S 36. *The Electronic Interpretation of the Strecker Degradation.*

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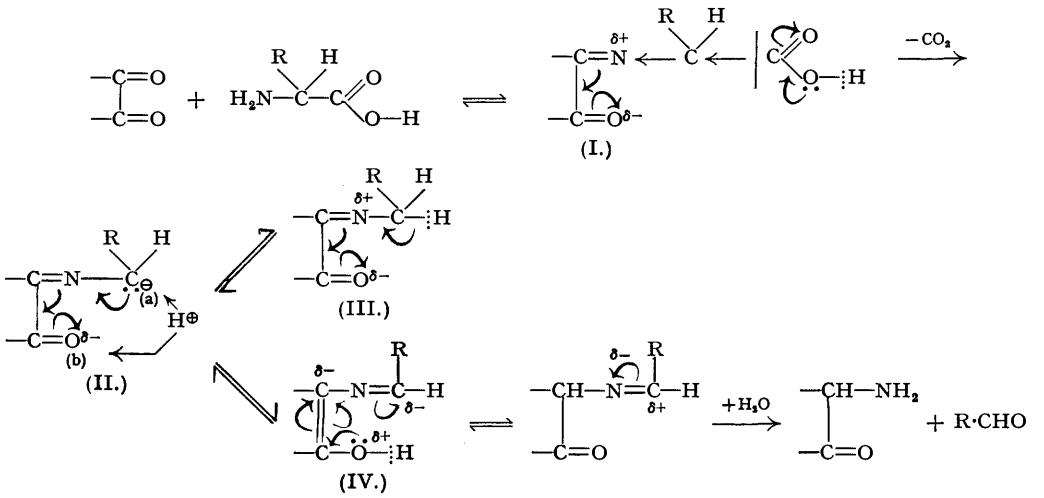
The mechanism suggested by Schönberg, Moubasher, and Mostafa (*J.*, 1948, 176) to explain the degradation of α-amino-acids to the corresponding aldehydes or ketones, containing one less carbon atom, by the action of certain carbonyl compounds is interpreted electronically. Besides the compounds listed in Table I (Schönberg *et al.*, *loc. cit.*) *o*-, *m*-, and *p*-nitrobenzaldehyde are found to effect the degradation of alanine, α-amino*iso*butyric acid, and α-aminophenylacetic acid to acetaldehyde, acetone, and benzaldehyde respectively. *N*-*o*-Nitrobenzylidene-ethylamine (IX, R = Me) gives acetaldehyde on refluxing with 50% glycerol, whereas *N*-*p*-nitrobenzylidenebenzylamine (VIII, R = H; R_1 = Ph) gives benzaldehyde when refluxed with pyridine followed by hydrolysis with dilute sulphuric acid.

In a recent publication, Schönberg, Moubasher, and Mostafa (*loc. cit.*) concluded from a study of the Strecker degradation of α-amino-acids, with certain carbonyl compounds, to the corresponding aldehydes or ketones with one less carbon atom, that the following two conditions must be satisfied: (1) The two hydrogen atoms attached to the nitrogen atom must be unsubstituted. (2) The carbonyl compound should contain the grouping ·CO·[CH:CH]$_n$·CO· where n = 0 or an integer, and that at least one ·CO· group must be aldehydic or ketonic.

The mechanism put forward by the above authors [see scheme B, *loc. cit.*] (cf. Herbst, *J. Amer. Chem. Soc.*, 1936, **58**, 2239; Herbst and Rittenberg, *J. Org. Chem.*, 1943, **8**, 380) is electronically interpreted and can be symbolised as follows :



The mesomeric displacement of electrons initiated by the carbonyl group in (I) will place a positive charge on the imino-nitrogen atom which facilitates the elimination of carbon dioxide as shown. Either the liberated proton or one from the medium can attack either of the two negative centres (a) and (b) in (II) to give (III) or (IV) respectively. The proportion in which material in the intermediate state (II) undergoes change to (III) or (IV) would depend on the relative rates with which the mesomeric anion (II) takes up the proton. The dotted lines indicate the fate of electron pairs originally forming the bonds.

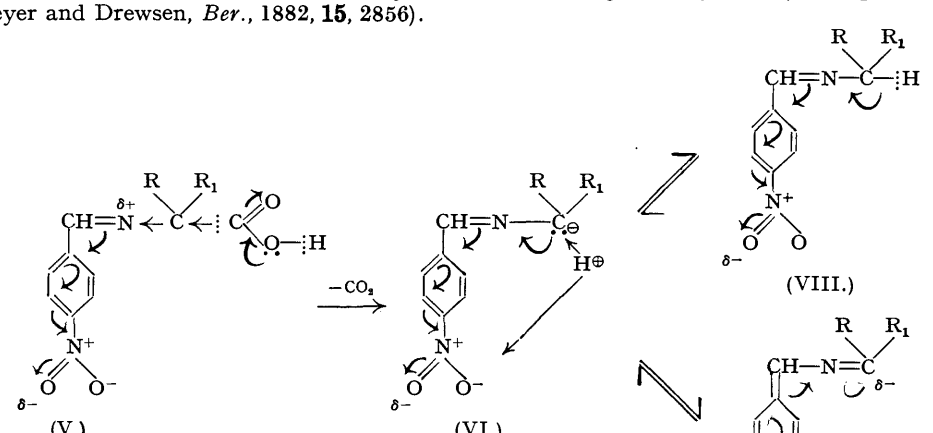
The decarboxylation of (I) and the mesomeric displacement of electrons in (II) are enhanced by any electron-attracting group which facilitates the release of the proton and at the same time forms a suitable seat for the remaining negative charge. Such a group must be preferably directly attached to or conjugated with the imino-carbon atom in (I). The fact that these conditions are fulfilled by all the compounds listed in Table I and not by most of those in Table II of Schönberg's communication (*loc. cit.*) is strong evidence for this electronic interpretation.

Further proof of its validity was obtained in the present investigation. According to the above mechanism one would expect that any carbonyl compound in which the carbonyl group is directly attached to or conjugated with any strong electron-attracting group (other than ·CO·), which fulfils the above requirements (*e.g.* NO_2), would effect the Strecker degradation.

o- and *p*-Nitrobenzaldehyde were chosen since in these compounds the nitro-group is conjugated with the carbonyl group through the benzene nucleus. They are also known to condense both with primary amines (Andree, *Ber.*, 1902, **35**, 420: Ingold and Piggott, *J.*, 1922, **121**, 2381) and with α-amino-acids (Bergmann, Ensslin, and Zervas, *Ber.*, 1925, **58**, 1034). As expected, they were found to react with alanine, α-amino*iso*butyric acid, and α-aminophenylacetic acid when refluxed in 50% aqueous glycerol in an atmosphere of carbon dioxide, to give appreciable amounts of acetaldehyde, acetone, and benzaldehyde respectively. However, when a mixture of *p*-nitrobenzaldehyde and alanine was either heated with 50% aqueous glycerol on the water-bath or refluxed with water, traces only of acetaldehyde were liberated. When the above solvents were replaced by 75% aqueous pyridine and the mixture heated on the water-bath, the acetaldehyde was more quickly liberated and its yield enormously increased.

m-Nitrobenzaldehyde, however, reacted very slowly with alanine, α-amino*iso*butyric acid, and α-aminophenylacetic acid in boiling 50% aqueous gycerol, giving poor yields of acetaldehyde, acetone, and benzaldehyde respectively. Although the yield of acetaldehyde and acetone increased enormously when glycerol was replaced by 75% aqueous pyridine, it was much less than that obtained with *o*- and *p*-nitrobenzaldehyde. This was expected since in *o*- and *p*-nitrobenzaldehyde, the nitro-group operates both by its strong tautomeric effect ($-T$) and by its relatively weak inductive effect ($-I$). In *m*-nitrobenzaldehyde, the nitro-group is not conjugated with the carbonyl group and, therefore, can only operate by its relatively weak inductive effect ($-I$). The yield of acetaldehyde and acetone in the case of *o*-nitrobenzaldehyde

was less than that in case of the *p*-derivative. This may probably be due to the condensation of *o*-nitrobenzaldehyde with both acetaldehyde and acetone to give indigo-blue (see Experimental) (Baeyer and Drewsen, *Ber.*, 1882, **15**, 2856).



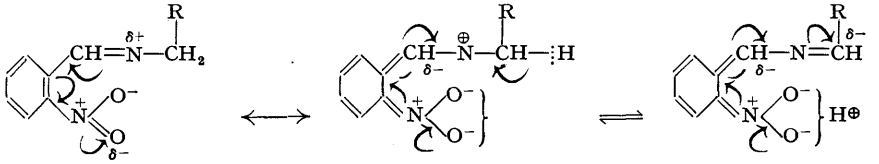
(V.) (VI.) (VIII.) (VII.)

(R = H or Me; R_1 = H, Me, or Ph)

The enhancing effect of pyridine cannot be merely one of solubility, for although the mixture of alanine and *p*-nitrobenzaldehyde is more soluble in boiling water or in 40% aqueous pyridine than in 75% aqueous pyridine, yet in the first two cases the yield of acetaldehyde was much poorer.

It is, therefore, more probably due to its basic property (nucleophilic character), which makes it a good proton acceptor. This would favour the condensation of the aldehyde with the α-amino-acid (Gulland and Mead, *J.*, 1935, 211), facilitate the decarboxylation, and enhance the mesomeric displacement of electrons in (VI).

The suggested mechanism was further supported by the fact that *N*-*o*-nitrobenzylideneethylamine (IX; R = Me) (Andree, *loc. cit.*) liberated acetaldehyde on refluxing with 50% aqueous glycerol in a stream of carbon dioxide. The imine (IX; R = Me) dissolves in ice-cold dilute hydrochloric acid, but decomposes slowly on standing at room temperature, or quickly on warming, to *o*-nitrobenzaldehyde and ethylamine hydrochloride (Ingold and Piggott, *loc. cit.*). The extra stability of the imine (IX; R = Me) in neutral or alkaline media is caused by its resonance with structure (IXa; R = Me). This resonance is inhibited in acid medium by the addition of a proton to the imino-nitrogen atom. The imine (IX; R = Me) is a methyleneazomethine system and its hydrolysis to acetaldehyde by neutral or alkaline media requires the prototropic interconversion between the tautomerides (IX) and (X) (Ingold *et al.*, *J.*, 1935, 1778; Baker, Nathan, and Shoppee, *J.*, 1935, 1847; Shoppee, *J.*, 1931, 1225; 1932, 696).



(IX.) (IXa.) (X.)

When *N*-*p*-nitrobenzylidenebenzylamine (VIII; R = H; R_1 = Ph) was refluxed with 75% aqueous glycerol and the product hydrolysed with dilute sulphuric acid and steam distilled, it gave only traces of benzaldehyde which could not be isolated as pure phenylhydrazone. This was not unexpected since Ingold and Piggott (*loc. cit.*), and Shoppee (*J.*, 1931, 1225) have shown that this methyleneazomethine is a non-mobile system. However, when it was refluxed with

dry pyridine for 6 hours followed by hydrolysis with dilute sulphuric acid, an appreciable amount of benzaldehyde was obtained. Under these conditions the prototropic change of (VIII) to (VII) must have occurred. The ease of degradation of alanine and α-aminophenylacetic acid with *o*- and *p*-nitrobenzaldehyde as compared with the low mobility of the methyleneazomethine system (IX; R = Me, and VIII; R = H, R_1 = Ph) is due to a great extent to the mobile nature of the intermediate anion (VI). The mobility of the methyleneazomethine system during decarboxylation is now under investigation.

Experimental.

The degradation of α-amino-acids was carried out in a carbon dioxide atmosphere in an apparatus similar to that used by Schönberg *et al.* (*loc. cit.*). In the case of alanine and α-amino*iso*butyric acid the delivery tube from the upright condenser was directly dipped into a wide test-tube containing a solution of 2 : 4-dinitrophenylhydrazine hydrochloride in 2N-hydrochloric acid, cooled in ice-cold water. The reagent was prepared by dissolving the hydrazine (1·0 g.) in hot 2N-hydrochloric acid (400 c.c.), cooling the solution in ice, and filtering.

Degradation of Alanine with o-, m-, *and* p-*Nitrobenzaldehyde.*—This was carried out using a mixture of alanine (0·3 g.; 1 mol.) and the nitrobenzaldehyde (0·5 g.; 1 mol.) either in 50% (v/v) aqueous glycerol (20 c.c.) or in 75% (v/v) aqueous pyridine (20 c.c.). The heating was continued for 3 hours and the liberated acetaldehyde reacted directly with the reagent, precipitating its 2 : 4-dinitrophenylhydrazone. This was filtered off in a sintered glass crucible, washed with dilute hydrochloric acid, then with water, and dried to constant weight. It was identified by its m. p. and mixed m. p. with an authentic specimen.

The yields mentioned are reproducible within ±10%, although they are of no quantitative significance. They only indicate the order of reactivity of the three nitrobenzaldehydes.

(a) *In* 50% *aqueous glycerol.* The mixture of the α-amino-acid, nitrobenzaldehyde, and glycerol was gently refluxed on a sand-bath in a stream of carbon dioxide. With *p*- and *o*-nitrobenzaldehyde the acetaldehyde 2 : 4-dinitrophenylhydrazone started to be precipitated after ¼—½ hour, whereas with the *m*-derivative traces were precipitated after 1 hour. The total yields collected, after 3 hours' heating, were approximately 0·10, 0·04, and 0·02 g. respectively. In case of the *o*-derivative the colour of the reaction mixture changed to dark bluish-green, probably due to the formation of indigo-blue.

(b) *In* 75% *aqueous pyridine.* The mixture of the α-amino-acid, nitrobenzaldehyde, and pyridine was heated on a boiling water-bath for 3 hours. With *p*- and *o*-nitrobenzaldehyde precipitation of the hydrazone started after ¼—½ hour, whereas with the *m*-derivative precipitation started after ½—¾ hour. The yields were 0·15, 0·15, and 0·06 g. respectively. In the case of the *p*- and *o*-aldehydes the insoluble amino-acid went slowly into solution with an obvious change in colour of the mixture; this indicated the condensation of the aldehyde with the α-amino-acid to give the corresponding Schiff's base (McIntire, *J. Amer. Chem. Soc.*, 1947, **69**, 1377).

(c) *In water or* 40% *aqueous pyridine.* A mixture of *p*-nitrobenzaldehyde and alanine was either refluxed with water (100 c.c.) or heated with 40% aqueous pyridine on the water-bath. In both cases a small amount of acetaldehyde was liberated.

Degradation of α-*Amino*isobutyric *Acid with* o-, m-, *and* p-*Nitrobenzaldehyde.*—The mixture of the α-amino-acid (0·35 g.; 1 mol.) and the nitrobenzaldehyde (0·5 g.; 1 mol.) was either refluxed with 50% aqueous glycerol (20 c.c.) or heated on the water-bath with 75% aqueous pyridine (20 c.c.). The reaction was carried out as in the case of alanine, and the precipitated acetone 2 : 4-dinitrophenylhydrazone was identified by its m. p. and mixed m. p. with an authentic specimen.

(a) *In* 50% *aqueous glycerol.* The yield of acetone was in the order *p*- > *o*- > *m*-(traces). In case of the *o*-derivative the colour of the reaction mixture turned to indigo-blue.

(b) *In* 75% *aqueous pyridine.* The yield of acetone was much higher than in the case of (a), and was again least with the *m*-derivative.

Degradation of α-*Aminophenylacetic Acid with* o-, m- *and* p-*Nitrobenzaldehyde.*—A mixture of α-aminophenylacetic acid (0·5 g.; 1 mol.), the nitrobenzaldehyde (0·5 g.; 1 mol.), and 50% aqueous glycerol (20 c.c.) was refluxed for 3 hours in a carbon dioxide atmosphere. Water (20 c.c.) was added and the mixture distilled in a stream of carbon dioxide. The first fraction of the distillate (*ca.* 10 c.c.) was treated with an aqueous solution of phenylhydrazine hydrochloride and warmed on the water-bath and the precipitated hydrazone crystallised from dilute alcohol. It was identified as benzaldehyde phenylhydrazone by its m. p. and mixed m. p. with an authentic specimen. Although no yields are given, as the hydrazone was usually contaminated with traces of that of the nitrobenzaldehyde, yet the yield was definitely least in case of the *m*-derivative. The degradation was effected with *o*-, *m*- and *p*-nitrobenzaldehyde even after one hour's refluxing.

Under the above-mentioned conditions alanine, and α-aminophenylacetic acid alone, with piperonal, or with benzoin did not degrade to the corresponding aldehydes.

Decomposition of N-o-*Nitrobenzylidene-ethylamine* (IX; R = Me).—The imine (0·5 g.), prepared according to Andree (*loc. cit.*) without subjecting it to distillation, was refluxed with 50% aqueous glycerol (20 c.c.) in a carbon dioxide atmosphere for three hours. The liberated acetaldehyde was identified as its 2 : 4-dinitrophenylhydrazone (yield *ca.* 0·07 g. ±0·01 g.). The liberation of acetaldehyde was, however, slower than in the case of *o*-nitrobenzaldehyde and alanine.

Isomerisation of N-p-*Nitrobenzylidenebenzylamine* (VIII; R = H, R_1 = Ph).—The imine (0·5 g.) (Ingold and Piggott, *loc. cit.*) was refluxed with dry pyridine (20 c.c.) for 6 hours in a dry carbon dioxide atmosphere. Dilute sulphuric acid (50—60 c.c.; 4N) was added until the solution became slightly acidic, and the mixture refluxed for 10 minutes. It was then distilled in a stream of carbon dioxide and the first fraction of the distillate (*ca.* 10 c.c.) was treated with an aqueous solution of phenylhydrazine hydrochloride. An appreciable amount of benzaldehyde phenylhydrazone was deposited, and was

identified by its m. p. and mixed m. p. The fraction of the distillate collected after that gave a mixture of the hydrazones of benzaldehyde and *p*-nitrobenzaldehyde.

Refluxing for 4 hours only caused isomerisation, but to a less extent.

When the above imine was refluxed with 75% aqueous glycerol for 4 hours, it gave only traces of benzaldehyde which could not be obtained as its pure phenylhydrazone, being admixed with much *p*-nitrobenzaldehyde.

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