analyzed by immersing a thermometer in the refluxing liquid, observing the b.p. and comparing with the previously determined b.p.–composition curve for mixtures of the two isomers.[4] Superheating was negligible compared with the difference in b.p. of the isomers (11.9°). The barometric correction was 0.04 deg./mm. for both compounds.

Typical results are shown in Table I.

(4) George L. Jones, Jr., Thesis, University of Virginia, 1950.

COBB CHEMICAL LABORATORY
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CHARLOTTESVILLE, VA. RECEIVED FEBRUARY 9, 1951

The Preparation of Certain *s*-Trithianes[1,2]

BY IRWIN B. DOUGLASS AND WILLIAM R. HYDRO

In the course of recent work in this Laboratory[3] it was desired to find a method for the preparation of 2,4,6-tribenzyl-*s*-trithiane. The ordinary methods yielded chiefly a gummy, ill-smelling product but the procedure outlined below proved to be highly satisfactory. Fractional crystallization of the crude product from acetone yielded the α- and β-forms which structural theory would lead one to expect.

When the same procedure was applied to the preparation of 2,4,6-triphenyl-2,4,6-trimethyl-*s*-trithiane, a good yield was obtained in a much shorter time than by the best previous method.[4]

Experimental

2,4,6-Tribenzyl-s-trithiane (Trithiophenylacetaldehyde), $(C_6H_5CH_2CHS)_3$.—Dry hydrogen chloride was passed into 400 ml. of absolute alcohol contained in a three-neck flask fitted with mechanical stirrer and maintained at 0° or lower until 262 g. had been adsorbed. The solution was then cooled to −10 to −12° and hydrogen sulfide was passed in for 30 minutes following which the flow of hydrogen sulfide was continued while 132 g. of a 50% solution of phenylacetaldehyde in alcohol was added dropwise over a two- to three-hour period. The temperature was kept below −10° during the entire operation. The increase in weight due to hydrogen sulfide was 19 g.

After the last of the phenylacetaldehyde had been added the slurry of crystals was stirred for 15 min. longer and was then filtered. The filtrate was placed in the ice-chest overnight and then separated from the crystals which had formed. Concentration of the mother liquor and cooling further increased the yield. The combined crystals, after washing with cold alcohol, yielded 70 g. (73%) of practically odorless product melting 105–140°.

Separation of α- and β-Forms.—Ten grams of the dry reaction product was dissolved in 50 ml. of acetone and filtered while hot. The solution was covered and set aside to crystallize slowly. After several hours about 20 ml. of fresh acetone was added to the felted mass of crystals and the mixture was stirred and warmed. When the fine needles had dissolved the acetone solution was decanted from a residue of less soluble prismatic crystals. Cooling of the acetone solution and repeated recrystallization of the fine needles which separated gave the pure α-form with m.p. 122–123° (cor.).

Anal. Calcd. for $C_{24}H_{24}S_3$: C, 70.5; H, 5.92; S, 23.5; mol. wt., 408.6. Found: C, 70.1; H, 6.10; S, 22.5; mol. wt., 386.

Repeated recrystallization of the prismatic crystals from acetone gave the pure β-form with m.p. 168–169° (cor.).

Anal. Calcd. for $C_{24}H_{24}S_3$: C, 70.5; H, 5.92; S, 23.5; mol. wt., 408.6. Found: C, 70.4; H, 5.96; S, 23.6; mol. wt., 438.

Several separations, as above, indicated that the crude reaction mixture contained 14–22% of the higher melting β-form.

2,4,6-Triphenyl-2,4,6-trimethyl-*s*-trithiane, $(C_6H_5CSCH_3)_3$, (Trithioacetophenone).—One hundred fifty ml. of absolute alcohol was saturated with 99 g. of hydrogen chloride at 0 to 5° as previously described. Hydrogen sulfide was passed into the mixture for 30 min., the temperature was lowered to −10 to −12° and a solution of 25 g. of acetophenone dissolved in an equal weight of alcohol was added dropwise over a 2–3-hour period as described above.

The solution first turned a deep purple color and later began to precipitate white crystals. The mixture was stirred 15 min. after adding the last acetophenone and then filtered. After standing overnight additional crystals formed and on concentration of the liquors the yield was further increased. After washing the crude product in alcohol and drying 22.8 g. (80%) of white material was obtained which melted at 118–121°. Recrystallization of a portion gave a pure product melting at 121–122° and at the same temperature when mixed with an authentic sample of trithioacetophenone.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MAINE
ORONO, MAINE RECEIVED FEBRUARY 26, 1951

Reactions of Ethylene Thiourea

BY NELSON R. EASTON, ALEX HLYNSKY AND HAROLD FOSTER

Very few S-substituted-2-imidazolidinethiones have been reported in the literature. The preparation of S-carboxymethyl-2-imidazolidinethione hydrochloride has been accomplished by the reaction of ethylene thiourea with chloroacetic acid[1] and S-carboethoxymethy-2-imidazolidinethione has been prepared by the action of ethyl chloroacetate on ethylene thiourea in the presence of sodium ethoxide.[2] The synthesis of S-dodecyl-2-imidazolidinethione has also been reported.[3]

We have prepared the S-benzyl, S-*p*-nitrobenzyl, S-*p*-chlorobenzyl and S-*o*-chlorobenzyl derivatives by condensing the appropriate halide with ethylene thiourea[4] and the treatment of the resulting salt with ammonium hydroxide. Due to its instability, however, the benzyl derivative could not be obtained in an analytically pure state. Table I gives the melting points and analyses.

TABLE I

S-2-IMIDAZOLIDINETHIONES

	M.p., °C.	Nitrogen, % Calcd.	Found
Benzyl-	68–70	14.57	14.0, 14.1
p-Nitrobenzyl-	158	17.70	17.70
o-Chlorobenzyl-	63–64	12.36	12.35, 12.25
p-Chlorobenzyl-	100–103	12.36	12.50

Hydrochlorides

				Yield, %
Benzyl-	173.4	12.25	12.32	82
p-Nitrobenzyl-	191	15.35	15.40	86
o-Chlorobenzyl-	214–215	10.63	10.54	97 crude
p-Chlorobenzyl-	172.5–175	10.63	10.67, 10.68	73

Experimental

Preparation of the S-Substituted-2-imidazolidinethione Hydrochlorides.—A mixture of 0.25 mole of ethylene thiourea and 0.25 mole of the halide in 90 ml. of ethanol was

(1) This note describes a portion of the work done on project NR 055 165 under contract N8onr77000 with the Office of Naval Research, United States Navy.

(2) Taken from a master's thesis presented by William R. Hydro.

(3) Douglass and Martin, *J. Org. Chem.*, **15**, 795 (1950).

(4) Reid, "A Study in the Chemistry of Thiones," Doctoral Thesis, Indiana University, Bloomington, Indiana, 1946.

(1) Johnson and Edens, THIS JOURNAL, **64**, 2706 (1942).

(2) Wilson, Baird, Burr, Munra and Stephen, *J. Roy. Tech. Coll. (Glasgow)*, **2**, no. 1, 56 (1929).

(3) Puetzen, U. S. Patent 2,156,193.

(4) Received through the kindness of Rohm and Haas Co., Philadelphia, Penna.

heated under reflux for one hour. At the end of this time the hot reaction mixture was filtered rapidly through a hot Buchner funnel. The filtrate on cooling deposited crystals of the desired hydrochloride. Completion of the precipitation was accomplished by adding ether. The product was recrystallized from ethanol.

Preparation of the S-Substituted-2-imidazolidinethiones.—A solution of 0.1 mole of the hydrochloride in 50 ml. of water was cooled in an ice-bath and treated with 35 ml. of a 25% solution of ammonium hydroxide. The precipitate which appeared immediately was collected on a Buchner funnel and was recrystallized from ethanol or better from a mixture of benzene and methylcyclohexane.

DEPARTMENT OF CHEMISTRY
LEHIGH UNIVERSITY
BETHLEHEM, PENNA. RECEIVED FEBRUARY 26, 1951

Optical Rotation of Peptides. I. Glycine and Alanine Dipeptides[1]

BY BERNARD F. ERLANGER AND ERWIN BRAND

The optical rotation of peptides may be considered an additive function of the contributions of the asymmetric carbon atoms of the constituent amino acid residues. It can be interpreted on the assumption that the contributions to the total rotation by an L- and by a corresponding D-amino acid residue are numerically the same, but opposite in sign.[2] As a first approach to this problem, a number of isomeric glycine and alanine dipeptides were synthesized and their optical rotation determined in the state NH_3^+, COO^- (in H_2O) and also in the state NH_3^+, COOH (in HCl). These dipeptides were first synthesized in the early years of this century by Emil Fischer[3] from α-halogen acid halides and about thirty years later by Bergmann[3] and collaborators from carbobenzoxy amino acid chlorides. We have used as starting materials the carbobenzoxy hydrazides of glycine and of alanine. These stable hydrazides are converted by the Bergmann technique[3] into their azides, which are coupled with amino acid ethyl or benzyl esters to yield carbobenzoxy dipeptide esters. The ethyl esters are either converted into carbobenzoxy dipeptide hydrazides or saponified to carbobenzoxy dipeptides, which are hydrogenated to the free dipeptides. The carbobenzoxy dipeptide benzyl esters are directly hydrogenated to dipeptides.

The specific rotation of six dipeptides, in H_2O and in 0.5 *N* HCl, is shown in Table II; the values in H_2O agree with those found by Emil Fischer[3] and Max Bergmann.[3] More detailed data on the specific rotation of these peptides and on the *residue rotations*[2] of alanine residues will be reported subsequently.

Experimental

Starting Materials. Carbobenzoxyamino Acid Hydrazides.—The preparation and properties of the glycine and alanine derivatives are reported, since these compounds have not been previously described.[4] The procedures used follow in a general way those given by Bergmann[5] for the corresponding lysine derivative. The carbobenzoxy hydrazides of glycine and of alanine are stable compounds.

1. **Carbobenzoxyglycine Hydrazide.**—Into a 500-cc. 3-neck flask equipped with a stirrer and immersed in an ice–salt-bath are placed 13.0 g. (0.1 mole) glycine ethyl ester hydrochloride, 75 cc. of water and 180 cc. of $CHCl_3$. With vigorous stirring, 5.2 g. (0.13 mole) of MgO is added in three portions over a period of 30 minutes, while 22.2 g. (0.13 mole) of carbobenzoxy chloride is dropped in. Stirring is continued for another 30 minutes, when 5 cc. of pyridine is added, followed in five minutes by acidification (congo) with 5 *N* HCl. The $CHCl_3$ layer is separated, washed first with 0.5 *N* HCl, then successively with water, 5% $NaHCO_3$, and water, dried over Na_2SO_4 and taken down *in vacuo*. The resulting oil is repeatedly (three times) treated with 50 cc. of anhydrous ethanol, which each time is distilled off *in vacuo*. The oil (carbobenzoxyglycine ethyl ester) is then dissolved in 100 cc. of anhydrous ethanol, 7 g. of hydrazine hydrate added, and the mixture allowed to stand overnight at room temperature. Most of the hydrazide crystallizes; it is filtered off, washed with cold anhydrous ethanol and dried; yield 15.2 g., m.p. 115°. Another 3.5 g. is recovered from the mother liquor; total yield 84%, based on glycine ethyl ester hydrochloride. For analysis the product is recrystallized from ethyl acetate; m.p. 115.5° (all m.p. cor.).

Anal. Calcd. for $C_{10}H_{13}O_3N_3$ (223.2): N, 18.8. Found: N, 18.9.

2. **Carbobenzoxy-L-alanine Hydrazide.**—The specific rotation $[\alpha]^{25}D$ of the alanine used in these and other syntheses varied from +14.5 to +14.7° for the L-isomer and from −14.4 to −14.7° for the D-isomer (2% in 6 *N* HCl). Most of the L- and D-alanine was prepared from acetyl-DL-alanine by Greenstein's enzymic resolution method[6] which made possible the preparation of relatively large batches.[7]

The carbobenzoxy hydrazide of L-alanine is prepared by the procedure described above for the corresponding glycine derivative and recrystallized from ethyl acetate. Total yield from 15.4 g. (0.1 mole) of L-alanine ethyl ester hydrochloride equals 18.7 g. (79%); m.p. 138.5°; $[\alpha]^{25}D$ −28.6° (2% in 0.5 *N* HCl).

Anal. Calcd. for $C_{11}H_{15}O_3N_3$ (237.3): N, 17.7. Found: N, 17.8.

3. **Carbobenzoxy-D-alanine Hydrazide.**—This compound is obtained from D-alanine ethyl ester hydrochloride by the same procedure and in the same yield as the corresponding L-derivative; m.p. 138.5°; $[\alpha]^{25}D$ +28.7° (2% in 0.5 *N* HCl).

Anal. Found: N, 17.7.

Amino Acid Benzyl Esters.—The use of amino acid benzyl esters[8] simplifies the "Carbobenzoxy" method for peptide synthesis, which involves the coupling of carbobenzoxy chlorides or azides with free amino acid esters. As is well known, the benzyl esters save one step in this synthesis, because the benzyl group is removed simultaneously with the N-carbobenzoxy groups by catalytic hydrogenation to yield free peptides, whereas other ester groups have to be saponified before hydrogenation. Moreover, the saponification of methyl and ethyl esters of carbobenzoxy peptides becomes increasingly difficult as the peptide chain is lengthened and the number of N-carbobenzoxy groups increased.[9]

The benzyl ester hydrochlorides of hydroxyproline,[10] of glycine and of cysteine (hydro-iodide[11]) have been well characterized. The γ-benzyl esters of both L- and D-glutamic acid were recently synthesized by Hanby, *et al.*,[12] by esterification of the amino acid with benzyl alcohol in the presence of constant-boiling hydriodic acid. Hydroxyproline[10] can be esterified with benzyl alcohol and dry HCl, but

(1) This report is part of a dissertation submitted by Bernard F. Erlanger in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A.C.S., Chicago, Ill., September, 1950.

(2) Brand and Erlanger, THIS JOURNAL, **72**, 3314 (1950).

(3) For references *cf.* Fruton, *Adv. Prot. Chem.*, **5**, 1 (1949).

(4) Since this paper went to press, Simmons, Harris and Fruton (*J. Biol. Chem.*, **188**, 251 (1951)) have reported the synthesis of carbobenzoxyglycinhydrazide (m.p. 116–117°) by a somewhat different procedure.

(5) Bergmann, Zervas and Greenstein, *Ber.*, **65**, 1692 (1932).

(6) Fodor, Price and Greenstein, *J. Biol. Chem.*, **178**, 503 (1949).

(7) For some enzyme preparations we are indebted to Armour and Company. We gratefully acknowledge the coöperation of Dr. Greenstein, who gave us part of the alanine and helped B.F.E. prepare the rest in the National Cancer Institute laboratories.

(8) Bergmann, Zervas and Ross, *J. Biol. Chem.*, **111**, 245 (1935), footnote 1.

(9) Braxd and Erlanger, unpublished experiments.

(10) Smith and Bergmann, *J. Biol. Chem.*, **153**, 627 (1947); they did not obtain proline benzyl ester in analytically pure form.

(11) Harington and Mead, *Biochem. J.*, **30**, 1598 (1936).

(12) Hanby, Waley and Watson, *J. Chem. Soc.*, 3239 (1950).