Reaction of β-aminopropionohydroxamic acid with aldehydes and ketones

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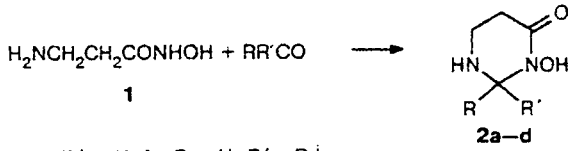
β-Aminopropionohydroxamic acid reacts with aliphatic aldehydes or ketones to give 2-substituted 1-hydroxytetrahydropyrimidin-6-ones, while its reaction with aromatic carbonyl compounds leads to either the same products or Schiff's bases, which can exist in tautomeric equilibrium in solution.

Key words: β-aminopropionohydroxamic acid, 1-hydroxytetrahydropyrimidin-6-ones, aldehydes, ketones, Schiff's bases, reaction, tautomeric equilibrium.

The reaction of *o*-aminobenzohydroxamic acid with aliphatic or aromatic aldehydes is of general character and affords derivatives of 3-hydroxy-1,2-dihydroquinozalin-4-one.[1]

We studied the reaction of β-aminopropionohydroxamic acid (**1**) with a series of aliphatic, aromatic, and aliphatic-aromatic aldehydes and ketones with the aim of extending this reaction to aliphatic β-aminohydroxamic acids. It was established that the treatment of aminohydroxamic acid (**1**) with formaldehyde, isobutyral, acetone, or cyclohexanone leads to 1-hydroxytetrahydropyrimidin-6-one or its 2-substituted derivatives (Scheme 1, Table 1).

Scheme 1



a: R = R' = H; **b**: R = H; R' = Pr^i; **c**: R = R' = Me; **d**: R—R' = $(CH_2)_5$

The structures of the products was confirmed by data from elemental analysis and ^1H and ^{13}C NMR spectroscopy as well as by a positive reaction with $FeCl_3$ for the hydroxamic fragment. The signals of the methylene or methine protons at C-2 (δ 4.1—4.2) are present in the ^1H NMR spectra of compounds **2a,b** in DMSO, while signals corresponding to the Schiff's bases (in the range of δ 8.2) are absent. In addition, the signals for C-2 (δ 75—80) were observed in the ^{13}C NMR spectra of compounds **2b,c,d**, while only one signal of a carbonyl group appeared at δ > 100 (δ 164—167) (Tables 2 and 3).

The reaction of aminohydroxamic acid (**1**) with aromatic aldehydes and ketones is much more ambiguous. In the case of benzaldehyde, its 2-, 3-, and 4-nitroderivatives, and 4-methoxybenzaldehyde, the cor-

Table 1. Melting points, yields, and data from elemental analysis of 1-hydroxy-2-R-2-R'-tetrahydropyrimidin-6-ones (**2**, **3**, **5**) and Schiff's bases RR'C=NCH$_2$CH$_2$CONHOH (**4**)

Compound	R	R'	M.p. /°C	Yield (%)	Found / Calculated (%) C	H	Molecular formula
2a	H	H	147—149	48	41.0 / 41.4	6.90 / 6.89	$C_4H_8N_2O_2$
2b	H	Pr^i	123—126	53	52.7 / 53.2	8.84 / 8.86	$C_7H_{14}N_2O_2$
2c	Me	Me	140—142	49	49.7 / 50.0	8.30 / 8.33	$C_6H_{12}N_2O_2$
2d		—$(CH_2)_5$—	137—139	53	58.8 / 58.6	8.60 / 8.69	$C_9H_{16}N_2O_2$
3a	H	Ph	149—150	74	61.9 / 62.5	6.29 / 6.25	$C_{10}H_{12}N_2O_2$
3b	H	2-$NO_2C_6H_4$	168—169	72	50.4 / 50.6	4.89 / 4.64	$C_{10}H_{11}N_3O_4$
3c	H	3-$NO_2C_6H_4$	138—139	65	49.4 / 50.6	4.79 / 4.64	$C_{10}H_{11}N_3O_4$
3d	H	4-$NO_2C_6H_4$	148—149	67	50.5 / 50.6	4.65 / 4.64	$C_{10}H_{11}N_3O_4$
3e	H	4-$MeOC_6H_4$	103—105	26	—	—	$C_{11}H_{14}N_2O_3$
4a	H	2-HOC_6H_4	86—89	34	56.6 / 57.7	6.18 / 5.77	$C_{10}H_{12}N_2O_3$
4b	H	2-HO-3-AllC_6H_3	97—99	28	—	—	$C_{13}H_{16}N_2O_2$
4c	H	3-$MeOC_6H_4$	117—118	53	58.7 / 59.5	6.28 / 6.31	$C_{11}H_{14}N_2O_3$
4d	H	4-Me_2N-C_6H_4	140—141	26	61.8 / 61.3	7.78 / 7.23	$C_{12}H_{17}N_3O_2$
4e	H	9-$C_{14}H_9$	151—153	48	73.7 / 74.0	5.52 / 5.48	$C_{18}H_{16}N_2O_2$
5	Me	Ph	118—120	32	63.7 / 64.1	6.78 / 6.80	$C_{11}H_{14}N_2O_2$

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Table 2. ^{1}H NMR spectra of 1-hydroxy-2-R-2-R'-tetrahydropyrimidin-6-ones (**2, 3, 5**)

Compound	Solvent	δ					
		NOH	R'		H(4)	H(5)	R
			H(2)	Me			
2a	DMSO-d_6	—	4.19 (s)	—	2.9 (t)	2.27 (t)	—
2b	DMSO-d_6	—	4.18 (d)	—	2.7 (m); 3.0 (m)	2.1—2.5 (m)	0.8 (d, 3 H); 0.93 (d, 3 H); 2.2—2.3 (m, 1 H)
2c	DMSO-d_6	5.3 (br.s)	—	1.32 (s)	2.87 (m)	2.3 (t)	1.35 (s, 6 H)
2d	DMSO-d_6	5.3 (br.s)	—	—	2.82 (t)	2.3 (t)	1.05 (m, 1 H); 1.4—1.6 (m, 7 H); 1.9 (m, 2 H)
3a	$CDCl_3$	—	5.57 (s)	—	3.1—3.3 (m)	2.28 (t)	7.5 (s, 5 H)
	DMSO-d_6	—	5.3 (s)	—	2.85 (t)	2.35 (m)	7.35 (s, 5 H)
3b	DMSO-d_6	—	6.0 (s)	—	2.8 (m); 2.7 (m)	2.4 (t)	7.55 (m, 2 H); 7.7 (t, 1 H); 8.0 (m, 1 H)
3c	DMSO-d_6	—	5.5 (s)	—	2.9 (t)	2.4 (m)	7.65 (m, 1 H); 7.70 (m, 1 H); 8.2 (m, 2 H)
3d	DMSO-d_6	9.45 (br.s)	5.45 (d)	—	2.9 (m)	2.4 (m)	7.65 (d, 2 H); 8.35 (d, 2 H)
	$CDCl_3$	1.2 (s)	5.65 (s)	—	3.15 (s)	2.7 (s)	7.6 (d, 2 H); 8.3 (d, 2 H)
3e	DMSO-d_6	—	5.35 (s)	—	2.85 (br.s)	2.35 (br.s)	7.25 (d, 2 H); 6.85 (d, 2 H); 3.75 (s, 3 H)
	$CDCl_3$	3.9 (s)	5.5 (s)	—	3.0—3.2 (m)	2.6 (t)	7.3 (d, 2 H); 6.9 (d, 2 H); 3.7 (s, 3 H)
5	DMSO-d_6	—	—	1.7 (s)	2.5;* 2.7 (br.s)	2.4 (s)	7.4 (s, 4 H); 7.8 (s, 1 H)
	$CDCl_3$	—	—	1.9 (s)	2.6—2.8 (m); 3.0 (m)	2.5 (m); 2.6—2.8 (m)	7.4 (s, 5 H)

* The signal is overlapped by the solvent signals.

Table 3. ^{13}C NMR spectra of 1-hydroxy-2-R-2-R'-tetrahydropyrimidin-6-ones (**2, 3, 5**) in DMSO-d_6

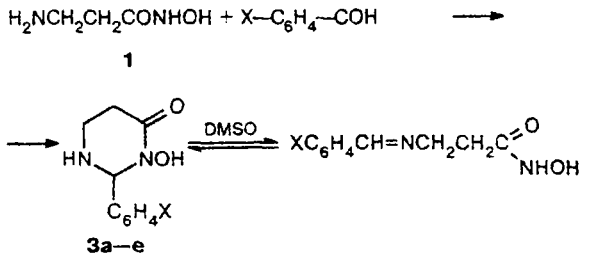
Compound	δ					
	C(2)	C(4)	C(5)	C(6)	R'	R
2b	79.75	39.08	35.125	167.04	28.00; 18.41; 14.58	—
2c	75.69	36.38	34.79	164.69	25.52	25.52
2d	77.59	35.62	34.78	164.67	32.40; 25.02; 22.00	
3a	78.05	39.02	34.87	166.43	127.26; 127.85; 127.92. 128.03; 128.65; 139.77	—
3b	73.03	37.91	34.56	165.96	124.48; 128.55; 129.35; 132.31; 149.07; 157.39	—
5	80.12	36.47	34.33	165.2	126.56; 127.11; 127.82; 128.00; 128.15; 143.48	26.95

responding condensation products could be isolated. The quite narrow melting ranges of these products (see Table 1) suggest that they do not contain considerable amounts of their isomeric forms. However, the signals of both 2-arylsubstituted 1-hydroxytetrahydropyrimidin-6-ones and the isomeric Schiff's bases were observed in the NMR spectra of these compounds in DMSO (Tables 2—5). Their ratio depends on the type and position of the substituent in the aromatic ring. The presence of electron-acceptor substituents favors the cyclic form, while the presence of electron-donor ones favors the linear form (the Schiff's base form). The latter is also stabilized if the substituent is present in the *ortho*-position (Table 6). The ^{1}H NMR spectra of the condensation products of acid **1** with benzaldehyde, 4-nitrobenzaldehyde, and 4-methoxybenzaldehyde in $CDCl_3$ exhibit only signals of cyclic isomers, which exist in DMSO in tautomeric equilibrium with the isomeric Schiff's bases (Scheme 2).

Table 4. ^{1}H NMR spectra of Schiff's bases RR'C=NCH$_2$CH$_2$CONHOH in DMSO-d_6

R	R'	δ			
		R	R'	NCH_2	CH_2CO
H	Ph	8.35 (s)	7.4 (s, 3 H); 7.7 (s, 2 H)	3.80 (t)	2.40 (m)
H	2-$NO_2C_6H_4$	8.65 (s)	7.73 (m, 1 H); 7.77 (m, 2 H); 7.9 (1 H)	3.85 (m)	2.40 (m)
H	3-$NO_2C_6H_4$	8.52 (s)	7.7 (s, 1 H); 8.12 (s, 1 H); 8.4 (d, 1 H); 8.52 (d, 1 H)	3.85 (t)	2.40 (m)
H	4-$NO_2C_6H_4$	8.5 (s)	7.95 (d, 2 H); 8.3 (d, 2 H)	3.85 (t)	2.45 (m)
H	2-HOC_6H_4	8.55 (s)	6.85 (m, 2 H); 7.3 (t, 1 H); 7.4 (d, 1 H)	3.85 (t)	2.40 (s)
H	2-HO-3-All-C_6H_3	8.55 (s)	3.35 (d, 2 H); 5.05 (m, 2 H); 6.0 (m, 1 H); 6.85 (t, 1 H); 7.2 (d, 1 H); 7.3 (d, 1 H)	3.85 (t)	2.40 (t)
H	3-$MeOC_6H_4$	8.5 (s)	3.7 (s, 3 H); 6.8 (2 H); 6.95 (d, 1 H); 7.05 (s, 1 H)	3.85 (t)	2.40 (t)
H	4-$MeOC_6H_4$	8.35 (s)	3.75 (m, 3 H); 7.0 (d, 2 H); 7.65 (d, 2 H)	3.80 (t)	2.30 (br.s)
H	4-$Me_2NC_6H_4$	8.2 (s)	2.9 (s, 6 H); 6.72 (d, 2 H); 7.5 (d, 2 H)	3.70 (t)	2.30 (t)
H	$C_{14}H_9$	9.50 (s)	7.55 (s, 4 H); 8.10 (s, 2 H); 8.5—8.7 (m, 3 H)	4.12 (s)	2.57 (s)
Me	Ph	2.20	7.3 (s, 4 H); 7.75 (s, 1 H)	3.65 (br.s)	2.38 (s)

Scheme 2

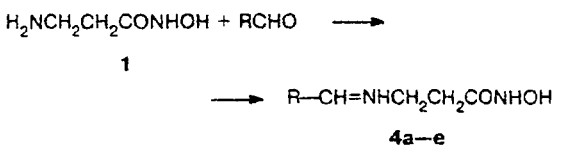


3a–e

a: X = H; **b:** X = 2-NO_2; **c:** X = 3-NO_2; **d:** X = 4-NO_2; **e:** X = 4-MeO

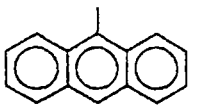
In the case of aromatic aldehydes containing the HO or MeO groups in the *ortho*- and *meta*-position and the Me_2N group in the *para*-position as well as with 9-anthraldehyde, only Schiff's bases are formed (Scheme 3).

Scheme 3



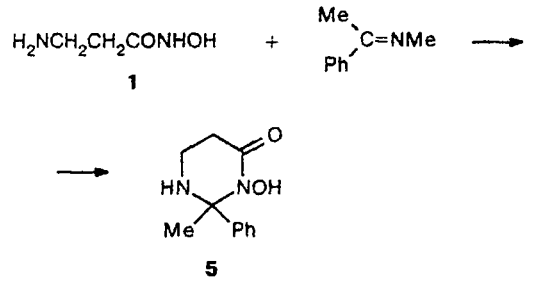
4a–e

a: R = 2-HOC_6H_4; **b:** R = 2-OH-3-AllC_6H_3; **c:** R = 3-$MeOC_6H_4$; **d:** R = 4-$Me_2NC_6H_4$; **e:** R =



Attempts to obtain condensation products with acetophenone or benzophenone under the same conditions failed. However, the condensation product with acetophenone (but not with benzophenone) was synthesized by heating acid **1** with acetophenone *N*-methylimine (Scheme 4).

Scheme 4



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The latter, like products **3a,e,d**, is an individual cyclic isomer in $CDCl_3$, while in DMSO it exists as a tautomeric mixture with its linear isomer in the ratio ~1/1.5 (Scheme 5).

Table 5. ^{13}C NMR spectra of Schiff's bases RR′C=$NCH_2CH_2CONHOH$ in DMSO-d_6

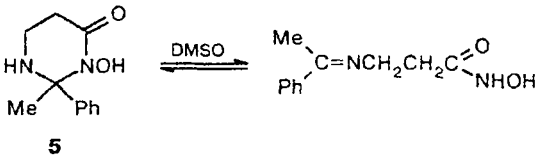
R	R′	δ			
		$CH_2(N)$	$CH_2(CO)$	R	R′
H	Ph	56.41	33.83	—	136.01; 130.66; 129.15; 128.03; 127.92; 127.23
H	2-$NO_2C_6H_4$	56.48	33.57	—	157.37; 149.07; 133.43; 131.22; 129.35; 124.12
H	2-HOC_6H_4	54.37	33.57	—	160.74; 132.36; 131.71; 118.65; 118.5; 116.52
Me	Ph	47.57	34.17	15.03	126.00; 126.35; 127.67; 127.86; 129.25; 140.33

Table 6. The composition of condensation products of aminohydroxamic acid **1** with aromatic carbonyl compounds $RCOC_6H_4$—X in different solvents (%)*

R	X	DMSO	$CDCl_3$
H	*p*-NO_2	87/13	100/—
H	*m*-NO_2	83/17	—
H	*o*-NO_2	75/25	—
H	H	60/40	100/—
Me	H	40/60	100/—
H	*p*-MeO	40/60	100/—
H	*m*-MeO	—/100	—/100
H	*p*-Me_2N	—/100	—
H	*o*-OH	—/100	—

* Cyclic isomer/Schiff's base.

Scheme 5



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Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker-300 AM instrument. Melting points were measured on a Kofler stage. Aminohydroxamic acid **1** (see Ref. 2) and acetophenone *N*-methylimine[3] were obtained according to procedures described earlier.

Synthesis of 1-hydroxytetrahydropyrimidin-6-ones 2a–d, 4e (general procedure). To a solution of aminohydroxamic acid **1** (0.2 g) in 5 mL of anhydrous MeOH an equimolar amount of an aldehyde or ketone was added. The mixture was refluxed for 3 h (with aldehydes) or for 6 h (with ketones), and the solvent was removed. The residue was recrystallized from Pr^iOH (**2a,b** and **4e**) or acetone (**2c,d**).

1-Hydroxytetrahydropyrimidin-6-ones 3a–d were obtained by the reaction of equimolar amounts of an aldehyde and acid **1** in EtOH. After refluxing for 3 h, the solutions were cooled to ~20 °C. The crystals that formed were filtered off and recrystallized from EtOH.

1-Hydroxytetrahydropyrimidin-6-one 3e. Anisaldehyde (0.25 mL) was added to a solution of acid **1** (0.1 g) in 5 mL of Pr^iOH. The mixture was kept for 4 h and the solvent was evaporated. The residue was washed with ether several times, and a small amount of THF was added. The resulting solution was left overnight. The crystals that formed were filtered off and recrystallized from $CHCl_3$.

Imines 4a,b were synthesized by analogy with product **2**. After the solvent was removed, the residue was washed with ether several times and left overnight. The crystals that formed were washed with petroleum ether and recrystallized from the same solvent.

Imine 4c. *m*-Methoxybenzaldehyde was added to a solution of acid **1** (0.2 g) in 5 mL of Pr^iOH. After refluxing for 3 h, the solution was cooled, and the precipitate that formed was filtered off and recrystallized from Pr^iOH.

Imine 4d. 4-*N*,*N*-Dimethylaminobenzaldehyde (0.12 g) was added to a solution of acid **1** (0.1 g) in 4 mL of anhydrous MeOH, and the mixture was left overnight at ~20 °C. The mixture was then refluxed with activated carbon, concentrated to dryness, and THF was added. The solid residue was filtered off and recrystallized from THF.

1-Hydroxytetrahydropyrimidin-6-one 5. Acetophenone *N*-methylimine was added to a solution of acid **1** (0.1 g) in MeOH (molar ratio 1.3 : 1). The mixture was refluxed for 4 h, and the solvent was evaporated. The product was repeatedly extracted from the residue with hot petroleum ether and recrystallized from the same solvent.

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