C-ALKYLATION OF HETEROCYCLIC ENAMINES*

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The composition of C-alkylation products in the thermal isomerisation of 1,1,2-trimethyl-2-pyrrolinium bromide (*VIIa*), 1,1-diethyl-2-methyl-2-pyrrolinium bromide (*VIIb*) and of their equimolecular mixture was determined by reduction of the isomerisation products with formic acid to saturated compounds which were identified by gas–liquid chromatographic comparison with authentic samples. Intermolecular mechanism of the isomerisation was proved.

Enamines can react with electrophilic reagents either at the nitrogen atom to give quaternary ammonium salts *I* or at the β-carbon atom under formation of immonium salts *II*. The reaction course of this reaction was studied mostly for protonation and alkylation and it was shown that it depends on the structure, basicity of the enamine, on the alkylating agent, solvent polarity and on the geometry of the transition state[1].

Addition of proton to heterocyclic enamines takes place almost exclusively at the β-carbon of the enamine grouping. The results of alkylation are not so unequivocal. Alkylation of 1-methyl-2-ethylidenepyrrolidine (*III*) with methyl iodide affords only product of β-alkylation, 1-methyl-2-isopropylidenepyrrolidine[2] (*IV*). Also alkylation with ethyl bromoacetate[3] proceeds similarly. On the other hand, methylation of enamines, derived from 1-azabicycloalkanes, leads to a mixture of products of alkylation both on nitrogen and β-carbon[4,5]. It has not been hitherto unequivocally proved whether the β-alkylation products arise directly or by isomerisation of the primarily formed products of N-alkylation. We tried to solve this problem in this communication.

Several years ago Lukeš and Červinka[6] indirectly prepared a quaternary ammonium salt derived from 1,2-dimethyl-2-pyrroline by the reaction of N,N-dimethyl-2-bromomethylpyrrolidinium bromide with base. We used this quaternary salt in the study of the course of isomerisation of an N-alkylated salt to a C-alkylated product. Using ^{1}H-NMR spectroscopy we confirmed our previous finding that the reaction of N,N-dimethyl-2-bromomethylpyrrolidinium bromide (*Va*) with silver oxide, followed by neutralisation with hydrobromic acid, leads to the quaternary salt *VI*

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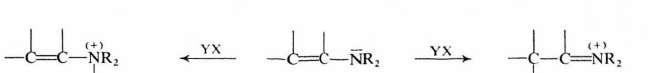
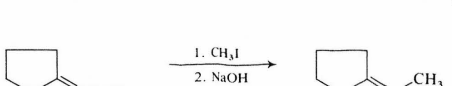
with exocyclic double bond whereas the reaction with sodium hydroxide affords the salt *VIIa* in which the double bond is endocyclic.



I *II*

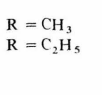


III *IV*

VIIa, R = CH_3
VIIb, R = C_2H_5

Va, R = CH_3
Vb, R = C_2H_5

VIa, R = CH_3
VIb, R = C_2H



VIIIa, $R^1 = R^2 = CH_3$; $R^3 = H$
VIIIb, $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = H$
VIIIc, $R^1 = R^2 = R^3 = CH_3$
VIIId, $R^1 = C_2H_5$, $R^2 = CH_3$; $R^3 = H$
VIIIe, $R^1 = C_2H_5$, $R^2 = n\text{-}C_3H_7$, $R^3 = H$
VIIIf, $R^1 = CH_3$, $R^2 = n\text{-}C_3H_7$, $R^3 = H$
VIIIg, $R^1 = R^2 = C_2H_5$, $R^3 = H$

The isomerisation was carried out by heating the quaternary salt briefly above its melting point in a closed flask. In order to identify all the reaction products, the isomerisation mixture was reduced with formic acid to saturated bases which were identified by gas–liquid chromatographic comparison with authentic standards. We found that the thermal isomerisation of the compound *VIIa* led to a mixture of salts of unsaturated bases which on reduction with formic acid afforded 1,2-di-

methylpyrrolidine (*VIIIa*), 1-methyl-2-ethylpyrrolidine (*VIIIb*) and 1,2,3-trimethylpyrrolidine (*VIIIc*). Since compound *VIIa* on heating with formic acid under the same conditions and on subsequent basification did not afford any steam-volatile base, we assume that the compound *VIIIa* arose during the isomerisation as a result of a mere loss of methyl bromide.

In order to decide whether the thermal isomerisation is an intramolecular or an intermolecular process we studied the analogous reaction of 1,1-diethyl-2-methyl-2-pyrrolinium bromide (*VIIb*) which after similar work-up afforded a mixture of 1-ethyl-2-methylpyrrolidine (*VIIId*), 1-ethyl-2-propyl-pyrrolidine (*VIIIe*) and a base which probably was 1,3-diethyl-2-methylpyrrolidine; the structure of this compound could not be proved since no authentic compound was available. Finally, thermal isomerisation of a mixture of both the quaternary salts *VIIa* and *VIIb* was carried out which led to the pyrrolidines *VIIIa*–*VIIIg* and an unidentified base with the longest retention time of the products. The principal products were *VIIId*, *VIIIf* and *VIIIg*; it is obvious that the latter two compounds could arise only by intermolecular isomerisation.

The quaternary salts *Va* and *Vb* were prepared by bromination-cyclisation[6] of the corresponding N,N-dialkyl-4-pentenylamines. N,N-Dimethyl-4-pentenylamine was obtained by cleavage of N,N-dimethylpiperidinium hydroxide, its diethyl analogue by reduction of N,N-diethyl-4-pentenamide with lithium aluminium hydride. The comparison samples of pyrrolidines were prepared by reaction of the corresponding 1-alkyl-2-pyrrolidones with Grignard reagents[7] followed by reduction of the obtained unsaturated bases with formic acid[8] or by reduction of their perchlorates with lithium aluminium hydride[9].

Thus, we proved that thermal isomerisation of quaternary ammonium salts derived from 2-pyrrolines *VIIa,b* affords a mixture of unsaturated bases which are products of alkylation at the β-carbon. The products contain bases the formation of which confirms the intermolecular reaction course.

EXPERIMENTAL

The melting and boiling points are uncorrected. ^{1}H-NMR spectra were measured on a Varian 100 instrument. Gas–liquid chromatographic analyses were performed on a Chrom-2 chromatograph at 100°C, using 15% Carbowax 6000 or 15% Tridox on Chromaton N/AW-DMCS.

1,1,2-Trimethyl-2-pyrrolinium Bromide (*VIIa*)

Eschweiler methylation of piperidine (50 g) with 38% formaldehyde (55 g) and formic acid (82 g) afforded N-methylpiperidine (32 g; 55%), b.p. 105°C. Treatment with methyl iodide (32 g) in ether gave the methoiodide (64 g; 81%) which was transformed into the quaternary hydroxide by the action of silver oxide. The hydroxide was heated to 170–180°C/20 Torr and N,N-dimethyl-4-pentenylamine which distilled at 117–119°C was collected (21 g; 70%). Addition of bromine (30 g) in chloroform (250 ml) afforded the compound *Va* (24 g), m.p. 237–239°C.

This salt (16·6 g) was heated with 25% sodium hydroxide (80 g) to 130°C for 5 min and the product was taken up in chloroform, yielding 5 g (44%) of the bromide *VIIa*, m.p. 236–237°C (ethanol). ^{1}H-NMR spectrum ($CDCl_3$), δ: 2·0, s, 3 H, ($CH_3C{=}C$); 2·8, m, 2 H ($-CH_2-C_{(4)}$); 3·7, s, 6 H ($N(CH_3)_2$); 4·5, t, 2 H ($-CH_2-C_{(5)}$); 6·0, m, 1 H ($-CH{=}C$).

1,1-Diethyl-2-methyl-2-pyrrolinium Bromide (*VIIb*)

4-Pentenoic acid, b.p. 88°C/20 Torr, prepared by alkaline hydrolysis of ethyl 4-pentenoate[10,11], was transformed into its chloride, b.p. 130–133°C, by treatment with thionyl chloride in dimethylformamide. This chloride (21 g) was dissolved in ether (80 ml) and a solution of diethylamine (38 g) in ether (100 ml) was added dropwise under cooling. After standing for one day the separated diethylamine hydrochloride was filtered off and the ether was evaporated. Distillation of the residue afforded N,N-diethyl-4-penteneamide (24 g; 86%), b.p. 118°C/20 Torr. For $C_9H_{17}NO$ (155·2) calculated: 68·60% C, 11·03% H, 9·03% N; found: 69·67% C, 11·08% H, 9·18% N.

A solution of this amide (24 g) in ether (130 ml) was added dropwise to a suspension of lithium aluminium hydride (5·9 g) in ether (300 ml). After heating for 3 h the mixture was decomposed by addition of water (6 ml), 15% sodium hydroxide (5 ml) and water (18 ml). The hydroxides were filtered off, the ethereal solution shaken with dilute hydrochloric acid and the bases liberated from the aqueous layer by addition of 5M sodium hydroxide. The aqueous layer was saturated with solid sodium hydroxide, the amine was separated and the aqueous layer extracted with ether (3 × 30 ml). The combined extracts were dried over potassium hydroxide and taken down. Distillation of the residue afforded 10 g (45%) of N,N-diethyl-4-pentenylamine, b.p. 154–155°C. This was dissolved in chloroform (100 ml) and a solution of bromine (12 g) in chloroform (120 ml) was added dropwise under stirring and cooling with ice. The solvent was evaporated and the remaining crystals were crystallized from ethanol, affording 1,1-diethyl-2-bromomethylpyrrolidinium bromide (*Vb*) as very hygroscopic crystals, m.p. 234–239°C; yield 16·9 g (79%).

Heating the salt *Vb* (16 g) with 25% sodium hydroxide solution (80 ml) for 5 min to 130°C and extraction with chloroform gave 3·6 g (31%) of *VIIb*, m.p. 230–240°C. For $C_9H_{18}BrN$ (220·1) calculated: 49·10% C, 8·24% H, 6·36% N; found: 48·96% C, 8·41% H, 5·97% N. ^{1}H-NMR spectrum ($CDCl_3$), δ: 1·4, t, 6 H ($N(CH_2C\underline{H}_3)_2$); 2·1, s, 3 H ($CH_3C{=}C$); 2·8, m, 2 H($-CH_2-C_{(4)}$); 4·0, m, 6 H ($C\underline{H}_2CH_3$ and $-CH_2-C_{(5)}$); 6·2, m, 1 H ($-CH{=}$).

Thermal Isomerisation of Quaternary Salts and the Reduction with Formic Acid

The bromide *VIIa* (0·9 g) was heated for 20 min to 240°C. After cooling, 98% formic acid (5 ml) and fused potassium formate (5 g) were added the mixture refluxed for 4 h, made alkaline, the bases steam-distilled and the distillate titrated with 1M hydrochloric acid and taken down. The bases were liberated by addition of sodium hydroxide solution, and taken up in ether, dried over solid potassium hydroxide, the solution taken down and the residue analysed by chromatography. Thermal isomerisations of 1,1-diethyl-2-methyl-2-pyrrolinium bromide (*VIIb*) (1·1 g) and of the mixture of *VIIa* (1·0 g) and *VIIb* (1·0 g) were carried out in an analogous manner.

1-Ethyl-2-methylpyrrolidine (*VIIId*)

1-Ethyl-2-methyl-2-pyrroline was obtained by reaction of methylmagnesium iodide with 1-ethyl-2-pyrrolidone (from butyrolactone and ethylamine). Perchlorate, m.p. 203–210°C. For $C_7H_{14}.ClNO_4$ (211·6) calculated: 39·71% C, 6·62% H, 6·62% N; found: 39·43% C, 6·57% H, 6·41% N. The liberated base was reduced with formic acid to the saturated amine *VIIId*, b.p. 53–55°C.

1,2-Diethylpyrrolidine (*VIIIg*)

Reaction of ethylmagnesium bromide with 1-ethyl-2-pyrrolidone afforded 1,2-diethyl-2-pyrroline. Perchlorate, m.p. 203—208°C; for $C_8H_{16}ClNO_4$ (225·7) calculated: 42·57% C, 7·15% H, 6·21% N; found: 42·75% C, 7·23% H, 6·31% N. The perchlorate was reduced with lithium aluminium hydride to 1,2-diethylpyrrolidine, b.p. 75—78°C/107 Torr. For $C_8H_{17}N$ (127·2) calculated: 75·52% C, 13·47% H, 11·01% N; found: 75·47% C, 13·62% H, 11·07% N.

1-Ethyl-2-propylpyrrolidine (*VIIIe*)

This compound was prepared analogously as described in the preceding experiment. Perchlorate, m.p. 190—198°C. For $C_9H_{18}ClNO_4$ (239·7) calculated: 45·09% C, 7·57% H, 5·84% N; found: 45·14% C, 7·64% H, 5·61% N. The saturated base *VIIIe* boils at 97°C/75 Torr. For $C_9H_{19}N$ (141·2) calculated: 76·52% C, 13·56% H, 9·92% N; found: 76·33% C, 13·61% H, 10·18% N.

Preparation of the Comparison Samples

1,2-Dimethylpyrrolidine (*VIIIa*) and 1,2,3-trimethylpyrrolidine (*VIIIc*) were prepared by reduction of the corresponding 2-pyrrolines with formic acid. 1-Methyl-2-ethylpyrrolidine (*VIIIb*), b.p. 122—123°C, and 1-methyl-2-propylpyrrolidine (*VIIIf*), b.p. 147—148°C, were already described.[9]

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