

The Prins Reaction of 2-Phenylbicyclo[2.2.1]hept-2-ene

KALLE MANNINEN and SEPPO PARHI

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

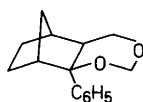
We have studied the reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde in the presence and absence of diisopropylammonium chloride and with acetic acid as solvent. The main reaction type is the Prins, leading to two unexpected esters in addition to the normal products. The Mannich side reaction produces an expected secondary amine. The course of the reaction routes is discussed and the mechanism for the formation of the unexpected esters is described.

When 2-phenylbicyclo[2.2.1]hept-2-ene is allowed to react with formaldehyde and a secondary amine such as dimethylamine¹ or diethylamine,² most of the products are combinations of all three starting materials. The main reaction is an unusual Mannich condensation involving 1,5-hydride shifts. When diisopropylamine is used instead of the amines

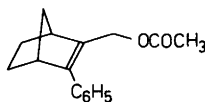
mentioned, the reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with only formaldehyde (Prins type reaction) becomes predominant, as reported recently.³ The Mannich reaction in this case proceeds only to a very small extent. The Prins type products are 1–5 and the other products 6 and 7. Here we present the complete results from our preliminary report,³ and discuss the possible pathways to the products of this complex reaction.

RESULTS

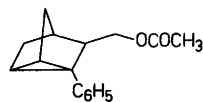
In the first experiments 2-phenylbicyclo[2.2.1]hept-2-ene was heated with paraformaldehyde and diisopropylammonium chloride in boiling acetic acid for 24–48 h. The main component among the neutral products was then (according to spectral



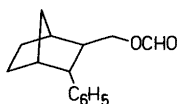
1



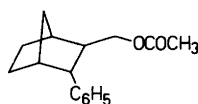
2



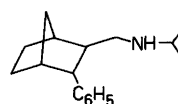
3



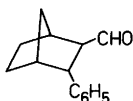
4



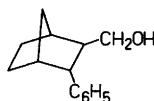
5



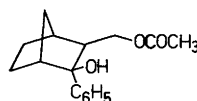
6



7



8



9

data) the saturated ester 5. Its structure was confirmed by reduction of the aldehyde 7, known from previous studies,^{1,2,4} to the corresponding alcohol 8 and acetylation of 8 with acetic anhydride to yield 5. Of the several other neutral products we isolated only the aldehyde 7. The product in the amine part was the secondary amine 6. Its mass and NMR spectra were in agreement with the expected structure, which is analogous to the structures of the secondary amines from 2-phenylbicyclo[2.2.1]hept-2-ene, formaldehyde and dimethyl- or diethylamine.^{1,2}

When 2-phenylbicyclo[2.2.1]hept-2-ene, formaldehyde and diisopropylammonium chloride were stirred at room temperature and then slowly heated to 70–80 °C to prevent polymerization, which in the first experiments was appreciable, there was only one main component in the neutral part of the products and only 50% of the starting alkene had reacted. On the basis of spectral data the product was identified as 1,3-dioxane 1. When 2-phenylbicyclo[2.2.1]hept-2-ene, formaldehyde and diisopropylammonium chloride were allowed to react in boiling acetic acid for 5–7 h, the main component in the neutral product mixture was the unsaturated acetate 2. The second most abundant product was the tricyclic acetate 3. An important result of this experiment was the discovery of the formate 4 among the neutral products. The ¹³C NMR spectrum of the mixture shows, in addition to the peaks of 1, 2, 3 and 5, also the same peaks as 4 prepared through ester interchange from 8 and ethyl formate. The separation of 4 from the product mixture for structure elucidation was hence not necessary.

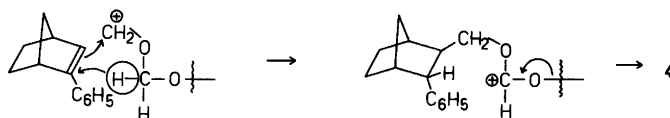
To study the influence of diisopropylammonium chloride on the reaction, 2-phenylbicyclo[2.2.1]hept-2-ene was heated alone with formaldehyde in acetic acid. When the heating time was 3 h, the main products were the expected dioxane 1 plus a hydroxy acetate, which spectral data showed to have the structure 9. Heating 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde in acetic acid for a longer time led to the same neutral products as the prolonged heating of these starting materials in the presence of diisopropylammonium chloride. After heating for 170 h, the main products were 2, 5 and 3 and the minor products 1, 4 and 7. The amount of polymers was negligible.

DISCUSSION

The results above show that the primary product of 2-phenylbicyclo[2.2.1]hept-2-ene and formaldehyde in acetic acid both in the presence and in the absence of diisopropylammonium chloride is dioxane 1, which is a typical Prins reaction product (cf. Ref. 5). The formation of 1 is reversible. This is probably due to the phenyl group, which stabilizes the positive charge on the benzylic carbon in the intermediate, in both the forming and breaking down of 1. Likewise the product 9, which we observed to form in the absence of diisopropylammonium chloride, is a typical Prins reaction product. The other normal Prins reaction products are the unsaturated acetate 2 and the tricyclic acetate 3. We believe that the former is a primary Prins reaction product and the latter is formed from it through isomerization. Our conclusion is supported by the observation that isomerization from 2 to 3 takes place during gas chromatographic separation on a metal column.

The formation of the secondary amine 6, although in very low yield, is in agreement with our previous proposals for the 1,5-hydride shifts associated with the reactions of bicyclo[2.2.1]hept-2-ene^{6,7} and 2-phenylbicyclo[2.2.1]hept-2-ene^{1,2} with formaldehyde and some secondary amines in acetic acid. The low yield of 6 is most probably due to steric factors. The bulky isopropyl groups of diisopropylamine retard the hydride shift from amine to the benzylic carbon of 2-phenylbicyclo[2.2.1]heptane skeleton, which must proceed for the formation of 6. The hindrance is so strong that the Prins reaction becomes predominant over the Mannich reaction.

The most interesting products arising from 2-phenylbicyclo[2.2.1]hept-2-ene and formaldehyde, both in the presence and in the absence of diisopropylammonium chloride, are the esters 4 and 5. To our knowledge these bicyclic esters with a lower oxidation state than 2, 3, or 9 are new product types in the Prins reaction. Following the experiments gas chromatographically shows that the formate (4) is formed first. When the reaction is allowed to proceed longer, however, the amount of 4 is diminished and the amount of 5 increased. Where diisopropylammonium chloride is present and the reaction time long, 5 is the main product. We believe that 4 forms from 2-phenylbicyclo[2.2.1]hept-2-ene and formaldehyde through a hydride shift from a formaldehyde dimer or oligomer to the bicyclic skeleton, as suggested in Scheme 1. Compound 4



Scheme 1. The formation of the formate of *endo*-3-phenylbicyclo[2.2.1]heptane-*exo*-2-methanol (4) from 2-phenylbicyclo[2.2.1]hept-2-ene and formaldehyde.

reacts then with water and acetic acid to give 5. The mechanism in Scheme 1 is supported by an observation that we made while allowing 2-phenylbicyclo[2.2.1]hept-2-ene to react with perdeuterioformaldehyde in the presence of diisopropylammonium chloride in acetic acid: We found deuterium at the benzylic carbon and in the methylene group of the side chain of 5. The hydrogen at the benzylic carbon must thus come from formaldehyde. In the secondary amine 6, isolated from the same experiment, the benzylic carbon is not deuterated and only the methylene group between the bicyclic skeleton and nitrogen contains deuterium, in agreement with the proposals regarding the 1,5-hydride shifts associated with the formation of secondary norbornanemethanamines mentioned above.

The use of diisopropylammonium chloride in the reaction of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde has an effect on both the rate of the reaction and the stability of the products. In its presence the reaction clearly proceeds faster. The normal Prins reaction products polymerize and the abnormal Prins reaction product 5 can be separated by distillation in nearly pure form. The separation of the hydroxy acetate 9 is possible only when the reaction is carried out without the amine hydrochloride.

EXPERIMENTAL

Mass spectra were measured with a Perkin Elmer RMU 6E double focussing mass spectrometer. ^1H and ^{13}C NMR spectra were determined with a Jeol FX-100 instrument. Infrared spectra were taken on a Perkin Elmer 257 spectrometer.

Heating of 2-phenylbicyclo[2.2.1]hept-2-ene with formaldehyde in the presence of diisopropylammonium chloride in acetic acid. Typical procedures. (a) Heating time 24 h. 2-Phenylbicyclo[2.2.1]hept-2-ene (25.5 g, 0.15 mol), paraformaldehyde (4.5 g, equivalent to 0.15 mol of formaldehyde) and diisopropylammonium chloride (20.6 g, 0.15 mol) were heated in acetic acid (75 ml) for 24 h at 115 °C. Water (225 ml) and ether (40 ml) were added and the neutral products

and amines separated by extraction as in previous work.¹

Evaporation of the extract containing neutral products left a residue of 25.3 g, which was distilled in a bulb tube oven. Fraction 100–140 °C/2.7 Pa, yield 3.5 g, was collected. The polymeric distillation residue of 20.3 g was not examined further. From the distillate was separated by preparative gas chromatography as the main (62 %) component the acetate of 3-*endo*-phenylbicyclo[2.2.1]heptane-2-*exo*-methanol (5, $\text{C}_{16}\text{H}_{20}\text{O}_2$, mol. wt. 244.34).

MS [IP 70 eV; m/e (% rel. int.)]: 184 (100, M – CH_3COOH), 155 (47), 143 (39), 130 (33), 117 (24), 115 (30), 106 (22), 91 (53), 77 (13), 67 (20), 43 (54).

^1H NMR (100 MHz, CDCl_3): δ 7.25 (5 H, s phenyl protons), 3.98 (2 H, d, J 7.7 Hz, CH_2 of side chain), 2.71 (1 H, t, benzylic proton), 2.45 and 2.21 (2 H, broad s, protons at C 1 and C 4), 1.99 (3 H, s, –O–COCH₃), 2.08–1.90 (1 H, m, proton at C 2), 1.69–1.29 (6 H, the other protons). IR (0.1 mm in CCl_4): 1735 (s, CO).

^{13}C NMR [25.06 MHz, CDCl_3]: δ 170.9 (C=O), 141.4, 127.8, 125.6 (Ph), 67.4 (CH_2 of side chain), 50.2 (C 3), 45.2 (C 2), 42.5 (C 4), 39.6 (C 1), 37.3 (C 7), 29.6 (C 6), 22.5 (C 5), 20.9 (CH_3).

The mass and ^1H NMR spectra are identical with those of the reference compound prepared as described below. From the minor components in the distillate, *endo*-3-phenylbicyclo[2.2.1]heptane-*exo*-2-carboxaldehyde (7) (5 %) was separated as a 2,4-dinitrophenylhydrazone. Its infrared spectrum is similar to that of the reference compound prepared from 7 in earlier work.¹

Distillation of the extract containing amines gave, after a prerun of unreacted diisopropylamine, 0.24 g *N*-isopropyl-3-*endo*-phenylbicyclo[2.2.1]heptane-2-*exo*-methanamine (6, $\text{C}_{17}\text{H}_{24}\text{N}$, mol. wt. 243.40).

MS [IP 70 eV; m/e (% rel. int.)]: 243 (12, M), 228 (3), 184 (5), 169 (3), 155 (4), 119 (7), 117 (7), 91 (12), 72 (100).

^1H NMR (100 MHz, C_6D_6): δ 7.15 (5 H, phenyl protons), 2.61 (1 H, benzylic proton), 2.44 (2 H, d, J 7.6 Hz, CH_2 of side chain), 2.26 (2 H, broad s, protons at C 1 and C 7), 2.1–1.8 (1 H, *endo*-proton at C 2).

^{13}C NMR [25.06 MHz, C_6D_6]: δ 53.4 (CH_2 of side chain), 52.9 (CH of side chain) 48.9 (C 3), 47.5 (C 2), 43.4 (C 4), 41.0 (C 1), 38.0 (C 7), 30.5 (C 6), 23.4 and

23.2 (CH₃ of side chain), 22.9 (C 5).

(b) Reaction time 45 min. 2-Phenylbicyclo[2.2.1]-hept-2-ene (10.2 g, 0.06 mol), paraformaldehyde (1.8 g, equivalent to 0.06 mol of formaldehyde) and diisopropylammonium chloride (8.24 g, 0.06 mol) were stirred in 30 ml of acetic acid at room temperature for 15 min. Then the temperature of the mixture was allowed to increase over 30 min to 76 °C, at which point the mixture was homogeneous. The mixture was cooled quickly and the neutral products isolated from the amines by extraction. The neutral part was distilled over in the bulb tube oven at 100–120 °C/2.7 Pa. Yield 9.5 g. Inspection of the gas chromatogram showed the distillate to contain 2-phenylbicyclo[2.2.1]hept-2-ene and only one product, in a ratio of about 1:1. The product was isolated by preparative gas chromatography and it was found from spectral data to be the 2-*endo*-phenyl-*exo*-tricyclo[6.2.1.0^{2,7}]3,5-dioxaundecane (1, C₁₅H₁₈O₂, mol. wt. 230.31, m.p. 43.5–44.5 °C).

MS [IP 70 eV; *m/e* (% rel. int.)]: 230 (15, M), 200 (7), 155 (5), 142 (8), 133 (26), 115 (10), 105 (100), 91 (14), 77 (35).

¹H NMR (100 MHz, CDCl₃): δ 7.46–7.25 (5 H, m, phenyl protons), 4.80 and 4.42 (2 H, 2 d, AB-system of C 3 protons, *J* = 4.2 Hz), 3.99–3.65 (2 H, m, C 6 protons), 2.63–0.65 (9 H, the other protons).

¹³C NMR [25.06 MHz, CDCl₃]: δ 139.9, 127.8, 127.6, 127.1 (Ph), 88.0 (C 4), 84.5 (C 2), 64.4 (C 6), 48.9 (C 7), 44.9 (C 1), 41.3 (C 8), 36.5 (C 11), 29.9 (C 9), 22.3 (C 10).

(c) Reaction time 6 h. 2-Phenylbicyclo[2.2.1]hept-2-ene (5.1 g, 0.03 mol), paraformaldehyde (0.9 g, equivalent to 0.03 mol of formaldehyde) and diisopropylammonium chloride (4.2 g, 0.03 mol) were heated in 15 ml of acetic acid for 6 h. Distillation of the neutral part of the product mixture in the bulb tube oven gave 2.55 g of liquid. The main component (about 50%) of the distillate was separated by preparative gas chromatography in a packed glass column and was found to be the acetate of 3-phenylbicyclo[2.2.1]hept-2-ene-2-methanol (2, C₁₆H₁₈O₂, mol. wt. 242.32).

MS [IP 75 eV; *m/e* (% rel. int.)]: 242 (15, M), 182 (24), 167 (10), 154 (100), 115 (26), 91 (25), 43 (28).

¹H NMR (100 MHz, CDCl₃): δ 7.25 (5 H, m, phenyl protons), 4.79 (2 H, s, the methylene protons of the side chain), 3.19 and 3.05 (2 H, two broad s, the bridgehead protons), 2.09 (3 H, s, the methyl protons), 1.96–1.26 (6 H, the other protons).

¹³C NMR [25.06 MHz, CDCl₃]: δ 170.8 (C=O), 136.6 (C 2 or C 3), 135.7 (C 2 or C 3), 145.8, 128.0, 127.8, 126.8 (Ph), 60.6 (CH₂ of side chain), 47.5 (C 4), 47.0 (C 7), 45.5 (C 1), 26.2 (C 5 or C 6), 25.9 (C 5 or C 6), 21.0 (CH₃).

The distillate of this experiment contained, in addition to the main component 2 and the side components 1, 2, 3 and 5, also a product which from

comparison of its ¹³C NMR spectrum with a reference compound could be identified as the formate of 3-*endo*-phenylbicyclo[heptane-*exo*-2-methanol (4).

The attempts to purify 2 by preparative gas chromatography using an aluminium column led to isomerization to the acetate of 2-phenyltricyclo[2.2.1.0^{2,6}]heptane-3-methanol (3, C₁₆H₁₈O₂, mol. wt. 242.32), which in a small amount was present in the distillate of this experiment.

MS [IP 75 eV; *m/e* (% rel. int.)]: 242 (32, M), 182 (87, M – CH₃COOH), 167 (100), 154 (58), 141 (52), 130 (72), 115 (48), 91 (74).

¹H NMR (100 MHz, CDCl₃): δ 7.20 (5 H, s, phenyl protons), 4.20–3.60 (2 H, methylene protons of the side chain), 1.95 (3 H, s, methyl protons) 2.40–1.29 (8 H, the other protons).

¹³C NMR [25.06 MHz, CDCl₃]: δ 170.3 (C=O), 139.4, 127.8, 127.7, 125.3 (Ph), 63.3 (CH₂ of side chain), 47.1 (C 3), 33.9 (C 7), 33.3 (C 4), 30.0 (C 5), 29.5 (C 2), 23.9 (C 6), 20.6 (CH₃), 17.0 (C 1).

Heating of 2-phenylbicyclo[2.2.1]hept-2-ene only with formaldehyde in acetic acid. (a) Heating time 3 h. 2-Phenylbicyclo[2.2.1]hept-2-ene (1.7 g, 0.01 mol) and paraformaldehyde (0.6 g, equivalent to 0.02 mol of formaldehyde) were allowed to react in 5 ml of acetic acid for 3 h. Water (15 ml) was added and the products extracted with ether. The ether solution was washed with potassium carbonate solution and dried with calcium sulfate. After evaporation of the solvent the residue was distilled in the bulb tube oven.

The fraction 100–120 °C/6.7 Pa, yield 0.7 g, was mainly the dioxane 1.

The fraction 120–150 °C/6.7 Pa, yield 0.74 g, was purified by preparative gas chromatography and on the basis of spectral data was identified as the acetate of *exo*-3-hydroxy-*endo*-3-phenylbicyclo[2.2.1]heptane-*exo*-2-methanol (9, C₁₆H₂₀O₃, mol. wt. 260.34).

MS [IP 75 eV; *m/e* (% rel. int.)]: 200 (18), 133 (26), 105 (100), 91 (9), 77 (28), 67 (10), 55 (15), 43 (32).

¹H NMR (100 MHz, CDCl₃): δ 7.41–7.25 (5 H, m, phenyl protons), 4.30 (2 H, d, *J* 8 Hz, the doublets have a fine splitting of about 2 Hz probably due to hindered rotation of the side chain methylene group), 2.49 (2 H, broad s, bridgehead protons), 1.96 (3 H, s, methyl protons), 2.14–0.90 (8 H, the other protons).

IR (0.1 mm in CCl₄): 3590, 3580, 3440 (m, OH), 1735 (s, CO).

¹³C NMR [25.06 MHz, CDCl₃]: δ 170.7 (C=O), 144.4, 127.1, 127.2, 126.7 (Ph), 80.5 (C 3), 64.9 (CH₂ of side chain), 49.0 (C 2 or C 4), 48.9 (C 2 or C 4), 39.4 (C 1), 35.1 (C 7), 29.2 (C 6), 23.0 (C 5), 21.0 (C 6).

(b) Heating time 170 h. 2-Phenylbicyclo[2.2.1]hept-2-ene (10.2 g, 0.06) and paraformaldehyde (3.6 g, 0.12 mol formaldehyde) were heated in 30 ml of

acetic acid for 170 h. Work up of the product gave 8.95 g of a liquid that boiled from 80 °C/13 Pa to 150 °C/66 Pa. The residue from distillation was small.

The main components in the distillate were the unsaturated acetate 2 (51 %), the saturated acetate 5 (16 %), the tricyclic acetate 3 (13 %) and the minor components (total 20 %) dioxane 1, formate 4 and the aldehyde 7.

Preparation of the reference compounds. (a) *Acetate of 3-endo-phenylbicyclo[2.2.1]heptane-2-exo-methanol (5).* *endo-3-Phenylbicyclo[2.2.1]heptane-exo-2-carboxaldehyde (7)*¹ (4.47 g, 0.022 mol) was reduced with sodium borohydride (0.43 g, 0.011 mol) in 50 ml of methanol to 3-endo-phenylbicyclo[2.2.1]heptane-2-exo-methanol (8, C₁₄H₁₈O, mol. wt., 202.28) which was recrystallized from petroleum ether. M.p. 77.5–78 °C.

MS [IP 75 eV; *m/e* (% rel. int.)]: 202 (48, M), 184 (100, M–H₂O), 169 (18), 156 (66), 143 (44), 130 (43), 115 (50), 105 (24), 91 (100).

¹H NMR (100 MHz, CDCl₃): δ 7.25 (5 H, s, phenyl protons), 3.53 (2 H, d, *I* 7 Hz, the methylene protons of the hydroxymethyl group), 2.40 and 2.27 (2 H, broad s, the bridgehead protons), 2.1–1.8 (1 H, endo-proton at C–2) 1.6–1.29 (6 H, the other protons).

IR (0.1 mm in CCl₄): 3605, 3450, 3315 (m, OH), 1030 (s, C–O).

¹³C NMR [25.05 MHz, CDCl₃]: δ 141.4, 127.9, 127.8, 125.6 (Ph), 66.6 (CH₂ of side chain), 50.1 (C3), 48.9 (C2), 42.7 (C4), 39.3 (C1), 37.4 (C7), 29.8 (C6), 22.6 (C5). The alcohol 8 (42.5 mg, 0.21 mmol) was treated with acetic anhydride (81 mg, 0.8 mmol) in dry pyridine for 15 h to produce 30 mg of the acetate of 3-endo-phenylbicyclo[2.2.1]heptane-2-exo-methanol (5).

(b) *Formate of 3-endo-phenylbicyclo[2.2.1]heptane-exo-2-methanol (4).* The alcohol 8 (1.11 g, 5.5 mmol) was heated with ethyl formate (4.2 g, 57 mmol) in the presence of a catalytical amount of *p*-toluene sulfonic acid for 15 h. Work up and distillation in a bulb tube oven at 125 °C/13 Pa gave 0.88 g of the formate of 3-endo-phenylbicyclo[2.2.1]heptane-exo-2-methanol (4, C₁₅H₁₈O₂, mol. wt. 230.31).

MS [IP 75 eV; *m/e* (% rel. int.)]: 230 (4, M), 184 (100, M–HCOOH), 169 (11), 157 (38), 143 (30), 130 (27), 106 (118), 91 (55).

¹H NMR (100 MHz, CDCl₃): 7.98 (1 H, s, formyl proton), 7.24 (5 H, s, phenyl protons), 4.05 (2 H, d, *J* 7.6 Hz, methylene protons of the side chain), 2.70 (1 H, broad signal, benzylic proton), 2.42 and 2.22 (2 H, broad signals, bridgehead protons), 2.20–1.27 (6 H, the other protons).

IR (0.1 mm in CCl₄): 1720 (s, CO).

¹³C NMR (25.06 MHz, CDCl₃): 160.7 (C=O), 141.1, 127.9, 127.7, 125.7 (Ph), 66.8 (CH₂ of side chain), 50.1 (C3), 45.0 (C2), 42.6 (C4), 39.6 (C1), 37.3 (C7), 29.5 (C6), 22.4 (C5).

REFERENCES

1. Manninen, K. and Haapala, J. *Acta Chem. Scand. B* 28 (1974) 433.
2. Manninen, K. *Finn. Chem. Lett.* (1980) 146.
3. Manninen, K. and Parhi, S. *Kem. Kemi* 5 (1978) 349.
4. Manninen, K. *Acta Chem. Scand. B* 32 (1978) 691.
5. Adams, D. A. and Bhatnagar, S. P. *Synthesis* (1977) 661.
6. Krieger, H. and Manninen, K. *Tetrahedron Lett.* (1966) 6483.
7. Manninen, K. *Acta Univ. Oul. A 2 Chem.* 1 (1972).

Received August 20, 1980.