[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

THE AMIDES OF THE 3-(*p*-BROMOBENZOYL)-3-METHYL-ACRYLIC ACIDS

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I. THE COMPOUNDS DERIVED FROM AMMONIA

The object of this investigation was the preparation of a series of amides of a typical α,β-unsaturated γ-ketonic acid. Interest centers in the study of the ring-chain tautomerism and the possibility of isomerism in the *cis* compounds where the spatial juxtaposition of the two functional groups permits and facilitates the formation of cyclic structures. While a limited amount of pertinent work has been done on nitrogen derivatives of certain of the ortho aldo and keto benzoic acids, very little has yet been reported in connection with the closely analogous *cis*-β-acyl and β-aroylacrylic acids and their derivatives.

The 3-bromobenzoyl-3-methylacrylic series was selected for the initial investigation in this field for the following reasons: The open-chain and cyclic esters and the acid chloride of the *cis* acid have already been made and studied, as well as the *trans* compounds, which are necessarily open-chain and which are desirable for purposes of reference (1). The 3-methyl group has a definite stabilizing influence on the configurations and permits the existence of both *cis* and *trans* forms, but nevertheless allows interconversions between the two types to take place under suitable conditions. The tendency to form cyclic derivatives in this series is marked but not as strong as in the 2,3-dimethyl series (2). The 3-methyl group has a noticeable damping effect on the reactivity of the α,β-unsaturated ketone system and to some extent hinders addition reactions. The para bromine atom favors the formation of crystalline derivatives, thus facilitating manipulations.

The action of aqueous ammonium hydroxide on the open-chain and pseudo methyl esters (I and II) and on the acid chloride (III) of 3-bromobenzoyl-3-methylacrylic acid gave in each case the same product, which has been formulated as the lactamol[2] (cyclic amide) or 5-hydroxypyr-

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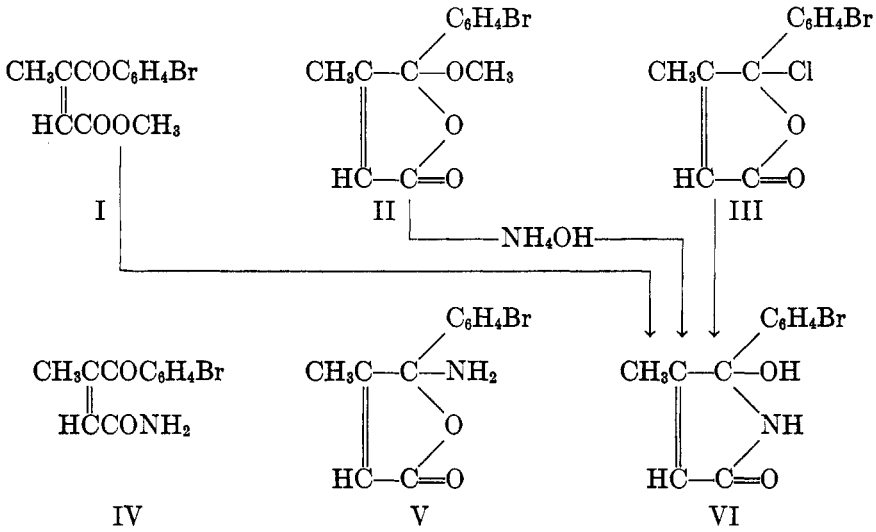
[2] The meaning of the term lactamol is self evident (*cf.* the term lactonol, Ref. 2b, footnote 3).

rolinone (VI). The alternative structural possibilities which must be considered are the open-chain true amide form (IV) and the cyclic pseudo amide or lactonamine (V) (better expressed perhaps as a 5-amino-2-furanone[3]). All of these three types of formulation (IV—VI) have been suggested for various compounds reported in the literature (*cf.* 3) but in few cases has there been given real proof of structure and in several cases it seems probable that the formulations assumed are erroneous (some of these are being reinvestigated in this laboratory). The structure we have assigned to this amide (VI) is based on the following considerations, some of which alone do not constitute good evidence but nevertheless add to the total and are consistent with the picture suggested.

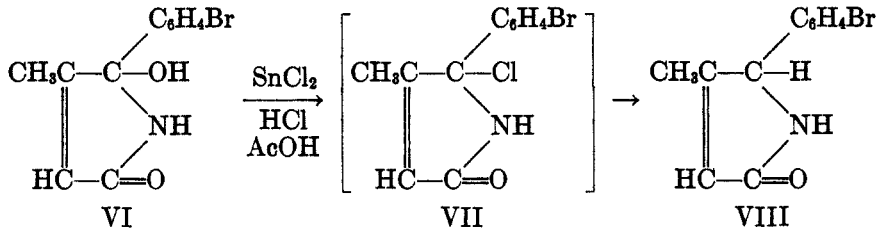


The amide is readily soluble in sodium hydroxide, in contrast with the *trans* amide (XI), which is not, and it is precipitated unchanged by acid. This property is consistent with formula VI. The weak acidity of the hydroxyl is comparable with that in the 2-hydroxy-3-furanones[3] (4) and is characteristic of the anilides in the *o*-benzoylbenzoic acid series (3h) which are supposed to be of the same cyclic type. Also, it is characteristic of a series of hydroxypyrrolidones which have recently been prepared from the enol lactone of β-benzoylpropionic acid (3k).

The resistance of the amide towards reduction with zinc and acetic acid or sodium hydrosulfite is an argument against the open-chain formula (IV) with its reactive conjugated 1,4-dicarbonyl system. Stannous

[3] The term furanone is obviously a misnomer. More properly it should be dihydrofuranone and numbered to indicate the positions involved. However, since a true furanone is impossible and since the abbreviated term has been extensively used (4), it will be retained here, but the expanded and proper term dihydrofuranone will be used whenever it is necessary to indicate the carbons involved.

chloride in hydrochloric and acetic acids, however, reduces the amide easily, eliminating an oxygen atom and giving a compound which is evidently the unsaturated lactam or α-pyrrolinone (VIII). This product gives a rapid reaction with Tollens' reagent as do the oxygen analogs, for example, 3,4-dimethyl-5-xenylfuranone-2 (2). Evidently the reduction has proceeded through the chloride (VII) and follows a course parallel with the reduction under similar conditions of oxygen analogs such as 2,3-dimethyl-3-xenoylacrylic acid which is believed to function in the cyclic form (2). The alternative cyclic formulation for the amide, as the 5-aminofuranone (V), would not be consistent with these facts because in that case reductive elimination of the nitrogen rather than the oxygen would be expected.

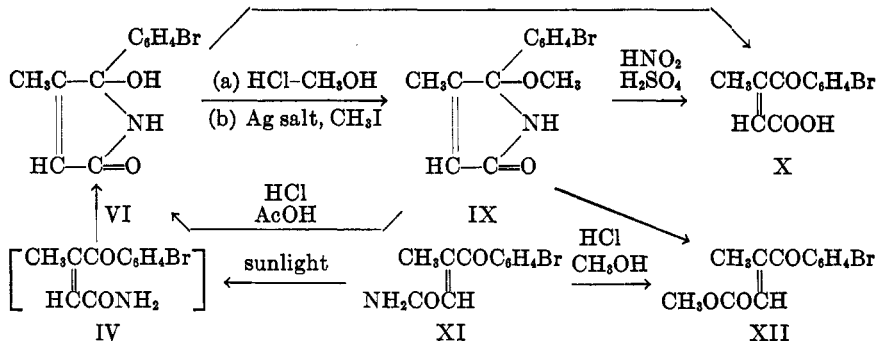


VI VII VIII

Methylation with methanolic hydrogen chloride readily converted the amide into a methyl ether (IX) which was easily hydrolyzed by conc'd hydrochloric and acetic acids. This methylation was not brought about by the action of dimethyl sulfate on the sodium salt, but it was effected in very small yield by the action of methyl iodide on the silver salt. Diazomethane, on the other hand, was without any action on the compound. These results cannot be explained on the basis of the 5-aminofuranone formula (V), are consistent with the properties which would be expected of a 5-hydroxypyrrolinone such as VI, but, of course, do not in themselves preclude the open-chain structure (IV). Analogous results are obtained with some of the 2-hydroxy-3-furanones (4) and are partly duplicated in the case of some of the *cis* aroylacrylic acids which function as 5-hydroxy-2-furanones (2). The failure to react with diazomethane clearly indicates a weakly acidic or hindered hydroxyl analogous to the hydroxyl in the 2-hydroxy-3-furanones (4). The methylation of the silver salt may (and probably does) involve the cyclic structure just as appears to happen in the methylation of the silver salts of certain of the 2-hydroxy-3-furanones (4).

The stability of the amide VI under hydrolytic conditions supports the hydroxypyrrolinone formulation (the open-chain amide IV should be easily hydrolyzable, as also should the aminofuranone form V). Unfortunately, the amide is sensitive, and is converted under many of the acid hydrolytic conditions into a complex high-melting nitrogen-containing

substance which is non-crystalline. Hydrolysis was finally effected by nitrous acid in conc'd sulfuric acid, and gave the *cis* acid (X).



Under extended treatment of the amide or its methyl ether with methanolic hydrogen chloride, inversion as well as methanolysis occurred, giving the *trans* ester (XII), which was obtained also directly from the *trans* amide (XI) by methanolysis under similar conditions. In this reaction inversion must precede methanolysis, since it is known that the *cis* acid and the *cis* (open-chain) ester are both converted into the cyclic (or pseudo) *cis* methyl ester under these conditions and, therefore, could not have been involved in intermediate steps. We are studying this reaction further in the hope of finding out something more about the mechanism of the changes.

Attempts to acylate or benzoylate were unsuccessful, as also were attempts to make the chloride (VII) with phosphorus pentachloride. Thionyl chloride reacted but caused chlorination of the methyl group, as will be described below.

Attempts to invert the *cis* amide to the *trans* isomer through the action of sunlight on a chloroform solution containing iodine as a catalyst were without avail, blocked perhaps by the stabilizing influence of the cyclic structure. This result calls to mind the inversion of the open-chain *cis*-3-bromobenzoyl-2- and -3-methylacrylic esters and the 2- (but not the 3-) methyl acid (1) to the *trans* isomers under these conditions. The failure of the 3-methyl acid to undergo inversion perhaps is due, as suggested, to the dominance of the cyclic structure in solution (1d).

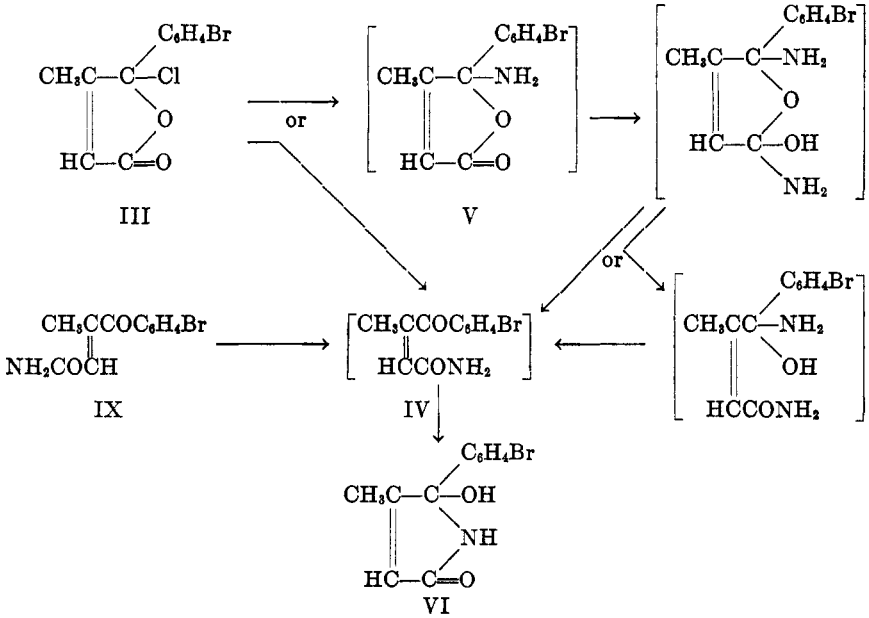
Ozonization of the methyl ether (IX) was carried out in the hope of isolating a nitrogen-containing fragment. Actually, such a compound was obtained, but in insufficient quantity for study. The chief products were *p*-bromobenzoic acid and *p*-bromophenyl methyl diketone, $BrC_6H_4COCOCH_3$.

In connection with these experiments the *trans* amide (XI) was made by the action of ammonium hydroxide on the *trans* acid chloride. It is insoluble in sodium hydroxide, in contrast with the *cis* isomer (VI). It

undergoes methanolysis to give the *trans* ester (XII), but acetic and hydrochloric acids convert it into an amorphous nitrogen-containing product similar to that obtained from the *cis* compound. Sunlight converts it into the *cis* amide (VI), which has been shown to be cyclic. Evidently the hypothetical open-chain isomer (IV) which must first be formed in the reaction undergoes spontaneous cyclization to the hydroxypyrrolinone form (VI).

Assuming the correctness of the formulation VI for the *cis* amide, it follows from the above described facts that the hypothetical open-chain form (IV) is inherently unstable and has a stronger tendency to cyclize than does the *cis* acid itself.

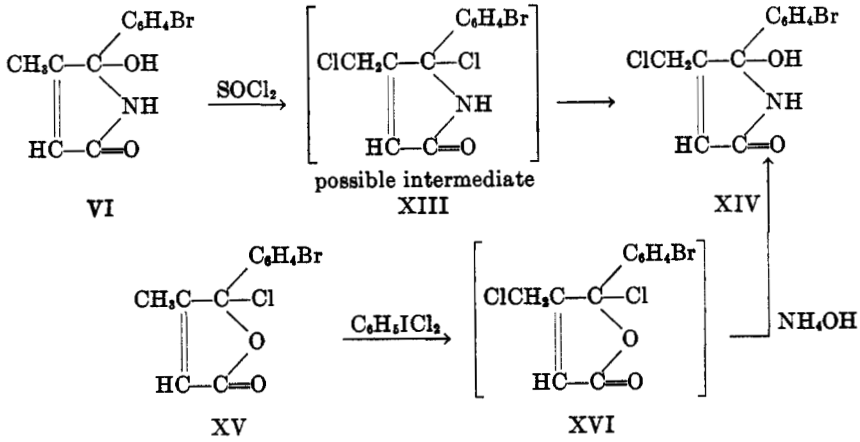
The reaction between ammonia and the pseudo acid chloride[4] (III) may proceed either by a 1,2-mechanism to give the aminofuran (V) as the primary product, or, as seems less likely, 1,4 to give first the open-chain amide (IV). Rearrangement or cyclization, respectively, must then follow. The transformation of the aminofuranone (V) into the hydroxypyrrolinone (VI) might involve first addition and elimination of ammonia to give the open-chain form (IV) as intermediate. The open-chain form (IV), produced either in this way or directly by a 1,4-reaction, would certainly cyclize to the hydroxypyrrolinone (VI), as must happen in the transformation of the *trans* isomer into VI by the action of sunlight alone. The following diagram outlines these possibilities, which are typical.



[4] Of course, the reaction might be expressed more simply in terms of a mobile tautomerism between the open-chain and cyclic forms of the chloride as in the case of succinoyl chloride, but it seems probable that here the cyclic structure (III) is fixed (*cf.* 1a).

Incidentally, it should be noted that actual migration or 1,3-shift of an amino group might occur in reaction, for example, from the 5 to the 2 positions of the cyclic form (V) to give momentarily the open-chain form (IV). However, there is little reason to suppose this, particularly since the anilino and the N-methylanilino groups do not migrate, as will be shown later (4c).

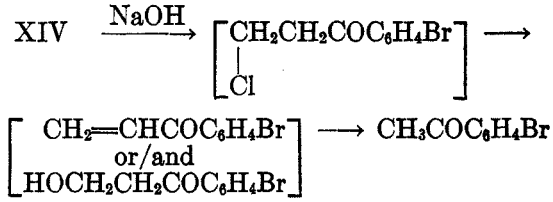
In attempting to make the 5-chloro-2-pyrrolinone by treating the cyclic *cis* amide (VI) with thionyl chloride, substitution of chlorine for hydrogen took place instead of replacement of the hydroxyl, and a crystalline monochloro derivative (XIV) was obtained. There is ample analogy for this type of reaction where thionyl chloride acts as a chlorinating agent, for example, the chlorination of hydroxycodeinone by this reagent (5). Presumably, in the reaction under discussion, the replacement of the hydroxyl was also involved to give XIII but attempts to isolate the dichloro compound failed. The reaction is formulated as follows:



The chloro amide (XIV) was prepared in a second way by the action of phenyl iododichloride on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (XV), followed by treatment with ammonium hydroxide.

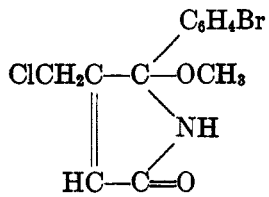
The proof of the position of the chlorine in the final product (XIV) was demonstrated as follows. Oxidation with potassium permanganate gave *p*-bromobenzoic acid, excluding the possibility that the chlorine was in the aryl group. Reduction with stannous chloride eliminated the chlorine and one oxygen and gave the unsaturated lactone or α-pyrrolinone (VIII) which had already been obtained from the parent amide (VI), thus showing the chlorine to be in an aliphatic combination. Alkaline hydrolysis gave *p*-bromoacetophenone, which was isolated and identified; this reaction evidently involved hydrolytic cleavage at the double bond (a reversal of

aldol condensation) followed by hydrolysis or elimination of hydrogen chloride, and a second hydrolytic cleavage to give *p*-bromoacetophenone, as follows:



If the chlorine had been on the ethylene linkage, hydrolytic cleavage could not have produced *p*-bromoacetophenone but might have given *p*-bromopropiophenone [which actually has been obtained in a similar hydrolysis of *cis*-3-bromobenzoyl-3-methylacrylic acid itself (1a)].

The chloro amide XIV shows reactions which are parallel with those of the parent amide VI, and which support the cyclic formulation. The compound is soluble in dilute sodium hydroxide and may be recovered unchanged on acidification. It is converted into the easily hydrolyzable methyl ether (XVII), and as mentioned above, is easily reduced by stannous chloride to the α-pyrrolinone, VIII.



XVII

The above mentioned chlorinations at the methyl group are of interest as demonstrating an activity at this point which is due presumably to conjugation through the intervening ethylene linkage with the carbonyl group.

EXPERIMENTAL[5]

5-(p-Bromophenyl)-5-hydroxy-4-methylpyrrolinone-2 (VI). A solution 70 g. of freshly prepared acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (III) in 250 cc. of dry dioxane was mechanically stirred and treated with 225 cc. of 16 *N* ammonium hydroxide, added gradually. The mixture was stirred for 3.5 hours at room temperature followed by refluxing for 1.5 hours. The solution was then cooled and evaporated in an air stream to remove the bulk of the dioxane. When the precipitation appeared to be complete, the product was filtered, washed with

[5] All melting points reported in this paper are "corrected". We are indebted to Mrs. James A. L. Mathers for many of the microanalyses.

water, and dried in a vacuum desiccator; yield 67 g. (96%). It was purified by repeated crystallization from 60% ethanol, from benzene, and from water, and melted at 174.5° (decomp.).

Anal. Calc'd for $C_{11}H_{10}BrNO_2$: C, 49.3; H, 3.8; N, 5.2.
Found: C, 49.2; H, 4.0; N, 5.1, 5.3.

Poorer yields were obtained when the *cis* acid chloride (III) was allowed to stand in saturated alcoholic ammonia for 48 hours.

The open-chain methyl ester (I) suspended in 16 *N* ammonium hydroxide reacted completely in 48 hours (and partially in 36 hours) to give the amide (VI). The pseudo ester (II) required longer standing, 70 hours, to complete the reaction (some unchanged material could be recovered after standing for only 48 hours).

Hydrolysis. A mixture of conc'd acetic acid to which a small amount of conc'd hydrochloric acid had been added, had no action on the amide (VI) at room temperature, but at refluxing temperature under the same conditions or with conc'd acetic acid continually saturated with hydrogen chloride, a high-melting amorphous solid which contained nitrogen was produced. Alkaline hydrolysis (refluxing 10% sodium hydroxide) gave non-crystalline products. The amide was dissolved in cold conc'd sulfuric acid and treated with sodium nitrite [the method of Bouveault (6)], the mixture then being warmed until evolution of gas ceased, and finally diluted with water; the *cis* acid (X) was produced in 50% yield.

Methanolysis of 10 g. of the amide (VI) by refluxing with 250 cc. of methanol and 30 cc. of conc'd hydrochloric acid for 3.5 hours, followed by evaporating in an air stream and cooling, gave as the first crop 2.2 g. of material which was identified as the *trans* ester (XII); yield 22%. Further evaporation gave 5.5 g. of crude solid which was filtered and washed with 10% sodium hydroxide; it was purified and identified as the methyl ether (IX); yield 25%. From the alkaline filtrate upon acidification 3 g. (30%) of unreacted amide was recovered. Wide variation in conditions, concentrations, and period of refluxing failed to improve the yield of the *trans* ester.

Reduction of the amide (VI) with zinc and conc'd acetic acid at 70° for a few minutes was without action but refluxing produced a high-melting amorphous material. Sodium hydrosulfite in 80% ethanol (refluxing for 1 hour) was without effect.

Chlorination with phosphorus pentachloride under various conditions gave only resinous products.

Diazomethane was without action, as also was dimethyl sulfate acting on a 10% sodium hydroxide solution.

Acylation with acetic anhydride or acetyl chloride at room temperature gave largely unchanged material, but under more drastic conditions (refluxing) or using pyridine, only a high-melting amorphous product was obtained.

Benzoylation. A mixture of 0.4 g. of the amide (VI) in 3 cc. of pyridine and 3 cc. of benzoyl chloride was allowed to stand at 0° for 20 hours. Hydrolysis gave 0.26 g. of product, which was washed with sodium carbonate and crystallized from methanol. It melted at 205–206°. (*Anal.* Calc'd for $C_{26}H_{20}BrNO_5$: C, 61.6; H, 3.95; N, 2.8. Found: C, 61.5, 61.3; H, 3.9, 3.9; N, 2.75). Treatment of this product with 10% sodium hydroxide (1 hour at 70–80°) was without action. This compound has not yet been identified.

5-(p-Bromophenyl)-5-methoxy-4-methylpyrrolinone (IX). This ether was prepared best by controlling the conditions of methanolysis of the amide (VI) as follows. The ratio of reactants was 4 g. of the amide, 60 cc. of methanol, and 1 cc. of conc'd hydrochloric acid. The mixture was refluxed 1 to 2 hours and allowed to stand for 3–12 hours. Water was then added up to the point of precipitation, and the solution was evaporated in an air stream until precipitation appeared to be complete. The

product was filtered and washed with 10% sodium hydroxide and water, small amounts of unchanged amide being removed (on the order of 1%). The yields varied from 95–99%. The compound crystallized from 60% ethanol and melted at 118–119°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3; N, 5.0; Br, 28.4; OCH_3, 11.0.
Found: C, 51.3; H, 4.1; N, 5.2, 5.0; Br, 28.2; OCH_3, 11.2.

The ether was also prepared as follows: A solution of the amide in sodium hydroxide was neutralized to the point of precipitation with dilute nitric acid, and silver nitrate was added, causing precipitation of the silver salt, which was filtered, washed with methanol, and digested (shaking) with methanol and methyl iodide for 2 hours. Largely unchanged material was recovered (90–95%), and a 5–10% yield of the methyl ether was isolated by taking advantage of its insolubility in alkali.

Hydrolysis was effected by the action of a 10:1 conc'd acetic-hydrochloric acid mixture upon standing for 24 hours at room temperature. The amide VI was obtained in quantitative yield. Using the sulfuric-nitrous acid method (6) as described above under the free amide (VI), the *cis* acid (X) was obtained in 60% yield.

Methanolysis of 0.4 g. with methanol and conc'd hydrochloric acid (refluxing for 3.5 hours) gave 0.1 g. (25%) of *trans*-3-bromobenzoyl-3-methylacrylic ester (XII).

Reaction with thionyl chloride. No reaction occurred on standing at room temperature but refluxing for 1 hour caused demethylation and also chlorination at the 4-methyl group to give XIV (see below).

Ozonization of 2 g. in 40 cc. of dry chloroform at 0° for 5 hours was followed by evaporation of the solvent, hydrolysis with water, and extraction with sodium bicarbonate and ether. From the sodium bicarbonate layer on acidification, 0.025 g. of *p*-bromobenzoic acid precipitated and was identified. From the ether solution, 0.55 g. of yellow crystals was obtained and then distilled in the vacuum oven. This was identified as *p*-bromophenyl methyl diketone [known (7); identified by melting point and analysis: Calc'd for $C_9H_8BrO_2$: C, 47.6; H, 3.1. Found: C, 47.6, 47.8; H, 3.2, 3.3]. From the non-acidic residues of the experiment a small amount of crystalline material was obtained by evaporation in the vacuum oven at 125°. It melted at 189–190°. Analysis indicated the formula to be C_8H_8BrNO, but not enough material was obtained for study.

5-(p-Bromophenyl)-4-methyl-2,5-dihydropyrrolone-2 (VIII). A solution of 0.5 g. of the amide (VI) in 10 cc. of conc'd acetic acid was added slowly to a freshly prepared suspension of 4 g. of stannous chloride in a mixture of 20 cc. of conc'd acetic and 5 cc. of conc'd hydrochloric acids, with stirring at room temperature for 1 hour. The mixture was diluted with water and extracted with ether. Upon evaporation of the ether and extraction of the acidic residue with sodium carbonate, a white crystalline residue remained, which was washed with hot methanol; yield 35%. After vacuum evaporation onto a cold finger, followed by repeated crystallization from methanol, it melted at 184–186°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: C, 52.4; H, 4.0; N, 5.55.
Found: C, 52.3; H, 4.2; N, 5.5.

The compound gave an immediate positive test with Tollens' reagent, whereas the parent amide (VI) did not react at all under the same conditions.

5-(p-Bromophenyl)-4-chloromethyl-5-hydroxypyrrolinone-2 (XIV). Thionyl chloride was added dropwise to 1 g. of the amide (VI) until no further reaction occurred, and then 10 cc. of benzene was added, followed by ligroin (about 50 cc.) added dropwise with scratching until crystallization set in. The mixture was concentrated by an air stream to complete crystallization and the product was then filtered and washed with ligroin; yield 95%; melting point 152–154° (decomp.). Repeated crys-

tallization from benzene raised the melting point to 183–184° (decomp.), and then crystallization from 75% acetic acid raised it to 218–219° (decomp.).

Anal. Calc'd for $C_{11}H_9BrClNO_2$: C, 43.7; H, 3.0; N, 4.6.
Found: C, 43.8, 43.7; H, 3.3, 3.05; N, 4.9.

An alternative preparation was as follows: Five grams of freshly prepared acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (1a) in 10 cc. of dry chloroform was treated with 5 g. of phenyl iododichloride (8), refluxing for 3 hours. The solution was then evaporated in a current of air. The resulting oil (containing iodobenzene) was treated directly with 25 cc. of 16 *N* ammonium hydroxide and the mixture was allowed to stand for 16 hours. The pasty mass was leached with warm 10% sodium hydroxide and the alkaline layer was decanted, cooled in ice, and acidified with hydrochloric acid. After precipitation was deemed complete, the product was filtered, washed with water, and dried; yield, 4.1 g. (80%).

The same product was obtained when a sample of the methyl ether of the amide (IX) was treated with thionyl chloride (refluxing), followed by hydrolysis.

The compound dissolved in 10% sodium hydroxide and was precipitated unchanged by hydrochloric acid. Reduction by stannous chloride in acetic-hydrochloric acid solution at room temperature in the way described above produced the dihydropyrrolone (VIII). Zinc and conc'd acetic acid (stirring 1 hour at room temperature) was without action. Oxidation of 0.2 g. with 10 cc. of aqueous 10% sodium hydroxide and potassium permanganate, followed by treatment with sulfur dioxide, gave 0.05 g. of *p*-bromobenzoic acid.

Hydrolytic fission by steam distilling 0.9 g. in 50 cc. of 10% sodium hydroxide until 500 cc. of distillate collected, gave a solid volatile product (0.12 g; 20%) which melted at 49–50° and was identified as *p*-bromoacetophenone by comparison with an authentic sample.

The methyl ether (XVII) was prepared in several ways. Thionyl chloride was added dropwise to 1 g. of the amide (VI) until no further reaction occurred, the excess then being evaporated *in vacuo* at 50°. To this was added 8 cc. of 2 *N* sodium methoxide in methanol, then 5 cc. of methanol. (In another experiment, 10 cc. of 10% methanolic potassium hydroxide was used instead, and with equal success). The sodium chloride was filtered off and the filtrate was cooled and acidified with conc'd hydrochloric acid. The solution was then concentrated (air blast) and filtered when crystallization appeared to be complete; yield nearly pure, 1 g. (97%). This was purified by heating in benzene with decolorizing carbon to remove persistent color, and was crystallized by adding ligroin to the filtrate and concentrating. Repeated crystallization from 50% methanol gave a product of m.p. 159.5–161°.

Anal. Calc'd for $C_{12}H_{11}BrClNO_2$: C, 45.5; H, 3.5; OCH_3, 9.8.
Found: C, 46.0, 45.5; H, 3.4, 3.2; OCH_3, 9.6.

In another experiment the crude freshly prepared chlorination-product was treated with 20 cc. of methanol (acid conditions through generation of hydrogen chloride) with equally good results.

In another preparation, a solution of 1 g. of the chloro derivative (XIV) in 20 cc. of methanol and 0.3 cc. of conc'd hydrochloric acid was refluxed for 1.5 hours and allowed to stand for 24 hours. After cooling and concentrating in a current of air, a crystalline mass was obtained. This was crystallized by dissolving in 10 cc. of methanol and adding water dropwise with scratching and seeding; the product was washed on the filter with 10% methanol; yield, 8.7 g. (86%).

Hydrolysis of 0.3 g., upon standing for 24 hours in 10:1 conc'd acetic-hydrochloric acid, gave 0.25 g. (83%) of the chloro amide (XIV). Heating with aqueous sodium hydroxide, as with the chloro amide itself (XIV), gave *p*-bromoacetophenone.

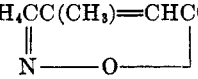
trans-*3*-(p-*Bromobenzoyl*)-*3-methylacrylic acid amide* (XI). The mixture made by treating 1 g. of the *trans* acid with 1 g. of phosphorus pentachloride and evaporating the bulk of the phosphorus oxychloride, was taken up in 3 cc. of dry dioxane (decanting from unchanged phosphorus pentachloride), and was then cooled and treated dropwise with an excess of 16 *N* ammonium hydroxide (with vigorous stirring). The mixture after standing for 16 hours was diluted with water and the resulting crystalline and nearly pure product was filtered off (0.7 g. or 70%). Repeated crystallization from benzene gave an analytical sample melting at 136.5–137.5°.

Anal. Calc'd for $C_{11}H_{10}BrNO_2$: C, 49.3; H, 3.8; N, 5.2.
Found: C, 49.1; H, 3.8; N, 5.45.

A solution of 0.1 g. of the amide (XI) in 15 cc. of methanol was exposed for 5 hours to the action of bright sunlight, and on concentration of the solution, an 85% yield of the *cis* isomer (cyclic, VI) was obtained.

The *trans* amide (XI) is insoluble in 10% sodium hydroxide. Methanolysis in a 15:1 methanol-conc'd hydrochloric acid mixture (refluxed for 10 hours) gave the *trans* methyl ester (XII). Hydrolysis of 0.2 g. in 10 cc. of conc'd acetic acid and 7 drops of conc'd hydrochloric acid (refluxed for 1 hour) gave an amorphous high-melting product.

3-(p-*Bromobenzoyl*)-*3-methylacrylic acid oxime anhydride*,



A solution of 0.7 g. of either the open-chain or pseudo *cis* ester of 3-bromobenzoyl-3-methylacrylic acid in 10 cc. of methanol was treated with 1 g. of hydroxylamine hydrochloride in 3 cc. of water, and then 10% sodium carbonate until the reaction became basic to litmus. Water and methanol alternately were added until solution of the materials involved was complete. After standing for 60 hours, crystals appeared. Using the cyclic or pseudo ester, the reaction was slower than with the open-chain isomer. After repeated crystallization from 60% ethanol, the product melted at 142–143°.

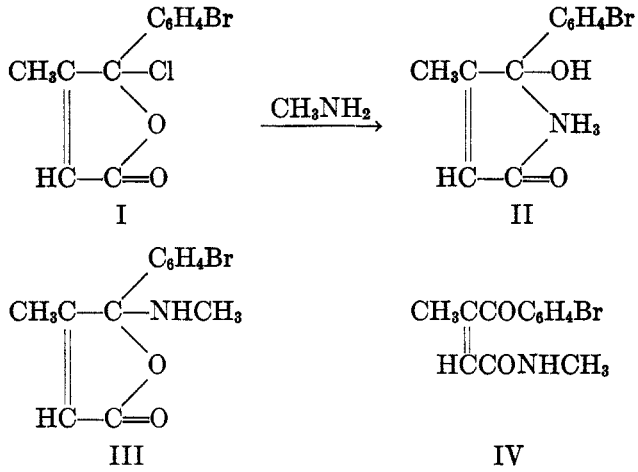
Anal. Calc'd for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.0; N, 5.3.
Found: C, 49.56; H, 2.9; N, 5.2.

II. THE COMPOUNDS DERIVED FROM METHYLAMINE

The amides made from methylamine have been studied in order to determine the effect of an aliphatic group at the nitrogen on the tendency to form ring compounds. It was expected that the N-methyl group would have little influence and that the compounds of this series would prove, as they did, to be analogous to those derived from ammonia.

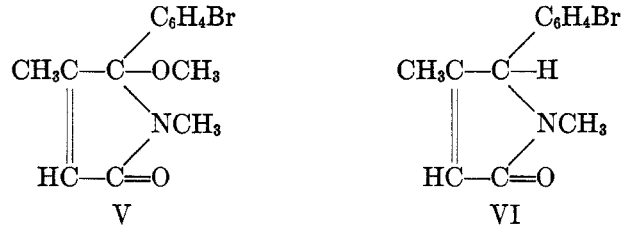
Aqueous methylamine reacted with the acid chloride (I) of *cis*-3-bromobenzoyl-3-methylacrylic acid to give an amide which exhibited all of the characteristics of an unsaturated lactamol or hydroxypyrrolinone and has therefore been assigned the structure II rather than the alternatives III or IV.

The compound is soluble in cold dilute aqueous sodium hydroxide and is precipitated unchanged by acids. It is stable towards boiling concentrated acetic and hydrochloric acid mixture in contrast to the ammonia analog which is quickly attacked under these conditions.



I II III IV

Methylation with methanol and hydrochloric acid gives a methyl ether (V) which is readily hydrolyzed by hydrochloric and acetic acids. However, extended treatment with the methanol-hydrochloric acid reagent is without action on the compound in contrast with the inversion and methanolysis which results when the ammonia analog is subjected to these more drastic conditions. Evidently, the N-methyl group makes for greater stability in this respect.



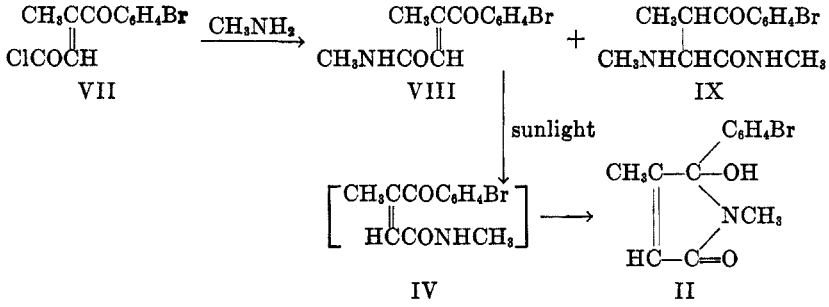
V VI

Stannous chloride reduction of the N-methylamide (II) in a mixture of conc'd acetic and hydrochloric acids gave a typical unsaturated lactam or α-pyrrolinone (VI) which showed the characteristic positive test with Tollens' reagent.

An unsuccessful attempt was made to isomerize the amide (II) into the *trans* isomer (VIII) by the action of sunlight on a chloroform solution containing iodine.

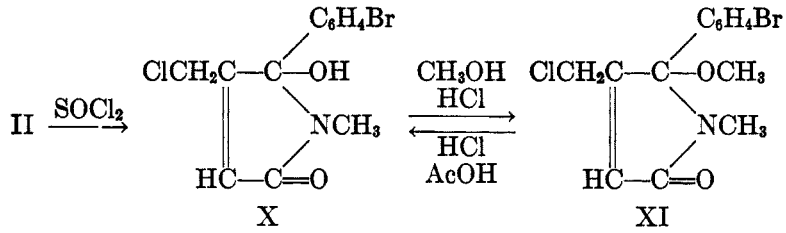
The *trans* amide (VIII) was made from the *trans* acid chloride (VII) by the action of aqueous methylamine; but the amide was not the sole product, the reaction differing in this respect from the analogous reaction with ammonia. Two other compounds were obtained besides the amide,

one of which appeared from analyses and chemical character to be the methylamine addition-compound, IX; these two compounds will be investigated further.



The *trans* amide (VIII), when subjected to the action of sunlight, was transformed into the hydroxypyrrolinone (II), presumably through the primary formation of an unstable open-chain *cis* form (IV), followed by cyclization.

Chlorination of the *cis* compound (II) with thionyl chloride produced a chloro derivative (X) which is analogous to that derived similarly from the ammonia analog, with chlorine replacing a hydrogen of the methyl group. This compound was soluble in dilute sodium hydroxide and was readily converted into the easily hydrolyzable methyl ether (XI).



Further work is being done in both this and the ammonia series in an effort to obtain the aminofuranone forms (III) which, it is believed, should be capable of independent existence.

EXPERIMENTAL[5]

5-(p-Bromophenyl)-1,4-dimethyl-5-hydroxypyrrolinone-2 (the lactamol of *cis*-3-(bromobenzoyl)-3-methylacrylic acid) (II). A solution of 10 g. of the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) in 100 cc. of dry dioxane was cooled in an ice-bath and treated with 30 cc. of 33% aqueous methylamine, added gradually with constant stirring. The solution was allowed to stand for 16 hours and was then heated on a water-bath for 3 hours. It was cooled, diluted with water to the point of crystallization, and concentrated by evaporation with an air blast. When precipitation appeared to be complete, the white crystals were filtered and washed

with water; yield 9.4 g. (93%) melting at 190–193°. Repeated crystallization from 50% methanol raised the melting point to 192.5–193.5°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3.
Found: C, 51.2; H, 4.3. (A quantitative estimation showed no methoxyl.)

The compound dissolved in 10% sodium hydroxide and was precipitated unchanged by hydrochloric acid. It was recovered unchanged after treatment with 30:1 conc'd acetic-hydrochloric acid (refluxing for 1 hour). It was recovered to the extent of 90% when allowed to stand for 15 hours at room temperature in methanol saturated with hydrogen chloride. Zinc dust and conc'd acetic acid for 1 hour at room temperature was without action. Attempts to benzoylate with benzoyl chloride and pyridine (standing 20 hours) and with benzoyl chloride and the sodium salt, were without success, the starting material being recovered almost quantitatively. Only starting material was obtained after treatment with phosphorus pentachloride in dry dioxane, followed by methanolysis. The compound was recovered in quantitative yield after treatment with acetic anhydride and a small amount of conc'd sulfuric acid (room temperature). At 60° for 10 min. only resinous products were obtained. Similarly, unchanged material was obtained when acetyl chloride and pyridine was used. No change was observed when a sample in chloroform containing a visible trace of iodine was subjected to the action of bright sunlight for 5 hours.

5-(p-Bromophenyl)-1,4-dimethyl-5-methoxypyrrolinone-2 (V). A solution of 0.75 g. of the hydroxypyrrolinone (II) in 30 cc. of methanol and 1 cc. of conc'd hydrochloric acid was allowed to stand for 12 hours and then refluxed for 10 hours. Upon cooling, neutralizing with sodium carbonate, and diluting with water (while mechanically stirred), flaky crystals were obtained. The product was filtered and washed with water; yield 0.54 g. (72%) melting at 69–71°. It was purified by vacuum evaporation onto a cold-finger condenser and melted at 71–72°.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: OCH_3, 10.5. Found: OCH_3, 10.7, 10.4.

Hydrolysis of 0.3 g. upon standing for 24 hours in 10 cc. of conc'd acetic and 1 cc. of conc'd hydrochloric acids at room temperature gave 0.21 g. (70%) of the hydroxypyrrolinone (II).

5-(p-Bromophenyl)-1,4-dimethyl-2,5-dihydropyrrolone-2 (VI). A solution of 0.5 g. of the hydroxypyrrolinone (II) in 10 cc. of conc'd acetic acid was added slowly to a suspension of 4 g. of finely powdered stannous chloride in a mixture of 5 cc. of conc'd hydrochloric and 20 cc. of conc'd acetic acids. The mixture was stirred for 1 hour at room temperature and then was diluted with water and concentrated by an air stream. The partially crystalline precipitate was separated by decanting the mother liquors and was dissolved in a small amount of alcohol. Crystallization was induced by adding a few drops of water; yield 0.28 g. (56%), melting point 99–100°. Recrystallization from 50% methanol raised the melting point to 100–101°.

Anal. Calc'd for $C_{12}H_{12}BrNO$: C, 54.1; H, 4.6.
Found: C, 53.8; H, 4.6.

The compound gave an immediate black precipitate when an ethanol solution was treated with ammoniacal silver nitrate solution.

trans-*3-(p-Bromobenzoyl)-3-methylacrylic N-methylamide* (VIII). In a number of preparations under varied conditions a mixture of three compounds invariably was obtained. A typical experiment follows.

One gram each of finely powdered phosphorus pentachloride and *trans*-3-bromobenzoyl-3-methylacrylic acid was mixed, and after the reaction subsided the phosphorus oxychloride was evaporated under reduced pressure. The residual oil was dissolved in 15 cc. of dry dioxane and decanted from unchanged phosphorus penta-

chloride (rinsing with 10 cc. more dioxane). The cooled solution was treated with 4 cc. of 33% aqueous methylamine with vigorous stirring, the solution then being allowed to warm to room temperature. It was poured into 100 cc. of water and after standing 0.5 hours was partially evaporated in an air stream until precipitation appeared to be complete. The solution was decanted from the partly crystalline mass and the residue was leached with several portions of boiling benzene. The insoluble residue (0.2 g.) was crystallized repeatedly from 10% ethanol, and melted at 211–224° (decomp.). The material was not the amide and gave the *anal.*, calc'd for $C_{12}H_{12}BrNO_2$: N, 5.0. Found: N, 5.35. It has not yet been investigated.

The benzene extracts, on cooling, deposited fine white crystals (0.2 g.), which on recrystallization from this solvent melted at 169.5–170.5°. This compound gave the *anal.*, calc'd for $C_{12}H_{17}BrN_2O_2$: N, 9.3; found: N, 9.15. It was formulated as IX and has as yet not been studied.

The benzene filtrate from the above on concentrating and standing deposited a more soluble compound (0.2 g.) which was purified by repeated crystallization from 1:1 benzene-ligroin, and melted at 112–113°.

Anal. Calc'd for $C_{12}H_{12}BrNO_2$: C, 51.1; H, 4.3; N, 5.0.
Found: C, 51.3; H, 4.6; N, 4.9.

Inversion was brought about in 50% yield by exposure in methanol solution to the action of bright sunlight for 5 hours. The product was the hydroxypyrrolinone (II).

5-(p-Bromophenyl)-4-chloromethyl-5-hydroxy-1-methyl-pyrrolinone-2 (X). Ten cubic centimeters of thionyl chloride was added to 1 g. of the hydroxypyrrolinone (II) and the mixture was heated on a water-bath for 10 minutes. On cooling and hydrolyzing in ice and water, a white crystalline powder was obtained; 0.55 g. (54%). It was purified by repeated crystallizations from 75% acetic acid and melted at 198–200° (decomp.).

Anal. Calc'd for $C_{12}H_{11}BrClNO_2$: C, 45.5; H, 3.5; N, 4.4; ClBr, 36.5.
Found: C, 45.1; H, 3.7; N, 4.3; ClBr, 35.7.

The compound dissolved slowly in cold and rapidly in warm (60–70°) 10% sodium hydroxide and was precipitated unchanged upon acidification with hydrochloric acid.

5-(p-Bromophenyl)-4-chloromethyl-5-methoxy-1-methyl-pyrrolinone-2 (XI). A solution of 0.5 g. of the hydroxypyrrolinone (II) in 5 cc. of thionyl chloride was allowed to stand at room temperature for 15 minutes and evaporated in a stream of dry air. Ten cubic centimeters of methanol was added, and the mixture heated at 60° for 1 hour. One cubic centimeter of water was then added, and on cooling and concentrating by an air stream, crystallization occurred; yield 0.5 g. (80%) melting at 100–105°. Repeated crystallization from methanol and vacuum evaporation onto a cold finger gave a pure product melting at 110–110.5°.

Anal. Calc'd for $C_{13}H_{13}BrClNO_2$: C, 47.25; H, 4.0; OCH_3, 9.4.
Found: C, 47.4; H, 4.3; OCH_3, 9.4.

This compound was obtained also in good yield by treating 0.25 g. of the chloro derivative (X) with 7 cc. of methanol and 0.1 cc. of conc'd hydrochloric acid, refluxing for 1.5 hours and standing at room temperature for 24 hours.

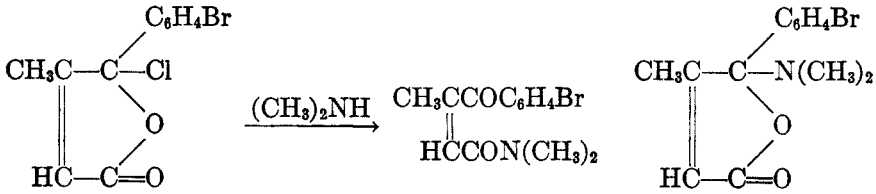
Hydrolysis of 0.5 g. in 10 cc. of conc'd acetic and 1 cc. of conc'd hydrochloric acids (24 hours at room temperature) gave 0.45 g. (95%) of the chloro derivative (X).

III. THE COMPOUNDS DERIVED FROM DIMETHYLAMINE

The N-dimethylamide is of particular interest because it cannot exist in the hydroxypyrrolinone form. Although the investigation of the com-

pounds in this series is incomplete, a preliminary report is being made at this time in order to supplement the discussion of the N-methylanilino series (4c), where all of the theoretically possible isomers have been obtained.

The compound made by the action of aqueous dimethylamine on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I), as would be expected, is unlike the compounds made similarly with ammonia or methylamine (9). Of the two possible formulations of the product, as the open-chain amide (II) or the N-dimethylaminofuranone (III), the former has been assigned, although the evidence is not as strong or as complete as could be desired.



I II III

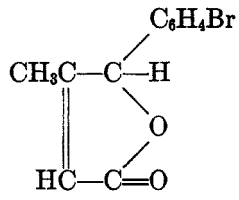
The structure of the amide does not follow from the synthesis because various mechanisms are possible, involving 1,2 or 1,4[6]-reactions as well as interchanges between II and III in either direction through addition and elimination of dimethylamine which was present in excess. The 1,4-reaction mechanism, however, is improbable since both aniline and methylaniline appear to react exclusively 1,2 (4c).

The amide is resistant towards acid hydrolysis, a property hardly to be expected of an aminofuranone such as III. It is reduced, with some difficulty, giving a non-crystalline nitrogen-containing product which has not yet been obtained pure and characterized. No evidence was observed of the formation of the nitrogen-free unsaturated lactone (IV) or the saturated ketonic acid which would be formed from it by hydrolysis, a result which would have been expected if the aminofuranone formulation were correct.[7] In this connection it should be noted that the unsaturated lactone or furanone (IV) has now been synthesized by dehydration of β-bromobenzoyl-β-methylpropionic acid, and if it had been formed in the reduction under discussion, it would have been isolated as such, or as

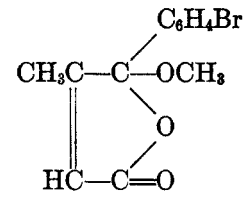
[6] *Cf.* the discussion of this type of reaction, Ref. 2.

[7] *Cf.* the reductions of the ammonia and methylamine compounds to the corresponding unsaturated lactams (9) and the reduction of *cis*-2,3-dimethyl-3-xenoylacrylic acid to the unsaturated lactone (2).

the saturated ketonic acid. The foregoing results, while favoring formula II over III, obviously are inconclusive.



IV



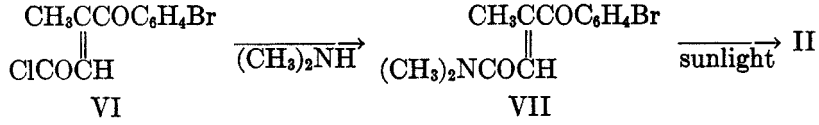
V

Alkaline hydrolysis proceeds very slowly, with cleavage of the molecule and production of *p*-bromopropiophenone, a type of reaction already observed with the *cis* acid itself (1a).

Methanolysis with methanol and hydrochloric acid eliminated the nitrogen and produced the cyclic or pseudo methyl ester (V), a result which would be expected on the basis of either formula II or III; stereochemical inversion did not occur as happens in the methanolysis of the ammonia anolog (4c).

Unsuccessful attempts were made to isomerize the dimethylamide by the action of sunlight on a chloroform solution with iodine as a catalyst, a common procedure for the *cis* to *trans* inversion. This evidence might be regarded as negative and favoring the cyclic structure (III), but little significance can be attached to the point because of the uncertainty in this type of reaction.

Positive evidence in favor of the open-chain formulation (II) is found in the study of the *trans* amide (VII) which was made from the *trans* acid chloride (VI) by the action of aqueous dimethylamine. Unfortunately,



VI VII

this product was not obtained in crystalline form, but its existence was demonstrated by subjecting the best sample, in methanol solution, to the action of bright sunlight; the result was conversion in good yield into the same amide obtained directly from the *cis* acid chloride (I) by the action of dimethylamine. This synthesis constitutes strong evidence in favor of formula II rather than III, since it is very unlikely (although not excluded) that the N-dimethylamino group of the primary open-chain product (II) would migrate under these conditions to give a cyclic compound such as

III [the analogous N-methylanilino group actually does not so migrate under these conditions as has now been shown (4c)].

Further studies are being undertaken in this series, particularly in an effort to obtain the isomeric amide of structure III.

EXPERIMENTAL

cis-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-dimethylamide* (II). A solution of 70 g. of the *cis* acid chloride (I) in 150 cc. of dry dioxane was treated with a solution of 22 g. of dimethylamine hydrochloride in 50 cc. of 20% sodium hydroxide, added slowly with mechanical stirring. The temperature was maintained at 50° with continued stirring for 1 hour. The solution was then poured into ice. A current of air was used to evaporate some of the dioxane, and the oil which separated was washed by decantation with 10% sodium carbonate. The oil by that time had crystallized; this material was filtered, pulverized, and again leached with sodium carbonate solution. The crude yield was 38.3 g. (54%). Repeated crystallization from 50% methanol gave slender needles melting at 116–117°.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: C, 52.7; H, 4.8.
Found: C, 52.55; H, 4.8.

The sodium carbonate extracts (above) on acidification gave 31 g. (45%) of *cis*-β-bromobenzoyl-β-methylacrylic acid, thus accounting for practically all of the material.

When II was boiled with 10% sodium hydroxide, dimethylamine was expelled and an oily product remained. This was removed by extraction with ether, and on steam distillation, it gave a small amount of *p*-bromopropiophenone which was identified by mixture melting point with an authentic sample.

The *cis* amide (II) was recovered unchanged after treatment with 20:1 conc'd acetic and hydrochloric acids (refluxing 1 hour). Methanolysis with 30:1.5 methanol-conc'd hydrochloric acid (refluxing 10 hours) gave a small amount of the *cis* pseudo ester (V).

Chlorination by thionyl chloride gave a non-crystalline product.

Reduction. The *cis* amide (II) was reduced in three ways: (a) by stannous chloride in 5:1 conc'd acetic-hydrochloric acid mixtures, refluxing for 1.45 hours (at room temperature no reduction took place); (b) by sodium hydrosulfite in 70% ethanol, refluxing for 3, 10, or 37 hours (three experiments); and (c) by zinc dust in conc'd acetic acid (1 hour at room temperature). The products in all cases were oils and these separately were evaporated in the vacuum oven at temperatures of 180–200° at 10 mm. [the sample from (c) distilled at a lower temperature, 131–136°, but at a lower and unknown pressure]. The products were collected dropwise on a cold-finger condenser, the refractive index being determined on successive drops. The data obtained for the main fractions which showed constant refractive indices follow:

(a) n_D^{27} 1.5690–1.5700. *Anal.* N, 2.5, 2.4.
(b) n_D^{27} 1.5693–1.5699. *Anal.* N, 2.5, 2.4.
(c) n_D^{27} 1.5439. *Anal.* N, 3.9, 4.0.

These oils gave no reaction with Tollens' reagent and attempts to isolate the unsaturated lactone (IV) failed.

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-dimethylamide* (VII). One gram of *trans*-β-bromobenzoyl-β-methylacrylic acid and 1 g. of phosphorus pentachloride were intimately mixed. Rapid reaction occurred without evolution of much heat. The phosphorus oxychloride was evaporated under reduced pressure and the residual

oil [the *trans* acid chloride (VI)] was taken up in 7 cc. of dry dioxane. A solution of 2 g. of dimethylamine hydrochloride in 9.5 cc. of 9.5% sodium hydroxide was added, the mixture being allowed to stand at room temperature for 16 hours. Dilution with water and partial evaporation in a current of air gave a yellow oil which could not be induced to crystallize. Repetition of the reaction in benzene, using a 5% solution of dimethylamine in benzene, produced the same result.

A solution of 0.55 g. of the oily product in 40 cc. of methanol was exposed to bright sunlight for 8 hours. On concentrating by a current of air, a white crystalline precipitate appeared; 0.37 g. (67%). It was purified by crystallization from benzene-ligroin mixtures and was identified by mixture melting point as the *cis* amide (II).

5-(p-Bromophenyl)-4-methyl-2,5-dihydrofuranone-[8]*2* (IV). A suspension of 2 g. of β-bromobenzoyl-β-methylpropionic acid (1a) in 10 cc. of acetyl chloride was refluxed for 1.5 hours. The resulting solution was evaporated and the solid residue washed with water; yield, 1.87 g. (96%) melting at 76–81°. After repeated crystallization it melted at 88.5–89.5°. It decomposed upon standing for several months.

Anal. Calc'd for $C_{11}H_9BrO_2$: C, 52.2; H, 3.6.
Found: C, 52.5; H, 3.7.

It was insoluble in sodium carbonate and gave a black precipitate when treated in the usual way with Tollens' reagent.

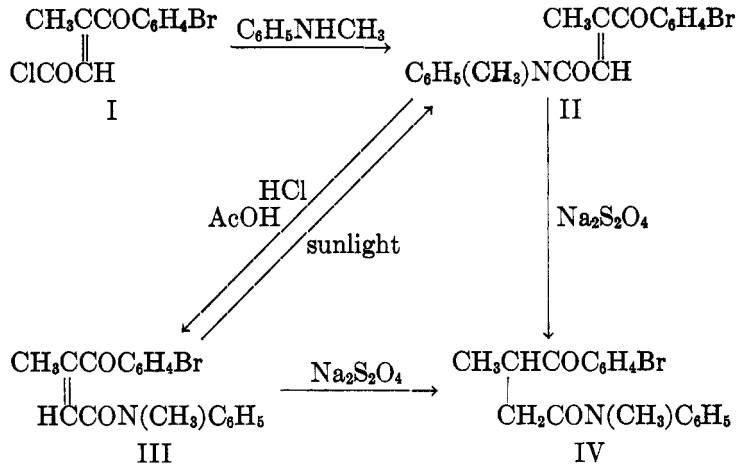
IV. THE COMPOUNDS DERIVED FROM METHYLANILINE

The amides made from methylaniline, a typical secondary amine, have been studied because it was expected that the two possible types in this series would be stable and would both be obtained by the methods which were only partially successful in the analogous N-dimethylamine series. Attention was turned to this series now, rather than to the completion of the investigation of the N-dimethylamino compounds, because here the products proved to be much more amenable to study and because there was immediate prospect of success in obtaining the complete series of derivatives in crystalline condition.

The *cis* (open-chain) N-methylanilide (III) was made from the *trans* isomer (II), which is necessarily open-chain, through inversion by sunlight. The *trans* N-methylanilide was made in good yield and without side reactions from the *trans* acid chloride (I). Both the *cis* and *trans* isomers were reduced easily and in excellent yields to the same compound, 3-bromobenzoyl-3-methylpropionic N-methylanilide (IV). Both isomers proved to be very resistant towards acid hydrolysis, and the action of refluxing conc'd hydrochloric and acetic acids served only to cause partial stereochemical inversion of the *cis* into the more stable *trans* form. In connection with the latter transformation, however, it should be noted that the action of sunlight on a chloroform solution of the *cis* isomer, with iodine as catalyst, was without effect, but of course little significance can be

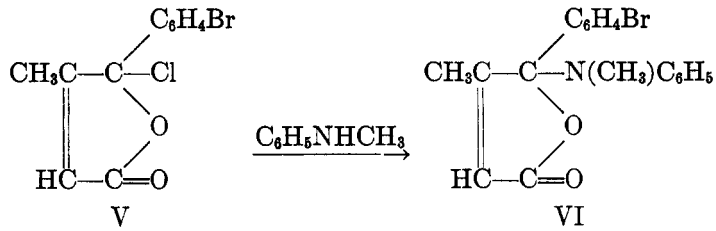
[8] Here the expanded and more proper term is used (rather than the commonly used abbreviation "furanone")in order to distinguish between this form and the isomeric enol lactone (*cf.* 9).

attached to this negative evidence in view of the uncertainty in this particular type of reaction.



The formulation of these compounds and reactions as given in the above diagram is supported by the mode of formation of the compounds involved, particularly (a) the formation of the *cis* amide (III) under conditions which would hardly be expected to permit rearrangement by actual migration of the N-methylanilino group (to give VI); (b) the reverse transformation from the labile *cis* to the stable *trans* form (which indicates the absence of a restrictive cyclic structure); and (c) the ease of reduction of both the *cis* and *trans* isomers by sodium hydrosulfite, a reaction which is characteristic and indicative of the unsaturated 1,4-dicarbonyl system.

An isomeric *cis* N-methylanilide was obtained by the interaction of the *cis* (pseudo) acid chloride of 3-bromobenzoyl-3-methylacrylic acid (V) and methylaniline. Since it is different from the open-chain *cis* methylanilide (III), it must be given the only alternative formulation as the methylanilinofuranone (VI). In turn, the existence of this isomer leaves no room for doubt concerning the structure of the open-chain isomer (III).



As would be expected from this formulation, the product (VI) is not easily reduced and is not affected by sodium hydrosulfite under the condi-

tions which are effective in reduction of the open-chain *cis* isomer and the *trans* isomer. The action of boiling conc'd acetic and hydrochloric acids converted this compound in excellent yield into a new nitrogen-containing substance which has not yet been identified and which is now under investigation.

In the methylanilides, then, we have been able to obtain all of the three possible types of compounds, the *cis* and *trans* isomers and the methylanilinofuranone form of the *cis* compound; furthermore, the modes of formation and reactions leave no doubt as to the structures which have been assigned.

EXPERIMENTAL[5]

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-methylanilide* (II). A sample of the non-crystalline *trans* acid chloride (I) was made in the usual way from 6 g. of the acid and phosphorus pentachloride, the phosphorus oxychloride being removed by evaporation under reduced pressure. This was taken up in 60 cc. of dry dioxane and treated with 6 cc. of methylaniline at 60° for 0.5 hours. Upon cooling and diluting with water, followed by partial evaporation in an air stream, 8.4 g. of II, m.p. 73–78° was obtained. Repeated crystallization from 9:1 ligroin-benzene mixtures raised the melting point to 96–97.5°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5.
Found: C, 60.6; H, 4.76.

cis-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic N-methylanilide* (III). A solution of 0.5 g. of the *trans* isomer (II) in 50 cc. of methanol was exposed to bright sunlight for 12 hours. Addition of water dropwise, with scratching, induced crystallization. The yield was 0.46 g. (92%) of nearly pure product melting at 124–125°. Repeated crystallization from 4:1 ligroin-benzene mixture raised the melting point to 125.5–126.5°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5.
Found: C, 60.3; H, 4.3.

A sample was recovered quantitatively after exposure to the action of bright sunlight for 12 hours in chloroform solution containing a visible amount of iodine.

Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave a non-crystalline product.

Inversion. A solution of 0.2 g. of the *cis* compound (III) in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid was refluxed for 1 hour, giving 0.12 g. (60%) of crude *trans* methylanilide (II) which was recrystallized and identified by mixture melting point.

3-(p-*Bromobenzoyl*)*butyric N-methylanilide* (3-bromobenzoyl-3-methylpropionic N-methylanilide) (IV). A mixture of 1 g. of sodium hydrosulfite, 20 cc. of 20% ethanol, and 0.3 g. of either the *cis* or the *trans* N-methylanilides (II or III) was refluxed for 1 hour. It was then diluted with water and partially concentrated by a current of air. When precipitation appeared to be complete, the white crystalline product was filtered. The yields of material (melting at 100–102°) were identical in both cases (0.28 g. or 93%). Repeated crystallization from ligroin raised the melting point to 103–104°.

Anal. Calc'd for $C_{18}H_{18}BrNO_2$; C, 60.0; H, 5.0.
Found: C, 59.9; H, 5.1.

5-(p-*Bromophenyl*)-*4*-*methyl*-*5*-(*N-methylanilino*)*furanone-2* (VI). A solution of

25 g. of the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (V) in 20 cc. of dry dioxane was treated with 20 cc. of methylaniline and the mixture maintained at 50–55° for 0.5 hours and then for 12 hours at room temperature. The crude product precipitated as a resin upon diluting with water; it was digested with 10% sodium carbonate solution and washed with water (by decantation). It was then crystallized from methanol; yield 11.85 g. (34%) melting at 138–144°. Repeated crystallization from 9:1 ligroin-benzene mixtures raised the melting point to 146–148°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.36; H, 4.5.
Found: C, 60.05; H, 4.2.

Reduction. Sodium hydrosulfite in 70% ethanol (refluxing for 2 hours with further additions of reducing agent) was without effect, 90% of the material being recovered unchanged. Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave an intractable oil.

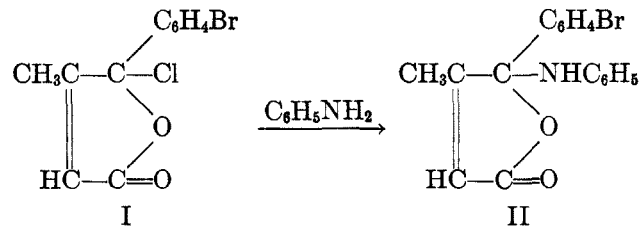
Acid hydrolysis or *methanolysis*, by refluxing for 1 hour in a mixture of 0.2 g. in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid (or in methanol and hydrochloric acid with 7 hours refluxing) gave the same product, in practically quantitative yield in the first case and 80% in the second. Upon repeated crystallization from a 9:1 mixture of ligroin and benzene, it melted at 137–138°.

Anal. Calc'd for $C_{18}H_{16}BrNO$: C, 60.4; H, 5.1; N, 4.4.
Found: C, 60.1; 60.2; H, 5.0; 4.7; N, 4.6; 4.5.

V. THE COMPOUNDS DERIVED FROM ANILINE

Since no series of amides would be completely representative without the anilides, this type has also been investigated. It was expected that the N-phenyl group would tend to stabilize the compounds in some degree and it was hoped that all of the possible isomers might be obtained. This hope was realized in part.

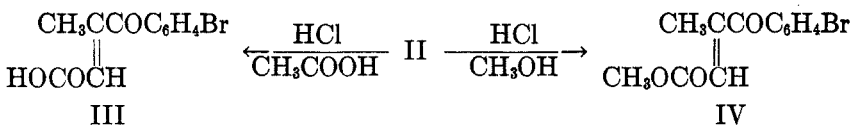
The action of aniline on the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) produced in good yield a compound in which the anilino group had replaced the chlorine. From analogy to the reactions with ammonia and methylamine (9) and the reaction between aniline and the pseudo acid chloride of *o*-benzoylbenzoic acid (3h), one might have expected this product to be the hydroxy-N-phenylpyrrolinone (X). But upon investigation, it quickly became evident from the properties, and from the isolation of the isomer [the true hydroxypyrrolinone (X) described below], that this compound is the anilinofuranone (II), the reaction being analogous to that with methylaniline and to that between aniline and opianic acid (3f).



I II

This anilinofuranone (II) was slightly acidic. It reacted with aqueous sodium hydroxide to give an oil which evidently was the sodium salt since it dissolved when the mother liquor containing the excess of sodium hydroxide was decanted and water was added. The original compound was precipitated unaltered from the solutions upon acidification.

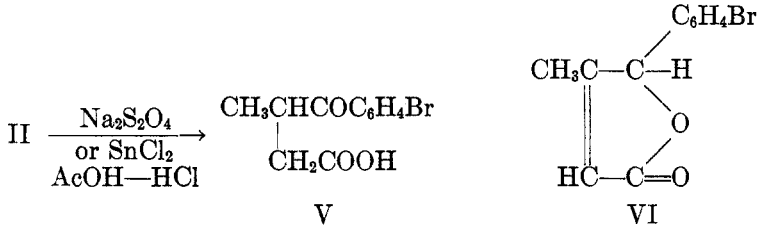
The anilinofuranone was easily hydrolyzed by hydrochloric acid in conc'd acetic acid at room temperature, but curiously the product was the *trans* acid (III), inversion of the configuration having taken place also. This reaction is in sharp contrast with the resistance towards hydrolysis by this reagent at refluxing temperature of the hydroxypyrrolinones, including the N-phenyl derivative (X), described below. The ease of hydrolysis in this case supports the anilinofuranone formulation (II).



The action of methanol and hydrochloric acid on the anilinofuranone (II) produced the *trans* ester (IV), involving both methanolysis and inversion of the configuration. This reaction is analogous to the hydrolysis and inversion described above, and is in striking contrast to the conversion under comparable conditions of the true hydroxypyrrolinones [including the anilino derivative (X) described below] into the corresponding methyl ethers. This reaction also is consistent with and supports formula II.

The two reactions, hydrolysis and methanolysis, as described above, present an interesting problem of mechanism, in that the inversion apparently cannot involve the *cis* acid, the open-chain or pseudo *cis* esters, or the *trans* anilide. Further work on this problem is in progress.

The reduction of the anilinofuranone (II) was accomplished by either stannous chloride or sodium hydrosulfite, the product being 3-bromobenzoyl-3-methylpropionic acid (V).

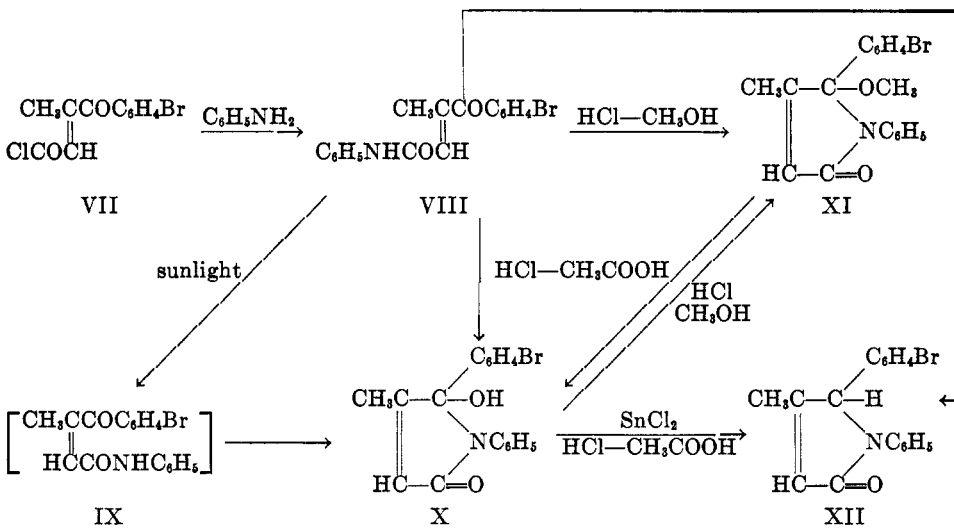


The elimination of nitrogen in both reductions is significant. The acid conditions involved in the stannous chloride reduction are sufficient to cause hydrolysis and inversion, and the *trans* acid (III) is therefore very

probably an intermediate. In the sodium hydrosulfite reduction, however, it seems likely that another mechanism may be involved, perhaps reductive elimination first of the nitrogen to give an unsaturated lactone (VI), followed by hydrolysis to the acid V. The results of these reductions are to be contrasted with the course of the reductions of the hydroxypyrrolinones, including the N-phenyl derivative (X) described below. The formula II explains the results satisfactorily.

From the foregoing facts the anilinofuranone structure (II) seems established. The compound is analogous to the methylanilino derivative, but is quite different in character from the dimethylamino compound. It is to be presumed that in the preparation of all three types from the *cis* pseudo acid chloride (I) the reactions are initially direct (9, 3h) but that with the more reactive dimethylamine a secondary reaction occurs, with rearrangement taking place through addition and elimination of dimethylamine, which is present in excess.

An isomeric anilide, which proved to be the hydroxypyrrolinone (X) has been prepared from the *trans* acid chloride (VII) through the *trans* anilide (VIII). The last step of the transformation, which involved inversion, was accomplished in two ways, by sunlight, and with hydrochloric acid. The intermediate and primary product of the sunlight reaction, of course, must be the true *cis* anilide (IX) but the properties of the compound obtained indicated that immediate cyclization to the hydroxy-N-phenylpyrrolinone (X) had followed.



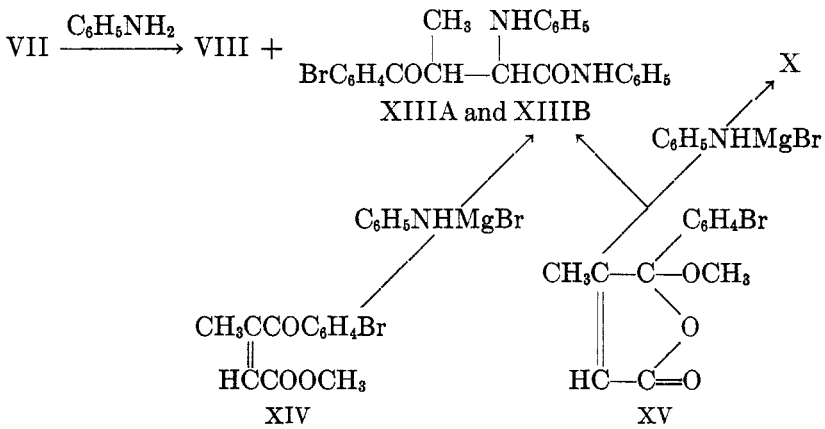
The compound is soluble in dilute sodium hydroxide and is precipitated unchanged upon acidification, as would be expected from the structure X.

The isomerization of the compound by hydrochloric acid, in the direction *trans* to *cis*, is explicable only on the basis of the cyclic formulation (X). The tendency to form the stable ring evidently constitutes the driving force overbalancing the natural tendency of the hypothetical open-chain *cis* form to undergo rearrangement to the thermodynamically more stable *trans* isomer. In contrast to this, as already shown, the *trans methyl*anilide is not affected by hydrochloric acid, presumably because the *cis* form can not cyclize directly, whereas the *cis* isomer, which must be open-chain, will undergo rearrangement to the *trans* in the normal way under these conditions. These differences between the anilide and the methylanilide constitute evidence for the cyclic formulation of the former (X).

Methanol and hydrochloric acid convert the hydroxypyrrolinone (X) into a methyl ether (XI); this reaction is characteristic of the type. The *trans* anilide (VIII) also is converted into this same methyl ether (XI), cyclization evidently being the driving force which is responsible for rearrangement in this direction. This latter reaction is in contrast with the transformation in the opposite direction under these conditions of the *cis* to the *trans* methylanilide. The methyl ether (XI) is easily hydrolyzed by hydrochloric acid in concentrated acetic acid. The hydroxypyrrolinone itself, however, is very resistant towards acid hydrolysis, and thus far attempts to eliminate the nitrogen have been unsuccessful.

Reduction of the hydroxypyrrolinone (X) with stannous chloride in concentrated acetic and hydrochloric acids gives a typical unsaturated lactam, the pyrrolinone (XII). This type of reduction, involving loss of an oxygen, but retention of the nitrogen, is characteristic of this class of compounds and lends further support to the formulation X. Incidentally, the *trans* anilide (VIII) also is converted into the pyrrolinone (XII) under the same conditions, but this reaction must involve first rearrangement to the hydroxypyrrolinone (X) since this change is known to occur readily under the general reaction conditions.

It is perhaps significant that the anilinofuranone (II) is produced in good yield from the *cis* acid chloride (I) by the reaction with aniline without the noticeable formation of secondary aniline addition compounds. The *trans* anilide (VIII), when first obtained by the action of aniline on the *trans* acid chloride (VII), was accompanied by three secondary products, although the yield of the true anilide (VIII) could be made almost quantitative under controlled conditions. Of the three secondary products, two contained two nitrogens each and evidently were stereoisomers of XIII, aniline having added to the α,β-unsaturated ketone system present [a similar addition compound is formed in the reaction with methylamine (9)]. The third compound contained three nitrogens. These compounds have not yet been investigated.



An obvious and probable explanation for the failure of secondary addition of aniline to occur in the reaction with the *cis* pseudo acid chloride (I) is that no reactive α,β-unsaturated ketone system is present in the compounds involved or in the final product (II).

In this connection some experiments should be described dealing with an attempt to prepare the anilides through the action of anilinomagnesium bromide on the open-chain and cyclic *cis* esters (XIV and XV). With the open-chain ester (XIV) only a small amount of one of the anilide addition compounds (XIIIB) was obtained, but when the pseudo ester XV was used, the yield of this same secondary product (XIIIB) was almost 60% and in addition a yield of approximately 40% of the hydroxypyrrolinone (X) was isolated, no other product being obtained.

In summary of the foregoing results, it may be stated that three of the four possible anilides have been made, namely, the *trans* isomer (IV), and the two cyclic forms in the *cis* series, the anilinofuranone (II) and the hydroxypyrrolinone (X). It has not been possible to obtain the true open-chain *cis* amide, and it seems very unlikely that this compound would be stable enough to exist under ordinary conditions.

EXPERIMENTAL[5]

5-Anilino-5-(p-*bromophenyl*)*-4-methylfuranone-2* (II). A solution of 88.6 g. of the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid (I) in 125 cc. of dry dioxane was treated with 70 cc. of aniline diluted with 25 cc. of dioxane. The mixture was maintained at 50–60° with continual stirring for 1.5 hours. The solution was poured into a large volume of water containing 100 cc. of conc'd hydrochloric acid. The resinous product was allowed to coagulate, separated by decantation, and digested with boiling methanol. The product solidified and was filtered; crude yield 117.5 g. (95%). Repeated crystallization from methanol, or benzene (in which it is more soluble), gave an analytical sample melting at 169.5–170.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1; Br, 23.2.
Found: C, 58.8, 58.8; H, 4.1, 4.05; N, 4.2, 4.0; Br. 23.55.

The compound reacts with 10% sodium hydroxide, giving an oil which was separated by decantation; it then dissolved readily in water. Acidification regenerated the anilinofuranone.

Hydrolysis of 0.2 g. in 12 cc. of conc'd acetic acid and 5 drops of conc'd hydrochloric acid (at room temperature or refluxed for 1 hour) gave 0.13 g. (92%) of nearly pure *trans* acid (III) which was purified and identified. When run on a larger scale as a method of preparing the *trans* acid (III), the yields were not as good, and when run at room temperature there usually was recovered some unchanged material, which could easily be separated by taking advantage of its insolubility in sodium bicarbonate.

Methanolysis of 0.5 g. in 30 cc. of methanol and 2 cc. of conc'd hydrochloric acid (refluxing for 7 hours and standing for 12 hours at room temperature) gave 0.22 g. (57%) of nearly pure *trans* ester (IV). The product was isolated by concentrating the solution and cooling.

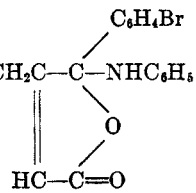
Reduction. A solution of 0.5 g. in 10 cc. of conc'd acetic acid and 10 cc. of ethyl acetate was added to a suspension of 4 g. of stannous chloride in 5 cc. of conc'd hydrochloric acid and 20 cc. of conc'd acetic acid, with vigorous stirring for 1 hour at room temperature. Dilution with water gave 0.31 g. of crude solid (81% yield) from which a pure sample of β-bromobenzoyl-β-methylpropionic acid was obtained upon crystallization; m.p. 94–94.5°; identified by mixture melting point with an authentic sample (1a). A similar result was obtained when sodium hydrosulfite in 80% ethanol was used (refluxing 3 hours).

Reduction with zinc dust, added to a well-stirred solution of the anilinofuranone (II) in conc'd acetic acid and with continued stirring for 1 hour at room temperature, gave a viscous, non-acidic oil which was evaporated in the vacuum oven and collected dropwise on the cold finger. The middle fraction, coming over at an oven temperature of 205–215°, was pale yellow and gave a microanalysis for nitrogen of 3.35%.

Reaction with thionyl chloride gave an amorphous solid product which was purified by repeated precipitation from methanol by addition of water. It melted at 178–179.5° (decomp.).

Anal. Calc'd for $C_{17}H_{13}BrClNO_2$: N, 3.7. Found: N, 3.7.

Evidently simple chlorination had occurred. The following formula is suggested for this product:



Phosphorus pentachloride converted a sample of the anilinofuranone in good yield into the *trans* acid.

Attempts to methylate the salts failed, only unchanged material being recovered in the following experiments: (a) Dimethyl sulfate was added dropwise to II in 2.5% sodium hydroxide, and (b) methyl iodide was added dropwise with stirring to a 1% sodium methoxide solution, followed by refluxing for 2 hours.

When methyl iodide was added to a carefully prepared sample of the silver salt in methanol with shaking for 2 hours, an intractable oil was obtained. The silver salt was made by adding silver nitrate to an aqueous solution of the sodium salt, filtering, and washing with water and methanol.

A new method of synthesis of trans-*3*-(p-*bromobenzoyl*)-*3*-*methylacrylic acid* (III).

The above described hydrolysis and inversion of the anilinofuranone (II) to the *trans* acid (III) has proved to be very useful in preparing quantities of the *trans* acid. The earlier method of synthesis started with citraconic anhydride and in seven steps through citraconic acid, mesaconic acid, the diester, the monoester, the monoester monoacid chloride, and the *trans*-3-bromobenzoyl-3-methylacrylic ester (IV), followed by hydrolysis, gave over-all yields of less than 10% (1a). The new synthesis starting from citraconic anhydride proceeds directly to *cis*-3-bromobenzoyl-3-methylacrylic acid, and then through the acid chloride (I) and the anilinofuranone (II), and involves only four steps with an over-all yield of approximately 50%.

trans-*3*-(p-*Bromobenzoyl*)-*3*-*methylacrylic anilide* (VIII). The oily acid chloride (VII) obtained in the usual way by the action of phosphorus pentachloride on 1 g. of the acid (III), with evaporation of the phosphorus oxychloride, was dissolved in 25 cc. of dry dioxane and cooled to 0–5°. One cubic centimeter of aniline was added dropwise and the temperature maintained at 5° for 1 hour. The mixture was then allowed to come to room temperature over a period of 0.5 hour. When poured into water and ice a precipitate formed, and 1.4 g. of material melting at 135–141° was obtained. Repeated crystallization from methanol brought the melting point to 143–144.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1.
Found: C, 59.4, 59.55; H, 4.1, 4.1; N, 4.2.

Reduction with zinc dust and conc'd acetic acid (1 hour at room temperature) gave a non-crystalline product. Sodium hydrosulfite in 80% ethanol (refluxing for 3 hours) gave a mixture of solid products which have not been identified.

Secondary products. When the acid chloride from 1 g. of the acid (III) was treated with an excess of aniline in dioxane and the mixture was allowed to stand for 18 hours at room temperature, 1.16 g. of crystalline material was obtained. It melted at 46–92°. Leaching with hot ethyl acetate gave a residue which melted at 151–161° (decomp.) and which was repeatedly crystallized from ethanol. This compound then melted at 163–165° and is probably a stereoisomer of XIII. It will be designated as isomer-A.

Anal. Calc'd for $C_{23}H_{21}BrN_2O_2$; N, 6.4. Found: N, 6.5.

The ethyl acetate filtrate (above) was evaporated to a gum which was taken up in ethanol; crystallization followed giving 0.2 g. of product melting at 213–215° (decomp.). Repeated crystallization from ethanol gave short white needles melting at 221–222° (decomp.). This is designated as isomer-B (it is presumably the stereoisomer of XIIIA).

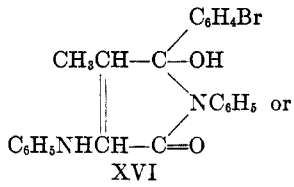
Anal. Calc'd for $C_{23}H_{21}BrN_2O_2$: N, 6.4. Found: N, 6.3.

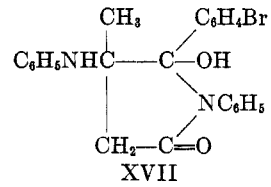
In a second run on this reaction (with the time of standing reduced to 1 hour) the products were worked up as above. Ethyl acetate, however, dissolved all of the material. Recrystallization from benzene and a little ligroin gave a new compound which crystallized from ethanol as short white needles and melted at 193–197° (decomp.).

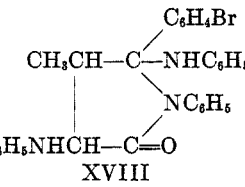
Anal. Calc'd for $C_{29}H_{28}BrN_3O_2$: N, 7.9. Found: N, 8.04.

The filtrate from this was concentrated and gave a sample of the *trans* anilide (VIII).

Alternative structural possibilities for one or both of the dianilino derivatives XIIIA and XIIIB are the following (XVI and XVII), and possibilities for the compound containing three nitrogens would be these structures with anilino replacing the hydroxyl, for example, XVIII.


XVI


XVII


XVIII

5-(p-Bromophenyl)-5-hydroxy-4-methyl-N-phenylpyrrolinone-2 (X). This compound was prepared in three ways as follows. (a) *By inversion of the* trans *anilide under acid conditions.* A solution of 0.1 g. of the *trans* anilide (VIII) in 10 cc. of conc'd acetic acid and 6 drops of conc'd hydrochloric acid was refluxed for 1 hour and diluted with ice and water. A quantitative yield of nearly pure hydroxypyrrolinone (X) precipitated.

(b) *By sunlight inversion of the* trans *anilide.* A solution of 0.1 g. of the *trans* anilide (VIII) in 15 cc. of methanol was exposed to bright sunlight for 6 hours. Upon evaporation and washing the residue with 10% methanol a quantitative yield of the *cis* compound (X) was obtained (m.p. 206-207°). Repeated crystallization from 65% ethanol raised the melting point slightly to 207-207.5°. The reaction worked equally well on a larger scale using 1 g. to 100 cc. of methanol.

Anal. Calc'd. for $C_{17}H_{14}BrNO_2$: C, 59.3; H, 4.1; N, 4.1.
Found: C, 59.1; H, 4.1; N, 4.2.

(c) *By the action of aniline magnesium bromide on the pseudo methyl ester of* cis-*3-bromobenzoyl-3-methylacrylic acid.* An ethereal solution containing approximately 4 g. of phenylmagnesium bromide was added to 20 cc. of dry benzene in a three-necked flask, mechanically stirred and maintained under an atmosphere of dry nitrogen. A solution of 5 cc. of aniline in 10 cc. of dry benzene was added dropwise with stirring, followed by stirring for 0.5 hour. A solution of 2 g. of the pseudo *cis* methyl ester of 3-bromobenzoyl-3-methylacrylic acid (XV) in 20 cc. of dry benzene was then added dropwise with stirring and the mixture finally heated at 50-60° for 1 hour. The solution was treated with ice-water, washed with dilute hydrochloric acid, 5% sodium hydroxide and then water. Evaporation gave a solid residue which was digested with ethanol and filtered; yield 2.1 g. (81%) melting at 161-165°. Extraction with boiling methanol gave a residue (1.26 g., 60%) of nearly pure aniline addition product, XIIIB, melting at 207-216° (identified by mixture melting point). From the methanol filtrate, on cooling, 0.8 g. (40%) of the hydroxypyrrolinone (X) was obtained and identified.

When the open-chain *cis* ester (XIV) of 3-bromobenzoyl-3-methylacrylic acid was used in a comparable experiment, only a 15% yield of the addition compound (XIIIB) was obtained, and no other crystalline product was isolated.

The hydroxypyrrolinone (X) is soluble in an excess of sodium hydroxide and is precipitated unchanged by acid. It is stable towards conc'd acetic acid and added conc'd hydrochloric acid (refluxed for 1 hour). Zinc dust and conc'd acetic acid (1 hour at room temperature) were without any action, the compound being recovered quantitatively. Exposure of a solution in chloroform with a visible amount of iodine to strong sunlight for 6 hours was without effect.

5-(p-Bromophenyl)-5-methoxy-4-methyl-N-phenylpyrrolinone-2 (XI). A solution of the hydroxypyrrolinone (X) in 20 cc. of methanol and 1 cc. of conc'd hydrochloric acid was refluxed for 7 hours. Then, after standing overnight, a few drops of water were added and the solution concentrated by an air stream. A partly crystalline mass appeared and was crystallized from isopropanol by adding a few drops of water

and allowing the solution to evaporate slowly. A yield of 0.13 g. (65%) of material melting at 92–95° was thus obtained. It was difficult to crystallize, usually coming down as an oil. It crystallized best from isopropanol or isopropanol-ethanol mixtures; melting point 92–95°.

Anal. Calc'd for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5; OCH_3, 8.6.
Found: C, 60.6; H, 4.6; OCH_3, 8.2, 7.9.

Similar results were obtained when the above reaction was carried out on the *trans* anilide (VIII).

Hydrolysis of 0.1 g. with 6 cc. of conc'd acetic acid and 12 drops of conc'd hydrochloric acid (standing for 18 hours at room temperature) gave 0.1 g. of nearly pure product which was purified and identified by mixture melting point as the hydroxypyrrolinone (X).

5-(p-Bromophenyl)-4-methyl-N-phenyl-2,5-dihydropyrrolone-2 (XII). A solution of 0.2 g. of the hydroxypyrrolinone (X) in 10 cc. of conc'd acetic acid was added slowly to a suspension of 2 g. of powdered stannous chloride in a mixture of 10 cc. of conc'd acetic and 2 cc. of conc'd hydrochloric acids. The mixture was stirred mechanically for 1 hour at room temperature, and was then diluted with water and extracted with ether. Evaporation of the ether and neutralization of the acetic acid with sodium bicarbonate was followed by leaching with two portions of boiling methanol. The methanol solution, on concentration, gave 0.2 g. of product which on repeated crystallization from 80% ethanol melted at 172–173.5°.

Anal. Calc'd for $C_{17}H_{14}BrNO$: C, 62.2; H, 4.3.
Found: C, 62.3; H, 4.2.

A similar result was obtained when the *trans* anilide (VIII) was substituted in the above reaction.

This compound gave a black precipitate when an alcohol solution of it was treated with Tollens' reagent. The hydroxypyrrolinone (X) in a similar test did not react.

SUMMARIES

I

The same amide was obtained from both the open-chain and pseudo esters and the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid. It has been assigned the unsaturated lactamol or hydroxypyrrolinone structure on the basis of alkali solubility, resistance towards reduction, elimination of the oxygen by the action of stannous chloride, conversion by methanolic hydrogen chloride into the easily hydrolyzable methyl ether, stability towards hydrolysis, and failure to undergo inversion into the *trans* isomer.

The action of sulfuric and nitrous acids caused elimination of the nitrogen and gave the *cis* acid. Extended treatment with methanol and hydrochloric acid gave the *trans* methyl ester by inversion of the configuration and elimination of the nitrogen. Ozonization gave *p*-bromobenzoic acid and *p*-bromophenyl and methyl diketone.

The amide of *trans*-3-bromobenzoyl-3-methylacrylic acid was made by the action of ammonia on the acid chloride. It underwent methanolysis

to the *trans* ester with elimination of the nitrogen. The action of sunlight converted it by inversion and cyclization into the same hydroxypyrrolinone as was obtained from the *cis* acid.

The action of thionyl chloride on the hydroxypyrrolinone brought about substitution of chlorine in the methyl group. The location of the chlorine was demonstrated by degradations. The hydroxypyrrolinone structure was shown by the reactions which paralleled those of the parent amide. The easily hydrolyzable methyl ether was made by the action of methanolic hydrogen chloride.

II

The amide obtained by the action of methylamine on the acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid evidently has the lactamol or hydroxypyrrolinone structure. It gives an easily hydrolyzable methyl ether and is reduced by stannous chloride to the simple pyrrolinone or unsaturated lactam.

The *trans* amide was made from the corresponding *trans* acid chloride. It was converted by the action of sunlight into the hydroxypyrrolinone through inversion and cyclization.

Thionyl chloride converted the hydroxypyrrolinone into a chloro derivative, the chlorine entering the methyl group. The easily hydrolyzable methyl ether of this compound was made.

III

The action of dimethylamine on the pseudo acid chloride of *cis*-3-(*p*-bromobenzoyl)-3-methylacrylic acid gives apparently the true open-chain *cis* dimethylamide. The evidence for the open-chain formulation of the product is the synthesis of this same compound by sunlight inversion of the *trans* dimethylamide which was obtained from the *trans* acid chloride by the action of dimethylamine.

IV

The *trans* N-methylanilide was made through the *trans* acid chloride. It was converted into the *cis* isomer by the action of sunlight. The reverse transformation from *cis* to *trans* was brought about by hydrochloric acid. Both the *cis* and *trans* isomers were reduced to the same N-methylanilide of 3-bromobenzoyl-3-methylpropionic acid. The structure follows from the reactions involved.

The isomeric N-methylanilinofuranone form of the *cis* methylanilide was made from the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid.

V

The action of aniline on the pseudo acid chloride of *cis*-3-bromobenzoyl-3-methylacrylic acid produced the anilinofuranone, the structure of which was shown by the ease of hydrolysis and methanolysis with inversion of configuration to give, respectively, the *trans*-3-bromobenzyol-3-methylacrylic acid and its ester. Reduction eliminated nitrogen giving 3-bromobenzoyl-3-methylpropionic acid.

The above hydrolytic inversion made possible a greatly improved synthesis of the *trans* acid.

The *trans* anilide was made by the action of aniline on the acid chloride, the reaction proceeding in quantitative yield under controlled conditions, but otherwise giving three secondary products, two containing two nitrogens each, and the other, three. The action of hydrochloric acid converted the *trans* anilide into the hydroxypyrrolinone by inversion and cyclization.

The isomeric cyclic anilide (the hydroxy-N-phenylpyrrolinone) was made through the *trans* anilide by isomerization by sunlight or hydrochloric acid. The evidence for the cyclic structure is the formation of the compound through rearrangement of the *trans* isomer by hydrochloric acid, methylation to an easily hydrolyzable methyl ether, and reduction to the unsaturated N-phenyllactam or pyrrolinone.

The true open-chain *cis* anilide was not obtained and is evidently incapable of existence.

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