Synthesis of 3-Hydroxy-4-Imidazolidinones (1a,b)

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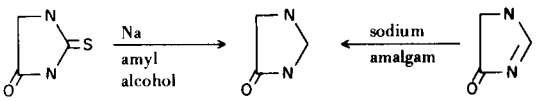
So far very little work has been reported on the preparation and properties of 4-imidazolidinones **1**. The known methods involve reduction of either thiohydantoins **2** (2) or 4 (5)-imidazolones **3** (3). In this paper we wish to report a rather convenient synthesis of 3-hydroxy-4-imidazolidinones (**6a-6l**), which is based on the reaction of aliphatic α-aminohydroxamic acids with aromatic aldehydes.

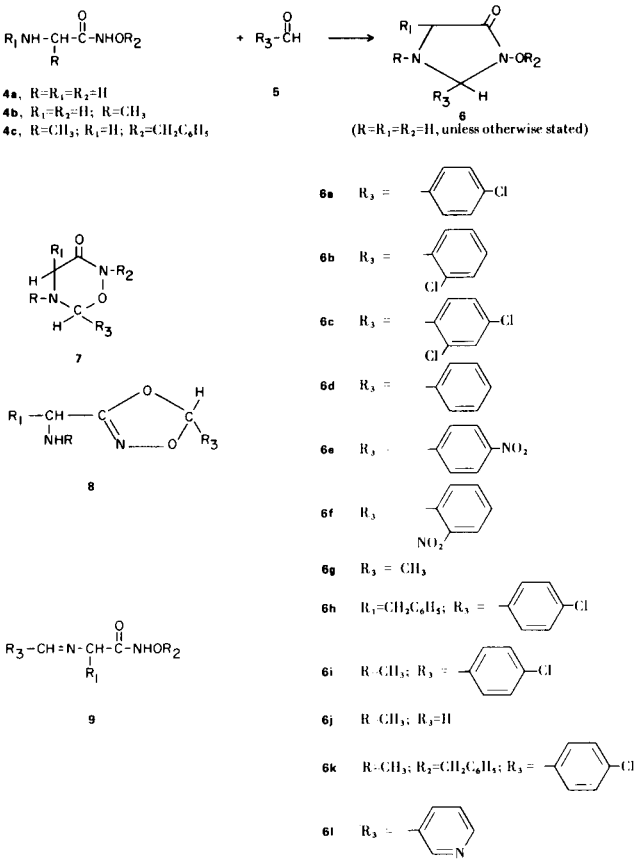


2 **1** **3**

Glycine hydroxamic acid (**4a**) was prepared by the procedure of Jones and Sneed (4), whereas, sarcosine hydroxamic acid (**4b**) and *O*-benzylsarcosine hydroxamic acid (**4c**) were prepared by the reaction of ethyl sarcosinate with hydroxylamine and benzyloxyamine, respectively. The reaction of these α-aminohydroxamic acids (**4a-4c**) with a number of aldehydes (**5**) was conducted by refluxing the mixture in absolute methanol during 2-4 hours. The resulting crystalline 3-hydroxy-4-imidazolidinones (**6a-6l**) were isolated in 70-90% yields, as shown in Scheme I. The structure proof of these compounds rested on satisfactory elemental analyses and spectroscopic data (nmr, ir and mass) as discussed below.

Theoretically, the reaction of an aldehyde with an α-aminohydroxamic acid can lead to the formation of several compounds. But many of the possible structures could be easily ruled out simply on the basis of elemental analyses. Therefore, only the structures **6**, **7**, **8** and **9** were considered as likely possibilities. The oxadiazole structure **7** was found to be unacceptable on the basis of ir spectra (presence of a fragment at m/e 17, characteristic of the hydroxyl group). Hydroxamic acids are known to react with aldehydes through the hydroxamic acid end of the molecule (5). If α-aminohydroxamic acids reacted analogously they would form compounds having the structure **8**. However, the nmr spectra (Table I, experimental section) and the ir spectra (presence of C=O absorption at 1675-1725 cm^{-1}) ruled out this possibility. Furthermore, the ability of *O*-benzylsarcosine hydroxamic acid (**4c**) to

SCHEME I



successfully react with *p*-chlorobenzaldehyde to afford the compound **6k** precluded any possibility of cyclization through the hydroxyl group (structures **7** and **8**). Therefore, the only possible structures for the products obtained from the reaction of α-aminohydroxamic acids with aldehydes are the ring form (structure **6**) and/or the open-chain form (structure **9**). The distinction between these ring-chain isomers was made by nmr spectroscopy. The azomethine protons in the nmr spectra of authentic Schiff bases with *p*-chloro- and *p*-bromobenzaldehydes, absorbed as singlets at τ 1.64 and τ 1.76, respectively (6). Similarly, the azomethine proton in 4-amino-5-(*p*-chlorobenzylidene-aminoethyl)-2-methylpyrimidine (**10**) resonated at τ 1.5 (singlet) whereas the methine protons in the corresponding

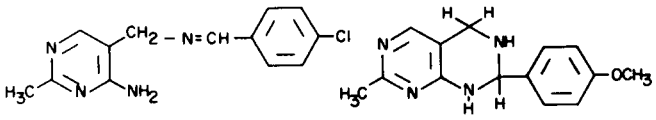
TABLE I

Analytical and Spectral Data for 3-Hydroxy-4-imidazolidinones

Compound	M.p. (°C) (a)	Empirical Formulae	Analyses Calcd.	Analyses Found	IR Data (cm^{-1}) NH	IR Data (cm^{-1}) C=O	NMR Data (τ)
6a	155-156	$C_9H_9ClN_2O_2$	C 50.84 H 4.27 N 13.17	C 50.83 H 4.33 N 12.97	3200	1675	6.70 (m, 1, N*H*), 6.62 (s, 2, CH_2), 4.76 (s, 1, ArC*H*), 2.60 (m, 4, Ar*H*), 0.8 (m, 1, O*H*)
6b	154-156	$C_9H_9ClN_2O_2$	C 50.84 H 4.27 N 13.17	C 50.67 H 4.44 N 13.32	3235	1700	6.62 (s, 2, CH_2), 5.90 (m, 1, N*H*), 4,30 (s, 1, ArC*H*, 2.64 (s, 4, Ar*H*), 0.6 (m, 1, O*H*)
6c	150-151	$C_9H_8Cl_2N_2O_2$	C 43.75 H 3.26 N 11.34	C 43.82 H 3.23 N 11.20	3250	1680	6.68 (m, 2, CH_2), 6.6 (m, 1, N*H*), 4.38 (m, 1, ArC*H*), 2.54 (m, 3, Ar*H*), 0.5 (m, 1, O*H*)
6d	147-150	$C_9H_{10}N_2O_2$	C 60.66 H 5.66 N 15.72	C 60.50 H 5.78 N 15.51	3250	1700	6.66 (s, 2, CH_2), 6.0 (m, 1, N*H*), 4.80 (s, 1, ArC*H*), 2.66 (s, 5, Ar*H*), 1.0 (m, 1, O*H*)
6e	156-157	$C_9H_9N_3O_4$	C 48.43 H 4.06 N 18.83	C 48.27 H 4.05 N 18.64	3300	1715	6.58 (s, 2, CH_2), 5.8 (m, 1, N*H*), 4.52 (s, 1, ArC*H*), 2.10 (m, 4, Ar*H*), 0.4 (m, 1, O*H*)
6f	160-161	$C_9H_9N_3O_4$	C 48.43 H 4.06 N 18.83	C 48.42 H 4.10 N 18.84	3190	1695	6.62 (s, 2, CH_2), 5.6 (m, 1, N*H*), 4.00 (s, 1, ArC*H*), 2.36 (m, 4, Ar*H*), 0.8 (m, 1, O*H*)
6g	146-148	$C_4H_8N_2O_2$	C 41.37 H 6.94 N 24.13	C 41.59 H 7.14 N 23.90	3220	1680	8.77 (d, 3, J=4cps, CH_3), 6.80 (d, 2, J=2.5 cps, CH_2), 5.70 (, 4, J=4.0, C*H*), 4.4 (m, 2, O*H* and N*H*)
6h	154-156	$C_{16}H_{15}ClN_2O_2$	C 63.47 H 4.99 N 9.25	C 63.31 H 4.95 N 9.09	3300	1700	7.0 (m, 2, CH_2), 6.8 (m, 1, N*H*), 6.26 (m, 1, ArC*H*), 4.80 (m, 1, ArC*H*), 2.80 (s, 8, Ar*H*), 0.52 (m, 1, O*H*)
6i	142-145	$C_{10}H_{11}ClN_2O_2$	C 52.99 H 4.89 N 12,36	C 53.14 H 4.82 N 12.23	---	1690	7.8 (s, 3, CH_3), 6.68 (m, 2, CH_2), 5.30 (m, 1, C*H*), 2.60 (s, 4, Ar*H*), 0.54 (m, 1, O*H*)
6j	115-116	$C_4H_8N_2O_2$	C 41.37 H 6.94 N 24.13	C 41.19 H 6.96 N 24.27	---	1690	7.64 (s, 3, CH_3), 6.90 (s, 2, CH_2), 5.90 (s, 2, CH_2), 1.0 (m, 1, O*H*)
6k	99-100	$C_{17}H_{17}ClN_2O_2$	C 64.46 H 5.41 N 8.84	C 64.62 H 5.63 N 9.01	---	1725	7.80 (s, 3, CH_3), 6.62 (m, 2, CH_2), 5.30 (m, 3, ArCh, ArCH_2), 2.70 (m, 9, Ar*H*)
6l	185-186	$C_8H_9N_3O_2$	C 53.60 H 5.03 N 23.44	C 53.51 H 5.26 N 23.35	3200	1700	7.5 (m, 2, CH_2), 6.25 (m, 2, N*H*, O*H*), 4.6 (s, 1, C*H*), 2.5 (m, 4, Ar*H*)
12+13	156-157	$C_9H_{10}N_2O_3$	C 55.67 H 5.19 N 14.43	C 55.50 H 5.17 N 14.20	3190	1690	7.5 (m, 2, CH_2), 6.6 (m, 3, N*H*, O*H*), 4.6 (s, 0.34, methine *H*), 3.0 (m, 4, Ar*H*, 1.5 (s, 0.66, azomethine *H*)

(a) Decomposition Point.

ring isomer, tetrahydropyrimido(4,5-*d*)pyrimidines (**11**) absorbed at τ 4.58 (singlet) (6). The nmr spectra of compounds **6a-6l** showed a singlet at τ 4.00-5.00 which integrated for one proton (characteristic of the methine proton). This suggested that the reaction of the α-aminohydroxamic acids **4a-4c** with the aldehydes **5** afforded only the corresponding ring isomers, 3-hydroxy-4-imidazolidinones (**6a-6l**). However, the reaction of glycine



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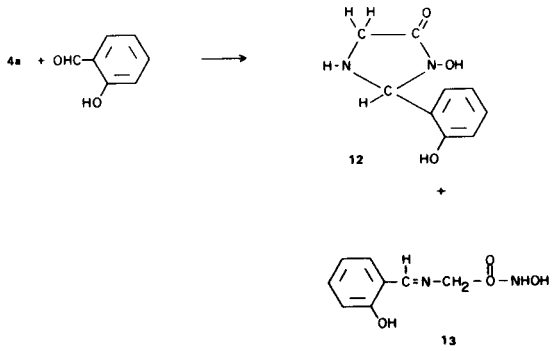
hydroxamic acid (**4a**) with salicylaldehyde afforded a mixture of the 3-hydroxy-4-imidazolidinone **12** and the Schiff base **13** as shown in Scheme II. This was confirmed by

SCHEME II



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13

the nmr spectrum of the mixture which showed absorptions characteristic of both the ring and the chain isomers, **12** and **13** respectively. The peak at τ 4.6 (methine proton, structure **12**) integrated for 0.34 H, whereas the peak at τ 1.5 (azomethine proton, structure **13**) integrated for 0.66 H. This suggested the approximate composition of the mixture to be 34% **12** and 66% **13**.

Conclusion.

The reaction of α-aminohydroxamic acids with a variety of aromatic aldehydes afforded 3-hydroxy-4-imidazolidinone (**6a-6l**). However, the reaction between glycine hydroxamic acid (**4a**) and salicylaldehyde yielded a mixture of 3-hydroxy-4-imidazolidinone **12** and the corresponding Schiff base **13**.

EXPERIMENTAL

The melting points were taken on a Thomas-Hoover Unimelt apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The nmr spectra were obtained with a Varian A-60 spectrometer using DMSO-d_6 as solvent. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The mass spectra were obtained on an Atlas CH-4 mass spectrometer. Glass plates coated with Silica Gel G. were used for tlc. Glycine hydroxamic acid (**4a**) was prepared by the procedure of Jones and Sneed (4). Ethyl sarcosinate hydrochloride was obtained by the procedure of Staudt (7).

Sarcosine Hydroxamic Acid (**4b**).

A solution of ethyl sarcosinate hydrochloride (30.7 g., 0.20 mole) in absolute methanol (70 ml.) was mixed with a solution of potassium hydroxide (11.2 g., 0.20 mole) in absolute methanol (70 ml.). The mixture was cooled at -5° overnight and the precipitated potassium chloride was removed by filtration. Similarly a solution of hydroxylamine hydrochloride (21.0 g., 0.30 mole) in hot absolute methanol (140 ml.) was mixed with a solution of potassium hydroxide (16.8 g., 0.20 mole) in absolute methanol (70 ml.). The mixture was cooled at -5° overnight and the precipitated potassium chloride was removed by filtration. The filtrates from these two reactions containing the free ethyl sarcosinate and hydroxylamine, respectively, were mixed together and cooled at -5° overnight. The solution was concentrated to about 200 ml. and cooled again at -5° overnight. Filtration afforded 16.0 g. (77%) colorless crystals of sarcosine hydroxamic acid (**4b**) m.p. 135-140° dec. The crude product, on purification by washing with hot water, gave 14.0 g. (66.6%) colorless crystals of **4b** m.p. 139-141° dec. The analytical sample was prepared by one recrystallization from distilled water, m.p. 140-141° dec.

Anal. Calcd. for $C_3H_8N_2O_2$: C, 34.61; H, 7.75; N, 26.91. Found: C, 34.85; H, 7.77; N, 26.84.

O-Benzylsarcosine Hydroxamic Acid (**4c**).

Benzyloxyamine was prepared from its hydrochloride (20.0 g., 0.0125 mole) by neutralizing the hydrochloride with excess base, extracting with ether and drying (magnesium sulfate). The ether solution of the free amine was mixed with 150 ml. of absolute methanol and most of the ether removed by evaporation under diminished pressure. A methanol solution (150 ml.) of ethyl sarcosinate, obtained from neutralization of its hydrochloride (12.0 g., 0.079 mole), was mixed with the methanol solution of benzyloxyamine and the mixture was cooled at -5° overnight. The filtration afforded 5.0 g. (33.0%) of the crude product, m.p. 97-100°. Recrystallization from ethanol-water yielded colorless crystals of **4c** m.p. 104-196°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.41. Found: C, 61.62; H, 7.36; N, 14.33.

General Procedure for the Reaction of α-Aminohydroxamic Acids (**4a-4c**) with Aldehydes (**5**).

A mixture of the α-aminohydroxamic acid **4a-4c** (0.02 mole) and the aldehyde **5** (0.02 mole) in absolute ethanol (60 ml.) was refluxed for 2-4 hours with stirring. Then the reaction mixture was filtered while hot, concentrated under diminished pressure and cooled at -5° overnight. Crystalline 3-hydroxy-4-imidazolidinones (**6a-6l**) were obtained in 70-90% yields by filtration and recrystallization of the solid from absolute ethanol. The same procedure was used for the reaction of **4a** with salicylaldehyde. The products were recrystallized from absolute ethanol and submitted for nmr and elemental analyses. The melting points, yields, elemental analyses and spectral data are summarized in Table I.

Acknowledgment.

This work was supported by Grant CA-06140 from the National Cancer Institute.

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Received September 29, 1969 Kalamazoo, Michigan 49001