New Derivatives of Ethyl 1-Methyl-1*H*-imidazole-2-glyoxylate. Synthesis and Properties of α-Hydroxyimino and α-Methoxyimino Double-Bond Stereoisomers

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Synthetic routes for the preparation of ethyl α-hydroxyimino and α-methoxyimino-1-methyl-1*H*-imidazole-2-acetate are reported. Separation and characterization of the double-bond stereoisomers are described.

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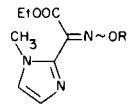
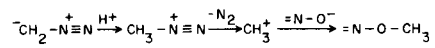
As part of a program on the synthesis of new 7β-acylaminoceph-3-em-4-carboxylic acids, (*Z*)-α-methoxyimino-1-methyl-1*H*-imidazole-2-acetic acid was desired as starting material. This paper reports the condensation of hydroxylamine with the known (1) ethyl 1-methyl-1*H*-imidazole-2-glyoxylate, and deals with the separation of the two isomeric α-hydroxyimino derivatives **1** and **2** and with the preparation of the two *O*-methyl ethers **3** and **4**.



1 and 2 R = H
3 and 4 R = CH_3

The formation of **1** and **2** in different ratios can be affected by varying the reaction conditions in the condensation of hydroxylamine with the α-ketoester. A preferential formation of the more polar α-hydroxyimino isomer **1** was observed if the reaction was carried out at room temperature and in aqueous acetic acid plus one equivalent of sodium hydroxide, while the yield of the other isomer **2** prevailed in refluxing ethanol and in the presence of pyridine. Both geometrical isomers have been *O*-alkylated to **3** and **4** either with diazomethane or with methyl iodide. It was observed that the reaction rate with diazomethane depends strictly on the configuration of the α-hydroxyimino ester. In fact, the more polar compound reacted much more rapidly than its isomer; this behaviour has been correlated with a greater acidity and an easier ionization.

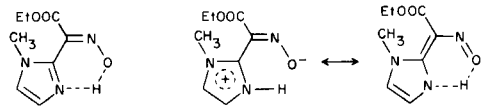


Alkylation with methyl iodide in the presence of potassium fluoride or sodium methoxide was affected by a side-reaction that led to an imidazolium derivative (**5**). The yields for the *O*-alkylations were always unsatisfactory. In the reaction with methyl iodide plus sodium methoxide in methanol, a complete transesterification (**6** and **7**) was observed.

Configurational Considerations.

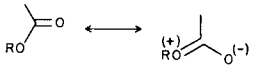
Configurational assignments have been made for all the geometrical isomers. The assignments are reasonable but must remain tentative until more data are available.

An (*E*)-configuration has been assigned to the more polar α-hydroxyimino ester with the higher melting point, the more acidic properties (it can be titrated with standard sodium hydroxide in an aqueous-alcoholic solution, whereas the titration of the other stereoisomer requires sodium methoxide in benzene-dimethylformamide), and the greater reactivity towards diazomethane. A hydrogen-bonded structure like **1** or rather an equilibrium between **1** and the zwitterion form **1a** has been proposed to account

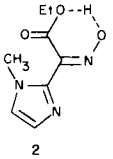


1 1a

for the infrared absorption bands near 2600-2500 cm^{-1} (broad) and at 1900 cm^{-1} (broad). These bands are present, for example, in the infrared spectra of 2-methyl-5-pyridinecarboxylic acid (2) and of 4-carbethoxy-1*H*-imidazole-1-acetic acid (unpublished data from this laboratory). The low frequency (1712 cm^{-1}) found for the ester carbonyl stretching vibration may be due to a resonance effect as shown.



A(*Z*)-configuration has been assigned to the other geometrical isomer **2**. An intramolecular H bond



2

formation was suggested by the broad ν OH band around 2700 cm^{-1} and the side of chelation was indicated by the

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high frequency of the ester carbonyl stretching vibration at 1745 cm^{-1}. The same high frequency for the ν C=O in a strongly chelated system has already been found for lactic acid ethyl ester (3). Furthermore, the lower acidity and the reduced polarity of **2** in comparison with those of **1** are typical properties of a chelated molecule and have been found in other compounds as, for example, in 4(7)-nitrobenzotriazole (4). A band near 935 cm^{-1} associated with the N-OH stretching vibration and present in both isomers was of weaker intensity in the spectrum of **1** with the assigned (*E*)-configuration. This is in accord with the data given by A. Ahmad (5) for two different pairs of geometrical isomers of α-hydroxyimino acids.

Another important difference was found in the uv absorption spectra of the two isomers. The more polar compound **1** has λ max 270 nm (ε 2,305), whereas the other had λ max 276 nm (ε 11,244). The abnormally low intensity observed for the formed isomer may be explained with a reduced conjugation between the ring and the side chain, or with an s-*cis* conformation in the side chain. Baas and Cerfontain (6) observed a striking difference in the uv absorption of two isomeric α-ethoxyimino ketones with s-*trans* and s-*cis* conformations, respectively.

The nmr spectra (DMSO-d_6) of the two stereoisomers show three-proton sharp singlets at 3.45 and at 3.78 ppm, associated with the *N*-methyl groups in **1** and **2**, respectively, whereas the ring protons are centered at 6.88 and 7.10 ppm in **1** and at 6.88 and 7.17 ppm in **2**. The hydroxyimino (OH) proton signal occurs as a sharp singlet at 11.83 ppm in the case of **2**, whereas a very broad flat band is seen for **1** with ill-defined chemical shift.

For the $=N\text{-}O\text{-}CH_3$ esters **3** and **4**, we found the signal of the methoxyimino group (deuteriochloroform) at 4.07 ppm for **3** (*E*) and at 3.95 ppm for **4** (*Z*). Identical chemical shifts in the same solvent have been observed (unpublished data from this laboratory) for the pairs of stereoisomeric esters of (*E*)-α-methoxyimino-2-furanacetic acid and (*Z*)-α-methoxyimino-2-thiophenacetic acid (4.07 ppm), and of (*Z*)-α-methoxyimino-2-furanacetic acid and (*E*)-α-methoxyimino-2-thiopheneacetic acid (3.95 ppm), with the same configurations at the double bond. The data given by R. Bucourt, *et al.* (7), agree well with our findings.

The characteristic triplets-quartets of the ethylester groups are practically superimposable, but in the (*E*)-isomers they are always at higher fields both in deuteriochloroform and in DMSO. R. Bucourt (7) also reported similar differences for analogous pairs of isomers. We have synthesized the reported compounds (7) and reconfirmed the published chemical shifts, always finding at higher fields the triplet and the quartet of the ethylester group belonging to the isomer with the α-hydroxyimino (or methoxyimino) *anti* to the ethoxycarbonyl group.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Ultraviolet spectra were recorded on a Beckman DB-T spectrophotometer and maxima are reported in nanometers. Nmr spectra were determined with a Varian 60 MHz instrument with TMS as internal standard. Thin layer chromatograms were run on silica gel plates which were developed with chloroform-methanol (9:1). No effort was made to improve the yields.

Ethyl 1-Methyl-1*H*-imidazole-2-glyoxylate.

This compound was prepared by the method of E. Regel, et al., (1); ir (nujol): ν 1740 (C = O ester), 1670 (C = O ketone) cm^{-1}; uv (ethanol): λ max nm 294 (ε 13,650); nmr (deuteriochloroform): δ 4.0 (s, 3H, NCH_3), 7.1 and 7.17 (2H, imidazole-H); nmr (DMSO-d_6): δ 4.0 (s, 3H, NCH_3), 7.23 (d, 1H, imidazole-H), 7.61 (d, 1H, imidazole-H).

(*E*)-Ethyl α-Hydroxyimino-1-methyl-1*H*-imidazole-2-acetate (**1**).

Hydroxylamine hydrochloride (1.50 g., 21.6 mmoles) was added to 2.36 g. (13 mmoles) of ethyl 1-methyl-1*H*-imidazole-2-glyoxylate in acetic acid (4 ml.). The solution was stirred and cooled in an ice-bath and 14 ml. of 1*N* sodium hydroxide were added. After being stirred at 0° for 2 hours and then at room temperature for 27 hours, the solution (*p*H 4.0) was continuously extracted with ethyl acetate. The organic phase which separated was washed with saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give an oil which solidified when washed with a little ethyl acetate and petroleum ether. The crude brown solid was shown by tlc to consist of a major spot at R_f 0.45 and a minor spot at R_f 0.50, in addition to an immobile spot (by-products). It was recrystallized from ethanol to give 1.10 g. of **1** with R_f 0.45, m.p. 158-160°; ir (potassium bromide): 2600-2500 and 1900 (broads, C=N-), 1712 (C=O) cm^{-1}; uv (ethanol): λ max 270-271 nm (ε 2,305); nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_3), 3.45 (s, 3H, NCH_3), 4.17 (q, 2H, CH_2), 6.88 (d, 1H, imidazole-H), 7.10 (d, 1H, imidazole-H).

Anal. Calcd. for $C_6H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31; mol. wt., 197.19. Found: C, 48.53; H, 5.56; N, 21.20; mol. wt. (NaOH), 196.31.

(*Z*)-Ethyl α-Hydroxyimino-1-methyl-1*H*-imidazole-2-acetate (**2**).

A mixture of 1.82 g. (10 mmoles) of ethyl 1-methyl-1*H*-imidazole-2-glyoxylate, 0.90 g. of hydroxylamine hydrochloride and 2 ml. of pyridine in ethanol (10 ml.) was stirred and heated under reflux for 3 hours. The solvent was removed by evaporation to 4 ml., and 17 ml. of water were added. The solid that separated (*p*H *ca.* 5.0) was filtered after adjusted the the *p*H of the mixture to 6.5 with 1*N* sodium hydroxide. The solid was washed with water and dried to give 1.5 g., which consisted of a mixture of **2** and **1** in a molar ratio of 2:1, as seen by tlc and as determined by nmr analysis [comparative integrations of peaks at δ 3.45 (NCH_3 of **1**) and at δ 3.78 (NCH_3 of **2**)].

The solid was dissolved in chloroform and placed on a column of silica gel. Elution with chloroform and then chloroform-methanol provided 1.0 g. of white crystals, nearly pure **2** with R_f 0.50; m.p. 132-135°; ir (potassium bromide): 2700 (OH bonded), 1745 (C=O) cm^{-1}; uv (ethanol): λ max 276 nm (ε 11,244); nmr (DMSO-d_6): δ 1.27 (t, 3 H, CH_3), 3.78 (s, 3H, NCH_3), 4.23 (q, 2H, CH_2), 6.88 (d, 1H, imidazole-H), 7.17 (d, 1H, imidazole-H), 11.83 (s, 1H, OH).

Anal. Found: C, 48.23; H, 5.51; N, 21.10; mol. wt. (CH_3ONa), 194.

(*E*)-Ethyl α-Methoxyimino-1-methyl-1*H*-imidazole-2-acetate (**3**).

Method A. *O*-Methylation with Diazomethane.

To a cooled solution of 1.97 g. (10 mmoles) of **1** in 70 ml. of ethyl acetate, were added dropwise 42 ml. of an ethereal solution (1%) of diazomethane (10 mmoles). The solution was left at room temperature and was monitored by tlc. The starting material **1** was found to rapidly disappear with concomitant appearance of a compound at R_f 0.65 and by-products at R_f 0.0. At the end of 3 hours no more **1** was present. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with dichloromethane and

dichloromethane-methanol (99:1) furnished pure **3** (1.48 g.) as an oil; nmr (deuteriochloroform): δ 1.33 (t, 3H, CH_3), 3.48 (s, 3H, NCH_3), 4.07 (s, 3H, OCH_3), 4.28 (q, 2H, CH_2), 6.88 (1H, imidazole-H), 7.05 (1H, imidazole-H).

Anal. Calcd. for $C_9H_{13}N_3O_3$ (211.22): C, 51.17; H, 6.20; N, 19.90. Found: C, 50.96; H, 6.30; N, 19.80.

Method B. *O*-Methylation with Methyl Iodide (Potassium Fluoride).

To an ice-cooled mixture of 789 mg. (4 mmoles) and of **1** and 1.16 g. of potassium flouride in 20 ml. of dimethylformamide was added dropwise 1 ml. (16 mmoles) of methyl iodide. The brown mixture was allowed to come to room temperature and at the end of 4 hours of stirring it was poured into 40 ml. of water and extracted with ethyl acetate (4 × 25 ml.). The organic layer was dried and taken to dryness. The residue was washed well with petroleum ether and chromatographed as in method A to yield 250 mg. of pure **3**.

Method C. *O*-Methylation with Methyl Iodide (Sodium Methoxide).

A solution of 5.6 g. (28.4 moles) of **1**, 30 ml. of 0.92*N* sodium methoxide, 30 ml. of methanol and 3.5 ml. of methyl iodide (56.8 mmoles) was stirred at room temperature for 3 hours. After concentration *in vacuo*, a brown residue was obtained which was dissolved in 20 ml. of water and extracted with ethyl acetate (8 × 20 ml.). The combined organic layer was dried and monitored by tlc. The presence of two major products could be detected with R_f 0.62 and R_f 0.59. Both spots were isolated by repeated column chromatography. The higher R_f spot corresponded to (*E*)-methyl α-methoxyimino-1-methyl-1*H*-imidazole-2-acetate **6**. The lower R_f spot was a brownish oil (**5**) containing small amounts of impurities; nmr (deuteriochloroform): δ 1.23 (t, 3H, CH_3), 3.50 (s, 3H, NCH_3), 4.20 (s, 3H), 4.20 (q, 2 H, CH_2), 6.88 (1H, imidazole-H), 7.0 (1H, imidazole-H). Pure **6** was a nearly colorless oil; nmr (deuteriochloroform): δ 3.52 (s, 3H, NCH_3), 3.85 (s, 3H, $COOCH_3$), 4.07 (s, 3H, $NOCH_3$), 6.88 (d, 1H, imidazole-H), 7.05 (d, 1H, imidazole-H).

Anal. Calcd. for $C_8H_{11}N_3O_3$ (197.19): C, 48.72; H, 5.62; N, 21.31. Found: C, 48.52; H, 5.65; N, 21.25.

(*Z*)-Ethyl α-Methoxyimino-1-methyl-1*H*-imidazole-2-acetate (**4**).

The procedure and the quantities were the same as described for **1** in method A, with the modification that ethanol was used as solvent for **2**. The starting product **2** was found to react much slowly than **1**, and at the end of 12 hours another portion of diazomethane (5 mmoles) was added. At the end of a total of 24 hours no more **2** was present. Workup gave, after chromatography, 1.1 g. of **4** as an oil; R_f 0.69; ir (liquid film): ν 1750 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.37 (t, 3H, CH_3), 3.78 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.37 (q, 2H, CH_2), 6.83 (1H, imidazole-H), 6.98 (1H, imidazole-H).

Anal. Found: C, 50.87; H, 6.15; N, 19.80.

(*Z*)-Methyl α-Methoxyimino-1-methyl-1*H*-imidazole-2-acetate (**7**).

Working with one tenth of the quantity given for **1** in method C, approximately 100 mg. of **7** has been obtained from **2** as a colorless oil; R_f 0.67; nmr (deuteriochloroform): δ 3.80 (s, 3H, NCH_3), 3.88 (s, 3H, $COOCH_3$), 3.95 (s, 3H, $NOCH_3$), 6.83 (d, 1H, imidazole-H), 6.98 (d, 1H, imidazole-H).

Anal. Found: C, 49.01; H, 5.66; N, 21.20.

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