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Synthesis of Enantiomerically Pure Forms of Trans-3-Phenylglycidic Acid.

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Abstract:Trans-(2R,3S)- and (2S,3R)-3-phenylglycidic acids were obtained as pure crystals. The optical properties and chemical stability were characterized. The absolute configuration of the trans-(+)- and trans-(-) isomers was established by means of chemical correlation.

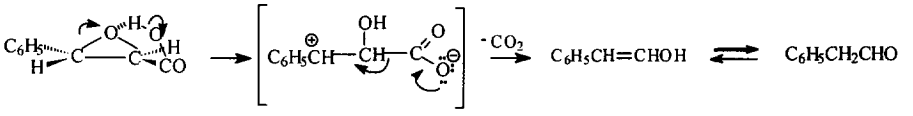
The optically active glycidic acids and their aromatic derivatives substituted in position 3 are well known as structurally important fragments of numerous biologically active substances. The esters of cis- and trans-3-phenylglycidic acids were used in the spectacular synthesis of taxol and taxotere [1,2,3] - currently the most intriguing anticancer substances. Both esters were applied to the synthesis of N-acylisoserine which is connected to the polycyclic portion of the taxol molecule at position 13 *via* the ester bond; this side chain proved to play a substantial function in conveying cytotoxicity to cancerous cells.

The racemic sodium salts and esters of the variously substituted *cis*- and *trans*- phenylglycidic acids in the aromatic ring were used as the basic substrates in the syntheses of the chinoline derivatives designed as 5-lipoxygenase inhibitors or leucotriene antagonists which play an important role as mediator of inflammatory and allergic reactions.[4] Methyl *trans*-3-(p-methoxy)phenylglycidate was a substrate for the synthesis of diltiazem hydrochloride, known as a very effective channel blocker, and applied in the treatment of angina pectoris.[5] Methyl *trans*-3-phenylglycidate was used in the synthesis of dehydroclausenamide.[6] This valuable hepatoprotective drug was obtained solely through aqueous extractions of dry leaves of *Clausena lansium* in minute quantities. (2S,3R)-3-phenylglycidic acid esters are important as synthetic intermediates of 1,5-benzothiazepine derivatives [7] having coronary blood vessel vasodilating activity or platelet aggregation-inhibiting activity.

Numerous methods aimed at synthesis of optically active 3-substituted esters and salts of *trans*- and *cis*-arylglycidic acids have been developed. These are: Sharpless enantioselective epoxidation,[8] Sharpless asymmetric dihydroxylation ,[9] auxiliary-controlled Darzens type condensation ,[10] enantioselective hydrogenation of 2-chloro-3-keto esters,[5] microbial asymmetric chlorohydrin synthesis and subsequent epoxidation with base,[11] microbial enantioselective hydrolysis of epoxy esters.[7] All these procedures lead to the ester form of the respective glycidic acids. However, the isolation of free, optically active isomers of 3-arylglycidic acids was

a difficult task due to the extended deterioration of the compound; that is spontaneous decarboxylation accompanied by opening of the oxirane ring, and therefore they were not known as chemically pure substances.[13,14,15,16] We think that the free carboxylic group may serve as a catalyst itself (3-arylglycidates are comparatively stable) by means of promoting the protonation of the oxirane ring (scheme 1), concurrently, an aromatic substitution in position 3 would aid the reaction due to the effect of the mesomeric stabilization of the intermediate cation.

Scheme 1



RESULTS

Enantiomerically pure *trans*(+)- and *trans*(-)-3-phenylglycidic acids were isolated for the first time in our laboratory. Their chemical stability and storage conditions were established, the chemical correlation of absolute configuration was unambiguously determined and application in syntheses of cystein protease inhibitors was investigated. The activation of the carboxylic group of trans-3-phenylglycidic acid for the amide bond formation (data will be published) was accomplished with 2-(-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) in slightly basic conditions in which the stable, carboxylate ion was predominantly present. In such mild conditions the yields of expected peptides were high and the opening of the oxirane ring kept at a minimum owing to short reaction times and low temperature conditions. We believe that the conditions for the isolation and storage of both enantiomers of *trans*-3-phenylglycidic acids will be applicable to a variety of glycidic acids substituted in position 3 with different aromatic substituents.[17] In many reaction pathways, some of them described at the beginning, a free acid might serve as the source of acylating agent which is more effective on the activation by means of TBTU or PyBOP, than methyl or ethyl esters which are rather poor electrophiles.[18]

EXPERIMENTAL

Optical rotations were measured on a JASCO J-2 spectropolarimeter. ^{1}H NMR spectra were recorded on TESLA BF 567A at 100MHz with TMS as the internal standard.

Sodium trans-3-phenylglycidate, (1). Benzaldehyde, 51cm^3 (0.5mol) and ethyl chloroacetate, 58.5cm^3 (0.5mol) were added dropwise over a period of 0.5h, at 0°C to a stirred solution of sodium methoxide, prepared

from sodium, 25.3g (1.1 mol) and methanol anh., 250cm^3. The reaction was continued for 0.5h at 0°C and then at room temperature for a further 2h. The precipitated sodium chloride was filtered off and washed with a small volume of methanol. The filtrate was cooled to 0°C and water (10cm^3) was added slowly to a well stirred solution. The mixture was stirred for the next 2h at 0°C, the precipitate of sodium *trans*-3-phenylglycidate was filtered and washed thoroughly with absolute diethyl ether. A new portion of fresh ether was added to the precipitant and after a few hours of stirring a salt was filtered (the operation should be performed twice), dried in a desiccator and stored in a refrigerator. Yield:87g (93%). ^{1}H NMR (D_2O): d(ppm) 3.36(d,1H,CHCOO,J=1.8Hz,trans), 4.07(d,1H,CHC$_6$H$_5$,J=1.8Hz,trans), 7.55(s,5H,Ar).

Racemic trans-3-phenylglycidic acid, (2). The racemic sodium *trans*-3-phenylglycidate, **1**, 9.3g (50mmol) was dissolved in a small volume of ice-water, diethyl ether was added and the water solution was acidified cautiously while stirring to pH 3-4. The extraction was repeated 3-4 times, the ether layers were combined, washed with ice-water and dried over anh. $MgSO_4$ at 4°C. The solution was then concentrated at low temperature to ca. 25% of the initial volume, n-hexane was added and left for the crystals to precipitate, in a refrigerator. Yield: 6.9g (85%). ^{1}H NMR ($CDCl_3$): d(ppm) 3.47(d,1H,CHCOOH,J=1.8Hz,trans), 3.95(d,1H,CHC$_6$H$_5$,J=1.8Hz,trans), 7.25(s,5H,Ar), 8.12(s,COOH).The crystals were then stored at 4°C for the subsequent resolution to enantiomers.

Optically pure trans-(+)-(2S,3R)- and trans-(-)-(2R,3S)-3-phenylglycidic acids, (3) and (4). A solution of **2**, 4.9g (30mmol) in cold anh. diethyl ether (60cm^3) was treated with a cold ethereal solution of (+)- ephedrin obtained from 7.03g (35mmol) of its hydrochloride. n-Pentane was added dropwise to start the precipitation, and the solution was left in a refrigerator. The precipitated crystals, 5.6g, of a diastereoisomeric salt were filtered (the solution was left in a refrigerator in order to isolate the other isomer), washed with cold abs. diethyl ether and again recrystallized at 0°C. Yield: 4.8g(46%), mp. 151-152°C, $[\alpha]_D^{24}$=+113° (c 0.5, EtOH). The crystals were dissolved in brine at 4°C, cold ether was added and to a stirred mixture $NaHSO_4$ was added dropwise to pH 3-4. The ether layer was removed and the extraction repeated twice. The organic layers were washed with cold brine, water, dried over $MgSO_4$ in a refrigerator and evaporated to one third of the original volume without warming. n-Pentane was then added and the solution was concentrated under vacuum at 0°C. A new portion of cold n-pentane was repeatedly poured to initialize a crystallization process. The crystals of **3** were left in the refrigerator overnight, filtered off, dried in a desiccator under high vacuum and stored in a refrigerator for a few weeks without decomposition.[17] Yield: 1.8g (40%), $[\alpha]_{546}^{22}$+100° (c1, Et_2O).

The correlation of configuration:[12] To the ethereal solution of 164mg (1mmol) of **3,** the diazomethane in ether was added until a bright, yellow colour was maintained. The solution was washed with $NaHCO_3$, H_2O and dried over $MgSO_4$. The solvent was evaporated to dryness and the identity of the compound was checked by ^{1}H NMR spectroscopy in $CDCl_3$: d(ppm), 3.55(d,1H,CHCO,J=1.8Hz,tans); 3.85(s,3H,OCH$_3$); 4.12 (d,1H,CHC$_6$H$_5$,J=1.8Hz,trans), 7.37(s,5H,Ar), $[\alpha]_D^{24}$=+197° (c 0.7, $CHCl_3$). Lit.[12]: $[\alpha]_D^{20}$= -173.3° (c 1.15, $CHCl_3$), methyl trans-(2R,3S)-3-phenylglycidate. The other enantiomer, **4**, was crystallized as a (-)-ephedrine salt and isolated in the form of a free acid : $[\alpha]_{546}^{22}$= -100° (c1, Et_2O). The optical rotation of the respective

methyl ester $[\alpha]_D^{24}$= -180° (c 0.6, $CHCl_3$).

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17. The optically pure trans-3-phenylglycidc acids can be stored as crystals for several weeks in a refrigerator (<0°C), in dry conditions.HPLC test on the stability of the acids in benzene solution at RT, indicates c.a. 20% of decomposition after 1hr. The complete deterioration of the sample is observed within minutes, at 50°C.
18. Therefore, the oxirane ring may serve as a competitive electrophilic center causing by-product formation.

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