IODOCYCLIZATION OF 2-ALLYLCYCLOHEXANOLS

Yu. I. Gevaza, I. P. Kupchik, V. I. Staninets,
V. N. Kalinin, and A. G. Bratolyubova

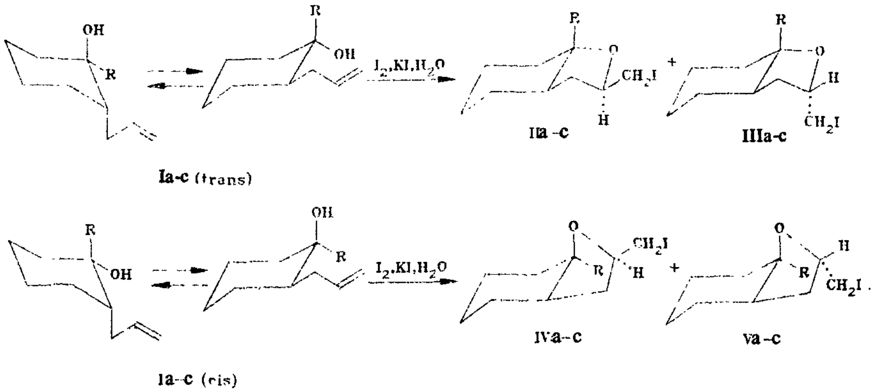
UDC 547.593.211'728:542.944.1'941:
541.632

Iodination of 2-allylcyclohexanol and its 1-methyl and 1-phenyl derivatives gives the corresponding 2-(iodomethyl)octahydrobenzofurans. These are reduced by $LiAlH_4$ to the stereoisomeric 2-methyloctahydrobenzofurans. The rate of iodination of 2-allylcyclohexanols is largely independent of their configuration.

Continuing an examination of the effects of α-substituents on the reactivity of unsaturated alcohols in the electrophilic cyclization reaction [1, 2], we have studied the iodocyclization of the isomeric 2-allylcyclohexanols (Ia-c).

As in the mercuration of 2-allylcyclohexanols [3], iodination of the alcohols (Ia-c) gives, according to their configuration, mixtures of the stereoisomeric octahydrobenzofurans (II-V).

In view of the instability of the 2-(iodomethyl)octahedrobenzofurans (II-V), and the complexity of their PMR spectra, we were unable to determine directly the compositions of the mixture of stereoisomers (II-V).



I—V a R=H; b $R=CH_3$; c $R=C_6H_5$

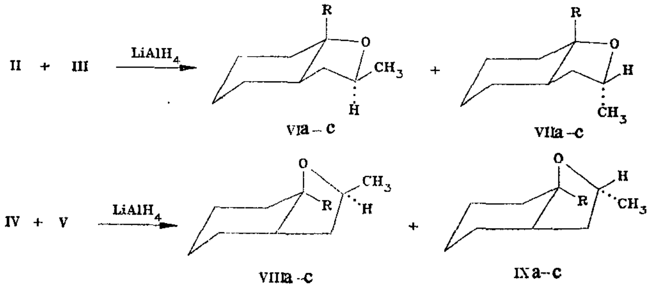
For this reason, the cyclization products (II-V) were reduced with $LiAlH_4$ to the 2-methyloctahydrobenzofurans (VI-IX). The isomer rates of the latter were determined by gas—liquid chromatography.

Iodination of trans-2-allylcyclohexanol (Ia) followed by reduction of the iodocyclization products gave a mixture of the two stereoisomers of 2-methyloctahydrobenzofuran (VIa and VIIa) in a ratio of 1:4. It appears that of the two conformers of the trans-alcohol (Ia) which are present in equilibrium, the conformers with the equatorial—equatorial positions of the reacting groups are iodinated preferentially.

Reduction of the iodination products of cis-2-allylcyclohexanol gives the stereoisomers of 2-methyloctahydrobenzofuran (VIIIa and IXa) in a ratio of 1:5. In this instance it is probably the conformer with the axial hydroxyl group which is iodinated.

Reduction of the iodocyclization products of cis-2-allyl-1-methylcyclohexanol (Ib) affords only the trans-2,7a-dimethyloctahydrobenzofuran (IXb).

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev 252660. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 170-172, February, 1985. Original article submitted June 19, 1983.



VI—IX a R=H; b R=CH$_3$; c R=C$_6$H$_5$

Reduction of the iodination products of the cis-alcohol (Ic) gives a mixture of cis- and trans-2-methyl-7a-phenyloctahydrobenzofuran (VIIIc, IXc) in a ratio of 1:6. In this case, it is the conformer with an axial hydroxyl group which reacts, since the phenyl substituent in the cyclohexanone ring preferentially occupies the equatorial position [4].

From the kinetic and thermodynamic data given in Table 1, it will be seen that the rates of iodination of (Ia) and (Ib) are an order of magnitude greater than those of penten-4-ol and 1-methylpenten-4-ol [1, 2]. The reason for this is evidently that the entropy factor for the cyclization of 2-allylcyclohexanols is more favorable than for substituted penten-4-ols.

The lower rate of iodocyclization of the cyclohexanol (Ic) is due to steric hindrance by the bulky phenyl group to the formation of the cyclic transition state during ring formation.

It has therefore been shown that the iodocyclization of 2-allylcyclohexanols is stereoselective, and results preferentially in the formation of trans-octahydrobenzofurans. The rate of iodination of 2-allylcyclohexnols is greater than that of penten-4-ols and is largely independent of the configuration of the original alcohols, being mainly dependent on the nature of the substituent in the 1 position.

EXPERIMENTAL

The IR spectra were recorded in a UR-20 spectrophotometer; the PMR spectra, on a Tesla BS-487B (80 MHz) instrument in CCl$_4$ (internal standard TMS). The purity and isomeric composition of the alcohols and the products were determined on a Tsvet-4 chromatograph with a katharometer detector, column length 3 m, internal diameter 3 mm, sorbent 10% Tween-80 on Chromaton N-AW-DMCS (0.25–0.315 mm). Evaporator temperature 250°C, column temperature 140-180°C. The cis-alcohol (Ib) was isolated on a PAKhV-02 preparative chromatograph. Column combination: length 2 m, internal diameter 10 mm, and length 7 m, internal diameter 6 mm; sorbent TTsEP on Chromaton N-AW (silanized with 20% dimethylchlorosilane); column temperature 115°C; carrier gas (nitrogen) flow rate 60 ml/min.

2-Allylcyclohexanol (Ia) (35% cis and 63% trans) was obtained by reducing 2-allylcyclohexanone with LiAlH$_4$ [3].

cis-2-Allylcyclohexanol was isolated by chromatography of the mixture of stereoisomers on alumina, n_D^{20} 1.4755 [3].

trans-2-Allylcyclohexanol was synthesized from 1,2-epoxycyclohexane and allylmagnesium bromide, bp 95–97° (15 mm); n_D^{20} 1.4772 [3].

2-Allyl-1-methylcyclohexanol (Ib) (84% cis and 16% trans) was obtained by the Grignard synthesis from 2-allylcyclohexanone and methyl iodide, yield 43%, bp 66-68°C (2 mm): n_D^{20} 1.4784 [5]. cis-2-Allyl-1-methylcyclohexanol was isolated by preparative chromatography from the mixed isomers, n_D^{20} 1.4770.

cis-2-Allyl-1-phenylcyclohexanol (Ic) was obtained by the Grignard reaction from 2-allylcyclohexanone and bromobenzene, yield 46%, bp 108–110° (2 mm); n_D^{20} 1.5380, d_4^{20} 1.0045. Found: C 83.0; H 9.1%; MR$_D$ 67.4. C$_{15}$H$_{20}$O. Calculated: C 83.3; H 9.3%; MR$_D$ 67.0.

Iodination of the alcohols (Ia-c) was carried out as for the iodination of hex-4-en-2-ol [1, 2]. The iodomethyl derivatives were reduced with LiAlH$_4$ in dry ether.

TABLE 1. Kinetic and Activation Parameters for the Iodocyclization of 2-Allylcyclohexanols

Compound	R	$k_{20°}$, liters/mole·sec	$E^{\neq}$, kJ/mole	$-\Delta S^{\neq}$, J/mole °K	lg *A*
cis -Ia	H	27,5±1,5	49,7±2,1	54,8±7,1	38,5±1,6
trans -Ia	H	25,9±1,5	51,8±2,1	48,1±7,1	40,1±1,5
cis -Ib	CH_3	67,0±2,0	45,1±2,5	63,5±8,4	35,5±1,9
cis -Ic	C_6H_5	2,3±0,2	38,0±1,0	116,3±3,5	29,5±1,1

2-(Iodomethyl)octahydrobenzofuran (IIa + IIIa) was obtained by iodinating the trans-alcohol (Ia), yield 92%, bp 95° (2 mm); n_D^{20} 1.5448. Found: C 40.7; H 5.7; I 48.1%. $C_9H_{15}IO$. Calculated: C 40.6; H 5.7; I 47.7%.

2-(Iodomethyl)octahydrobenzofuran (IVa + Va) was obtained by iodocyclization of the cis-alcohol (Ia), yield 90%, bp 93–95° (2 mm); n_D^{20} 1.5445. Found I 48.0%. $C_9H_{15}IO$. Calculated: I 47.7%.

2-(Iodimethyl)-7a-methyloctahydrobenzofuran (IVb + Vb) was synthesized by iodination of the cis-alcohol (Ib), yield 92%, bp 108–110° (2 mm)n_D^{20} 1.5361. Found: C 42.6; H 6.0; I 45.5%. $C_{10}H_{17}IO$. Calculated: C 42.8; H 6.1; I 45.3%.

2-(Iodomethyl)-7a-phenyloctahydrobebzofuran (IVc + Vc) was obtained by iodinating the cis-alcohol (Ic), yield 91%, mp 63°C (from methanol). Found: C 52.8; H 5.5; I 37.2%. $C_{15}H_{10}IO$. Calculated: C 52.6; H 5.6; I 37.1%.

2-Methyloctahydrobenzofuran (VIa + VIIa) was obtained by reducing 2-(iodomethyl)octahydrobenzofuran (IIa + IIIa). Ratio of cis to trans isomers, 1:4. Yield 56%, bp 75–78° (17 mm), n_D^{20} 1.4610 [3]. PMR spectrum: 1.22 (3H, d, J = 6.5 Hz, CH_3), 3.08 (1H, m, CH–O); 4.10 ppm (1H, m, $CH–CH_3$).

2-Methyloctahydrobenzofuran (VIIIa + IXa) was prepared by reducing the mixture of (IVa) + (Va). Ratio of cis to trans isomers, 1:5. Yield 58%, bp 74–76° (16 mm); n_D^{20} 1.4605. PMR spectrum: 1.23 (3H, d, J = 6.5 Hz, CH_3), 3.10 (1H, m, CH–O), 4.18 ppm (1H, m, $CH–CH_3$).

trans-2,7a-Dimethyloctahydrobenzofuran (VIIIb + IXb) was synthesized by reducing the mixture (IVb + Vb). Yield 62%, bp 56–58° (2 mm); n_D^{25} 1.4590. PMR spectrum: 1.16 (3H, d, J = 6.2 Hz, $CH–CH_3$), 1.14 (3H, d, J = 8.5 Hz, $CH_3–C–CH_3$), 4.08 ppm (1H, m, $CH–CH_3$), Found: C 77.4; H 11.7%. $C_{10}H_{18}O$. Calculated: C 77.9; H 11.8%.

2-Methyl-7a-phenyloctahydrodihydrobenzofuran (VIc + VIIb) was obtained by reducing the mixture (IIc + IIIc). Ratio of cis to trans isomers, 1:6. Yield 60%, mp 142-144°C. PMR spectrum: 1.18 (3H, d, J = 6.5 Hz, $CH–CH_3$), 4.38 ppm (1H, m, $CH–CH_3$). IR spectrum: 1090 (C–O–C), 1585 cm^{-1} (C_6H_5). Found: C 82.5; H 8.6%. $C_{15}H_{20}O$. Calculated: C 83.3; H 9.3%.

The kinetic measurements (Table 1) were carried out as described in [6], in a phosphate buffer over the pH range 6.8–7.5, concentrations of alcohols (Ia-c) and iodine 1.25–5.0·10^{-3}, and of potassium iodide 0.03–1.0 mole/liter. The rate of iodocyclization of the cyclohexanols (Ia-c) is given by the kinetic equation $-d[I_2]/dt = k_2[HC]\cdot[I_2]$, where [HC] is the analytical concentration of the unsaturated alcohol, and $[I_2]$ the concentration of molecular iodine.

LITERATURE CITED

1. Yu. I. Gevaza, I. P. Kupchik, and V. I. Staninets, Khim. Geterotsikl. Soedin., No. 1, 32 (1981).
2. Yu. I. Gevaza, I. P. Kupchik, M. Yu. Kornilov, and V. I. Staninets, Ukr. Khim. Zh., 48, 72 (1982).
3. V. Speziale, M. Amat, and A. Lattes, J. Het. Chem., 13, 349 (1976).
4. V. M. Potapov, Stereokhimiya, Khimiya, Moscow (1976).
5. J. Colonge and F. Colomby, Bull. Soc. Chim. France, No. 2, 241 (1951).
6. V. I. Staninets and Yu. I. Gevaza, Ukr. Khim. Zh., 39, 589 (1973).