Stereochemistry of Reactions of 7-Norbornenyl Anions

R. R. SAUERS AND R. M. HAWTHORNE, JR.

The School of Chemistry, Rutgers, The State University, New Brunswick, New Jersey

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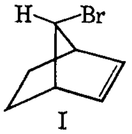
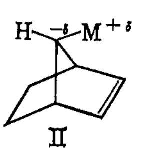
The action of magnesium and lithium on *syn*-7-bromonorbornene has been investigated. Carbonation of the organometallic reagents led to a 2:1 mixture of the corresponding *anti-syn* carboxylic acids. Oxidation of the Grignard reagent led to a 2:1 mixture of *anti-syn*-7-norbornenol.

In view of the striking differences in the products and rates of solvolysis of 7-*syn*- and -*anti*-norbornenyl derivatives,[1] in which partial positive charges are developed at the 7-position, it was of interest to devise experiments which would develop partial negative charge at this position in the norbornene skeleton. Of particular interest were the possibilities of rearrangements or cyclizations and the effects of the double bond on the relative stability of the two isomeric carbanions at C-7.

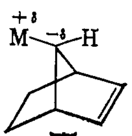
To this end, it was decided to investigate the action of magnesium and lithium on *syn*-7-bromonorbornene[2] (I). This halide should serve as a potential source of both possible anions, II and III, in view of the well-known racemization of optically active halides by these metals.[3] Information on the structure of the organometallic reagents could be gained by determination of the structure of the products formed on carbonation and oxidation reactions.



I



II

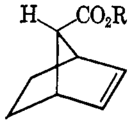


III

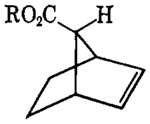
Results and Discussion

Treatment of *syn*-7-bromonorbornene with magnesium in diethyl ether followed by carbonation gave a 40% yield of a mixture of carboxylic acids. The mixture was converted to methyl esters and found (g.l.c.) to contain two components in a ratio of 2:1. Careful fractional distillation gave two isomeric esters, both of which showed strong infrared absorption at *ca.* 14 μ, indicating the presence of *cis* olefins.[4] The nuclear magnetic resonance spectra of both isomers strongly suggested that they were the *syn*- and *anti*-7-carbomethoxynorbornenes, IV and V.

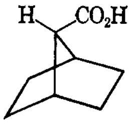
Verification of the presence of the norbornene skeleton in both isomers was accomplished by conversion of both isomers to a known norbornane derivative. Basic hydrolysis of the two esters gave two carboxylic acids, VI and VII, both of which absorbed 1 mole of hydrogen to produce the known[2] 7-carboxynorbornane (VIII). The only remaining problem was to determine which pair of isomers was *syn* and which pair was *anti*.



IV, R = CH_3
VI, R = H

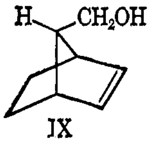


V, R = CH_3
VII, R = H

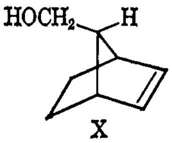


VIII

Several approaches to the problem of assigning the stereochemistry were investigated. The recent interest[5] in the use of infrared spectroscopy to detect intramolecular hydrogen bonding with π-electrons[6] offered the possibility of a relatively simple and unambiguous solution. It would only be necessary to convert the two esters to the corresponding unsaturated alcohols IX and X and determine which of them exhibited intramolecular hydrogen bonding. Only the *syn* isomer (IX) would be expected to show an interaction between the hydroxyl group and the double bond. Unfortunately, both isomers showed only a single hydroxyl absorption and no bonded hydroxyl absorption[7] (see Experimental). Apparently, in the *syn* isomer the conformation of the hydroxyl group in which the hydrogen is close enough to interact with the double bond is sterically unfavorable and the O-H bond is directed away from the double bond.



IX



X

Gas chromatography has also been used recently[8] to assign configurations to isomeric unsaturated alcohols. In the case at hand, it was found that one of the isomers had a retention time of 62 min. and the other a retention time of 83 min. It is tempting to assign structure IX to the more rapidly eluted isomer and structure X to the isomer which has the freer hydroxyl group and thus is bound more strongly to the column. In view of the results of the infrared measurements, however, it did not seem prudent to rely solely on these results for a structure proof.

A more convincing demonstration of the identity of the two series of isomers was provided by some data on

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[1] S. Winstein, A. H. Lewin, and K. C. Pande, *J. Am. Chem. Soc.*, **85**, 2324 (1963); H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); S. Winstein, M. Shatavsky, C. J. Norton, and R. B. Woodward, *ibid.*, **77**, 4183 (1955).

[2] H. Kwart and L. Kaplan, *ibid.*, **76**, 4072 (1954).

[3] See D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962), for a discussion and references.

[4] H. B. Henbest, G. D. Meakins, B. Nicholls, and R. A. L. Wilson, *J. Chem. Soc.*, 997 (1957); E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *ibid.*, 4073 (1956).

[5] I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958); D. S. Trifan, J. L. Weinmann, and L. P. Kuhn, *J. Am. Chem. Soc.*, **79**, 6566 (1957); A. W. Baker and A. T. Shulgin, *ibid.*, **80**, 5358 (1958); P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *ibid.*, **80**, 6691 (1958); R. West, *ibid.*, **81**, 1614 (1959); *cf.* R. Picolini and S. Winstein, *Tetrahedron Letters*, **13**, 4 (1959).

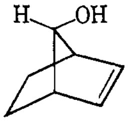
[6] A. M. Buswell, W. H. Rodebush, and R. M. Whitney, *J. Am. Chem. Soc.*, **69**, 770 (1947).

[7] We are indebted to Professor P. von R. Schleyer, Princeton University, for these measurements. Interestingly, the 8,8-dimethyl analog does show internal bonding in the *syn* form (see ref. 9).

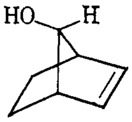
[8] C. H. DePuy and P. R. Story, *Tetrahedron Letters*, **6**, 20 (1959); *cf.* K. Mislow and J. C. Berger, *J. Am. Chem. Soc.*, **84**, 1956 (1962).

the retention times of the esters on a silver nitrate column. The two isomers were cleanly separated on a 2-ft. column of diethylene glycol on Celite. The lower boiling ester had a retention time of 25 min. compared with 59 min. for the higher boiling isomer. Under identical conditions of flow rate and temperature the retention times then were determined on a 2-ft. column packed with Celite which was impregnated with a saturated solution of silver nitrate in diethylene glycol. On the silver nitrate–glycol column the higher boiling ester had about the same retention time as before (50 min.), but the lower boiling ester now had a retention time of 71 min. This striking reversal in the order of retention times allows a definite assignment of configuration to be made. The silver ion would be expected to affect the retention time of only the isomer with the unhindered double bond (*i.e.*, *anti*); therefore the low-boiling ester is V. The fact that the *syn* isomer (IV) has nearly the same retention time on either column serves as a double check on the conclusions, since it excludes the possibility of any specific interaction between the ester functions and silver nitrate.[9]

Oxidation of the Grignard reagent was also investigated. A 33% yield of alcohols was obtained which was shown to contain *syn*-7-norbornenol (XI) and *anti*-7-norbornenol (XII) in a ratio of 28:72.



XI



XII

Preparation of the lithium reagent from *syn*-7-bromonorbornene proved to be erratic. The best results, which could not be duplicated, gave a 54% yield of acids on carbonation. Coincidentally, the *syn–anti* ratio of the acids was also about 1:2.

Rationalization of these results is difficult in view of the uncertainties in the structure of these reagents and the stereochemistry of their reactions.[10] A simple but not completely rigorous explanation of the results would be to assume that the organometallic reagent is produced in a thermodynamically controlled step. Assuming that carbonation proceeds with retention of configuration,[3,10d] two explanations are possible depending on the rates of the carbonation steps *vs.* the rates of interconversion of the *syn* and *anti* isomers. If the carbonation steps are very fast, the product ratio reflects differences in stability of the two anions. If rates of inversion are very fast, the product ratio reflects differences in transition state energies. In either case it appears that the *anti* form is more stable than the *syn* form of the organometallic derivatives. Presumably, this would be a result of the repulsion of the negative charge on the anion by the π-electrons of the double bond.[9] Steric effects do not appear to be responsible for the predominant formation of the *anti* isomer since it was shown that, in the case of the esters, the *syn* ester (IV) is slightly more stable than the *anti* ester (V).

In any case, it is clear that the 7-norbornenyl anion behaves differently from other allylcarbinyl anions. The Grignard reagent from allylcarbinyl chloride, for example, gives products which indicate scrambling of the methylene carbons, presumably *via* the cyclopropylcarbinyl system.[11] Similarly, 5-bromonorbornene yields only nortricyclyl products from Grignard reactions.[12] In the case of the cholesteryl Grignard reagent, no cyclization was observed, the carbonation product being 3β-carboxycholestene.[13] The effect of the double bond on the stereochemistry of this reaction is not known since the Grignard reagent from 3-chlorocholestanes also leads to 3β acid on carbonation.

It was of considerable interest to investigate the solvolytic behavior of *p*-toluenesulfonate derivatives of alcohols IX and X. It was anticipated that products and rates of reaction would be markedly different for the two. In actuality, the *syn* isomer did solvolyze somewhat faster than the *anti* isomer in glacial acetic acid. Of even greater interest is the lack of rearrangement of both systems.[14]

The n.m.r. spectral data of the compounds used in this study are summarized in Table I.

TABLE I

N.M.R. SPECTRAL DATA

Compound (no.)	Proton assignment,[a] τ-values: 2,3	1,4	7	Other
anti-CO_2CH_3 (V)	4.0 (t, 2.0)	7.0	7.7 (m, 1.5)	6.4 (OCH_3)
anti-CO_2H (VII)	4.0 (t, 2.0)	6.9	7.6	
anti-CH_2OH (X)	4.0 (t, 2.0)	7.3		6.8 (CH_2O; d, 8.0)
anti-OH (XII)	4.1 (t, 2.3)	7.5	6.5	
syn-Br(I)	4.05 (s, 0.9)	7.0	6.2	
syn-CO_2CH_3 (IV)	4.05 (t, 1.9)	6.9	7.7 (t, 1.5)	6.5 (OCH_3)
syn-CH_2OH (IX)	4.0 (t, 1.9)	7.3		6.8 (CH_2O; d, 7.0)
syn-CO_2H (VI)	4.0 (t, 2.0)	6.8	7.6	
syn-OH (XI)	4.1 (m)	7.3	6.4	

[a] The multiplicity appears in parentheses followed by the coupling constants, c.p.s. (d = doublet, t = triplet, s = sextet, m = multiplet). In addition, all of these compounds exhibited two sets of multiplets centered at *ca.* τ 8.2 and 9.0, respectively.

There appears to be some long-range coupling between the 7-proton of ester V and the *endo*-5,6 protons. A comparison of the spectra of the *syn* and *anti* esters shows that the 7-proton of the *anti* isomer is coupled to protons in addition to those of the bridgeheads. The olefinic protons cannot be responsible since they appear as triplets in both cases. The doubling of the high-field peaks at *ca.* τ 9.0 strongly suggests that it is the *endo* protons[15] of the ethylene bridge which are responsible.[16]

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[9] The configurations reported herein and in our preliminary communication of this work [R. R. Sauers, *Chem. Ind.* (London), 176 (1960)] have recently been confirmed by R. K. Bly and R. S. Bly [*J. Org. Chem.*, **28**, 3165 (1963)].

[10] (a) R. R. Sauers and G. T. Kwiatkowski, *ibid.*, **27**, 4049 (1962); (b) G. M. Whitesides, F. Kaplan, and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 2167 (1963); (c) G. Fraenkel, D. G. Adams, and J. Williams, *Tetrahedron Letters*, **12**, 767 (1963); (d) H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **83**, 2595 (1961).

[11] M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *ibid.*, **82**, 2646 (1960).

[12] J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

[13] E. J. Corey and R. A. Sneen, *ibid.*, **75**, 6234 (1953); G. Roberts, C. W. Shoppee, and R. J. Stephenson, *J. Chem. Soc.*, 2705 (1954).

[14] These results have been substantiated recently by R. S. Bly, R. K. Bly, and J. E. Goldberg, Abstracts of Papers, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964, p. 6C.

[15] R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

[16] Similar couplings have been observed; see J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963).

Experimental[17]

***syn*- and *anti*-7-Carbomethoxynorbornene (IV and V).**—A solution of 43 g. (0.25 mole) of *syn*-7-bromonorbornene[2] in 300 ml. of dry ether was added over 28 hr. to 20 g. (0.82 g.-atom) of magnesium under 200 ml. of ether an an atmosphere of nitrogen. The temperature was maintained at *ca.* 28° throughout the addition. Dry carbon dioxide was bubbled into the resulting mixture for 30 min. The reaction mixture was poured onto saturated ammonium chloride solution and acidified with cold, concentrated hydrochloric acid. The aqueous layer was extracted three times with ether and the combined ether layers were extracted with potassium hydroxide solution. Nine grams of neutral material remained in the ether phase (probably coupling products). Acidification of the basic extract followed by ether extraction, drying, and evaporation of the ether gave 13.6 g. (40%) of a mixture of the acids VI and VII. Treatment of the mixture with ethereal diazomethane gave a mixture of the esters (12 g.) which was analyzed directly on a 2-ft. column of silicone (SF-96) on Celite at 165°. The ratio of areas under the peaks was approximately 2:1. This mixture of esters was combined with 11.6 g. of esters from another run; the total was fractionated on a 460 × 10 mm. column of glass helices. There was obtained 11.7 g. of the *anti* isomer (b.p. up to 92.5° at 25 mm.) which was contaminated with a small amount of the *syn* isomer, 7.2 g. of the *syn* isomer (b.p. up to 95.5° at 25 mm.) which was contaminated with a small amount of the *anti* isomer, and 1.25 g. of a mixture containing nearly equal amounts of the two isomers. The pure isomers were obtained by redistillation of the first two fractions.

***anti*-7-Carbomethoxynorbornene** (7.5 g.) had b.p. 93–93.5° (30 mm.) and $n^{25}\text{D}$ 1.4705.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.44; H, 8.03.

***syn*-7-Carbomethoxynorbornene** (6.2 g.) had b.p. 95.5° (25 mm.) and $n^{25}\text{D}$ 1.4688.

Anal. Found: C, 70.86; H, 7.86.

The gas chromatography measurements were carried out at 97° and a flow rate of 138 ml. of helium/min. Retention times on a 2-ft. column of 40% diethylene glycol–Celite were for IV, 59 min., and V, 25 min. Retention times on a 2-ft. column of 40% diethylene glycol saturated with silver nitrate–Celite were for IV, 50 min., and V, 71 min.

Equilibration of the esters was carried out by refluxing 1.75 g. of a mixture of esters rich in *anti* isomer for 136 hr. in 12 ml. of methanol in which a small piece of sodium had been dissolved. The recovered esters (1.3 g.) were analyzed on a 5-ft. silicone–Celite column at 165°: *syn*, 55%, and *anti*, 45%. Equilibration of a mixture containing 80% *anti* isomer gave the same mixture of isomers.

***syn*-7-Carboxynorbornene (VI).**—Hydrolysis of 2.0 g. of the *syn* ester in 15 ml. of methanol with 1 g. of potassium hydroxide gave 1.35 g. (74%) of acid VI after purification by sublimation, m.p. 91–96°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.45; H, 7.59.

The benzylisothiouronium salt crystallized as plates from aqueous ethanol and had m.p. 170.5–171.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21. Found: C, 62.84; H, 6.76; N, 9.35.

***anti*-7-Carboxynorbornene (VII).**—Hydrolysis of 2.0 g. of ester V gave 1.2 g. (66%) of acid VII after sublimation, m.p. 70–73°.

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.63; H, 7.37.

The benzylisothiouronium salt crystallized as plates from aqueous ethanol and had m.p. 168.5–169.5°.

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.25; H, 6.84; N, 9.06.

7-Carboxynorbornane (VIII).—Reduction of 0.138 g. (0.0010 mole) of either VI or VII with hydrogen in 10 ml. of methanol in the presence of 20 mg. of 10% palladium-charcoal resulted in quantitative uptake of 0.0010 mole of hydrogen in both cases. The product (0.109 g., 78%) from the *syn* acid melted at 74–75.5° (lit.[2] m.p. 77.5–78.5°) after sublimation. The product from the *anti* acid (0.102 g., 73%) melted at 76–77° after sublimation. A melting point of a mixture of the two products was 74–76.5°. The infrared spectra of the two were identical and corresponded closely with the published data for this compound.[2]

***syn*-7-Methylolnorbornene (IX).**—Reduction of 2.0 g. of ester IV with 0.5 g. of lithium aluminum hydride in 30 ml. of ether gave 1.5 g. (92%) of alcohol IX, b.p. 52° (0.06 mm.), $n^{27}\text{D}$ 1.4935, O–H absorption at 3633 cm.$^{-1}$.[7]

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.62; H, 9.95.

The **tosylate** was prepared from tosyl chloride and pyridine, m.p. 38.5°–39.5° (needles from pentane).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52. Found: C, 64.64; H, 6.50.

***anti*-7-Methylolnorbornene (X).**—Reduction of 2.0 g. of ester V as above gave 1.6 g. (98%) of alcohol X, b.p. 61° (0.25 mm.), $n^{27}\text{D}$ 1.4970, O–H absorption at 3630 cm.$^{-1}$.[7]

Anal. Calcd. for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.12; H, 9.78.

The **tosylate** was prepared from tosyl chloride and pyridine, m.p. 60–61° (needles from pentane).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.73; H, 6.52. Found: C, 64.51; H, 6.39.

The alcohols were analyzed on a 2-ft. column of polyethylene glycol (300) on Celite at 165° and a flow rate of 82 ml./min. Alcohol IX had a retention time of 62 min. and alcohol X had a retention time of 83 min.

Solvolysis of *p*-Toluenesulfonates of Alcohols IX and X.—The tosylates (0.56 g.) were dissolved in 25 ml. of glacial acetic acid which contained 0.20 g. of anhydrous sodium acetate and 1 ml. of acetic anhydride. The mixtures were heated to reflux for 4 days. Addition of ice was followed by ether extraction. Inspection of the infrared spectra of the crude products indicated that the *syn* isomer had solvolyzed completely while the *anti* isomer still showed strong bands associated with the tosylate. The crude acetates were reduced with lithium aluminum hydride in ether and the resulting alcohols were analyzed by gas chromatography (6-ft. Carbowax 20M, 148°). The products in both cases were essentially unrearranged alcohols as shown by retention times and comparative infrared spectra.

Oxidation of the Grignard Reagent.—The reagent was prepared as above from 2.30 g. (0.095 g.-atom) of magnesium and 5.60 g. (0.032 mole) of *syn*-7-bromonorbornene in 75 ml. of ether. The solution was cooled to 0–5° and oxygen was passed through the solution for 1 hr. Addition of saturated ammonium chloride solution was followed by ether extraction. The alcohols (1.16 g., 33%) were separated from the other neutral material (1.9 g.) by chromatography on alumina. The ratio of *syn–anti*-norbornenols was shown to be unaffected by this treatment. The *syn* isomer (28%) was identified by preparation of the phenylurethan derivative, m.p. 125–126° (lit.[18] m.p. 125–126°). The *anti* isomer (72%) was identified by its melting point, 117.5–118.5° (lit.[19] m.p. 118–119°). Infrared absorption at 13.9 (*syn*) and 14.1 μ (*anti*) and the n.m.r. spectra (Table I) also support these structures.

Carbonation of the Lithium Reagent of *syn*-7-Bromonorbornene.—Lithium metal (0.50 g., 0.072 g.-atom) was cut into small pieces and dropped into a flask containing 50 ml. of dry tetrahydrofuran under nitrogen. A few drops of a solution of 5.00 g. (0.029 mole) of *syn*-7-bromonorbornene in 45 ml. of tetrahydrofuran was added to the reaction mixture at room temperature. The reaction flask was then cooled to *ca.* −80° and the remainder of the bromide solution was added slowly over 3 hr. The resulting solution was stirred at −80° for 15 hr. and then poured over Dry Ice to effect carbonation. Addition of saturated ammonium chloride solution destroyed the complexes and was followed by ether extraction. The acidic product was separated by washing the combined ether extracts with potassium hydroxide solution. Acidification yielded 2.15 g. (54%) of a mixture of the *syn* and *anti* acids. Gas chromatographic analysis (see above) indicated a *syn* to *anti* ratio of 33:67.

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[17] Melting points are corrected. Analyses were by G. Robertson, Florham Park, N. J. N.m.r. spectra were run in carbon tetrachloride on a Varian A-60 spectrometer.

[18] S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

[19] S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956).