[CONTRIBUTION NO. 331 FROM THE CHEMICAL DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

Synthesis of 2,2'-Bis-[5(4H)-oxazolones]

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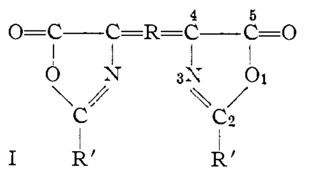
RECEIVED JUNE 16, 1954

Several members of a little studied class of azlactones, 2,2'-bis-[5(4H)-oxazolones], have been prepared. The compounds were obtained in good yields by ring-closure with acetic anhydride of N,N'-diacylbis-(α-amino acids). The latter were synthesized by Schotten–Baumann condensation of diacyl chlorides with α-amino acids.

Azlactones have received much study. Two articles[1,2] summarize the important chemistry of these compounds through 1949. Less well known are the bis-[5(4H)-oxazolones] or diazlactones. These compounds may be divided into four general classes which depend on the position of coupling (2 or 4) and the presence or absence of an exocyclic double bond at position 4.

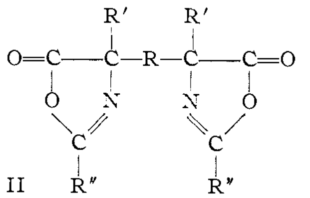
Type Structure

4,4'-bis-[5(4H)-oxazolone] (unsaturated)



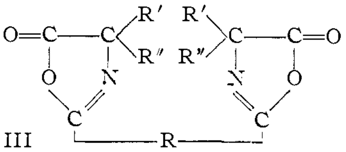
I

4,4'-bis-[5(4H)-oxazolone] (saturated)



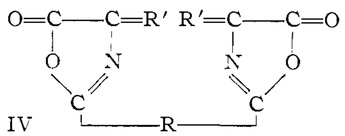
II

2,2'-bis-[5(4H)-oxazolone] (saturated)



III

2,2'-bis-[5(4H)-oxazolone] (unsaturated)



IV

Examples of Class I[3-5] have been synthesized by an erlenmeyer condensation of dialdehydes with hippuric acid in the presence of sodium acetate and acetic anhydride. Two examples of Class II have been synthesized[2] by the oxidative coupling of 2-phenyl-4-alkyl-5(4H)-oxazolones with mercuric acetate. Examples of Class IV have not been noted in the literature but should be obtainable by erlenmeyer condensations of aldehydes with N,N'-diacylbis-(glycines). A few examples of Class III compounds have been mentioned,[6,7] but the properties of this interesting class of substances have not been described. The compounds appeared particularly suitable as difunctional intermediates in polyamide syntheses.[8]

A general route to the Class III 2,2'-diazlactones has now been developed and is outlined below.

$$\mathrm{ClOC{-}R{-}COCl} + 2\mathrm{NH_2{-}CR'R''{-}COOH} \longrightarrow \qquad \text{(a)}$$

$$\underset{\mathrm{V}}{\mathrm{HOOC{-}CR'R''{-}NHCO{-}R{-}CONH{-}CR'R''{-}COOH}}$$

$$\mathrm{V} \xrightarrow{-2\,\mathrm{H_2O}} \mathrm{III} \qquad \text{(b)}$$

The specific synthesis conditions, properties and yields of the N,N'-diacylbis-(α-amino acids) (V) have been detailed in the Experimental Section, Part I. The specific conditions for the preparation of the diazlactone (III), yields and properties have been detailed in the Experimental Section, Part II. Additional information concerning both steps is given below.

N,N'-Diacylbis-(α-amino Acids).—Reaction (a) is an example of the Schotten-Baumann reaction. When *aliphatic* diacyl chlorides and α-amino acids were combined, the use of alkali hydroxides in the reaction was found to give better yields of products than did magnesium oxide, pyridine or alkali carbonates. In the reaction of *aromatic* diacyl chlorides with α-amino acids, the use of magnesium oxide afforded good yields of products. When an insoluble α-amino acid was used, such as DL-leucine, better yields of the N,N'-diacylbis-(α-amino acids) were realized by adding a trace of wetting agent to the aqueous alkali reaction mixture. This modification probably permitted better contact between the α-amino acid and diacyl chloride. Other techniques for combining diacyl chlorides with α-amino acids, such as reaction in anhydrous pyridine, ether or dioxane, usually gave low yields of the desired N,N'-diacylbis-(α-amino acid). Similarly, the reaction of diacyl chlorides with α-amino acid derivatives such as the α-amino acid ester or α-amino nitrile afforded low yields of the final N,N'-diacylbis-(α-amino acid), usually because of losses during the subsequent hydrolysis step.

2,2'-Bis-[5(4H)-oxazolones].—Reaction (b) was carried out in hot acetic anhydride. The concentration of acetic anhydride, temperature of reaction and time were critical when α-hydrogen atoms were present in the α-amino acid. Degradation occurred in these instances, presumably *via* the Dakin–West reaction,[9] if longer times, higher temperatures and smaller quantities of acetic anhydride were used.

To avoid long contact times, the N,N'-diacylbis-

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[1] "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, Chapter 5, p. 198–239.

[2] H. T. Clark, J. R. Johnson and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 730–848.

[3] M. T. Bogert and R. A. Gortner, THIS JOURNAL, **32**, 119 (1910).

[4] P. Ruggli and O. Schetty, *Helv. Chem. Acta*, **23**, 718 (1940).

[5] R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 3173 (1931).

[6] I. G. Patent Application 79,856-IVc/39c, dated November 11, 1941, microfilmed as P.B. report 19,922; issued as French Patent 887,530 (1943).

[7] B.I.O.S. Final Report No. 1472, Item No. 22.

[8] C. S. Cleaver and B. C. Pratt, THIS JOURNAL, **77**, 1541 (1955).

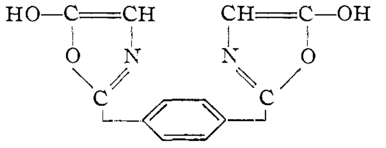
[9] H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 745 (1928).

(α-amino acid) was added to preheated acetic anhydride. Occasionally, the crystalline acetate salts of the diazlactones were obtained if insufficient acetic anhydride was used for ring-closure.

Other techniques of ring-closure were also examined and included the use of phosphorus tribromide,[2] thionyl chloride, trifluoroacetic anhydride, ketene, concentrated sulfuric acid,[10] and heating in an inert solvent. Although indications of ring-closure were obtained in most cases, acetic anhydride gave highest yields in all instances.

N,N′-Oxalylbis-(α-amino acids) failed to dehydrate to the corresponding diazlactones. Carter and Hinman[11] noted a similar behavior, in that N-carbobenzoxy and N-*p*-toluenesulfonyl derivatives of α-amino acids failed to undergo ring-closure with phosphorus tribromide. This suggests that only the usual N-acyl derivatives of α-amino acids may be dehydrated to azlactones.

2,2′-*p*-Phenylenebis-[5(4H)-oxazolone] was readily synthesized and exhibited remarkable stability for a compound containing four highly activated α-hydrogen atoms (the glycine residues). Such stability seemed more likely for the resonance-stabilized enolic form of the molecule VI.



VI

However, an infrared absorption spectrum showed the presence of bands at 5.5 and 6.0 μ (characteristic for lactone carbonyl and C=N bonds). It is therefore concluded that the molecule exists in the usual azlactone structure.

Experimental Section

I. Synthesis of N,N′-Diacylbis-(α-amino Acids). N,N′-Succinoylbis-(α-aminoisobutyric Acid).—Twenty grams of succinoyl chloride (0.129 mole) and 65 ml. of 4 *N* sodium hydroxide (0.26 mole) were added slowly and simultaneously to a solution of 28 g. of α-aminoisobutyric acid (0.32 mole) in 30 ml. of 4 *N* sodium hydroxide (0.12 mole) while keeping the temperature of the solution at 0°. The reaction mixture was then slowly acidified with concentrated hydrochloric acid to yield 14 g. (38% yield) of small white crystals, m.p. 270–272°, which were insoluble in hot water, ethyl alcohol and dioxane.

Anal. Calcd. for $C_{12}H_{20}N_2O_6$: N, 9.73; neut. equiv., 144. Found: N, 9.58; neut. equiv., 131.

N,N′-Adipoylbis-(α-aminoisobutyric Acid).—A solution of 50 g. of adipoyl chloride (0.27 mole) in 150 ml. of dioxane and a solution of 75 g. of potassium carbonate (0.54 mole) in 100 ml. of water were added as above to a solution of 65 g. of α-aminoisobutyric acid (0.63 mole) in 200 ml. of 3 *N* potassium hydroxide. Upon acidification, white crystals were obtained which were recrystallized from water to yield 42 g. (49% yield), m.p. 232–234°.

Anal. Calcd. for $C_{14}H_{24}N_2O_6$: N, 8.87; neut. equiv., 158. Found: N, 9.09; neut. equiv., 158.

N,N′-Adipoylbis-(1-aminocyclohexanecarboxylic Acid).—Twenty grams of adipoyl chloride (0.11 mole) and 55 ml. of 4 *N* sodium hydroxide were added as above to a solution of 33 g. of 1-aminocyclohexanecarboxylic acid in 30 ml. of 4 *N* sodium hydroxide. After acidification and slurrying the precipitate in boiling water, there was obtained 18 g. (42% yield) of white crystals, m.p. 209–212°.

Anal. Calcd. for $C_{20}H_{32}N_2O_6$: N, 7.08; neut. equiv., 198. Found: N, 7.18; neut. equiv., 185.

N,N′-Terephthaloylbis-(*dl*-alanine).—A solution of 20 g. of terephthaloyl chloride (0.098 mole) in 100 ml. of dioxane was added over a two-hour period to a well stirred, ice-cooled vessel containing 20 g. of *dl*-alanine (0.225 mole) and 10 g. of magnesium oxide (0.25 mole) in 150 ml. of water. After addition of the acid chloride was complete, stirring was continued at ice-bath temperature for 15 minutes, and finally at room temperature for 15 minutes. Concentrated hydrochloric acid was then added dropwise to the reaction vessel until a *p*H of 1.0–2.0 was obtained. The insoluble N,N′-terephthaloylbis-(*dl*-alanine) was then filtered from solution and, while still moist, was slurried in 500 ml. of boiling water. The product was then filtered, washed with water and dried overnight in a vacuum oven at 65°, yield 24 g. (79%) of crude N,N′-terephthaloylbis-(*dl*-alanine), m.p. 290–292°.

Anal. Calcd. for $C_{14}H_{16}N_2O_6$: N, 9.08. Found: N, 8.54.

N,N′-Terephthaloylbis-(glycine).—A solution of 50 g. of terephthaloyl chloride (0.246 mole) in 300 ml. of dioxane was treated as above with a solution of 50 g. of glycine (0.66 mole) and 35 g. of magnesium oxide (0.88 mole) in 200 ml. of water. Recrystallization of the product from water afforded 60 g. of white crystals (87% yield), m.p. 266–268°.

Anal. Calcd. for $C_{12}H_{12}N_2O_6$: N, 10.00; neut. equiv., 140. Found: N, 9.01; neut. equiv., 152.

N,N′-Terephthaloylbis-(α-aminoisobutyric Acid).—A solution of 20 g. of terephthaloyl chloride (0.098 mole) in 150 ml. of dioxane was treated as above with a solution of 25 g. of α-aminoisobutyric acid (0.24 mole) and 12 g. of magnesium oxide (0.3 mole) in 200 ml. of water. After slurrying the product in boiling water, there was obtained 28 g. of white crystals, m.p. 300° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O_6$: N, 8.34; neut. equiv., 168. Found: N, 7.57; neut. equiv., 164.

N,N′-Terephthaloylbis-(*dl*-leucine).—A solution of 198 g. of terephthaloyl chloride (0.98 mole) in 720 ml. of dioxane was treated as above with a solution of 300 g. of *dl*-leucine (2.3 mole), 180 g. of magnesium oxide (4.5 moles) and 1 g. of Aerosol OT in 2400 ml. of water. Recrystallization of the product from glacial acetic acid yielded 350 g. (90% yield) of white crystals, m.p. 259–261°.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: N, 7.14; neut. equiv., 196. Found: N, 7.17; neut. equiv., 193.

The melting points of the N,N′-diacylbis-(α-amino acids) were usually so high that some decomposition occurred before or during the melting process. Therefore, melting points were a poor criterion of purity. For melting points above 210°, small samples of the compounds were placed on a Maquenne block, and the temperature noted at which decomposition and/or melting occurred.

Several N,N′-diacylbis-(α-amino acids) were very insoluble and hence were difficult to recrystallize. In these instances, however, it was found sufficient for purification to slurry the compounds in an excess of boiling water to remove water-soluble impurities. The compounds thus treated gave good yields of the corresponding diazlactones when subsequently treated with acetic anhydride. Nitrogen analyses of the N,N′-diacylbis-(α-amino acids) were frequently more precise and reproducible by the Dumas method than by the Kjeldahl technique.

II. Synthesis of 2,2′-Bis-[5(4H)-oxazolones]. 2,2′-*p*-Phenylenebis-[4-methyl-5(4H)-oxazolone].—Acetic anhydride (400 ml., 4 moles) was heated on a hot plate to near boiling. Crude N,N′-terephthaloylbis-(*dl*-alanine) (50 g., 0.16 mole) was then added rapidly, and the reaction mixture was swirled vigorously and maintained near the boiling point for ten minutes. During this time, the N,N′-terephthaloylbis-(*dl*-alanine) rapidly dissolved to give a light yellow solution. The reaction mixture was then rapidly cooled by being swirled vigorously in an ice-bath. Small, almost colorless crystals slowly precipitated from solution over a one-hour period. The crystals were filtered, washed with several small portions of anhydrous diethyl ether, and recrystallized from hot benzene; yield 24 g. of small white crystals, m.p. 180–181°. Additional material was obtained by combining the acetic anhydride and benzene filtrates and concentrating them at 60° (20 mm.) on a steam-bath to a 100-ml. volume and cooling. The resulting material

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[10] J. L. O'Brien and C. Niemann, This Journal, **72**, 5348 (1951).

[11] H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

was recrystallized from benzene to give an additional 11.5 g. of colorless crystals. Total yield was 35.5 g. (80%).

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.8; H, 4.42; N, 10.30. Found: C, 61.93; H, 4.60; N, 10.37.

2,2'-*p*-Phenylenebis-[4-isobutyl-5(4H)-oxazolone].—Fifty grams of N,N'-terephthaloylbis-(*dl*-leucine) (0.128 mole) was treated with 250 ml. of acetic anhydride as above to yield 30 g. (65% yield) of large white crystalline flakes after recrystallization from benzene, m.p. 167°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.7; N, 7.87. Found: C, 67.6; H, 6.92; N, 8.00.

2,2'-*p*-Phenylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Fifty grams of N,N'-terephthaloylbis-(α-aminoisobutyric acid) (0.149 mole) was heated in 500 ml. of acetic anhydride at 120° for one-half hour. During this time, the solid failed to dissolve but became more crystalline in appearance. After recrystallization from chloroform, there was obtained 32 g. (72% yield) of small white crystals, m.p. 260° (sublimes).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: N, 9.34. Found: N, 9.12.

2,2'-*p*-Phenylenebis-[5(4H)-oxazolone].—Two grams of N,N'-terephthaloylbis-(glycine) (0.071 mole) was heated in 40 ml. of refluxing acetic anhydride for 15 minutes. The solid failed to dissolve but became more crystalline in appearance. After recrystallization from a large volume of dioxane, there was obtained essentially a quantitative yield of white crystals, m.p. 245° dec.

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.28; N, 11.49. Found: C, 58.9; H, 3.43; N, 11.53.

2,2'-Tetramethylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Ten grams of N,N'-adipoylbis-(α-aminoisobutyric acid) (0.0316 mole) was warmed with 25 ml. of acetic anhydride on a steam-bath for 20 minutes. After cooling and recrystallization from benzene, there was obtained 8 g. (82% yield) of crystals, m.p. 108–109°.

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.15; N, 10.00. Found: C, 59.29; H, 7.07; N, 10.04.

2,2'-Dimethylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Two grams of N,N'-succinoylbis-(α-aminoisobutyric acid) (0.07 mole) was treated as above with 20 ml. of acetic anhydride and the product recrystallized from a benzene–petroleum ether mixture to yield about 0.5 g. of white crystals (*ca.* 25% yield), m.p. 102–103°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.2; H, 6.35; N, 11.10. Found: C, 57.3; H, 6.40; N, 11.5.

2,2'-Tetramethylenebis-(spiro-[cyclohexane-1,4'-oxazol]-5'(4'H)-one).—Five grams of N,N'-adipoylbis-(1-aminocyclohexanecarboxylic acid) (0.013 mole) was treated as above with 20 ml. of acetic anhydride and the product recrystallized from a benzene–petroleum ether mixture to yield *ca.* 2.5 g. of white crystals (*ca.* 60% yield), m.p. 109–111°.

Anal. Calcd. for $C_{20}H_{28}N_2O_4$: C, 66.66; H, 7.78; N, 7.78. Found: C, 66.76; H, 7.88; N, 7.85.

Evidence was also obtained for the synthesis of 2,2'-tetramethylenebis-[4-isobutyl-5(4H)-oxazolone] and 2,2'-tetramethylenebis-[5(4H)-oxazolone]. These products were liquids which decomposed during distillation, and complete purification was not effected.

Acknowledgment.—The authors wish to thank Dr. W. A. Gregory of the Grasselli Chemicals Department for suggesting this route to diazlactones.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

A Novel Route to Certain 2-Pyrrolecarboxylic Esters and Nitriles[1,2]

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RECEIVED SEPTEMBER 7, 1954

Diethyl oximinomalonate undergoes reduction and condensation with certain β-diketones and a β-ketoaldehyde to give 2-pyrrolecarboxylic esters. Similarly, ethyl oximinocyanoacetate and certain β-diketones afford 2-pyrrolecarbonitriles. The method has been applied to the synthesis of five previously known pyrroles: 2-carbethoxy-3,5-dimethylpyrrole, 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole, 5-carbethoxy-2,4-dimethyl-3-pyrrolepropionic acid, 2-carbethoxy-3,4-dimethylpyrrole and 4-ethyl-3,5-dimethyl-2-pyrrolecarbonitrile. This synthetic approach constitutes the most direct route to four of these five pyrroles. A sixth and previously unreported pyrrole, 3,5-dimethyl-2-pyrrolecarbonitrile, also has been prepared by this method.

A little more than a decade ago Fischer and Fink,[3] while attempting a Knorr-type reductive condensation[4] of ethyl α-oximinoacetoacetate with the diethyl acetal of 3-oxobutyraldehyde, observed the unexpected formation of 2-carbethoxy-5-methylpyrrole. Thus it became apparent that in this instance a new type of pyrrole ring-synthesis involving the cleavage of the acetyl group of ethyl α-oximinoacetoacetate was occurring in preference to the anticipated Knorr condensation. Reinvestigation of the reductive condensation of ethyl α-oximinoacetoacetate with 2,4-pentanedione (II) by these same workers[3] revealed that in the case of this β-diketone the new condensation does in fact compete, though very unsuccessfully, with the Knorr cyclization. As has long been known, this reaction affords the Knorr product, 4-acetyl-3,5-dimethyl-2-carbethoxypyrrole, in good yield. From the mother liquor, however, Fischer and Fink[3] were able to isolate 2-carbethoxy-3,5-dimethylpyrrole (V), the product arising from the new-type condensation, in a yield amounting to a few tenths of 1%. A subsequent publication[5] by these investigators reports that two more β-ketoaldehydes have been found to undergo the new-type condensation, and Cookson[6] recently has elucidated a further example of a cyclization of this same general type.

In the interest of achieving a more direct synthetic route to certain 2-pyrrolecarboxylic esters which are important intermediates in the preparation of porphyrins and other polypyrryl compounds, it was decided to attempt a series of condensations closely related to those reported by Fischer and Fink,[3,5] but employing diethyl oximinomalonate (I) rather than ethyl α-oximinoacetoacetate. It was anticipated that the use of I by precluding the possibility of competing Knorr-type cyclizations would both widen the scope of the con-

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[1] Studies in the Pyrrole Series, XXVII. Paper XXVI, A. H. Corwin and K. W. Doak, THIS JOURNAL, **77**, 464 (1955).

[2] This work was carried out under a research grant from the National Science Foundation.

[3] H. Fischer and E. Fink, *Z. physiol. Chem.*, **280**, 123 (1944).

[4] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, pp. 3–5.

[5] H. Fischer and E. Fink, *Z. physiol. Chem.*, **283**, 152 (1948).

[6] G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).