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61. Hydrazide as a Carboxyl Protecting Group Deprotection by Acidolysis

by **Jörg Schnyder**[1]) and **Max Rottenberg**
Pflanzenphysiologisches Institut, Altenbergrain 21, 3013 Bern, Switzerland
and Laboratorium GRD, 3752 Wimmis, Switzerland

(23. XII. 74)

Summary. Elimination of the hydrazide group was studied with the model compounds N-benzoyl-glycine hydrazide and N-benzoyl-L-phenylalanine hydrazide, using phosphorus oxychloride, hydrogen bromide or hydrogen chloride in acetic acid, or 60% perchloric acid. It was found that treatment of N-benzoyl-L-phenylalanine hydrazide with perchloric acid gave N-benzoyl-L-phenylalanine in 100% yield and without racemisation.

During an attempted synthesis of phosphohomoserine [1] we found that treatment of Z-Hse hydrazide[2]) with $POCl_3/H_2O$ [2] resulted in elimination of the hydrazide group and formation of the lactone, thus preventing phosphorylation. It was thought that lactone ring formation [3] might be responsible for the ready elimination. In order to test this hypothesis we studied the reaction with other hydrazides that could not form a lactone.

Previous workers have already suggested or used hydrazides [4–6] as carboxyl protective groups. However, their methods of deprotection are either accompanied by side reactions or are troublesome in the isolation stage. We now describe a method that is free from these drawbacks.

Using either Bz-Gly hydrazide (**I**) or Bz-Phe hydrazide (**III**) as model compounds, and $POCl_3/H_2O$; HBr or HCl/AcOH, and $HClO_4$ as acidolytic reagents we tested the deprotection both qualitatively and quantitatively.

With the three reagents, $POCl_3/H_2O$, HCl/AcOH, and HBr/AcOH, elimination of hydrazine went to no more than 94% completion, and was accompanied by partial or total racemisation of Bz-Phe. With $HClO_4$, on the other hand, cleavage of the hy-

[1]) Taken in part from the Doctoral Dissertation to be submitted by *J. Schnyder*. Present address: Research Institute, *Wander* SA., 3001 Bern, Switzerland.

[2]) Standard abbreviations [12] are used for amino acids and protecting groups. In addition, Hse stands for homoserine.

drazide was quantitative, and the product Bz-Phe was optically pure, although this compound is known to be highly susceptible to racemisation.

Using this simple deprotection method, hydrazides might become useful as blocked carboxyl derivatives of simple carboxylic acids such as N-acyl amino acids. Whether this technique will be suitable for manipulation of higher peptides remains to be investigated.

Experimental Part

General: See [1].

N-Benzoylglycine methyl ester was prepared according to [7]. M.p. 77–79° (Lit. [7], m.p. 83°).

Syntheses of model compounds. – *N-Benzoyl glycine hydrazide* (**I**). 1.93 g (10 mmol) Bz-Gly-OMe in 10 ml MeOH was treated in portions of 0.1 ml with a total of 1.14 ml (24 mmol) hydrazine hydrate and stirred at room temperature for 6 h. After addition of 10 ml ether the crystals were collected and dried: 1.72 g (88%). After recrystallization from EtOH/ether the product had m.p. 159.5–160.5° (Lit. [8] m.p. 162.5°). Rf 0.01 (A), 0.09 (C), 0.88 (E). – NMR. (d_6-DMSO): 3.43 (br/2H */—NNH_2); 3.9 (*d*/2H */—N—CH_2—CO—); 7.8 (*m*/5H/—Ph); 8.4 (*t*/br/1H/—NH—C—); 8.8 (*s*/1H/-NNH—).

$C_9H_{11}N_3O_2$ (193.2) Calc. C 55.95 H 5.74 N 21.75% Found C 55.76 H 5.97 N 22.03%

N-Benzoyl-L-phenylalanine methyl ester (**II**). To 2.16 g (10 mmol) L-Phe-OMe suspended in 20 ml H_2O and 2.3 ml (20 mmol) N-methylmorpholine at 0° was added dropwise 1.6 ml (10 mmol) benzoyl chloride. Stirring was continued for 30 min at 0°, and then overnight at room temperature. The crystalline precipitate was collected and dried: 2.72 g (96%). Recrystallized from ether/hexane. M.p. 78.5–80° (Lit. [8], m.p. 83.6–84.6°). $[\alpha]_D^{25} = +25.09°$ and $[\alpha]_{546}^{25} = +30.70°$ ($c = 0.57$, dioxane) (Lit. [9] $[\alpha]_D^{25} = +24.22°$ and $[\alpha]_{546}^{25} = 28.79°$). Rf 0.72 (A), 0.77 (C), 0.95 (E).

N-Benzoyl-L-phenylalanine hydrazide (**III**). Prepared from **II** and hydrazine as in **I**. Yield 97.2%. M.p. 190–191° (Lit. [10] m.p. 193–198°). $[\alpha]_D^{25} = -46.34°$ and $[\alpha]_{546}^{25} = -55.64°$ ($c = 1.51$, DMF) (Lit. [10] $[\alpha]_D^{25} = -45.8°$). Rf 0.05 (A), 0.24 (C), 0.91 (E). Hydrazine equivalent (Lit. [11]). Calc. 283.31 mg/meq, found 284.99 mg/meq. – NMR. (d_6-DMSO): 3.1 (*d*/2H/—CH_2—PH); 3.43 and 4.25 (br/2H */—NNH_2); 4.75 (*q*/1H */—N—CH—); 7.6 (*m*/5H/—CO—Ph and 5H/—C—Ph); 8.3 (*d*/1H/—NH—C—); 9.05 (*s*/br/1H/—HNN—).

$C_{16}H_{17}N_3O_2$ (283.32) Calc. C 67.82 H 6.05 N 14.83% Found C 67.76 H 5.97 N 14.95%

Cleavage of hydrazide. – 1. *Quantitative test.* For each analytical run *ca.* 15 mg of **III** was cooled in an ice-bath and treated with 0.2 ml 60% $HClO_4$. It was then incubated at 40° in a stoppered test tube for various lengths of time. The reaction mixture was transferred with EtOH/H_2O 1:1 into a 50 ml volumetric flask, and 50 μl aliquots were taken for estimation of hydrazine as in [11]. See table.

Cleavage yields of hydrazine at different times

mg **III**	h	Absorbance	nmol calc.	nmol found	% cleavage
13.45	1/2	0.04	47.5	4.2	8.84
14.4	1	0.105	50.8	9.0	17.72
13.6	2	0.188	48.0	15.3	31.88
15.80	24	0.730	55.77	56.72	101.7
15.05	24	0.690	53.12	53.66	101.02
14.00	24	0.623	49.41	48.55	98.26
14.40	24	0.644	50.83	50.15	98.66
					Average 99.91

2. *Preparative run.* 283.6 mg (1 mmol) **III** was mixed in an ice-bath with 5 ml 60% $HClO_4$-solution in 0.5 ml portions. After 1 day incubation at 48° the mixture was cooled in an ice-bath

* Signals overlap; integral approximatively only.

while a large excess of H_2O was added. The solution was extracted with EtOAc to separate the liberated organic acid which was further purified by taking it up in 2M $KHCO_3$, acidifying, and again extracting with EtOAc. This solution was washed with H_2O until neutral, dried (Na_2SO_4), and filtered. After evaporation of the solvent the residue was crystallized from $EtOH/H_2O$, giving analytically pure Bz-L-Phe, 227 mg (84%). M.p. 134–134.5° (Lit. [9] m.p. 142–143°). $[\alpha]_D^{25} = +37.96°$ and $[\alpha]_{546}^{25} = +45.92°$ ($c = 1.6$, dioxane) (Lit. [9] $[\alpha]_D^{25} = +38.74°$ and $[\alpha]_{546}^{25} = +45.73°$).

$C_{16}H_{15}NO_3$ (269.2) Calc. C 71.36 H 5.61 N 5.20% Found C 71.52 H 5.75 N 5.20%

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62. A Chemical Study of *Burley* Tobacco Flavour (*Nicotiana tabacum* L.) V. Identification and Synthesis of the Novel Terpenoid Alkaloids 1,3,6,6-Tetramethyl-5,6,7,8-tetrahydro-isoquinolin-8-one and 3,6,6-Trimethyl-5,6-dihydro-7*H*-2-pyrindin-7-one[1][2]

by **Edouard Demole** and **Cécile Demole**

Firmenich SA, Research Laboratory, 1211 Geneva 8

(20. XII. 74)

Summary. GLC. allowed the isolation of 1,3,6,6-tetramethyl-5,6,7,8-tetrahydro-isoquinolin-8-one (*A*) and 3,6,6-trimethyl-5,6-dihydro-7*H*-2-pyrindin-7-one (*D*) from *Burley* tobacco condensate (about 0.1% each). The structures and syntheses of these novel terpenoid alkaloids are described, and a possible way for their formation in tobacco is suggested.

The new compounds **A** and **D** were isolated[3] by subjecting subfractions B2-PN-j and B3-PN-i from *Burley* tobacco condensate to GLC. separations[4]. The former subfraction was found to contain 3.21% of **D**, the latter 0.37% of **D** and 1.52% of **A**,

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[1] For the 4th publication of this series see [1].

[2] Part of this work was included in a paper presented by *E. D.* at the VIth International Congress of Essential Oils (San Francisco, Calif., Sept. 8–12, 1974).

[3] We thank Mr. *D. Berthet* for this isolation work.

[4] *Burley* tobacco condensate and subfraction B2-PN-j were obtained and investigated as previously described [2]. Compound **D** was eluted between 1,5,5-trimethyl-9-oxabicyclo-[4.3.0]nonan-3-one and nicotyrine on Carbowax at 220° (see *Scheme 13* in paper [2]). The preparation and study of subfraction B3-PN-i will be described in a future paper.