isolated (identified by m. p. and mixed m. p.) from reactions of the dichloride and the sodium salt of acetoxime in absolute ethanol. The solid product isolated from a similar reaction with potassium benzohydroxamate appeared to be impure II; the oily products gave only III on hydrolysis with hydrochloric acid, as did similar oils obtained from reactions with potassium hydroxylaminedisulfonate. Most of I was recovered from attempted reactions with sodium cyanide in acetone or ethanol or potassium cyanide in acetone; dark solutions resulted when ethanol was used with potassium cyanide and no pure product could be isolated. Aqueous potassium silver cyanide and I gave 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine (identified by m. p. and analysis). Treatment of the crude diiodide with ammoniacal silver cyanide, followed by hydrolysis with hydrochloric acid, gave only III. No pure substance was isolated from the reactions with sodio acetoacetic ester.

Summary

3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine is dehydrohalogenated rapidly by treatment with ethanolic sodium hydroxide. The reaction provides a convenient preparation of 3,6-divinyl-2,5-diketopiperazine. The only reaction observed when the dichlorodiketopiperazine is treated with the sodium salt of acetoxime is dehydrohalogenation. The readiness with which this reaction occurs probably accounts for the failure of replacement reactions with other hydroxylamine derivatives, with alkali cyanides, and with sodio acetoacetic ester. Replacement of the chlorine atoms of the dichlorodiketopiperazine occurs readily when the substance is treated with sodium benzyl mercaptide, morpholine or piperidine, and less readily with potassium thiocyanate.

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[CONTRIBUTION FROM THE NOYES LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Non-Markownikoff Addition in Reactions of 3,6-Divinyl-2,5-diketopiperazine

BY H. R. SNYDER AND M. E. CHIDDIX[1]

The dehydrohalogenation of 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine[1a] proceeds under such mild conditions as to suggest an analogy to reactions of β-halocarbonyl compounds. In this paper are recorded some reactions of the dehydrohalogenation product (3,6-divinyl-2,5-diketopiperazine, I) which show its properties to resemble those of α,β-unsaturated carbonyl compounds.

The divinyldiketopiperazine (I) was found to undergo the addition of hydrogen chloride readily. The product so obtained had physical properties identical with those of the 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (II), from which the divinyl compound was prepared. Since the yield of the addition product was good, and since the divinyl compound was halogen-free, it is not possible that the dichloro compound isolated was present as an impurity in the unsaturated substance (I). That the addition product is indeed 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine was proved by converting it to the known methionine anhydride (III)[2] and the known 3,6-*bis*-(β-benzylthiolethyl)-2,5-diketopiperazine (IV).[3] The same derivatives were prepared from the original dichloro compound as well, and mixed melting point determinations were made. In addition, both samples of methionine anhydride were hydrolyzed and samples of benzoylmethionine (V) were prepared. All these derivatives had approximately the melting points ascribed to them in the literature, and in no instance was there a depression of melting point on mixing of the derivatives from the two sources. The racemic and *meso* forms of S-benzylhomocysteine anhydride (IV) have been characterized[3] as melting at 165 and 176°, respectively. The samples obtained in this work melted at about 175°, so it seems likely that the diketopiperazine II is the *meso* form, or that this form preponderates if both it and the racemic variety are present in the samples of II. The only discrepancy in melting points was encountered with *dl*-S-benzylhomocysteine (VI); the sample prepared by hydrolysis of IV melted with decomposition at about 230°, whereas the recorded[4] melting point is 190–191°. The sample of VI had the expected composition.

The divinyldiketopiperazine (I) underwent addition of hydrogen bromide to give the dibromo analog of II. The 3,6-*bis*-(β-bromoethyl)-2,5-diketopiperazine (VII) so formed was identified by conversion to methionine anhydride (III). The dibromodiketopiperazine decomposed readily. It dissolved slowly in hot alcohol or hot water to give strongly acid solutions. In an experiment in which a sample was heated with water the amount of acid generated was determined by titration; it corresponded to a neutral equivalent of 181, as compared to the theoretical value of 164 calculated on the assumption that one molecule of VII yields two molecules of hydrogen bromide. The formation of the acid may be due either to dehydrohalogenation or to hydrolysis.

Treatment of the divinyldiketopiperazine with hydrogen sulfide gave an addition product containing two atoms of sulfur. Attempts to direct the reaction by carrying it out in the dark, to favor Markownikoff addition, and under strong

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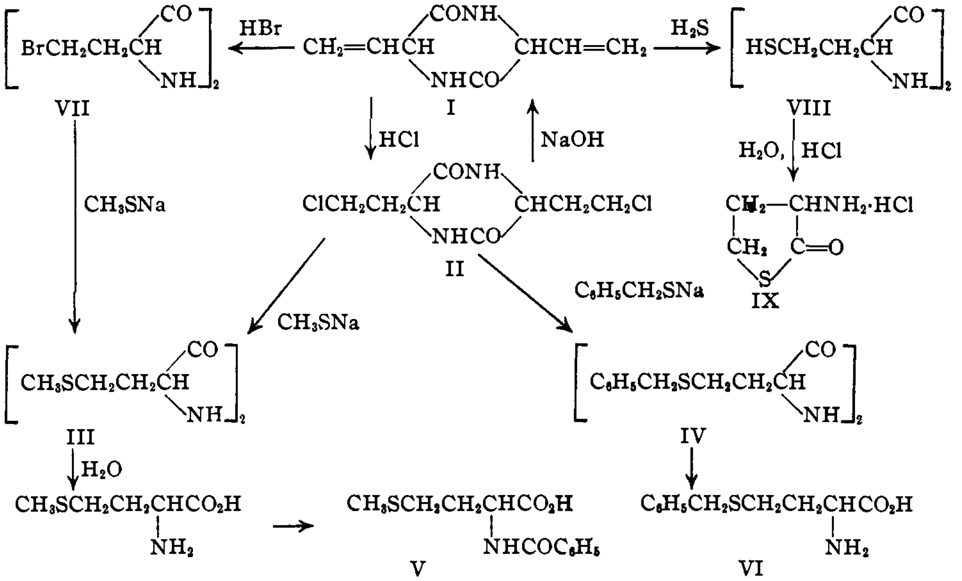
(1a) See preceding paper, THIS JOURNAL, **66**, 1000 (1944).

(2) Snyder, Andreen, Cannon and Peters, *ibid.*, **64**, 2082 (1942).

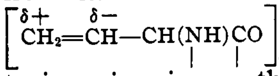
(3) du Vigneaud, Patterson and Hunt, *J. Biol. Chem.*, **126**, 217 (1938).

(4) Butz and du Vigneaud, *ibid.*, **99**, 135 (1932).



ultraviolet irradiation, to favor non-Markownikoff addition,[5] were unsuccessful, the same product being obtained in all instances. The reaction product was hydrolyzed to homocysteine thiolactone hydrochloride (IX) in good yield, so evidently the addition of hydrogen sulfide occurred in the non-Markownikoff fashion. The addition product, although of analytical purity, melted with decomposition at a temperature much lower than the recorded[3] melting point of either the *meso* or racemic homocysteine anhydride. It is possible that the material is a mixture of the two forms.

The non-Markownikoff addition observed in these instances cannot be ascribed to an effect of peroxides, since reactions of hydrogen chloride and olefins are not susceptible to such influence. An explanation can be based on the assumption that the group —CH(NH)CO— of the diketopiperazine ring polarizes the double bond of the attached vinyl group by withdrawing electrons from it. The reactive form thus would be



$$\left[\overset{\delta+}{C}H_2{=}\overset{\delta-}{C}H{-}CH(NH)CO\right]_2$$

. The effect of the diketopiperazine ring on the double bond is similar to that of a *m*-directing group in producing the polarization.[6] On this basis the addition of halogen acid is to be regarded as strictly comparable to the non-Markownikoff addition of hydrogen bromide to divinylsulfone,[7] in which the addition to the double bond is directed by a *m*-orienting group which cannot participate in 1,4-addition. It is of interest to note that in the nitration of phenylglycine the side-chain is strongly *m*-directing.[8] During the occurrence of this reaction the side-chain must be in the form of the salt —CH(NH$_3^+$)CO$_2$H. It is not surprising that this group should be *m*-directing, inasmuch as the group —CH$_2$NH$_3^+$ is *m*-orienting[6] and incorporation of the carbonyl group would be expected to increase its effectiveness in this regard. The addition of halogen acids to the divinyldiketopiperazine (I) may involve preliminary salt formation. However, the non-Markownikoff addition of hydrogen sulfide in the absence of strong acids and in the absence of ultraviolet irradiation and the extraordinary ease[1a] of dehydrohalogenation of the dichlorodiketopiperazine (II) suggest that the free diketopiperazine ring has a strong polarizing effect on groups attached at the 3 and 6 positions.

Experimental

(1) **Addition of Hydrogen Chloride to 3,6-Divinyl-2,5-diketopiperazine.**—Dry hydrogen chloride was bubbled into a solution of 17.5 g. of 3,6-divinyl-2,5-diketopiperazine[1a] in 150 cc. of 100% acetic acid until the gain in weight was 9.0 g. The mixture was allowed to stand for one hour, after which period it was heated on the steam-bath until a clear solution resulted. The solution was allowed to cool and the crude 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (II) was collected and washed with water, alcohol, and ether. It weighed 14.9 g. (59%) and melted at 233–234° (cor., with decomp.; lit.,[3] 231–232°); the melting point was not lowered by admixture of authentic II. The divinyldiketopiperazine was regenerated by heating the hydrogen chloride addition product with alcoholic sodium hydroxide.[1a]

(2) **Preparation of Methionine Anhydride (III).**—The product from the preceding experiment was treated with sodium methyl mercaptide according to the procedure described previously.[2] Methionine anhydride melting at 230–231° (lit.,[2] 231–232°) was obtained, and its melting point was not depressed by admixture of an authentic sample.

Anal. Calcd. for $C_{10}H_{18}N_2O_2S_2$: C, 45.77; H, 6.92. Found: C, 46.26; H, 7.13.

(3) ***dl*-Methionine and Benzoyl *dl*-Methionine.**—The methionine anhydride so obtained was hydrolyzed as described previously. The methionine was analyzed.

Anal. Calcd. for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43. Found: C, 40.71; H, 7.51.

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(5) Vaughan and Rust, *J. Org. Chem.*, **7**, 472 (1942).

(6) Price, *Chem. Rev.*, **29**, 37 (1941).

(7) Alexander and McCombie, *J. Chem. Soc.*, 1913 (1931).

(8) Plöchl and Loë, *Ber.*, **18**, 1179 (1885).

Benzoyl *dl*-methionine was prepared by the procedure of Windus and Marvel.[9] It melted at 151–151.5° (cor., lit.,[9] 143–145°).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97. Found: C, 56.86; H, 6.20.

The derivative prepared from authentic methionine melted at 149–150.5° (cor.) and a mixture of the two samples also melted at this temperature.

(4) **Preparation of 3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine (IV).**—The previously described method[1a] was used with the hydrogen chloride addition product obtained in (1). The product melted at 177–178° (cor.) and this melting point was not depressed by admixture of IV prepared from authentic II.[1a]

Anal. Calcd. for $C_{22}H_{26}N_2O_2S_2$: C, 63.73; H, 6.33. Found: C, 64.27; H, 6.34.

(5) **Hydrolysis of 3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine.**—A mixture of 2 g. of the anhydride (IV) prepared in (4), 15 cc. of water and 45 cc. of concentrated hydrochloric acid was heated under reflux for seven hours, then filtered. The filtrate was diluted with 100 cc. of water and evaporated to dryness under diminished pressure. The white solid residue was dissolved in 20 cc. of hot absolute ethanol; the solution was clarified with charcoal and treated with 2 cc. of pyridine. The solid which separated was collected and recrystallized from water. It melted at 226–230° (cor., with dec.; lit.[4] 190–191°).

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.72. Found: C, 58.98; H, 6.75.

Exactly the same results were obtained in the hydrolysis of the anhydride[1a] prepared from authentic 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine. The yield was about 75% in both instances.

(6) **3,6-*bis*-(β-Bromoethyl)-2,5-diketopiperazine (VII).**—A cold solution of 2.4 g. of dry hydrogen bromide in 6 cc. of glacial acetic acid was added slowly to a cold, stirred solution of 1.12 g. of the divinyldiketopiperazine (I) in 7 cc. of glacial acetic acid. The solution was allowed to stand without cooling for one hour, during which time crystallization occurred. The mixture was stirred in 80 cc. of cold water and the solid was collected and recrystallized from glacial acetic acid. The product (VII) melted at 221–222° (cor., with dec.) and was obtained in yields of about 50%.

Anal. Calcd. for $C_8H_{12}Br_2N_2O_2$: C, 29.27; H, 3.69. Found: C, 29.74; H, 3.69.

A sample of 0.20 g. of VII was dissolved in 20 cc. of water by heating on the steam-bath for five minutes. The clear solution was cooled and titrated with 0.0445 *N* sodium hydroxide and phenolphthalein. The end-point was fugitive. The partly neutralized solution was heated for a few minutes longer, then cooled and titrated to a permanent end-point (23.85 cc. of the standard solution required).

A mixture of 0.4 g. of the dibromo compound (VII) and a solution of 0.186 g. of sodium methyl mercaptide in 15 cc. of absolute ethanol was shaken mechanically for five hours, then allowed to stand three hours, and finally heated to boiling until a clear solution resulted. The crystals which separated when the solution was cooled were collected, washed with water, and recrystallized from 10 cc. of absolute ethanol. The yield of methionine anhydride (III), m. p. 231–232° (cor.), was about 30%; the melting point was not depressed by admixture of authentic (III).

Anal. Calcd. for $C_{10}H_{18}N_2O_2S_2$: C, 45.77; H, 6.92. Found: C, 46.09; H, 6.99.

(7) **Addition of Hydrogen Sulfide to 3,6-Divinyl-2,5-diketopiperazine.**—A solution of 10 g. of the divinyldiketopiperazine (I) and 2 cc. of glacial acetic acid in 250 cc. of absolute ethanol was saturated at 0° with hydrogen sulfide. The container was closed by a wired-on stopper and the mixture allowed to stand at room temperature overnight. A crystalline, light green solid was collected, washed with ethanol, and dried in the air (wt., 6.94 g.). The mother liquor was resaturated with hydrogen sulfide and allowed to stand as before to give a second crop of 1.0 g. of light blue crystals. The combined product was nearly colorless after recrystallization from ethanol; m. p. 185–186° (cor., with dec.).

Anal. Calcd. for $C_8H_{14}N_2O_2S_2$: C, 41.01; H, 5.98. Found: C, 41.14; H, 6.13.

The substance dissolved in 2.5% aqueous sodium hydroxide and could be regenerated by saturation of the solution with carbon dioxide. It gave a positive sulfhydryl test with sodium nitroprusside.

In similar experiments in which acetic acid was not added to the mixtures the reaction was very slow, requiring about four days to proceed to a 50% yield. No difference could be detected between runs carried out in quartz apparatus under an ultraviolet lamp and those carried out in the dark. The crude products from these runs were of darker green color than that described above, but the purified materials were nearly colorless.

(8) **Homocysteine Thiolactone Hydrochloride.**—A solution of 4 g. of the dithiol (VIII) in 60 cc. of concentrated hydrochloric acid was heated under reflux for two hours, then diluted with 100 cc. of water and evaporated to dryness under diminished pressure. The residue was dissolved in 150 cc. of water and after decolorization the solution was again evaporated under diminished pressure. The residue was washed well with absolute ethanol; the thiolactone salt (IX) weighed 3.2 g. and melted at 199–200° (lit.,[10] 200–201°).

Anal. Calcd. for C_4H_8ClNOS: C, 31.28; H, 5.25. Found: C, 31.82; H, 5.64.

Summary

3,6-Divinyl-2,5-diketopiperazine undergoes addition of hydrogen chloride, hydrogen bromide and hydrogen sulfide in the manner opposite to that predicted from Markownikoff's rule. In this regard the double bonds resemble that of an α,β-unsaturated carbonyl compound. The abnormal orientation may be attributed to polarization of the double bond by the attached —CH(NH)CO— group of the diketopiperazine ring.

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[9] Windus and Marvel, THIS JOURNAL, **53**, 3490 (1931).

[10] Riegel and du Vigneaud, *J. Biol. Chem.*, **112**, 149 (1935–1936).