from alcohol. The hydrochloride of the tripeptide was obtained in 94.2% yield (1.49 g.). A sample was recrystallized from alcohol, forming clusters of colorless needles.

Calcd. for $C_{13}H_{18}O_4N_3Cl$: neut. equiv., 316. Found: neut. equiv., 312.

A solution of 316 mg. (1 millimole) of the hydrochloride in approximately 200 ml. of water was passed slowly through a 12 × 250 mm. column packed with Amberlite IR-4B resin. From the chloride-free effluent 260 mg. (96.8%) of the tripeptide was recovered by evaporation; m. p., 221–223° (dec.) (Sigmund and Wessely[13] reported m. p. 225–230° (dec.)).

Summary

A new method for the synthesis of peptides has been devised in which the amino group of an amino acid is protected by formation of the phthalyl derivative. This is converted to the corresponding phthalimidoacyl chloride which is used to acylate a second amino acid or peptide. Removal of the protecting group from the resulting phthalyl peptide is effected by treatment with hydrazine hydrate under conditions which do not affect the peptide linkage.

Procedures are given for the synthesis in good yield of glycine anilide (70%), glycylglycine (60%), glycyl-DL-phenylalanine (61%), glycyl-L(+)-cysteine hydrochloride (60%) and DL-phenylalanylglycylglycine (53%).

The advantages of the phthalyl protecting group in peptide syntheses are discussed.

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NOTES

The Isoxazolines and Isoxazoles from Benzal-*p*-bromoacetophenone and *p*-Bromobenzalacetophenone

BY A. H. BLATT

In a study of the configuration and rearrangement of the oximes of α,β-unsaturated ketones published in THIS JOURNAL,[1] some attention was given to the formation of the isoxazoline (III) from benzal-*p*-bromoacetophenone (I) and its oximes (II), and to the formation of the isoxazole (VIII) from the dibromide of benzal-*p*-bromoacetophenone (IV) and its oxime (VII). The reactions involved are shown in diagram I.

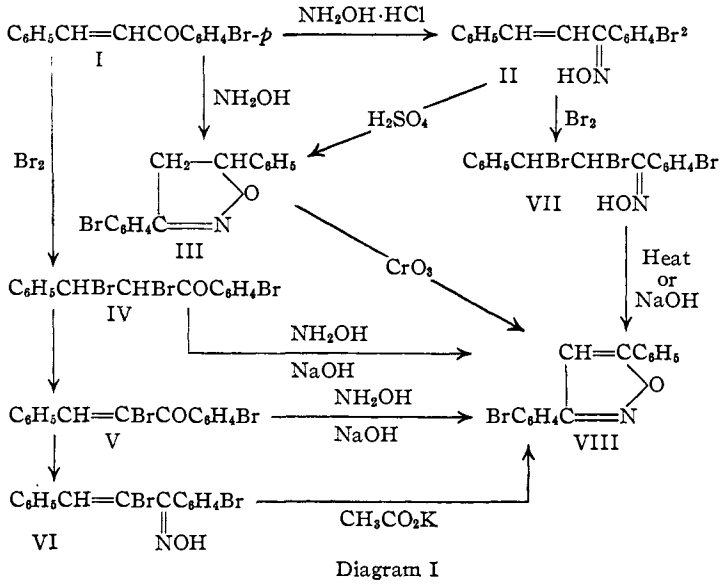


Diagram I

(1) Blatt, THIS JOURNAL, **53**, 1133 (1931); Blatt and Stone, *ibid.*, **53**, 4134 (1931).

(2) Only one of the pair of isomeric oximes is shown

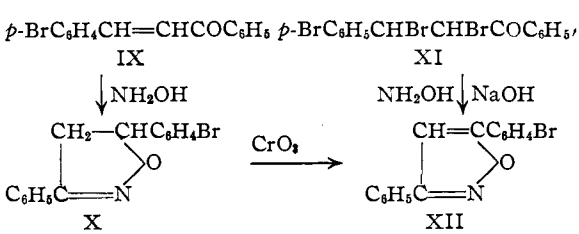
At the time it was pointed out that the obvious and attractive mechanism for the formation of an isoxazoline from an α,β-unsaturated ketone and hydroxylamine was by a simple 1,4-addition of the reagent to the conjugated system followed by elimination of a molecule of water and the shift of a hydrogen atom from nitrogen to carbon. This mechanism could not be accepted, however, because it led to a structure for the isoxazoline that was contradicted by the chemical evidence. The 1,4-addition of hydroxylamine to benzal-*p*-bromoacetophenone would furnish the isoxazoline (X) below, in which the nitrogen atom is attached to what was the β-carbon atom of the conjugated system in the unsaturated ketone. The isoxazoline obtained, however, is III, above, with the nitrogen atom attached to what was the carbonyl carbon atom in the unsaturated ketone. This structure is established for the isoxazoline (III) by its formation from the oxime (II), and by its conversion to the isoxazole (VIII), whose structure in turn is established by its formation from the oximes (VI) and (VII).

It is necessary for us to reopen this old work because of the appearance of a set of papers by Barnes and his co-workers[3] which deals *inter alia* with the formation and structures of the isoxazolines and isoxazoles obtained from a number of

(3) (a) Barnes, Pierce and Cochrane, THIS JOURNAL, **62**, 1084 (1940); (b) Barnes and Cochrane, *ibid.*, **64**, 2262 (1942); (c) Barnes and Brandon, *ibid.*, **65**, 1070 (1943); (d) Barnes and Dodson, *ibid.*, **65**, 1585 (1943); (e) Barnes and Dodson, *ibid.*, **67**, 132 (1945); (f) Barnes and Spriggs, *ibid.*, **67**, 134 (1945); (g) Barnes and Snead, *ibid.*, **67**, 138 (1945); (h) Barnes, Pinkney and DaCosta, *ibid.*, **69**, 3129 (1947); (i) Barnes and Read, *ibid.*, **69**, 3132 (1947); (j) Barnes, Goodwin and Cotten, *ibid.*, **69**, 3135 (1947).

α,β-unsaturated ketones and β-diketones. In these papers frequent reference is made to our early work as showing that isoxazolines are formed by the 1,4-addition of hydroxylamine to α,β-unsaturated ketones—precisely the mechanism which we had shown was not valid for the α,β-unsaturated ketones with which we had worked. In the fifth paper of their series,[3e] Barnes and Dodson deal with the isoxazolines and isoxazoles obtained from benzal-*p*-bromoacetophenone (I) and *p*-bromobenzalacetophenone (IX). Their experimental work confirmed our earlier results; but, since they believe it is logical for isoxazoline formation to take place by 1,4-addition, they assigned the isomeric structure X to the isoxazoline from benzal-*p*-bromoacetophenone which we had shown to have the structure III. Similarly, since they believe it is logical for the formation of an isoxazole from the dibromide (IV) and hydroxylamine to proceed through 1,4-addition to the α-bromo ketone (V) they assigned the isomeric structure XII to the isoxazole which we had shown to have the structure VIII. It is particularly to be noted that Barnes and Dodson offered no evidence for revising the structures we had assigned, and revised them solely on the assumption that the compounds had been formed by a simple 1,4-addition process.

We have reëxamined our earlier work because with the publication of Barnes and Dodson's article two conflicting structures for the isoxazoline and the isoxazole from benzal-*p*-bromoacetophenone now appear in the literature, and because one new fact in the Barnes and Dodson article made it possible that our earlier work contained an error. Barnes and Dodson found that the isoxazole from *p*-bromobenzalacetophenone melts at 178–179°; the isomeric isoxazole from benzal-*p*-bromoacetophenone melts at 180–181°, and mixtures of the two isoxazoles show such a small lowering of the melting point that the establishment of their non-identity by this method is not certain. Since our proof of the identity of the isoxazole (VIII) obtained from the dibromo oxime (VII), the α-bromo oxime (VI), the dibromo ketone (IV) and the isoxazoline (III) was by means of mixed melting points it was possible that this identification was not valid.



For the certain identification of the isoxazoles we have now converted them to the isoxazolium chloride–ferric chloride salts by treatment with methyl sulfate, then hydrochloric acid and ferric chloride.[4] These salts are sparingly soluble, crystallize well and have characteristic sharp melting points. The ferric chloride salt (XIII) from the isoxazole (VIII) melts at 139–140°; the ferric chloride salt (XIV) from the isoxazole (XII) melts at 143–144°; mixtures of the two salts melt between 110–120°.

The new experiments confirm the earlier work. In the benzal-*p*-bromoacetophenone series the isoxazoline (III) is converted by oxidation to the isoxazole (VIII) which is identical with the isoxazole obtained from the dibromo ketone (IV), the α-bromo oxime (VI) and the dibromo oxime (VII). In the *p*-bromobenzalacetophenone series the isoxazoline (X) is converted by oxidation to the isoxazole (XII) which is identical with the isoxazole obtained from the dibromo ketone (XI). The conclusion is that the structures originally assigned to the isoxazoline (III) and the isoxazole (VIII) derived from benzal-*p*-bromoacetophenone are correct, and that the isoxazoline and isoxazole derived from *p*-bromobenzalacetophenone have the structures (X) and XII, respectively.

Experimental

The ferric chloride salts were prepared by heating on the steam-bath for four hours, 0.5 g. of the isoxazole and 1.5 ml. of freshly distilled methyl sulfate. The reaction mixture was cooled and 5 ml. of a mixture of equal parts of water and concd. hydrochloric acid was added. After allowing a half-hour for conversion of the methosulfate to the chloride, an excess of concd. ferric chloride solution (1 part water:2 parts ferric chloride hexahydrate) was added. The yellow crystals of the salt were filtered, dried and purified by crystallization from glacial acetic acid.

2-Methyl-3-*p*-bromophenyl-5-phenylisoxazolium chloride–ferric chloride (XIII) melts at 139–140°. Calcd. for $C_{16}H_{13}BrCl_4FeNO$: C, 37.44; H, 2.6. Found: C, 37.79; H, 2.68.

2-Methyl-3-phenyl-5-*p*-bromophenylisoxazolium chloride–ferric chloride (XIV) melts at 143–144°. Calcd. for $C_{16}H_{12}BrCl_4FeNO$: C, 37.44; H, 2.6. Found: C, 37.6; H, 2.75.

Samples of the isoxazole (VIII) prepared by oxidation of the isoxazoline (III), by heating the dibromo oxime (VII), by the action of potassium acetate on the α-bromo oxime (VI), and by the action of alkali and hydroxylamine on benzal-*p*-bromoacetophenone dibromide (II) were converted to the ferric chloride salt (XIII). Mixtures of the ferric chloride salt obtained from these sources showed no depression of the melting point. Samples of the isoxazole (XII) prepared by oxidation of the isoxazoline (X) or by the action of alkali and hydroxylamine on the dibromide of *p*-bromobenzalacetophenone (XI) were converted to the ferric chloride salt (XIV). Mixtures of this salt obtained from these two sources showed no depression of the melting point. Mixtures of the ferric chloride salt (XIII) and the isomeric salt (XIV) melted over the range 110–120°.

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(4) Kohler and Blatt, THIS JOURNAL, **50**, 1217 (1928).