# SYNTHESIS OF BRIDGEHEAD BICYCLO[2.2.2]OCTANOLS

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The paper describes syntheses of bicyclo[2.2.2]octan-1-ol, its 4-methyl and 4-phenyl derivatives, and bicyclo[2.2.2]octane-1,4-diol.

Study of reactions at bridgehead carbon atoms of bicyclic systems has fundamental importance for understanding of discrete configuration of transition states (reactive intermediates) in the course of organic reactions[1]. Therefore, much attention was paid to methods of preparation of the bicyclo[2.2.2]octanes substituted at 1- and/or 4-positions[2]. The interest in this group of compounds still increased in the course of studies of transfer of the non-conjugated polar effects[3,4] and those of through--bond interactions[5] for which the 1- and/or 4-substituted bicyclo[2.2.2]octane derivatives represent an ideal model. The bridgehead substituents of various bicyclic systems inclusive of the bicyclo[2.2.2]octane system are extremely inert to nucleophilic substitution. Therefore, the 1- and/or 4-substituted bicyclo[2.2.2]octanes were usually prepared by transformation of 1-carboxylic group (for more details see ref.[4]). Later several papers appeared dealing with preparation of bicyclo[2.2.2]octan-1-ol (*VI*) and its 4-substituted derivatives[6,7] and bicyclo[2.2.2]octane-1,4-diol[8,9] (*IX*).

We considered it useful to develop simple methods of preparation of the bridgehead bicyclo[2.2.2]octanols, because these compounds could be potential starting materials for preparation of various bridgehead bicyclo[2.2.2]octane derivatives. This paper gives preparations of bicyclo[2.2.2]octan-1-ol (*VI*), its 4-methyl and 4-phenyl derivatives, and bicyclo[2.2.2]octane-1,4-diol (*IX*). They served as starting materials for further transformations of hydroxyl group[10–12,26–28].

Bicyclo[2.2.2]octan-1-ol (*VI*) was prepared earlier[13,14] *via* hydrolysis of the 1-bromo derivative with calcium carbonate; we have now used the reaction sequence: The carboxylic acid[14] *I* was transformed into the chloride *II* (identified as the corresponding amide[15]) which on reaction with diethyl ethoxymagnesiummalonate and subsequent hydrolysis to *III* (not isolated) gave 1-acetylbicyclo[2.2.2]octane (*IV*). The Bayer–Villiger oxidation of *IV* gave 1-acetoxybicyclo[2.2.2]octane (*V*) which was transformed without isolation to bicyclo[2.2.2]octan-1-ol (*VI*).



*I*, X = OH
*II*, X = Cl
*III*, X = $CH(COOC_2H_5)_2$
*IV*, X = $CH_3$

*V*, R = $COCH_3$

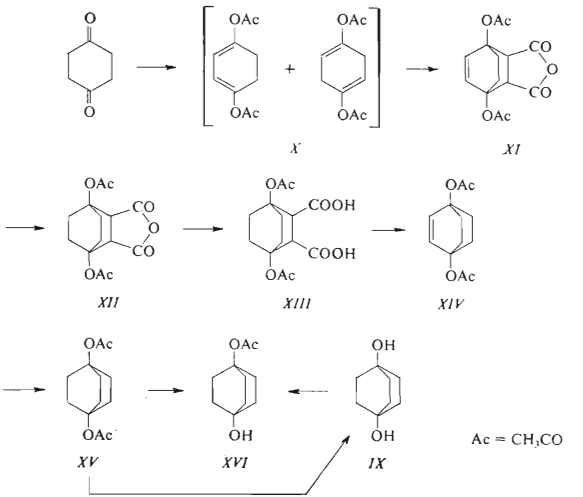
*VI*, R = H
*VII*, R = $CH_3$
*VIII*, R = $C_6H_5$

4-Methyl- (*VII*) and 4-phenylbicyclo[2.2.2]octan-1-ol (*VIII*) were prepared from the corresponding 3-oxo derivatives accessible from 4-substituted 4-acetylcyclohexanones[16]. The key step of the synthesis of *VII* and *VIII* consisted in the Wolff–Kizhner reduction of the 3-carbonyl group, which in usual way of preparation gives relatively low yields[6,7] due obviously to retro-aldol opening of the bicyclo[2.2.2]octane skeleton. We have found the reduction yields to be substantially increased by first preparing the hydrazone *in situ* and its subsequent treatment with KOH in triethylene glycol.

Bicyclo[2.2.2]octane-1,4-diol (*IX*) was prepared[8,9] *via* hydrolysis of the respective 1,4-dichloro derivative. This synthesis of *IX* necessitates high pressures (diene addition at 100 MPa)[8,17] hardly realizable in laboratory. Kauer has already shown[9,18,19] that *IX* is a suitable starting material for preparation of various bridgehead substituted bicyclo[2.2.2]octane derivatives *via* transformation of hydroxyl groups. The reaction sequence chosen for preparation of *IX* is given in Scheme 1. Acid-catalyzed reaction of isopropenyl acetate with 1,4-cyclohexanedione gives (besides 1,4-diacetoxy-1,4-cyclohexadiene) 1,4-diacetoxy-1,3-cyclohexadiene (*X*) which undergoes diene addition with maleic anhydride to give 1,4-diacetoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (*XI*). Hydrogenation of *XI* gave the saturated *XII* which was hydrolyzed to the corresponding dicarboxylic acid *XIII*. Oxidative decarboxylation of *XIII* with lead tetraacetate in pyridine in the presence of oxygen gave 1,4-diacetoxybicyclo[2.2.2]oct-2-ene (*XIV*) which on hydrogenation and subsequent hydrolysis *via* diacetate *XV* gave satisfactory yields of *IX*. Partial hydrolysis of *XV* or partial acetylation of *IX* gave the monoacetate of *IX*, *i.e.* 4-acetoxybicyclo[2.2.2]octan-1-ol (*XVI*).

## EXPERIMENTAL

The temperature data were not corrected. The IR spectra were measured with a grating spectrophotometer (Brückl, Munich, GFR). The $^1$H-NMR spectra were measured with a Varian A 60 apparatus (tetramethylsilane, in hexadeuteriodimethyl sulphoxide), and the mass spectra were measured with a MCH-1303 apparatus (USSR) and were published elsewhere[20].




SCHEME 1

Bicyclo[2.2.2]octane-1-carboxylic Acid (*I*)

The compound was prepared according to Grob[14]; m.p. 140—141°C, ref.[14] gives m.p. 140·5 to 142°C. The corresponding chloride *II* was prepared from 15·4 g (0·1 mol) *I* by refluxing in 50 ml thionyl chloride for 2 h. The excess thionyl chloride was evaporated, and the residue was distilled in vacuum, the fraction boiling within 103—105°C at 1·6 kPa being taken. Yield 16·1 g (94%). For identification purposes a sample of the chloride *II* was transformed into the respective amide; m.p. 176—177°C (ref.[15] gives m.p. 177—178°C).

1-Acetylbicyclo[2.2.2]octane (*IV*)

The compound was prepared from the chloride *II* by a modified preparation method of 1-acetyladamantane[21] in the yield 70%. B.p. 92—96°C at 1·5 kPa; $n_D^{24.5}$ 1·4821 (ref.[15] gives b.p. 94—98°C at the same pressure and $n_D^{23}$ 1·4846).

Bicyclo[2.2.2]octan-1-ol (*VI*)

7·6 g (50 mmol) *IV* in 11 ml 10% sulphuric acid was oxidized with about 20 g perbenzoic acid in 250 ml chloroform according to the procedure given[22] for 20-ketosteroid. The oxidation proceeded 7 days (longer time does not affect the yield) in dark at room temperature. Then the

mixture was diluted with 250 ml ether, the organic layer was washed with water, with 5% aqueous sodium carbonate, and again with water until neutral; thereafter it was dried over anhydrous $MgSO_4$, and the solvents were evaporated. The residue was treated with methanol and solution of sodium hydroxide (15 g NaOH in 15 ml $H_2O$ and 125 ml methanol) and refluxed 2 h. After evaporation of methanol the residue was diluted with 150 ml water and extracted three times with 50 ml ether. Usual procedure gave 4·3 g solid which was purified by sublimation at 110—120°C at 1·3 kPa. Yield 3·9 g (62%) *VI*, m.p. 213—215°C (sealed capillary); refs[13,14] give m.p. 214 to 215°C.

4-Methylbicyclo[2.2.2]octan-1-ol (*VII*)

5 g 1-Hydroxy-4-methylbicyclo[2.2.2]octan-3-one[16] and 10 ml 80% hydrazine hydrate were refluxed 2 h. After addition of 30 ml triethylene glycol and 3 g KOH, the mixture was heated at 220°C 1 h with simultaneous distillation. After cooling the whole apparatus was rinsed with ether (which was then added to the combined ether extracts), the distillate was combined with the distillation residue, diluted with 150 ml water, and extracted twice with 40 ml ether. The combined extracts were washed with water, 2 N-HCl, and again with water. Drying over anhydrous $MgSO_4$ and evaporation of ether at room temperature gave 4·1 g needles, m.p. 96—98° (sealed capillary). Sublimation at 70—90°C at 1·7—2·0 kPa gave 3·5 g (77%) pure *VII*, m.p. 102—103°C (sealed capillary); refs[7,23,24] give m.p. within 98 to 104°C. Boiling of 1 g *VII* in 15 ml acetanhydride for 1/2 h gave the acetate in the yield 62%. B.p. 85—87°C at 2·0 kPa, $n_D^{27.5}$ 1·4605. Ref.[7] gives b.p. 100—102°C at the same pressure. For $C_{11}H_{18}O_2$ (182·3) calculated: 72·48% C, 9·95% H; found 72·36% C, 10·23% H.

4-Phenylbicyclo[2.2.2]octan-1-ol (*VIII*)

The compound was prepared from 1-hydroxy-4-phenylbicyclo[2.2.2]octan-3-one[16] in analogy to *VII*. Sublimation at 120°C at 1·3 kPa gave 60% yield of the product melting at 122—123°C (sealed capillary); refs[23,24] give m.p. 122—123°C and 115—117°C, respectively. Boiling of *VIII* with acetanhydride gave 91% yield of the acetate, m.p. 91—92°C (aqueous ethanol 2 : 1). For $C_{16}H_{20}O_2$ (244·3) calculated: 78·65% C, 8·25% H; found: 78·86% C, 8·34% H.

1,4-Diacetoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Acid Anhydride (*XI*)

1,4-Cyclohexanedione, isopropenyl acetate and maleic anhydride (molar ratio 1 : 3 : 1) with a small amount of anhydrous *p*-toluenesulphonic acid were heated at a temperature max. 150°C, and the acetone formed was distilled off through a column. After removal of all acetone the mixture solidified, the crystalline product was collected by suction and washed with ethanol. M.p. 206—209°C. Repeated crystallization from benzene gave pure *XI*, m.p. 210—211·5°C (ref.[25] gives m.p. 209—210·5°C), yield 50—55%. For $C_{14}H_{14}O_7$ (294·2) calculated: 57·14% C, 4·80% H; found: 57·21% C, 4·95% H. IR spectrum (KBr): 1790, 1780, 1755, 1735, 1370, 1230, 1080 920 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, $\delta$, ppm): 1·7—1·95 (m, 4 H, —$CH_2$—), 2·1 (s, 6 H, $CH_3$—), 4·2 (s, 2 H, C—H), 6·3 (s, 2 H, —CH=).

1,4-Diacetoxybicyclo[2.2.2]octane-2,3-dicarboxylic Acid Anhydride (*XII*)

5 g *XI* was hydrogenated in 40 ml tetrahydrofurane using a $PtO_2$ catalyst. Yield 5 g (99%) *XII*, m.p. 184—185·5°C (acetone). For $C_{14}H_{16}O_7$ (296·3) calculated: 56·75% C, 5·44% H; found: 56·62% C, 5·26% H. IR spectrum (KBr): 1785, 1735, 1370, 1235, 1070, 915 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, $\delta$, ppm): 1·98 (s, 8 H, —$CH_2$—), 4·45 (d, 2 H, C—H).

1,4-Diacetoxybicyclo[2.2.2[octane-2,3-dicarboxylic Acid (*XIII*)

3·5 g *XII* in 15 ml 20% aqueous $KHCO_3$ was heated on water bath with stirring until dissolution. Cooling and acidification with concentrated hydrochloric acid caused precipitation of a solid which on crystallization from 50% acetic acid gave 3·5 g (94%) pure *XIII*, m.p. 189·5—190°C. For $C_{14}H_{18}O_8$ (314·3) calculated: 53·50% C, 5·77% H; found: 53·46% C, 5·71% H. IR spectrum (KBr): 1785, 1735, 1375, 1235, 1065, 910 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, $\delta$, ppm): 2·0 (s, 8 H, —$CH_2$—), 4·45 (d, 2 H, C—H).

1,4-Diacetoxybicyclo[2.2.2]oct-2-ene (*XIV*)

Oxygen was bubbled through 160 ml pyridine for 15 min, whereafter 20 g (63·6 mmol) *XIII* and 42·5 g (95 mmol) lead tetraacetate were added, and the mixture was heated at 65—70°C with continuous introduction of oxygen for 10 min. After cooling the mixture was decomposed with an excess of diluted $HNO_3$ (1 : 2) and extracted with ether. The combined ether extracts were washed with $KHCO_3$ solution, saturated NaCl solution, and dried over anhydrous $MgSO_4$. Ether was evaporated, and the residue was crystallized from 50% acetic acid and then sublimed at 80°C at 1·3 kPa. Yield of pure *XIV* was 8·7 g (61%); m.p. 85—87°C. For $C_{12}H_{16}O_4$ (224·2) calculated: 64·27% C, 7·19% H; found: 64·39% C, 7·21% H. IR spectrum (KBr): 2880, 1730, 1375, 1245, 1085 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, $\delta$, ppm): 1·83 (s, 8 H, —$CH_2$—), 2·0 (s, 6 H, $CH_3$—), 6·23 (s, 2 H, C—H).

1,4-Diacetoxybicyclo[2.2.2]octane (*XV*)

The compound was prepared by hydrogenation of 1·8 g *XIV* in 10 ml tetrahydrofuran using a $PtO_2$ catalyst. After usual treatment the crystalline residue was sublimed at 90°C at 1·3 kPa. Yield 1·8 g (99%) *XV*, m.p. 91—93°C (sealed capillary). For $C_{12}H_{18}O_4$ (226·3) calculated: 63·70% C, 8·01% H; found: 63·91% C, 8·09% H. IR spectrum (KBr): 2880, 1730, 1380, 1360, 1260, 1245, 1055, 925 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, $\delta$, ppm): 1·91 (s, 6 H, $CH_3$—), 2·06 (s, 12 H, —$CH_2$—).

*Partial hydrolysis* of XV: Mixture of 0·45 g *XV* and solid sodium ethoxide (from 50 mg Na) in 5 ml ether was refluxed with stirring for 1/2 h. Ether was distilled off, the residue was treated with 7 ml benzene, and the mixture was refluxed with stirring 3 h. After cooling and dilution with 15 ml ether the mixture was decomposed with water, the organic layer was extracted with diluted hydrochloric acid (1 : 4), solution of $NaHCO_3$, and water. After drying and evaporation of the solvents the crystalline residue was sublimed at 100°C at 1·3 kPa. Yield 0·27 g (73·5%) 4-acetoxybicyclo[2.2.2]octan-1-ol (*XVI*), m.p. 69·5—71·5°C (sealed capillary). For $C_{10}H_{16}O_3$ (184·2) calculated: 65·19% C, 8·75% H; found: 65·13% C, 8·57% H.

Bicyclo[2.2.2]octane-1,4-diol (*IX*)

Solution of 1·6 g *XV* in 25 ml methanol containing 2 g NaOH and 2 ml water was refluxed 2 h. After cooling and acidification with diluted hydrochloric acid the mixture was evaporated in vacuum. The residue was extracted with boiling anhydrous acetone, and evaporation of the solvent gave a crystalline residue which was sublimed at 180—190°C at 1·3 kPa to give 0·7 g (70%) *IX*, m.p. 282—284°C (sealed capillary); refs[8,9] give m.p. 281—283°C. IR spectrum (KBr): 3300, 2945, 2870, 1465, 1350, 1115, 1095, 920, 825, 650 $cm^{-1}$. $^1$H-NMR spectrum ($(CD_3)_2SO$, ppm): 1·58 (s, 12 H, —$CH_2$—), 3·95 (s, 2 H, HO—).

*Partial acetylation of* IX: Solution of 0·4 g *IX* in 5 ml acetanhydride was left to stand 30 min at room temperature and then refluxed for another 5 min. The solid obtained on cooling (0·1 g) was collected (the unreacted *IX*), and the filtrate was decomposed with water and extracted with ether. Usual treatment gave 0·25 g (48%) product identical with the monoacetate *IX* obtained by the partial hydrolysis of *XV*.

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