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UNSYMMETRICAL CONNECTIVE OLEFINATION BY KORNBLUM NITRO-SYNTHESIS : APPLICATIONS IN PHYTUBERIN CHEMISTRY*

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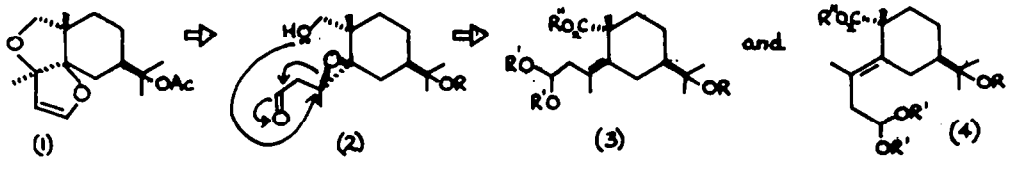
Abstract - Kornblum unsymmetrical olefin synthesis employing radical-anion chain crossed-coupling (light catalysed) of a mono- and a gem-di-nitro-compound, followed by reductive NO_2 removal, is examined in the context of a hindered olefin structure required for phytuberin synthesis. Whilst successful for a tetrasubstituted olefin model (for which a Wittig approach failed), increasing substitution on the ß-position of the mono-nitro component supressed the coupling reaction, presumably for steric reasons. An alternative coupling involving a bromonitro-cyclohexane and a mononitroacetal caused symmetrical coupling of the mononitro-component in high yield, rather than a crossed reaction.

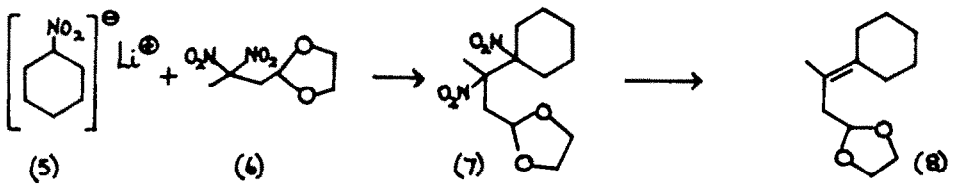
Reductive elimination (using Na_2S/DMF) from either rac.- or meso- 1,2-dinitro-1,2-diphenylethane leads to (E)-stilbene [> 98% (E)] probably through a stabilised radical or anion. A convenient preparation of triphenylisoxazoline-N-oxide is reported.

In connexion with synthetic work on the stress metabolite of potato, phytuberin (1),[1,2] intermediate (2) was considered as a precursor and the (Z) and (E) olefins (3) and (4) became of interest (Scheme 1). The latter have hindered tetrasubstituted double bonds and methods for the formation of such systems,[3] particularly in the presence of functionality, are scarce. Beyond a report that Kornblum's olefin synthesis[4,5] is not an attractive proposition for the synthesis of seco-steroids,[6] it has not been employed in natural product work, but its reported insensitivity to steric hindrance appeared to be an attractive feature for our purpose. In addition, the methodology is compatible with a number of useful functional groups.



Scheme 1. Phytuberin Retrosynthesis.

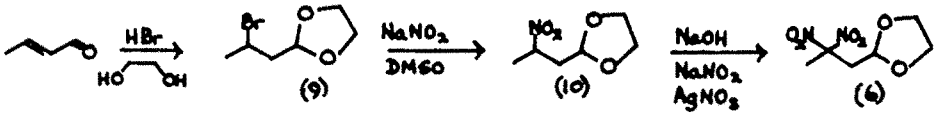
* This paper is dedicated to Professor R.A. Raphael F.R.S. on the occasion of his 65th birthday.



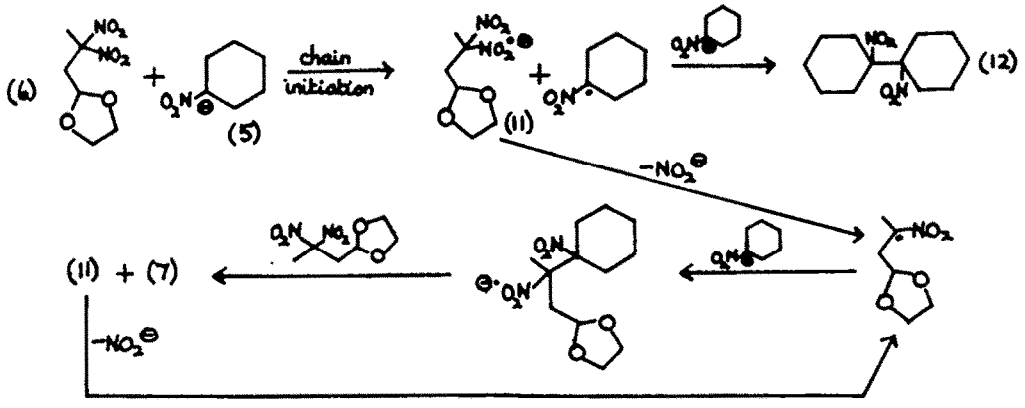
Scheme 2. Kornblum Olefin Synthesis.

Our first objective was the model olefin-acetal (8) and the principle of the Kornblum synthesis, as applied to our situation, is shown in scheme 2. Nitrocyclohexane was prepared (80%) by peracetic acid oxidation of cyclohexylamine,[7] whilst the dinitro-acetal (6) was made according to Scheme 3. Treatment of crotonaldehyde with HBr in ethylene glycol[8] gave the bromodioxolan (9) (69%) which has better keeping qualities than the dimethyl or diethyl acetal and at 0°C remains stable for long periods. Both dimethylformamide (containing urea to solubilise sodium nitrate) or dimethylsulphoxide were used as solvents for formation of (10) and best conditions were 5 days in DMSO at 20°C (46%). Phloroglucinol was used as a nitrite ester scavenger to check the side-reaction producing pseudonitrole. Oxidative nitration using silver nitrate/sodium nitrite,[9] a non-chain electron transfer substitution which proceeds with elimination of silver metal,[10] was used to convert the mono-nitroacetal (10) into the dinitro-(6). Literature conditions gave low yields (often < 20%), but adjustments to ensure complete initial formation of the sodium salt raised this to 81%.

Initially the lithium salt of nitrocyclohexane was generated in situ (LiOMe/DMSO) and treated with the gem-dinitroacetal (6) under nitrogen and with irradiation (quartz halogen lamp) to give the vicinal dinitroacetal (7) in 41% yield, along with the symm. - vicinal dinitro-product (12). On development of the reaction conditions however, in particular by isolating the lithium salt of the



Scheme 3. Synthesis of the Dinitroacetal.

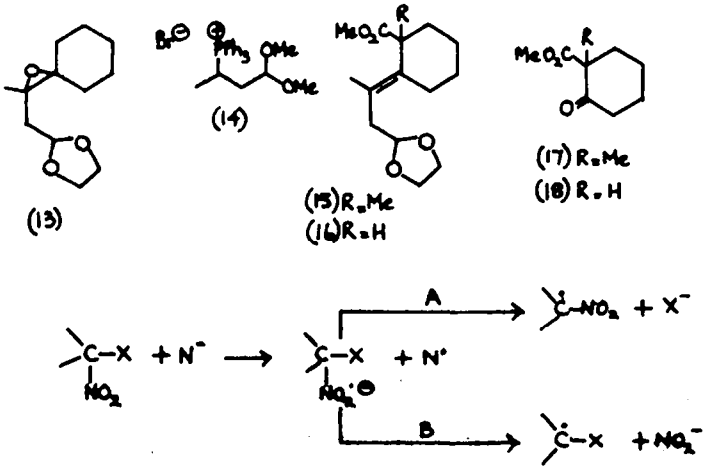


Scheme 4. Radical-Anion Chain Leading to Dinitroacetal (7).

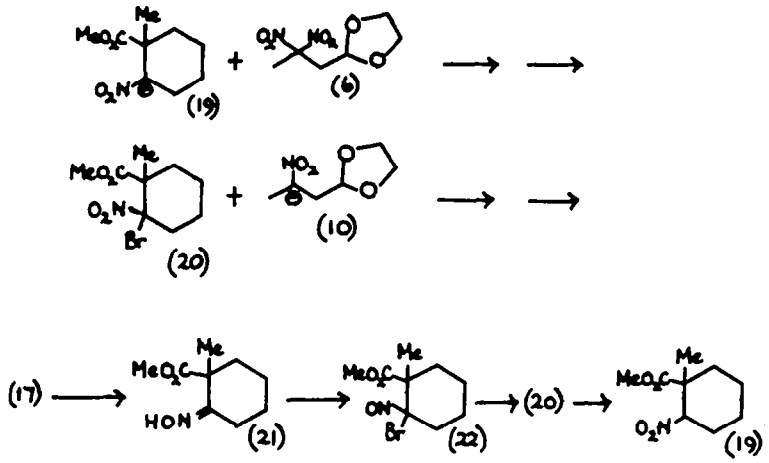
mono-nitro compound as a fine powder prior to coupling (Experimental), it was found that the yield of (7) could be almost doubled (80%). The mechanistic course of the reaction, which is photochemically accelerated, is considered to involve chain initiation via electron transfer between anion (5) and the gem-dinitro compound (6), the chain being sustained by the propagation sequence shown in Scheme 4.[11,12]

Experiments on the reductive elimination of the nitro-groups in (7) using calcium amalgam[5,13] under heterogeneous conditions initially gave poor yields of olefin. Neither increase in amalgam/substrate ratio, nor elevation of the temperature (up to 100°C) had much effect on either the nature or the yield of product. However, lengthened reaction times caused significant improvements and with a 6 day reaction period and good stirring yields of (8) ranging between 50% and quantitative were recorded in a single pass reaction. Recovered material can be recycled, and irradiation with a quartz halogen lamp accelerated the reaction (all starting material disappeared in 3 days). The model compound (8) could be epoxidised using m-chloroperbenzoic acid[14] to give the epoxide (13) in almost quantitative yield. In a comparison with the Kornblum reaction, the ylide formed from (14) with n-butyl lithium was treated with cyclohexanone but no Wittig reaction ensued presumably because of susceptibility to steric effects: even with benzaldehyde as ketonic component the yield was only ∿ 14%.

Attention was then turned to (15) as a closer model for (4), containing similar hindering substituents. The cyclic β-keto ester (18) was methylated to form (17) (84%) using the DMSO method of Née et al.[15] However, using an alternative procedure by Chuang,[16] but extending reaction time and using a larger volume of solvent, the claimed yield (80%) could be increased to 93% and since the method employs only 1:1 mol of methyl iodide as opposed to the 10 fold excess used by Née, this was preferred. Conversion of a carbonyl into a nitro group can be effected by oxidation of the oxime with trifluoroperactic acid (though the reaction is sensitive to steric hindrance).[17] A second method involves reduction of the oxime to an amine followed by peracid oxidation.[7,18,19] A third method,[20] conversion of the oxime to a bromonitroso compound, oxidation to the bromonitro compound, and then reductive debromination appeared particularly attractive as it is reportedly less subject to steric hindrance and the bromonitro intermediate gives flexibility in permitting an alternative nitro-coupling mode. The Kornblum coupling, using a



Scheme 5. Pathways for the Radical Anion Decomposition.

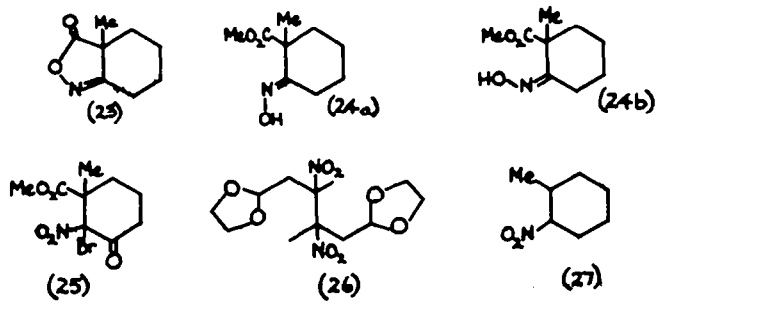


Scheme 6. Ketone → Nitro Conversion.

di- and a mono-nitro compound is a specific example of a more general type of reaction in which a radical anion derived from an α-substituted nitroalkane may fragment in two ways (Scheme 5).[11,12] When X = Cl, Br, I, $ArSO_2$ path A is followed: when X = CO_2R, COR, CN, NO_2 path B is followed. Thus coupling modes involving pairs (19) and (6) or (20) and (10) are feasible.

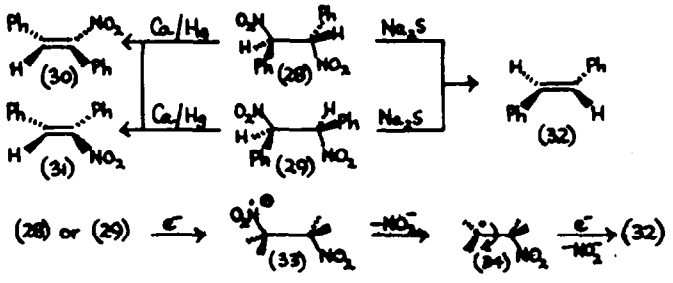
Careful study of conditions permitted formation of oxime (21) in 67% yield. The use of an aqueous medium at 70°C with reaction times of > 1 h, or addition of methanol, led to marked decreases in yield and best yields were obtained by a slow reaction (19 h) in water at 19°C, using very vigorous stirring. Yields were decreased by formation of an isoxazalone[21] by-product (23). However, attempts to form (23) by refluxing the oxime (as isolated) in light petroleum (b.p. 80-100°C), treatment with pyridine, or 30% methanolic potash, or subliming the oxime *in vacuo*, all failed, and it was concluded that this must be the (*E*)-oxime (24a), the (*Z*)-(24b) having cyclised readily during formation to isoxazalone. Formation of the bromonitroso product (22) was effected by adding a saturated solution of oxime (24a) in dioxan to a vigorously stirred suspension of *N*-bromosuccinimide (3 mol) in aqueous sodium bicarbonate. The blue nitroso-oil (22) was completely formed in 16 h and was oxidised [conc. nitric acid or conc. nitric acid/30% hydrogen peroxide/(1:1)] as a pentane solution yielding (20) (81% based on oxime). The product consisted of a pair of diastereomers (~ 1:1) which could be separated either by hplc or by tlc. Reduction of the bromonitro compound (20) with sodium borohydride gave the nitro ester (19) in 85% yield. A side product from the nitric acid oxidation, formed in 2% yield, was identified as the bromonitro ketone (25).

Unfortunately attempts to cross couple the nitro-ester anion (19) with the *gem*-dinitroacetal (6) at 20°C using irradiation from either a quartz lamp or

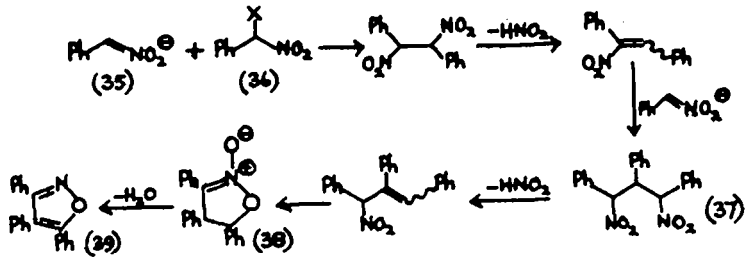


fluorescent tubes failed. Other attempts at 65°C, or employing crown ether, also failed and it was concluded that steric effects due to the β-carbon substitution had become prohibitive. However, the introduction of the ester function in (19) might also have adverse effects on anion reactivity and so Path A of Scheme 5, i.e. (20) + (10), was also tried using diastereomer-A of (20). Again, no crossed coupled product was isolated, only debrominated ester (19) and the symmetrically coupled acetal (26) (71%). The latter could be separated chromatographically into meso- and racemic forms (∿ 1:1). A second reaction using diastereomer-B of (20) also gave debrominated ester (19) and the symmetrical dinitroacetal (26) (80%, ∿ 1:1 diastereomers). Though not leading to the desired (15), the high yield of (26) is interesting. Attempts were now made to reduce steric interactions further by using the anion of methyl nitrocyclohexane (27) in a reaction with dinitro-acetal (6) but again the desired crossed-coupling did not take place. The reaction thus appears to be unable to surmount the steric crowding that this route to structures (15) and (16) presents.

In connexion with aliphatic examples, Kornblum reported that where the possibility exists, (Z)- and (E)-olefin mixtures were isolated from the reduction of vicinal dinitro compounds.[5] Since (Z)- and (E)- stilbenes are well known, it was decided to ascertain the position when diastereomeric 1,2-dinitro-1,2-diphenylethanes were reduced with calcium amalgam. Racemic material (29) was isolated by treating the sodio-derivative of phenylnitromethane with iodine in potassium iodide[22] and Schechter's stereochemical assignment[23] was confirmed by an X-ray single-crystal structure.[24] The meso-form (28) was made by treating stilbene with nitrogen dioxide.[25] Attempts to eliminate both nitro groups with Ca/Hg led instead to elimination of nitrous acid, possibly during work-up, giving α-nitrostilbenes. Both rac- and meso- forms gave a mixture of (Z)- and (E)-α-nitrostilbenes, (30) and (31). However, treatment with sodium sulphide nonahydrate in DMF caused successful denitration and it is reported that tin II chloride is also effective.[13] Each diastereomer gave almost pure (E)-stilbene (32) [< 2% of (Z)] and isomerisation of (Z)- to (E)-stilbene was ruled out by treating pure (Z)-stilbene with sodium sulphide under the reaction conditions (Scheme 7). It has been suggested that elimination of the two nitro-groups from a vic-dinitro compound by sodium sulphide involves generation of a radical anion (33) followed by loss of nitrite anion giving radical (34).[4] The benzyl stabilised radical, or anion after electron transfer, may in this example have a sufficiently long life-time to permit rotation leading to mainly (E)-stilbene from each diastereomer. A similar view is held by Fukunaga.[13] The stereochemistry in particular eliminations of this kind may therefore depend on radical or anion stabilities and the subject requires further investigation.



Scheme 7. Elimination Products from rac.- and meso-1,2-Dinitro-1,2-diphenylethanes.



Scheme 8. Origins of Triphenylisoxazoline N-oxide (38).

Both rac- and meso-1,2-dinitro-1,2-diphenylethane gave 3,4,5-triphenylisoxazole (39) when refluxed with 30% aqueous sodium hydroxide. The precursor of (39) is doubtless 3,4,5-triphenylisoxazoline N-oxide (38) which gives the former on heating. Its formation from α-nitrostilbene and phenylnitromethane under base catalysed conditions was studied by Worrall[26] and others and is believed to follow Scheme 8. More recently Fukunaga[27] has obtained (38) in 48% yield by treating sodium or potassium phenylmethylnitronate (35) with silver nitrate in DMSO for 2 h. During the present work we found simple alternative conditions for making the compound. Treatment of phenylnitromethane with lithium methoxide in anhydrous DMF followed by iodine in DMF gave 3,4,5-triphenylisoxazoline N-oxide in 50% yield: presumably the initial reaction is between (35) and (36, X=I).

EXPERIMENTAL

Analytical thin layer chromatography (tlc) employed silica gel HF254 on 5 x 20 cm glass plates: preparative tlc similarly involved 20 x 20 cm, 20 x 40 cm and 40 x 40 cm plates: visualisation used iodine vapour or λ254 or λ336 nm light. Gas-liquid chromatography (glc) involved a Pye 104 instrument, whilst high performance liquid chromatography (hplc) employed Waters analytical and preparative equipment and silica columns. Reactions were irradiated with a Daray 1200 quartz-halogen lamp.

2-(2-Bromopropyl)-1,3-dioxolane (9). - Ethylene glycol (12.4 g, 0.2 mol) was cooled in ice - salt and hydrogen bromide was passed to give a weight increase of 8 g. Crotonaldehyde (14.0 g, 0.2 mol) was added slowly with stirring, continuing passage of HBr until 12 g more had dissolved (total 20 g, 0.25 mol). The mixture was stirred at 5°C for 2 h, kept at 5°C for 15 h and then at 20°C for 2 h. The mixture was extracted with ether and the product was distilled to give the dioxolane (9) (26.9 g, 69%), b.p. 83-84°C/13 mm Hg, n_D^{20} 1.4787 (Lit.[8] b.p. 76-78°C/10 mm Hg, n_D^{15} 1.4799). (Found: C, 36.85; H, 5.75. Calc. for $C_6H_{11}BrO_2$: C, 36.9; H, 5.65%).

2-(2-Nitropropyl)1,3-dioxolane (10) - Sodium nitrite (21.6 g, 0.31 mol, dried at 120°C) in dimethylsulphoxide (DMSO, 200 ml, distilled from calcium hydride) was stirred with phloroglucinol (23.6 g, 0.24 mol, dried at 105°C). The above bromoacetal (30 g, 0.15 mol) in DMSO (10 ml) was added and the solution was stirred (5 days) at 20°C. Work up using ice-water and $CHCl_3$ gave the dioxolane (10) (11.7 g, 47%), b.p. 92-93°C/3 mm Hg, n_D^{22} 1.4482. (Found: C, 44.7; H, 7.2; $(M-1)^+$ 160.0599. $C_6H_{11}NO_4$ requires C, 44.7; H, 6.85%; (M-1) 160.0609) δ($CDCl_3$) 5.08 (1H, t, J 4 Hz, O.CH.O), 4.92 (1H, q of t, J 7 Hz, 2 Hz, .$CHNO_2$), 4.04 (4H, m, .$O(CH_2)_2O$.), 2.64 (d of d of d of d, J, 15 Hz, 8 Hz, 4 Hz, .CH(H)), 2.04 (1H, d of t, J 16 Hz, 5 Hz, .CH(H), 1.67 (3H, d, J 7 Hz, Me).

2-(2,2-Dinitropropyl)-1,3-dioxolane (6). - The β-nitroacetal (10) (11.0 g, 68 mmol) was dissolved in water (27 ml) containing sodium hydroxide (2.73 g, 68 mmol) at 60-70°C and then sodium nitrite (7.07 g, 102 mmol) was dissolved. The cooled solution was added to a rapidly stirred ice-cold solution of silver nitrate (25.41 g, 137 mmol) in water (47 ml) layered with ether (55 ml) and containing a few drops of sodium hydroxide (enough to cause brown silver oxide just to appear). A precipitate which darkened and coagulated appeared. The ice-bath was removed and the mixture was stirred (1.5 h) at 20°C. The black solids were filtered off and washed with ether (50 ml). The aqueous layer was

extracted with ether (2 x 50 ml) and after washing with brine the combined organic extracts were evaporated and distilled to give the dinitrodioxolane (6) (9.91 g, 70%), b.p. 121-122°C/2.5 mm Hg, n_D^{22} 1.4651. (Found: C, 34.8: H, 4.7; N 13.25; (M-1)⁺ 205.0475. $C_6H_{10}N_2O_6$ requires C, 34.95; H, 4.85; N, 13.6% (M-1) 205.0461. δ($CDCl_3$): 5.04 (1H, t, J 4 Hz, .OCHO.), 3.94 (4H, m, .O(CH_2)$_2$O.), 2.96 (2H, d, J 4 Hz, .CH_2), 2.24 (3H, s, Me).

Lithium Salt of Nitrocyclohexane (5). - Nitrocyclohexane was made from cyclohexylamine (21.9 g) by Emmons' procedure[7] in 80% yield b.p. 88-90°C/16 mm Hg, n_D^{20} 1.4634. (Lit.[7] b.p. 109°C/40 mm Hg, n_D^{25} 1.4620). Dry methanol (30 ml) was treated with lithium chips (0.2 g, 28 mg atom) at 0°C under nitrogen. Nitrocyclohexane (3.70 g, 29 mmol) was added and stirring was continued at 20°C for 25 min. Evaporation and addition of dry ether (60 ml) gave a solid which was washed under dry nitrogen with ether (60 ml). Drying by rotation under vacuum (1 mm Hg at 60°C for 14 h) gave the salt (5) as a pale yellow free flowing powder.

vic-Dinitrodioxolane (7) - Lithium salt of nitrocyclohexane (5)(1.05 g, 78 mmol) was covered with dry DMSO (15 ml, distilled from calcium hydride) under a blanket of dry nitrogen and vigourously stirred. 2-(2,2-Dinitropropyl)-1,3- dioxolane (1.60 g, 78 mmol) in DMSO (2 ml) was syringed into the suspension and stirred under anhydrous conditions with exclusion of air (6 h). During this period the mixture was irradiated with a quartz halogen lamp. The product was poured into ice-water and extracted with ether benzene. Evaporation and chromatography (pressure column) on silica eluting with chloroform-ether mixtures gave the vicinal dinitro acetal (7) (1.76 g, 79%) which crystallised as colourless plates from methanol m.p. 88.5-89.5°C. (Found: C, 50.05; H, 6.9; N, 9.45; (M-1)⁺ 287.1221. $C_{12}H_{20}N_2O_6$ requires C, 50.0; H, 6.95; N, 9.7%; (M-1) 287.1243). δ($CHCl_3$): 4.94 (1H, t, J 5 Hz, .OCHO.), 3.88 (4H, m, .O(CH_2)$_2$O.), 2.89 (1H, d of d, J 15 Hz, 5 Hz, .CH(H)), 2.62 (2H, br.d, J 12 Hz, ring .CH(H).C(NO_2)$_2$), 2.28 (1H, d of d J 15 Hz, 5 Hz, .CH(H)), 2.03-1.20 (8H, br.m, ring .CH), 1.72 (3H, s, Me). 1,1'-Dinitrobicyclohexane (12) (71 mg, 7%) was also isolated from the chromatogram, needles from acetone m.p. 209-218°C (decomp.) (Lit.[28] m.p. 214-220°C). (Found: C, 56.15; H, 7.85; H, 10.75; (M-NO_2)⁺ 210.1510 (M-N_2O_3)⁺ 180.1512. Calc. for $C_{12}H_{20}N_2O_4$: C, 56.25; H, 7.8; N, 10.95%: (M-NO_2) 210.1494; (M-N_2O_3) 180.1514). δ($CDCl_3$): 2.61 (4H, br. d, J 12 Hz, CH(H).C.NO_2), 1.96-1.00 (16H, br. m, ring CH.).

Olefinic Dioxolane (8). - Mercury (II) chloride (15.96 g, 59 mmol) in anhydrous DMF(12 ml) and HMPA (60 ml) was added under argon to vigorously stirred calcium shot (ALFA, 7.51 g, 188 mg atom) in HMPA (60 ml, distilled from CaH_2) the temperature being kept below 55°C (ice-bath). After 2 h, the vic. dinitrodioxolane (7) (16.9 g, 59 mmol) was added and stirring continued for 6 days at room temperature with irradiation (quartz halogen lamp). The mixture was poured into ice-water and extracted with ether/benzene (1:1). Washing, evaporation and distillation gave the olefinic dioxolane (8) (6.41 g, 56%) as a colourless oil b.p. 90-91°C/1 mm Hg, n_D^{14} 1.4945, pure by glc (1% OV 17 at 120°C). (Found: C, 73.45; H, 10.1; M⁺ 196.1451. $C_{12}H_{20}O_2$ requires C, 73.45; H, 10.2%; M 196.1463). δ($CDCl_3$): 4.91 (1H, t, J 5 Hz, .OCHO.), 3.92 (4H, m, .O(CH_2)$_2$O.), 2.43 (2H, d, J 5 Hz, CH_2), 2.19 (4H, br. s, ring CH_2), 1.76 (3H, s, Me), 1.54 (6H, br. s, ring CH_2). On a smaller scale yields near theoretical were sometimes recorded. The granular size and activity of the calcium is important and material from some suppliers was ineffective.

Epoxy Dioxolane (13). - Olefin (8) (1.96 g, 10 mmol) in dichloromethane (100 ml) and 0.5M aqueous sodium bicarbonate (30 ml) was treated slowly with m-chloroperbenzoic acid (3.05 g, 15 mmol). After stirring at 20°C (2 h) the organic layer was washed with M-sodium hydroxide and then water, and dried and evaporated to give the epoxide (13) (2.19 g, quantitative) as a colourless oil which was almost pure by glc (1% OV 17, 150°C). (Found: C, 67.45; H, 9.27; (M-1)⁺ 211.1353. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.4%; (M-1) 211.1334. δ($CDCl_3$): 5.02 (1H, t, J 4 Hz, .OCHO.), 3.92 (4H, m,.O(CH_2)$_2$), 1.98 (2H, m, .CH(H)),1.64 (10H, br. m, ring .CH_2), 1.42 (3H, s, Me).

2-Methyl-2-carbomethoxycyclohexanone (17) - Sodium (1.39 g, 60 mg atom) dissolved in dry methanol (14 ml) was added to a mixture of the β-keto-ester (18) (9.36 g, 60 mmol) and methyl iodide (9.36 g, 66 mmol) at 0°. The reaction mixture was stirred for 2 days at 5°C and then poured into water (50 ml). Extraction with ether followed by washing (15% aqueous KOH), evaporation and distillation gave the methylated ester (17) (9.52 g, 93%), b.p. 88-89°C/7 mm Hg, n_D^{23} 1.4574. Lit. n_D^{29} b.p. 69-72°C/0.4 mm Hg, n_D^{25} 1.4570). (Found: C, 63.55; H, 8.4; M⁺ 170.0941. Calc. for $C_9H_{14}O_3$: C, 63.55; H, 8.25%; M 170.0943). Purity was verified by glc (5% SE30 at 120°C) ν_{max} 1735 (CO_2Me), 1715 (.C=O) cm^{-1}: δ($CDCl_3$): 3.72 (3H, s, .OMe), 2.62-1.42 (8H, br. m, ring .CH_2), 1.30 (3H, s, Me).

2-Methyl-2-carbomethoxycyclohexanone oxime (24a) - β-Keto-ester (17) (50 g, 0.29 mol) was added to vigorously stirred hydroxylamine hydrochloride (30.7 g, 0.44 mol) and sodium acetate (28.9 g, 0.35 mmol) in water (120 ml) and stirring was continued for 19 h at room temperature. The white solid was filtered off and crystallised from n-hexane giving the oxime (24a) (36.7 g, 67%), needles m.p. 102-102.5°C (Found: C, 58.45, H, 8.30; N, 7.4; M⁺ 185.1047. $C_9H_{15}NO_3$

requires C, 58.4; H, 8.1; N, 7.55%; M 185.1052). ν_{max}1720 (CO_2Me), 1665 (w, C=N str.). $\delta(CDCl_3)$: 9.24 (1H, br. s, =NOH, exchg. D_2O, position and shape varied with conc.), 3.78 (3H, s, OMe), 3.26 (1H, br. d., J 12 Hz, ring -CH(H)), 2.42 (1H, br. d, J 12 Hz, ring-CH(H)), 2.24-1.48 (6H, br. m, ring .CH_2), 1.40 (3H, s, Me).

The aqueous reaction mixture was extracted with ether (3 x 50 ml), combined with liquors from the oxime crystallisation, evaporated and distilled (twice) to give isoxazolone (23) (6.9 g, 15%), b.p. 100-103°C/1 mm Hg, n_D^{20} 1.4808. (Found: C, 62.8; H, 7.4; N, 9.1: M^+ 153.0793. $C_8H_{11}NO_2$ requires C, 62.75; H, 7.2; N 9.15%, M 153.0790). ν_{max}(liq.film) 1780 (C=O), 1620 (w, C=N str) cm^{-1} $\delta(CDCl_3)$ 2.79-1.19 (8H, m, ring CH_2), 1.43 (3H, s, Me).

Bromonitro-esters (20) (Stereoisomers A and B). - N-Bromosuccinimide (66.3 g, 0.37 mol, freshly crystallised from water) was suspended in sodium bicarbonate (31.5 g, 0.38 mol) in water (350 ml) and cooled to 5°C. Oxime (24a) (23 g, (0.12 mol) in dioxan (80 ml) was added, the blue reaction mixture being stirred (17 h) and then extracted with n-pentane (4 x 100 ml). Evaporation gave a blue oil (39 g) to which n-pentane (50 ml) and conc. nitric acid (150 ml) was added after cooling in ice-salt. After the initial exothermic reaction had subsided, the solution was allowed to warm up to room temperature and stirred for 18 h. The reaction mixture was then cooled and water (150 ml) added. The lower oily layer was separated and the aqueous layer extracted thoroughly with n-pentane. Oil and pentane extracts were combined and washed with 5% sodium hydroxide, then water. Drying and evaporation gave a pale yellow oil (28.4 g, 81%) which was distilled, b.p. 95-109°C/0.4 mm Hg to give a colourless oil (26.2 g) containing two major compounds (tlc, elutant benzene). Hplc using benzene elution and R.I. detection afforded two isomeric bromonitro-esters (20A) and (20B) together with the more highly oxidised by-product (25).

Isomer (20A) (9.3 g, 27%), a viscous oil, had b.p. 95-96°C/0.1 mm Hg, n_D^{18} 1.5079 (Found: C, 39.05; H, 5.4; N, 4.75 $(M-NO_2)^+$ 233.0187. $C_9H_{14}NO_4Br$ requires C, H, 5.0%; N, 5.0%; $(M-NO_2)$ 233.0187). ν_{max} (liq.film), 1720 (CO_2Me), 1565 and 1350 (NO_2) cm^{-1}. $\delta(CDCl_3)$: 3.72 (3H, s, OMe), 2.74 (2H, br. m, ring CH_2) 2.24-1.04 (6H, br. m, ring CH_2), 1.80 (3H, s, Me).

Isomer (20B) (12.7 g, 37%), a viscous oil b.p. 107-110°C/0.5 mm Hg, n_D^{19} 1.5106, crystallised on keeping: recrystallised from light petroleum (b.p. 40-60°) it had m.p. 44-44.5°C (Found: C, 38.7; H, 4.95; N, 4.95; $(M-NO_2)^+$ 233.0190). $C_9H_{14}NO_4Br$ requires C, 38.55; H 5.0; N, 5.0%; $(M-NO_2)$ 233.0178) ν_{max}(liq.film), 1720 (CO_2Me), 1570 and 1350 (NO_2) cm^{-1}. $\delta(CDCl_3)$ 3.76 (3H, s, OMe), 3.04-1.56 (8H, br, m, ring CH_2), 1.52 (3H, s, Me). The A and B isomers were also characterised by ^{13}Cmr spectra.

Oxidation product (25) was isolated by hplc (0.64 g, 1.8%) and was crystallised from n-hexane, then cyclohexane, m.p. 105-106°C. (Found: C, 36.9; H, 4.25; N, 4.65; $(M-OMe)^+$ 261.9750. $C_9H_{12}NO_5Br$ requires C, 36.85; H 4.1; N, 4.8%; $(M-OMe)$ 261.9715. ν_{max} ($CHCl_3$): 1740 (CO_2Me), 1720 (C=O), 1570 and 1345 (NO_2) cm^{-1}. $\delta(CDCl_3)$ 3.80 (3H, s, OMe), 3.36-1.52 (6H, br. m, ring CH_2), 1.48 (3H, s, Me).

2-Methyl-2-carbomethoxynitrocyclohexane (19).-Bromonitro-ester (20A) (1.25 g, 4.5 mmol) in methanol (2 ml) was added to ice-cold sodium borohydride (1.71 g, 45 mmol) in methanol (24 ml) and water (8 ml) and stirred at 20°C for 26 h. Methanol was evaporated and the aqueous solution was acidified with 15% aqueous hydroxylamine hydrochloride. The product was extracted with pentane and evaporated to give a pale yellow oil (0.88 g, 98%) which was almost pure by tlc (elutant benzene) or glc (5% SE30 at 150°C) criteria. Distillation gave the nitro-ester (19) b.p. 120-122°C/5.5 mm Hg, n_D^{16} 1.4764 (Found: C, 53.85; H, 7.55; N 6.55; $(M-NO_2)^+$ 155.1071. $C_9H_{15}NO_4$ requires C, 53.75; H 7.45; N, 6.95% $(M-NO_2)$ 155.1072 ν_{max} (liq.film) 1720 (.CO_2Me) 1560, 1380 (.NO_2) cm^{-1} Nmr showed the product to be a mixture of two isomers. The major one (84%) had ($CDCl_3$): 4.98 (1H, d of d, J 11 Hz, 4 Hz, .CH(NO_2), 3.80 (3H, s, OMe), 2.44-1.36 (8H, br. m, ring CH_2), 1.28 (3H, s, Me). Corresponding data for the minor isomer (16%) were $\delta(CDCl_3)$: 4.63 (1H, t, J 5 Hz), 3.70 (3H, s, OMe), 2.44-1.36 (8H) and 1.36 (3H).

A similar result was obtained on reductive debromination of the isomeric bromonitro ester (20B) which gave (19) in 87% yield.

Treatment of bromonitro-ester (20) with the anion of β-nitroacetal (10) - Bromonitro ester (20A) (1.4 g, 5 mmol) was treated with β-nitroacetal (10) (0.8 g 5 mmol) and lithium methoxide (0.38 g, 10 mmol) in DMSO (10 ml) for 24 h. The reaction mixture was worked up to give a yellow oil (846 mg) and the oil was separated by preparative layer chromatography (elutant ether) to give two diastereomeric vicinal dinitroacetals (26) (71%) isolated as rac. - and meso-forms (though not stereochemically identified) and the debrominated nitro-ester (19) (21%) (identical with an authentic specimen).

Isomer (26A) (258 mg, 32%) crystallised from methanol after further preparative tlc (elutant chloroform), m.p. 84.5-85°C. (Found: C, 45.05; H, 6.45; N, 8.5; $(M-1)^+$ 319.1128. $C_{12}H_{20}N_2O_8$ requires C, 45.0; H, 6.25; N, 8.75%; (M-1) 319.1141). $\delta(CDCl_3)$: 4.92 (2H, d of d, J 7 Hz, 5 Hz, .OCHO.), 3.84 (8H, br.m, .$O(CH_2)_2O$.) 2.84 (2H, d of d, J 14 Hz, 6 Hz, .CH(H)), 2.54 (2H, d of d, J 16 Hz, 4 Hz, .CH(H)), 1.64, s, Me).

Isomer (26B) (310 mg, 39%) crystallised from methanol m.p. 109.5-110.5°C (Found: C, 44.95; H 6.35; N, 8.35; (M-1)$^+$ 319.1151. $C_{12}H_{20}N_2O_8$ requires C, 45.0; H 6.25; N 8.75% (M-1) 319.1141). δ($CDCl_3$) 4.90 (2H, t, J 5 Hz, .OCHO.) 3.84 (8H, br. m, .O(CH_2)$_2$O.), 2.88 (2H, d of d, J 16 Hz, 4 Hz, .CH(H)), 2.09 (2H, d of d, J 17 Hz, 5 Hz., CH(H)), 1.76 (6H, s, Me).

A similar result was obtained using the isomeric bromonitro-ester (20B), (26) being obtained as an ~1:1 mixture of diastereoisomers (80%): the nitro-ester (19) (13%) was also isolated.

2-Methylnitrocyclohexane (27) - 1-Bromo-1-nitro-2-methylcyclohexane was prepared[20] (6.64 g, 37% from 2-methylcyclohexanone oxime), and bulb distilled (oven 60°C/0.4 mm Hg, n_D^{12} 1.5084. (Found: 37.6; H, 5.35; N, 6.45; Br, 35.35. Calc. for $C_7H_{12}NO_2Br$: C, 37.85; H, 5.4; N, 6.3, Br 36.05%). Prepared[22] by sodium borohydride reduction of the bromonitro-compound (6.00 g), the nitro-compound (27) (2.08 g, 54%) had b.p. 72-74°C/4mm Hg, n_D^{16} 1.4648 (Found: C, 58.4; H, 9.35; N, 9.35; (M-NO_2)$^+$ 97.1010. Calc. for $C_7H_{13}NO_2$: C, 58.75; H, 9.1; N 9.8%; (M-NO_2) 97.1017).

Phenylnitromethane (36, X=H) - Prepared according to the literature[30] in 43% yield this had b.p. 110°C/12 mm Hg, n_D^{17} 1.5330 (Lit.[30] b.p. 76°C/2 mm Hg, n_D^{20} 1.5316. It was pure as judged by glc (1% OV 17, 100°C).

Phenyldinitromethane (36, X=NO_2) - Benzaldoxime[31] was formed in 87% yield, m.p. 30-33°C (Lit.[32] m.p. 35°C). Benzaldoxime was converted into phenyldinitro-methane by treatment with dinitrogen tetroxide according to a literature method.[33] Crystallised from n-hexane (32% yield) it had m.p. 79-80°C (Lit.[33] m.p. 79-80°C). (Found: C, 46.05; H, 3.05; N, 15.15; (M-NO_2)$^+$ 136.0391. Calc. for $C_7H_6N_2O_4$: C, 46.15; H, 3.3; N 15.4%; (M-NO_2) 136.0399).

rac.-1,2-Dinitro-1,2-diphenylethane (29) - Iodine (3.08 g, 12 mmol) dissolved in a minimum of saturated aqueous potassium iodide was added to the sodium salt of phenylnitromethane (3.82 g, 24 mmol) in water (20 ml) with stirring for 3.5 h at 20°C. Extraction with benzene gave a paste (1.45 g) which was crystallised from ethanol giving the racemic compound (29) (430 mg), needles m.p. 148-153°C (Lit.[22] m.p. 151-153°C). (Found: C, 61.55; H, 4.35; N, 10.0; (M-HNO_2)$^+$ 225.0793. Calc. for $C_{14}H_{12}N_2O_4$: C, 61.75; H, 4.4; N, 10.3%; (M-HNO_2) 225.0790). δ($CDCl_3$): 7.40 (10-H, s, Ph), 6.52 (2H, s, .CH).

meso-1,2-Dinitro-1,2-diphenylethane (28) - Nitrogen dioxide (prepared by heating dry lead (II) nitrate in nitrogen) was passed into a stirred solution of (E)- stilbene (1.0 g) in benzene (10 ml) until saturated. The product was filtered off and crystallised from ethanol to give the meso-compound (28), m.p. 230-232°C (Lit.[26] m.p. 230-233°C). (Found: C, 61.9; H, 4.3; N, 10.05; (M-HNO_2)$^+$ 225.0803. Calc. for $C_{14}H_{12}N_2O_4$: C, 61.75; H, 4.4; N, 10.3%; (M-HNO_2) 225.0790.

When either rac.-(29) or meso-(28) was heated on a steam bath in 30% aqueous sodium hydroxide for 3 h, 3,4,5-triphenylisoxazole (39), m.p. 214-215°C was obtained.

Treatment of meso- and rac- 1,2-dinitro-1,2-diphenylethane with calcium amalgam. - Calcium shot (108 mg, 2.7 mg atom) in HMPA (1 ml) was stirred under under argon with mercury II chloride (223 mg, 0.8 mmol) in HMPA (1 ml) and DMF (0.3 ml). After 2 h, the meso-compound (28) (215 mg, 0.8 mmol) in HMPA (0.6 ml) and DMF (0.3 ml) was syringed in and stirred for 4 h. The reaction mixture was poured into water and extracted with ether/benzene. Evaporation gave a yellow oil (140 mg, 78%) which on preparative tlc (elutant ether-hexane, 1:1) gave yellow needles of (Z)- nitrostilbene, m.p. 73.5-74.5°C (Lit.[34] m.p. 74-75°C) and flat yellow prisms of (E)-α-nitrostilbene m.p. 124-127°C (Lit.[34] m.p. 127-128°C). Authentic specimens of the (E) and and (Z)-compounds were made according to the method of Freeman and Stevens.[34] Similar treatment of the meso-compound (28) gave a mixture of (E)- and (Z)-α-nitrostilbene.

Denitration of meso- and rac- 1,2-dinitro-1,2-diphenylethane with sodium sulphide. - A stirred mixture of rac.-1,2-dinitro-1,2-diphenylethane (55 mg, 0.2 mmol) and sodium sulphide nonahydrate (120 mg, 0.5 mmol) in anhydrous DMF (1 ml), under nitrogen, was irradiated with a quartz halogen lamp for 4 h at room temperature. The product was poured into water and worked up to give a white solid (34 mg, 95%) shown to be almost pure (E)-stilbene containing 1.5% (Z)-stilbene by glc comparison (1% OV 17 at 160°C) using authentic reference samples. Recrystallisation gave (E)-stilbene m.p. 123.5-124.5°C (Lit.[23] m.p. 124°C). (Found: C, 93.25; H, 6.55; M$^+$ 180.0919. Calc. for $C_{14}H_{12}$: C, 93.35; H, 6.65%; M 180.0939. δ($CHCl_3$) 7.82-7.22 (10H, br. m, 2 x Ph), 7.18 (2H, s, =CH). The meso-diastereomer similarly gave (E)-stilbene (96% yield) m.p. 124-125°C containing a trace of (Z)-isomer.

Triphenylisoxazoline-N-oxide (38) - Phenylnitromethane (36, X=H) (686 mg, 5 mmol) in DMF (1 ml) was added under nitrogen to lithium methoxide (191 mg, 5 mmol) in anhydrous DMF (4 ml) and stirred for 15 min. The mixture was cooled in ice and iodine (635 mg, 2.5 mmol) in DMF (4 ml) added. Stirring was then continued at room temperature for 2 h and the product was poured into brine (75 ml) and extracted with ether/benzene (1:1). The extracts were washed with sodium metabisulphite solution, then water, and dried and evaporated to give

the N-oxide (38) (264 mg, 50%) which was crystallised first from methanol, then cyclohexane, m.p. 160-161°C (Lit.[26] m.p. 161-162°C) (Found: C 79.35; H, 5.45; N, 4.5; M^+ 315.1265. Calc. for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4; N 4.45%; M 315.1259). δ($CDCl_3$): 7.96 (2H, m), 7.50 (13H, br, m, Ph), 5.51 (1H, d, J 4 Hz, -CH), 4.91 (1H, d, J 4 Hz, -CH).

A similar experiment using bromine in place of iodine gave the N-oxide (38) in 31% yield, m.p. 161-162°. together with 3,4,5-triphenylisoxazole (39) (15%) m.p. 214-215.5° (Lit.[26] m.p. 214-215°C). (Found: C, 84.95; H, 5.35; N, 4.5; M^+ 297.1164. Calc. for $C_{21}H_{15}NO$: C, 84.95; H, 5.05, N 4.7%, M 297.1154). Melting the N-oxide for a few min gave the isoxazole (39) m.p. 216-217°C.

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