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Application of the Arndt-Eistert Synthesis to the Preparation of Dipeptides of β-Amino Acids

D. Fleš and A. Markovac-Prpić

Research Department »Pliva« Pharmaceutical and Chemical Works, Zagreb
and
Chemical Institute, Faculty of Science, University of Zagreb, Strossmayerov trg 14, Zagreb, Croatia, Yugoslavia

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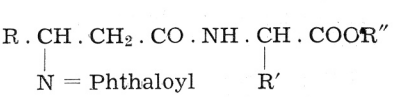
After it has been discovered by Balenović[1] that the Arndt-Eistert synthesis can be applied to the *N*-phthaloyl amino acids, many papers have appeared relating to the problem of synthesis of β-amino acids. The Wolff rearrangement of diazomethyl-*N*-phthaloyl-aminoalkyl ketones was generally performed in alcohols[2], although in some preparations the aniline was used and the corresponding anilides were obtained as primary products[3]. However many other protonic reagents (water, ammonia, substituted amines etc.) were used in the Arndt-Eistert synthesis and the different derivatives of carboxylic acids could be isolated in this way.[4]

So far as we know the Arndt-Eistert synthesis has not been performed in the presence of esters of amino acids. In the course of our studies on the synthesis of dipeptides of homologous amino acids we outlined a direct synthesis of dipeptides by rearranging diazomethyl-*N*-phthaloyl-aminoalkyl ketones in the presence of esters of amino acids. The reaction was accomplished in dioxane in the presence of silver oxide as a catalyst. A vigorous evolution of nitrogen occured at 60—70° and the dipeptides of the phthalimido-homoacids were isolated in a yield ranging from 20—60%. In all preparations except in the preparation of the compound II, the racemic amino acids were used. The synthesis of the compound II was accomplished by rearranging the diazomethyl-*N*-phthaloyl-aminomethyl ketone in the presence of L-alanine ethyl ester, and the optically active dipeptide was thus obtained.

TABLE I



I	R = R′ = H	R″ = CH_3	
II	R = H	R′ = CH_3	R″ = C_2H_5
III	R = H	R′ = CH_2OCH_3	R″ = C_2H_5
IV	R = R″ = CH_3	R′ = H	
V	R = CH_3	R′ = CH_2OCH_3	R″ = C_2H_5

The most important side reaction was that leading to the formation of diketopyperazines, especially if methyl ester of glycine was used in the reaction.

There is an appreciable difference in the rates with which various diazoketones rearrange and form dipeptides. With the diazoketone of glycine the

reaction was complete in ten minutes, while with alanine it took about an hour.

We consider that the method described in this paper represents a convenient route for the preparation of dipeptides of β-amino acids, since the compounds described in the experimental part of this communication can be easily converted to the dipeptides according to the standard methods[5, 6]

EXPERIMENTAL*

N-*Phthaloyl-β-alanyl-*L-*alanine ethyl* (II)

A mixture of 1.2 g. of diazomethyl-*N*-phthaloyl-aminomethyl ketone[1], 1.5 ml. of L-alanine ethyl ester and 6 ml. of purified dioxane was heated on the water-bath at 60° and the freshly prepared suspension of silver oxide in dioxane was added gradually. A vigorous evolution of nitrogen occured and the reaction was accomplished in about ten minutes. The reaction mixture was cooled, silver oxide removed by filtration under suction, washed with ethyl acetate and the yellow solution evaporated under reduced pressure to a semicrystalline residue. The crude product was dissolved in 50 ml. of ethyl acetate, washed with 20 ml. of *N*-hydrochloric acid, neutralized with 10 ml. of a saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of ethyl acetate afforded 1.5 g. of a crystalline product which was crystallized from 5 ml. of ethyl acetate and 3 ml. of petroleum ether. A yield of 0.9 g. (53.9%) of white needles was obtained; m. p. 144—147°. A sample for analysis was crystallized twice from a mixture of ethyl acetate and petroleum ether to a melting point of 150—151°; $[\alpha]_D^{19}$ —1.5° ± 0.15° (c 10.3% in dioxane).**

Anal. 12.64 mg. subst: 28.00 mg. CO_2, 6.32 mg. H_2O
3.41 mg. subst.: 0.274 ml. N_2 (29°, 758 mm.)
$C_{16}H_{18}O_5N_2$ (318.22) calc'd.: C 60,37; H 5.70; N 8.80%
found: C 60.45; H 5.59; N 9.05%

N-*Phthaloyl-β-alanyl-glycine methyl ester* (I)

The compound I was prepared from 1.24 g. of diazomethyl-*N*-phthaloyl-aminomethyl ketone and 1.5 ml. of glycine methyl ester in 6 ml. of dioxane. The crude dipeptide (1.1 g., m. p. 149—156°) was crystallized from 10 ml. of ethanol to give 0.75 g. (47.8%) of white needles melting at 157—159°. A sample for analysis was recrystallized twice from ethyl acetate to a melting point of 162—162.5°.

Anal. 14.01 mg. subst. 29.68 mg. CO_2, 5.86 mg. H_2O
4.83 mg. subst.: 0.412 ml. N_2 (25°, 754 mm.)
$C_{14}H_{14}O_5N_2$ (290.27) calc'd.: C 57.93; H 4.86; N 9.65%
found: C 57.81; H 4.68; N 9.68%

N-*phthaloyl-β-alanyl-*O-*methyl-*DL-*serine ethyl ester* (III)

The compound III was prepared from 0.45 g. of diazomethyl-*N*-phthaloyl-aminomethyl ketone and 0.5 ml. of *O*-methyl-DL-serine ethyl ester in 2 ml. of dioxane The crude product (0.5 g., m. p. 143—145°) was crystallized from 4 ml. of ethyl acetate to give 0.41 g. (59.8%) of needles melting at 149—152°. A sample for analysis was crystallized from ethyl acetate to a melting point of 152—153.°.

Anal. 11.59 mg. subst.: 24.79 mg. CO_2, 5.61 mg. H_2O
3.94 mg. subst.: 0.284 ml. N_2 (26°, 756 mm.)
$C_{17}H_{20}O_6N_2$ (348.35) calc'd.: C 58.61; H 5.79; N 8.04%
found: C 58.37; H 5.41; N 8.18%

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* The melting points are uncorrected

** A sample of *N*-phthaloyl-β-alanyl-L-alanine ethyl ester, prepared according to the standard method[7] had a specific rotation of $[\alpha]_D^{20}$ —.1.3° (c 10.0% in dioxane) and gave no depression of melting point when mixed with the compound II.

DL-N-*Phthaloyl-β-aminobutyryl-glycine methyl ester* (IV)

The compound IV was prepared from 1.4 g. of diazomethyl-*N*-phthaloyl-α-aminoethyl ketone[1] and 1.5 ml. of glycine methyl ester in 6 ml. of dioxane. The crude semicrystalline product (1.1 g.) was dissolved in 3 ml. of ethanol and left at room temperature overnight. 0.2 g. of almost pure diketopyperazine was obtained by filtration under suction. The alcoholic mother liquor was evaporated under reduced pressure and the oily residue was dissolved in a mixture of 5 ml. of benzene and 5 ml. of petroleum ether. After standing for several days at room temperature a crop of 0.5 g. of white crystals separated. Yield 28.5%;* m. p. 110—115°. A sample was purified for analysis from a mixture of benzene and petroleum ether (1 : 1) to a melting point of 119—120°.

Anal. 17.00 mg. subst.: 36.95 mg. CO_2, 7.89 mg. H_2O
4.58 mg. subst.: 0.372 ml. N_2 (26°, 754 mm.)
$C_{15}H_{16}O_5N_2$ (304.29) calc'd.: C 59.20; H 5.30; N 9.21%
found: C 59.31; H 5.19; N 9.20%

DL-N-*Phthaloyl-β-aminobutyryl-O-methyl-*DL-*serine ethyl ester* (V)

The compound V was prepared from 1.1 g. of diazomethyl-*N*-phthaloyl-α-aminoethyl ketone and 1.4 ml. of O-methyl-DL-serine ethyl ester in 6 ml. of dioxane at 80°. The crude oily product (1 g.) was dissolved in 3 ml. of ethyl acetate and 5 ml. of petroleum ether were added. After standing overnight at room temperature a crop of 0.25 g. was obtained. Yield 15.4%*; m. p. 118—119°. A sample for analysis was crystallized from a mixture of ethyl acetate and petroleum ether (1 : 2). White needles, m. p. 125—126°.

Anal. 11.90 mg. subst.: 26.01 mg. CO_2, 6.22 mg. H_2O
8.03 mg. subst.: 0.549 ml. N_2 (28°, 755 mm.)
$C_{18}H_{22}O_6N_2$ (362.37) calc'd.: C 59.66; H 6.12; N 7.73%
found: C 59.64; H 5.84; N 7.69%

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IZVOD

Pripravljanje dipeptida β-amino kiselina primjenom Arndt-Eistert-ove reakcije

D. Fleš i A. Markovac-Prpić

Ako se Wolff-ovo pregrađivanje diazometil-*N*-ftaloil-aminoalkil ketona provede u prisutnosti estera amino kiselina, dobiju se pripadni derivati dipeptida β-amino kiselina. Reakcija se provodi u dioksanu uz srebrni oksid kao katalizator.

* No attempt has been made so far to recover more of the dipeptide from the mother liquors.

Priređeni su slijedeći dipeptidi: N-*ftaloil*-β-*alanil*-*glicin metilni ester* (I), bijele iglice iz etil acetata, t. t. 162—162,5°; N-*ftaloil*-β-*alanil*-L-*alanin etilni ester* (II), bijele iglice iz smjese etil acetata i petrol etera, t. t. 150—151°, $[\alpha]_D^{19}$ —1.5°; N-*ftaloil*-β-*alanil*-O-*metil*-DL-*serin etilni ester* (III), iglice iz etil acetata, t. t. 152—153°; DL-N-*ftaloil*-β-*aminobutiril*-*glicin metilni ester* (IV), t. t. 119—120°; DL-N-*ftaloil*-β-*aminobutiril*-O-*metil*-DL-*serin etilni ester* (V), bijele iglice iz smjese etil acetata i petrol etera (1 : 2), t. t. 125—126°.

ISTRAŽIVAČKI INSTITUT
»PLIVA« TVORNICA FARMACEUTSKIH I KEMIJSKIH PROIZVODA
I
KEMIJSKI INSTITUT
PRIRODOSLOVNO-MATEMATIČKI FAKULTET
ZAGREB

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