NEW METHOD FOR THE REDUCTION OF BENZOFURANS

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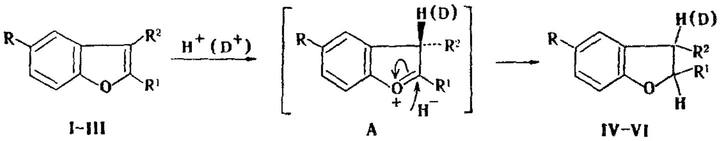
A new method for the reduction of benzofurans with potassium and sodium borohydrides in CF_3COOH was developed. It is shown by gas–liquid chromatography and PMR spectroscopy that mixtures (∿2:3) of the cis and trans isomers of dihydro derivatives of benzofuran are formed in the reduction. The mechanism of the reduction includes intermolecular transfer of a hydride ion to the protonated form of the benzofuran.

The problem of the smooth and unambiguous preparative reduction of benzofurans to 2,3-dihydrobenzofurans by accessible reagents has not yet been completely solved (for example, see [1, 2]), whereas the direct conversion of benzofurans to 2,3-dihydrobenzofurans in many cases could be the most efficient method for the synthesis of the latter, particularly in the search for biologically active substances; one must take into account the fact that the 2,3-dihydrobenzofuran fragment is included in the structure of a number of effective pharmacological agents, including morphine.

In contrast to indoles, benzofurans have not been heretofore reduced by binary hydrides. Of the reducing agents of the hydride type, triethylsilane in trifluoroacetic acid has been used [3].

We have developed a new method for the reduction of benzofurans by potassium and sodium borohydrides in solution in CF_3COOH in the case of I-III.

The reduction of benzofurans proceeds via a mechanism involving intermolecular transfer of a hydride ion to the C_2 atom of the protonated form of the benzofuran compounds (A) (see [4-6] for information regarding the structures of the compounds formed in the reaction of alkali metal borohydrides with CF_3COOH) via the scheme:



I, IV $R=H$, $R^1=C_2H_5$, $R^2=CH_3$; II, V $R=H$, $R^1+R^2=(CH_2)_4$; III, VI $R=HO$, $R^1+R^2=(CH_2)_4$

This mechanism is confirmed by the formation of the β-deuterated benzofuran system of VI in the case of reduction of benzofuran III in CF_3COOD.

The reduction of I leads to a mixture (∿2:3) of the cis and trans isomers of dihydro derivative IV.

The establishment of the configurations of 2,3-disubstituted 2,3-dihydrobenzofurans is not an easy task. To accomplish this we used PMR spectroscopic methods (see, for example, [7-16]), sometimes in conjunction with gas–liquid chromatography (GLC) (see, for example, [1, 10, 16]) or with chemical transformations [7, 10-12]; roentgenoscopy [7-14] was used in individual studies.

Contradictory data exist with respect to the spin–spin coupling constants (SSCC) of the protons attached to the C_2 and C_3 atoms in cis- and trans-2,3-disubstituted 2,3-dihydrobenzofurans. It is more often assumed that the SSCC are considerably greater (6.5-10.8 Hz) for the cis isomers than for the trans forms [7, 10, 12-14, 17].

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We have established that the J_{2-3} values of the cis and trans isomers of IV differ little from one another (8.0 ± 0.2 and 7.5 ± 0.2 Hz, respectively); this is in agreement with the data on the virtually identical SSCC for 2,3-dimethyl-2,3-dihydrobenzofuran [16] (8.2 Hz) and 2-phenyl-3-methyl-2,3-dihydrobenzofurans [11] (8 Hz).

As in the case of other 2,3-dialkyl-2,3-dihydrobenzofurans [10, 14-16], the assignment of the isomers of IV to the cis and trans series can be realized by a joint examination of the data from GLC and the PMR spectra. As compared with the trans isomer, the cis isomer has a longer retention time in GLC analysis, a weaker-field location of the signals of the protons attached to the C_2 and C_3 atoms, and a greater chemical shift of the signal of the protons attached to the $3\text{-}CH_3$ group.

Hexahydrodibenzofurans II and VI are stereochemically homogeneous (according to the GLC and PMR spectral data) and are probably the cis isomers.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 or C_6D_6 were recorded with Varian HA-100 and T-60 spectrometers with tetramethylsilane as the internal standard; the SSCC were determined in experiments with double resonance with respect to the methyl and methylene groups. Analysis by GLC was carried out with an LKhM-89 chromatograph with a column (l = 30 m, d = 2 mm) filled with SE-30, nitrogen as the carrier gas, a temperature of 100°C, and a pressure of 0.4 atm.

2-Ethyl-3-methylbenzofuran (I). A mixture of 15 g (0.11 mole) of O-phenylhydroxylamine hydrochloride and 12 g (0.14 mole) of diethyl ketone was refluxed in 100 ml of a 13% alcohol solution of hydrogen chloride for 2 h, after which it was poured into water, and the aqueous mixture was extracted with ether. The ether solution was washed with 5% potassium hydroxide solution and water and dried with magnesium sulfate. The solvent was removed by distillation, and the residue was distilled *in vacuo* to give 10.5 g (66%) of I with bp 94-96°C (14 mm) and n_D^{20} 1.5449. Found: C 82.8; H 7.2%. $C_{11}H_{12}O$. Calculated: C 82.5; H 7.2%. According to the data in [18], this compound had bp 110-111.5°C (15 mm) and n_D^{20} 1.5440.

1,2,3,4,4a,9b-Hexahydrodibenzofuran (V). A 3.7-g (0.07 mole) sample of potassium borohydride was added gradually in the course of 2 h to a mixture of 3 g (0.017 mole) of II [19] in 30 ml of trifluoroacetic acid (TFA), after which the mixture was poured into water, and the aqueous mixture was extracted with ether. The ether solution was washed with 5% potassium hydroxide solution and water and dried with magnesium sulfate. The solvent was removed by distillation, and the residue was distilled to give 2 g (67%) of V with bp 119-120°C (12 mm). Found: C 82.5; H 8.1%. $C_{12}H_{14}O$. Calculated: C 82.7; H 8.1%. According to the data in [20], this compound had bp 140-142°C (20 mm).

8-Hydroxy-1,2,3,4,4a,9b-hexahydrodibenzofuran (VI). A 6.5-g (0.2 mole) sample of potassium borohydride was added in small portions in the course of 3 h to a mixture of 5 g (0.027 mole) of III [21] in 25 ml of TFA, after which the mixture was poured into water, and the aqueous mixture was extracted with ether. The ether solution was washed with sodium bicarbonate and dried with magnesium sulfate. The solvent was removed by distillation to give 2.6 g (52%) of VI with mp 63-65°C (from heptane). PMR spectrum (in CCl_4: 3.0 (m, H_{9b}; this signal was absent in a sample deuterated in the 9b position) and 4.5 ppm (m, H_{4a}). Found: C 75.7; H 7.3%. $C_{12}H_{14}O_2$. Calculated: C 75.8; H 7.4%.

2-Ethyl-3-methyl-2,3-dihydrobenzofuran (IV). Compound V was similarly obtained from 8.5 g (0.056 mole) of I and 6 g (0.11 mole) of potassium borohydride after distillation of the residue *in vacuo* to give 5 g (63%) of a mixture of cis and trans isomers of IV with bp 104-106°C (14 mm). Found: C 81.8; H 8.5%. $C_{11}H_{14}O$. Calculated: C 81.4; H 8.7%.

The reaction product prior to and after vacuum distillation contained more of the trans isomer (according to data from GLC and the PMR spectra, the ratios of the cis and trans isomers were 2:3 and 1.9:3.1, respectively). PMR spectrum (in CCl_4): 0.86 (q, $^3J_{3\text{-}H\text{-}CH_3}$ = 7.2 Hz, $3\text{-}CH_3$ in cis-IV), 1.0 (q, $^3J_{3\text{-}H\text{-}CH_3}$ = 7.0 Hz, $3\text{-}CH_3$ in trans-IV), 2.8 (m, 3-H in trans-IV), 3.0 (m, 3-H in cis-IV), 4.0 (dt, $^3J'_{2,3}$ = 7.6, $^3J''_{2\text{-}H\text{-}CH_2}$ = 6.2 Hz, 2-H in trans-IV; in solution in C_6D_6: J' = 7.5 and J'' = 5.5 Hz), and 4.28 ppm (dt, $^3J'_{2,3}$ = 7.8, $^3J''_{2\text{-}H\text{-}CH_2}$ = 5.1 Hz in cis-IV; in solution in C_6D_6: J' = 8.0, J'' = 5.0 Hz).

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