SELECTIVE *N*-ALKYLATION OF *(E)*-UROCANIC ACID†

Nancy Lauth-de Viguerie, Natalia Sergueeva, Monique Damiot, Hiba Mawlawi, Monique Riviere, and Armand Lattes*

Laboratoire des Interactions Moléculaires et Réactivité Chimique et Photochimique URA au CNRS 470, Université Paul Sabatier, 118 route de Narbonne, F 31062 Toulouse, France

Abstract- Various methods of selective alkylation of the $N(\tau)$- and $N(\pi)$-nitrogen atoms of *(E)*-urocanic acid derivatives are reported. Solid-liquid phase transfer catalysis gave the best results for $N(\tau)$-alkylation of urocanic acid alkyl esters. Liquid-liquid phase transfer catalysis allowed direct $N(\tau)$-alkylation of urocanic acid itself. The $N(\pi)$-nitrogen atom was alkylated after protection of the $N(\tau)$-nitrogen with a phenacyl group.

INTRODUCTION - *(E)*-3-(1*H*-Imidazol-4-yl)-2-propenoic acid or *(E)*-urocanic acid is a metabolite of histidine found in the skin and excreted in sweat. This compound has interesting biological properties:

-it acts as a natural photoprotecting agent,[1-3]

-the *(Z)*-isomer has been found to have immunosuppressive activity,[4-6] although the mechanism has yet to be elucidated.

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† The authors dedicate this paper to Professor Alan R. Katritzky (University of Florida) on the occasion of his 65th birthday.

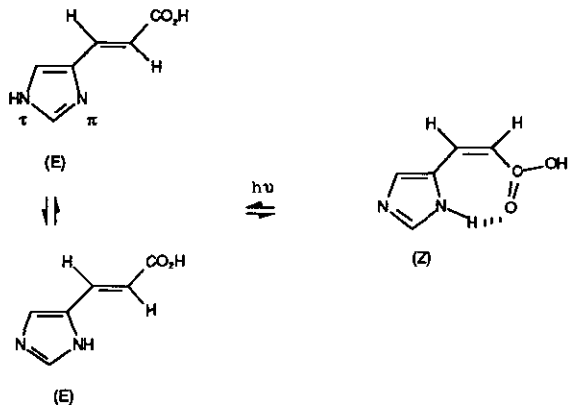


Figure 1

The study of the relationship between structure and activity hinges on the synthesis of numerous derivatives of urocanic acid in order to :

- improve the solubility and so facilitate the formulation;
- study structure-activity relationships in immunology;
- investigate cycloaddition reactions in organized media used as models of biological systems.

As urocanic acid exists in two tautomeric forms (Figure 1), *N*-alkylation can occur at two sites : the *N*(τ) and *N*(π) nitrogen atoms.[7](Figure 2).

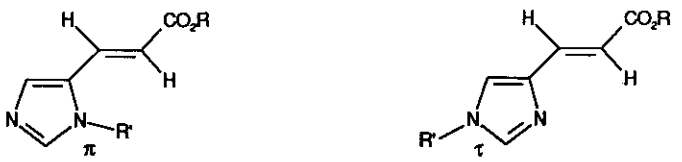


Figure 2

This question is related to the general problem concerning the *N*-alkylation of imidazole derivatives substituted in position 4(5). According to the literature, when the substituent in position 4(5) is a withdrawing group, *N*-alkylation occurs essentially on the *N*(τ) nitrogen atom.[8] This is observed for histidine, the biological precursor of urocanic acid, specially when the substituent is sterically hindered.[9] A preliminary study in our laboratory has demonstrated selective *N*-alkylation of urocanic acid alkyl esters to be possible.[10-12] We report here a study of several *N*-alkylation methods in

order to determine a facile way to selectively obtain $N(\tau)$ or $N(\pi)$-substituted urocanic acid.

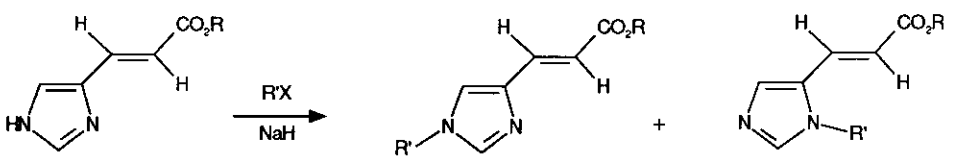
I.- $N(\tau)$-ALKYLATION

First we studied the alkylation reaction in a homogeneous phase and then in a heterogeneous phase.

1.- Alkylation in a homogeneous phase

Urocanic acid is insoluble in organic solvents, so the reaction in a homogeneous phase utilized urocanic alkyl esters as starting material.

To our knowledge, there have been no descriptions of the selective *N*-alkylation of urocanic acid alkyl esters by non-activated halides, apart from methylation which generally gives rise to mixtures.[13-15] Direct *N*-alkylation was not possible and a modification of a method previously described by Ienaga *et al.*[16] was developped[10] : R'X=alkyl bromide solvent=dimethylformamide, temperature=20°C, reaction duration=1 h (Figure 3).The yields were excellent.



1 R=CH_3
2 R=C_2H_5
3 R=$C_{12}H_{25}$

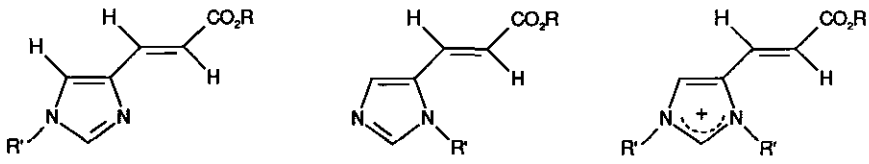
4 R'=C_2H_5, **5** R'=C_7H_{15}, **6** R'=$C_{12}H_{25}$
7 R'=C_2H_5, **8** R'=C_7H_{15}, **9** R'=$C_{12}H_{25}$

Figure 3

In all these reactions a single *N*-alkylated product was isolated and only small amounts of a second one were detected by thin layer chromatography.

A structural study [10,11] showed that the *N*-alkylated esters synthesized using this method had a 1,4-disubstituted imidazole ring. This *N*-alkylation was regioselective for the alkyl bromides examined.

When the reaction was carried out with allyl bromide or methyl iodide, mixtures of products were obtained, due to the substitution at either $N(\tau)$- or $N(\pi)$-nitrogen atoms and to disubstitution (Figure 4).



R:C_2H_5, R':$CH_2CH{=}CH_2$ **9** **10** **11**

R:C_2H_5, R':CH_3 **12** **13** **14**

Figure 4

In order to obtain a good regioselectivity with all alkyl halides, mild reaction conditions in heterogeneous systems were examined.

2- Alkylation in solid-liquid systems

In the presence of anhydrous potassium carbonate in a heterogeneous phase, we studied the action of allyl bromide on urocanic acid ethyl ester in different experimental conditions (Table 1).

Table 1.- Reaction of allyl bromide with urocanic acid ethyl ester

Solvent	temperature (°C)	duration (h)	yield **10** (%)	yield **11** (%)	yield **12** (%)
toluene	20	18	30	-	-
toluene	110	18	50	-	-
acetone	20	18	80	-	-
acetone	40	18	70	10	10
acetone([a])	40	18			100
acetonitrile	20	18	70		
ethanol/water,1/1 v/v	20	18	40		

([a]) Excess of allyl bromide.

The results described in the Table 1 show that the best yields and selectivities were obtained in polar aprotic solvents at room temperature. At 40°C, the reaction was not selective, and when the reaction was carried out with an excess of allyl bromide, the $N(\tau),N(\pi)$-diallyl compound was obtained in a 100% yield. As the $N(\tau)$-allyl derivative did not rearrange in the reaction conditions, it seems that there is a competition between the three reactions observed and that dialkylation is faster than $N(\pi)$-monoalkylation. The reaction in acetone (or acetonitrile) at room temperature led to the $N(\tau)$-allyl urocanic acid ethyl ester with an 80% yield The reaction conditions were later applied to various other halides. The results recorded in Table 2 show that these conditions gave good yields only with reactive alkyl halides.

Table 2.- Alkylation of urocanic acid alkyl esters in solid-liquid systems

R	R'X	solvent	temperature (°C)	duration (h)	yield (%)	compound
CH_2CH_3	CH_3I	acetone	20	18	80	**13**
CH_2CH_3	CH_3I	acetonitrile	20	18	90	**13**
CH_2CH_3	$C_6H_5COCH_2Cl$	acetonitrile	20	18	90	**16**
CH_2CH_3	$(C_6H_5)_3CCl$	acetonitrile	20	18	90	**17**
CH_3	$C_{12}H_{25}Br$	acetone	reflux	240	22	**6**
CH_3	$C_{12}H_{25}Br$	DMF	100	7	39	**6**
CH_3	$C_{12}H_{25}Br$	THF*	20	3	96	**6**

* with 18-crown-6 ether

For the long chain bromide we decided to use **solid-liquid phase transfer catalysis conditions**. The solvent chosen was tetrahydrofuran (THF) which allows a good solubilisation of urocanic acid methyl ester and of the *N*-dodecyl derivative. Potassium carbonate was used as solid phase and the 18-

crown-6 as catalyst. The reaction at 20°C was fast, regiospecific, facile and gave quantitative yields.

Solid-liquid phase tranfer catalysis proved to be an excellent method for the *N*(τ)-alkylation of urocanic acid alkyl esters, but it cannot be used for urocanic acid itself, insoluble in organic solvents. Liquid-liquid phase transfer conditions were then considered.

3- Alkylation by liquid-liquid phase transfer catalysis

The use of **liquid-liquid phase transfer catalysis** in the *N*-alkylation of heterocycles has already proved its value. Good yields of *N*-alkylated pyrroles or indoles have been obtained with aqueous potassium hydroxide solution as base, a crown ether [17] or a tetraalkylammonium salt [18] as phase transfer catalyst. Dou *et al.* [19] used these reaction conditions for *N*-alkylation of imidazole, the yields obtained were very low for long chain halides. Using different experimental conditions, Lattes *et al.* [20] succeeded in alkylating imidazole with long chain alkyl halides. They used an 18M aqueous sodium hydroxide solution, benzene and tetraethylammonium bromide. Imidazole and benzimidazole have also been alkylated by liquid-liquid phase transfer catalysis with various polyethylene glycols.[21]

We report here a study concerning the reaction of dodecyl bromide and urocanic acid in liquid-liquid phase transfer conditions. Many *O*-alkylations of carboxylate anions using liquid-liquid phase transfer catalysis have been described.[22] So, in the case of urocanic acid, *N*- and *O*-alkylations might be expected. Five phase transfer catalysts were used : polyethylene glycol 600 (PEG 600), 18-crown-6 (18-CR-6), tetrabutylammonium bromide (TBuAB), benzyldimethyldodecylammonium bromide (BDMAB) and polyoxyethylene 23 lauryl ether (BRIJ 35). Only long chain catalysts gave good alkylation yields (Table 3) and, depending on the conditions, one or two compounds were obtained.

- compound (**18**) corresponding to an *N*(τ)-alkylation;
- compound (**9**) corresponding to a *N,O*-dialkylation (Figure 5).

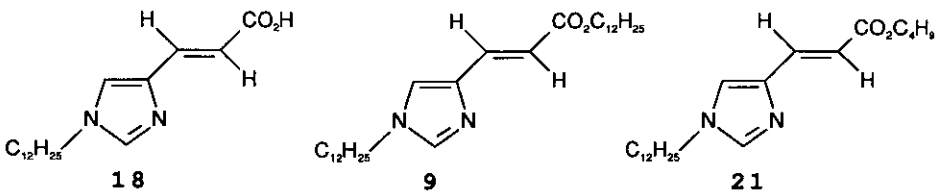


Figure 5

Table 3.- Liquid-liquid phase transfer catalyzed reaction of dodecyl bromide on urocanic acid

Entry No	R'X	[R'X]/[U.A.]	catalyst	solvent	tempera-ture°C	duration h	total yield %	**18** yield %	**9** yield %
1	$C_{12}H_{25}Br$	1	BDMAB	toluene	110	15	30	93	7
2	$C_{12}H_{25}Br$	2	BDMAB	toluene	110	45	40	75	25
3	$C_{12}H_{25}Br$	3	BDMAB	toluene	110	45	75	60	40
4	$C_{12}H_{25}Br$	4	BDMAB	toluene	110	45	75	60	40
5	$C_{12}H_{25}Br$	3[a]	BDMAB	toluene	110	45	50	90	10
6	$C_{12}H_{25}Br$	2	BDMAB	$C_2H_4Cl_2$	83	45	15	0	100
7	$C_{12}H_{25}Br$	2	BRIJ 35	toluene	90	59	40	0	100
8	$C_{12}H_{25}Br$	2	TBuAB	toluene	110	45	15	0	100
9	$C_{12}H_{25}Br$	2	18-CR-6	toluene	110	15	0		
10	$C_{12}H_{25}Br$	2	PEG 600	toluene	110	15	0		

a : final value of R'X which was added in three parts at t = 0 h, t = 24 h, t = 36 h
U.A. : urocanic acid

Discussion : According to the reaction conditions a mixture of the two compounds (**18** and **9**) was obtained (Table 3, Entries No 1 to 5) or only the *N,O*-dialkylated compound (**9**) (Table 3, Entries No 6 to 8). The results can probably be explained by the behaviour of the dianion involved in the reaction. This dianion is likely to be anchored at the interface (use of concentrated sodium hydroxide solution) by the carboxylate function rather than by the imidazoyl group (Figure 6). The anchoring of the carboxylate function at the interface favors *N*(τ)-alkylation at the less hindered

nitrogen atom. This alkylation increases the solubility in the organic phase and *O*-alkylation can then occur.

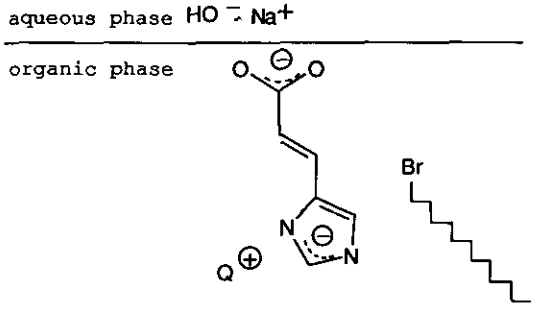


Figure 6

The solvent and the catalyst are likely to have an equal influence on the initial anchoring at the interface and on the subsequent solubilisation in the organic phase. So, the relative rates of the heteroalkylations depend on the nature of the solvent and of the catalyst. It is important to note that the best results are obtained with the long-chain catalysts :

- the cationic catalyst (BDMAB) favors *N*(τ)-alkylation (Table 3, Entries No 1 to 5) ;
- the non ionic catalyst (BRIJ 35) favors *N,O*-dialkylation (Table 3, Entries No 6 to 8).

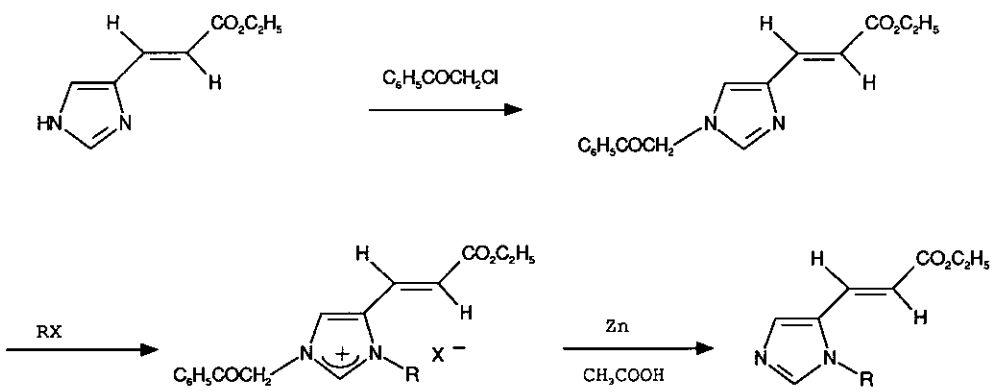
These hypotheses were confirmed by two additional experiments using liquid-liquid phase transfer catalysis : urocanic acid methyl ester was not alkylated and *N*(τ)-dodecyl urocanic acid (**18**) was *O*-alkylated by butyl bromide to give compound (**21**).

II- *N*(π)-ALKYLATION

The results described above indicate that the *N*-substitution occurs essentially on the *N*(τ) nitrogen. Thus, in order to alkylate the *N*(π) nitrogen, the *N*(τ) nitrogen must be protected.

The triphenylmethyl or phenacyl groups, which are commonly employed as protective groups on histidine [9] were therefore tested for the preparation of $N(\pi)$-methyl and $N(\pi)$-allyl urocanic acid ethyl ester.

The action of the triphenylmethyl chloride on urocanic acid ethyl ester led to the $N(\tau)$-substituted compound with an excellent yield (paragraph I). However, during the subsequent substitution reaction, the protective group tended to be eliminated giving a mixture of the $N(\tau)$-substituted and $N(\tau),N(\pi)$-disubstituted products.



R = $CH_2CH=CH_2$ **19** **11**
R = CH_3 **20** **14**

Figure 7

The phenacyl group appeared less labile and the reaction of $N(\pi)$-phenacyl urocanic acid ethyl ester (**16**) with allyl iodide or methyl bromide led to the corresponding $N(\tau),N(\pi)$-disubstituted products (**19**) and (**20**).

Deprotection with Zn in acid medium at 0°C led to the $N(\pi)$-alkylated products (**11**) and (**14**) (Figure 7) in good yields. When the reaction was carried out at 25°C, hydrogenation of the ethylenic chain was also observed.

CONCLUSION - Selective *N*-alkylations of urocanic acid were obtained in different ways.

Solid-liquid phase transfer catalysis appeared to be the best method for alkylation of the urocanic acid alkyl esters.

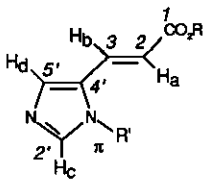
Liquid-liquid phase transfer catalysis allowed direct *N*-alkylation of urocanic acid and also one-pot synthesis of long chain *N*-alkyl urocanic acid alkyl esters.

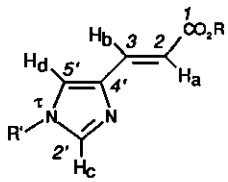
EXPERIMENTAL PART

Urocanic acid, methyl iodide, alkyl bromides and phenacyl chloride were obtained from Aldrich.

The ^1H nmr spectra were recorded on Bruker AC 80 spectrometer. The uv spectra were recorded on a HP 8451 A spectrophotometer, and the ir spectra were recorded on a Perkin Elmer 683 instrument.

The structure of products was determined according to references.[10-12]





Urocanic Acid Alkyl Esters (1 and 2)

A solution of urocanic acid (3 g, 21.7 mmol) in dry corresponding alcohol (100 ml) was saturated by HCl gas and refluxed through a Soxhlet thimble containing activated 3Å sieves for 2.5 h. The solvent was removed under reduced pressure giving the ester hydrochloride . The residue was neutralized by a saturated aqueous $NaHCO_3$ solution, extracted with ethyl acetate and dried over sodium sulfate . Evaporation of ethyl acetate left urocanic acid alkyl ester (**1** or **2**) in a 85% yield.

*Compound (**1**)* : mp 95-96°C; ir (potassium bromide) ν 1720(C=O), 1650(C=C) , 2800-3400(broad band NH) cm^{-1}; ^1H nmr (DMSO-d6) δ 3.68 (s, 3H, CH_3), 6.34 (AB, J=16 Hz, 1H, H_a), 7.55 (AB, J=16 Hz, 1H, H_b), 7.53 (s, 1H, H_d), 7.77 (s,

1H, H_c) ppm ; m/z=153, MH^+(100%) . Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found : C, 55.10; H, 5.19; N, 18.38.

Compound (2) : mp 79°C; ir (potassium bromide) ν 1730(C=O), 1618(C=C), 3100(broad band NH) cm^{-1}; uv (ethanol) λmax 288 nm (ε 18945); ^1H nmr ($CDCl_3$) δ 1.30 (t, J=7.1 Hz, 3H, CH_3-CH_2), 4.16 (q, J=7.1 Hz, 2H, OCH_2), 6.50 (AB, J=16 Hz, 1H, H_a), 7.50 (AB, J=16 Hz, 1H, H_b), 7.20 (s, 1H, H_c), 7.67 (s, 1H, H_d) ppm . Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.86. Found : C, 57.90, H, 5.95; N, 16.7.

Compound (3) was prepared from the *p*-toluenesulfonate of urocanic acid.[23]

ALKYLATION ON *N*(τ)-NITROGEN ATOM

General Procedure for *N*(τ)-Alkylation in Homogeneous Phase

A solution of alkylurocanate (3.26 mmol) in dry dimethylformamide (40 ml) was added dropwise to a stirred suspension of 95% sodium hydride (0.123 g, 4.89 mmol) in dry dimethylformamide (10 ml) under a dry and inert atmosphere. Alkyl bromide (3.26 mmol) was added to the mixture. The reaction was followed by thin-layer chromatography on 2.5 x 7.5 cm silica gel 60 Å plates (250 μm layer, Whatman) with uv detection at 254 nm. The solvent was a chloroform-ethanol mixture (95:5, v/v). The reaction was stopped on the disappearance of the starting ester, only small amounts of secondary products were detected. The reaction mixture was filtered through celite 545 (Fluka) and the filtrate was evaporated to dryness. The residue was purified on a 20 x 2 cm I.D. column of silicagel (250-400 mesh, Fluka) using chloroform-ethanol (90:10, v/v) as eluent affording the *N*(τ)-alkylated urocanic acid alkyl esters.

N(τ)-Ethyl Urocanic Acid Methyl Ester (4) : 90% yield (0.530 g) ; mp 52°C ; R_f($CHCl_3$/EtOH:9/1) 0.67; uv ($CHCl_3$) λmax 290 nm (ε 21476); ir υ 1710(C=O), 1650(C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.66 (s, 3H, OCH_3), 3.85 (q, J=7.3 Hz, 2H, NCH_2), 6.40 (AB, J=16 Hz, 1H, H_a), 7.38 (AB, J=16 Hz, 1H, H_b), 7.36 (s, 1H,

H_c), 7.05 (s, 1H, H_d) ppm . Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71 ; N, 15.55. Found : C, 60.10; H, 7.00; N, 15.71.

N(τ)-Heptyl Urocanic Acid Methyl Ester (5) : 88% yield (0.72 g) ; mp 75°C; R_f($CHCl_3$/EtOH:9/1) 0.66; uv ($CHCl_3$) λmax 290 nm (ε 21319) ; ir υ 1710(C=O), 1650(C=C) cm^{-1} ; ^1H nmr ($CDCl_3$) δ 3.75 (s, 3H, OCH_3), 3.85 (t, J=6.7 Hz, 2H, NCH_2), 6.48 (AB, J=16 Hz, 1H, H_a), 7.53 (AB, J=16 Hz, 1H, H_b), 7.04 (s, 1H, H_d), 7.42 (s, 1H, Hc) . Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found : C, 67.12; H,8.90; N, 11.09.

N(τ)-Dodecyl Urocanic Acid Methyl Ester (6): 90% yield (0.94 g) ; mp 74°C; R_f($CHCl_3$/EtOH:9/1) 0.67 ; uv ($CHCl_3$) λmax 290 nm (ε 19973); ir υ 1710(C=O), 1650(C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.87 (m, 3H, CH_3-$(CH_2)_{11}$), 3.78 (s, 3H, OCH_3), 3.81 (t, J=6.3 Hz, 2H, NCH_2), 6.51 (AB, J=16 Hz, 1H, H_a), 7.55 (AB, J=16 Hz, 1H, H_b), 7.48 (s, 1H, H_c), 7.05 (s, 1H, H_d) . Anal. Calcd for $C_{19}H_{32}N_2O_2$: C; 71.21; H, 10.06; N, 8.74. Found : C, 71.08; H, 10.10; N,8.75.

N(τ)-Ethyl Urocanic Acid Dodecyl Ester (7) : 81% yield (0.88 g) ; mp 55°C; R_f($CHCl_3$/EtOH:9/1) 0.68 ; uv ($CHCl_3$) λmax 290 nm (ε 18708) ; ir υ 1710(C=O), 1650(C=C) cm^{-1} ; ^1H *nmr* ($CDCl_3$) δ 4.14 (t, J=7 Hz, 2H, OCH_2) , 3.97 (q, J=7.3 Hz, 2H, NCH_2), 6.50 (AB, J=16 Hz, 1H, H_a) , 7.43 (AB, J=16 Hz, 1H, H_b), 7.49 (s, 1H, H_c), 7.06 (s, 1H, H_d). Anal. Calcd for $C_{20}H_{35}N_2O_2$: C, 71.60; H, 10.51; N, 8.35 . Found : C, 71.77; H, 10.74; N, 8.25.

N(τ)-Heptyl Urocanic Acid Dodecyl Ester (8) : 70% yield (0.93 g) ; mp 57°C ; R_f($CHCl_3$/EtOH:9/1) 0.65 ; uv ($CHCl_3$) λmax 290 nm (ε 19480) ; ir υ 1710(C=O), 1650(C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.14 (t, J=6.7 Hz, 2H, OCH_2), 3.92 (t, J= Hz, 2H, NCH_2), 6.55 (AB, J=16 Hz, 1H, H_a), 7.48 (AB, J=16 Hz, 1H, H_b), 7.57 (s, 1H, H_c), 7.03 (s, 1H, H_d). Anal. Calcd for $C_{25}H_{44}N_2O_2$: C, 74.21; H, 10.96; N, 6.92 . Found : C, 74.30; H, 10.92; N, 6.87.

N(τ)-Dodecyl Urocanic Acid Dodecyl Ester (9) : 92% yield (1.43 g) ; mp 72°C ; R_f($CHCl_3$/EtOH:9/1) 0.66; uv ($CHCl_3$) λmax 290nm (ε 25517) ; ir υ 1710(C=O), 1650(C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.13 (t, J=6.7 Hz, 2H, OCH_2), 3.90 (t, J=

7.2 Hz, 2H, NCH_2), 6.53 (AB, J=16 Hz, 1H, H_a), 7.46 (AB, J=16 Hz, 1H, H_b), 7.55 (s, 1H, H_c), 7.03 (s, 1H, H_d) . Anal. Calcd for $C_{30}H_{54}N_2O_2$: C, 75.90; H, 11.46; N, 5.90. Found : C, 75.92; H, 11.43; N, 5.70.

General Procedure for Solid-Liquid N(τ)-Alkylation

Potassium carbonate (0.83 g, 6 mmol) was added to compound (**2**) (1 g, 6 mmol) in 10 ml of acetonitrile. Alkyl halide (5.8 mmol) was added dropwise to this suspension. The mixture was stirred at room temperature for 18 h, filtered and the filtrate was evaporated. The appropriate working of the various residues then yielded the *N*-alkylated products.

*N(τ)-Allyl Urocanic Acid Ethyl Ester (**10**)* : The residue was recristallized in CCl_4 to afford compound (**10**) in 80% yield (0.96 g) ; mp 76°C; uv(ethanol) λmax 290nm (ε 20800) ; ^1H nmr ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H, CH_2-$C\underline{H}_3$), 4.21 (q, J=7.1 Hz, 2H, $C\underline{H}_2$-CH_3), 6.53 (AB, J=16 Hz, 1H, H_a), 7.53 (AB, J=16 Hz, 1H, H_b), 7.48 (s, 1H, H_c), 7.08 (s, 1H, H_d), 5.21 (m, 2H, $=CH_2$), 4.50 (m, 2H, NCH_2), 5.91 (m, 1H, $C\underline{H}=CH_2$) ppm ; ^{13}C nmr ($CDCl_3$) δ 167.6 (C_1), 116.3 (C_2), 135.8 (C_3), 138.4 ($C_{4'}$), 121.3 ($C_{5'}$), 138.3 ($C_{2'}$), 49.6 ($N\underline{C}H_2$), 132.1 ($\underline{C}H_2=$), 119.3 ($=\underline{C}H$), 60.3 ($O\underline{C}H_2$), 14.3 ($\underline{C}H_3$) ppm . Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.07; H, 6.79; N, 13.59. Found : C, 63.91; H, 6.79; N, 13.40

*N(τ)-Methyl Urocanic Acid Ethyl Ester (**13**)*: 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 (**13**) in 90% yield (0.94 g) ; mp 98°C, ir (potassium bromide) ν 1730(C=O), 1610 (C=C), 3100(NH); uv (ethanol) λmax 288 nm (ε 17991) ; ^1H nmr ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H, CH_2-$C\underline{H}_3$), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 3.60 (s, 3H, NCH_3), 6.50 (AB, J=16 Hz, 1H, H_a), 7.51 (AB, J=16 Hz, 1H, H_b), 7.03 (s, 1H, H_d), 7.40 (s, 1H, H_c) ppm ; ^{13}C nmr ($CDCl_3$) δ 167.5 (C_1), 139 ($C_{2'}$), 138.3 ($C_{4'}$), 135.6 (C_3), 122.3 ($C_{5'}$), 116.4 (C_2), 61.2 ($O\underline{C}H_2$), 33.6 ($N\underline{C}H_3$), 14.2 ($\underline{C}H_3$) ppm.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found : C, 60.22; H, 6.67; N, 15.58.

N(τ)-Phenacyl Urocanic Acid Ethyl Ester (16) : The residue was recrystallized in ether to afford compound (**16**) in 90% yield (1.49 g) ; mp 124°C, ir ν 1730(C=O), 1680(C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H, $C\underline{H}_3$-CH_2), 4.31 (q, J=7.1 Hz, 2H, OCH_2), 5.39 (s, 2H, NCH_2), 6.50 (AB, J=16 Hz ,1H ,H_a), 7.55 (AB, J=16 Hz, 1H, H_b), 7.91 (s, 1H, H_c), 7.12 (s, 1H, H_d), 7.5-7.6 (m, 5H, phenyl) ppm ; ^{13}C nmr ($CDCl_3$) δ 190.9 ($\underline{C}O$), 167.7 (C_1), 139.3 (C_2'), 138.5 (C_4'), 135.8 (C_3), 134.6-129.22-128.0 ($\underline{C}_6H_5$), 122.5 (C_5'), 116.4 (C_2), 60.3 ($O\underline{C}H_2$), 14.3 ($\underline{C}H_3$) ppm . Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found : C, 67.23, H, 5.60; N, 9.60.

N(τ)-Triphenylmethyl Urocanic Acid Ethyl Ester (17) : The residue was recrystallized in ether affording compound (**17**) in 90% yield (2.13 g) ; mp 138°C, ir ν 1730(C=O), 1680 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H, $C\underline{H}_3$-CH_2), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 6.51 (AB, J=16 Hz, 1H, H_a), 7.50 (AB, J=16 Hz, 1H, H_b), 7.01 (s, 1H, H_d), 7.2-7.3 (m, 15H, phenyl), 7.46 (s, 1H, H_c) ppm . Anal. Calcd for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86. Found : C, 79.16, H, 5.81; N, 5.90.

Solid-Liquid Phase Transfer Catalysed *N*(τ)-Alkylation

N(τ)-Dodecyl Urocanic Acid Methyl Ester (6)

Potassium carbonate (21.6 g, 157.6 mmol) and 18-crown-6 (0.57 g, 1.97 mmol) was added to (3 g, 19.7 mmol) of compound (**1**) in 50 ml of dry THF. Dodecyl bromide (9.82 g, 39.4 mmol) in 10 ml of THF was added dropwise to this suspension. The mixture was refluxed under stirring for 2 h, filtered and the filtrate was evaporated to dryness. The residue was recrystallised in n-hexane and stored at 4°C overnight to afford compound (**6**) with a 96% yield (6.00 g).

Liquid-Liquid Phase Transfer Catalysed *N*(τ)-Alkylation

The procedure corresponding to Entry No3 only will be described here. A solution of NaOH (4 g, 0.1 mol) and of urocanic acid (1.38 g, 0.01 mol) in

30 ml of water was mixed with a solution of benzyldodecyldimethylammonium bromide (0.385 g, 0.001 mol) and of dodecyl bromide (7.5 g, 0.03 mol) in 30 ml of toluene. The mixture was stirred for 45 h at 110°C. After cooling the two phases were separated. The organic phase was washed with water, then dried over sodium sulfate and evaporated. The residue was partially dissolved in boiling n-hexane (60 ml). The n-hexane solution was separated from the remaining solid and purified on a silica gel Kieselgel Riedel de Haën 31612 (70-230 mesh) column eluted first with ether and after with chloroform/ethanol (95/5, v/v) affording product (**9**) with a 30% yield (1.42 g) .

The aqueous phases were neutralized with formic acid giving a precipite which was filtered. The solid was extracted with 40 ml of chloroform. The extract was dried over sodium sulfate and evapored. The solid obtained and the solid remaining after the above n-hexane treatment were recrystallized from an acetone/petroleum ether (1/1,v/v) mixture, affording compound (**18**) with a 45% yield (1.38 g) ; mp 116°C, ir ν 1710 (C=O), 1645 (C=C) cm^{-1}, uv($CHCl_3$) λmax 290 nm (ε 21335) ; ^1H nmr ($CDCl_3$) δ 0.87 (t, J= 6.5 Hz, 3H, CH_2-C<u>H</u>$_3$), 1.0-1.5 (m, 18H, (C<u>H</u>$_2$)$_9$$CH_3$), 1.5-1.9 (m, 2H, NCH_2-C<u>H</u>$_2$), 3.87 (t, J=7 Hz, 2H, NCH_2), 6.56 (AB, J=16 Hz, 1H, H_a), 7.09 (s, 1H, H_d), 7.60 (s, 1H, H_c), 7.62 (AB, J=16 Hz, H_b) . Anal. Calcd for $C_{18}H_{30}N_2O_2$: C, 70.55; H, 9.87; N, 9.14 . Found : C, 70.31; H,10.05; N, 9.02.

The same conditions applied to the reaction of compound (**18**) with butyl bromide afforded *N*(τ)-dodecyl urocanic acid butyl ester (**21**) in a 15% yield, mp 45-46°C, R_f($CHCl_3$/ethanol:95/5, v/v) 0.48, ir ν 1700(C=O), 1640(C=C) cm^{-1}; uv($CHCl_3$) 290 nm (ε 22618) ; ^1H nmr ($CDCl_3$) δ 0.86 (t, J=7.2 Hz, 3H, (CH_2)$_{11}$C<u>H</u>$_3$), 0.94 (t, J=5 Hz, 3H, (CH_2)$_3$C<u>H</u>$_3$), 1.2-1.4 (m, 20H, (C<u>H</u>$_2$)$_9$$CH_3$ and (CH_2)$_2$C<u>H</u>$_2$$CH_3$), 1.6-1.9 (m, 4H, NCH_2-C<u>H</u>$_2$ and OCH_2-C<u>H</u>$_2$), 3.90 (t, J=7 Hz, 2H, NC<u>H</u>$_2$), 4.16 (t, J=7 Hz, 2H, OC<u>H</u>$_2$), 6.52 (AB, J=16 Hz, 1H, H_a), 7.07 (s, 1H, H_d), 7.45 (s, 1H, H_c), 7.53 (AB, J=16 Hz, 1H, H_b) ppm . Anal. Calcd for $C_{22}H_{38}N_2O_2$: C, 72.88; H, 10.56; N, 7.73. Found : C, 72.99; H, 10.87; N, 7.65.

ALKYLATION ON N(π)-NITROGEN ATOM

*N(π)-Allyl Urocanic Acid Ethyl Ester (**11**)*

- An excess of allyl bromide (2.12 g, 17.5 mmol) was added to a solution of (1 g, 3.5 mmol) of compound (**16**) in 30 ml of dry acetonitrile. The mixture was stirred for 2 days at 40°C. The residue, obtained after evaporation of the solvent, was washed with ether giving compound (**19**) with an 80% yield (1.1 g) ; ^{1}H nmr ($CDCl_3$) δ 1.3 (t, J=7.1 Hz, 3H, CH_2-C<u>H</u>$_3$), 4.17 (q, J=7.1 Hz, 2H, OCH_2), 4.91 (m, 2H, $N_\pi CH_2$), 5.35 (m, 2H, CH_2=), 5.91 (m, 1H, C<u>H</u>=CH_2), 6.21 (s, 2H, $N_\tau CH_2$), 6.32 (AB, J=16 Hz, 1H, H_a), 7.3-7.9 (m ,1H+5H, H_b+phenyl), 8.31 (s, 1H, H_d), 9.92 (s, 1H, H_c) ppm.

- An excess of Zn (0.64 g, 9.84 mmol) was added at 0°C to a solution of (0.56 g, 1.4 mmol) of compound (**19**) in 20 ml of acetic acid. The mixture was stirred for 10 min and filtered over celite. The solution was concentrated, neutralized with $HNaCO_3$ and extracted with ethyl acetate. The organic solution was dried oversodium sulfate. Compound (**11**) was obtained with a 98% yield (0.283 g) after evaporation of ethyl acetate; mp 120°C ; ^{1}H nmr ($CDCl_3$) δ 1.27 (t, J=7.1 Hz, 3H, C<u>H</u>$_3$-CH_2), 4.24 (q, J=7.1 Hz, 2H, OCH_2), 4.51 (m, 2H, $N_\pi CH_2$), 5.18 (m, 2H, CH_2=), 5.83 (m, 1H, -C<u>H</u>=CH_2), 6.21 (AB, J=16 Hz, 1H, H_a), 7.41 (AB, J=16 Hz, 1H, H_b), 7.45 (s, 1H, H_d), 7.61 (s, 1H, H_c) ppm ; ^{13}C nmr ($CDCl_3$) δ 166.2 (C_1), 129.1 ($C_{4'}$), 131.1 (C_3), 121.4 ($C_{5'}$), 140.5 ($C_{2'}$), 119.4 (C_2), 51.4 (N<u>C</u>H_2), 60.3 (OCH_2), 14.3 (<u>C</u>H_3) ppm.

*N(π)-Methyl Urocanic Acid Ethyl Ester (**14**)*

- An excess of methyl iodide (1.99 g, 14 mmol) was added to a solution of (0.40 g, 1.4 mmol) of compound (**16**) in 10 ml of dry acetone. The mixture was stirred for 3 days at room temperature. Evaporation of acetone left an orange oil, compound (**20**) precipited as a yellow powder with a 70% yield (0.42 g) by adding ether; mp 202°C; ^{1}H nmr (DMSO-d6) δ 1.31 (t, J=7.1 Hz, 3H, CH_2-C<u>H</u>$_3$), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 6.11 (s, 2H, NCH_2), 4.04 (s, 3H, NCH_3), 6.69 (AB, J=16 Hz, 1H, H_a), 7.71 (AB, J=16 Hz, 1H, H_b), 7.6-8.1 (m,

5H, phenyl), 8.31 (s, 1H, H_d), 9.21 (s, 1H, H_c) ppm . Anal. Calcd for $C_{17}H_{19}N_2O_3I$: C, 47.90; H, 6.57; N, 4.49. Found : C, 47.54, H, 6.49; N, 4.38. - Deprotection was carried out as for compound (**19**) affording product (**14**) with a 98% yield ; ir ν 1700(C=O), 1680(C=C) cm^{-1}; uv (CH_3OH) λmax 300nm (ε 20875) ; ^1H nmr ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H, CH_3-CH_2), 4.30 (q, J=7.1 Hz, 2H, OCH_2), 3.71 (s, 3H, NCH_3), 6.32 (AB, J=15 Hz, 1H, H_a), 7.48 (AB, J=15 Hz, 1H, H_b), 7.41 (s, 1H, H_d), 7.51 (s, 1H, H_c) ppm ; ^{13}C nmr ($CDCl_3$) δ 166.4 (C_1), 140.1 ($C_{2'}$), 129.0 ($C_{5'}$), 128.5 (C_3), 118.5 (C_2), 61.4 (CH_2), 32.9 (NCH_3), 14.2 (CH_3) ppm . Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55 . Found : C, 60.16, H, 6.75; N, 15.68.

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