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PREPARATION OF 1-SUBSTITUTED BICYCLO[3.2.1]OCTANES BY A REARRANGEMENT REACTION

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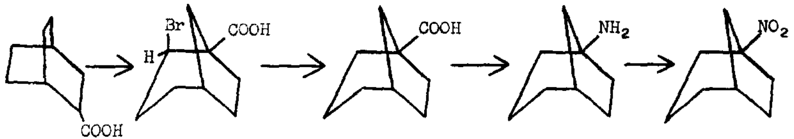
The rearrangement of a bicyclo[2.2.2]octane system to a bicyclo[3.2.1]-octane system was first reported by Doering and Farber.[1] Since then a large number of publications have appeared dealing with the interconversion of these two systems.[2]

We wish to report a simple procedure for preparing bicyclo[3.2.1]-octanes with substituents on a bridgehead carbon via the rearrangement of the readily available bicyclo[2.2.2]octane-2-carboxylic acid[3] (I) to 2-axial-bromobicyclo[3.2.1]octane-1-carboxylic acid (II). II was converted to bicyclo[3.2.1]octane-1-carboxylic acid (III) in an overall yield (from I) of 49%.



I II III IV V

When bicyclo[2.2.2]octane-2-carboxylic acid (I) was subjected to Hell-Volhard Zelinsky bromination,[4,5] a bromo acid, to which we have assigned the axial configuration II, was obtained* in 57% yield. After

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* Compounds II, III and IV gave satisfactory elemental analyses.

two recrystallizations from benzene-pentane this acid had a m.p. of 153-154°. Thin layer chromatographic analysis* of II gave only a single spot. G.l.c. analysis** of the methyl ester of II did not give meaningful results, because of the facile thermal isomerization[6] of the 2-axial isomer to the 2-equatorial isomer. However, our g.l.c. data did not reveal any unidentified components, but only the two which we assigned to the 2-axial and 2-equatorial isomers. The n.m.r.*** characteristics indicated an axial bromo configuration for II (*vide infra*).

Hydrogenolysis of II with Pd/C under basic conditions[5,6] gave bicyclo[3.2.1]octane-1-carboxylic acid (III) in 86% yield. After repeated sublimations *in vacuo*, III melted at 69.5-70.5° (reported[6] 73.5-74.5°). Its n.m.r. spectrum showed only a complex envelope between δ 1.3 and 1.5.

To confirm the structure of the bicyclo[3.2.1]octane-1-carboxylic acid (III), it was converted by the Schmidt reaction to 1-bicyclo[3.2.1]-octylamine (IV) in 63% yield as the hydrochloride, m.p. 311-314° (dec.). G.l.c. showed the free amine to be homogeneous. Oxidation of amine IV with permanganate[7] gave 1-nitrobicyclo[3.2.1]octane (V) in 35% yield, m.p. 77.5-78.5° (sealed capillary). S. J. Etheredge[8] reported a m.p. of 80-81° (sealed capillary) for a sample of V prepared by a different route. The infrared spectrum of our sample was identical with that of V

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* Thin layer chromatography was carried out with the methyl ester of II using ascending method on silica gel G. Moving phase = methanol. R_f 0.75.

** All g.l.c. analyses were carried out with an F&M Gas Chromatograph using a 6', 1/4" stainless steel column packed with 5% silicone gum rubber SE 30 on 60-80 mesh Chromosorb W.

*** Varian A-60 spectrophotometer, $CDCl_3$ as solvent, tetramethylsilane as internal standard.

prepared by Etheredge.[+]

Since an earlier report by Vaughan[6] gave a m.p. of 188° for the 2-axial-bromobicyclo[3.2.1]octane-1-carboxylic acid, we have examined the properties and purity of our bromo acid II (m.p. 153-154°) rather carefully. Like Vaughan's material, II was readily isomerized (methyl ester in refluxing 48% HBr) to an acid, m.p. 217-219°[*], presumably the more stable 2-equatorial-bromobicyclo[3.2.1]octane-1-carboxylic acid (reported[6] m.p. 218.5-219.5°). However, in contrast to Vaughan's statement that the axial and equatorial acids gave strikingly similar infrared and n.m.r. data, the infrared spectrum of II was decidely different from that of the 2-equatorial-bromo acid. Likewise, the n.m.r. spectra were different. The n.m.r. spectrum of II showed, in addition to a complex envelope at δ 1.5-2.5, a poorly resolved signal at δ 4.70. The width of the δ 4.70 signal at half height was approximately 6 cps, consistent with an equatorial proton.[9] The n.m.r. spectrum of the 2-equatorial-bromo acid showed a complex envelope between δ 1.5-2.8 and a broad multiplet (approximate width at half height, 18 cps) with two predominant peaks centered at δ 4.08 (doublet) and δ 4.25 (doublet), consistent with an axial proton. The lower field position of the equatorial proton signal with respect to that of the isomeric axial proton is in agreement with expectation for a rigid cyclohexane system.[10]

Since we suspected contamination of the various preparations of the axial bromo acid by the equatorial isomer, we have looked for the presence of this isomer in our sample II. The integrated n.m.r. spectra of the two

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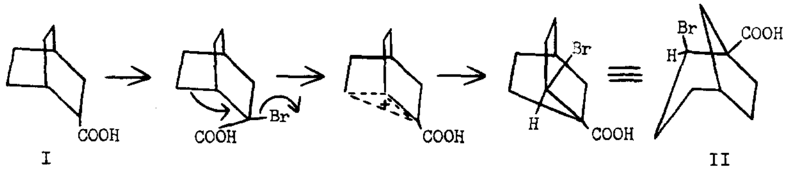
[+] We wish to thank Miss S. J. Etheredge and Professor G. Stork for an infrared spectrum of compound V.

[*] This material gave a satisfactory elemental analysis and its methyl ester appeared as only one component on g.l.c.

isomeric bromo acids, and artificial mixtures of the same, proved to be useful in estimating the purity of II. Comparison of the integrals between δ 4.0-4.5 (*equatorial* proton) and between δ 4.5-5.0 (*axial* proton) allowed us to estimate that our sample II contained less than 3% of the *equatorial* isomer. These data lead us to conclude that our sample II is essentially pure 2-*axial*-bromobicyclo[3.2.1]octane-1-carboxylic acid.[*]

The mechanisms for the brominative rearrangement of I to II may be interpreted as a Wagner-Meerwein type involving the stereospecificity associated with a 'non-classical' carbonium ion.



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[*] Conceivably Vaughan's sample was a mixture of the 2-*axial* and 2-*equatorial* bromo acids. This speculation is partially supported by m.p.'s of artificial mixtures of the 2-*equatorial* isomer and II (Ratio of *equatorial* to *axial*, m.p.: 90/10, 192-200°; 85/15, 185-191°; 80/20, 181-186°).

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