826. *Triad Prototropic Systems. Part IV.* The Effect of Substituents on the Mobility of the Azomethinecarboxylic Acids derived from Ketones.*

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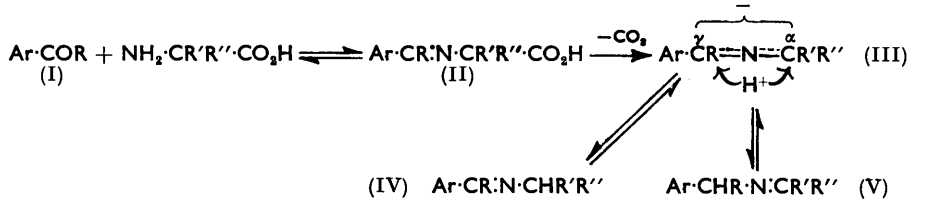
The degradation of α-amino-acids by ketones such as fluorenones, benzophenones, and acetophenones is governed by temperature and by the polar character of the substituents present in the ketone, and of those attached to the α-carbon atom of the amino-acid. Thus, the percentage of degradation increases when an electron-attracting group (*e.g.*, NO_2) is attached at the *para*-position to the carbonyl group of the ketone, or by rise of temperature. The increase by these two factors appears to be due to a similar increase in the percentage of decarboxylation of the intermediate azomethinecarboxylic acids. Substituted benzophenones and acetophenones are less effective than the corresponding aldehydes.

This investigation is a continuation of the study of the effect of decarboxylation, and of substituents, on the mobility of the azomethinecarboxylic acids derived from the condensation of ketones such as fluorenones, benzophenones, and acetophenones with α-amino-acids. It supports the previous assumption by Baddar and Iskander,[1] that the reaction



between α-amino-acids and carbonyl compounds is reversible,[2] since the amount of degradation of alanine with fluorenone increased on increase in the molecular proportion of fluorenone (cf. Table 1). It reached its maximum value (63%) when 1 mol. of alanine was heated with 1 mol. of fluorenone for 30 hr., or with 4 mols. for 3 hr. The results also support the same authors' conclusion that the decarboxylation of the intermediate acid (II) to the mesomeric anion (III) is favoured by rise of temperature,[3] and increase in the electron-attracting power [4] of the groups Ar, R, and R′ (cf. Table 5).

The fact that the percentage of decarboxylation of phenylglycine with 4 : 4′-dinitrobenzophenone and 4-nitroacetophenone was found to be the same, in spite of the fact that R in the former ketone is an electron-attracting and in the latter is an electron-repelling group, may be attributed to steric factors, which inhibit the formation of the azomethinecarboxylic acid in the former case.

The relative rates at which a proton is taken up at the two positions in the mesomeric anion (III) to give isomers (IV) and (V) depends on (1) the electron density at the α- and γ-carbon atoms, and (2) the relative stabilities of the resulting Schiff's bases. These two factors may operate together, favouring the formation of one of the isomers (*e.g.*, when Ar = R = *p*-NO_2·C_6H_4, and R′ = Ph), or may oppose each other, favouring the formation of a different isomer (*e.g.*, when Ar = R = *p*-NO_2·C_6H_4, and R′ = Me).

The greater percentage of degradation of phenylglycine with 4-nitroacetophenone than with 4 : 4′-dinitrobenzophenone (Table 3A), although both decarboxylated it to the same extent (Table 5), may be attributed to the lower stability of isomer (IV; R = Me) than of isomer (IV; R = *p*-NO_2·C_6H_4).

* Part III, *J.*, 1954, 209.

[1] Baddar and Iskander, *J.*, 1954, 203.
[2] Cf. Gulland and Mead, *J.*, 1935, 210.
[3] Brown, *Quart. Reviews*, 1951, **5**, 131.
[4] Cf. McIntire, *J. Amer. Chem. Soc.*, 1947, **69**, 1377.

p-Methoxyphenylglycine was found to be more easily degraded with strong degrading agents, and less so with weak degrading agents, than phenylglycine (cf. Table 3). This may be due to the fact that, with the former agents, decarboxylation is nearly complete (cf. Table 5), and thus, the percentage of degradation will be directly proportional to the electron density at the γ-carbon atom in the anion (III). With weak degrading agents the rate of decarboxylation will be a controlling factor.

The previous assumption by Baddar and Iskander [1] that the increase in the percentage of degradation, on rise of temperature, is mainly due to a corresponding increase in the percentage of decarboxylation is supported by the following fact: the percentage increase in degradation of phenylglycine with 4 : 4′-dinitrobenzophenone, caused by rise of temperature from 100° to 115—120° (cf. Table 3A), was nearly the same as the percentage increase in decarboxylation (cf. Table 5).

The increase in the degrading power of the ketones studied in the present investigation by the introduction of nitro-groups cannot be due to an oxidising action of the nitro-group, since tetranitrodiphenylmethane failed to degrade alanine.

In general, benzaldehydes are stronger degrading agents than the corresponding benzophenones and acetophenones (cf. the present results with those in Parts I [6] and II [1]). Similarly, the percentage of decarboxylation of phenylglycine by benzaldehydes was higher than that by benzophenones (cf. Table 5). This may be mainly due to a greater tendency of amino-acids to condense with aldehydes than with ketones.

Experimental

Degradation of Alanine.—A mixture of alanine (0·089 g., 0·001 mole) and the required ketone (0·001 mole) in 75% (v/v) aqueous pyridine or in dry pyridine (10 ml.) was heated in an oil-bath at 115—120°, or on a boiling-water bath, under carbon dioxide for 3 hr. (cf. Baddar and Iskander [1]). The liberated acetaldehyde was estimated as its 2 : 4-dinitrophenylhydrazone. The efficiency of the apparatus was determined by a method similar to that mentioned in Part II; [1] in two experiments recovery of acetaldehyde from paraldehyde was 93·36 and 93·65%.

The results, although not of absolute quantitative significance, are reproducible within ±5%. The results (each the mean of at least two runs) are in Table 1.

Table 1.

	Degradation (%) in		
Degrading ketone	75% C_5H_5N (115—120°)	C_5H_5N (115—120°)	75% C_5H_5N (water-bath)
2 : 3 : 6 : 7-Tetranitrofluorenone	18·6	—	14·9
2 : 4 : 7-Trinitrofluorenone	16·3	—	10·7
Fluorenone	15·8 [a]	—	8·9 [b]
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	4·2	—	1·8
4 : 4′-Dinitrobenzophenone	3·1	—	1·4
3 : 3′-Dinitrobenzophenone	0	—	—
4-Nitrobenzophenone	0	1·4	—
4 : 4′-Dichlorobenzophenone	0	—	—
Benzophenone	0	—	—
4-Nitroacetophenone	Trace	16·4	—
3-Nitroacetophenone	0	13·2	—
4-Chloroacetophenone	0	2·5	—
2-Chloroacetophenone	0	2·5	—
2 : 4 : 2′ : 4′-Tetranitrodiphenylmethane	0	—	—

[a] Three experiments were carried out, the proportions (in moles) of alanine and fluorenone respectively being: (*a*) 0·001, 0·002; (*b*) 0·002, 0·001; (*c*) 0·001, 0·004. The percentages of degradation were 43·4, 42·5, and 63·5, respectively. [b] This experiment was repeated and the heating was continued until no more acetaldehyde was liberated (63·2% after 30 hr.).

Degradation of α-Aminoisobutyric Acid.—A mixture of this acid (0·21 g., 1 mol.) and the degrading ketone (1 mol.) in 75% (v/v) pyridine (10 ml.) was treated as with alanine. The liberated acetone was collected as its 2 : 4-dinitrophenylhydrazone. In a control experiment, a known weight of pure "AnalaR" acetone was treated identically. In four experiments the

[5] Baddar, *J.*, 1949, s 163.
[6] *Idem*, *J.*, 1950, 136.

recovery of acetone was 66·6, 64·3, 65·7, and 65·1%. The mean (65·4%) was used in the calculation of the values in Table 2A, which were reproducible within ±5% (based on the weight of the 2 : 4-dinitrophenylhydrazone). It appeared that the low recovery was due to the solubility of acetone 2 : 4-dinitrophenylhydrazone in 2N-hydrochloric acid.

Degradation of 1-*Aminocyclohexanecarboxylic Acid.*—The α-amino-acid [1] (0·14 g., 1 mol.) was heated with the requisite ketone as in the preceding experiment. The reaction mixture was acidified with 2N-hydrochloric acid (100 ml.) and distilled in a stream of carbon dioxide. The *cyclo*hexanone was determined by a similar procedure to that used by Baddar and Iskander.[1] Recovery of *cyclo*hexanone in two experiments was 91·56 and 92·1 (mean 91·8%). The results are in Table 2B.

TABLE 2.

	Degradation (%) in 75% C_5H_5N			
	A		B	
Degrading ketone	(115—120°)	(water-bath)	(115—120°)	(water-bath)
Isatin	57·6 [a]	40·8	—	—
2 : 3 : 6 : 7-Tetranitrofluorenone	18·5	1·9	20·6	13·5
2 : 4 : 7-Trinitrofluorenone	0	—	6·0	0·8
Fluorenone [c]	0	—	0 [c]	—
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	2·7	1·4	10·0	4·2
4 : 4′-Dinitrobenzophenone	0	—	*ca.* 0·4	—
3 : 3′-Dinitrobenzophenone	—	—	0	—
4-Nitrobenzophenone	—	—	0	—
4 : 4′-Dichlorobenzophenone	—	—	0	—
4-Nitroacetophenone [c]	0 [b]	—	0	—

[a] Cf. Baddar and Iskander.[1] [b] When the experiment was carried out in dry pyridine no degradation took place. [c] These ketones could be distilled in steam, and the distillate gave a 2 : 4-dinitrophenylhydrazone, which proved to be that of the original ketone.

Degradation of Phenylglycine.—Phenylglycine (0·15 g., 1 mol.) was heated with the degrading ketone (1 mol.) in 75% pyridine (10 ml.) in the usual manner. For the estimation of benzaldehyde produced (Table 3A), the following procedures were adopted.

(i) For ketones which were not volatile in steam, such as nitrofluorenones and benzophenones, and for nitro-ketones which were volatile in steam, procedures (i) and (ii), respectively, adopted by Baddar and Iskander [1] were used. Control experiments with benzaldehyde gave 82·0% and 92·1% recovery, respectively.

(ii) For fluorenone, the mixture was distilled with 2N-hydrochloric acid (200 ml.) until 10—15 ml. remained in the flask. The distillate was extracted with ether (80 ml.), then treated with saturated aqueous sodium hydrogen sulphite (20 ml.). The sulphite layer was warmed with excess of 2 : 4-dinitrophenylhydrazine reagent, and the precipitated benzaldehyde hydrazone was dried and weighed. Control experiments with benzaldehyde gave 74·9% and 75·1% recovery.

TABLE 3.

	Degradation (%) in 75% C_5H_5N			
	A		B	
Degrading ketone	(115—120°)	(water-bath)	(115—120°)	(water-bath)
Isatin	—	—	100·0	98·3
2 : 3 : 6 : 7-Tetranitrofluorenone	54·9	20·7	23·0	11·2
2 : 4 : 7-Trinitrofluorenone	8·0	2·5	5·6	5·6
Fluorenone	15·6	13·6	8·6	4·5
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	27·8	4·2	9·7	4·7
4 : 4′-Dinitrobenzophenone	9·2	2·6	8·4	4·7
3 : 3′-Dinitrobenzophenone	0	—	0	—
4-Nitrobenzophenone	5·0	3·0	4·9	3·6
4 : 4′-Dichlorobenzophenone	0	—	0	—
3 : 3′-Dibromobenzophenone	0	—	0	—
4-Nitroacetophenone	26·0	13·2	14·6	5·6
3-Nitroacetophenone	3·8	2·4	3·5	2·8
p-Nitrodeoxybenzoin	0	—	—	—

Degradation of p-*Methoxyphenylglycine.*—*p*-Methoxyphenylglycine (0·18 g., 1 mol.) was heated with the carbonyl compound (1 mol.) in 75% pyridine as usual. For the estimation of *p*-anisaldehyde produced (Table 3B), the procedure was as for benzaldehyde except that 200 ml.

of 2N-hydrochloric acid were used instead of 100 ml. The α-amino-acid was found to be stable under the conditions of the experiments, and in absence of degrading agents.

The recoveries for (i) isatin, nitrofluorenones, and benzophenones, (ii) fluorenone, and (iii) nitroacetophenones were 97·1, 70·5, and 91·5%, respectively.

Degradation of m-*Nitrophenylglycine.*—*m*-Nitrophenylglycine (0·034 g.; 1 mol.) and the carbonyl compound (1 mol.) in 75% (v/v) aqueous pyridine (10 ml.) were heated in the usual manner.

(i) With ketones which were not volatile in steam, the reaction mixture was treated with 2N-hydrochloric acid (200 ml.), and distilled until no more *m*-nitrobenzaldehyde came over. It was estimated as its 2 : 4-dinitrophenylhydrazone. Control experiments showed that *m*-nitrophenylglycine was degraded in absence of the ketones to the extent of 5·8% and 5·1% at 115—120° and on a boiling-water bath, respectively. Control experiments with *m*-nitrobenzaldehyde gave 92·5% recovery.

With fluorenone the *m*-nitrobenzaldehyde was determined by an indirect method similar to that used in the case of chlorobenzaldehyde,[1] *i.e.*, reduction of *m*-nitrobenzaldehyde with stannous chloride before steam-distillation. Control experiments gave 78·4% recovery of fluorenone. Results are in Table 4.

TABLE 4.

Degrading ketone	Degradation (%) in 75% C_5H_5N (115—120°)	(water-bath)
Isatin	42·9	42·9
2 : 3 : 6 : 7-Tetranitrofluorenone	31·3	28·2
2 : 4 : 7-Trinitrofluorenone	42·9	42·4
Fluorenone	17·1	13·0
2 : 4 : 2′ : 4′-Tetranitrobenzophenone	31·4	31·6
4 : 4′-Dinitrobenzophenone	35·8	35·7
3 : 3′-Dinitrobenzophenone	17·7	16·8
4-Nitrobenzophenone	30·9	29·4
4 : 4′-Dichlorobenzophenone	1·3	—
3 : 3′-Dibromobenzophenone	0	—

Decarboxylation of α-Amino-acids with Carbonyl Compounds.—The experiments were carried out in an apparatus composed of (i) a reaction flask attached to an inlet for pure nitrogen, and to a condenser ending with a trap of concentrated sulphuric acid, and (ii) absorption tubes containing soda-lime (similar to those used in quantitative analysis) attached to the trap.

Equimolecular amounts of the carbonyl compound and the amino-acid were placed in the reaction flask, and the air was swept out by a current of pure nitrogen (½ hr.). 75% Pyridine (10 ml.) was added, the absorption tubes were connected, and the reaction mixture was heated for 3 hr. on a boiling-water bath (unless otherwise stated), in a current of pure nitrogen. The reaction flask was then cooled in ice, and the current of nitrogen was passed for a further ½ hr. A control experiment to determine the efficiency of the apparatus was made by decomposing a known weight of " AnalaR " oxalic acid with potassium permanganate in presence of dilute sulphuric acid (recovery factor = 97·6%). The results are in Table 5.

TABLE 5.

Carbonyl compound	Decarboxylation (%) * 1	2	3	4	5	6
Isatin	—	81·5	92·6	—	—	95·5
2 : 3 : 6 : 7-Tetranitrofluorenone	—	2·3	34·9	—	—	16·3
Fluorenone	97·8	—	23·3	—	58·2 †	7·0
4 : 4′-Dinitrobenzophenone	—	—	23·3	69·9	—	—
3 : 3′-Dinitrobenzophenone	—	—	0	—	59·0	—
4-Nitroacetophenone	—	—	23·3	72·0	—	—
p-Nitrobenzaldehyde	—	—	100·0	—	—	—
2-Chloro-5-nitrobenzaldehyde	—	—	100·0	—	—	—
m-Nitrobenzaldehyde	—	—	22·0	58	—	—
o-Chlorobenzaldehyde	—	—	75·0	—	—	—
m-Chlorobenzaldehyde	—	—	58·0	—	—	—

* (1) Alanine heated for 30 hr. (2) α-Amino*iso*butyric acid. (3) Phenylglycine. (4) Phenylglycine at 115—120° for 3 hr. (5) *m*-Nitrophenylglycine. (6) *p*-Methoxyphenylglycine.

† The same value was obtained in absence of fluorenone.

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