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INVESTIGATION ON ALKALINE CLEAVAGE OF N-NITROSO-N-CARBOMETHOXY AMINO ACID ESTERS

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Abstract. Alkaline cleavage of L(+) N-nitroso-N-carbomethoxy-alanine methyl ester and N-nitroso-N-carbomethoxy-1-phenyl-2, 2, 2-trifluoroethylamine methyl ester yielded substitution and denitrosation products. A reaction mechanism has been proposed.

Reaction of aliphatic amines with nitrous acid is known to involve diazotisation followed by deamination¹ to give rise to varying products depending on substrate and reaction conditions. Investigations have been carried out to establish the nature of the intermediate diazoalkanes and their mode of decomposition.³ N-Alkylnitrosoamides and N-carbamates on basic hydrolysis give products which were attributed to diazonium ions and were shown to be dependent on the nature of the solvent. base and alkyl groups.3'4 Solvolysis of methyl-(S)-N-nitroso (phenethyl) N-carbamate methyl ester in methanol yields 1-methoxy-1-phenylethane with partial inversion of configuration and 1phenyl-ethanol with predominant retention of configuration.⁵ It was not clear whether the intermediate diazonium ion had decomposed by a concerted process or whether ion-pairs were involved in such reactions leading to partial racemisation of products. For such an investigation, substitution by suitable groups capable of exerting an electron attracting effect should make the resulting diazonium ion susceptible to alkaline cleavage and provide an answer to the preceding question. Thus, replacing a methyl group with a trifluoromethyl group which is approximately the same size, but exerting the opposite inductive effect on substitution of carbomethoxy group for the phenyl group in methyl-N-nitrosc-(1-phenethyl)-N-carbamate methyl ester should render a strong impact in this respect. Hence L(+)-N-nitroso-N-carbomethoxyalanine methyl ester and N-nitroso-N-carbomethoxy-1-phenyl-2, 2, 2-trifluoroethylamine methyl ester were selected as models to observe the effect of carboxymethyl group or a CF3 group on the stability of the resulting diazoniumion and the effect this has upon the substitution products arising thereafter.

Results and Discussion

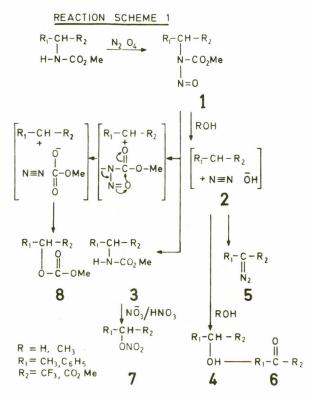
The results have shown that diazoesters were formed under the reaction conditions (Table 1). The stability of these esters was considered to be due to the carboxymethyl or trifluoromethyl substituent groups whose negative inductive-effects increase the $C \rightarrow N_2$ bond strength. Since deamination reaction did not proceed appreciably, as a result the products were formed in low yield and were difficult to collect pure in sufficient amounts for recording of optical rotation. Hence, the stereochemical consequences of the reaction are unknown. However, most of the products produced in low yields were collected by preparative GLC and compared with authentic samples by GLC. These fractions were also used for recording of IR, NMR, or mass spectra for structure elucidation. The following general scheme accounts for the products produced in these reactions (Scheme I).

TABLE 1

CO2 Me	ALKALI	PRODUCT CO2 Me	PERCENT
$CH_3 - CH - N - CO_2 Me$ N = 0	Na OMe/Me OH or Na OH/Me OH	CH3-CH-OCH3 CO2Me	3.0
	haony he on	$CH_3 - C = N_2$ CO_2Me	16.85
		CH ₃ -CH-N-CO ₂ M	e 76.44
CF3 C6H5-CH-N-CO2 Me N=0	NaO Me / Me OH or	$C_6 H_5 - C - CF_3$	13.6
N=O	NaOH/MeOH	C ₆ H ₅ -CHOH-CF ₃	15.7
		CF_{3} $ C_{6} H_{5} - C = N_{2}$ CF_{3}	43.17
		$C_{6} H_{5} - C \equiv N_{2}$ C_{5} $C_{6} H_{5} - C H - N - CO_{2} N$ $C_{6} H_{5} - C H - N - CO_{2} N$	1e 14.15
		C6H5-CH-OCO2M6	
		CF_3 I_3 C_6 H_5 - CH - ONO_2	2.8

N-Nitroso-N-carbomethoxy methyl ester¹ on reaction in a hydroxy solvent gave either an ionpair² or a denitrosation reaction, thus producing N-carbomethoxy derivative³ and hydroxy derivative.⁴ The former ion-pair resulted in the formation of diazoester⁵ which was one of the major products of the reaction. Ketone⁶ was produced by oxidation in air or with N₂O₄. The denitrosation reaction which has produced derivative³ further produced nitrate⁷ and carboxymethylate⁸ derivatives as secondary products of the reaction involving N-carboxymethyl—2,2, 2trifluoroethylamine by reaction with HNO₃ or NO₃ ion produced *in situ* and ion-pair rearrangement followed by substitution respectively.¹⁵

ALKALINE CLEAVAGE OF N-NITROSO-N-CARBOMETHOXY AMINO ACID ESTERS



Experimental

Materials. All chemicals used were research grade and solvents were analar. Purifications were carried out by preparative GLC or low temperature vacuum distillation techniques. Gas chromatographic analysis were carried out on a Fraktometer F-6 (Perkin-Elmer) by using capillary columns of various lengths. The columns used were 10% or 20% apiezon-L, carbowax, silicone oil, GEGA or PPG coated on celite. IR spectra were recorded on a Unicam SP 200 spectrophotometer. NMR spectra were produced on an R-10 60 MHz (Perkin-Elmer) instrument and mass spectra were recorded with AEI MS 12 instrument coupled with or without the Fraktometer and CH-5 Varimat mass spectrometers.

General Procedure. To the methyl ester of N-nitroso-N-carbomethoxy amino acid (0.1M) was added portionwise excess of NaOH or NaOMe (1N) at room temperature in a flask connected with a gas trap. The rate of evolution of the gas (N_2) was very slow which indicates slow hydrolysis of the substrates with alkali. Hence, the deamination reaction occurs with difficulty. After 48 hours of continuous stirring, the reaction mixture was extracted with ether, washed with water and dried over anhydrous MgSO4. Ether was removed - by distillation and the remaining yellow-brown concentrate was resolved on a suitable column by GLC and the separated fractions were identified with the help of NMR, IR, MS and combined GLC mass spectrometric techniques.

L(+)Alanine Methyl Ester Hydrochloride. This salt was prepared by Fischer esterification⁶ of L(+)alanine with anhydrous methanol and dry HCl gas. After removal of excess methanol, the viscous syrup crystallized and was dried under vaccum, m.p. 152° (reported m.p. 158-158.5°,7 yield, quantitative. The structure of the compound was supported by IR and NMR and was found indentical with an authentic sample.⁸

L(+)N-Carbomethoxyalanine Methyl Ester. To a well stirred ice-cold solution of L(+)alanine methyl ester hydrochloride mixed with potassium carbonate solution and benzene, methyl chloroformate was added dropwise⁹. The mixture was stirred for 2 hr and the benzene layer was removed. After washing with water the benzene solution was dried over anhydrous MgSO₄ and benzene was distilled. The viscous liquid retained in the flask was distilled, b.p. 74-76°/3mm., as a colourless syrup. Anal. Calculated for C₆HN₁₁O₄. Calc. C 44. 72%, H 6.83%, N 8.69%. Found: C 44.82%, H 6.83%, N 8.75%. The structure of the compound was supported by IR and NMR spectrum. The IR principal absorptions recorded were in the

region 1070 cm⁻¹ (C-O-C), 1700 cm⁻¹ (-C-), 2900 cm⁻¹ (C-H), 2940 cm⁻¹ (CH₃) and 3310 cm⁻¹ (N-H). NMR spectrum revealed the presence of a methyl, an amino (NH), two methoxy and a methine protons in the ratio of 3:1:3:3:1 at δ 1.21, 1.84, 3.6, 4.02 and 5.01 respectively.

L(+) N-Nitroso-N-Carbomethoxyalanine Methyl Ester. After dissolving L(+)N-Carbomethoxyalanine methyl ester (3 g) in dry ether (200 ml) in a flask, anhydrous sodium acetate (3g) was added and the suspension was cooled to -30° and stirred continuously by keeping the flask in an acetone-cardice bath. Redistilled N2O4 (4g) dissolved in (10 ml) dry ether was slowly dropped into the reaction flask and stirred for 2 hr and gradually temperature was increased to 0°. By continuous stirring for another 2 hr, the reaction flask was brought to room temperature. After distilling the ether, the crude nitroso derivative was collected as the residual golden yellow oil and purified by passing over a silica gel column with a chloroform-ether mixture (50:50).' A single fraction of light yellow colour was collected after it was checked by TLC. The IR spectrum of the compound supports the assigned structure, showing an IR band at 1500 cm⁻¹ for the -N-N=O grouping, and absence of NH bond at 3310 cm⁻¹. The NMR spectrum also supports the assigned structure.

N-Nitroso-N-Carbomethoxy-1-Phenyl-2, 2, 2-Trifluoroethylamine Methyl Ester. Synthesis of the compound was achieved by a new route¹⁰ and its carbomethoxy methyl ester was prepared by a known procedure⁷. The yield was quantitative, m.p. 96°, recrystallized from n-pentane. Its structure was supported by IR, NMR and mass spectrum. Anal. Calculated for $C_{10}H_{10}F_3NO_2$. Cal. C 51.50%, H 4.29%, N 6.01% Found : C 51.48%, H 4.29%, N 6.0%. The N-nitroso derivative of the N-carbomethoxy methyl ester was prepared by a procedure described earlier in this paper. Other compounds were synthesized for the present investigation included, α-methoxy-methyl lactate,¹¹ trifluoroacetophenone,¹² l-phenyl-2, 2, 2-trifluoromethylethanol,¹³ l-phenyl-2, 2, 2-trifluoromethyldiazoethane,¹⁴ l-phenyl-2, 2, 2-trifluoroethanol methyl carbonate and l-phenyl-2, 2, 2-trifluoroethyl nitrate,¹⁵

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