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Peptide Synthesis *via* *N*-Acylated Aziridinone. I. The Synthesis of 3-Substituted-1-benzyloxycarbonylaziridin-2-ones and Related Compounds[1)]

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Optically-active 3-substituted-1-benzyloxycarbonylaziridin-2-ones were synthesized from the corresponding benzyloxycarbonyl L-amino acids by the use of a dehydrating agent, such as phosgene, thionyl chloride, or phosphorus oxychloride. The reaction was carried out in THF at −20—−30°C using triethylamine to neutralize the reaction solution exactly. Among the other *N*-protecting groups used in peptide chemistry, *p*-bromobenzyloxycarbonyl and *p*-chlorobenzyloxycarbonyl amino acids also gave the corresponding aziridinones quantitatively. Some of these *N*-acylated aziridinones were obtained in the crystalline form. A reaction mechanism was also described.

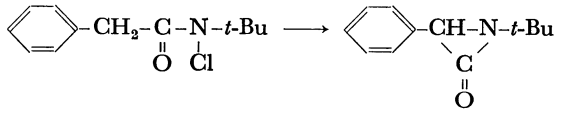
In 1908, Leuchs[2)] proposed aziridinone as a reactive intermediate when his *N*-carboxy-α-amino acid anhydride (NCA) rapidly lost carbon dioxide on heating to form polypeptide. Since then, aziridinone has been suggested as a possible reactive intermediate in peptide synthesis, though it has never been isolated from either amino acid or peptide derivatives.

In 1961, in the course of his studies of the Favorskii-

1) A part of this study has been reported in a preliminary communication. This Bulletin, **43**, 3321 (1970). Also presented at the 8th Symposium on Peptide Chemistry, Osaka, Nov. 1970, and at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971.

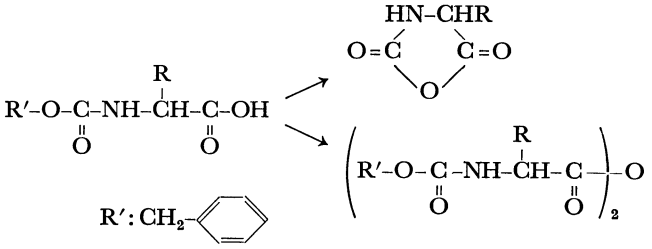
2) H. Leucks and W. Geiger, *Ber.*, **41**, 1721 (1908).

type rearrangement of *N*-*t*-butyl-*N*-chloroamide, Baumgarten[3] first detected an aziridinone as the intermediate; though it could not be isolated in a pure form, it showed a carbonyl band at 1847 cm^{-1} in IR spectra. One year later, he[4] succeeded in isolating *N*-*t*-butyl-3-phenyl-aziridinone.

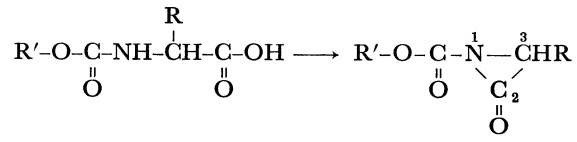


Recently, some of the aziridinones have been synthesized and their physical and chemical properties have also been clarified[5-9] to some extent. The typical synthetic routes reported so far are attributed to the dehydrohalogenation of either *N*-haloamides or α-haloamides, and it has been revealed that the *N*-substituent decisively influences the ease of ring formation and the stabilization of the corresponding aziridinone. All the aziridinones synthesized to date have the *N*-substituent, which is an electron-donating and sterically bulky alkyl group. Among them, *N*-*t*-butyl and *N*-adamantyl aziridinones have both been isolated in the pure form.

On the other hand, the reaction of an amino acid with phosgene ($COCl_2$) or thionyl chloride ($SOCl_2$) has been widely studied since Leuchs first obtained NCA. In 1950, Katchalski and Ben-Ishai[10] reported an improved route of synthesizing NCA by the use of benzyloxycarbonyl L-amino acid (Z-AA) and excess $SOCl_2$ at 40—60°C. One year later, Wieland and Bernhard[11] reported that Z-AA reacted with $COCl_2$ at 0°C in the presence of a *t*-amine to form Z-amino acid anhydride. The variety of products formed in each reaction depends upon both the reaction temperature and the presence or absence of the *t*-amine.



In the present paper, I wish to report a new synthesis of *N*-acylated aziridinones, which have an optically-active asymmetric carbon at *C*-3, from the corresponding L-acylamino acid. Some of them are isolated in the crystalline form.



Results and Discussion

Synthesis of 3-Substituted-1-benzyloxycarbonylaziridin-2-ones. Z-AA dissolved in tetrahydrofuran (THF) did not react with an equivalent $COCl_2$ under stirring at −20——30°C during the first 30 minutes. As an equivalent triethylamine (TEA) in ether was added drop by drop, triethylamine hydrochloride (TEA–HCl) was formed, and a thin-layer chromatograph (tlc) developed in the buffer solution ($CHCl_3$: AcOEt: AcOH, 85: 15: 3) showed a new spot (R_f 0.4), which was detected by ninhydrin. When another equivalent TEA was added, drop by drop, to the mixture at the same temperature and the reaction solution was neutralized exactly, a different spot (R_f 0.9) appeared almost quantitatively. The IR spectra of the reaction solution at each reaction step are summarized in Table 1.

Table 1. IR of the reaction solution

Reaction solution	R_f	IR (cm^{-1})
Z-AA	0.5	$\nu_{C=O}$ 1715, 1690 ν_{NH} 3300
After adding an eq. TEA	0.4	$\nu_{C=O}$ 1790, 1720 ν_{NH} 3200
After adding two eq. TEA	0.9	$\nu_{C=O}$ 1840, 1690 ν_{NH} —

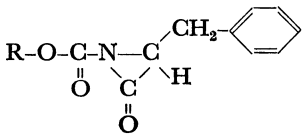
In order to isolate the final product of this reaction, ether was added to the reaction mixture at −20°C, the mixture was then quickly filtered to remove the TEA–HCl formed, and the filtrate was evaporated under reduced pressure on an ice-bath. Then to the residue were added ether and petroleum ether, and the mixture was kept in a refrigerator overnight. A small amount of the remaining Z-AA and the TEA–HCl precipitated was filtered off, and the filtrate was evaporated again. This procedure was repeated a few times, until the tlc of the solution showed a single spot at R_f 0.9. Attempts to crystallize the oil obtained after concentration did not succeed in most cases, though the oil in each case was rather stable at low temperatures.

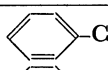
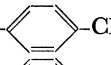
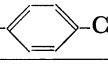
Fortunately, when Z-L-phenylalanine (Z-Phe) was treated in the same manner, the product was obtained in the crystalline state in a refrigerator; it was subsequently recrystallized from ether and petroleum ether to afford colorless needles with mp of 73.0—73.5°C. $[\alpha]_D^{20}$ −36.0° (*c* 1, THF). IR: $\nu_{C=O}$; 1840, 1690 cm^{-1}. The results of elementary analysis agreed with the dehydration product of Z-Phe, and its structure was confirmed to the 3-benzyl-1-carbobenzoxyaziridin-2-one (I) from these results and other observations, which will be discussed later.

From a further study of this dehydration reaction, it was found that 3-substituted-1-benzyloxycarbonyl-

3) H. E. Baumgarten, R. L. Zey, and U. Krolls, *J. Amer. Chem. Soc.*, **83**, 4469 (1961).
4) H. E. Baumgarten, *ibid.*, **84**, 4975 (1962).
5) H. E. Baumgarten and J. F. Fuerholzer, *ibid.*, **85**, 3303 (1963).
6) J. C. Sheehan and I. Lengyel, *ibid.*, **86**, 1356 (1964); J. C. Sheehan and J. H. Beeson, *ibid.*, **89**, 362 (1967); J. C. Sheehan and M. M. Nafissi-V, *ibid.*, **91**, 1176 (1969); J. C. Sheehan and I. Lengyel, *Angew. Chem.*, **80**, 27 (1968).
7) I. Lengyel and D. B. Uliss, *Chem. Commun.*, **1968**, 1621.
8) K. Bott, *Tetrahedron Lett.*, **1968**, 3323.
9) E. R. Talaty and A. E. Dupuy, Jr., *Chem. Commun.*, **1968**, 790; E. R. Talaty and C. M. Utermoehlen, *ibid.*, **1970**, 473; E. R. Talaty, C. M. Utermoehlen, and L. H. Stekoll, *ibid.*, **1971**, 543.
10) E. Katchalski and D. Ben-Ishai, *J. Org. Chem.*, **15**, 1067 (1950).
11) T. Wieland and H. Bernhard, *Ann. Chem.*, **572**, 190 (1951).

Table 2. Analytical data of aziridinones



R	Mp (°C)	$[\alpha]_D^{20}$ in THF	Analysis (Calcd) C	H	N	
(I) 	73—73.5	−36.0	(72.58) 72.60	(5.37) 5.33	(4.98) 5.11	
(II) 	86—87	−11.0	(56.68) 56.58	(3.92) 4.00	(3.89) 3.89	Br (22.19) 21.79
(III) 	81—82	−26.5	(64.66) 64.40	(4.47) 4.46	(4.44) 4.45	Cl (11.23) 11.27

aziridin-2-ones were also synthesized by the same treatment using $SOCl_2$ or phosphorus oxychloride ($POCl_3$) instead of $COCl_2$. When Z-Phe was used as the starting material, the corresponding crystalline aziridinone was obtained; it was identified with the specimen afforded above.

When $SOCl_2$ was used as the dehydrating agent, one more equivalent TEA was required for the neutralization of the reaction solution to form a brown-colored SO_2–TEA complex.[12]

Synthesis of Other N-*Acylated Aziridinones.* Various *N*-protecting groups commonly used in peptide chemistry were examined by the treatment and reaction conditions used for Z–AA. A remarkable difference among them was observed.

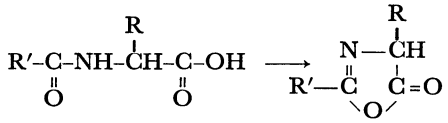
Ring formation to the aziridinone proceeded when *p*-bromobenzyloxycarbonyl (Br–Z) and *p*-chlorobenzyloxycarbonyl (Cl–Z) amino acids were used. The dehydration of Br-Z-L-phenylalanine and Cl-Z-L-phenylalanine was carried out successfully, with the aid of equivalent $COCl_2$ in THF at −20°C, by the dropwise addition of two equivalent TEA in the way described above. Then the corresponding *N*-acylated aziridinones were obtained in the respective crystalline forms. The analytical data of these aziridinones are listed in Table 2.

When tosyl amino acid was used, considerable amounts of the corresponding *N*-acylated aziridinone were isolated, but it failed to crystallize.

On the contrary, in the case of the *p*-methoxybenzyloxycarbonyl group (PMZ), which is sterically very similar to the analogous carbobenzoxy groups mentioned above, the ring formation of PMZ amino acid proceeded with little detection.

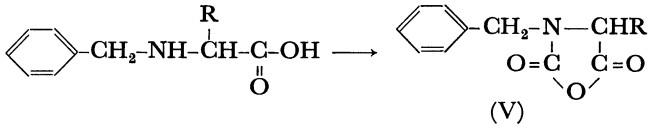
In the cases of the *t*-butyloxycarbonyl (BOC) and *t*-amyloxycarbonyl (AOC) groups, which are widely used in solid-phase peptide synthesis, the corresponding expected aziridinones could not be detected.

When other acyl groups, such as benzoyl and acetyl, were used for the *N*-protection of amino acids, the ring compounds resulting from the treatment described above were found not to be aziridinone, but azlactone. From benzoyl-L-phenylalanine and acetyl-L-phenylalanine, the corresponding 2-substituted-4-benzyl-azlactones were obtained in good yields.



R′: CH_3, C_6H_5 (IV)

If *N*-benzyl L-amino acid was used as the starting material, optically-active benzylamino-*N*-carboxyanhydrides (*N*-Bzl-NCA) were synthesized under the same reaction condition; some of them were obtained in the crystalline form.

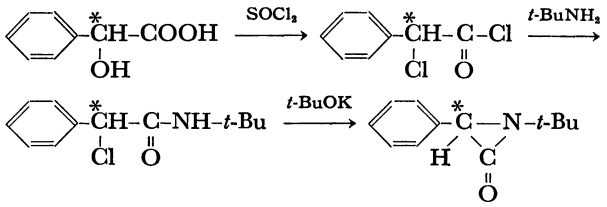


(V)

In any case, it is interesting to note that the *N*-substituents of amino acids leading to the formation of the corresponding *N*-acylated aziridinones are limited in some urethan-type groups (Z, Br–Z, Cl–Z) and the tosyl group investigated so far in this study.

Retention of Optical Activity. The aziridinones obtained to date have been synthesized by the dehydrohalogenation of *N*-haloamides or α-haloamides. Besides this type of reaction, the only optically-active aziridinone obtained *via* the optically-active α-haloamide was reported by Baumgarten[5] *et al.*

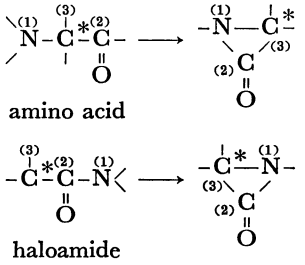
In the above route, a chance of partial racemization still remains during the abstraction of the chlorine atom on the asymmetric carbon at *C*-3.



On the contrary, the new route to synthesize the *N*-acylated aziridinone reported here may be carried out by intramolecular dehydration between carboxyl and amino groups in L-acylamino acids. This new route involves no abstraction on the asymmetric carbon during the cyclization reaction, because the atomic sequence of the starting material in this study is in

12) L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, **1944**, 243.

striking contrast to that of haloamide.



Accordingly, there is every possibility of retaining the whole optical activity in this new route. This fact is confirmed by deriving the aziridinones to the known optically-active amino acid derivatives.

Spectral Assay. Sheehan and Beeson[6] reported that *N*,3-di-*t*-butylaziridinone showed a carbonyl absorption band at 1835 cm^{-1} in the IR spectra. Later, the same band for *N*,3-di-adamantylaziridinone was observed at 1830 cm^{-1} by Talaty *et al.*[9]

All the *N*-acylated aziridinones obtained in this study show a carbonyl band due to the ring at 1840 cm^{-1} and the acyl carbonyl at 1690 cm^{-1}, and no amino band is detected in the range of 3100—3300 cm^{-1}. The IR spectra of II and III, which are typical examples of these aziridinones, are shown in Fig. 1.

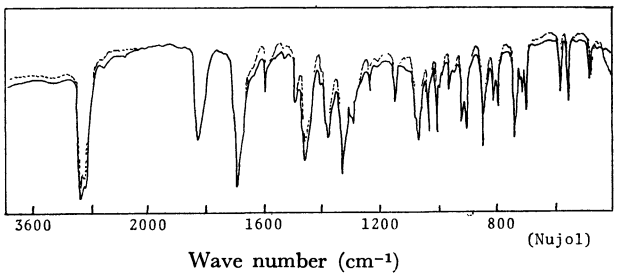


Fig. 1. IR spectra of aziridinones
—— II; ------III

The NMR data of the three crystalline aziridinones and Z-Phe which is the starting material of I, are shown in Table 3 and Fig. 2.

The triplet of the methine proton on the *C*-3 of I at 4.55 (δ) is caused only by the AB-type coupling with the methylene proton of the benzyl group. On the contrary, the methine proton of Z-Phe shows a quartet at 4.67 (δ) due to the adjacent amino proton.

The mass spectrum of the parent molecular ion of

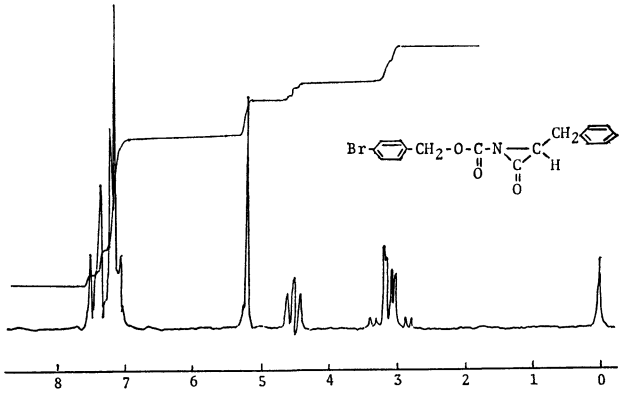
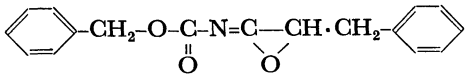


Fig. 2. NMR spectrum of II

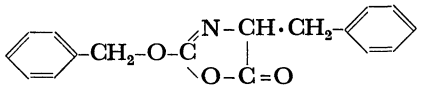
I shows *m/e* 281 ($C_{17}H_{15}NO_3$). The *m/e* 253, which is derived from the fisson of the aziridinone ring, and *m/e* 238, 209, 192, 181, 162, 146, 128, 118, 117, and 91 ions are observed. Some of these assignments are shown in Scheme 1.

The mass spectra of II and III show M^+ 362 ($C_{17}H_{14}NO_3 \cdot Br$) and 315 ($C_{17}H_{14}NO_3 \cdot Cl$) respectively; the *m/e* ion values observed can also probably be identified with that of I mentioned above.

Isomeric Structures. The other possible isomeric structures, such as an epoxide (VI) and an azlactone must be taken into consideration with regard to the dehydration product from Z-Phe.



(VI)



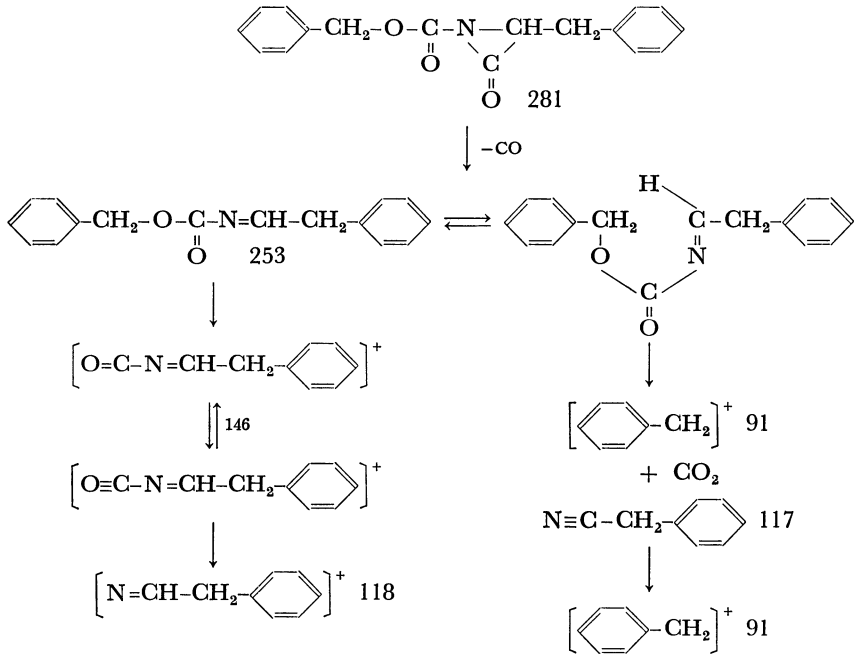
(VII)

With regard to VI, Sheehan and Beeson[6] reported the thermal decomposition of *N*,3-di-*t*-butylaziridinone at 175°C; they discussed the isomerization of the aziridinone to epoxide in order to explain the formation of pivalaldehyde and *t*-butyronitrile as the main products.

Azlactone would be another isomeric structure, though it has never yet been synthesized. Siemion

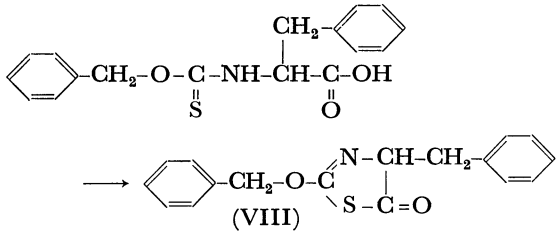
Table 3. NMR data of aziridinones
(δ, $CDCl_3$, 60 MHz)

Compound	NH	CH	CH_2- 	OCH_2- 	
I	—	4.55(*t*)	3.26(*dd*)	5.30(*s*)	7.21(*bs*)
			3.03(*dd*)		7.37(*bs*)
II	—	4.58(*t*)	3.22(*dd*)	5.26(*s*)	7.17(*bs*)
			2.95(*dd*)		7.40(*m*)
III	—	4.58(*t*)	3.23(*dd*)	5.27(*s*)	7.18(*bs*)
			2.96(*dd*)		7.38(*m*)
Z-Phe	5.45(*d*)	4.67(*q*)	3.10(*d*)	5.04(*s*)	7.18(*bs*)
					7.26(*bs*)



Scheme 1.

et al.[13] reported the only example of thiourethan-type azlactone (VIII), which was derived from benzyloxythiocarbonyl-L-phenylalanine; it was completely optically-inactive as had been expected. The IR spectra showed 1630 cm^{-1} ($\nu_{C=N}$) and 1720 cm^{-1} ($\nu_{C=O}$).



(VIII)

It has widely been accepted that the racemization during the peptide-coupling reaction must be caused by the formation of an azlactone.[14] Therefore, along with the results observed by the spectral assay, the retention of the whole optical activity in the dehydration product from Z–AA strongly supports that its structure should be the *N*-acylated aziridinone. To confirm the structure definitely, an X-ray analysis of Br-Z-aziridinone (II) is now in progress.

Reaction Mechanism. In the present study, dehydration of Z–AA to form 3-substituted-1-benzyloxycarbonylaziridinones took place by the use of $POCl_3$ as well as $COCl_2$ and $SOCl_2$, which contain two reactive halogen atoms in the molecule. Therefore, the pathway of this reaction may be partially similar to that of "the phosphorus oxychloride method" reported by Wieland and Heinke.[15]

A mechanistic approach was carried out using $SOCl_2$ as the dehydrating agent. In this case, three equivalent TEA are required to neutralize the reaction mixture exactly, because one more TEA is consumed for the neutralization of SO_2, as has been described earlier. The SO_2–TEA complex formed in the course of the reaction is brown and is insoluble in the THF–ether contained in the reaction system. Accordingly, by cutting off the reaction at each step when the addition of every equivalent TEA is over, the entire reaction may be divided into three steps. The TEA–HCl or SO_2–TEA complex precipitated at the end of each step of the reaction is collected by filtration.

It was found that an equivalent TEA–HCl was recovered almost quantitatively at the end of the first step, and that during this step the tlc of the reaction solution showed no aziridinone at R_f 0.9. At the end of the second step, when another equivalent TEA was added, the mass collected by filtration was rather small in amount and was still colorless, while tlc showed that the reaction proceeded about a half. A mixture of the rest of the TEA–HCl and an equivalent SO_2–TEA complex, which was brown in color, was obtained quantitatively in the last step of the reaction, when the reaction solution was neutralized exactly and the formation of the aziridinone was accomplished.

It is evident that $SOCl_2$ does not act as a chlorinating agent, but as a dehydrating one, at the lower temperatures treated in this study, and that the reaction proceeds *via* a mixed anhydride resulting from dehydrohalogenation between Z–Phe and $SOCl_2$ with the aid of TEA.

It should be noted that the use of ethylchloroformate or benzenesulfonyl chloride, commonly used as the mixed anhydride reagents in peptide chemistry, did not cause the ring closure under the above reaction conditions. Thus, another halogen atom containing in the intermediate mixed anhydride formed from Z–Phe and $SOCl_2$ must play an essential role as an effective leaving group in forming such a strained aziridinone. The abstraction of the hydrogen atom from the amino

13) I. S. Siemion, D. Konopinska, and Dzugaj, *Roczniki Chemii, Ann. Soc. Chim. Polonorum*, **43**, 989 (1969); I. Z. Siemion and D. Konopinska, *ibid.*, **44**, 785 (1970).

14) Optically active 2-phenyl-L-4-benzyl-azlactone was reported. M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964).

15) T. Wieland and B. Heinke, *Ann. Chem.*, **599**, 70 (1956).

nitrogen may take place by TEA, accompanied by the formation of TEA–HCl. Consequently, the nucleophilic attack of nitrogen to the carbonyl carbon would lead to the formation of an aziridinone ring.

The ease of abstraction of the hydrogen atom in the amino nitrogen may also be connected with the electronegativity of the nitrogen atom itself caused by the effect of *N*-substituents. The fact that PMZ–AA gave scarcely any of the corresponding aziridinone may be attributed to the relatively greater electronegative property of the urethan oxygen of the PMZ group in comparison with that of the Z group. The above electronegativity of the urethan oxygen of the PMZ group would affect the electron density of the amino nitrogen enough to prevent the abstraction of the hydrogen atom under the circumstances used in this study. It is well known that PMZ–AA is cleaved much more easily than Z–AA under mild acidic conditions. Similarly, in the cases of BOC–AA and AOC–AA, which are also easily cleaved under the same acidic conditions, the corresponding aziridinones were not obtained.

Experimental

The melting points are uncorrected. Thin-layer chromatography (tlc) was performed with silica gel G (Merck), and the spots were detected by ninhydrin on heating at 100°C after developing in a buffer solution ($CHCl_3$: AcOEt: AcOH, 85: 15: 3). The IR spectra were obtained using a Shimadzu IR-27G apparatus. The NMR spectra were recorded at 60 MHz in $CDCl_3$ with TMS as the internal standard using a Hitachi R-20A apparatus. The mass spectra were obtained by means of a Hitachi RMS-4 mass spectrometer. The optical rotations were measured with a Yanagimoto OR-100 apparatus.

The THF, ether and petroleum ether used throughout this experiment were dried over sodium metal wire after distillation. The $COCl_2$ gas was absorbed in dry ether to prepare the $COCl_2$–ether solution which was then stored in a refrigerator. The $SOCl_2$, $POCl_3$, and TEA were purified by distillation before use.

3-Benzyl-1-benzyloxycarbonylaziridin-2-one (I). (a) To a solution of Z-Phe (14.95 g, 0.05 mol) in 200 ml of THF was added $COCl_2$–ether solution (25 ml, containing 0.05 mol of $COCl_2$) at −20°C. TEA (7 ml, 0.05 mol) in 15 ml of ether was then added drop by drop to the solution over a period of 30 min, with stirring at −20°C. Tlc showed a spot at R_f 0.4. After 30 min, TEA (7 ml, 0.05 mol) in 15 ml of ether was added again to the reaction mixture under the same conditions as above. A spot appeared at R_f 0.9 on tlc. After an additional 30 min of stirring, 200 ml of ether was added to the reaction mixture. The TEA-HCl thus precipitated in a quantitative yield was removed by filtration, and the filtrate was evaporated under reduced pressure on an ice-bath. To the residue were added ether (200 ml) and petroleum ether (100 ml), then the mixture was stored in a refrigerator overnight. After the removal of a small amount of precipitate by filtration, the filtrate was evaporated again in the same manner as above. Then, ether (100 ml) and petroleum ether (300 ml) were added to the residue, which was then crystallized in a refrigerator for three days. The crude products thus formed were collected by filtration to afford 10.2 g (73%). For recrystallization, to the crude product was added 100 ml of ether at 0°C. After the removal of a small amount of undissolved material by filtration, petroleum ether (200 ml) was added to the filtrate, which was stored again in a refrigerator for several days to afford colorless needles (6.74 g, 48%). Recrystallization was then repeated once more in the same manner to give an analytical sample.

(b) Freshly distilled $SOCl_2$ (5.95 g, 0.05 mol) in 30 ml of ether was added to a solution of Z-Phe (14.95 g, 0.05 mol) in 200 ml of THF at −30°C. To the solution was added TEA (14 ml, 0.1 mol) in 30 ml of ether, drop by drop, over a period of 1 hr with stirring. Tlc showed two spots, at R_f 0.4 and 0.9. Then TEA (7 ml, 0.05 mol) in 15 ml of ether was added drop by drop to the reaction mixture at the same temperature. The reaction mixture gradually turned brown. After an additional 30 min, ether was added to the mixture; the mixture was subsequently filtered to romove quantitative yields of the TEA-HCl and SO_2-TEA complex thus precipitated; the yellowish filtrate, which showed a spot at R_f 0.9 on tlc, was then worked up in the manner described in (a). Subsequent recrystallization from ether and petroleum ether gave colorless needles (3.5 g, 25%), which were identified with those afforded by (a).

*3-Benzyl-1-*p*-bromobenzyloxycarbonylaziridin-2-one (II).* Br-Z-Phe[16] was prepared by a Schotten-Baumann reaction with L-phenylalanine and *p*-bromobenzyloxycarbonyl chloride. Mp 107—109°C. $[\alpha]_D^{20}$ −8.9° (*c* 1, MeOH). To a solution of Br-Z-Phe (7.56 g, 0.02 mol) in 50 ml of THF was added the $COCl_2$–ether solution (10 ml, containing 0.02 mol of $COCl_2$) at −20°C. TEA (5.6 ml, 0.04 mol) in 12 ml of ether was then added over a period of 1.5 hr to neutralize the reaction mixture at −20°C in the same manner as had been described above. Colorless prisms of II (3.2 g, 44%) were obtained after recrystallization.

*3-Benzyl-1-*p*-chlorobenzyloxycarbonylaziridine-2-one (III).* Cl-Z-Phe was synthesized with L-phenylalanine and *p*-chlorobenzyloxycarbonyl chloride in the same manner as Br-Z-Phe. Mp 80.5—82.0°C. $[\alpha]_D^{20}$ −7.5° (*c* 1, MeOH). To a solution of Cl-Z-Phe (6.66 g, 0.02 mol) in 50 ml of THF was added the $COCl_2$–ether solution (10 ml, containing 0.02 mol of $COCl_2$) at −20°C; TEA (5.6 g, 0.04 mol) in 12 ml of ether was subsequently added in the same manner as above to afford III as colorless needles (2.3 g, 37%) after recrystallization.

4-Benzyl-2-phenyl-5-oxazolone (IV). To a solution of benzoyl-L-phenylalanine (26.9 g, 0.1 mol) in 200 ml of THF was added the $COCl_2$–ether solution (50 ml, containing 0.1 mol of $COCl_2$) at −30°C. TEA (28 ml, 0.2 mol) in 80 ml of ether was then added dropwise over a period of 1.5 hr in order to completely neutralize the reaction mixture at the same temperature. A 200 ml portion of ether was then added to the reaction mixture, which was subsequently filtered to remove the TEA-HCl precipitated; the filtrate was evaporated *in vacuo* on an ice-bath. To the residue was added 300 ml of ether; the mixture was washed with an ice-cold 5% sodium bicarbonate aqueous solution and dried over magnesium sulfate. The organic layer was evaporated to about half its volume, and 150 ml of petroleum ether was added to the solution, which was then stored in a refrigerator overnight to afford 19.4 g of IV (73.3%). Recrystallization from ether and petroleum ether gave colorless needles (14.7 g, 58.6%). Mp 72—74°C. IR $\nu_{C=O}$ 1830, 1815 cm^{-1}. $\nu_{C=N}$ 1655 cm^{-1}. NMR (δ) 7.27 (bs, 5H), 7.69 (m, 4H), 4.68 (t, 1H), 3.42 (dd, 2H), 3.13 (dd, 2H). Found: C, 76.13; H, 5.18; N, 5.38%. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22;

16) D. M. Channing, P. B. Turner, and G. T. Young, *Nature*, **167**, 487 (1951).

N, 5.57%. $[\alpha]_D^{20}$ 0° (*c* 1, THF).

3-Benzyl-4-phenyl-2,5-oxazolidinedione (V). A Schiff base from L-phenylglycine and benzaldehyde was reduced by catalytic hydrogenation to afford *N*-benzyl-L-phenylglycine. Mp 222—224°C. $[\alpha]_D^{20}$ +92.4° (*c* 1, AcOH). To a solution of *N*-benzyl-L-phenylglycine (4.8 g, 0.02 mol) in 15 ml of THF was added the $COCl_2$–ether solution (10 ml, containing 0.02 mol of $COCl_2$) at −30°C. TEA (5.6 ml, 0.04 mol) in 12 ml of ether was then added, drop by drop, in the manner described above. After the removal of the TEA–HCl precipitated by filtration, the filtrate was evaporated *in vacuo* on an ice-bath. To the residue was then added 300 ml of ether, and the mixture was washed with an ice-cold 5% sodium bicarbonate aqueous solution and dried over magnesium sulfate. Crystallization from ether and petroleum ether (1 : 2) gave 2.6 g of V. Mp 120—122°C. IR $\nu_{C=O}$ 1850, 1760 cm^{-1}. NMR (δ) 7.04—7.55 (m, 10H), 4.90 (s, 1H), 4.44 (q, 2H). Found: C, 71.79; H, 5.08; N, 5.28%. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24%. $[\alpha]_D^{20}$ +124.0° (*c* 1, THF).

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