Wave length, $m\mu$	O.D. differences before solvolysis	O.D. differences after solvolysis	Net change in differences
242	0.000	0.008	0.008
243	− .002	.004	.006
244	.012	.003	.008
245	.009	.004	− .005
246	.017	.007	− .010

than 20 half-lives for this compound as estimated from known rates in other solvents using the Winstein–Grunwald equation.[58]

The neutral and basic solutions obtained after solvolysis were examined spectroscopically and the optical density differences are tabulated in column 3 of Table IX.

Subtraction of the difference in column 2 from those in column 3 gives column 4. The net differences in column 4 represent the spectral contributions of any phenolic species present after solvolysis which were not present before, i.e., any cleavage product. These net differences are very small (within experimental error of zero), and since 2-p-hydroxyphenylethanol has a maximum at 241 $m\mu$ (ϵ 10,150) in basic solution, it can be estimated from these differences that less than 0.2% of the 2-p-anisylethyl p-toluenesulfonate undergoes cleavage during solvolysis.

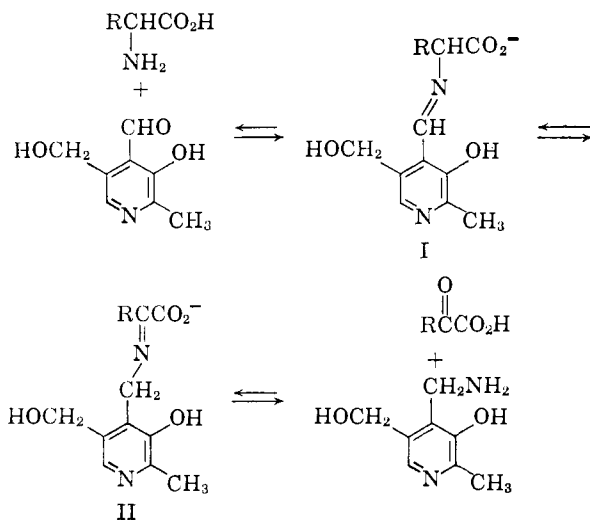(58) S. Winstein, E. Grunwald and H. W. Jones, J. Am. Chem. Soc., 73, 2700 (1951).

Azomethine Chemistry. II. Formation of Peptides from Oxazolidine-5-ones[1,2]

By Richard G. Hiskey and James M. Jung[3-5]

Treatment of N-arylidene salts of α-amino acids with phthaloylglycyl chloride has provided 65–85% yields of 2-aryl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones. These oxazolidine-5-ones afford tripeptides in 30–50% yield when treated with α-amino acid esters. Acylation of the azomethines with the p-nitrophenyl ester of N-carbobenzoxyglycine or the mixed carbonic anhydride of phthaloyl glycine also proceeds but in lower yield.

In an earlier report[1] model compounds resembling the azomethine intermediate II in the pyridoxal-catalyzed transamination reaction were generated and catalytically hydrogenated. The addition of hydrogen was shown to proceed stereospecifically and afford optically active α-amino acids from the corresponding α-keto acid. In order to obtain a more complete understand-

ing of the possible reactions of pyridoxal in biological systems, model compounds related to the azomethine intermediate I have also been studied.

The condensation of α-amino acids, in the form of carboxylate salts, with aryl aldehydes is well known.[6,7] Using a modification of the earlier method[7] of preparation, azomethine salts of a number of α-amino acids could be obtained in good yield (Table I). The salts

(1) Part I of this series, R. G. Hiskey and R. C. Northrop, J. Am. Chem. Soc., 83, 4798 (1961).

(2) This work was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is hereby made to the donors of this fund.

(3) Abstracted in part from a dissertation by J. M. Jung submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June, 1962.

(4) Petroleum Research Fund Fellow, 1959-1961.

(5) Tennessee Eastman Corporation Fellow, 1961-1962.

(6) O. Gerngross, Biochem. Z., 108, 84 (1920); O. Gerngross and E. Zuhlke, Ber., 57, 1482 (1924).

(7) M. Bergman, H. Ensslin and L. Zervas, ibid., 58, 1034 (1925).

Table I

Schiff Base Salts of Amino Acids

X	R	Yield, %	X	R	Yield, %
H−	−H	95.7	CH₃O−	−CH₃	84.0
H−	−CH₂OH	96.5	CH₃O−	−CH(CH₃)₂	71.2
H−	−CH₂C₆H₅	74.5	CH₃O−	−CH₂CH(CH₃)₂	89.3
CH₃O−	−H	90.0	CH₃O−	−CH₂SCH₂C₆H₄	80.0
CH₃O−	−CH₂C₆H₅	96.0	HO−	−H	98.0

are sensitive to moisture and evolve the aldehyde on exposure to air. Consequently the salts were usually generated immediately prior to use. The Schiff base salts decomposed rather than melted. The criterion of purity used was the complete disappearance of the carboxyl OH band and the appearance of azomethine and carboxylate peaks in the 1640 and 1625 cm.$^{-1}$ regions, respectively.

Of interest was an earlier experiment[7] in which barium N-benzylideneglycinate (IIIa, Ar = C₆H₅, R = H) was reported[8] to yield 2-phenyl-3-acetyloxazolidine-5-one (IVa, Ar = C₆H₅, R = H, R′ = CH₃) with either acetyl chloride or acetic anhydride in refluxing carbon tetrachloride. More recently a similar reaction
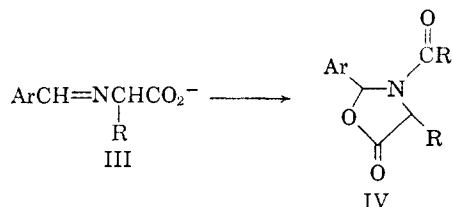

using trifluoroacetic anhydride[9] provided 2-phenyl-3-trifluoroacetyloxazolidine-5-one (IVb, Ar = C₆H₅, R = H, R′ = CF₃). In view of the close relationship between I and III and the fact that a number of biological processes involve acylation (usually by "active esters") it seemed possible that oxazolidine-5-

(8) H. Scheibler and P. Baumgarten, ibid., 55, 1358 (1922), prepared IVa by the action of acetic anhydride on sodium N-benzylideneglycinate. The proposed betain structure was subsequently revised.

(9) F. Weygand and E. Leising, ibid., 87, 248 (1954).

ones might arise from pyridoxal. A reaction of the type visualized would involve the conversion of I to V with an "active ester" of an α-amino acid. However, if a substance such as V were present biologically, it might be expected to react further. For example, IVa

I+YNHCHOZ →

V
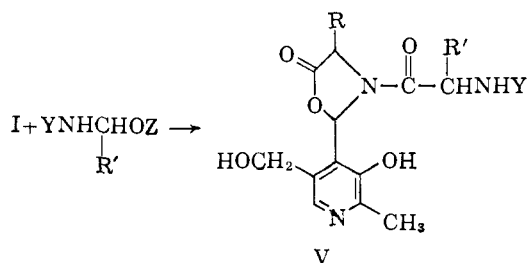
was found to yield N-acetylglycine and benzaldehyde when treated with water.[7] Micheel[10] has provided several examples of dipeptide formation using various oxazolidine-5-ones prepared from N-tosyl-α-amino acids (Fig. 1). Ethyl N-trifluoroacetylglycylglycinate was also prepared[9] by the action of ethyl glycinate on IVb.
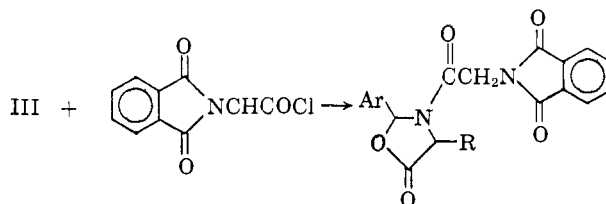

Figure 1.
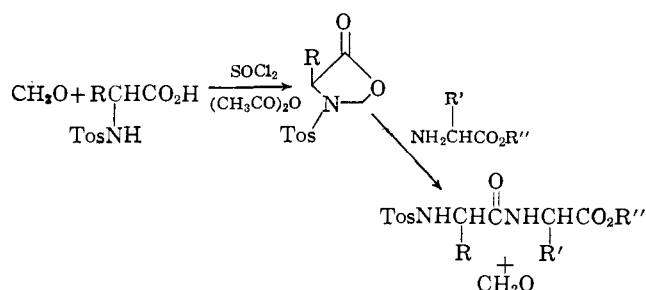
Thus it appeared likely that acylation of I or III with a suitably protected α-amino acid derivative would provide an oxazolidine-5-one, e.g., V, which would couple with a third α-amino acid and provide a tripeptide. The anticipated over-all sequence is shown below. This report concerns preliminary acylation studies with
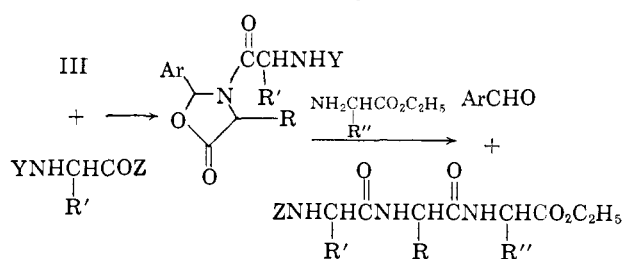

the azomethine salts in Table I and the general aspects of the above sequence. Experiments with I and azomethine models more closely resembling I will be discussed separately.

When IIIa was treated with acetyl chloride as previously described, IVa was obtained in low yield. However, acylation of the sodium salt, rather than the barium salt, in refluxing methylene chloride afforded IVa in 72.7% yield. In a similar manner acylation of IIIa with phthaloylglycyl chloride afforded 2-phenyl-3-phthaloylglycyloxazolidine-5-one (VIIa, Ar = C_6H_5, R = H) in 66.7% yield. The yield of oxazolidinone was increased when a p-methoxy substituent was employed in III; VIIb (Ar = p-$CH_3OC_6H_4$, R = H) was obtained in 78.5% yield from IIIb (Ar = p-CH_3-OC_6H_4). Cyclization of IIIc (Ar = p-HOC_6H_4) afforded 40.6% of VIIc (Ar = HOC_6H_4, R = H) while a similar reaction with the azomethine salt derived from cyclo-

(10) F. Micheel and W. Meckstroth, Ber., 92, 1675 (1959); F. Micheel and H. Haneke, ibid., 92, 309 (1959); F. Micheel and S. Thomas, ibid., 90, 2906 (1957); F. Micheel and H. Haneke, ibid., 95, 1009 (1962).

III +

VII

hexanone and glycine gave only 20.1% of the oxazolidine-5-one VIII. A 35.5% yield of VIIb resulted from acylation of the N,N-dicyclohexylamine salt of IIIb and therefore the sodium N-p-methoxybenzylidene salts of the amino acids were employed throughout the remainder of the study.
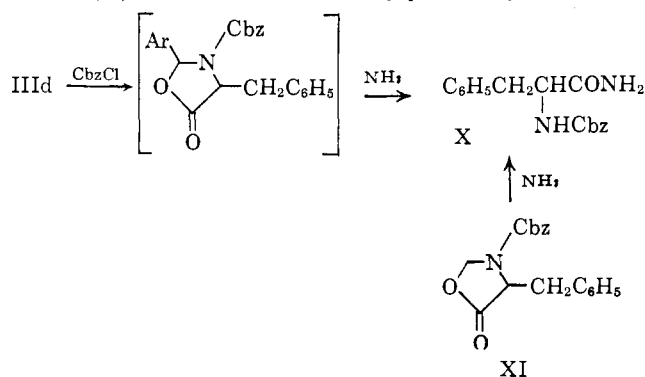

VIII
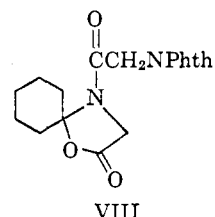
Several of the N-p-methoxybenzylidene derivatives were treated with phthaloylglycyl chloride. The resulting 2-p-methoxyphenyl-3-phthaloylglycyl-4-alkyloxazolidene-5-ones are listed in Table II. The cyclized products exhibited a characteristic carbonyl absorption band at 1800–1810 cm.$^{-1}$ and in some cases rather large specific rotations. In contrast to IVa which is rapidly hydrolyzed in water, the oxazolidine-5-ones containing a phthaloyl group could be precipitated from N,N-dimethylformamide solution by addition of water.

Treatment of the 2-p-methoxyphenyl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones with ethyl glycinate provided the N-phthaloyl tripeptide esters IX. The rather low yields of the tripeptides obtained (Table III) probably reflect isolation problems rather than difficulties associated with oxazolidinone ring opening. The optical activity associated with the oxazolidine-5-ones (Table II) and the optically active tripeptides obtained

VII + $NH_2CH_2CO_2C_2H_5$ →
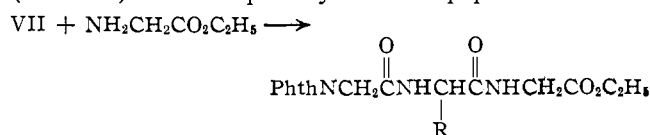
(Table III) preclude complete racemization in the overall reaction sequence. The present data do not allow an estimate of the amount of racemization. However, in a single experiment sodium N-p-methoxybenzylidene-L-phenylalanate (IIId, Ar = p-$CH_3OC_6H_4$, R = CH_2-C_6H_5) was treated with carbobenzoxy chloride and then with ammonia. N-Carbobenzoxy-L-phenylalanine amide (X) was obtained in 88% yield, $[\alpha]^{24}D$ +11.0°.

XI

The amide X was previously prepared by Ben-Ishai[11]

(11) D. Ben-Ishai, J. Am. Chem. Soc., 79, 5736 (1957).

Table II

2-*p*-Methoxyphenyl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones

$$p\text{-}CH_3OC_6H_4CH{=}NCHCO_2Na \;+\; PhthNCH_2COCl \;\longrightarrow$$

(with R below N in reactant)

R	Yield, %	M.p., °C.	Specific rotation[a] n_{tD} (c)	t, °C.	Calculated	Found
-H	78.5	168			C, 63.15; H, 4.24; N, 7.37	C, 62.74; H, 4.16; N, 7.43
-CH₃	71.2	197.5	+171.3 (1.02)	26	C, 63.95; H, 4.60; N, 7.10	C, 64.24; H, 4.93; N, 7.02
-CH₂CH(CH₃)₂	78.7	186	+205.5 (0.4)	29	C, 66.05; H, 5.54; N, 6.42	C, 65.71; H, 5.54; N, 6.28
-CH₂C₆H₅	66.5	199.5	+562 (0.4)	29	C, 68.93; H, 4.71; N, 5.96	C, 68.64; H, 4.71; N, 5.89
-CH₂SCH₂C₆H₄	85.5	192.5	+ 8.69 (0.78)	22	C, 65.09; H, 4.68; N, 5.42; S, 6.21	C, 64.82; H, 4.95; N, 5.25; S, 6.20

[a] All rotations were taken in acetone.

Table III

Tripeptides Obtained from 2-*p*-Methoxyphenyl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones

$$\xrightarrow{\;H_2NCH_2CO_2C_2H_5\;}\qquad PhthNCH_2\overset{O}{\overset{\|}{C}}NHCHC\overset{O}{\overset{\|}{N}}HCH_2CO_2C_2H_5$$

(with R below)

R	Yield, %	M.p., °C.	Specific rotation n_{tD} (c)	t, °C.	Calculated	Found
-H	98	232.5			C, 55.33; H, 4.93; N, 12.10	C, 55.18; H, 4.83; N, 11.91
-CH₃	41.7	249.5	+18.8[a] (0.25)	24	C, 56.50; H, 5.30; N, 11.63	C, 56.41; H, 5.45; N, 11.56
-CH₂CH(CH₃)₂	34.4	217.5	-12.7[a] (0.4)	24	C, 59.54; H, 6.25; N, 10.52	C, 59.69; H, 6.43; N, 10.44
-CH₂C₆H₅	44.7	230	-9.62[b] (0.42)	22	C, 63.15; H, 5.30; N, 9.61	C, 62.97; H, 5.58; N, 9.67
-CH₂SCH₂C₆H₅	49.6	208.5	+44.0[b] (0.48)	22	C, 59.61; H, 5.20; N, 8.69; S, 6.63	C, 59.79; H, 5.28; N, 8.98; S, 6.58

[a] Rotation taken in acetone.　[b] Rotation taken in N,N-dimethylformamide.

by amminolysis of either 3-carbobenzoxy-4-benzyl-oxazolidine-5-one (XI) or N-carbobenzoxyphenylalanyl chloride. Both preparations had specific rotations of $[\alpha]^{24}$D +12.0°.

Although acylation of III proceeded readily with acid chlorides, varying results were obtained with other acid derivatives. Treatment of IIIb with the mixed anhydride[12] derived from phthaloylglycine and ethyl chloroformate afforded only 13% of VIIb. Acylation of IIIb with N-carbobenzoxyglycine *p*-nitrophenyl ester (XII) followed by hydrolysis of the resulting oil provided a 23.8% yield of N-carbobenzoxy-glycylglycine (XIII). Several attempts to acylate III with N-carbobenzoxy amino acid azides gave no trace of the oxazolidinones. When IIIb was treated with N-carbobenzoxyglutamic anhydride (XIV) an oil re-

sulted whose spectra suggested the presence of the desired oxazolidine-5-one (XV). Hydrolysis of the oil afforded N-carbobenzoxy-γ-glutamylglycine (XVI) in 24% yield. N-Carbobenzoxyglutamic anhydride is

(12) J. R. Vaughan and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

known[13] to yield mixtures of the α- and γ-acylated products; the α-isomer of XVI may have been produced but was not isolated.
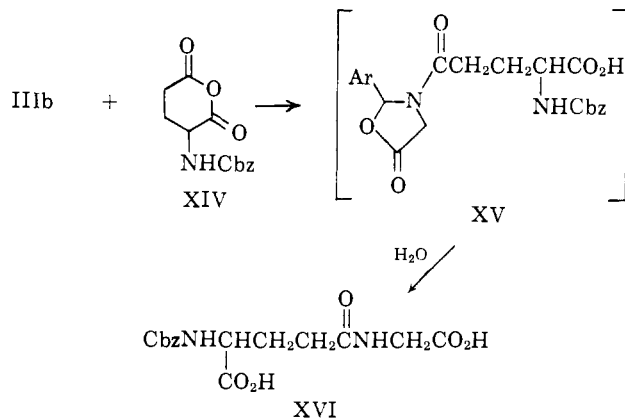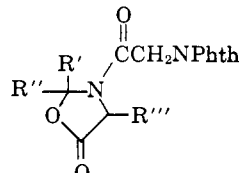
The formation of VII from α-amino acids other than glycine gives rise to two asymmetric centers. It might be anticipated that an equimolar mixture of the two possible diastereoisomers would result. However, in the cases studied only a single isomer was isolated. Thus in the absence of some equilibration process the ring closure leading to VII would appear to be reasonably stereospecific. At least two possible mechanistic pathways for ring closure may be considered. One would involve direct acylation of III to produce the iminium salt XVII which could then cyclize to IV. A second scheme would involve initial formation of the mixed anhydride XVIII which could give XVII by

(13) W. J. LeQuesne and G. T. Young, *J. Chem. Soc.*, 24 (1952); 1959 (1950).

TABLE IV

OTHER OXAZOLIDINONES PREPARED via AZOMETHINES

$$\begin{array}{c} O \\ \| \\ R' \quad CCH_2NPhth \\ R''{-}N \\ O \quad {-}R''' \\ \| \\ O \end{array}$$

R'	R''	R'''	Yield, %	M.p., °C.	Calculated	Found
H	C_6H_5	H	66.7	229–231	C, 65.15; H, 4.03; N, 8.00	C, 65.31; H, 4.20; N, 8.00
	$-(CH_2)_5-$	H	20.1	202.5	C, 63.15; H, 5.30; N, 8.18	C, 63.19; H, 5.57; N, 8.08
H	p-HOC_6H_4	H	40.6	243 dec.	C, 62.20; H, 3.85; N, 7.65	C, 61.62; H, 4.00; N, 7.68
H	C_6H_5	$CH_2C_6H_5$	35.4	223.5 dec.	C, 70.90; H, 4.58; N, 6.36	C, 70.77; H, 4.59; N, 6.53

either an intra- or intermolecular process. The present data cannot distinguish between the two possibilities.

$$\begin{array}{ccc}
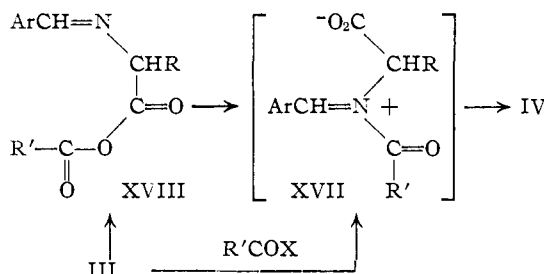\text{ArCH}{=}\text{N} & & \left[\begin{array}{c} {^-}O_2C \\ \diagdown \text{CHR} \end{array} \right. \\
\diagdown \text{CHR} & & \text{ArCH}{=}\overset{+}{\text{N}}\;+ \\
\overset{|}{\text{C}}{=}O & \longrightarrow & \overset{|}{\text{C}}{=}O \\
R'{-}\text{C}{-}O & & \left. \begin{array}{c} \\ \overset{|}{\text{C}}{=}O \\ \overset{|}{R'} \end{array} \right] \longrightarrow \text{IV} \\
\overset{\|}{O} \quad \text{XVIII} & & \text{XVII} \\
\uparrow & & \uparrow \\
\text{III} & \overset{\text{R'COX}}{\longrightarrow} &
\end{array}$$

The conversion of III to IV may be considered as a specific example of a more general reaction exhibited by azomethines. Attack of an electrophile on an azomethine containing a nucleophilic group Y would provide the iminium ion XIX. Ring closure could then give the cyclic product XX. Thus, depending on the nature of Y and the electrophile, a number of intermediates could be produced. Whether the cyclic products would be stable under biological conditions or decompose as in the conversion of VII to IX would depend on the nature of the intermediate.

$$\begin{array}{ccccc}
\overset{Y}{\diagdown} & & \overset{Y}{\underset{\downarrow}{\diagdown}} & & \overset{Y}{\diagdown} \\
{-}\text{C}{=}\text{N} & \overset{E^+}{\longrightarrow} & {-}\text{C}{=}\overset{+}{\text{N}} & \longrightarrow & {-}\text{C}{-}\text{N} \\
| & & | \quad \diagdown E & & | \quad \diagdown E \\
& & \text{XIX} & & \text{XX}
\end{array}$$
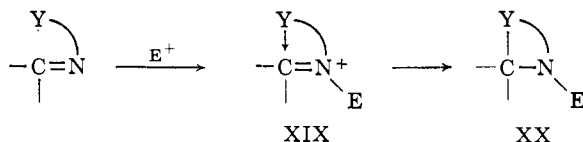
Experimental[14]

2-Phenyl-3-acetyloxazolidine-5-one (IIIa).—To 2.0 g. (0.01 mole) of potassium N-benzylideneglycinate suspended in 200 ml. of methylene chloride was added 0.79 g. (0.01 mole) of acetyl chloride. The reaction mixture was stirred under reflux for 6 hours, filtered and evaporated to an oil which solidified on cooling. Recrystallization from carbon tetrachloride gave 1.49 g. (72.7%) of IIIa, m.p. 99.5–102°; reported[7] m.p. 103°. The infrared spectrum of IIIa exhibited characteristic absorption peaks at 1650 and 1800 cm.$^{-1}$.

N-Acetylglycine from 2-Phenyl-3-acetyloxazolidine-5-one (IIIa).—A 100-mg. (0.49 mmole) sample of IIIa was treated with 5 ml. of boiling water. The solution was cooled after 2 minutes, washed with ether and evaporated in vacuo. The solid was recrystallized from dilute ethanol to afford 56 mg. (97.9%) of N-acetylglycine, m.p. 202–204°; reported[15] m.p. 206°.

N-Acetylglycylglycine Ethyl Ester from 2-Phenyl-3-acetyloxazolidine-5-one (IIIa).—A solution of 200 mg. (0.976 mmole) of IIIa in 25 ml. of dry tetrahydrofuran was treated with a three molar excess of ethyl glycinate. After 2 hours at reflux the solvent was removed and the solid mass recrystallized from ethanol to yield 140 mg. (70.0%) of N-acetylglycylglycine ethyl ester, m.p. 151–152°; reported[16] m.p. 151°.

(14) Amino acids were obtained from the Mann Research Laboratories, New York, N. Y. and are of the L-configuration. Optical rotations were performed on a Rudolf model 80 polarimeter equipped with a model 200 photoelectric attachment. Elemental analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Micro-Tech Laboratories, Skokie, Ill. The melting points are uncorrected.

(15) R. Radenhausen, J. prakt. Chem., 52, 437 (1895).

(16) E. Fischer, Chem. Ber., 35, 1101 (1902).

Preparation of Schiff Base Salts of Amino Acids.—To the amino acid (0.01 mole) was added one molar equivalent of 1 N sodium hydroxide. Addition of ethanol and gentle warming was sometimes necessary to effect solution. The solution was then evaporated under reduced pressure on the rotatory evaporator until solid began to appear at which time one molar equivalent of the aryl aldehyde was added. Evaporation was continued until the reaction mixture solidified. Ethanol was added and the solid filtered, washed thoroughly with ether and dried in vacuo over phosphorus pentoxide. This procedure afforded the Schiff base salts in 85–95% yield. The infrared spectrum exhibited characteristic absorption peaks at 1640 and 1625 cm.$^{-1}$.

Preparation of 2-Aryl-3-phthaloylglycyl-4-alkyloxazolidine-5-ones (VII).—A 2.23-g. (0.01 mole) sample of phthaloylglycyl chloride[17] was dissolved in 50 ml. of methylene chloride and added in one portion to a stirred suspension of freshly prepared Schiff base salt (0.01 mole) in 200 ml. of methylene chloride. The suspension was brought to reflux and in ca. 15 minutes an almost clear solution was obtained, which slowly became cloudy. After 8–12 hours the turbid reaction mixture was concentrated and dried. The resulting solid was washed with water, 5% sodium bicarbonate, sodium bisulfite and water. The dried residue was recrystallized from aqueous acetone and afforded the oxazolidine-5-one in 70–85% yield. The infrared spectrum exhibited characteristic absorption peaks at 1667 and 1800–1810 cm.$^{-1}$.

Ring Opening of the Oxazolidinone with Ethyl Glycinate. Preparation of Protected Tripeptides.—To 0.01 mole of oxazolidinone in 50 ml. of N,N-dimethylformamide was added 0.03 mole of glycine ethyl ester hydrochloride and 0.03 mole of triethylamine. The reaction mixture was magnetically stirred for 8–12 hours at 90°. The solvent was removed in vacuo and the residue dissolved in ethyl acetate and filtered. The filtrate was washed with dilute hydrochloric acid, water, sodium bisulfite and water. Removal of the solvent and recrystallization of the residue from ethanol afforded 40–90% yields of the tripeptide esters.

Acylation of Sodium N-p-Methoxybenzylideneglycinate (IIIb) with p-Nitrophenyl Carbobenzoxyglycinate (XII).—A suspension of 4.0 g. (0.019 mole) of IIIb and 6.15 g. (0.019 mole) of p-nitrophenyl carbobenzoxyglycinate was refluxed with stirring for 67 hours in 150 ml. of methylene chloride. Filtration and evaporation afforded a yellow oil which was treated with 1 N hydrochloric acid. The resulting solid was washed with water and dried to afford 1.20 g. (23.8%) of product melting at 175°. A mixture melting point with an authentic sample of XIII was not depressed; reported[18] m.p. 178–179°.

Acylation of Sodium N-p-Methoxybenzylideneglycinate (IIIb) with a Mixed Carboxylic–Carbonic Anhydride.—Phthaloylglycine (4.1 g., 0.02 mole) was suspended in 100 ml. of dry chloroform and 2.1 g. (0.02 mole) of triethylamine was added to the stirred suspension. The solution was cooled to −15° and 2.3 g. (0.02 mole) of ethyl chloroformate was added. The solution was stirred for 25 minutes and then added to a precooled stirred suspension of 4.3 g. (0.02 mole) of IIIb in 50 ml. of chloroform. After 9.5 hours the solvent was removed and the resulting yellow oil was taken up in methylene chloride, washed with water and dried. Removal of the solvent afforded a solid which was recrystallized from dilute ethanol to yield 1.0 g. (13%) of VIIb, m.p. 166°. The infrared spectrum of the product was identical with that of an authentic sample.

Carbobenzoxyglutamic Anhydride (XIV) was obtained in 88% yield by the procedure of LeQuesne and Young[13]; m.p. 92–93°, reported[13] 93–94°.

Acylation of Sodium N-p-Methoxybenzylideneglycinate (IIIb) with Carbobenzoxyglutamic Anhydride (XIV). Carbobenzoxy-γ-glutamylglycine (XVI).—A suspension of 5.53 g. (0.026 mole) of IIIb in 100 ml. of methylene chloride was treated with 5.73 g.

(17) J. C. Sheehan and V. S. Frank, J. Am. Chem. Soc., 71, 1856 (1949).

(18) M. Bergmann and L. Zervas, Chem. Ber., 65, 1192 (1932).

(0.022 mole) of XIV in 100 ml. of methylene chloride. The suspension was stirred at reflux for 7 hours, cooled and evaporated. The oil was washed with 3 N hydrochloric acid, extracted with chloroform and the organic layer dried and evaporated. The resulting oil was treated with 100 ml. of 2 N sodium hydroxide at room temperature for 10 hours. The alkaline solution was washed with methylene chloride, acidified with 6 N hydrochloric acid and extracted with ethyl acetate. The organic layer was evaporated and the resulting solid recrystallized from ethyl acetate and n-heptane to yield 2.01 g. (24.3%) of carbobenzoxy-γ-glutamylglycine, m.p. 158–160°; reported[13] m.p. 159–161°.

2-p-Methoxy-3-phthaloylglycyloxazolidine-5-one (VIIb) from the Dicyclohexylamine Salt of N-p-Methoxybenzylideneglycine.—To 0.75 g. (0.01 mole) of glycine was added 10 ml. of a 1 molar solution of dicyclohexylamine in dioxane. Water was added to dissolve the solid and the solution was evaporated on the rotatory evaporator to near dryness. Anisaldehyde (1.36 g., 0.01 mole) was then added and the Schiff base salt was isolated in the usual manner.

The crude salt was suspended in 100 ml. of methylene chloride and treated with 2.23 g. (0.01 mole) of phthaloylglycyl chloride in 25 ml. of methylene chloride. The suspension was stirred overnight. Work-up in the usual manner afforded 1.35 g. (35.5%) of VIIb, m.p. 165–167°. A mixture melting point with an authentic sample was not depressed.

Carbobenzoxyphenylalanine Amide (X).—Sodium N-p-methoxybenzylidenephenylalanate (IIId, 4.4 g., 0.015 mole) was suspended in 100 ml. of methylene chloride and 2.45 g. (0.015 mole) of carbobenzoxy chloride in 25 ml. of methylene chloride was

added to the stirred suspension. After 10 hours at room temperature the solvent was removed in vacuo and the resulting oil carefully dried in vacuo over sodium hydroxide. The oil was dissolved in 50 ml. of absolute ethanol and treated with 5 ml. of concentrated ammonium hydroxide. The solution was stirred 6 hours at room temperature, evaporated and the residue dissolved in chloroform. The extract was washed with water, 1 N hydrochloric acid, 5% sodium bicarbonate, sodium bisulfite and water. Removal of the solvent and recrystallization of the residue from chloroform and n-heptane afforded 2.08 g. (88% based on 0.34 g. of recovered Schiff base salt) of X, m.p. 165–166°; $[\alpha]^{24}$D +11.0° (c 1.0 in chloroform); reported[11] m.p. 167°, $[\alpha]^{20}$D +12° (c 1.0 in chloroform).

Phthaloylglycyl-D,L-serine from Sodium N-Benzylidene-D,L-serinate.—To 0.75 g. (3.5 mmoles) of sodium N-benzylidene-D,L-serinate suspended in 50 ml. of methylene chloride was added 0.78 g. (3.5 mmoles) of phthaloylglycyl chloride. The mixture was shaken mechanically for 44 hours at room temperature. The solvent was evaporated and the oily residue steam distilled. The aqueous solution in the distillation flask was evaporated and the residue recrystallized from dilute ethanol to afford 140 mg. (13.7%) of dipeptide, m.p. 192–192.5°; reported[19,20] m.p. 199 and 191°.

Anal. Calcd. for $C_{13}H_{12}N_2O_6$: C, 53.45; H, 4.14; N, 9.56. Found: C, 53.50; H, 4.28; N, 9.46.

(19) F. E. King, J. W. Clark-Lewis and G. R. Smith, J. Chem. Soc., 1046 (1954).

(20) F. E. King, J. W. Clark-Lewis and R. J. Wade, ibid., 880 (1957).

[Contribution from the Department of Chemistry, Cornell University, Ithaca, N. Y.]

Peracid Reactions. III.[1] The Oxidation of Bicyclo[2.2.1]heptadiene[2]

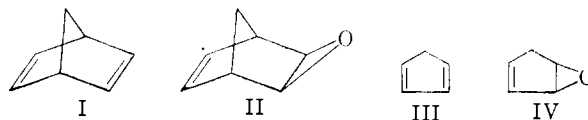By Jerrold Meinwald,[3] Santokh Singh Labana and Mohindra Singh Chadha

The peracid oxidation of bicyclo[2.2.1]heptadiene (I) gives bicyclo[3.1.0]hex-2-ene-6-endo-carboxaldehyde (VIIIa) rather than the expected epoxide II. Further transformations of this aldehyde establish its structure and stereochemistry, and a mechanism for its formation is suggested. This rearrangement of bicyclo[2.2.1]heptadiene provides ready access to a group of compounds which is otherwise inaccessible.

Introduction

Ever since bicyclo[2.2.1]heptadiene (I) became readily available, there has been extensive interest in its reactions and properties.[4] We were interested in the possibility of preparing its monoepoxide II, and although the peroxidic oxidation of I has been studied in several laboratories, conditions which might have been appropriate for the isolation of II do not seem to have been selected.[5] We wish to report the unusual course of the peracid oxidation of bicycloheptadiene, which promises to be of synthetic usefulness, although not in the way originally intended.

Discussion

One promising approach to our goal was provided by the work of Korach, Nielsen and Rideout,[6] who developed a convenient procedure for the conversion of cyclopentadiene (III) into its monoepoxide IV using peracetic acid and sodium carbonate in a two-phase system. When this technique was applied to I, a neutral product with the expected empirical formula,

(1) For parts I and II of this series, see J. Meinwald, M. C. Seidel and B. C. Cadoff, J. Am. Chem. Soc., 80, 6303 (1958), and J. Meinwald and E. Frauenglass, ibid., 82, 5235 (1960).

(2) This work was supported in part by research grants from the National Institutes of Health.

(3) Fellow of the Alfred P. Sloan Foundation.

(4) See, for example, G. S. Hammond, N. J. Turro and A. Fischer, J. Am. Chem. Soc., 83, 4674 (1961); W. G. Dauben and R. L. Cargill, Tetrahedron, 15, 197 (1961); C. F. Wilcox, S. Winstein and W. G. McMillan, J. Am. Chem. Soc., 82, 5450 (1960); L. Schmerling, J. P. Lewis and R. W. Welch, ibid., 78, 2819 (1956); also papers cited in ref. 5.

(5) N. A. Milas and P. P. H. L. Otto, J. Org. Chem., 25, 2225 (1960); J. P. Schaefer, J. Am. Chem. Soc., 82, 4091 (1960); G. T. Youngblood, C. D. Trivette and P. Wilder, J. Org. Chem., 23, 684 (1958).

(6) K. M. Korach, R. D. Nielsen and H. W. Rideout, J. Am. Chem. Soc., 82, 4328 (1960).

I   II   III   IV

C_7H_8O, was isolated in ca. 70% yield. That this product was not the desired one was revealed immediately by the presence of a strong carbonyl stretching band at 5.92 μ in its infrared spectrum. This carbonyl group was part of an aldehydic function, as shown by the presence of a prominent doublet (J = 3 c.p.s.) in the n.m.r. spectrum, centered at 0.70 τ.[7] Chemical confirmation of this conclusion was provided by the smooth silver oxide oxidation of this product to a crystalline acid, $C_7H_8O_2$. This acid readily decolorized bromine and must, therefore, have at least one double bond.

Two possible pairs of structures for the aldehyde and acid which would accommodate these observations may be derived as shown in Chart 1. Epoxidation of I to give II, followed by acid-catalyzed ring opening to give the resonance-stabilized cation V, or direct conversion of I into V without the intermediacy of the epoxide itself, may be pictured as a plausible first step. The contraction of V (focusing on the contributing Va) to give bicyclo[2.1.1]hex-2-ene-5-carboxaldehyde (VI) finds some analogy in epoxide chemistry,[8] although the facile generation of such a highly strained ring system in this particular instance would be rather surprising. Alternatively, the opening of the C_1–C_2 bond in the

(7) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.

(8) For a convenient review of several early cases of epoxide rearrangement of this type, see S. Winstein and R. B. Henderson in R. C. Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1.