sequently to solidify as Form I at −13.5°. This unsaturated monoglyceride, previously prepared in this Laboratory by Dr. T. R. Wood and one of us (A. R. B.), when exposed for a short time to air at room temperature, quickly developed a film and a decrease in iodine value. The rates of oxidation of the glycerides reported in this paper are being studied and will be reported at a later date.

Two polymorphic forms (Fig. 3) were also found for 1-monolinolein, Form II melting at −22.8 and Form I at 12.3°. While other forms were anticipated for each 1-monolinolein and 1-monolinolenin on the basis of previous experience, evidence for these forms could not be found from thermometric measurements. It is interesting to note that the melting points of both Form II and Form I for 1-monolinolenin are higher than for 1-monolinolein.

Summary

Physical and chemical data are reported for two new synthetic glycerides, 1-monolinolenin and trilinolenin.

Melting point data for the polymorphic forms of 1-monolinolein, 1-monolinolenin, trilinolein and trilinolenin are also reported.

Bromination of 1-monolinolenin and trilinolenin produced two new crystalline bromides.

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Synthetic Amino Acids. Some Reactions of 3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine

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

In a continuation of a study[2] of the preparation of amino acids from the easily available 3,6-*bis*-(β - chloroethyl) - 2,5 - diketopiperazine[2b] (I), this substance has been treated with a number of reagents with which it might be expected to react metathetically. In previous work the dichloro compound has been found to react normally with sodium methyl mercaptide and with thiourea. It now has been found that the substance is unexpectedly susceptible to dehydrohalogenation by alkali, a circumstance which may account for the failure of certain projected syntheses depending upon replacement of the chlorine by interaction with alkaline reagents. For example, attempts to prepare the dicyano derivative (a potential glutamic acid intermediate) by treatment of the dichloro compound with alkali cyanides were unsuccessful. Previous treatment of the dichloride with potassium iodide in acetone, to effect replacement of most of the chlorine by iodine, did not improve the reaction, nor did substitution of silver cyanide for the alkali cyanide.

Attempted syntheses of canaline intermediates from the dichlorodiketopiperazine, with or without previous treatment with potassium iodide, and the sodium salt of acetoxime, potassium benzohydroxamate or potassium hydroxylaminedisulfonate likewise were unsuccessful, despite the fact that the closely related reaction of α-benzamido-γ-iodobutyric acid and potassium benzohydroxamate is reported to occur readily.[3]

The dichlorodiketopiperazine reacted readily with sodium hydroxide in refluxing ethanol to form the divinyldiketopiperazine (II). When the chloro compound was present in slight excess the reaction mixture became neutral within twenty to thirty minutes. Although some of the experiments referred to above were carried out after the properties of the divinyl compound were known, the substance was definitely isolated as a product only from the reactions with the sodium salt of acetoxime. However, some of the impure reaction products, from which no unchanged dichlorodiketopiperazine could be recovered, did yield the hydrochloride of α-amino-γ-butyrolactone when subjected to hydrolysis with hydrochloric acid. Both the *bis*-chloroethyl- and divinyldiketopiperazines are converted to the aminolactone by this treatment. In one of the attempted reactions between the dichloro compound and potassium silver cyanide the product isolated was 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine. This substance also would yield the aminolactone hydrochloride on hydrolysis with hydrochloric acid.

Certain replacements of the halogen atoms in the dichlorodiketopiperazine were effected without difficulty. Piperidine and morpholine gave the corresponding *bis*-tertiary amines (IV and V). The sodium salt of benzylmercaptan reacted to give the *bis*-benzylthioldiketopiperazine (VI). Potassium thiocyanate reacted to give the *bis*-thiocyano derivative (VII) in low yield. Attempts to alkylate acetoacetic ester were unsuccessful.

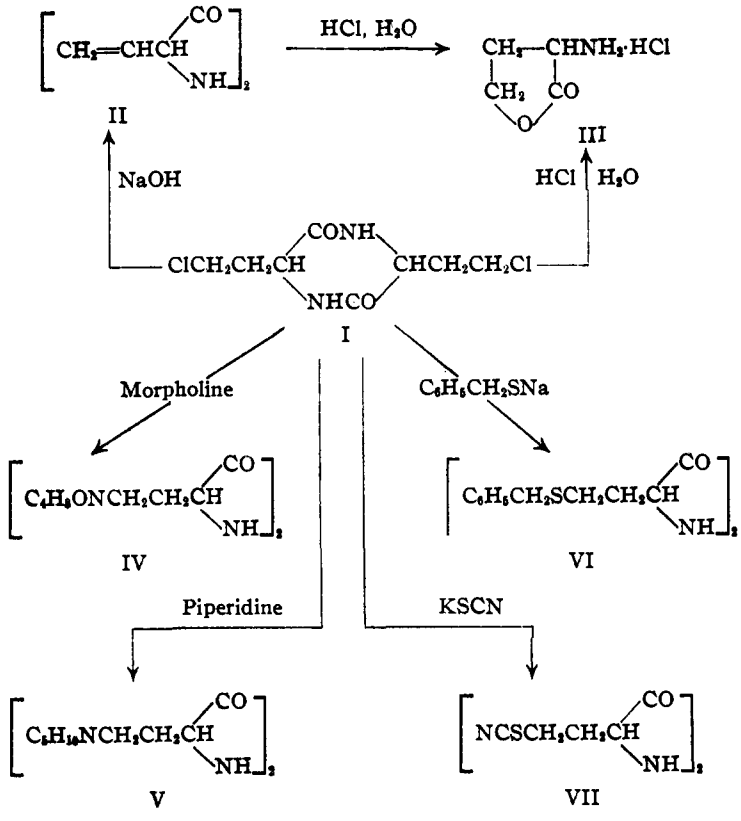
Experimental

3,6-*bis*-(β-N-Morpholinoethyl)-2,5-diketopiperazine (IV).—A mixture of 5 g. of the dichloride (I) and 15 cc. of morpholine was heated on the steam-bath to 85°. A clear dark solution resulted and the temperature rose to 125°. The mixture was allowed to cool and the crystals were separated by dilution of the liquid portion with ether

(1) Present address, General Aniline and Film Corp., Easton, Pa.

(2) (a) Snyder and Cannon, THIS JOURNAL, **66**, 511 (1944); (b) Snyder, Andreen, Cannon and Peters, *ibid.*, **64**, 2082 (1942).

(3) Kitagawa, *J. Agr. Chem. Soc. Jap.*, **12**, 871 (1936); *C. A.*, **31**, 1362 (1937).



and filtration. The solid was extracted with two 50-cc. portions of chloroform, and the residue from evaporation of this solvent was recrystallized from 95% ethanol. The yield of the product, m. p. 229–232° (cor.), was about 40%.

Anal. Calcd. for $C_{16}H_{28}N_4O_4$: N, 16.45. Found: N, 16.48.

3,6-*bis*-(β-N-Piperidinoethyl)-2,5-diketopiperazine (V) was prepared in much the same way from 2 g. of the dichloride and 5 g. of piperidine. Piperidine hydrochloride and piperidine were separated from the product by water extraction, and the substance was purified by recrystallization from 60% ethanol. It melted at 242–243° (cor.).

Anal. Calcd. for $C_{18}H_{32}N_4O_2$: C, 64.20; H, 9.59. Found: C, 64.26; H, 9.63.

3,6-*bis*-(β-Thiocyanoethyl)-2,5-diketopiperazine (VII).—A mixture of 10 g. of the dichloride (I), 10 g. of potassium thiocyanate and 100 cc. of acetone was shaken mechanically at room temperature for forty hours and then heated under reflux for twenty hours. The hot mixture was filtered and the residue from the evaporation of the filtrate was extracted with hot water and recrystallized from 33% acetic acid. The yield of product, m. p. 207–208° (cor.), was about 15%.

Anal. Calcd. for $C_{10}H_{12}N_4O_2S_2$: C, 42.24; H, 4.23. Found: C, 42.51; H, 4.45.

3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine (VI).—A mixture of 5 g. of the dichloride and 100 cc. of an absolute ethanol solution containing 3.25 g. of sodium ethoxide and 6 g. of benzyl mercaptan was heated under reflux for one hour. The hot solution was filtered and the filtrate was cooled. The crystals were separated and the mother liquor was used in a second hot extraction of the original residue. The process was repeated until no additional crop was obtained. The product so obtained melted at 173–174° (cor.) after recrystallization from ethanol (lit.,[4] 165°, 176°). The yield was about 50%.

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

Anal. Calcd. for $C_{22}H_{28}N_2O_2S_2$: C, 63.73; H, 6.33. Found: C, 63.65; H, 6.49.

3,6-Divinyl-2,5-diketopiperazine (II).—A mixture of 88 g. (0.37 mole) of the dichloride (I) and a cold solution of 26.8 g. (0.67 mole) of sodium hydroxide in 400 cc. of absolute ethanol was stirred mechanically and gradually heated to boiling over a period of about thirty minutes. After being heated under reflux for twenty minutes, the hot mixture was filtered and the filtrate was distilled to dryness under diminished pressure. The yellow crystalline residue was dissolved in 100 cc. of hot chloroform and the solution was filtered. Dilution with 100 cc. of hot carbon tetrachloride and cooling caused crystallization. The solid was collected and washed with a mixture of chloroform and carbon tetrachloride (volume ratio, 1:2), and then with a mixture of ethanol and ether (volume ratio, 1:3). Evaporation of the filtrate and washings gave an additional crop which was treated in the same way. For complete removal of the solvents it was necessary to dry the product under a pressure of 2 mm. or less. The yield of pure, colorless 3,6-divinyl-2,5-diketopiperazine was 38 g. (62%). In ordinary melting point determinations the material darkened slowly and decomposed at temperatures above 240°; however, it melted at 192.5° (cor.) to a clear liquid when the sample tube was immersed in a bath at this temperature. The yields were inferior when other ratios of reactants were used or when sodium ethoxide was substituted for the hydroxide.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.06. Found: C, 58.07; H, 6.24.

Hydrochloride of α-Amino-γ-butyrolactone (III).—A solution of 4 g. of the divinyldiketopiperazine in 30 cc. of a mixture of equal volumes of concentrated hydrochloric acid and water was heated on the steam cone for eight hours. The solution was concentrated under diminished pressure and the sirupy residue was dissolved in 50 cc. of water. The resulting solution was concentrated to a colorless crystalline residue. This was recrystallized from 95% ethanol. The lactone hydrochloride weighed 3.9 g. (59%) and melted at 199–200° (cor.) (lit.,[5] 198–200°).

Anal. Calcd. for $C_4H_8ClNO_2$: C, 34.92; H, 5.86. Found: C, 35.15; H, 6.08.

The same product was obtained when the dichlorodiketopiperazine was refluxed for two and one-half hours with 15 volumes of concentrated hydrochloric acid. The reaction mixture was diluted with water and worked up as above, to give a product of the same analysis and melting point.

Attempted Preparation of 3,6-*bis*-(β-Iodoethyl)-2,5-diketopiperazine.—Reaction occurred when the dichlorodiketopiperazine was refluxed with an acetone solution containing a slight excess of sodium iodide. The crude iodide decomposed at about 240°. A solvent for recrystallization was not found, and the pure substance was not isolated. A sample recrystallized from methylcellosolve (with apparent decomposition in the hot solvent) was free of inorganic materials and had a carbon content of 26.85% (calcd. for the diiodide, 22.75; for I, 40.0%).

Attempted Reactions of the Dichlorodiketopiperazine (I) with Inorganic Cyanides, with Derivatives of Hydroxylamine and with the Sodium Derivative of Acetoacetic Ester.—Numerous experiments with each reagent were carried out, usually with both the dichloride and the crude diiodide. The divinyldiketopiperazine (II) was definitely

(5) Feofilaktov and Onishchenko, *J. Gen. Chem.* (U. S. S. R.), **9**, 304, 314 (1939); *C. A.*, **34**, 378 (1940).

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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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).