Tetrahedron Letters, Vol. 33, No. 34, pp. 4875-4878, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SYNTHESIS OF NOVEL CAGE QUATERNARY SALTS VIA NUCLEOPHILIC SUBSTITUTION OF 1,3-DIIODOBICYCLO[1.1.1]PENTANE. FURTHER EVIDENCE FOR A STABLE 3-IODO-1-BICYCLO[1.1.1]PENTYL CATION.

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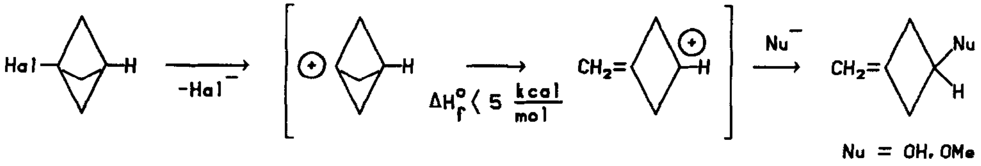
Summary: Nucleophilic substitution of 1,3-diiodobicyclo[1.1.1]pentane by tertiary amines and pyridines was investigated. The structure of cage quaternary salts obtained together with the observation of the competitive addition of pyridine in the reaction of [1.1.1]propellane with iodine indicate the existence of a relatively stable "hot intermediate" very close in its structure to a stabilized 3-iodo-1-bicyclo[1.1.1]pentyl cation.

Nucleophilic substitution of halogen and other reactions involving "bridgehead" carbocations are of great interest from both experimental and theoretical points of view.[1a-d] The most interesting cation of this type (and the simplest one) is the 1-bicyclo[1.1.1]pentyl cation, which has received significant attention these last few years. As a result, many theoretical investigations[2a-e] as well as experimental attempts at trapping this moiety[3a,b] have been done. Both "protonated propellane"[2d] and "CH^+-trimethylenemethane complex"[2a] calculated structures have been proposed for this cation, but there is still doubt of its existence: the cation was predicted[2c,e] and found[3a-d] to rearrange without significant barrier to methylenecyclobutyl cation with relief of strain energy (Scheme 1).

SCHEME 1



However, recently the existence of a relatively stable 3-iodo-1-bicyclo[1.1.1]pentyl cation (1) has been claimed for the reactions of 1,3-diiodobicyclo[1.1.1]pentane (2) with methoxide and azide anions.[3e]

Because of the great importance of the 1-bicyclo[1.1.1]pentyl cation to the chemistry of bicyclo[1.1.1]pentanes, we investigated the reactions of 1,3-diiodobicyclo[1.1.1]pentane (2) with tertiary amines and pyridines. The main objective of this study was to determine whether the stable cationic intermediate 1 might be produced as well as to prepare a new family of quaternary bicyclo[1.1.1]pentyl salts.

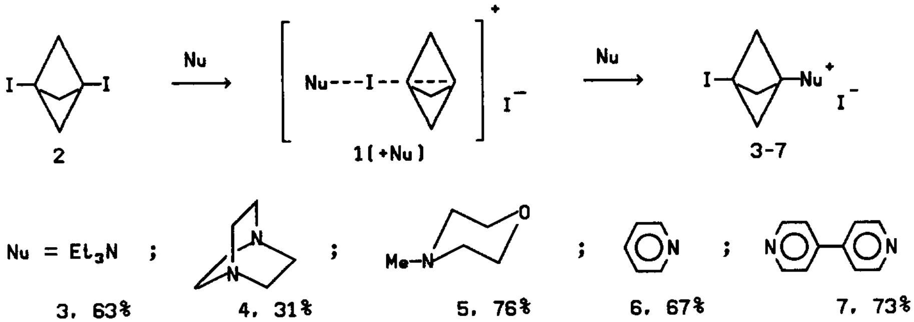
We found that 1,3-diiodide 2 reacts with these nucleophiles at room temperature in methanol, hexane, benzene, ethyl ether, acetonitrile, but best in acetone to give exclusively the unrearranged 3-iodobicyclo[1.1.1]pentyl salts 3-7 in good yield and high purity (Scheme 2).[4,5]

The reaction rate of 2 increases in polar solvents. Furthermore, when the reaction was carried out in methanol, a detectable amount of 1-methoxy-3-iodobicyclo[1.1.1]pentane was obtained indicating nucleophilic attack by the solvent.

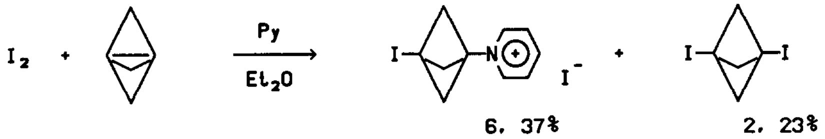
The above findings strongly support the contention of Wiberg and McMurdie[3e] that the reaction of 2 with nucleophiles goes through some "hot intermediate", close in its structure to cation 1. However, the reaction of diiodide 2 with pyridine is a first order reaction in the nucleophile, in contrast to the behavior of known bridgehead halides[1d,e] in a cationic S_N1 process. Thus, when the concentration of pyridine in acetone was increased 5 times, the rate of the reaction was enhanced 5.6±0.8 times. In our opinion, this may be attributed to the participation of pyridine in stabilization of the transition state. If this is the case, this transition state may be best rationalized as a complex of cation 1 with nucleophile

(Scheme 2).

SCHEME 2



An alternative scheme may involve a formation of [1.1.1]propellane as an intermediate.[3e] Indeed, we found that the reaction of iodine with [1.1.1]propellane in the presence of pyridine afforded a mixture of diiodide 2 and substitution product 6.[6]



Nevertheless we assume the direct formation of Nu-stabilized cation 1 (Scheme 2) in the reactions of 2 with pyridine is more likely since neither pyridine nor the solvent used (e.g. ether) can abstract I_2 from diiodide 2 effectively[7] to give [1.1.1]propellane.

We were not successful in substitution of the remaining iodine in 3-6 with an excess of the tertiary amine to produce dicationic species. Other iodobicyclo[1.1.1]pentanes, e.g. 1-trifluoromethyl-3-iodobicyclo[1.1.1]-pentane, did not react with our chosen nucleophiles.

As a result of present work a new class of cage quaternary salts 3-7 has been obtained. This class of strained cage compounds have unusual structural and chemical characteristics (e.g. the shortest nonbonding C^1-C^3 cage distance ever documented[8]) and deserve additional attention.

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4. Structures of all new compounds have been elucidated on the basis of NMR ^{1}H and ^{13}C spectra and confirmed by HRMS.
5. *In a typical procedure,* diiodide 2 (3.2 g, 10 mmol) was dissolved in 70 ml of dry acetone and pyridine (7.9 g, 100 mmol) was added. The resulting solution was allowed to stand for 3 days at room temperature with occasional shaking. The precipitate formed was filtered and recrystallized from the minimum volume of hot water to afford 6 (2.7 g, 67%) as cream colored crystals: ^{1}H NMR (DMSO-D_6) δ 8.95 (d, 2 H, α-*H*), 8.54 (t, 1 H, γ-*H*), 8.07 (t, 2 H, β-*H*), 2.86 (s, 6 H, CH_2); ^{13}C NMR (DMSO-D_6) δ 146,6 (α-*C*), 142,4 (γ-*C*); 127,8 (β-*C*), 61.2 (C-N^+), 60,7 (CH_2), -4.8 (*C*-I); HRMS (FAB) *m/e* calcd for $C_{10}H_{11}NI$ (M-I) 271.9936, found 271.9929.
6. In an independent experiment pyridine when reacted with diiodide 2 under the same conditions gave only traces of 6.
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(Received in USA 26 March 1992; accepted 10 June 1992)