On the Use of 2-Amino-1-phenyl-propane (Benzedrine) for Optical Resolution of Acids

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The optical resolution of a racemic acid is usually performed by fractional crystallisation of its salt with some suitable, optically active alkaloid. There are less than ten such alkaloids commercially available and often only some of them will give crystalline salts with the acid in question. As the resolving power of these common alkaloids is rather capricious, it is not always possible to separate both the antipodes or even to prepare one of them in an optically pure condition without an unreasonable number of recrystallisations. In such cases where the common alkaloids fail to give satisfactory results α-phenylethylamine is often found to be useful. However, the disadvantage of this amine is that its optically active forms are not easily available as the resolution is carried out by means of the expensive (−)-malic acid [1]. For that reason the author has investigated the homologous 2-amino-1-phenyl-propane as regards its fitness for optical resolutions. The racemic base, which is also known as benzedrine, is rather cheap and the (+)-form is commercially available. The resolution is easily carried out by means of tartaric acid; recrystallisation of the bitartrate yields the (+)-form and the neutral tartrate the (−)-form [2].

The results from a series of experiments on resolution of different acids have been

Table 1. Experiments on resolution of some acids by means of (+)-2-amino-1-phenyl-propane. If not otherwise stated the optical activity refers to ethanolic solution.

Acid	Solvent	First salt fraction Yield in %	$[\alpha]_D$ of the acid		Excess of active acid %
			found	lit.	
α-Phenoxypropionic	50 % Benzene--petr. ether	50	−4.9°	−39.3°	12
α-(2-Naphthoxy)propionic	85 % Ethanol	34	−79.7°	−93.3°	85
α-(2-Methyl-4-chlorophenoxy)propionic	20 % Ethanol	73	0.0°	+19°	0
α-(2,4-Dichlorophenoxy)-propionic	20 % Ethanol	oil	—		
α-(3,4-Dichlorophenoxy)-propionic	30 % Ethanol	66	−5.8°	−39.3°	15
α-(2,4,5-Trichlorophenoxy)propionic	35 % Ethanol	55	−20.1°	−49.7°	40
α-Phenoxy-*n*-butyric	10 % Ethanol	35	+3.6°	+51.2°	7
α-(1-Naphthoxy)-*n*-butyric	40 % Ethanol	oil	—		
α-(2-Naphthoxy)-*n*-butyric	96 % Ethanol	30	−64.1°	−90.8°	71
α-(2,4-Dichlorophenoxy)--*n*-butyric	30 % Ethanol	oil	—		
α-(2-Naphthylmethyl)-propionic	35 % Ethanol	47	+5.7°[a]	+32.0°[a]	18
Propylsulphidesuccinic (acid salt)	10 % Ethanol--acetone	54	−13.2°	−137.2°[b]	10
β-Hydroxy-β-phenyl-pivalic	96 % Ethanol	42	−2.6°[b]	−9.0°[b]	29
α-Bromopropionic	Acetone	41	−6.7°	−29.5°[c]	20−25

a) in acetone b) in acetic acid c) homogenous

summarised in Table 1. It is notable that crystalline salts were obtained in all cases except three. Also it may be pointed out that most of the acids used in these experiments have rather small tendencies to yield crystalline salts with the common alkaloids. The acids liberated from the first fraction of the (+)-amine salts were obtained in very different degrees of optical purity. In two cases no or very small activity could be detected while in three cases the acids were obtained in a fairly high degree of optical purity. In the remaining six cases the products contained from 10 to 30 % excess of active acid which in many cases is enough to render a resolution possible by repeated recrystallisations. In view of this the use of 2-amino-1-phenylpropane for optical resolution of acids seems to be of great value as a complement to the common alkaloids and as a substitute for α-phenylethylamine.

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1. *Org. Syntheses, Collective Vol.* **II**, New York 1947, p. 506.
2. Nabenhauer, F. P. *U. S. P.* 2 276 508, 2 276 509 (1942).

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Volume Changes Accompanying Enzymatic Reactions with Ribonuclease and Deoxyribonuclease

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Previous investigations by Chantrenne, Linderstrøm-Lang and Vandendriessche [1] and Vandendriessche [2] have shown that the enzymatic breakdown of ribose nucleic acid (RNA) by ribonuclease is accompanied by volume changes that cannot be explained solely in terms of a hydrolytic splitting of an ester bond between a phosphate group and a hydroxyl group in ribose. In fact, the splitting of such a bond would produce a decrease in volume of about 2 ml/eq. at pH 4.6, while actually a contraction of 14 ml/eq. is found. Moreover, at certain temperatures (*e.g.* 30° C) this contraction is preceded by a very rapid increase in volume (curve 1, Fig. 1).

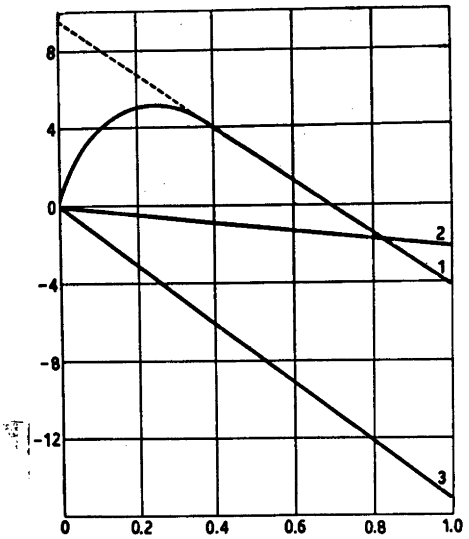

Fig. 1. Relation between volume changes and titration values (pH 4.6—30° C). Absc.: Base consumption in equivalents per mole (P_4 in case of nucleic acids). Ord.: Volume changes in ml per mole (id.).

1. *Yeast ribose nucleic acid and ribonuclease.*
2. *Thymus deoxyribose nucleic acid and deoxyribonuclease.*
3. *Ammonium uridine-2′—3′-phosphate and ribonuclease.*

Several explanations have been proposed for these phenomena, *viz.* that the dilatation is due to the breakdown of a superstructure, and that the contraction is caused by dipole formation. However, in the light of further experiments at other temperatures and pH-values (Vandendriessche [2]), none of the explanations offered were wholly satisfactory. It has now been found that the enzymatic break-