Reaction of 3-(*o*-Chlorobenzylidene)-2,4-dioxopentanoic Acid with Hydroxylamine Hydrochloride. Revised Structure for Azeto[3,2-*d*]isoxazoline (1)

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Reaction of 3-(*o*-chlorobenzylidene)-2,4-dioxopentanoic acid (**1**) with hydroxylamine hydrochloride in acetic acid gave 5-(*o*-chlorophenyl)-3-methyl-4-(α-hydroxyimino)isoxazolineglyoxylic acid (**5**) and 3-(*o*-chlorobenzylidene)-4-hydroxyimino-2-oxopentanoic acid (**2**) in 57% and 7% yields. Pyrolysis of **5** afforded 5-(*o*-chlorophenyl)-3-methylisoxazole-4-carbonitrile (**8**), *cis*- and *trans*-5-(*o*-chlorophenyl)-3-methylisoxazoline-4-carbonitriles (**9,10**), and 5-(*o*-chlorophenyl)-3-methylisoxazoline-4-carboxamide (**11**).

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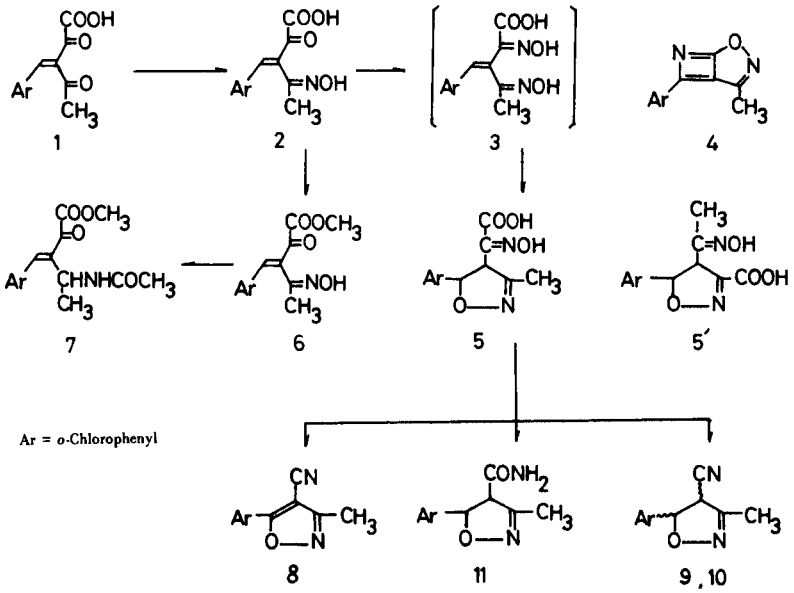
Recently we have reported (1) the reaction of 3-(*o*-chlorobenzylidene)-2,4-dioxopentanoic acid (**1**), prepared by the Knoevenagel condensation of *o*-chlorobenzaldehyde with ethyl acetopyruvate (2), with hydroxylamine hydrochloride to give 4-(*o*-chlorophenyl)-3-methylazeto[3,2-*d*]-isoxazoline (**4**), its dihydro isomers (*cis*- and *trans*-azetino[3,2-*d*]isoxazolines), and 4-(α-amino-*o*-chlorobenzyl)-3-methylisoxazolin-5-one *via* decarboxylation of 3-(*o*-chlorophenyl)-2,3,3a,6a-tetrahydro-4-methylisoxazolo[4,5-*d*]isoxazole-6a-carboxylic acid. However, there were errors in the structural assignments, and these were corrected by Rees in a recent short communication (3). In this paper we wish to report the correction of our preliminary communication (1).

A reaction of the diketoacid (**1**) with two moles of hydroxylamine in acetic acid at 50° afforded 5-(*o*-chlorophenyl)-3-methyl-4-(α-hydroxyimino)isoxazolineglyoxylic acid (**5**) and 3-(*o*-chlorobenzylidene)-4-hydroxyimino-2-oxopentanoic acid (**2**) in 57% and 7% yields, respectively. The structure of **2** was determined by the following reactions. Reduction of the methyl ester (**6**), obtained from the reaction of **2** with diazomethane, with zinc in acetic acid containing acetic anhydride afforded the 4-acetamino derivative (**7**) in 50% yield. The structure **7** was verified from the nmr spectrum (deuteriochloroform) which shows a doublet at δ 1.05, due to CH_3CH protons (J = 7 Hz), a multiplet at δ 4.65 assigned to CH_3CH proton and a NH signal (broad doublet) at δ 8.00. This

Scheme I



result clearly indicated that the hydroximino group in compound **2** is located at C_4.

Treatment of **2** with an equivalent amount of hydroxylamine in acetic acid gave **5** in 75% yield. Therefore, the diketoacid (**1**) would be expected to lead *via* the monoxime **2** followed by the dioxime **3**, which could not be isolated, to **5**. The structure assignment of **5** was based on ir and nmr spectral evidence, and elemental analysis. The ir spectrum (potassium bromide) of **5** showed the absorption bands at 3600, 3480, 3100, 3000, 2880, and 1700 cm^{-1}. The nmr spectrum (deuteriodimethylsulfoxide) of **5** displayed a broad doublet at δ 4.77 (1H, b.d, $J_{4,5}$ = 10 Hz, C_4-*H*) which was collapsed to a doublet by irradiation of the methyl protons, and other peaks at δ 1.85 (3H, s, CH_3), δ 5.95 (1H, d, $J_{5,4}$ = 10 Hz, C_5-*H*) and δ 12.80 (1H, b.s, N*H*).

Compound **5** was readily transformed into the cyanoisoxazoline by decarboxylation and dehydration. As a matter of fact, pyrolysis of **5** afforded 5-(*o*-chlorophenyl)-3-methylisoxazole-4-carbonitrile (**8**) (m.p. 70-71°), which was identified by comparison with the sample synthesized by the route of Rees (3), *cis*- and *trans*-5-(*o*-chlorophenyl)-3-methylisoxazoline-4-carbonitriles (**9,10**) which were converted to **8** by refluxing in acetic acid, and 5-(*o*-chlorophenyl)-3-methylisoxazoline-4-carboxamide (**11**). Reaction of **1** with hydroxylamine in acetic acid under refluxing condition gave **8** and **11** in 38% and 5% yields.

Finally in the nmr spectra of **9**, **10**, and **11**, the signal of the C_4-proton showed the same pattern as that in **5**, and this finding excluded the possibility of the structure **5'** shown in Scheme I.

EXPERIMENTAL

Melting points are uncorrected. Infrared (ir) and ultraviolet (uv) spectra were taken with a JASCO Model IRA-1 and a Schimadzu UV-200 spectrophotometers. Nuclear magnetic resonace (nmr) spectra were recorded with a Hitachi R-24A, and mass spectra were recorded with a Hitachi Mass Spectrophotometer RMU-7L.

3-(*o*-Chlorobenzylidene)-2,4-dioxopentanoic Acid (**1**).

A mixture of *o*-chlorobenzaldehyde (14.1 g., 0.1 mole), ethyl acetopyruvate (15.8 g., 0.1 mole) and piperidine (5 drops) was allowed to stand for 24 hours at 40° to give a pasty solid. Benzene (50 ml.) was added, and the mixture was stirred with cooling. The precipitate was collected by filtration and recrystallized from methanol to give **1** (16.6 g., 66%) as colorless needles, m.p. 189-190°; ir ν max (potassium bromide): 1800, 1690, 1665 cm^{-1}; uv λ max (ethanol): 272 (log ϵ 3.97), 325 (3.66) nm; nmr δ (deuteriodimethylsulfoxide): 2.41 (3H, s, $COCH_3$), 6.40 (1H, s, =C*H*).

Anal. Calcd. for $C_{12}H_9ClO_4$: C, 57.04; H, 3.58. Found: C, 57.32; H, 3.74.

Reaction of Diketoacid (**1**) with Hydroxylamine Hydrochloride in Acetic Acid.

A. At 50°.

A mixture of **1** (12.6 g., 0.05 mole) and hydroxylamine hydrochloride (6.9 g., 0.1 mole) in acetic acid (100 ml.) was stirred for 24 hours at 50°. After evaporation of the solvent under reduced pressure, the residue was agitated in the mixture of chloroform and water (1:1) (50 ml.). The resulting precipitate was collected by filtration and recrystallized from 50% methanol to give **5** (7.64 g., 57%) as colorless needles, m.p. 168-169°.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_4$: C, 50.98; H, 3.92; N, 9.91. Found: C, 50.84; H, 3.72; N, 10.31.

The separated chloroform layer was dried (sodium sulfate), and evaporated to give a crystalline residue, which was recrystallized from methanol-benzene to give **2** (980 mg., 7%) as colorless needles, m.p. 147-149°; ir ν max (potassium bromide): 3380, 1758, 1680 cm^{-1}; nmr δ (deuteriodimethylsulfoxide): 2.20 (3H, s, CH_3), 6.48 (1H, s, =C*H*), 11.45 (1H, s, NO*H*).

Anal. Calcd. for $C_{12}H_{10}ClNO_4$: C, 53.84; H, 3.76; N, 5.23. Found: C, 54.04; H, 3.65; N, 5.12.

B. At Refluxing Temperature.

A mixture of **1** (12.6 g., 0.05 mole) and hydroxylamine (6.9 g., 0.1 mole) in acetic acid (100 ml.) was refluxed for 24 hours. After evaporation of the solvent under resuced pressure, the residue was neutralized with saturated sodium bicarbonate solution and extracted with chloroform. The extract was washed with water, dried (sodium sulfate), and evaporated to give a viscous oil, which was submitted on an alumina column chromatography. The fraction eluted with benzene showed one spot on thin layer chromatography (alumina) was evaporated to give crystalline residue (3.7 g., 38%), which was recrystallized from petroleum ether to give **8** as colorless needles, m.p. 70-71°; ir ν max (potassium bromide): 2270 (CN), 1620 cm^{-1}; uv λ max (ethanol): 262 (log ϵ 4.01) nm; nmr δ (deuteriochloroform): 2.52 (3H, s, CH_3), 7.04-7.70 (4H, m, aromatic protons); mass mass spectrum: m/e 218 (M^+).

Anal. Calcd. for $C_{11}H_7ClN_2O$: C, 60.42; H, 3.22; N, 12.81. Found: C, 60.58; H, 3.00; N, 12.79.

The next fraction eluted (benzene-methanol, 9:1) was evaporated to give a crystalline residue, which was recrystallized from methanol to give **11** (595 mg., 5%) as colorless prisms, m.p. 259-260° dec.; ir ν max (potassium bromide): 3400, 3250, 1690 ($CONH_2$) cm^{-1}; nmr δ (deuteriodimethylsulfoxide): 1.92 (3H, s, CH_3), 3.95 (1H, d, J = 8 Hz, C*H*), 5.95 (1H, d, J = 8 Hz, C*H*).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$: C, 55.35; H, 4.64; N, 11.73. Found: C, 55.46; H, 4.82; N, 11.66.

Methyl 3-(*o*-Chlorobenzylidene)-4-hydroxyimino-2-oxopentanoate (**6**).

To a ether solution (50 ml.) of diazomethane, prepared from nitrosomethylurea (5 g.), was added **2** (1.33 g., 0.005 mole) under ice cooling. The mixture was stirred for 2 hours under cooling. The ether was evaporated, and the residue was recrystallized from benzene-ligroin to give **6** (1.19 g., 85%) as colorless needles, m.p. 124-125°; ir ν max (potassium bromide): 3400 (OH), 1742 (CO) cm^{-1}; nmr δ (deuteriodimethylsulfoxide): 2.15 (3H, s, CH_3), 4.15 (3H, s, $COOCH_3$), 6.45 (1H, s, =C*H*), 8.10 (1H, s, NO*H*).

Anal. Calcd. for $C_{13}H_{12}ClNO_4$: C, 55.42; H, 4.29; N, 4.97. Found: C, 55.62; H, 4.41; N, 5.00.

Methyl 4-Acetamino-3-(*o*-chlorobenzylidene)-2-oxopentanoate (**7**).

To a solution of **6** (1 g., 0.0035 mole) in acetic acid (50 ml.) and acetic anhydride (4 ml.) was added zinc dust (3 g.) and the mixture was heated under vigorous stirring for 7 hours. After

filtration of the zinc dust, the filtrate was evaporated under reduced pressure. The residue was neutralized with saturated sodium bicarbonate solution and extracted with chloroform. The extract was washed with water, dried (sodium sulfate) and evaporated to give a crystalline residue, which was recrystallized from ethanol to give **7** (0.55 g., 50%) as colorless needles, m.p. 183-184°; ir ν max (potassium bromide): 3300 (NH), 1765 (CO), 1640 (NHCO) cm^{-1}; nmr δ (deuteriodimethylsulfoxide): 1.05 (3H, d, J = 7 Hz, CH_3CH), 1.80 (3H, s, $COCH_3$), 4.00 (3H, s, $COOCH_3$), 4.65 (1H, m, CH_3CH), 6.23 (1H, s, =CH), 8.00 (1H, b.d., J = 6 Hz, NH).

Anal. Calcd. for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.21; N, 4.52. Found: C, 58.28; H, 5.05; N, 4.26.

Reaction of **2** with Hydroxylamine Hydrochloride.

A mixture of **2** (267 mg., 1 mmole) and hydroxylamine hydrochloride (69 mg., 1 mmole) in acetic acid (10 ml.) was heated for 24 hours at 50°. After evaporation of the solvent, the residue was stirred in the mixture of chloroform and water (1:1) to give a fine powder, which was collected by filtration and recrystallized from methanol to give **5** (225 mg., 72%). This was identical with the authentic sample by comparison of their ir spectra.

Pyrolysis of **5**.

Carboxylic acid **5** (2.82 g., 0.01 mole) was heated in a preheated oil bath (170-175°) until the end of gas evolution to give viscous brownish oil. Ethyl acetate was added and the resulting precipitate was collected by filtration. The precipitate was recrystallized from methanol to give **11** (240 mg.), which was identical with the authentic sample by comparison of their ir spectra. The solvent was evaporated under reduced pressure, and the residual oil was submitted on an alumina column chromatography. Evaporation of the *n*-hexane eluate gave **8** (470 mg.), which was identical with the authentic sample in all aspects. Secondly, evaporation of the benzene eluate gave colorless needles. Fractional recrystallization from petroleum ether gave **9** (170 mg.) from the more soluble part and **10** (260 mg.) from the less soluble part.

Compound **9** had m.p. 56-57°; ir ν max (potassium bromide): 2270 (CN) cm^{-1}; nmr δ (deuteriochloroform): 2.15 (3H, s, CH_3), 3.95 (1H, d, J = 6 Hz, CH), 6.10 (1H, d, J = 6 Hz, CH); mass spectrum m/e: 220 (M^+).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.88; H, 4.24; N, 12.75.

Compound **10** had m.p. 112-114°; ir ν max (potassium bromide): 2290 (CN) cm^{-1}; nmr δ (deuteriochloroform): 2.20 (3H, s, CH_3), 4.60 (1H, d, J = 12 Hz (4), CHO, 6.05 (1H, d, J = 12 Hz, CH); mass spectrum m/e: 220 (M^+).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; N, 12.69. Found: C, 59.74; H, 3.98; N, 12.67.

Dehydration of **9** and **10**.

A mixture of **9** and **10** (0.2 g.) was refluxed in acetic acid (20 ml.) for 10 hours. After evaporation of the solvent, the residue was dissolved in chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution, dried (sodium sulfate), and evaporated. The residue was purified by passing through an alumina column using *n*-hexane as the eluent to give pure **8** (120 mg.), which was identical with the authentic sample in all respects.

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