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Stereochemical Correlation of Diastereomeric 3-Amino- with 3-Arylamino Acids, and Their Derivatives via Stereospecific N-Phenylation by Diphenylhalonium Salts

Short Communication

Bogdan Kurtev, Ekaterina Simova*, Maya Victorova, Nikolina Berova,
and **Stefanka Christoskova**

Faculty of Chemistry, University of Sofia, 1126 Sofia, Bulgaria

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Diphenylhalonium salts were used in stereospecific N-phenylation of racemic and optically active 3-amino-2,3-diphenyl-1-propanols leading to 3-anilino-2,3-diphenyl-1-propanols. The absolute configurations of the latter and of genetically related compounds were established.

(Keywords: Absolute configuration; 3-Aminopropanols)

Stereochemische Korrelation von diastereomeren 3-Amino- mit 3-Arylaminosäuren bzw. ihrer Derivate durch stereospezifische N-Phenylierung mit Diphenylhaloniumsalzen (Kurze Mitteilung)

Durch stereospezifische N-Phenylierung mit Hilfe von Diphenylhaloniumsalzen werden racemische sowie optische aktive 3-Amino-2,3-diphenyl-1-propanole in die entsprechenden 3-Anilino-2,3-diphenyl-1-propanole übergeführt. Auf Grund dieser Umwandlung wird die absolute Konfiguration der Aminoalkohole und davon abgeleiteter Derivate ermittelt.

3-Amino- and especially 3-arylamino-2-phenylpropanoic acids and their derivatives are relatively easily accessible. Convenient synthetic methods for their preparation have been developed on the basis of base- or acid-catalyzed aldol-type reactions of carbanions from carboxylic acids or their derivatives and imines (cf.[1]). Although the application of 3-arylamino compounds is rather limited, they can be used as starting materials in stereospecific syntheses of N-heterocyclic compounds (cf.[2–10]).

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Assignment of configurations (relative or absolute) to 3-amino acids and their derivatives by chemical correlations presents no difficulties. For example, the absolute configurations of the (—)-menthyl esters of the four optically active 3-amino-2,3-diphenylpropanoic acids and of the two enantiometric pairs of 3-amino-2,3-diphenyl-1-propanols derived from the esters[11] were successfully correlated with the known configurations of the (—)-menthyl esters of the enantiomeric 2,3-diphenylpropanoic acids[12]. However, the absolute configurations of the easily accessible (—)-menthyl ester of *erythro*-3-anilino-2,3-diphenylpropanoic acid **5**, as well as of (—)-*erythro*-3-anilino-2,3-diphenyl-1-propanol **4** and (—)-*cis*-2-oxo-3,4,5-triphenyl-tetrahydro-1,3-oxazine **6**, obtained from the former by stereospecific transformations[13] have not yet been established due to the limited number of N-phenylated compounds of known absolute configuration (cf.[14]).

A tempting possibility for a generally applicable stereochemical correlation between amino- and arylamino compounds should involve a stereospecific N-arylation of the amino compounds. Consequently we studied the behaviour of the above mentioned amino compounds towards diphenylhalonium fluoroborates. These reagents are known to phenylate compounds with a heteroatom carrying an unshared electron pair[15]. This property of $Ph_2X\mathrm{BF}_4$ is due to their heterolytic dissociation when heated in a polar solvent thereby generating phenyl cations[16].

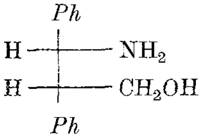
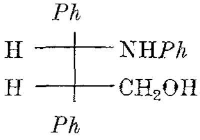
The experimental procedure consisted in heating the amino compound with a small molar excess of $Ph_2X\mathrm{BF}_4$ ($X = \mathrm{I}$, Br) in boiling acetonitrile. For following the reaction course and detecting the reaction products we used the TLC-technique described in[17]. The products were isolated by preparative TLC of the reaction mixtures on $\mathrm{Al_2O_3}$-TLC cards. The results are summarized in Table 1.

Phenylation of the methyl esters of the diastereomeric (±)-3-amino-2,3-diphenylpropanoic acids (±)-*erythro*-**1** and (±)-*threo*-**1** gave low yields of the corresponding methyl esters of (±)-3-anilino-2,3-diphenylpropanoic acids (±)-*erythro*-**3** and (±)-*threo*-**3**. When $Ph_2\mathrm{IBF}_4$ was used and the reaction time extended isomerisation took place as established by TLC.

Previously we had proved that only 3-anilinoesters, but no 3-aminoesters undergo retroaldol degradation and isomerisation in the presence of $\mathrm{AlCl_3}$[1]. Therefore it may be assumed that the phenylation step is not connected with isomerisation. The latter takes place subsequently, most probably under the influence of $\mathrm{BF_3}$ generated from the fluoroborate salts.

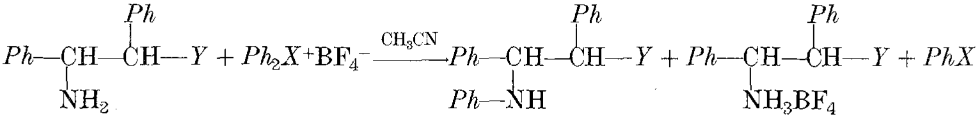
The desired stereospecific N-phenylation was successful when we used the configurationnally stable diastereomeric 3-amino-2,3-diphenyl-1-propanols. i.e. (±)-*erythro*-**2**, (±)-*threo*-**2**[18] and optically active (+)-*erythro*-**2**[12]. They were converted into the corresponding 3-anilino-2,3-diphenyl-1-propanols **4**, i.e. (±)-*erythro*-**4**[19], (±)-*threo*-**4**[20] and (—)-*erythro*-**4**[13] (see Table 1).

Table 1. *Phenylation of the methyl esters of 3-amino-2,3-diphenylpropanoic acid* (**1**) *and of 3-amino-2,3-diphenyl-1-propanols* (**2**)

Starting Compound		$Ph_2X^+BF_4^-$		Reaction Time	Phenylated Product	
Formula; Configuration	mmol	*X*	(mmol)	(h)	Formula; Configuration	Yield %
(±)-*erythro*-**1**	0.20	Br	0.26	3	(±)-*erythro*-**3**	10
(±)-*threo*-**1**	0.20	Br	0.26	3	(±)-*threo*-**3**	9
(±)-*erythro*-**2**	0.22	Br	0.28	1	(±)-*erythro*-**4**	50
(±)-*erythro*-**2**	0.22	I	0.26	4	(±)-*erythro*-**4**	17
(±)-*threo*-**2**	0.22	Br	0.28	1	(±)-*threo*-**4**	45
(±)-*threo*-**2**	0.50	I	0.60	4	(±)-*threo*-**4**	9
 (+)-*erythro*- (2*R*, 3*R*)-**2** $[\alpha]_D = +27.8°$ [a]	0.22	Br	0.28	1	 (—)-*erythro*- (2*R*, 3*R*)-**4** $[\alpha]_D = -49.1°$ [b]	50

[a] See Ref.[12]; [b] see Ref.[13].

This chemical correlation confirms the relative configurations of the diastereomeric (±)-3-anilino-2,3-diphenylpropanoic acids and derivatives, deduced before on the basis of qualitative conformational analysis[21].

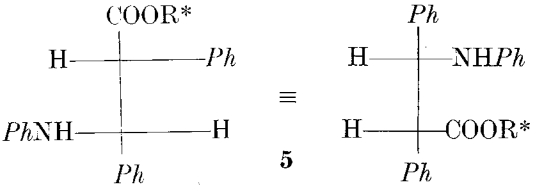


$$Ph\text{—}\underset{NH_2}{CH}\text{—}\overset{Ph}{CH}\text{—}Y + Ph_2X^+BF_4^- \xrightarrow{CH_3CN} Ph\text{—}\underset{Ph\text{—}NH}{CH}\text{—}\overset{Ph}{CH}\text{—}Y + Ph\text{—}\underset{NH_3BF_4}{CH}\text{—}\overset{Ph}{CH}\text{—}Y + PhX$$

1, **2** **3**, **4**

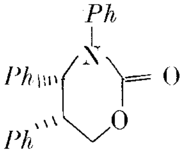
X = I or Br; $Y = COOCH_3$ (**1**, **3**) or CH_2OH (**2**, **4**)

Since N-phenylation is stereospecific and no change occurs in the priority of the substituents at the two chiral centers in the newly obtained compounds, we can assign *erythro*-**4** the same absolute configuration as in *erytro*-**2**, as established before, namely 2*R*, 3*R*. Consequently the absolute configurations of the chiral centers in **5** are 2*R*, 3*R* and 4*R*, 5*R* in **6**.



5

R* = (—)-menthyl



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Therefore diphenylhalonium fluoroborates may be used successfully in stereochemical correlations of 3-amino and 3-arylamino compounds of the above mentioned type and most probably in stereochemical N-phenylations of other types of amino compounds.

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