

SYNTHESIS OF BRIDGEHEAD FLUOROBICYCLO[2.2.2]OCTANES

Jan KOPECKÝ and Jaroslav ŠMEJKAL

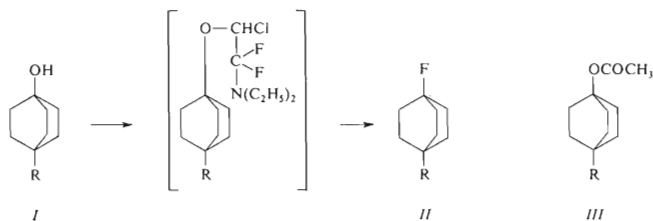
*Institute of Hygiene and Epidemiology,**Centre of Occupational Hygiene and Occupational Diseases, 100 42 Prague 10*

Received November 14th, 1979

The paper describes preparation of bridgehead, *i.e.* 1 and/or 4-fluorobicyclo[2.2.2]octanes from the respective bicyclo[2.2.2]octanols with the Yarovenko reagent.

Introduction of methods for measurement of chemical shifts by ^{19}F -NMR caused that 1 and/or 4-fluorobicyclo[2.2.2]octanes became a useful group of compounds, because the mentioned method allows to study on this model the influence of non-conjugation polar effects and their transmission to the reaction centre^{1,2} as well as the through-bond interactions^{3,4}. As the synthetical accessibility of the bridgehead fluorobicyclo[2.2.2]octanes has been relatively difficult so far⁵⁻⁷, we considered it useful to study possibility of application of easily available bridgehead hydroxybicyclo[2.2.2]octanes for this synthesis.

The first fluorobicyclo[2.2.2]octane was prepared by Suzuki and Morita⁵ by reaction of 1-methoxybicyclo[2.2.2]octane with excess acetyl fluoride in the presence of catalytic amount tin tetrachloride. However, this reaction produced a mixture of 1-fluoro- and 1-chlorobicyclo[2.2.2]octanes. Using a complex of boron trifluoride and phosphoric acid instead of tin tetrachloride, the authors⁶ obtained pure 1-fluorobicyclo[2.2.2]octanes. The method given by Kauer⁷ is based on conversion of bridgehead hydroxybicyclo[2.2.2]octanes into respective fluoroformates which could be converted into the fluoro derivatives by action of SF_4 in anhydrous hydrogen fluoride. We found earlier⁸⁻¹⁰ that the bridgehead hydroxybicyclo[2.2.2]octanes can easily be converted into chloro, bromo or iodo derivatives by action of the corresponding inorganic (alkali) halides in orthophosphoric or polyphosphoric acid, but this method cannot be applied to preparation of the fluoro derivatives. Out of the methods used for introduction of fluorine atom by the way of splitting of C—O bond¹¹ the most promising seemed to be that introduced by Yarovenko¹². The latter method is based on reaction of hydroxy compounds with 1,1-difluoroalkylamines, especially 2-chloro-1,1,2-trifluorotriethylamine, and subsequent thermic splitting of the formed ether^{13,14}. We found that in the case of the 1-hydroxybicyclo[2.2.2]octanes (*Ia–If*) the reaction needs higher temperatures (60–140°C) to be successful. The corresponding fluorobicyclo[2.2.2]octanes (*IIa–IIg*, except for *IIe*) are then formed in the yields 50 to 60% (ref. ¹⁵).



I, II, a, R = H; *b*, R = CH₃; *c*, R = C₆H₅; *d*, R = OCOCH₃; *e*, R = OH; *f*, R = NO₂C₆H₄
Ilg, R = F, *IIf*, R = 4-NH₂C₆H₄; *IIIa*, R = C₆H₅; *IIIb*, R = 4-NO₂C₆H₄

1-Fluoro-4-(4-X-phenyl)bicyclo[2.2.2]octanes represent an interesting model for study of non-conjugated *vs* conjugated polar effects by measuring the fluorine chemical shifts using ¹⁹F-NMR. Recently these compounds were also studied by Adcock and Khor^{16,17}. We prepared 1-fluoro-4-(4-nitrophenyl)bicyclo[2.2.2]octane (*II f*) and 1-fluoro-4-(4-aminophenyl)bicyclo[2.2.2]octane (*II h*) from 1-acetoxy-4-phenylbicyclo[2.2.2]octane (*III a*). Nitration of *III a* with nitric acid in acethanhydride gave the 1-acetoxy-4-(4-nitrophenyl) derivative (*III b*) which gave 1-hydroxy-4-(4-nitrophenyl)bicyclo[2.2.2]octane (*I f*) on boiling with methanolic hydroxide. The compound *I f* was converted (60% yield) into 1-fluoro-4-(4-nitrophenyl)bicyclo[2.2.2]octane (*II f*) by the Yarovenko reaction. Reduction of *II f* with sodium borohydride in the presence of Pd/C gave 1-fluoro-4-(4-aminophenyl)bicyclo[2.2.2]octane (*II h*).

EXPERIMENTAL

The temperature data were not corrected. The infrared spectra were measured with a UR 10 apparatus (Zeiss, Jena). The ¹H-NMR spectra were measured with a Varian A 60 apparatus (tetramethylsilane) and the mass spectra were measured with a MCH-1303 (SSSR); both were published elsewhere¹⁸.

1-Fluoro-4-R-bicyclo[2.2.2]octanes (*II a—II g*, except for *II e*)

The starting hydroxybicyclo[2.2.2]octanes *I a—I f* were heated with 2-chloro-1,1,2-trifluoro-triethylamine at 60—140°C for 30 to 90 min. No solvent was used; if the starting compound was solid, then excess reagent was used. After cooling the whole apparatus was rinsed with ether which was then combined with the ether extract of the reaction mixture. The combined ether extracts were washed with 5% KHCO₃ solution and water and dried with MgSO₄. Ether was evaporated, and the residue was purified by column chromatography (Al₂O₃/pentane or light petroleum); the product was then purified by distillation or sublimation in vacuum of water pump. The reaction conditions, yields, m.p. and spectral characteristics of the compounds prepared are given in Table I.

TABLE I
Reaction Conditions, Yields, Melting (boiling) Points and Spectral Characteristics of the Prepared Fluorobicyclo[2.2.2]octanes

Compound Molar ratio ^a	Temperature, °C Time, min	M.p. ^b (b.p.), °C Yield, %	IR (CCl ₄), cm ⁻¹	¹ H-NMR (CCl ₄), ppm
<i>Ila</i> 1 : 2	60—65 60	182—184 ^c (63.5)	2 950, 2 920, 2 865, 1 460, 1 340, 1 070, 920	1.67; 1.74
<i>Ilb</i> 1 : 1.5	120 30	(148—150) ^d (50)	2 950, 2 920, 2 860, 1 460, 1 330, 1 060	0.79; 1.6
<i>Ilc</i> 1 : 2.2	130—140 60	132—133 ^e (56.5)	3 080, 3 060, 3 030, 2 950, 2 920, 2 870, 1 495, 1 460, 1 335, 1 330, 1 065, 1 035	1.9; 1.93; 7.05—7.25
<i>Ild</i> 1 : 1.1	120—130 60	57—58.5 (49.5)	2 960, 2 925, 2 875, 1 735, 1 460, 1 370, 1 350, 1 240, 1 078	1.85; 1.9—2.2
<i>Ile</i> ^f —	—	235—236 (94)	3 590, 3 015, 2 950, 2 920, 2 870, 1 460, 1 348, 1 230, 1 110, 1 090, 1 055	1.85; 1.92 ^g
<i>Ilf</i> 1 : 2	130 90	119—121 ^h (59.5)	3 080, 3 065, 2 955, 2 920, 2 870, 1 605, 1 530, 1 460, 1 350, 1 075	2.0; 7.34; 8.1
<i>Ilg</i> 1 : 2.2	100 60	193—195 (49)	2 960, 2 930, 2 870, 1 460, 1 350, 1 310, 1 110, 1 080	1.86; 1.92; 1.97
<i>Ilh</i> ^b —	—	202—204 (93)	3 470, 3 430, 3 020, 2 955, 2 920, 2 870, 1 625, 1 460, 1 355, 1 285, 1 060 ⁱ	1.95; 3.5; 6.6; 8.06 ⁱ

^a Hydroxybicyclo[2.2.2]octane; 2-chloro-1,1,2-trifluorotriethylamine; ^b the m.p. were determined in a sealed capillary; ^c ref. ⁶ gives m.p. about 152°C; ^d ref. ⁶ gives b.p. 165—170°C; ^e ref. ¹⁷ gives m.p. 131—132.5°C; ^f prepared by hydrolysis of *Ild*; ^g ref. ¹⁷ gives m.p. 121.5—123°C; ^h prepared by reduction of *Ilg*; ⁱ in CDCl₃ and CHCl₃, respectively.

1-Fluoro-4-hydroxybicyclo[2.2.2]octane (*Ile*)

Solution of 110 mg (0.59 mmol) *IId* and 0.2 g NaOH in 3 ml wet methanol (0.2 ml H₂O) was refluxed 1 h. After evaporation of methanol the residue was diluted with water and extracted with ether. The extract was dried with MgSO₄, ether was evaporated and the residue was sublimed under the pressure $2 \cdot 10^3$ Pa, the bath temperature 100–110°C. Yield 80 mg (94%) *Ile*, m.p. 235–236°C (sealed capillary).

1-Acetoxy-4-(4-nitrophenyl)bicyclo[2.2.2]octane (*IIIb*)

Fuming nitric acid (13 ml) was added drop by drop to solution of 22 g 1-acetoxy-4-phenylbicyclo[2.2.2]octane¹⁹ (*IIIa*) in 220 ml acetonitrile at 25°C during 20 min. The mixture was stirred 4 h, treated with water and extracted with benzene. After evaporation of the solvent the residue was crystallized from benzene. Yield 16.5 g (66%) *IIIb*, m.p. 150–151°C (ethanol). For C₁₆H₁₉NO₄ (289.3) calculated: 4.84% N; found: 4.60% N.

1-Hydroxy-4-(4-nitrophenyl)bicyclo[2.2.2]octane (*If*)

3.85 g *IIIb* was dissolved in methanolic hydroxide (1.5 g NaOH and 1.5 ml water in 12 ml methanol). The mixture was refluxed 2 h, diluted with about 100 ml water, acidified with hydrochloric acid, and extracted with benzene. After evaporation of benzene the residue was crystallized from aqueous ethanol (2:1). Yield 3.3 g (100%) *If*, m.p. 139–141°C. The sample for analysis was crystallized from 70% ethanol and melted at 140.5–142°C. For C₁₄H₁₇NO₃ (247.3) calculated: 5.66% N; found: 5.43% N.

1-Fluoro-4-(4-aminophenyl)bicyclo[2.2.2]octane (*IIIh*)

Solution of 1.6 g *IIf* in 100 ml methanol under nitrogen was added dropwise under stirring and cooling to suspension of 70 mg 10% Pd/C and 1.4 g NaBH₄ in 7.5 ml water. After 2.5 h stirring the catalyst was collected by suction and washed with ether. The filtrate was diluted with water and extracted with ether. The combined ether extracts were extracted with 2M-HCl, and the acid aqueous extracts were alkalinized with 2M-NaOH. The precipitated solid was collected by suction, washed with water and reprecipitated. Yield 1.3 g (93%) *IIIh*, m.p. 202–204°C; ref.¹⁷ gives m.p. 190°C.

The authors are indebted to van't Hoff foundation for financial support enabling a part of the described research. They also are indebted to Dr D. Sardela, Department of Chemistry, Boston College, USA, for measurements of the ¹H-NMR spectra, to Dr V. Hanuš, Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, Prague, for measurements of the mass spectra, and to Dr K. Boček of our Institute for measurements of the IR spectra.

REFERENCES

1. Anderson G. L., Stock L. M.: J. Amer. Chem. Soc. 90, 212 (1968).
2. Ritchie C. D., Lewis E. S.: J. Amer. Chem. Soc. 84, 591 (1962).
3. Hoffmann R.: Accounts Chem. Res. 4, 1 (1971).
4. Heilbronner E.: Pure Appl. Chem. 7, 9 (1971).
5. Suzuki Z., Morita K.: J. Org. Chem. 32, 31 (1967).
6. Suzuki Z., Morita K.: Bull. Chem. Soc. Jap. 41, 1724 (1968).

7. Anonymous: Chem. Eng. News March 9, 39 (1970).
8. Kopecký J., Šmejkal J.: Tetrahedron Lett. 1967, 1931.
9. Kopecký J., Šmejkal J.: Tetrahedron Lett. 1967, 3889.
10. Kopecký J., Šmejkal J.: This Journal 45, 2965 (1980).
11. Knunyanc I. L., Polishchuk V. R.: Usp. Khim. 44, 685 (1975).
12. Yarovenko N. N., Raksha M. A.: Zh. Obsch. Khim. 29, 2159 (1959).
13. Liška F.: Chem. Listy 66, 189 (1972).
14. Bailey E. J., Fazakerley H., Hill M. E., Newall G. P., Phillips G. H., Stephenson L., Tulley A.: Chem. Commun. 1970, 106.
15. Kopecký J., Šmejkal J., Hudlický M.: Chem. Ind. (London) 1969, 271.
16. Adcock W., Khor T. C.: Tetrahedron Lett. 1976, 3063.
17. Adcock W., Khor T. C.: J. Org. Chem. 42, 218 (1977).
18. Stenhagen E., Abrahamsson S., McLafferty F. W.: *Registry of Mass Spectral Data*. Wiley, New York 1974.
19. Kopecký J., Šmejkal J., Hanuš V.: This Journal, in press.

Translated by J. Panchartek.