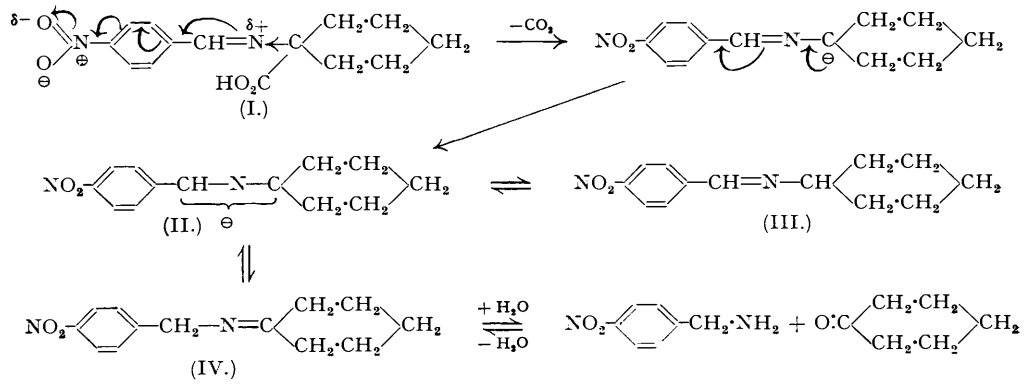
29. *Triad Prototropic Systems. Part I. The Mobility of the Azomethine System during Decarboxylation.*

By Fawzy G. Baddar.

Whereas *p*-nitrobenzylidene-ethylamine and -cyclo*hexylamine*, and *o*-chlorobenzylidene-*cyclo*hexylamine and -ethylamine do not undergo tautomerism when refluxed with 50% glycerol or even dry pyridine, 1-amino*cyclo*hexane-1-carboxylic acid and alanine are readily degraded, when heated with *p*-nitro- or *o*-chloro-benzaldehyde in 75% pyridine, to *cyclo*hexanone and acetaldehyde, respectively. This shows that the anion (cf. II and VI) resulting from the decarboxylation of the corresponding azomethine-carboxylic acid (cf. I and V), which is supposed to be formed as an intermediate product, is more mobile than the corresponding azomethine (cf. III and VII). Further, *m*-chlorobenzaldehyde and dichloroacetone degrade alanine and α-amino*iso*butyric acid to acetaldehyde and acetone, respectively. In all cases the degradation is facilitated by replacing 50% glycerol by 75% pyridine.

In a previous publication (Baddar, *J.*, 1949, S 163), the degradation of α-amino-acids by certain carbonyl compounds was interpreted electronically. According to this interpretation the degradation can be effected by any carbonyl compound, in which the carbonyl group is preferably directly attached to, or conjugated with, strong electron-attracting groups. The azomethine systems are known to be immobile (cf. Ingold and Piggott, *J.*, 1922, **121**, 2381) and tautomerism in these systems requires strong nucleophilic reagents such as sodium ethoxide (cf. Ingold, Shoppee, and Thorpe, *J.*, 1926, 1477; Ingold and Shoppee, *J.*, 1929, 1199). The degradation of α-amino-acids with certain carbonyl compounds is supposed to take place by the condensation of the carbonyl compound with the α-amino-acid to give an azomethine-carboxylic acid (cf. I), which is then decarboxylated to an intermediate anion (cf. II). This, owing to its mobility, can combine with a free proton to give a mixture of the two possible tautomerides (cf. III and IV).



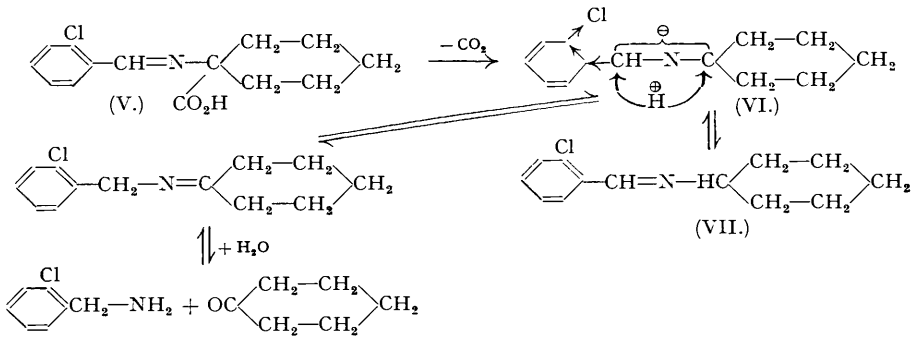
In the present investigation the author made a comparative study of the effect of decarboxylation on the mobility of these systems. It was found that, whereas certain azomethines are immobile even in presence of strong nucleophilic reagents such as sodium ethoxide, the system becomes mobile, even in presence of a weak nucleophilic reagent such as pyridine, if decarboxylation is expected to take place as an intermediate step. Thus, whereas, *p*-nitrobenzylidene-ethylamine, and -*cyclo*hexylamine (III) gave practically no acetaldehyde or *cyclo*hexanone respectively when refluxed with 50% glycerol or even with dry pyridine, alanine (cf. Baddar, *loc. cit.*) and 1-amino*cyclo*hexane-1-carboxylic acid gave, when refluxed with 50% glycerol, acetaldehyde, and *cyclo*hexanone respectively.

Similarly, whereas *o*-chlorobenzylidene-*cyclo*hexylamine (VII) and -ethylamine did not undergo tautomerism when refluxed with dry pyridine or, in the case of the former compound, with

alcoholic sodium ethoxide, 1-amino*cyclo*hexane-1-carboxylic acid and alanine were degraded with *o*-chlorobenzaldehyde, when heated with 75% pyridine, to *cyclo*hexanone and acetaldehyde respectively.

If the azomethine-carboxylic acids (I) and (V) are formed as intermediate products and the ionic nature of decarboxylation is accepted (cf. Brown and Hammick, *J.*, 1949, 173), the corresponding azomethine-carboxylate ions afford on decarboxylation the mesomeric azomethine anions (II) and (VI) respectively. This naturally requires much less energy than that necessary for the extraction of a proton from the azomethine systems (III) and (VII).

o-Nitrobenzaldehyde with 1-amino*cyclo*hexane-1-carboxylic acid gave an indigo-blue compound, but no *cyclo*hexanone was isolated. The nature of this compound, as well as those similarly obtained from alanine and α-amino*iso*butyric acid (cf. Baddar, *loc. cit.*), is under investigation. The yield of *cyclo*hexanone liberated from 1-amino*cyclo*hexane-1-carboxylic acid with *m*-nitrobenzaldehyde was much less than that with *p*-nitrobenzaldehyde. This supported the previous assumption by Baddar (*loc. cit.*) that in *m*-nitrobenzaldehyde the nitro-group operates only by its relatively weak inductive effect ($-I$), whereas, in *p*-nitrobenzaldehyde it operates by both its inductive ($-I$) and its strong tautomeric ($-T$) effect.



In *o*-chlorobenzaldehyde the chlorine atom appears to operate only by its strong inductive effect ($-I$), thus effecting the decarboxylation of the azomethine-carboxylic acid (V) and enhancing the mesomeric shift of electrons in the intermediate anion (VI). The electromeric effect ($+E$) of the chlorine atom appears not to operate in this degradation, as the yield of acetaldehyde and acetone liberated from alanine and α-amino*iso*butyric acid, respectively, by *o*-chlorobenzaldehyde was slightly higher than that liberated by *m*-chlorobenzaldehyde under the same conditions.

The above observations, however, add a further proof to the ionic nature of prototropy (cf. Ingold, Shoppee, and Thorpe, *loc. cit.*; Ingold and Shoppee, *loc. cit.*; Shoppee, *J.*, 1931, 1225).

The degradation of alanine and α-amino*iso*butyric acid to acetaldehyde and acetone respectively was effected also by *s*-dichloroacetone in boiling water. The yield increased when water was replaced by 50% glycerol. This showed that the effect of glycerol in increasing the yield is not merely to aid dissolution or wetting but is probably caused by its higher boiling point and its greater nucleophilic character. Under similar conditions *s*-dichloro*iso*propyl alcohol failed to effect this degradation. This showed that the carbonyl group in *s*-dichloroacetone is involved, probably by a mechanism similar to that mentioned above. In *s*-dichloroacetone the two chlorine atoms exert more electron-attraction on the system than the one chlorine atom in the chlorobenzaldehydes, and thus cause an easier degradation.

Experimental.

The degradation of α-amino-acids was carried out as mentioned by Baddar (*loc. cit.*). The liberated carbonyl compounds were identified as their 2 : 4-dinitrophenylhydrazones. Yields are reproducible within ±10%, although they are of no quantitative significance as the hydrazones were contaminated with traces of those of the original carbonyl compounds.

Degradation of Alanine with o- *and* m-*Chlorobenzaldehyde.*—(i) *o*-Chlorobenzaldehyde (0·46 g., 1 mol.) and alanine (0·3 g., 1 mol.) were heated on a boiling water-bath with 75% pyridine (20 c.c.) in a carbon dioxide atmosphere for 3 hours. The liberated acetaldehyde was precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·09 g.) (Found : C, 43·2; H, 3·7; N, 24·8. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0%), which was crystallised from alcohol and identified by its m. p. and mixed m. p. with an authentic specimen.

(ii) The experiment was repeated using *m*-chlorobenzaldehyde, and the liberated acetaldehyde was

precipitated as its 2 : 4-dinitrophenylhydrazone (*ca.* 0·065 g.) and identified as above (Found : N, 25·4, 24·8%).

When the degradation was carried out with *o*-chlorobenzaldehyde (0·46 g.) in 50% glycerol (cf. Baddar, *loc. cit.*), only *ca.* 0·01 g. of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected, which after two crystallisations were identified as above.

Degradation of Alanine with s-*Dichloroacetone.*—A mixture of dichloroacetone (0·84 g., 1 mol.), alanine (0·6 g.), and water (20 c.c.) was refluxed in a carbon dioxide atmosphere for 3 hours. The precipitated hydrazone (*ca.* 0·07 g.) was crystallised from dilute alcohol and identified as above (Found : C, 42·9; H, 3·6; N, 24·3%).

When water was replaced by 50% glycerol, the yield of acetadehyde enormously increased. Pyridine could not be used as it appeared to react with dichloroacetone.

α-Amino*iso*butyric acid, when similarly treated, gave acetone.

Under similar conditions *s*-dichloro*iso*propyl alcohol failed to effect the degradation of alanine.

Degradation of α-Aminoisobutyric Acid with o- *and* m-*Chlorobenzaldehyde.*—A mixture of the chlorobenzaldehyde (0·46 g., 1 mol.), α-amino*iso*butyric acid (0·35 g., 1 mol.), and 75% pyridine (20 c.c.) was heated for 3 hours as above.

(i) With *o*-chlorobenzaldehyde, the precipitated derivative (*ca.* 0·1 g.) was crystallised from dilute alcohol and identified as acetone 2 : 4-dinitrophenylhydrazone (Found : C, 45·5, 45·3; H, 4·1, 4·3; N, 23·0. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2, N, 23·95%), by its m. p. and mixed m. p. with an authentic specimen.

(ii) With *m*-chlorobenzaldehyde, the precipitated acetone 2 : 4-dinitrophenylhydrazone (*ca.* 0·55 g.) was identified as above (Found : C, 45·8; H, 4·3; N, 23·5, 23·4%).

With 50% glycerol practically no acetone was liberated.

Degradation of 1-*Amino*cyclo*hexane*-1-*carboxylic Acid with* p- *and* m-*Nitrobenzaldehyde.*—The amino-acid (0·5 g., 1 mol.) and the nitrobenzaldehyde (0·5 g., 1 mol.) were heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere. Water was added and the product distilled in a carbon dioxide atmosphere. The distillate was treated with a solution of 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with boiling alcohol, filtered from the insoluble derivative of the nitrobenzaldehyde, diluted with water, and allowed to crystallise. In case of *p*-nitrobenzaldehyde, the yield of the crystalline derivative was about 0·15 g., and was identified as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone by m. p. and mixed m. p. (Found : C, 51·7, 52·0; H, 5·2, 5·0; N, 20·6, 20·1. Calc. for $C_{12}H_{14}O_4N_4$: C, 51·8; H, 5·0; N, 20·1%).

With *m*-nitrobenzaldehyde, traces of the *cyclo*hexanone derivative were isolated and were identified by m. p. and mixed m. p.

o-Nitrobenzaldehyde gave an indigo-blue compound but practically no *cyclo*hexanone came over on distillation (cf. Baddar, *loc. cit.*).

Degradation of 1-*Amino*cyclo*hexane*-1-*carboxylic Acid with* o-*Chlorobenzaldehyde.*—A mixture of *o*-chlorobenzaldehyde (0·3 g.), the α-amino-acid (0·3 g.), and 75% pyridine (20 c.c.) was treated as above. The reaction mixture was acidified with dilute hydrochloric acid and distilled. The distillate was treated with 2 : 4-dinitrophenylhydrazine hydrochloride, the precipitated derivative extracted with hot alcohol, and the solution filtered. The filtrate was diluted with water and allowed to crystallise. The product was recrystallised from dilute alcohol and identified by m. p. and mixed m. p. as *cyclo*hexanone 2 : 4-dinitrophenylhydrazone. The fraction insoluble in alcohol crystallised from acetic acid in orange-red crystals, m. p. 208·5—209·5°, undepressed on admixture with an authentic specimen of *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone.

When the degradation was carried out in 50% glycerol instead of 75% pyridine, practically no *cyclo*hexanone was liberated.

o-*Chlorobenzylidene-ethylamine.*—*o*-Chlorobenzaldehyde (5·0 g.) was treated with anhydrous ethylamine (6 c.c.) in the cold. Heat was evolved and the aldehyde dissolved. The mixture was left overnight at room temperature, diluted with water, and extracted with ether. The *o-chlorobenzylidene-ethylamine* was dried (Na_2SO_4) and distilled, to give a colourless oil, b. p. 84·5°/3 mm. (Found : C, 64·4; H, 6·0; N, 8·0, 8·3; Cl, 21·4, 21·5. $C_9H_{10}NCl$ requires C, 64·5; H, 6·0; N, 8·4; Cl, 21·2%). It was soluble in dilute hydrochloric acid, and decomposed to give the original aldehyde on warming.

p-*Nitrobenzylidene*cyclo*hexylamine* (III).—An ethereal solution of *p*-nitrobenzaldehyde (1 g.) and *cyclo*hexylamine (0·66 g.) was set aside overnight. The ethereal solution was washed with 2% acetic acid and with sodium hydrogen carbonate solution, and then dried (Na_2SO_4). Evaporation of the ether left a *benzylidene* derivative (*ca.* 1·5 g.), which crystallised from light petroleum (b. p. 60—70°) in colourless prismatic needles, m. p. 85·5—86° (Found : C, 67·4, 66·9; H, 6·9, 6·9; N, 11·8, 12·2. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

o-*Chlorobenzylidene*cyclo*hexylamine* (VII).—An ethereal solution of *o*-chlorobenzaldehyde (2·8 g.) and *cyclo*hexylamine (2·0 g.) was treated as above. The dry product was distilled in a vacuum, to give *o-chlorobenzylidene*cyclo*hexylamine* as a colourless oil, b. p. 135—136°/3 mm. (*ca.* 3·8 g.) (Found : C, 70·0, 70·6; H, 7·0, 7·3; N, 6·4, 6·3; Cl, 16·5, 15·6. $C_{13}H_{16}NCl$ requires C, 70·4; H, 7·2; N, 6·3; Cl, 16·0%). It dissolved in dilute hydrochloric acid and decomposed on warming.

p-*Nitrobenzylidene-ethylamine.*—A mixture of *p*-nitrobenzaldehyde (0·5 g.) and 30% aqueous ethylamine (4 c.c.) was heated for few minutes on a water-bath. The mixture was diluted with water, and the precipitated *product* (0·55 g.) was filtered off and crystallised from light petroleum (b. p. 60—70°) in colourless silky needles, m. p. 76—77° (Found : C, 61·0, 60·7; H, 5·7, 5·4; N, 15·4, 15·5%; *M*, 176. $C_9H_{10}O_2N_2$ requires C, 60·7; H, 5·6; N, 15·7%; *M*, 178).

Tautomerism of o-*Chlorobenzylidene-ethylamine.*—(i) When *o*-chlorobenzylidene-ethylamine (0·5 g.) was heated with 50% glycerol (20 c.c.) for 3 hours in a carbon dioxide atmosphere, practically no acetaldehyde was liberated. A similar result was obtained when glycerol was replaced by dry pyridine and the mixture refluxed for 6 hours, followed by acidification with dilute sulphuric acid and distillation in a carbon dioxide atmosphere.

(ii) The azomethine (0·5 g.) was refluxed with alcoholic sodium ethoxide (1 g. of sodium in 20 c.c. of

absolute alcohol) for 5 hours. The solution was acidified with dilute sulphuric acid, and the liberated acetaldehyde was driven off by a stream of carbon dioxide. An appreciable amount of acetaldehyde 2 : 4-dinitrophenylhydrazone was collected and identified by its m. p. and mixed m. p. However, a similar result was obtained when the experiment was repeated with ethylamine itself.

Tautomerism of p-*Nitrobenzylidene-ethylamine and* -cyclo*hexylamine.*—The azomethines were refluxed with 50% glycerol or dry pyridine as stated above. The product was acidified with dilute sulphuric acid and distilled. Practically no acetaldehyde or *cyclo*hexanone was obtained.

Tautomerism of o-*Chlorobenzylidene*cyclo*hexylamine.*—The azomethine was similarly refluxed with 50% glycerol, dry pyridine or sodium ethoxide. The acidified solution was distilled, and the distillate treated with 2 : 4-dinitrophenylhydrazine hydrochloride. The precipitated derivative was extracted with hot alcohol, and the extract filtered, diluted with water, and allowed to crystallise. The precipitated product, *o*-chlorobenzaldehyde 2 : 4-dinitrophenylhydrazone (trace), melted at 200—202°.

M. p.s are not corrected. Microanalyses were carried out by Drs. Weiler and Strauss of Oxford.

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