Investigation of the Retro-Diels–Alder Reaction as a Method for the Generation of Nitroso-olefins

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N-Methyltetrahydrocarbazole (1) reacts with ethyl 2-nitrosopropenoate and with 3-nitrosobut-3-en-2-one to give the fused oxazines (2) in good yields. These adducts, when heated in xylene, undergo retro-Diels–Alder reaction to give the starting carbazole and the nitroso-olefins, which are intercepted by indole. Thermolysis of the adduct (2a) in pentanol results in the formation of the oximinoketone (6) in good yield. α-Nitrosostyrene also forms an adduct (2c) with *N*-methyltetrahydrocarbazole, but gives in addition the nitrone (3) and a 2 : 1 adduct, which is assigned the structure (4). The oxazine (2c) failed to undergo the retro-Diels–Alder reaction when heated in xylene. Attempts to induce a retro-Diels–Alder reaction of the adducts (8) formed from hexamethylbicyclo[2.2.0]hexa-2,5-diene and 3-nitrosobut-3-en-2-one were also unsuccessful.

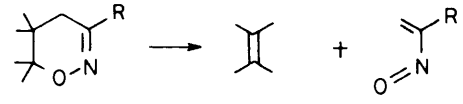
Nitroso-olefins can be generated by the 1,4-elimination of hydrogen halide from oximes of α-halogenoaldehydes and α-halogenoketones. Some of these compounds have been characterised spectroscopically [1] but many others, particularly those bearing only hydrogen at the β-carbon atom, are too short-lived in solution to be detected. We have investigated different methods of generating these intermediates, in order to provide additional evidence for their existence and alternatives to the halogeno-oximes as precursors for their use in synthesis. This paper concerns an investigation of an approach based on the retro-Diels–Alder reaction.

The retro-Diels–Alder reaction has been used to generate a wide variety of reactive species in a synthetically useful manner.[2] Some nitroso compounds, including the highly reactive nitrosocarbonyl compounds, are conveniently generated in this way.[3] We considered that the cleavage of 5,6-dihydro-4*H*-1,2-oxazines (Scheme) might provide a viable route to some nitroso-olefins.

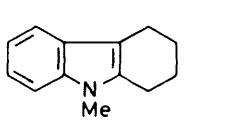
There is a fairly good precedent for this reaction, in that the structurally similar 3,4-dihydro-2*H*-pyrans are known to fragment at high temperatures: for example, the parent system is cleaved to ethylene and acrolein at temperatures above 500 °C.[4] On the other hand, it was known from earlier work that different modes of fragmentation of 5,6-dihydro-4*H*-1,2-oxazines, involving cleavage of the N–O bond, could occur at moderate temperatures (below 200 °C).[5] The type of ring-cleavage envisioned in the Scheme could not therefore be a completely general process, and special structural features would be required to favour it.

The retro-Diels–Alder reaction is facilitated when one of the fragments is a stable aromatic system. We have previously found that some nucleophilic heteroaromatic compounds undergo cycloaddition reactions with nitroso-olefins of the general structure $H_2C{=}C(R)NO$ to give fused 1,2-oxazines in good yields. Alkyl substituted indoles are excellent partners in reactions of this type.[6] We therefore chose to investigate the thermal properties of adducts derived from a 1,2,3-trialkyl substituted indole, in which the possibilities of unwanted isomerisation to open-chain oximes would be minimised. 9-Methyl-1,2,3,4-tetrahydrocarbazole (1) [7] was prepared as a suitable substrate.

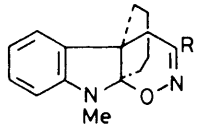
Its adducts (2a) and (2b) with 3-nitrosobut-3-en-2-one and with ethyl 2-nitrosopropenoate were isolated in high yields as crystalline solids. Reaction of the carbazole with α-nitrosostyrene gave the oxazine (2c) in lower yield (46%), together with two other products. One of these, another 1 : 1 adduct, was assigned the nitrone structure (3) on the basis of its spectroscopic properties; in particular, the ^1H n.m.r. spectrum



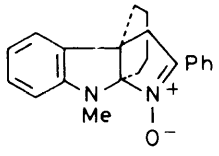
Scheme.



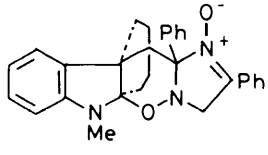
(1)



(2) a ; R = COMe
b ; R = CO_2Et
c ; R = Ph



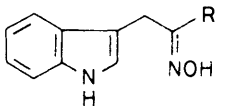
(3)



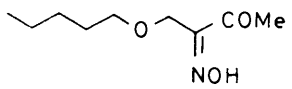
(4)

shows downfield shifts for the signals due to the hydrogen atoms of the methylene group in the five-membered ring, and for the *ortho*-hydrogens of the phenyl group, in comparison with those of the oxazine (2c). These downfield shifts have been observed before in other nitrones of this type.[8] The third product proved to be a 2 : 1 adduct of the nitroso-olefin and the carbazole. It is tentatively assigned structure (4) by analogy with other 2 : 1 adducts derived from α-nitrosostyrene which have been isolated by Mackay and Watson.[9]

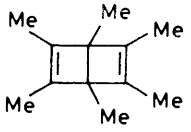
Evidence for the retro-diene process was sought by heating the oxazines (2) in an inert solvent in the presence of indole, which is a good reagent for intercepting these nitroso-olefins.[6] The adducts (2a) and (2b), when heated in *o*-xylene (140 °C) in the presence of indole, slowly gave the indole adducts (5). Even after 3—4 days, substantial amounts of the starting oxazines were recovered and the indole adducts were isolated only in low yields (16 and 24%, respectively). *N*-Methyltetrahydrocarbazole and unchanged indole were also isolated from each reaction mixture. The yields of transfer products (5) were not increased by the use of a higher boiling solvent, nor of a dipolar aprotic solvent (dimethylformamide): in both cases



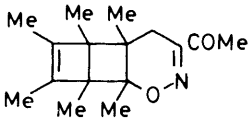
(5) a ; R = COMe
b ; R = CO_2Et



(6)



(7)



(8) (*exo* and *endo*)

more unidentified decomposition products were found. It was found that the adduct (2a) partially dissociated when it was briefly heated in the melt at 180—200 °C. *N*-Methyltetrahydrocarbazole was formed, but other products were not identified. The oxazine (2c) derived from α-nitrosostyrene failed to give the retro-diene reaction when heated with indole in xylene for up to 7 days, but slowly decomposed during this period. There was no evidence for its thermal conversion into the nitrone (3) nor into the 2 : 1 adduct (4).

It appeared possible that the retro-diene reaction of the oxazines (2a) and (2b) might be more efficient than was indicated by these experiments in that the *N*-methyltetrahydrocarbazole was competing with the indole for the intermediates and thus reversing the process. In order to intercept the intermediate more effectively, pentanol was used as both solvent and nucleophile. The adduct (2a) was heated in pentanol (b.p. 136 °C) for 48 h and the expected product of nucleophilic addition to the nitroso-olefin, the oxime (6), was isolated in 67% yield by column chromatography. *N*-Methyltetrahydrocarbazole was also isolated (63%).

This experiment indicates that the cleavage of the adduct (2a) at 140 °C takes place quite cleanly, but because *N*-methyltetrahydrocarbazole is itself such a good reaction partner, and cannot readily be removed from the medium, the practical uses of the retro-diene process are limited.

In an attempt to overcome this problem we prepared adducts of hexamethylbicyclo[2.2.0]hexa-2,5-diene (7) and 3-nitrosobut-3-en-2-one. The reaction gave a mixture of two 1 : 1 adducts which were formulated as the *endo*- and *exo*-oxazines (8). One of the isomers was isolated pure by fractional crystallisation and was fully characterised. It was assumed that if the retro-diene reaction of these adducts took place, either thermally or in the presence of a catalyst, then the hydrocarbon fragment would be hexamethylbenzene which would not add readily to the nitroso-olefin. Unfortunately no suitable conditions could be found to bring about the retro-Diels–Alder reaction. The adducts (8) were heated in the presence of indole, with and without a silver(I) catalyst, but none of the transfer product (5a) was detected.

Thus, although the viability of the thermal cleavage outlined in the Scheme has been demonstrated, the adducts (2) are not ideal substrates from a practical point of view, and other compounds, possibly based on the addition to more volatile heteroaromatics, need to be developed.

Experimental

^1H N.m.r. spectra were obtained at 220 MHz in $CDCl_3$. Mass spectra were recorded at 70 eV using a direct insertion probe. I.r. spectra were recorded as mulls in liquid paraffin. Flash column chromatography was carried out using silica gel 80–100 mesh (Whatman). Hexamethyl-dewarbenzene(-bicyclo-[2.2.0]hexa-2,5-diene) was supplied by the Aldrich Chemical Co. Ltd. 9-Methyl-1,2,3,4-tetrahydrocarbazole was prepared by a modification of the general method described by Gale and Wilshire,[7] the sodium salt of tetrahydrocarbazole being prepared by heating the latter with sodium hydride in dimethylformamide at 100 °C for 5 h.

Addition of Nitroso-olefins to 9-Methyl-1,2,3,4-tetrahydrocarbazole.—(*a*) *3-Nitrosobut-3-en-2-one.* To a solution of 1-chlorobutane-2,3-dione 2-oxime [6] (1.36 g, 10 mmol) and *N*-methyltetrahydrocarbazole (3.70 g, 20 mmol) in dry dichloromethane (100 cm^3) was added dry powdered sodium carbonate (7 g, excess) and the suspension was stirred at 20 °C for 18 h. The reaction mixture was filtered and the filtrate, after evaporation, was subjected to column chromatography (silica). Gradient elution with light petroleum (b.p. 60—80 °C) and ethyl acetate gave (i) *N*-methyltetrahydrocarbazole (2.10 g, 11.3 mmol) and (ii) *3-acetyl-9-methyl-4,4a,9,9a-tetrahydro-4a,9a-butano[1,2]oxazino[6,5-b]indole* (2a) (2.24 g, 79%), m.p. 163—164 °C (from dichloromethane–hexane) (Found: C, 71.7; H, 7.0; N, 9.9. $C_{17}H_{20}N_2O_2$ requires C, 71.8; H, 7.0; N, 9.9%); $\nu_{max.}$ 1 692 and 1 602 cm^{-1}; δ 1.30—1.75 (7 H, m), 2.20—2.30 (1 H, m), 2.28 (3 H), 2.46 (1 H, d, *J* −19.5 Hz), 2.90 (1 H, d, *J* −19.5 Hz), 2.93 (3 H), and 6.55—7.17 (4 H, m); *m/z* 284 (M^+).

(*b*) *Ethyl 2-nitrosopropenoate.* Ethyl bromopyruvate oxime [6] (2.90 g, 13.8 mmol), *N*-methyltetrahydrocarbazole (2.30 g, 12.4 mmol, 0.9 equiv.), and sodium carbonate (10 g), gave, by the method described in (*a*), *3-ethoxycarbonyl-9-methyl-4,4a,9,9a-tetrahydro-4a,9a-butano[1,2]oxazino[6,5-b]-indole* (2b) (3.39 g, 87%), m.p. 101—102 °C (from dichloromethane–hexane) (Found: C, 68.6; H, 7.0; N, 8.8. $C_{18}H_{22}N_2O_3$ requires C, 68.8; H, 7.0; N, 8.9%); $\nu_{max.}$ 1 720 and 1 610 cm^{-1}; δ 1.23 (3 H, t, *J* 6.2 Hz), 1.3—1.7 (7 H, m), 2.10—2.25 (1 H, m), 2.55 (1 H, d, *J* −19.4 Hz), 2.86 (3 H), 2.89 (1 H, d, *J* −19.4 Hz), 4.22 (2 H, q, *J* 6.2 Hz), and 6.5—7.15 (4 H, m); *m/z* 314 (M^+).

(*c*) *α-Nitrosostyrene.* α-Chloroacetophenone oxime (4.00 g, 23.6 mmol), *N*-methyltetrahydrocarbazole (4.00 g, 21.6 mmol), and sodium carbonate (15 g), gave, by the method described in (*a*), (i) the *9-methyl-3-phenyl-4,4a,9,9a-tetrahydro-4a,9a-butano[1,2]oxazino[6,5-b]indole* (2c) (3.20 g, 46.5%), m.p. 102.5—104 °C (from ethyl acetate–hexane) (Found: C, 79.2; H, 7.0; N, 8.7. $C_{21}H_{22}N_2O$ requires C, 79.25; H, 6.9; N, 8.8%); $\nu_{max.}$ 1 608 and 1 592 cm^{-1}; δ 1.25—2.10 (8 H, m), 2.66 (1 H, d, *J* −17.1 Hz), 2.85 (3 H), 2.89 (1 H, d, *J* −17.1 Hz), 6.4—7.2 (4 H, m), 7.25—7.35 (3 H, m), and 7.50—7.58 (2 H, m); *m/z* 318 (M^+); (ii) *6-methyl-2,11a-diphenyl-4,5a,6,10b,11,11a-hexahydro-5a,10b-butano-3H-imidazo[1′,2′: 2,3][1,2]oxazino-[6,5-b]indole 1-oxide* (4) (0.67 g, 7%), m.p. 190—192 °C (from ethyl acetate–hexane) (Found: C, 77.0; H, 6.5; N, 9.3. $C_{29}H_{29}N_3O_2$ requires C, 77.2; H, 6.4; N, 9.3%); $\nu_{max.}$ 1 608 and 1 495 cm^{-1}; δ 1.00—1.85 (8 H, m), 2.69 (1 H, d, *J* −14.6 Hz), 2.88 (3 H), 2.91 (1 H, d, *J* −14.6 Hz), 4.31 and 4.44 (ABq, *J* −19.5 Hz), 6.11—6.15 (2 H, m), 6.39—6.45 (1 H, m), 6.9—7.2 (9 H, m), and 8.12—8.16 (2 H, m); *m/z* 451 (M^+); (iii) *8-methyl-2-phenyl-3,3a-8,8a-tetrahydro-3a,8a-butanopyrrolo-[2,3-b]indole 1-oxide* (3) as an amorphous solid (0.73 g, 10%) contaminated with intractable polar material. Crystallisation gave the pure nitrone (0.22 g, 3%), m.p. 163—165 °C (decomp.) (from ethyl acetate–hexane) (Found: C, 79.0; H, 6.8; N, 8.8. $C_{21}H_{22}N_2O$ requires C, 79.25; H, 6.9; N, 8.8%); $\nu_{max.}$ 1 606 and 1 488 cm^{-1}; δ 1.15—2.10 (7 H, m), 2.71—2.74 (1 H, m), 3.22 (1 H, d, *J* −17.1 Hz), 3.26 (3 H), 3.34 (1 H, d, *J* −17.1 Hz), 6.50—6.75 (2 H, m), 7.04—7.17 (2 H, m), 7.30—7.40 (3 H, m), and 8.23—8.32 (2 H, m); *m/z* 318 (M^+).

Addition of 3-Nitrosobut-3-en-2-one to Hexamethyldewarbenzene.—1-Chlorobutane-2,3-dione 2-oxime (4.18 g, 30.9 mmol), hexamethyldewarbenzene (5.00 g, 30.9 mmol), and sodium carbonate (15 g) were stirred in dichloromethane (600 cm^3) at 20 °C for 18 h. The mixture was filtered and the filtrate was evaporated. Flash column chromatography of the residue gave a mixture of *adducts* (8) in a *ca.* 1 : 1 ratio (by n.m.r.). Bulb-to-bulb distillation gave the mixture of the isomers of (8) in an analytically pure state (Found: C, 73.6; H, 9.0; N, 5.4. $C_{16}H_{23}NO_2$ requires C, 73.6; H, 8.8; N, 5.4%). The mixture partly solidified on standing; crystallisation gave the less soluble isomer, m.p. 93—95 °C (from hexane); $\nu_{max.}$ 1 695 and 1 592 cm^{-1}; δ 0.64 (3 H), 0.84 (3 H), 1.07 (3 H), 1.29 (3 H), 1.53 (1 H, d, J −15.9 Hz), 1.53 (3 H), 1.56 (3 H), 2.58 (3 H), and 2.79 (1 H, d, J −15.9 Hz); m/z 261 (M^+). The ^1H n.m.r. spectrum of the other isomer, obtained from that of the mixture, had δ 0.81 (3 H), 0.90 (3 H), 0.98 (3 H), 1.12 (3 H), 1.17 (3 H), 1.18 (3 H), 1.66 (1 H, d, J −14.6 Hz), 2.44 (3 H), and 3.60 (1 H, d, J −14.6 Hz).

Thermolysis of Oxazines.—*Oxazine* (2a). (*a*) The oxazine (0.568 g, 2.0 mmol) and indole (0.234 g, 2.0 mmol) were heated in *o*-xylene under N_2 at 140 °C for 72 h. The complex reaction mixture was evaporated and the residue was subjected to column chromatography (silica), which gave, using light petroleum and ethyl acetate mixtures, (i) *N*-methyltetrahydrocarbazole (0.126 g, 34%), (ii) the oxazine (2a) (0.204 g, 36%), (iii) indole (0.192 g, 82%), and (iv) 1-(indol-3-yl)butane-2,3-dione 2-oxime (0.084 g, 16%), m.p. 120—121 °C (from dichloromethane–hexane) (lit.,[6] m.p. 120—121 °C), which was identified by comparison with an authentic specimen.

(*b*) The oxazine (2a) (0.568 g, 2.0 mmol) was dissolved in freshly distilled pentan-1-ol (30 cm^3) and the solution was heated under reflux under dry N_2 for 48 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica) which gave (i) *N*-methyltetrahydrocarbazole (0.232 g, 63%), (ii) the oxazine (2a) (0.035 g, 12%), and (iii) 1-pentyloxybutane-2,3-dione 2-oxime (6) as a yellow oil (0.251 g, 67%), b.p. 102—104 °C at 0.02 mmHg; $\nu_{max.}$ 3 300 and 1 692 cm^{-1}; δ 0.80—0.90 (3 H, m), 1.20—1.40 (4 H, m), 1.50—1.65 (2 H, m), 2.37 (3 H), 3.49 (2 H, t), 4.41 (2 H), and 10.80 (1 H). The n.m.r. spectrum was identical with that of a specimen prepared from 1-chlorobutane-2,3-dione 2-oxime, pentan-1-ol, and sodium carbonate. It was characterised as its 3-(2,4-*dinitrophenylhydrazone*), m.p. 157—159 °C (Found: C, 49.0; H, 5.9; N, 19.15. $C_{15}H_{21}N_5O_6$ requires C, 49.05; H, 5.7; N, 19.1%).

(*c*) A small sample of the oxazine (2a) was heated at 180—200 °C for 3 min. The presence of *N*-methyltetrahydrocarbazole and of the oxazine (2a) was revealed by t.l.c.; no other components were detected. The mixture was not examined further.

Oxazine (2b). A solution of the oxazine (1.570 g, 5.0 mmol) and indole (3.340 g, 20 mmol) in *o*-xylene (60 cm^3) was heated under reflux under N_2 for 96 h. The solvent was removed and the residue was subjected to column chromatography, which gave (i) *N*-methyltetrahydrocarbazole (0.857 g, 93%), (ii) indole (2.548 g), and (iii) a brown oil (0.636 g) which on trituration followed by crystallisation gave ethyl 2-hydroxyimino-3-(indol-3-yl)propionate (5b) (0.300 g, 24%), m.p. 155—157 °C (from dichloromethane–hexane) (lit.,[6] m.p. 155—157 °C), which was identified by comparison with an authentic specimen.

Oxazine (2c). A solution of the oxazine (1.000 g, 3.14 mmol) and indole (1.000 g, 8.55 mmol) in *o*-xylene (60 cm^3) was heated under reflux under N_2 for 7 days. The solvent was removed and the residue was subjected to column chromatography, which gave (i) *N*-methyltetrahydrocarbazole (0.040 g, 7%), (ii) the oxazine (2c) (0.662 g, 66%), and (iii) indole (0.985 g, 98.5%).

Oxazines (8). A mixture of the isomeric oxazines (8) (0.522 g, 2.0 mmol) and indole (1.170 g, 10.0 mmol) in 1,2-dichlorobenzene (40 cm^3) was heated under reflux under N_2 for 72 h. The oxazines slowly decomposed (t.l.c.) but none of the oxime (5a) was detected. Silver tetrafluoroborate (0.01 g) was added and the reaction mixture was heated for a further 72 h, but, again, none of the oxime (5a) was detected.

Acknowledgements

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