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FASCINATING PROBLEMS IN ORGANIC REACTION MECHANISMS—VI[1]

BROMONITROCAMPHANE ANHYDROBROMONITROCAMPHANE REARRANGEMENT

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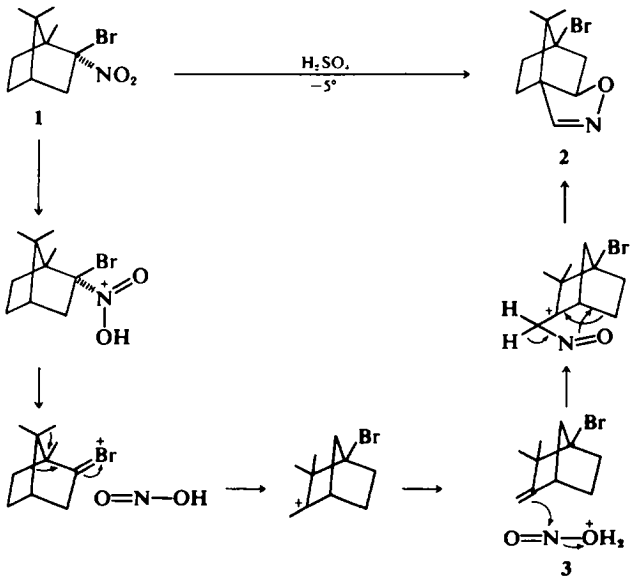
Abstract—The fascinating bromonitrocamphane(**1**)→anhydrobromonitrocamphane(**2**) change has been examined in detail. The structure of **2** has been confirmed by X-ray analysis and other physical data. The **1**→**2** transformation belongs to the rather uncommon fragmentation-rearrangement-recombination pathway and the three distinct stages involved, namely, the loss of the nitro group, the rearrangement of the bornane cation so generated to 4-bromocamphene(**3**) and the subsequent reacceptance of elements of the lost nitro group, have been confirmed on basis of experimental data, particularly employing ^{15}N sodium nitrite. The remarkable bromonitrocamphane(**1**)→4-bromotricyclene acid(**8**) change, the useful camphene→**9** transformation and the amusing **15**→**16** change have been discovered. The concerted nature of the camphene→**11** reaction has been established with optically active camphene and this study has helped in identifying the stage where optical activity is lost in the **1**→**2** change. Kinetic studies have shown that in the highly strained tricyclic isoxazolines **11**, **2** and **16**, the 4-substituents, through inductive effect, greatly affect the stability of the isoxazoline ring. The facile rupture of such isoxazolines have provided an efficient route to doubly functionalized bornanes.

INTRODUCTION

At the turn of the century, Forster, in the course of pioneering investigations related to camphor and its derivatives, isolated compound $C_{10}H_{14}NOBr$ on treatment of bromonitrocamphane(**1**)—prepared from camphor oxime and hypobromite—with sulphuric acid.[2] The structure of this product—named anhydrobromonitrocamphane—was suggested to be **2** in 1957[3] mainly on basis of chemical studies and the **1**→**2** change was rationalized on the basis of initial loss of nitro group with subsequent reunion as a nitrosating agent.†

This fragmentation-rearrangement-recombina-

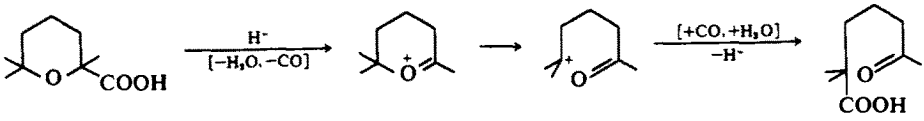
†The original mechanism has been slightly modified to accommodate the real stereochemistry of **1**.



tion route, graphically represented as,

$$AL \xrightarrow{-L} A \longrightarrow B \xrightarrow{+L} C$$

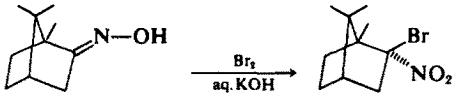
is indeed quite rare in systems lacking a π framework and the only well established member of this class is the classical, although less complicated, sulfuric acid induced α-cinenic acid→geronic acid change, so beautifully demonstrated by Meinwald:[4]



In view of the novel feature of this route, it was considered desirable to unequivocally establish the structure of anhydrobromonitrocamphane(2) and the proposed route as well as the novel reactions envisaged in the mechanistic scheme, namely, the loss of a protonated nitro group as nitrous acid and the transformation of systems such as 3 to isoxazolines by reacceptance of elements of the lost nitrous acid. Further, since the 1→2 change could, in principle, be rationalized by pathways not involving the loss of nitro group, the confirmation of, by various criteria, the fragmentation-rearrangement-recombination was required.

Structure of anhydrobromonitrocamphane(2)

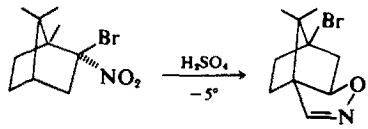
2-Bromo-2-nitrobornane (bromonitrocamphane; 1) was prepared in 60% yields according to the original procedure of Forster:[2]



4 1

The crude product (m.p. 185–220°) could be chromatographed over silica gel to give snow white samples (m.p. 220° dec) without much loss in yields. The NMR and IR* of the crude material was essentially identical to that of the purified sample, thus indicating that in the 4→1 change, the acceptance of elements of Br^+ takes place exclusively from the more hindered *exo* side!† The sulfuric acid "dehydration" of bromonitrocamphane could be smoothly effected in 40% yields to give the beautifully crystalline 2.

The spectral data compiled in the present work are in excellent agreement with the isoxazoline structure 2. The NMR ($\delta CDCl_3$ 0·87 (*anti* Me), 0·93



1 2

(*syn* Me), 4·10 (d,d *endo* t-proton), 7·07 (isoxazoline proton)) eventually turned out to be characteristic of systems exemplified by 2. The MS exhibited relatively weak (0·71%) molecular ion peaks at 243 and 245. The most abundant peak corresponded to the loss of bromine at 164 followed by a less abundant one (69%) corresponding to the loss of hydrogen bromide. The UV maximum at 226 nm (ϵ 2200), typical of 2-isoxazolines, was used to study transformations of systems related to 2 (*vide infra*).

A complete X-ray analysis of anhydrobromonitrocamphane has been carried out[5] and the results are in total agreement with structure 2. Crystals of anhydrobromonitrocamphane are orthorhombic, space group $p2_12_12_1$. The dimensions of the unit cell, comprising 4 molecules, were found to be a = 10·364, b = 9·408, c = 10·499A°, z = 4. The bond angles and bond lengths, tabulated below, provide for the first time the consequences of augmentation of the strain inherent in bicycloheptanes with another ring. Surprisingly, from examination of similar results from bornanes,[6] it appears that in the formation of the third ring, the isoxazoline ring bears the brunt of the additional strain as reflected by the tremendously distorted 4-10-N angle (101°) and the rather long N—O and O—3 bonds. It is no surprise that this ring bursts open under the slightest provocation!

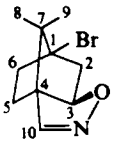
The fragmentation rearrangement-recombination path

The operation of this pathway in the 1→2 change was convincingly demonstrated employing ^{15}N sodium nitrite ($^{15}N > 95\%$). Bromonitrocamphane(1) was transformed to anhydrobromonitrocamphane(2) under the usual conditions with added two moles of ^{15}N sodium nitrite. The incorporation of the label in a highly purified sample became evident on comparison of molecular ion peaks from this experiment with authentic 2. The most prominent change in the mass spectrum, relative to that of 2, was the enhancement of the *m/e* 165 peak corresponding to loss of bromine from ^{15}N anhydrobromonitrocamphane. The percentage of incorporation has been calculated based on the changes of intensities of peaks at *m/e* 163, 164 and

*Routine physical data are presented in the experimental section.

†The stereochemistry has been rigorously established as in 1 and this work will form a separate paper.

Table 1.



Bond distances (in Å)

Bonds	Distance	Bonds	Distance	Bonds	Distance
1–2	1·51	6–1	1.57	4–10	1·50
2–3	1·54	1–7	1·49	10–N	1·33
3–4	1·55	4–7	1·58	N–O	1·51
4–5	1·56	8–7	1·53	O–3	1·46
5–6	1·50	9–7	1·51	1–Br	1·93

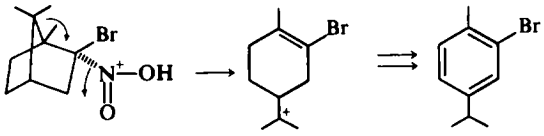
Bond angles (in degrees)

Bonds	Angle	Bonds	Angle	Bonds	Angle
1–2–3	102	7–1–Br	118	7–4–10	120
2–3–4	102	6–1–Br	110	3–4–10	113
3–4–5	104	1–7–4	91	4–10–N	101
4–5–6	104	9–7–8	115	10–N–O	113
5–6–1	102	9–7–4	112	N–O–3	110
6–1–2	108	8–7–1	115		96
2–1–7	105	5–4–7	102		

165 relative to standard and the method of calculation is described in the Experimental. The extent of incorporation was found to be 34%. The labelling experiment has been carried out twice and the results were quite comparable. From a preparative standpoint, the yield of the isoxazoline in the **1**→**2** change can be nearly doubled by addition of excess solid sodium nitrite to the reaction mixture. All these observations are in excellent accord with the pathway envisaged. The individual steps in the overall path were then subjected to scrutiny.

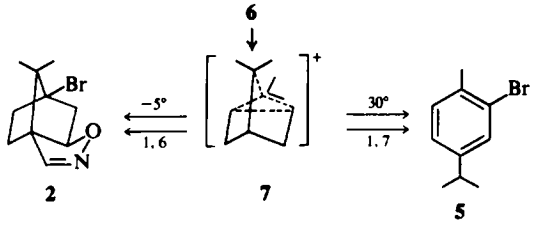
Fragmentation—the loss of the protonated nitro group

The **1**→**2** transformation is carried out at −5° in sulfuric acid–hexane system. It was found that when the reaction was conducted at ~30° a 55% yield of 2-bromo-*p*-cymene(**5**) was obtained.* The crude product was at least 95% pure (VPC)! significantly, under these conditions no anhydrobromonitrocamphane(**2**) could be detected. At 10°, **2** could be isolated along with, as the major product, **5**. Conversely, under the conditions of the **1**→**2** change (−5°) no 2-bromo-*p*-cymene is produced. The **1**→**5** change has preparative value also, since the available procedure for **5**[7] was found to yield mixtures which proved recalcitrant to fractionation. The ready formation of **5** is best explained on the basis of loss of nitro group *via* the protonated intermediate **6**, assisted by the stereochemically favourably disposed 1,7 bond.† There is no parallel to such a ready loss of the nitro group and the **1**→**5** change should be considered unusual particularly in view of the fact that we have shown recently[8] that generally *gem* bromonitro compounds on treatment with sulfuric acid, under the conditions of the **1**→**5** change, lose elements of Br^+ and not nitrous acid! The possibility for 1,7 bond participation present in **6** drives the reaction to 2-bromo-*p*-cymene and the nitrous acid produced obligingly brings about the aromatization:[9]



6 **5**

The remarkable temperature dependence of 1,7 *vs* 1,6 participation strongly implicate the common intermediate **7**:



2 **7** **5**

Rearrangement

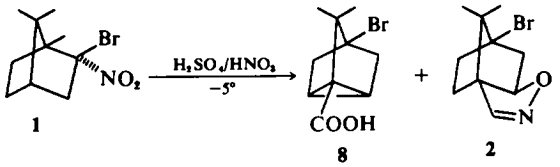
The bromocamphene intermediate **3**. Having established that the bromonitrocamphane(**1**) can readily lose elements of nitrous acid, attempts were made to identify the bromocamphene intermediate **3**. These, involving the use of large excess of hexane and the use of ammonium sulfate to destroy the nitrous acid, were unsuccessful. The reason for the failure became apparent on attempted monitoring of the **1**→**2** change by NMR. A sample of **1** was dissolved in neat sulphuric acid and during the brief interval between making the solution and recording the spectra, **1** was totally consumed to yield what is believed to be anhydrobromonitrocamphane(**2**).‡ It should be concluded that the further reactions of the camphene intermediate **3** are most efficient and that it is most unlikely that any significant amounts of **3** are built up in the reaction. In the hope of intercepting the camphene intermediate with nitronium ion, bromonitrocamphane was reacted with nitric acid/sulfuric acid (nitrating mixture!). This reaction, conducted under conditions employed in

*Routine spectral and analytical data are presented in the Experimental.

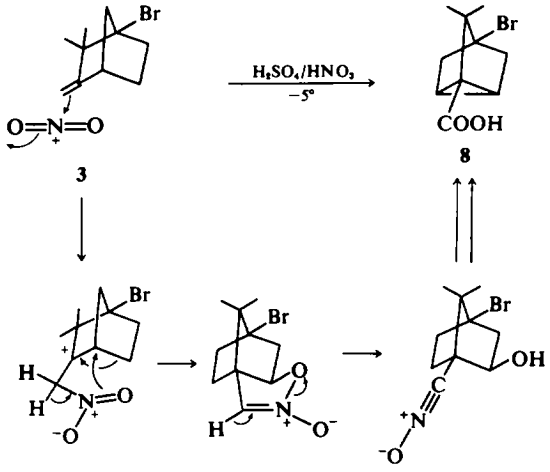
†The formation of **5** in minor yields, in the course of preparation of **2** from large amounts of **1** have been reported (M. O. Forster, *J. Chem. Soc.* **75**, 1141 (1899)).

‡NMR H_2SO_4: 5·12 (d,d *endo* proton), 7·91 (s, isoxazoline proton); the d,d pattern is chacteristic of isoxazolines of type **2**. The significant downfield shift of this proton and the isoxazoline proton relative to **2** could be due to solvent (or protonation?).

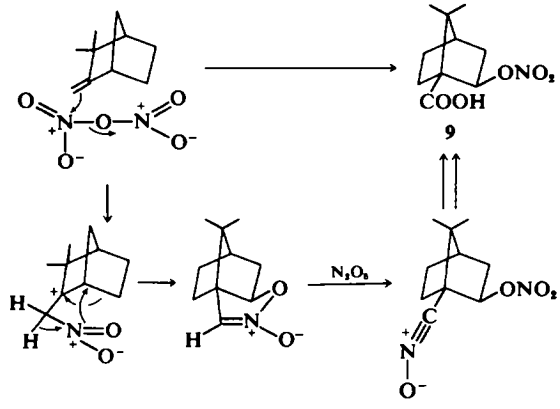
the 1→2 change, gave in addition to **2** (12%), the highly insoluble bromotricyclene acid **8** (5%). The structural assignment is supported by analysis, IR, NMR and MS.*



Careful model experiments confirmed that **2** is not involved in the transformation to **8** and that **8** is not formed during the usual sulfuric acid 1→2 change, Consequently, the formation of **8** must involve the predicted acceptance of nitronium ion species and a reasonable pathway for this fascinating change is outlined:

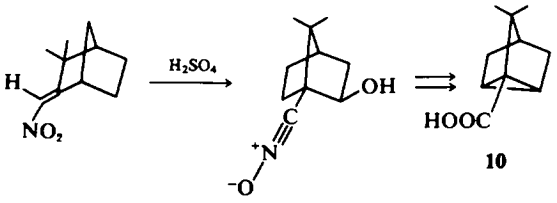


This rather unusual sequence derives much support from the known transformation of camphene to the acid **9** by N_2O_5/chloroform[10] which we rationalize by an analogous path:



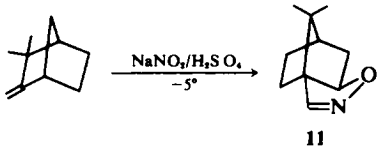
*Routine analytical and spectral data are presented in the Experimental.

Additionally we have recently established that the sulfuric acid initiated transformation of ω-nitrocamphene to tricyclenic acid **10** proceeds by a pathway similar to that envisaged for the 1→8 change:[11]

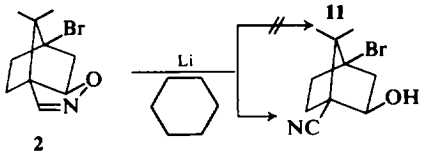


Recombination

The transformation of the bromocamphene intermediate to isoxazoline **2**: This step was dramatically demonstrated by the transformation of camphene to isoxazoline **11**, the parent of tricyclic systems to which anhydrobromonitrocamphane belongs:[1]



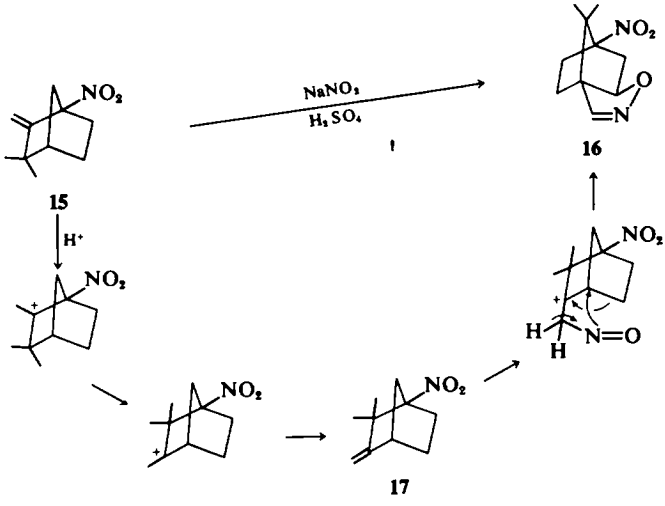
Further, the camphene→**11** transformation, brought about under conditions of the 1→2 change, provides a facile route to doubly functionalized bornanes. The structural assignment for **11** is supported by analysis, IR, NMR and UV* and, as expected, these are strikingly similar to anhydrobromonitrocamphane(**2**). Parenthetically, the isoxazoline **11** is formed only under very narrowly defined conditions. Reaction of camphene with sodium nitrite–acetic acid, addition of N_2O_3 to camphene, reduction of ω-nitrocamphene with zinc–acetic acid, all failed to give **11**. Attempted transformation of anhydrobromonitrocamphane(**2**) to **11** by debromination led instead to isoxazoline rupture (*vide infra*):



The camphene→**11** change can be rationalized on the basis of further transformation of electron deficient species **12**, *via* 1,6-σ-participation, O—C bond formation and proton loss. It has been found that optically active camphene gives optically active **11**, thus indicating that the O—C bond formation must be synchronous with σ-participation. If σ-participation were to precede O—C bond forma-

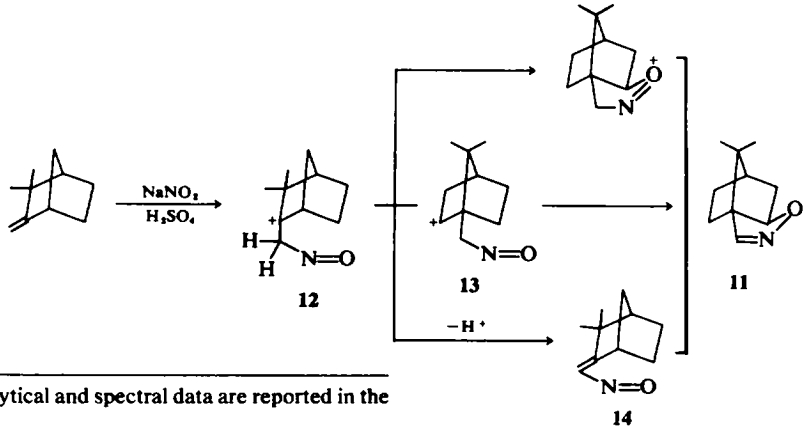
tion, the resulting intermediate bornane cation **13** would certainly racemize *via* very rapid hydride shifts.[12] Consequently, the earlier rationalization[3] of the racemization that occurs during the bromo-nitrocamphane-anhydrobromonitrocamphane rearrangement on basis of a non-concerted transformation of the bromocamphene intermediate **3** should be revised in view of results from the closely related camphene-**11** change. It is quite likely that the bromocamphene intermediate **3** itself undergoes racemization as has been clearly demonstrated with camphene.[13] The question as to whether deprotonation succeeds or precedes the concerted change cannot be answered. If the latter were to be the case, the isoxazoline formation would be, formally, a $\pi 4s + \sigma 2s$ change involving the novel $\alpha\beta$-unsaturated nitroso system **14**, which has been demonstrated to behave as powerful 1,4-dipoles:[14]

An amusing event took place, when in attempts to discourage the 1,6 σ-participation and thus make the intermediacy of the α,β-unsaturated nitroso system more apparent, 1-nitrocamphene (**15**) was reacted with sodium nitrite-sulfuric acid, under the conditions of the **1**→**2** change. This reaction gave, as the sole isolable product, the 4-nitro isoxazoline **16**. The **15**→**16** change must involve the prior acid induced isomerization of 1-nitrocamphene to 4-nitro camphene (**17**):

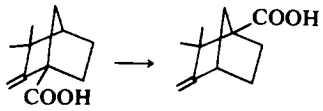


The structural assignment for **16** is supported by analysis, IR and typical NMR.* The proposed **15**→**17** change is analogous to the reported acid induced 1-carboxy camphene-4-carboxy camphene[15] change and may well be general for camphenes substituted in the 1-position with electron withdrawing groups.

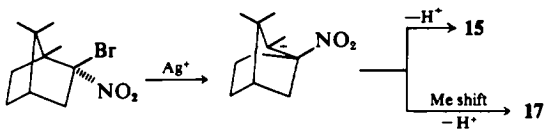
The structure of **15** has been quite well established[16] and our attempts to demonstrate the **15**→**17** change in $CF_3COOH(D)$ employing NMR led to no



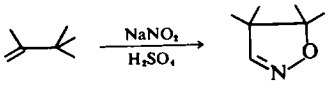
*Routine analytical and spectral data are reported in the Experimental.



conclusive results. Interestingly, bromonitrocamphane(**1**) on chromatography over silver nitrate impregnated silica gave in small yields a mixture of 4-nitrocamphene and 1-nitrocamphane in the ratio 2:1!



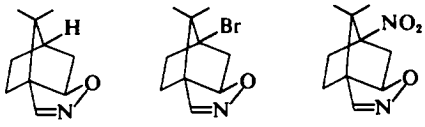
The structural assignment for **17** is supported by analysis, IR and NMR.* We have found that the camphene→**11** change could be generalized in terms of **18**→**19** and this aspect will be treated separately.



18 **19**

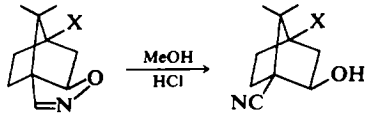
Reactions of tricyclic isoxazolines

In the course of the present work three tricyclic isoxazolines, namely, **11**, **2** and **16** became available for comparative study:



11 **2** **16**

The isoxazoline ring in these systems opens up under a variety of conditions, thus leading to a practical route to 1,2-di-functionalized bornanes. A novel feature of the tricyclic isoxazolines is their ready and clean rupture to corresponding cyano hydroxy compounds **21**, **22** and **23** in presence of acids. This property has been noted even in the early investigations of Forster,[2] in the course of study of **2**. The ring opening can be effected by bases and also thermally, but with much complications.

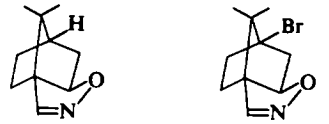


11: X = H
2: X = Br
16: X = NO_2

21: X = H
22: X = Br
23: X = NO_2

*Routine analytical and spectral data are reported in the Experimental.

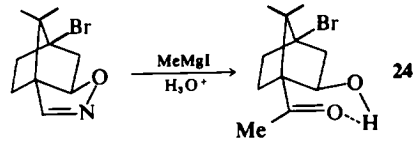
The structural assignments for the cyano hydroxy compounds are supported by analysis, IR and NMR.* Initially, from qualitative observations, it became evident that the substituents exert a profound influence on the acid induced ring rupture. For example, the **11**→**21** change was found to be quite rapid whilst the **16**→**23** change was slowest with the **2**→**22** coming in between. The isoxazolines are characterized by a UV maximum at 228 nm, a feature that was found to be lacking in the products. This property has enabled estimation of the rates of opening of **11** and **2** in excess methanolic hydrochloric acid. The $\pi-\pi^*$ transition of the nitro group overlaps with the isoxazoline band, thus making **16** not suitable for this study. The disappearance of the 228 nm band was followed as a function of time. From the clean first order plots thus obtained the rate constant was determined:



$3{\cdot}8 \times 10^{-4}$ sec^{-1} $4{\cdot}1 \times 10^{-5}$ sec^{-1}

Thus the bromine substitution slows down the opening by a factor of 9. We explain this substituent effect on the basis of the importance of the heterolytic N—O stretching over proton loss.

The reaction of anhydrobromonitrocamphane(**2**) with excess MeMgI is reported to yield a compound m.p. 117° having an unusual bromoiminocarbinol structure.[17] Surprisingly this compound obtained according to the procedure described, has been found to be N free and is assigned structure **24**:

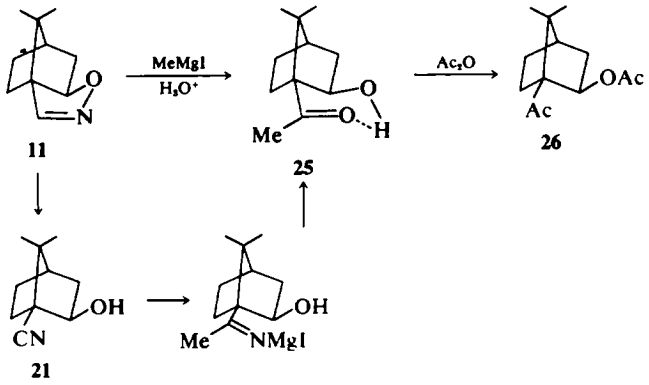


24

The structural assignment for **24** is supported by analytical and spectral data.* Similarly, 2-*exo*-hydroxy-1-acetyl apocamphane **25** can be obtained from isoxazoline **11** in good yields.

Compound **25** could be readily acetylated to **26** and the structural assignment for both the compounds are supported by analytical and spectral data.* Finally in accordance with the proposed mechanism, the cyano hydroxy compound **21** could be smoothly converted to **25**.

In conclusion, the bromonitrocamphane-anhydrobromonitrocamphane rearrangement can now be classified as belonging to the fragmentation-rearrangement-recombination path. Further, this work has brought to light the operation of subtle stereochemical factors, several novel transfor-



mations and has led to the development of a rational synthesis of tricyclic isoxazolines and through these a practical route to di-functionalized bornanes.

EXPERIMENTAL

General. M.ps were taken on a Fisher–John m.p. apparatus and are uncorrected. Capillary m.ps were taken in a Thomas Hoover capillary m.p. apparatus. IR spectra were recorded either on a Perkin Elmer 700 or 137 or Perkin Elmer 521 spectrophotometer. NMR spectra were determined either with chloroform-d_1 or CCl_4 or trifluoroacetic acid solns on a Varian-A60 or A60D spectrometer at 60 mc/s 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, unless otherwise stated, are optically inactive.

Anhydrobromonitrocamphane (2). A standardized procedure is described below. Initially all the three stages gave trouble.

(a) *Camphoroxime.* A stirred mixture of camphor (30·4 g, 0·2 mole) in EtOH (600 ml) was heated on a water bath. A soln of hydroxylamine hydrochloride (30·4 g, 0·435 mole) in minimum quantity of water was added followed by careful addition of NaOH pellets (45 g, 1·12 mole). The mixture was stirred for 2½ hr and concentrated by removal of 250 ml EtOH. The mixture was poured on to a 2 l beaker surrounded by ice, neutralized by careful addition of 2N HCl (pH 2·5) and kept in the refrigerator overnight. The ppt was filtered off through a sintered funnel washed with cold water and then dried in a vacuum desiccator. The crude product had the m.p. 114–5°. It was recrystallized from hot light petroleum (65–67°) to give white crystals of camphor oxime; yield, 28 g (84%); m.p. 115–6° (lit.[18] 118°). IR: ν_{max} (KBr)(cm^{-1}): 3360–3300 (OH), 1670 (C=N), 915 (C—N); NMR: δ_{CCl_4}: 0·82, 0·92, 1·00 (s, C—CH_3).

(b) *2-Bromo-2-nitrocamphane* (1). To a thin paste of camphoroxime (50 g, 0·299 mole) and water (100 ml) contained in a 500 ml beaker was added ice cold KOH aq (107 g, 1·91 mole, 250 ml). The suspension was stirred with a glass rod and transferred to a 2 l round bottommed flask, surrounded by ice. To this mixture stirred magnetically was added an ice-cold soln of potassium hypobromite (prepared by slow addition of Br_2 (310 g, 1·937 mole) to ice-cooled KOH (310 g, 5·353 mole, 500 ml)). After leaving aside with stirring ovenight, the green mass was filtered through a sintered funnel and was repeatedly washed with cold water till the final washing was neutral to litmus. The crude pale greenish product was dried on a porous dish overnight: yield, 59·6 g.

20 g of the crude product was chromatographed using silica gel (200 g). Elution with light petroleum gave 14·4 g (55%) of pure snow white 2-bromo-2-nitrocamphane, m.p. 220 (dec) (lit.[19] 220°). TLC: Single spot (R_f: 0·33 hexane); IR: ν_{max}(Nujol)(cm^{-1}): 1560 (NO_2 asym), 1360 (NO_2, sym): NMR: δ_{CCl_4}: 1·00, 1·28; 1·36 (s, methyls).

(c) *Reaction of bromonitrocamphane with sulfuric acid at −5°: Preparation of anhydrobromonitrocamphane* (2). A soln of bromonitrocamphane (4·3 g, 0·01640 mole) in hexane (10 ml) was slowly added to a stirred mixture of conc H_2SO_4 (98%, 30 ml) and hexane (5 ml), kept below −5°. Addition was done at such a rate that the temp did not rise above −3°. The mixture was stirred at this temp for an additional 1 hr, poured on to crushed ice, filtered and washed with dilute ammonia soln. The crude product was recrystallized from hot EtOH to give colourless crystals of pure anhydrobromonitrocamphane; yield: 1·5 g (38%), m.p. 240–2° (dec). TLC: Single spot (R_f: 0·56, benzene:EtOAc (1:1)); UV: λ_{max}(CH_3OH): 228 nm, IR: ν_{max} (KBr)(cm^{-1}): 1575 (C=N—O); NMR: δ_{CDCl_3}: 7·07 (s, isoxazoline proton), 4·10 (d,d, *endo* proton, J_{AX} = 8 Hz, J_{BX} = 4·5 Hz), 0·93 (syn, Me), 0·87 (anti Me); MS: *m/e* 243, 245.

(d) *Reaction of bromonitrocamphane with* ^{15}*N-sodium nitrite* (^{15}N > 95%). Into a small centrifuge tube surrounded by ice salt mixture was added conc H_2SO_4 (0·4 ml, 98–100%). After about 10 min 3 drops of light petroleum were added. When bath temp was about −8°, a mixture of bromonitrocamphane (0·066 g, 0·00025 mole) and ^{15}N-sodium nitrite (0·035 g, 0·0005 mole) was introduced. The temp of bath was maintained at −5° and the mixture intermittently stirred for additional 1 hr, diluted carefully with water and the ppt crude centrifuged, repeatedly washed with dilute ammonia and then with water, and dried. The crude material was repeatedly crystallized to give 0·017 g (27%) of anhydrobromonitrocamphane.

Extent of incorporation of label. Although the incorporation of label became evident on comparison of molecular ion peaks from this experiment with authentic anhydrobromonitrocamphane, the much more abundant peaks at 164 (M^+–Br) and 163 (M^+–HBr) were chosen to calculate the extent of incorporation. The extent of incorporation of ^{15}N can be obtained by comparison of changes of the intensities of 163, 164 and 165 ions with that of reference. The percentage distribution of these ions in 2

and of sample obtained in the label experiment 2 + 2* are as follows:

m/e ions	2	2+2*
163	33·34	25·11
164	58·50	49·78
165	8·16	25·11
	100·00	100·00

The 165 satellite in 2 arises mainly from ^{13}C abundance ($10 \times 1{\cdot}1\% = 11\%$). The significant enhancement of this peak in (2 + 2*) is due to incorporation of label.

Let the % of incorporation be X then

$$25{\cdot}11 = \underset{\uparrow}{\frac{58{\cdot}5 \times X}{100}} + \underset{\uparrow}{\frac{8{\cdot}16\,(100 - X)}{100}}$$

$\uparrow$ 165 peak ($2^{*+} - Br$); $\uparrow$ remaining satellite of ($2^{+} - Br$)

$X = 33{\cdot}67 = \sim 34$

This value can be used to calculate the expected percentage distribution of the remaining peaks in the 2 + 2* experiment:

$$164\text{ peak} = \underset{\uparrow}{\frac{33{\cdot}34 \times 34}{100}} + \underset{\uparrow}{\frac{58{\cdot}5\,(100 - 34)}{100}} = 49{\cdot}94; \quad \text{Found} = 49{\cdot}78$$

($2^{*+} - HBr$); ($2^{+} - Br$)

$$163\text{ peak} = \underset{\uparrow}{\frac{33{\cdot}34\,(100 - 34)}{100}} = 22{\cdot}04; \quad \text{Found} = 25{\cdot}11$$

($2^{+} - HBr$)

∴ the percentage of incorporation is in good agreement with a value of 34%.

Reaction of bromonitrocamphane with sulfuric acid at 25°: Isolation of 2-bromo-p-cymene (**5**). A heterogeneous mixture of bromonitrocamphane (1 g, 0·00381 mole), conc H_2SO_4 (10 ml) and light petroleum (65–7°, 50 ml) was shaken for 0·5 hr at room temp (> 25°). The hexane layer was separated washed several times with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and solvents evaporated to give 2-bromo-*p*-cymeme (purity 95% by VPC on a silicone rubber column) as the sole isolable product; yield, 0·4910 g (55%). No anhydro-bromonitrocamphane could be detected. IR: ν_{max} (neat) (cm^{-1}): 1605 (Ph), 1495 (Ph), 820 (2 adjacent H in phenyl ring); NMR: δ_{CCl_4}: 1·25, 1·16 (d, isopropyl Me's, J = 7 Hz), 2·31 (s, aromatic Me), 2·8 (unresolved heptet, t-proton, J = 7 Hz), 7·30 (s, proton near to Br).

The structural assignment was further confirmed by comparison (IR, NMR, VPC retention times) with an authentic sample of 2-bromo-*p*-cymene prepared in poor yields by bromination of p-cymene in presence of iodine.[7]

Interception of bromocamphene intermediate with NO_2^+—species: Isolation of 4-bromotricyclenic acid (**8**) *under nitration conditions*

Reaction of bromonitrocamphane with nitric acid–sulfuric acid mixture. Under ice salt cooling, bromonitrocamphane (1 g, 0·0038 mole) was stirred for 6 hr with a nitrating mixture, prepared from conc H_2SO_4 (10 ml) and conc HNO_3 (1·1 ml). The mixture was poured on to crushed ice, the ppt filtered off, washed with dilute ammonia, dried and extracted with chloroform to give the acid as the insoluble residue; yield, 0·0500 g (5%), m.p. 259–60°. (Found: C, 49·08; H, 5·27. Calcd for $C_{10}H_{13}BrO_2$ (M. wt. 245): C, 48·97; H, 5·31%); IR: ν_{max} (KBr) (cm^{-1}): 3150–2500 (OH, H-bonded), 1675 (COOH, H-bonded); NMR: δ CF_3CO_2H: 1·15 (s, dimethyl), 2·06 (m, 4 protons), 2·20 (br, 2 protons); MS: *m/e* 244, 246. The IR and NMR spectra were similar to that of tricyclenic acid. The chloroform extract on evaporation gave anhydrobromonitrocamphane (12%). Anhydrobromonitrocamphane under identical reactions conditions did not give any 4-bromotricyclenic acid.

Demonstration of the isoxazoline formation with camphene

Isolation 3a,4,5,6,7,7a-*hexahydro*-3a,6-*methano*-8,8-*dimethylbenzisoxazole* (**11**). To ice-salt cooled (− 5°) and stirred mixture of conc H_2SO_4 (98%, 100 ml) and light petroleum (65-70°, 12 ml) and added solid $NaNO_2$ (11·2 g, 0·1623 mole) in batches, maintaining the temp below − 5°. Subsequently a soln of camphene (10 g, 0·0733 mole) in light petroleum (65–70°, 25 ml) was added at such a rate that the temp did not rise above − 5°. After additional 1 hr stirring, the mixture was poured on to crushed ice, filtered, washed with dilute ammonia and dried to yield 5·5 g of crude isoxazoline. Sublimation gave pure product; yield 3·6500 g (33%), m.p. 210° (dec). (Found: C, 72·95; H, 9·20; N, 8·73. Calc for $C_{10}H_{15}NO$ (M. wt. 165): C, 72·72; H, 9·09; N, 8·48%). UV: λ_{max}: 224 nm; IR: ν_{max}(KBr)(cm^{-1}): 1563 (C=N—O); NMR: δ_{CCl_4}: 0·95, 1·00 (*gem*-dimethyl), 4·20 (d, d *endo* proton), 7·00 (s, isoxazoline proton).

The above reaction was repeated with optically active pure camphene, prepared from camphor involving a sequence of reduction and dehydration. Therefore, the optical purity was only 57% $(\alpha)_D^{30} = +10$. The sublimed product, having NMR and IR identical to racemic **11**, showed a rotation of $(\alpha)_D^{30} = -5$. In another experiment with a sample of commercial, optically active camphene $(\alpha)_D^{20} = +47$; optical purity 82%) a rotation of $(\alpha)_D^{20} = -2$ was observed for a highly purified sample of the isoxazoline. The levelling effect observed is attributed to racemization of camphene prior to the reaction.[13] All rotations were measured in chloroform (1%) solns.

Reaction of 1-nitrocamphene with sodium nitrite–sulfuric acid: Isolation of 3a,4,5,6,7,7a-*hexahydro*-6-*nitro*-3a,6-*methano*-8,8-*dimethylbenzisoxazole* (**16**)

(a) *A vastly improved procedure for the preparation of 1-nitrocamphene* (**15**). Under protection from light, $AgNo_3$ (5 g, 0·0294 mole) was added in batches over 1 hr to a refluxing soln of bromonitrocamphane (3 g, 0·0114 mole) in EtOH (20 ml) and trifluoroacetic acid (0·5 ml). After 27 hr, the mixture was filtered, solvents evaporated and the residue extracted with light petroleum. The organic extracts on evaporation gave 1·4940 g of crude product. Chromatography over silica employing benzene : hexane (1 : 4) as eluent gave pure 1-nitrocamphene; m.p. 66–70°; yield: 1·5 g (83%). IR: ν_{max}(neat)(cm^{-1}): 1660 (C=C), 1540 (NO_2, asym), 1380 (NO_2, sym), 910 (terminal methylene), 877 (C—N), NMR: δ_{CCl_4}: 1·20, 1·19 (*gem*-dimethyl), 4·97, 4·88 (olefinic protons).

The NMR and IR were identical to sample prepared in 30% yield by the available procedure.[16] The m.p. of this preparation, as reported, was 54–55. Both the samples gave isoxazoline **16**.

(b) *Reaction of* 1-*nitrocamphene with sodium nitrite–sulfuric acid: Isolation of* 3a,4,5,6,7,7a-*hexahydro*-6-*nitro*-3a,6-*methano*-8,8-*dimethylbenzisoxazole.* A hexane soln of 1-nitrocamphene (0·2300 g, 0·001326 mole, 1·5 ml) was added to a stirred mixture of conc H_2SO_4 (98%, 3 ml) and hexane (0·5 ml) cooled in an ice-salt bath (~ −5°). After additional 1 hr stirring at the same temp and mixture was poured on to crushed ice, the white ppt collected, washed intermittently with dilute ammonia to yield 0·1500 g (55%) of a crude isoxazoline. Recrystallization from MeOH gave sample; m.p. 195–200° (dec). (Found: C, 56·40; H, 6·66. Calc for $C_{10}H_{15}N_2O_3$ (M. wt. 211): C, 56·87; H, 7·10%). IR: ν_{max}(KBr)(cm^{-1}): 1563 (C=N—O), 1527 (NO_2, asym), 1359 (NO_2, sym); NMR: δ_{CDCl_3}: 1·13 (s, C—CH_3, 6 protons), 4·35 (d,d *endo* proton), 7·21 (s, isoxazoline proton).

(c) *A study of* 1-*nitrocamphene* 4-*nitrocamphene transformation.* 1-Nitrocamphene was unaffected when allowed to stand in trifluoroacetic acid or trifluoroacetic acid(D) as evidenced by NMR. However chromatography of **1** over $AgNO_3$ impregnated silica and involving elution with hexane gave a 2:1 mixture of **17** and **15** in ~ 1% yield. (Found: C, 66·53; H, 8·44; N, 7·53. Calc for $C_{10}H_{15}NO_2$ (M. wt. 181): C, 66·30; H, 8·30; N, 7·73%). IR: ν_{max}($CHCl_3$)(cm^{-1}): 1660 (C=C), 1520 (NO_2, asym), 1370 (NO_2, sym); NMR: δ_{CCl_4}: 1·1, 1·32 (C—CH_3, 4-nitrocamphene), 1·20, 1·18 (C—CH_3, 1-nitrocamphene), 4·82, 4·66 (olefinic protons due to 4-nitrocamphene), 4·9, 4·8 (olefinic protons due to 1-nitrocamphene).

1-*Cyano*-2-exo-*hydroxy-apocamphane* (**21**). A soln of **11** (0·100 g, 0·00061 mole) in EtOH (0·8 ml) was mixed with HCl (12N, 0·4 ml) and the resulting mixture refluxed for 1·5 hr. Solvents were evaporated and the residue diluted and extracted with ether. The organic extract was washed with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and evaporated to give 1-cyano-2-*exo*-hydroxy compound; yield, 0·0800 g (80%); m.p. 205–6° (dec, sealed capillary). (Found: C, 73·12; H, 9·10; N, 9·23. Calc for $C_{10}H_{15}NO$ (M. wt. 165): C, 72·72; H, 9·09; N, 8·48%). IR: ν_{max} (KBr) (cm^{-1}): 3472 (OH); 2222 (C≡N, saturated); NMR: δ_{CDCl_3}: 1·30, 1·09 (s, *gem*-dimethyls), 4·08 (m, *endo* proton).

1-*Cyano*-2-exo-*hydroxy*-4-*bromoapocamphane* (**22**). A soln of anhydrobromonitrocamphane (0·122 g, 0·005 mole) in EtOH (0·8 ml) was mixed with HCl (12N, 0·4 ml) and the mixture refluxed for 1·5 hr. Solvents were evaporated and the residue diluted and extracted with ether. The organic extract was washed with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and evaporated to give the 1-cyano-2-*exo*-hydroxy-4-bromoapocamphane in nearly quantitative yield: m.p. 244–5° (lit.[3] 244–5°). IR; ν_{max}(KBr)(cm^{-1}): 3480 (OH), 2230 (C≡N, saturated); NMR: δ_{CCl_4}: 1·30, 1·11 (s, *gem*-dimethyls), 4·0 (m, *endo* proton).

1-*Cyano*-2-exo-*hydroxy*-4-*nitroapocamphane* (**23**). A mixture resulting from crude **16** (0·120 g, 0·00571 mole), HCl (1 ml, 12N) and EtOH (95%, 2 ml) was refluxed for 1·5 hr. Solvents were removed, the residue treated with water and extracted with ether. The ether extract was washed with $NaHCO_3$ aq, water, dried ($MgSO_4$), solvents evaporated to give 0·040 g (33%) of 1-cyano-2-*exo*-hydroxy-4-nitroapocamphane. IR: ν_{max}(KBr)(cm^{-1}): 3413 (OH), 2247 (CN, saturated), 1534 (NO_2, asym), 1368 (NO_2, sym).

1-*Acetyl*-2-exo-*hydroxyapocamphane* (**25**)

(a) *By reaction of* 3a,4,5,6,7,7a-*hexahydro*-3a,6-*methano*-8,8-*benzisoxazole.* To stirred MeMgI (prepared by cautious addition of MeI (2·5 ml, 5·7 g, 0·04 mole) to a suspension of Mg turnings (0·75 g, 0·03 mole) in ether (30 ml), containing small amounts of I_2) was added a dry ether soln of **11** (1·5 g, 0·00909 mole, 10 ml). There was a vigorous reaction. The mixture was refluxed for 7 hr, diluted with water (15 ml) and then with dil H_2SO_4 (15 ml), stirred for 0·5 hr and the layers separated. The ether layer was washed with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and evaporated to give 1·0 g (61%) of nearly pure 1-acetyl-2-hydroxy-apocamphane as a low melting solid. (Found: C, 72·81; H, 10·05. Calc for $C_{11}H_{18}O_2$ (M. wt. 182): C, 72·52; H, 9·89%). IR: ν_{max}(neat)(cm^{-1}): 3367 (OH), 1667 (C=O). (Both are indicating strong H-bonding). NMR: δ_{CDCl_3}: 2·16 (s, —C(=O)—CH_3), 1·13, 103 (bridgehead Me), 4·85 (d,d, with small additional coupling, *endo* proton).

(b) *By reaction of* 1-*cyano*-2-exo-*hydroxyapocamphane with methyl-magnesium iodide.* To stirred MeMgI (prepared by addition of MeI, 1·14 g, 0·008 mole) to a suspension of Mg turnings (0·25 g, 0·01 mole) in dry ether (10 ml) containing small amounts of I_2) was added a dry ether soln of **21** (0·500 g, 0·00303 mole, 2·5 ml). The soln was refluxed for 7 hr, the complex hydrolyzed by addition of water (5 ml) and dil H_2SO_4 (5 ml) and stirring for 0·5 hr. The ether layer was separated, washed with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and evaporated to give 0·35 g (64%) of 1-acetyl-2-hydroxy-apocamphane as a low melting solid. The IR was superimposable on that from the previous experiment.

Preparation of 1-*acetyl*-2-*acetoxyapocamphane* (**26**). A soln of **25** (0·120 g, 0·00066 mole) in Ac_2O-pyridine (6 drops: 3 drops) was left aside overnight. Solvents were removed *in vacuo* to give essentially pure (TLC) acetyl derivative in quantitative yield. The crude derivative was subjected to evaporative distillation to give a liquid product. (Found: C, 69·55; H, 9·10. Calc for $C_{13}H_{20}O_3$ (M. wt. 224): C, 69·64; H, 8·92%). IR: ν_{max}(neat)(cm^{-1}): 1733 (O—C(=O)—CH_3), 1689 (C=O); NMR: δ_{CCl_4}: 1·11, 1·02 (s, C—CH_3), 2·05, 2·00 (s, s, —OCOCH_3, —COCH_3), 5·5 (d,d with additional small coupling, *endo* proton).

1-*Acetyl*-2-exo-*hydroxy*-4-*bromoapocamphane* (**24**). To stirred MeMgI prepared from 0·25 g (0·01 mole) Mg turnings and MeI (1 g, 0·00704 mole) in dry ether (10 ml as described for the Br_2 free case) was added a soln of anhydrobromonitrocamphane (0·500 g, 0·00205 mole) in dry ether (2·5 ml). After additional 7 hr stirring, the Grignard complex was decomposed by addition of water followed by dil H_2SO_4, the organic layer separated, washed with sat $NaHCO_3$, water, dried ($MgSO_4$) and solvents evaporated to give large transparent crystals of the acetyl hydroxy compound; m.p. 120–1° (sublimed sample); yield, 0·3 g (60%). (Found: C, 50·71; H, 6·81. Calc for $C_{11}H_{17}BrO_2$ (M. wt. 261): C, 50·57; H, 6·51%). IR: ν_{max} (KBr): 3425 (OH), 1689 (C=O); NMR: δ_{CCl_4}: 1·09, 1·00 (C—CH_3), 2·12 (s, —COCH_3), 4·7 (d,d with additional small coupling, *endo* proton).

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