Prins reaction in the synthesis of lignin model compounds. I. Synthesis of guaiacylglycerol and veratrylglycerol

R. BREŽNÝ and J. ALFÖLDI

Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava

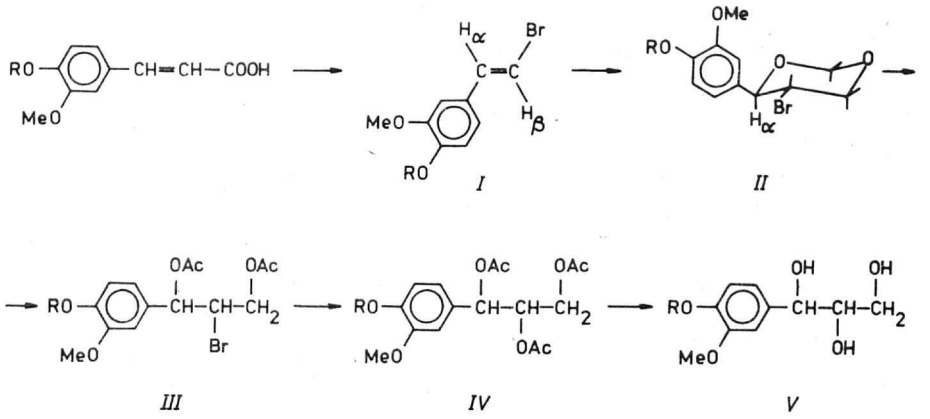
Received 1 April 1977

A simple new route leading to *erythro,threo*-1-(3,4-dimethoxyphenyl) and -(4-hydroxy-3-methoxyphenyl) glycerol is described. The starting β-bromostyrenes were converted to the corresponding 1,3-dioxans by means of a newly modified Prins reaction. Opening of the dioxan ring by acetolysis followed by the exchange of bromine atoms for acetoxy groups, and final deacetylation gave the title substances. The stereochemical course of the Prins reaction is discussed on the basis of p.m.r. data. Mass spectral characteristics and p.m.r. data for the synthetic intermediates are also given.

Описывается новый способ простого приготовления *эритро, трео*-1-(3,4-диметоксифенил)- и -(4-гидрокси-3-метоксифенил)глицеролов. Исходные β-бромстиролы были превращены в соответствующие 1,3-диоксаны при помощи новой модификации реакции Принса. Указанные вещества были обнаружены после раскрытия диоксанового кольца ацетолизом, а замещения атома брома на ацетоксильную группу и дезацетилирования. Стереохимическое течение реакции Принса обсуждается на основании данных ^{1}H-ЯМР. Приводятся данные спектров ^{1}H-ЯМР и масс-спектров для промежуточных продуктов.

A number of lignin model substances belong to the class of compounds bearing an α,γ-diol arrangement in the side-chain of the arylpropane unit. The so far described procedures leading to this type of system involved reduction with complex metal hydrides [1—4]. Potential 1,3-diol grouping can be formed from 1,2-unsaturated substances by Prins reaction which, to our knowledge, has not yet been applied in the synthesis of lignin model substances. An example of such an application is the present synthesis (Scheme 1) of two 1-arylglycerols.

The addition of formaldehyde to *trans*-β-bromostyrenes was carried out in dichloromethane in the presence of a catalytic amount of boron trifluoride



a) R = Me, *b*) R = $COCH_3$, *c*) R = H.

Scheme 1

etherate. The reaction proceeded smoothly at room temperature and with the starting β-bromostyrenes was complete in 2 h. Pronounced regioselectivity was observed with substrates having the phenolic group free which normally show tendency to hydroxymethylation on the aromatic ring and/or to form phenol-formaldehyde resins. Under the conditions described herein the olefinic double bond reacted almost exclusively to give substituted 1,3-dioxans. The p.m.r. spectra confirmed that the products belonged to the *threo* series showing thus, that in the case of our substrates the addition of formaldehyde was a *syn* addition.

The *trans*-β-bromostyrenes were obtained from the corresponding substituted cinnamic acids [2]. 4-Hydroxy-3-methoxystyryl bromide (*Ic*), unstable in contact with air, can be conveniently isolated and stored as its acetate *Ib* having good crystallizing properties. The isomeric purity of the obtained *trans*-β-bromostyrenes *Ia* and *Ib* was confirmed by their p.m.r. spectra showing a coupling constant $J_{\alpha,\beta}$ 13.5 Hz for the *trans*-oriented H_α and H_β. The *trans*-β-bromostyrene *Ib* was unreactive under the conditions of the newly modified Prins reaction and, therefore, prior to the reaction with formaldehyde, it was deacetylated. Deblocking of the phenolic group resulted in high yield of the corresponding 1,3-dioxan *IIc*, isolated as the acetate *IIb*. The comparison of the integrated p.m.r. spectra of *Ia* and *Ib*, namely of the signals assigned to O—CH_2—O and H_α, showed that both these substances were *threo*-1,3-dioxans. The configurational assignment was based on the $H_{\alpha,\beta}$ coupling constant characteristic of the diaxial arrangement.

The opening of the 1,3-dioxan ring was most conveniently achieved by perchloric acid-catalyzed acetolysis. A mixture of *threo* and *erythro* isomers was invariably formed by this reaction as a result of the intermediate formation of benzylium cations. Compounds *IIIa* and *IIIb* gave similar p.m.r. spectra. The presence of isomeric mixtures was obvious from pairs of overlapping H_α doublets found in the

spectra, which were assigned to the individual stereoisomers on the basis of the observed coupling constants [5]. The p.m.r. spectra showed also that an approximately equal amount of stereoisomers was present in both *IIIa* and *IIIb*.

The bromine atoms in *IIIa* and *IIIb* were replaced by acetoxy groups by their treatment with silver acetate in acetic acid [2] giving acetylated *threo,erythro*-1--arylglycerols *IVa* and *IVb*. Their p.m.r. spectra were interpreted in the above-described manner. As expected, the amount of the stereoisomers present in *IVa* and *IVb* was similar to that present in their precursors. Following deacetylation with sodium methoxide in methanol of veratrylglycerol triacetate *IVa* was a smooth reaction. On the other hand, similar deacetylation of guaiacylglycerol tetraacetate *IVb* did not result in the formation of the wanted derivative *Vc*, which was then obtained in good yield by deacetylation of *IVb* with ammonia in methanol. The structure of *Vc* was confirmed by its acetylation giving the parent substance, and by methylation with diazomethane which produced veratrylglycerol *Va*. The identity of the derivatives with the expected substances was confirmed by spectral methods.

Experimental

Melting points were determined on a Kofler hot-stage. P.m.r. spectra (80 MHz) for solutions in chloroform-d and acetone-d_6 were recorded with a Tesla BS 487 B spectrometer at 25°C. Proton-signal assignments were made by the Indor technique. Mass spectra (74 eV) were measured with a JMS-100 D instrument at an emission of 300 μA. The temperature in the site of evaporation was 130—150°C. All reactions were monitored by thin-layer chromatography on Silica gel G (Merck, A.G., Darmstadt) coated glass slides. The given R_f values refer to the reaction products. Detection was performed by charring with 5% (v/w) sulfuric acid in ethanol. Preparative chromatography was carried out on columns of dry-packed [6, 7] Silica gel 60 (Merck, A.G., Darmstadt) which, prior to packing, was equilibrated with 40% of the mobile phase. The solvents used for chromatography were: *A*. benzene—ethyl acetate 10:1, and *B*. chloroform—methanol 10:1. Chloroform solutions were dried with anhydrous sodium sulfate, decolorized with a little silica gel, filtered and concentrated at 40°C/2 kPa.

trans-3,4-Dimethoxystyryl bromide (Ia)

A solution of bromine (2.2 ml) in acetic acid (100 ml) was added at 10—15°C to a suspension of methylferulic acid (9 g) in acetic acid (100 ml). Anhydrous potassium acetate (7 g) was added at 20 °C to the colourless solution and stirring was continued for 4 h. The mixture was filtered, the filtrate concentrated to dryness with the addition of toluene, and the solution of the residue in chloroform was washed with saturated aqueous sodium hydrogen carbonate solution. The product (R_f 0.62, solvent *A*), when crystallized from

isopropyl ether—heptane, showed m.p. 63—65°C; Ref. [1] m.p. 63—65°C. Further crop of the same material (total amount 8.8 g, 84%) was obtained by chromatography of the mother liquors. P.m.r. data ($CDCl_3$): H_α (7.04 p.p.m., doublet), H_β (6.60 p.p.m., doublet, $J_{\alpha,\beta}$ 13.5 Hz), H_{arom} (6.88 p.p.m., multiplet).

trans-4-Acetoxy-3-methoxystyryl bromide (Ib)

Chloroform (7 ml) was added to a suspension of ferulic acid (5 g) in acetic acid (50 ml) and, after cooling (0°C), bromine (1.3 ml) in a mixture of acetic acid—chloroform (50:7; 57 ml) was added dropwise with stirring. After addition of anhydrous potassium acetate (5 g) at 20°C to the colourless solution the stirring was continued for 4 h. The mixture was filtered and, after concentration of the filtrate with codistillation with toluene, the solution of the product in chloroform was washed with cold water and processed in the usual manner. Acetylation of the product with acetic anhydride (10 ml) in pyridine (100 ml) overnight gave crude *Ib*, a solution of which in benzene was decolorized with a little silica gel. Crystallization from isopropyl ether or methanol gave 4.9 g (86%) of the title substance (R_f 0.67, solvent *A*) melting at 108—110°C; Ref. [2] 109—110°C. P.m.r. data ($CDCl_3$): H_α (7.06 p.p.m., doublet), H_β (6.67 p.p.m., doublet, $J_{\alpha,\beta}$ 13.5 Hz), H_{arom} (6.88 p.p.m., multiplet).

threo-5-Bromo-4-(3,4-dimethoxyphenyl)-1,3-dioxan (IIa)

Boron trifluoride etherate (0.75 ml) was added to a mixture of *Ia* (5 g) and paraformaldehyde (1.4 g) in dichloromethane (100 ml), and the reaction mixture was stirred for 2 h at 20°C. After this time t.l.c. (solvent *A*) showed the presence of a product having R_f 0.42. The mixture was diluted with chloroform, shaken with saturated aqueous sodium hydrogen carbonate solution and the organic phase was processed in the usual manner. Purification by chromatography and crystallization from isopropyl ether—heptane gave 5 g (80%) of *IIa* melting at 73.5—75°C. P.m.r. data (acetone-d_6): O—CH_2—O (two doublets at 5.11 and 4.86 p.p.m.), H_α (4.50 p.p.m., doublet, $J_{\alpha,\beta}$ 9 Hz). Mass spectral data (*m/e*, I_{rel}): 304 (11.6), 302 (11.6), 167 (100), 166 (26.8), 150 (10.7), 94 (12.5), 76 (16.1).

For $C_{12}H_{15}O_4Br$ (303.16) calculated: 47.54% C, 4.99% H, 26.36% Br; found: 47.66% C, 5.08% H, 26.50% Br.

threo-5-Bromo-4-(4-acetoxy-3-methoxyphenyl)-1,3-dioxan (IIb)

A 5% (w/v) solution of sodium in methanol (2 ml) was added with stirring to a solution of *Ib* (2 g) in methanol (100 ml) and after 2 h at 20°C t.l.c. (solvent *A*) showed that the conversion of the starting material to the product (R_f 0.58) was complete. The mixture was deionized with a cation-exchange resin, filtered, concentrated, and paraformaldehyde (600 mg) followed by boron trifluoride etherate (0.2 ml) was added to the solution of the residue in dichloromethane (30 ml). The reaction was complete after 2 h at 20°C, as showed

by t.l.c. (solvent *A*, R_f 0.35). The mixture was diluted with chloroform, washed with aqueous sodium hydrogen carbonate solution and processed in the usual manner. The product, which could not be crystallized, was isolated (2 g, 85%) as the acetate *IIb* (R_f 0.42, solvent *A*), m.p. 79—81°C (from ethyl acetate—heptane). P.m.r. data ($CDCl_3$): O—CH_2—O (two doublets at 4.83 and 5.20 p.p.m.), H_α (4.49 p.p.m., doublet, $J_{\alpha,\beta}$ 9 Hz). Mass spectral data (*m/e*, I_{rel}): 332 (2.6), 330 (2.6), 289 (23.1), 287 (25.6), 153 (15.4), 152 (100), 151 (23.1), 43 (43.6).

For $C_{13}H_{15}O_5Br$ (331.17) calculated: 47.15% C, 4.57% H, 24.13% Br; found: 47.30% C, 4.50% H, 23.91% Br.

erythro,threo-2-Bromo-1-(3,4-dimethoxyphenyl)-1,3-propanediol diacetate (IIIa)

Perchloric acid (70%; 0.1 ml) was added to a solution of *IIa* (1 g) in a mixture of acetic acid—acetic anhydride (1:1; 16 ml). After 1 h at 20°C, at which time t.l.c. (solvent *A*) showed that the starting material disappeared and that only one product (R_f 0.27) was present, the mixture was poured into a solution of sodium hydrogen carbonate (2 g) in water (200 ml) and left for 1 h. The mixture was shaken with chloroform and the organic layer was processed in the usual manner. The obtained sirupy product (1.2 g, ~100%) was chromatographically almost homogeneous and sufficiently pure for the next step. P.m.r. data (acetone-d_6): *erythro* isomer: H_α (5.99 p.p.m., doublet, $J_{\alpha,\beta}$ 5.5 Hz); *threo* isomer: H_α (5.98 p.p.m., doublet, $J_{\alpha,\beta}$ 7 Hz). Mass spectral data (*m/e*, I_{rel}): 375 (13.5), 373 (13.5), 293 (12.5), 193 (76.9), 192 (28.8), 167 (100), 139 (22.1), 43 (>100).

For $C_{15}H_{19}O_6Br$ (375.22) calculated: 48.01% C, 5.10% H, 21.30% Br; found: 48.25% C, 4.88% H, 21.40% Br.

erythro,threo-2-Bromo-1-(4-acetoxy-3-methoxyphenyl)-1,3-propanediol diacetate (IIIb)

Acetolysis of bromodioxan *IIb* (1 g) at 60—65°C in the manner described above in the preparation of *IIIa* gave 1.2 g (~100%) of a chromatographically almost pure (R_f 0.21, solvent *A*) sirup, the p.m.r. spectrum (acetone-d_6) of which showed the same chemical shift for H_α and the same $J_{\alpha,\beta}$ as found in the spectrum of *IIIa*. Mass spectral data (*m/e*, I_{rel}): 404 (2.5), 402 (2.5), 362 (8.2), 360 (8.2), 281 (9.1), 222 (4.8), 221 (8.2), 179 (26.1), 178 (15.2), 153 (34.1), 43 (100).

For $C_{16}H_{19}O_7Br$ (403.23) calculated: 47.66% C, 4.75% H, 19.82% Br; found: 47.62% C, 4.47% H, 20.02% Br.

erythro,threo-(3,4-Dimethoxyphenyl) (IVa) and -(4-acetoxy-3-methoxyphenyl) glycerol triacetate (IVb)

Dry silver oxide [8] (0.6 g) was added to a solution of *IIIa* or *IIIb* (0.5 g) in acetic acid—acetic anhydride (5:1; 12 ml) and the mixture was refluxed for 3 and 5 h, respective-

ly. T.l.c. after this showed the presence of *IVa* (R_f 0.15, *cf.* R_f 0.13 for *IVb*, solvent *A*; in more polar solvents the stereoisomers can be clearly distinguished). After filtration and concentration of the filtrate, the residue was chromatographed to give the two title substances in 75 and 71% yield, respectively.

IVa: P.m.r. data (acetone-d_6): *erythro* isomer — H_α (5.91 p.p.m., doublet, $J_{\alpha,\beta}$ 5.25 Hz); *threo* isomer — H_α (5.90 p.p.m., doublet, $J_{\alpha,\beta}$ 7 Hz). Mass spectral data (*m/e*, I_{rel}): 354 (8.6), 294 (7.9), 209 (8.6), 193 (13.8), 192 (34.5), 168 (12.4), 167 (100), 139 (17.6), 43 (93.1).

For $C_{17}H_{22}O_8$ (354.35) calculated: 57.62% C, 6.26% H; found: 57.60% C, 6.21% H.

IVb: P.m.r. data (acetone-d_6): *erythro* isomer — H_α (5.96 p.p.m., doublet, $J_{\alpha,\beta}$ 5.5 Hz), *threo* isomer — H_α (5.98 p.p.m., doublet, $J_{\alpha,\beta}$ 7 Hz). Mass spectral data (*m/e*, I_{rel}): 382 (4.5), 340 (9.7), 282 (5.4), 281 (26.9), 278 (37.1), 238 (5.8), 195 (17.7), 153 (100), 43 (>100).

For $C_{18}H_{22}O_9$ (382.36) calculated: 56.54% C, 5.80% H; found: 56.37% C, 5.57% H.

erythro,threo-1-(3,4-Dimethoxyphenyl) glycerol (Va)

Deacetylation of *IVa* with sodium methoxide in methanol gave in a virtually theoretical yield *Va* (R_f 0.35, solvent *B*) melting at 104—108°C (from chloroform—ether). Ref. [4] gives m.p. 92—93 and 109—110°C for *erythro* and *threo* isomer, respectively. Mass spectral data (*m/e*, I_{rel}): 228 (16.2), 167 (100), 166 (66.2), 139 (78.4), 124 (52.7), 108 (36.5), 77 (33.8), 65 (23.0).

erythro,threo-1-(4-Hydroxy-3-methoxyphenyl) glycerol (Vc)

Gaseous ammonia was bubbled for 15 min at 0°C through a solution of *IVb* (300 mg) in dry methanol (20 ml) and the solution was concentrated after 2 1/2 h at 0°C. Chromatography gave 110 mg (65%) of sirupy *Vc* (R_f 0.1, solvent *B*).

Methylation at 10°C of *Vc* (in methanol) with diazomethane in dichloromethane gave more than 90% of *Va*, which was confirmed by its melting point and mass spectrum.

Acetylation of *Vc* with acetic anhydride in pyridine gave high yield of *IVb*.

Acknowledgements. The authors thank V. Mihálov and J. Mrva for mass spectrometry and P. Kováč for helpful discussions.

References

1. Adler, E. and Björkquist, K. J., *Acta Chem. Scand.* **5**, 241 (1951).
2. Adler, E. and Björkquist, K. J., *Acta Chem. Scand.* **7**, 561 (1953).
3. Stumpf, W. and Rumpf, G., *Justus Liebigs Ann. Chem.* **599**, 51 (1956).

4. Adler, E. and Gustafson, B., *Acta Chem. Scand.* ***17***, 27 (1963).
5. Inch, T. D., *Annual Review of NMR Spectroscopy*, Vol. *2.* (Mooney, E. S., Editor.) Pp. 35—82. Academic Press, London, 1969.
6. Kováč, P., Anderle, D., Dubnický, J., and Kučera, Z., *PV 5271-75.*
7. Loev, B. and Goodman, M. M., *Chem. Ind.* (London) ***1967***, 2026.
8. Hirst, L. L. and Percival, E., *Methods Carbohyd. Chem.* ***2***, 145 (1963).

Translated by P. Kováč