[Contribution from the Chemical Institute, Faculty of Science, University of Zagreb]

REACTION OF N-DISUBSTITUTED GLYCYL CHLORIDES WITH DIAZOMETHANE. A NEW SYNTHESIS OF SOME β-ALANINE DERIVATIVES. AMINO ACIDS. V[1]

K. BALENOVIĆ, N. BREGANT, D. CERAR, and M. TKALČIĆ

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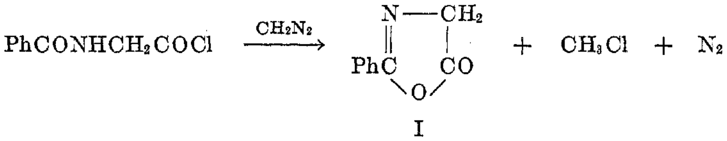
It has been shown (1) that N-monosubstituted glycyl chlorides, *e.g.* hippuryl chloride, do not react with diazomethane to give diazoketones, but give, instead oxazolones (I).



I

RCH_2COCl II

RCH_2COCHN_2 III

$RCH_2CH_2COOC_2H_5$ IV

$R = N(CO)_2C_6H_4$ in all cases

RCH_2COCH_2R'

V $R' = Cl$

VI $R' = OH$

VII $R' = OCOCH_3$

VIII $R' = OCH_3$

IX $R' = OC_6H_5$

X $R' = OC_6H_2(NO_2)_3$

We have applied this reaction with diazomethane to a disubstituted glycyl chloride, N-phthaloylglycyl chloride (II), and obtained, as was expected, the normal diazoketone (III) (2). From this diazoketone a compound was prepared by the Arndt-Eistert reaction which was identical with the previously known ethyl ester of β-phthalimidopropionic acid (IV) (3). We have also prepared from the same diazoketone, 1-chloro-3-phthalimidopropanone (V) (4), 1-hydroxy-3-phthalimidopropanone (VI) (5), and 1-acetoxy-3-phthalimidopropanone (VII) (6)—compounds which have been earlier prepared by other methods (4–6). The following new compounds were prepared: 1-methoxy-3-phthalimidopropanone (VIII), following the method of Casanova and Reichstein (7); 1-phenoxy-3-phthalimidopropanone (IX) from diazoketone and phenol; and 1-(2,4,6-trinitrophenoxy)-3-phthalimidopropanone (X), from diazoketone and picric acid.

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EXPERIMENTAL

N-Phthaloylglycyl chloride (II) was prepared by a slight modification of Gabriel's procedure (8). N-Phthaloylglycine (7 g.) was refluxed with 12 ml. of thionyl chloride during 1 hour and the solution distilled under reduced pressure, b.p. 190–192°/15 mm. Recrystallized from benzene, m.p. 84–85°.

1-Diazo-3-phthalimidopropanone (III). A solution of 7.5 g. of the recrystallized N-phthaloylglycyl chloride in 500 ml. of anhydrous ether was added gradually to a 500-ml.

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[1] Paper IV, *Helv. Chim. Acta*, **34**, 744 (1951).

ethereal solution of diazomethane (from 30 g. of nitrosomethylurea) during 15 minutes at 0°. Crystals of the diazoketone separated at once. After standing overnight the crystals were collected, m.p. 168° (decomp.), yield 5.8 g. (75%). After recrystallization from ethyl acetate the m.p. was unchanged.

Anal. Calc'd for $C_{11}H_7N_3O_3$: N, 18.34. Found: N, 18.13.

N-Phthaloyl-β-alanine ethyl ester (IV). To a warm solution of 2.5 g. of the diazoketone (III) in 30 ml. of ethanol was added a freshly prepared suspension of 0.1 g. of silver oxide in 5 ml. of ethanol. The reaction mixture was heated during 2 hours, until nitrogen evolution ceased, treated with a little charcoal, filtered, and evaporated under reduced pressure. The residual viscous yellow oil was repeatedly extracted with hot petroleum ether (b.p. 30–50°). From the petroleum ether extract 1.1 g. (35%) of white needles separated, m.p. 72–73°; lit. 73.5° (3).

Anal. Calc'd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67.
Found: C, 63.02; H, 5.34; N, 5.85.

1-Chloro-3-phthalimidopropanone (V). A suspension of 4.6 g. (0.02 mole) of the diazoketone (III) in 25 ml. of glacial acetic acid was treated with 5 ml. of concentrated hydrochloric acid. The reaction took place at room temperature, and crystallization occurred at once. After standing for a short time the reaction mixture was diluted with 200 ml. of water and the colorless crystals collected, m.p. 138°, yield: 4.12 g. (87.5%). On recrystallization from aqueous acetone the m.p. remained unchanged. Reported, m.p. 139.5° (4).

Anal. Calc'd for $C_{11}H_8ClNO_3$: C, 55.59; H, 3.39.
Found: C, 55.70; H, 3.11.

1-Hydroxy-3-phthalimidopropanone (VI). To a suspension of 6.9 g. of the diazoketone (III) (0.03 mole) in 30 ml. of ethanol previously heated to 60–70°, 25 ml. of water and 0.1 ml. of concentrated sulphuric acid were added. The reaction took place with evolution of nitrogen, and was completed in 15 minutes. At the end of the reaction all the components were in solution. On cooling, white crystals separated. Yield 5.4 g. (66%), m.p. 121°. On recrystallization from benzene and ethanol, a constant m.p. of 142° is obtained. Reported, m.p. 141–142° (5).

Anal. Calc'd for $C_{11}H_9NO_4$: N, 6.39. Found: N, 6.40.

1-Acetoxy-3-phthalimidopropanone (VII). The diazoketone (III, 3 g.) was gradually added to 20 ml. of glacial acetic acid previously heated to 50–60°. The reaction took place at once with evolution of nitrogen. The reaction mixture was then brought to the boiling point, heated 15 minutes, and left standing overnight. Yield 2.04 g. (59.7%), m.p. 135–136°. By diluting the mother liquor with an equal volume of water an additional yield of 0.55 g. (16.4%) of crystals, m.p. 125–131° was obtained. The substance was recrystallized from ether.

Anal. Calc'd for $C_{13}H_{11}NO_5$: N, 5.36. Found: N, 5.34.

1-Methoxy-3-phthalimidopropanone (VIII). The diazoketone (III, 3 g.), 100 ml. of methanol, and, according to procedure of Casanova and Reichstein (7), 1.5 g. of powdered cupric oxide, were refluxed during 4 hours. The mixture was treated with a little charcoal, filtered, and evaporated under reduced pressure. The residue was extracted with benzene. After the evaporation of benzene, 2.9 g. (95%) of white crystals remained, m.p. 88°. Recrystallized from petroleum ether, m.p. 89.5°.

Anal. Calc'd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75.
Found: C, 61.52; H, 4.72.

Semicarbazone, from VIII and semicarbazide acetate in methanol, m.p. 203°.

Anal. Calc'd for $C_{13}H_{14}N_4O_4$: C, 53.78; H, 4.86.
Found: C, 53.71; H, 5.04.

2,4-Dinitrophenylhydrazone, recrystallized from benzene-petroleum ether, m.p. 207°.

Anal. Calc'd for $C_{18}H_{15}N_5O_7$ C, 52.30; H, 3.66.
Found: C, 52.46; H, 4.05.

1-Phenoxy-3-phthalimidopropanone (IX). The diazoketone (III, 3 g.) was dissolved in 30 g. of phenol and held at 60° till the nitrogen evolution ceased (2–3 hours). The reaction mixture was then poured into a tenfold volume of water, left standing overnight at 0°, and the crystals collected and recrystallized from ethanol (charcoal). Yield 1.7 g. (48%) of colorless prisms, m.p. 159°.

Anal. Calc'd for $C_{17}H_{14}NO_4$: C, 68.91; H, 4.76; N, 4.73.
Found: C, 68.98; H, 4.51; N, 4.74.

1-(2,4,6)-Trinitrophenoxy-3-phthalimidopropanone (X). To a suspension of 2.29 g. (0.01 mole) of the diazoketone (III), 2.29 g. (0.01 mole) of picric acid was added. The mixture was refluxed for 30 minutes on a steam-bath, at which time the nitrogen evolution ceased. The new compound separated from the hot solution. Yield 1.90 g. (44%) of pale yellow needles. The substance was recrystallized from acetone, m.p. 207°.

Anal. Calc'd for $C_{17}H_{10}N_4O_{10}$: C, 47.45; H, 2.34; N, 13.03.
Found: C, 47.49; H, 2.30; N, 12.89.

SUMMARY

It is shown that N-disubstituted glycyl chlorides such as N-phthaloylglycyl chloride, do not react with diazomethane as hippuryl chloride, giving 5-oxazolones, but that 1-diazo-3-phthalimidopropanone (III) is obtained instead. A number of substituted phthalimidopropanones were prepared from III; compounds (VIII–X) are new.

ZAGREB, YUGOSLAVIA

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