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STEREOSELECTIVE REACTION BETWEEN ACETANTHRANIL AND RACEMIC AMINE

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ABSTRACT

Racemic amines 1-phenyl-ethylamine and 1-amino-2-propanol were found to undergo kinetic resolution in the stereoselective reaction with acetanthranil. The residual amines have optical rotation of (+) 5.2° and (+) 4.5° which correspond to optical purity of about 15.7% and 18% for 1-phenylethylamine and 1-amino-2-propanol, respectively. The effect of temperature, reaction time, solvent, concentration of amine and catalyst were examined on the kinetic resolution.

INTRODUCTION

In certain transformations, optical antipodes react with different velocities. One of the antipodes react more rapidly and predominate in the reaction product and the second prevails in the unreacted residual product. There have been a few reports on the kinetic resolution of amines (1) such as, the kinetic resolution of 1-phenylethylamine using an optically active morpholin-2-one (2-4).

On the other hand, several 4-quinazolinones were reported to possess antibacterial activity against a wide variety of micro-organisms (5,6). Also, quinazolinone and its derivative have potential activities as analgesics, antimalarials, antispasmotics, anticonvulsants and long acting sedatives(7-9).

In the present work, an enantioselective reaction of acetanthranil **I** with certain racemic amines is reported. The kinetic resolution of these racemates as well as study of the effect of solvent, temperature, reaction time, concentration and catalyst on such kinetic resolution have been investigated.

EXPERIMENTAL

All melting points were uncorrected. Optical rotation was taken on Carl Zeis Jena; IR spectra (KBr) were recorded on Perkin Elmer 710B spectrophotometer. ^{1}H-NMR spectra were measured in DMSO-d_6 on JNM-PUX 6-NMR spectrometer (TMS as internal standard). Elemental analysis was performed in the Micro-analysis Center, Faculty of Science, Cairo University.

Reaction of acetanthranil I with (±)1-phenylethylamine (±)1-amino-2-propanol :

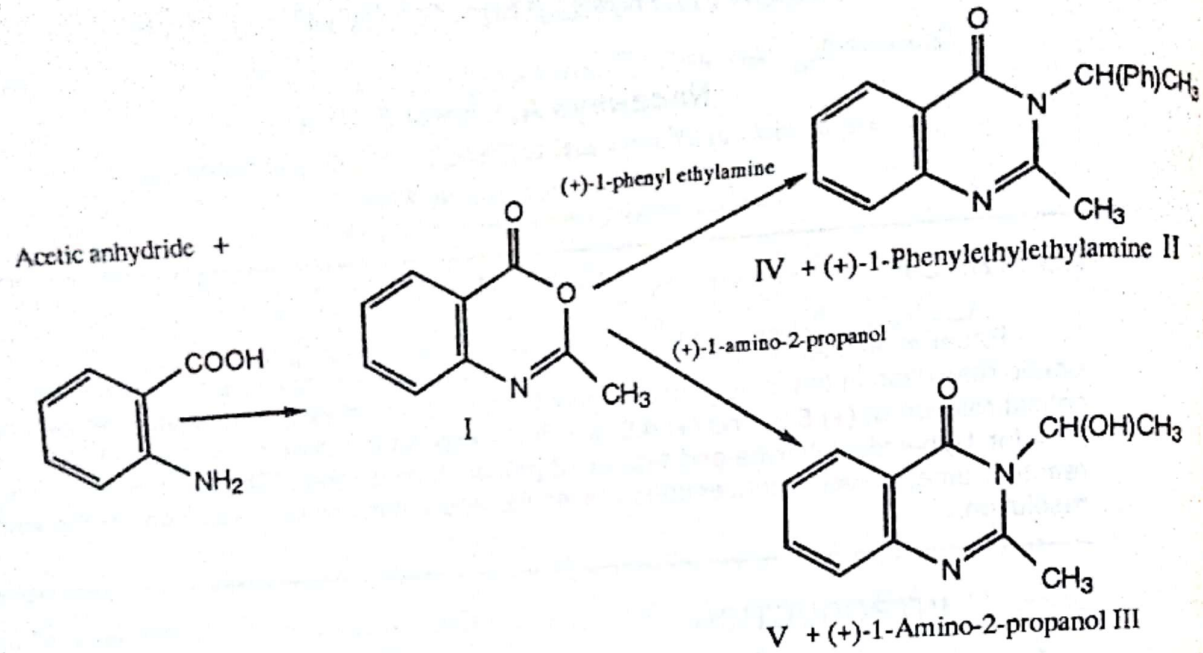
A mixture of 1 mole of acetanthranil **I** and 10 moles of the racemic amine was heated at 100°C for 24 hrs. When the reaction was completed, it was allowed to cool at room temperature. The mixture was filtered and the residual solid was recrystallized (from ethanol) to give : 3-(1-phenylethyl)-2- methyl-4-(3H)-quinazolinone **VI** with mp. 270°C; IR (KBr) : n1665 Cm^{-1}; ^{1}H-NMR (δ, DMSO-d_6) ; 1.5 (δ, CH_3), 2 (S, CH_3) ,3(m, CH), 7-8 (m, Ar).

Analysis for ($C_{17}H_{16}N_3O$) :

Calcd C : 77.3, H: 6.1, N: 10.6

Found C: 77.5, H: 6.5, N: 11

For Compound (V) 3-(2-hydroxy-



Scheme 1

propyl)-2-methyl-4(3H)-quinazolinone m.p. 250°C; IR(KBr) : n1450, 1670 Cm^{-1}; ^{1}H-NMR (δ, DMSO-d_6) : 2 (S, CH_3); 2.3 (d, CH_3), 3.3 (m, CH), 4.4 (δ, CH_2) 7-7.8 (m, Ar).

Analysis for ($C_{12}H_{14}H_2N_2O_2$) : Calcd : C : 66.05, H: 6.4, N: 12.8

Found : C: 66.5, H: 6.9, N: 13.

The filtrate was subjected to column chromatography using of silica gel (1 for 70 g silica gel); ethanol : chloroform (3:1) mixture as eluent. Pure fractions (one spot) were collected and evaporated under vacuum. The optical rotation of compounds was determined using a special polarimeter (Carl Zeis Jena). In the case of compound **IV** the [α] of the residual amine is (+) 5.2° (15.7%) and the [α] of **V** was (+) 4.5° (18%).

RESULTS AND DISCUSSION

Acetanthranil **I** was prepared by the reaction of anthranilic acid and acetic anhydride **II.** Treatment of acetanthranil **I** with 10 moles of (±) 1-phenylethylamine (II), or (±) 1-amino-2-propanol **III** for 24 hrs. at 100°C gave 4-quinazolinone derivatives **IV, V** and optically active residual amines.

The quinazolinone derivatives were separated by filtration and washed with alcohol several times. The filtrate was evaporated to about 5 ml and the product was cleaned up using a column chromatography. The separated amines have optical rotation of (+) 5.2° and (+) 4.5° with corresponding optical purity of 15.7% and 18% for 1-phenylethyl-amine and 1-amino-2-propanol, respectively.

From the obtained results it appeared that acetanthranil reacted rapidly with (-)-antipode than the (+) one.

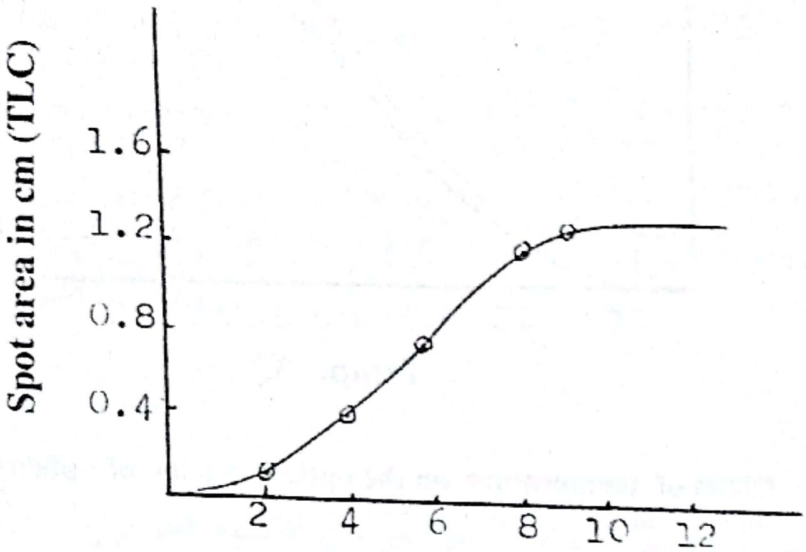


Fig. (1): Effect of concntration of 1-phenylethylamine on the rate of the reaction.

Effect of different variables on the kinetic resolution :

a- Concentration of racemic amines :

On the treatment of acetanthranil with different concentrations of racemic amines from 1-9 equivalents, a gradual increase in the rate of reaction was observed (TLC spotting). Therefore, all subsequent experiments were carried out with 10 molar equivalents of amines. (Fig. 1).

b- Reaction time and temperature :

The same reaction was carried out at various times and temperatures (20-100°C). The experiment showed that the most suitable time which gave the maximum optical purity was 24 hrs. (Fig. 3). Also, the most favourable temerature was 100°C to obtain the highest optical purity (Fig. 2).

c- Solvent :

The reaction was performed in various solvents. The highest optical purity and high yield were obtained when the reaction was carried out without a solvent. In aprotic solvents, e.g. acetonitrile and tetrahydrofuran, no change in stereoselectivity was observed. Moreover, a decrease in the reaction rate was observed in protic solvents like ethanol.

d- Catalyst :

The same reaction was achieved using different catalysts. When a strong base such as sodium methoxide was used as catalyst, a moderate yield with no stereoselectivity was obtained. The acidic catalyst, e.g. p-toluene sulphonic acid gave lower yield with no increase in stereoselectivity when compared with catalyst free experiments.

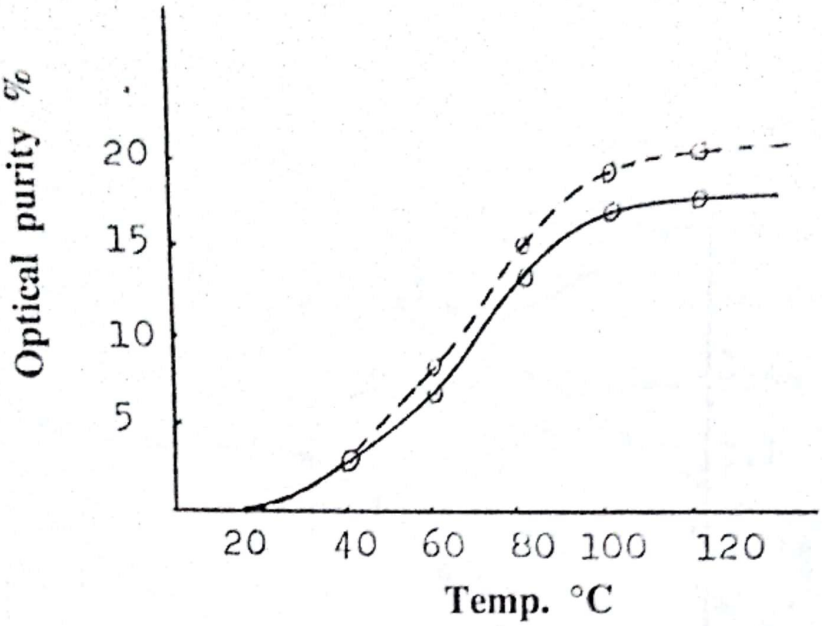


Fig. (2): Effect of temperature on the optical purity of l-phenylethylamine (–) and 1-amino-2-propanol (- - -).

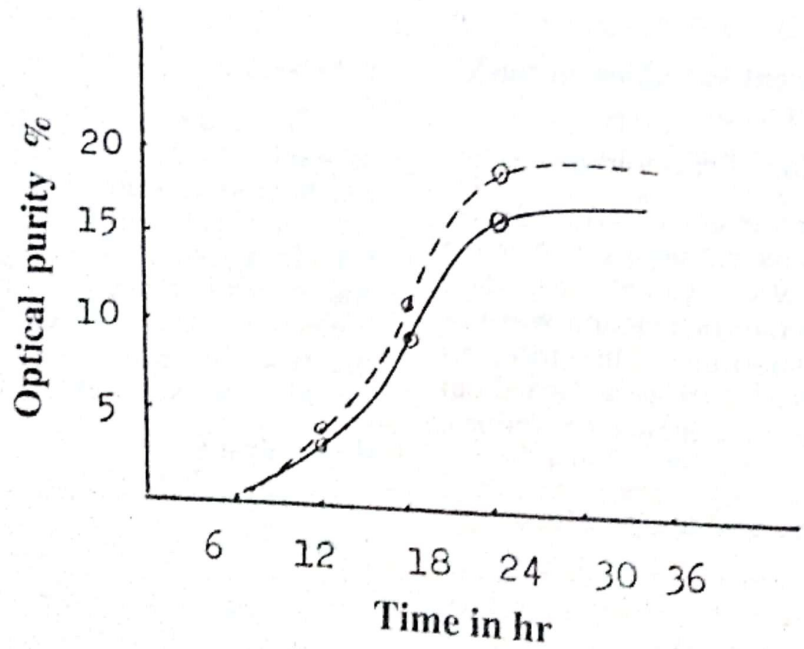


Fig. (3): Effect of time on the optical purity of 1-phenyl ethyl amine (–) and 1-amino-2-propanol (- - -).

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التفاعل الانتقائى للتشكيل الفراغى بين الأسيتا انثرانيل والأشكال الراسيمية للأمين

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تم فى هذا البحث فصل الأشكال الراسيمية للأمين ١-فينيل ايثيل أمين و ١-اميتو-٢-بروبانول بالتفاعل الانتقائى للتشكيل الفراغى مع الاسيتا انثرانيل عن طريق الفصل الحركى.

وقد وجد أن قوة التدوير النوعية للأمين المتبقى بعد التفاعل هى + ٥ ، + ٥ر٤ وهذا يماثل نقاء ضوئى حوالى ٧ر١٥٪ ، ١٨٪ لكل من ١-فينيل ايثيل أمين و ١-امينو-٢-بروبانول على التوالى.

كما تم دراسة تأثير كل من الحراره ، وقت التفاعل ، نوع المذيب ، تركيز الأمين ، ونوع العامل المساعد على عملية الفصل الحركى.