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The Reaction of α,β-Dibromo Acid Esters with Benzylamine

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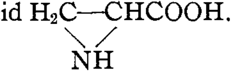
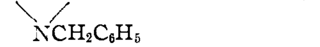
Methyl α,β-dibromopropionate and methyl α,β-dibromobutyrate react with benzylamine in a manner similar to that of α,β-dibromo ketones. Based upon this analogy, and upon chemical reactions, molar refraction and infrared spectra, the reaction products obtained are formulated as N-benzylethyleniminecarboxylic acid esters.

Ethyleniminecarboxylic acids (aziridinecarboxylic acids) have not as yet been described in the literature. These acids are isomeric with dehydro amino acids which have been extensively studied in connection with their interest for protein chemistry.[1] Theoretically, ethyleniminecarboxylic acids can be constructed by elimination of one molecule of water from β-hydroxyamino acids. Serine, for instance, would be the parent substance of the simplest cycloimino acid 

An attempt was made to synthesize members of this class of compounds in order to obtain some information about their stability and reactivity. The basis for the method of synthesis employed in the present work is the preparation by Cromwell, *et al.*,[2] of the structurally related ethylenimine ketones by the reaction of primary amines with α,β-dibromo ketones.

Methyl α,β-dibromopropionate and butyrate, respectively, were treated with 3 moles of benzylamine. The reaction was expected to proceed according to the equation

$$RCHBrCHBrCOOCH_3 + 3C_6H_5CH_2NH_2 =$$

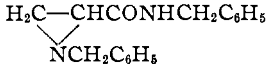


I R = H
II R = CH_3

From the reaction mixtures, colorless oils whose analysis corresponded to the structures I and II, respectively, were isolated by high-vacuum distillation in 50% yield.

The yield of product I could be raised to 75% when a mixture of one mole of benzylamine and two moles of triethylamine, instead of three moles of benzylamine, was allowed to react with one mole of methyl α,β-dibromopropionate. Tarry by-products, probably formed by polymerization of the three-membered ring compound, could not be vacuum distilled.

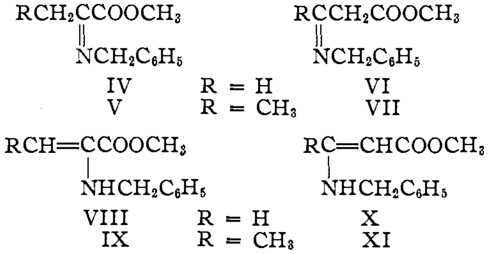
A solid by-product of the interaction between methyl α,β-dibromopropionate and benzylamine was formed in a yield of 0.5–1%. It has a melting point of 252–254°, and its empirical formula agrees with the structure



III

It is evident, from the isolation of this compound, that the reaction of the ester with benzylamine proceeds to a small extent with alkylamide formation.

The ring structures I, II and III were assigned to the products obtained because of their formation from α,β-dibromo esters and benzylamine, which is analogous to the formation of ethylenimine ketones, observed by Cromwell.[2] The formulations as ring structures are confirmed by the molar refractions found. These were identical with the values calculated for the ethylenimine derivatives I and II, and different from those calculated for the other non-cyclic isomeric structures IV to XI. Particularly, the Schiff bases IV through VII had to be considered as possibly formed by rearrangement of I and II.



$$\underset{\textstyle NCH_2C_6H_5}{RCH_2\overset{}{C}COOCH_3} \qquad \underset{\textstyle NCH_2C_6H_5}{R\overset{}{C}CH_2COOCH_3}$$

IV R = H VI
V R = CH_3 VII

$$\underset{\textstyle NHCH_2C_6H_5}{RCH{=}CCOOCH_3} \qquad \underset{\textstyle NHCH_2C_6H_5}{RC{=}CHCOOCH_3}$$

VIII R = H X
IX R = CH_3 XI

The ethyl ester of V has been described in Beilstein as having a melting point of 79–80°. The methyl ester V probably melts some degrees higher. If an appreciable amount of it were present in the reaction product derived from the methyl α,β-dibromobutyrate it would have been expected to crystallize; however, no crystals were obtained when the reaction product was permitted to stand at −20° over a long period of time.

To obtain more proof for the proposed structures, the infrared absorption spectra of these compounds were compared with those of ethylenimine and 1-benzyl-2-methylethylenimine. The absence of absorption bands characteristic for N–H stretching (2.8–3.2 μ) and C=C and C=N (5.9–6.3 μ) in the spectra of the isolated compounds show that structures of the types IV, V, VI, VII, VIII, IX, X and XI are not present.

The infrared spectra of ethylenimine and substituted ethylenimines have been studied recently.[3,4] Kissman and Tarbell[4] have stated that they provisionally regard a strong band at 1089 $cm.^{-1}$ (9.2 μ) as a characteristic of the ethylenimine ring. 1-Benzyl-2-methylethylenimine (XII) which we prepared by adaptation of the method of Wenker[5] shows a band at 9.1 μ. The compound derived from methyl α,β-dibromopropionate displays a strong band at 9.2 μ, which is in accordance with

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[1] J. P. Greenstein, *Advances in Enzymology*, **8**, 117 (1948).

[2] N. H. Cromwell, *et al.*, THIS JOURNAL, (a) **65**, 312 (1943); (b) **67**, 2235 (1945); (c) **69**, 258 (1947); (d) **71**, 708, 711 (1949); (e) **73**, 1044, 2803, 5929 (1951).

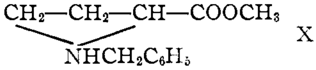
[3] H. T. Hoffman, Jr., *et al.*, *ibid.*, **73**, 3028 (1951).

[4] H. M. Kissman and D. S. Tarbell, *ibid.*, **74**, 4317 (1952).

[5] J. Wenker, *ibid.*, **57**, 2328 (1935).

the assigned structure I. However, the spectrum of the compound derived from methyl dibromobutyrate does not produce this band. The infrared spectra obtained by Cromwell, *et al.*,[2e] of *cis* and *trans* forms of ethylenimine ketones show a strong band at 9.2 μ for the *cis*-form only. This suggests that our compound II, lacking the 9.2 μ band, might be present in the *trans* form.

An absorption band near 7.2 μ, which might be attributed to C–CH_3 deformation, was present in the spectrum of XII and of the compound with the proposed structure II. However, the presence of a similar band in the spectrum of compound I makes such an assignment dubious. In addition to structure II, an isomeric 4-membered ring structure XIII, without a C–CH_3 group, is conceivably an alternate formulation for the reaction product of methyl α,β-dibromobutyrate and benzylamine

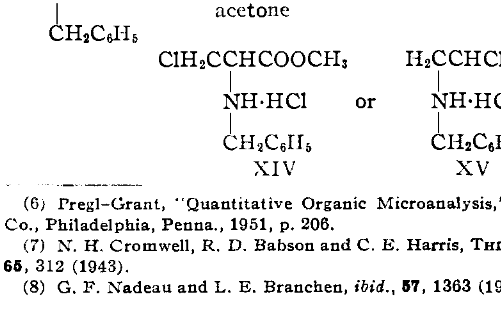

XIII

The molar refraction does not permit distinction between these two possibilities. Therefore we tried to obtain proof for the presence or absence of a methyl group attached to carbon by application of the method of R. Kuhn and H. Roth.[6] The reaction product obtained from methyl dibromobutyrate upon chromic acid oxidation yielded one mole of volatile acid (CH_3–COOH) which seems to confirm formula II.

I and II reacted very slowly with permanganate and with bromine in chloroform. 1-Benzyl-2-phenyl-3-benzoylethylenimine[7] was prepared for comparison and found to be very similar in its reactivity toward the above mentioned reagents. III does not decolorize bromine in chloroform solution and reacts slowly with permanganate.

I and II, as well as the 1-benzyl-2-phenyl-3-benzoylethylenimine ketone of Cromwell, are not alkaline to litmus in dilute alcohol. This behavior would be expected for structures like IV and VII but did not seem to be compatible with the assumed cyclic formulations. However, the basic character of I could be detected by titration with perchloric acid in glacial acetic acid, according to the method of Nadeau and Branchen.[8] One mole of $HClO_4$ was neutralized by one mole of I.

A strong argument in favor of a three-membered ring structure for I is the addition of hydrogen chloride in acetone. A crystalline hydrochloride was isolated, corresponding to one of the formulas XIV or XV.

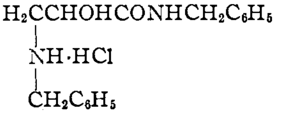


XIV XV

Formula XIV is preferred since the HCl addition product did not release iodine from an acidified acetone solution of potassium iodide, as α-chloroesters and α-chloroketones, but not β-chloroketones, do.[9]

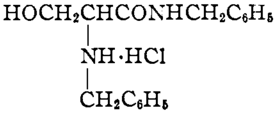
When I was boiled with 6 *N* hydrochloric acid, benzylamine hydrochloride could be isolated. The ethyleneimine ketones also react with aqueous HCl to split off the amine moiety, and in such cases 1,2-diketones[7] are formed from the rest of the molecule.

When the substance with the proposed formula III was heated with a mixture of 6 *N* hydrochloric acid and acetic acid, a product with a melting point of 207–209° was obtained. Analysis indicated this product to be the hydrochloride of a hydration product of III. A compound with the structure III might be expected to lead to such compounds as XVI and/or XVII.



$$\begin{array}{l} H_2CCHOHCONHCH_2C_6H_5\\ |\\ NH\cdot HCl\\ |\\ CH_2C_6H_5 \end{array}$$

XVI



$$\begin{array}{l} HOCH_2CHCONHCH_2C_6H_5\\ \quad\quad\quad\;\, |\\ \quad\quad\quad NH\cdot HCl\\ \quad\quad\quad\;\, |\\ \quad\quad\quad CH_2C_6H_5 \end{array}$$

XVII

Similar compounds in the ketone series, which were prepared from the water–alcohol hydrolysis of chloroamino ketones, have been reported by Cromwell and Wankel.[9]

By treatment of II with alkyl halides, the benzyl group is split out of the molecule. For instance dibenzylamine hydrobromide was obtained by reaction with benzyl bromide.

The benzyl group could not be detached from the nitrogen by shaking I in a hydrogen atmosphere with palladium–charcoal in alcohol or with platinum oxide in acetic acid. Treatment with sodium in toluene, followed by decomposition of the alkali metal with alcohol yielded crystalline substances which appears to be dimerization products. However their precise structure has not been investigated.

Experimental

1-Benzyl-2-carbomethoxyethylenimine (I).—A solution of 36.9 g. (0.15 mole) of methyl α,β-dibromopropionate in 100 ml. of dry benzene was cooled to 5° in a round-bottom flask equipped with a reflux condenser. A mixture of 16.1 g. (0.15 mole) of benzylamine and 30.1 g. of triethylamine (0.30 mole) in 150 ml. of dry benzene was added in several portions. A precipitate of triethylamine hydrobromide formed immediately with evolution of heat. After the contents of the flask had refluxed for 3 hr., the triethylamine hydrobromide was removed by filtration. The filtrate was washed with water and dried over sodium sulfate.

The solvent was removed from the filtrate under reduced pressure and the oil remaining was distilled in a high vacuum. Upon redistillation, the main fraction, boiling at 96–98° (0.2 mm.), yielded 20.8 g. or 74% of pure product.

A dilute alcoholic solution of this product was slightly acid to litmus. No picrate could be obtained. The substance is stable when protected from light; molar refraction found, 52.81; calcd., 52.77, on the basis of that of N-methylethylenimine[11]; molar refractions, calculated for formula IV or VI 54.05, for formula VIII and X 54.33.

Anal. Calcd. for $C_{11}H_{13}O_2N$ (191.2): C, 69.1; H, 6.85; N, 7.0; equiv. wt., 191.2. Found: C, 69.2; H, 6.8; N, 7.0; equiv. wt.,[10] 181; $n^{25}D$ 1.5238; d^{25} 1.1074.

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(6) Pregl–Grant, "Quantitative Organic Microanalysis," Blakiston Co., Philadelphia, Penna., 1951, p. 206.

(7) N. H. Cromwell, R. D. Babson and C. E. Harris, THIS JOURNAL, **65**, 312 (1943).

(8) G. F. Nadeau and L. E. Branchen, *ibid.*, **57**, 1363 (1935).

(9) N. H. Cromwell and R. A. Wankel, *ibid.*, **70**, 1321 (1948); **71**, 711 (1949).

(10) Titration with 0.1 *N* perchloric acid in glacial acetic acid, according to the method of Nadeau and Branchen.[8]

(11) W. Marckwald and O. Frobenius, *Ber.*, **34**, 3552 (1901).

Bromination.—A 0.4934-g. portion (2.6×10^{-3} mole) of substance I, dissolved in 10 ml. of chloroform, was titrated with a solution of bromine in chloroform (0.0312 g./ml.). After 2 ml. of the chloroform solution had been added there was no more immediate decolorization of bromine. However, the solution did decolorize additional quantities of bromine after standing for several minutes.

A total amount of 14 ml. of bromine solution was used. To reach the end-point of the titration, the theoretical amount calculated for two bromine atoms per molecule of I is 13.4 ml.

Attempted Hydrogenation.—Five and one-half grams of substance I dissolved in 100 ml. of abs. alcohol and 2 ml. of glacial acetic acid were shaken at room temperature in a hydrogen atmosphere at a pressure of 60 lb./sq. inch in the presence of 200 mg. of platinum oxide. The pressure dropped 2.5 lb. in a period of 2 hr. Two ml. of a basic oil was isolated, which distilled at 91–93° (0.25 mm.), n^{29}D 1.5117.

Anal. Calcd. for $C_{11}H_{15}O_2N$ (193.2): C, 68.4; H, 7.8; N, 7.25. Found: C, 68.5; H, 7.1; N, 7.0.

The product according to the low hydrogen value probably was only partially hydrogenated. After standing for several hours a small amount of crystals deposited from the oil. After washing with petroleum ether and ether they melt at 88–90°. There was not enough material for analysis.

HCl Addition in Acetone.—Two grams of 1-benzyl-2-carbomethoxyethylenimine (I) was dissolved in 10 ml. of dry acetone. An excess of HCl in absolute ether was added with efficient cooling. A precipitate formed immediately. The reaction mixture was kept in the refrigerator overnight. The precipitate was isolated by filtration and washed with absolute ether. The material was recrystallized from a mixture of absolute alcohol and absolute ether until a constant melting point of 138–140° was obtained (formula XIV or XV).

Anal. Calcd. for $C_{11}H_{15}NO_2Cl_2$ (264.1): C, 50.0; H, 5.7; N, 5.3; ionic Cl, 13.5. Found: C, 50.1; H, 5.8; N, 5.3; ionic Cl, 13.4.

Reaction with Aqueous HCl.—Two grams of N-benzyl-2-carbomethoxyethylenimine I was refluxed for 2 hr. with 16 ml. of 6 *N* HCl. The excess HCl was evaporated and the resulting oil was dissolved in absolute alcohol and precipitated with absolute ether. The product, after repeated recrystallizations from a mixture of absolute alcohol and absolute ether, had a m.p. of 256–257°. Benzylamine hydrochloride melts at 255–258° ("Beilstein," Vol. XII, p. 1013).

Anal. Calcd. for $C_7H_9N \cdot HCl$ (143.6): C, 58.5; H, 7.0; N, 9.75. Found: C, 57.7; H, 6.7; N, 9.7.

Benzylamide of 1-Benzyl-2-carboxyethylenimine (III).—Methyl α,β-dibromopropionate was permitted to react with 3 moles of benzylamine in benzene in a manner similar to the method given before in which benzylamine and triethylamine were used.

The dark brown residue remaining after the distillation of the crude 1-benzyl-2-carbomethoxyethylenimine was extracted with boiling benzene. The insoluble white crystalline material obtained was twice recrystallized by dissolving the substance in hot glacial acetic acid and precipitating with absolute ethanol, whereupon it melted at 252–254°. The substance, dried at 100°, was analyzed.

Anal. Calcd. for $C_{17}H_{18}N_2O$ (266.2): C, 76.7; H, 6.85; N, 10.5. Found: C, 76.2; H, 6.89; N, 10.2.

This substance when dissolved in chloroform, did not take up bromine in a chloroform solution. In glacial acetic acid it reduced potassium permanganate slowly.

Hydration Product of III.—Two-tenths gram of the benzyl amide of 1-benzyl-2-carboxyethylenimine (III) was refluxed with a mixture of 6 *N* hydrochloric acid (10 ml.) and glacial acetic acid (10 ml.). A white precipitate formed when the mixture was cooled. This material was recrystallized from a mixture of glacial acetic acid and absolute ether (m.p. 207–209°). The substance is insoluble in water and dilute nitric acid but soluble in concentrated nitric acid; on addition of a 1% $AgNO_3$ solution AgCl precipitates.

Anal. Calcd. for $C_{17}H_{20}N_2O_2HCl$ (320.7): C, 63.6; H, 6.6; N, 8.7; Cl, 11.1. Found: C, 63.9; H, 6.4; N, 8.7; Cl, 10.9.

1-Benzyl-2-methyl-3-carbomethoxyethylenimine (II).—The synthesis, using the methyl ester of α,β-dibromobutyric acid and benzylamine, was carried out with equimolar concentrations, and following the same procedure as described for I.

After redistillation, the main fraction was colorless and boiled at 91–93° (0.4 mm.). The yield was 50%, based on the methyl α,β-dibromobutyrate. Only a very small amount of bromine in chloroform was decolorized instantaneously by this compound. No picrate was obtained. A diluted alcoholic solution reacted almost neutral; molar refraction found, 57.37; calcd., 57.47, on the basis of a derivative of ethylenimine.[11]

Anal. Calcd. for $C_{12}H_{15}O_2N$ (205.2): C, 70.2; H, 7.3; N, 6.8; CH_3 (to C), 7.33. Found: C, 70.0; H, 7.0; N, 6.7; CH_3 (to C), 7.15; n^{25}D 1.5144; d^{25}_{4} 1.067.

Probably not all of the volatile acid found by oxidation of II with chromic acid and expressed as CH_3 (to C) is acetic acid, since compound I, which does not contain a C–CH_3 group, produced $^1/_3$ of a mole of volatile acid per mole of substance. Presumably some benzoic acid is formed by oxidation of the benzyl group in I and II. In contrast, N,N-dimethylbenzylamine under the same conditions gave only 0.08 mole of volatile acid per mole of the base.

Reaction with Benzyl Bromide.—Five grams (0.025 mole) of II and 4.3 g. (0.025 mole) of benzyl bromide were refluxed for 4 hr., during which time a precipitate formed. The isolated crystals were dissolved in hot acetone and a small amount of ether was added to the solution. The precipitated material, on recrystallization from absolute ethanol, melted at 257–258° (uncor.). For dibenzylamine hydrobromide melting points of 266 and 250° are recorded in the literature ("Beilstein," Vol. XII, p. 1035).

Anal. Calcd. for $C_{14}H_{14}N \cdot HBr$: N, 5.05; Br, 28.9. Found: N, 4.8; Br, 29.0.

N-Benzylisopropanolamine.—Propylene oxide (7.4 g.) was slowly added to a solution of 53.5 g. of benzylamine in 150 ml. of 95% ethanol. The reaction mixture was warmed for 2 hr. at 40–50° and then heated to the boiling point of the alcohol. The solution was cooled and kept at room temperature for 24 hours. The alcohol and excess benzylamine were distilled off under reduced pressure and the resulting oil was distilled at 93–95° (0.2 mm.), n^{27}D 1.5270.

Anal. Calcd. for $C_{10}H_{15}ON$ (165.1): C, 71.6; H, 9.2; N, 8.5. Found: C, 72.3; H, 9.2; N, 8.7.

N-Benzylisopropanolamine Sulfate.—A mixture of 14.5 g. of N-benzylisopropanolamine and 8.2 g. of H_2SO_4 (concd.) was heated to 250° and, after some decomposition occurred, was permitted to cool slowly. The solid product was ground with 95% alcohol in a mortar and the precipitate was filtered and washed several times with alcohol.

1-Benzyl-2-methylethylenimine (XII).—To 6 g. of N-benzylisopropanolamine sulfate, 2.5 g. of NaOH, dissolved in 18 g. of water, was added. The mixture was heated on a water-bath until an exothermic reaction started. Heat was withdrawn and, when the reaction subsided, was applied again. When the bath temperature reached 100° an oil separated. The temperature was maintained for 30 min. and the oil was removed with a pipet, dissolved in absolute ether and dried over KOH pellets. After the ether was removed under reduced pressure a light yellow oil remained which was distilled at 58° (2 mm.), n^{27}b 1.5113.

Anal. Calcd. for $C_{10}H_{13}N$ (147.1): C, 81.5; H, 8.9; N, 9.5; CH_3 (to C), 10.20. Found: C, 81.5; H, 8.9; N, 9.5; CH_3 (to C), 10.41.

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