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THE PREPARATION AND TRANSFORMATIONS OF 2-AZA-3-OXABICYCLO [2.2.1] HEPTENE HYDROCHLORIDE

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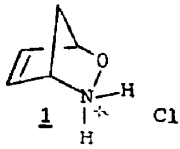
Abstract - Reaction of 1-chloro 1-nitroso cyclohexane with *excess* freshly prepared cyclopentadiene in ether: ethanol gives the crystalline 2-aza 3-oxabicyclo (2.2.1) heptene hydrochloride (**1**) in 89% yields. 2-Aza 3-oxabicyclo (2.2.1) heptene (**2**), generated *in situ* with pyridine, can be acylated with a variety of acid chlorides and anhydrides, thus providing a novel and convenient route to diverse oxazabicycloheptenes. The free base **2** generated with $NaHCO_3$ in a two phase system, readily reacts with formalin leading to the Mannich base adduct **16**, with PhNCS to the thiourea **19** and with i-AmONO to the nitroso compound **20**. PGG → PGE type cleavage is observed on reaction of the *in situ* generated **2** with excess benzoylchloride, MsCl and TsCl. Surprisingly, the reaction of **1** with ArCHO in presence of pyridine gives N-α-chloroaryl compounds possessing a highly reactive halogen. Diimide reduction of **2** gives the parent oxazabicycloheptane system-related to PG-endoperoxides which was characterized as the hydrochloride or the benzoyl derivative.

The recognition that 2,3-dioxabicyclo (2.2.1) heptanes are precursors to prostaglandins, thromboxanes and prostacyclins, has led to interest in bicyclic compounds arising from sequestration of cyclopentane with a heterobridge.[1] Whilst systems carrying the N-N are well studied, those that incorporate either a N-O or a O O bridge are of recent origin. The $\pi 4S + \pi 2S$ addition of cyclic 1,3-dienes with singlet oxygen or the equivalent nitroso grouping offers the most attractive entry to these frameworks. The presence of the nitrogen substituent in the nitroso adducts has enabled their use in the synthesis of heterocyclic systems[2] and in the stereocontrolled generation of contiguous asymmetric centres.[3]

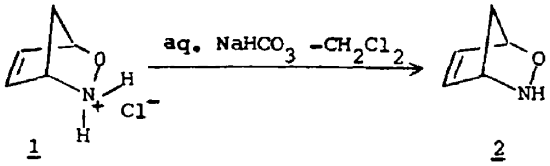
The focus of the work presented in this paper is on the preparation and transformations of the novel 2-oxazabicyclo heptene hydrochloride **1**.



1

The white crystalline hydrochloride **1**, m.p. 83-85 (dec), was prepared in 89% yields by reaction of chloronitrosocyclohexane with a ten fold excess of cyclopentadiene in ether ethanol.[4] The formation of **1** is rationalized on the basis of further transformations of the initially formed nitroso adduct. As anticipated, the nitrogen function in the initially formed oxazabicycloheptene is quite basic and this factor is responsible for the further transformations leading to **1**. (Scheme 1) This facet finds support in the transformations of **1** with aldehydes to chloro-compounds, closely related to the chloronitroso-cyclohexane-cyclopentadiene adduct (*vide infra*), (Scheme 4). The structural assignment for **1** is supported by spectral and analytical data.[5]

Five to ten gram lots of **1** can be prepared conveniently and stored under dry and cold conditions. The hydrochloride **1** was smoothly transformed to the free base **2** by reaction with aqueous bicarbonate in a two phase system.



1 **2**

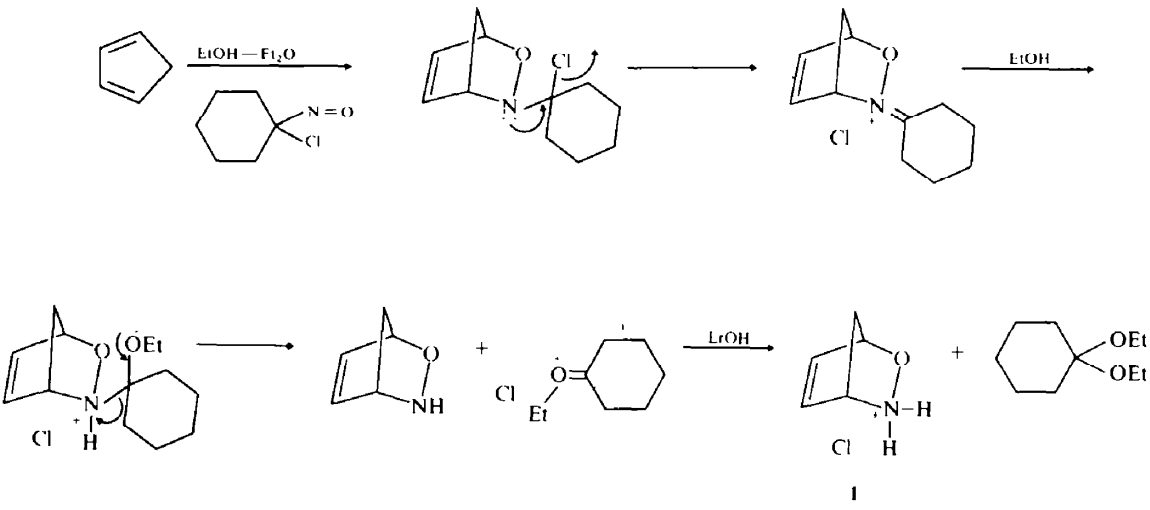
The free base **2** decomposed on standing. Fortunately, for most of the reactions, it could be generated *in-situ* from the hydrochloride **1**. However, in the case of some reactions, **2** was prepared and used immediately.

With the delineation of a convenient route to **1**, its properties were examined as a precursor to oxazabicycloheptenes and heptanes. Further, the thermal and photochemical behaviour of representative systems were studied, in order to, *inter alia*, draw comparison with PG-endoperoxides.

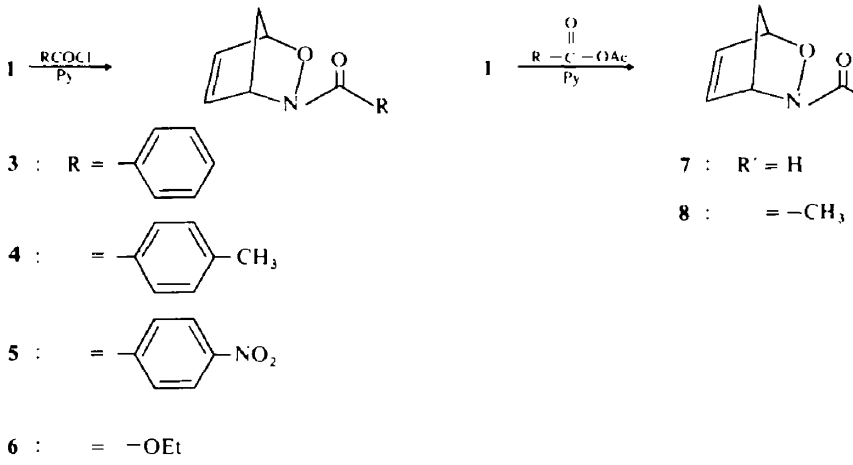
The reaction of **1** with benzoyl chloride pyridine in dry benzene gave the crystalline N-benzoyl oxazabicycloheptene **3** in 80% yields (Scheme 2).[6]

Hitherto, **3** was prepared by cycloaddition of cyclopentadiene with *in-situ* generated nitrosocarbonylbenzene. Whilst the original report[7] referred to **3** as a liquid, that spontaneously decomposed, a more recent one[8] again from cyclopentadiene-PhCONO cycloaddition, identifies this, like that reported in the present work, as a stable crystalline solid m.p. 74-75. The structural assignment for **3** is supported by analytical, IR, NMR and MS data and by comparison with an authentic sample. The procedure for **3** described in the present work is not only more versatile but very much more convenient and rapid.

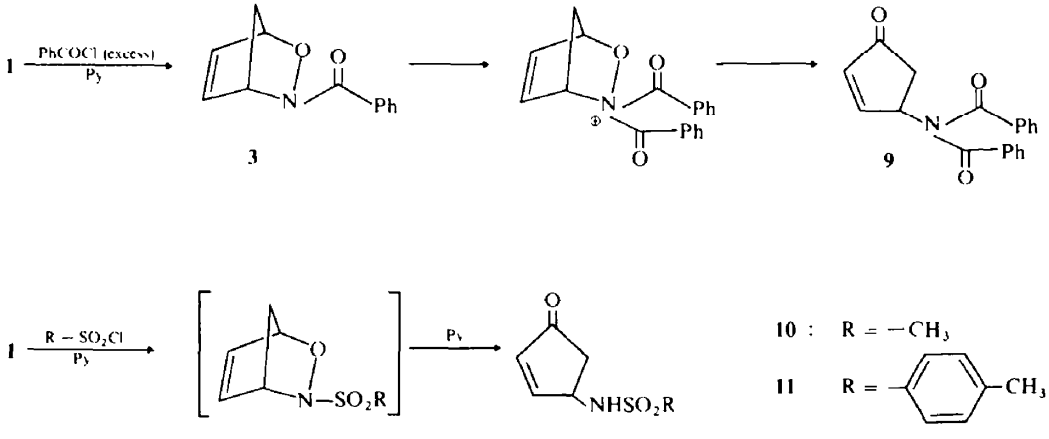
Compound **1** proved to be a convenient source for acylated oxazabicycloheptenes as illustrated with the preparation of N-(*p*-toluoyl), N-(*p*-nitrobenzoyl), N-



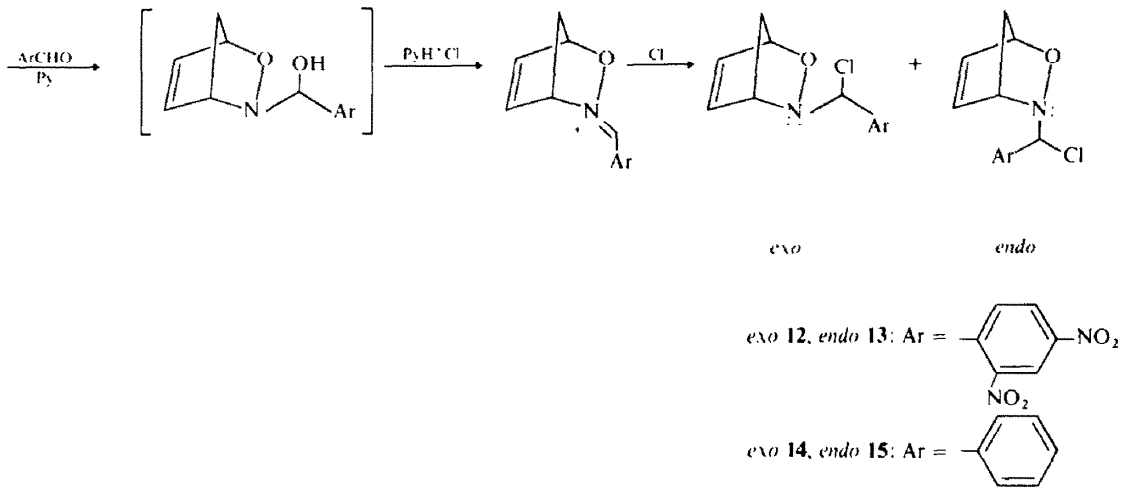
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

carbethoxy, N-formyl and N-acetyloxazabicyclo (2.2.1) heptenes, **4**–**8** (Scheme 2). The ready formation of N-formyloxazabicyclo (2.2.1) heptene (**7**) further illustrates the usefulness of **1** in the preparation of N-functionalized oxazabicycloheptenes not easily accessible by conventional cycloaddition procedures.

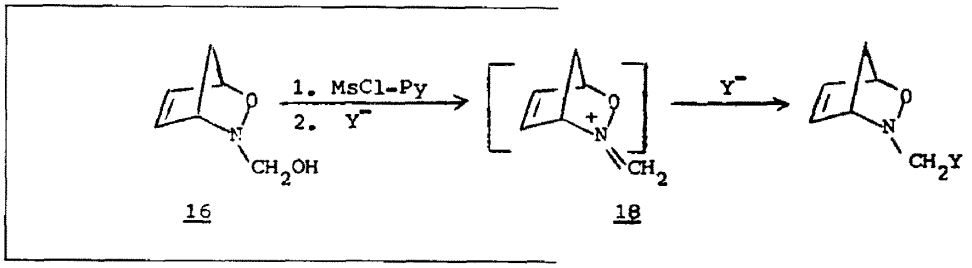
In contrast to the smooth acylations reported above, **1** on standing for 24 hr at rt in presence of benzoyl chloride–pyridine gave as the sole isolable product, the highly crystalline 4-(N,N-di-benzoylamino) cyclopentenone (**9**). The formation of **9** is rationalized on the basis of rupture of N O bond of the dibenzoylated intermediate. This rupture is similar to PG-endoperoxide → PGE transformation (Scheme 3). The structural assignment for **9** is based on IR, NMR, MS, analytical data and by preparation from **3** with additional benzoyl chloride-pyridine. Interestingly, even in the preparation of **3**, compound **9** is formed as a minor product.

As anticipated, such N–O fragmentations occur readily and exclusively on treatment of the salt **1** with either methanesulfonylchloride-pyridine or *p*-toluenesulfonylchloride-pyridine leading to, respectively, **10** and **11** (Scheme 3). These compounds were unstable and decomposed on standing.

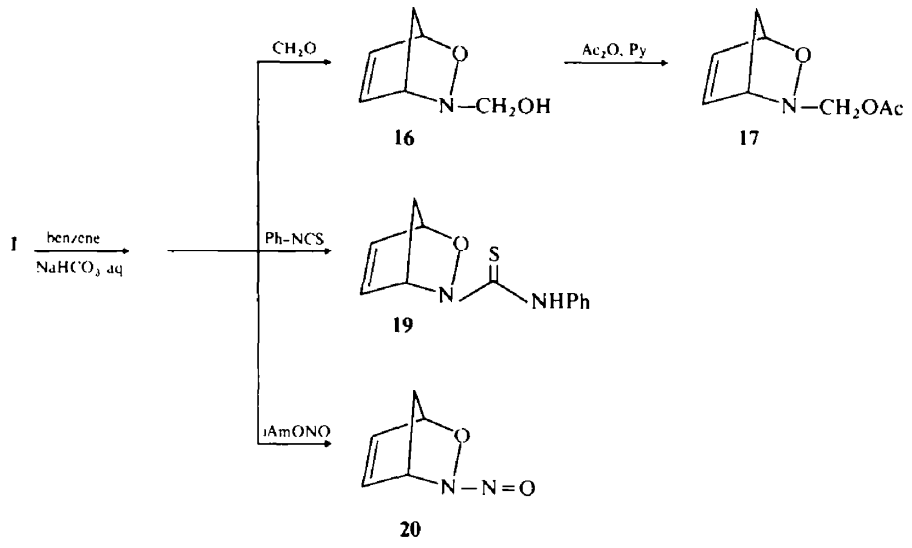
An unusual transformation of **1** was observed during efforts to rupture the N–O bond by SN_i' processes.[9] Thus, the salt **1** on treatment with one equivalent of pyridine followed by 2,4-dinitrobenzaldehyde gave two crystalline compounds m.p. 111 12 and 131–132 , in respectively, 26 % and 3 % yields. These are assigned structures **12** and **13** (Scheme 4).[10] The minor isomer **13** can be thermally transformed, although not cleanly, to **12**. Similarly, the reaction of benzaldehyde with **1** gave products m.p. 71 (31 %) and 113 (4 %) identified as **14** and **15** (Scheme 4). The pathways envisaged in Scheme 4 rationalizing the formation of **12**–**15** incorporate mechanistic facets associated with the generation of the hydrochloride **1** itself from chloronitrosocyclohexane and cyclopentadiene involving a key, electrophilic, alkylated nitrone intermediate. Compounds **12** to **15** possess a highly active C–Cl bond and readily precipitate AgCl from methanolic $AgNO_3$ solutions; further their MS exhibit only $(M\ Cl)^+$ peaks.

The free base, oxazabicycloheptene **2**, could also be used advantageously. Thus, the reaction of **2**, generated *in situ* from the hydrochloride **1** with aqueous bicarbonate, gave with formalin, in 85 % yields, N-hydroxymethyloxazabicyclo (2.2.1) heptene **16** as a syrupy liquid, further characterised as the acetate **17** (Scheme 5).

Hitherto, the functionalization of nitrogen in oxazabicycloheptene was carried out by interaction with electrophilic reagents. The ready availability of **16** opens up a novel route to N-functionalized oxazabicycloheptenes *via* nucleophilic addition to the *in situ* generated electrophile **18**. In sum, these would constitute novel examples of the Mannich reaction.



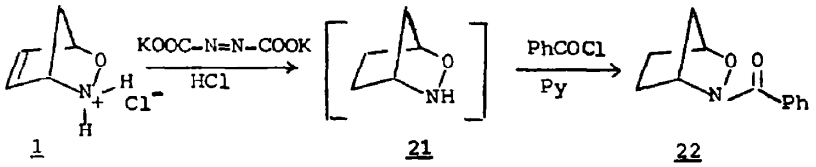
Urea formation with an optically active isothiocyanate followed by separation of diastereomers and thermolytic reversal[11] would constitute a practical method for the resolution of oxazabicycloheptanes. That, this is feasible was demonstrated with the ready formation of the crystalline thiourea **19** by reaction of the free base **2** with phenylisothiocyanate (Scheme 5).



Scheme 5.

Attempts to transform **1** to cyclopentadienone *via* N–O rupture followed by elimination, have been, thus far, not fruitful. Reaction of the free base, generated in a two phase medium, with excess methyl iodide in presence of either Et_3N or K_2CO_3 gave complex mixtures but not the expected cyclopentadienone dimer. Yet another route to cyclopentadienone envisaged the further decomposition of the readily isolable (from reaction of the free base **2** with Am^{i}ONO) N-nitroso adduct **20** (Scheme 5). The fragmentation of **20** to cyclopentadienone by N_2O extrusion is yet to be realized. Preliminary experiments gave complex mixtures.

Oxazabicycloheptane **21**, directly related to PG-endoperoxide, was prepared from the hydrochloride **1** by di-imide reduction. Compound **21** was characterized as its crystalline hydrochloride[12] and via benzoylation to **22**. The structural assignment for **22** is supported by IR, NMR, MS, analytical data and by comparison with an authentic sample prepared by di-imide reduction of N-benzoyloxazabicycloheptene **3**.



Work thus far presented, demonstrates that the readily available hydrochloride **1** is a highly versatile compound that could be gainfully used for the preparation of an unlimited variety of oxazabicycloheptenes. These, in turn, can be restructured to diverse molecular types. Novel pyrolytic transformations of **3** and **22** are presented in the following paper.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on Perkin Elmer Model 337 and 580 spectrophotometers as neat liquids or solids as KBr discs. NMR spectra were obtained on approximately 10–15% solns mostly in $CDCl_3$ on A-60D and TR-90 spectrometers. The chemical shifts are reported in ppm downfield from internal TMS at 0.00 as internal standard. Elemental analysis were carried out in Coleman automatic C, H and N analysers. Silica-gel (ACME) was used for tlc and column chromatography was done on silica-gel (ACME), columns being prepared from its slurry in petroleum ether (60 66). Reactions were monitored, whenever possible, by tlc.

2-Aza-3-oxabicyclo(2.2.1)hept-5-ene hydrochloride (**1**). Chloronitrosocyclohexane was prepared by chlorination of cyclohexanone oxime.[13]

To a stirred and ice-chilled soln of chloronitrosocyclohexane (5.8 g, 0.039 mol) in EtOH: dry ether (1:3, 100 ml) was added, in drops, freshly cracked cyclopentadiene (25 g, 0.378 mol). The mixture was left stirred for 3 hr during which the blue color of the reagent completely disappeared—the separated white crystalline hydrochloride was collected, washed with ether and dried; yield 4.656 g (89%); mp 83–85°. (Found C, 45.19; H, 5.7; Calc. for C_5H_8ClNO: C, 44.94; H, 5.99%); IR: ν_{max} (KBr) (cm^{-1}): 3380 (br, NH); NMR: $\delta_{(D_2O)}$: 6.95, 6.75 (m, m, olefinic protons), 5.75 (br, 1-H), 5.35 (br, 4-H), 2.35 (m, $-CH_2-$).

2-Aza-3-oxabicyclo (2.2.1) *hept-5-ene* (**2**). A mixture of hydrochloride **1** (1.952 g, 0.0146 mol), CH_2Cl_2 (100 ml) and $NaHCO_3$ aq (50 ml, 10%) was vigorously shaken in a separatory funnel, the CH_2Cl_2 layer separated, dried ($MgSO_4$) and evaporated to give **2** as a yellow oil in 100% yield. IR: ν_{max} (neat) (cm^{-1}): 3320 (br, NH); NMR: $\delta_{(CDCl_3)}$: 6.4–5.88 (m, olefinic protons), 4.88 (br, 4-H), 4.11 (br, 1-H), 1.5 (m, CH_2–).

N-Benzoyl-2-aza-3-oxabicyclo (2.2.1) *hept-5-ene* (**3**). An ice-cooled and stirred mixture of benzoyl chloride (4.8 g, 0.034 mol), pyridine (6.32 g, 0.08 mol) and dry benzene (25 ml) was gradually admixed with **1** (2.67 g, 0.02 mol) and left stirred for 0.5 hr. The mixture was cautiously diluted with cold water (25 ml), extracted with CH_2Cl_2 (4 × 30 ml), the

combined organic extracts washed with HCl aq (3 × 30 ml, 10%), water (2 × 30 ml), dried ($MgSO_4$) and evaporated to yield 4.674 g of a crude residue. Chromatography over silica gel and elution with CH_2Cl_2 gave 3.2 g (80%) of pure **3**; mp 74–75 . (Found: C, 71.93; H, 5.29; N, 7.16%; Calc. for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.96%); IR: ν_{max} (KBr) (cm^{-1}): 1620 ("amide I" band); NMR: $\delta_{(CDCl_3)}$: 7.72, 7.39 (m, m, aromatic protons), 6.41 (m, olefinic protons), 5.28 (br, 1-H and 4-H), 1.9 (m, CH_2-); MS: *m/e*: 201

Authentic N-benzoyl-2-aza-3-oxabicyclo (2.2.1) *hept-5-ene* (**3**). Benzhydroxamic acid was prepared by reaction of methylbenzoate with NH_2OHHCl[14] and tetraethyl ammonium periodate from freshly prepared 25% Et_4NOH and paraperiodic acid.[15]

Under stirring and ice-cooling, a soln of freshly cracked cyclopentadiene (0.66 g, 0.01 mol) in EtOAc (25 ml) was added, in drops, to a soln of Et_4NIO_4 (4.83 g, 0.015 mol) in acetate buffer (25 ml, 0.02 M; pH 7), followed by, in drops, a solution of benzydroxamic acid (3.15 g, 0.022 mol) in EtOAc (120 ml). The mixture was left stirred for 6 hr, the layers separated, the aqueous layer extracted with EtOAC (3 × 40 ml), the combined extracts washed with water, brine, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc: benzene (20:80) gave, in a single fraction, the adduct **3** which was crystallized from benzene-petroleum ether; yield 0.871 g (44%); m.p. 72 73 .

N-p-*Toluoyl 2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**4**). To an ice-cooled and stirred suspension of **1** (1.33 g, 0.01 mol) and pyridine (0.79 g, 0.01 mol) in dry benzene (30 ml) was added, in drops, *p*-toluoyl chloride (1.54 g, 0.01 mol) in benzene (5 ml) followed by another equiv of pyridine (0.79 g, 0.01 mol). The mixture was left stirred for 1.5 hr, washed repeatedly with cold water, dried ($MgSO_4$) and the solvents evaporated to give 1.12 g (52%) of **4** as a thick syrup. (Found: C, 72.04; H, 6.20; Calc. for: $C_{13}H_{13}NO_2$, C, 72.55; H, 6.04%); IR: ν_{max} (neat) (cm^{-1}): 1635 ("amide I" band); NMR: $\delta_{(CDCl_3)}$: 7.6, 7.1 (d, d, J_{ortho} = 8 Hz aromatic protons), 6.3 (br, olefinic protons), 5.2 (br, 1-H and 4-H), 2.31 (s, Ar-CH_3), 1.9 (m, $-CH_2$).

N-p-*Nitrobenzoyl-2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**5**). The reaction of **1** with *p*-nitrobenzoyl chloride and pyridine, as described in the previous experiment, gave, after crystallization from benzene-petroleum ether, 61% yield of **5**; m.p. 113–114 . (Found: C, 58.68; H, 3.65; Calc. for: $C_{12}H_{10}N_2O_4$; C, 58.53; H, 4.06%; IR: ν_{max} (KBr) (cm^{-1}): 1660 ("amide I" band), 1510, 1345 (nitro); NMR: $\delta_{(CDCl_3)}$: 8.08, 7.92 (d, d, J_{ortho} = 8 Hz, aromatic protons), 6.36, 6.62 (m, olefinic protons), 5.36 (br, 1-H and 4-H), 2.0 (m, CH_2-).

N-*Ethoxy carbonyl-2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**6**). Pyridine (0.79 g, 0.01 mol) was added, in drops, to an ice-cooled and stirred suspension of **1** (1.33 g, 0.01 mol) in dry benzene (50 ml). After 0.25 hr, a soln of ethylchloro formate (1.08 g, 0.01 mol) in benzene (20 ml) was introduced followed by another equiv of pyridine (0.79 g, 0.01 mol). The mixture was left stirred for 2 hr, the organic layer washed with water, dried ($MgSO_4$), solvents evaporated under vacuum and the crude product (0.9 g) purified by preparative tlc (EtOAc: C_6H_6, 1:9) to yield 0.8 g (47%) of **6** as a colourless oil. (Found: C, 57.1, H, 5.7; Calc. for $C_8H_{11}O_3N$: C, 56.9, H, 6.1%; IR: ν_{max} (neat) (cm^{-1}). 1630, 1700, 1740; NMR: $\delta_{(CDCl_3)}$: 6.4 (m, olefinic protons), 5.23, 5.05 (br, br, 1-H and 4-H), 4.2 (q, O CH_2 CH_3), 1.9 (m, $-CH_2-$), 1.25 (t, CH_2-CH_3).

N-*Formyl-2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**7**). A freshly prepared sample of acetic-formic anhydride[16] (0.037 mol, prepared from 3.5 ml of Ac_2O) was added to an ice-cooled and stirred suspension of **1** (1.33 g, 0.01 mol) and pyridine (1.18 g, 0.015 mol). The mixture was left stirred for 2 hr, admixed with $NaHCO_3$ aq (10 ml, 10%, 0.11 mol), stirred for 0.5 hr, extracted repeatedly with CH_2Cl_2, dried ($MgSO_4$), solvents evaporated and the crude product chromatographed on silica gel. Elution with EtOAc: benzene (9:1) gave 0.9 g (72%) of the light yellow liquid aldehyde **7**. (Found: C, 57.16; H, 5.70, Calc for $C_6H_7NO_2$; C, 57.60; H, 5.60%); IR: ν_{max} (neat) (cm^{-1}): 1680 ("amide I" band); NMR; $\delta_{(CDCl_3)}$: 8.23 (s, N-CHO), 6.47 (m, olefinic protons), 5.47 (br, 4-H), 5.17; (br, 1-H), 1.95 (m, CH_2-).

N-*Acetyl-2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**8**). To an ice-cooled and stirred mixture of **1** (1.33 g, 0.01 mol) and pyridine (1.18 g, 0.015 mol) was added, in drops, a soln of Ac_2O (3.78 g, 0.037 mol) in benzene (5 ml), followed by another lot of pyridine (1.18 g, 0.015 mol). After 2 hr, $NaHCO_3$ aq (20 ml, 10%, 0.022 mol) was introduced and the stirring continued for further 0.5 hr. The layers were separated and the aqueous portion extracted with CH_2Cl_2, the combined extracts dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc: benzene (1:1) gave 1.1 g (79%) of **8** as a liquid. (Found. C, 60.97; H, 6.12; Calc. for $C_7H_9NO_2$: C, 60.43; H, 6.47%); IR: ν_{max} (neat) (cm^{-1}): 1675 ("amide I" band); NMR: $\delta_{(CDCl_3)}$: 6.5 (m, olefinic protons), 5.3 (m, br, 1-H and 4-H), 2.0 (s, N-CO-CH_3), 2.0 (m, $-CH_2-$).

4-*Dibenzoylaminocyclopentenone* (**9**). An ice-cooled and stirred mixture of benzoylchloride (2.810 g, 0.02 mol) and pyridine (3.16 g, 0.04 mol) in dry benzene (35 ml) was gradually admixed with **1** (1.335 g, 0.01 mol) and left stirred for 24 hr at rt (35). The mixture was treated with HCl aq (20 ml, 10%), extracted with benzene (3 × 40 ml), the organic layer washed with $NaHCO_3$ (2 × 30 ml, 8%), water (2 × 30 ml), dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with CH_2Cl_2 gave 1.397 g (46%) of **9**. A sample was crystallized from benzene petroleum ether; m.p. 47–50 . (Found: C, 74.30; H, 4.68; Calc. for $C_{19}H_{15}NO_3$: C, 74.75; H, 4.91%); IR: ν_{max} (KBr) (cm^{-1}): 1723 (α, β unsaturated cyclopentenone carbonyl); NMR: $\delta_{(CDCl_3)}$: 7.82–6.78 (m, aromatic protons), 5.65 (m, olefinic protons), 3.85 (br, N-CH-C=), 2.18 (m, CH_2 C=O).

4-*Metha nesulfonylaminocyclopentenone* (**10**). Dry pyridine (0.79 g, 0.01 mol) was added, in drops, to an ice-cooled and stirred suspension of **1** (1.33 g, 0.01 mol) in benzene (50 ml). After 0.25 hr a soln of mesylchloride (1.14 g, 0.01 mol) in benzene (5 ml) was added followed by pyridine (0.79 g, 0.01 mol). The mixture was left stirred for 4 hr, washed with cold water, dried ($MgSO_4$), the solvents evaporated *in vacuo* and the residue chromatographed on silica gel. Elution with EtOAc: benzene (1:4) gave 0.5 g (28%) of **10** as a viscous liquid which decomposed on standing. (Found: C, 40.83; H, 4.68; Calc for $C_6H_9NO_3S$: C, 41.14; H, 5.14%); IR: ν_{max} (neat) (cm^{-1}): 3300 (NH), 1720 (α, β unsaturated cyclopentenonecarbonyl), 1370, 1175 (SO_2–N); NMR: $\delta_{(CDCl_3)}$: 5.84, 5.65 (m, olefinic protons), 5.25–4.95 (m, CH NH-SO_2), 3.15 (s, CH_3 SO_2), 2.95 (m, CH_2-C=O).

4-(p-*Tosylamino*) *cyclopentenone* (**11**). Pyridine (0.79 g, 0.01 mol) was added, in drops, to an ice-cooled and stirred suspension of **1** (1.33 g, 0.01 mol) in dry benzene (50 ml). After 0.25 hr a soln of freshly crystallized *p*-tosylchloride (1.9 g, 0.01 mol) in benzene (20 ml) was introduced followed by another equiv of pyridine (0.79 g, 0.01 mol). The mixture was left stirred for 5 hr, the organic layer washed with water, dried ($MgSO_4$), solvents evaporated under vacuum and residue chromatographed on silica gel.

Elution with EtOAc: benzene (2:3) gave **11** (0.2 g, 8%) as a light yellow unstable liquid. IR: ν_{max} (neat) (cm^{-1}): 1710 (α,β-unsaturated cyclopentenone CO), 1310, 1140 (SO_2–N); NMR: $\delta_{(CDCl_3)}$: 7.72, 7.34 (m, m, aromatic protons), 6.2–5.6 (br, olefinic protons), 4.42 (br, N-CH-CH=CH), 2.44 (s, C_6H_4 CH_3).

exo and endo-*N-(α-Chloro-2,4-dinitrobenzyl) 2-aza-3-oxabicyclo* (2.2.1) *hept-5-ene* (**12** and **13**). Dry pyridine (0.79 g, 0.01 mol) was added to an ice-cooled and stirred suspension of the hydrochloride **1** (1.33 g; 0.01 mol) in benzene (50 ml) followed by, in drops, a soln of 2,4-dinitrobenzaldehyde (1.96 g; 0.01 mol) in benzene (5 ml). The mixture was left stirred for 5 hr, washed repeatedly with cold water, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel.

Elution with EtOAc: benzene (1:4) gave 0.85 g (26%) of **12**, m.p. 111 112 . (Found: C, 46.44; H, 2.80; N, 13.20; Calc. for

$C_{12}H_{10}ClN_3O_5$: C, 46.22; H, 3.21; N, 13.48%); IR: ν_{max} (KBr) (cm^{-1}): 1523, 1350 (nitro), 776 (C Cl); NMR: $\delta_{(CDCl_3)}$: 9.26 (d, J = 8 Hz, aromatic o-proton), 8.69 (d, J = 2 Hz, aromatic m-proton), 8.34 (dd, J_{ortho} = 8 Hz, J_{meta} = 2 Hz, aromatic m-proton), 8.15 (s, N–CHCl–Ar), 6.23, 5.92 (m, m, olefinic protons), 5.39, 5.11 (br, br, 1-H and 4-H), 2.7 (o, o, $-CH_2-$); MS: *m/e*: 276 $(M-Cl)^+$.

Further elution with EtOAc: benzene (3:2) gave 0.1 g (3%) of **13**; m.p. 131–132°. (Found: C, 46.53; H, 2.88; N, 13.11; Calc for $C_{12}H_{10}ClN_3O_5$: C, 46.22; H, 3.21; N, 13.48%); IR: ν_{max} (KBr) (cm^{-1}): 1520, 1345 (nitro), 772 (C Cl); NMR: $\delta_{(CDCl_3)}$: 9.24 (d, J = 8 Hz, aromatic o-proton), 8.67 (d, J = 2 Hz, aromatic m-proton), 8.32 (dd, J_{ortho} = 8 Hz, J_{meta} = 2 Hz, aromatic m-proton), 8.31 (s, N–CHCl–Ar), 6.28, 6.0 (m, m, olefinic protons), 5.08, 4.87 (1-H and 4-H), 2.7 (m, $-CH_2-$); MS: *m/e*: 276 $(M-Cl)^+$.

exo *and* endo-*N*-(α-*Chlorobenzyl*)2-*aza*-3-*oxabicyclo* (2.2.1) *hept*-5-*ene* **14** *and* **15**. The salt **1** (1.33 g; 0.01 mol) was reacted with benzaldehyde (1.06 g; 0.01 mol) as described above. Elution with EtOAc: benzene (1:4) gave 0.7 g (31%) of the *exo*-product **14** which on crystallization from benzene-petroleum ether gave colorless crystals; m.p. 71–72°. (Found: C, 65.40; H, 5.37; Calc. for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.41%); IR: ν_{max} (KBr) (cm^{-1}): 750 (C–Cl); NMR: $\delta_{(CDCl_3)}$: 8.16 (s, N–CHCl–Ph), 7.46 (m, aromatic protons), 6.32, 6.06 (m, m, olefinic protons), 5.30 (br, 1-H and 4-H), 2.9 (o, o, $-CH_2-$); MS: *m/e*: 186 $(M-Cl)^+$.

Further elution with EtOAc: benzene (1:1) gave 0.1 g (4.4%) of the *endo*-product **15**; m.p. 113–114°. (Found: C, 64.71; H, 5.27; Calc. for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.41%); IR: ν_{max} (KBr) (cm^{-1}): 750 (C–Cl); MS: *m/e* 186 $(M-Cl)^+$.

N-Hydroxymethyl 2-aza-3-oxabicyclo (2.2.1) *hept-5-ene* (**16**). $NaHCO_3$ aq (10 ml, 10%, 0.011 mol) was introduced, in drops, to an ice-cooled and stirred soln of **1** (1 g, 0.0074 mol) in formalin (10 ml, 40%). The mixture was left stirred for 50 hr, extracted with CH_2Cl_2, washed with water, brine, dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc: benzene (7:3) gave 0.8 g (85%) of **16** as a thick syrupy liquid, which was characterized as the acetate **17** (*vide infra*); IR: ν_{max} (neat) (cm^{-1}): 3380 (OH); NMR: $\delta_{(CDCl_3)}$: 5.8 (m, olefinic protons), 5.24 (m, 4-H), 4.75 (m, 1-H), 2.5 (m, $-CH_2-$).

N-Acetoxymethyl 2-aza-3-oxabicyclo (2.2.1) *hept-5-ene* (**17**). A mixture of **16** (0.381 g, 0.003 mol), Ac_2O (0.459 g, 0.0045 mol) and pyridine (0.355 g, 0.0045 mol) was left aside at room temp for 24 hr. Solvents were evaporated *in vacuo* to give **17** as a colourless liquid; yield 100%. (Found: C, 56.42; H, 6.35; Calc. for $C_8H_{11}NO_3$: C, 56.80; H, 6.50%); IR: ν_{max} (neat) (cm^{-1}): 1740 (ester); NMR: $\delta_{(CDCl_3)}$: 5.82 (m, olefinic protons), 5.2 (br, 4-H), 4.8 (m, 1-H), 4.2 (m, N–CH_2), 2.05 (s, $-OCOCH_3$).

N-(N'-Phenylaminothiocarbonyl) oxazabicyclo (2.2.1) *hept-5-ene* (**19**). To an ice-water-cooled and stirred soln of the free base **2** in benzene (50 ml)—generated from the hydrochloride **1** (1.33 g, 0.01 mol) by $NaHCO_3$ aq—was added, in drops, phenylisothiocyanate (1.35 g, 0.01 mol). The mixture was stirred for 5 hr at ~10°, solvents evaporated *in vacuo* and the nearly pure **19** (1.8 g, 76%) on crystallization from benzene–petroleum ether gave white crystals; m.p. 93–94°. (Found: C, 62.45; H, 4.58; Calc. for $C_{12}H_{12}N_2O_5$: C, 62.06; H, 5.17%); IR: ν_{max} (KBr) (cm^{-1}): 3325 (NH), 1495 (thiocarbonyl); NMR: $\delta_{(CDCl_3)}$: 8.4 (br, S=C–NH C_6H_5), 7.2 (m, aromatic protons), 6.56, 6.33 (m, m, olefinic protons), 5.8 (br, 1-H), 5.26 (br, 4-H), 1.9 (m, $-CH_2-$).

N-Nitroso 2-aza-3-oxabicyclo (2.2.1) *heptene* (**20**). To an ice water cooled and stirred soln of the free base **2** in benzene (30 ml)—generated from the hydrochloride **1** (1.6 g, 0.0120 mol) by $NaHCO_3$ aq—was added, in drops, i-AmONO (1.8 g, 0.0154 mol). The mixture was left stirred for 3 hr and solvents evaporated without heating to give 0.8 g (61%) of pure (tlc) **20** as a yellow gum. IR: ν_{max} (neat) (cm^{-1}): 1550 (N–N=O).

N-Benzoyl-2-aza-3-oxabicyclo (2.2.1) *heptane* (**22**): *in situ benzoylation of 2-aza-3-oxabicyclo* (2.2.1) *heptane* (**21**). To an ice-cold and stirred suspension of potassium azodicarboxylate[7] (1.1 g, 0.0056 mol) and the hydrochloride **1** (0.29 g, 0.0021 mol) in abs MeOH (10 ml) was added, in drops, conc HCl (0.42 g, 0.01 mol) in MeOH (20 ml). The mixture was stirred for 4 hr, solvents evaporated *in vacuo* without heating and the resulting white cake suspended in dry benzene (25 ml). To this ice-cooled and stirred suspension was added, in drops, pyridine (0.8 g, 0.0101 mol) followed by benzoyl chloride (0.7 g, 0.0101 mol), the mixture left stirred overnight at ~5°, diluted with water, extracted with benzene (4 × 50 ml), the organic layer washed with $NaHCO_3$ (2 × 50 ml, 10%), HCl (2 × 50 ml, 10%), water (50 ml), dried ($MgSO_4$), solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc: benzene (1:4) gave 0.034 g (8%) of **3** and 0.209 g (48%) of the desired dihydro adduct **22** which crystallized on standing in the refrigerator, m.p. 35–36°. Tlc and IR of **22** was found to be identical to that of an authentic sample. (Found: C, 70.90; H, 6.55; N, 7.00; Calc. for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.89%); IR: ν_{max} (neat) (cm^{-1}): 1630 ("amide I" band); NMR: $\delta_{(CDCl_3)}$: 7.68, 7.4 (m, m, aromatic protons), 4.81 (br, 1-H and 4-H), 1.86 (m, $-CH_2-$).

Authentic N-benzoyl 2-aza-3-oxabicyclo (2.2.1) *heptane* (**22**). A soln of glacial AcOH (3.6 g, 0.06 mol) in abs MeOH (25 ml) was added, in drops, to an ice-cooled and stirred suspension of potassium azodicarboxylate (5.82 g, 0.03 mol) and **3** (1.5 g, 0.0074 mol) in abs MeOH (50 ml). The mixture was left stirred for 9 hr, solvents evaporated *in vacuo* without heating, and the white residue admixed with water (50 ml), extracted with CH_2Cl_2 (4 × 40 ml), dried ($MgSO_4$) and the solvents evaporated and the residue chromatographed on silica gel. Elution with EtOAc: benzene (1:4) gave 0.82 g (56%) of pure **22** as a viscous liquid which crystallized on standing in the refrigerator; m.p. 35–36°.

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[4]"Preliminary experiments using 1-chloro-1-nitrosocyclohexane as dienophile indicated that low temp reaction with cyclopentadiene gave a product which decomposed at −30° with formation of a black tar" G. Just and L. Cutrone, *Can. J. Chem.* **54**, 867 (1976).

[5]Analytical, IR, NMR and MS data are reported in the experimental section.

[6]Unless otherwise stated, only one pure isomer was obtained. NMR comparison of oxazabicycloheptenes possessing the tertiary amide function (**3–8**) with those which do not (**1**, **12–17**) indicate shielding of the bridge methylene in the former cases, thus implying *exo* stereochemistry for these products.

[7]G. Just and L. Cutrone, *Can. J. Chem.* **54**, 867 (1976).

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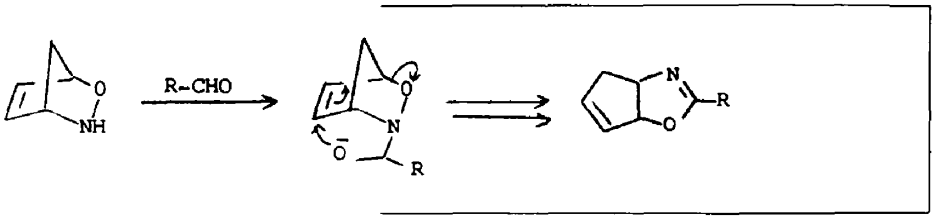
[9]This could, in principle, lead to bicyclio oxazolines:



[10]Since **2** is chiral, four compounds, namely, *exo* R, *exo* S, *endo* R and *endo* S could arise The identification of the products as the *exo*, *endo* pair is based on the completely different multiplicity of the bridge methylene (NMR). The possibility that **12–15** are in each case R, S mixtures can not be excluded, although they are crystalline solids and are pure (tlc).

The *exo-endo* barrier in the above systems can be expected to be quite high (K. Muller and A. Eschenmoser, *Helv. Chim. Acta* **52,** 1823 (1969).

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