# Oxymetallation. Part 18.[1] Extensive Rearrangement to a [4.2.1] Skeleton in the Bromodemercuriation of 2-Bromomercurio-9-oxabicyclo[3.3.1]nonane

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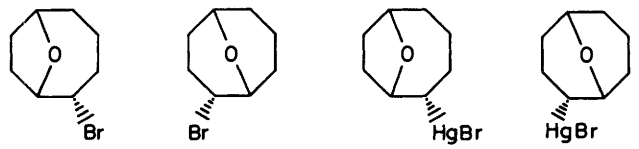
The distributions of isomeric 2-bromo-9-oxabicyclononanes obtained by the brominolysis of *trans*-2-bromomercurio-9-oxabicyclo[4.2.1]nonane and of *trans*-2-bromomercurio-9-oxabicyclo[3.3.1]nonane in methanol with added sodium bromide, in dichloromethane and in pyridine, and from the bromination of 5-trimethylsilyloxycyclo-octene and of 5-t-butyloxycyclo-octene have been determined using $^{13}C$ n.m.r. spectroscopy. Whereas the product distributions are generally in keeping with established mechanisms, the bromodemercuriation of the [3.3.1]mercurial in methanol with added sodium bromide affords the *trans*-[4.2.1]bromide as the major product. It is suggested that this novel skeletal rearrangement occurs *via* a sequence of deoxymercuriation and bromination.

In connection with our work on bicyclic peroxonium ions,[2] we required authentic samples of *trans*-2-bromo-9-oxabicyclo[4.2.1]nonane (**1a**) and *trans*-2-bromo-9-oxabicyclo[3.3.1]nonane (**2a**). Our approach to the synthesis of these compounds was to try to bring about configuration-preserving brominolyses of the corresponding organomercurials[3] *trans*-2-bromomercurio-9-oxabicyclo[4.2.1]nonane (**3**) and *trans*-2-bromomercurio-9-oxabicyclo[3.3.1]nonane (**4**) using bromine in methanol with added sodium bromide.[4]

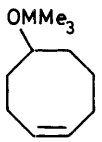
In the event, these conditions led to the additional formation of bromides with different 9-oxabicyclononane skeletons from those of the starting mercurials, *i.e.* (**1a**) from (**4**), and (**2a**) from (**3**). Moreover, rearrangement from a [3.3.1] to a [4.2.1] framework [(**4**) ⟶ (**1a**)] occurred to an unprecedentedly large extent (60%). This prompted us to investigate the bromodemercuriation of (**3**) and (**4**) in more detail, and to examine alternative ways of preparing the products (**1a**) and (**2a**).




(**1a**) *trans* [(**1b**) *cis*] (**2a**) *trans* [(**2b**) *cis*] (**3**) *trans* (**4**) *trans*

## Results

The brominolyses of (**3**) and (**4**) were carried out both in methanol with added sodium bromide and in dichloromethane.[4] The bromodemercuriations in dichloromethane afforded the expected product (**1a**) or (**2a**) plus substantial amounts of the corresponding *cis*-isomer (**1b**) or (**2b**) with little or no accompanying skeletal rearrangement. The brominolysis of compound (**4**) was also carried out in pyridine, and this was the only experiment to yield a product in which the *trans*-[3.3.1]bromide (**2a**) was the major component. The *trans*-[4.2.1]bromide (**1a**), containing little or no other isomer, was obtained by the bromination of 5-t-butyloxycyclo-octene (**6**) or 5-trimethylsilyloxycyclo-octene (**5**) [equation (1)]. The results are fully summarised in the Table.




(**5**) M = Si
(**6**) M = C

$$+ Br_2 \longrightarrow (1a) + Me_3MBr \qquad (1)$$

## Discussion

*Structural Assignments for the 2-Bromo-9-oxabicyclononanes* (**1**) *and* (**2**).—Each of the four isomers has a distinctive proton-decoupled $^{13}C$ n.m.r. spectrum (see Experimental section). Not

**Table.** Preparation of the 2-bromo-9-oxabicyclononanes (**1**) and (**2**)

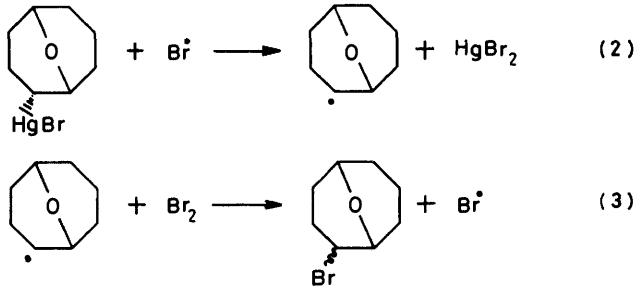
| Expt. | Starting material | Reaction conditions | Product distribution (%)[a] (**1a**) | (**1b**) | (**2a**) | (**2b**) |
|---|---|---|---|---|---|---|
| 1 | (**3**)[b] | $Br_2$ + NaBr in MeOH | 80 (80) | | 20 (20) | |
| 2 | (**4**) | $Br_2$ + NaBr in MeOH | 60 | | 30 | 10 |
| 3 | (**3**)[b] | $Br_2$ in $CH_2Cl_2$ | 55 (65) | 25 (30) | 10 (5) | 10 |
| 4 | (**4**) | $Br_2$ in $CH_2Cl_2$ | | | 30 | 70 |
| 5 | (**4**) | $Br_2$ in pyridine | 15 | | 85 | |
| 6 | (**5**) | $Br_2$ in $CCl_4$ | 100 | | | |
| 7 | (**6**) | $Br_2$ in $CCl_4$ | 95 | | 5 | |

[a] Estimated to the nearest 5% from the $^{13}C$ n.m.r. spectra of the product mixtures. [b] Contains 15% of (**4**) as estimated by $^{13}C$ n.m.r. spectroscopy. Product distribution in parentheses is that calculated (to the nearest 5%) for (**3**) alone by using the data obtained for (**4**) in the comparable experiment (immediately below).

only does this spectrum provide the best characteristic for identifying a given isomer, but it also gives a clear indication of structure.

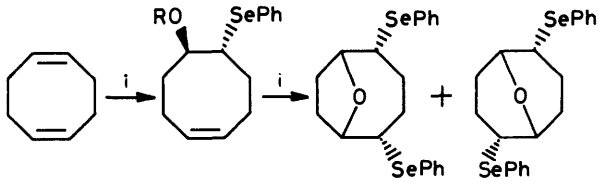
The bridgehead carbon nuclei of 9-oxabicyclo[4.2.1]nonanes, both unsubstituted[5,6] and with a 2-mercurio,[5] 2-bromo,[5] 2-hydroxy,[6] 2-amino,[6] or 2-phenylseleno[7] substituent, resonate in the range δ 76—85 p.p.m., whereas the corresponding nuclei in 9-oxabicyclo[3.3.1]nonanes resonate in the range δ 66—73 p.p.m. The two skeletal systems are thus readily distinguished by $^{13}C$ n.m.r. spectroscopy. Furthermore, a *cis*-hydroxy substituent at C-2 produces a markedly larger downfield shift in the C-1 resonance than does the corresponding *trans*-substituent, for both [4.2.1] and [3.3.1] types of ether.[6] If it is assumed that bromine has a parallel effect in the 2-bromo-9-oxabicyclononanes, then their configurations at C-2 can also be assigned on the basis of the $^{13}C$ data. That the magnitudes of the appropriate β-effects then calculated for bromine [4.3 p.p.m. in (**1a**), 3.7 p.p.m. in (**2a**), 7.3 p.p.m. in (**1b**), and 6.2 p.p.m. in (**2b**)] are very similar to those reported for the hydroxy group (3.8, 4.0, 7.0, and 6.4 p.p.m. respectively)[6] inspires confidence in the validity of this approach.

*Mechanistic Interpretation of the Product Distributions.*—The structural assignments arrived at on the basis of $^{13}C$ n.m.r. spectroscopy are supported by that fact that, *with the exception of the results for bromine in methanol with added sodium bromide*, the product distributions they indicate (Table) are, by and large, in harmony with mechanistic expectations. Brominolyses in dichloromethane are expected to proceed by a free radical chain process with stereochemical scrambling at C-2 [*e.g.* equations (2) and (3)], while an $S_E2$ mechanism with retention of configuration is expected for the reaction in pyridine;[8] brominations of the cyclo-oct-4-enol derivatives (**5**) and (**6**) are expected to proceed by a polar mechanism resulting in *trans* addition [equation (1)], as for iodination,[9,10] mercuriation,[3,9] and selenation.[7]




Thus, brominolysis of the [3.3.1]mercurial in dichloromethane (experiment 4, Table) gave a mixture of the [3.3.1]bromides with the *cis*-isomer predominating, and this is similar to a previous finding for the related iodinolysis in carbon tetrachloride.[9] Brominolysis in pyridine (experiment 5, Table), on the other hand, gave mainly the *trans*-[3.3.1]bromide and *none* of the *cis*-isomer. The formation of 15% of the *trans*-[4.2.1]bromide in this reaction suggests the intervention to a small extent of a mechanism similar to that which dominates the brominolyses in methanol with added sodium bromide (see later). Again, brominolysis of the [4.2.1]mercurial in dichloromethane (experiment 3, Table) gave a mixture of [4.2.1]bromides, but now with the *trans*-isomer predominant. The result is complicated by the fact that the mercurial contained 15% of the [3.3.1] isomer.* When allowance is made for this, there is still a small quantity (5%) of *trans*-[3.3.1]bromide which appears to be derived from the [4.2.1]mercurial. A similar amount of rearranged product was found previously in the related iodinolysis,[9] but no explanation was offered for its origin.

Bromination of the cyclo-oct-4-enol ethers (experiments 6 and 7, Table), as expected, gave exclusively *trans*-bromides. The observed high selectivity for the [4.2.1] product is interesting in view of an earlier report[11] that a 3:2 mixture of isomers was obtained from the analogous reaction with 5-methoxycyclo-octene. A similar trend has been noted before in the oxyselenation of cyclo-octa-1,5-diene in alcoholic solvents [equation (4)].[7]




*Reagents:* i, PhSeCN, ROH

Much more [4.2.1] ether was obtained in t-butyl alcohol than in methanol and this was accounted for in terms of greater kinetic control resulting because t-butyl is a better leaving group than methyl in the intermediate bicyclic trialkyloxonium ions.

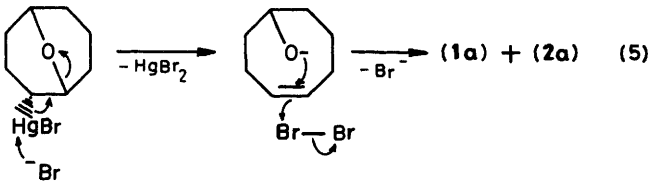
We must now discuss the results obtained for brominolysis in methanol with added sodium bromide. At first sight, the product distribution in experiment 1 (Table) appears to indicate that the desired $S_E2$ pathway for bromodemercuriation has been achieved. Thus, no *cis*-bromides were detected, and the ratio (80:20) of [4.2.1] to [3.3.1] isomers reflects very closely that (85:15) of the starting mercurials. However, this simple interpretation is called into question by the startling observation (experiment 2, Table) that, under these conditions, the [3.3.1]mercurial affords 60% of the *trans*-[4.2.1]bromide. This cannot arise from the isomerisation of reactant or product, since it is well established that 9-oxabicyclo[3.3.1]nonanes are thermodynamically more stable than the corresponding [4.2.1] isomers.[3,7] The skeletal rearrangement must therefore take place *during* the bromodemercuriation.

The formation of some *cis*-[3.3.1]bromide (**2b**) in experiment 2 (Table) suggests that homolytic bromodemercuriation occurs to a small extent (*cf.* ref. 4). Comparison with experiment 4 then indicates that about 5% of the *trans*-[3.3.1]bromide arises by this pathway. Taking this into account, the ratio of (**1a**) to (**2a**) attributable to heterolytic processes becomes 70:30, which closely resembles that (80:20) found in experiment 1. *The implication is that a major part of the polar bromodemercuriation of* (**3**) *and* (**4**) *in methanol with added sodium bromide proceeds via a common intermediate.* In fact, the results can be accommodated by a combination of 90% of a pathway involving a common intermediate which affords the products (**1a**) and (**2a**) in the ratio 78:22, plus 10% of an $S_E2$ pathway with retention.

We suggest that the main pathway for the bromodemercuriation of compounds (**3**) and (**4**) in methanol with added sodium bromide involves a sequence of deoxymercuriation and bromination [*e.g.* equation (5)].

It has been established that iodide ions can induce deoxymercuriation under neutral conditions.[12] Although bromide ions are expected to be less effective, the antiperiplanar arrangement of mercury and oxygen groups in compounds (**3**) and (**4**) should assist the postulated elimination. Bromination of the resultant cyclo-oct-4-enolate ion will afford only *trans*-

* It was originally reported[3] that the procedure used gives pure [4.2.1]mercurial, but other workers[9] have also detected minor amounts of the [3.3.1] isomer in the product.




bromides and can be expected to favour the [4.2.1] isomer (**1a**) by analogy with the brominations of cyclo-oct-4-enol ethers (experiments 6 and 7, Table).

## Experimental

*Materials.*—Cyclo-oct-4-enol was prepared from cyclo-octa-1,5-diene by monoepoxidation[13] then reduction,[14] and was purified by column chromatography ($SiO_2$; $CH_2Cl_2$). *trans*-2-Acetoxymercurio-9-oxabicyclo[4.2.1]nonane {$\delta_C$ 177.4, 81.0 (C-1), 76.5 (C-6), 54.0 ($^1J_{^{199}Hg,\ ^{13}C}$ 1 480 Hz, C-2), 35.4, 35.2, 30.5, (2 C), 26.5, and 23.7 p.p.m.; the presence of 15% of the [3.3.1] isomer was detected by signals at δ 70.5 (C-1), 67.6 (C-5), and 53.5 (C-2) p.p.m.} and *trans*-2-nitratomercurio-9-oxabicyclo[3.3.1]nonane were prepared from cyclo-oct-4-enol by Bordwell and Douglass's method,[3] and were converted into the corresponding organomercury(II) bromides (**3**) and (**4**) [$\delta_C$ 70.6 (C-1), 67.7 (C-5), 61.0 (C-2), 33.6, 33.1, 29.4, 27.2, and 19.6 p.p.m.] by treatment with aqueous sodium bromide.

5-*t-Butyloxycyclo-octene* (**6**).—This was prepared as follows. A mixture of cyclo-octa-1,5-diene (3.2 g) and mercury(II) trifluoroacetate[5] (3.12 g) in dry t-butyl alcohol (6 $cm^3$) was stirred for 5 days. The excess of t-butyl alcohol was then removed under reduced pressure, and the residue was dissolved in dichloromethane (20 $cm^3$). This solution was cooled to 0 °C, and stirred while aqueous sodium hydroxide (20 $cm^3$; 0.5M) was added followed, during 15 min, by a solution of sodium borohydride (0.75 g) in aqueous sodium hydroxide (20 $cm^3$; 3M). After 1 h, the dichloromethane layer was isolated, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography ($SiO_2$; $CH_2Cl_2$) of the crude product afforded the *cyclo-octene* (**6**) (0.265 g, 19%); $\delta_H$ 5.6 (m, 2 H), 3.5 (m, 1 H), 2.5—0.8 (m, 10 H), and 1.1 (s, 9 H); $\delta_C$ 130.0, 129.7, 73.2, 71.8, 37.4, 37.1, 28.4, 26.1, 25.0, and 22.9 p.p.m.; $\nu_{max.}(CCl_4)$ 3 030, 2 990, 2 950, 2 880, 1 470, 1 390, 1 365, 1 200, and 1 055 $cm^{-1}$ (Found: $M^+$, 182.1666. $C_{12}H_{22}O$ requires $M^+$, 182.1670).

*Bromodemercuriation.*—(*a*) *In methanol with added sodium bromide.* To a stirred and cooled suspension of the organomercury(II) bromide (**3**) or (**4**) (4 mmol) in methanol (10 $cm^3$) was added a mixture of sodium bromide (2 g) and bromine (4.5—5 mmol) in methanol (20 $cm^3$) rinsed in with more methanol (10 $cm^3$). The resulting mixture was stirred for 45 min in an open flask, water (25 $cm^3$) was then added, and the mixture was extracted with light petroleum (b.p. <35 °C; 3 × 20 $cm^3$). The extracts were combined, washed with aqueous sodium metabisulphite, dried ($MgSO_4$), and the light petroleum was removed under reduced pressure to afford the mixture of 2-bromo-9-oxabicyclononanes (65—75%).

(*b*) *In dichloromethane.* Bromine (4.5—5 mmol) dissolved in dichloromethane (10 $cm^3$) was added to a stirred solution of the organomercury(II) bromide (**3**) or (**4**) (4 mmol) in dichloromethane (30 $cm^3$). After 2.5 h, the solution was decanted from the precipitated mercury(II) bromide, washed with aqueous sodium metabisulphite, dried ($MgSO_4$), and the solvent removed under reduced pressure to afford the mixture of 2-bromo-9-oxabicyclononanes (65—75%).

(*c*) *In pyridine.* Bromine (8 mmol) was added to a stirred suspension of the organomercury(II) bromide (**4**) (8 mmol) in pyridine (15 $cm^3$). After 4 h, the pyridine was removed under reduced pressure and the resulting residue was dissolved in a mixture of dichloromethane (20 $cm^3$) and water (20 $cm^3$). The dichloromethane layer was isolated, dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting residue was extracted with pentane (3 × 20 $cm^3$) and the pentane removed under reduced pressure to afford the mixture of 2-bromo-9-oxabicyclononanes (40%).

*Bromination of Cyclo-oct-4-enol Ethers.*—(*a*) *5-Trimethylsilyloxycyclo-octene* (**5**). Bis(trimethylsilyl)acetamide (4 mmol) was added to a solution of cyclo-oct-4-enol (7 mmol) in carbon tetrachloride (10 $cm^3$) at 0 °C and the mixture was stirred for 1 h at room temperature while protected with a calcium chloride tube. More carbon tetrachloride (60 $cm^3$) was then added and the mixture was cooled in an ice-bath. A solution of bromine (8 mmol) in carbon tetrachloride (20 $cm^3$) was added dropwise with stirring during 15 min. The mixture was stirred for 30 min at room temperature, methanol (25 $cm^3$) was added, and stirring was continued for a further 30 min. The volatile material was removed under reduced pressure to afford a mixture of acetamide and *trans*-2-bromo-9-oxabicyclo[4.2.1]-nonane (**1a**) [$\delta_H(CCl_4)$ 4.75—4.3 (m, 2 H), 4.15 (m, 1 H), 2.65—1.1 (m, 10 H)].

(*b*) *5-t-Butyloxycyclo-octene* (**6**). A solution of bromine (0.85 mmol) in carbon tetrachloride (0.5 $cm^3$) was added dropwise to a stirred solution of (**6**) (0.85 mmol) in carbon tetrachloride (0.8 $cm^3$) at 0 °C. After 15 min, the volatile material was removed at 20 mmHg and collected in a cold trap; this was shown by $^1H$ n.m.r. spectroscopy to contain a high yield of t-butyl bromide and a small quantity of 1,2-dibromo-2-methylpropane, each compound being identified by peak enhancement upon addition of an authentic sample. The residue was a mixture of the *trans*-isomers (**1a**) and (**2a**) in quantitative yield.

*Determination of Product Distributions.*—The proportions of the isomeric 2-bromo-9-oxabicyclononanes in each product were determined by comparison of peak intensities in the $^1H$-decoupled $^{13}C$ n.m.r. spectrum. Using the signals due to carbon atoms attached to oxygen or bromine, three distributions were calculated from each spectrum. These were averaged and the averages rounded to the nearest 5%. The results are given in the Table. A similar technique has been used previously to determine isomer ratios for alkyl bromides[4] and for substituted 9-oxabicyclononanes.[7]

The $^{13}C$ n.m.r. spectra were measured at 20 MHz on a Varian CFT 20 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal reference. The chemical shift data for the individual isomers are given below and were independent (±0.05 p.p.m.) of the isomer distribution in the sample; $\delta_C$ (**1a**) 82.0 (C-1), 76.55 (C-6), 54.35 (C-2), 35.4, 35.0, 34.8, 24.45, and 22.9 p.p.m.; (**1b**) 85.05 (C-1), 78.1 (C-6), 59.4 (C-2), 35.9, 35.4, 31.45, 32.0, and 21.4 p.p.m.; (**2a**) 70.25 (C-1), 66.2 (C-5), 51.85 (C-2), 31.95, 31.3, 29.05, 23.8, and 18.5 p.p.m.; (**2b**) 72.8 (C-1), 66.6 (C-5), 54.0 (C-2), 29.3, 29.15, 27.9, 25.0, and 17.75 p.p.m.

An analytical sample of 2-bromo-9-oxabicyclononane, which contained all four isomers, was obtained by combining the products from several reactions and purifiying the mixture by column chromatography ($SiO_2$; $CH_2Cl_2$); mass spectrum *m/z* 41 (100%), 204 (6.9; $M^+$), and 206 [6.7; $(M + 2)^+$] (Found: C, 46.9; H, 6.3; Br, 39.6; $M^+$, 204.0145. $C_8H_{13}BrO$ requires C, 46.84; H, 6.39; Br, 38.96%; $M^+$, 204.0149).

## Acknowledgements

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