Pyrylium Salts with Long Alkyl Substituents, II [1]

2,4-Dimethyl-6-undecylpyrylium Perchlorate and Derived Pyridinium Salts

Mariana Bogatian, Calin Deleanu, Gheorghe Mihai, and Teodor Silviu Balaban*

Center of Organic Chemistry of the Roumanian Academy Splaiul Independentei 202 B, 71141 Bucharest, PO 15/258, Roumania

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Pyrylium Salts, Pyridinium Salts, Synthetic Amphiphiles, NMR Spectra

The crystalline title pyrylium salt was obtained by $SnCl_4$ catalysed acylation of mesityl oxide with lauroyl chloride followed by treatment with perchloric acid and column chromatography. This new pyrylium salt was converted in high yields into the corresponding pyridine and N-substituted pyridinium salts (N-methyl, N-phenyl, N-(4-*n*-butylphenyl), and N-dodecyl) whose proton (300 MHz) and carbon-13 (75 MHz) NMR spectra are presented.

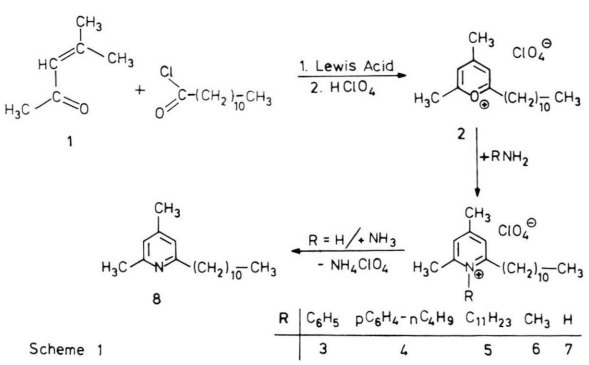
Introduction

One long aliphatic (lipophilic) chain attached to strongly polar (hydrophilic) groups leads to compounds with tensioactive properties. These are due either to micelar aggregates or to membranes. Two long lipophilic chains attached to one polar group lead to amphiphiles, which can form bilayer membranes [2]. Some such synthetic analogs of biomembranes have been prepared and their catalytic activity has been investigated and compared with that of phospholipids and lecithins [3]. Reviews on this field explored sistematically by Kunitake and coworkers are available [4].

Pyrylium salts substituted with long alkyl sidechains are of synthetic interest due to the easy conversion into pyridinium salts [5] which are analogs of the intensively studied ammonium salts amphiphiles [6]. Also, the rich pyrylium chemistry [7] allows functionalization to other a-, carbo- or hetero-cyclic compounds. The only pyrydinium compounds with lipophilic groups known until now had the alkyl chain bonded directly to the nitrogen atom, due to their easy preparation by quaternisation of the corresponding aromatic azines. In a previous paper [1] we have synthesized a pyrylium salt having an eleven carbon γ-alkyl side-chain stemming from hexahydropseudoionone, and some pyridinium salts derived therefrom. In the present paper we describe a pyrylium salt having a linear eleven carbon α-alkyl side-chain and pyridinium salts derived therefrom.

Results and Discussion

The acylation of mesityl oxide (**1**) was effected with lauroyl chloride of comercial source, by known methods [8]. When $AlCl_3$ was used as acylating catalyst, the yields were low (< 5%) due to the poor isolation of the desired title salt **2,** while with the weaker Lewis acid $SnCl_4$, the yields (of several runs) were consistently higher, although globaly modest (12–18%). However, the starting materials are cheap and available in bulk quantities. For other acylations of mesityl oxide with acyl chlorides and Lewis acids, the presence of carbon disulfide as solvent, or dispersion medium, was found to be beneficial for the yield in pyrylium salt [8c]. In our case, the use of carbon disulfide as solvent, did not improve the yields in which the desired reaction product could be isolated, irrespectively of the catalyst used ($AlCl_3$ or $SnCl_4$).



Scheme 1

* Reprint requests to Dr. T. S. Balaban, 1992–1993 Alexander von Humboldt fellow, Institut für Organische Chemie, Technische Hochschule Darmstadt, Petersenstraße 22, D-W-6100 Darmstadt.

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The fact that the title compound was not described before, albeit attempted preprations under similar conditions [9], may be due to the rather difficult separation of the desired salt from the complex acylation mixture, after aqueous decomposition. The main components of this mixture are the fatty acid formed by hydrolysis of unreacted lauroyl chloride and products arising from the intermolecular condensation of mesityl oxide. The latter components are usually of higher molecular mass and can be separated by filtration of the reaction mixture. The separation of the lauric acid from the pyrylium salt is more difficult and could be achieved only by column cromatography.

Reactions with ammonia or primary amines gave the corresponding pyridinium salts **3–7,** as shown in Scheme 1. The free pyridine **8** is obtained as an oil from its pyridinium salt **7,** by treatment with excess of ammonia.

Two methods were employed for the conversion into pyridinium salts: either the direct reaction of pyrylium salts with amines in boiling alcohol (Method A), or reaction at room temperature in methylene chloride in the presence of triethylamine (Method B), according to the method optimised by Katritzky [5]. The higher molecular mass pyridinium salts **4** and **5** could only be obtained by the latter method. The failure of the former procedure is due to the very high solubility of these salts, even in weakly polar solvents (such as diethyl ether) which are usualy used to precipitate organic salts from alcoholic solutions.

The N-dodecyl-2,4-dimethyl-6-undecylpyridinium salt **5,** is insoluble in deionized water but upon sonication (1 min) forms emulsions which are stable for several weeks, similarly to ammonium salts which were proven to form stable bilayer membranes [2,4,6].

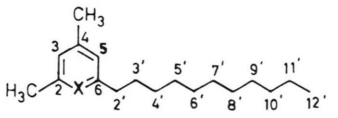
The good solubility in $CDCl_3$ of the pyrylium and pyridinium salts **2–7** allow a comparison of the NMR chemical shifts in these compounds without the need of taking into account solvent effects. Tables I and II present the proton and carbon-13 chemical shifts, respectively, for the new compounds.

The assignment of the proton signals was in most cases straightforward. The β-heteroaromatic ring protons were unambigously assigned from difference nOe spectra by irradiating the α-methyl and α-methylene groups in the salts **2** and **5.** For

Table I. ^{1}H NMR chemical shifts (δ, ppm) at 300 MHz of compounds **2–8** in $CDCl_3$.

Compound	**2**	**3**	**4**	**5**	**6**	**7**[a]	**8**
R	–	C_6H_5	pC_6H_4-C_4H_9	$C_{12}H_{25}$	CH_3	H	–
Protons							
3-H	7.82[b]	7.65	7.66	7.55[b]	7.50	7.35	6.80
5-H	7.73[b]	7.57	7.57	7.45[b]	7.39	7.35	6.80
2-CH_3	2.91	2.36	2.36	2.85	2.79	2.69	2.50
4-CH_3	2.73	2.65	2.64	2.54	2.53	2.59	2.28
2′-CH_2	3.11	2.54	2.56	2.98	3.02	2.91	2.72
3′-CH_2	1.84	1.59	1.58	1.77	1.74	1.74	1.68
4′-CH_2	1.38	1.15	1.17	1.47	1.45	1.27	1.30
5′···11′-CH_2	1.26	1.15 and 1.23	1.17 and 1.23	1.26	1.26–1.38	1.27	1.26
12′-CH_3	0.88	0.88	0.88	0.88	0.88	0.88	0.88
Aromatic – 2″, 6″		7.44	7.33[c]				
3″, 5″		7.67	7.45[c]				
4″		7.67	–				
Aliphatic – 1″-CH_2			2.74	4.28			
2″-CH_2			1.67	1.77			
3″-CH_2			1.40	1.47			
ω″-CH_3			0.96	0.88	4.08		

[a] Trifluoroacetic acid was added to a $CDCl_3$ solution of **8;** [b] assignment based on nOe difference spectra; [c] doublet, J = 8 Hz.



X = $O^{\oplus}$, $N^{\oplus}$–R, N

Table II. ^{13}C NMR chemical shifts (δ, ppm) at 75.48 MHz of compounds **2–8** in $CDCl_3$.

Compound	**2**	**3**	**4**	**5**	**6**	**7**[a]	**8**
R	–	C_6H_5	pC_6H_4–C_4H_9	$C_{12}H_{25}$	CH_3	H	–
Carbon atoms							
C-2	177.65[b]	154.88	155.03	154.20	155.19	152.91	157.05
C-4	174.58[b]	159.97	159.71	157.78[b]	158.05[d]	161.45	148.12
C-6	180.84[b]	158.45	158.60	157.34[b]	157.45[d]	157.19	161.44
C-3	124.26[c]	128.08	128.00[c]	129.04[c]	128.13	126.16	121.67
C-5	122.78[c]	126.52	126.52[c]	127.28[c]	126.60	124.98	120.57
2-CH_3	23.72	22.36[c]	22.34[c]	21.28[c]	21.65[d]	22.25	23.87[c]
4-CH_3	21.40	22.21[c]	22.15[c]	21.68[c]	21.93[d]	19.35	20.94[c]
2′-CH_2	34.79	34.02	33.95	33.13	34.02	33.79	38.00
3′-CH_2	27.05	28.64	28.69	28.78	27.68	28.78	30.25
10′-CH_2	31.88	31.88	31.87	31.91	31.90	32.20	31.95
11′-CH_2	22.66	22.66	22.65	22.68	22.67	22.94	22.70
12′-CH_3	14.09	14.09	14.08	14.11	14.11	14.11	14.12
Aromatic – 1″		137.93	135.26				
2″, 6″		126.09	125.80				
3″, 5″		131.76	130.70				
4″		131.75	146.76				
Aliphatic – 1″-CH_2			35.29	51.97			
2″-CH_2			33.17	28.78			
3″-CH_2			22.34	26.70			
ω″-CH_3			13.86	14.09	39.38		

[a] Trifluoroacetic acid was added to a $CDCl_3$ solution of **8;** [b] assignment based on COLOC spectra; [c] assignment based on H–C COSY spectra; [d] assignments may be interchanged.

the other compounds, the 3-proton is analogously presumed to be more deshielded than the 5-proton which is neighbouring the 6-undecyl group.

With the aromatic proton signals ascertained, the assignments for the 3 and 5 heterocyclic ring carbons could also be made unequivocally from H–C COSY spectra. The assignments for the other carbon atoms of the heterocyclic ring confirm the previous ones [10] in which the order of deshielding in pyrylium salts is $\alpha > \gamma$, while in pyridinium salts and alkyl substituted pyridines, the reverse is true (γ carbons more deshielded then α carbons).

The aromatic ring current of various aryl groups in N-aryl-2,4,6-trimethylpyridinium salts has been evaluated from the shielding of the 2- and 6-methyl groups in ^1H NMR spectra [11], or of the 2- and 6-carbon atoms in the ^{13}C NMR spectra [12]. In the N-phenyl-2,4-dimethyl-6-undecylpyridinium perchlorate **3,** the phenyl ring shields as expected, strongly (by more than 0.4 ppm), the protons of both the 2-methyl and the 6-methylenic groups (the latter is denoted in Table I as 2′-CH_2, in order to preserve the numbering of the lauric acid moiety), comparatively to the N-methyl or N-dodecyl pyridinium salts. When comparing the carbon chemical shifts of the same groups, these apparently suffer only minor (< 1 ppm) shieldings. Also the 2- and 6-carbon atoms are under 1 ppm more shielded in the N-phenyl substituted compounds **3** and **4** comparatively to the N-dodecyl (**5**) or N-methyl (**6**) pyridinium salts. We conclude that the proton spectra are better suited for judging the aromatic ring current in N-aryl-2,4,6-trimethylpyridinium salts than the carbon spectra where the shielding effects are much smaller. Conversely, if one looks at the shielding of the aromatic pyridinium ring which affects the N-phenyl ring in **3,** one notes that both the *ortho*-phenyl protons and carbons are more shielded, accounting for the assignments in Tables I and II.

In the carbon spectra, five of the eleven carbon atoms (2′, 3′, 10′, 11′ and 12′) of the undecyl sidechain have signals unambigously assigned from the H–C COSY spectra (as shown in Table II). For the remaining seven carbon atoms, as they res-

onate in a narrow range (< 1 ppm) around the value of 29 ppm, and for which five or six distinct peaks are observed, the assignment is not evident.

A detailed study of the $1/T_1$ relaxation rates of the carbon atoms in such side-chains will be informative for their mobility. Aggregation in solution is expected to affect this mobility. We hope to learn more about membranar and micellar agregates, which are also of biochemical importance, from future relaxation rate studies on such simple model compounds, with known tensioactive properties.

Experimental

Routine proton NMR spectra were recorded at 60 MHz on a Varian A-60A instrument while the high field spectra were recorded on a superconducting Varian Gemini 300 apparatus operating at 300 MHz for protons and 75.48 MHz for ^{13}C nuclei. Mass spectra for the pyridine **8** were recorded on a 70-SE VG-Analytical GC-MS instrument. Infrared and ultraviolet spectra were run on Zeiss instruments (UR 20 and SPECORD, respectively). Melting points were measured in open capillary tubes (for the low melting compounds) or on a hot-stage melting point apparatus equipped with a polarizor to check for nematic properties.

2,4-Dimethyl-6-undecylpyrylium perchlorate (**2**)

Anhydrous $SnCl_4$ (96 g, 0.37 moles) was added under stirring and with external cooling (ice and water bath) to lauroyl chloride (80.5 g, 0.37 moles). Then mesityl oxide (30 g, 0.3 moles) was added so that the temperature was maintained between 22 and 25 °C (the ice was removed from the cooling bath). Stirring was continued after completion of addition for seven hours, then the mixture was left over night. The evolution of hydrogen chloride ceased after final heating for five hours at 40 °C under stirring. The reaction mixture was decomposed by pouring over 120 g crushed ice, 12 ml of concentrated aqueous hydrochloric acid and 100 ml diethyl ether. The aqueous layer was separated and extracted twice with 25 ml diethyl ether. The combined organic layers were washed four times with small portions of dilute aqueous hydrogen chloride, after which concentrated (about 70%) aqueous perchloric acid was added. This led to the separation of an upper oily layer which was collected, washed with distilled water and extracted three times with methylene chloride. These extracts were then dried and concentrated. Filtration through a sintered glass frit affords an oil which is transferred to a short, thick, silica gel (Merck) chromatography column. The lauric acid was eluted first (hexane : diethyl ether = 7:1) after which the pyrylium perchlorate **2** was eluted with a mixture of hexane : diethyl ether : methanol = 7:5:0.5. From this fraction, after concentration, the pyrylium salt crystallized as colourless microcrystals (16.6 g), in 12.5% yield (based on mesityl oxide) having m.p. of 66–67 °C.

IR (KBr), cm^{-1}: 625 m, 1100 s, 1550 m, 1640 m, 2850 w, 2920 w.

UV (EtOH), λ_{max}: 242 and 345.

$C_{18}H_{31}ClO_5$ (362.89)
Calcd C 59.57 H 8.61 Cl 9.77%,
Found C 59.35 H 8.77 Cl 10.02%.

Conversion of pyrylium salt **2** *into pyridinium salts* **3** *and* **6** *(Method A)*

A 1.33 molar excess of amine was added to an alcoholic solution of **2** which became instantly deep red. Heating for 30 to 60 min under gentle reflux faded the colour of the reaction mixture into cognac. After cooling, the pyridinium salts were precipitated with hexane and **6** was recrystallized from isopropanol (m.p. 76 °C), while **3** afforded an oil at room temperature which solidified on cooling below −20 °C. The yields in **3** and **6** were 75% and 78%, respectively.

UV (EtOH), λ_{max} (nm): 212, 273 and 330 sh for **3;** 227 and 273 for **6.**

IR (CH_2Cl_2), cm^{-1}: 625 ms, 1100 s, 1600 mw, 1635 m, 2860–3100 w for **3.** IR (KBr), cm^{-1}: 625 ms, 1100 s, 1635 m, 2860 w, 2930 w for **6.**

3: $C_{24}H_{36}ClNO_4$ (438.01)
Calcd N 3.19%,
Found N 3.09%.

6: $C_{19}H_{34}ClNO_4$ (375.93)
Calcd N 3.72%,
Found N 3.65%.

Conversion of pyrylium salt **2** *into pyridinium salts* **4** *and* **5** *(Method B)*

The pyrylium salt **2** (1.3 g, 3.6 mmoles) was dissolved in 25 ml dry methylene chloride to which freshly distilled amine (for **5,** 0.78 g, 4.2 mmoles of dodecylamine) were added. The deep red solution was stirred at room temperature for two hours after which acetic acid (0.65 g, 10.8 mmoles) were added. After stirring for another hour, the orange-brown reaction mixture was treated with 50 ml dilute (1%) hydrochloric acid. The methylene chlo-

ride layer was washed twice with saturated aqueous ammonium chloride solution (to avoid formation of stable emulsions) and dried over anhydrous magnesium sulphate. Solvent evaporation left salt **5** (1.7 g, 85% yield) as a waxy oil which crystallized slowly in the refrigerator (m.p. 35 °C).

UV (EtOH), λ_{max} (nm): 220, 276 and 303 sh for **4;** 227 and 273 for **5.**

IR (CH_2Cl_2), cm^{-1}: 1100 s, 1465 m, 1635, 2855 ms, 2930 s for both **4** and **5. 4** has an additional weak band at 3080 cm^{-1}.

5: $C_{30}H_{56}ClNO_4$ (530.23)
Calcd N 2.64%,
Found N 2.97%.

2,4-Dimethyl-6-undecylpyridine **8**

Pyrylium salt **2** (0.4 g, 1.1 mmoles) was treated with excess aqueous ammonia (20%). Extraction into diethyl ether, drying over NaOH pellets and concentration in vacuo yielded the pyridine **8** as an yellow oil (0.24 g, 83.5%).

IR (CCl_4), cm^{-1}: 1370 m, 1400 m, 1470 m, 1600 ms, 2855 s, 2925 vs.

UV (EtOH), λ_{max}, nm: 220 and 277. On addition of HCl these maxima remain unchanged and a shoulder appears at about 310 nm. GC/MS (*m/z*): 261 (M^+), 232, 204, 190, 176, 162, 148, 134, 121 (100%), 106, 79, 55, 43, 41, 29. The base peak (*m/z*) 121 corresponds to a benzylic type radical cation (or 2,4-dimethyl-aza-tropylium) after a McLafferty fragmentation of the undecyl group and ellimination of decene ($C_{10}H_{20}$).

$C_{18}H_{31}N$ (261.45)
Calcd N 5.32%,
Found N 5.28%.

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