Pakistan J. Sci. Ind. Res. Vol 25, Nos 1–2, February – April 1982

REACTION PRODUCTS FROM NITROUS ACID DEAMINATION OF L(+) ALANINE METHYL ESTER HYDROCHLORIDE IN ACETIC ACID

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(Received July, 1977; revised December 1981)

Deamination of L–(+)–alanine methyl ester or of its acid salts with sodium nitrite in acetic acid gave substitution products predominantly with retention of configuration. Angles of optical rotation under varying conditions and added salts have been recorded. The present composition of substitution and elimination products has been studied followed by a discussion on the results. An ion-pair mechanisam has been proposed for the reaction.

INTRODUCTION

Reactions of aliphatic amines with nitrous acid have been discussed and reviewed as systems involving 'ion-pair' to explain stereochemistry of the products dependent of solvents, nucleophile or leaving group. It is known that nitrous acid deaminatin of amino acids proceeds with retention of configuration due to neighbouring group participation of the carboxylate ion or form substitution products with net retention while migration reactions proceed with net inversion at the migration terminii. [1 – 6]. Amino acid esters are reported to give either substitution products with net inversion or recemization together with inversion about the asymmetric carbon atom due to the lack of the participation of the neighbouring ester group and substitution products from nitrous acid deamination as in case of isoleucine methyl ester are formed with the retention of configuration [7 – 9]. Amino acid esters, therefore, gave reaction products by either retaining configuration at optical centre, inversion of configuration or recemisation of substitution products overwhelemed by the nucleophilicity of reaction, medium, substitution at α-or N- or participation of substituent group in rearrangement of products. However, the alkaline cleavage of N-nitroso-alanine methyl ester yielded denitrosation, elimination and rearranged products [10], whereas the N-carbamates gave esters involving ion-pair [11]. Aspartic acid dimethyl ester deaminates via diazo ester intermediate followed by a carbonium ion formation to yield predominantly elimination products [12]. In the present investigation, deaminative cleavage of L–(+)–alanine methyl ester or its acid salts in acetic acid has been studied with respect to stereochemical consequences of the reaction as well as the effect of counter ions such as sodium acetate or lithium chloride on the course of such a reaction.

EXPERIMENTAL

Materials. All he chemicals used were research grade and the solvents were analar. Purifications were carrid out by the low temperature vacuum distillation technique or by a preparative GLC. The chromatographic analyses were carried out on a Fraktometer F-21 (Perkin-Elmer) by using 10 % SE 30 and 10 % PPG capillary columns. Spectra were recorded on Unicam SP 200 IR, R-10 60 MH_z NMR and AEI MS 12 and CH-5 Varimat spectrometers. Optical rotation were recorded on a polarimeter (Perkin – Elmer 241) with automatic digital recorder.

REACTION PROCEDURE

In a double necked round bottom flask fitted with a condenser and kept in ice bath, containing methyl alaninate (0.5 M) or methyl alaninate hydrochloride (0.5 M) which excess of galcial acetic acid (Expt. 1 a; 3. b; 4. b; 10 b; 14 c, 15 d) or with excess of glacial acetic acid and sodium acetate (Expt. 5 b) or containing only LiCl (Expt. 11 b – 13 b) was added (dropwise) cold aqueous solution of sodium nitrite (0.5 ml). When evolution of gases has ceased from the reaction mixture it was stirred for 2 hr at room temperature. It was then extracted with diethyl ether several times and the etheral fraction were dried over anhydrous K_2CO_3. After distilling ether on water bath the remaining concentrate was analysed by GLC. From an

aliquot sample, pure fractions were separated by the preparative GLC and characterised with the help of IR, NMR, MS, combined GLC – MS techniques and optical rotations were recorded in 1 dm cell.

L–(+)–Alanine Methyl Ester Hydrochloride. The ester salt was prepared [13], dried under vacuum and crystallized from methanol, m.p. 154° (reported m.p. 158°) [6]

L–(+)–Alanine Methylester. Free ester was prepared and its structure was anlysed by IR and mass spectrum [13]
m/e 104 (M + 1 11
m/e 104 (M + 1 11%), 88 (17%, M^+–NH_2), 72(7%, M^+ – OCH_3); 59 (10%, M – CO_2), 55 (35%, *m/e* 72 – NH_3). 44(M^+ – CO_2CH_3); 43 (100%, M^+ – HCO_2CH_3),42(5%, *m/e* 59 – NH_3).

Methyl Acrylate; A colourless liquid fraction was collected by preparative GLC from the reaction mixture and was found to have identical [14] IR and NMR with an authentic sample from the reagent bottle.

Methyle Lactate. It was prepared by te diazotisation of lactic acid with CH_2N_2 and a pure sample was collected with the help of preparative GLC and its sturcture was supported by IR and NMR techniques. A colourless fraction collected from the reaction mixture showed identical retention time, IR, and NMR with the synthesised material.

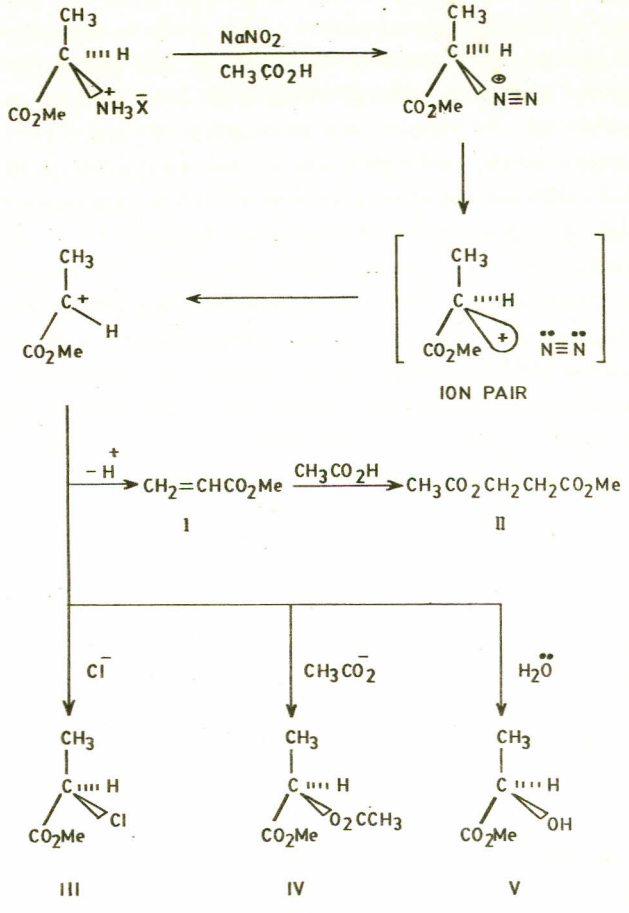
Methyl – α – Chloropropinate. A colourless oily fraction, collected from the reactin mixture by preparative GLC and shown identical IR and NMR spectra with an authentic sample from the reagent bottle. Analogous bormoester was synthesised and was found to have similar retention time, IR and NMR as of a liquid fraction from the reaction mixture [15].

Methyl – α – Acetoxypropionate.. This ester was synthesised [16] and a colourless fraction was collected from the reaction mixture by preparative GLC. The fraction recorded identical IR and NMR as of the authentic sample.

Methyl–3–Acetoxypropionate. Authantic sample was prepared by refluxing methyl acrylate with galcial acetic acid in the presence of small amount of pyridine [17]. A viscous oil distilled under vacuum, was collected and purified by preparative GLC. The last fraction from the reaction mixture was collected as pure sample by preparative GLC and was found to have the same IR and NMR spectra as the authentic material. Mass spectrum showed (M + I) molecular ion peak at *m/e* 147, characteristic of esters and mass break-down pattern recorded was *m/e* 147, (M + I, 6%), 117 (2%, $M^+ - C_2H_6$), 115 (2%, $M^+ - CH_3OH$); 87 (38%, $M^+ - CO_2CH_3$), 75 (8%, $M^+ - C_3H_4O_2$), 73 (5%, $M^+ - CH_3CO_2CH_3$); 59 (12%, *m/e* 87 – C_2H_4); 45 (10%, *m/e* 73 – C_2H_4), 44 (100%, $M^+ - C_5H_{11}CO_2$).

RESUTLS AND DISCUSSION

Deamination of L– (+) – alanine methyl ester hydrochloride with sodium nitrite in acetic acid gave methyl acrylate (1), methyl-3-acetoxypropionate (II), methyl-α-chloropropionate (III), methyl-α-acetoxypropionate (IV) and methyl lactate (V) as reaction products (Scheme 1). The present composition of these products and the angle of rotation of optically active substances varied due to effect of the medium, the counter ion or common ion and the ester salts. (Table 1). Increasing volume of glacial acetic acid (Expt. 3b, 4b) the angle of rotation as well as



Scheme 1.

Table 1. Deamination of L–(+) alanine methyl ester and its salts with sodium nitrite.

Expt. No.	Reactants AME + $NaNO_2$		Percent product composition					α 589		$[\alpha]_D^{20}$		per cent retention	
	CH_3COOH (ml)	Added Salt (M)	I	III	IV	V	II	III	IV	III	IV	III	IV
1.a	300	–	3.5	–	86.0	3.5	6.5	–	12.263	–	+ 11.292	–	20.73
2.a.	"	NaAc 1.0	4.11	–	82.56	7.83	5.57	–	9.950	–	+ 9.162	–	16.82
3.b.	300	–	11.5	23.0	59.4	–	6.2	+ 18.280	+ 25.092	+ 16.102	+ 23.092	57.92	42.39
4.b.	150	–	5.75	30.36	57.56	–	3.24	+ 11.125	+ 18.362	+ 9.810	+ 16.908	35.28	31.04
5.b.	–	NaAc 0.5	15.94	46.26	11.59	–	0.61	+ 9.107	+ 14.473	+ 8.03	+ 13.327	28.89	24.47
6.b.	300	" 0.1	26.4	27.8	42.9	–	2.9	–	+ 17.649	+ –	+ 16.242	–	29.82
7.b.	"	" 0.5	12.07	12.53	72.09	–	3.3	–	+ 14.403	–	+ 13.262	–	24.35
8.b.	"	" 1.0	10.0	5.0	79.8	–	5.2	–	+ 12.483	–	+ 11.488	–	21.09
9.b.	"	" 1.5	14.38	3.3	77.4	–	4.96	–	+ 10.881	–	+ 10.014	–	18.38
10.b.	–	–	32.56	54.0	–	13.41	–	+ 20.147	–	+ 17.76	–	49.18	–
11.b.	–	LiCl 0.5	9.21	83.75	–	7.0	–	+ 21.480	–	+ 18.94	–	63.88	–
12.b.	–	" 1.0	14.8	80.36	–	8.15	–	+ 21.924	–	+ 19.35	–	68.12	–
13.b.	–	" 1.5	11.61	83.97	–	4.45	–	+ 21.582		+ 19.98	–	69.62	–
14.c.	150	–	6.38	42.51*	45.12	–	2.46	+ 19.765*	+ 11.309	+ 13.22	+10.413	–	19.12
15.d.	150	–	2.5	–	84.0	3.0	8.0	–	+ 13.201	–	+ 12.156	–	22.32

AME = Alanine methyl ester a = AME b = AME. HCl c = AME. HBr d = AME. $HClO_4$ * = Methyl-α-bromopropionate
10.b. = AME + $NaNO_2$ (Neat experiment), All α 589 were recorded of GLC pure liquids

the retention of the configuration of methyl-α-chloropropionate and methyl-α-acetoxypropionate has shown considerable increase whereas their percent composition did not change, however methylacrylate (I) and methyl-3-acetoxy ester (II) were doubied in their yield and the chloroester (III) was less produced. These results interpreted that the nucleophilic attack by increasing the acetate ions retained configuration otherwise competition between the acetate ions and the chloride ions would have occurred. In absence of acetic acid when only sodium acetate was added (Expt. 5b) where chloride ion and the acetate ion were competing the relative polariability of the chloride ion and its increase in the relative nucleophilic strength [18] as compared to the acetate ion, the nucleophilic attack by the chloride ion became evident in competition. Thus, the yield of methyl-α-chloropropionate (III) was increased and that of acetoxy ester (IV) decreased, but angle of rotation and percent retention of these esters had decreased. Due to slow addition of the acetate moiety on methyl acrylate (I) the change in percent composition for methyl acrylate (I) and methyl-3-acetoxypropionate (II) was recorded. Addition of sodium acetate (Expt. 6b–9b) in presence of excess of acetic acid the product compositon remained unchanged except for emthyl-α-acetoxy propionate (IV) which indicated that the addition of common ions decreased retention of configuration due to weaker basic nature of the acetate ion, its poor nucleophilicity and greater covalent radii of sodium as conjugate ion. Similarly the addition of lithium chloride in absence of acetic acid (Expt. 11b–13b) enhanced the yield, angle of rotation and percent retention for chloroester due to common ion effect. The alanine methyl ester salts with HCl, HBr and $HClO_4$ (Expt. 4b, 14c, 15d) on deamination showed increase in ester (IV) yield as well as the specific rotation and retention of configuration due to the nature of the acid used. Since substitution products were significantly produced instead of elimination products which indicated that carbocation species produced in the course of such reaction were more stable due to inductive and hyperconjugative effects for favourable attack by the incoming nucleophile as in the case of ethyl-(1-carboxymethyl) and iso-butyl-(1-carboxybenzyl) carbonium ions whereas 3-phenylpropyl-(2-carboxymethyl), iso-pentane-(4-carboxymethyl), ethyl-(1,2-dicarboxymethyl) and propyl-(1,3-dicarbosymethyl) carbonium ions all gave olefin product by ready loss of a proton (Table 2) because relatively unstable carbonium ions were involved during these solvolytic processes. Moreover, the neighbouring group participation by the bulky carboxymethyl group were helpful and prevented the attack by the solvent from the rear thus retaining configuration. Since L–(+)–alanine methyl ester acid salts retained configuration at an optically active centre under different conditions it has been thus concluded that such deaminations involve ion-pairs in diazonium ion formation as well as predominant retention of configuration occurs via front side attack of the carbocation by the incoming nucleophile. These

Table 2

Carbonium ion	Substitution (S)	Elimination (S)	Ratio S/E	Reference
Ethyl-(1-Carboxymethyl)	Major	Minor	24.5 (86/3)	Present investigation
iso-Ethyl-(1-Carboxybenzyl)	"	"	2.5 (55/22)	8
3-Phynylpropyl-(2.Carboxymethyl)	Minor	Major	0.31 (21/68)	8
Ethyl-(1,2-dicarboxymethyl)	"	"	0.04 (4/96)	12
Propyl-(1,3-dicarboxymethyl)	"	"	0.32 (14/44)	12
iso-Pentane-(4-Carboxymethyl)	"	"	0.21 (8/39)	9

reactions shows similarities to the other solvolytic reactions and do not involve hot carbonium ions or other high energy speices.

Acknowledgement. Author is thankful to the Alexander von Humboldt Foundation, Federal Republic of Germany for a fellowship and Prof. Dr. W. Kirmse for providing laboratory space research facilities and guidance throughout the progress of this work.

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