

# Research on Heterocyclic Compounds. XIII. Synthesis of 4,5-Dihydro-5-oxo-3-isoxazoleacetic Acid and Related Compounds

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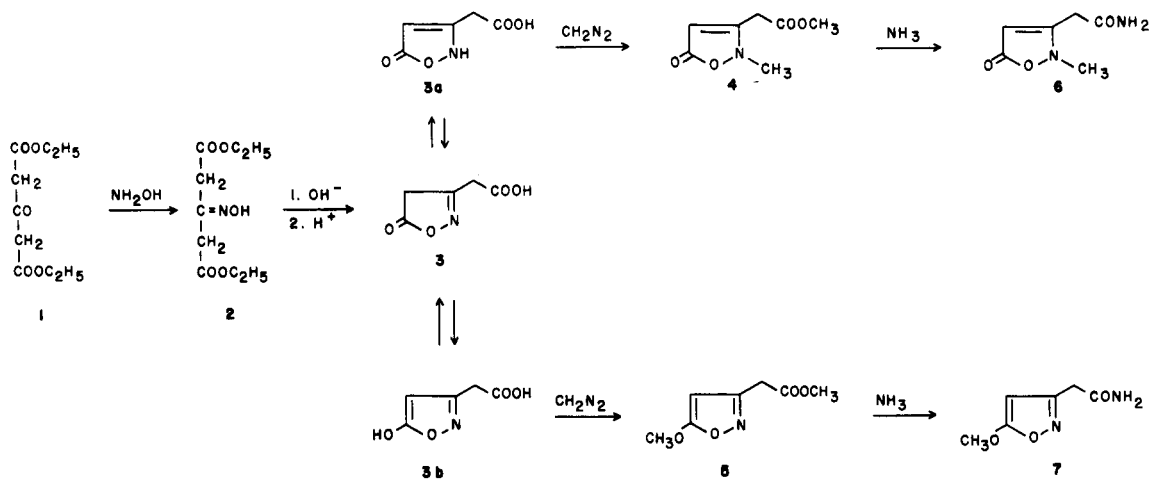
Some new 4,5-dihydro-5-oxoisoxazole derivatives were synthesized as part of a study to prepare potential antiinflammatory agents. The reaction of the diethyl ester of 3-oxopentanedioic acid with hydroxylamine afforded the 3-hydroxyimino derivative, which was then cyclized to the title compound. This reacted with diazomethane to give a couple of isomeric methyl derivatives, namely methyl 2,5-dihydro-2-methyl-5-oxo-3-isoxazoleacetate and methyl 5-methoxy-3-isoxazoleacetate. Reaction of these compounds with ammonia gave the corresponding acetamides. All compounds were characterized by elemental analysis, uv, ir, and  $^1\text{H}$ -nmr spectra.

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In the context of our research on the synthesis of heterocyclic compounds with an acidic moiety as well as on the relationships between their chemical structure and antiinflammatory activity [1], we have taken into consideration the possibility to prepare some acidic derivatives of 4,5-dihydro-5-oxoisoxazole. In view of the chemical structure and reactivity of such compounds, they should be able to interact with the prostaglandin synthetase cyclooxygenation site according to the mechanism of action proposed by Gund and Shen [2] for the antiinflammatory arylacetic acids.

At present, only a few carboxylic derivatives of 4,5-dihydro-5-oxoisoxazole are known [3], like ethyl 4,5-dihydro-5-oxo-3-isoxazolecarboxylate, which was synthesized by Piutti [4,5], and some other derivatives with an ester or carboxamide moiety [6], whereas no acetic derivatives are known.

In view of the remarkable pharmacological activity shown by a number of heteroarylacetic acids we synthesized in the past, we thought it was interesting to prepare 4,5-dihydro-5-oxo-3-isoxazoleacetic acid (**3**). Such compound was obtained starting from the diethyl ester of 3-oxopentanedioic acid **1**, which was reacted with hydroxylamine hydrochloride in aqueous methanol to give the 3-hydroxyimino derivative **2**. Both the reaction and the following isolation and purification procedure of the product had to be carried out carefully controlling temperature, because rapid decomposition occurred above  $40^\circ$ . 4,5-Dihydro-5-oxo-3-isoxazoleacetic acid (**3**) was directly obtained from **2** by treatment with aqueous methanolic sodium hydroxide solution at  $0^\circ$ . In such reaction conditions, both the closure of the isoxazolone ring and the hydrolysis of the carbethoxy moiety not involved in the cyclization took place. The elemental analytical data and uv, ir, and  $^1\text{H}$



nmr spectra confirmed the proposed structure **3**.

From a pharmacological viewpoint, also some derivatives of the acid **3** should be interesting, particularly its amide: in fact, during our previous researches we have observed that some heteroarylcarboxamides and acetamides surpassed the corresponding acids in antiinflammatory activity [7,8]. Therefore, we have tried to prepare an ester of the acid **3**, but all the attempts we made with the usual esterification methods were unsuccessful. Consequently it was decided to try to prepare the methyl ester of **3** by treatment with diazomethane.

Treatment of an ethereal methanolic solution of **3** with an ethereal diazomethane solution (molar ratio 1:3) gave a mixture of two liquid products, which showed Rf 0.75 and 0.48, respectively, on silica gel thin layer eluting with chloroform-methanol 9:1. They were separated by column chromatography and showed different boiling points. The elemental analytical data proved that these two products had the same empirical formula,  $C_7H_9NO_4$ . The nmr spectra were similar both in deuteriochloroform and in hexadeuteriodimethyl sulfoxide: both products showed two singlets (3 protons each) in the  $\delta$  3-4 range, a singlet for 2H in the same region, and another singlet (1H) at about  $\delta$  5. To this couple of products we have therefore assigned the isomeric structures **4** and **5**, which arose by exhaustive methylation of the tautomeric forms **3a** and **3b** of the acid **3**.

The correct assignment of either structure to these products was mainly made on the basis of nmr spectra in deuteriotrifluoroacetic acid. In such solvent the proton in the 4 position exchanged with deuterium and the corresponding signal at about  $\delta$  5 disappeared from both spectra, but at a sharply different rate. The H-4 proton of the low-boiling product with Rf 0.75 exchanged slowly and the corresponding peak was still perceptible two hours after the preparation of the solution, whereas in the case of the high-boiling product with Rf 0.48 the H-4 peak became no more visible in the spectrum within ten minutes, because of its much higher exchange rate. Consequently, we have assigned to the latter product the structure **4** (methyl 2,5-dihydro-2-methyl-5-oxo-3-isoxazoleacetate), which accounts for the higher acidity of the proton in the 4 position in that it is adjacent to a carbonyl group. Therefore, the former product is methyl 5-methoxy-3-isoxazoleacetate **5**.

Such structural assignments were also confirmed by other experimental data. The ir spectrum of **5** showed a strong sharp band at  $1750\text{ cm}^{-1}$  due to the carboxylic C=O group, and other strong bands in the range  $1600\text{--}1500\text{ cm}^{-1}$  due to the double bonds of the aromatic isoxazole ring. These latter bands were absent in the spectrum of compound **4**, which showed a strong broad band centered at  $1740\text{ cm}^{-1}$  arising by the overlap of stretching frequencies of two carbonyl groups (COOH and 5-CO). As regards

uv spectra, compound **4** exhibited a high intensity absorption band with  $\lambda_{\text{max}}$  267 nm, whereas compound **5** had a band of medium intensity at a markedly lower wavelength.

The assigned structures are also in accordance with the difference observed both in the boiling point and in the chromatographic behaviour: in fact, the methoxy derivative **5** had a lower boiling point and a higher Rf in comparison with **4**. It has to be pointed out that there is a close similarity between the 5-oxoisoxazole derivatives **3** and **4** as regards ir and uv spectra.

The methyl esters **4** and **5** were reacted with concentrated ammonia to obtain the corresponding acetamides **6** and **7**, respectively. Analytical and spectral features of these compounds were in agreement with those of the corresponding esters, as reported in detail in the experimental section.

## EXPERIMENTAL

Melting points were determined in open capillary tubes using an Electrothermal apparatus and applying no correction. Thin layer chromatography was run on Merck precoated silica gel 60 F254 plates, and detection of components was made by ultraviolet light. Column chromatographic separations were performed using Merck silica gel 60 (70-230 mesh ASTM). The uv spectra were obtained with a Cary 219 spectrophotometer. The ir spectra were recorded on a Beckman Microlab 620MX spectrophotometer. The  $^1\text{H}$ -nmr spectra were recorded on a Varian EM-360 60 MHz spectrometer, using TMS as an internal standard. The elemental analyses were performed using a Perkin Elmer Elemental Analyzer model 240.

### 3-Hydroxyiminopentanedioic Acid Diethyl Ester (**2**).

To a stirred solution of 20.6 g (0.102 mole) of 3-oxopentanedioic acid diethyl ester **1** [9] in 270 ml of methanol, a solution of 18.3 g (0.263 mole) of hydroxylamine hydrochloride in 30 ml of water was added at room temperature; stirring was carried on for 6 hours following the addition. The solvent was then completely removed at  $40^\circ$  under reduced pressure. The resulting residue was treated with ethyl acetate, the filtered solution was dried over anhydrous sodium sulfate and the solvent removed *in vacuo*. The resulting oily residue was stirred with *n*-hexane to remove traces of the starting product. After removal of *n*-hexane, 19 g (86%) of an oil was obtained; this product was chromatographically pure (as shown by tlc on silica gel eluting with benzene-ethyl acetate 8:2) and was not redistilled *in vacuo*, because all attempts made to distill the product caused fast decomposition; nmr (deuteriochloroform):  $\delta$  1.6 and 1.65 (two triplets,  $\text{CH}_3$ , 6H), 3.9 (s, 2- and 4- $\text{CH}_2$ , 4H), 4.55 (m, ethyl  $\text{CH}_2$ , 4H).

Anal. Calcd. for  $\text{C}_7\text{H}_{15}\text{NO}_5$ : C, 49.7; H, 6.9; N, 6.4. Found: C, 49.9; H, 7.0; N, 6.2.

### 4,5-Dihydro-5-oxo-3-isoxazoleacetic Acid (**3**).

A mixture of 18 g (0.083 mole) of **2** and 180 ml of 1.5 *N* sodium hydroxide solution in water-methanol 2:1 was stirred at  $0^\circ$  for 3 hours. Methanol was then removed by distillation at  $40^\circ$  under reduced pressure. The residual alkaline aqueous solution was cooled at  $0^\circ$  and acidified with diluted hydrochloric acid. The acid solution was extracted three times with ethyl acetate; the combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to dryness *in vacuo* giving a viscous oil which was treated with diethyl ether to afford pale pink crystals. Two recrystallizations first from ether and then from ethyl acetate gave 8 g (67%) of white crystals, mp  $89\text{--}91^\circ$ ; Rf 0.42 (ethanol-water 85:15); uv (95% ethanol):  $\lambda_{\text{max}}$  256 nm ( $\epsilon$  3,550;  $E_1\%$  248); ir (potassium bromide):  $\text{cm}^{-1}$  1800 and 1715 strong (5-C=O and carboxylic C=O), 1620 medium (C=N); nmr (hexadeuteriodimethyl sulfoxide):  $\delta$  3.5 (s,  $\text{CH}_2$ ).

*Anal.* Calcd. for  $C_5H_5NO_4$ : C, 41.9; H, 3.5; N, 9.8. Found: C, 42.2; H, 3.6; N, 9.8.

Methyl 2,5-Dihydro-2-methyl-5-oxo-3-isoxazoleacetate (4).

An ethereal solution of 6.3 g (0.15 mole) of diazomethane was added dropwise to a solution of 7.15 g (0.05 mole) of **3** in 10 ml of methanol and 50 ml of diethyl ether cooled in a freezing mixture of common salt and crushed ice. After standing overnight, the solvent was evaporated to obtain an oil. This crude product was examined by tlc (chloroform-methanol 9:1), which showed the presence of two components with Rf 0.75 and 0.48, respectively. This mixture was chromatographed on a silica gel column packed with chloroform, eluting the first eight fractions with the same solvent and the following fractions with chloroform-methanol 9:1. Fractions 2-8 contained the product with Rf 0.75 (**5**); fraction 9 contained both products and was discarded; fractions 10-12 containing the product with Rf 0.48 (**4**) were combined and evaporated *in vacuo*. The residue was redissolved in methanol, filtered and evaporated *in vacuo* to obtain 2 g of an oil which was distilled with a mercury diffusion pump, affording 1.5 g (17.5%) of **4**, bp 148-150°/1  $\mu$ ;  $n_D^{20} = 1.5285$ ; uv (95% ethanol):  $\lambda$  max 267 nm ( $\epsilon$  11,167;  $E_1^{1\%}$   $_{1\text{cm}}^{1\text{cm}}$  652); ir (liquid film):  $cm^{-1}$  1740 broad, strong (two C=O); nmr: a) in deuteriochloroform:  $\delta$  3.48 (s, 2H,  $CH_2$ ), 3.31 (s, 3H) and 3.71 (s, 3H) (two  $CH_3$ ), 5.12 (s, 1H, H-4); b) in hexadeuteriodimethyl sulfoxide:  $\delta$  3.18 (s, 2H,  $CH_2$ ), 3.26 (s, 3H) and 3.58 (s, 3H) (two  $CH_3$ ), 5.09 (s, 1H, H-4); c) in deuteriotrifluoroacetic acid:  $\delta$  3.8 (s, 2H,  $CH_2$ ), 3.68 (s, 3H) and 3.84 (s, 3H) (two  $CH_3$ ); the H-4 peak was absent in the latter spectrum which was recorded 10 minutes following the preparation of the solution.

*Anal.* Calcd. for  $C_7H_9NO_4$ : C, 49.1; H, 5.3; N, 8.2. Found: C, 48.9; H, 5.3; N, 8.0.

Methyl 5-Methoxy-3-isoxazoleacetate (5).

Fractions 2-8 obtained in the above procedure were combined and worked up in the same manner described for **4**, obtaining 4.2 g (49%) of redistilled **5**, bp 92-94°/1  $\mu$ ;  $n_D^{20} = 1.4905$ ; uv (95% ethanol):  $\lambda$  max 224 nm ( $\epsilon$  7,300;  $E_1^{1\%}$   $_{1\text{cm}}^{1\text{cm}}$  426); ir (liquid film):  $cm^{-1}$  1750 strong (C=O), 1620, 1520 strong (aromatic); nmr: a) in deuteriochloroform:  $\delta$  3.53 (s, 2H,  $CH_2$ ), 3.67 (s, 3H) and 3.9 (s, 3H) (two  $CH_3$ ), 5.24 (s, 1H, H-4); b) in hexadeuteriodimethyl sulfoxide:  $\delta$  3.23 (s, 2H,  $CH_2$ ), 3.6 (s, 3H) and 3.9 (s, 3H) (two  $CH_3$ ), 5.5 (s, 1H, H-4); c) in deuteriotrifluoroacetic acid:  $\delta$  3.94 (s, 2H,  $CH_2$ ), 3.83 (s, 3H) and 4.12 (s, 3H) (two  $CH_3$ ), 5.17 (s, H-4: this peak integrated for nearly 1H ten minutes following the preparation of the solution, and for about 0.1H after 2 hours).

*Anal.* Calcd. for  $C_7H_9NO_4$ : C, 49.1; H, 5.3; N, 8.2. Found: C, 48.7; H, 5.5; N, 8.3.

2,5-Dihydro-2-methyl-5-oxo-3-isoxazoleacetamide (6).

A mixture of 1.3 g (7.5 mmoles) of **4** and 5 ml of concentrated ammonia was heated on a boiling water bath for 15 minutes. The reaction mixture was then evaporated to dryness *in vacuo*, obtaining an oily residue which became a crystalline solid by treatment with a little amount of ethanol. The crude product was recrystallized twice from anhydrous ethanol to give 0.5 g (42%) of white crystals, mp 127-128°; Rf 0.53 (ethanol-water 8:2); uv (95% ethanol):  $\lambda$  max 266 nm ( $\epsilon$  11,495;  $E_1^{1\%}$   $_{1\text{cm}}^{1\text{cm}}$  736); ir (potassium bromide):  $cm^{-1}$  1730 broad, strong (two C=O); nmr (deuteriotrifluoroacetic acid):  $\delta$  3.79 (s, 2H,  $CH_2$ ), 3.7 (s, 3H,  $CH_3$ ), 5.5 (s, H-4: this peak

completely disappeared from the spectrum within 20 minutes after the preparation of the solution).

*Anal.* Calcd. for  $C_6H_8N_2O_3$ : C, 46.1; H, 5.2; N, 17.9. Found: C, 46.4; H, 5.3; N, 17.8.

5-Methoxy-3-isoxazoleacetamide (7).

A mixture of 3.5 g (0.02 mole) of **5** and 10 ml of concentrated ammonia was heated on a boiling water bath for 20 minutes. A solid product precipitated from the reaction solution after cooling. The precipitate was filtered, dried and then recrystallized twice from ethanol to obtain 2.4 g (77%) of white crystals, mp 134-135°; Rf 0.57 (ethanol-water 8:2); uv (95% ethanol):  $\lambda$  max 224 nm ( $\epsilon$ , 7,180;  $E_1^{1\%}$   $_{1\text{cm}}^{1\text{cm}}$  460); ir (potassium bromide):  $cm^{-1}$  1710 strong (C=O), 1620, 1515 strong (aromatic); nmr (deuteriotrifluoroacetic acid):  $\delta$  3.91 (s, 2H,  $CH_2$ ), 4.09 (s, 3H,  $CH_3$ ), 5.65 (s, H-4: this peak integrated for nearly 1H ten minutes following the preparation of the solution, and for about 0.1H after 2 hours).

*Anal.* Calcd. for  $C_6H_8N_2O_3$ : C, 46.1; H, 5.2; N, 17.9. Found: C, 46.1; H, 5.4; N, 17.5.

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