Short Communications

The Reaction of 2-Phenylbicyclo-[2.2.1]hept-2-ene with Formaldehyde and Methylammonium Chloride in Acetic Acid

KALLE MANNINEN

Department of Chemistry, University of Oulu, SF-90570 Oulu 57, Finland

The reaction of 2-phenylbicyclo[2.2.]hept-2-ene with formaldehyde and dimethylammonium chloride in molar ratio 1:1:1 with acetic acid as solvent has been found to give amino alcohol *1*, aldehyde *2*, and secondary amines *3* and *4* as the main products. Minor products in this reaction are the unsaturated tertiary amine *5*, tricyclic amine *6* and tertiary amines *7* and *8*.[1] Products *1*, *5* and *6* are normal aminomethylation products of an alkene (*cf.* Ref. 2), whereas *2*, *3* and *4* are anomalous, involving a 1,5- or 1,3-hydride shift in an intermediate step of the reaction.[3] Amines *7* and *8* are Eschweiler methylation products of *3* and *4*.

Hydride shifts in the reaction of an alkene with formaldehyde and a secondary amine have been found for bicyclo[2.2.]hept-2-ene,[4,5] 2,6,6-trimethylbicyclo[3.1.1]hept-2-ene,[6] 6,6-dimethyl-2-methylenebicyclo[3.1.1]heptane,[6] 2-methylenebicyclo[2.2.1]heptane [7] and 2-methylbi-

cyclo[2.2.1]hept-2-ene,[7] in addition to 2-phenylbicyclo[2.2.1]hept-2-ene. A transannular hydride abstraction leading to an unsaturated amino ketone has been reported for the reaction of cyclodecenone with formaldehyde and monomethylamine.[8] The investigation described in this paper deals with the reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde and methylammonium chloride in acetic acid. The principal purpose was to find out which route is predominant in this case: the usual one leading to an amino alcohol, an amino alkene or an oxazine (*cf.* Ref. 2), or the special one associated with hydride shifts and leading to saturated amines.[4,5]

To test the two possibilities, 2-phenylbicyclo[2.2.1]hept-2-ene was heated with paraformaldehyde and methylammonium chloride in acetic acid for 10 min. The gas chromatogram of a neutralized sample of the reaction mixture showed one main and several minor components. The main component was identified as oxazine *9* from its ^{1}H NMR and mass spectra. The ^{13}C NMR spectrum of *9*, which was run after the actual structure elucidation, is in accordance with the presented formula.

The experiment was then repeated using a longer reaction time. The gas chromatographic analysis of the product mixture after several minutes again showed oxazine *9* to be the main component. After a reaction time of 1 h a second main component was found. The proportion of *9* was decreased and the proportion of the
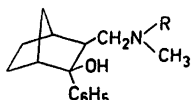
1, R = CH₃
13, R = H
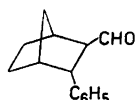
2
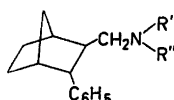
3, R' = H R'' = CH₃
7, R' = R'' = CH₃
12, R' = R'' = H
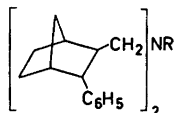
4, R = H
8, R = CH₃
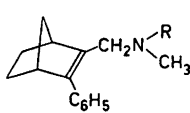
5, R = CH₃
10, R = H
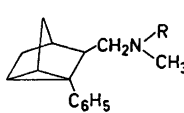
6, R = CH₃
11, R = H
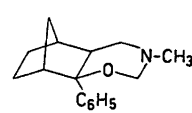
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new main component increased as the heating was continued. After 3 h, the heating was discontinued and the reaction mixture worked up. The new main component and six other basic products were separated by preparative gas chromatography. On the basis of the mass and ¹H NMR spectral data, the structure *10* was proposed for the main product and the structures *3*, *5*, *6*, *7*, *11* and *12* for the minor basic products. To confirm the structure analysis of *10*, it was converted into the tertiary amine *5* by Eschweiler-Clarke methylation.

The previously unreported, tricyclic secondary amine *11*, was isolated in pure state only for mass spectral analysis. The assignment of the structure *11* was confirmed by converting the compound into the known tricyclic tertiary amine *6* via Eschweiler-Clarke methylation.

The other products isolated, the primary amine *12*, secondary amine *3*, and tertiary amines *5*, *6* and *7*, have been described earlier.[1] The theoretically possible amino alcohol *13* could not be isolated from the reaction mixture. The impurity peaks in the mass spectrum of the primary amine *12* at m/e 231, 213 and 44, which are not present in the mass spectrum of the authentic *12*,[1] show, however, that *13* could be present in the reaction mixture. The peak m/e 231 could be the molecular ion peak, 213 could be due to loss of water and 44 could represent the CH_3NHCH_2 group of *13*.

Examination of the above results shows that the principal route in the reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde and monomethylammonium chloride in acetic acid is the usual one, leading mainly to an oxazine *9* and an unsaturated amine *10*. If the reaction is controlled kinetically, the faster forming *9* can be isolated as the main product; but by allowing the reaction to approach equilibrium, the proportion of *10* is rendered most. The proportion of these main products, the side product *11* formed in a similar way, and the methylation products *5* and *6*, is about 90 %. The proportion of primary amine *12* formed via a hydride shift and its methylation products *3* and *7* is only about 10 %. Hence the route involving hydride shifts is only a side reaction in the aminomethylation of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde and methylammonium chloride. Because methylamine could have been methylated as well under the reaction conditions used, (cf. Ref. 9) it cannot be stated conclusively that all of the secondary amine *3* and the tertiary amine *7* were formed from the primary amine *12* via methylation. Dimethylamine produced by the methylation of methylamine would react with 2-phenylbicyclo[2.2.1]hept-2-ene and formaldehyde to form *3*, as was pointed out earlier.[1] The products *5* and *6* might also form, in addition to the ways presented above, from 2-phenylbicyclo[2.2.1]hept-2-ene, formaldehyde and any dimethylamine formed from methylamine.

Experimental. The mass and ¹H NMR spectra were recorded and the gas chromatographic analyses and separations performed as described earlier.[1] The ¹³C NMR spectrum of oxazine *9* was run on a Jeol FX-100 instrument.

Reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde and methylammonium chloride. 2-Phenylbicyclo[2.2.1]hept-2-ene (20.4 g, 0.12 mol), paraformaldehyde (3.8 g, equivalent to 0.12 mol of formaldehyde) and methylammonium chloride (6.5 g, 0.10 mol) were heated in 40 ml of acetic acid for 10 min. After cooling to room temperature, the reaction mixture was poured into 400 ml of water. The unreacted starting materials and the neutral products were separated from the basic products by extraction, as described earlier.[1] The neutral products, yield 12.4 g, were not examined more closely. Distillation of the basic fraction (12.4 g) twice gave as the main component (90 %) oxazine *9* ($C_{16}H_{21}NO$, mol. wt. 243.34), yield 7.40 g (48 %), b.p. 125−127 °C/20 Pa.

MS[70 eV; m/e (% rel. int.)]: 243 (33, M), 171 (34), 170 (34), 142 (85), 105 (58), 77 (44), 73 (41), 58 (75), 44 (100, [CH_3NHCH_2]), 42 (47).

¹H NMR (60 MHz, CCl_4): δ 7.33 (5 H, broad s, Ph protons), 3.81 and 3.58 (2 H, AB-system of $O−CH_2−N$ protons, J 7 Hz), 2.68−2.17 (5 H, m), 2.05 (3 H, s, NCH_3), 1.63−0.95 (6 H, broad signal).

¹³C NMR [25.06 MHz, $CDCl_3$]: 141.1, 127.9, 127.8 and 127.0 (Ph carbons), 84.6 (benzylic carbon), 81.2 ($O−CH_2−N$), 53.7 (CH_2N), 49.8 (CH), 44.1 (CH), 42.9 (CH), 41.5 (CH_3N), 37.0 (CH_2), 30.6 (CH_2), 22.4 (CH_2).

The experiment was repeated as above, but with a heating time of 3 h. Distillation of the amine fraction (11.2 g) gave 7.5 g of mixture, boiling range 135−160 °C/50 Pa. The products were separated by preparative gas chromatography. The main component (60 %) was N-methyl-3-phenylbicyclo[2.2.1]hept-2-ene-2-methamine *(10)* ($C_{15}H_{19}N$, mol. wt. 213.31).

MS [IP 70 eV; m/e (% rel. int.)]: 213 (100, M), 198 (10, M−CH_3), 184 (96), 172 (61), 155 (17), 141 (17), 115 (24), 108 (24), 70 (44), 44 (49).

¹H NMR (60 MHz, CCl_4): δ 7.23 (5 H, s, Ph protons), 3.34 (2 H, s, CH_2N), 3.11 (2 H, broad s, bridgehead protons), 2.40 (3 H, s, CH_3N), 2.32−1.08 (6 H, complex signal), 0.89 (1 H, s, NH). Eschweiler-Clarke methylation of *10* gave the known tertiary amine *5*.

Oxazine *9* comprised about 16 % of the fraction; the other compounds separated and identified were:

N-Methyl-*endo*-3-phenylbicyclo[2.2.1]heptane-*exo*-2-methanamine *(3*, 8 %)*, whose mass and ¹H NMR spectra are identical with those of an authentic sample.[1]

N-Methyl-1-phenyltricyclo[2.2.1.0²,⁶]heptane-7-methanamine *(11*, 7 %, $C_{15}H_{19}N$, mol. wt. 213.31).

MS [IP 70 eV; m/e (% rel. int.)]: 213 (16, M), 198 (1, [M−CH_3]), 170 (7), 142 (8) 128 (4), 115 (4), 91 (6), 77 (3), 70 (5), 44 (100, [CH_3NHCH_2]).

The Eschweiler-Clarke methylation of *11* gave the tertiary amine *6* described below.

N,N-Dimethyl-3-phenylbicyclo[2.2.1]hept-2-ene-2-methanamine (*5*, 3 %, $C_{16}H_{21}N$, mol. wt. 227.33), which has been described earlier.[1]

MS [IP 70 eV; *m/e* (% rel. int.)]: 227 (75, M), 212 (23, [M−CH₃]), 198 (40), 186 (39), 155 (35), 115 (23), 91 (27), 84 (72), 67 (29), 58 (100).

¹H NMR (60 MHz, CCl₄): δ 7.24 (5 H, s, Ph protons), 3.13 (2 H, broad s, bridgehead protons), 2.98 (2 H, s, CH₂N), 2.20 [6 H, s, N(CH₃)₂], 2.11 − 1.00 (6 H, complex signal).

N,N-Dimethyl-1-phenyltricyclo[2.2.1.0²,⁶]-heptane-7-methanamine (*6*, 3 %, $C_{16}H_{21}N$, mol. wt. 227.33), whose structure was confirmed earlier.[1]

MS [IP 70 eV; *m/e* (% rel. int.)]: 227 (8, M), 115 (3), 91 (2), 84 (1), 77 (1), 58 (100, [(CH₃)₂-NCH₂]).

N,N-Dimethyl-*endo*-3-phenylbicyclo[2.2.1]-heptane-*exo*-2-methanamine (*7*, 2 %), whose ¹H NMR spectrum is identical with that reported in the literature.[10]

endo-3-Phenylbicyclo[2.2.1]heptane-*exo*-3-methanamine (*12*, 1 %), whose mass spectrum has the same peaks as that of an authentic sample.[1]

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Received June 9, 1978.

Preparation of *gem*-Dibromocyclopropyl Aldehydes and Acids from Conjugated Dienes

KJELL H. HOLM, DONALD G. LEE and LARS SKATTEBØL

Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, Oslo 3, Norway

The *gem*-dibromocyclopropyl unit is an allene synthon,[1] and we were interested in compounds where it is connected to a carbonyl function, particularly an aldehyde group. No useful method for the preparation of aldehydes of the general structure *1* has been described. The addition of dihalocarbenes to α,β-unsaturated aldehydes is not a feasible reaction, but addition to the corresponding acetals takes place albeit in poor yields.[2] Subsequent hydrolysis of the acetals afforded the aldehydes and the parent compound, 2,2-dibromocyclo-

	1	*2*
a	R = H	R = H
b	R = Me	R = Me
c	R = Ph	R = Ph
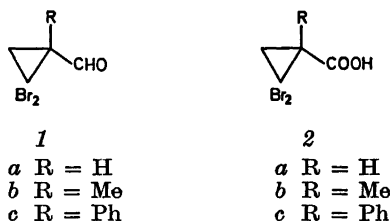
propylcarbaldehyde (*1a*), was first prepared in this way,[3] but no yields were reported. In the present work we describe convenient synthetic routes to the aldehydes *1* and the corresponding acids *2* starting from conjugated dienes.

Conjugated dienes react with dibromocarbene, generated by various methods, to give the monoadducts *3* in good yields.[4] Addition to the second double bond will also take place to a certain extent depending on the structure of the diene, but provided an excess of diene is used the amount of bis-adducts becomes insignificant in most cases. Furthermore, separation of the adducts usually creates no problem. In the present work dibromocarbene was generated from bromoform and 50 % aqueous sodium hydroxide by the phase transfer method[5] or from bromoform and potassium *t*-butoxide. These monoadducts are conveniently oxidized to the aldehydes *1* in good yields by either ruthenium dioxide − sodium *meta*-periodate (method A) or by ozone (method B).

By method A the oxidation was carried out in dilute water−carbon tetrachloride mixture using catalytic amounts of ruthenium dioxide.[6] In the aqueous phase the latter was oxidized to the tetroxide by sodium *meta*-periodate which was used in excess. The rate of oxidation