391. *The Polymerization of 3-Substituted Oxazolidine-2,5-diones.*

By C. H. Bamford, H. Block, and A. C. P. Pugh.

The tertiary amine-catalysed polymerization of sarcosine-*N*-carboxy-anhydride in the presence of 3-methylhydantoin has been shown to be similar to the catalysis by lithium chloride reported previously. Use of 3-phenyloxazolidine-2,5-dione as the cyclic anhydride has permitted isolation and characterization of 3-methyl-1-*N*-phenylglycylhydantoin as the product from both these reactions. The isolation of this compound, which is a stable member of a family of generally reactive kinetic intermediates, indicates the nature of the paths in these reactions, and, by analogy, the nature of the reaction paths in the polymerization, catalysed by tertiary amines or lithium chloride, of oxazolidine-2,5-diones unsubstituted in the 3-position. A generalized reaction scheme for the polymerization of oxazolidine-2,5-diones is given.

The mechanism of the polymerization of oxazolidine-2,5-diones catalysed by tertiary bases and by lithium chloride has been discussed in earlier papers.[1a,b] It has been suggested that both reactions proceed through the formation of a bifunctional intermediate of type (I) which cannot occur with a 3-substituted oxazolidine-2,5-dione. There is abundant experimental evidence [1a,b,2a,b,3] that polymerization of sarcosine-*N*-carboxy-anhydride is not induced by tertiary bases. Apparent indications to the contrary such as the observations by Bilek *et al.*[4] (recently cited again by Katchalsky and Sela [5]) can almost certainly be attributed to the presence of small quantities of active impurities, particularly water. L-Proline-*N*-carboxy-anhydride, which we show to be extremely sensitive to traces of impurities, has given far more varied results in its ability to be polymerized by tertiary bases. However, under the most rigorous and testing conditions only low rates of polymerization are observed.

Although sarcosine-*N*-carboxy-anhydride is not polymerized by lithium chloride alone, polymerization does occur in the presence of 3-methylhydantoin. It has been suggested that an intermediate (II) is involved,[1a] with structure analogous to (I). That 1,3-dimethylhydantoin does not produce any reaction is consistent with this.[2a] In view

[1] (*a*) Ballard, Bamford, and Weymouth, *Proc. Roy. Soc.*, 1955, *A*, **227**, 155; (*b*) Ballard and Bamford, *J.*, 1956, 381; (*c*) Ballard, Bamford, and Elliott, *Makromol. Chem.*, 1960, **35**, 222; (*d*) Ballard and Bamford, *Proc. Roy. Soc.*, 1954, *A*, **223**, 495; (*e*) Ballard and Bamford, *J.*, 1958, 355.

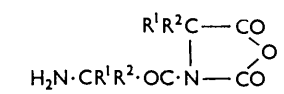
[2] (*a*) Bamford, *Chem. Soc. Special Publ.* No. 2, 1955, p. 45; (*b*) Schlögl, *ibid.*, p. 47.

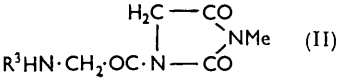
[3] Hargitay and Buyle, personal communication.

[4] Bilek, Derkosch, Michl, and Wessely, *Monatsh.*, 1953, **84**, 717.

[5] Katchalski and Sela, *Adv. Protein Chem.*, 1958, **13**, 243.

of the similarity of the hydantoin and oxazolidine-2,5-dione rings it was therefore natural to suppose that the polymerization of oxazolidine-2,5-diones which are not *N*-substituted proceeds through (II) and resembles that initiated by tertiary bases.[1a]

(I) 

 (II)

In the present paper we complete the analogy by showing that sarcosine-*N*-carboxy-anhydride polymerizes readily in the presence of a tertiary base if 3-methylhydantoin is added. Further, we establish unequivocally the existence of intermediates of type (II) by the isolation of 3-methyl-1-*N*-phenylglycylhydantoin (II; $R^3 = Ph$) from reaction mixtures containing 3-methylhydantoin and 3-phenyloxazolidine-2,5-dione together with a tertiary base or lithium chloride. Such intermediates are not formed in the presence of primary bases. These observations support the mechanism which we have previously proposed, and we show later that the essentials of this mechanism are consistent with all the available observations. The reactions of primary, secondary, and tertiary bases with oxazolidine-2,5-diones can now be fitted into a self-consistent scheme.

Experimental

Materials.—Sarcosine-*N*-carboxy-anhydride, prepared by the method of Hanby *et al.*,[6] was purified as described by Ballard *et al.*[1a]

L-Proline-*N*-carboxy-anhydride, kindly supplied by Mr. A. A. Randall of this laboratory, was sublimed at 35—40°/10^{-4} mm. immediately before use.

3-Phenyloxazolidine-2,5-dione [7] was recrystallized from ethyl acetate–light petroleum (b. p. 60—80°) and was sublimed at 100—110°/10^{-4} mm. immediately before use.

3-Methylhydantoin [8] was twice recrystallized from ethanol and was sublimed at 150°/10^{-4} mm. before use.

Triethylamine, from Judex Co., Ltd., was treated with acetic anhydride (10% v/v) for 0·5 hr. The triethylamine was distilled off at 89—90°, left over solid sodium hydroxide for 12 hr., and redistilled.

Tributylamine, from Eastman-Kodak Corp., was treated with acetic anhydride (10% v/v) for 0·5 hr. The anhydride was distilled off and the tributylamine distilled at *ca.* 10 mm. After drying (NaOH; 12 hr.) the product was redistilled at *ca.* 10 mm.

Lithium chloride, from May and Baker Ltd., was used without purification. It was dried as described below.

Hexylamine, from L. Light & Co., Ltd., was dried (NaOH) and fractionated under reduced pressure.

NN-Dimethylformamide, from Honeywill & Stein Ltd., was dried (P_2O_5) and fractionated at 25° under reduced pressure, the middle fraction being collected. Repetition of this procedure resulted in a pure and dry sample as shown by its inability to cause measurable polymerization of sarcosine-*N*-carboxy-anhydride over a substantial period.

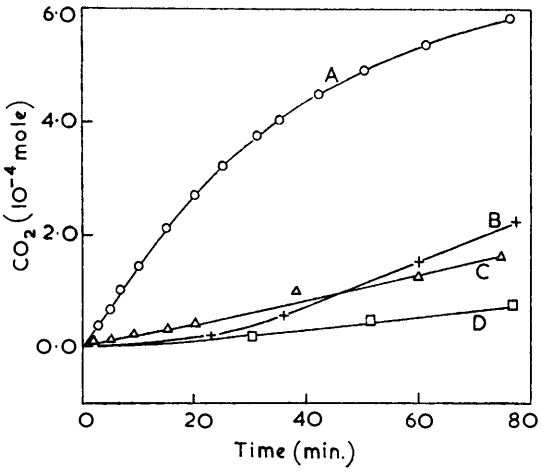
All materials, after purification were not allowed to come into contact with the air except in a dry box.

Results.—(a) *System: sarcosine-N-carboxy-anhydride, 3-methylhydantoin, tertiary base.* Kinetic experiments were carried out in a two-limbed vessel in which, before the experiment, the anhydride and other reagents were kept in separate limbs. The reaction vessel was connected to a constant-volume manometric system [1d] by means of a tapered joint, and rotation of the vessel about the joint resulted in the mixing of the reactants and in the start of the polymerization. Mixtures were shaken in a thermostat bath at 25·0°. The results are shown in the Figure.

[6] Hanby, Waley, and Watson, *J.*, 1950, 3009.
[7] Fuchs, *Ber.*, 1922, **55**, 2943.
[8] Siemonson, *Annalen*, 1904, **333**, 113.

An intermediate (II; R^3 = Me) was sought from triethylamine, 3-methylhydantoin, and sarcosine-*N*-carboxy-anhydride in the molar ratios 100 : 10 : 1 but only polysarcosine was isolated.

(b) *System:* L-*proline-*N*-carboxy-anhydride, tertiary base.* Polymerization was markedly slower in the system L-proline-*N*-carboxy-anhydride, tributylamine in *NN*-dimethylformamide (Figure) if reagents were freshly distilled and dried by azeotropic distillation with benzene.



Conversion–time curves for reactions of oxazolidine-2,5-diones with tributylamine in NN*-dimethylformamide at* 25°.

Concns. (mole/l.): sarcosine-*N*-carboxy-anhydride, (A) 0·332, (B) 0·317, (D) 0·289; 3-methylhydantoin, (A), 0·178, (B) 0·185, (D) 0; tributylamine, (A) 0·042, (B) 0, (D) 0·262. Curve C is for L-proline-*N*-carboxy-anhydride (0·291) and tributylamine (0·129 mole/l.).

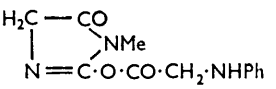
Complete conversion for 0·332 mole/l. of sarcosine-*N*-carboxy-anhydride yields 10^{-3} mole of CO_2.

In the absence of such precautions results were very varied; in one instance polymerization was complete in 8 min.

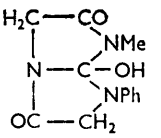
(c) *Isolation and characterization of intermediates of type* (II), *with base-catalysis.* Reaction occurred when tributylamine was added to a solution of 3-phenyloxazolidine-2,5-dione and 3-methylhydantoin in *NN*-dimethylformamide. The carbon dioxide evolved was frozen out at −196°; a yield of 96% was estimated by measuring the pressure in a vessel of known volume and temperature.

A solution of 3-phenyloxazolidine-2,5-dione (3 g.), 3-methylhydantoin (2 g.), and triethylamine (20 ml.) in *NN*-dimethylformamide (30 ml.) was concentrated after 2 hr. at reduced pressure to *ca.* 50 ml.; it deposited crystalline 3-*methyl*-1-N-*phenylglycylhydantoin* (II; R^3 = Ph) (2·2 g.), m. p. 227—228° (from benzene) (Found: C, 58·1; H, 5·3; N, 16·5. $C_{12}H_{13}N_3O_3$ requires C, 58·3; H, 5·3; N, 17·0%).

This compound (0·1 g.) was hydrolysed for 0·5 hr. in refluxing 2N-sodium hydroxide (5 ml.). Paper chromatography with butanol–pyridine–water for development, and Reindel and Hoppe's technique [9] for rendering the spots visible, with a control 1 : 1 mixture of *N*-phenylglycine and 3-methylhydantoin in 2N-sodium hydroxide at the concentrations expected from the hydrolysis, showed these materials to be the hydrolysis products.



(III)



(IV)

The infrared spectrum of compound (II; R^3 = Ph), in a potassium chloride disc, recorded on a Perkin-Elmer Infracord spectrophotometer, showed absence of the ester doublet in the region 1000—1200 cm.$^{-1}$, thus eliminating structure (III) for this compound.

Compound (II; R^3 = Ph) (0·2 g.) was refluxed in acetyl chloride (10 ml.) for 1½ hr. The *acetyl derivative* separated; recrystallized from chloroform–light petroleum (b. p. 60—80°), it (0·15 g.) had m. p. 230° (Found: C, 58·0; H, 5·5; N, 14·4. $C_{14}H_{15}N_3O_4$ requires C, 58·1; H, 5·2; N, 14·5%). Formation of this derivative is strong evidence against structure (IV) (tertiary

[9] Reindel and Hoppe, *Chem. Ber.*, 1954, **87**, 1103.

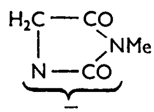
alcohol). The infrared spectrum (KCl disc) supports this conclusion since the absence of the ester doublet in the region 1000—1200 cm.$^{-1}$ eliminates ester formation.

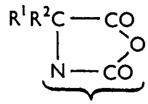
(d) *System: hexylamine, 3-phenyloxazolidine-2,5-dione, 3-methylhydantoin.* 3-Phenyloxazolidine-2,5-dione (2 g.), 3-methylhydantoin (1·3 g.), and hexylamine (1·2 g.) in *NN*-dimethylformamide (25 ml.) were allowed to react for 12 hr. Precipitation with ice-water resulted in a solid (presumably the hexylamide) which was extremely soluble in ether. The fact that 3-methyl-1-*N*-phenylglycylhydantoin is only sparingly soluble in this solvent showed that this intermediate was not present in concentrations greater than 1%.

(e) *Isolation of an intermediate* (II) *in reaction with catalysis by lithium chloride.* Reaction catalysed by lithium chloride between 3-phenyloxazolidine-2,5-dione and 3-methylhydantoin is very strongly inhibited by traces of water, so the reagents were dried by removing the benzene–water azeotrope. 3-Methylhydantoin (0·6 g.) and lithium chloride (0·3 g.) were refluxed with sodium-dried benzene in *NN*-dimethylformamide (30 ml.) under a Dean–Stark head until no more water was removed. During the drying, the *NN*-dimethylformamide was heated, and since slight decomposition to dimethylamine under these conditions was possible, the solvents were removed on a water-bath under reduced pressure and finally at 100°/10^{-4} mm. 3-Phenyloxazolidine-2,5-dione (1 g.) was similarly dried. The three compounds were then dissolved in *NN*-dimethylformamide (30 ml.) and left for 12 hr., carbon dioxide being evolved. Addition to ice afforded 3-methyl-1-*N*-phenylglycylhydantoin which, recrystallized from benzene, had m. p. 226° (0·5 g.) (Found: C, 58·2; H, 5·5; N, 16·6%) and an infrared spectrum identical with that of the sample prepared as described in (c) above.

Discussion

The results shown in the Figure confirm previous observations that the initial rate of reaction of sarcosine-*N*-carboxy-anhydride in the presence of tertiary base or of 3-methylhydantoin is of the same low order as the rate of decomposition of sarcosine-*N*-carboxy-anhydride in pure solvent. When tertiary base and 3-methylhydantoin are both present a much higher rate is observed; therefore, kinetically, tertiary bases behave very similarly to lithium chloride [1a] in these systems. The parallelism is emphasized by the isolation of the intermediate (II; R^3 = Ph) in both cases. These observations show definitely that the 3-methylhydantoin anion (V) is an intermediate in both reactions, and strongly suggest that with oxazolidine-2,5-diones which are not *N*-substituted the anion (VI) is involved in the corresponding reactions.

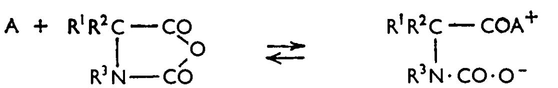
(V) 

 (VI)

The marked variation in the rate of polymerization of L-proline-*N*-carboxy-anhydride when treated with tertiary base, together with the observation that reaction may be slow, indicates that the well-known rapid polymerization of this anhydride by a tertiary base is an impurity effect. The sensitivity of this anhydride to impurities is not unexpected since it is extremely reactive.[1e] We do not consider that the low polymerization rate observed with our purest materials is any proof of a mechanism involving only tertiary base and anhydride since traces of impurities may still be present. This reaction is being investigated further.

The above and other evidence is consistent with the following mechanisms for polymerization involving initiation by primary base and catalysis by tertiary base and lithium chloride.

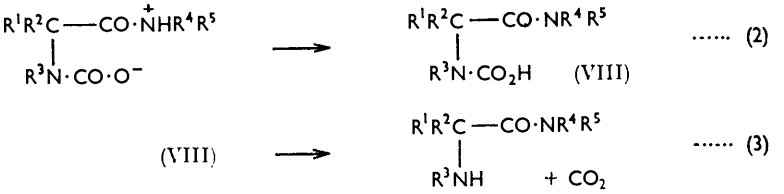
(i) A rate-determining (reversible) association between the initiator and the oxazolidine-2,5-dione:



(VII) ······(1)

where A represents $R^4R^5R^6N$ or Cl^- and the ion (VII) is an equivalent representation of the mesomeric or tautomeric forms previously described.[1b]

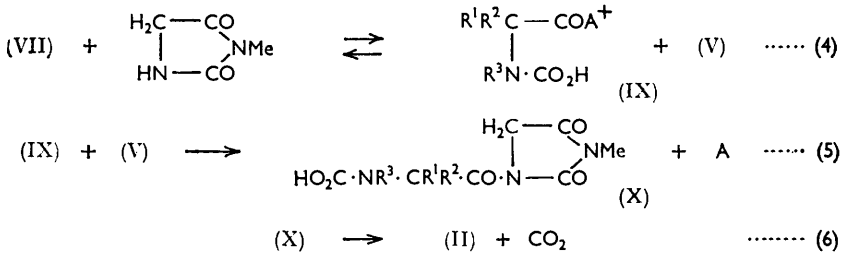
(ii) If A is an amine, and any or all of R^4, R^5, R^6 are hydrogen, proton transfer from A to the *N*-carboxy-anion occurs, followed by decomposition of the unstable carbamic acid (VIII), *e.g.*:



The proton transfer is faster than reactions (4) and (7) described below; hence the reactions described in sections (iv) and (v) do not occur with primary bases. Reactions (1), (2), and (3) describe the normal polymerization initiated by a primary or secondary base.

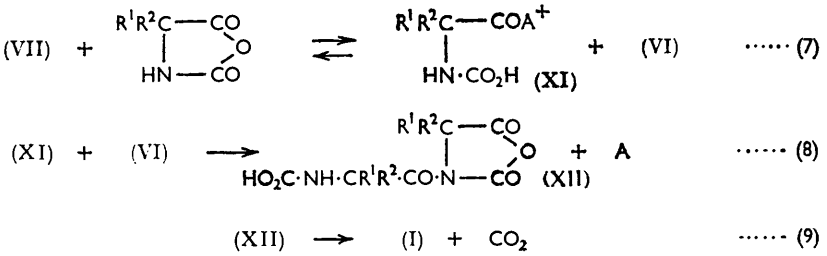
(iii) If A is a tertiary amine or a weakly basic anion such as Cl^- in *NN*-dimethylformamide and R^3 is not hydrogen, no further reaction will occur, and it is presumed that the ion (VII) is in equilibrium with the catalyst and anhydride. This equilibrium is analogous to that between hydantoin and hydantoic acid. In the case of L-proline-*N*-carboxy-anhydride this equilibrium presumably results in higher concentrations of ion (VII) than occur with sarcosine-*N*-carboxy-anhydride or 3-phenyloxazolidine-2,5-dione. Protonating impurities would then cause more rapid polymerization with L-proline-*N*-carboxy-anhydride. That initiation by lithium chloride involves primarily the chloride anion rather than the lithium cation is shown by the fact that lithium perchlorate does not initiate the polymerization of γ-benzyl-L-glutamate-*N*-carboxy-anhydride.[1c]

(iv) If to the equilibrium mixture described in (iii) 3-methylhydantoin is added, reactions (4)—(6) take place. Of these, (5) would be expected to be very fast.



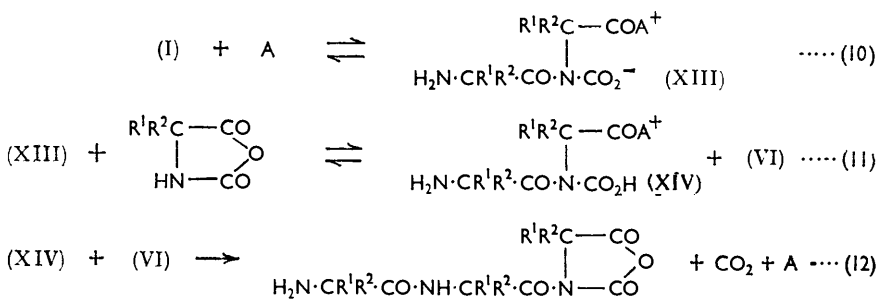
For compound (II; R^3 = Ph) the substituted aniline derivative is too weak a secondary base to enter into further propagation reactions, and it is therefore possible to isolate the intermediate in this case.

(v) If R^3 = H, the intermediate (VII) can react with oxazolidine-2,5-dione as in (7). Reactions (7)—(9) are analogous to reactions (4)—(6).



Further polymerization can now occur (*a*) by the normal primary-base mechanism involving the basic group of compound (I) and either the initial anhydride or the anhydride end of a second molecule (I), or (*b*) by the scheme (vi). In the latter the anhydride portion of compound (I) enters into reactions similar to those in (i) and (v).

(vi)



Reactions (1) and (7)—(9) lead to a mechanism essentially similar to that proposed for initiation by a tertiary base,[1b] while (vi) is an additional mode of propagation from the anhydride end of the bifunctional intermediate.

We believe that the formation of ions (V) and (VI) occurs by reaction of 3-methylhydantoin or oxazolidine-2,5-dione with (VII) rather than with tertiary base, since in this manner a closer similarity in mechanism between primary, secondary, and tertiary bases can be achieved. In the case of lithium chloride there is no such indication of the actual reaction path and ionization of 3-methylhydantoin or oxazolidine-2,5-dione may be the initial step.

The original mechanism for catalysis by a tertiary base proposed by Ballard and Bamford [1b] was criticized by Katchalski and Sela [5] on three counts. The first, that the experimental evidence does not support the idea that tertiary bases cannot initiate the polymerization of *N*-substituted anhydrides, has been shown above to be without foundation. Indeed, the low rate of reaction between tertiary bases and sarcosine- or L-proline-*N*-carboxy-anhydride is inconsistent with the various rapid ionic mechanisms which have been advanced.[5,10] The second criticism was that no experimental evidence for intermediates of type (I) existed and that " it may be anticipated that the isolation and characterization of such compounds could be achieved without difficulty." However, the experimental evidence previously published [1b] is supported by the findings described in this paper. We cannot agree that the isolation and characterization of a compound (I), which was postulated as a reactive kinetic intermediate, would present no difficulty. Thirdly, these authors state that " it should be emphasized that the tertiary amine initiated polymerizations usually proceed considerably faster than the corresponding primary or secondary amine initiated polymerizations. It can, therefore, hardly be visualized that both types of polymerization proceed by the same amine propagation mechanism." This entirely disregards the possibility fully discussed in the paper referred to [1b] that the tertiary base may act as a catalyst in a manner similar to that given above (equations 7 and 8). In our comprehensive scheme the concentration of (VII), which determines the rate of reaction in all cases, can build up to a much higher value under these conditions. This is true even if reactions (7) and (8) have rates of the same order as the association (1). The rate of the latter would be expected to be comparable for all amines of the same base strength which do not differ appreciably in the steric shielding of the nitrogen lone pair.

Kopple,[11] in considering the reactions of oxazolidine-2,5-diones, doubted whether the ring system is sufficiently acidic to allow the formation of the ion (VI); this doubt could obviously be applied to the formation of an ion (V) from 3-methylhydantoin and

[10] Wieland, *Angew. Chem.*, 1951, **63**, 7; 1954, **66**, 507.
[11] Kopple, *J. Amer. Chem. Soc.*, 1957, **79**, 6442.

can now hardly be maintained. Moreover, this author himself postulates the formation of anions of type (VI). We consider that both ions (V) and (VI) are formed to kinetically significant extents as transient intermediates, a hypothesis which is consistent with the heterocyclic ring systems' being extremely weak acids.

We do not consider a reaction scheme such as that proposed by Kopple, involving isocyanate intermediates in polymerization by a tertiary base, to be applicable, since if initiation by a primary base followed this presumably faster route urea derivatives would be expected, together with low yields of carbon dioxide and loss of primary end groups.

We thank Mr. D. R. Boreham, Mrs, S. J. Kapur, and Mrs. Z. Watson for technical assistance.

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[*Received, October 21st*, 1960.]