[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF BUFFALO]

THE OXIMES OF ALPHA, BETA-UNSATURATED KETONES AND THE BECKMANN REARRANGEMENT. II

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In a recent article[1] we presented evidence to show that the oximes of certain α,β-unsaturated ketones possessed the *syn*[2] configuration (I) and underwent a *trans* shift in the Beckmann rearrangement, and that the closely related and isomeric isoxazolines (II) were not formed through a

I II

process which involved these oximes as intermediates. After this article had been submitted to THIS JOURNAL there appeared a paper on the same subject by Auwers and Seyfried[3] in which, on the basis of essentially similar experimental evidence, exactly opposite conclusions were reached. Although we believed that our conclusions were correct, we nevertheless preferred not to recall our article in order to add a discussion of Auwers' work since we felt that such a discussion, involving as it must matters of interpretation rather than fact, would certainly be futile and might lead to controversy. Since that time, however, we have been able to accumulate additional evidence concerning the problem at issue which we believe to be decisive. In this article we shall present our new evidence and then discuss certain phases of Auwers' work.

In our earlier paper we described the *syn* oxime of benzal-*p*-bromoacetophenone and reported that it furnished as a result of the Beckmann rearrangement the *p*-bromoanilide of cinnamic acid. A further and more detailed study of this rearrangement confirmed these observations and disclosed one additional and significant fact: if the entire crude rearrangement product or if the mother liquors from the crystallization of this crude product are subjected to an alkaline hydrolysis one obtains—in addition to the hydrolysis products of the anilide, *p*-bromoaniline and cinnamic acid—small amounts of ammonia and *p*-bromobenzoic acid. These latter two products, the ones to be expected from the isomeric *anti* oxime, might have been formed as a result of any one of three causes. The original oxime might have undergone both a *cis* and a *trans* shift on rearranging, or it might have been transformed into its isomer before rearranging or, finally, it might itself have been a mixture of the *syn* and *anti* isomers. A decision

[1] Blatt, THIS JOURNAL, **53**, 1133 (1931).

[2] We use "*syn*" following the suggestion of Auwers[3] to designate the unsaturated oximes in which the hydroxyl group is adjacent to the ethylenic double bond.

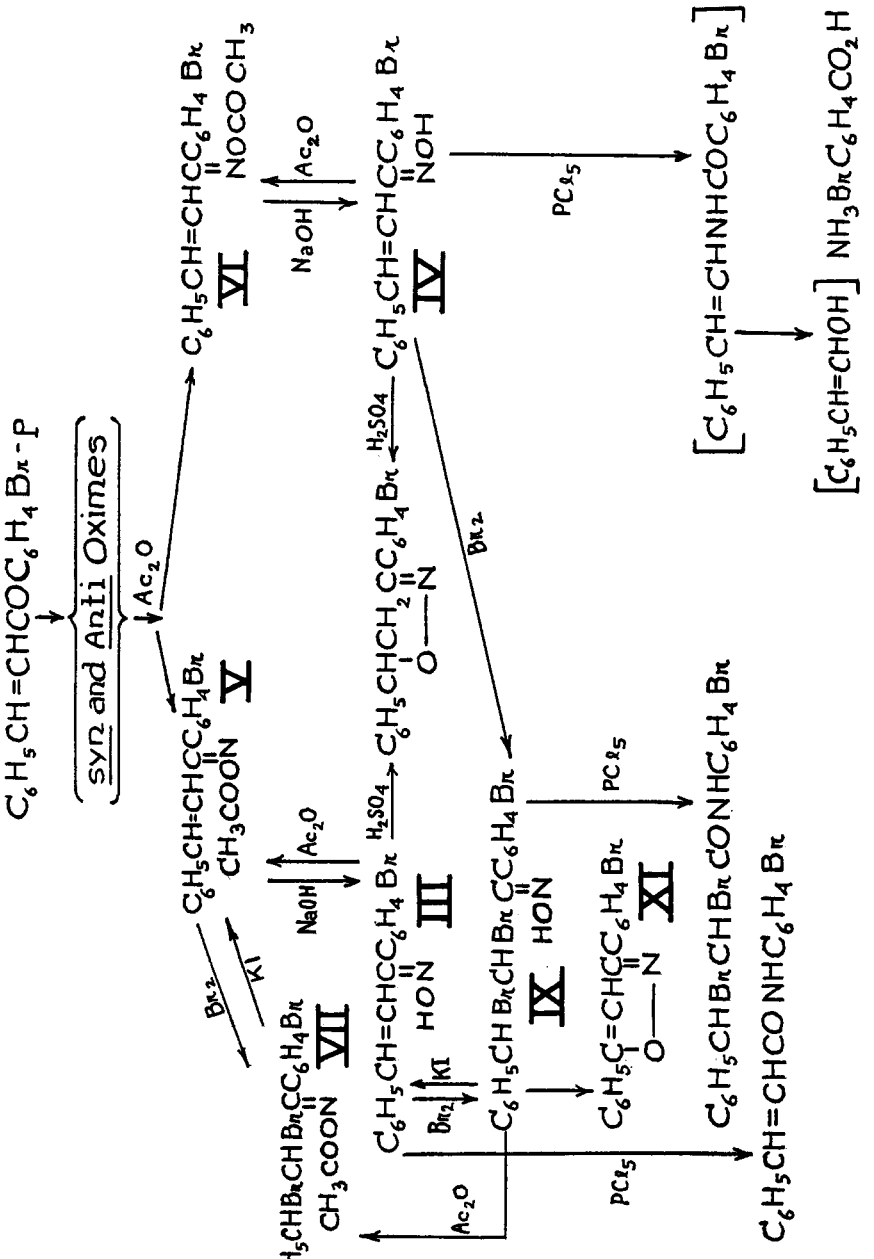
[3] Auwers and Seyfried, *Ann.*, **484**, 178 (1930).

between these alternatives was, of course, essential. We were at first unsuccessful in making such a decision because we were unable by fractional crystallization of the original material either to obtain two isomeric oximes or to obtain a fraction which gave a completely homogeneous rearrangement product. However, when we acetylated the original oxime (a procedure employed by Auwers for purifying similar oximes) it was possible to separate two isomeric acetyl derivatives and by hydrolyzing these acetates to obtain both the *syn* and the *anti* oximes of benzal-*p*-bromoacetophenone. It was thus evident that the material previously described as the *syn* oxime of benzal-*p*-bromoacetophenone is in reality a mixture consisting predominantly of the *syn* oxime (III) but also containing small amounts of the *anti* oxime (IV).

The *syn* and *anti* oximes of benzal-*p*-bromoacetophenone are the first examples of isomeric oximes so far obtained from unsaturated ketones of the type of benzalacetophenone. The *syn* oxime (III) we are confident is a homogeneous chemical individual; the *anti* oxime may contain at most traces of the *syn* isomer. The two oximes are remarkably similar in their physical properties and if they are taken as representative of α,β-unsaturated oximes in general, then their similarity accounts well for the fact that such isomers have not been isolated heretofore. The pure *syn* oxime (III) is deceptively similar in physical properties to the previously described mixture; chemically it differs only in that it yields homogeneous products on acetylation and in the Beckmann rearrangement. The *anti* oxime (IV) parallels the *syn* isomer in its behavior on heating and toward sulfuric acid. Thus both the *syn* and *anti* oximes melt over a wide temperature range and they both melt over almost the same range. This peculiar behavior on heating is certainly connected with the decomposition of the material; it is perhaps due also in part to an interconversion of one isomer into another. With sulfuric acid both isomers yield the same 3-*p*-bromophenyl-5-phenyl isoxazoline. The differences between the *syn* and *anti* isomers are exhibited, as we have already stated, in their behavior on acetylation and on rearrangement. The behavior of the two isomers toward bromine will be considered later.

The evidence upon which we based the configuration of the *syn* oxime in our earlier paper consisted essentially in the addition of bromine to that oxime to form a dibromide (IX) which behaved similarly to the original oxime in the Beckmann rearrangement and which on heating lost hydrogen bromide to form the isoxazole (XI). The argument was that the isoxazole formation indicated that the oximino hydroxyl group in the dibromide was *syn* to the halogen and that therefore in the unsaturated oxime this hydroxyl group was *syn* to the double bond. The assumption was that the unsaturated oxime and the dibromo oxime derived from it possessed the same configuration. The facts involved have been verified using the pure

syn oxime. The assumption involved has been verified in two separate ways. In the first place we brominated the *syn* acetate (V) and obtained a



syn dibromoacetate (VII). Then by acetylating the *syn* dibromide (IX) we obtained the same dibromoacetate. This evidence renders the possibility of rearrangement during bromination slight. More convincing, however, is the second method of proof, kindly suggested to us by Professor E. P. Kohler, which consists in going back from the saturated dibromo compounds to the ethylenic compounds from which they were originally made. Thus the *syn* dibromide (IX) on treatment with potassium iodide in acetone furnishes cleanly the *syn* oxime (III), while the *syn* dibromoacetate (VII) with the same reagent yields the *syn* acetate (V).

Having thus definitely established the validity of the method used for determining the configuration of the *syn* oxime, we proceeded to the application of this method to the *anti* isomer. Here a surprising result was encountered. The *anti* oxime (IV) when brominated yields the *syn* dibromide (IX). This shift in configuration and concomitant disappearance of isomerism when the ethylenic double bond is saturated is of interest in connection with the explanation of Raikowa[4] for the non-existence of isomers of oximes having a methylene group adjacent to the erstwhile carbonyl group. It is not possible to say as yet whether the shift in configuration on bromination is actually due to the saturation of the double bond or to a specific isomerizing action of the reagent. In view of Raikowa's theory, experiments on the addition of reagents other than bromine to the ethylenic double bond of *anti* oximes of this type would be of considerable interest.[5] Whatever the cause of the shift of configuration on bromination the fact that such a shift takes place made the *anti* oxime of much less value to us than we had hoped. At the same time, however, it made clear why the presence of the *anti* oxime was not discovered when formerly we brominated the mixture of isomers.

The remainder of our work was concerned chiefly with the sulfuric acid cyclicization of α,β-unsaturated oximes and with the mechanism of isoxazoline formation, but before taking up these two topics it is necessary to consider briefly some α-bromo oximes such as (X). We extended our work to include the α-bromo oxime (X) because of the suggestion, made in a private communication from Professor Auwers, that the heat decomposition of the saturated dibromo oxime (IX) to yield the isoxazole (XI) might proceed through the α-bromo oxime (X). Since this would involve a shift in configuration, it would invalidate the heat decomposition as

$$C_6H_5CH{=}CBrC({=}NOH)C_6H_4Br \quad \text{X}$$

[4] Raikowa, *Ber.*, **62**, 1626, 2142 (1929).

[5] Experiments apparently of this type were made by Merz, *ibid.*, **63**, 2951 (1930), who studied the catalytic reduction of the "*syn*" and "*anti*" oximes of benzalacetophenone and dypnone and found that with each pair one was reduced and the other unaffected. However, the substances studied by Merz were not isomeric oximes but were in each case an oxime and an isoxazoline, as was shown by Auwers, *Ann.*, **484**, 180 (1930), and ourselves, THIS JOURNAL, **53**, 1134 (1931).

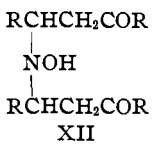
evidence. We therefore prepared the α-bromo oxime (X) and studied its behavior on heating. This oxime, like the saturated dibromo oxime, does decompose on melting but, unlike the saturated dibromo oxime, it does not yield any isoxazole. Consequently, the heat decomposition of the dibromo oxime does not involve the α-bromo oxime.

The α-bromo oxime (X), like the α-bromo oximes studied by Auwers, yields on a Beckmann rearrangement a product resulting from a shift of the unsaturated part of the molecule. In this respect it and all other known α-bromo oximes are similar to the *anti* oxime of benzal-*p*-bromoacetophenone (IV). By analogy, therefore, we suggest for the α-bromo oximes the *anti* configuration. This configuration we do not consider as established but there does exist some inferential support for it in the formation of the oximes themselves. Thus when α-bromobenzal-*p*-bromoacetophenone is treated with hydroxylamine hydrochloride, the oxime formation is strikingly slower than when benzal-*p*-bromoacetophenone is treated with the same reagent under the same conditions. This same slow rate of oxime formation is shown by α-bromobenzalacetophenone. This effect is not confined to ketones having a bromine atom in the α-position since benzaldesoxybenzoin, having a phenyl group in the α-position, also forms an oxime very slowly. It appears logical to attribute this slowness of oxime formation to steric factors—to the hindrance due to the large substituent in the α-position. And a natural continuation of this reasoning suggests that the oximes of these α-substituted ketones would possess the configuration less subject to the hindrance—that is, the *anti* configuration. We wish to emphasize that we consider these ideas on the configuration of the α-substituted oximes as indicative rather than conclusive.

In our first paper we discussed the isomerization of *syn* α,β-unsaturated oximes into isoxazolines which results when the oximes are dissolved in sulfuric acid. In an attempt to determine whether this reaction, like the Beckmann rearrangement, is related to oxime configuration we tried the action of sulfuric acid on certain *anti* oximes. The α-bromo oxime (X) and the oxime of α-bromobenzalacetophenone were unaffected by solution in sulfuric acid. Benzaldesoxybenzoin oxime was attacked but did not yield either of the two known 3,4,5-triphenyl isoxazolines. At this point it appeared that the sulfuric acid cyclicization was quite specific for *syn* oximes. Unfortunately, however, for such a clean-cut differentiation we found that the *anti* oxime of benzal-*p*-bromoacetophenone (IV), like the *syn* isomer, does yield an isoxazoline with sulfuric acid. It would seem therefore that the sulfuric acid rearrangement is conditioned by the substituents present in the oxime molecule rather than by the configuration of the oxime itself.

The mechanism of isoxazoline formation was also discussed in our first paper. Isoxazolines are formed from α,β-unsaturated ketones and hy-

droxylamine only in alkaline solution. The reaction is an unusually complex affair and Fleck,[6] using benzalacetophenone, obtained seven products. We were interested only in learning whether the isoxazolines are formed through an oxime or as a result of some type of 1,4-addition. Having available both the *syn* and *anti* oximes of benzal-*p*-bromoacetophenone, we tried the action of alkali on these oximes and found that neither one furnished an isoxazoline. We then attempted to relate the isoxazoline formation to 1,4-addition by seeing whether a ketone so substituted as to render 1,4-addition negligible would yield an isoxazoline with hydroxylamine and alkali. β-Phenylbenzalacetophenone satisfied our requirements because with the Grignard reagent it furnishes but little 1,4-addition product[7] and because the analogously constituted β-phenylcinnamic ester in contrast to cinnamic ester adds hydroxylamine very reluctantly.[8] When we treated β-phenylbenzalacetophenone with hydroxylamine and alkali we obtained only the oxime. No isoxazoline was found. Since, then, isoxazoline formation does not take place unless 1,4-addition is possible and since the isoxazoline formation is not a result of simple 1,4-addition,[9] the most obvious source of the isoxazolines is some complex dimolecular 1,4-addition product such as (XII). Fleck isolated such a product from the reaction between benzalacetophenone and hydroxylamine and found that this product on further treatment with hydroxylamine did yield an isoxazoline. We did not attempt to isolate a product analogous to (XII) from benzal-*p*-bromoacetophenone since in view of the complex nature of the alkaline reaction we were satisfied with showing the probable course of the isoxazoline formation.



XII

In conclusion it is necessary to consider certain phases of Auwers' work on α,β-unsaturated oximes in order to point out why he and ourselves have come to such diametrically opposite conclusions in the interpretation of our results. Auwers studied unsaturated oximes which correspond in behavior to our *syn* oximes, their dibromides, certain α-bromo oximes which correspond to our oxime (X), and some β-bromo oximes. We shall consider only two of these classes of compounds.

Because the oximes of α-bromo unsaturated ketones are converted into isoxazoles by alkali, while the unhalogenated oximes are unaffected and because these α-bromo oximes lose halogen with alkali more rapidly than do the α-bromo ketones, Auwers assigns a *syn* configuration to the α-bromo oximes. This conclusion does not seem to us to be justified for two reasons. First, an inspection of the formula of an α-bromo oxime (XIII) suffices to

[6] Fleck, "Dissertation," Leipzig, 1903.

[7] E. P. Kohler, *Am. Chem. J.*, **38**, 515 (1907).

[8] Posner, *Ann.*, **389**, 34 (1912).

[9] Auwers and Seyfried, *ibid.*, **484**, 187 (1930); Blatt, THIS JOURNAL, **53**, 1136 (1931).

show that, irrespective of the configuration of the oxime, the isoxazole formation cannot be a simple reaction; it must either involve several steps or else a rearrangement in order to account for the presence of the hydrogen atom in the 4-position of the isoxazole (XIV). Second, work on the most closely related compounds, the α-bromo ketones, has shown that in the reaction between these ketones and alcoholic alkali the first step consists always of addition to the double bond.[10] And if the first step in the action of alcoholic alkali on the α-bromo oximes also consists in saturation of the double bond then, in view of our results with the addition of bromine to the *anti* oxime (IV), one would expect a shift from the *anti* to the *syn* configuration at this stage.

$$\text{RCH=CBrC(NOH)R'} \quad \text{XIII}$$

$$\begin{array}{l} \text{RC=CHCR'} \\ \quad | \quad\quad \| \\ \text{O}\text{——}\text{N} \end{array} \quad \text{XIV}$$

The configuration of the saturated dibromo oximes is not considered by Auwers as definitely established. He assigns them provisionally the *anti* configuration because they are prepared from the halogen-free oximes by bromination and because they behave similarly to these halogen-free oximes in the Beckmann rearrangement. In order to reconcile the *anti* configuration of the dibromo oximes with the fact that they, like the α-bromo oximes, yield isoxazoles with alkali, Auwers concludes that the alkaline reaction is not trustworthy in the case of the dibromo oximes because of the possibility that it proceeds through an α-bromo oxime with a consequent shift in configuration. However, the assumption of an α-bromo oxime in this alkaline reaction seems hardly warranted, for the dibromide of benzalacetophenone oxime loses hydrogen bromide to form an isoxazole on treatment with sodium acetate while the corresponding α-bromo oxime is unaffected by this reagent.[11] It appears to us preferable to consider that the first step leading toward an isoxazole on treatment of a dibromo oxime with alkali is the loss of halogen acid to form a bromo-isoxazoline which would then lose halogen acid very rapidly to yield an isoxazole. This would account for Auwers' striking observation that on treatment of the dibromide of benzalacetophenone oxime with one mole of sodium acetate the products are unchanged oxime and isoxazole.

From this discussion it is apparent that the explanation of the divergent conclusions reached by Auwers and ourselves lies in the different emphasis and interpretation placed on the reactions of the bromo oximes and alkali. In our opinion these alkaline reactions are complex processes and, while they may well possess considerable significance for assigning configurations, a great deal more information concerning the intimate course of the reactions is necessary before they can be safely used for that purpose. At present the available facts can be interpreted at least as well and, it seems

[10] Dufraisse and Gerald, *Bull. soc. chim.*, [4] **31**, 1285 (1922); Kohler and Addinall, THIS JOURNAL, **52**, 3728 (1930).

[11] Auwers and Seyfried, *Ann.*, **484**, 201–202 (1930).

to us, better in the opposite sense to that chosen by Auwers. Since these alkaline reactions are being investigated by Auwers and others, we have not attempted to study them and do not propose to do so.

The expenses of this investigation have been defrayed by funds privately contributed.

Experimental Part

$C_6H_5CH{=}CHCOC_6H_4Br$-*p*.—The previously described oxime[12] obtained by the action of hydroxylamine hydrochloride on this ketone is a mixture of the *syn* and *anti* isomers, as is shown by its behavior in the Beckmann rearrangement. When 1.0 g. of the crude oxime was rearranged[13] the product was a sticky solid. It was dissolved in alcohol and furnished 0.35 g. of the *p*-bromoanilide of cinnamic acid. The alcoholic filtrate from the purification of the anilide was yellow in color and when boiled with sodium hydroxide it turned dark red while a steady stream of ammonia was evolved.[14] When no more ammonia was given off the reaction mixture was diluted with water and extracted with ether. The aqueous layer, after the usual treatment, yielded an acid which melted partially at 105–130°, the balance at 190–215°. This acid was dissolved in dilute carbonate and oxidized cold with permanganate. The odor of benzaldehyde was evident during the oxidation. Finally the solution was acidified, cleared with bisulfite and the organic acid filtered and dried. It melted at 200–220°; mixed with *p*-bromobenzoic acid (246°) the melting point was 220–235°.

Attempts to separate the crude oxime into its components by fractional crystallization using alcohol and water and also benzene and petroleum ether were unsuccessful. Rearrangements of the various fractions followed by hydrolyses indicated that the *syn* oxime was accumulating in the less soluble fractions but we were unable to secure a product which was free from the *anti* isomer. The more soluble fractions consistently yielded oils. The separation of the oxime mixture was finally effected by means of the acetyl derivatives.

For acetylation 50 g. of the crude oxime of benzal-*p*-bromoacetophenone was heated on the steam-bath for three and a half hours, with 100 cc. of acetic anhydride. The resulting clear, pale yellow solution was cooled and poured into 500 cc. of cold water. The crude acetylation mixture, composed of small almost colorless lumps, weighed 54.5 g. and melted at 75–130°.

Fifty grams of this mixture was dissolved in 100 cc. of boiling ethyl acetate. The filtered solution when chilled in ice deposited 28 g. of fairly pure acetate of the *syn* oxime. The filtrate from this first crop of crystals was concentrated to about 30 cc., then diluted with petroleum ether and subjected to the usual fractionation. The separation, which

[12] Blatt, THIS JOURNAL, **53**, 1138 (1931).

[13] Since in the course of this work it was necessary to perform a large number of these rearrangements we shall, in order to save space, describe here the general procedure employed and omit details in the succeeding pages except in the cases where a special procedure was used. We dissolved or suspended the oxime in absolute ether and added an excess of phosphorus pentachloride. The reaction mixture was kept cold at the outset and gradually allowed to warm to room temperature. After an appropriate time—generally three hours, always long enough to allow any insoluble intermediate to redissolve—the reaction mixture was poured on ice and the ether removed in an air stream. The rearrangement product if a solid was filtered, if a liquid taken up in ether.

[14] We assured ourselves by separate experiments that neither the oxime nor the pure *p*-bromoanilide of cinnamic acid yields ammonia when boiled with alcoholic alkali.

is a tedious process at best, can be accelerated somewhat by leaching the intermediate fractions with cold ethyl acetate which extracts the low melting soluble *anti* acetate. Operating in this fashion it is possible to obtain from the original 50 g. of crude acetate some 30–33 g. of almost pure *syn* acetate melting at 142–144°, and about 10–12 g. of impure *anti* acetate melting at 85–100°. The purification of these isomers is described later.

Derivatives of the Syn Series

The acetate of syn benzal-*p*-bromoacetophenone oxime (V) obtained from the above fractionation is purified by crystallization from ethyl alcohol or ethyl acetate. The pure product melts at 145°. It forms triclinic crystals showing parallel extinction with crossed nicols.[15] To the unaided eye these crystals appear as stout opaque rods or as small clumps of extremely fine needles. The acetate is moderately soluble in ethyl acetate, benzene, acetone and acetic acid and crystallizes well from these solvents. It is only slightly soluble in methyl and ethyl alcohols and ether, insoluble in petroleum ether. In ethyl alcohol 1.0 g. requires about 20 cc. for solution at the boiling point and 0.9 g. is recovered on chilling the solution. In ethyl acetate 5.0 g. will dissolve in about 20 cc. at the boiling point and on chilling the solution 4.5 g. is recovered.

Anal. Calcd. for $C_{17}H_{14}O_2NBr$: C, 59.3; H, 4.1. Found: C, 59.3; H, 4.4.

Bromination of the Syn Acetate (V).—We dissolved 6.88 g. of the acetate in 50 cc. of chloroform and added a solution of 3.2 g. of bromine in the same solvent. After the reaction was completed, the solvent and slight excess of bromine were removed in an air stream and the resulting brown solid was ground with alcohol, which removed the color. The product, 8.6 g., was crystallized from benzene and petroleum ether.

Anal. Calcd. for $C_{17}H_{14}O_2NBr_3$: Br, aliphatic, 31.7. Found: Br, 31.4, 31.6.

The syn dibromoacetate (VII) melts at 146–147°. It is quite soluble in the common organic solvents save alcohol, ether and petroleum ether. The use of alcohol in crystallizing this and other saturated dibromo compounds in this series is inadvisable for occasionally, due perhaps to traces of alkali, these compounds react with the solvent. The *syn* dibromoacetate is identical (mixed melting point) with the product obtained by the action of acetic anhydride on the *syn* dibromide (IX) (see later).

Action of Potassium Iodide on the Syn Dibromoacetate (VII).—When 0.5 g. of this material was dissolved in 20 cc. of acetone and a solution of 0.5 g. of potassium iodide in 2 cc. of water was added, there was an immediate liberation of iodine. A small amount of apparently inorganic material precipitated. After fifteen minutes the iodine was removed with concd. thiosulfate solution and then the reaction mixture was cautiously diluted with water. The resulting precipitate, after filtration and drying, weighed 0.32 g. and melted at 130–138°. Mixed with the *syn* acetate (145°) the melting point was 139–143°. By crystallization from 6 cc. of alcohol there was obtained 0.25 g. of pure *syn* acetate whose identity was shown by a mixed melting point.

Hydrolysis of the Syn Acetate (V).—When 13.8 g. of the *syn* acetate was suspended in 200 cc. of alcohol and a solution of 5.0 g. of potassium hydroxide in 25 cc. of water was added, a yellow color developed almost immediately. The reaction was stirred for one hour, during which time all of the material went into solution, then warmed so that it could be diluted with enough hot water to destroy the color. (The disappearance of color on dilution apparently indicates the hydrolysis of the sodium salt.) On cooling, 10.0 g. of fine needles of the *syn* oxime separated; yield 80%. The balance of the oxime can be obtained by further dilution of the filtrate.

[15] Dr. R. H. Pegrum was kind enough to examine carefully the crystals of both the *syn* and *anti* acetates and the corresponding oximes. To economize space we are giving only part of his observations.

The syn oxime of benzal-*p*-bromoacetophenone (III) thus regenerated from its acetyl derivative is deceptively similar to the mixture previously described as the *syn* oxime. Its behavior on heating, on solution in sulfuric acid and on bromination parallels our previous description. The melting point of the pure oxime is not sharp and depends upon the rate of heating. We prefer the figure 145–158°. During the heating the material develops a yellow color and the odor of an aromatic nitrile is apparent.

Attempts to convert the *syn* oxime into its *anti* isomer were only partially successful. Since the melting points of the oximes are not sufficiently sharp for identification, it was necessary to follow each experiment with a Beckmann rearrangement and then hydrolyze the entire product to see if ammonia and *p*-bromobenzoic acid were formed. Operating in this manner it was possible to show that prolonged boiling with alcoholic alkali, heating with formic acid, and conversion into the bromomagnesium salt by means of cold ethylmagnesium bromide followed by decomposition with ammonium chloride, all resulted in a partial conversion into the *anti* isomer. The conversion, however, was never clean cut or useful.

Beckmann Rearrangement of the Syn Oxime (III).—When 1.0 g. of the regenerated oxime was rearranged, the yield of crude product was quantitative. On crystallization this product furnished 0.6 g. of the *p*-bromoanilide of cinnamic acid, while the mother liquors from the crystallization furnished on hydrolysis only *p*-bromoaniline (identified as tribromoaniline) and cinnamic acid. There was no ammonia evolved. The cinnamic acid melted sharply at 132–133°, with no high melting residue and gave a negative Beilstein test for halogen.

Acetylation of the Syn Oxime (III).—In order to further demonstrate the homogeneity of the regenerated *syn* oxime and to determine whether the formation of the isomeric *anti* acetate might be due to the isomerizing action of acetic anhydride on the *syn* oxime, we acetylated 6.0 g. of the regenerated *syn* oxime. The acetylation was carried out exactly as described for the crude oxime mixture. On pouring the reaction mixture into cold water, there was an immediate separation of the characteristic stout rods of the *syn* acetate. The crude acetylation product melted at 143–145° and weighed 6.75 g.; yield, 98%.

Bromination of the Syn Oxime (III).—When the *syn* oxime was brominated exactly as described in our previous paper, the results were identical with those reported before. We have found, however, that the resulting *syn* dibromo oxime (IX) can be crystallized from benzene and petroleum ether. The melting point of this dibromo oxime, which is also a decomposition point, varies with the rate of heating. Our earlier melting point was, by an excess of caution, too low; 173° is a better figure.

Beckmann Rearrangement of the Syn Dibromo Oxime (IX).—When 0.7 g. of the dibromo oxime was rearranged, the yield of crude product was quantitative. On crystallization from benzene it melted at 194°. The identity of the material as the *p*-bromoanilide of dibromocinnamic acid was established by a mixed melting point with a synthetic specimen of that anilide. The synthetic anilide was prepared both by treating dibromocinnamoyl chloride with *p*-bromoaniline and by bromination of the *p*-bromoanilide of cinnamic acid. For analysis the anilide was crystallized from benzene, from which it separates in extremely fine needles melting at 195–196°.

Anal. Calcd. for $C_{15}H_{12}ONBr_3$: C, 39.0; H, 2.8. Found: C, 39.1; H, 2.8.

Action of Potassium Iodide on the Syn Dibromo Oxime (IX).—When 1.0 g. of the dibromo oxime was dissolved in 25 cc. of acetone and a concd. aqueous solution of potassium iodide (1.5 g. KI) was added, the liberation of iodine began at once and was accompanied by the formation of a precipitate of inorganic material. After fifteen minutes the iodine was removed with concd. thiosulfate solution, which, however, did not render the solution completely colorless. Water was then added and the inorganic salt

dissolved. On further dilution with water the *syn* oxime was thrown out as an oil which soon solidified. The yield of crude product was 0.65 g. Mixed melting points indicated that the product was the *syn* oxime (III) but in order to be certain a portion of the material was acetylated and the balance rearranged and hydrolyzed. On acetylation the *syn* acetate (V) was obtained. On rearrangement and hydrolysis there was only insignificant traces of ammonia.

Acetylation of the Syn Dibromo Oxime (IX).—When 2.0 g. of the dibromo oxime was heated for three and a half hours with an excess of acetic anhydride and the reaction mixture was poured into water the yield of crude dibromo acetate (VII) was quantitative. The crude material melted at 138–143° and after crystallization from benzene and petroleum ether at 147°. The mixed melting point of this material and that obtained by the action of bromine on the *syn* acetate (V) showed no depression.

Derivatives of the Anti Series

The acetate of the anti oxime benzal-*p*-bromoacetophenone (VI) obtained in an impure state by the fractionation of the mixed acetates (p. 4142) is contaminated with small amounts of the slightly soluble *syn* acetate and of the unsaturated ketone, benzal-*p*-bromoacetophenone, which has persisted through the oxime formation and acetylation. The removal of these impurities is a difficult process and is, because of the extreme solubility of the *anti* acetate in the few effective solvents, accompanied by large losses of material. Purification can be accomplished by persistent fractionation from ethyl acetate and petroleum ether but this method is less satisfactory than a very slow crystallization from the same solvents. If the slow crystallization is properly done the resulting crystals are large enough to permit a separation by hand. The crystals of the *anti* acetate, which are triclinic, present themselves as stout prisms often as large as 4 mm. on a side. They are easily distinguished from the opaque rods of the *syn* acetate both by their appearance and by their transparency. The transparent plates of the unsaturated ketone are easily identified by their yellow color. The final purification of the *anti* acetate is effected by crystallization from ethyl acetate and petroleum ether and the pure product melts at 105–106°. A mixture of the *syn* and *anti* acetates melts at 90–100°. The *anti* acetate is quite soluble in the common organic solvents save ethyl alcohol and petroleum ether. Unfortunately the impurities which accompany the *anti* acetate are also only slightly soluble in alcohol and we were unable to effect any purification using that solvent.

Anal. Calcd. for $C_{17}H_{14}O_2NBr$: C, 59.3; H, 4.1. Found: C, 59.2; H, 4.4.

Hydrolysis of the Anti Acetate (VI).—We suspended 1.7 g. of the acetate in 25 cc. of alcohol, added a solution of 0.5 g. of sodium hydroxide in 3 cc. of water and stirred for forty-five minutes at room temperature. During this time a yellow color developed in the solution, all of the acetate dissolved and a precipitate of extremely fine silky needles appeared. The solution was diluted with 125 cc. of cold water, which destroyed the yellow color and precipitated the *anti* oxime quantitatively. An alternate procedure consists in adding ether and water to the alcoholic reaction mixture, washing the ether extract with water, calcium chloride and water. On evaporation of the ether the *anti* oxime is obtained.

Anal. Calcd. for $C_{15}H_{12}ONBr$: C, 59.6; H, 4.0. Found: C, 59.7; H, 4.3.

The anti oxime of benzal-*p*-bromoacetophenone (IV) is very soluble in ether, acetone and ethyl acetate, moderately soluble in benzene and alcohol. It crystallizes in very fine silky needles when its solutions in cold acetone are diluted with petroleum ether. These needles are so small, averaging 0.05 mm. in length and 0.008 in width, that it was not possible to determine their crystal system. The melting point of the

anti oxime is not sharp and is always accompanied by the appearance of a yellow color in the melt. We prefer the value 150–163°. Mixed with the pure *syn* oxime (145–158°), the melting point is 135–150°. We hesitate to state that the *anti* oxime is completely free from all traces of the *syn* isomer for there is in the case of the *syn* isomer no such sensitive test for small amounts as is furnished by the evolution of ammonia on hydrolysis of the rearrangement product of the *anti* oxime. That our *anti* oxime certainly contains only minimal amounts of the *syn* oxime is shown by its behavior on acetylation, which yields the *anti* acetate accompanied occasionally with traces of higher melting material, and on rearrangement which is described in detail subsequently. With sulfuric acid the *anti* oxime furnishes an orange solution—in contrast to the clear yellow solution obtained from the *syn* oxime. This orange solution when poured on ice after four hours of standing yields, like the solution of the *syn* oxime, 3-*p*-bromophenyl-5-phenyl isoxazoline.

Beckmann Rearrangement of the Anti Oxime (IV).—When 1.5 g. of the oxime was rearranged, a yellow precipitate formed which did not dissolve after four hours' standing. Consequently the reaction mixture was decomposed with ice and it furnished, on evaporation of the ether, 1.5 g. of a dirty yellow solid. This product was difficult to handle and on crystallization yielded only 0.25 g. of solid material melting at 204°—presumably the styryl amide of *p*-bromobenzoic acid (see below). The alcohol filtrate from this crystallization was boiled for seven hours after the addition of 3.0 g. of sodium hydroxide in 10 cc. of water. There was an immediate and steady stream of ammonia evolved. Finally ether and water were added to the dark red solution and the aqueous layer, after filtration to remove some tarry material, yielded on acidification 0.75 g. of *p*-bromobenzoic acid. The acid melted at 205–220°; mixed with a pure specimen (m. p. 246°) the melting point was 225–235°. The *p*-bromobenzoic acid was dissolved in carbonate solution and treated with permanganate. Only a trace of permanganate was reduced and there was no odor of benzaldehyde—indicating the absence of cinnamic acid. It is our opinion that the third hydrolysis product, phenylacetaldehyde, polymerizes and furnishes the tarry material which is responsible for the low melting point of the *p*-bromobenzoic acid.

Since the primary rearrangement product was so intractable, we did not attempt to purify it but contented ourselves with the hydrolysis of the 0.25 g. of once recrystallized material obtained from the reaction.[16] The material behaved in exactly the same fashion as did the alcoholic mother liquors from which it was obtained. Ammonia was evolved and, after the usual treatment, 0.15 g. of *p*-bromobenzoic acid was isolated. The acid melted at 215–238°, and when mixed with pure *p*-bromobenzoic acid at 225–240°.

Bromination of the Anti Oxime (IV).—When 3.0 g. of the *anti* oxime was suspended in 40 cc. of chloroform and treated with 1.6 g. of bromine in the same solvent, a clear solution containing a slight excess of bromine resulted. The solvent and excess bromine were evaporated in a current of dry air and the yellow solid which remained was crystallized from benzene and petroleum ether. It then melted at about 165° with decomposition (yielding 3-*p*-bromophenyl-5-phenyl isoxazole) and its melting point on admixture with a sample of the purest *syn* dibromo oxime (173°) was raised to 169°. To complete the identification of the bromination product of the *anti* oxime as the *syn* dibromide, the material was heated with acetic anhydride in the usual fashion and furnished the *syn* dibromoacetate (VII). A mixed melting point of this material and that obtained by the bromination of the *syn* acetate exhibited no depression.

[16] In connection with some other work we have obtained an easily handled substance of the same type as this product—that is, an acyl derivative of an unsaturated aliphatic amine. We hope to describe this interesting type of substance in more detail later.

Preparation of the α-Bromo Oxime (X).—In our first preparation we followed the procedure of Auwers[17] for the oxime of α-bromobenzalacetophenone which involves the isolation and purification of the α-bromo ketone. From 6.2 g. of α-bromobenzal-*p*-bromoacetophenone[18] and 2.8 g. of hydroxylamine hydrochloride dissolved in 50 cc. of alcohol and 15 cc. of water we obtained 5.0 g. of oxime, a yield of 75%. The reaction is quite slow and to obtain this yield it was necessary to boil the solution for four days, a fresh crop of oxime being obtained each day.

We found later that the preparation of this oxime and the corresponding oxime from α-bromobenzalacetophenone could be simplified as follows. The dibromo ketone is boiled with alcoholic potassium acetate but the α-bromo ketone need not be isolated. Instead, ether is added to the reaction mixture and the inorganic salts and acetic acid are thoroughly washed out with water. After drying, the ether is replaced with alcohol, hydroxylamine hydrochloride is added and on boiling the solution the α-bromo oxime is formed. The reaction cannot, however, be carried out in one step by treating the dibromo ketone with hydroxylamine hydrochloride and potassium acetate together as the resulting solution is so acidic that no α-bromo ketone is formed.

The α-bromo oxime, obtained by either method, is moderately soluble in ether and acetone, slightly soluble cold in benzene, chloroform and alcohol. For analysis it was crystallized from alcohol, from which it separates in fine, white needles melting at 163–164°.

Anal. Calcd. for $C_{15}H_{11}ONBr_2$: C, 47.3; H, 2.9; Br (aliphatic), 21.0. Found: C, 47.5; H, 3.2; Br (Volhard), 20.65.

Beckmann Rearrangement of the α-Bromo Oxime (X).—When 2.0 g. of the oxime was rearranged the product was a yellow oil which could not be made to crystallize. Consequently it was dissolved in 30 cc. of alcohol and a solution of 5.0 g. of potassium hydroxide in 10 cc. of water added. Immediately the solution turned dark and, on heating, ammonia was evolved. After ten hours' boiling, when no more ammonia was given off, ether and water were added and the two layers separated. The ether layer was extracted with dilute acid and this acid extract gave no precipitate with bromine; hence, there was no *p*-bromoaniline present. The alkaline extract after the usual treatment furnished an acid which was shown to be *p*-bromobenzoic acid by comparison with an authentic specimen.

Action of Heat on the α-Bromo Oxime (X).—When 0.75 g. of the oxime was heated a few degrees above its melting point, it turned brown, then suddenly decomposed with a single vigorous puff. The gaseous decomposition product was hydrogen bromide (litmus, silver nitrate). The residue, which had the characteristic odor of an aromatic nitrile, dissolved in alcohol and ether, leaving a small tarry residue. From the alcohol–ether solution sodium carbonate extracted *p*-bromobenzoic acid. The alcohol–ether solution after this extraction was boiled with potassium hydroxide. Ammonia was evolved and, after the usual treatment, *p*-bromobenzoic acid was obtained. No isoxazole could be detected.

The oxime of α-bromobenzalacetophenone behaves similarly when heated. The products isolated from the thermal decomposition of this oxime were hydrogen bromide, ammonia and benzoic acid. No isoxazole could be found.

Action of Sulfuric Acid on the Oxime (X).—When 10 cc. of sulfuric acid was added to 1.0 g. of the oxime, an orange-yellow solution resulted. After half an hour this solution was poured on ice and the resulting precipitate filtered as soon as it had coagulated. It melted, after drying, at 162–163° and a mixture with the original oxime (163–164°)

[17] Auwers, *Ber.*, **62**, 1322 (1929).

[18] Kohler and Addinall, THIS JOURNAL, **52**, 3732 (1930).

melted at the same place. The recovery was quantitative. In a check experiment similar results were obtained after the oxime had been left for twenty-six hours in the acid solution.

In another experiment we dissolved 0.5 g. of the oxime of α-bromobenzalacetophenone in sulfuric acid. After standing for four hours the solution was worked up and the oxime was recovered unchanged.

$$C_6H_5CH{=}C(C_6H_5)COC_6H_5$$

Benzaldesoxybenzoin Oxime.—Knoevenagel and Weissgerber[19] heated benzaldesoxybenzoin, hydroxylamine hydrochloride and alcohol in sealed tubes at 180° for five hours and obtained a product melting at 208° which they considered to be either the oxime or the isomeric 3,4,5-triphenyl isoxazoline. Later, Kohler and Barrett[20] reported that the product obtained in this way is in reality triphenyl isoxazole. We used a procedure less drastic than that of Knoevenagel and obtained the desired oxime—after a certain amount of confusion occasioned by the fact that this oxime also melts at 208°. A solution of 2.1 g. of hydroxylamine hydrochloride in the minimum amount of water was added to 4.26 g. of benzaldesoxybenzoin dissolved in 45 cc. of alcohol. After two and a half hours' boiling, glistening plates began to separate from the solution. After six hours the hot solution was filtered and 0.9 g. of oxime was obtained. The filtrate on cooling deposited more crystals which were chiefly unsaturated ketone (needles) mixed with a small amount of oxime (plates). This precipitate with the filtrate was boiled for five hours and left over the week-end. The solid then obtained was again a mixture of oxime and ketone. By taking advantage of the very slight solubility of the oxime in alcohol, it was possible to separate the oxime by a single crystallization from that solvent. The filtrate from the crystallization was added to the original solution and boiled for an additional eight hours. By continued repetition of this process it is possible to secure an excellent yield of the oxime.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 83.9; H, 5.8.

Benzaldesoxybenzoin oxime melts at 208°. It is only slightly soluble in the ordinary solvents. A Zerewitinoff determination showed the presence of an active hydrogen atom and a Beckmann rearrangement completed the proof that the material was the desired oxime. When 1.0 g. of the oxime was rearranged, the product was a yellow oil. This oil was dissolved in alcohol, 10 cc. of 30% potassium hydroxide solution was added and the reaction mixture boiled for seven hours until no more ammonia was evolved. Ether and water were added and from the aqueous and ethereal layers there were obtained benzoic acid and desoxybenzoin. The products were identified by mixed melting points.

Action of Sulfuric Acid on Benzaldesoxybenzoin Oxime.—The oxime dissolves in sulfuric acid to furnish a clear yellow solution. If this solution is poured on ice at once the oxime is recovered. However, on standing the solution turns cherry-red and if this red solution is poured on ice only a red oil is obtained. From this oil we could not isolate either of the two known 3,4,5-triphenyl isoxazolines.[21]

$$(C_6H_5)_2C{=}CHCOC_6H_5$$

Preparation of β-Phenyl Benzalacetophenone Oxime.—This oxime, which has already been described,[22] can be obtained from the ketone using either hydroxylamine

[19] Knoevenagel and Weissgerber, *Ber.*, **26**, 443 (1893).

[20] Kohler and Barrett, THIS JOURNAL, **46**, 2110 Reference (1924).

[21] Ref. 20, pp. 2111–2112.

[22] Dilthey and Last, *J. prakt. chem.*, [2] **94**, 51 (1916); Vorländer, Osterburg and Meye, *Ber.*, **56**, 1136 (1923).

hydrochloride or the hydrochloride and excess alkali. When the ketone (0.02 mole in 50 cc. of alcohol) is boiled for seven hours with two equivalents of hydroxylamine hydrochloride and the hot solution diluted with water, an 85% yield of the oxime is obtained. The preparation in alkaline solution was followed more closely. A solution of 2.1 g. of hydroxylamine hydrochloride and 3.0 g. of potassium hydroxide in the minimum amount of water was added to 4.26 g. of ketone dissolved in 35 cc. of alcohol. After the reaction mixture had been boiled for six hours it was diluted with water. On standing overnight 3.4 g. of oxime was obtained. The filtrate poured into water furnished an additional 0.85 g. The yield of crude oxime was 94%. The filtrate from the second crop of oxime was acidified with hydrochloric acid but the resulting precipitate was insignificant in amount, showing that the complex products generally obtained from unsaturated ketones and hydroxylamine were not formed in this case. The oxime can be crystallized from alcohol or, better, from benzene plus two volumes of petroleum ether. It melts from 149–153°.

Action of Sulfuric Acid on β-Phenyl Benzalacetophenone Oxime.—When 1.5 g. of the oxime was shaken with 15 cc. of sulfuric acid, a clear yellow solution resulted. This was poured on ice and the white precipitate filtered, dried and crystallized from alcohol. It melted at 139°; yield, 1.2 g. For analysis the material was crystallized a second time from alcohol.

Anal. Calcd. for $C_{21}H_{17}ON$: C, 84.3; H, 5.7. Found: C, 84.0; H, 5.9.

3,5,5-Triphenyl isoxazoline crystallizes in fine white needles melting at 140–141°. It is quite soluble in the common organic solvents save alcohol and petroleum ether.

Beckmann Rearrangement of the Oxime.—When 3.0 g. of the oxime was rearranged, the yield of crude anilide was quantitative. For analysis the material was crystallized from ethyl acetate and petroleum ether and from alcohol and water.

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

β-Phenyl cinnamanilide is quite soluble in the common solvents with the exception of petroleum ether. It crystallizes in splendid fan-shaped clusters of fine white needles melting at 130–131°. The structure of the anilide was established by its hydrolysis, which is extremely slow, to yield aniline. The aniline was identified as tribromoaniline.

Summary

As a result of a continued study of the reaction of hydroxylamine hydrochloride and benzal-*p*-bromoacetophenone, it has been possible to isolate both the *syn* and the *anti* oximes of that ketone. The configuration of the predominant oxime, which corresponds to the only oxime so far isolated from other α,β-unsaturated ketones of this type, has been established as *syn* to the double bond. The isomeric oxime is *anti* to the double bond. Knowing the configuration of the oximes and the products which they furnish in the Beckmann rearrangement, it follows that these oximes undergo a *trans* shift on rearranging.

Certain α-substituted unsaturated oximes were studied and the *anti* configuration suggested but not established for them.

The study of the sulfuric acid cyclicization of α,β-unsaturated oximes has been extended to include some *anti* oximes and it is shown that this cyclicization is conditioned by the substituents in the oxime molecule rather than by the configuration of the oximes.

The formation of isoxazolines from α,β-unsaturated ketones has been shown not to proceed through an oxime as an intermediary and has been shown inferentially to proceed through a complex dimolecular 1,4-addition process.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME, INC.]

AMINO ALCOHOLS. VII. PHENOLIC ARYLPROPANOLAMINES

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Studies on compounds that produce a rise in blood pressure, *i. e.*, with ephedrine, epinephrine, tyramine and related substances, indicate that certain pharmacological effects are unquestionably associated with definite elemental groups in the structure of the active molecule. For example, it has been established that: (1) the optimum skeleton for pressor activity is found in compounds having a phenyl and an amino group (or a substituted amino group) attached to adjacent carbons of an aliphatic chain.[1] (2) Compounds containing two or three carbons in the aliphatic chain possess maximum pressor activity.[2] (3) Compounds with the three-carbon side chain are active on the blood pressure after oral administration.[2b,1c,3] (4) A secondary alcoholic hydroxyl attached to the carbon bearing the phenyl serves to detoxicate very markedly and perhaps to increase the activity of the molecule.[2a,1c,1a,4] (5) Primary amines tend to be more active and less toxic than the corresponding methylated secondary amines, and if the amino group is further methylated or if the size of the alkyl is increased, there is a corresponding decrease in activity and increase in toxicity.[2a,5]

These conclusions are based chiefly on results obtained from compounds in which the aromatic nucleus of the molecule is a phenyl group. A most significant difference, however, between the structure of epinephrine (I) and ephedrine (II) is that the former has two hydroxyls substituted in the phenyl portion, and these contribute very substantially toward its characteristic action. It was in order to determine more specifically the effect of phenolic groups in molecules of this type that the synthesis of a series of hydroxyaryl derivatives and their pharmacological study was undertaken, and to confine as nearly as possible any change in activity solely to phenolic

[1] (a) Barger and Dale, *J. Physiol.*, **41**, 19 (1910); (b) Hasama, *Arch. exptl. Path. Pharmakol.*, **153**, 165 (1930); (c) Hartung and Munch, THIS JOURNAL, **53**, 1875 (1931).

[2] (a) Chen, Wu and Henriksen, *J. Pharmacol.*, **36**, 363 (1929); (b) Hartung, Munch Deckert and Crossley, THIS JOURNAL, **52**, 3317 (1930).

[3] Piness, Miller and Alles, *J. Am. Med. Assn.*, **94**, 790 (1930).

[4] Tainter, *Quart. J. Pharm. Pharmacol.*, **3**, 584 (1930).

[5] Curtis, *J. Pharmacol.*, **35**, 321 (1929).