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Abstract

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SYNTHESIS OF THE HEXAHYDRO-(3,4 : 3 ,4)-FUROFURAN SYSTEM–THE BASIC NUCLEUS OF NATURAL RESINOLS

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The heterocyclic fused hexahydro-(3,4 : 3 ,4)-furofuran system forms the basis of a certain group of natural substances, the so-called phenolic resinols or lignans.

Among such compounds are: pinoresinol ((I), $R_1 = CH_3O$; $R_2 = OH$; $R_3 = H$), eudesmin ((I), $R_1 = R_2 = CH_3O$; $R_3 = H$), sesamin $\left((I),\ R_1R_2 = H_2C\begin{matrix}/O-\\ \backslash O-\end{matrix};\ R_3 = H\right)$, and syringaresinol ((I), $R_1 = R_3 = CH_3O$; $R_2 = OH$).

structural formula (I)

This series of substances is of definite interest from the standpoint of biological action; in particular, one representative of these compounds, sesamin, exhibits bacteriostatic activity toward pathogenic bacteria, especially toward *Mycobacterium tuberculosis*, the growth of which sesamin inhibits at a dilution of $1 : 10^{-7}$ ([1,2]). Sesamin also considerably enhances the insecticidal action of pyrethrin ([3,4]).

It was of interest to determine the possibility of obtaining by synthesis the basic nucleus of the resinols (I)–2,5 -diphenylhexahydro-(3,4 : 3 ,4)-furofuran ($R_1 = R_2 = R_3 = H$), since in nature only aromatic derivatives of hexahydrofurofurans are encountered, having substituents in the benzene ring, and the transition from these to compounds with other substituents is difficult.

For the synthesis of 2,5 -diphenylhexahydro-(3,4 : 3 ,4)-furofuran we chose scheme (A), which is also applicable to compounds substituted in the benzene nuclei, and by this scheme carried out the synthesis both of 2,5 -diphenylhexahydro-(3,4 : 3 ,4)-furofuran and of its structural isomer, the 2,5-diphenyl-substituted compound.

$$\underset{\substack{C_6H_5-CO-CH-COOC_2H_5\\ |\\ C_6H_5-CO-CH-COOC_2H_5}}{\text{(II)}} \xrightarrow{LiAlH_4} \underset{\substack{C_6H_5-CH(OH)-CH-CH_2OH\\ |\\ C_6H_5-CH(OH)-CH-CH_2OH}}{\text{(IV)}} \xrightarrow{-2H_2O} \text{(VI)}$$

$$\underset{\substack{C_6H_5-CO-CH-COOC_2H_5\\ |\\ C_2H_5OOC-CH-CO-C_6H_5}}{\text{(III)}} \xrightarrow{LiAlH_4} \underset{\substack{C_6H_5-CH(OH)-CH-CH_2OH\\ |\\ HOH_2C-CH-CH(OH)-C_6H_5}}{\text{(V)}} \xrightarrow{-2H_2O} \text{(VII)}$$

(A)

The starting material in the synthesis of 2,5 - and 2,5-diphenylhexahydro-(3,4 : 3 ,4)-furofurans is dibenzoylsuccinic ester, obtained by Knorr' s method ([5]) in the form of two isomers: the β ester (m.p. 128-130°) and the γ ester (m.p. 74-78°).

After reduction of these compounds to the corresponding tetrahydric alcohols, formation of isomeric tetraols was to be expected. Elimination of water from the latter leads to 2,5 -diphenylhexahydro-(3,4 : 3 ,4)-furofuran and, respectively, 2,5-diphenylhexahydro-(3,4 : 3 ,4)-furofuran.

Reduction of the β isomer of dibenzoylsuccinic ester with lithium aluminum hydride in ether at 0° led to the preparation of β-2,3-di-(α-hydroxybenzyl)-butanediol-1,4, designated β-tetraol (IV), in a yield of 50% based on β-dibenzoylsuccinic ester. Prisms from dichloroethane, m.p. 137-138.5°.

$C_{18}H_{22}O_4$.	Found, %:	C 71.82; H 7.58; OH 22.25
	Calculated, %:	C 71.52; H 7.28; OH 22.50

Tetraacetate, m.p. 112-113°.

$C_{26}H_{30}O_8$.	Found, %:	C 65.98; H 6.47; $COCH_3$ 31.8
	Calculated, %:	C 66.38; H 6.38; $COCH_3$ 36.6

Tetrabenzoate, m.p. 258-259°.

$C_{46}H_{38}O_8$.	Found, %:	C 76.44; H 5.68
	Calculated, %:	C 76.88; H 5.29

The γ-dibenzoylsuccinic ester was reduced with lithium aluminum hydride under the same conditions as the β isomer. γ-2,3-Di-(α-hydroxybenzyl)-butanediol-1,4 (V), designated γ-tetraol, was obtained in a yield of 31% based on γ-dibenzoylsuccinic ester. From dichloroethane—colorless prisms with m.p. 147.5-148°.

$C_{18}H_{22}O_4$.	Found, %:	C 71.56; H 7.26; OH 23.36
	Calculated, %:	C 71.52; H 7.28; OH 22.50

In the reduction of racemic dibenzoylsuccinic ester, it was possible to obtain three racemates of 2,3-di-(α-hydroxybenzyl)-butanediol-1,4, and from meso-dibenzoylsuccinic ester—two meso forms and one racemate.

We succeeded in isolating from the reduction products of both forms one crystalline tetrahydric alcohol each, the β- and γ-tetraols. The oily substances remaining after their isolation also contained hydroxyl groups; possibly they contained other isomers as well.

The β- and γ-isomeric tetraols obtained were subjected to dehydration. From the tetraol obtained by reduction of the meso form of dibenzoylsuccinic ester, dehydration was expected to give 2,5-diphenylhexahydro-(3,4 : 3 ,4)-furofuran, since only in this case, upon closure of one tetrahydrofuran ring, do the remaining primary alcohol groups occupy a cis position relative to each other. Accordingly, the tetraol obtained by reduction of racemic dibenzoylsuccinic ester should give 2,5 -diphenylhexahydro-(3,4 : 3 ,4)-furofuran. Elimination of water from the β-tetraol was carried out in vacuo at a residual pressure of 9 mm and a bath temperature of 110–170° in the presence of potassium bisulfate. After the separation of water had ceased, the main amount of the substance distilled over at 9 mm and 220–230° as a yellow syrup. Trituration with dry ether caused crystallization. The isolated substance, recrystallized from alcohol, had m.p. 88.5–90° and by elemental analysis corresponded to the composition of diphenylhexahydro-(3,4 : 3 ,4)-furofuran, designated β-bicycle; the substance contained no hydroxyl groups either by analytical determinations or by investigation of the infrared spectrum. The yield was 54%.

$C_{18}H_{18}O_2$.	Found, %:	C 81.09; H 6.69
	Calculated, %:	C 81.21; H 6.77

Dehydration of the γ-tetraol was also carried out by slow heating in the presence of potassium bisulfate in vacuo at 13 mm and a bath temperature of 150–200°. Diphenyl-hexahydro-(3,4 : 3 ,4)-furofuran, called the γ-bicycle, distilled at 13 mm and 220–280° as a thick red-orange oil, which, on cooling and treatment with dry ether, crystallized in fine needles; from alcohol, m.p. 72.5–74.5°, yield 25.6%.

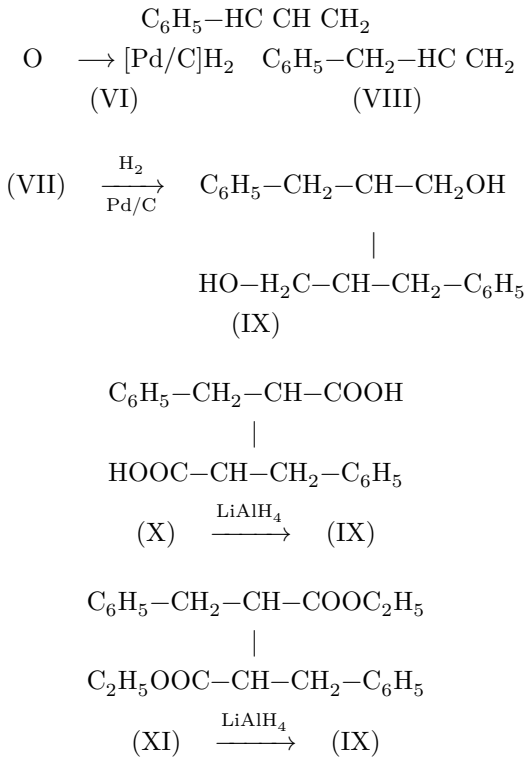
	Found, %:	C 81.29; H 7.04
$C_{18}H_{18}O_2$.	Calculated, %:	C 81.21; H 6.77

Determination by the Tserevitinov method and the infrared spectrum of the compound showed the absence of hydroxyl groups.

For identification of the 2,5-, 2,5 -diphenyl-hexahydro-(3,4 : 3 ,4)-furofurans synthesized by us, and for determination of the positions of the substituents in them, catalytic hydrogenation of these compounds was undertaken in glacial acetic acid in the presence of palladium on charcoal at atmospheric pressure and room temperature. Under these conditions, owing to the influence of the phenyl groups, cleavage of the ether bond occurs between the oxygen and secondary carbon atoms (scheme (B)), as has been shown experimentally, for example, for the reductive cleavage of 2-phenyl- and 2,3-diphenyl-dioxane (6).

reaction scheme: hydrogenation and reductions of compounds VI, VII, VIII, IX, X, XI

(B)



On hydrogenation of the β-bicycle under the conditions indicated above, a substance with m.p. 65.5-67°, yield 79%, was obtained. According to the analytical data and the absence of hydroxyl groups (determination by the Tserevitinov method), this compound was 2,3-dibenzyl-tetrahydrofuran (VIII).

Found, %:		C 85.64; H 7.92
$C_{18}H_{20}O$.	Calculated, %:	C 85.71; H 7.94

Consequently, the β-bicycle is 2,5-diphenyl-hexahydro-(3,4 : 3 ,4)-furofuran (VI).

Under the same conditions the γ-bicycle was subjected to hydrogenation; a thick oily substance was obtained, which crystallized after drying in vacuo and rubbing with dry ether. The dl-2,3-dibenzylbutanediol-1,4 (IX) isolated in 49% yield had m.p. 87–88° (from ligroin); a mixed sample of it with dl-2,3-dibenzylbutanediol-1,4, obtained by reduction with lithium aluminum hydride of dl-2,3 -dibenzylsuccinic acid, showed no depression of the melting point.

Found, %:		C 80.19; H 7.92; OH 13.07
$C_{18}H_{22}O_2$.	Calculated, %:	C 79.90; H 8.20; OH 12.60

Diacetate, m.p. 73.5–74.5° (from alcohol).

Found, %:		C 74.92; H 7.53
$C_{22}H_{26}O_4$.	Calculated, %:	C 74.53; H 7.40

The structure of *dl*-2,3-dibenzylbutanediol-1,4 was proved by counter-synthesis starting from *dl*-2,3-dibenzylsuccinic acid (X) (7) or its diethyl ester (m.p. 80–81.5°) (XI), which were reduced with lithium aluminum hydride in ether. After the usual work-up, a difficultly crystallizable oily substance was obtained. By distillation in vacuo at 195–210°/1.6 mm, a crystalline compound was isolated, m.p. 87–88°.

Found, %:		C 79.82; H 8.17
$C_{18}H_{22}O_2$.	Calculated, %:	C 79.90; H 8.20

Thus, the structure of racemic 2,3-dibenzylbutanediol-1,4 (IX) was confirmed, and consequently the structure of the γ-bicycle synthesized by us was shown to be 2,5-diphenylhexahydro-(3,4 : 3 ,4)-furofuran (VII).

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Note: Figure translations are in progress. See original paper for figures.