loses hydrocyanic acid with effervescence and passes into the anhydro compound. It is exceedingly soluble in organic solvents. The ethereal solution soon smells of hydrocyanic acid and if it is allowed to stand for some time in a closed vessel the cyanide gradually changes into an isomeric compound.

B. The Open Chained Compounds

The anhydro compound and the substances that are obtained from it by addition or hydrolysis constitute a class of compounds with properties entirely different from those of the cyclic compounds. All of the latter are readily converted into each other and all are also easily transformed into the anhydro compound, but neither the anhydro compound itself nor any of its derivatives or addition products can be changed into one of the cyclic compounds. The distinction between the two classes, therefore, presents no difficulties.

The Anhydro Compound, Ethylidene-α,β-diphenyl-β-benzoyl-vinylamine, $C_6H_5COC(C_6H_5)=C(C_6H_5)N=CHCH_3$.—The anhydro compound is formed from the pseudo base by loss of water, from the methyl ether by loss of alcohol and from the cyanogen compound by loss of hydrocyanic acid. Owing to the ease with which it is hydrolyzed, it is difficult to get a pure product by any procedure. In order to avoid this hydrolysis as far as possible it is important to decompose these substances at the lowest possible temperature, to remove the volatile product as rapidly as possible and to crystallize the residue without undue contact with the air of the laboratory.

Thus 4 g. of the pseudo base was heated at 120° under 3 mm. pressure for ten minutes, at the end of which time effervescence ceased. The residue was dissolved in the minimum quantity of alcohol-free ether, the solution immediately diluted with an equal volume of petroleum ether and cooled in a freezing mixture. It deposited 3.2 g. of yellow needles melting at 105°. After several recrystallizations the melting point rose to 110° but the substance was still quite yellow. Rapid solution in methyl alcohol followed by immediate chilling in a freezing mixture finally gave needles which were almost colorless and melted at 112°.

Anal. Calcd. for $C_{23}H_{19}ON$: C, 84.7; H, 5.8. Found: C, 84.9; H, 5.9.

The anhydro compound is readily soluble in all organic solvents except low-boiling petroleum ether. Although it combines with alcohol it can be recrystallized from methyl alcohol provided that this is entirely free from bases. It reduces permanganate and it is readily ozonized.

α-Methoxyethyl-α,β-diphenyl-β-benzoyl-vinylamine, $C_6H_5COC(C_6H_5)=C(C_6H_5)NHCH(OCH_3)CH_3$.—When the anhydro compound is dissolved in boiling methyl alcohol which contains a trace of base, the solution almost immediately turns yellow and in a comparatively short time a pale yellow addition product begins to crystallize. The same substance is formed with equal rapidity by similar treatment of the cyanogen compound (XVIII) and, more slowly, also from the methyl ether (XVII). It was purified by recrystallization from methyl alcohol, from which it separates in yellow plates melting at 140°. Above the melting point it loses methyl alcohol and reverts to the anhydro compound.

Anal. Calcd. for $C_{24}H_{23}O_2N$: C, 80.7; H, 6.4. Found: C, 80.6; H, 6.5.

α-Cyano-ethyl-α,β-diphenyl-β-benzoyl-vinylamine, $C_6H_5COC(C_6H_5)=C(C_6H_5)NHCH(CN)CH_3$.—When a saturated ethereal solution of the cyanogen compound XVIII was kept in a stoppered flask at the ordinary temperature, it slowly deposited a more sparingly soluble substance which separated in large, very pale yellow prisms which melt at 130°. Like the methoxyl compound it decomposes above the melting point and reverts to the anhydro compound and like it, also, it is easily ozonized and hydrolyzed. With concentrated hydrochloric acid, the products of hydrolysis are phenyl dibenzoyl methane and alanine hydrochloride.

Anal. Calcd. for $C_{24}H_{20}ON_2$: C, 81.8; H, 5.7. Found: C, 82.0; H, 5.7.

Addition of Methyl Magnesium Iodide, *Iso*propyl-α,β-diphenyl-β-benzoyl-vinylamine, XXIV.—The anhydro compound obtained by heating 2.2 g. of the methyl ether to 150° under diminished pressure was added to a solution of methyl magnesium iodide containing one g. of magnesium. The solution became hot and deposited a colorless, crystalline magnesium derivative. This was separated by decanting the supernatant liquid, washed with ether and stirred into cracked ice and ether. The ethereal layer and washings yielded 1.7 g. of a yellow solid which was purified by recrystallization from ether and from methyl alcohol.

Anal. Calcd. for $C_{24}H_{23}ON$: C, 84.5; H, 6.7. Found: C, 84.9; H, 7.1.

The amine is readily soluble in all organic solvents except petroleum ether. It crystallizes in yellow needles and melts at 115°. Its structure was established by hydrolysis. For this purpose a small quantity of concd. hydrochloric acid was added to a solution of 1 g. of the substance in boiling methyl alcohol. The solution was diluted with an equal volume of hot water; then set aside until it was colorless. It deposited phenyl dibenzoyl methane. The filtrate from the diketone was thoroughly extracted with ether and then evaporated to dryness. It left a hydrochloride which after one recrystallization from dry methyl alcohol and anhydrous ether melted at 152–153°. This hydrochloride when treated first with sodium nitrate and then with an alkaline solution of iodine gave iodoform. It is therefore the hydrochloride of *iso*-propylamine.

Hydrolysis of the Anhydro Compound, α,β-Diphenyl-β-benzoyl-vinylamine, XXV.—The pure solid anhydro compound is not altered by air but when it is not quite pure or when its solutions are not securely protected against contamination by acids, it is hydrolyzed to the corresponding amine. In petroleum ether this hydrolysis is very slow. It occurs most rapidly when solutions in moist ether are exposed to the air of the laboratory. The product separates as a bright yellow solid. This was purified by recrystallization from acetone and methyl alcohol.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 84.2; H, 5.9.

The amine is sparingly soluble in methyl alcohol, moderately soluble in ether and very readily soluble in acetone. It crystallizes in needles and melts at 162°. Its structure was established by ozonization and by hydrolysis.

Ozonization.—A current of ozone was passed for several hours through a solution of the amine in carbon tetrachloride. The ozonide was decomposed with ice, the solvent pumped off and the residue dissolved in ether. After the removal of a small quantity of benzoic acid with sodium carbonate the ethereal solution was dried and allowed to evaporate slowly. It deposited first a white solid which was purified by sublimation and identified as benzamide, and then pale yellow prisms, identified as benzil.

Hydrolysis.—When the anhydro compound is triturated with cold concd. aqueous hydrochloric acid the hydrolysis stops at the amine. In alcohol both the anhydro compound and the amine undergo further hydrolysis. Thus when a drop of concd. hydrochloric acid was added to a solution of 0.5 g. of the amine in methyl alcohol, the color gradually faded and the solution deposited an almost equal quantity of a colorless solid which was identified as phenyl dibenzoyl methane. A similar solution was boiled. It became colorless in a few minutes but gave, in addition to the diketone, methyl benzoate and desoxybenzoin.

Isomeric Amine.—In one experiment in which a considerable quantity of crude methylene anhydro compound[8] which had been kept in a vial for several years was recrystallized from ether without protection against the acid in the air, a more sparingly soluble yellow compound made its appearance. This separated from ether in small prisms and melted at 208°.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 84.7; H, 5.8.

This new product is isomeric with the amine melting at 162°. It is hydrolyzed

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[8] Ref. 2, p. 1224.

under the same conditions as the lower melting substance and also gives the same products—phenyl dibenzoyl methane and ammonium chloride. It is therefore difficult to comprehend how it can be anything except a geometrical isomer of the lower melting compound. There is, however, one grave objection to this interpretation. When the lower melting amine is treated with standardized methyl magnesium iodide, it consumes two moles of reagent, liberates two moles of gas, and is recovered when the magnesium derivative is decomposed. The higher melting amine likewise dissolves in the reagent but it consumes only one mole of it and it liberates only one mole of gas. It also is recovered when the resulting magnesium compound is decomposed.

Synthesis.—In order to secure more of this isomer we hydrolyzed both the methylene and the ethylidene anhydro compounds in different solvents and under varying conditions. All these attempts ended in the lower melting amine. We therefore turned to synthesis. Amines of this type have been obtained by Claisen,[9] who found that some isoxazoles react with phenyl magnesium bromide to form compounds to which he assigned this structure. We added triphenyl isoxazole to a solution of phenyl magnesium bromide containing 5 equivalents of the reagent. The isoxazole is sparingly soluble and the reaction was extremely slow. After boiling for sixty-four hours the mixture was decomposed in the usual manner. It gave, besides unchanged isoxazole, only the amine melting at 162°.

Although methyl magnesium iodide seldom acts as a reducing agent, we found that it reacts with triphenyl isoxazole much more rapidly than phenyl magnesium bromide. The sole product in this case also was the lower melting amine. This amine was also the only product obtained in an entirely different method of synthesis which started with the nitrile of benzoyl-phenyl-acetic acid: $C_6H_5CH(COC_6H_5)CN \longrightarrow C_6H_5CH(COC_6H_5)C(C_6H_5){=}NMgBr \longrightarrow C_6H_5C(COC_6H_5){=}C(C_6H_5)NH_2$.

II. Experiments with Diphenyl *p*-Bromophenyl Isoxazoles

As outlined in the introduction, the first step in the preparation of the brominated isoxazoles was the condensation of nitrostilbene and *p*-bromophenyl nitromethane. In the earlier experiments this condensation was conducted in such a manner as to give the best yield of isoxazoline oxides. When it became evident that the separation of the oxides is not feasible, the conditions were changed in order to secure the isoxazoles instead of the oxides. The procedure then was as follows.

A solution of one g. of sodium in 75 cc. of methyl alcohol was added in the course of a few minutes to a boiling solution of 9.0 g. of nitrostilbene and 8.6 g. of bromophenyl nitromethane in the same solvent. After boiling for about five minutes, during which it became filled with a mass of solid oxide, it was treated with sodium methylate from 8 g. of sodium dissolved in 125 cc. of methyl alcohol and boiled for three to four hours. It was then cooled and filtered. The yield of crude washed and dried product melting at 168–171° was 105 g. from 90 g. of nitrostilbene. Recrystallization from ether raised the melting point to 172–173° where it became constant, but ozonization showed that the recrystallized product was a mixture.

Ethylation.—The mixture of isoxazoles was ethylated by exactly the same procedure that had been employed with the unbrominated compound and thus converted into a mixture of ferric chloride double salts. This was subjected to fractional recrystallization from ethyl bromide. The least soluble component separated from cold solutions in greenish yellow needles, and from boiling solutions in brown plates or

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[9] Claisen, *Ber.*, 59, 150 (1926).

tables. Both forms melt at 172–174° and the yellow slowly passes into the brown form if it is allowed to remain in contact with the mother liquor. From 22 g. of the mixed isoxazoles was obtained 34 g. of crude, washed and dried ferric chloride double salts; of this approximately 50% was later isolated in the form of the salt V.

Anal. Calcd. for $C_{23}H_{19}ONBrCl_4Fe$: C, 45.8; H, 3.2; Cl, 23.5. Found: C, 45.7; H, 3.1; Cl, 24.2.

3,4-Diphenyl-5-bromophenyl Isoxazole, II.—In order to locate the bromophenyl group it was necessary to convert the double salt into the isoxazole. To this end an ethereal solution of the corresponding pseudo base was prepared by shaking 8 g. of the powdered double salt with a mixture of 50 cc. of 20% sodium hydroxide, 50 g. of ice and 100 cc. of ether. This ethereal solution was repeatedly extracted with small quantities of concd. hydrochloric acid which had been diluted with an equal volume of water until the ether left no residue when evaporated. The combined acid extracts when chilled in a freezing mixture and freed from ether by evaporation in a draught deposited a hydrated chloride in colorless needles. The chloride was collected on a glass filter and partially dried by suction, then transferred to a flask and heated in a rapid current of air. As the temperature rose the chloride melted, lost first water then ethyl chloride, resolidified and finally melted again at about 170°. The product was recrystallized from acetone and methyl alcohol.

Anal. Calcd. for $C_{21}H_{14}ONBr$: C, 67.0; H, 3.7. Found: C, 67.4; H, 3.9.

The isoxazole is readily soluble in acetone, moderately soluble in ether, sparingly soluble in methyl alcohol. It crystallizes in needles and melts at 172–173°, almost exactly the melting point of the mixture of the two isomeric isoxazoles. In open vessels it sublimes freely at its melting point.

Ozonization.—The isoxazole was ozonized in ethyl bromide in the usual manner, the solvent removed under diminished pressure and the pasty residue shaken with ice water for two hours, during which most of it solidified. Solid and oil were then dissolved in ether. From the ethereal solution sodium carbonate extracted only a trace of *p*-bromobenzoic acid. The dried ethereal solution on evaporation deposited small colorless prisms that melted at 145–146°.

Anal. Calcd. for $C_{21}H_{14}O_3NBr$: C, 61.8; H, 3.4. Found: C, 61.6; H, 3.7.

β-Benzilmonoxime-*p*-bromobenzoate, VIII.—The ozonization product was readily hydrolyzed both with acids and with bases. Acids gave mainly benzil, hydroxylamine and *p*-bromobenzoic acid, while sodium methylate formed mainly benzonitrile and methyl *p*-bromobenzoate. In order to determine whether, as is usual in the case of phenylated isoxazoles, ozonization results in a derivative of β-benzil monoxime, the substance was synthesized by shaking 1.7 g. of β-benzil monoxime with 2.5 g. of *p*-bromobenzoyl chloride in 20 cc. of pyridine for two hours. The product melted at 145–146° and a mixture of the two substances melted at the same temperature.

The Pseudo Base, 2-Ethyl-3,4-diphenyl-5-bromophenyl-5-hydroxy Isoxazoline, XIII.—From the ferric chloride double salt the brominated pseudo base was obtained by the method previously employed for getting its unbrominated analog. It crystallized in colorless prisms and melted with effervescence at about 105°.

Anal. Calcd. for $C_{23}H_{20}O_2NBr$: C, 65.4; H, 4.7. Found: C, 66.0; H, 4.7.

Ozonization.—Two grams of the pseudo base was ozonized in ethyl bromide for two hours. After removing the solvent the pasty residue was boiled with water for a short time, then cooled and dissolved in ether. From the ethereal solution sodium carbonate extracted benzoic acid and a very small quantity of *p*-bromobenzoic acid which, like the analysis, indicated that the base was contaminated with a small quantity of the unbrominated compound. The ethereal solution on evaporation deposited pale yellow needles. After repeated recrystallization from petroleum ether containing a few drops of ether these melted at 89–90°.

Anal. Calcd. for $C_{14}H_9O_2Br$: C, 58.1; H, 3.1. Found: C, 58.9; H, 3.4.

p-Bromobenzil, **XXI**, is readily soluble in all organic solvents. It has a pronounced tendency to separate from solution as an oil and consequently is extremely difficult to purify. The analyses show that our sample was contaminated with benzil. Our melting point, therefore, is doubtless a little too low but the fact that the substance readily formed a quinoxaline derivative and was oxidized to equivalent quantities of benzoic and *p*-bromobenzoic acids by alkaline hydrogen peroxide leaves no doubt as to its character.

The Anhydro Compound, Ethylidene-α,β-diphenyl-β-bromobenzoyl-vinylamine, XX.—The anhydro compound was made like its bromine-free analog. It crystallizes from ether and from methyl alcohol in very pale yellow needles and melts at 102°.

Anal. Calcd. for $C_{23}H_{18}ONBr$: C, 68.3; H, 4.5. Found: C, 68.7; H, 4.7.

Ozonization.—The substance was ozonized in ethyl bromide. The products, isolated in the same manner as those from the bromine-free compound, were *p*-bromobenzil and benzamide.

Hydrolysis. α,β-Diphenyl-β-bromobenzoyl-vinylamine, XXVI.—Like its bromine-free analog, the anhydro compound is hydrolyzed with the utmost ease to acetaldehyde and a yellow, unsaturated amine. The amine was purified by recrystallization from acetone and methyl alcohol. It is readily soluble in acetone, moderately soluble in ether, sparingly soluble in methyl alcohol. It crystallizes in deep yellow needles and melts at 172°.

Anal. Calcd. for $C_{21}H_{16}ONBr$: C, 66.7; H, 4.2. Found: C, 67.4; H, 4.7.

Summary

This paper contains a description of the isolation of two pseudo bases in the triphenyl isoxazole series, an account of their properties, an opinion as to their structure, and a discussion of the mechanism by which such pseudo bases are formed from their salts.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

PARA-CYMENE STUDIES. XI. PARA-CYMYL-2-CARBITHIOIC ACID

BY ALVIN S. WHEELER AND CHARLES L. THOMAS[1]

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Fleischer[2] was the first to make a dithio acid, the dithio-benzoic acid. Two years later Engelhardt, Latschinoff and Malyscheff[3] obtained its lead salt by the action of benzoyl chloride on lead sulfide. Klinger[4]

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[1] This paper is an abstract from a Bachelor's Thesis presented to the Faculty of the University of North Carolina in June, 1928.

[2] Fleischer, *Ann.*, **140**, 241 (1866).

[3] Engelhardt, Latschinoff and Malyscheff, *Z. Chem.*, **1868**, 353; *Jahresb. über der Fortschritte der Chemie*, **1868**, 595.

[4] Klinger, *Ber.*, **15**, 862 (1882).