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THE INVENTION OF RADICAL CHAIN REACTIONS. PART XIV. A DECARBOXYLATIVE RADICAL ADDITION TO QUINONES

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Abstract - Irradiation of esters 3 derived from aliphatic or alicyclic carboxylic acids and N-hydroxy-2-thiopyridone in the presence of various quinones gives high yields of the corresponding adducts (e.g. 9) with net loss of carbon dioxide.

Quinone and hydroquinone subunits occur in a wide variety of important natural products including the ubiquinones, vitamins E and K, the tetracycline antibiotics and the anticancer anthracyclines.[1] It is therefore not surprising to find that a tremendous effort has been expended in search of ways for the introduction and further modification of these substructures.[1] Curiously, however, radical additions to quinones have not attracted much attention. Only scattered reports have thus appeared concerning such additions using radicals produced photochemically,[2] by decomposition of boranes[3] or by hydrogen abstraction by the highly reactive alkoxy radicals.[4] Other systems that have also been employed include thermal decomposition of diacylperoxides[5] and decarboxylation of carboxylic acids with lead tetraacetate[6] or with a combination of a silver salt and persulfate.[7]

Although the yields of desired adducts are sometimes high, these various procedures are really limited to rather simple substrates capable of withstanding the harsh and usually strongly oxidative conditions necessary for the generation of the carbon radical. The more useful radical sources based on the chemistry of stannanes and organomercury compounds[8] operate under reducing conditions and are therefore, on the whole, incompatible with the mildly oxidising quinones.

We have recently shown that esters (3 and 4), derived from carboxylic acids and N-hydroxy-2-thiopyridone 1 or N-hydroxythiazolinethione 2 respectively, undergo a smooth decarboxylative rearrangement to sulphides 5 when heated or irradiated.[9] This reaction, which follows the simple radical chain mechanism depicted in Scheme 1 (path A) (illustrated for esters of type 3) has turned out to

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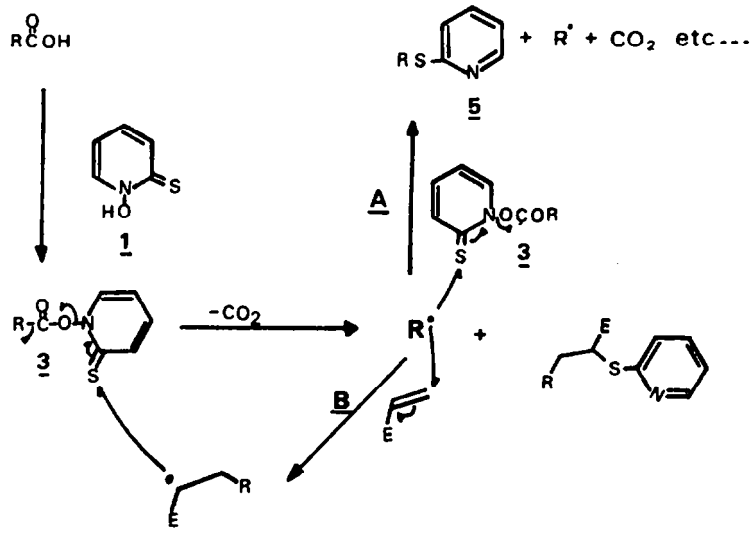
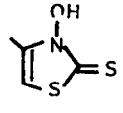
be an exceptionally convenient source of carbon radicals. Primary, secondary and tertiary aliphatic and alicyclic carboxylic acids were shown to undergo a variety of useful transformations based on radical chemistry. For example, in the presence of an electrophilic olefin, the decarboxylation is followed by carbon-carbon bond formation as outlined in Scheme 1, path B.



Scheme 1

As part of our study of this system, we undertook to examine, on one hand, the compatibility of the reaction with quinones and, on the other, the efficiency of an eventual radical addition as compared with the synthetically trivial formation of sulphide 5 through path A. The latter (background reaction) is always in competition with the desired pathway (e.g. path B).

Initial experiments with quinones were disappointing.[9b] Thus reacting the palmitic acid derivative 4a with benzoquinone or 1,4-naphthoquinone gave a complex mixture from which a poor yield of the corresponding adducts 7a (27%) and 8a (26%) could be isolated along with variable amounts of sulphide 6 (18-28%). However, in the course of a parallel mechanistic study[10], we observed that the formation of sulphides (e.g. 6) via the background reaction was quite temperature sensitive and thus could be to some extent, controlled. Furthermore, our initial experiments with the quinones could have been complicated by various redox processes occuring after the radical addition had taken place. If this were true, a lowering of the reaction temperature would probably lead to a simpler mixture more amenable to analysis.



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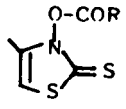

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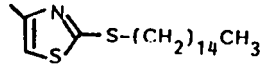
4a R = $CH_3(CH_2)_{14}$-



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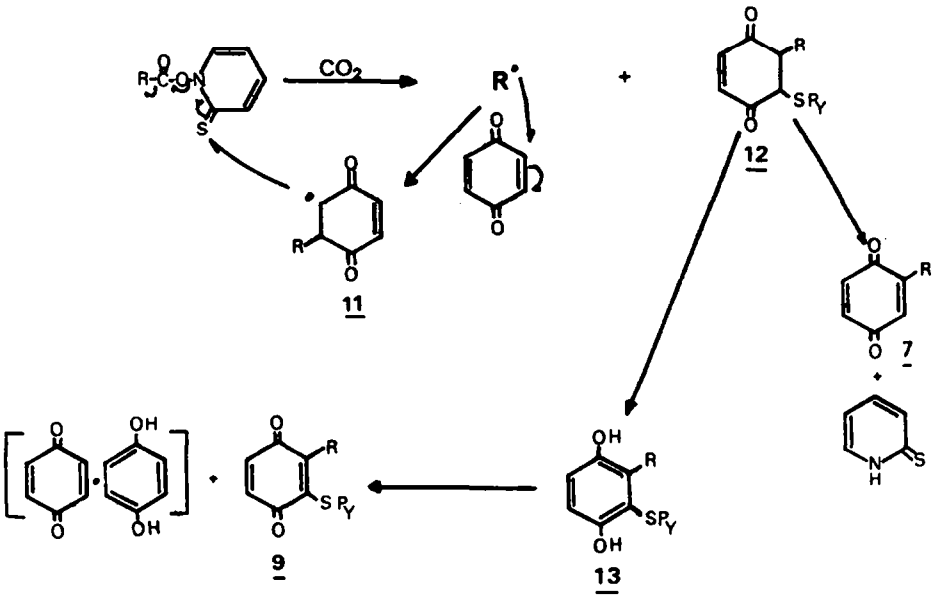
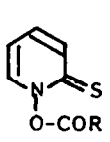
Low temperature decarboxylations are best performed using esters of type 3 which can be conveniently decomposed with visible light from a tungsten lamp. In contrast, derivatives 4 with the thiazoline nucleus, although easier to handle, require U.V. irradiation, which could be a potential complicating factor in this case.

In the event, irradiation of palmitoyl ester 3a at 0°C in dichloromethane in the presence of 5 equivalents of benzoquinone resulted in a much cleaner reaction. The major product, however, turned out to be 9a (77%) and not 7a, as in the initial experiments. The latter was only a minor product (10%) under the present conditions. Quinhydrone was also observed. The mechanism outlined in Scheme 2 is a plausible explanation of the facts. Thus radical addition to the quinone followed by reaction of the intermediate radical 11 with ester 3a produces the "normal" adduct 12. Two pathways are then possible : either aromatisation to give the hydroquinone derivative 13a or elimination of 2-thiopyridone to yield the mnosubstituted benzoquinone 7a. The former process appears to predominate at low temperature. Further oxidation of 13 by the excess benzoquinone leads finally to the isolated quinone 9a and to quinhydrone. The following observation is in accord with such a reaction scheme. If only a slight excess of benzoquinone (1.1 eq.) is employed, the reaction furnishes two main products : 9a (minor) and a more polar major compound identified as the intermediate hydroquinone derivative 13. When the latter is mixed with 3 eq. of benzoquinone in dichloromethane a rapid reaction ensues to give 9a and quinhydrone. This conversion reflects the higher oxidation potential of benzoquinone as compared with a substituted quinone such as 9a.[1]



Scheme 2



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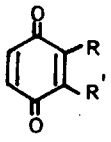
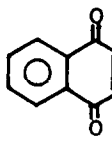
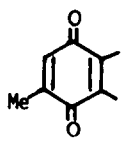


7 R' = H
9 R' =



8 R' = H
10 R' =



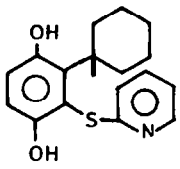
15 R' = H
16 R' =

3, 7, 8, 9, 10, 15, 16

a, R = $CH_3(CH_2)_{14}$-
b, R = Ph_2CHCH_2-
c, R = cyclohexyl
d, R = $(PhCH_2)_2CH$-
e, R = 1-methylcyclohexyl

The scope of the radical addition was next examined using a variety of esters 3 and quinones. The results are collected in the Table. Yields are generally high and, on the whole, a similar pattern of products is obtained as with the first experiment. One exception is with ester 3e derived from 1-methyl cyclohexane carboxylic acid (Table, entry 5). The reaction in this case does not proceed beyond the substituted hydroquinone 14 stage. The oxidation step is presumably impeded by the steric bulk of the newly formed quaternary centre. With 2-methyl-benzoquinone one regioisomer of 15 or 16 is observed resulting from radical attack at position 5 which is the most favoured sterically and electronically.[7b]

Another subtle facet of the reaction was revealed on examination of 2-methylnaphthoquinone as the radical trap. When the crude reaction mixture was first subjected to column chromatography, the adduct 17 was isolated in only 20% yield. Further elution with a more polar solvent gave fractions which also contained the desired product. This behaviour suggested the presence of an unstable intermediate undergoing decomposition on the silica. Indeed repeated chromatography raised the yield to over 50%. The presence of this intermediate, of probable structure 18 was not detected by TLC because of strong interference by the excess of the highly coloured 2-methylnaphthoquinone. Again for steric reasons, departure of 2-thiopyridone is hampered under normal reaction conditions, but is facilitated by contact with the slightly acidic silica.



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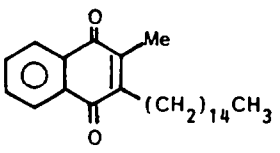

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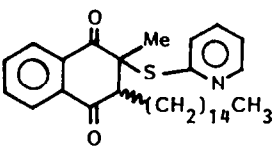

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Entry	Ester 3	Quinone (equivalents)	Products Yield (%)
1	3a	Benzoquinone (5)	7a (10), 9a (77)
2	3b	" (7)	7b (10), 9b (80)
3	3c	" (5)	7c (10), 9c (78)
4	3d	" (5)	7d (7), 9d (83)
5	3e	" (5)	14 (79)
6	3a	Naphthoquinone (5)	8a (12), 10a (77)
7	3b	" (5)	8b (13), 10b (69)
8	3a	2-Methylbenzoquinone (5)	15a (15), 16a (71)
9	3b	" (5)	15b (25), 16b (60)
10	3c	" (5)	15c (21), 16c (21)
11	3a	2-Methylnaphtoquinone (5)	17 (20)

The general absence of sulphides 5, arising by decarboxylative rearrangement, reflects the strong radicophilicity of the quinones in accord with known kinetic data.[11] It also confirms our earlier observations concerning the dramatic effect of temperature on the course of the decarboxylation process.

The synthetic potential of the reaction is clearly evident. The nature of the products may be easily altered by simply varying the amounts of quinones. In addition, the mildness of the reaction conditions coupled with the demonstrated compatibility of the decarboxylation method with a wide variety of functional groups should allow the elaboration of more complex and even fragile quinonoid systems. In addition, the attachment of the 2-thiopyridyl residue to the quinone may well permit further interesting chemistry of either a radical or a nucleophilic nature. Further oxidation to sulphoxide or to sulphone would further enrich the gamut of reactions which are possible.

Experimental

Melting points are uncorrected. Unless otherwise stated, NMR data (60 MHz) are for deuterochloroform solutions with tetramethylsilane as internal standard. I.R. spectra are of dichloromethane solutions unless stated to the contrary. N-Hydroxypyridine-2-thione 2 and its sodium salt are available commercially.

General Procedure for the Preparation of Esters 3.- (Note : These compounds are sensitive to light and moisture. The reaction vessel, chromatography column etc... should therefore be covered with aluminium foil). To a solution of the carboxylic acid chloride (100 mmole; prepared from the corresponding acid and oxalyl chloride using standard methods) in dry, degassed dichloromethane (50 ml) was added the sodium salt of N-hydroxypyridine-2-thione 2 (10.5 mmole). After stirring for 1-2 hours at room temperature under an inert atmosphere, the reaction mixture was rapidly filtered and the solvent evaporated under vacuum without heating. The yellow residue may be used as such or further purified by filtration through a short silica column.

General Method for the Preparation of Quinone Derivatives.- An ice-cold stirred solution of ester 3 (1 mmole) and the appropriate quinone (5-7 mmoles, see Table) in degassed dichloromethane (20 ml) was irradiated with a 300 W tungsten lamp for 30 min. under an inert atmosphere. The solvent was then evaporated under reduced pressure and the residue purified by chromatography on silica using a solvent gradient, generally pentane:dichloromethane then dichloromethane then dichloromethane:ethyl acetate mixtures. In some cases, analytical samples of the substituted quinones produced could not be easily secured. Use was therefore made of high resolution mass spectrometry.

3-(1-pentadecyl)-2-(pyridine-2-thiyl) 1,4-benzoquinone 9a.- Irradiation of ester 3a (143 mg, 0.39 mmole) and p-benzoquinone (290 mg, 2.7 mmole) gives 9a (130 mg, 77%) as orange red crystals after chromatography using dichloromethane:pentane mixtures (1:1 -> 9:1); m.p.: 49-53°C (from methanol); ν_{max} : 1665, 1610, 1585 cm^{-1}; m/e: 427 (M^+); δ_H: 6.80-8.55 (4H, m), 6.81 (2H, m), 2.46 (2H, m), 0.87-1.3 (29H, m) (Found: C, 72.80; H, 8.55. Calc. for $C_{26}H_{37}NO_2S$: C, 73.02; H, 8.72%).

A small amount of quinone 7a (12.5 mg, 10%) was isolated from the first fractions (m.p.: 70-72°C from methanol; lit.[9b] m.p.: 71-72°C).

3-(2,2-Diphenylethyl)-2-(pyridine-2-thiyl)-1,4-benzoquinone 9b.- This compound (150 mg, 80%) was isolated as orange crystals after chromatography (dichloromethane:ethyl acetate 7:3) from the reaction of ester 3b (172 mg) and p-benzoquinone; m.p.: 131-135°C (from methanol); ν_{max} : 1665, 1600, 1580 cm^{-1}; δ_H: 8.24 (1H, d), 6.90-7.80 (13H, m), 6.67 (2H, bs), 4.36 (1H, t, J = 7.5 Hz), 3.57 (2H, d, J = 7.5 Hz); m/e (M^+): found 397.1144; calc. for $C_{25}H_{19}NO_2S$: 397.1137.

Less polar fractions (dichloromethane:pentane 1:1) yielded small amounts of 7b (10 mg, 7%) as a yellow oil. This product was identified spectroscopically; ν_{max} : 1665, 1610, 1585 cm^{-1}; m/e: 288 (M^+); δ_H: 7.28 (10H, m), 6.80 (2H, m), 6.32 (1H, m), 4.18 (1H, t, J = 8 Hz), 3.22 (2H, d, J = 8 Hz).

3-Cyclohexyl-2-(pyridine-2-thiyl)-1,4-benzoquinone 9c.- This compound (179 mg, 83%) was isolated as red crystals after chromatography (dichloromethane:ethyl acetate 4:1) from the reaction of ester 3c (171 mg) and p-benzoquinone (390 mg); m.p. 100-101°C (from methanol); ν_{max} (Nujol): 1665, 1585, 1565 cm^{-1}; δ_H: 8.12 (1H, m), 6.85-7.60 (3H, m), 6.65 (2H, bs), 3.20 (1H, m), 0.9-2.31 (10H, m); m/e (M^+): found 299.0970; calc. for $C_{17}H_{17}NO_2S$: 299.0980.

The less polar fractions (dichloromethane:pentane 1:1) gave small amounts of 7c as a yellow oil (9 mg, 7%); ν_{max} : 1665, 1605 cm^{-1}; m/e: 190 (M^+); δ_H: 6.85 (2H, bs), 6.63 (1H, m), 2.75 (1H, m), 0.85-2.05 (10H, m).

3-(1,3-Diphenylpropan-2-yl)-2-(pyridine-2-thiyl)-1,4-benzoquinone 9d.- This compound was obtained as orange-red crystals (129 mg, 78%) after chromatography (dichloromethane:ethyl acetate 9:1) from the reaction of ester 3d (140 mg) and p-benzoquinone (220 mg); m.p.: 114-115°C (from methanol); ν_{max} : 1665, 1585, 1565 cm^{-1}; δ_H: (200 MHz); 8.29 (1H, bs), 7.19 (10H, bs), 6.90-7.80 (3H, m), 6.74 (2H, bs), 4.19 (1H, m), 3.20 (4H, m); m/e (M^+): found: 411.1292; calc. for $C_{26}H_{21}NO_2S$: 411.1292.

The minor 7d (12 mg, 10%) was isolated from the less polar fractions (dichloromethane:pentane 1:1) as yellow crystals. It had a m.p. of 87-90°C (from methanol); ν_{max} : 1665, 1605 cm^{-1}; δ_H: (200 MHz): 7.27 (10H, m), 6.96 (2H, bs), 6.45 (1H, m), 3.55 (1H, qn, J = 7 Hz), 2.91 (4H, m); m/e (M^+) : found 302.1310; calc. for $C_{21}H_{18}O_2$: 302.1307.

3-(1-Methylcyclohexyl)-2-(pyridine-2-thiyl)-1,4-dihydroxybenzene 14.- This compound was obtained a a yellow oil (190 mg, 79%) after chromatography (dichloromethane:ethyl acetate) from the reaction of ester 3e (192.5 mg) and p-benzoquinone (415 mg); ν_{max} :3350, 1605 (weak), 1585, 1565 cm^{-1}; δ_H (200 MHz): 8.45 (1H, m), 7.50 (1H, m), 7.10 (2H, m), 6.78 (1H, d, J = 10 Hz), 6.68 (1H, d, J = 10 Hz), 1.2-1.7 (10H, broad), 1.00 (3H, s)); m/e (M^+): found 315.1287; calc. for $C_{18}H_{21}NO_2S$: 315.1293.

3-Pentadecyl-2-(pyridine-2-thiyl)-1,4-naphthoquinone 10a.- This compound was obtained as yellow crystals (141 mg, 77%) after chromatography (dichloromethane: ethyl acetate) from the reaction of ester 3a (139 mg) and 1,4-naphthoquinone (300 mg); m.p.: 83-85°C (from methanol); ν_{max} (nujol): 1670, 1600 cm^{-1}; δ_H: 8.60 (1H, bd), 6.81-8.19 (6H, m), 2.88 (2H, m), 0.86-1.26 (26H, m); m/e (M^+): found 477.2690; calc. for $C_{30}H_{39}NO_2S$: 477.2701.

From the less polar fractions (dichloromethane:pentane) a small amount of 8a (17 mg, 12%) could be isolated as yellow crystals with a m.p. of 71°C (from methanol; lit.[9b] m.p.: 71-72°C).

3-(2,2-Diphenylethyl)-3-(pyridine-2-thiyl)-1,4-naphthoquinone 10b.- This compound was isolated as yellow crystals (240 mg, 69%) after chromatography (dichloromethane:ethyl acetate 4:1) from the reaction of ester 3b (259 mg) and 1,4-naphthoquinone (610 mg); m.p.: 122-127°C (from methanol); ν_{max} : 1670, 1600, 1580, 1565 cm^{-1}; δ_H (200 MHz): 7.09-8.35 (18H, m), 4.54 (1H, t, J = 7 Hz), 3.78 (2H, d, J = 7 Hz). (Found: C, 77.99; H, 5.02. Calc. for $C_{29}H_{19}NO_2S$: C, 77.84; H, 4.73%).

From the less polar fractions (dichloromethane:pentane 1:1) a small amount of 8b (34 mg, 13%) was isolated as yellow crystals with a m.p. of 95-100°C (from methanol); ν_{max} : 1670, 1625 cm^{-1}; δ_H (200 MHz): 7.05-8.08 (14H, m), 6.46 (1H, s), 4.39 (1H, t, J = 7 Hz), 3.34 (2H, d, J = 7 Hz); m/e (M^+): found 338.1304; calc. for $C_{24}H_{18}O_2$: 338.1307.

6-Methyl-3-pentadecyl-2-(pyridine-2-thiyl)-1,4-benzoquinone 16a.- This compound was obtained as orange crystals (90 mg, 71%) after chromatography (dichloromethane:ethyl acetate 4:1) from the reaction of ester 3a and 2-methyl 1,4-benzoquinone; m.p.: 50-52°C (from methanol); ν_{max} : 1665, 1585, 1565 cm^{-1}; δ_H: 6.98-8.63 (4H, m), 6.73 (1H, m), 2.81 (2H, m), 2.07 (3H, m), 0.87-1.26 (29H, m); m/e (M^+): found 441.2725; calc. for $C_{27}H_{39}NO_2S$: 441.2702.

From the less polar fractions, a small amount of 15a was obtained as pale yellow crystals (15 mg, 15%) with a m.p. of 38-40°C (from methanol); ν_{max} : 1665, 1620, 1605 cm^{-1}; δ_H: 6.67 (1H, s), 6.50 (1H, m), 2.40 (2H, m), 2.02 (3H, s), 0.87-1.30 (29H, m); m/e (M^+): found 332.2719; calc. for $C_{22}H_{36}O_2$: 332.2716.

3-(2,2-Diphenylethyl)-6-methyl-2-(pyridine-2-thiyl)-1,4-benzoquinone 16b.- This compound was obtained as red-orange crystals (211 mg, 60%) after chromatography (dichlromethane:ethyl acetate 4:1) from the reaction of ester 3b (287 mg) and 2-methyl benzoquinone (520 mg); m.p.: 65-68°C (from ethanol); ν_{max} : 1665, 1645, 1605, 1585, 1565 cm^{-1}; δ_H: 7.12-8.20 (14H, m), 6.38 (1H, m), 4.31 (1H, t, J = 8 Hz), 3.48 (2H, d, J = 8 Hz), 1.90 (3H, m); m/e: 411 (M^+).

From the less polar fractions, a small amount of 15b was obtained as a red oil (64 mg, 25%), ν_{max} : 1660, 1605, 1585 cm^{-1}; δ_H: 6.92 (10H, m), 6.51 (1H, s), 6.38 (1H, m), 4.00 (1H, t, J = 7 Hz), 3.12 (2H, d, J = 7 Hz), 2.02 (3H, d).

3-Cyclohexyl-6-methyl-2-(pyridine-2-thiyl-)-1,4-benzoquinone 16c.- This compound was obtained as orange crystals (270 mg, 64%) after chromatography from the reaction of ester 3c (319 mg) and 2-methyl-1,4-benzoquinone (820 mg); m.p.: 75-80°C (from methanol); ν_{max} : 1665, 1605, 1585, 1565 cm^{-1}; δ_H (400 MHz); 6.80-8.20 (4H, m), 6.48 (1H, m), 3.15 (1H, m), 2.01 (3H, m), 0.95-2.20 (10H, m); m/e (M^+): found 313.1132; calc. for $C_{18}H_{19}NO_2S$: 313.1136.

A small amount of 15c was isolated from the less polar fractions as a yellow oil (60 mg, 21%); ν_{max} : 1665, 1620 cm^{-1}; δ_H: 6.75 (1H, s), 6.60 (1H, m), 2.74 (1H, m), 2.14 (3H, m), 0.82-2.32 (10H, m).

3-Methyl-2-pentadecyl-1,4-naphtoquinone 17.- This compound was obtained as pale yellow crystals (50 mg, 20%) after chromatography (dichloromethane-pentane) from the reaction of ester 3a (240 mg) and 2-methyl-1,4-naphthoquinone (565 mg); m.p. 92-95°C (from methanol); ν_{max} 1675, 1630, 1605 cm^{-1}; δ_H: 7.40-8.05 (4H, m), 2.55 (2H, m), 2.13 (3H, s), 0.83-1.28 (29H, m); m/e: 382 (M^+).

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