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# REACTIONS OF BICYCLO[n,2,1]ALKANONES WITH DIAZOMETHANE

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Our knowledge of the behaviour of bridged bicyclic ketones towards diazoalkanes is very scanty in spite of the potential synthetic and theoretical interest of such reactions.[2] This contrasts with the current widespread interest in many other reaction types of bicyclic systems. As it has frequently occurred in alicyclic chemistry, a deeper understanding of a given reaction class can be expected from the investigation of such reactions in bridged polycyclic systems.

To cover this major gap we started an investigation in this area and we report now here some results which serve to delineate well the course of the reactions of diazomethane with the norcamphor family ketones.

Reaction of (II) with great excess of N-nitrosomethylurethane allows the isolation (preparative v.p.c.) of bicyclo[3,2,1]octan-3-one (V),[3] bicyclo-[4,2,1]nonan-3-one (IV),[4] and the new bicyclo[5,2,1]decan-3-one (VI)[†] in nearly equimolar amounts, whereas when the reaction is carried out with only 1-3 equivalents of N-nitrosomethylurethane bicyclo[3,2,1]octan-2-one (I)[5] and bicyclo[4,2,1]nonan-2-one (III)[4] can be isolated.

Spiro-epoxides from (II)[6] are not formed in any detectable amount (less than 1% with respect to reacted (II) could have been detected).

Competitive experiments allow one to establish the reactivity scale towards diazomethane (under methanol catalysis) shown in the Chart.

In order to establish the order of migratory aptitudes, either (II) or (I) was treated with 0.1 equivalents of diazomethane to give, respectively, (I) and (V) or (III) and (IV) in a ratio of 2:1.

It is clear from the above that the reactivity of small bridged bicyclics is primarily determined by the position of the carbonyl group and not by the

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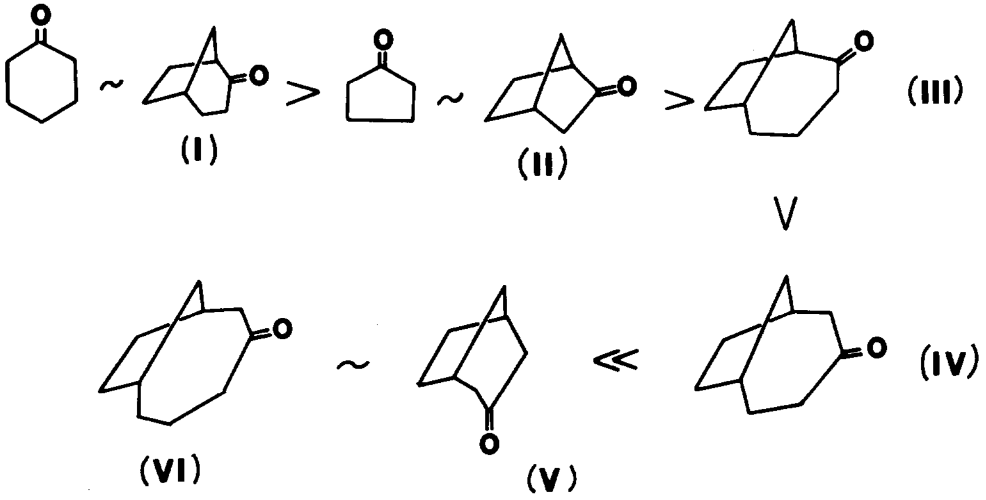
[†] The structure is supported by satisfactory elemental and spectral analysis of both the ketone (which shows also the expected molecular ion) and of its 2,4-dinitrophenylhydrazone (mp 148-150°), by the fact that (VI) upon treatment with $CH_3OD$/Na incorporates four deuteriums and, finally, by the fact that (VI) originates from either (III) or (IV) upon treatment with diazomethane. The unknwon bicyclo[5,2,1]decan-4-one is also probably formed besides (VI) in the latter reaction. Its isolation was not attempted, however.

strain of the bicyclic skeleton. Bicyclics with the carbonyl group adjacent to the bridghead display the "normal" reactivity of cycloalkanones while their isomers with the carbonyl group farther removed from the bridghead have a reduced reactivity. Such a difference is most pronounced with the smallest bicyclics such that (V) requires strong catalysis $(BF_3)$[7] to react appreciably with diazomethane.



CHART

Bicyclics tend to lose these peculiarities with increasing size and it would be interesting to devise a method of synthesis of the unknown 2-one isomer of (VI) (which is not formed in a sufficient quantity from the reaction of (II) with diazomethane) to investigate its reactivity towards diazomethane.[†]

All the above observations can be rationalised consistently on the basis of a mechanism whereby rate-determining nucleophilic attack at the carbonyl carbon gives origin to a betaine intermediate such as (IIi) or (Vi) in the case of the reactions of (II) or (V), respectively, Here it is assumed that *exo* attack greatly prevails over *endo* attack by analogy with attack of other reagents such as Grignard reagents.[8] Moreover the oxygen atom in the betaine

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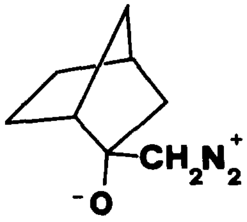
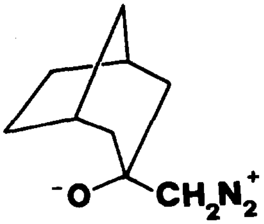
[†] In the reaction of (II) with diazomethane most of (VI) originates from (III) owing to the low reactivity of (IV). This is also the reason why in this reaction bicyclo[5,2,1]decan-4-one could have been formed with an extremely small yield, if any.



(IIi)



(Vi)

intermediates should be hydrogen bonded to methanol as all bicyclic ketones shown in the Chart above fail to react appreciably with diazomethane in ether without the addition of acidic catalysts such as methanol.

Such a mechanism allows us to rationalize the fact that although the strain of the bicyclic does not determine the rate, it directs the nature of the reaction products. It seems, in fact, reasonable to assume that lack of formation of epoxides is due to C-C bond migration with release of the strain of the bicyclic being faster than closure of a new (oxirane) ring. This seems to us to be an important general factor determining the ratio of epoxides vs ring enlarged ketones (for example, epoxides are important products in the case of unstrained ketones such as open chain ketones or of cyclohexanones[2]) which has not been hitherto taken into account.[2,†] These results indicate that the double reaction path suggested by others[9] is not needed here, at least in the case of (II).

Also, the pattern of reactivity shown in the Chart above can be accounted for in terms of the mechanism proposed here. In fact, the order of reactivity (I) > (II) > (III) runs parallel to the reactivity order cyclohexanone > cyclopentanone > cycloheptanone towards both diazomethane[2] and other nucleophilic reagents which, like sodium borohydride, bring about an $sp^2 \rightarrow sp^3$ change at the reaction center.[10] Therefore, the order of reactivity (I) > (II) > (III) encountered here may be explained along the same lines as the reactivity order cyclohexanone > cyclopentanone > cycloheptanone through a rate-determining transition state of the betaine type shown above.

A cyclohexanone, cyclopentanone, or cycloheptanone character is thus envisaged for (I), (II), or (III), respectively. A cyclopentanone character

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[†] Alternatively, lack of spiro-epoxide formation from (II) could be attributed to the *trans*-coplanar transition state required for nucleophilic displacement of nitrogen by oxygen from (IIi) being disfavoured by repulsions between the *syn*-7-hydrogen and nitrogen. However, molecular models indicate this to be very unlikely.

for (II) had already been recognized in sodium borohydride reductions.[10a]

It is clear that to explain the low reactivity of (V) a new factor, that cannot be either the ring strain or the ring size, is required. This may be tentatively proposed as the repulsive interactions between the oxygen and the two endo hydrogens in the transition state leading from the reagents to (Vi).

Also, migratory aptitudes in the reaction of (II) seem to be determined more by bond eclipsing forces (the $C_3$-$C_2$ bond which bears the fully eclipsed substituents in the intermediate migrates preferentially) than by the chair-like or boat-like nature of the transition state[11] leading from the betaine intermediate to ring enlarged products.

Finally, we would like to emphasize the preparative interest of these reactions. Besides (I) and (III)-(V), the available syntheses of which are very laborious,[3,7] the new (VI) is easily obtained. (VI) would be difficult to prepare by the available methods for his congeners which would lead to a bridgehead substituted skeleton.

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