[CONTRIBUTION FROM THE CHEMICAL INSTITUTE, FACULTY OF SCIENCES, UNIVERSITY OF ZAGREB]

SOME DERIVATIVES OF OPTICALLY ACTIVE α-AMINO ALDEHYDES. AMINO ACIDS. X.[1,2]

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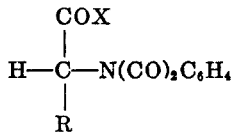
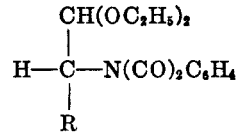
α-Amino aldehydes, the corresponding aldehydes of naturally occurring amino acids, have in several instances been suggested as precursors of certain naturally occurring compounds.

Neuberg (1) for example, has connected the formation of pyrazine and its homologs during the process of alcoholic fermentation with the reduction of amino acids to α-amino aldehydes.

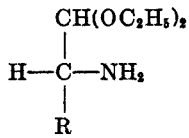
More recently, Delbrück (2) propounded a theory for the biogenesis of proteins, especially viruses. According to this idea, the Schiff's bases resulting from the combination between amino aldehydes are enzymatically hydrated and dehydrogenated to peptides.



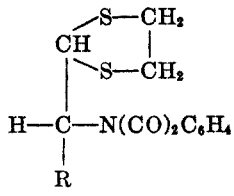
I X = Cl
II X = H



III



IV



V

(a) R = CH_3; (b) R = CH_2SPh; (c) R = p-$(CH_3O)PhCH_2$;

Earlier papers describe only two well defined aldehydes derived from naturally occurring amino acids. Fischer and Kametaka (3) obtained L-α-aminopropionaldehyde diethyl acetal by the reduction of L-alanine ethyl ester with sodium amalgam in an acid medium. These authors had applied to L-alanine a method described independently by Neuberg (1) and Fischer (4). The reduction of glycine ester hydrochloride and the acetalization of the resulting aldehyde gave aminoacetaldehyde diethyl acetal in a low yield: from L-alanine and *d,l*-phenylalanine, α-aminopropionaldehyde diethyl acetal and *d,l*-α-amino-β-phenylpropionaldehyde diethyl acetal respectively were obtained.

[1] See note, *J. Chem. Soc.*, 3316 (1952).

[2] Presented at the II International Congress of Biochemistry, Paris, July, 1952.

The same method of reduction was applied more recently by Akabori (5) and by Bullerwell and Lawson (6) to a number of amino acids; the resulting amino aldehydes were, however, not isolated, but used as starting materials for the syntheses of imidazole derivatives. The well defined *p*-nitrophenylosazones of these aldehydes were prepared.

Radde (7) was the first to apply another method, and he obtained crystalline phthalimidoacetaldehyde from glycine by the Rosenmund-Zetzsche reduction (8) of N-phthaloylglycyl chloride. Radde also described, but with incomplete experimental data, the reduction of *d,l*-alanine to *d,l*-phthalimidopropionaldehyde.

In the present paper a description is given of the Rosenmund-Zetzsche reduction of the optically active N-phthaloyl acyl chlorides (I) derived from naturally occurring amino acids. Crystalline N-phthaloyl derivatives of α-amino aldehydes (II) were obtained in good yields, and their rotatory power remained unimpaired. We thus obtained N-phthaloyl-L-alanine aldehyde (IIa), S-benzyl-N-phthaloyl-L-cysteine aldehyde (IIb), and O-methyl-N-phthaloyl-L-tyrosine aldehyde (IIc) from the corresponding acyl chlorides (Ia–c).

These N-phthaloyl aldehydes were converted by Claisen's method (9) to diethyl acetals (III) using ethyl orthoformate in absolute ethanol, and after splitting off the phthaloyl group with a solution of hydrazine hydrate in ethanol (10), optically active α-amino aldehyde diethyl acetals (IV) were obtained. In this manner we prepared L-alanine aldehyde diethyl acetal (IVa) from IIa, $[\alpha]_D$ +17.8°; S-benzyl-L-cysteine aldehyde diethyl acetal (IVb) from IIb, $[\alpha]_D$ −2.6°; and O-methyl-L-tyrosine aldehyde diethyl acetal (IVc) from IIc, $[\alpha]_D$ −79.1°.

N-Phthaloyl aldehydes (II) gave with ethanedithiol crystalline N-phthaloyl aldehyde ethylene mercaptals (V). The splitting off of the phthaloyl group took place under action of hydrazine hydrate, and α-amino aldehyde ethylene mercaptals were thus obtained. N-Phthaloyl-L-alanine aldehyde ethylene mercaptal (Va) gave L-alanine aldehyde ethylene mercaptal, $[\alpha]_D$ +18.5°; S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene mercaptal (Vb) gave S-benzyl-L-cysteine aldehyde ethylene mercaptal, $[\alpha]_D$ −19.2°.

Other derivatives of N-phthaloyl aldehydes were also prepared, notably the semicarbazones, the 2,4-dinitrophenylhydrazones, and the thiosemicarbazones.

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EXPERIMENTAL

All melting points are uncorrected.

Microanalyses were carried out by Dr. L. Filipović in our laboratory.

Preparation of N-phthaloyl aldehydes (II). (*General procedure*). A solution of the N-phthaloyl acyl chloride (about 15 g.) in xylene (50–70 ml.) was reduced following the Rosenmund-Zetzsche method (8) with palladium on barium sulfate (palladium content 5%) at 110–130° (the hydrogen was introduced through the sintered glass bottom of the reaction flask). After 80–90% of the theoretical amount of hydrochloric acid was evolved, the catalyst was filtered off, the reaction mixture washed with ether, and the ether removed under reduced pressure. After standing at 0° the aldehyde generally crystallized from the xylene

solution. Additional yields were obtained from the mother liquor by precipitating with petroleum ether. Yields were above 60%.

N-Phthaloyl-L-alanine aldehyde. (1-α-phthalimidopropionaldehyde) (IIa). A solution of N-phthaloyl-L-alanyl chloride (Ia, 15 g.) prepared following the method described by Balenović, Cerar, and Fuks (11) in xylene (60 ml.) was reduced with Pd-$BaSO_4$ catalyst (2.5 g.) at 110° during 10 hours. Yield 6.5 g. of N-phthaloyl-L-alanine aldehyde, m.p. 107–108°, $[\alpha]_D$ −30°. After precipitation with petroleum ether an additional yield was obtained from the mother liquor (1.8 g.). Total yield 65%. Recrystallized from benzene-petroleum ether (1:1), m.p. 112°, $[\alpha]_D^{17}$ −29.9° ± 0.4° (*c*, 2.16 in benzene). Sublimation at 95–100°/0.04 mm./1 hour gave the partially racemized aldehyde with $[\alpha]_D$ −7°.

Anal. Calc'd for $C_{11}H_9NO_3$ (203.19): C, 65.02; H, 4.47.
Found: C, 65.12; H, 4.56.

Semicarbazone, from IIa and semicarbazide acetate in methanol, recrystallized from methanol, m.p. 226°.

Anal. Calc'd for $C_{12}H_{12}N_4O_3$ (260.25): C, 55.38; H, 4.65.
Found: C, 55.44; H, 4.74.

2,4-Dinitrophenylhydrazone, recrystallized from benzene, m.p. 203–204°.

Anal. Calc'd for $C_{17}H_{12}N_5O_6$ (383.31): C, 53.26; H, 3.42.
Found: C, 53.08; H, 3.57.

S-Benzyl-N-phthaloyl-L-cysteine aldehyde (IIb). A solution of S-benzyl-N-phthaloyl-L-cysteinyl chloride (Ib, 2.0 g.) prepared following the procedure described by Balenović and Fleš (12) in xylene (10 ml.) was reduced with Pd-$BaSO_4$ catalyst (1 g.) at 100–110° during 4 hours. The reaction mixture was filtered and the crude aldehyde was precipitated from the filtrate by adding petroleum ether (60 ml.); yield 1.2 g. (67%), $[\alpha]_D^{18}$ −5.0° ± 0.5° (*c*, 2.0 in benzene). After distillation at 180°/0.03 mm. the compound crystallized and partially racemized, $[\alpha]_D^{22}$ −1.8° ± 0.5° (*c*, 4.03 in benzene). Recrystallized from benzene, m.p. 119–120°.

Anal. Calc'd for $C_{18}H_{15}NO_3S$ (325.37): C, 66.44; H, 4.65.
Found: C, 65.90; H, 4.14.

Semicarbazone, from IIb and semicarbazide acetate in methanol, recrystallized from methanol, m.p. 205–206.5°.

Anal. Calc'd for $C_{19}H_{18}N_4O_3S$ (382.43): C, 59.67; H, 4.74.
Found: C, 59.74; H, 4.89.

O-Methyl-N-phthaloyl-L-tyrosine aldehyde (IIc). A solution of O-methyl-N-phthaloyl-L-tyrosinyl chloride (Ic, 22.5 g.) prepared following the method described by Balenović, Thaller, and Filipović (13) in xylene (60 ml.) was reduced with Pd-$BaSO_4$ catalyst (3 g.) at 110° during 14 hours. After adding petroleum ether (30 ml.) and a few drops of ethanol to the reaction mixture, crystallization occurred. O-Methyl-N-phthaloyl-L-tyrosine aldehyde was obtained, yield 20.5 g. (100%), m.p. 88°, $[\alpha]_D^{18}$ −150° ± 1° (*c*, 0.30 in ethanol).

Anal. Calc'd for $C_{18}H_{15}NO_4$ (309.31): C, 69.89; H, 4.89.
Found: C, 69.60; H, 5.02.

If this reduction was carried out under the same conditions, but at 135–140°, only 50% of O-methyl-N-phthaloyl-L-tyrosine aldehyde was obtained, and the residue was a yellow oil from which a small amount of optically inactive yellow compound separated, m.p. 126°.

Anal. Found: C, 72.98; H, 5.15; N, 5.21.

Semicarbazone, from IIc and semicarbazide acetate in methanol, recrystallized from methanol, m.p. 227–229°.

Anal. Calc'd for $C_{19}H_{18}N_4O_4$ (366.37): C, 62.28; H, 4.95.
Found: C, 62.54; H, 4.95.

Preparation of N-phthaloyl-α-amino aldehyde diethyl acetals (III). *(General procedure).* The acetals were prepared according to Claisen's procedure (9). To a solution of N-phthaloyl-α-amino aldehyde (1 mole) and ethyl orthoformate (1.1 mole) in the minimum quantity of absolute ethanol, dry ammonium chloride (0.01 mole) was added and the mixture was left at room temperature for 8 days. This mixture was then diluted with water to which

a few drops of 25% ammonia had been previously added, and was repeatedly extracted with ether, washed with water, and dried (Na_2SO_4). After evaporating the ether under reduced pressure, the crude diethyl acetal remained, which crystallized from a mixture of dichloromethane and petroleum ether.

N-Phthaloyl-L-alanine aldehyde diethyl acetal (IIIa). Following the general procedure, N-phthaloyl-L-alanine aldehyde diethyl acetal was obtained, yield 76%. Recrystallized from petroleum ether, m.p. 53°, $[\alpha]_D^{20}$ −2.7° ± 0.3° (*c*, 3.70 in absolute ethanol).

Anal. Calc'd for $C_{15}H_{19}NO_4$ (277.31): C, 64.96; H, 6.91.

Found: C, 64.44; H, 6.75.

S-Benzyl-N-phthaloyl-L-cysteine aldehyde diethyl acetal (IIIb). Following the general procedure, S-benzyl-N-phthaloyl-L-cysteine diethyl acetal was obtained as an oil, yield 97%. Distilled at 200–220°/0.04 mm., $[\alpha]_D^{24}$ −4.7° ± 1.4° (*c*, 1.5 in benzene). After standing for 24 hours, crystallization occurred, m.p. 73°.

Anal. Calc'd for $C_{22}H_{25}NO_4S$ (399.49): C, 66.14; H, 6.31.

Found: C, 66.02; H, 6.17.

O-Methyl-N-phthaloyl-L-tyrosine aldehyde diethyl acetal (IIIc). Following the general procedure, O-methyl-N-phthaloyl-L-tyrosine aldehyde diethyl acetal was obtained as an oil, yield 81%. After passing through an Al_2O_3 column (activity IV according to Brockmann)[4] the compound was distilled at 160°/0.03 mm., $[\alpha]_D^{19}$ −108° ± 0.4° (*c*, 2.36 in ether). Distillation had no influence on the $[\alpha]_D$.

Anal. Calc'd for $C_{22}H_{25}NO_5$ (383.43): C, 68.91; H, 6.57.

Found: C, 69.06; H, 6.20.

Preparation of N-phthaloyl-α-amino aldehyde ethylene mercaptals (V). (*General procedure*). A solution of N-phthaloyl-α-amino aldehyde (1 mole) and ethanedithiol (1.1 moles) in a tenfold volume of dioxane containing 3% of dry hydrogen chloride was left at room temperature for four days. The mixture was then evaporated under reduced pressure at 40°, water was added, and the mixture again evaporated *in vacuo*. The residue thus freed from the excess ethanedithiol was washed with a small amount of cold methanol, and the ethylene mercaptal generally crystallized.

N-Phthaloyl-L-alanine aldehyde ethylene mercaptal (Va). Following the general procedure, N-phthaloyl-L-alanine aldehyde ethylene mercaptal was obtained from IIa $[\alpha]_D$ −30°. From cold methanol crystals of the racemate separated in a 25% yield, m.p. 96°.

Anal. Calc'd for $C_{13}H_{13}NO_2S_2$ (279.36): C, 55.88; H, 4.69.

Found: C, 55.86; H, 4.63.

Distillation of the mother liquor at 160–170°/0.03 mm. gave the oily, optically active N-phthaloyl-L-alanine aldehyde ethylene mercaptal, $[\alpha]_D$ +48.7° ± 0.4° (*c*, 2.16 in benzene), yield 70%.

Anal. Found: C, 56.02; H, 4.82.

S-Benzyl-N-phthaloyl-L-cysteine aldehyde ethylene mercaptal (Vb). Following the general procedure, the oily S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene mercaptal was obtained from IIb ($[\alpha]_D$ −1.8°), yield 72.3%, which distilled at 230–235°/0.04 mm., $[\alpha]_D^{21}$ −60.14° ± 1° (*c*, 2.67 in benzene). After standing for a time, the oil crystallized, m.p. 98–100°.

Anal. Calc'd for $C_{20}H_{19}NO_2S_3$ (401.54): C, 59.82; H, 4.77.

Found: C, 60.12; H, 4.84.

O-Methyl-N-phthaloyl-L-tyrosine aldehyde ethylene mercaptal (Vc). Following the general procedure O-methyl-N-phthaloyl-L-tyrosine aldehyde ethylene mercaptal was obtained from IIc ($[\alpha]_D$ −150°) as a crystalline solid, yield 89%. Recrystallized from methanol, m.p. 103°, $[\alpha]_D^{18}$ −105° ● 0.8° (*c*, 0.18 in dichloromethane).

Anal. Calc'd for $C_{20}H_{19}NO_3S_2$ (385.48): C, 62.31; H, 4.97.

Found: C, 62.26; H, 4.97.

Hydrazinolysis of N-phthaloyl-L-alanine aldehyde diethyl acetal. L-*Alanine aldehyde diethyl acetal* (IVa). A solution of N-phthaloyl-L-alanine aldehyde diethyl acetal (IIIa, 2.16 g., $[\alpha]_D$ −2.7°) in ethanol (15 ml.) was refluxed for 30 minutes with a molar solution of

hydrazine hydrate in ethanol (9.7 ml.). After cooling, the phthalyl hydrazide formed during the reaction was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residual oily L-alanine aldehyde diethyl acetal was distilled at 95–105° (oil bath)/18 mm., yield 0.36 g., (36%), $[\alpha]_D^{22}$ +17.8° ± 0.3° (*c*, 1.32 in 0.1 *N* HCl).[3]

Anal. Calc'd for $C_7H_{17}NO_2$ (147.21): C, 57.10; H, 11.64.

Found: C, 56.96; H, 11.37.

Hydrazinolysis of S-benzyl-N-phthaloyl-L-cysteine aldehyde diethyl acetal. S-benzyl-L-cysteine aldehyde diethyl acetal (IVb). A solution of *S*-benzyl-N-phthaloyl-L-cysteine aldehyde diethyl acetal (IIIb, 1.1 g., $[\alpha]_D$ −4.7°) in ethanol (10 ml.) was refluxed with a molar solution of hydrazine hydrate in ethanol (4.6 ml.). Following the procedure given for the corresponding L-alanine derivative, S-benzyl-L-cysteine aldehyde diethyl acetal was obtained, which distilled at 135–140°/0.04 mm., yield 0.6 g. (84%), $[\alpha]_D^{18}$ −2.6° ± 0.2° (*c*, 2.49 in dichloromethane).

Anal. Calc'd for $C_{14}H_{23}NO_2S$ (269.39): C, 62.41; H, 8.60.

Found: C, 62.61; H, 8.59.

Hydrazinolysis of O-methyl-N-phthaloyl-L-tyrosine aldehyde diethyl acetal. O-Methyl-L-tyrosine aldehyde diethyl acetal (IVc). A solution of O-methyl-N-phthaloyl-L-tyrosine aldehyde diethyl acetal (IIIc, 1.9 g., $[\alpha]_D$ −109°) in ethanol (15 ml.) was refluxed for 30 minutes with a molar solution of hydrazine hydrate in ethanol (5 ml.). After removing the phthalyl hydrazide and evaporating the reaction mixture to dryness the residue was dissolved in dichloromethane and an additional amount of phthalyl hydrazide was separated. After evaporation of the solvent, the residue was dissolved in benzene and chromatographed on Al_2O_3 (20 g., activity III according to Brockmann).[4] Fractions of 15 ml. were collected, the second fraction containing the pure O-methyl-L-tyrosine aldehyde diethyl acetal (1.1 g., 86.5%), $[\alpha]_D^{19}$ −79.2° ± 0.1° (*c*, 0.73 in chloroform). Distillation of the compound at 160°/0.02 mm. resulted in partial racemization.

Anal. Calc'd for $C_{14}H_{23}NO_3$ (253.33): C, 66.37; H, 9.15.

Found: C, 66.64; H, 8.64.

Hydrazinolysis of N-phthaloyl-L-alanine aldehyde ethylene mercaptal. L-Alanine aldehyde ethylene mercaptal. A solution of N-phthaloyl-L-alanine aldehyde ethylene mercaptal (Va, 1.45 g., $[\alpha]_D$ +48°) in ethanol (10 ml.) was refluxed with a molar solution of hydrazine hydrate in ethanol (6.5 ml.) for 4 hours. After cooling, the precipitated phthalyl hydrazide was filtered off, the reaction mixture was evaporated to dryness under reduced pressure, and *N* HCl (40 ml.) was added to the residue. After standing overnight at 0° an additional amount of phthalyl hydrazide separated and was filtered off; the filtrate was basified with concentrated aqueous ammonia and extracted with three 50-ml. portions of ether. The extracts were dried (Na_2SO_4) and the ethereal extracts were evaporated to dryness. The residue distilled at 145–155°/12 mm., yield 0.52 g. (67%) of L-alanine aldehyde ethylene mercaptal, $[\alpha]_D^{19}$ +18.5° ± 0.2° (*c*, 1.98 in dichloromethane).

Anal. Calc'd for $C_5H_{11}NS_2$ (149.27): C, 40.23; H, 7.43.

Found: C, 40.42; H, 7.37.

Hydrazinolysis of N-phthaloyl-*d,l*-alanine aldehyde ethylene mercaptal (Va, m.p. 96°) gave *d,l*-alanine aldehyde ethylenemercaptal.

Anal. Found: C, 40.26; H, 7.30.

Hydrazinolysis of S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene mercaptal. S-Benzyl-L-cysteine aldehyde ethylene mercaptal. In the same manner as described above, S-benzyl-N-phthaloyl-L-cysteine aldehyde ethylene mercaptal (Vb, 0.6 g., $[\alpha]_D$ −60° was treated with a molar solution of hydrazine hydrate in ethanol for 4 hours, and ultimately S-benzyl-L-cysteine aldehyde ethylene mercaptal was obtained, which distilled at 150–180°/0.04 mm., $[\alpha]_D^{26}$ −19.2° ± 1° (*c*, 0.924 in benzene).

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[3] Fischer and Kametaka (3) gave $[\alpha]_D$ +14.3° under the same conditions. (Calculated for the hydrochloride.)

[4] Brockmann and Schodder, *Ber.*, **74**, 73 (1941).

Anal. Calc'd for $C_{12}H_{17}NS_2$ (271.44): C, 53.10; H, 6.31.
Found: C, 52.96; H, 6.27.

SUMMARY

The Rosenmund-Zetzsche reduction was applied to the optically active N-phthaloyl acyl chlorides (Ia–c) of the naturally occurring amino acids. The crystalline N-phthaloyl derivatives of these aldehydes (IIa–c) were converted into diethyl acetals (IIIa–c) and ethylenemercaptals (Va–c). Hydrazinolysis of the diethyl acetals and the ethylene mercaptals gave the corresponding α-amino aldehyde diethyl acetals (IVa–c) and α-amino aldehyde ethylene mercaptals. All of these compounds are optically active.

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