Studies Directed Toward the Synthesis of Conformationally Restricted Neurotransmitter Analogs: The Addition of *N*-Hydroxyimides to Ethyl Propiolate

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N-Hydroxyimides were found to add readily to ethyl propiolate to yield the imidooxyacrylates in both protic and aprotic solvents. The *trans* isomer only was formed in aprotic solvents while both isomers were formed in protic solvents.

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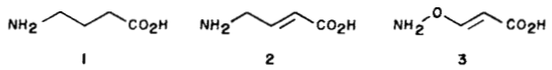
In conjunction with our attempts to synthesize conformationally restricted aminooxy analogs of the inhibitory neurotransmitter γ-aminobutyric acid (GABA, **1**) we have studied the reaction of *N*-hydroxyimides, *N*-hydroxyamides, and *N*-hydroxycarbamates with ethyl propiolate.

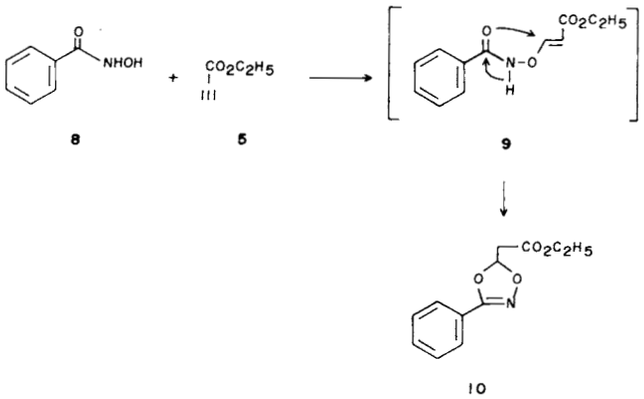


1 **2** **3**

Recently it has been shown that the conformationally restricted GABA analog, *trans*-4-amino crotonate **2** is a better substrate for the pyridoxal phosphate dependent enzyme GABA aminotransferase (GABA-T) than the natural substrate GABA [1]. This may indicate that the extended conformation may be necessary for optimum GABA aminotransferase activity. Aminooxy analogs of amino acids are known to inhibit amino transferases [2]. Although conformationally restricted aminooxy analogs such as **3** are unknown it is possible that the *trans* isomer **3** would be a potent inhibitor for GABA aminotransferase. Our synthetic approach to this new class of compounds is based upon the Michael addition of suitably blocked hydroxylamines (*e.g.* *N*-hydroxyimides, amides, and carbamates) to ethyl propiolate to give the desired blocked aminooxy acrylates.

We have found that *N*-hydroxy imides such as *N*-hydroxysuccinimide and *N*-hydroxyphthalimide readily add to ethyl propiolate in protic solvents such as ethanol to give a mixture of *cis* and *trans* isomers in violation of Truce's rule of *trans* addition [3]. For example, when *N*-hydroxysuccinimide **4** and ethyl propiolate **5** were heated in ethanol for several hours a mixture of the expected *cis* isomer **6** which results from *trans* addition and the *trans* isomer **7** which results from *cis* addition was isolated. The results for the addition of *N*-hydroxyimides **4** and **5** in refluxing ethanol are summarized in Table I.

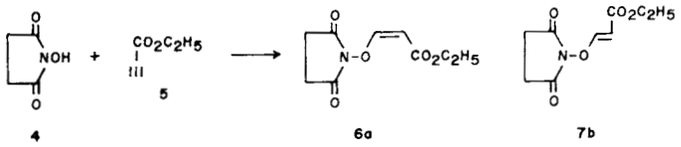
N-Hydroxybenzamide was also found to readily add to **5** in ethanol. However, the desired acrylate **9** was not



8 **5** **9** **10**

isolated. Instead the dioxazole **10** resulting from an intramolecular Michael addition of the intermediate acrylate **9** was isolated in excellent yield. Previously it has been shown that dioxazoles such as **10** can be formed in poor yield by the sodium hydride catalyzed reaction of **5** with **8** [4]. Interestingly, under the same conditions *N*-methyl-*N*-hydroxybenzamide did not react with **5**. Similarly the *N*-hydroxycarbamates, *N*-hydroxyurethane and *N*-hydroxybenzyl carbamate did not react with **5** under these conditions.

The base catalyzed addition of *N*-hydroxyimides in aprotic solvents was also investigated. For example, *N*-hydroxyphthalimide was found to add to **5** in *N,N*-dimethylformamide (DMF) using a catalytic amount of triethylamine. In this case only the desired *trans* isomer **7b** resulting from *cis* addition was isolated. A similar solvent dependence of product stereochemistry was also

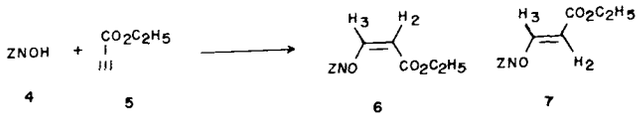


4 **6a** **7b**

4b **5** **7b**

Table I.

The Reaction of *N*-Hydroxyimides **4** with Ethyl Propiolate **5**



4 5 6 7

				Spectral Data					
			(6:7)		**6** (*cis*)			**7** (*trans*)	
4	ZN	Yield (%)	*cis:trans*	**6** H_2 (δ)	H_3 (δ)	J (Hz)	**7** H_2 (δ)	H_3 (δ)	J (Hz)
a	succinimide	89	44:56	**a** 5.2	6.5	7	**a** 5.3	7.6	13
b	phthalimide	71	36:64	**b** 5.1	6.8	7	**b** 5.2	7.8	13

observed by Dolfini for the reaction of aziridine with ethyl propiolate [5].

In summary, we have found that *N*-hydroxyimides **4** add readily to ethyl propiolate **5** to give the imidooxyacrylates both with and without base catalysis. The stereochemistry of addition was found to be solvent dependent. In protic solvents such as alcohols both the *cis* and *trans* adduct were formed while only the *trans* isomer was formed in *N,N*-dimethylformamide. The analogous acrylate was not isolated when *N*-hydroxybenzamide **8** was reacted with **5** but instead the dioxazole **10** resulting from an intramolecular Michael addition was the isolated product.

EXPERIMENTAL

The *N*-hydroxyimides, *N*-hydroxybenzamide, *N*-hydroxyethylcarbamate, *N*-hydroxyurethane, and ethyl propiolate were purchased from Aldrich Chemical Co. *N*-Hydroxy-*N*-methylbenzamide, *N*-hydroxy-*N*-methyl-4'-nitrobenzamide, and *N*-hydroxybenzylcarbamate were prepared using literature methods. Melting points were determined using a Laboratory Devices Melt-Temp Apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded using a Varian T-60 with tetramethylsilane as an internal standard. Elemental analyses were performed by Atlantic Microlabs, Inc.

Ethyl 3-Succinidooxyacrylate **6a,7a**.

An ethanol (100 ml) solution of ethyl propiolate (9.8 g, 0.1 mole) and *N*-hydroxysuccinimide (11.5 g, 0.1 mole) was refluxed for 3 hours. The solvent was then removed under reduced pressure, the residue dissolved in methylene chloride, and extracted with water (2 x, 200 ml) to remove the excess *N*-hydroxysuccinimide. The solvent was then evaporated *in vacuo* to give the crude product as a 44:56 gummy solid (19.0 g, 89%) mixture of the *cis* and *trans* isomer. The *cis* isomer was isolated free of the *trans* isomer by fractional crystallization from diethyl ether as a white crystalline solid (8.0 g, 38% isolated) which was analytically pure, mp 116-118°; nmr (deuteriochloroform): δ 1.3 (t, 3H, ethyl Ch_3), 2.8 (broad s, 4H, succinimide CH_2), 4.2 (q, 3, ethyl CH_3), 5.2 (d, 1H, C-2 H, J = 7 Hz) 6.5 (d, 1H, C_3H, J = 7 Hz).

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.19; N, 6.57. Found: C, 50.67; H, 5.20; N, 6.56.

The mother liquor was concentrated *in vacuo* to give an oil which contained only a trace of the *cis* isomer (10.2 g, 48%); nmr (deuteriochloroform): δ 1.3 (2 overlapping t, 3H, ethyl CH_3), 2.9 (m, 4H, succinimide CH_2), 4.2 (2 overlapping 9, 2H, ethyl CH_2), 5.1 (d, J = 7 Hz, *cis* C_2-H), 5.3 (J = 13 Hz, *trans* C_2-H), 6.5 (d, J = 7 Hz, *cis* C_3-H), 7.6 (d, J = 13 Hz, *trans* C_3-H).

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.19; N, 6.57. Found: C, 50.65; H, 5.25; N, 6.58.

Ethyl 3-Phthalimidooxyacrylate **6b,7b** (Method A).

N-Hydroxyphthalimide (16.3 g, 0.1 mole) and a catalytic amount of triethylamine (1 ml) were dissolved in *N,N*-dimethylformamide (100 ml) in a 250 ml round bottom flask equipped for magnetic stirring. Ethyl propiolate (9.8 g, 0.1 mole), dissolved in *N,N*-dimethylformamide (50 ml), was then added dropwise during 10 minutes. The dark red solution warmed as a vigorous exothermic reaction ensued. The solution was allowed to stir at room temperature for 2 hours and then poured onto 800 g of crushed ice. The resulting orange precipitate was collected by filtration, washed with water (3 x, 500 ml), and air dried. Recrystallization from ethanol gave 10.4 (40%) of the analytically pure *trans* acrylate, mp 115-118°. Concentration of the mother liquor gave a second crop. When the recrystallization solvent was removed *in vacuo* the *cis* isomer was not observed; nmr (deuteriochloroform): δ 1.3 (t, 3H, ethyl Me), 4.1 (q, 2H, ethyl CH_2), 5.6 (d, 1H, alkene H, J = 13 Hz), 7.7 (d, 1H, alkene H, J = 13 Hz), 7.9 (broad s, 4H, Ar-H).

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 59.76; H, 4.24; N, 5.36. Found: C, 59.58; H, 4.25; N, 5.33.

Compound **7b**.

Ethyl propiolate (9.8 g, 0.1 mole) and *N*-hydroxyphthalimide (16.3 g, 0.1 mole) were refluxed in ethanol for 3 hours. Removal of the solvent *in vacuo* gave the crude product which was recrystallized from a small volume of ethanol (50 ml). The crystalline product 18.6 g (71%) was a 26:74 of the *cis:trans* isomers, mp 103-109°; nmr (deuteriochloroform): δ 1.3 (2 overlap t, 3H, ethyl CH_3), 4.3 (2, overlap 9, 2H, ethyl CH_2), 5.1 (d, J = 7 Hz, *cis* C_2-H), 5.5 (d, J = 13 Hz, *trans* C_2-H), 6.8 (d, J = 7 Hz, *cis* C_3-H), 7.8 (d, J = 13 Hz, *trans* C_3-H_4), 8.0 (broad s, 4H, Ar-H).

Ethyl 5-phenyl-2-dioxazoleacetate **10**.

Ethyl propiolate (9.8 g, 0.1 mole) and *N*-hydroxybenzamide (15.1 g, 0.11 mole) were dissolved in ethanol and the solution refluxed for 3 hours. The solution was allowed to cool and the solvent removed *in vacuo*. The resulting oil was dissolved in methylene chloride (25 ml) and then carbon tetrachloride (100 ml) added to precipitate the unreacted *N*-hydroxybenzamide. The filtrate was then washed with water to remove (100 ml, 3 x) to remove any remaining *N*-hydroxybenzamide, dried with anhydrous magnesium sulfate, and concentrated *in vacuo* to give 15.1 g (64%) of the oily product; nmr (deuteriochloroform): δ 1.3 (t, 3H, ethyl CH_3), 3.0 (d, 1H, dioxazole H), 4.3 (q, 2H, ethyl CH_2), 6.5 (t, 2H, acetate CH_2), 7.6 (m, 5H, Ar-H).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.92. Found: C, 61.15; H, 5.57; N, 5.94.

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