Amino-Protecting Groups Removable by Neighboring-Group Assistance. II.[1] The *o*-Phenazophenoxyacetyl Moiety

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The *o*-phenazophenoxyacetyl moiety has been found to be an effective amino-protecting group for several amino esters. It can be introduced *via* acylation of the amino ester with an appropriate carboxylic acid. The removal of this blocking group was easily accomplished by reduction of the azo portion using potassium borohydride and palladium on carbon followed by acidification of the reaction mixture. An intramolecular rearrangement occurred which was followed by fragmentation into a benzoxazinone and the regenerated amino ester. Both the introduction and removal of this amino-protecting group were completed in higher yields than those obtained in previous procedures which employed the *o*-nitrophenoxyacetyl blocking group.

The rapid removal of the *o*-nitrophenoxyacetyl amino-protecting group by neighboring group assistance was recently reported.[1] The procedure involved the reduction of the nitro portion to the hydroxylamino stage using zinc and ammonium chloride. The blocking group was then removed as a result of the attack of the nucleophilic hydroxylamino moiety on the neighboring amide linkage. The overall yields of this procedure ranged from 45 to 78% depending on which amino acid was involved.

The mild conditions and the simplicity of this procedure led us to extend the investigation to other functional groups which are also capable of intramolecular participation. As a result, we have found that the *o*-phenazophenoxyacetyl moiety was superior in almost every way when compared with the *o*-nitro compound. Specifically, we used two phenazo blocking groups, one derived from α-methyl-α-(4,5-dimethyl-2-phenazophenoxy)propionic acid (**1**, herein named the DAZ group) and the other derived from α-methyl-α-(4-methyl-2-phenazophenoxy)propionic acid (**2**, herein named the MAZ group). Either of these compounds were easily coupled to the amino portion of several amino acid esters *via* the EEDQ procedure[2] in excellent yield (Scheme I). The protected amino esters **3** and **4** were generally obtained as highly colored oils or glasses that were homogeneous products according to their thin layer chromatograms. Characterization of these intermediates (**3** and **4**) was made from spectral data (uv, ir, nmr) and from subsequent chemical reactions.

The conversion of the phenazo group in **3** or **4** to a nucleophilic reduction product, **5** or **6**, was accomplished using several reducing agents. Zinc dust and ammonium hydroxide and aluminum amalgam were both found to effect the desired reduction. However, the preferred reagent was potassium borohydride and palladium on carbon, which rapidly and completely reduced **3** or **4** within 45 min at 5°.

The phenylhydrazo (**5**) or the anilino (**6**) intermediates were not isolated and characterization was difficult because of their unstable nature. The method of reduction of **3** or **4** could yield either or both of these intermediates and either would be expected to be an effective nucleophile[3] in the subsequent fragmentative cyclization.

The 45-min reduction of **3** or **4** with potassium borohydride and palladium on carbon was immediately followed by acidification of the reaction mixture. An assisted cleavage of the amide bond resulted and two products were isolated and identified. One was the deblocked amino ester hydrochloride **7** and the other was a 3,4-dihydro-2,2-dimethyl-2*H*-1,4-benzoxazin-3-one, **8** or **9**. The formation of **8** and **9** indicated that the reduction of the phenazo group of **3** or **4** apparently proceeded all the way to the amino stage. It is still unclear at what point the phenylhydrazo moiety in **5** fragmented: before or after the acidification step. Aniline was never isolated from the reaction mixture and did not interfere with the main object of the experiment: the deblocking of an amino ester.

The starting materials **1** and **2** were prepared by the following reaction scheme (Scheme II). The 2-phenylazo-4,5-xylenol (**10**) was obtained from a commercial source (however, it is no longer available). The 2-phenylazo-4-cresol (**11**) was prepared by a classical diazotization and coupling experiment.[4] The preparations of the phenazophenoxypropionic acids, **1** and **2**, from **10** and **11** were accomplished using a procedure that has been previously employed in the preparation of a variety of α-aryloxy aliphatic carboxylic acids.[5]

Deblocking experiments were performed on five different amino esters which were each protected with the DAZ and MAZ groups. The MAZ-amino esters **4** were found to be deblocked in better yield than the DAZ-amino esters **3** in every case. Table I summarizes the results of these experiments. For comparison purposes, this table also contains the results of the reduction and subsequent deblocking of DAZ-amino esters with other reducing agents.

The yields of amino ester hydrochlorides **7** obtained by the reductive fragmentation of MAZ-amino esters (Table I) are the results of one-run experiments in most cases. The present procedure of preparing and removing amino-protecting groups has advantages other than high yields. The protected amino esters **3** and **4** are very deeply colored derivatives of the colorless amino acids or amino esters with characteristic ultraviolet and visible spectra (intermediate **1** has an ultraviolet maximum at 333 mμ). The starting materials are inexpensive and the chemical conversions involved are simple procedures which give uniformly high yields. The present method, therefore, represents a simple, rapid,

(1) Paper I: C. A. Panetta, *J. Org. Chem.*, **34**, 2773 (1969).

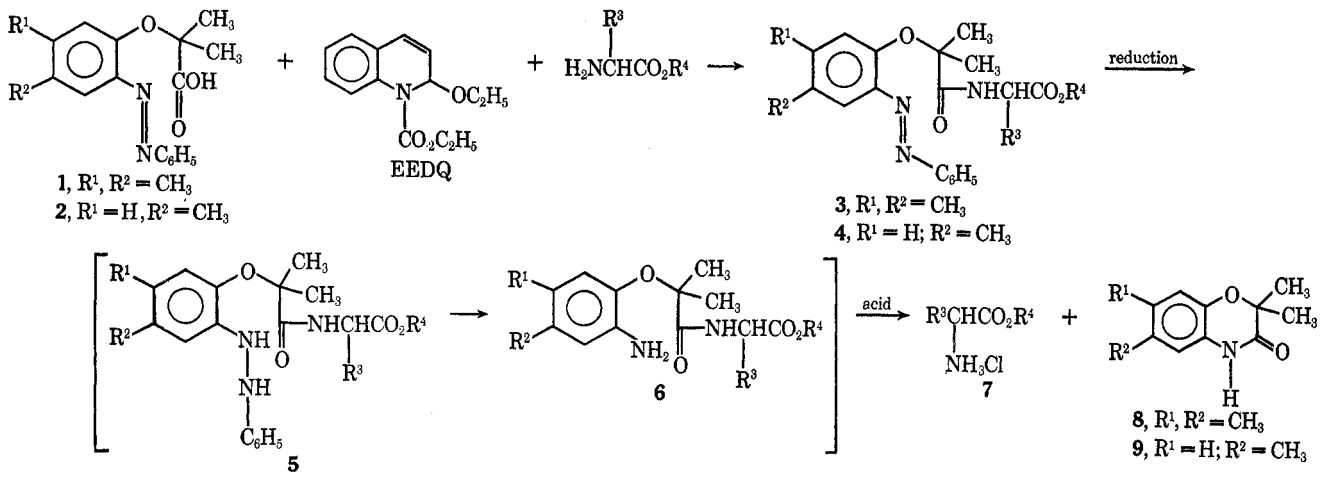
(2) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, **90**, 1651 (1968).

(3) For a report on the nucleophilic amino group in a similar reaction, see R. W. Holley and A. D. Holley, *ibid.*, **74**, 3069 (1952).

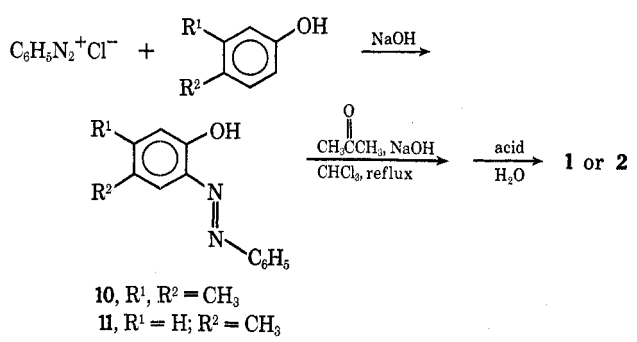
(4) E. Nölting and O. Kohn, *Ber.*, **17**, 351 (1884); C. Liebermann and St. V. Kostanecki, *ibid.*, **17**, 876, (1884).

(5) W. G. M. Jones, J. M. Thorp, and W. S. Waring, British Patent 860,303 (Feb 1, 1961); *Chem. Abstr.*, **55**, 24680b (1961).

SCHEME I



SCHEME II



and effective procedure for the temporary protection of amino groups found in amino acids or amino esters.

Experimental Section[6]

2-Phenylazo-4-cresol (11).—This starting material was prepared using a published procedure.[4] It was obtained in quantitative yield and melted at 105–106° (lit.[4] mp 105–106°).

α-Methyl-α-(4-methyl-2-phenylazophenoxy)propionic Acid (2).—A mixture of 6.36 g (0.03 mol) of 2-phenylazo-4-cresol, 12.1 g (0.03 mol) of sodium hydroxide, and 33.9 g (0.58 mol) of acetone was heated to reflux. Chloroform, 8.4 g (0.07 mol), was added dropwise and, after the addition was complete, the resulting mixture was heated to reflux for 5–6 hr. The solvents were removed by distillation at reduced pressure and the residue was then distributed between water and chloroform at pH 2. The dried chloroform extract was concentrated to a small volume under reduced pressure and the concentrate was eluted on a silicic acid (100-mesh) column with benzene. Crystals were obtained, 4.3 g (48.1%), mp 83–84°.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.56; H, 5.90; N, 9.49. Found: C, 68.45; H, 6.04; N, 9.39.

General Procedure for the Preparation of MAZ-Amino Esters 4.—The following procedure was used essentially unchanged for the preparation of all of the MAZ-amino esters. The amino ester hydrochloride (3.3 mmol) was dissolved in water and extracted with chloroform at pH 9.0. The chloroform solution was dried and the solvent was removed by distillation under reduced pressure. The residual oil was dissolved in 50 ml of THF. To the resulting solution was added 1.0 g (3.3 mmol) of α-methyl-α-(4-methyl-2-phenylazophenoxy)propionic acid (2) and 0.82 g (3.3 mmol) of EEDQ.[2] The reaction mixture was stirred at ambient temperature for 5–6 hr. The solvent was removed *in vacuo* and the residue was purified by silicic acid column chromatography with benzene as the eluting solvent. The MAZ-amino esters were obtained as deep red or orange colored oils or glasses that were homogeneous according to thin layer chromatography on silica gel coated plates using benzene–ethyl acetate (90:10) as the eluting solvent. The ir and nmr spectra of these products were consistent with the structure given 4. The yields obtained for the various MAZ-amino esters are as follows: MAZ-glycine ethyl ester, 93.7%; MAZ-leucine ethyl ester, 91.2%; MAZ-valine methyl ester, 94.2%; MAZ-phenylalanine methyl ester, 96.9%; and MAZ-alanine ethyl ester, 82.9%.

General Procedure for the Deblocking of MAZ-Amino Ester 4.—A solution of 3.8 mmol of the MAZ-amino ester 4 in 50 ml of methyl isobutyl ketone was added dropwise to a stirred and chilled mixture of 46.5 mmol of KBH_4 and 0.17 g of 5% Pd on carbon in 50 ml of water. The mixture was stirred for 1 hr after the addition was completed. It was filtered through Celite and the pH of the filtrate was adjusted to 1.0. The organic layer was separated and dried and the methyl isobutyl ketone was removed by distillation under reduced pressure. The crystalline residue was recrystallized from EtOAc and petroleum ether (bp 30–60°) to afford pure 3,4-dihydro-2,2,6-trimethyl-2*H*-1,4-benzoxazin-3-one (9), mp 153–154°; homogeneous according to thin layer chromatography on silica gel coated plates using benzene–ethyl acetate (90:10) as the eluting solvent. The ir and nmr spectra were consistent with the structure of 9. The yields obtained in five different experiments are listed in Table I.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found: C, 69.33; H, 7.00; N, 7.40.

The pH 1.0 aqueous layer was adjusted to pH 11–12 and extracted with ether, and the resultant ether extract was dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the filtrate was then treated with gaseous HCl until it was thoroughly saturated. An oily solid at first separated and then slowly crystallized. It was recrystallized from ether–ethanol to yield the pure deblocked amino ester hydrochloride 7. This was characterized by direct comparison of thin layer chromatogram R_f values and ir spectral properties with those of authentic samples. The chromatograms were run on silica gel coated plates and the eluting solvent was CH_3OH–NH_4OH (98:2). The ir spectra were run on Nujol mulls. The yields obtained in deblocking experiments on five different MAZ-amino esters are listed in Table I. Two amino ester hydrochlorides (valine and phenylalanine) required chromatography on silicic acid (100-mesh) columns (eluent, methanol) before they were obtained as homogeneous products.

α-Methyl-α-(4,5-dimethyl-2-phenylazophenoxy)propionic Acid (1).—2-Phenylazo-4,5-xylenol (10) (Aldrich Chemical Co.) was treated with NaOH, $CHCl_3$, and acetone in essentially the same manner as was 2-phenylazo-4-cresol (above). Chromatography on a silicic acid column was performed first with petroleum ether (bp 30–60°) as the eluting solvent, in order to remove some starting material, and then with a 1:1 mixture of petroleum ether and benzene which eluted the product. The latter was recrystallized from petroleum ether (bp 30–60°) to afford pure 1, mp 125–126°; ir and nmr spectra were consistent with the structure of 1.

Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.32; H, 6.58; N, 9.13.

(6) Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., or by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany. Melting points were not corrected.

TABLE I

SUMMARY OF RESULTS OF DEBLOCKING EXPERIMENTS ON SEVERAL MAZ- AND DAZ-AMINO ESTERS

Protected amino ester[a]				Benzoxazinone		
Formula no.	R^3	R^4	% yield of deblocked amino ester hydrochloride **7**	% yield	Formula no.	Reducing agent
4	H	C_2H_5	89.4 (glycine)	47.0	9	KBH_4
4	$(CH_3)_2CHCH_2$	C_2H_5	87.6 (leucine)	40.0	9	KBH_4
4	$(CH_3)_2CH$	CH_3	83.5 (valine)	51.0	9	KBH_4
4	CH_3	C_2H_5	89.2 (alanine)	31.0	9	KBH_4
4	$C_6H_5CH_2$	CH_3	79.8 (phenylalanine)	36.0	9	KBH_4
3	H	C_2H_5	61.8 (glycine)	35.0	8	KBH_4
3	$(CH_3)_2CHCH_2$	C_2H_5	53.0 (leucine)	75.0	8	KBH_4
3	$(CH_3)_2CH$	CH_3	72.7 (valine)	34.0	8	KBH_4
3	CH_3	C_2H_5	48.0 (alanine)	30.0	8	KBH_4
3	C_6H_5CH	CH_3	53.3 (phenylalanine)	29.0	8	KBH_4
3	H	C_2H_5	45 (glycine)	36.0	8	Zn + NH_4OH
3	$(CH_3)_2CHCH_2$	C_2H_5	45 (leucine)	39.0	8	Zn + NH_4OH
3	H	C_2H_5	44 (glycine)	42.0	8	Al(Hg)
3	$(CH_3)_2CHCH_2$	C_2H_5	33 (leucine)	37.0	8	Al(Hg)

[a] The L isomer of each amino ester (except glycine) was used.

DAZ-L-Valine Methyl Ester [3, R^3 = $(CH_3)_2CH$; R^4 = CH_3] and DAZ-L-Phenylalanine Methyl Ester (3, R^3 = $C_6H_5CH_2$; R^4 = CH_3).—These amino ester derivatives were prepared by the EEDQ method.[2] The procedure was essentially the same as the general procedure described in detail above for the preparation of MAZ-amino esters. Benzene–EtOAc (90:10) was employed as the eluting solvent for chromatography on a silicic acid column. These DAZ-amino esters were obtained as deep red or orange colored oils or glasses that were homogeneous according to thin layer chromatography (same conditions as those used with the MAZ-amino esters). The ir and nmr spectra of these products were consistent with their proposed structures (**3**). The DAZ-L-valine methyl ester and the DAZ-L-phenylalanine methyl ester were obtained in 98.5 and 98.7% yields, respectively.

DAZ-Glycine Ethyl Ester (3, R^3 = H; R^4 = C_2H_5), DAZ-L-Leucine Ethyl Ester [3, R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5], and DAZ-L-Alanine Ethyl Ester (3, R^3 = CH_3; R^4 = C_2H_5).—These amino ester derivatives were prepared by a general carbodiimide procedure which is described below. A mixture of 6.7 mmol of the amino ester hydrochloride, 60 ml of acetonitrile, 6.7 mmol of triethylamine, and 6.7 mmol of α-methyl-α-(4,5-dimethyl-2-phenylazophenoxy)propionic acid (**1**) was treated with 6.7 mmol of 1-cyclohexyl-3-(2-morphalinoethyl)carbodiimide metho-*p*-toluenesulfonate (Aldrich Chemical Co.) in one portion. The resultant mixture was stirred at 40–50° for a period of 12 hr. The acetonitrile was replaced with $CHCl_3$ and the $CHCl_3$ solution was washed successively with water, aqueous HCl, Na_2CO_3, and water. The dried organic solution was distilled under reduced pressure until all of the solvent was removed and the residue was chromatographed on a silicic acid (100 mesh) column. Elution with benzene–EtOAc (90:10) separated a yellow fraction which afforded the DAZ-amino ester as a homogeneous highly colored glass. The ir and nmr spectra of these products were consistent with the proposed structures (**3**). The yields were 60.0, 31.0, and 73.0%, respectively.

General Procedure for the Deblocking of DAZ-Amino Esters 3.—The deblocking of DAZ-amino esters with KBH_4 and 5% Pd on carbon was accomplished by essentially the same procedure as that used on the MAZ-amino esters which was described in detail above. The crystalline, cyclic by-product, 3,4-dihydro-2,2,6,7-tetramethyl-2*H*-1,4-benzoxazin-3-one (**8**) melted at 201–202°. Table I lists the yields of **8** obtained in five different experiments.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.31; N, 6.83. Found: C, 70.22; H, 7.26; N, 6.80.

The yields of amino ester hydrochlorides **7** obtained in deblocking experiments on five different DAZ-amino esters are listed in Table I.

Deblocking DAZ-Glycine Ethyl Ester (3, R^3 = H; R^4 = C_2H_5) and DAZ-Leucine Ethyl Ester [3, R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5]. A. Zn and NH_4OH.—The following procedure was used for both of these DAZ-amino esters. Zinc dust (46 mg-atoms) was added in one portion to a stirred solution of 3.8 mmol of DAZ-amino ester **3**, 50 ml of methanol, and 5 ml of NH_4OH. The resultant mixture was stirred at room temperature for 4 hr and was then filtered. The filtrate was adjusted to pH 1.0 and some inorganic salts precipitated which were removed by filtration. The resulting filtrate was distilled under reduced pressure until a solid residue was obtained. This was chromatographed on a silicic acid (100-mesh) column using a mixture of benzene and EtOAc (50:50) as the eluting solvent. This procedure washed the benzoxazinone **8** from the column first. The amino ester hydrochloride **7** was then collected after the eluting solvent was changed to methanol. The yields of each of these products are listed in Table I.

B. Aluminum Amalgam.—Al(Hg) was prepared by dipping strips of Al foil (75 mmol) in a 5% aqueous solution of $HgCl_2$ and then washing the treated strips successively in EtOH and ether. The Al(Hg) was then added to a stirred solution of the DAZ-amino ester (2.5 mmol) in 40 ml of THF and 15 ml of water during a 30-min period. The amalgam dissolved and the mixture was filtered. The filtrate was concentrated under reduced pressure until all of the THF was removed. The aqueous residue was adjusted to pH 1.0 and then extracted with EtOAc. The organic layer afforded the benzoxazinone **8**. The aqueous layer was adjusted to pH 7.0 and extracted with ether. The dried ether extract was saturated with HCl gas and the amino ester hydrochloride **7** precipitated. The yields of the two products are listed in Table I.

Registry No.—**1**, 29851-38-5; **2**, 29851-39-6; **3** (R^3 = H; R^4 = C_2H_5), 29851-42-1; **3** (R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5), 29851-43-2; **3** (R^3 = $(CH_3)_2CH$; R^4 = CH_3), 29851-44-3; **3** (R^3 = CH_3; R^4 = C_2H_5), 29851-45-4; **3** (R^3 = $C_6H_5CH_2$; R^4 = CH_3), 29851-46-5; **4** (R^3 = H; R^4 = C_2H_5), 29851-47-6; **4** (R^3 = $(CH_3)_2CHCH_2$; R^4 = C_2H_5), 29851-48-7; **4** (R^3 = $(CH_3)_2CH$; R^4 = CH_3), 29851-49-8; **4** (R^3 = CH_3; R^4 = C_2H_5), 29851-50-1; **4** (R^3 = $C_6H_5CH_2$; R^4 = CH_3), 29851-51-2; **8**, 29851-52-3; **9**, 29936-64-9.

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