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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Synthesis of Chiral 1,3-Dihydroisobenzofurans (Phthalans) Containing Functional Substituents in the 1-Position

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Abstract—Chiral 3-methyl-1,3-dihydroisobenzofurans (phthalans) having a carbonyl or α-hydroxybenzyl group in position *1* were synthesized by cyclization of the corresponding trimethyl[(S)-1-phenylethyl]ammonium iodides. The configuration of the chiral centers in the products was determined by X-ray analysis.

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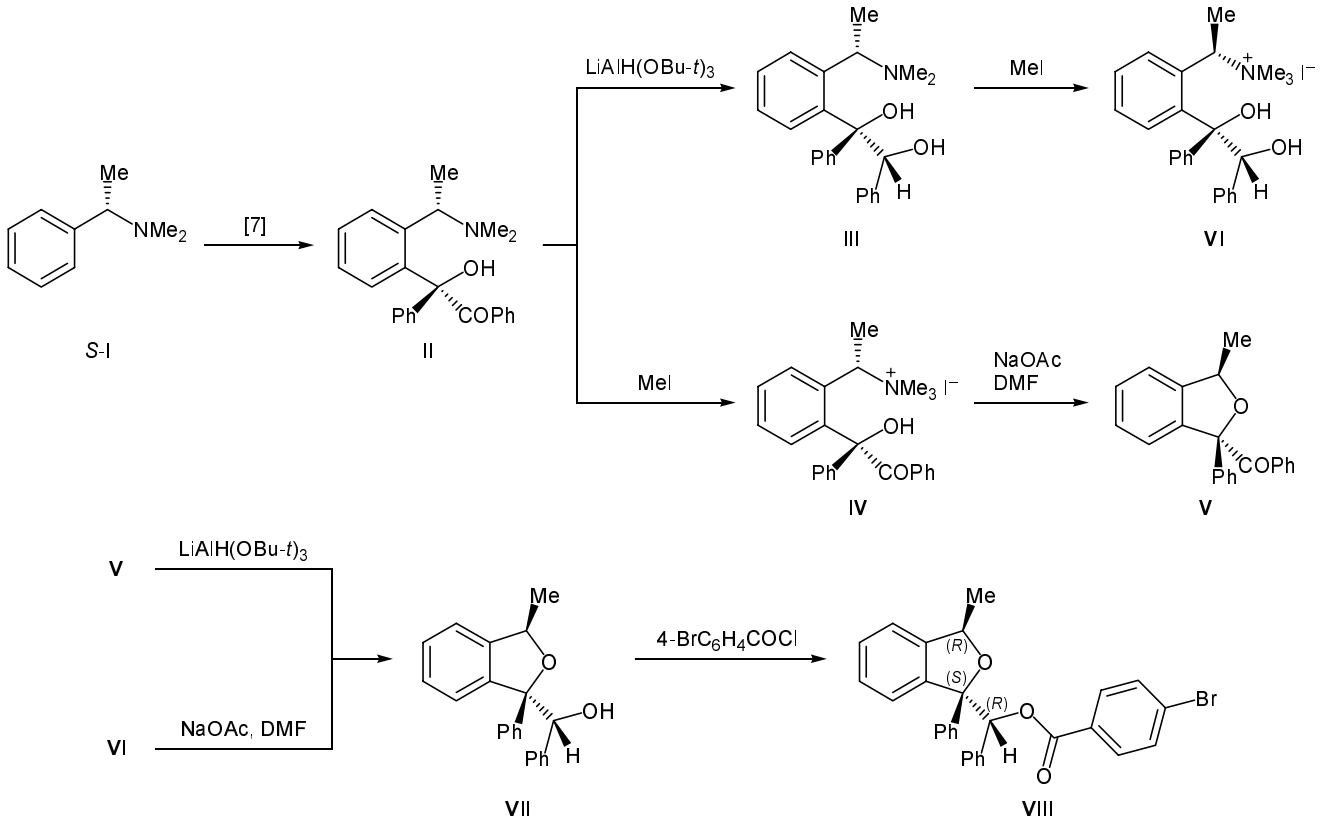
In the preceding communications [1, 2] we described the synthesis of chiral phthalans via cyclization of δ-amino alcohols derived from *N*,*N*-dimethyl-(*S*)-(–)-1-phenylethanamine (**I**) via *ortho*-lithiation followed by condensation with aryl ketones [3, 4]. We presumed that the reaction occurs as intramolecular S_N2 substitution which should be accompanied by inversion of configuration of the chiral center in the initial amine. However, the obtained products had no functional groups; therefore, their subsequent utilization was strongly restricted. On the other hand, compounds possessing a phthalan fragment may be interesting from the practical viewpoint; some phthalan derivatives are known to exhibit biological activity [5]. Published data on chiral phthalans are very limited [6].

With a view to synthesize phthalan derivatives having a functional substituent in the 1-position we used as starting compounds trifunctional compounds with a known configuration, namely amino hydroxy ketone **II** [7] and amino diol **III** [8] which were prepared previously from amine **I** (Scheme 1). Quaternary ammonium iodide **IV** obtained from compound **II** underwent cyclization on heating in dimethylformamide in the presence of sodium acetate to give phthalan **V** having a benzoyl group on C^1. The structure of product **V** was confirmed by the ^{1}H NMR and IR spectra and X-ray diffraction data (see table, Fig. 1). As follows from the X-ray diffraction data, the C^1 and C^3 atoms in molecule **V** have different configurations; this means that the cyclization was accompanied by inversion of configuration of one of the chiral centers, presumably at the ammonium group as we presumed in [1]. It was impossible to determine the absolute configuration of **V**, for the error in the determination of the Flack parameter [9] exceeded the parameter itself (see table).

Amino diol **III** contains two hydroxy groups capable of being involved in cyclization to give five- or six-membered oxygen-containing heteroring. Heating of quaternary ammonium iodide **VI** derived from amino diol **III** in dimethylformamide in the presence of sodium acetate gave phthalan **VII** having a side-chain hydroxy group as a result of closure of five-membered ring. The structure of **VII** was confirmed by the ^{1}H NMR spectrum. Phthalan **VII** was converted into *p*-bromobenzoyl derivative **VIII**, and the absolute configuration of the C^1 and C^3 atom in the latter was determined by X-ray analysis. The X-ray diffraction data confirmed the formation of five-membered ring in the cyclization of iodide **VI**. The configurations of the C^1 and C^3 chiral centers as *S* and *R*, respectively, were determined in two ways: (1) relative to the (*R*)-chiral center in the initial diol, which is not involved in the cyclization; and (2) from anomalous X-ray scattering due to the presence of a heavy bromine atom in molecule **VIII** {the Flack parameter was equal to 0.00(2);

Scheme 1.



see table, Fig. 2) [9]}. We thus confirmed that replacement of the dimethylamino group in δ-hydroxy ammonium iodides derived from amine **I** is accompanied by inversion of configuration, i.e., it occurs according to the S_N2 mechanism.

Phthalane **VII** was also synthesized by reduction of benzoylphthalan **V** with sodium tetrahydridoborate and lithium tris(*tert*-butoxy)hydridoaluminate. In the first case, the reaction was not stereoselective, and a 1 : 1 mixture of disatereoisomeric α-hydroxybenzyl-substi-

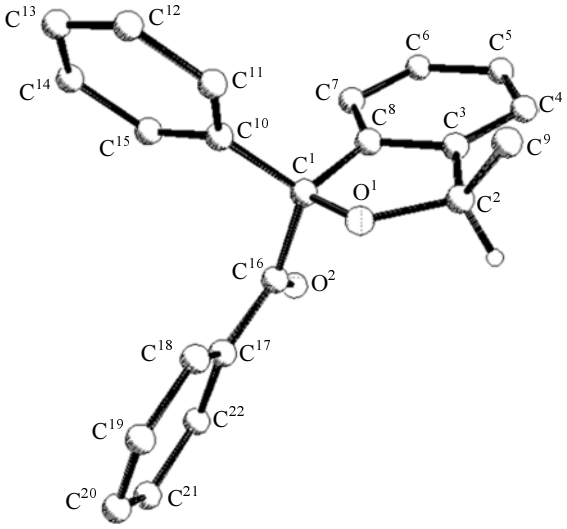


Fig. 1. Structure of the molecule of (1*S*,3*R*)-1-benzoyl-3-methyl-1-phenyl-1,3-dihydroisobenzofuran (**V**) according to the X-ray diffraction data.

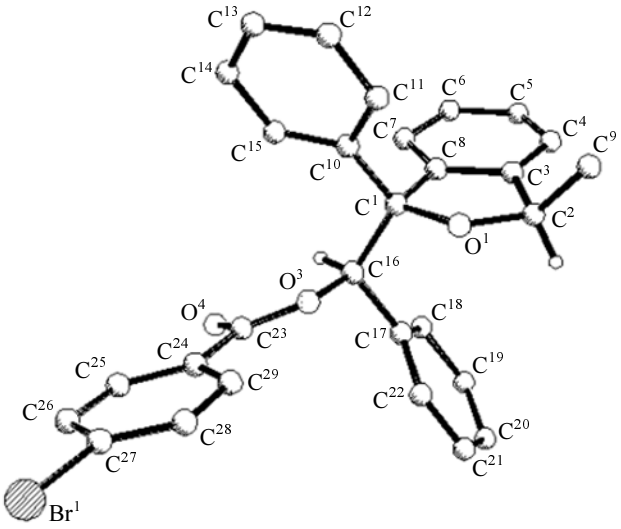


Fig. 2. Structure of the molecule of (*R*)-[(1*S*,3*R*)-3-methyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl]phenylmethyl 4-bromobenzoate (**VIII**) according to the X-ray diffraction data.

Crystallographic data and parameters of X-ray diffraction experiments for compounds **V** and **VIII**

Parameter	**V**	**VIII**
Formula	$C_{22}H_{18}O_2$	$C_{29}H_{23}BrO_3$
Molecular weight	314.36	499.38
Diffractometer	Siemens P3/PC	Syntex $P2_1$/PC
Wavelength λ, Å	0.71073	0.71073
Temperature, K	293(2)	195(2)
Crystal system	Monoclinic	Rhombic
Space group	*C*2	$P2_12_12_1$
a, Å	15.511(3)	9.862(2)
b, Å	8.653(2)	12.108(2)
c, Å	12.754(3)	20.135(4)
α, deg	90	90
β, deg	90.92(3)	90
γ, deg	90	90
V, Å^3	1711.6(6)	2404.3(8)
Z	4	4
d_{calc}, g/cm^3	1.220	1.380
θ range, deg	3.10–26.06	1.96–28.05
Number of reflections	3599	3269
Number of independent reflections	1803	3267
Completeness of data acquisition	99.7%	99.4%
Refinement procedure	Full-matrix least squares procedure (with respect to F^2)	Full-matrix least squares procedure (with respect to F^2)
Number of reflections/limits/parameters	1803/1/217	3267/0/299
S factor (F^2)	1.02	1.09
R factor [$I > 2\sigma(I)$]	$R_1 = 0.0359$ $wR_2 = 0.0934$	$R_1 = 0.0605$ $wR_2 = 0.1377$
R factor (all reflections)	$R_1 = 0.0451$ $wR_2 = 0.0975$	$R_1 = 0.0857$ $wR_2 = 0.1479$
Absolute structure parameter	–0.6(16)	0.00(2)
Δρ, *e*/Å^3, max/min	0.148/–0.155	0.667/–1.108

tuted phthalans was obtained. The reduction with $LiAlH(BuO\text{-}t)_3$ was strictly stereoselective, and the product was identical to that obtained by cyclization of dihydroxy ammonium iodide **VI**.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films or dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian XL-400 instrument (400 MHz) using tetramethylsilane as internal reference. The conditions of X-ray diffraction experiments and crystallographic parameters of compounds **V** and **VIII** are collected in table. The specific optical rotations were measured on a VNIEKIPRODMASh EPO 1A polarimeter. The elemental compositions were determined at the Microanalysis Laboratory, Faculty of Chemistry, Moscow State University.

(1*S*)-1-{2-[(1*S*)-1-Hydroxy-2-oxo-1,2-diphenylethyl]phenyl}ethyl(trimethyl)ammonium iodide (IV). Methyl iodide, 0.04 mol, was added dropwise to a solution of 0.01 mol of amino alcohol **II** in 50–100 ml of anhydrous acetone under stirring and cooling to 0°C. If necessary, an additional portion of methyl iodide, 0.04 mol, was added after 12 h. The progress of the reaction was monitored by TLC (benzene–acetone, 6:1), following disappearance of the initial amino alcohol. The product was filtered off and washed with anhydrous diethyl ether. Yield 90%, mp 176°C (decomp.), $[\alpha]_D = -205.0°$ (*c* = 2, EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.02 d (3H, CHC**H**$_3$), 3.20 s (9H, NMe_3), 5.38 q (1H, C**H**CH_3), 5.65 br.s (1H, OH), 7.01–8.05 m (14H, H_{arom}).

(1*S*,2*R*)-1-{2-[(1*S*,2*R*)-1,2-Dihydroxy-1,2-diphenylethyl]phenyl}ethyl(trimethyl)ammonium iodide (VI) was synthesized in a similar way from amino alcohol **III**. Yield quantitative, mp 200°C (decomp.), $[\alpha]_D = -70.0°$ (*c* = 2, EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05 d (3H, CHC**H**$_3$), 3.25 s (9H, NMe_3), 5.55 q (1H, C**H**CH_3), 6.25 s (1H, C**H**OH), 6.85 br.d (2H, OH), 7.20–8.10 m (14H, H_{arom}).

(1*S*,3*R*)-1-Benzoyl-3-methyl-1-phenyl-1,3-dihydroisobenzofuran (V). A solution of 0.01 mol of compound **IV** and 0.05 mol of fused sodium acetate in 50–100 ml of freshly distilled DMF was heated for 10 h under reflux. The solvent was distilled off under slightly reduced pressure, and the residue was treated with a 2 N solution of sodium hydroxide and extracted with diethyl ether. The extract was washed with 2 N hydrochloric acid (to remove the corresponding amino alcohol) and water and dried over $MgSO_4$, and the solvent was distilled off. Yield 70%, mp 155°C (from EtOH), $[\alpha]_D = -361.1°$ (*c* = 1, CH_2Cl_2). IR spectrum: ν(CO) 1680 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm:

1.69 d (3H, CHC**H**$_3$), 5.37 q (1H, C**H**CH$_3$), 7.20–7.90 m (14H, H$_{arom}$). Found, %: C 84.29; H 5.74. $C_{22}H_{18}O_2$. Calculated, %: C 84.09; H 5.73.

(*R*)-[(1*S*,3*R*)-3-Methyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl]phenylmethanol (VII) was synthesized in a similar way from ammonium iodide **VI**. The product was isolated by column chromatography on silica gel (Silicagel 60, benzene–acetone, 6:1). Yield 78%, oily substance, R_f 0.4, $[\alpha]_D$ = 91.6° (*c* = 1, EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 d (3H, CHC**H**$_3$), 4.80 q (1H, C**H**CH$_3$), 5.40 d (1H, C**H**OH), 7.00 d (1H, OH), 7.05–7.80 m (14H, H$_{arom}$).

Anhydrous *tert*-butyl alcohol, 23.23 mmol, was slowly added dropwise to a suspension of 7.74 mmol of lithium tetrahydridoaluminate in 25 ml of anhydrous diethyl ether at 0°C under argon. The mixture was stirred for 30 min, and 1.94 mmol of compound **V** in 50 ml of diethyl ether was added. The progress of the reaction was monitored by TLC (benzene–acetone, 6:1; R_f 0.4). The reduction was complete in 12 h. The mixture was then treated with 30 ml of water on cooling, saturated with sodium chloride, and extracted with diethyl ether. The extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to column chromatography on silica gel (Silicagel 60, benzene–acetone, 6:1). Yield 85%, oily substance, R_f 0.4, $[\alpha]_D$ = 91.4° (*c* = 1, EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 d (3H, CHC**H**$_3$), 4.80 q (1H, C**H**CH$_3$), 5.40 d (1H, C**H**OH), 7.00 d (1H, OH), 7.05–7.80 m (14H, H$_{arom}$).

(*R*)-[(1*S*,3*R*)-3-Methyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl]phenylmethyl 4-bromobenzoate (VIII). *p*-Bromobenzoyl chloride, 0.74 mmol, was added to a mixture of 0.74 mmol of compound **VII** and 3 ml of freshly distilled pyridine. The mixture was heated until it became homogeneous, kept for 18 h, poured onto ice, and neutralized to pH <7 by adding concentrated hydrochloric acid in a dropwise fashion. The mixture was extracted with diethyl ether, the extract was washed with a 2 N solution of sodium hydroxide and water and dried over $MgSO_4$, and the solvent was distilled off. Yield 50%, mp 192°C (from EtOH), $[\alpha]_D$ = 205° (*c* = 0.5, EtOAc). IR spectrum: ν(CO) 1710 cm^{-1}. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.50 d (3H, CHC**H**$_3$), 4.75 q (1H, C**H**CH$_3$), 6.60 s (1H, OCH), 6.90–7.80 m (14H, H$_{arom}$).

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