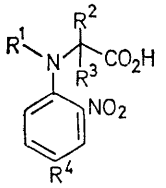
Thermolysis of *N*-*o*-Nitrophenyl- and *N*-2,4-Dinitrophenyl-α-amino-acids

By **R. S. Goudie** and **P. N. Preston,*** Department of Chemistry, Heriot-Watt University, Edinburgh EH1 1HX

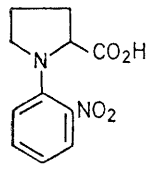
The products of thermolysis of two 2,4-dinitrophenyl- and six *o*-nitrophenyl-α-amino-acids have been investigated. Benzimidazolone and derivatives thereof were isolated in four of the reactions investigated and the mechanism of these conversions is discussed. In general the products are different from those reported for photochemical decomposition.

CERTAIN ring-closure reactions [1] of *N*-2,4-dinitrophenyl derivatives of α-amino-acids (I; $R^4 = NO_2$) have been used for amino-acid identification in the progressive degradation of polypeptides. One important reaction [2] is the pH-dependent photochemical decomposition, which can produce 5-nitrobenzimidazole 3-oxides (III; $R^3 = NO_2$) at low pH or 4-nitro-2-nitrosoanilines (IV) and an aldehyde at high pH. The mechanism of these reactions remains unclear. Needle and Pollitt [1] have

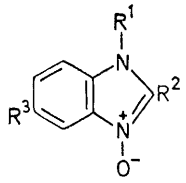


(I)

	R^1	R^2	R^3	R^4
a;	H	H	H	NO_2
b;	Ph	H	H	NO_2
c;	H	H	H	H
d;	Me	H	H	H
e;	H	Me	H	H
f;	H	Me	Me	H
g;	H	Ph	H	H

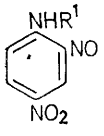


(II)

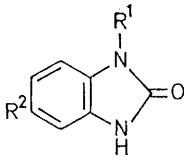


(III)

a; $R^1 = R^3 = H$, $R^2 = Ph$
b; $R^1 = R^2 = R^3 = H$
c; $R^1 = Me$, $R^2 = R^3 = H$



(IV)



(V)

a; $R^1 = H$, $R^2 = NO_2$
b; $R^1 = Ph$, $R^2 = NO_2$
c; $R^1 = R^2 = H$
d; $R^1 = Me$, $R^2 = H$

suggested a scheme involving initial decarboxylation *via* direct interaction between the *o*-nitro-group and the carboxy-system. During the present work this mechanism was contested by Meth-Cohn; [3] on the basis of related work [4] he suggested that one important step is initial nucleophilic attack of the amine nitrogen at the oxygen atom of the *o*-nitro-group. Subsequent rearrangement of the reduced furoxan intermediate followed by decarboxylation and dehydration provides a rationale for the formation of the two products.

Since the detailed mechanism of the photochemical reaction is in doubt we considered it of interest to study the thermolysis of these compounds and now report the decomposition modes of 2,4-dinitro- (Ia and b) and *o*-nitrophenyl-α-amino-acids (Ic—g). Most of the pyrolyses, unless otherwise stated, were carried out at 200° for materials as *ca.* 2% mixtures with acid-washed sand; in view of the photolability of the amino-acids all reactions were carried out in the dark and under nitrogen as a precaution against photo-oxidation.

The results (see Table) indicate that the nature of the

Major products from the pyrolysis of 2,4-dinitro- and *o*-nitrophenyl-α-amino-acids

Compound	Products and yield (%)
(Ia)	(Va) 60, (VIa) 15
(Ib)	(Vb) 60, (VIb) 8, (VIIb) 15
(Ic)	(Vc) 60, (VIc) 5, (VId) 5, (VIIc) 10
(Id) *	(Vd) 42, (VIc) 7, (VIIa) 4, (VIId) 8
(Ie)	(VId) 10, (VIIe) 65, (IXa) 10
(If)	(VId) 30
(Ig) †	(VIIf) 40, (IIIa) 30, (VId) 10
(II)	(VIII) 35, (VId) 4

* Benzaldehyde (*ca.* 5%) also produced. † *o*-Nitrophenol (*ca.* 8%) also produced.

thermolysis products is sensitive to the substituents (I; R^{1-3}) in the amino-acid and that in many cases the products are different from those [(III) and (IV) only] from the photochemical reaction.

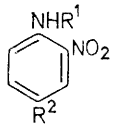
Pyrolysis of the unsubstituted compound, *o*-nitrophenylglycine (Ic), provided a mixture of benzimidazolone (Vc) in good yield (60%) together with smaller amounts of *N*-methyl-*o*-nitroaniline (5%), *o*-nitroaniline (5%), and benzimidazole (VIIa) (10%); 2,4-dinitrophenylglycine (Ia) behaved similarly in that the major product was 5-nitrobenzimidazolone (Va) (60%), formed together with 2,4-dinitroaniline (15%).

The product distribution was not markedly modified by introduction of an *N*-methyl or *N*-phenyl group. *o*-Nitrophenylsarcosine (Id) and *N*-phenyl-2,4-dinitrophenylglycine (Ib) afforded as major products the appropriate benzimidazolone derivatives (Vd) (42%) and (Vb) (60%), respectively. Replacement of hydrogen by alkyl or aryl (R^2 or R^3) completely repressed the formation of benzimidazolone; *o*-nitrophenyl-α-alanine (Ie) afforded 2-methylbenzimidazole (65%)

[1] G. W. H. Cheeseman, *Adv. Heterocyclic Chem.*, 1963, 210.
[2] D. J. Needle and R. J. Pollitt, *J. Chem. Soc.* (*C*), 1969, 2127.
[3] O. Meth-Cohn, *Tetrahedron Letters*, 1970, 1235.
[4] R. Fielden, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Letters*, 1970, 1229.

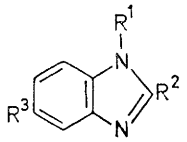
as the major product together with *o*-nitroaniline (10%) and, interestingly, 2,2′-bibenzimidazolyl (IXa) (10%).

A more striking change is observed with *o*-nitrophenyl-α-aminoisobutyric acid (If), which provides *o*-nitroaniline as the only identifiable product. Thermolysis of *o*-nitrophenyl-α-aminophenylacetic acid (Ig)



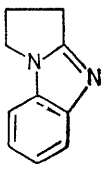
(VI)

a; $R^1 = H$, $R^2 = NO_2$
b; $R^1 = Ph$, $R^2 = NO_2$
c; $R^1 = Me$, $R^2 = H$
d; $R^1 = R^2 = H$

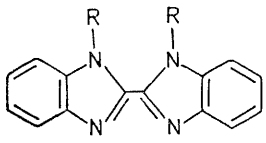


(VII)

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = Ph$, $R^2 = H$, $R^3 = NO_2$
c; $R^1 = R^2 = R^3 = H$
d; $R^1 = Me$, $R^2 = R^3 = H$
e; $R^1 = R^3 = H$, $R^2 = Me$
f; $R^1 = R^3 = H$, $R^2 = Ph$

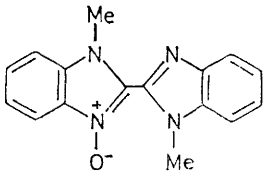


(VIII)

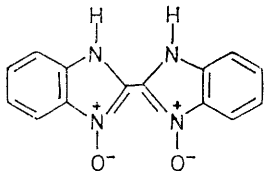


(IX)

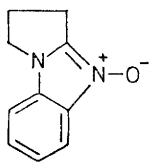
a; R = H
b; R = Me



(X)



(XI)

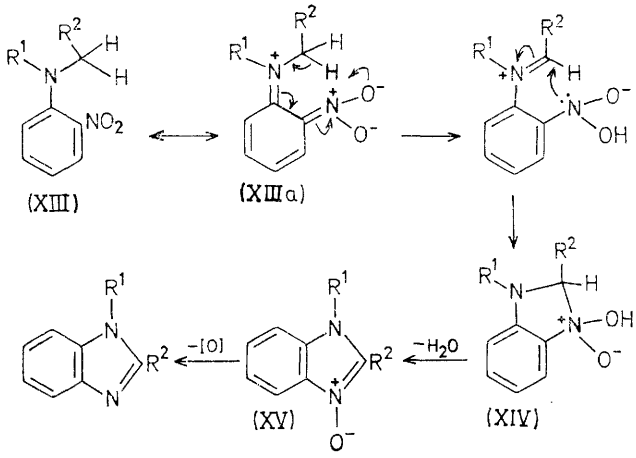


(XII)

produced 2-phenylbenzimidazole *N*-oxide (IIIa) (30%) together with 2-phenylbenzimidazole (VIIf) (40%) and *o*-nitroaniline (10%).

In one experiment it was demonstrated that decomposition can occur efficiently in solution; when *o*-nitrophenylglycine (Ic) was heated under reflux in nitrobenzene the major product was benzimidazolone (Vc) (60%), formed together with smaller quantities of benzimidazole (7%), *N*-methyl-*o*-nitroaniline (7%), *o*-nitroaniline (7%), and an unidentified orange material (10%).

The formation of benzimidazoles in all but one of the reactions is easily rationalised on the basis of studies by Suschitzky and Sutton [5] on the thermal conversion of *NN*-disubstituted *o*-nitroanilines into benzimidazoles at 220—240°. The mechanism they have proposed



(XIII) (XIIIa) (XV) (XIV)

SCHEME

(Scheme) requires the intermediacy of a benzimidazole *N*-oxide. The situation in pyrolysis of the amino-acid (XIII; $R^2 = CO_2H$) allows for two distinct decomposition modes, depending on the timing of decarboxylation. The possibility of an initial decarboxylation was eliminated since *N*-methyl-*o*-nitroaniline was recovered quantitatively when subjected to the conditions used for decomposition of *o*-nitrophenylglycine (Ic). Since the possibility existed that the amino-acid pyrolyses might be subject to acid catalysis (by $-CO_2H$), *N*-methyl-*o*-nitroaniline was also thermolysed in the presence (separately) of 3-phenylpropionic acid and glacial acetic acid: in each case the amine was recovered almost quantitatively. Evidently replacement of H for CO_2H within structure (XIII; $R^2 = CO_2H$) facilitates initial nucleophilic attack, as depicted within the canonical form (XIIIa). Decarboxylation can then occur at any subsequent step in the process; indeed it would be anticipated that this step would be particularly easy within structures of type (XIV) or (XV) in which the carboxy-group is adjacent to an *N*-oxide system.

Whereas Suschitzky and his co-workers [4,6] were able to synthesise benzimidazole *N*-oxides by acid-catalysed thermal or photochemical reactions of *NN*-dialkyl *o*-nitroanilines, they did not isolate such products from purely thermal reactions. One important aspect of the present work, therefore, is the isolation of 2-phenylbenzimidazole *N*-oxide (IIIa) (30%) from pyrolysis of the corresponding amino-acid. Presumably the lower working temperatures used for the amino-acid pyrolyses prevent, for this case at least, complete conversion into the benzimadazole or other products.

The formation of benzimidazolone derivatives in four of the reactions is additional evidence that *N*-oxides are formed at some stage. von Niementowski,[6,7]

[5] H. Suschitzky and M. E. Sutton, *Tetrahedron Letters*, 1967, 3933.

[6] R. Fielden, O. Meth-Cohn, D. Price, and H. Suschitzky, *Chem. Comm.*, 1969, 772.

[7] St. von Niementowski, *Ber.*, 1910, **43**, 3012.

and later Kuhn and Blau,[8] reported that benzimidazolone (Vc) is obtained by heating benzimidazole *N*-oxide (IIIb) with water in a sealed tube at 180°. The hydrolytic rearrangement of 1-methylbenzimidazole 3-oxide (IIIc) to 1-methylbenzimidazolone (Vd) is especially ready, and can be effected[9] in acetone or chloroform under reflux or by leaving at room temperature for a few weeks. Since water is produced in the amino-acid pyrolyses the formation of benzimidazolones can presumably arise from intermediate *N*-oxides either hydrolytically or by thermal rearrangement. Products of this type were not isolated by Suschitzky and Sutton[5] since the structures of the intermediate *N*-oxides [*e.g.* (XII)] prohibited conversion into the ketone.

In our hands however, *NN*-dimethyl-*o*-nitroaniline was converted after 2 hr. at 240° into a mixture of *N*-methylbenzimidazolone (Vd) (35%), *N*-methylbenzimidazole (VIId) (12%), and benzimidazole (8%); conversion was shown to be high by recovery of *ca.* 40% of the starting material. When the reaction temperature was reduced to 200° a large amount (*ca.* 70%) of the starting material was recovered and only one product [*N*-methylbenzimidazolone (11%)] was isolated.

The formation of 2,2′-bibenzimidazolyl (IXa) from the decomposition of *o*-nitrophenylalanine (Ie) has precedent also in the work of Kuhn[8] and Takahashi[9] and their co-workers, and may be a further consequence of the intermediacy of *N*-oxides. Thus the hydrolytic reaction[8] of benzimidazole *N*-oxide produces 2,2′-bibenzimidazolyl 3,3′-dioxide (XI) in 30% yield as well as benzimidazolone; pyrolysis[9] of 1-methylbenzimidazole *N*-oxide (IIIc) without solvent at 130° gave a mixture of small amounts of 1,1′-dimethyl-2,2′-bibenzimidazolyl 3-oxide (X) and 1,1′-dimethyl-2′2′-bibenzimidazolyl (IXb). However, the formation of compound (IXa) by a route of this type requires an unusual loss of two methyl groups, and the mechanism of this process remains unclear in the absence of further work.

EXPERIMENTAL

2,4-Dinitrophenyl-α-amino-acids (Ia) and (Ib) were prepared by the method of Sanger.[10]

General Procedure for the Preparation of o-*Nitrophenyl-α-amino-acids.*—Acids (Ie—g) and (II) were prepared by a modification of the method of Sanger;[10] *e.g.* for (Ie) a solution of alanine (4·0 g., 0·045 mole) and sodium hydrogen carbonate (18 g.) in water (100 ml.) was added to *o*-nitrofluorobenzene (7·0 g., 0·05 mole) in ethanol (180 ml.). The mixture was heated under reflux in the dark for 8 hr., then evaporated to *ca.* 80 ml. at 5 mm. The remaining solution was extracted with ether to remove excess of *o*-nitrofluorobenzene and the aqueous portion was acidified to pH 1 to precipitate *o*-nitrophenylalanine (Ie) (8·4 g., 90%), m.p. 144°.

Satisfactory analytical data were obtained for these compounds, the m.p.s of which were (Ic) 199° (Id) 75°, (If) 142°, (Ig) 175°, and (II) 57°.

Pyrolyses.—(a) *In nitrobenzene.* *o*-Nitrophenylglycine (3·0 g., 0·015 mole) was heated under reflux with nitrobenzene (100 ml.) for 3 hr. The cooled solution deposited an off-white solid, which yielded benzimidazolone (0·9 g., 43%), m.p. 308° (from ethanol) (lit.,[11] 311°); the i.r. spectrum was identical with that of an authentic sample prepared[12] from *o*-phenylenediamine and urea. Nitrobenzene was removed from the filtrate by evaporation at 150°/2 mm., and the resultant dark brown oil was extracted with benzene to leave a buff coloured solid; recrystallisation of this from ethanol gave benzimidazolone (0·36 g., total yield 60%). The benzene extract was evaporated and the remaining brown oil was purified by preparative t.l.c. with chloroform as eluant; the following were eluted, in order of increasing R_F value: benzimidazole, m.p. 170° (lit.,[13] 170) (7%); an unidentified orange material (10% by weight); *o*-nitroaniline. m.p. 71·5° (lit.,[14] 71·5) (7%); and *N*-methyl-*o*-nitroaniline, m.p. 37° (lit.,[15] 37°) (7%).

(b) *In sand.* All pyrolyses were carried out for 3 hr. at 200° in the dark under nitrogen for *ca.* 2% mixtures with acid-washed sand (B.D.H.). On completion of the reaction the sand was extracted (Soxhlet) with hot solvent.

o-Nitrophenylglycine (Ic) (2·0 g., 0·01 mole) gave a product which was extracted with hot acetone. Evaporation of the extract left a brown oil which was treated as already described to give benzimidazolone (0·84 g., 60%), benzimidazole (10%), *o*-nitroaniline (5%), and *N*-methyl *o*-nitroaniline (5%).

2,4-Dinitrophenylglycine (Ia) (2·0 g., 0·008 mole) gave a brown solid after extraction of the product with hot acetone. This solid was extracted with hot water; on cooling a yellow solid precipitated which was digested with sodium hydroxide (10 ml.). The insoluble portion was 2,4-dinitroaniline (0·23 g., 15%), m.p. 180° (lit.,[16] 180°). The alkaline solution was acidified with 2N-hydrochloric acid and extracted with ether; evaporation of the extract provided 5-nitrobenzimidazolone (Va) (0·90 g., 60%), m.p. 306° (lit.,[1] 306°), identical (i.r. spectrum) with an authentic sample prepared[17] by nitration of benzimidazolone.

2,4-Dinitrophenyl-*N*-phenylglycine (Ib) (2·0 g., 0·006 mole) gave an acetone extract which was purified by preparative t.l.c. with chloroform as eluant. Of the eight compounds observed the following were isolated, in order of increasing R_F value: (i) *5-nitro-1-phenylbenzimidazolone* (Vb) (0·94 g., 60%), m.p. 262°, which was identified mass spectrometrically (A.E.I. MS902) (Found: *M*, 255. $C_{13}H_{13}N_3O_3$ requires *M*, 255); the mass spectrum was similar to that of 5-nitrobenzimidazolone and showed the following transitions: *m/e* 255 ⟶ 225 ($M^{\cdot+}$ — NO), 255 ⟶ 209 ($M^{\cdot+}$ — NO_2), and 209 ⟶ 181 ($M^{\cdot+}$ — NO_2 — CO); *cf.* *m/e* 179 ⟶ 149, 179 ⟶ 133, and 133 ⟶ 105 for 5-nitrobenzimidazolone; (ii) 5-nitro-1-phenylbenzimidazole (0·23 g., 15%), m.p. 160° (lit.,[18]

[8] von R. Kuhn and W. Blau, *Annalen*, 1958, **615**, 99.
[9] S. Takahashi and H. Kano, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 783.
[10] F. Sanger, *Biochem. J.*, 1946, **39**, 507.
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[12] L. S. Efros, B. A. Porai-Koshits, and S. G. Farbenshtein, *Zhur. obshchei Khim.*, 1953, **23**, 1691.
[13] Ref. 11, vol. 1, p. 335.
[14] Ref. 11, vol. 4, p. 2426.
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[16] N. M. Cullinane, O. E. Embrey, and D. R. Davies, *J. Chem. Soc.*, 1932, 2362.
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[18] L. Joseph and J. Julca, *J. Org. Chem.*, 1962, **27**, 1102.

162°) (Found: C, 65·0; H, 4·0; N, 16·9. Calc. for $C_{12}H_9N_3O_2$: C, 65·25; H, 3·8; N, 17·55%); and (iii) *N*-2,4-dinitrophenylaniline (0·13 g., 8%), m.p. 157° (lit.,[19] 158°).

o-Nitrophenyl-α-aminophenylacetic acid (Ig) (2·6 g., 0·0017 mole) gave a black semi-solid from the chloroform extract: treatment of this material with acetone left an insoluble portion which gave 2-phenylbenzimidazole *N*-oxide (IIIa) (0·47 g., 30%), m.p. 225° (from acetone) (lit.,[20] 225°) (Found: C, 73·7; H, 4·75; N, 13·1. Calc. for $C_{13}H_{10}N_2O$: C, 74·2; H, 4·75; N, 13·35%). The acetone-soluble portion was purified by preparative t.l.c. with benzene as eluant to give 2-phenylbenzimidazole (VIIf) (0·29 g., 40%), m.p. 292° (lit.,[21] 291°), and *o*-nitroaniline (0·12 g., 10%). Benzaldehyde (5%) was estimated by conversion into its 2,4-dinitrophenylhydrazone.

o-Nitrophenyl-α-alanine (Ie) (1·6 g., 0·008 mole) gave a dark brown solid after chloroform extraction which was shown to contain eight compounds by qualitative t.l.c. Three compounds isolated by preparative t.l.c. with ether as eluant were: (i) 2-methylbenzimidazole (VIIe) (0·69 g., 65%), m.p. 176° (lit.,[22] 175°); (ii) 2,2′-bibenzimidazolyl (IXa) (0·17 g., 10%), sublimes *ca.* 300°, *m/e* 234 (77%, $M^{\cdot+}$), 143 (7%), 142 (7%), 117 (7%) ($M^{\cdot+} - C_7H_5N_2^{\cdot}$), 105 (100%, $C_6H_5N_2^{\cdot+}$), and 77 (53%); $\nu_{max.}$ (KBr) 425w, 445w, 745s, 950m, 1143m, 1180m, 1270m, 1345s, 1395s, and 2750—3060s cm.$^{-1}$ (*cf.* ref. 25); and (iii) *o*-nitroaniline (0·11 g., 10%).

o-Nitrophenylsarcosine (Id) (2·2 g., 0·01 mole) provided a product, purification of which by preparative t.l.c. (benzene eluant) gave (order of decreasing R_F value) *o*-nitrophenol (0·11 g., 8%), *N*-methyl-*o*-nitroaniline (0·11 g., 7%), and 1-methylbenzimidazolone (0·59 g., 42%), m.p. 187° (lit.,[23] 186°) (Found: C, 64·5; H, 5·3; N, 18·6. Calc. for $C_8H_8N_2O$: C, 64·9; H, 5·4; N, 18·9%). The material extracted from the origin of the t.l.c. plate was re-run with ether as eluant to give 1-methylbenzimidazole (0·11 g., 8%), m.p. 65° (lit.,[24] 63—65°), and benzimidazole (0·05 g., 4%), m.p. 170° (lit.,[13] 170°).

o-Nitrophenylproline (II) (2·4 g., 0·01 mole) gave a chloroform extract which was digested with acetone. The solution was evaporated and the residual oil was purified by preparative t.l.c. with chloroform as eluant to give 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (VIII) (0·56 g., 35%), m.p. 105—107° (lit.,[25] 100°) (Found: C, 74·9; H, 6·7; N, 17·4. Calc. for $C_{10}H_{10}N_2$: C, 75·5; H, 6·9; N, 17·65%), *o*-nitrophenol (0·04 g., 3%), and *o*-nitroaniline (0·05 g., 4%).

o-Nitrophenyl-α-aminoisobutyric acid (If) (0·64 g., 0·003 mole) provided an acetone extract which was shown by t.l.c. to contain six compounds; only *o*-nitroaniline (0·12 g., 30%) could be isolated by preparative t.l.c. with ether as eluant.

N-Methyl-*o*-nitroaniline was recovered almost quantitatively after being heated either alone in sand for 3 hr. at 200° or with (separately) equimolar quantities of 3-phenylpropionic acid and glacial acetic acid for 3 hr. at 200°.

NN-Dimethyl-*o*-nitroaniline was converted into a mixture of *N*-methylbenzimidazolone (35%), *N*-methylbenzimidazole (12%), and benzimidazole (8%) after 2 hr. at 240°; 40% of the starting material was recovered. After 2 hr. at 200° benzimidazolone (11%) and starting material (*ca.* 70%) were recovered.

[0/1379 *Received, August 10th,* 1970]

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