98-3; *N*-[β-(3-indolylethyl)]-β-ethylenedioxyglutarimide, 32367-47-8.

Acknowledgment.—Thanks are due the Charles Pfizer and Company for a generous initial supply of β-oxoglutaric acid. Thanks are also due the National Institute of Mental Health for Public Health Grant MH-10106-01,02 and in addition to George M. J. Slusarczuk, Joseph Wreen, and John Harrison for their preparative assistance.

The Condensation of Aldehydes and Ketones with Dipeptides[1]

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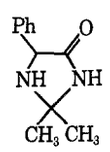
The interaction of simple peptides and carbonyl compounds has been investigated and found to be a fairly general reaction in weakly alkaline media. The reaction appears to be reversible and the most stable products have been obtained using alicyclic and acyclic ketones and acyclic aldehydes. In the present work, the sodium salts of several dipeptides were treated with ketones or aldehydes in refluxing methanolic or aqueous solutions. The products were shown to be imidazolidinyl peptides. This is apparently the first general investigation of what appears to be a common reaction of peptides.

The condensations of aldehydes and ketones with substances containing both amide and amine functional groups have been reported in the literature. The products of these reactions are generally heterocyclic compounds which have both the amide and amine nitrogen atoms in the new ring system.

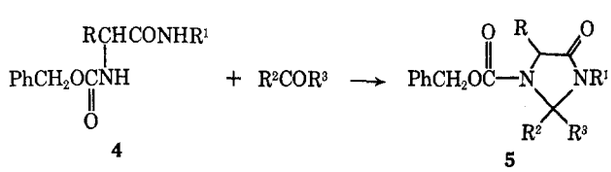
Davis and Levy[2] described the condensation of acetone with the α-phenylglycine amide (**1**) to yield an oxazolidine **2**, which rearranged, after treatment with pyridine, to a 4-imidazolidinone **3**. Similarly, other

1 **2**



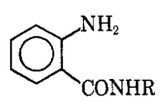
3

workers[3] found that isobutyraldehyde, benzaldehyde, and cyclohexanone reacted with the amides of carbobenzoxyamino acids **4** in the presence of a sulfonic acid catalyst to afford 1-carbobenzoxy-4-imidazolidinones **5** and other products. Primary and secondary amides



4 **5**

of 2-aminobenzoic acids **6** undergo the same type of condensation reaction with aldehydes[4] and ketones.[5] 1,2,3,4-Tetrahydro-4-quinazolones **8** were obtained after isomerization of the initially formed imine **7**. An imidazolidinone known as hetacillin (**10**) has been reported in other work.[6] It was prepared by the action of acetone on the commercially important penicillin,



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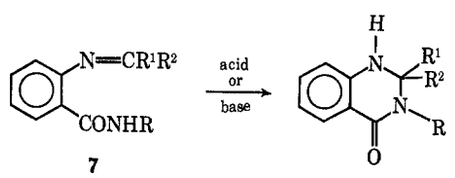
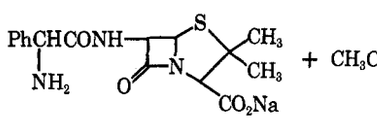


7 **8**

ampicillin (**9**), in a weakly basic aqueous medium. Aldehydes and other ketones were also successfully condensed with **9**.



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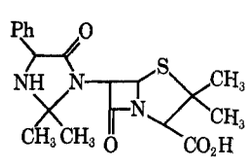

10

The reaction of formaldehyde with proteins and peptides has been reviewed[7] and the formation of 4-imidazolidinone derivatives was postulated in some of the cases. Aside from this work, however, there has been no systematic and thorough study of the interaction of carbonyl compounds with peptides.

In this paper, we report on what appears to be a general condensation reaction of aldehydes and ketones with a variety of dipeptides. The reaction is appar-

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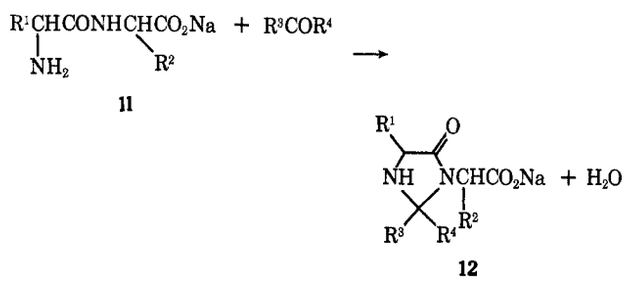
TABLE I
IMIDAZOLIDINYL PEPTIDES 12

Dipeptide sodium salt 11	Carbonyl compd	Registry no.	Imidazolidinyl peptides 12 R1	R2	R3	R4	Mp, °C	Infrared[c] carbonyl absorption frequency,[a] cm⁻¹		Calcd, %[b] C	H	N	Found, %[b] C	H	N
Diglycine	Acetone	32380-90-8	H	H	CH_3	CH_3	120–125	1675	1601	43.29	5.67	14.43	43.16	5.78	14.28
Glycyl-DL-phenylalanine	Acetone	32380-96-4	H	bz	CH_3	CH_3	175–180	1670	1605	59.15	5.98	9.86	58.95	6.15	10.02
L-Leucylglycine	Acetone	32319-33-8	*i*-Bu	H	CH_3	CH_3	85–90	1670	1601	52.80	7.60	11.20	52.95	7.73	11.11
DL-Alanylglycine	Acetone	32319-34-9	CH_3	H	CH_3	CH_3	150–155	1675	1602	46.15	6.25	13.46	46.28	6.41	13.32
Diglycine	Cyclohexanone	32380-97-5	H	H	$-(CH_2)_5-$		210–215	1660	1610	51.20	6.45	11.95	51.14	6.39	11.84
Diglycine	Isobutyraldehyde	32319-35-0	H	H	*i*-Bu	H	195–200	1675	1602	44.15[d]	6.45[d]	12.90[d]	44.51	6.45	12.46
Diglycine	Cyclopentanone	32319-36-1	H	H	$-(CH_2)_4-$		162–167	1675	1610	46.60[e]	6.22[e]	12.10[e]	46.65	5.92	12.40

[a] All products show no amide II band in region 1525–1565 cm⁻¹. [b] Microanalyses were performed by Alfred Bernhardt, 5251 Elbach, Germany. [c] Infrared spectra were prepared using Nujol mull. [d] Calculations based on the hemihydrate of the imidazolidinyl peptide. [e] Calculation based on the two-thirds hydrate of the imidazolidinyl peptide.

ently reversible and the products are 4-imidazolidinones according to elemental analysis, spectral properties, and comparison with products obtained in previous and related work (some of which is cited above).

Alkali metal salts of several dipeptides **11** were



11 **12**

treated with carbonyl compounds in methanolic or aqueous solution. The salt was probably necessary in order to keep the concentration of the zwitterionic form of the dipeptide as low as possible. This postulation was supported by the observation that little or no condensation occurred when the reaction was attemped in weakly alkaline solution.

The reactivity of the carbonyl compounds used in this condensation reaction varied greatly depending on certain structural features of these reagents. For example, acetaldehyde reacted exothermically and almost violently with diglycine (**11**, R^1, R^2 = H) to yield a very complex reaction mixture that resisted attempts to separate it into its components. Acetone, cyclopentanone, cyclohexanone, and isobutyraldehyde condensed readily with several dipeptides to afford stable and characterizable imidazolidinyl peptides **12**. Benzaldehyde, *p*-nitrobenzaldehyde, and acetophenone were reactive toward diglycine but the products were labile and easily reverted to the starting materials when attempts were made to isolate and identify them. Fluorenone and camphor did not react with diglycine at any observable rate.

The nature of the groups R^1 and R^2 in the dipeptide **11** also show a marked influence on the rate of the condensation reaction. If R^1 was smaller in size than R^2 [DL-alanyl-DL-phenylalanine (**11**, R^1 = CH_3; R^2 = $PhCH_2$); glycyl-L-leucine (**11**, R^1 = H; R^2 = $(CH_3)_2CHCH_2$); and glycyl-DL-alanine (**11**, R^1 = H; R^2 = CH_3)], the reaction resulted in a complex mixture and the products were unstable and/or not easily isolated. An exception to this was glycyl-DL-phenylalanine (**11**, R^1 = H; R^2 = $PhCH_2$), which produced a stable imidazolidinyl peptide with acetone (see Table I). On the other hand, if R^1 was the same size as, or larger in size than R^2 [diglycine (**11**, R^1, R^2 = H); L-leucylglycine (**11**, R^1 = $(CH_3)_2CHCH_2$; R^2 = H); DL-alanylglycine (**11**, R^1 = CH_3; R^2 = H)], the reaction mixture contained essentially one product which was usually, but not always, easy to isolate and purify. DL-Phenylalanyl-DL-alanine (**11**, R^1 = $PhCH_2$; R^2 = CH_3) was an exception to this rule. This was not completely unexpected since it is a mixture of diastereoisomers. These results appear to indicate the bulky R^2 groups offer steric hindrance to the formation of a bond with the amide nitrogen atom and thus prevent the formation of stable cyclic products. Alternatively, large R^1 groups facilitate the cyclization process.[8]

Table I lists all of the condensation products that were stable enough to be isolated in pure form and characterized. The imidazolidinone ring structure was supported mainly by infrared spectra. All of the compounds showed a carbonyl stretching band for a cyclic tertiary amide (amide I band) at about 1675 cm⁻¹. This frequency was in agreement with that (1695 cm⁻¹) reported for the γ-lactam carbonyl stretching band of the potassium salt of hetacillin (**10**).[6] The carbonyl stretching absorption for the carboxylate group appeared at about 1605 cm⁻¹ (1620, 1610 cm⁻¹ in the potassium salt of hetacillin[6]) and the amide II band[9] (amide NH deformation), which was a strong band found between 1525 and 1565 cm⁻¹ in the spectra of the dipeptide starting materials **11**, was significantly absent in those of the products **12**.

The nmr spectra of the imidazolidinyl peptides **12**, were prepared and were in agreement with the types and numbers of protons found in the proposed structures. Unlike the infrared data, however, the nmr information could not be used to exclude the possibility that the products had the Schiffs base (imine) structure.

The present research has uncovered a new class of group-specific reagents for use in peptide and, possibly, in protein chemistry. These reagents are simple aldehydes (isobutyraldehyde) and ketones (acetone, cyclopentanone, cyclohexanone) and the group for which they are specific is the α-aminoamide moiety found in almost all peptides and proteins. Group-specific rea-

(8) For a review of the literature concerning the beneficial effect of alkyl substituents on the ease of ring closure, see B. Capon, *Quart. Rev. Chem. Soc.*, **18**, 109 (1964).

(9) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co., 1968, pp 286, 287.

gents have been chiefly responsible for the elucidation of structure-activity correlations in proteins.

Continuing work on this project is concerned with the stereochemistry of the products **12** which have been prepared from optically active carbonyl compounds and dipeptides **11**.

Experimental Section[10]

General Procedure for the Preparation of Imidazolidinyl Peptides (12).—This procedure was used for the preparation of all of the imidazolidinyl peptides listed in Table I except that prepared from diglycine and cyclopentanone. The dipeptide free acid (10.0 mmol) was dissolved (or suspended) in a small amount of water and the resultant mixture was treated with 10 ml of 1 *N* NaOH. The aqueous solvent was removed by distillation under reduced pressure and the residual solid (dipeptide sodium salt, **11**) was found to be homogeneous by thin layer chromatography (the R_f of **11** was always greater than that of the dipeptide-free acid). The dipeptide sodium salt **11** (10.0 mmol) was dissolved in about 30 ml of methanol. The resultant solution was then treated with 20–25 mmol of the appropriate aldehyde or ketone and this was followed by heating of the reaction mixture to the reflux temperature for 3 hr. Thin layer chromatographic inspection indicated that an equilibrium between the reactants and the products was established during this time period and that further heating beyond 3 hr did not increase the yield of the products (usually two new tlc zones were observed with larger R_f values than those of the reactants). The reaction mixture (now light yellow to dark brown) was concentrated by distillation under reduced pressure until all of the solvent was removed. The oily residue was then dissolved in a minimum amount of MeOH–EtOAc or MeOH–acetone (both 50:50) and this solution was placed on a column of silica gel (E. Merck, 70–375 mesh). The column was eluted with the same solvent that was used to dissolve the oily residue. The w/w ratio of adsorbent to sample was about 66 to 1. The column fractions were collected and combined according to their thin layer chromatograms. Usually the original oily reaction product which was placed on the column was separated into two homogeneous products, one of which was obtained in a much greater yield than the other. The foregoing manipulations were performed as quickly as possible in order to avoid undue decomposition which was known to occur spontaneously with some of the products. The major product eluted from the column was usually an oil. It was stored in a desiccator (hygroscopic) for several hours, during which time it usually crystallized. Recrystallization was accomplished from a mixture of methanol and petroleum ether (bp 30–60°). Infrared, elemental analysis, and melting point data for the products are listed in Table I. Accurate calculations of yields were made in the experiments involving diglycine–isobutyraldehyde (57.5%), diglycine–cyclohexanone (36.0%), and diglycine–acetone (40.2%). The yields of products from the other experiments were estimated to be in the same range.

Condensation of Diglycine and Cyclopentanone. Preparation of an Imidazolidinyl Peptide in an Aqueous Medium.—Diglycine (10.0 mmol) and an equimolar amount of CH_3ONa were mixed and stirred in a small amount of dry methanol for a few minutes. The methanol was removed under reduced pressure and the residual solid (**11**, R^1, R^2 = H) was homogeneous according to tlc. This diglycine sodium salt and 10.0 mmol of cyclopentanone were added to 15 ml of distilled water and the resultant mixture was stirred at room temperature for 24 hr. After this time, the brownish-red product was isolated, chromatographed, crystallized, and recrystallized exactly as described in the general procedure. The physical constants for this product are listed in Table I. The estimated yield was similar to the yields obtained in the general procedure.

(10) Thin layer chromatograms of the reactions mixtures were run on 20 × 20 cm glass plates coated with a 250-μ thick layer of silica gel (Camag DF-5). Spotting was performed using 2 μl of a 1% solution and the developing solvent system was one of the following: methylene chloride–methanol (70–30 or 50–50) or ethyl acetate–methanol (50–50). The eluted zones were detected as colored areas after spraying with a 0.3% solution of ninhydrin in 1-butanol–2,4,6-collidine (95–5) followed by heating.

Acknowledgment.—Support of this work under a National Institutes of Health Research Project Grant No. AM 12761-03 is gratefully acknowledged.

Reactions of 7-*tert*-Butylnorbornadiene. Synthesis of *syn*- and *anti*-7-*tert*-Butylnorbornenes[1]

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7-*tert*-Butylnorbornadiene was synthesized from the corresponding 7-*tert*-butoxy compound and *tert*-butyllithium. Hydroboration and oxymercuration of the *tert*-butyldiene occurred exclusively with the sterically unencumbered anti double bond *via* exo,cis addition. Diimide reduction and catalytic hydrogenation occurred preferentially with the anti double bond even though both exo,cis and endo,cis additions were involved. The study of these various reactions has provided synthetic routes from the *tert*-butyl diene to the isomeric *syn*- and *anti*-7-*tert*-butylnorbornenes. The chemistry of 7-*tert*-butylnorbornadiene has been contrasted with that of norbornadienes substituted in the 7 position with an oxygen radical.

Previous papers from these and other laboratories have illustrated the preference of norbornadienes and norbornenes substituted in the 7 position with an oxygen-bearing substituent to experience electrophilic addition to the syn double bond[2–7] (eq 1). This preference has been ascribed to "chelation" of the entering electrophile by the syn double bond and the 7 substituent, which stabilizes the transition state.[3–5] In this way, the potentially adverse steric inhibition presented by the syn-7 substituents was overcome by this electronic effect.

The proposition was subsequently advanced that, in reactions where this electronic effect was nonoperative, steric factors would become dominant.[4] Catalytic hydrogenation of the syn and anti isomers was shown to be controlled by steric parameters ($k_{anti} \gg k_{syn}$); similar reduction of the norbornadiene derivatives was less sensitive to steric control and was influenced primarily by coordination control.[3,9]

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