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Preparation of β-Amino*iso*butyric Acid from Glycine *via* the Wolff Rearrangement of Diazoethylketones*

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A description is given of the conversion of 3-diazo-1-phthalimidobutan-2-one (Ia) into β-phthalimido*iso*butyranilide (IIa) *via* the Wolff rearrangement[7], in aniline solution, and further rearrangement to β-amino*iso*butyric acid. The same rearrangement in (-)-α-phenylethylamine solution is also described.

The following new compounds have been prepared from 3-diazo-1-phthalimidobutan-2-one: 3-bromo-1-phthalimidobutan-2-one, 3-hydroxy-1-phthalimidobutan-2-one, 3-acetoxy-1-phthalimidobutan-2-one, 3-(2,4,6-trinitrophenoxy)-1-phthalimidobutan-2-one, and *N*-[2-oxo-1-phthalimidobutyl(3)] pyridinium bromide.

On the basis of unpublished experiments[1] Eistert outlined some time ago the suitability of the Wolff rearrangement[2] of diazoethylketones for the conversion of carboxylic acids into their α-methyl homologues.

Wilds and Meader[3] used rearrangements at 170—180° in the presence of dimethylaniline and benzyl alcohol for obtaining benzyl esters of the rearranged acids. They applied this procedure to the diazoketones derived from aromatic carboxylic acids and diazomethane, diazoethane and diazopropane.

By successive addition of an ethanolic solution of aniline (1 mole) and of a 10 percent aqueous silver nitrate solution to an ethanolic solution of benzoyldiazoethane (1 mole), at 70°, Baddeley, Holt and Kenner[4] obtained β-anilinopropiophenone.

Later Newman[5] found that alpha hydrogen was necessary for this improved Wolff rearrangement of diazoketones in homogeneous medium; consequently, such treatment left benzoyldiazoethane (Ib) unchanged.

Franzen[6] has shown that α,β-unsaturated ketones having the formula $RCOCH=CHR_1$ can be obtained from diazoketones with the formula

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$RCOC(N_2)CH_2R_1$ in aqueous dioxane at room temperature, in the presence of catalytic amounts of silver oxide

$RCOC(N_2)CH_3$ (I) $\qquad$ $RCH(CH_3)CONHC_6H_5$ (II)

a, $R = C_6H_4(CO_2)NCH_2$

$RCH(CH_3)COOH$ (III) $\qquad$ a, $R = NH_2CH_2$; b, $R = Ph$

$C_6H_5(CH_3)CHNHCOC_6H_4CONHCH_2CH(CH_3)CONHCH(CH)C_6H_5$ (IV)

$C_6H_4(CO)_2NCH_2CONHCH(CH_3)C_6H_5$ (V)

We have successfully carried out the conversion of carboxylic acids RCO_2H into the α-methyl homologous acids (III) *via* the Wolff rearrangement of the corresponding diazoethylketone (I) in aniline for 15—20 minutes, at 90—100°, in the presence of catalytic quantities of silver oxide[7]. Acid hydrolysis of the anilide (II) thus obtained gave the α-methyl homologous acid (III).

In this manner we prepared β-amino*iso*butyric acid (IIIa) from glycine *via* the Arndt-Eistert synthesis[8], α-phenyl propionanilide (IIb) from benzoic acid, and several optically active α-methyl-β-amino acids from *N*-phthaloyl derivatives[9] of natural amino acids[10].

Our attempts to carry out the Wolff rearrangement of diazoethylketones with benzyl alcohol and silver oxide at 90—100° were unsuccessful, which is in agreement with other authors.

We attempted the Wolff rearrangement of 3-diazo-1-phthalimidobutan-2-one (Ia) in optically active α-phenylethylamine, anticipating the possibility of obtaining the optically active β-phthalimido*iso*butyric acid, but the hydrolysis of the reaction product, which proved to be a substituted phthalamic acid (IV), gave the inactive β-amino*iso*butyric acid. For identification purposes, (-)-*N*-phthaloylglycyl-(α-phenylethyl)amide (V) was also prepared.

DL-β-Aminoisobutyric acid has been previously synthesised[11, 12, 13]; the (-)-antipode has been isolated from urine[14].

The following new compounds have also been prepared from 3-diazo-1-phthalimidobutan-2-one: 3-bromo-1-phthalimidobutan-2-one, 3-hydroxy-1-phthalimidobutan-2-one, 3-acetoxy-1-phthalimidobutan-2-one, 3-(2,4,6-trinitrophenoxy)-1-phthalimidobutan-2-one, and *N*-[2-oxo-1-phthalimidobutyl(3)] pyridinium bromide.

EXPERIMENTAL

All melting points are uncorrected, unless otherwise stated.

3-Diazo-1-phthalimidobutan-2-one (Ia)

To an ethereal solution of diazoethane (2.05 g., 0.097 mole, in 800 ml. of ether; prepared from about 30 g. of nitrosoethylurea) finely powdered phthalylglycyl chloride (10 g., 0.044 mole) was added, with stirring, at 0°. The precipitate of *3-diazo-1-phthalimidobutan-2-one* immediately separated, and after standing overnight at 0° the separation was complete. Yield 65—75%, m. p. 135°. The analytical sample

was recrystallized from ethyl acetate, and yellow platelets with the unchanged m. p. were obtained.

Anal. 10.90 mg. subst.: 23.77 mg CO_2, 3.67 mg. H_2O
$C_{12}H_9O_3N_3$ (243.22) calc'd.: C 59.26; H 3.73%
found: C 59.51; H 3.77%

Benzoyldiazoethane (Ib)

This compound was prepared from an ethereal diazoethane solution (2 moles) and freshly distilled benzoyl chloride (1 mole) at 0°. After standing overnight the ether was removed *in vacuo* at room temperature, and the remaining oily yellow benzoyldiazoethane was used without further purification.

β-Phthalimidoisobutyranilide (IIa)

A mixture of 3-diazo-1-phthalimidobutan-2-one (Ia, 30 g., 0.123 mole) and freshly distilled aniline (300 ml.) was heated in a 1 l. round-bottomed flask in the presence of a small quantity of freshly prepared silver oxide (previously washed with water, absolute methanol, and finally with aniline). At 90° the evolution of nitrogen began, which was intensified by occasional addition of fresh quantities of silver oxide. When the evolution of nitrogen got vigorous the heating was discontinued, since the temperature rose spontaneously to 110—120°. The reaction was complete after 15 minutes, and the reaction mixture was heated for another 15 minutes at 130°. It was then poured into a mixture of finely crushed ice (1 kg.), and concentrated hydrochloric acid (350 ml.), and after standing for a few hours filtered and washed with water. The crude *β-phthalimidoisobutyranilide* was obtained in yields of 28.9—31.5 g. (76—83%), and showed the m. p. 159—162°. Recrystallization from ethanol gave 20 g. (53%) of colourless needles, m. p. 180°. The analytical sample was recrystallized several times from ethanol, the m. p. remained unchanged.

Anal. 10.75 mg. subst.: 27.74 mg. CO_2, 5.30 mg. H_2O
$C_{18}H_{16}O_3N_2$ (308.32) calc'd.: C 70.12; H 5.23%
found: C 70.41; H 5.52%

α-Phenylpropionanilide (IIb)

This compound was prepared in the same manner as IIa. α-Diazopropiophenone (obtained from 1.2 g. of benzoyl chloride) gave 0.55 g. (28%) of crude *α-phenylpropionanilide*. Recrystallization from dichloromethane-petroleum ether gave colourless prisms, m. p. 131°. Lit. m. p. 133—134° [15].

Anal. 7.88 mg. subst.: 23.11 mg. CO_2, 4.81 mg. H_2O
$C_{15}H_{15}ON$ (225.28) calc'd.: S 79.97; H 6.71%
found: C 80.08; H 6.83%

β-Aminoisobutyric Acid

β-Phthalimidoisobutyranilide (IIa, 20 g.) was refluxed for ten hours in a mixture of glacial acetic acid (120 ml.) and 47% hydriodic acid (60 ml.). After standing overnight the phthalic acid was filtered off and washed with a few milliliters of glacial acetic acid. The filtrate was evaporated *in vacuo* to dryness, dissolved in redistilled water (250 ml.), and again evaporated to dryness. The residue was again dissolved in water (300 ml.), and shaken with ether to remove traces of phthalic acid. The aqueous solution was evaporated to dryness *in vacuo*, and the mixture of aniline hydriodide and β-aminoisobutyric acid dissolved in redistilled water (750 ml.), treated with charcoal, and filtered. The charcoal was washed with 1 l. of redistilled water, and the combined filtrates diluted to 6 l. This solution was passed through a column (3.6 × 73 cm.) of Amberlite IR-4B (20—50 mesh, 290 g., 600 ml.), and washed with 3 l. of redistilled water. The filtrate was evaporated to dryness *in vacuo*, and the residue dried in high vacuum at 80°. *β-Aminoisobutyric acid* was obtained in a yield of 6.69 g. (100%), and showed the m. p. 172—174° (decomp.). The analytical sample

was repeatedly recrystallized from aqueous acetone (1:5), and colourless platelets with the m. p. 179° were obtained. Lit. m. p. 180° [11].

Anal. 9.29 mg. subst.: 15.96 mg. CO_2, 7.39 mg. H_2O
$C_4H_9O_2N$ (103.12) calc'd.:C 46.59; H 8.80%
found: C 46.90; H 8.90%

Rearrangement of 3-Diazo-1-phthalimidobutan-2-one in (-)-α-Phenylethylamine. Isolation of the Reaction Product IV.

A solution of 3-diazo-1-phthalimidobutan-2-one (4.8 g., 0.02 mole) in (-)-α-phenylethylamine (16 g., $[\alpha]_D^{18}$ — 35°, prepared according to Cumming et al.[16]) was treated with silver oxide (0.25 g.) at 100° in the same manner as described for β-phthalimidoisobutyranilide. The phthalic acid diamide IV was extracted from the crude reaction mixture with acetone, and after evaporation of the solvent 8.2 g. (89%) of the compound IV remained, showing $[\alpha]_D^{18}$ — 50°. Several recrystallizations from methanol gave thin colourless needles with the constant m. p. 221° (corr.), and showed $[\alpha]_D^{17}$ — 68° ± 7° (c, 0.118 in ethanol).

Anal. 7.21 mg. subst.: 19.43 mg. CO_2, 4.48 mg. H_2O
5.17 mg. subst.: 0.4008 ml. N_2 (18.8°, 750 mm.)
$C_{28}H_{31}O_3N_3$ (456.97) calc'd.: C 73.46; H 6.82; N 9.18%
found:C 73.54; H 6.95; N 8.90%

Hydrolysis of the Reaction Product IV to β-Aminoisobutyric Acid

Hydrolysis of IV and the isolation of β-aminoisobutyric acid was carried out in the same manner as described for β-phthalimidoisobutyranilide. The β-aminoisobutyric acid obtained was optically inactive, and was identified by m. p., mixed m. p., R_f values and analysis.

(-)-N-Phthaloylglycyl-(α-phenylethyl)amide (V)

A mixture of phthalylglycyl chloride (1 mole) and (-)-α-phenylethylamine (2 moles) was left overnight at room temperature. Next morning the reaction mixture was dissolved in acetone and poured into the tenfold quantity of cold 10% hydrochloric acid. The *(-)-N-phthaloylglycyl-(α-phenylethyl)amide* was filtered off and recrystallized from methanol until the constant m. p. 241° (corr.) was obtained, and it showed $[\alpha]_D^{17}$ — 143° ± 8° (c, 0.10 in ethanol).

Anal. 6.77 mg. subst.: 17.39 mg. CO_2, 3.34 mg. H_2O
$C_{18}H_{16}O_3N_2$ (308.32) calc'd.: C 70.11; H 5.22%
found.: C 70.09; H 5.52%

3-Hydroxy-1-phthalimidobutan-2-one

A solution of 3-diazo-1-phthalimidobutan-2-one (Ia, 2 g., 0.008 mole) in glacial acetic acid (10 ml.) was treated with 48% hydrobromic acid (3 ml.), under cooling. The reaction took place with evolution of nitrogen. After 20 minutes water (150 ml.) was added, and the reaction mixture left at 0° overnight. The precipitate was filtered off and dried. The yield of crude *3-bromo-1-phthalimidobutan-2-one* was 1.6 g. (66.6%), m. p. 93—95°. Repeated recrystallization from dichloromethane-petroleum ether (1:5) gave colourless prisms showing the m. p. 101°.

Anal. 10.07 mg. subst.: 18.05 mg. CO_2, 3.23 mg H_2O
$C_{12}H_{10}O_3NBr$ (296.12) calc'd.: C 48.67; H 3.40%
found: C 48.94; H 3.59%

3-Hydroxy-1-phthalimidobutan-2-one

A mixture of 3-diazo-1-phthalimidobutan-2-one (Ia, 1.22 g., 0.005 mole), benzoic acid (0.61 g., 0.005 mole) and dioxane (10 ml.) was heated on a water bath (95—100°)

for 3 hours. Water (10 ml.) was then added, and the reaction mixture left at 0° for 4 hours. Instead of 3-benzoyloxy-1-phthalimidobutan-2-one, *3-hydroxy-1-phthalimidobutan-2-one* was obtained as a yellow oil. Several recrystallizations from benzene gave colourless leaflets of the m. p. 161°.

Anal. 8.75 mg. subst.: 19.88 mg. CO_2, 3.74 mg. H_2O
$C_{12}H_{11}O_4N$ (233.22) calc'd.: C 61.80; H 4.75%
found: C 62.03; H 4.78%

3-Acetoxy-1-phthalimidobutan-2-one

A mixture of 3-diazo-1-phthalimidobutan-2-one (Ia, 1.22 g., 0.005 mole) and glacial acetic acid (7.5 ml.) was heated to 40°, and the heating discontinued when the temperature rose spontaneously to 70—80°, with evolution of nitrogen. After 15 minutes water (50 ml.) was added and the mixture left at 0° overnight. The precipitate was filtered off, and 0.92 g. (67%) of crude *3-acetoxy-1-phthalimidobutan-2-one* was obtained, showing the m. p. 108—120°. After repeated recrystallization from aqueous acetone (1:1) the compound the sublimed at 110°/0.02 mm.; colourless needles of the m. p. 119—120° were obtained.

Anal. 6.32 mg. subst.: 14.17 mg. CO_2, 2.79 mg. H_2O
$C_{14}H_{13}O_5N$ (275.25) calc'd.: C 61.09; H 4.76%
found: C 61.18; H 4.94%

1-Phthalimido-3-(2,4,6-trinitrophenoxy)butan-2-one

A mixture of 3-diazo-1-phthalimidobutan-2-one (Ia, 0.49 g., 0.002 mole) and picric acid (0.46 g., 0.002 mole) was dissolved in acetone (5 ml.). Evolution of nitrogen occurred. After 10 minutes a few drops of water were added, and the reaction mixture left at room temperature for half an hour. The separated *1-phthalimido-3-(2,4,6-trinitrophenoxy)butan-2-one* was filtered off, and washed with ethanol. Yield 0.37 g. (41.6%) of pale yellow crystals, m. p. 180—183°. Repeated recrystallization from benzene gave colourless needles with the m. p. 187° .

Anal. 8.08 mg. subst.: 14.40 mg. CO_2, 1.96 mg. H_2O
$C_{18}H_{12}O_{10}N_4$ (444.31) calc'd.: C 48.66; H 2.72%
found: C 48.94; H 2.73%

N-[2-Oxo-1-phthalimidobutyl-(3)]pyridinium bromide

To a solution of 3-bromo-1-phthalimidobutan-2-one (0.6 g., 0.002 mole) in acetone (6 ml.) pyridine was added (0.27 g., 0.0034 mole) and the mixture left for two days at room temperature. The precipitate was filtered off and washed with acetone; yield 0.49 g. (67%) of crude *N-[2-oxo-1-phthalimidobutyl-(3)]pyridinium bromide*, m. p. 158—160°. Recrystallization from absolute ethanol gave the monohydrate as colourless platelets, showing the m. p. 171—172°.

Anal. 9.73 mg. subst.: 18.55 mg. CO_2, 3.90 mg. H_2O
$C_{17}H_{17}O_4N_2Br$ (393.24) calc'd.: C 51.92; H 4.36%
found: C 52.05; H 4.49%

Drying at 100° and 0.01 mm. for 5 hours gave the anhydrous compound.

Anal. 10.20 mg. subst.: 20.25 mg. CO_2, 3.83 mg. H_2O
$C_{17}H_{15}O_3NBr$ (375.22) calc'd.: C 54.41; H 4.03%
found: C 54.20; H 4.20%

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IZVOD

Preparacija β-aminoizomaslačne kiseline iz glicina Wolffovim premještajem diazoetilketona

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3-Diazo-1-ftalimidobutan-2-on (Ia) je Wolffovim premještajem[7] u anilinu preveden u β-ftalimidoizobutiranilid (II) i dalje u β-aminoizomaslačnu kiselinu. Opisan je isti premještaj u (-)-α-feniletilaminu.

Iz 3-diazo-1-ftalimidobutan-2-ona priređeni su ovi novi spojevi: 3-bromo-1-ftalimidobutan-2-on, 3-oksi-1-ftalimidobutan-2-on, 3-acetoksi-1-ftalimidobutan-2-on, 3-(2,4,6-trinitrofenoksi)-1-ftalimidobutan-2-on i N-[2-okso-1-ftalimidobutil(3)]piridinium bromid.

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