riod of 15 minutes; stirring is continued for an additional 20 minutes. From the undissolved excess PCl_5 the solution is filtered into a still and the ether removed *in vacuo* (bath temperature maintained throughout at 60°). In order to remove $POCl_3$, 75 cc. of ethyl acetate is added and then distilled off. The ethyl acetate treatment is repeated four times. The last portion of ethyl acetate is distilled off *in vacuo* until about 40 cc. of distillate has been collected. The residue is cooled in an ice-bath and treated with 25 cc. of petroleum ether. After one hour the supernatant is removed by suction and the residue (mostly dense crystals of glycine carbamino anhydride[17]) washed twice with 25 cc. of petroleum ether. The anhydride is then transferred with 30 cc. of benzyl alcohol to a 500-cc. flask containing 200 cc. of ether, previously saturated with HCl at 0°. On warming to 25° while stirring magnetically, CO_2 evolution begins and the benzyl ester hydrochloride starts to crystallize as long needles, while the anhydride dissolves. After continuing magnetic stirring overnight at 25°, the hydrochloride is filtered off without special precautions and washed with ether (9.5 g., m.p. 137–138°). Recrystallization from anhydrous methanol–ether yields 8.8 g. (70% based on carbobenzoxyglycine); m.p. 140°.

Anal. Calcd. for $C_9H_{11}O_2N\cdot HCl$ (201.7): N, 7.0; HCl, 18.1. Found: N, 7.0; HCl, 18.1.

5. **L-Alanine Benzyl Ester Hydrochloride.**—Alanine carbamino anhydride[17] is obtained more easily than the corresponding glycine derivative. Following the method of Hunt and du Vigneaud[18] with minor changes (stirring, etc.), 22 g. (0.1 mole) of carbobenzoxy-L-alanine[16] is treated with 25 g. (0.12 mole) of PCl_5. The carbobenzoxy-L-alanyl chloride is converted, at a bath temperature of 40–45°, into the well-crystallizing anhydride. After washing with petroleum ether, the anhydride is dissolved in 50 cc. of benzyl alcohol and added to 500 cc. of ether previously saturated with HCl at 0°. After standing at 25° overnight, 16 g. (m.p. 137–138°) of benzyl ester hydrochloride is obtained, which yields 15 g. on recrystallization from anhydrous methanol–ether (70% based on carbobenzoxyalanine); m.p. 140°; $[\alpha]^{25}D$ −10.9° (2% in 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}O_2N\cdot HCl$ (215.7): N, 6.5; NH_2-N, 6.5; HCl, 16.9. Found: N, 6.5; NH_2-N, 6.5; HCl, 17.0.

6. **D-Alanine Benzyl Ester Hydrochloride.**—This compound is obtained from carbobenzoxy-D-alanine with the same procedure and yield as the L-isomer; m.p. 139–140°; $[\alpha]^{25}D$ +10.5° (2% in 0.1 *N* HCl).

Anal. Found: N, 6.6; NH_2-N, 6.5; HCl, 16.9.

Carbobenzoxydipeptide Esters (Compounds 7–16).—In a mixture of 60 cc. of glacial acetic acid, 24 cc. of 5 *N* HCl and 250 cc. of water, 0.05 mole of a carbobenzoxy amino acid hydrazide is dissolved and cooled to −5°. On adding in one portion a cold, concentrated, aqueous solution of sodium nitrite (0.053 mole), the azide precipitates as a sirup[19] and is taken up in 300 cc. of cold ether. The ether layer is kept cold while washing successively with water, 3% $NaHCO_3$, and again with water. After brief drying over sodium sulfate, the azide solution is added in one portion to a dry, cold, ethereal solution of an amino acid ester (previously prepared from 0.07 mole of the amino acid ester hydrochloride). After standing for about 20 hours at room temperature, the reaction mixture is washed successively with 0.5 *N* HCl, water, 3% $NaHCO_3$ and water; after drying over sodium sulfate and removing the ether *in vacuo*, crystalline products are obtained, which are recrystallized from ethyl acetate–petroleum ether; yield of pure compounds is 65–70% based on the hydrazide used.

Carbobenzoxy-dipeptide Hydrazides (Compounds 17–20).—For the preparation of a hydrazide, 0.05 mole of carbobenzoxy dipeptide ethyl ester is dissolved in 80–100 cc. of hot, absolute alcohol, 0.10–0.13 mole of hydrazine hydrate added, and the solution refluxed for one hour. After standing for about 20 hours at room temperature, most of the hydrazide has crystallized; only small amounts can be obtained from the mother liquor after cooling and addition of ether. Recrystallization from ethyl alcohol–ether yields 80–90% of pure carbobenzoxy dipeptide hydrazide.

Carbobenzoxy Dipeptides (Compounds 21–24).—The carbobenzoxy dipeptide ethyl esters are saponified in acetone–*N* NaOH (about 15–20% excess of NaOH) for about ½ hour. After addition of a slight excess of *N* HCl, the mixture is concentrated *in vacuo*. Compounds 21, 22 and 24 are recrystallized from ethyl acetate–petroleum ether, 23 from hot water. The yield of pure compounds is somewhat variable, 65–85%. The neutralization equivalent (neut. equiv.) is obtained by titration in alcohol.[20]

Dipeptides (Compounds 25–30).—Hydrogenolysis of of 0.02 mole of a carbobenzoxy dipeptide is carried out in about 100 cc. of methanol containing a few drops of acetic acid with palladium black as catalyst in a rapid stream of hydrogen. About 6 cc. of palladium black suspension (0.5 g. Pd) in the appropriate solvent is used per 0.01 mole of the group to be reduced (carbobenzoxy or benzyl). Water is added, if necessary, to keep the peptide in solution during hydrogenation. After about two hours the hydrogenation of carbobenzoxy dipeptides is complete, as indicated by cessation of CO_2 evolution. Carbobenzoxy dipeptide benzyl esters are then hydrogenated for an additional two hours. Concentration *in vacuo* of the filtrate and washings results in crystallization of the peptides, which are recrystallized from water-alcohol. The yield of pure peptides varies from 70 to 85%; it is larger in the case of the benzyl esters, where the yield may be as high as 95%.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 122–260).

(17) The carbamino anhydrides (oxazolid-2,5-diones) of glycine and alanine were recently synthesized directly from the amino acids by treatment with carbonyl chloride by Farthing (*J. Chem. Soc.*, 3213 (1950)). This author, incidentally, states that preparation of benzyl chloroformate according to Bergmann,[16] using a toluene solution of carbonyl chloride, gave colored crude products. Such reports from the United Kingdom have come to our attention previously. However, investigators in this country have no trouble in obtaining colorless pure benzyl chloroformate by Bergmann's method. The reason for this discrepancy remains unexplained.

(18) Hunt and du Vigneaud, *J. Biol. Chem.*, **124**, 699 (1938).

(19) Carbobenzoxyglycine azide is crystalline.

(20) Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April 1950, Abstracts p. 56-C.

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Optical Rotation of Peptides. II. Glycine and Alanine Tripeptides[1]

BY ERWIN BRAND, BERNARD F. ERLANGER, HOWARD SACHS AND JEROME POLATNICK

The first paper in this series dealt with the synthesis and specific rotation of dipeptides of alanine.[2] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of nine glycine and alanine tripeptides are presented. More detailed data on their specific rotations and on the *residue rotations*[3] of alanine residues will be reported subsequently.

Experimental

The synthesis and properties of most of the starting materials have been previously described[3]: L- and D-alanine, benzyl esters of glycine and of L- and D-alanine (ref. 2, Compounds 4–6), four isomeric carbobenzoxy-alanyl-alanine hydrazides (ref. 2, Compounds 17–20). Carbobenzoxy-glycyl-L-alanine hydrazide and its D-isomer were prepared according to Bergmann.[4]

Carbobenzoxy Tripeptide Esters (Compounds 1–13).—The coupling of the azides of carbobenzoxy dipeptide hydrazides (0.025 mole) with amino acid esters (0.0375 mole) is carried out as described in detail for the synthesis of dipeptide esters[2] with the following changes: only 0.025 mole of a carbobenzoxy dipeptide hydrazide is dissolved in the

(1) Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A. C. S., Chicago, Ill., September, 1950.

(2) Erlanger and Brand, THIS JOURNAL, **73**, 3508 (1951).

(3) Brand and Erlanger, *ibid.*, **72**, 3314 (1950).

(4) Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936).

TABLE I

GLYCINE AND ALANINE TRIPEPTIDE DERIVATIVES

Number	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
	Carbobenzoxy tripeptide esters					
1	Z.Gly-Ala-Gly.OEt (L)	$C_{17}H_{23}O_6N_3$	365.4	145	11.5	11.3
2	Z.Gly-Ala-Gly.OBz (L)	$C_{22}H_{25}O_6N_3$	427.4	144	9.8	9.9
3	Z.Gly-Ala-Gly.OBz (D)	$C_{22}H_{25}O_6N_3$	427.4	144	9.8	9.9
4	Z.Gly-Ala-Ala.OEt (L-L)	$C_{18}H_{25}O_6N_3$	379.5	128	11.1	11.0
5	Z.Gly-Ala-Ala.OEt (L-D)	$C_{18}H_{25}O_6N_3$	379.5	126	11.1	11.2
6	Z.Ala-Ala-Ala.-OEt (3L)	$C_{19}H_{27}O_6N_3$	393.4	192	10.7	10.7
7	Z.Ala-Ala-Ala.OEt (L-D-L)	$C_{19}H_{27}O_6N_3$	393.4	142	10.7	10.6
8	Z.Ala-Ala-Ala.OEt (L-L-D)	$C_{19}H_{27}O_6N_3$	393.4	176	10.7	10.7
9	Z.Ala-Ala-Ala.OBz (3L)	$C_{24}H_{29}O_6N_3$	455.5	201.5	9.2	9.4
10	Z.Ala-Ala-Ala.OBz (3D)	$C_{24}H_{29}O_6N_3$	455.5	201.5	9.2	9.3
11	Z.Ala-Ala-Ala.OBz (L-D-L)	$C_{24}H_{29}O_6N_3$	455.5	148–9	9.2	9.2
12	Z.Ala-Ala-Ala.OBz (L-L-D)	$C_{24}H_{29}O_6N_3$	455.5	180.5	9.2	9.4
13	Z.Ala-Ala-Ala.OBz (D-L-L)	$C_{24}H_{29}O_6N_3$	455.5	173	9.2	9.3
	Carbobenzoxy tripeptide hydrazides					
14	Z.Ala-Ala-Ala.$NHNH_2$ (3L)	$C_{17}H_{25}O_5N_5$	379.4	235	18.5	18.3
15	Z.Ala-Ala-Ala.$NHNH_2$ (L-D-L)	$C_{17}H_{25}O_5N_5$	379.4	194	18.5	18.6
16	Z.Ala-Ala-Ala.$NHNH_2$ (L-L-D)	$C_{17}H_{25}O_5N_5$	379.4	205	18.5	18.5
	Carbobenzoxy tripeptides					
17	Z.Gly-Ala-Ala.OH (L-L)[b]	$C_{16}H_{21}O_6N_3$	351.5	172	12.0	12.0
18	Z.Gly-Ala-Ala.OH (L-D)[c]	$C_{16}H_{21}O_6N_3$	351.5	146	12.0	12.0

[a] The following abbreviations are used (*cf.* ref. 2, Table I, Footnote *a*): Z: carbobenzoxy, $C_6H_5\cdot CH_2OCO$; Gly: NH-(CH_2)CO; Ala: NH($CHCH_3$)CO; peptide linkage indicated by hyphen: -; Et: C_2H_5; Bz: $C_6H_5CH_2$; configuration follows compound in parentheses; *e.g.*, carbobenzoxy-L-alanyl-D-alanpl-L-alanine benzyl ester: Z.Ala-Ala-Ala.OBz (L-D-L); carbobenzoxy-L-alanyl-L-alanyl-L-alanine hydrazide: Z.Ala-Ala-Ala.$NHNH_2$ (3L); D-alanyl-L-alanyl-L-alanine: H.Ala-Ala.OH (D-L-L). [b] N.E. = 353 (N.E.: neutralization equivalent obtained by titration in alcohol (*cf.* Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April, 1950, Abstracts p. 56-C)). [c] N.E. = 351.

TABLE II

GLYCINE AND ALANINE TRIPEPTIDES

Analytical data and specific rotation in 0.5 *N* HCl

Number	Compound[a]	Molecular formula	Mol. wt.	Nitrogen, % Calcd.	Found	Amino N,[c] % Calcd.	Found	Neut. equiv.[b] Found	$[\alpha]^{23}D$ (c = 2)
19	H.Gly-Ala-Gly.OH (L)[d]	$C_7H_{13}O_4N_3$	203.2	20.7	20.5			Insol.	− 65.3[e]
20	H.Gly-Ala-Gly.OH (D)	$C_7H_{13}O_4N_3$	203.2	20.7	20.6			Insol.	+ 65.5[e]
21	H.Gly-Ala-Ala.OH (L-L)	$C_8H_{15}O_4N_3$	217.2	19.3	19.5			219	−103.0
22	H.Gly-Ala-Ala.OH (L-D)	$C_8H_{15}O_4N_3$	217.2	19.3	19.2			219	− 21.7
23	H.Ala-Ala-Ala.OH (3L)[f,g]	$C_9H_{17}O_4N_3$	231.3	18.2	18.2	6.1	5.9	230	− 85.4
24	H.Ala-Ala-Ala.OH (3D)[g]	$C_9H_{17}O_4N_3$	231.3	18.2	18.1	6.1	6.0	231	+ 85.9[e]
25	H.Ala-Ala-Ala.OH (L-D-L)	$C_9H_{17}O_4N_3$	231.3	18.2	18.0	6.1	5.9	232	+ 37.0
26	H.Ala-Ala-Ala.OH (L-L-D)	$C_9H_{17}O_4N_3$	231.3	18.2	18.2	6.1	6.0	231	− 4.6
27	H.Ala-Ala-Ala.OH (D-L-L)	$C_9H_{17}O_4N_3$	231.3	18.2	18.0	6.1	6.0	231	−115.2

[a,b] See Table I. [c] Incorrect values for terminal glycine amino groups omitted.[2] [d] Previously prepared (Fischer, *Ber.*, 41, 850 (1908)) with $[\alpha]^{20}D$ −64.3° (4.3% in H_2O); we find $[\alpha]^{24}D$ −63.7° (2% in H_2O). [e] At 24°. [f] Previously prepared (Abderhalden and Gohdes, *Fermentforschung*, 13, 56 (1933)) with analytical data to fit 1/2 mole of water which could not be removed in high vacuum at 130°, $[\alpha]^{18}D$ −70.2° (3.5% in 2 *N* HCl). Our tripeptide analyzed correctly without water and showed $[\alpha]^{25}D$ −79.2° (2% in 2 *N* HCl). [g] X-Ray studies on these crystals carried out by Dr. R. E. Pasternak in Dr. Pauling's Laboratory at the California Institute of Technology will be published by these authors.

mixture of 50 cc. of glacial acetic acid, 25 cc. of 5 *N* HCl and 200 cc. of water, treated with $NaNO_2$ (0.0275 mole) and extracted with 200 cc. of 1:1 (v/v) ether–ethyl acetate. The cold, dry solution of the azide is added in one portion to the previously prepared, cold, dry ethereal solution of amino acid ester; crystals of the coupling product begin to appear within a few minutes. After standing at 25° for about 20 hours, the mixture is cooled to −5°, the crystals are collected, washed with ether and recrystallized from ethanol. The yield of pure compounds is 70–75%, based on the hydrazide used.

Carbobenzoxy-Tripeptide Hydrazides (Compounds 14–16).—The hydrazides were prepared with hydrazine hydrate from carbobenzoxy tripeptide ethyl esters as described for carbobenzoxy dipeptide hydrazides.[2] Recrystallization from ethanol–ether results in pure compounds with 80–90% yield.

Carbobenzoxy Tripeptides (Compounds 17–18).—The carbobenzoxy tripeptide ethyl esters are saponified in methanol–2 *N* NaOH (about 10% excess of NaOH) for one hour at 37°. After acidification, the methanol is completely removed *in vacuo* with repeated additions of water. The oily residue is extracted with hot ethyl acetate and the warm (40°) solution dried with sodium sulfate. The dry ethyl acetate solution is cooled to −5° and crystallization induced by the addition of petroleum ether. Recrystallization from ethyl acetate–petroleum ether yields 80–85% of the pure compounds.

Tripeptides (Compounds 19–27).—Hydrogenolysis with palladium black as catalyst is carried out as previously described.[2] Methanol is the solvent used for carbobenzoxy tripeptides, while carbobenzoxy tripeptide benzyl esters are hydrogenated in 80% acetic acid (150 cc. per 0.015 mole).

The yield of pure, recrystallized (water–ethanol) peptides is 85–90%.

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Dipole Moments of Central-Atom Molecules

BY A. D. FRANKLIN

The general equation for the mean square dipole moment of a molecule with a rigid skeleton given by Eyring[1] may be solved in detail for the case of a central atom to which several different rotating polar groups are attached. An example is ethyl orthocarbonate. The observed moment should correspond to the square root of this mean square moment.

Eyring's equation in this case reduces to

$$\overline{\vec{\mu}^2} = m^2 + \sum_i s_i^2 + 2\sum_i \overline{(\vec{m}\cdot\vec{s_i})} + 2\sum_{i>j} \overline{(\vec{s_i}\cdot\vec{s_j})}$$

where the subscript i refers to the i^{th} group, $\vec{m} = \sum_i (\vec{m_i} + \vec{r_i})$, $\vec{m_i}$ is the moment associated with the bond joining the group to the central atom, and $\vec{r_i}$ and $\vec{s_i}$ are the components of the group moment along and perpendicular to this bond, respectively. The averages, which drop out for the case of free rotation, are to be taken over the various orientations of the polar groups.

In Table I are gathered the observed moments and those calculated assuming free rotation for several examples of this type of molecule.

TABLE I

Et represents the ethyl group; Me the methyl; and Ph the phenyl group.

Compound	Debye units Calcd.	Obsd.
$(EtO)_3SiH$	2.8	1.78[2]
$(EtO)_4Ti$	2.1	1.41[3]
$(EtO)_4Si$	2.1	1.70[4]
$(EtO)_4C$	2.1	1.1[5]
$(MeO)_4C$	2.1	0.8[5]
$(EtO)_3TiCl$	1.8	2.87[3]
$(PhO)TiCl_3$	1.3	2.97[3]
$(CH_2Cl)_4C$	2.8	0[5]
$(CH_2Br)_4C$	2.6	0[5]
$(CH_2I)_4C$	2.3	0[5]
$(EtO)_2SO$	3.0	2.96[4]
$(EtO)_3PO$	2.9	3.07[4]

All bond angles about the C, Si, Ti, P and O atoms were assumed to be tetrahedral. The configuration of $(EtO)_2SO$ was taken as identical to $SOCl_2$.[6] Bond moments were either taken from Smyth and co-workers[7,8,9] or else calculated from Pauling's[10] electronegativity values, and the equations given by Hannay and Smyth.[11]

There is no agreement evident in the table, the observed values lying below the calculated in most cases. It has been suggested that this trend is due to an increase in the bond angle at the polar group.[3,12] Although this may occur with the Ti and Si compounds, it is not likely to be the cause of the zero moment observed with the neopentyl compounds. Since it can readily be shown that dipole–dipole interaction alone is of the same order as kT, and combined with steric hindrance would tend to exclude configurations with large moments, sufficient reason for the low moments can be found in lack of free rotation. Yamasaki, *et al.*,[13] came to the same conclusion regarding $(MeO)_4Si$ on the basis of electron diffraction studies.

Until more is known about the interactions between rotating groups upon the same molecule, it can only be concluded that calculations based upon free rotation in these molecules are unsatisfactory, and although the dipole results do not rule out the possibility of a wider oxygen bond angle in the Ti and Si molecules, neither do they give any real information on this point.

(1) H. Eyring, *Phys. Rev.*, **39**, 746 (1932).
(2) H. Spauschus, A. Mills, J. Scott and C. MacKenzie, THIS JOURNAL, **72**, 1377 (1950).
(3) R. Crowe and C. Caughlan, *ibid.*, **72**, 1694 (1950).
(4) W. Svirbely and J. Lander, *ibid.*, **70**, 4121 (1948).
(5) L. Ebert, R. Eisenschitz and H. V. Hartel, *Naturwissenschaften*, **15**, 668 (1927).
(6) K. Palmer, THIS JOURNAL, **60**, 2360 (1938).
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(10) L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1939, p. 64.
(11) N. Hannay and C. P. Smyth, THIS JOURNAL, **68**, 171 (1946).
(12) R. Sauer and D. Mead, *ibid.*, **68**, 1794 (1946).
(13) K. Yamasaki, A. Kotera, M. Yokoi and Y. Ueda, *J. Chem. Phys.*, **18**, 1414 (1950).

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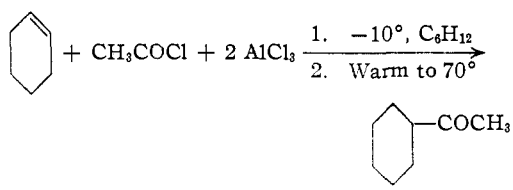
A Rearrangement in the Nenitzescu Reaction of Cycloheptene with Acetyl Chloride and Aluminum Chloride

BY S. L. FRIESS AND REX PINSON, JR.

In the course of preparation of a series of acetylcyclanes an attempt was made to synthesize methyl cycloheptyl ketone (I) using the acylation procedure of Nenitzescu and Cioranescu.[1] In the general procedure for the reaction, two moles of aluminum chloride are added in portions to a mixture of the olefin and acid chloride in cyclohexane solvent at about −10°, and upon warming slowly to 70°, HCl is evolved and the saturated ketone is obtained. For example



Nenitzescu found that the reaction progresses quite satisfactorily for 5- and 6-membered cyclic olefins, with the solvent acting as the ultimate hydrogen donor for the production of the saturated

(1) C. D. Nenitzescu and E. Cioranescu, *Ber.*, **69B**, 1820 (1936).