The Epimeric *syn*-Bicyclo[3.2.1]octane-2,8-diols[1]

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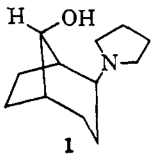
Received December 26, 1963

The isomeric *syn*-8-hydroxybicyclo[3.2.1]octan-2-one and *exo*(axial)-2-hydroxybicyclo[3.2.1]octan-8-one have been obtained by unique oxidative degradations of known intermediates. Reduction of these ketols with sodium borohydride afforded *endo*(equatorial)-*syn*-bicyclo[3.2.1]octane-2,8-diol and *exo*(axial)-*syn*-bicyclo-[3.2.1]octane-2,8-diol, respectively. The reaction sequence from 2-methyl-2-aza-3-oxatricyclo[3.3.2.^{4,8}0^{1,5}]decane to the *exo-syn* diol represents a simple, versatile synthetic application of the intramolecular nitrone–olefin addition.

In the course of investigations of synthetic routes to bicyclo[3.2.1]oct-2-en-8-yl derivatives,[4] several observations were made which provided the basis for a stereospecific synthesis of *exo-syn-* and *endo-syn*-bicyclo[3.2.1]-octane-2,8-diol. At the risk of undue prolificacy, we have chosen to report these results because they provide a rather striking illustration of the utility of intramolecular nitrone–olefin cyclizations for synthetic and structural studies.

Mercuric acetate oxidation[5] of the *syn*-amino alcohol **1**[4] gave, in poor yield, an unstable enamino alcohol (**2**) which could not be easily purified (the presence of **3** in the product mixture is conceivable, though no indication of its presence was found). Hydrolysis of the product afforded the crystalline *syn*-bicyclo[3.2.1]octan-8-ol-2-one (**4**) whose stereochemistry is confirmed by establishment of the *syn* configuration for the 8-hydroxyl substituent of its precursor.[4] Reduction of ketol **4** with sodium borohydride gave a major diol **5a** as evidenced by the excellent yield of a sharp melting product, and the preparation of a bis-*p*-nitrobenzoate (**5b**). The hydroxyl group at C-2 was assigned the *endo*(equatorial) configuration because of the established preference for hydride reductions of unhindered ketones to give thermodynamically more stable equatorial alcohols,[6] and/or possible complexation of the reducing species with the *syn*-8-hydroxyl group.[7] Moreover, the physical properties of **5a** were distinctly different from those reported[8] for *exo*(axial)-*syn*-bicyclo-[3.2.1]octane-2,8-diol (**6a**).



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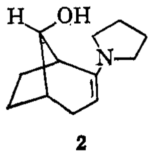

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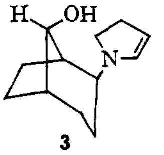

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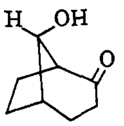

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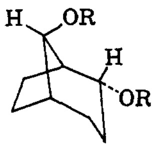
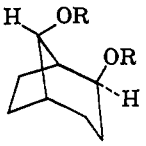


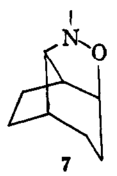
5a, R = H
b, R = $p\text{-}NO_2C_6H_4\underset{\underset{\displaystyle O}{\|}}{C}-$



6a, R = H
b, R = $p\text{-}NO_2C_6H_4\underset{\underset{\displaystyle O}{\|}}{C}-$

It was noted that some confusion had existed in the literature as to the structure of diol **6a**. Initially, a synthesis of *trans*-bicyclo[2.2.2]octane-2,3-diol was reported,[9] but later the product obtained by employment of the same procedure was assigned as **6a**.[8] We repeated the preparation of **6a** *via* formolysis of bicyclo[2.2.2]-octene oxide.[8] Again a single, sharp-melting diol was isolated. This product (**6a**) gave a negative periodate test as expected for a 1,3-diol; however, like its epimer **5a**, it failed to show appreciable reaction with *p*-nitrobenzaldehyde. The diols **5a** and **6a** were different compounds as shown by infrared spectra, mixture melting point, and comparison of bis-*p*-nitrobenzoates.

The assignment of **6a** as *exo-syn*-bicyclo[3.2.1]octane-2,8-diol seems unambiguous in view of the detection of intramolecular hydrogen bonding[8]; however, we can now provide an interesting degradative sequence which supports this assignment and which promises to have additional, valuable application. The condensation of Δ^4-cycloheptene carboxaldehyde and N-methylhydroxylamine has been reported to produce the tricyclic isoxazolidine **7** in good yield.[10] Oxidative cleavage of **7** could be effected with peracetic acid.[11] The product was a semisolid oil which could not be purified. It was assigned the hydroxynitrone structure **8** (stereochemistry uncertain) on the basis of its infrared spectrum and by analogy with the results of other studies.[11] The acidic hydrolysis of **8** further verified the proposed structure, as *exo*-bicyclo[3.2.1]octan-2-ol-8-one (**9**) was the only neutral product isolated. The ketol **9** was found to be quite unstable to base; for example, sodium bicarbonate washing of an ether solution of the hy-



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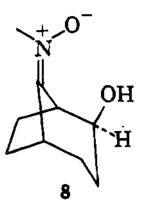

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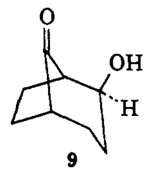

9

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[1] This work was supported by a generous grant from the National Science Foundation.

[2] Alfred P. Sloan Foundation Fellow, 1961–1965.

[3] U. S. Public Health Predoctoral Fellow, 1961–1963.

[4] N. A. LeBel and L. A. Spurlock, *Tetrahedron*, **20**, 215 (1964).

[5] For a summary of references dealing with the mercuric acetate oxidations of tertiary amines, see N. J. Leonard and F. P. Hanck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

[6] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

[7] An examination of Dreiding models indicates that steric hindrance to hydride attack at C-2 in ketol **4** is quite similar in magnitude for both *exo* and *endo* directions. The cited effect, coupled with the greater thermodynamic stability of **5a** over its C-2 epimer (**6a**), could easily account for the nearly exclusive production of **5a**.

[8] H. M. Kwart and G. C. Gatos, *J. Am. Chem. Soc.*, **80**, 881 (1958).

[9] H. M. Walborsky and D. F. Loncrini, *ibid.*, **76**, 5396 (1954).

[10] N. A. LeBel, G. M. J. Slusarczuk, and L. A. Spurlock, *ibid.*, **84**, 4360 (1962).

[11] The scope, mechanism, and other applications of this interesting reaction will be reported elsewhere.

drolysis material resulted in the isolation of only viscous oil instead of the crystalline product. This is undoubtedly the result of a facile retro-aldol condensation of **9**, and supplied supporting evidence for the β-hydroxy ketone structure. The infrared spectrum of **9** showed a typical split carbonyl absorption (1742 and 1748 cm.$^{-1}$) similar to that reported for bicyclo[3.2.1]octan-8-one.[12]

Reduction of **9** with sodium borohydride provided a striking confirmation of structure for the three reaction sequences employed. The product was, as in the reduction of the isomeric ketol **4**, a single diol. Identical infrared spectra, melting points and mixture melting point with the diol from formic acid treatment of bicyclo[2.2.2]octene oxide, and a comparison of bis-*p*-nitrobenzoate derivatives confirmed the structure of both compounds as *exo-syn*-bicyclo[3.2.1]octane-2,8-diol (**6a**). That reduction of **9** should take place preferentially from the side of the two-carbon bridge was anticipated from results obtained with bicyclo[3.2.1]-octan-8-one itself[12] and several analogs.[4,12,13]

The observation that the *exo-syn* diol **6a** did not form a *p*-nitrobenzilidine derivative under normal conditions might be considered unusual. This result is, however, not surprising when consideration is taken of the relative geometry of C-2 and C-8 substituents in this bicyclic ring system. The oxygen–oxygen bond distance is somewhat shorter in compound **6a** than in the corresponding *exo-syn*-bicyclo[2.2.1]heptane-2,7-diol as evidenced by hydrogen bonding studies[8] and by formation of slightly more stable cuprammonium complex.[8] However, the latter complex prefers an O–Cu–O bond angle close to 90°. Introduction of a carbon atom between the two oxygens *via* an equilibrium reaction (to form an additional bridged six-membered heteroring) is unfavorable because additional strain would be introduced into the over-all skeleton.[14]

Experimental[15]

2-N-Pyrrolidylbicyclo[3.2.1]oct-2-en-8-ol.—A solution of 9.75 g. (0.05 mole) of amino alcohol **1**[4] and 75 g. (0.24 mole) of mercuric acetate in 200 ml. of 5% aqueous acetic acid was heated with stirring on a steam bath for 2 hr. Precipitation was apparent after 20 min. The precipitate was removed by filtration and was washed with 5% aqueous acetic acid solution. The combined filtrate and washings were saturated with hydrogen sulfide, and the precipitate of mercuric sulfide was removed by filtration. The filtrate was made basic with potassium carbonate. A layer of ether was added, and the solution was saturated with potassium carbonate. The layers were separated and the aqueous layer was extracted with two more portions of ether. The extracts were dried and concentrated affording 1.70 g. (18%) of crude enamino alcohol (**2**). No attempt was made at further purification.

syn-**Bicyclo[3.2.1]octan-8-ol-2-one** (**4**).—The crude enamino alcohol **2** was dissolved in 60 ml. of 10% hydrochloric acid. The solution was boiled for a few minutes to remove hydrogen sulfide and was then allowed to stand on the steam bath for 30 min. The cooled solution was saturated with sodium chloride and was continuously extracted with ether. After drying, concentration of the extract gave 1.5 g. of crude material which could be sublimed at 125° (100 mm.) to give 1.05 g. (66%) of pure hydroxy ketone (**4**), m.p. 197–198°; infrared spectrum (CCl_4): 3600, 3413, 1712, 1163, 1147, and 1087 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.30; H, 8.82.

The **2,4-dinitrophenylhydrazone** crystallized from absolute ethanol as orange needles, m.p. 163–165° dec.

endo-syn-**Bicyclo[3.2.1]octane-2,8-diol** (**5a**).—To 0.400 g. (2.8 mmoles) of **4** in 20 ml. of absolute methanol was added 0.109 g. (2.9 mmoles) of sodium borohydride, and the solution was stirred for 3 hr. at 15–20°. One milliliter of water followed by 2 ml. of 15% potassium hydroxide were added, and the mixture was concentrated to a volume of approximately 10 ml Water (15 ml.) was again added and the resulting suspension was continuously extracted with ether. The extract was dried and concentrated to give 0.412 g. of crude alcohol which was crystallized by dessication. Recrystallization from ether afforded 0.363 g. (90%) of pure diol, m.p. 250.2–251.0°; infrared spectrum ($CHCl_3$): 3610, 3413, 1088, 1071, 1024, and 1006 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.64; H, 9.69.

The **bis-*p*-nitrobenzoate** (**5b**) was crystallized from chloroform–ether, m.p. 191.2–191.8°.

Anal. Calcd. for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36. Found: C, 59.82; H, 4.71; N, 6.27.

exo-**Bicyclo[3.2.1]octan-2-ol-8-one** (**9**).—To 1.00 g. (6.5 mmoles) of isoxazolidine **7** stirred at 0° was added dropwise 1.24 g. (6.6 mmoles) of 40% peracetic acid. The temperature was not allowed to rise above 5°. The solution was stirred for 2 hr. at 0° and then was neutralized with sodium bicarbonate. Ether (10 ml.) and 10 ml. of 1% hydrochloric acid were added; and the resulting mixture was stirred vigorously for 1 hr. The ether layer was separated, dried, and concentrated, giving 0.415 g. of crude material. The crude hydroxy ketone was sublimed at 115–120° (100 mm.) and was recrystallized from a mixture of ether and pentane affording 0.365 g. (40%) of pure material, m.p. 179.5–180.2°; infrared spectrum (CCl_4): 3390, 1748, 1742, 1285, 1080, and 990 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.66.

The **2,4-dinitrophenylhydrazone** was crystallized from absolute ethanol as orange plates, m.p. 113–115° dec.

In a separate experiment, 0.40 g. (2.6 mmoles) of **7** in 2 ml. of chloroform was treated with a solution of 0.40 g. (2.9 mmoles) of perbenzoic acid in 8.9 ml. of chloroform. The mixture was stirred for 18 hr. and was then washed with saturated sodium bicarbonate solution, dried, and concentrated. The yellow semisolid (0.797 g.) could not be purified without excessive decomposition. The presence of hydroxynitrone **8** was confirmed by the infrared spectrum (mull): 3322 and 1170 cm.$^{-1}$.

exo-syn-**Bicyclo[3.2.1]octane-2,8-diol** (**6a**).—By a procedure similar to that employed with the isomeric ketol **4**, 0.070 g. (0.5 mmole) of **9** was treated with 0.125 g. (3.3 mmoles) of sodium borohydride in 6 ml. of methanol. The product was recrystallized from ether–pentane giving 0.065 g. (92%) of pure diol, m.p. 267.0–268.0° (lit.[8] m.p. 255–257°); infrared spectrum ($CHCl_3$): 3610, 3401, 1182, 1087, 1045, 993, and 928 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.36; H, 9.82.

The **bis-*p*-nitrobenzoate** was crystallized from chloroform–ether, m.p. 220.0–220.5°.

Anal. Calcd. for $C_{22}H_{20}N_2O_8$: C, 60.00; H, 4.58; N, 6.36. Found: C, 60.00; H, 4.72; N, 6.21.

2,3-Epoxybicyclo[2.2.2]octane.—The epoxide was prepared from bicyclo[2.2.2]octene and peracetic acid[16] in 85% yield, m.p. 189–191°, lit.[16] m.p. 190–192°.

exo-syn-**Bicyclo[3.2.1]octane-2,8-diol.**—The diol was prepared from the epoxide and formic acid in 61% yield, m.p. 267–268°, lit.[8] m.p. 255–257°. Mixture melting point with diol **5a** was 255–258°, and that with diol **6a** was 267–268°.

The **bis-*p*-nitrobenzoate** was prepared and was crystallized from chloroform–ether, m.p. 219.5–220.5°. A mixture melting point with bis-*p*-nitrobenzoate **5b** showed 174–177°, and with **6b** was 219.5–220.5°.

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(12) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 4299 (1960).

(13) C. S. Foote and R. B. Woodward, *Tetrahedron*, in press.

(14) For example, the tetrahydrooxazine formally derived from condensation of formaldehyde and *exo-syn*-8-[N-methylamino]bicyclo[3.2.1]-octan-2-ol is very unstable to hydrolytic conditions (L. A. Spurlock, unpublished observations).

(15) Melting points are corrected and boiling points are uncorrected. Analyses were by Midwest Microlabs, Inc., Indianapolis, Ind. Infrared spectra were obtained with a Beckman Instruments, Inc., Model IR-4, or a Perkin-Elmer Corp. Infracord spectrometer, both with sodium chloride optics.

(16) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *J. Am. Chem. Soc.*, **83**, 988 (1961).

Attempted Preparation of *exo-syn*-Bicyclo[3.2.1]octyl-2,8-*p*-nitrobenzylidine Acetal.—To a solution of 0.220 g. (1.45 mmoles) of *p*-nitrobenzaldehyde in 2.5 ml. of dry benzene was added 0.200 g. (1.40 mmoles) of diol **6a** and a catalytic amount of *p*-toluenesulfonic acid. The solution was heated at reflux for 8 hr., and then the solvent was removed *in vacuo*. The resulting yellow semicrystalline mass was triturated with ether until most of the yellow color was removed. The residual solid was recrystallized from ethanol–ether, affording 0.175 g. (88%) of starting diol **6a**, m.p. 265–268°.

The Mannich Reaction with 2-Methylcyclopentanone and 2-Methylcyclohexanone[1a]

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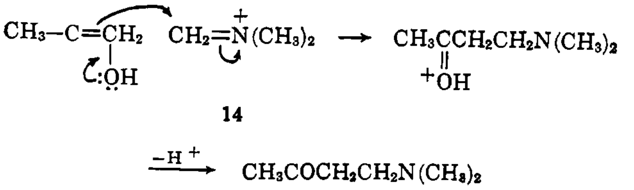
The Mannich reaction of dimethylamine and formaldehyde with 2-methylcyclopentanone yields 2-dimethylaminomethyl-2-methylcyclopentanone (**15**). The corresponding reaction with 2-methylcyclohexanone yields a mixture of structurally isomeric amino ketones **5** and **16** in which 2-dimethylaminomethyl-2-methylcyclohexanone (**16**) is the predominant product. These orientations are contrary to what has previously been reported for the Mannich condensation with these ketones.

As part of a study of the Michael reaction we wished to prepare an authentic sample of 2-(2-carboxyethyl)-5-methylcyclopentanone (**12**) and elected to follow a synthetic path (see Chart I) analogous to that previously employed[2] for the corresponding cyclohexanone derivative **13**. Both of these preparative procedures were intended to make use of the reported[3] Mannich condensations of 2-methylcyclopentanone (**1**) and 2-methylcyclohexanone (**2**) at the less highly substituted position to form Mannich bases **4** and **6**. Although the reported orientation in these two Mannich condensations has been widely accepted as correct,[2,4] the current view that Mannich reactions in slightly acidic media involve an electrophilic attack of an imminium salt such as **14** on the enol form of the ketone[5] is difficult to reconcile with the reported[3] orientation since the more highly substituted enols of 2-methylcyclopentanone and 2-methylcyclohexanone are expected to be the more stable.[6]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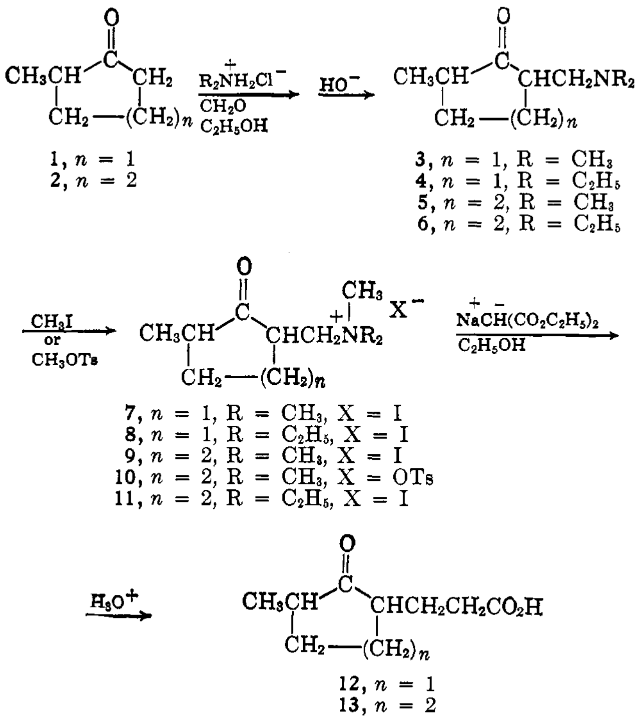
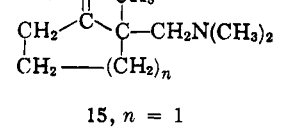
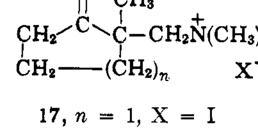
Our initial attempt to prepare acid **12** utilized the previously described[3] Mannich base derived from 2-methylcyclopentanone (**1**), diethylamine hydrochloride, and formaldehyde. Neither the previous investigators nor we were able to obtain the base (reported to be **4**) or its methiodide (reported to be **8**) as crystalline solids. From the reaction of this crude methiodide with diethyl sodiomalonate as previously described,[2] we were unable to isolate any of the desired keto acid **12**, only a small amount of methylmalonic acid being recovered.

CHART I


1, $n = 1$
2, $n = 2$
3, $n = 1$, $R = CH_3$
4, $n = 1$, $R = C_2H_5$
5, $n = 2$, $R = CH_3$
6, $n = 2$, $R = C_2H_5$
7, $n = 1$, $R = CH_3$, $X = I$
8, $n = 1$, $R = C_2H_5$, $X = I$
9, $n = 2$, $R = CH_3$, $X = I$
10, $n = 2$, $R = CH_3$, $X = OTs$
11, $n = 2$, $R = C_2H_5$, $X = I$
12, $n = 1$
13, $n = 2$

The Mannich reaction was, therefore, repeated with dimethylamine hydrobromide to form a Mannich base which readily yielded a crystalline methiodide in an over-all yield of 89%. However, the n.m.r. spectrum (see Experimental) of this crystalline product left no doubt that it was not the methiodide **7** but rather had structure **17**. The n.m.r. spectrum of the original Mannich base indicated that at least 80% of this material had structure **15** and not **3**. Thus, our earlier failure to prepare the keto acid **12** was not surprising.


15, $n = 1$
16, $n = 2$


17, $n = 1$, $X = I$
18, $n = 2$, $X = I$
19, $n = 2$, $X = TsO$

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[1] (a) This research has been supported in part by Grant No. RG-8761 from the National Institutes of Health; (b) National Science Foundation Predoctoral Fellow, 1963–1964.

[2] (a) R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

[3] E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

[4] (a) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); (b) B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959; (c) R. Jacquier, M. Mousseron, and S. Boyer, *Bull. soc. chim. France*, 1653 (1956).

[5] (a) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (b) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

[6] H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).