High-sensitivity Optical Resolution of Amines by Gas Chromatography

By B. HALPERN and J. W. WESTLEY

(*Department of Genetics, Stanford Medical School, Palo Alto, California*)

MOLECULAR architecture is the controlling factor in crystal growth, hence preparative chemical resolutions often rely on fractional crystallization of diastereoisomeric salts.[1] Reagents employed for this purpose are derived from both natural (alkaloids) and synthetic sources (prior resolution of racemates). While most naturally occurring resolving agents are sterically pure, synthetic reagents are of unknown purity. The usual criterion for steric purity, optical rotation, has limited precision.[1] Failing a reliable enzyme assay one must use a laborious isotopic dilution method to estimate racemic contamination.[2]

We have now found that gas–liquid chromatography (g.l.c.) of diastereoisomers[3–5] can be used to estimate quantitatively the steric purity of many resolving agents. On the basis of some preliminary experiments with a representative compound 2-amino-1-phenylpropane (amphetamine) (Table I), TFA-L-prolyl chloride[6] was used to analyze many racemic amines, and in most cases quantitative separation of the diastereoisomers was achieved on packed columns.

In typical assays (Table II) an excess of TFA-L-prolyl chloride in an inert solvent was added to a cooled solution of the amine in methylene chloride and the reaction mixture neutralized with triethylamine. After being washed (H_2O) and dried (Na_2SO_4), part of the solution (1 μl., containing approx. 1 μg. of the amine) was injected into the gas chromatograph.

Finally, we have used g.l.c. to monitor the steric purity of diastereoisomeric fractions obtained from classical resolution techniques. Thus the (+)-tartrate salt of an amine (5 mg.) was added to an excess of TFA-L-prolyl chloride in methylene chloride and the suspension neutralized with triethylamine. The analysis showed that all the amines could be resolved with (+)-tartaric acid, but at least five recrystallizations of the salt were

TABLE I

*Gas-chromatographic separation of diastereoisomeric N-acyl-1-phenyl-2-aminopropanes**

Acyl group	Separation temperature (°C)	Retention times of diastereoisomers (min.)		Ratio of retention times
2-Chloro-3-methylbutanoyl	159	17·8	18·5	1·04
2-Chloro-4-methylpentanoyl	170	13·5	14·85	1·10
2-Cyclohexylbutanoyl	180	22·3	23·8	1·07
2-Phenylbutanoyl	190	20·6	22·5	1·08
N-Trifluoroacetylprolyl	190	15·65	19·4	1·24

* G.l.c. analyses were carried out on a Wilkens 705 Aerograph equipped with a flame-ionization detector. The 15-foot steel column was packed with 0·75% DEGS/0·25% EGSS-X on acid-washed Chromosorb W and during analysis the nitrogen flow was 67 ml./min.

TABLE II

Gas-chromatographic separation of racemic amines as their N-trifluoracetyl-L-prolyl derivatives

Amine	Column*	Separation temperature (°C)	Retention times of diastereoisomers (min.)† L-(−)	L-(+)	Ratio of retention times
2-Aminobutane	A	140	11·7	12·4	1·06
2-Amino-3-methylbutane	A	140	12·4	14·0	1·13
2-Aminopentane	A	140	15·2	17·6	1·16
2-Amino-4-methylpentane	A	140	12·8	15·8	1·23
	B	140	10·4	11·75	1·13
2-Amino-octane	A	155	16·1	19·25	1·20
	B	155	16·25	18·45	1·13
2-Amino-1-phenylpropane	A	185	19·9	24·95	1·25
	B	185	13·4	14·7	1·09
trans-1-Amino-2-phenylcyclopropane	B	200	15·35	16·55	1·08
1-Amino-1-phenylethane	A	185	23·0	17·6	1·31
	B	185	12·95	10·65	1·22
1-Amino-1-α-naphthylethane	B	225	15·25	12·25	1·24

* Column A ($\frac{1}{4}$ in. × 15 ft.) was packed with 0·75% DEGS/0·25% EGSS-X on acid-washed Chromosorb W and during analysis the nitrogen flow was 67 ml./min.
Column B ($\frac{1}{8}$ in. × 5 ft.) was packed with 5% SE 30 on Chromosorb W and during analysis the nitrogen flow was 37 ml./min.
† The sign refers to optical rotation of the pure amine.

necessary for optical purity greater than 95%. For example, the (+)-tartrate of 2-amino-4-methylpentane, after five recrystallizations from methanol, was sterically pure as shown by g.l.c. This was confirmed by liberating the free amine with sodium hydroxide, extracting with ether, and distilling. The fraction boiling at 105—108° gave $[\alpha]_D^{23}$—10·78° (lit.[7]—10·73°).

In the 2-aminoalkane series, our g.l.c. results with amines of known optical rotation suggest that retention data may be used to assign absolute configuration. As (+)-2-amino-3-methylbutane and (+)-2-amino-4-methylpentane have already been related to the absolute L-configuration of the α-amino-acids[8] it appears that all (+)-aliphatic-2-aminoalkanes of this homologous series have the absolute L-configuration.

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