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

SYNTHESIS OF AMINOALKYLGLYOXAL DERIVATIVES. II[1]. AMINOALKYLGLYOXAL DERIVATIVES OF L-ALANINE, β-ALANINE, AND L-TYROSINE

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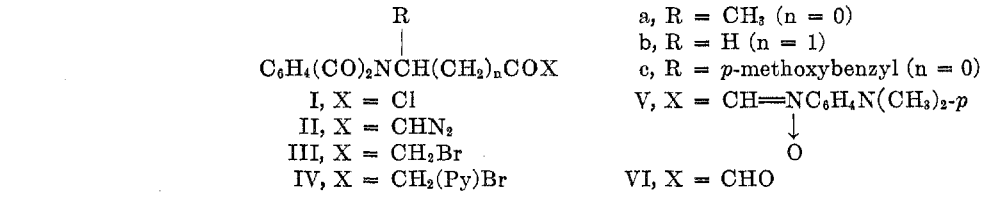
Derivatives of aminomethylglyoxal, the simplest of the series of aminoalkylglyoxals, have recently been prepared using glycine as starting material (1).

We have now prepared, following the same method and starting with L-alanine, β-alanine, and L-tyrosine, the derivatives of the corresponding aminoalkylglyoxals (VIa–c).

From the above mentioned amino acids, the N-phthaloylacyl chlorides (Ia–c), the diazoketones (IIa–c), and the bromoketones (IIIa–c) were prepared, from which, following the method of Kröhnke and Börner (2), the glyoxals (VIa–c) were obtained through the reaction stages IV–VI in the form of their N-phthaloyl derivatives.



The bisethylenemercaptals and quinoxaline derivatives of these glyoxals were also prepared.

α-Phthalimidoethylglyoxal (VIa) derived from L-alanine, and α-(phthalimido)-β-(*p*-methoxyphenyl)ethylglyoxal (VIc) derived from O-methyl-L-tyrosine are optically active, showing $[\alpha]_D$ +8.7° and $[\alpha]_D$ −1.4° respectively.

The N-phthaloylglyoxals (VIa–c) were obtained after filtration through a column of Al_2O_3 and high vacuum distillation as yellow oils; the glyoxals of L-alanine and β-alanine ultimately crystallized.

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EXPERIMENTAL

All melting points are uncorrected.

(−)-*1-Bromo-3-phthalimidobutan-2-one* (IIIa). To a suspension of (−)-1-diazo-3-phthalimidobutan-2-one (IIa, 5 g.) prepared following Balenović, Cerar, and Fuks (3) in glacial acetic acid (27.5 ml.), 48% hydrobromic acid (5.3 ml.) was added with stirring. After standing for an hour at room temperature the reaction was complete. The mixture was then diluted with 300 ml. of water and the crystals were collected. Yield, 6 g. (98.5%) of (−)-1-bromo-3-phthalimidobutan-2-one; recrystallization from ether-petroleum ether gave the pure compound, m.p. 66°, $[\alpha]_D^{19}$ −34.7° ± 1° (c, 0.14 in acetone).

[1] Paper I, Balenović and Bregant, *J. Org. Chem.*, **17**, 1328 (1952).

Anal. Calc'd for $C_{12}H_{10}BrNO_3$ (269.12): C, 48.66; H, 3.40.
Found: C, 49.05; H, 3.39.

(−)-1-Bromo-3-phthalimido-4-(p-methoxyphenyl)butan-2-one (IIIc). To a suspension of (−)-1-diazo-3-phthalimido-4-(*p*-methoxyphenyl)butan-2-one (IIc, 3.5 g.) prepared according to Balenović, Thaller, and Filipović (4) in glacial acetic acid (19 ml.), 48% hydrobromic acid (3.8 ml.) was added. The reaction mixture was treated in the same manner as described for the preparation of IIIa. Yield, 4.0 g. (100%) of (−)-1-bromo-3-phthalimido-4-(*p*-methoxyphenyl)butan-2-one, m.p. 75°, recrystallized from acetone, m.p. unchanged, $[\alpha]_D^{20}$ −177.6° ± 0.5° (*c*, 3.26 in benzene).

Anal. Calc'd for $C_{19}H_{16}BrNO_4$ (402.24): C, 56.73; H, 4.01.
Found: C, 57.17; H, 4.03.

Pyridinium salt of IIIa (IVa). The bromoketone IIIa (7.8 g.) and anhydrous pyridine (33 ml.) were refluxed for 15 minutes. After cooling, the crystals were collected and washed with petroleum ether; yield of hygroscopic pyridinium salt, 9.7 g. (98%), m.p. 85° (decomp.). Recrystallization from absolute ethanol did not change the m.p.; $[\alpha]_D^{15}$ −7.94° ± 0.1° (*c*, 0.32 in absolute ethanol).

Anal. Calc'd for $C_{17}H_{15}BrN_2O_3$ (375.22): C, 54.41; H, 4.03.
Found: C, 54.53; H, 4.48.

Pyridinium salt of IIIb (IVb). 1-Bromo-4-phthalimidobutan-2-one (IIIb, 5.3 g.) prepared following Jones, Kornfeld, and McLaughlin (5) and anhydrous pyridine (22 ml.) were treated in the same manner as described for the preparation of IVa. Yield, 6.7 g. (100%) of hygroscopic pyridinium salt, m.p. 225° (decomp.).

Anal. Calc'd for $C_{17}H_{15}BrN_2O_3$ (375.22): C, 54.41; H, 4.03.
Found: C, 54.48; H, 4.31.

Pyridinium salt of IIIc (IVc). (−)-1-Bromo-3-phthalimido-4-(*p*-methoxyphenyl)butan-2-one (IIIc, 7.0 g.) and anhydrous pyridine (28 ml.) were treated in the same manner as described for the preparation of IVa. Yield 7.7 g. (92%) of hygroscopic pyridinium salt, m.p. 215° (decomp.), $[\alpha]_D^{20}$ −83.3° ± 0.6° (*c*, 0.18 in absolute ethanol).

Anal. Calc'd for $C_{24}H_{21}BrN_2O_4$ (481.35): C, 59.87; H, 4.40.
Found: C, 59.42; H, 5.15.

α-(Phthalimido-L-alanyl)-N-(p-dimethylaminophenyl)nitrone (Va). A mixture of a solution of IVa (5.1 g., 0.014 mole) in water (15 ml.) and ethanol (4 ml.) and a solution of *p*-nitrosodimethylaniline (2.1 g., 0.014 mole) in ethanol (70 ml.) was cooled to −5°. To this mixture 0.014 mole of *N* NaOH was gradually added during 30 minutes with occasional stirring. The orange-yellow nitrone was left at the same temperature for an additional 30 minutes, then filtered and washed with a cold mixture of ethanol and water (2:5). Yield, 2.5 g. (50%) of α-phthalimido-L-alanyl)-N-(*p*-dimethylaminophenyl)nitrone, recrystallized from dioxane-water, orange-yellow prisms, m.p. 153°.

Anal. Calc'd for $C_{20}H_{19}N_3O_4$ (365.39): C, 65.74; H, 5.24.
Found: C, 66.13; H, 5.45.

α-(β-Phthalimidoalanyl)-N-(p-dimethylaminophenyl)nitrone (Vb). The pyridinium salt IVb (3.9 g., 0.01 mole) and *p*-nitrosodimethylaniline (1.6 g., 0.01 mole) were treated in the same manner as described for the preparation of Va. Yield, 3.2 g. (86%) of α-(β-phthalimidoalanyl)-N-(*p*-dimethylaminophenyl)nitrone; recrystallization from dioxane-water gave orange-yellow needles, m.p. 154°.

Anal. Calc'd for $C_{20}H_{19}N_3O_4$ (365.39): C, 65.74; H, 5.24.
Found: C, 65.52; H, 5.42.

α-(O-Methyl-N-phthaloyl-L-tyrosinyl)-N-(p-dimethylaminophenyl)nitrone (Vc). The pyridinium salt IVc (6 g., 0.012 mole) and *p*-nitrosodimethylaniline (2.5 g., 0.017 mole) were treated in the same manner as described for the preparation of Va. Yield, 5.5 g. (92%) of α-(O-methyl-N-phthaloyl-L-tyrosinyl)-N-(*p*-dimethylaminophenyl)nitrone; recrystallization from dioxane-water gave orange-yellow needles, m.p. 156°.

Anal. Calc'd for $C_{27}H_{25}N_3O_5$ (471.50): C, 68.78; H, 5.35.
Found: C, 68.71; H, 5.36.

(−)-*α-Phthalimidoethylglyoxal* (VIa). To a suspension of the powdered nitrone Va (1.5 g.) in water (3.5 ml.) in a separatory funnel, 5 *N* H_2SO_4 (15 ml.) and pure ether (15 ml.) were added. This mixture was thoroughly shaken until the nitrone dissolved. The water layer was extracted six times with ether and the combined ethereal extracts were washed twice with 5 *N* H_2SO_4, and then with water. After evaporating the ether under reduced pressure, the yellow oily residue (0.9 g.) was dissolved in benzene (30 ml.) and filtered through a column containing 3 g. of Al_2O_3.[2] The column was washed with benzene (30 ml.), and the combined filtrate and washings were evaporated under reduced pressure. The remaining oily α-phthalimidoethylglyoxal (0.7 g., 80%) showed $[\alpha]_D^{18}$ −1.34° ± 0.4° (*c*, 1.12 in dry ether). After high vacuum distillation a greenish-yellow oil was obtained, which crystallized on standing for a time.

Anal. Calc'd for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.93.
Found: C, 62.72; H, 4.09.

(+)-*2-(α-Phthalimidoethyl)quinoxaline*. A mixture of (−)-α-phthalimidoethylglyoxal (VIa, 1.15 g.), an equimolar amount of *o*-phenylenediamine, and glacial acetic acid (15 ml.) was refluxed for 2 hours, and cooled. On addition of water (200 ml.), 1.05 g. (70%) of crude (+)-2-(α-phthalimidoethyl)quinoxaline separated. Recrystallization from ethanol and sublimation at 150°/0.01 mm. yielded white prisms, m.p. 119°, $[\alpha]_D^{17}$ +9.38° ± 0.1° (*c*, 0.85 in absolute ethanol).

Anal. Calc'd for $C_{18}H_{13}N_3O_2$ (303.31): C, 71.29; H, 4.32.
Found: C, 71.23; H, 4.02.

β-Phthalimidoethylglyoxal (VIb). A suspension of the powdered nitrone Vb (2.2 g.) in water (6 ml.) was treated in the same manner as described for the preparation of VIa. Yield, 1.3 g. (93%) of β-phthalimidoethylglyoxal, obtained as a yellow oil which, after filtration through a column of Al_2O_3 (as with VIa) and high vacuum distillation, gave yellow needles, m.p. 96.5°.

Anal. Calc'd for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.93.
Found: C, 62.43; H, 4.35.

2-(β-Phthalimidoethyl)quinoxaline. A mixture of β-phthalimidoethylglyoxal (VIb, 0.6 g.), an equimolar amount of *o*-phenylenediamine, and glacial acetic acid (10 ml.) was refluxed for two hours and cooled. On addition of water (50 ml.), 0.61 g. (78%) of crude 2-(β-phthalimidoethyl)quinoxaline separated. Recrystallization from ethanol and sublimation at 150°/0.02 mm. gave white prisms, m.p. 143°.

Anal. Calc'd for $C_{18}H_{13}N_3O_2$ (303.31): C, 71.29; H, 4.32.
Found: C, 71.44; H, 4.35.

Bisethylenemercaptal of β-phthalimidoethylglyoxal. β-Phthalimidoethylglyoxal (VIb, 1.0 g., 0.004 mole) and ethanedithiol (1.5 ml., 0.01 mole) were dissolved in a 3% solution of anhydrous hydrochloric acid in dioxane (14 ml.). After standing at room temperature for four days, the solution was evaporated to dryness. Yield, 1.6 g. (100%) of bisethylenemercaptal; recrystallization from benzene gave the pure compound in the form of white needles, m.p. 212°.

Anal. Calc'd for $C_{16}H_{17}NO_2S_4$ (383.54): C, 50.10; H, 4.47.
Found: C, 50.28; H, 4.56.

(+)-*α-(Phthalimido)-β-(p-methoxyphenyl)ethylglyoxal* (VIc). A suspension of the powdered nitrone Vc (4.5 g.) in water (10 ml.) and 5 *N* H_2SO_4 (40 ml.) was treated in the same manner as described for the preparation of VIa. Yield, 2.4 g. (76%) of yellow oily (+)-α-(phthalimido)-β-(*p*-methoxyphenyl)ethylglyoxal, which after filtration through a column of Al_2O_3 (as with VIa), and high vacuum distillation at 160°/0.01 mm. showed $[\alpha]_D^{17}$ +8.75° ± 0.5° (*c*, 1.50 in benzene).

Anal. Calc'd for $C_{19}H_{15}NO_5$ (337.32): C, 67.65; H, 4.48.
Found: C, 67.55; H, 4.52.

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[2] Neutral Al_2O_3 was prepared following Reichstein's procedure (6). Activity IV–V according to Brockmann.

Quinoxaline derivative of (+)-α-(*phthalimido*)-β(*p-methoxyphenyl*)*ethylglyoxal.* A mixture of (+)-α-(phthalimido)-β-(*p*-methoxyphenyl)ethylglyoxal (VIc, 0.45 g.), an equimolar amount of *o*-phenylenediamine and glacial acetic acid (7.5 ml.) was refluxed for two hours, and cooled. On addition of water (100 ml.), 0.3 g., (56%) of crude quinoxaline derivative separated. Recrystallization from ethanol and sublimation at 165°/0.02 mm. gave white prisms, m.p. 126°, $[\alpha]_D^{18}$ −42.4° ± 0.9° (*c*, 0.10 in absolute ethanol).

Anal. Calc'd for $C_{25}H_{19}N_3O_3$ (409.43): C, 73.34; H, 4.68.
Found: C, 73.29; H, 4.65.

Bisethylenemercaptal of (+)-α-(*phthalimido*)-β-(*p-methoxyphenyl*)*ethylglyoxal.* (+)-α-(Phthalimido)-β-(*p*-methoxyphenyl)ethylglyoxal (VIc, 0.82 g.) and ethanedithiol (0.9 ml.) were dissolved in a 3% solution of anhydrous hydrochloric acid in dioxane (12.5 ml.). After standing at room temperature for four days, the solution was evaporated to dryness. Yield, 0.98 g. (82%) of crude bisethylenemercaptal; recrystallization from benzene gave the bisethylenemercaptal crystallized with one molecule of solvent, m.p. 72°. Dried at 120°/760 mm. to constant weight, the solvent-free compound had m.p. 146°, $[\alpha]_D^{19}$ −40° ± 0.6° (*c*, 0.40 in acetone).

Anal. Calc'd for $C_{23}H_{23}NO_3S_4$ (488.66): C, 56.41; H, 4.74.
Found: C, 56,80; H, 4.79.

SUMMARY

A description is given for the preparation of phthalimidoalkylglyoxals (VIa–c) through the reaction stages I–VI. The starting materials were L-alanine, β-alanine and L-tyrosine.

α-Phthalimidoethylglyoxal (VIa) and α-(phthalimido)-β-(*p*-methoxyphenyl)-ethylglyoxal (VIc) are optically active.

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