Alkoxycarbonylnitrenes as Selective Intramolecular CH-Insertion Reagents in Alicyclic Chemistry

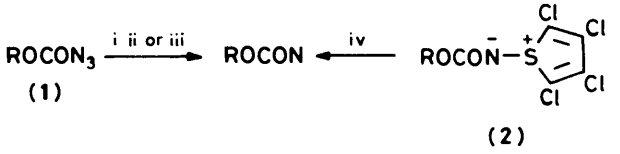
Pierre C. Marais and Otto Meth-Cohn*
National Chemical Research Laboratory, Council for Scientific and Industrial Research, P.O. Box 395, Pretoria 0001, Republic of South Africa

Intramolecular CH-insertion of cyclohexyl, *cis*- and *trans*-4-t-butylcyclohexyl, and *cis*- and *trans*-2-methylcyclohexyl nitrenoformates have been studied. The nitrenes were generated by vapour-phase (spray) pyrolysis or solution thermolysis of the corresponding azides, or by photolysis of tetrachlorothienyl S,N-ylides derived from the azides. The product ratios were principally (and predictably) dependent upon reaction temperatures (and thus conformational equilibria), these varying in the range 10—500 °C. 17-Substituted estrone-derived nitrenoformates inserted either into the 12β (from 17β) or 14α (from 17α) CH sites while 17-derivatives with the nitrene on the end of a long inert group abstracted hydrogen from the steroid B-ring.

CH-Insertion reactions are characteristic of only the most reactive singlet nitrenes, and proceed with 100% retention of configuration.[1] Despite the uniqueness of this high-yield process, it has been infrequently used in synthesis, probably because of its lack of selectivity. Thus it is known[2] that ethoxycarbonylnitrene inserts preferably in tertiary > secondary > primary sites (typically 32:10:1 ratio for intermolecular solution thermolysis). Furthermore, five-membered (oxazolidinone) ring formation is preferred over six-membered (oxazinone) in intramolecular insertions, with no evidence for large or small rings being formed.[3] This data suggests an early-collision insertion by a highly reactive and short-lived intermediate singlet nitrene.

The present work is a study of the application of CH-insertion in synthesis and an attempt to discover the factors allowing greater selectivity in these reactions. To this end we have examined: (*a*) some simple model cyclohexyl azidoformates to define more clearly the role of conformation in intramolecular insertions; (*b*) some estrone-based 17α- and 17β-azidoformates to exemplify the functionalisation of unactivated sites; and (*c*) some estrone-based systems with 17-attached 'long-arms' terminating in an azidoformate group to examine the potential of nitrenes for remote functionalisation.

Early indications showed that the most crucial factor determining product ratios was temperature. To this end we generated the nitrenes in a range of 10—500 °C by one of the methods illustrated in Scheme 1.



(1) (2)

(**a**); R = C_6H_{11}
(**b**); R = *trans*-2-Methylcyclohexyl
(**c**); R = *cis*-2-Methylcyclohexyl

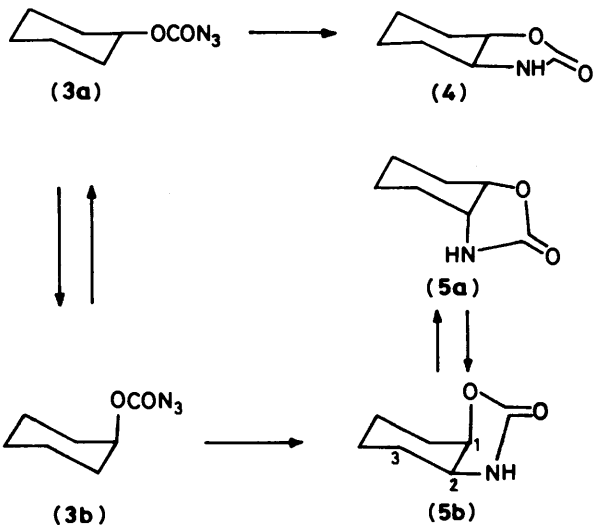
Scheme 1. *Reagents and conditions:* Method i, Heat, $Cl_2CHCHCl_2$ or CH_2Cl_2, 130—150 °C; ii, heat, spray pyrolysis, 250—500 °C; iii, heat, solution catalysis; iv, *hν*, 10 °C, CH_2Cl_2.

Solution thermolyses were conducted either in a Teflon-lined autoclave or in refluxing tetrachloroethane, an inert solvent. The 'spray pyrolysis' technique has been described elsewhere[4] and the tetrachlorothiophene S,N-ylides (**2**) have been shown to be efficient photo-sources of pure singlet nitrenes using Pyrex-filtered u.v. light.[5] Attempts to conduct metal-catalysed decompositions using iron carbonyls, copper acetylacetonate or phthalocyanine, or rhodium acetate proved totally ineffective.

Cyclohexyl azidoformate has been thermolysed in dichloromethane at 140 °C to give *cis*- (**5**) and *trans*-oxazolidinones (**4**) in 30 and 29% yield (*i.e.* ~ 1:1) respectively while photolysis at 25 °C gave the products in 30 and 25% (~ 1.2:1).[6]

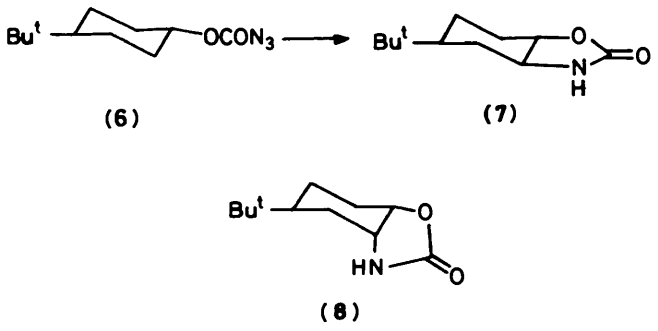
Since the equatorial to axial conformational equilibrium moves from (**3a**) ⟶ (**3b**) with temperature and since the axial cyclohexyl azidoformate (**3b**) could only yield the *cis*-oxazolidinone (**5**), the ratio of *cis* to *trans* isomers should increase with temperature. We thus compared isomer yields with equilibrium ratios (Scheme 2). Using the literature equilibrium data for cyclohexyl acetate[7] as a model for cyclohexyl azidoformate (**3**) and data for cyclohexyl *p*-nitrobenzoate[8] as an analogue of the ylide (**2**; R = cyclohexyl) the predicted *cis-trans* ratios based on equilibrium data showed remarkable accord with the experimental data (Scheme 2). (These calculations presume small entropy changes with temperature and assume that nitrene insertion is rapid compared to the conformational interconversions—both assumptions are vindicated by the excellent accord of theory and fact.) Since the CH-N proton reveals an axial coupling (*J* 12 Hz) in its ^1H n.m.r. spectrum, we conclude that the *cis*-oxazolidinone exists in the conformation (**5b**). The isomers are easily separated chromatographically and readily hydrolysed (KOH in triethylene glycol, 160 °C, 5 min) into 2-aminocyclohexanols in over 80% yield, making this insertion a useful synthetic reaction.

We next examined the conformationally rigid 4-t-butylcyclohexyl azidoformates [(**6**) and (**9**)]. The *trans*-isomer (**6**) should yield oxazolidinones in a ratio determined solely by geometric factors. Shingaki has shown that in intermolecular reactions of azidoformates with cyclohexanes, a preference for equatorial over axial insertion is observed (1.3:1 at 120 °C) reflecting the steric effects of axial 3- and 5-hydrogens in the latter case.[9] As expected, a similar preference is shown in this intramolecular case (1.4:1); this preference decreases with increasing temperature and is indicative of a less discriminating intermediate (Scheme 3). The unexpected small but reproducible reverse in isomer ratio at higher temperature could reflect the involvement of a twist-boat conformation to a small extent. No more than 0.4% of a *trans*-diaxial conformer of (**6**) should exist at 300 °C using the literature data[7] as before, whereas our yields suggest that up to 6% of the twist-boat conformer could be involved at 300 °C.



Method	Temp. (°C)	Calc. ratio of (3a):(3b)	Oxazolidinone (%) Overall	Ratio *cis*:*trans*	Ratio Calc.
hv, CH_2Cl_2	10	83.4:16.6	74	52:48	51:49
Heat, $Cl_2CHCHCl_2$	145	69.7:30.3	76	58:42	59:41
Spray pyrolysis	250	66.1:33.9	58	69:31	69:31
Spray pyrolysis	300	64.8:35.2	73	70:30	69:31
Spray pyrolysis	500	61.1:38.9	52	71:29	71:29

Scheme 2.



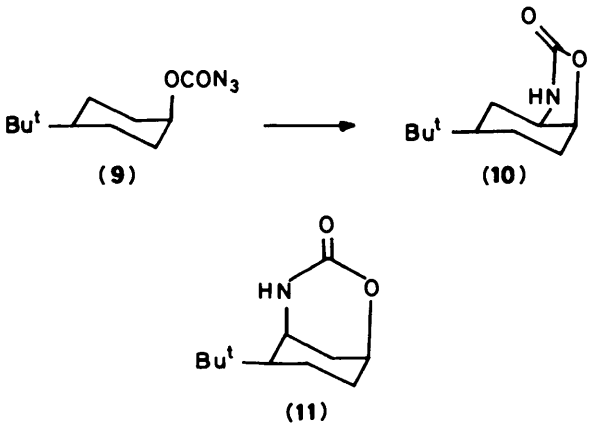
Method	Temp (°C)	Overall %	Ratio (7):(8)
Heat, $Cl_2CHCHCl_2$	140	62	59:41
Spray pyrolysis	300	59	47:53

Scheme 3.

The isomeric *cis*-4-t-butylcyclohexyl azidoformate reveals another aspect of nitrene selectivity not seen in the fluxional cyclohexyl azidoformate, namely the preference of five- over six-membered ring formation in the insertion process (Scheme 4). The known preference for five-membered ring formation is again followed, with the expected loss of discrimination at the higher temperature. However, since formation of the five-membered product (**10**) involves an equatorial insertion and the six-membered an axial insertion, the true extent of preference should be adjusted by at least the amount already indicated (1.4:1 at 140 °C and 0.9:1 at 300 °C) for the equatorial over axial insertion bias (Scheme 3).

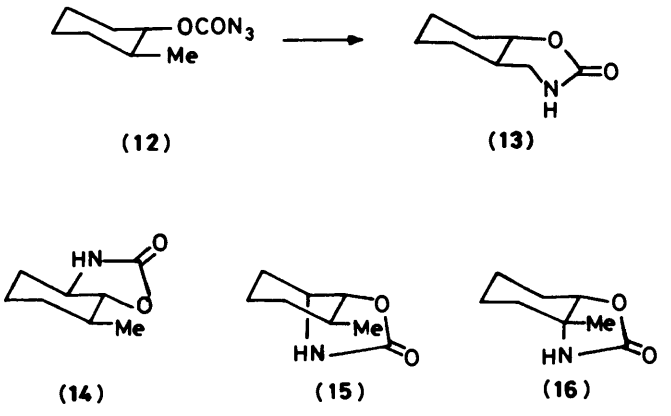
In order to test the intramolecular bias for primary, secondary, or tertiary insertions we next examined 2-methylcyclohexyl azidoformates (**12**) and (**17**). The four possible insertion products (**13**)—(**16**) from the *trans*-isomer (**12**) were all formed (Scheme 5) in ratios varying slightly with temperature. In order to relate these ratios to the 1°:2°:3° ratio of a typical acyclic insertion (*e.g.* 1:10:32—see introduction) the observed ratios need correcting for (*a*) the number of primary, secondary, and tertiary insertion sites available (*b*) the 5:6 membered preference observed in Scheme 4 and (*c*) the equatorial:axial bias observed in Scheme 3. However, the unknown factor relating the ease of insertion into a freely rotating methyl group relative to equatorial and axial insertions renders actual ratios difficult to determine. The approximate corrected ratio would be of the order 1°:2°:3° as 1:2:9 (10 °C) for the photoreaction and 1:2:6 (150 °C) for the thermal one. In other words a very considerable difference exists between inter- and intra-molecular insertion preferences, the latter reflecting significant extra steric interactions in insertion transition states, resulting in an evening-up of site preference.

Examination of the *cis*-2-methylcyclohexyl azidoformate decomposition suggests that six different insertion products are possible, four each from the two conformers (**17a**) and (**17b**) with two products being common to both conformers (Scheme 6). In fact only five of them were found. The conformer ratio [(**17a**):(**17b**)] using data for *cis*-2-methylcyclohexyl acetate[7] and *p*-nitrobenzoate[8] as a basis, as before, is also shown in the scheme. Several features of this reaction deserve comment: (*a*) The tertiary-insertion product (**22**) can only be formed from the minor conformer (**17b**) and clearly accounts for the bulk of product from that precursor. The absence of the oxazolidinone (**23**) is no doubt due to unfavourable interactions of the lone-pair oxygen orbitals of the C–O group with the adjacent axial



Method	Temp. (°C)	Overall %	Ratio (10):(11) %	Ratio (5):(6)
Heat, $Cl_2CHCHCl_2$	136	61	81:19	4.3:1
Spray pyrolysis	300	59	72:28	2.6:1

Scheme 4.



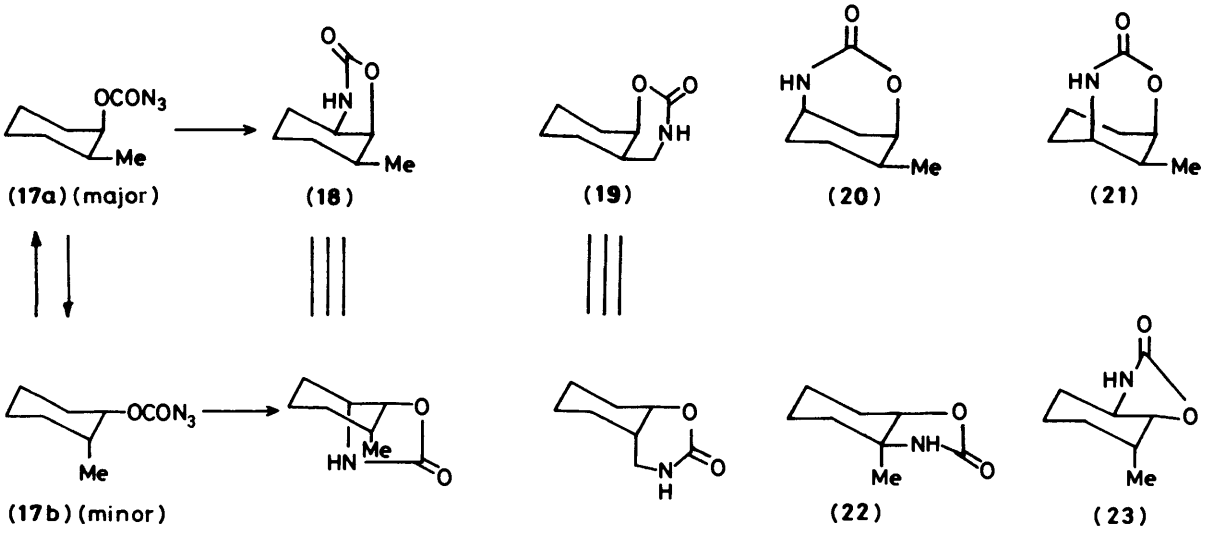
Method	Temp. (°C)	Overall %	(13):(14):(15):(16)	10 : 20 : 30
$h\nu$, CH_2Cl_2	10	61	6 29 10 55	1.0 6.5 9.2
Heat, CH_2Cl_2	150	83	8 27 12 53	1.0 4.9 6.5

Scheme 5.

methyl group in the transition state leading to secondary insertion. (*b*) Once again, low temperature favours maximum selectivity, in this case for *cis*-insertion in an adjacent equatorial bond to give the oxazolidinone (**18**). The ratio of five- to six-membered-ring products decreases from 4:1 to 2:1 and to 3:2 as the temperature is raised from 10 °C to 150 °C to 300 °C respectively. Thus one can conclude that, as with *cis*-4-t-butylcyclohexyl azidoformate (**9**), optimum selectivity for five-membered insertion requires as low a temperature as possible. (*c*) The sensitivity of the nitrene to small conformational effects at lower temperatures is further underlined by variation of the ratio of the two oxazinones [(**20**) and (**21**)] with temperature (at 10 °C, 150 °C, and 300 °C the ratios are approximately 3:1, 2:1, and 1:1 respectively). Insertion into an axial CH from an axial nitrenoformate will prefer to occur through an *exo*-conformation to limit axial interactions. With the transition state leading to (**20**) this raises secondary steric problems with the methyl group.

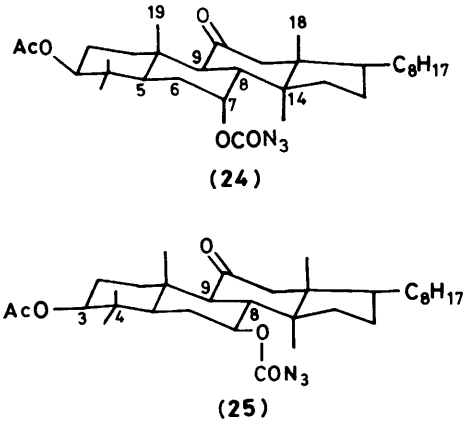
With the above considerations in mind we turned our attention to steroidal azidoformates in order to attempt useful specific functionalisations at unactivated sites. The principle impression from the work with cyclohexyl systems is that the insertion products are primarily a reflection of the conformer population of the azide prior to decomposition.

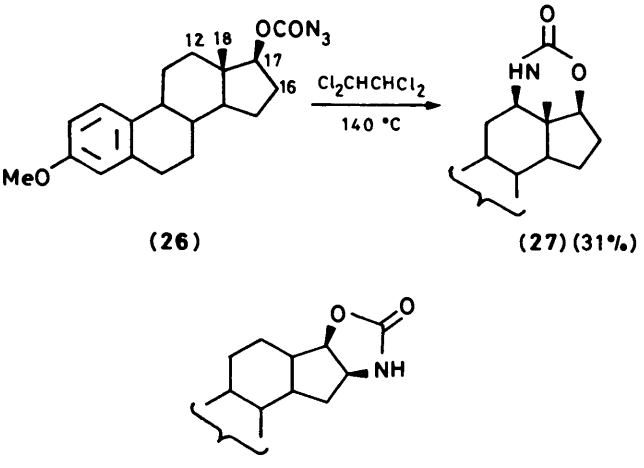
Several steroidal azidoformates have been investigated as vehicles for functionalising paraffinic sites. Thus Edwards and Paryzek [10] noted that the lanostanyl azidoformate (**24**) yielded only two insertion products on thermolysis at 140—142 °C in CCl_4, namely at the 6α- (52%) and 5- (9%) positions. It is evident from our results that attack of the axial **9-CH** is strongly disfavoured and that lowering the temperature would render 6α-insertion even more preferred. The corresponding 7β-epimer (**25**) underwent insertion into both 6α- and 6β-positions (78% overall) (2:1) as well as the 8-position (7%) under the same conditions.[10] Again the axially disposed 18- and 19-methyl groups disfavour the attack at the tertiary position. Other



Method	Temp. (°C)	Ratio (17a):(17b)	Overall %	Products (%) (18)	(19)	(20)	(21)	(22)	(23)
hv, CH_2Cl_2	10	80:20	50	67	6	10	3	14	0
Heat, CH_2Cl_2	150	77:23	55	48	10	16	8	19	0
Spray pyrolysis	300	71:29	62	39	10	16	13	22	0

Scheme 6.





workers[11] noted that the related 3β-lanostanyl azidoformate yielded products of insertion into the 4α-methyl group (35%) and 2α- (30%) position on thermolysis at 125 °C while at 180 °C the same products were formed in 14 and 51% yield respectively.[12] The authors were not able to explain this difference but it is clear from our data that conformational factors diminish in significance at higher temperatures. 4α-Methyl group insertion should be optimum at low temperature. The analogous Δ^8-lanosteryl azidoformate also favoured the latter insertion (55%) over the former (25%) at 125 °C. The surprisingly high extent of primary insertion again results from the disfavoured conformation for secondary insertion because of the neighbouring *gem*-dimethyl group. The lack of axial insertion due to related conformational problems is again evident. Related data for a 4,4,10β-trimethyl-*trans*-decalin-3β-ol azidoformate was observed by other workers.[12]

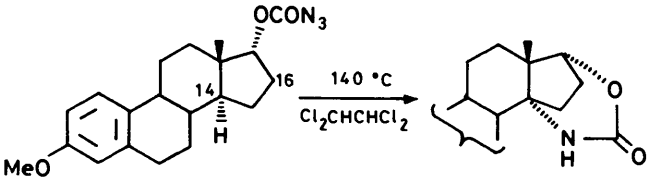
We first examined the decomposition of easily accessible 17-azidoformates of estradiol 3-methyl ether. The 17β-epimer (**26**) has available the 16β-site (giving rise to an oxazolidinone) and the 12β- and 18-positions (resulting in oxazinones) for insertion. In fact only two insertion products [(**27**) and (**28**)] were isolated and the oxazinone (**27**) was readily hydrolysed as before to give a 70% yield of the corresponding 12β-aminoestradiol, a useful functionalisation. As often is the case in nitrene decompositions, minor amounts of estrone 3-methyl ether and the triplet-nitrene-derived estradiol carbamate (**26**; NH_2 in place of N_3) were also isolated.[10]

In a similar manner the epimeric azidoformate (**29**) gave two insertion products, the oxazolidinone (**31**) and oxazinone (**30**). Attempts to hydrolyse the oxazinone proved unsuccessful. It would seem feasible that, given a suitable removable blocking group in the 16-position, the formation of oxazinones (**27**) and (**30**) could be optimised. To date we have only examined the 16β-bromo derivative of (**29**) which, through the well-known heavy-atom effect[13] undergoes only triplet reaction giving the corresponding carbamate in 59% yield.

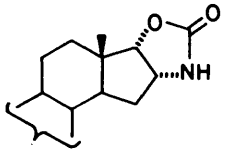
The excellent work of Breslow's group on remote

Table 1. Experimental details for the preparation of azidoformates and ylides

Alcohol	Chloroformate: Reaction time (h)	Chloroformate: Dimethylaniline added	Azidoformate: Product	Azidoformate: Reaction conditions	Azidoformate: Yield (%) (from alcohol)	TCT *S,N*-ylide: Product	TCT *S,N*-ylide: Reaction time (h)	TCT *S,N*-ylide: Yield (%) (from azidoformate)
Cyclohexanol	5		(3)	6 h reflux	80	(2a)	0.5	16
trans-4-t-Butylcyclohexanol	5		(6)	6 h reflux	86			
cis-4-t-Butylcyclohexanol	7		(9)	6 h reflux	80			
trans-2-Methylcyclohexanol	16		(12)	1.5 h room temp.	78	(2b)	1.5	15
cis-2-Methylcyclohexanol	20		(17)	0.75 h room temp.	62	(2c)	1	17
3-Methoxyestra-1,3,5(10)-trien-17β-ol	21		(26)	6 h reflux	93			
3-Methoxyestra-1,3,5(10)-trien-17α-ol	4, 5	√	(29)	3 h room temp.	71			
3-Methoxyestra-1,3,5(10)-trien-17α-yl β-hydroxypropionate	3	√	(32)	2.5 h room temp.	79			



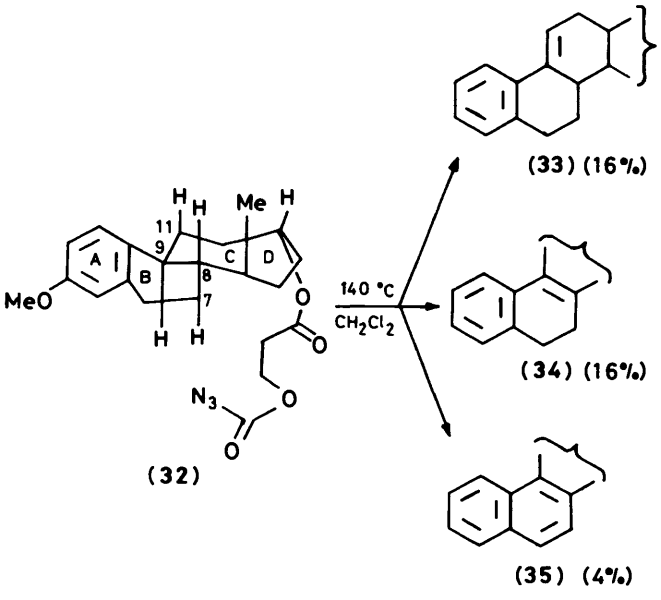
(29) (30) (31%)



(31) (43%)

Table 2. Data for cyclohexyl azidoformates

Azidoformate	M.p. (°C)	$\nu_{max.}$/cm^{-1}	δ_H (multiplicity, *J*/Hz, assignment)
(3)	Oil	2 180, 2 130, 1 720	4.90—4.64 (m, 1-H)
(6)	39—41	2 185, 2 130, 1 735	4.82—4.42 (m, 1-H) and 0.84 (s, Bu^t)
(9)	34—37	2 180, 2 130, 1 730	5.10 (m, 1-H) and (s, Bu^t)
(12)	Oil	2 170, 2 120, 1 720	4.57—4.23 (m, 1-H) and 0.93 (d, 5.7, Me)
(17)	Oil	2 160, 2 120, 1 720	4.95 (m, 1-H) and 0.93 (d, 6, Me)



(32) (33) (16%) (34) (16%) (35) (4%)

functionalisation in the steroid field, features only one (unsuccessful) attempt utilising nitrenes.[14] They employed the extremely potent phosphoryl nitrenes but obtained no products of insertion into or abstraction from the steroid skeleton. Part of the problem in designing a suitable substrate is to fashion a 'long arm' inert to attack by the nitrene. Since nitrenes do not insert into alkane groups adjacent to carbonyls (*e.g.* acetic acid) or hetero-atoms we devised the groups $-COCH_2OCON_3$ and $-COCH_2CH_2OCON_3$ as chain-extended azidoformates to attach to the 17-oxygen atom of estradiol 3-methyl ether. They proved to be totally inert to nitrene attack. However, the first group was also too short to allow strain-free access to the steroid skeleton. Both 17α- and 17β-derivatives gave uncyclised carbamate *via* triplet abstraction in 24 and 32% yield respectively. The longer chain was, however, of greater interest. Dreiding models revealed that the nitrene derived from the 17α-azide (**32**) had strain-free access especially to the axial CH's of the steroid B-ring, the tertiary and benzylic 9-CH being particularly attractive. By contrast the 17β-analogue was inhibited from access to either face. In the event no insertion was observed but rather abstraction products were isolated, indicative of a triplet nitrene-mediated reaction. As well as the ubiquitous carbamate analogue of the azide (13%), three further unsaturated carbamates (**33**)—(**35**) were isolated, the first two being inseparable. It would seem most likely that conformational factors restrict the attack of the singlet nitrene within the timescale of its brief lifetime and that inter-system crossing to the long-lived triplet state ensues. Abstraction of the 9α-hydrogen could then give rise to the $\Delta^{8,9}$- and $\Delta^{9,11}$-carbamates (**34**). Further intermolecular abstraction could also lead to (**35**). Removal of the 17-side-chain [from a mixture of the three carbamates (**33**)—(**35**)] with lithium aluminium hydride yielded a mixture, very closely related spectroscopically to that reported recently by other workers[15] from an oxidation of the B-ring in a modified estradiol. Furthermore, the fact that heating

Table 3. Analytical and spectroscopic data for steroidal azidoformates

Azidoformate (Formula)	M.p. (°C)	Found (%) (Required) C	H	N	$\nu_{max.}$/cm^{-1}	δ_H (multiplicity, *J*/Hz, assignment)
(**26**) $C_{20}H_{25}N_3O_3$	94—96	67.6 (67.6)	7.05 (7.0)	11.7 (11.8)	2 125, 1 715	4.70 (dd, 9, 7.5, 17α-H), 3.74 (s, MeO), and 0.80 (s, 18-Me)
(**29**) $C_{20}H_{25}N_3O_3$	102—103	67.4	7.0	11.7	2 130, 1 715	4.86 (d, 6, 17β-H), 3.75 (s, MeO), and 0.77 (s, 18-Me)
(**32**) $C_{23}H_{29}N_3O_5$	Oil	M^+, 427.2107 (*M*, 427.2107)			2 170, 2 130, 1 715	4.94 (d, 6, 17β-H), 4.49 (t, 6, CH_2), 3.79 (s, MeO), 2.73 (t, 6, CH_2), and 0.81 (s, 18-Me)

Table 4. Analytical and spectroscopic data for TCT *S,N*-ylides

Ylide (formula)	M.p. (°C)	Found (%) (Required) C	H	N	S	Cl	$\nu_{max.}$/cm^{-1}	δ_H (multiplicity, *J*/Hz, assignment)
(**2a**) $(C_{11}H_{11}NO_2SCl_4)$	97—98	36.3 (36.4)	2.9 (3.05)	3.9 (3.9)	9.3 (8.8)	41.5 (39.1)	1 660, 1 570	4.74—4.41 (m, 1-H)
(**2b**) $(C_{12}H_{13}NO_2SCl_4)$	94—96	38.1 (38.2)	3.4 (3.5)	3.6 (3.7)	8.4 (8.5)	37.4 (37.6)	1 662, 1 571	4.50—4.08 (m, 1-H) and 0.92 (d, 5.7, Me)
(**2c**) $(C_{12}H_{13}NO_2SCl_4)$	105—107	37.9	3.3	3.8	8.8	37.6	1 660, 1 570	4.82 (m, 1-H) and 0.90 (d, 6.3, Me)

Table 5. Details of spray pyrolysis experiments

Azidoformate	Weight (g)	Pyrolysis conditions	Nitrene-derived products (yields %)
Cyclohexyl azidoformate (**3**)	3.9	over 5 h; 250 °C	(**4**) (18), (**5**) (40),
	0.5	over 1 h; 300 °C	(**4**) (22), (**5**) (51),
	3.0	over 3.5 h; 500 °C	(**4**) (15), (**5**) (37)
trans-4-t-Butylcyclohexyl azidoformate (**6**)	0.5	over 1 h; 300 °C	(**7**) (28), (**8**) (31)
cis-4-t-Butylcyclohexyl azidoformate (**9**)	0.5	over 0.75 h; 300 °C	(**10**) (42), (**11**) (17)
cis-2-Methylcyclohexyl azidoformate (**17**)	1.4	over 2 h; 300 °C	(**18**) (24), (**19**) (6), (**20**) (10), (**21**) (8), (**22**) (14)

Table 6. Details of solution thermolysis experiments

Azidoformate	Solvent*	Azidoformate concentration (mol l^{-1})	Reaction conditions	Nitrene-derived products (yields %)
(**3**)	TCE	0.06	1 h, 145 °C	(**4**) (32), (**5**) (44)
(**6**)	TCE	0.03	1 h, 145 °C	(**7**) (37), (**8**) (25)
(**9**)	TCE	0.02	1 h, 136 °C	(**10**) (49), (**11**) (12)
(**12**)	DCM	0.06	0.75 h, 150 °C	(**13**) (7), (**14**) (22), (**15**) (10), (**16**) (44)
(**17**)	DCM	0.05	1 h, 150 °C	(**18**) (26), (**19**) (6), (**20**) (9), (**21**) (4), (**22**) (10)
(**26**)	TCE	0.03	1 h, 140 °C	(**27**) (31), (**28**) (43)
(**29**)	TCE	0.04	0.75 h, 140 °C	(**30**) (37), (**31**) (43)
(**32**)	DCM	0.03	1 h, 140 °C	(**33**) (16), (**34**) (16), (**35**) (4)

* TCE = 1,1,2,2-tetrachloroethane, TCM = tetrachloromethane, DCM = dichloromethane.

a mixture of (**33**) and (**34**) under the thermolysis conditions caused no change, indicated that the equilenin (**35**) was not a disproportionation product. The possibility of a concerted abstraction of vicinal 9,11-hydrogens is also feasible in line with literature analogies.[2]

In conclusion, singlet nitrenoformates are capable of useful and predictable functionalisation at inert sites and the extent of selectivity is primarily dependent upon the proper selection of temperature. Low-temperature methods enhance selectivity significantly. The prospect for remote functionalisation by insertion is limited by the brief lifetime of singlet nitrenes and the tendency for the azide-containing side-chain to adopt an unfavourable conformation for insertion. However, triplet nitrene-mediated hydrogen abstraction seems a feasible process in these cases.

Experimental

M.p.s were recorded on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were obtained on a Perkin-Elmer 257

spectrophotometer and ^1H n.m.r. spectra on a Varian EM 390 (90 MHz) or Bruker WM 500 (500 MHz) instrument. The n.m.r. data refers to deuteriochloroform solutions relative to tetramethylsilane as internal standard. Mass spectra were taken on a Varian MAT 212 instrument. Chromatography was performed on silica; t.l.c. plates were Merck Silica Gel 60 F-254 while Merck Silica Gel 60 (70—230 mesh) was used for column chromatography. Light petroleum refers to that fraction with b.p. 60—80 °C. The spray pyrolysis apparatus has already been described in detail.[4]

Preparation of Azidoformates and Tetrachlorothiophene S,N-Ylides.—The azidoformates were prepared from the corresponding alcohols, and tetrachlorothiophene S,N-ylides were prepared from the azidoformates.

All alcohols are commercially available (Fluka) with the exception of 3-methoxyestra-1,3,5(10)-trien-17α-yl β-hydroxypropionate, which was prepared as follows: The procedure described by Fisher[16] was used for the preparation of β-benzyloxypropionyl chloride, b.p. 154—155 °C (0.5 mmHg), $\nu_{max.}$(liquid film) 1 790 (CO) cm^{-1}.

To a solution of 3-methoxyestra-1,3,5(10)-trien-17α-ol (2.0 g, 7 mmol) in dry pyridine was added dropwise β-benzyloxypropionyl chloride (1.67 g, 8.4 mmol). The mixture was stirred at 50 °C for 2 h after which water (20 ml) was added. The product was extracted into ether and the extract washed twice with 20% cold aqueous citric acid and once with water, dried ($MgSO_4$),

Table 7. Details of photolysis experiments: photolysis time 1 h

TCT *S,N*-ylide	TCT *S,N*-ylide concentration (mol l^{-1})	Nitrene-derived products (yields %)
(**2a**)	0.01	(**4**) (36), (**5**) (38)
(**2b**)	0.04	(**13**) (7), (**14**) (18), (**15**) (6), (**16**) (34)
(**2c**)	0.01	(**18**) (34), (**19**) (3), (**20**) (5), (**21**) (2), (**22**) (7)

Table 8. Analytical and spectroscopic data for nitrene-derived products

Product (Formula)	M.p. (°C)	Found (%) (Required) C	H	N	*m/z*	$\nu_{max.}$/cm^{-1}	δ_H (multiplicity, *J*/Hz, assignment)
(**4**) ($C_7H_{11}NO_2$)	101—102 (Lit.,[6] 101—103)	59.4 (59.6)	8.1 (7.9)	10.0 (9.9)	141 (M^+), 98, 82	3 260, 1 735	5.83 (br s, NH), 3.95 (td, 10.5,3, 1-H), and 3.37 (td, 10.5, 3, 2-H)
(**5**) ($C_7H_{11}NO_2$)	54—55 (Lit.,[6] 55—56)	59.55	7.85	10.0	141 (M^+), 98, 82	3 265, 1 735	6.70 (br s, NH), 4.60 (m, 1-H), and 3.80 (m, 2-H)
(**7**) ($C_{11}H_{19}NO_2$)	123—124	66.9 (67.0)	9.4 (9.7)	7.2 (7.1)	197 (M^+), 141, 100, 57, 41	3 240, 1 760	6.49 (br s, NH), 3.86 (td, 11.1, 3.9, 1-H), 3.36 (td, 11.1, 3, 2-H), and 0.88 (s, Bu^t)
(**8**) ($C_{11}H_{19}NO_2$)	147—148	66.9	9.4	7.1	197 (M^+), 141, 100, 57, 41	3 230, 1 741	6.32 (br s, NH), 4.65 (m, 1-H), 4.16 (m, 2-H), and 0.84 (s, Bu^t)
(**10**) ($C_{11}H_{19}NO_2$)	172—173	67.15 (67.0)	9.9 (9.7)	7.1 (7.1)	197 (M^+), 141, 100, 57, 41	3 265, 1 718	6.45 (br s, NH), 4.55 (m, 1-H), 3.61 (m, 2-H), and 0.83 (s, Bu^t)
(**11**) ($C_{11}H_{19}NO_2$)	165—166	67.0	9.75	7.1	197 (M^+), 154, 98, 82	3 225, 1 690	7.33 (br s, NH), 4.63 (m, 1-H), 3.84 (m, 3-H), and 0.92 (s, Bu^t)
(**13**) ($C_8H_{13}NO_2$)	184—185	61.2	8.55	8.7	155 (M^+), 127, 110, 96, 82	3 240, 1 690	6.93 (br s, NH), 3.84 (m, 1-H), 3.30 (m, CH adjacent to N), and 2.95 (t, 10.8, CH adjacent to N)
(**14**) ($C_8H_{13}NO_2$)	125—126	62.1	8.6	8.8	155 (M^+), 140, 112, 96	3 270, 1 745	6.33 (br s, NH), 3.55 (t, 11.4, 1-H), 3.37 (td, 11.4, 3.3, 2-H), and 1.05 (d, 6, Me)
(**15**) + (**16**) inseparable mixture					155 (M^+), 140, 112, 96	3 250, 1 740	6.51 [br s, NH (**15**) + (**16**)], 4.21 [m, 1-H (**16**)], 4.04 [m, 1-H and 2-H (**15**)], 1.30 [s, Me (**16**)], and 1.04 [d, 6, Me (**15**)]
(**18**) ($C_8H_{23}NO_2$)	95—97	61.6 (61.9)	8.6 (8.4)	9.1 (9.0)	155 (M^+), 140, 112, 96	3 200, 1 710	6.57 (br s, NH), 4.53 (dd, 6, 3, 1-H), 3.87—3.59 (m, 2-H), and 1.13 (d, 6, Me)
(**19**) ($C_8H_{13}NO_2$)	139—141	62.1	8.5	9.2	155 (M^+), 110, 82	3 240, 1 690	6.72 (br s, NH), 4.54 (m, 1-H), 3.51 (dd, 12.3, 5.4, CH adjacent to NH), and 3.08 (d, 12.3, CH adjacent to NH)
(**20**) ($C_8H_{13}NO_2$)	Oil	M^+, 155.0946			155 (M^+), 98, 69, 55	3 240, 1 680	7.07 (br s, NH), 4.41 (m, 1-H), 3.68 (m, 3-H), and 1.07 (d, 5.4, Me)
(**21**) ($C_8H_{13}NO_2$)	94—95	61.9	8.5	8.9	155 (M^+), 140, 112, 96	3 240, 1 690	7.07 (br s, NH), 4.35 (m, 1-H), 3.41 (m, 3-H), and 1.10 (d, 7.5, Me)
(**22**) ($C_8H_{13}NO_2$)	110—111	61.7	8.7	9.2	155 (M^+), 140, 112, 96	3 200, 1 725	6.14 (br s, NH), 4.22—3.93 (m, 1-H), and 122 (s, Me)
(**27**) ($C_{20}H_{25}NO_3 \cdot H_2O$)	124—128	69.3 (69.5)	7.7 (7.9)	4.0 (4.1)	327 (M^+), 284, 266, 251	3 220, 1 655	4.09 (m, 17α-H), 3.77 (s, MeO), 3.32 (dd, 12, 4.5, 12α-H), and 0.82 (s, 18-Me)
(**28**) ($C_{20}H_{25}NO_3$)	247—249	72.8 (73.4)	7.8 (7.7)	4.3 (4.3)	327 (M^+), 299, 282, 266, 251	3 237, 1 715	4.43 (d, 9, 17α-H), 4.20 (m, 16α-H), 3.76 (s, MeO), and 0.89 (s, 18-Me)
(**30**) ($C_{20}H_{25}NO_3$)	205—208	73.4 (73.4)	7.7 (7.7)	4.3 (4.3)	327 (M^+), 266, 251	3 220, 1 680	6.28 (br s, NH), 4.15 (m, 17β-H), 3.76 (s, MeO), and 0.95 (s, 18-Me)
(**31**) ($C_{20}H_{25}NO_3$)	299—300	73.3	7.9	4.3	327 (M^+), 266, 251	3 235, 1 705	7.70 (br s, NH), 4.56 (d, 7.5, 17β-H), 4.32 (m, 16β-H), 3.80 (s, MeO), and 0.82 (s, 18-Me)
(**33**) + (**34**) inseparable mixture					399 (M^+), 356, 266, 251	3 525, 3 418, 1 715	7.54 [d, 9, 1-H (**33**)], 7.14 [d, 9, 1-H (**34**)], 6.14 [m, 11-H (**33**)], 4.96 [m, NH_2 + 17β-H (**33**) + (**34**)], 4.33 [t, 6, side-chain CH_2, (**33**) + (**34**)], 3.79 [s, MeO (**33**) + (**34**)], 2.64 [t, 6, side-chain CH_2 (**33**) + (**34**)], and 0.177 and 0.75 [s, 18-Me (**33**) + (**34**)]

and evaporated to yield a crude product. This was chromatographed with light petroleum–ethyl acetate (7:1) as eluant to give *3-methoxyestra*-1,3,5(10)-*trien*-17α-*yl* β-*benzyloxypropionate* (1.4 g, 45%); $\nu_{max.}$($CHCl_3$) 1 730 (CO) cm^{-1}; δ_H (90 MHz; $CDCl_3$) 7.36 (5 H, s, Ph), 4.95 (1 H, d, *J* 6 Hz, 17β-H), 4.54 (2 H, s, benzylic CH_2), 3.80 (2 H, t, *J* 6.6 Hz, OCH_2), 3.78 (3 H, s, MeO), 2.64 (2 H, t, *J* 6.6 Hz, $COCH_2$), and 0.78 (3 H, s, 18-Me). This material was used without further purification. 3-Methoxyestra-1,3,5(10)-trien-17α-yl β-benzyloxypropionate (1.3 g, 2.9 mmol) was hydrogenolysed in ethyl acetate (30 ml) in the presence of 10% palladium-on-charcoal (0.1 g) in a Parr bomb. Filtration, solvent evaporation and column chromatography with light petroleum–ethyl acetate (3:1) as eluant yielded *3-methoxyestra*-1,3,5(10)-*trien*-17α-*yl* β-*hydroxypropionate* (0.91 g, 88%), m.p. 54—55 °C (from MeOH–H_2O) (Found: C, 73.75; H, 8.45. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%); $\nu_{max.}$($CHCl_3$) 3 560 (OH) and 1 700 cm^{-1} (CO); δ_H (90 MHz; $CDCl_3$) 4.95 (1 H, d, *J* 6 Hz, 17β-H), 3.77 (3 H, s, MeO), 2.59 (2 H, t, *J* 6 Hz), and 0.81 (3 H, s, 18-Me); *m/z* 358 (M^+) and 269 [M − $OCO(CH_2)_2OH$].

General Procedure for Azidoformate Preparation.—The alcohol was dissolved in a minimum of dry dichloromethane and added dropwise to a stirred 20% solution of phosgene (1.5 mol equiv.) in toluene at 0 °C. In some cases, the addition of 1 mol equiv. of *N,N*-dimethylaniline was required. The solution was allowed to warm to room temperature and monitored by t.l.c. until complete conversion of the alcohol was indicated. Excess of phosgene was removed by bubbling nitrogen through the solution for 20 min. The crude chloroformate obtained after evaporation of the solvent under reduced pressure was dissolved directly in dry acetone and sodium azide (2 mol equiv.) was added. The mixture was stirred at room temperature until t.l.c. indicated that the reaction was complete. Filtration and solvent evaporation gave the crude azidoformate which was chromatographed over silica using light petroleum–ethyl acetate to yield the required purified product. Further details are given in Table 1. Due to their volatility and thermal instability the cyclohexyl-derived azidoformates did not give satisfactory mass spectra or elemental analyses.

General Procedure for Tetrachlorothiophene S,N-*Ylide Preparation.*—The azidoformate was added dropwise to a tenfold molar excess of 2,3,4,5-tetrachlorothiophene (TCT) at 130 °C and stirred at this temperature until nitrogen evolution ceased. The excess of TCT was removed under reduced pressure (2 mmHg, 95 °C) and the residue chromatographed using light petroleum–chloroform as eluant. The required TCT *S,N*-ylide was recrystallised from light petroleum. Further details are given in Table 1.

Tables 2—4 contain analytical and spectroscopic data for azidoformates and TCT *S,N*-ylides.

Nitrene Generating Reactions.—Nitrenes were generated by the spray pyrolysis[4] or solution thermolysis of the azidoformate or by photolysis of the corresponding TCT *S,N*-ylide. Details of the experimental procedures appear below and in Tables 5—7.

Solution thermolysis reactions were conducted by dissolving the azidoformate in 1,1,2,2-tetrachloroethane and heating the stirred solution at the temperature given in Table 6. Alternatively, the azidoformate was dissolved in dichloromethane and heated in a high-pressure vessel.

Photolyses of the TCT *S,N*-ylides were conducted in dichloromethane in a Hanovia photochemical reactor with a medium-pressure mercury arc. The temperature was maintained at 10 °C externally with a solid CO_2–acetone bath.

Nitrene-derived products were isolated by careful column chromatography using light petroleum–ethyl acetate as eluant. Analytical and spectroscopic data are given in Table 8.

Thermolysis of Remotely Functionalised Steroidal Azides.—After solution thermolysis of the azide (**32**), column chromatography of the crude reaction mixture gave a fraction containing (**33**) and (**34**) as an inseparable mixture and a fraction containing (**35**) as the major product with traces of (**33**) and (**34**). In order to assign unambiguously the structures of (**33**), (**34**), and (**35**), these fractions were recombined and the β-(carbamoyloxy) propionate side-chain cleaved as follows. The recombined mixture of compounds (**33**), (**34**), and (**35**) (0.66 g) was added dropwise in dry tetrahydrofuran (THF) (50 ml) to a stirred slurry of lithium aluminium hydride (0.24 g, 6.3 mmol) in THF (50 ml). The mixture was stirred for 30 min and water (100 ml) added. Extraction with diethyl ether (2 × 75 ml), washing of the organic extract with water (2 × 50 ml), drying and solvent evaporation yielded the crude product mixture which was column chromatographed with light petroleum–ethyl acetate (4:1). Two fractions were collected with the first fraction containing a mixture (~1:1) of *3-methoxyestra*-1,3,5(10),9(11)-*tetraean*-17α-*ol* and *3-methoxyestra*-1,3,5(10),8-*tetraen*-17α-*ol* (0.183 g, 39%); $\nu_{max.}$($CHCl_3$) 3 600 (OH), 1 600 (C=C), and 807 ($\Delta^{9(11)}$ C–H bend); δ_H (90 MHz; $CDCl_3$) 7.61 (1 H, d, *J* 9 Hz, 1-H, $\Delta^{9(11)}$), 7.30 (1 H, d, *J* 9 Hz, 1-H, Δ^8), 6.25 (1 H, m, 11-H $\Delta^{9(11)}$), 3.85 (3 H, s, MeO, $\Delta^{9(11)}$ + Δ^8), and 0.81 and 0.79 (3 H, s, 18-Me, $\Delta^{9(11)}$ + Δ^8).

The second fraction contained *3-methoxyestra*-1,3,5(10),6,8-*pentaen*-17α-*ol* derived from (**35**) (0.025 g, 5%), m.p. 104—106 °C (Found: C, 80.6; H, 7.80. $C_{19}H_{22}O_2$ requires C, 80.82; H, 7.85%); δ_H (500 MHz; $CDCl_3$) 7.863 (1 H, d, *J* 9.2 Hz, 1-H), 7.554 (1 H, d, *J* 8.5 Hz, 6-H), 7.230 (1 H, d, *J* 8.5 Hz, 7-H), 7.143 (1 H, dd, *J* 9.2, 2.6 Hz, 2-H), 7.102 (1 H, d, *J* 2.6 Hz, 4-H), 3.989 (1 H, d, *J* 6.0 Hz, 17β-H), 3.900 (3 H, s, MeO), and 0.612 (3 H, s, 18-Me).

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