A NOVEL STEREOCHEMICAL CONTROL

A PERSISTENT PREFERENCE FOR EXO ELECTROPHILE ACCEPTANCE IN 2-BORNANES

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Abstract—The conjugate bases of camphor oxime and 2-nitro-bornane, possessing a π array, accept elements of H^+ and Br^+ selectively from the "crowded" *exo* side. The present work adds another facet towards the understanding of stereochemical controls inherent in the bornane framework, the other two related being the *endo* addition of nucleophiles to camphor and the *exo* electrophile acceptance by camphor enolates. The present work describes, *inter alia*, a practical route to 2-*endo* nitrobornane and the novel 2,2-dinitrobornane.
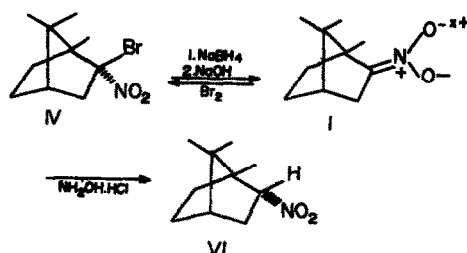
As a consequence of studies related to the bromo-nitrocamphane → anhydrobromonitrocamphane rearrangement,[1] the chemistry of 2-nitrocamphane with particular attention to the stereochemistry of acceptance of H^+ and Br^+ of bornane-2-nitronic acid (I) or its salts came under scrutiny. We feel that the work reported here adds a third facet to the understanding of the bornane framework, the other two being, the well studied electrophile acceptance of 2-bornene-2-ol (II) or its salts to camphor—which preferentially takes an *exo* course[2] and the thoroughly documented course of addition of nucleophiles to camphor (III) which shows an *endo* preference.[3] The significant observation that (I) under a variety of conditions preferentially accepts H^+ and Br^+ from the *exo* side has emerged from the present study.

I: X=H or Na

Y=H or Br

II: X=H or metal

III

Until 1967 it was generally believed that substitution in bornanes would show an *endo* preference due to the shielding influence of the C_7-gem-dimethyl groups.[4]

Indeed this concept was so deeply entrenched that considerable interest was aroused when in that year camphor was shown to exchange preferentially *exo*.[5] The same year Schleyer introduced a novel concept that would predict a torsional strain controlled *exo* electrophile acceptance for type II systems. The view was also expressed that this effect is inconsequential for processes involving the generation or destruction of *exo* π

systems where the stereochemistry would be controlled by steric effects leading to *endo* acceptance.[6] The crux of the torsional strain theory is the eclipsing of substituents as they move along the reaction coordinate. Over a period of years Schleyer's theory has been accorded varying degrees of acceptance and no significant alternate explanation has emerged.[7] The nitronic acid and its salts present an unusual situation not encountered in the earlier extensive investigations but which incorporate aspects of structures II and III.

2-Bromo-2-nitrobornane (IV) was prepared in 55% yields from camphor oxime (V) and hypobromite.[1] Our work as well as that from X-ray analysis[8] have established IV to be the *exo* bromo *endo* nitro isomer. The formation of IV demonstrates a clear preference to the *exo* acceptance of Br^+ by the intermediate Va.


V

Va

IV
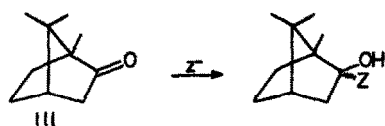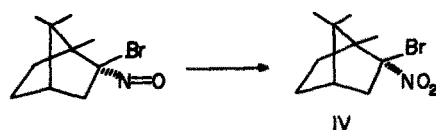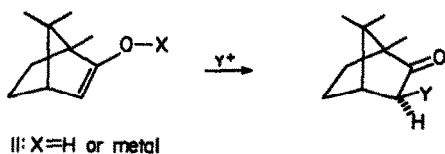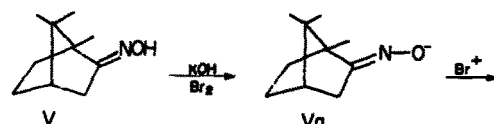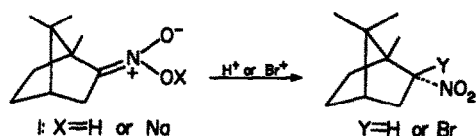
2-*endo* Nitrobornane (VI) can be prepared in quantitative yields by sodium borohydride reduction of IV that involves the quenching of the nitronate I(X = Na) with hydroxylamine hydrochloride.[9] The preference is for an *exo* proton acceptance. Further an aliquot containing I(X = Na) was poured onto bromine water. The precipitated solid was shown to be exclusively 2-*exo*bromo-2-*endo* nitrobornane IV (IR, NMR).


IV

I

VI

Under unequivocally kinetic conditions also the preference is for the formation of *endo*-2-nitrobornane. Thus, the potassium salt I(X = K), prepared using slight excess of KOtBu, was poured onto $3NH_2SO_4$ and then extracted with ether. Careful analysis of the reaction mixture showed that the product was *endo* 2-nitrobornane (VI).[10] In another experiment, the potassium salt was poured onto bromine water. The precipitated product was 2-*exo* bromo-2-*endo*-nitro bornane (IV).


VI

IV
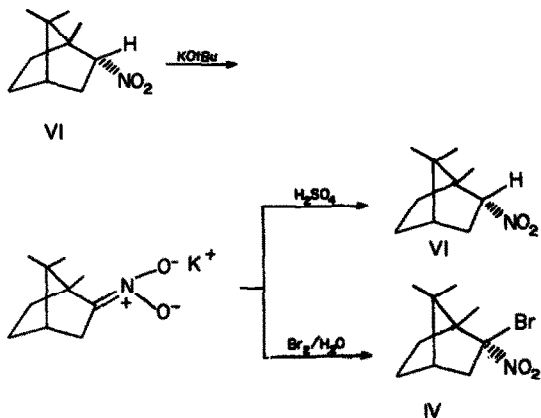
The *endo* assignment for VI is supported by its NMR spectrum.[11] Further, on hydrogenation VI furnished bornylamine. It appears that of the two possible 2-nitrobornanes, the *endo* isomer enjoys thermodynamic preference. This is brought out with the exclusive formation of 2-*endo* nitro-bornane (VI) in 32% yields from IV with ethanolic KOH.


IV

VI
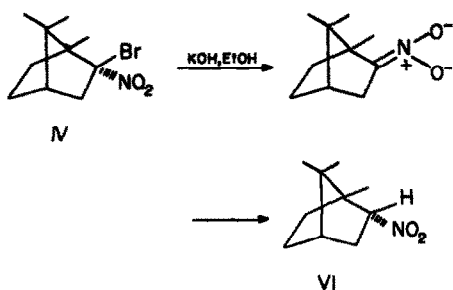
In a novel effort to discern preferences for the nitronic acid (I) → 2-nitrobornane (VI) change, the hydrogenolysis of 2,2-dinitrobornane (VII) was studied. It is known that *gem* dinitro compounds undergo rapid hydrogenolysis at normal pressure to give mono nitro compounds. The reduction virtually stops at this stage and leads to kinetically controlled products as exemplified with the VIII → IX change.[12]


VIII   IX
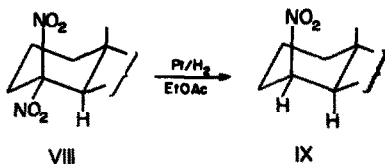
We rationalize this ready and clean change on the basis of active participation of the unreduced nitro function.
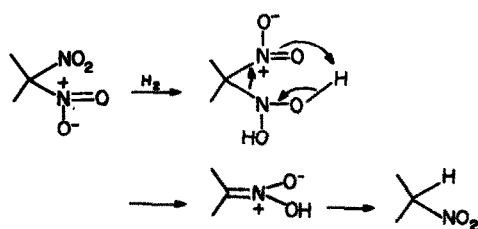
Nitration of camphor oxime with fuming HNO_3 is reported to yield 2-2-dinitrobornane m.p. 107°.[13] To our surprise the reaction gave a 37% yield of camphor nitrimine (X) and a 7% yield of VII m.p. 214°! The structural assignment for VII is fully supported by spectral and analytical data.

X 37%

VII 7%
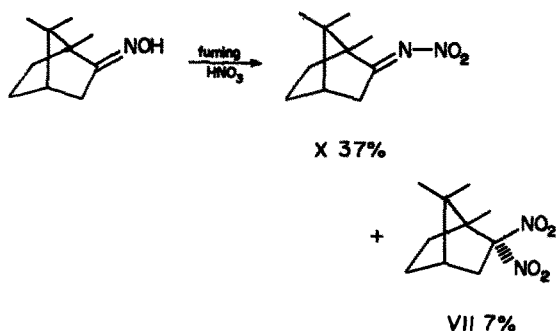
Hydrogenolysis of VII, gave as the sole isolable product, in 66% yields, *endo* nitrobornane (VI). There was no evidence for the formation of any of the isomeric compound.

VII   I

VI
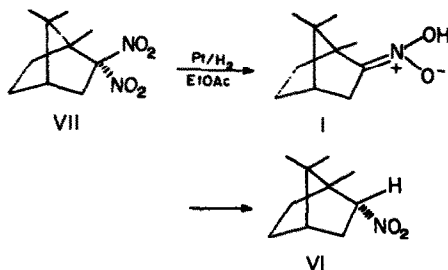
We believe that the VII → VI change constitutes an elegant demonstration of preference for kinetic *exo* proton acceptance.

Reaction of bornane[14,15] with dil. HNO_3 in sealed tube has been reported to yield *exo* 2-nitrobornane.[16] In our hands, however, the reaction was found to lead to a complex mixture[17] containing nitro and carbonyl functions. The only pure compound that could be isolated was *endo* nitrobornane. The isolation of VI was not entirely unexpected, since the reaction most probably proceeds via I. Thus, 2-*exo* nitrobornane remains elusive.

The present study has shown bornane-2-nitronic acid preferentially accepts electrophiles from the "crowded" *exo* side. Thus, irrespective of theories that would account for the experimental observations, the bornane system, similar to the parent bicyclo-[2.2.1]-heptane, shows distinct preference for acceptance of electrophiles from the *exo* side at 2-position.

Our results can be rationalized on the basis of a

product-like transition state wherein significant bond formation with the electrophile occurs only when the nucleophilic C_{-2} centre has considerable s-character which would place the 2-substituent in a progressively *endo* orientation. In a broader sense, in 2-substituted bornanes, a product-like transition state—whatever its finer descriptions ·may be—favours *exo* entry, and a starting material-like transition state an *endo* substitution.[18] All the observed stereochemical preferences that involve substitution at 2 and 3 positions of bornanes could be explained on this basis.

EXPERIMENTAL[a]

2-endo *Nitrobornane* ((VI)

To a mechanically stirred soln of $NaBH_4$ (2.7 g; 0.0713 mole) in MeOH: water (75:25; 50 ml), warmed with hot water, was introduced a soln of bromonitrobornane[1] (3.5 g; 0.01335 mole) in MeOH (17.5 ml). At first, a few drops were added cautiously. Vigorous exothermic reaction occurred accompanied by frothing, causing the MeOH to reflux. Subsequently the remaining soln was introduced rapidly. After additional stirring for 3 hr at room temp. the mixture was made distinctly alkaline by addition of KOHaq, and steam distilled to remove most of the MeOH. The residue was neutralized with aqueous hydroxylamine hydrochloride soln (15%; 25 ml) and again subjected to steam distillation. The 2-*endo* Nitrobornane crystallized on the walls of the condenser and was collected and dried; yield 1.75 g (92%) m.p. 147° (lit. 146–147°).[19] Tlc single spot (R_f: 0.7 benzene; 0.6 Benzene: hexane 1:1) IR: ν_{max}(CHCl$_3$) (cm^{-1}): 1545 (NO$_2$, asym), 1380 (NO$_2$, sym.), 865 (C–N). NMR: $\delta_{(CCl_4)}$: 4.65 (ill defined triplet, J = 7.50 Hz, non-bridgehead t-proton), 1.10 (s, C–CH$_3$), 0.97 (s, C–CH$_3$, 6 protons).

An aliquot after NaBH$_4$ reaction was added to excess Br-water and the precipitated solid collected, washed with water and dried to give sample identical in all respects (tlc, IR and NMR) to that of authentic 2-*exo*-bromo-2-*endo*-nitrobornane.

Acid quenching of potassium bornane-2-nitronate

Isolation of VI. To a stirred soln of t-BuOK in dry t-BuOH (0.6000 g, 0.00535 mole, 2 ml) was added a soln of 2-*endo*-nitrobornane, in t-BuOH (0.9150 g, 0.005 mole, 1 ml). After an additional 0.5 hr of stirring, the mixture was poured on to 3N H$_2$SO$_4$ (100 ml). The mixture was extracted with ether, the organic layer washed with bicarbonate and then with water, dried (MgSO$_4$) and evaporated and the crude product chromatographed on silica. Elution with petroleum ether, benzene (90:10) gave unchanged 2-*endo*-nitrobornane. One of the early fraction contained traces of isomer as evidenced by the presence of a 1570 cm^{-1} in addition to the major band at 1540 cm^{-1} attributed to NO$_2$ asym of the starting material.

Reaction of potassium bornane-2-nitronate with bromine-water

Isolation of IV. To a stirred soln of 2-*endo*-nitrobornane (0.915 g, 0.005 mole) in dry t-BuOH (15 ml) was added sublimed t-BuOK (0.7200 g, 0.00643 mole). After additional 0.5 hr stirring the mixture was poured onto Br-water (3 g, 0.019 mole, 100 ml), the precipitated crude bromonitrobornane was collected, washed with water and dried; yield, 1.0270 g (66%). The IR of this

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[a]M.ps were taken on a Fisher-John melting point apparatus and are uncorrected. Capillary m.ps were taken in a Thomas Hoover capillary melting point apparatus. IR spectra were recorded either on a Perkin–Elmer 700 or 137 or Perkin –Elmer 521 spectrophotometer. NMR spectra were determined with CHCl$_3$-d$_1$/CCl$_4$ solutions on a Varian-A60 or A60D spectrometer using TMS as internal standard. Silica gel G (Stahl) with calcium sulfate binder was used for tlc. Column chromatography was performed either with silica gel or with alumina. The compounds reported here, are optically inactive. Wherever possible, the reactions were monitored by tlc.

material was superimposable with that of 2-*exo*-bromo-2-*endo*-nitrobornane, prepared from camphoroxime with potassium hypobromite; further, the NMR was also identical with that of an authentic sample.

Hydrogenation of VI

Isolation of endo-2-*Aminobornane*. In a Parr hydrogenation apparatus, a soln of 2-*endo*-nitro-camphane in EtOAc (0.200 g, 0.00109 mole, 20 ml) was hydrogenated over PtO$_2$ catalyst at an initial pressure of 50 psi. After 5 hr, the mixture was filtered, washed thoroughly with EtOAc and the combined filtrates evaporated to give 0.1200 g (71%) of essentially pure bornylamine. IR: ν_{max} (CHCl$_3$) (cm^{-1}): 3300–3150 (NH$_2$, due to hydrogen bonding). NMR $\delta_{(CDCl_3)}$: 6.88 (broad –NH$_2$, exchanged in D$_2$O), 3.42 (dq, non-bridgehead t-proton), 1.06 (s, C–CH$_3$), 0.91 (s, C–CH$_3$, 6 protons).

Reaction of IV *with ethanolic KOH*

Isolation of 2-endo *nitrobornane* (VI). An aqueous soln of KOH (1 g, 0.018 mole) in minimum amount of water was added to a soln of bromonitrocamphane (5 g, 0.01908 mole) in EtOH (12.5 ml). The mixture was refluxed on a water bath overnight, concentrated, diluted with water and steam distilled. Crystals of 2-*endo*-nitrobornane, accumulated on the walls of the condenser were collected and dried; yield, 1.1 g (32%); m.p. 147° (lit.[19] 146–147°). IR: ν_{max} (KBr) (cm^{-1}): 1545 (NO$_2$, asym.), 1380 (NO$_2$, sym.), 865 (C–N). NMR: $\delta_{(CCl_4)}$: 4.62 (illdefined triplet, J = 8.00 Hz; non-bridgehead t-proton), 1.08 (s, C–CH$_3$), 0.93 (s, C–CH$_3$, 6 protons).

2 2-Dinitrobornane (VII). To a hand stirred soln of camphoroxime (10 g, 0.06 mole) in glacial AcOH (150 ml) was added pure fuming HNO$_3$ (6.4 ml, sp. gr. 1.5000) in the absence of direct light. After 10 min, water (500 ml) was added and the blue ppt collected, washed liberally with water and exposed to air for 8 hr and subsequently dried in vacuum; yield, 7.5 g; m.p. 86–95°. The crude product was chromatographed over silica gel (300 g). Elution with benzene: hexane (25:75) gave pure 2,2-dinitrobornane; yield, 1.0 g (7%); m.p. 214° (sealed capill) (lit. 107.5–108.5°).[13] TLC: Single spot (R_f: 0.79, benzene: hexane (1:1)). Found: C, 52.78; H, 7.20; N, 12.40. Calc. for C$_{10}$H$_{16}$N$_2$O$_4$ (M.Wt. 228): C, 52.63; H, 7.01; N, 12.28%. IR ν_{max} (KBr) (cm^{-1}): 1560 (NO$_2$, asym.), 1365 (NO$_2$, sym.), 848 (C–N). NMR: $\delta_{(CDCl_3)}$: 1.50, 1.03, 0.92 (S, C–CH$_3$).

Further elution using benzene–hexane (50:50) gave material which was subsequently identified as comphornitrimine, yield: 4.5 g (37%). TLC: Single spot (R_f: 0.65, benzene: hexane (1:1)). IR: ν_{max} (neat) (cm^{-1}): 1640 (C=N), 1570 (NO$_2$, asym.), 1325 (NO$_2$, sym.). NMR: $\delta_{(CCl_4)}$: 1.06, 1.00, 0.91 (s, C–CH$_3$).

IR and NMR spectra of this sample was identical to that of an authentic sample of camphornitrimine.

Hydrogenolysis of 2,2-dinitrobornane

Isolation of VI. In a semi-micro hydrogenation set-up a soln of dinitrobornane in EtOAc (0.1320 g, 0.000578 mole, 30 ml) was injected to a stirred suspension of Pt-catalyst in EtOAc (10 ml) kept under H$_2$. Theoretical amount of gas corresponding to one nitro group was consumed in 7 min. The mixture was twice filtered, washed thoroughly with EtOAc and evaporated to give 0.0700 g (66%) of crude 2-*endo*-nitrobornane; crystallization from hot aqueous EtOH gave 0.0500 g of pure product; m.p. 146–7° (lit.[19] 146–7°). There was no evidence for the formation of any of the isomeric 2-*exo*-nitrocamphane.

Tlc: Single spot (R_f: 0.52, benzene: hexane (1:1)). IR: ν_{max} (CHCl$_3$) (cm^{-1}): 1550 (NO$_2$, asym.), 1378 (NO$_2$, sym.), 865 (C–N); superimposable on that of the 2-*endo*-nitrocamphane obtained by borohydride reduction of bromonitrocamphane.

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[4a]"...... A different steric situation prevails in the Camphane System where the *exo* face of the molecule is strongly screened by the *gem* dimethyl group at C_7. As a result, this system is generally approached by reagents from the *endo* side ......".

E. L. Eliel, *Stereochemistry of Carbon Compounds*, p. 304. McGraw-Hill Book Co., Inc., New York (1962).

[5a]"...... The phenomenon of *exo* hydrogen exchange in the case of camphor must reflect the operation of some as yet unappreciated steric or stereoelectronic effect. It takes an additional, although somewhat vicarious, interest because this apparently general tendency of bicyclo 2,2,1 heptan-2-ones to suffer *exo* protonation in a group of reactions which certainly cannot involve carbonium ions mimics the tendency of 2-bicyclo 2,2,1 heptyl carbonium ions to yield *exo* substituted products .....". (Ref. 2).

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[10]2-Bornane nitronic acid readily tautomerises preferentially to the *endo* isomer (Toivonen, Heikki, *Suomen Kem.* B 1971, 44(2), 54–60, *Chem. Abstr.* **75**, 6120j (1971).

[11]NMR data given in "experimental". The *endo* nitro assignment is supported by the appearance of the bridge methyls as a single peak. Additionally, in the case of 2,2-dinitro bornane-where one of the nitro groups must be *exo*-these peaks are clearly separated.

[12]J. R. Bull, E. R. H. Jones and G. D. Meakins, *J. Chem. Soc.* 2601 (1965).

[13]S. Mitchell and R. Gordon, *Ibid.* 853 (1936).

[14]L. Wolf, *Ann.* **394**, 86 (1912).

[15]It was felt that desulfurization of 2-bornanone-thioketal will provide a very desirable route to bornane, compared to the one available, namely, the Wolff-Kishner reduction of bornanone under drastic conditions. The novel 2-bornanone thioketal was prepared in 85% yields by refluxing for 30 hr a mixture of camphor (6.0 g), ethane dithiol (17 ml), PTSA (0.8 g) in dry benzene (160 ml). Filtration followed by evaporation and distillation gave 7.7 g of the thioketal b.p. 122°/0.5 mm (NMR δ_{CCl_4}: 3.44–3.10 (m, 4H), 1.07, 1.02, 0.95 (CH₃). Surprisingly the thioketal could not be desulfurized.

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[17]For a similar observation see Ref. 10.

[18]The fact that tautomerization of bornane-3-nitronic acids proceeds with equal stereochemical preference is in excellent agreement with this observation (see Ref. 10).

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