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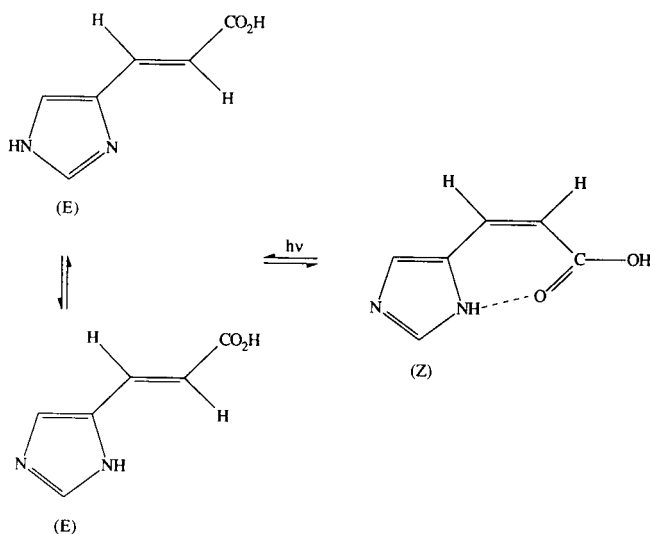
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Methods of selective methylation of the nitrogen atoms of the ethyl ester of 3-(1*H*-imidazol-4-yl)-2-propenoic acid are reported. The nitrogen atom α to the ethylenic chain was methylated after protection of the β nitrogen with a phenacyl group.

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(*E*)-3-(1*H*-Imidazol-4-yl)-2-propenoic acid or urocanic acid [1] is a metabolite of histidine found in the skin, and excreted in sweat. Under irradiation, this compound undergoes photoisomerization to give a mixture of the (*E*) and (*Z*) isomers (Scheme 1). The two isomers have a broad absorption band around 270 nm and high molar extinction coefficient. Urocanic acid thus may act as a natural photoprotector, and it has potential applications in the cosmetics industry [1-3]. The (*Z*) isomer has been found to have immunosuppressive activity [4-6], although the mechanism has yet to be elucidated.

Scheme 1



Study of the relationship between structure and immunological activity hinges on synthesis of numerous derivatives of urocanic acid. Several modifications of the imidazole ring, such as a change of heteroatom [6] or methylation of carbon 2 have been reported. However, *N*-alkylation has not so far been described. This substitution is of interest since intramolecular hydrogen bonding is blocked in the *N*-alkyl derivatives of the esters of the (*Z*) configuration, which is likely to have a marked influence on the biological activity.

We report here a study of the regioselective methylation of ethyl urocanate. The methylation reactions so far described [7-9] generally lead to mixtures of products due to dimethylation and substitution at either the *N*(α) or *N*(β) sites as shown in Figure 1.

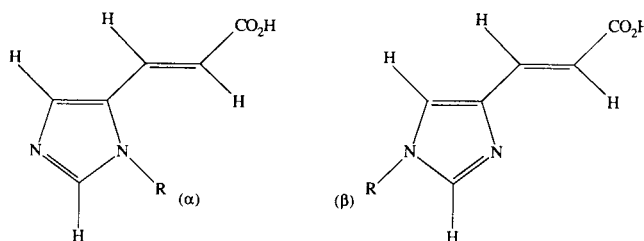


Figure 1

Methylation on the *N*(β) of the Ethyl Esters of (*E*) and (*Z*) Isomers of 3-(1*H*-Imidazol-4-yl)-2-propenoic Acid, (**1**) and (**2**).

Duke *et al.* [7] employed methyl sulfate to *N*-methylate methyl urocanate (*E*). Apart from the product *N*-methylated on the (β) nitrogen, this reaction also gives the *N,N'*-dimethylimidazolium salt from a second methylation reaction.

On the other hand, reflux of compound **1** with methyl iodide in the presence of sodium ethylate in ethanol affords a mixture of the ethyl esters of (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)-2-propenoic acid (**3**) and (*E*)-3-(1-methyl-1*H*-imidazol-5-yl)-2-propenoic acid (**8**) in the proportions 66/24 [8].

Using different experimental conditions, we succeeded in methylating compound **1** selectively on the (β) nitrogen. In the presence of a weaker base (anhydrous potassium carbonate) in a heterogeneous phase, the action of methyl iodide on a slight excess of ethyl urocanate in acetone at room temperature led to the ethyl ester of (*E*)-3-(1*H*-imidazol-4-yl)-2-propenoic acid (**3**) in a yield of around 80%. The structure of this compound was determined by comparison of its spectra parameters with those of similar compounds reported in the literature [7-9].

The corresponding ethyl ester of (*Z*)-3-(1*H*-imidazol-4-yl)-2-propenoic acid (**4**) was obtained using two different procedures: by irradiation at 300 nm of compound **3** in ethanol, giving a mixture of the two isomers, which were separated on a silica column (at photostationary equilibrium (*E*)/(*Z*) = 40/60; by methylation of compound **2** under identical conditions to those used for methylation of isomer **1**.

Methylation on the *N*(α) of the Ethyl Ester of 3-(1*H*-Imidazol-4-yl)-2-propenoic Acid.

The results described above indicate that the methylation occurs essentially on the least sterically hindered nitrogen. Thus in order to methylate the (α) nitrogen, the (β) nitrogen must be protected. The triphenylmethyl or phenacyl groups, which are commonly employed as protective groups on histidine [9], were therefore tested.

The action of triphenylmethyl chloride on ethyl urocanate led to the (β)-*N*-substituted compound in excellent yield. However, during the subsequent methylation reaction, the protective group tended to be eliminated giving a mixture of the mono and dimethylated products. The phenacyl group appeared less labile, and deprotection was carried out photochemically or in acid medium [9].

Deprotection with zinc in acid medium led to hydrogenation of the ethylenic chain, and so this was carried out photochemically. The reactions described on Scheme 2 gave rise to a mixture of the (*E*) and (*Z*) isomers of the ethyl ester of 3-(1-methyl-1*H*-imidazol-5-yl)-2-propenoic acid in the proportions **8**/**9** = 40/60. The two isomers were separated by chromatography on a silica column.

Determination of the Structures.

The structures were confirmed by ^1H and ^{13}C nmr spectroscopy. The site of *N*-alkylation was determined by the NOE effect. For compound **3**, the *N*-methyl signal interacts with the H_a and H_c proton signals, whereas in compound **8** it only interacts with the H_c proton signal. A more

detailed analysis of these results will be included in a future publication reporting a study of the conformations and configurations of a range of variously substituted derivatives of urocanic acid. Our assignments are in line with literature data [7,8,10].

Table
Chemical Shifts (ppm) of Protons in Deuteriochloroform

R	Compound	δH_a	δH_b	δH_c	δH_d
$\phi_3\text{C}$ (β)	5 (<i>E</i>)	6.50	7.50	7.46	7.01
		$J = 15 \text{ Hz}$			
ϕCOCH_2 (β)	6 (<i>E</i>)	6.50	7.55	7.90	7.12
		$J = 15 \text{ Hz}$			
CH_3 (β)	3 (<i>E</i>)	6.50	7.50	7.41	7.03
		$J = 15 \text{ Hz}$			
CH_3 (β)	4 (<i>Z</i>)	5.72	6.91	7.38	8.32
		$J = 12 \text{ Hz}$			
CH_3 (α)	8 (<i>E</i>)	6.20	7.50	7.50	7.40
		$J = 15 \text{ Hz}$			
CH_3 (α)	9 (<i>Z</i>)	5.85	6.60	7.60	8.25
		$J = 12 \text{ Hz}$			

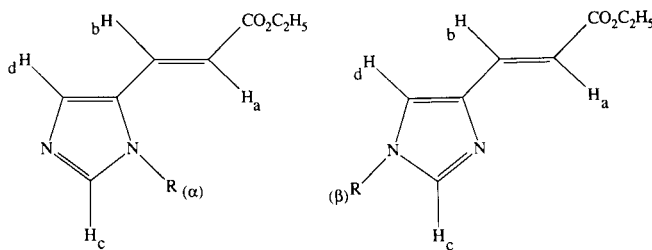
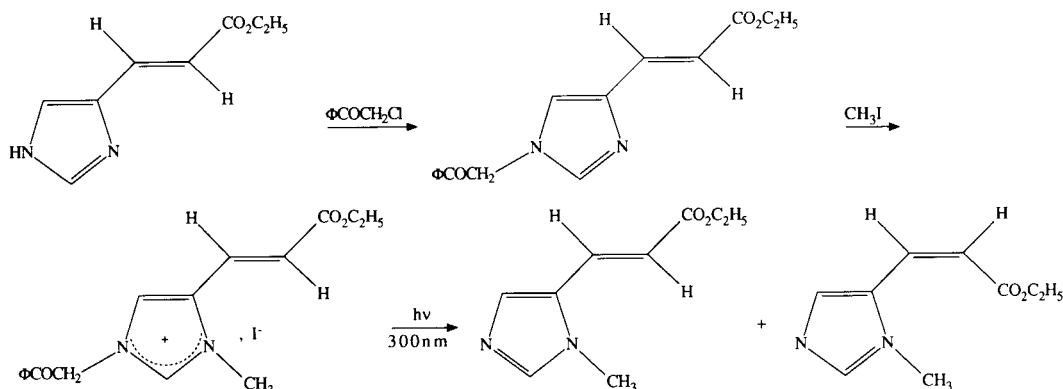


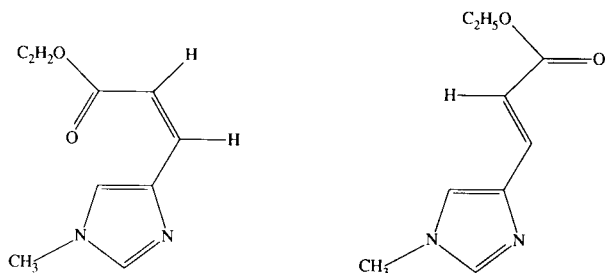
Figure 2

It should be noted that the H_c proton signal is little affected by the site of the *N*-alkylation and the configuration of the double bond. This is to be expected as these modifications have little influence on its immediate environment, whereas the H_a proton is strongly deshielded in the (*Z*) isomer by the carbonyl group (Figure 2). This is not observed in the non alkylated esters [11] where an intramo-

Scheme 2



lecular hydrogen bond constrains the molecule to the *s-trans* conformation at the junction between the ring and the ethylenic chain.



Conclusion.

The (*Z*) and (*E*) isomers of the ethyl esters of 3-(1*H*-imidazol-4-yl)-2-propenoic acid were methylated selectively in good yield. Methylation on the nitrogen atom α to the ethylenic chain influences the conformation of the (*Z*) isomers, an effect which is not observed with the non alkylated homologs where the conformation tends to be governed by intramolecular hydrogen bonding. This may have considerable significance for the biological activity.

EXPERIMENTAL

Urocanic acid, methyl iodide, thionyl chloride and phenacyl chloride were obtained from Aldrich. The ^1H nmr spectra were recorded on Bruker AC 80 and Bruker AM 300 WB (NOE effect) spectrometers. The uv spectra were recorded on an HP 8451 A spectrophotometer, and the ir spectra were recorded on a Perkin Elmer 683 instrument. Irradiation was carried out in a Rayonet type RPP 100 apparatus equipped with a turntable.

(*E*)-3-(1*H*-Imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**1**).

Thionyl chloride (15 ml) was added dropwise to a suspension of 0.054 mole of (*E*) urocanic acid in toluene (freshly distilled and kept over sodium) in the presence of triethylamine under an inert atmosphere. After stirring for 18 hours the excess thionyl chloride and toluene were evaporated under vacuum. Absolute ethanol (250 ml) was added to the residue, and the mixture was stirred for a further 48 hours. The excess ethanol was evaporated under vacuum, the residue was taken up in 50% sodium hydroxide solution, extracted with ethyl acetate and dried over sodium sulfate. After recrystallization from ether, compound **1** was obtained in 50% yield, mp 79°; ir (potassium bromide): ν 1730 (C=O), 1618 (C=C) cm^{-1} , 3100 (broad band NH); uv (ethanol): λ max 288 nm (ϵ 18945); ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_3\text{-CH}_2$), 4.16 (q, 2H, OCH_2), 6.5 (d, 1H, H_a , $J = 15$ Hz), 7.5 (d, 1H, H_b , $J = 15$ Hz), 7.2 (s, 1H, H_c), 7.67 ppm (s, 1H, H_d).

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.9; H, 5.95; N, 16.70.

(*Z*)-3-(1*H*-Imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**2**).

Compound **1** was irradiated in absolute ethanol in a quartz tube at 254 nm for 3 hours. A mixture of 60% (*Z*) and 40% (*E*) was obtained after evaporation under vacuum. The two isomers were separated by chromatography on a silica column eluted with

chloroform/ethanol (9/1, v/v), mp 77°; ir (potassium bromide): ν 1750 (C=O), 1610 (C=C) cm^{-1} , 3100 (NH); uv (ethanol): λ max 300 nm (ϵ 14282); ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_2\text{-CH}_3$), 4.16 (q, 2H, OCH_2), 5.6 (d, 1H, H_a , $J = 12$ Hz), 6.7 (d, 1H, H_b , $J = 12$ Hz), 7.72 (s, 1H, H_c), 7.38 ppm (s, 1H, H_d).

Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.9; H, 5.95; N, 16.70.

(*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**3**).

Potassium bicarbonate (6 mmoles) was added to 1 g (6 mmoles) of compound **1** in 10 ml of acetone. Methyl iodide (5.8 mmoles) was added dropwise to this suspension. The mixture was stirred at room temperature for 18 hours, filtered and the filtrate evaporated. The residue was taken up in chloroform. The chloroform phase was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was purified on a silica column eluted with chloroform/ethanol (9/1, v/v) affording product **3** in 80% yield, mp 98°; ir (potassium bromide): ν 1730 (C=O), 1610 (C=C) cm^{-1} , 3100 (NH); uv (ethanol): λ max 288 nm (ϵ 17991); ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_2\text{-CH}_3$), 4.2 (q, 2H, OCH_2), 3.6 (s, 3H, NCH_3), 6.5 (d, 1H, H_a , $J = 15$ Hz), 7.5 (d, 1H, H_b , $J = 15$ Hz), 7.03 (s, 1H, H_d), 7.4 ppm (s, 1H, H_c).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.22; H, 6.67; N, 15.58.

(*Z*)-3-(1-Methyl-1*H*-imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**4**).

This compound was prepared using two different methods:

a) Compound **3** was irradiated at 254 nm in ethanol for 3 hours giving a mixture of the two isomers [60% (*Z*) and 40% (*E*)] which were separated by chromatography on a silica gel column (70-230 mesh ASTM) eluted with hexane/ethanol (4/1, v/v).

b) Methyl iodide (0.25 ml) was added to a mixture of 3.6 mmoles of compound **2** and 3.6 mmoles of potassium bicarbonate in 10 ml of acetone (dried over a molecular sieve). The mixture was left to stand at room temperature for 18 hours. After filtration, the filtrate was evaporated under vacuum, and the residue taken up in chloroform. Evaporation of the chloroform left compound **4** in the form of an oil with a yield of 70%; ir: ν 1750 (C=O), 1610 (C=C) cm^{-1} ; uv (methanol): λ max 296 nm (ϵ 10000); ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_2\text{-CH}_3$), 4.2 (q, 2H, OCH_2), 3.66 (s, 3H, NCH_3), 5.72 (d, 1H, H_a , $J = 12$ Hz), 6.91 (d, 1H, H_b , $J = 12$ Hz), 7.38 (s, 1H, H_c), 8.32 ppm (s, 1H, H_d).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.98; H, 6.66; N, 15.55. Found: C, 60.30; H, 6.80; N, 15.60.

(*E*)-3-(1-Triphenylmethyl-1*H*-imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**5**).

A mixture of 6 mmoles of triphenylmethyl chloride and 6 mmoles of triethylamine in 5 ml of toluene was added to a solution of 6 mmoles of compound **1** in 20 ml of dry toluene under an inert atmosphere. The mixture was heated at 40° for 18 hours. The precipitate was filtered off and the toluene evaporated. The residue was taken up in water and extracted with ethyl acetate. Compound **5** was isolated after purification on a silica gel column (70-230 mesh) eluted with chloroform/ethanol (9/1, v/v) with a yield of 80%; mp 138°; ir: ν 1730 (C=O), 1680 (C=C) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_3\text{-CH}_2$), 4.2 (q, 2H, OCH_2), 6.5 (d, 1H, H_a , $J = 15$ Hz), 7.50 (d, 1H, H_b , $J = 15$ Hz), 7.01 (s, 1H, H_d), 7.2-7.3 (m, 15H, phenyl), 7.46 ppm (s, 1H, H_c).

Anal. Calcd. for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_2$: C, 79.39; H, 5.92. N, 6.86. Found: C, 79.16; H, 5.81; N, 6.90.

(*E*)-3-(1-Phenacyl-1*H*-imidazol-4-yl)-2-propenoic Acid Ethyl Ester (**6**).

A mixture of 6 mmoles of phenacyl chloride and 6 mmoles of triethylamine in 10 ml of toluene was added to a solution of 6 mmoles of compound **1** in 20 ml of dry toluene. The mixture was heated at 50° for 24 hours. The brown precipitate was filtered off under vacuum, and then dissolved in ethyl acetate by gentle warming. The solution was washed with water, and the organic phase was dried over sodium sulfate. Evaporation under vacuum left an orange oil, which afforded compound **6** in 75 % yield after recrystallization from ether, mp 124°; ir: ν 1730 (C=O), 1680 (C=C) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_3\text{-CH}_2$), 4.3 (q, 2H, OCH_2), 5.39 (s, 2H, NCH_2), 6.5 (d, 1H, H_a , $J = 15$ Hz), 7.55 (d, 1H, H_b , $J = 15$ Hz), 7.9 (s, 1H, H_c), 7.12 (s, 1H, H_d), 7.5-7.6 ppm (m, 5H, phenyl).

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$: C, 67.59; H, 5.63; N, 9.86. Found: C, 67.23; H, 5.60; N, 9.60.

(*E*)-3-(1-Phenacyl-3-methyl-1*H*-imidazol-4-ium)-2-propenoic Acid Ethyl Ester Iodide (**7**).

An excess of methyl iodide was added to a solution of 1.4 mmoles of compound **6** in 10 ml of dry acetone. The mixture was stirred for 3 days at room temperature. Evaporation of the acetone left an orange oil, which was dissolved in a minimum amount of ethanol. The compound **7** precipitated as a yellow powder in 70 % yield by adding diethyl ether, mp 202°; ^1H nmr ($\text{DMSO-}d_6$): δ 1.3 (t, 3H, $\text{CH}_2\text{-CH}_3$), 4.2 (q, 2H, OCH_2), 6.11 (s, 2H, NCH_2), 4.03 (s, 3H, NCH_3), 6.69 (d, 1H, H_a , $J = 15$ Hz), 7.7 (d, 1H, H_b , $J = 15$ Hz), 7.6-8 (m, 1H, H_c , $J = 15$ Hz, 5H, phenyl), 8.31 (s, 1H, H_d), 9.2 ppm (s, 1H, H_e), 6.57.

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{IN}_2\text{O}_3$: C, 47.90; H, 4.49; N, 6.57. Found: C, 47.54; H, 4.38; N, 6.49.

(*E*)-3-(1-Methyl-1*H*-imidazol-5-yl)-2-propenoic Acid Ethyl Ester (**8**) and (*Z*)-3-(1-Methyl-1*H*-imidazol-5-yl)-2-propenoic Acid Ethyl Ester (**9**).

A 3.10^{-5} M solution of compound **7** in absolute ethanol was irradiated at 300 nm for 3 hours. A mixture of the two products was obtained (60% of the (*Z*) isomer **9** and 40% of the (*E*) isomer **8**).

The two isomers were separated on a silica gel column (70-230 mesh) eluted with chloroform/methanol (97/3, v/v).

Compound **8**.

This compound had ir: ν 1700 (C=O), 1680 (C=C) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_3\text{-CH}_2$), 4.3 (q, 2H, OCH_2), 3.7 (s, 3H, NCH_3), 6.2 (d, 1H, H_a , $J = 15$ Hz), 7.48 (d, 1H, H_b , $J = 15$ Hz), 7.45 (s, 1H, H_c), 7.63 ppm (s, 1H, H_d).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.98; H, 6.66; N, 15.55. Found: C, 60.16; H, 6.75; N, 15.68.

Compound **9**.

This compound had ir: ν 1750 (C=O), 1680 (C=C) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.3 (t, 3H, $\text{CH}_3\text{-CH}_2$), 4.3 (q, 2H, OCH_2), 3.72 (s, 3H, NCH_3), 5.8 (d, 1H, H_a , $J = 12$ Hz), 6.60 (d, 1H, H_b , $J = 12$ Hz), 7.6 (s, 1H, H_c), 8.25 ppm (s, 1H, H_d).

Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_2$: C, 59.98; H, 6.66; N, 15.55. Found: C, 60.12; H, 6.80; N, 15.80.

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