An Anomalous Eschweiler-Clarke Reaction

Saïd Rahal* and Leïla Badache

Institut de Chimie, U.S.T.H.B., BP 32, El Alia, Bab Ezzouar, Alger, Algérie

Key-words : Eschweiler-Clarke reaction HCHO/HCO2H, reflux

<u>Abstract</u>: Reaction of b-alanine 1 with formaldehyde in the presence of formic acid under Eschweiler-Clarke conditions yields the corresponding betaine 3 instead of the expected N,N dimethyl β -alanine 2.

The Eschweiler-Clarke reaction^{1,2} is commonly used for methylation of primary or secondary amines by the action of formaldehyde in the presence of formic acid ; the mechanism involves formation of intermediate iminium ions, which are reduced by formic acid with liberation of carbon dioxide, leading always to tertiary amines without formation of quaternary alkylammonium salts.

This reaction can also work on amino-acids, and N,N-dimethylamino-acids have been prepared, even if authors² report failure in some cases. In our laboratory, we tested this reaction on various amino-acids³ and found it efficient for the soluble ones ; however, we obtained an unexpected Eschweiler-Clarke product with β -alanine 1, for which this reaction led to the corresponding betaine³⁴ (82% yield) instead of the anticipated N,N-dimethyl β alanine 2⁵.

This behaviour has never been reported in Eschweiler-Clarke reactions, and seems to be specific to the β -position of the amine function; no betaine has been obtained with the homologues glycine and α -aminobutanoic acid, which gave the corresponding N,N-dimethyl derivatives 4 and 5 in good yields (82 and 89 % respectively)⁶.

The mechanism probably involves further attack of N,N-dimethyl β -alanine 2 by formaldehyde, giving an equilibrium with the quaternary salt 6; an elimination would be favoured on this adduct, liberating acrylic acid 7 which would be attacked *in situ* by the generated trimethylamine to give the final betaine 3.

$$2 \xrightarrow{\text{CH}_2\text{OH}} (\text{CH}_3)_2\text{N-CH}_2\text{CH}_2\text{CO}_2\text{H}, \text{HCO}_2 \xrightarrow{-7} -H_2\text{O}$$

$$6 \xrightarrow{+} H_2\text{C=N(CH}_3)_2, \text{HCO}_2 \xrightarrow{-\text{CO}_2} \text{N(CH}_3)_3 \xrightarrow{7} 3$$

A β -lactone intermediate is not considered because γ -amino-acids would give also betaines under these conditions, γ -lactones being easier to generate.

A similar elimination has been reported by Watanabe et al⁷ who obtained an unsaturated diester **9** when they submitted the cyclic β -amino-diester **8** to the Eschweiler-Clarke methylation; in this case, betaines cannot be formed, the acid function being protected.



- 1. Eschweiler, W. Ber., 1905, 38, 880.
- 2. Clarke, H.T.; Gillespie, H.B. and Weisshauss, S.Z. J. Am. Chem. Soc., 1933, 55, 4571.
- 3. Conditions: 0.3 mol. of amino-acid, 65 ml of 37-40% HCHO and 75 ml of 90% HCO₂H are refluxed until CO₂ evolution ceases (6-17h). 30 ml concentrated HCl is added and the solution evaporated under reduced pressure. The resulting N,N-dimethylaminoacid hydrochlorides are crystallized in an ethanol/acetone mixture.

Treatment of the hydrochlorides with an equivalent quantity of freshly pricipitated silver oxide (ref.8), filtering and evaporating to dryness leads to the N,N-dimethylamino acids as solids, crystallized in ethanol/acetone.

- 4. **3** : m.p. 119-120°C ; n (KBr) 1600 cm⁻¹ ; d_H(D₂O) 3.57 (t, 2H, 7.3 Hz), 3.12(s, 9H), 2.67 (t, 2H, 7.3 Hz); m/e 132 (MH)⁺
- Betaine 3 melts at 119-120°C. Gresham et al⁹ have prepared this compound by the action of trimethyamine on β-propiolactone and reported as m.p.120-121°C. They also prepared N,N-dimethyl β-alanine 2, m.p. 140-142°C.
- 6. 4: m.p. 182-182.5°C; v(KBr) 1630 cm⁻¹; δH(D₂O) 3.74 (s, 2H), 2.94 (s, 6H); m/e 104 (MH)⁺
 5, HCl: m.p. 156-157°C; v(KBr) 1710 cm⁻¹; δH(D₂O) 3.46 (t, 2H, 5.5 Hz), 3 18 (s, 6H), 2.79 (t, 2H, 7.2 Hz), 2.28 (q, 2H, 7.2 Hz); m/e 132 (m-Cl)⁺
- 7. Watanabe, K. and Wakabayashi, T. J. Org. Chem., 1980, 45, 357.
- 8. Clarke, H.T. and Behr, L.D. Org. Syn. Coll. Vol, 1969, Vol.II, 19.
- Gresham, T.L.; Jansen, J.E.; Shaver, F.W.; Bankert, R.A. and Fiedorek, F.T. J. Am. Chem. Soc., 1951, 73, 3168.

(Received in France 16 April 1991)