A Novel Urocanic Acid Derivative from Skin Tissue Extracts; (*E*)-3-[1-(1,1-Dimethyl-3-oxobutyl)imidazol-4-yl]propenoic Acid

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A novel derivative of urocanic acid (**1**) had been isolated from acetone extracts of rabbit skin tissue. It proved to be (*E*)-3-[1-(1,1-dimethyl-3-oxobutyl)imidazol-4-yl]propenoic acid (**3c**), potentially a much better ultraviolet screening agent than urocanic acid. Sterical effect of dimethyl groups in the side chain adjacent to the imidazole ring of **3c** on its solubility is also discussed.

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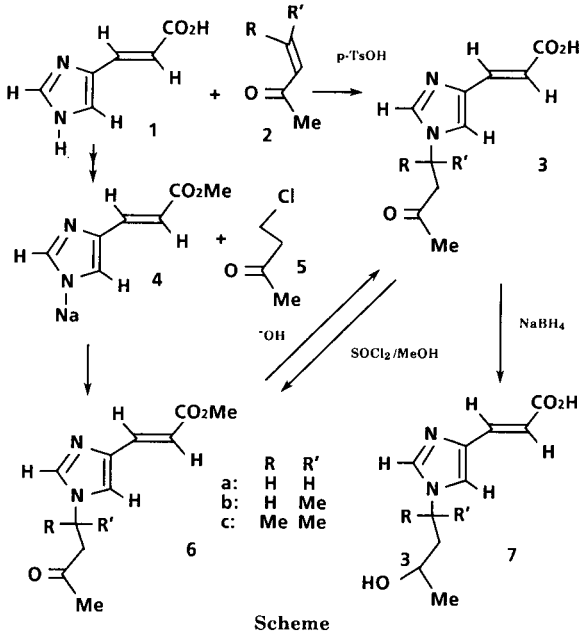
We have already reported [1,2] the isolation of several unique heterocyclic derivatives with plant growth regulating properties from the extraction of rabbit skin. During that work, a new imidazole spectrally akin to urocanic acid was observed in the acetone extracts. Purification by chromatography gave a crystalline compound, $C_{12}H_{16}N_2O_3$, which was identified tentatively as the urocanic acid derivative **3c** on the basis of its ^1H nmr, ^{13}C nmr and mass spectra. Thus the molecule showed most of the spectral features of urocanic acid as well as some for an attached portion which appeared to be a 1,1- rather than a 2,2-dimethyl-3-oxobutyl group and which gave a 3-hydroxy-1,1-dimethylbutylated product **7c** on sodium borohydride reduction. Since the molecule underwent normal esterification, the substituted-butyl group did not form part of an ester function and must have been attached at N1 or N3 of the imidazole ring. Comparison of its uv spectrum with those of 1- and 3-methylurocanic acid [3] gave no useful information but since nOe of the substituent's methyl groups increased both the H2 and H5 signals by *ca.* 10%, it was concluded that N1 rather than N3 was the point of attachment.

The compound **3c** was easily synthesized by prolonged heating of urocanic acid (**1**) with mesityl oxide (**2c**) in dimethyformamide containing *p*-toluenesulfonic acid. Similarly, the lower homologue **3b** was prepared from **1** and 3-pentene-2-one (**2b**). The unmethylated homologue **3a** was made by *N*-alkylation of methyl sodiourocanate (**4**) with 4-chloro-2-butanone (**5**), followed by alkaline hydrolysis of the crude ester **6a**.

As might be expected, the new dimethylated ketonic derivative **3c** and the dimethylated alcoholic derivative **7c** were immensely more soluble than urocanic acid in common solvents (Table 1); in contrast, the solubility of the unmethylated ketonic derivative **3a** was between **3c** and urocanic acid. And the monomethylated derivative **3b** showed high and nearly equal solubility like **3c**. These results showed that the α-methyl groups were the crucial



Scheme

Table 1

^1H NMR Spectra of Urocanic Acid and its Derivatives
(δ ppm and J Hz in deuterium oxide)

Compound	arom-*H* [a]	-HC=C*H*- [b]	Side Chain
1	7.60, 8.54	6.49, 7.27	
3a	7.67, 8.58	6.47, 7.24	2.25 (3H, s), 3.26 (2H, t, J = 6), 4.44 (2H, t, J = 6)
3b	7.75, 8.68	6.45, 7.22	1.54 (3H, d, J = 7), 2.16 (3H, s), 3.16 (1H, dd, J = 5, 18.5), 3.26 (1H, dd, J = 9, 18.5), 4.9-5.0 (1H, m)
3c	8.02, 8.97	6.52, 7.52	1.75 (6H, s), 2.15 (3H, s), 3.32 (2H, s)
6c	8.02, 8.96	6.54, 7.55	1.73 (6H, s), 2.14 (3H, s), 3.31 (2H, s), 3.83 (3H, s)
7c	7.87, 8.73	6.48, 7.21	1.09 (3H, d, J = 6.5), 1.69 (3H, s), 1.70 (3H, s), 2.0-2.1 (2H, m), 3.8-3.9 (1H, m)

[a] 1H, s. [b] 1H, d, J = 16.

Table 2

Solubilities of Urocanic Acid and its Derivatives at 24°

Compound	Maximal Solubilities (ml/g) in Water	Methanol	Ethanol	Acetone
1	328	364	741	8300
3a	73	91	370	641
3b	9	11	37	58
3c	9	5	15	22
7c	≪1	≪2	≪10	47

factor in such solubility. Preliminary tests of the dimethylated compounds **3c** and **7c**, which possesses clear enough lipophilicity as well as hydrophilicity to be ultraviolet screening agents, suggest that they may be considerably better than urocanic acid and its derivatives [4,5] in that respect.

In view of the formation of compound **3c**, its occurrence as a metabolite of urocanic acid or as artifact cannot be concluded on existing evidence.

EXPERIMENTAL

Melting points are uncorrected. Ultraviolet spectra were measured on a Cary-recording-Spectrometer, Model 118. The ^1H nmr and ^{13}C nmr spectra were measured in deuterium oxide on a Brucker AM-400 spectrometer; chemical shifts are in δ from *t*-butyl alcohol (1.23 ppm) for the former and TSP for the latter as internal standards.

(*E*)-3-[1-(3-Oxobutyl)imidazol-4-yl]propenoic Acid (**3a**).

The sodium salt **4** of methyl urocanate, prepared from methyl urocanate (3.0 g) and sodium hydride (0.92 g) in DMF (150 ml), was heated with 4-chloro-2-butanone (**5**) (4 ml) at 110° overnight. Evaporation *in vacuo* and purification by silica gel tlc (chloroform-ethanol; 9:1) gave the chromatographically pure oily substance **6a** (3.22 g). Without further purification, **6a** was treated with 1*N*-sodium hydroxide for 3 hours. After neutralization and evaporation *in vacuo*, the residue was applied to an XAD-7 column for desalinization. The methanol eluate was evaporated, and the crystalline solid recrystallized from ethanol to give the pure acid **3a** (45%), mp 169-171° dec; uv (water): λ max 266 nm (log ε 4.20); ms: m/z 208 (M^+, 9%), 164 (24), 138 (21), 121 (24), 94 (40), 71 (35), and 55 (100).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.3; H, 5.6; N, 13.2.

(*E*)-3-[1-(1-Methyl-3-oxobutyl)imidazol-4-yl]propenoic Acid (**3b**).

A mixture of urocanic acid (**1**) (10 g) and 3-pentene-2-one (**2b**) (50 ml) in DMF (150 ml), was heated at 80° for 15 hours in the presence of *p*-TsOH (140 mg). After evaporation *in vacuo*, application to an XAD-7 column, and washing with 0.1% TFA, a methanol eluate was evaporated to dryness to give white crystal (77%). The TFA salt was treated with Dowex 50 (H^+ form) column and Dowex 1 ($HCOO^-$ form) column, and the obtained crude crystals were recrystallized from ethanol to give **3b** (51%), mp 147-148° dec from ethanol; uv (ethanol): λ max 285 nm (log ε 4.33); ms: m/z 222 (M^+, 3%), 138 (30), 120 (17), 94 (55), 84 (31), 69 (100).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.4; N, 12.6. Found: C, 59.7; H, 6.6; N, 12.7.

(*E*)-3-[1-(1,1-Dimethyl-3-oxobutyl)imidazol-4-yl]propenoic Acid (**3c**).

(a) A phenol extract [1] from the rabbit skin tissue was prepared by a modification of the method of Aonuma *et al.* [6] After concentration, the solution was extracted with acetone, which was evaporated to give the crude extract. The residue was applied to an ion exchange column [Dowex 1 ($HCOO^-$ form)], and a 1*N*-formate eluate was collected and evaporated. The mixture was purified by using ODS-column chromatography (LC-SORB-ODS: 20 x 400 mm) in a linear gradient mode (methanol in 0.01% TFA; 0-50%) to yield white pure crystals of **3c**, mp 148-149° dec from ethanol; ^{13}C nmr (deuterium oxide): δ 29.4 (q), 33.3 (q), 54.4 (t), 62.7 (s), 123.6 (d), 124.2 (d), 131.9 (s), 132.0 (d), 138.0 (d), 172.1 (s), and 212.9 (s); uv (ethanol): λ max 283 nm (log ε 4.17); ms: m/z 236 (M^+, 6%), 192 (18), 138 (11), 120 (10), 98 (63), 94 (43), and 83 (100).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.0; H, 6.8; N, 11.9. Found: C, 60.9; H, 7.0; N, 11.8.

(b) A mixture of urocanic acid (**1**) (12 g) and mesityl oxide (**2c**) (200 ml) in DMF (300 ml), was heated at 110° overnight in the presence of *p*-TsOH (90 mg) to give as above white crystals of **3c** (40%), mp 148-149° dec.

Methyl (*E*)-3-[1-(1,1-Dimethyl-3-oxobutyl)imidazol-4-yl]propenoate (**6c**).

Thionyl chloride (26 g) was added at -10° to a suspension of **3c** (5.0 g) in methanol (100 ml), and the mixture was stirred at room temperature overnight. After removal of solvent, the residue was dissolved in a minimum amount of ethyl acetate and petroleum ether was added to the solution to yield crystalline hydrochloride of **6c** (83%), mp 228-229° dec. After neutralization of aqueous solution of the hydrochloride, chloroform extract was dried over sodium sulfate and evaporated to give oily free **6c**; uv (ethanol): λ max 279 nm (log ε 4.27); ms: m/z 250 (M^+, 86%), 219 (7), 152 (99), 121 (98), 93 (77), 66 (20), and 43 (100).

Anal. Calcd. for $C_{13}H_{18}N_2O_3 \cdot HCl$: C, 54.5; H, 6.9; N, 9.8. Found: C, 54.5; H, 7.0; N, 10.1.

(*E*)-3-[1-(3-Hydroxy-1,1-dimethylbutyl)imidazol-4-yl]propenoic Acid (**7c**).

A suspension of **3c** (10 g) and sodium borohydride (6.0 g) in 95% ethanol (100 ml) was stirred for 10 minutes. The mixture was added to water (100 ml) and acidified to *p*H 4.0. The residue from evaporation was desalinated on an XAD-7 column to yield a gum, which crystallized from ethyl acetate-ethanol to give the pure material **7c** (74%), mp 137-139° dec; λ max 286 nm (log ε 4.47); ms: m/z 238 (M^+, 19%), 194 (38), 162 (13), 138 (16), 120 (28), and 94 (100).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.5; H, 7.6; N, 11.8. Found: C, 60.8; H, 7.8; N, 11.9.

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