SYNTHESIS OF 4-(ζ -CARBOMETHOXYHEXYL)IMIDAZOLIN-2-ONE

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Previously [1] it was established that 4(5)-methylimidazolin-2-one (I) under the influence of AlCl₃ reacts with l-chloro-l-octen-3-one (II) in nitrobenzene to give trans-4-methyl-5-(3-keto-l-octenyl)imidazolin-2-one (III).



To use this reaction in the synthesis of the imidazole analogs of prostaglandins we developed a simple method for obtaining $4-(\zeta-\text{carbomethoxyhexyl})$ imidazolin-2-one (X) and studied its ketovinylation using chlorovinyl ketone (II).



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The acylation of 2-phenyloxazolin-5-one (IV) with the ethyl ester of suberyl chloride in benzene, in the presence of triethylamine, gave the O-acyl derivative (VI), which was then subjected to $0 \rightarrow C$ isomerization using γ -picoline in the presence of trifluoroacetic acid as described in [2] to give 2-phenyl-4-(ζ-carbethoxyenanthoyl)oxazolin-5-one (VII). Subsequent hydrolytic cleavage of ester (VII) with HCl gave 8-keto-9-aminopelargonic acid ` hydrochloride (VIII). The reaction of hydrochloride (VIII) with KCNO in aqueous solution and subsequent esterification of the intermediate acid (IX) with a mixture of methanol and BF_3 etherate gave ester (X) in an overall yield of 32% when based on the starting (IV). The reaction of ester (X) with chloride (II) in nitrobenzene, in the presence of AlCl₃, gave in low yield an imidazole analog of the prostaglandins, and specifically trans-4-(ζ carbomethoxyhexyl)-5-(3-keto-1-octenyl)imidazolin-2-one (XI), whose structure was confirmed via the UV and PMR spectra. The UV spectrum of (XI) has an absorption maximum at 360 nm, which is characteristic for the chromophore system of (III) [1]. The trans configuration of the double bond in (XI) is in agreement with the SSCC J $_{\rm H_A, H_B}$ = 16 Hz. Attempts to ketovinylate acid (IX) itself under the conditions of the Friedel-Crafts reaction proved unsuccessful.

EXPERIMENTAL

The UV spectrum was taken in alcohol on a Specord UV-VIS instrument, and the IR spectra were taken as KBr pellets on a UR-20 instrument. The PMR spectra were taken on a Varian DA-60-IL instrument, while the spectrum of (XI) was taken on a Bruker WM-250 instrument (250 MHz, internal standard = HMDS). The TLC was run on Silufol UV-254 (the substances were detected in UV light and by iodine vapors).

 $\frac{2-\text{Phenyl}-4-(\zeta-\text{carbethoxyenanthoyl}) \text{oxazolin}-5-\text{one (VII)}.}{\text{g of }2-\text{phenyloxazolin}-5-\text{one [3] and }6.86 \text{ g of the ethyl ester of suberyl chloride [4]} in 200 ml of benzene was gradually added 5 ml of Et_3N and the mixture was stirred for 10 min, the precipitate was filtered, and the mother liquor was evaporated in vacuo. With stirring and cooling (10-15°C), a solution of 1.8 ml of CF_3COOH in 30 ml of <math>\gamma$ -picoline was added to the residual 0-acyl derivative (VI) and the mixture was kept for 24 h at 0°C, poured on ice, acidified with 1:1 HCl solution to pH ~ 1, and the precipitate was filtered to give 9.1 g (84%) of (VII), mp 96-98°C (from ethyl acetate (EA)), R_f 0.70 (1:1 benzene-EA). PMR spectrum (CDCl₃, δ , ppm): 1.16 t (CH₃, J = 7 Hz); 1.37 m (CH₂CH₂CH₂CH₂): 2.21 m, 2.75 m (2CH₂); 4.03 q (OCH₂, J = 7 Hz); 7.21-7.53 m (m- and p-protons of aromatic ring); 7.63-8.11 m (o-protons of aromatic ring). Found: C 66.09; H 6.68%. C₁₉H₂₃NO₅. Calculated: C 66.07; H 6.71%.

 $4-(\zeta-Carboxyhexyl)$ imidazolin-2-one (IX). A mixture of 1.5 g of ketoester (VII) and 22 ml of 1:1 HCl solution was refluxed for 6 h, cooled to 20°C, the benzoic acid was filtered, and the mother liquor was evaporated in vacuo. The residue was treated with acetone and the obtained precipitate was filtered to give 0.65 g (67%) of 8-keto-9-aminopelargonic acid hydrochloride (VIII), decomposing above 250°C, which was used as such in the next step.

With stirring, KCNO was added to a solution of 1.9 g of hydrochloride (VIII) in 20 ml of water to pH 7 and the mixture was kept for 24 h at 20°C, acidified with 1:1 HCl solution to pH ~ 1, and the precipitate was filtered and dried in the air to give 1.45 g (81%) of (IX), mp 228-230°C (after reprecipitation with dilute HCl solution from soda solution), R_{f} 0.40 (alcohol-EA, 1:4). Found: C 56.10; H 7.88; N 13.64%. $C_{10}H_{16}N_{2}O_{3}$. Calculated: C 56.59; H 7.60; N 13.20%.

 $\frac{4-(\zeta-\text{Carbomethoxyhexyl})\text{imidazolin-2-one (X).}}{4-(\zeta-\text{Carbomethoxyhexyl})\text{imidazolin-2-one (X).}} With stirring, 1.2 g of acid (IX) was added to a mixture of 6 g of BF₃ etherate and 18 ml of MeOH and the mixture was kept for 96 h at 20°C, partially evaporated in vacuo, the residue was treated with soda solution to pH 8, and the precipitate was filtered and dried in the air to give 0.91 g (71%) of (X), mp 135-137°C (from alcohol), R_f 0.59 (1:4 alcohol-EA). Infrared spectrum (<math>\nu$, cm⁻¹): 1630, 1660, 1700, 1735. PMR spectrum (CF₃COOH, δ , ppm): 1.10-1.190 m (CH₂CH₂CH₂CH₂); 2.48 m (CH₂CO, CH₂C=C); 3.82 s (OCH₃); 6.46 m (H-C=C). Found: C 58.38; H 8.11; N 12.50%. C_{11H1eN2O3}. Calculated: C 58.39; H 8.02; N 12.38%.

 $\frac{\text{trans}-4-(\zeta-\text{Carbomethoxyhexyl})-5-(3-\text{keto}-1-\text{octenyl})\text{imidazoline}-2-\text{one (XI)}.}{\text{stirring, 0.44 g of AlCl_3 was gradually added at 0-6°C to a mixture of 0.25 g of ester (X) and 0.4 g of 1-chloro-1-octen-3-one (II) in 15 ml of nitrobenzene and the mixture was stirred for 1 h at 20° and for 48 h at 65-70°C. The mixture was poured on ice and the nitrobenzene layer was diluted with 500 ml of heptane and decanted from the deposited oil, which was dissolved in EA and washed with soda solution. The EA was evaporated in vacuo and the residue (0.27 g) was chromatographed on a column packed with silica gel 100/160 µm. Elution with acetone gave 0.03 g (8%) of (XI) as a viscous oil that is unstable when stored, R_f 0.33 (EA), and gives a dark color with FeCl_3 (presence of imidazolin-2-one ring). Ultraviolet spectrum: <math display="inline">\lambda_{max}$ 360 nm. Infrared spectrum (v, cm⁻¹): 970, 1580, 1610, 1710-1725, 3020, 3035. PMR spectrum (CDCl_3, δ , ppm): 0.89 t (CH_3, J = 5 Hz); 1.34 m (4CH_2); 1.62 m (3CH_2); 1.91 m (CH_2COOMe); 2.32 t (CH_2CO, J = 9 Hz); 2.55 t (CH_2C = C, J = 9 Hz), 3.66 s (CH_3O); 6.29 d (trans-CH = CHCO, J = 16 Hz), 7.24 d (trans-CH = CHCO, J = 16 Hz). Found: C 61.62; H 8.59%. C_{19}H_3ON_2O_4 \cdot H_2O. Calculated: C 61.93; H 8.75%.

CONCLUSIONS

 $4-(\zeta-Carbomethoxyhexyl)$ imidazolin-2-one was synthesized and it was shown that it can be trans-C-ketovinylated using 1-chloro-1-octen-2-one.

LITERATURE CITED

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