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The Reaction of Thionitrites with Barton Esters : a Convenient Free Radical Chain Reaction for Decarboxylative Nitrosation.§

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Abstract: Tertiary thionitrite esters react with primary and secondary O-acyl derivatives of N-hydroxy-2-thiopyridone to give *trans* nitroso dimers as the principal products of a free radical chain reaction.

There is considerable current research interest in the structure and chemical reactivity of thionitrite esters, particularly in view of their role as potential biocatalysts and reagents for the storage, transport, and release of biologically fundamental nitric oxide.[1] While an elegant series of studies by Williams[2] has established the vital role of copper ion in the induced homolysis of thionitrites, much less is known of their reactivity with simple carbon centered radicals in terms of the efficiency of nitric oxide transfer from sulphur to carbon.

With the above framework in mind, and also as a part of our interest in the development of new free radical chain reactions for organic synthesis, we now describe, in full detail,[3] the results of a study of the reactions of thionitrite esters with the O-acyl thiohydroxamate derivatives (**1**) of carboxylic acids. The selection of a Barton ester (**1**) as a substrate was made on the basis of their proven utility as precursors for the decarboxylative generation of carbon centered radicals under very mild conditions.[4] Thus, as shown for the propagation sequence outlined in Scheme 1, we reasoned that the addition of a thiyl radical to the radicophilic thiocarbonyl group of compound (**1**) would be followed by the normal decarboxylative sequence to give an alkyl radical which could then undergo either a direct S_H2 displacement reaction with the thionitrite, or, more probably, an addition-elimination sequence *via* (**2**) to produce in the first instance, a monomeric nitroso compound (**3**) with concomitant liberation of the chain carrying thiyl radical.

§ Respectfully dedicated to the memory of our dear friend and mentor, D. H. R. B.

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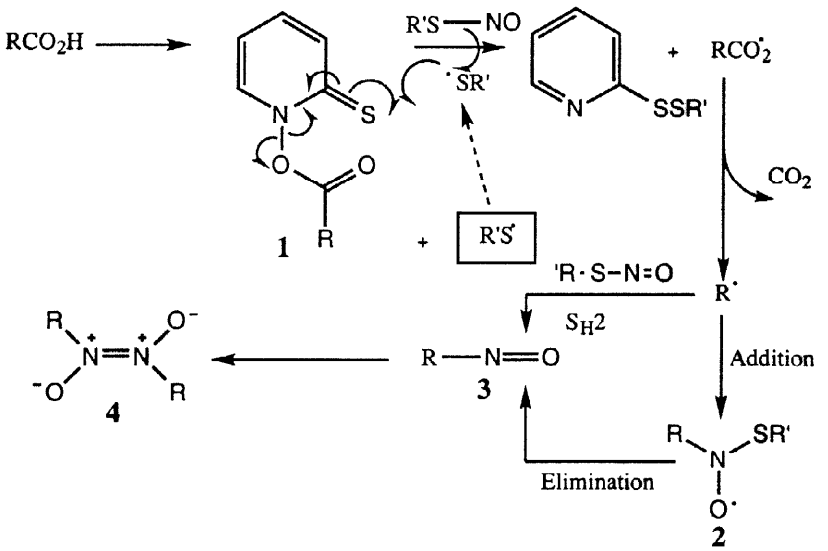


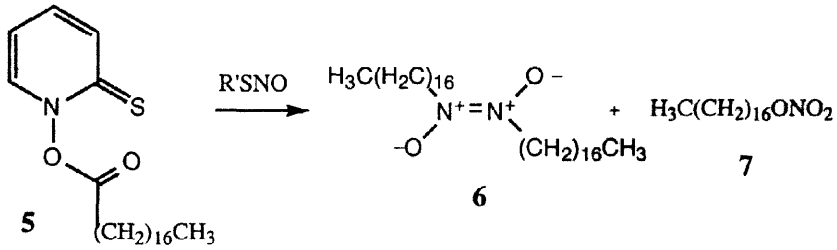
Scheme 1

At first sight, in view of the known propensity of monomeric nitroso compounds (**3**) to function as radical scavengers to give nitroxides, it could be argued that such a proposed chain sequence is severely flawed. Close examination of the Barton nitrite photolysis[5] however, which also leads to a nitroso intermediate as the primary product of a radical reaction, reveals that an unusually facile dimerisation to give (**4**) is the predominant fate of monomer (**3**), and is even the preferred pathway over tautomerisation to an oxime when this is a possible alternative.From a synthetic standpoint, the above reaction therefore provides a simple route for the replacement of a carboxylic acid by a new carbon nitrogen bond under neutral free radical conditions. Decarboxylative nitrosation has previously been accomplished *via* a Borodin-Hunsdiecker[6] like strategy involving *in situ* generation of acyl nitrites from the reaction of nitrosyl chloride with silver, lead or mercury salts of carboxylic acids. Most recently, a very intriguing and elegant non -chain radical reaction for decarboxylative amination using acylthiohydroxamates (**1**) in the presence of 3-phenyl-3-(trifluoromethyl)diazirine as a radical trap was reported by Barton.[7]

In the first instance, we elected to carry out a systematic study using the Barton ester (**5**) derived from n-octadecanoic acid and three different tertiary thionitrite esters which were readily prepared by nitrosation of the corresponding mercaptan. (Scheme 2 and Table). Examination of the results obtained confirms that the formation of the desired *trans* nitroso dimer (**6**) is the dominant process, and that the overall efficiency is not significantly influenced by the nature of the tertiary thionitrite. However, highly crystalline and readily prepared trityl thionitrite[8], since it was more stable than the other two tertiary thionitrites, proved to be the most practical reagent for routine use.

In common with other free radical reactions of Barton esters, reactions can be run either under photochemical conditions using the light from a 250 Watt tungsten lamp, or thermally.It was also of interest to note that reaction can occur, albeit over a four day period, at room temperature (20^0) in the dark (Method C). The progress of the reaction can be simply monitored by the disappearance of the dark green colour of the thionitrite until a pale yellow solution persists.

Even although carefully degassed solutions were used, we were intrigued by the formation of the nitrate ester (**7**) as a secondary byproduct. This was initially believed to arise from the capture of a carbon centered radical, first by adventitious oxygen and then by the thionitrite to give a pernitrite ester which underwent subsequent rearrangement. However, the observation that an experiment conducted using 2.2 molar equivalents of thionitrite reagent led to a significant decrease in the isolated yield of the nitroso dimer (**6**) together with a concomitant increase in the production of the nitrate ester (**7**) provides strong presumptive evidence that the known reaction[9] of a nitroso compound with two further molecules of nitric oxide, or an equivalent precursor thereof, to give a diazonium nitrate which then loses nitrogen may be a more reasonable explanation (Scheme 3). The unusual caveat that an excess of thionitrite as reagent should not be used therefore follows.

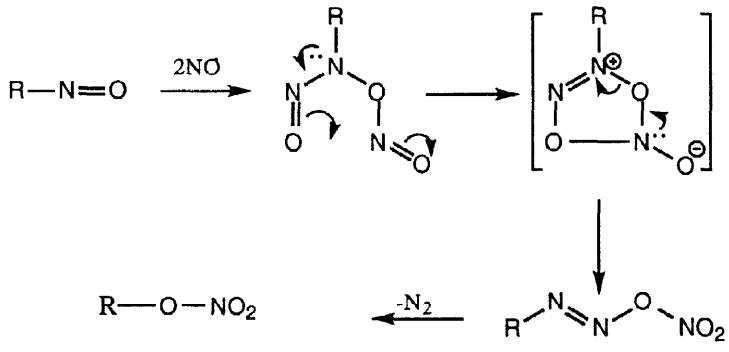


Scheme 2.

Table: The Reaction of Barton Ester (5) with Thionitrite Esters.

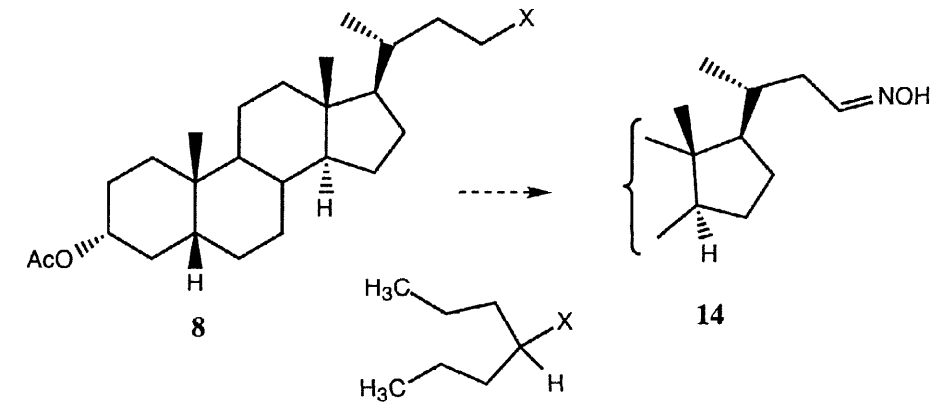
R'	Equiv. of R'SNO	Method	Yield (6) (%)	Yield (7) (%)
Ph_3C	1.03	A	47.3	4.4
Ph_3C	1.03	B	54.7	3.7
Ph_3C	2.2	B	15.7	15.8
Ph_3C	0.97	C	39.7	8.0
1-Adamantyl	0.91	B	52.5	5.4
tert-Dodecyl	1.03	B	41.6	8.8

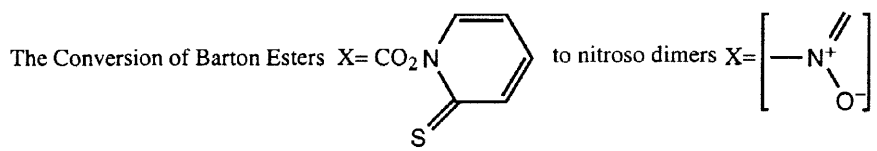
Reagents and Conditions R'SNO, degassed benzene, N_2.
Method A, Thermal 60-65^0.
Method B, Visible Light (250 Watt Tungsten Lamp).
Method C, Dark,Room Temperature, 4 days.



Scheme 3

Our attention was then directed towards a brief examination of the scope of the reaction using trityl thionitrite and a range of simple acylthiohydroxamates. The results, shown in Scheme 4, indicate that the reaction can also be applied to the Barton esters (**9**) and (**10**) derived from secondary carboxylic acids and the steroidal examples (**8**) and (**10**) also demonstrate that the overall transformation is compatible with the presence of ketonic and ester functionality. As anticipated for the chain mechanism outlined in Scheme 1, the reaction of (**10**) furnished a 1:1 mixture of bis-nitrosodiastereomers as the primary products. The lower yield of nitroso dimer obtained from (**9**) may be a reflection of the volatility of the corresponding nitroso monomer.

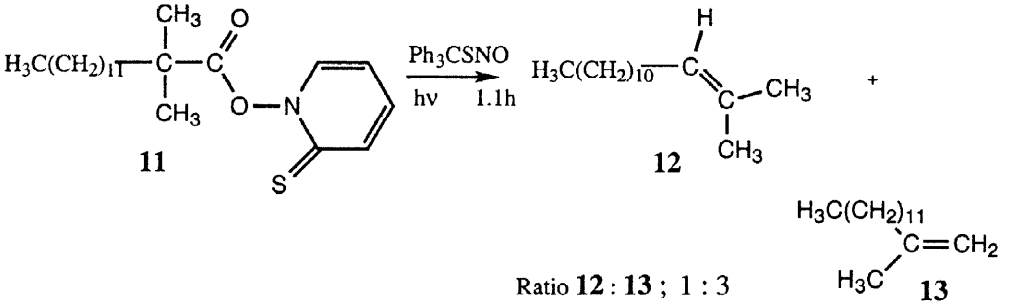




Substrate	Method	Yield (%)
(8)	A	62
	B	60
(9)	B	33
(10)	B	48

Scheme 4

The attempted application of this method to the Barton ester of the tertiary carboxylic acid (**11**) did not yield any products of decarboxylative nitrosation, and led instead to the isolation of a mixture of the isomeric alkenes (**12**) and (**13**) (Scheme 5). A plausible explanation for this observation almost certainly hinges on the known fact that the equilibrium for dimerisation of tertiary nitrosoalkanes is much less favourable. In addition to their behaviour as radical traps for carbon centered radicals, the nitroso monomer could also trap nitric oxide, as shown in Scheme 3, and the resultant diazonium nitrate or tertiary nitrate could then undergo subsequent elimination to give the observed alkenes.



Scheme 5

Clearly, the present strategy is therefore restricted to derivatives of primary and secondary carboxylic acids, a limitation which does not apply in the non chain diazirine method developed by Barton for decarboxylative amination.[7]

Nevertheless, from a synthetic viewpoint, the utility of the present decarboxylative nitrosation reaction does not lie in the production of the corresponding nitrosoalkane or its dimer, but in the variety of useful functional group transformations which can then be performed on these products, Thus for example, catalytic hydrogenation of the nitroso dimer (**6**) over a platinum oxide catalyst at atmospheric pressure afforded heptadecylamine in good yield (75%). The simple tautomerisation of the nitroso dimer *via* its monomer to the corresponding oxime is of course the most valuable transformation, given the potential either for reduction to the amine or for subsequent hydrolysis to the corresponding carbonyl compound. Initially, we had hoped that this reaction could be carried out *in situ* during decarboxylative nitrosation through the simple expedient of adding trifluoroacetic acid to the reaction medium. In the event however, a trial experiment using (**8**) as substrate led once again to the nitroso dimer and not the oxime. The most efficient method, which was then applied to the dimers obtained from (**8**) and (**10**) to give the desired oximes (**14**) and (**15**) respectively in essentially quantitative yield, was that used in the classical Barton nitrite ester photolysis[5] and consists of a simple reflux in isopropanol.

In summary, the present free radical chain reaction for decarboxylative nitrosation demonstrates that the reaction of carbon centred radicals with thionitrites is an effective process for the formal transfer of nitric oxide from sulfur to carbon. In preparative terms, although limited to primary and secondary carboxylic acids the reaction occurs under mild neutral conditions and, through the versatility of the nitroso group, provides a convenient method for the selective replacement of a carboxylic acid group by a new carbon nitrogen bond, thereby adding to the recent armoury of methods for formation of a carbon nitrogen bond under free radical conditions.[10]

EXPERIMENTAL

Melting points were determined on a Reichart hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 infrared spectrometer as a thin film or a dichloromethane solution. Ultraviolet spectra were recorded on a Perkin Elmer 554 UV-VIS spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded, in $CDCl_3$, at 400MHz and 100.6MHz respectively on a Varian VXR 400 with residual protic solvent used as the internal reference. Chemical shifts were measured in ppm and coupling constants J in

Hertz. Mass spectra were recorded by FAB (fast atom bombardment), CI (chemical ionization with NH_3) or EI (electron impact) on a VG 7070B mass spectrometer, m/z relative intensities (in %) in parentheses. Elemental analyses were performed by the staff of the University College Microanalytical Laboratory. Reaction solvents were dried and distilled according to standard procedures. Petrol refers to redistilled light petroleum ether (b.p. 40-60^{0}C) and ether to diethyl ether, Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh). All reactions unless otherwise stated were carried out in oven dried glassware and under a nitrogen atmosphere.

Preparation of Thionitrites: General Procedure

A solution of sodium nitrite (1.2 eq.) in water (4 ml for 1.20 g of nitrite) was added to a solution of mercaptan (1 eq.) in benzene or ether (8 ml). The reaction mixture was vigorously stirred and cooled to 5^{0}C. Dilute sulfuric acid (15%, d=1.1, 0.7 eq.) was then added dropwise and the resulting mixture vigorously stirred for 15 minutes in the dark. The solution was diluted with more benzene or ether (5 ml) and washed several times with water to remove sodium sulfate, and with 5% aqueous sodium hydrogen carbonate for very stable thionitrites.The organic phases were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude thionitrite was purified in the dark to minimize possible photolytic decomposition.

Triphenylmethylthionitrite

The title compound was prepared from triphenylmethylmercaptan (11.7 g, 42 mmol) in benzene (24 ml). The crude green solid obtained after work-up (12 g) was recrystallized from chloroform/ethanol in the dark to give bright green prisms (9.45 g, 73%); m.p. 100^{0}C (lit.[8] 100^{0}C); IR (CH_2Cl_2) 3088, 1956, 1932, 1815, 1777, 1597, 1490, 1446, 1040, 899, 786 cm^{-1}; ^{1}H NMR δ 7.14 (m, 6H), 7.30 (m, 9H); ^{13}C NMR δ 76,0 (*C* SNO), 127,61 (3C, C-4'), 128.17 (6C), 129.9 (6C), 143.60 (3C, C-1'); m/z (EI) 276 (0.6, Ph_3CSH), 275 (1.1, M^+ -NO), 274 (3.0), 244 (38.5, Ph_3CH), 243 (100, Ph_3C^+), 242 (79.6), 241 (80), 215 (24.5), 166 (37.3, Ph_2CH^+), 165 (100), 64 (47); m/z (FAB) 275 (20, M^+-NO), 244 (24.5), 243 (100, Ph_3C^+), 165 (17).

1-Adamantylthionitrite

The 1-adamantanethiol was prepared by refluxing, for three hours, a mixture of 1-bromoadamantane, thiourea, 48% HBr and glacial acetic acid[11] and the resulting isothiouronium bromide was then hydrolysed with 5% aqueous NaOH solution[12] to furnish the thiol in 65% overall yield; IR (CH_2Cl_2) 2907, 2837, 1449, 1043 cm^{-1}; ^{1}H NMR δ 1,67 (s, 7H, SH,3CH_2), 1.927 (s, 3H), 1.935 (s, 3H), 2.03 (s, 3H). The 1-adamantylthionitrite was prepared from the thiol (554 mg, 3.29 mmol) in benzene at 0^{0}C, for 40 minutes. Chromatography of the crude product, over silicagel (using a column covered with aluminium foil) with petrol gave the thionitrite as a green solid (473 mg, 73%), m.p. 58-60^{0}C, which proved to be less stable than triphenylmethylthionitrite and was subsequently used without further purification. IR (CH_2Cl_2) 2907, 2848, 1484, 1037, 650 cm^{-1}; ^{1}H NMR δ 1.94 (m, 6H), 2.29 (bs, 3H), 2.54 (s, 3H), 2.55 (s, 3H); ^{13}C NMR δ 29.96 (C-3), 36.24 (C-4), 43.45 (C-2), 55.6 (C-1).

tert- Dodecylthionitrite

The title compound was prepared from *tert*-dodecanethiol (mixture of isomers purchased from TC1, 4.70 ml, 20 mmol) in benzene (15 ml), at room temperature for 30 minutes. The organic phase was then washed with water (10 ml), aqueous 5% $NaHCO_3$ (10 ml), water (10 ml), dried over $MgSO_4$, and evaporated under reduced pressure. The green liquid (4.7 g) obtained was purified by flash chromatography (petrol) using a column covered with aluminium foil. The *tert*- dodecylthionitrite was obtained as a green-red liquid (3.54 g, 76.5%);b.p. 75-80^{0}C/0.5 Torr; IR (film) 2954, 2872, 1497, 1461, 1379, 1133, 672, 615 cm^{-1}, which proved to be less stable than triphenylmethylthionitrite and was subsequently used without further purification.

Preparation of O-Acyl Thiohydroxamic Acids: General Procedure

The acid chlorides were prepared immediately prior to use. To a solution of the carboxylic acid (1 mmol) in benzene (5 ml) was added oxalyl chloride (0.5 ml) and dimethylformamide (DMF) (1 drop) at room temperature under nitrogen and the resulting solution stirred for 2 hours. The reaction mixture was evaporatedto dryness, redissolved in benzene (5 ml) and evaporated to dryness again yielding the crude acid chloride which was used immediately without further purification.

A mixture of the acid chloride (1 mmol) and the sodium salt of N-hydroxypyridine-2-thione (1.05 mmol) in anhydrous dichloromethane (5 ml) was stirred in the dark under a nitrogen atmosphere for 2-4hours. A little dry ether was then added and the precipitated NaCl filtered off. The filtrate was concentrated under reduced pressure in the dark, without heating. The yellow residue was purified by flash chromatography over a silicagel column wrapped with aluminium foil, and then used without further purification, eluting with dichloromethane for the compound (**5**), with 0-3% ethyl acetate/dichloromethane for the compounds (**8**), (**9**), (**10**), and with 30-100% ether/petrol for the compound (**11**) Derivatives (**5**)[4], (**8**)[4], and (**10**)[11] have previously been prepared but used without spectral characterisation. dry ether was then added and the precipitated NaCl filtered off. The filtrate was concentrated under reduced pressure in the dark, without heating. The yellow residue was purified by flash chromatography over a silicagel column wrapped with aluminium foil, and then used without further purification, eluting with dichloromethane for the compound (**5**), with 0-3% ethyl acetate/dichloromethane for the compounds (**8**), (**9**), (**10**), and with 30-100% ether/petrol for the compound (**11**) Derivatives (**5**), (**8**), and (**10**) have previously been prepared but used without spectral characterisation.

N-Octadecanoyloxy-2-pyridinethione (**5**)

The title compound was prepared from stearic acid. Yield: 90%; IR (CH_2Cl_2) 2938, 2854, 1810, 1610, 1526, 1465, 1454, 1135, 1055, 869, 828 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J=7Hz, CH_3), 1.26 (bs, 26H), 1.40 (m, 2H), 1.82 (q, 2H, J=7.6Hz, CH_3), 2.72 (t, 2H, J=7.5Hz, CH_2CO_2), 6.64 (ddd, 1H, J=1.8, 7.0, 8.8Hz), 7.21 (ddd, 1H, J=8.8, 1.8, 7.0Hz), 7.57 (dd, 1H, J=7.0, 1,8Hz), 7.70)dd, 1H, J=8.8, 1.8Hz).

N-(3α-Acetoxy-24-nor-5βH-cholane-23-carboxyl)-2-pyridinethione (**8**)

The title compound was prepared from 3α-acetyl lithocholic acid chloride. Yield: (74%); IR (CH_2Cl_2) 2982, 2944, 2869, 1809, 1724, 1611, 1529, 1468, 1451, 1380, 1364, 1240, 1136, 1059, 1025, 909, 858, 828 cm^{-1}; ^1H NMR δ 0,67 (s, 3H, CH_3-18), 0.93 (s, 3H, CH_3-19), 0.99 (d, 3H, J=6.2Hz, CH_3-20), 2.04 (s, 3H, $OCOCH_3$), 2.63 (m, 1H, CH_aCO_2), 2.77 (m, 1H, CH_bCO_2), 4.72 (m, 1H, H-3β), 6.63 (ddd, 1H, J=1.8, 6.9, 8.7Hz), 7.21 (ddd, 1H, J=6.8, 1.5, 8.6Hz), 7.56 (dd, 1H, J=6.9, 1.0Hz), 7.70 (dd, 1H, J=8.9, 1.1Hz).

N-(1-Propylbutanoyloxy)-2-pyridinethione (**9**)

The title compound was prepared from the parent acid and used without further purification. Yield: (88%); IR (CH_2Cl_2) 2962, 2874, 1802, 1610, 1530, 1451, 1410, 1134, 1040, 919, 835cm^{-1}; ^1H NMR δ 0.96 (t, 6H, J=7.3Hz, CH_3), 1.47 (m, 4H, CH_2CH_3), 1.63 (m, 2H), 1,85 (m, 2H), 2.77 (m, 1H, $CHCO_2$), 6.61 (ddd, 1H, J=1.8, 6.9, 8.6Hz), 7.18 (ddd, 1H, J=8.4, 1.4, 6.8Hz), 7.47 (dd, 1H, J=6.9, 1.5Hz), 7.68 (dd, 1H, J=1.8, 8.8Hz).

N-(3β-Acetoxy-11-keto-5αH-pregnane-20-carboxyl)-2-pyridinethione (**10**)

The title compound was prepared from 3β-acetoxy-11-ketobisnorallocholanic acid chloride (1 eq.), N-hydroxy-pyridine-2-thione (1.2 eq.),triethylamine (1.15 eq.), dimethylamino-pyridine (0.1 eq.) in dry benzene (10 ml). ^1H NMR δ 0.70 (s, 3H, CH_3-18), 0.92 (td, 1H, J=4, 13Hz), 1.03 (s, 3H, CH_3-19), 1,12 (bs, 2H), 1.20-1.40 (m), 1.45 (d, 3H, J=7Hz, CH_3-21), 1.50-1.81 (m), 1.98-2.14 (m), 2.01 (s, 3H, $OCOCH_3$), 2.40 (d, 1H, J=12Hz, H-8b), 2.49 (dm, 2H, J=12Hz, H-9), 2.80 (qd, 1H, J=7, 10Hz, H-20), 4.66 (sept, 1H, J=5.6Hz, H-

3a), 6.63 (ddd, 1H, J=1.6, 6.8, 8.3Hz), 7.20 (ddd, 1H, J=8.2, 1.7, 6.8Hz), 7.46 (dd, 1H, J=7.2, 1.6Hz), 7.68 (dd, 1H, J=8.8, 1.4Hz)

N-(2,2-Dimethyl-tetradecanoyloxy)-2-pyridinethione (**11**)

The title compound was prepared from 2,2-dimethyltetradecanoic acid and used without further purification. Yield: (90%); IR (CH_2Cl_2) 2928, 2855, 1794, 1611, 1529, 1448, 1038 cm^{-1}; ^1H NMR δ 0.89 (t, 3H, J=7Hz, CH_3), 1.28 (s) and 1.30 (m, 18H), 1.39 (m, 2H), 1.44 (s, 6H, $(CH_3)_2$), 1.76 (m, 2H. $CH_2C(CH_3)_2$), 6.62 (ddd, 1H, J=1.8, 6.9 8.7Hz), 7.18 (ddd, 1H, J=6.8, 1.5, 8.6Hz), 7.46 (dd, 1H, J=6.9, 1.5Hz), 7.69 (dd, 1H, J=8.8,1.8Hz).

General Procedure for the Thermal Decarboxylation of O-Acylthiohydroxamates with Thionitrites
Method A

A solution.of triphenylmethylthionitrite (200 mg, 0.65 mmol) in benzene (7 ml), flushed with nitrogen for 10 minutes, was added *via* cannula to a pre-nitrogen flushed solution of the O-acyl thiohydroxamic acid in benzene (7 ml). The resulting solution was heated at 60-65^{0}C (oil bath) for 20 -35 minutes until the complete disappearance of the thionitrite green colour and the persistance of a yellow solution. The solution was then evaporated to dryness and the resulting residue chromatographed to give pyridyltriphenylmethyl disulfide, carboxylic acid, and the bis-nitroso compound.

General Procedure for the Photochemical Decarboxylation of O-Acylthiohydroxamic Acids with Thionitrites
Method B

A solution of the thionitrite (2 mmol) in benzene (15 ml) was flushed with nitrogen for 10 minutes and then added *via* cannula to a pre-nitrogen flushed solution of the O-acylthiohydroxamic acid (2-2.2 mmol) in benzene(15 ml). The resulting mixture was irradiated with a 250W tungsten lamp until complete disappearance of the thionitrite green colour and the persistance of a yellow solution(1 to 4 hours). The solution was then evaporated to dryness and the resulting residue chromatographed.

Decarboxylation of N-Octadecanoyloxy-2-pyridinethione (**5**) *with Triphenylmethylthionitrite*

The residue obtained after evaporation under reduced pressure of the reaction mixture of triphenylmethylthionitrite (610 mg, 2mmol) with the O-acylthiohydroxamic acid (**5**) (800 mg, 2mmol) in benzene (30ml) was diluted in cold dichloromethane. The precipitated bis-(1-nitrosoheptadecane) was filtered off (295mg, 54.7%). Column chromatography of the filtrate adsorbed onto silica (1%-20% ether/petrol) furnished in order of elution; 1-heptadecyl nitrate (22.2mg, 3.7%) and pyridyltriphenylmethyl disulfide (560mg, 70%).

1-Heptadecyl nitrate; UV (hexane) 224 (ε, 490), 270 (ε,140); IR (film) 2923, 2851, 1631, 1461, 1374, 1276, 1041, 979,861 cm^{-1}; ^1H NMR δ 0.90 (t, 3H, J=6.8Hz, CH_3), 1.28 (s) and 1.34 (m, 26H), 1.40 (m, 2H), 1.74 (q, 2H, J=6.8Hz), 4.46 (t, 2H, J=6.8Hz, CH_2ONO_2); ^{13}C NMR δ 14.12 (CH_3), 22.70, 25.63, 26.73, 29.11, 29.39, 29.50, 29.60, 29.64, 29.67, 29.69, 31.93, 73.46 (CH_2ONO_2);Anal. Calcd for $C_{17}H_{35}NO_3$: C, 67.73, H, 11.70, N, 4.64. Found: C, 68.01, H, 11.97, N, 4.48.

Pyridyltriphenylmethyl disulfide: m.p. 104^{0}C (dichloromethane/petrol); IR (CH_2Cl_2) 3030, 2927, 2854, 1955, 1911, 1809, 1694, 1596, 1577, 1561, 1491, 1446, 1119, 1083, 1044, 670, 630 cm^{-1}; ^1H NMR δ 6.88 (ddd, 1H, J=0.9, 4.8, 7.4Hz), 7.05 (dd, 1H, J=7.4, 0.8Hz), 7.10-7.17 (m, 9H), 7.24 (m, 1H), 7.34 (m, 6H), 8.23 (dd, 1H, J=4.8, 0.9Hz); m/z (CI,NH_3) 386 (MH^+), 354 (MH^+-S), 262 (24), 243 (100,Ph_3C^+), 167 (35), 112 (97).
Bis-(1-nitrosoheptadecane): m.p. 93-94^{0}C (CH_2Cl_2); UV (MeOH) 280 (slightly soluble); IR (CH_2Cl_2) 2912, 2861, 1461, 1261cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J=6.8Hz, CH_3), 1.26 (s, 22H), 1.34 (m, 6H), 1.87 (q, 2H,

J=6.7Hz), 4.26 (t, 2H, J=7.3Hz, CH_2NO); ^{13}C NMR δ 14.12 (CH_3), 22,69, 25.07, 26.60, 29.04, 29.36, 29.51, 29.60, 29.65, 29.69, 31.92, 58.91 (CH_2NO); m/z (FAB) 539 (17,MH^+), 521 (16), 376 (29), 350 (15), 270 (21), 256 (34), 243 (100); Anal. Calcd for $C_{34}H_{70}N_2O_2$: C 75.77, H 13.09, N 5.19. Found: C 75.78, H 12.90, N 5.19

Decarboxylation of N-Octadecanoyloxy-2-pyridinethione with 1-Adamantylthionitrite

The solution obtained from the reaction mixture of 1-adamantylthionitrite (428mg, 2.16mmol) with the O-acylthiohydroxamic acid (**5**) (939mg, 2.38mmol) in benzene (40ml) was cooled to room temperature and filtered to remove the white precipitated bis-(1-nitrosoheptadecane) (265mg, 45.5%). Column chromatography of the filtrate adsorbed onto silica (2%-20% ether/petrol) furnished in order of elution; 1-heptadecyl nitrate (35.5mg, 5.4%), adamantylpyridyl disulfide (262mg, 43.7%) and a second crop of bis-(1-nitrosoheptadecane) (41mg, 7%; total yield; 52.5%)

Adamantylpyridyl disulfide: m.p. 35-36^{0}C; IR (CH_2Cl_2) 2911, 2853, 1577, 1562, 1447, 1416, 1350, 1299, 1120, 1041, 977, 618cm^{-1}; ^1H NMR δ 1.63 (s, 6H), 1.85 (s, 3H), 1.86 (s, 3H), 2.02 (bs, 3H), 7.03 (ddd, 1H, J=1.0, 4.8, 7.3Hz), 7.6 (ddd, 1H, J=1.9, 7.37, 8.15Hz), 7.80 (dt, 1H, J=1.0, 8.1Hz), 8.39 (dm, 1H, J=0.9, 4.8Hz); ^{13}C NMR δ 29.78 (3xC-1), 35.85 (3xC-4), 42.26 (3xC-2), 50.77 (C-1), 119.40 and 120.10 (C-2', C-4'), 136.62 (C-3'), 148.93 (C-5'), 162.10 (C-1'); m/z (FAB) 279 (16), 278 (81, MH^+), 277 (11), 276 (12), 136 (11), 135 (100, $C_{10}H_{15}^+$),112 (10), 93 (9), 79 (11); Anal. Calcd for $C_{15}H_{19}NS_2$: C 64.94, H 6.90, N 5.05, S 23.11. Found: C 64.90, H 6.91, N 4.87, S 22.98.

Decarboxylation of N-Octadecanoyloxy-2-pyridinethione with tert-Dodecylthionitrite

The residue obtained after evaporation under reduced pressure of the reaction mixture of tert-dodecylthionitrite (231mg, 1mmol) with the O-acylthiohydroxamic acid (**5**) (383mg, 0.973mmol) in benzene (15ml) was diluted with cold dichloromethane. The precipated bis-(1-nitrosoheptadecane) was filtered off (109mg, 41.6%). Column chromatography of the filtrate adsorbed onto silica (1%-10% ether/petrol) furnished in order of elution: 1-heptadececyl nitrate (26mg, 8.8%) and pyridyl*tert*-dodecyl disulfide (160mg, 52.8%).
Pyridyl*tert*-dodecyl disulfide: IR (film) 2958, 2928, 2871, 1574, 1560, 1446, 1417, 1378, 1118, 1081, 1043, 986, 760, 718cm^{-1}; ^1H NMR δ 0.83 (m), 1.22 (m), 1.57 (m), 7.05 (dd, 1H, J=7.3, 5.0Hz), 7.61 (t, 1H, J=7.4Hz), 7.79 (m, 1H), 8.42 (d, 1H, J =3Hz),; m/z (FAB) 312 (32,MH^+), 298 (14), 146 (10), 145 (10), 144 (100). Anal. Calcd for $C_{17}H_{29}NS_2$; C 65.54, H 9.39, N 4.50, S 20.58. Found: C 65.67, H 9.44, N 4.61, S 20.28.

Decarboxylation of N-(3α-Acetoxy-24-nor-5βH-cholane-23-carboxyl)-2-pyridinethione (**8**) *with Triphenylmethylthionitrite*

The oily residue obtained after evaporation under reduced pressure of the reaction mixture of trityl thionitrite (410mg, 1.36mmol) with the O-acylthiohydroxamic acid (**8**) (790mg, 1.49mmol) in benzene (30ml) was adsorbed onto silica. Column chromatography (30-100% ether/petrol) furnished in order of elution; pyridyltriphenylmethyl disulfide (348mg, 60%), 3α-acetyl lithocholic acid (62.4mg, 10%) and bis-(3α-acetoxy-23-nitroso-24-nor-5βH-cholane (354mg, 60%)

Bis-(3α-acetoxy-23-nitroso-24-nor-5βH-cholane): m.p. 155-156^{0}C (ethyl acetate); $[\alpha]_D^{20}$ +69.5^0 (c=0.38, $CHCl_3$); IR (CH_2Cl_2) 2944, 2866, 1722, 1444, 1377, 1366, 1329, 1244, 1206, 1022cm^{-1}; ^1H NMR δ 0.64 (s, 3H, CH_3-18), 0.92 (s, 3H, CH_3-19), 0.98 (d, 3H, J=6.3Hz,CH_3-20), 1.00-1.91 (m), 1.95 (dm, 1H, J=11.7Hz), 2.02 (s, 3H, $OCOCH_3$), 4.25 (m, 2H, CH_2-23), 4.71 (m, 1H, H-3β); ^{13}C NMR δ 11.97 (*C*H_3-18), 18.5 (*C*H_3-20), 20.78, 21.43(*C*H_3-19), 23.29, 24.11, 26.26, 26.59, 26.96, 28.14, 30.97, 32.21, 33.84, 34.54, 35.1, 35.74, 40.36, 41.84, 42.78, 55.87, 56.41, 56.94 (*C*H_2-23), 74.31 (C-3), 170.55 ($OCOCH_3$); m/z (FAB) 808 (MH^+), 791, 748 (10), 688 (22,MH^+-AcOH), 402 (13), 344 (42), 313 (63), 107 (100). Anal. Calcd for $C_{50}H_{82}N_2O_6$; C 74.40, H 10.24, N 3.47. Found: C 74.12, H 9.93, N 3.25.

Decarboxylation of N-(1-propylbutanoyloxy)-2-pyridinethione (**9**) *with Triphenylmethylthionitrite*

The residue obtained after evaporation under reduced pressure of the reaction mixture of trityl thionitrite (610mg, 2mmol) with the O-acylthiohydroxamic acid (**9**) (562mg, 2,3mmol) in benzene (30ml) was diluted with 10% ether/petrol. The precipitated pyridyltriphenylmethyl disulfide was filtered off (460mg, 59%). The filtrate was concentrated under reduced pressure and chromatographed to give, in order of elution; bis-(4-nitrosoheptane) (85.4mg, 33%), and a second crop of pyridyltriphenylmethyl disulfide (132mg, 17%,total yield, 76%)

Bis-(4-nitrosoheptane): m.p. 44-45^{0}C; IR (CH_2Cl_2) 2964, 2933, 2871, 1461, 1384, 1189, 1113cm^{-1}; ^{1}H NMR δ 0.92 (t, 6H, J=7.3Hz, CH_3), 1.29 (m, 4H, J=2.0, 7.6Hz), 1.56 (m, 2H, CH_a), 1.87 (m, 2H, CH_b), 5.46 (m, 1H, J=4.2, 9Hz, CHNO); ^{13}C NMR δ 13.65, 19.13, 34.09, 66.07 (*C*HNO); m/z (FAB) 259 (21, MH^+), 228 (11), 161 (25), 130 (17), 57 (100).

Decarboxylation of N-(3β-Acetoxy-11-keto-5αH-pregnane-23-carboxyl)-2-pyridinethione (**10**) *with Triphenylmethylthionitrite*

The residue obtained after evaporation under reduced pressure of the reaction mixture of trityl thioniitrite (430mg, 1.4mmol) with the O-acylthiohydroxamic acid (**10**) (710mg, 1.4mmol) in benzene (30ml) was chromatographed to give, in order of elution; pyridyl triphenylmethyl disulfide (365mg, 66%), a 1:1 mixture of the bis-nitroso diastereoisomers (306mg) (56%).

Bis-(3β-acetoxy-20-nitroso-5αH-pregnan-11-one: The title compound was a mixture of diastereoisomers at position 20. IR (CH_2Cl_2) 2943, 2861, 1724, 1703, 1455, 1446, 1389, 1364, 1248, 1194, 1028cm^{-1}; ^{1}H NMR δ 0.57 (s, 3H) and 0.68 (s, 3H CH_3-18), 0.84 (td, 1H, J=3.3Hz), 0.87 (td, 1H, J=2.8Hz), 0.98 (s, 3H) and 1.00 (s, 3H, CH_3-19), 1.10 (m, 4H), 1.22 (d, 3H, J=6.5Hz, CH_3-20), 1.18-1.29 (m, 12H), 1.33 (d, 3H, J=6.5Hz, CH_3-20), 1.30-1.41 (m), 1.49-1.76 (m, H-19), 1.85 (d, 1H, J=12.5Hz), 1.92 (m, 1H), 1.99 (s,3H) and2.00 (s, 3H, $OCOCH_3$), 2.14 (bq, 1H, J=8.4Hz), 2.24-2.38 (m, 4H), 2.45 (tm, 2H J=3.4, 13.4Hz), 4.64 (m, 2H, J=5.6Hz, H-3α), 5.41 (qd, 1H, J=6.5, 10.7Hz) and 5.54 (m, 1H, J=6.5, 10.7Hz, H-20); ^{13}C NMR δ 11.9, 13.5, 14.1, 17.2, 21.4, 23.2, 23.4, 25.6, 25.7, 23.1, 27.8, 32.4, 33.4, 34.8, 34.9, 35.3, 36.3, 36.7, 44.6, 45.8, 46.0, 51.0, 52.8, 54.4, 55.0, 56.5, 57.1, 61.4, 63.0, 63.8, 63.9, 73.2 (*C*-20), 170.6 (*O*COCH3), 209.9 and 210.3 (*C*-11); m/z (FAB) 390 (2, MH^+/2), 359 (32), 299 (35, MH^+-AcOH), 154 (26), 43 (100). Anal. Calcd for $C_{46}H_{70}N_2O_8$; C 70.92, H 9.05, N 3.59. Found; C 70.65, H 9.26, N 3.29.

Decarboxylation of N-(2,2-Dimethyl-tetradecanoyloxy)-2-pyridinethione (**11**) ***with Triphenylmethylthionitrite***

The residue obtained after evaporation under reduced pressure of the reaction mixture of trityl thionitrite (620mg, 2.03mmol) with the O-acyl thiohydroxamic acid (**11**) (742mg, 2.03mmol) in benzene (20ml) was chromatographed (0%-50% ether/petrol) to give in order of elution: a mixture of unseparated 2-methyl-2-tetradecene and 2-methyl-1-tetradecene (109mg, 29.5%), 2,2-dimethyltetradecanoic acid (45mg, 10%), pyridyltriphenylmethyl disulfide (338mg, 50%) and the O-acyl thiohydroxamic acid starting material (11) (100mg, 87% conversion).

2-Methyl-2-tetradecene[12] and 2-Methyl-1-tetradecene[13]: These were obtained as a 1:3 mixture of isomers as shown by ^{1}H NMR. IR (film) 3073, 2956, 2924, 2854, 1649, 1466, 1375, 886, 721cm^{-1}; ^{1}H NMR δ 0.91 (t, CH_3), 1.29 (s, CH_2), 1.43 (m, CH_2), 1.62 (s, CH=C*Me*$_2$), 1.71 (s, CH=C*Me*$_2$), 1.73 (s, C*Me*=CH_2),1.95-2.01 (m, C*H*$_2$CH=CMe$_2$), 2.02 (m, C*H*$_2$CMe=CH_2), 4.69 (dm, J=8.7Hz, CMe=C*H*$_2$), 5.14 (tm, J=6.7Hz, CH_2C*H*=CMe$_2$); ^{13}C NMR δ 14.12 (CH_3 A+B), 17.63 (CH_3 A), 22.39 (CH_3 B), 22.73 (CH_2), 25.71 (CH_3 B), 27.69, 28.09, 29.38, 29.41, 29.60, 29.66, 29.70, 29.73, 29.95, 31.97, 37.88, 109.51 (CMe=*C*H$_2$ B), 124.99 (*C*H=CMe$_2$ A), 131.04 (CH=*C*Me$_2$ A), 146.27 (*C*Me=CH_2 B).

General Procedure for the Conversion of Bis-Nitroso Compounds into Oximes

A solution of the bis-nitroso compound was heated to reflux in isopropanol (15ml/mmol) for 4 hours for primary bis-nitroso compounds, and for 24 hours for secondary bis-nitroso compounds.

3α-Acetoxy-20-hydroxyimino-24-nor-5βH-cholane (**14**): m.p. 162-165^{0}C (MeOH); $[\alpha]_D^{20}$ +42^0 (c=0.61, $CHCl_3$); IR (CH_2Cl_2) 3578, 2933, 2855, 1722, 1444, 1377, 1355, 1261, 1022cm^{-1}; ^{1}H NMR δ 0.67 and 0.68 (s, 6H, CH_3-18), 0.94 (s, 6H, CH_3-19), 0.98 (d, 3H, J=5.9Hz) and 1.00 (d, 3H, J=5.7Hz, CH_3-20), 1.1-2.0 (m), 2.04 (s, 3H, $OCOCH_3$), 2.28 (m, 4H, CH_2-22), 4.73 (m, 2H, J=6.3, 4.8Hz,H-3β), 6.74 (bs, 1H, *H*C=NOH anti), 7.42 (m, 1H, J=5.6, 7.1Hz, *H*C=NOH syn), 8.20 (bs, 2H, OH); ^{13}C NMR δ 12.03, 18.98, 19.40, 20.78, 21.46, 23.30, 24.17, 26.28, 26.59, 26.98, 28.28, 28.31, 32.21, 34.07, 34.54, 35.0, 35.76, 35.85, 39.99, 40.35, 41.84, 42.79, 55.90, 56.18, 56.38, 56.42, 74.37 (C-3), 151.50 (C=N), 170.69 (*O*COCH3); m/z (FAB) 404 (MH^+), 402 ($(M-H)^+$), 344 (47, MH^+-AcOH), 154 (23), 43 (100).Anal. Calcd for $C_{25}H_{41}NO_3$; C 74.40, H 10.24, N 3.47. Found; C 74.30, H 10.34, N 3.16.

3β-Acetoxy-20-hydroxyimino-5αH-pregnan-11-one (**15**): m.p. 192-193^{0}C; $[\alpha]_D^{20}$ +41.9^0 (c=0.42, $CHCl_3$); IR (CH_2Cl_2) 3578, 3266, 2985, 2863, 1724, 1702, 1365, 1029cm^{-1}; ^{1}H NMR δ 0.57 (s, 3H, CH_3-18), 0.89 (m, 1H, J=13.7Hz), 1.03 (s, 3H, CH_3-19), 1.12 (m, 2H), 1.21 (d, 1H, J=6.1Hz), 1.27 (m, 3H), 1.37 (m, 1H, J=12.3Hz). 1.49-1.80 (m, 8H), 1.84 (s, 3H, CH_3-20), 2.02 (s, 3H, $OCOCH_3$), 2.12 (m, 1H), 2.34-2.52 (m, 4H), 4.67 (m, 1H, J=5Hz, H-3α), 8.77 (bs, 1H, OH); ^{13}C NMR δ 11.97 (CH_3), 14.10, 14.86, 21.40, 23.47, 23.59, 27.13, 27.83, 32.44, 33.45, 35.42, 36.91, 44.69, 47.45, 54.89, 55.51, 56.57, 64.23 (C-17), 73.25 (C-9), 157.34 (C-20), 170.70 (*O*COCH3), 210.15 (C-11); m/z (FAB) 390 (96, MH^+), 330 (23, MH^+-AcOH), 43 (100).Anal. Calcd for $C_{23}H_{35}NO_4$; C 70.92, H 9.05, N 3.59. Found; C 70.61, H 9.05, N 3.40.

Reduction of Bis-(1-nitrosoheptadecane) (**6**) *to 1-Heptadecylamine*

A solution of bis-(1-nitrosoheptadecane) (**6**) (114mg, 0.21mmol) in a mixture of chloroform (20ml) and ethanol (5ml), containing a catalytic amount of platinum dioxide (15mg), was hydrogenated at room temperature and atmospheric pressure for 2 days, with addition of fresh catalyst (15mg) after 24 hours. The resulting suspension was concentrated under reduced pressure and the residue diluted with water, and acidified with aqueous HCl. The aqueous layer was washed with ether, and saponified with aqueous NaOH, and then extracted with ether. The combined organic phases were washed several times with water, brine and dried over K_2CO_3. Evaporation of the solvent under reduced pressure gave 1-heptadecylamine as a white solid (80mg, 75%);m.p. 50^{0}C (lit.[14], 49^{0}C); IR (CH_2Cl_2) 3374, 3292, 2926, 2854, 1604, 1467, 1370, 1074, 848cm^{-1}; ^{1}H NMR δ 0.89 (t, 3H, J=7Hz, CH3), 1.21-1.35 (m), and 1.26 (s, 28H), 1.47 (m, 2H), 1.83 (bs, 2H, NH_2), 2.70 (bt, 2H, J=7Hz, CH_2NH_2); m/z (FAB) 256(MH^+).

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