Tetrahedron Vol. 41, No. 23, pp. 5507 to 5516, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

THE INVENTION OF NEW RADICAL CHAIN REACTIONS. PART X†. HIGH YIELD RADICAL ADDITION REACTIONS OF αβ-UNSATURATED NITROOLEFINS. AN EXPEDIENT CONSTRUCTION OFTHE 25-HYDROXY-VITAMIN D_3 SIDE CHAIN FROM BILE ACIDS.

Derek H.R. Barton, Hideo Togo and Samir Z. Zard

Institut de Chimie des Substances Naturelles, C.N.R.S.,
91190 Gif-sur-Yvette, France

(*Received in France* 18 *July* 1985)

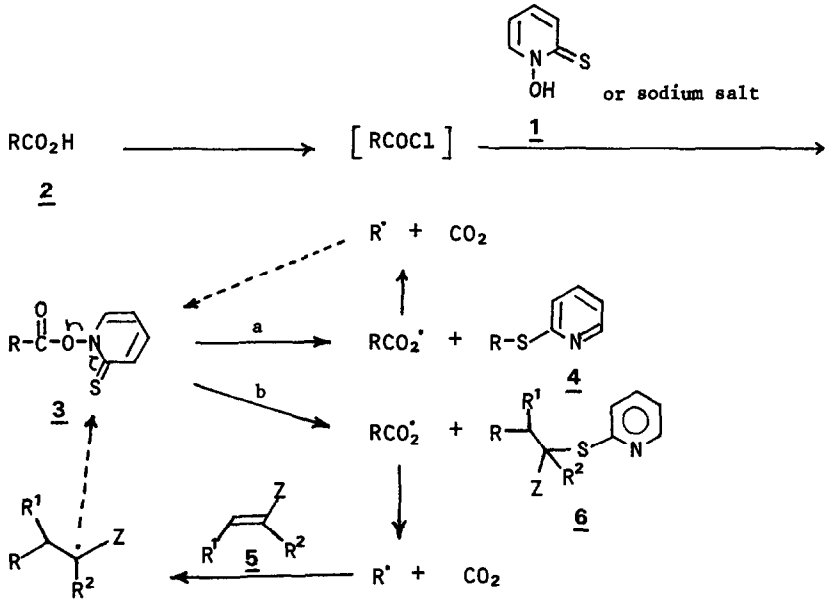
Abstract - *Radicals derived from thiohydroxamic esters* 3 *readily add to nitroolefins* 5 *(Z = NO_2) to give good yields of α-nitrosulphides. These adducts, where the structure permits, are easily oxidised to carboxylic acids* 8 *by treatment with alkaline hydrogen peroxide. Reductive cleavage to the corresponding aldehydes or ketones* 9 *is efficiently carried out by the action of $TiCl_3$. Addition of methyl magnesium iodide to the methyl ketone derived from 3α-acetoxy 11-oxo cholanic acid gives steroid* 10 *possessing the 25-hydroxycholesterol side chain of the vitamin D_3 metabolites. Radical additions to 1-phenylthio-2-nitropropene* 11 *have been briefly studied.*

Radical additions to olefins have been extensively studied, especially in connection with the crucial role they play in the production of polymers.[1] In recent times, however, such additions have also acquired importance as mild carbon-carbon bond forming reactions for low molecular weight compounds.[2] Since radical additions are strongly favoured by electron withdrawing groups, electron poor olefins have, predictably, found more general use. Nitro olefins, which are expected to be especially activated, have, however received scant attention. This is a consequence, perhaps, of anticipated difficulties associated with the manipulation of such reactive species. Nevertheless, we anticipated that radical addition to αβ-unsaturated nitroolefins should afford good yields of adducts if the complication of polymerisation could be avoided. In this paper we report our findings on this reaction as well as a number of synthetic applications.

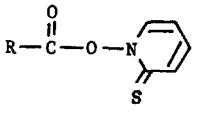
We recently described a radical chain decarboxylation of carboxylic acids via their esters (mixed anhydrides) with appropriate thiohydroxamic acids, e.g. 3.[3] The reaction proceeds by the simple radical chain mechanism depicted in Scheme 1 (path a) involving the intermediacy of carbon radicals. We have also shown that these intermediate radicals are easily intercepted by a variety of reagents, thus diverting the basic reaction in a number of synthetically useful ways. In particular, when the decarboxylation is performed in the presence of electron poor

† Part IX, D.H.R. Barton, D. Crich and G. Kretzschmar, J. Chem. Soc. (Perkin 1), in press.
†† This paper is dedicated with affection to Prof. H.H. Inhoffen on the occasion of his 80th birthday.

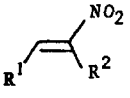
olefins, carbon-carbon bond formation occurs to give adducts such as 6 (Scheme 1, path b). A notable advantage of our system, apart from the commercial availability of the reagent 1, is the presence of the background reaction giving sulphide 4 (path a) as well as the radical chain nature of the process. These two factors allow complete control of the reaction. The intermediate carbon radicals either react with the "trap" to give the desired products or simply give sulphides 4. Unwanted reactions usually associated with radicals such as dimerisation, disproportionation, solvent attack etc. are avoided. One may conclude that the thiocarbonyl group exerts a salutary disciplinary effect on the otherwise unruly radicals.



Scheme 1



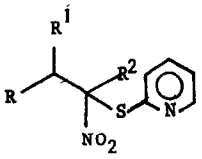
3

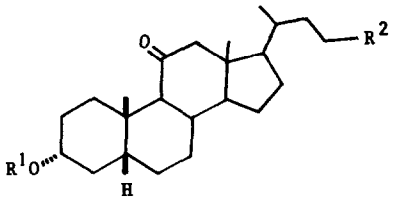


5

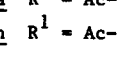
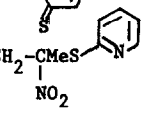
3a R = $CH_3(CH_2)_{14}$-
3b R = $-C(CH_3)_3$
3c R = cyclohexyl
3d R = 1-adamantyl
3e R = Ph_2CHCH_2-
3f R = $(PhCH_2)_2CHCO_2H$
3g R = 1-methylcyclohexyl

5a $R^1 = R^2 = H$
5b $R^1 = H$; $R^2 = Me$
5c $R^1 = Me$; $R^2 = H$





6a R = $CH_3(CH_2)_{14}$- ; $R^1 = R^2 = H$
6b R = $(CH_3)_3C$- ; $R^1 = R^2 = H$
6c R = cyclohexyl; $R^1 = R^2 = H$
6d R = 1-adamantyl ; $R^1 = R^2 = H$
6e R = $CH_3(CH_2)_{14}$- ; $R^1 = H$; $R^2 = Me$
6f R = 1-cyclohexyl; $R^1 = H$; $R^2 = Me$
6g R = Ph_2CHCH_2- ; $R^1 = H$; $R^2 = Me$
6h R = $(PhCH_2)_2CH$- ; $R^1 = H$; $R^2 = Me$
6i R = 1-methylcyclohexyl ; $R^1 = H$; $R^2 = Me$
6j R = 1-adamantyl; $R^1 = Me$; $R^2 = H$

2a R^1 = Ac- ; $R^2 = CO_2H$
3h R^1 = Ac- ; R^2 = 
6k R^1 = Ac- ; $R^2 = CH_2$-CMeS- 
9f $R^1 = H$; $R^2 = CH_2COCH_3$
10 $R^1 = H$; $R^2 = CH_2C(Me)_2OH$

Preliminary experiments with nitroethylene[3e] 5a involving radicals derived from palmitic, pivalic and cyclohexane carboxylic acids gave the expected adducts 6a, 6b, 6c, but only in moderate yields (45-53%). Increasing the amount of nitroolefin did not improve the results significantly. We initially ascribed the low yields to a competing radical induced polymerisation of the nitroethylene as for the other activated olefins (e.g. methyl methacrylate, acrylonitrile) which we examined. A survey of the literature, however, revealed that practically all reported polymerisations of αβ-unsaturated nitroolefins were ionic in character and generally base induced. Indeed, blank experiments showed that nitroethylene 5a and 2-nitropropene 5b to be resistant to polymerisation when heated in the presence of azo-bis-isobutyronitrile (AIBN). In all likelihood, traces of basic material in the reaction medium were responsible for the partial destruction of the nitroolefin in our previous experiments.[3e] If this were the case, added acid should have a beneficial effect on the yields. After performing the necessary blank experiments for compatibility, we undertook to reexamine the reaction in the presence of anhydrous camphorsulphonic acid. As an additional precaution we lowered the reaction temperature to -20°C - 0°C.

Thus, the acid 2 was converted to the acid chloride using oxalylchloride, and then to ester 3 by treatment with thiohydroxamic acid 1 in the presence of pyridine. After filtration of the pyridine hydrochloride and cooling, the camphorsulphonic acid was added followed by the nitroolefin. Irradiation with a tungsten lamp for a short time (~30 min) induced the desired reaction.

Under these modified experimental conditions, a considerable improvement in the yields was observed. For example, palmitic acid afforded 81% of α-nitrosulphide 6a as compared with only 53% in the absence of added camphorsulphonic acid. Other examples are listed in the Table.

Table

Entry	Ester 3	Nitroolefin (eq.)	α-Nitrosulphide (yield %)	Acid 8 (yield %)	Aldehyde or ketone 9 (yield %)
1	3a	5a (6.0)	6a (53)[a] (81)	8a (100)	-
2	3b	5a (1.2)	6b (52)[a]	-	-
3	3c	5a (2.1)	6c (45)[a] (70)	8b (89)	-
4	3d	5a (4.4)	6d (97)	8c (95)	9g (68)
5	3a	5b (3.6)	6e (65)	-	9a (70)
6	3c	5b (3.0)	6f (36)[b]	-	9b (100) (83)[c]
7	3e	5b (3.6)	6g (71)	-	9c (86) (81)[c]
8	3f	5b (3.6)	6h d	-	9d (75)[c]
9	3g	5b (3.6)	6i d	-	9e (55)[c]
10	3h	5b (3.6)	6k (100)	-	9f (90)
11	3d	5c (4.0)	6j (78)	-	-

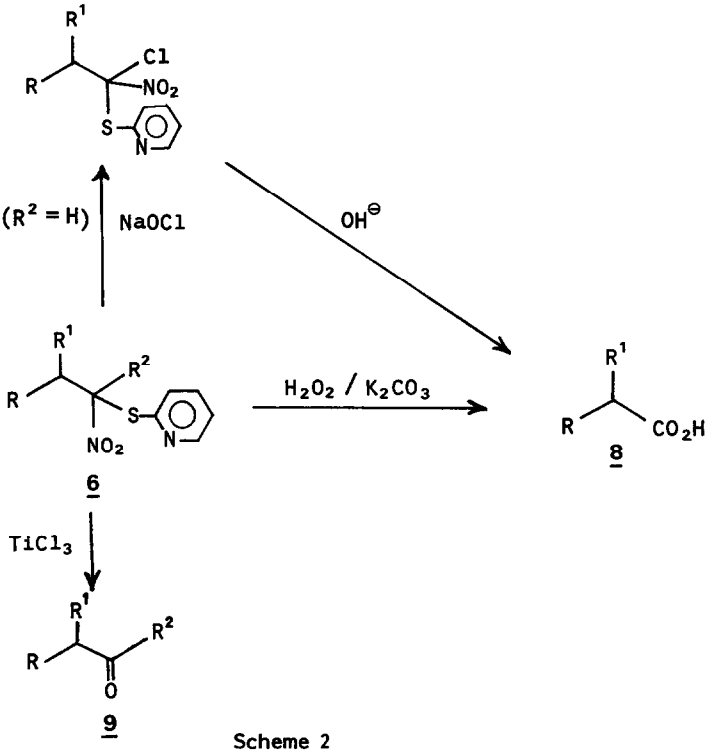
a. Preliminary experiments in the absence of added camphor sulphonic acid (see ref. 3). All other experiments performed in the presence of added acid.
b. Low yield due to instability of product. See text.
c. Overall yield without isolation of α-nitrosulphide 6.
d. No attempt at isolation was made in these cases.

2-Nitropropene gave equally satisfying results (Table). Noteworthy is the quantitative formation of α-nitrosulphide 6k from the steroid acid 2a. In the case of additions to 2-nitropropene, we noticed that adducts 6 derived from secondary and especially tertiary carboxylic acids were rather labile and difficult to purify. They decomposed on heating to 2,2'-dipyridyldisulphide 7 and other unidentified products. Bowman and co-workers,[4] who have prepared similar α-nitrosulphides by $S_{RN}1$ reaction of 2-pyridine thiolate with gem-dinitroalkanes, also noted the concomitant formation of 2,2'-dipyridyldisulphide. They proposed a radical-radical anion chain oxidative mechanism involving the α-nitrosulphide and the thiolate anion. In our case a radical disproportionation, sterically favoured in the case of adducts from secondary and tertiary carboxylic acids, may be operating. From a synthetic standpoint, we found it more convenient to convert the unstable α-nitrosulphides to the corresponding methyl ketones 9 *in situ* (*vide infra*).

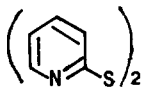
The activating effect of the nitro group is so powerful that even addition of adamantyl radicals to 1-nitropropene 5c to give 6j occurs normally (78% yield) despite the presence of the terminal methyl group. Previously β-alkyl substituents in the olefinic component were known to exert a considerable inhibitory action on radical additions, rendering β-substituted olefins almost useless for synthetic purposes.[1,2]

In addition to displaying interesting antifungal and antibacterial activity,[4] α-nitrosulphides are versatile synthetic intermediates. For example, adducts derived from nitro ethylene 5a are readily converted to the corresponding carboxylic acids 8 (Scheme 2) by exposure to alkaline hydrogen peroxyde[5] (Table). Chlorination with sodium hypochlorite followed by alkaline hydrolysis also achieves the same transformation, but less conveniently. Overall, this sequence, i.e. radical addition and oxidative cleavage, represents a mild conversion of a carboxylic acid into the next homologene, complementing therefore the classical Arndt-Eistert reaction,[6] which involves the use of diazomethane and hence not well adapted for large scale work.

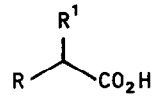
Another, perhaps even more useful transformation is the reductive cleavage with $TiCl_3$[7] to give the corresponding aldehyde or, in the case of α-nitrosulphides derived from 2-nitropropene 5b, the corresponding methyl ketone (Scheme 2). In practice, this is best carried out directly without isolation of the α-nitrosulphide. Indeed, purification of this intermediate is not only unnecessary but sometimes detrimental to the overall yield for reasons discussed above.



Scheme 2

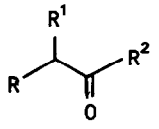


7



8

8a R = $CH_3(CH_2)_{14}$- ; R^1 = H
8b R = 1-cyclohexyl; R^1 = H
8c R = 1-adamantanyl; R^1 = H

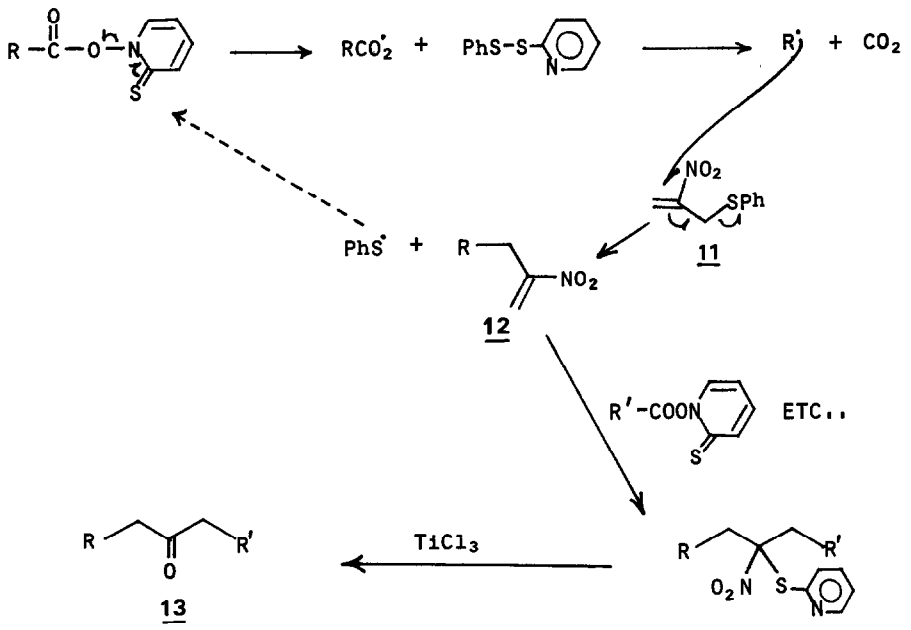


9

9a R = $CH_3(CH_2)_{14}$- ; R^1 = H ; R^2 = Me
9b R = 1-cyclohexyl; R^1 = H ; R^2 = Me
9c R = Ph_2CHCH_2 ; R^1 = H ; R^2 = Me
9d R = $(PhCH_2)_2CH$-; R^1 = H ; R^2 = Me
9e R = 1-methyl-1-cyclohexyl; R^1=H; R^2=Me
9g R = 1-adamantyl; R^1 = R^2 = H

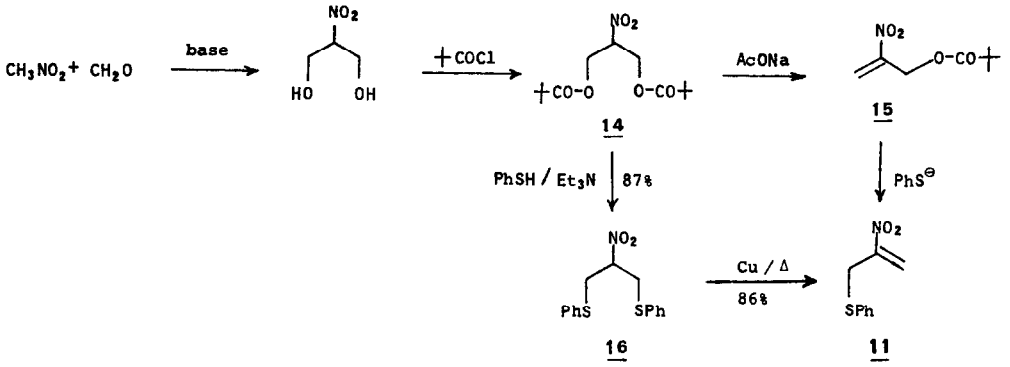
In the case of the steroid α-nitrosulphide 6k, treatment with $TiCl_3$ results in the cleavage of the 3α-acetoxy group as well as formation of the 25-keto group. Keto steroid 9f is thus obtained in 90% yield. Exposure of 9f to methyl magnesium iodide produces diol 10 (79%) having the important 25-hydroxy cholesteryl side chain of the vitamin D_3 metabolites.[8] This example nicely illustrates the ease with which a carboxylic acid function can now be manipulated to give useful products under mild conditions.

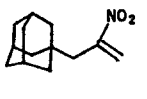
We have briefly examined the synthetic possibilities of a modified nitroolefin incorporating a good leaving group (in a radical sense). Addition of a radical on a nitroolefin such as 11, concerted with, or followed by, elimination of a phenylthiyl radical, which propagates the chain, should give another nitroolefin 12 (Scheme 3). In principle, a second radical addition on 12 would, after reductive cleavage, produce the symmetrical ketone 13, if the same radical is employed, or an unsymmetrical ketone if the second radical is different.



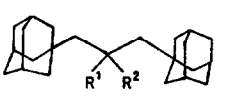
Scheme 3

Nitroolefin 11 had previously been prepared by Seebach and co-workers[9] by sequential elimination of pivalic acid from 14 to give 15 followed by addition of one equivalent of thiophenolate and finally loss of a second pivalic acid molecule (Scheme 4).





17



18 R^1 NO_2; R^2 = S-

19 $R^1 = R^2 = O$

Scheme 4

We have found the last two steps of this synthesis rather delicate. We therefore developed a more convenient route to 11 involving the treatment of dipivalate 14 with 2 equivalents of thiophenol in the presence of triethylamine to give the low melting sulphide 16 (87%). Heating with copper powder in a Kugelrohr apparatus under vaccum causes the elimination of one thiophenyl groups. The desired olefin 11 distilled as formed in 86% yield. After some experimentation, the addition of adamananyl radical to give 17 could be effected thermally in 77% yield. Double addition was somewhat less successful. Using a 3-4 fold excess of ester 3d, the expected ketone 19 was obtained in only ~35% yield after treatment with $TiCl_3$. We found, however, that $TiCl_3$ was not necessary. Mere exposure of the reaction mixture to air for 1 hour gave directly the ketone in ~40% yield. In this case, the corresponding α-nitrosulphide 18 is sufficiently hindered to undergo spontaneous disproportionation and capture of the intermediate carbon radicals with oxygen to give finally the ketone. This observation lends support to the radical nature of the decomposition of the hindered α-nitrosulphides noted above.

It is clear that radical additions to nitroolefins under controlled conditions can give in high yield intermediates of synthetic value. This is a reflection of the generality and mildness of our novel decarboxylation method as well as the extremely rich chemistry inherent in the nitro group itself.[10]

Experimental

M.p's were determiend with a Köfler hot stage apparatus. ^1H Nmr spectra are for deuteriochloroform solutions with tetramethylsilane as internal standard, unless otherwise stated. Optical rotations are for chloroform solutions. I.R. spectra are of nujol mulls unless stated to the contrary. Nitroolefins 5a, 5b and 5c were prepared by the method of Buckley and Scaife.[11]

N-(1-Adamantoyloxy)pyridine 2-thione 3d

[Note : Esters of this type are somewhat sensitive to laboratory lighting. It is advisable to cover reaction flask, chromatography column etc... with aluminium foil].

A mixture of 1-adamantane carboxylic acid (2.2 g), oxalyl chloride (4.1 g) and a trace of dimethylformamide in benzene was kept at room temperature for 1 hour under an inert atmosphere. The solvent and excess oxalyl chloride were evaporated off and the flask cooled in an ice bath. The hydroxamic acid 1 (1.7 g) in methylene chloride (10 ml) was added followed by a solution of pyridine (1 g) in methylene chloride (2 ml), added dropwise. The cooling bath was removed after 5 min. and the mixture kept at room temperature for 40 min. The solvent was evaporated under vacuum and the residue purified by chromatography on silica (methylene chloride) to give pure ester 3d, (3.5 g, 98%); m.p. 164-166°C (pentane-methylene chloride); ν_{max} 1782 cm^{-1}; δ_H: 7.0-7.8 (3H, m), 6.55 (1H, dd, J = 7 and 2 Hz), 1.7-2.3 (15H, m); m/e 289 (M^+) (Found: C, 66.55; H,6.69. Calc. for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62%)

General Procedure for the Preparation of Esters 3 and Radical Addition to Nitroolefin 5a, 5b, and 5c.

All operations are performed under an inert atmosphere with rigorous exclusion of moisture. Until irradiation is started (300 W tungsten lamp), the reaction vessels are best wrapped with aluminium foil.

A solution of the carboxylic acid (2 mmoles) in dry benzene (8 ml) was treated with excess oxalylchloride and a trace of dimethyl formamide. After keeping at room temperature overnight, the excess oxalyl chloride and solvent were removed in vacuo. The hydroxamic acid 1 (2.2 mmoles) was added with cooling (ice bath) followed by slow addition of pyridine (5 mmoles) in dry benzene (2 ml). The cooling bath was removed and stirring was continued at room temperature for 30 min. The pyridine hydrochloride was quickly filtered, camphor sulphonic acid (4 mmoles) was added and the resulting mixture cooled again to -20°- -10°C for reactions with nitroethylene 5a and to 0°C for 5b and 5c. The nitroolefin was added (see Table) as a solution in dry benzene (2 ml) and the reaction mixture irradiated for ca. 30 min. (disapperance of ester 3).

Concentration of the reaction mixture and chromatography on silica gave the pure α-nitrosulphides 6. Yields are recorded in the Table.

1-Nitro-1-(pyridine-2-thiyl)heptadecane 6a had m.p. 55-57°C (pentane-ether); ν_{max} 1555 cm^{-1}; δ_H: 8.45 (1H, m), 6.9-7.7 (3H, m), 6.55 (1H, t, J = 7 Hz), 2.30 (2H, m), 1.30 (28H, broad s), 0.90 (3H, broad t); m/e 348 ($M^+ - NO_2$) (Found: C, 67.92; H, 9.62. Calc. for $C_{22}H_{38}N_2O_2S$: C, 66.96; H, 9.62%).

2-Cyclohexyl-1-nitro, 1-(Pyridine-2-thiyl)ethane 6c had b.p. 180°C/0.2 mmHg (Lit.[3e], b.p. 180°C/0.2 mmHg); ν_{max} (neat) 1555 cm^{-1}; δ_H: 8.40 (1H, m), 6.9-7.7 (3H, m), 6.60 (1H, t, J = 8 Hz), 0.9-2.4 (13H, m); m/e 220 ($M^+ - NO_2$).

For the case of 2-(1-adamantyl)-1-nitro-1-(pyridine-thiyl)ethane 6d the intermediate ester 3d can be prepared separately and isolated as a crystalline solid in a high state of purity. It is sufficient to irradiate a mixture of 3d (2 mmoles) and nitroethylene (8.8 mmoles) in dichloromethane (5 ml) and toluene (3 ml) with only a small amount of camphorsulphonic acid (~40 mg) at -20°- -10°C. Purification as above furnished the pure α-nitrosulphide 6d in 97% yield, m.p. 100-101°C (pentane/ether); ν_{max} 1555 cm^{-1}; δ_H: 8.40 (1H, m); 7.3-7.7 (1H, m), 6.9-7.2 (2H, m), 6.55 (1H, t, J = 6 Hz), 1.3-2.2 (17H, m); m/e 272 ($M^+ - NO_2$) (Found: C, 63.88; H, 6.98; N, 9.05. Calc. for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80%).

2-Nitro-2-(Pyridine-2-thiyl)octadecane 6e had m.p. 54-55°C (pentane-ether); ν_{max} 1545 cm^{-1}; δ_H: 8.50 (1H, m), 7.0-7.7 (3H, m), 2.2 (2H, m), 2.0 (3H, s), 1.3 (28H, broad s), 0.9 (3H, broad t); m/e 362 ($M^+ - NO_2$) (Found: C, 67.79; H, 9.81; N, 7.06. Calc. for $C_{23}H_{40}N_2O_2S$: C, 67.60; H, 9.87; N, 6.86.%).

1-Cyclohexyl-2-nitro-2(pyridine-2-thiyl)-propane 6f was obtained as an oil. This compound was somewhat unstable and was not further purified but was used directly as such, ν_{max} (neat) 1550 cm^{-1}; δ_H (CCl_4): 8.50 (1H, m), 7.0-7.8 (3H, m), 2.2. (2H, m), 2.0 (3H, s), 0.8-2.0 (11H, m); m/e 234 ($M^+ - NO_2$).

5,5-Diphenyl-2-nitro-2-(pyridine-2-thiyl)pentane 6g was obtained as a somewhat unstable paste which was used without further purification; ν_{max} (neat) 1545 cm^{-1}; δ_H: 8.35 (1H, m), 7.7-6.9 (3H, m), 7.20 (10H, broad s), 3.80 (1H, t, J = 4 Hz), 2.0-2.3 (4H, m), 1.95 (3H, s); m/e 332 ($M^+ - NO_2$).

3α-Acetoxy, 25-nitro-25-(pyridine-2-thiyl)-11-oxo,27-nor-5β-cholestane 6k was obtained as a paste
and used without further purification, ν_{max} 1730, 1705, 1545 cm^{-1}; δ_H (CCl_4) 8.50 (1H, m), 7.0-7.8 (3H, m), 4.6 (1H, m), 2.0 (3H, s), 1.95 (3H, s), 1.15 (3H, s), 0.65 (3H, s); m/e 538 ($M^+ - NO_2$).

2-(1-Adamantyl)-1-nitro-1-(pyridine-2-thiyl)propane 6j was prepared with the same modification as for 6d. It had m.p. 110-112°C (ether); ν_{max} 1560 cm^{-1}; δ_H (before crystallisation; mixture of 2-diasteriomers) 8.7 (1H, m), 7.2-8.0 (3H, m), 7.2 (minor) and 7.1 (major) (1H, d, J = 2 Hz), 1.5-2.6 (16H, m), 1.20 (minor) and 1.15 (major) (3H, d, J = 8 Hz); m/e 286 ($M^+ - NO_2$) (Found: C, 65.27; H, 7.35; N, 8.58. Calc. for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43%).

Typical Procedure for the Conversion of Nitroethylene Adducts to Carboxylic Acids 8. *Preparation of 1-Adamanylacetic acid* 8c.

α-Nitro sulphide 6d (83 mg) was dissolved in methanol-tetrahydrofuran (1:1, 2.6 ml) and treated with aqueous potassium carbonate (300 mg in 0.7 ml of water) followed by 30% aqueous hydrogen peroxide (2 ml). The mixture was heated to 40°C for 15 hours. The temperature was then raised to 55-60°C, and additional portions of 30% hydrogen peroxide (2 ml then 1 ml) were added with vigorous stirring every 30 min. until consumption of all the starting material.

The reaction mixture was acidified with concentrated HCl and extracted with ether (3 x 20 ml). The combined organic layers were dried ($MgSO_4$), evaporated off and the residue purified by chromatography on silica (ether-dichloromethane 1:9) to give 1-adamantanylacetic acid (48 mg, 95%). m.p. 132-135°C (hexane) (lit.[12], m.p. 136°C).

Heptadecanoic acid 8a (100%) had m.p.58-60°C (hexane, lit.[13], 60-61°C).

Cyclohexylacetic acid 8b (89%) had b.p. 120°C/10 mmHg (lit.[13], b.p. 135/13 mmHg).

Preparation of Ketones 9.

A) Typical procedure for purified α-nitrosulphides.

3α-Hydroxy-27-nor-5β-cholestane-11,25-dione 9f.

A mixture of the nitrosteroid 6k (208 mg) and 15% aqueous $TiCl_3$ (1.1 g) in tetrahydrofuran (10 ml) was stirred under an inert atmosphere at room temperature overnight. The mixture was poured into water, extracted with ether (3 x 20 ml) and the combined organic layers dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography on silica (dichloromethane-ethylacetate 7:3) gave 9f (128 mg, 90%); m.p. 105-110°C (ether-pentane) $[\alpha]_D$ + 54° (c = 0.5); ν_{max} 3400, 1705 cm^{-1}; δ_H (CCl_4) 3.8 (1H, bs), 3.6 (1H, m), 2.1 (3H, s), 1.2 (3H, s), 0.65 (3H, s); m/e 402 (M^+) (Found: C, 76.64; H, 10.28. Calc. for $C_{26}H_{42}O_3$: C,77.56; H, 10.51%).

2-Octadecanone 9a (70%) had m.p. 45-50°C (methanol) (lit.[13], m.p. 52°C); ν_{max} 1710 cm^{-1}; δ_H: 2.45 (2H, t, J = 7 Hz), 2.2. (3H, s), 1.1-1.8 (28H, broad s), 0.9 (3H, t, J = 6 Hz); m/e 268 (M^+).

Cyclohexylacetone 9b *(100%)* had ν_{max} (neat) 1710 cm^{-1}; δ_H (CCl_4): 2.15 (1H, d, J = 6Hz), 2.10 (3H, s), 0.8-2.1 (11H, m); m/e 140 (m^+), semicarbazone m.p. 166-167.5°C (methanol), lit.[14], m.p. 166-166.5°C.

5,5 Diphenyl-2-pentanone 9c (81%) had m.p. 86-87.5°C (ether-pentane); ν_{max} 1705 cm^{-1}; δ_H (CCl_4) 7.2 (10H, bs), 3.85 (1H, t, J = 4 Hz), 2.2-2.4 (4H, m), 2.0 (3H, s); m/e 238 (M^+) (Found: C, 85.44; H, 7.60. Calc. for $C_{17}H_{18}O$: C, 85.67; H, 7.61%).

B) Typical Procedure Without Isolation of α-Nitrosulphide.

Radical addition to the nitroolefin was performed normally as described above. When irradiation was complete, the solvent and excess nitroolefin were evaporated under vacuum without heating (temperature preferably ≤10°C). To the residue, tetrahydrofuran (11 ml) and 15% aqueous $TiCl_3$ (21 g, 20 mmoles) were added and the mixture was stirred overnight under an inert atmosphere then poured into water, extracted with ether (3 x 20ml) and the organic layers combined and dried ($MgSO_4$). Evaporation and purification of the residue by chromatography on silica gave the corresponding ketones (yields are cited in the Table).

5-Phenyl-4-(Phenylmethyl)-2-pentanone 9d (75%) was a colourless liquid, ν_{max} (neat) 1710 cm^{-1}; δ_{H^+}7.3 (10H, bs), 2.6 (4H, bs), 2.2-2.8 (1H, m), 2.3 (2H, d, J = 2 Hz), 2.0 (3H, s); m/e 252 (M^+). This ketone was analysed as the semicarbazone, m.p. 134-135°C (ethanol) (Found: C, 73.54; H, 7.45; N, 13.56. Calc. for $C_{19}H_3N_3O$: C, 73.76; H, 7.49; N, 13.58%).

(1-Methylcyclohexyl)acetone 9e (55%) was a colourless oil, ν_{max} 1700 cm^{-1}; δ_H 2.35 (2H, s), 2.2 (3H, s), 2.5 (10H, bs), 1.05 (3H, s). It was analysed as the semicarbazone, m.p. 173-175°C (methanol) (Found: C, 62.69; H,9.91; N, 19.92. Calc. for $C_{11}H_{21}N_3O$: C, 62.53; H, 10.02; N, 19.89%).

(1-Adamantyl)-acetaldehyde 9g.

To a solution of the α-nitrosulphide 6d (42 mg) in a little methanol containing sodium methoxide (0.3 ml of a 0.5M methanolic solution) was added a mixture of 15% aqueous $TiCl_3$ (2 g) and ammonium acetate (1.63 g) in water (3 ml). After stirring for 8 min. at room temperature under argon, the reaction mixture was poured into water, extracted with ether (3 x 20 ml) and the organic layer dried ($MgSO_4$) and concentrated. Purification of the residue by flask chromatography (methylene chloride) gave the aldehyde 9g (16 mg, 68%) as an oil, ν_{max} (neat) 1720 cm^{-1}; δ_H: 9.80 (1H, t, J = 4 Hz), 2.15 (2H, d, J = 4 Hz), 1.5-2.3 (15H, m); m/e 178 (M^+). This was analysed as the semicarbazone, m.p. 214-215°C (methanol) (Found: C, 66.64; H, 9.00; N, 17.96. Calc. for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86%).

3α,25-Dihydroxy-5β-Cholestan-11-one 10.

Methyl magnesium iodide was prepared by the standard procedure from magnesium turnings (105 mg) and methyl iodide (720 mg) in ether (5 ml). The reaction mixture was cooled in ice and a solution of the ketosteroid 9f (96 mg) in dry ether (3 ml) was added dropwise under an inert atmosphere. After 20 min, the reaction mixture was quenched with water, acidified with 1N HCl, extracted with ether and the organic layer dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography on silica (ethylacetate-dichloromethane 3:7) gave the diol 10 (79 mg, 79%), m.p. 142-144°C (ethylacetate); $[\alpha]_D$ +52° (c = 0.4); ν_{max} 3350, 1700 cm^{-1}; δ_H 3.80 (1H, broad), 1.3 (6H, s), 1.20 (3H, s), 0.70; m/e 418 (M^+) (Found: C, 77.12; H, 10.71. Calc. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.07%).

1,3-Diphenylthio-2-nitropropane 16.

Triethylamine (0.74 g) was slowly added to a mixture of 2-nitro-1,3-propanediol dipivalate[9] 14 (1.00 g) and thiophenol (0.8 g) in ether (10 ml) and was cooled to 0°C. After 3 hours at the same temperature, the solvent was evaporated off and the residue purified by chromatography on silica (dichloromethane-pentane 3:2) to give the sulphide 16 (886 mg, 87%), m.p. 37-38°C (pentane-ether); ν_{max} 1550, 1370 cm^{-1}; δ_H: 7.20 (10H, b.s), 4.50 (1H, qn, J = 6 Hz), 3.35 (4H, d, J = 6 Hz); m/e 305 (M^+) (Found: C, 58.83; H, 5.00; N, 4.78. Calc. for $C_{15}H_{15}NO_2S_2$: C, 58.99; H, 4.95; N, 4.58%).

1-Phenylthio-2-nitropropene 11.

An intimate mixture of sulphide 16 (1.22 g) and copper powder (2.58 g) was heated to 180-200°C in a Kugelrohr apparatus under vacuum (0.2 mmHg). The nitroolefin 11 distilled slowly as formed in sufficient purity (usually >90%, remainder is starting material) (0.618 g, 80%). The spectral data are identical to those reported by Seebach et al.[9]

3-(2-Adamantyl)-2-nitropropene 17.

A solution of ester 3d (149 mg), a trace of camphorsulphonic acid (~10 mg) and nitroolefin 11 (525 mg, 93% pure) in benzene (3 ml) and dichloromethane (1 ml) was heated to reflux for 15 min (bath temperature 90°C) under an inert atmosphere. The solvent was evaporated off and the

residue purified by chromatography on silica (pentane-dichloromethane 1:1) to give the adamantane adduct 17 (88 mg, 77%), m.p. 92-93°C (hexane); ν_{max} 1522 cm^{-1}; δ_H 6.40 (1H, b.s), 5.40 (1H, b.s), 2.50 (2H, s), 1.2-2.2 (15H, m) (Found: C, 70.63; H, 8.58; N, 6.44. Calc. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33%).

1,3-Di-(1-adamantyl)-acetone 19.

A solution of 3-(2-adamantyl)-2-nitropropene 17 (43 mg) and ester 3d in benzene (3 ml) and dichloromethane (3 ml) was irradiated with a 300 W tungsten lamp at room temperature for 70 min. under an inert atmosphere. The mixture was then stirred under air for 60 min., the solvent removed and the residue purified by chromatography on silica (pentane-dichloromethane 1:1) to give the symmetrical ketone 19 (28 mg, 40%); m.p. 240-245°C (ethanol; lit.[15], m.p. 235-249°C); ν_{max} 1690 cm^{-1}; δ_H: 2.20 (4H, s), 1.5-2.2 (30H, m); m/e 326 (M^+).

The same ketone may be obtained directly (35% yield) by irradiating a solution of ester 3d (2 mmoles) and 3-phenylthio-2-nitropropene 11 (0.5 mmole) in the presence of a trace of camphorsulphonic acid (20°C, 1.5 hours).

Acknowledgements. We thank the C.N.R.S. for a post-doctoral Fellowship to one of us (H.T) and Roussel-Uclaf for generous financial assistance.

REFERENCES

1. P.A. Abell in "Free Radicals", J.K. Kochi Ed., Wiley-Interscience, New York, 1973; P.J. Flory, "Principles of Polymer Chemistry", Cornell University Press, Ithaca, 1953.
2. Inter alia, B. Giese and G. Kretzschmar, Angew. Chem. Intl. Ed., 20, 965 (1981); idem, Chem. Ber., 116, 3267 (1983); for a recent review see : B. Giese, Angew. Chem. Intl. Ed., 22, 753 (1983) and references therein.
3. a) D.H.R. Barton, D. Crich and W.B. Motherwell, J. Chem. Soc., Chem. Commun., 939 (1983); b) idem, Tetrahedron Letts., 4979 (1983); c) D.H.R. Barton and G. Kretzschmar, ibid., 5887 (1983); d) D.H.R. Barton, D. Crich and W.B. Motherwell, J. Chem. Soc., Chem. Commun., 242 (1984); e) D.H.R. Barton, D. Crich and G. Kretzschmar, Tetrahedron Letts., 1055 (1984); f) D.H.R. Barton and D. Crich, ibid., 25, 2787 (1984); g) D.H.R. Barton, D. Bridon and S.Z. Zard, Tetrahedron Letts., 25, 5777 (1984); h) D.H.R. Barton, D. Crich and G. Kretzschmar, J. Chem. Soc., Perkin 1), in press; i) D.H.R. Barton, D. Bridon and S.Z. Zard, J. Chem. Soc., Chem. Commun., in press.
4. W. Russell Bowman, D. Rakshit and M.D. Valmas, J. Chem. Soc. (Perkin 1), 2327 (1984) and references therein.
5. Adapted from a recently described method by G.A. Olah, M. Arvanaghi, Y.D. Vankar and G.K.S. Prakash, Synthesis, 662 (1980).
6. See inter alia: W.E. Bachmann and W.S. Struve, Org. React., 1, 38 (1942) and references therein; T. Aoyama and T. Shioiri, Chem. Pharm. Bull., 29, 3249 (1981) and references therein.
7. J.E. McMurry and J. Melton, J. Org. Chem., 38, 4367 (1973).
8. Previous syntheses of the 25-hydroxycholesterol side chain from bile acids have relied on the Arndt-Eistert reaction: W.H. Pearlman, J. Am. Chem. Soc., 69, 1475 (1947); H. Lettré, A. Egle, J. von Jena and K. Mathes, Liebigs Ann. Chem., 708, 224 (1967); H. Lettré, J. Greiner, K. Rutz, L. Hofmann, A. Egle and W. Bieger, ibid, 758, 89 (1972); B.I. Cohen, G.S. Tint, T. Kuramoto and E. Mosbach, Steroids, 25, 365 (1976); W.G. Dauben and P.H. Payot, J. Org. Chem., 21, 1299 (1956).
9. D. Seebach and P. Knochel, Helv. CHim. Acta, 67, 261 (1984).
10. For example see: D.H.R. Barton, W.B. Motherwell and S.Z. Zard, Bull. Soc. Chim. Fr. II, 61 (1983); for a review see: D. Seebach, E.W. Colvin, F. Lehr and T. Weller, Chimia, 33, 1 (1979).
11. G.D. Buckley and C.W. Scaife, J. Chem. Soc., 1471 (1947).
12. H. Stetter, M. Schwarz and A. Hirschhorn, Chem. Ber., 92, 1629 (1959).
13. Dictionary of Organic Compounds, I. Heilbron Ed., Eyre and Spottiswoode Pub., London, 1965.
14. J.T. Adams, B. Abramovitch and C.R. Hauser, J. Am. Chem. Soc., 65, 553 (1943).
15. H. Stetter and C. Becker, Liebigs Ann. Chem., 1992 (1976).