Kinetics of the Condensation of Glycine with Benzaldehyde in Ethanol

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Potassium hydroxide catalyzed condensation of glycine with benzaldehyde in ethanol at 25° to afford phenylserine has been studied kinetically by means of spectrophotometry of remaining benzaldehyde, giving a rate law: $v = k[\text{glycine}][\text{benzaldehyde}]^2([\text{KOH}]_{\text{total}} - [\text{glycine}]_{\text{initial}})$. An ir spectrum of the reaction solution indicates the presence of C=N bond, but the expected intermediate $PhCH{=}NCH_2COOH$ could not be isolated because of its easy decarboxylation. Ethyl glycinate can form the Schiff base with benzaldehyde, but the methylene compounds without primary α-amino group such as acetic acid, methoxyacetic acid or its ester, and *N*-methylglycine of the similar carbon acidity do not react practically with benzaldehyde. These results suggest a mechanism involving an attack of the carbanion of *N*-benzylideneiminoacetic acid on benzaldehyde, implying the activation of the methylene by an electron-withdrawing benzylideneimino group (PhCH=N).

Condensation of glycine with benzaldehyde in ethanolic potassium hydroxide gives the anil of phenylserine in a good yield.[1,2] The base-catalyzed condensations of activated methylenes with carbonyl compounds have been established to involve the carbanions.[3-5] In most cases, two electron-withdrawing groups such as cyano, acyl, carboxy, or amide are favorable to provide sufficient activation of methylene groups for condensation with carbonyl compounds. However, in some cases, a single nitro or carbonyl group is sufficient to effect condensation with carbonyl compounds, when its acidity is fairly high, *e.g.*, $pK_a = 13$ for nitromethane,[6] but a single carboxylate, cyano, or amide group does not seem to be sufficient for the condensation under moderately basic conditions such as in alcoholic potassium hydroxide, *e.g.*, $pK_a = 24$–25 for acetic acid or acetonitrile.[6] α-Amino group may act as a deactivator like α-alkoxy groups which act as deactivators in the carbanion formation.[7] The Schiff base is a possible intermediate in the condensation of glycine with carbonyl compounds, but the example for the activation of the methylene by a N=C group is unknown. The acidity of the methylene in glycine may be increased sufficiently by the complex formation with cobalt ion to effect the condensation with acetaldehyde.[8-10]

To obtain some informations on the mechanism of the condensation and the activation of the methylene by a benzylideneimino group, the potassium hydroxide catalyzed condensation of glycine with benzaldehyde in absolute ethanol at 25° has been studied kinetically by means of uv spectrophotometry.

Results and Discussion

Rate Law.—Glycine exists mainly as a zwitterion in a neutral solution, but in a potassium hydroxide solution it forms the potassium salt; hence excess potassium hydroxide (*i.e.*, $[\text{KOH}]_{\text{excess}} = [\text{KOH}]_{\text{total}} - [NH_2CH_2CO_2H]_{\text{initial}}$) may be the effective concentration of base. The apparent second-order rate coefficient, k_a, in a rate expression

$$v = k_a[\text{PhCHO}][NH_2CH_2CO_2^-] \quad (1)$$

was found to increase linearly with the initial concentration of benzaldehyde, while the third-order one, k_a', in a rate expression

$$v = k_a'[\text{PhCHO}]^2[NH_2CH_2CO_2^-] \quad (2)$$

was nearly constant, independent of the initial concentration of benzaldehyde, as shown in Table I. The value of k_a' is $(0.76 \pm 0.04) \times 10^{-3}\ M^{-2}\ \text{sec}^{-1}$ at 25°.

Figure 1 indicates the first-order dependence of the third-order coefficient on the concentration of excess potassium hydroxide. Hence, the rate of the reaction in absolute ethanol is expressed as

$$\frac{d[P]}{dt} = k[\text{KOH}]_{\text{excess}}[\text{PhCHO}]^2[NH_2CH_2CO_2^-] \quad (3)$$

where P denotes phenylserine.

In the reaction of benzaldehyde with ethyl glycinate instead of free glycine, the second-order rate coefficient increases with the initial concentration of benzaldehyde, but it does not show exactly the first-order dependence of the rate on added potassium hydroxide ($[\text{KOH}]_t$), since ethyl glycinate is partly hydrolyzed by potassium hydroxide.

Condensation of the Other Methylene Compounds.—If the carbanions can be produced sufficiently under basic conditions, the condensation with aldehyde should occur. Under the same conditions as for glycine–benzaldehyde condensation, acetic acid, methoxyacetic acid or its ethyl ester, and *N*-methylglycine underwent attempts to condense them with benzaldehyde in ethanolic potassium hydroxide (0.60 *M*); virtually none of them reacted. A little (below 5%) consumption of benzaldehyde in 2.5 hr may be ascribed to the Cannizzaro or the Tischenko reaction, while for the reaction of glycine the conversion to phenylserine was over 70%. Phenylacetonitrile reacted with benzaldehyde in ethanolic potassium hydroxide at 25° to give α-cyanostilbene with second-order rate constant of $2.3 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$ at $[\text{KOH}]_t = 0.30\ M$, which is larger than that for glycine ($k_2 = 0.38 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$). Phenylacetic acid did not react with benzaldehyde under the same conditions. The methylene group of phenylacetonitrile appears to be activated sufficiently by the presence of phenyl and cyano groups.

(1) W. A. Bolhofer, *J. Amer. Chem. Soc.*, **76**, 1322 (1954).
(2) K. N. F. Slaw and S. W. Fox, *J. Amer. Chem. Soc.*, **75**, 3421 (1953).
(3) G. Jones, *Org. React.*, **15**, 204 (1967).
(4) A. T. Nielsen and W. J. Houliham, *Org. React.*, **16**, 1 (1968).
(5) R. L. Reeves in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience, New York, N. Y., 1966, p 580.
(6) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 1.
(7) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **91**, 104 (1969).
(8) D. C. Berndt, *J. Org. Chem.*, **35**, 1129 (1970).
(9) D. H. Williams and D. H. Bush, *J. Amer. Chem. Soc.*, **87**, 4644 (1965).
(10) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Amer. Chem. Soc.*, **89**, 5133 (1967).

TABLE I

APPARENT SECOND- AND THIRD-ORDER RATE COEFFICIENTS FOR THE REACTION OF GLYCINE WITH BENZALDEHYDE IN ETHANOL AT 25°[a]

Initial concn						
$[NH_2CH_2CO_2H]$, M	$[PhCHO]$, M	$[KOH]_{added}$, M	$[KOH]_{excess}$, M	10^4k_a, M^{-1} sec^{-1}	$10^3k_a'$, M^{-2} sec^{-1}	$10^4k_a'/[KOH]_{excess}$, M^{-3} sec^{-1}
0.15	0.10	0.30	0.15	0.85	0.82	5.5
0.15	0.20	0.30	0.15	1.4	0.84	5.6
0.15	0.30	0.30	0.15	1.9	0.80	5.3
0.15	0.40	0.30	0.15	2.3	0.64	4.3
0.15	0.51	0.30	0.15	3.0	0.71	4.7
0.15	0.30	0.20	0.05		0.12	2.5
0.15	0.30	0.30	0.15		0.62	4.2
0.15	0.30	0.45	0.30	3.8	1.3	4.5
0.15	0.30	0.60	0.45		2.1	4.6
0.15	0.30	0.75	0.60		3.0	4.9

[a] See eq 1 and 2.

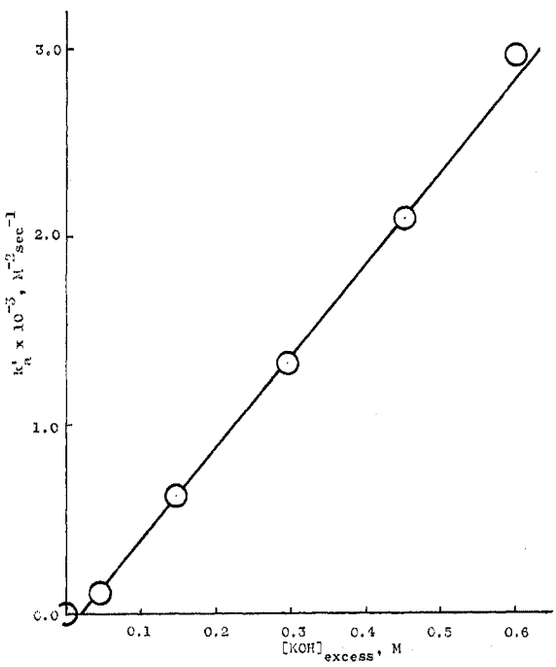


Figure 1.—Effect of excess KOH concentration on the third-order rate constant, k_a', for the condensation of glycine with benzaldehyde in ethanol at 25°: $[NH_2CH_2CO_2H]_{initial} = 0.15$ M; $[PhCHO]_{initial} = 0.30$ M.

Confirmation of the Schiff Base.—Condensation of ethyl glycinate with benzaldehyde in a benzene solution containing anhydrous magnesium sulfate as a dehydrating agent gives the Schiff base, *N*-benzylideneglycine ethyl ester, almost quantitatively. Reaction of the Schiff base with benzaldehyde in ethanolic potassium hydroxide at 25° gives phenylserine ethyl ester and its hydrolysis product, phenylserine.

On the other hand, we could not isolate the Schiff base, *N*-benzylideneglycine, from the condensation of glycine with benzaldehyde in a benzene or ethanolic solution containing anhydrous magnesium sulfate. The evaporated solution gave *N*-benzylidenemethylamine

$$PhCHO + NH_2CH_2CO_2H \xrightarrow[-H_2O]{} [PhCH{=}NCH_2CO_2H] \xrightarrow[-CO_2]{} PhCH{=}NCH_3$$

$$[PhCH{=}NCH_2CO_2H] \xrightarrow{+PhCHO} [PhCH{=}NCHCO_2H] \xrightarrow[-CO_2]{} PhCH{=}NCH_2CH(OH)Ph$$

$$PhCH{=}NCH_3 \xrightarrow{+PhCHO} PhCH{=}NCH_2CH(OH)Ph$$

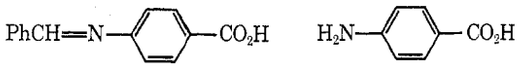
$$[PhCH{=}NCHCO_2H] \rightarrow PhCHOH$$

and *N*-benzylidene-(2-phenyl-2-hydroxylethyl)amine, which are decarboxylation products of *N*-benzylideneglycine and *N*-benzylidenephenylserine, respectively.

Further, an infrared spectrum of the ethanolic mixture of benzaldehyde, glycine, and potassium hydroxide at an early stage of reaction indicates C=N absorption at 1640 cm^{-1}. Hence the formation of the Schiff base is above suspicion.

Mechanism.—Following evidences support the intermediacy of the Schiff base for the condensation of glycine with benzaldehyde. (1) The second-order dependence of the rate on benzaldehyde precludes a simple reaction of one molecule of glycine with one molecule of the aldehyde or a nucleophilic catalysis involving a reaction of glycine with the Schiff base, but is explicable by a reaction between *N*-benzylideneglycine and benzaldehyde. (2) Ethyl *N*-benzylideneglycinate is obtained almost quantitatively from a reaction between ethyl glycinate and benzaldehyde, and its reaction with benzaldehyde gives phenylserine ethyl ester and its hydrolysis product, phenylserine. Though *N*-benzylideneglycine could not be isolated, *N*-benzylidenemethylamine and *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine were obtained, which suggests the formation of *N*-benzylideneglycine. Further, an infrared spectrum of the reaction mixture of glycine with benzaldehyde in ethanolic potassium hydroxide indicates the presence of *N*-benzylideneglycine. (3) Since the electron-releasing α-amino group in glycine suppresses the carbanion formation as the α-methoxy group[7] does, the acidity of glycine as a carbon acid would be slightly lower than that of acetic acid ($pK_a = 24$)[6] and comparable with those of methoxyacetic acid and *N*-methylglycine. Such methylene compounds of similar carbon acidity that cannot form Schiff bases did not condense with benzaldehyde. This fact suggests that the above methylenes cannot dissociate in ethanolic potassium hydroxide sufficiently to effect the condensation and this may be true for the methylene in glycine of similar carbon acidity. However, glycine can easily be converted under the reaction conditions into the Schiff base, *i.e.*, *N*-benzylideneiminoacetate ion, $PhCH{=}NCH_2CO_2^-$ (I), whose methylene may be activated sufficiently by both benzylideneimino and carboxylate groups, though no report on the activation by a $-N{=}CR_2$ group instead of $-CR{=}NR$ group is available. The acidity (pK_a) of *p*-benzylideneiminobenzoic acid (II) as a carboxylic acid is reported to be

almost equal to that of *p*-aminobenzoic acid (III),[11] but the inductive effects of amino and imino substituents

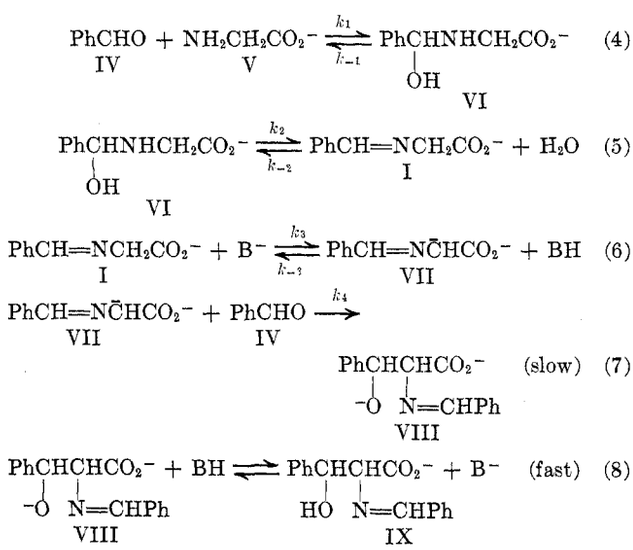


II III

would be small because of the longer distance between the substituent and the acidic proton compared with glycine, and the extent of n–π conjugation in II would be comparable with that in III, since II has a double planar configuration with a dihedral angle of *ca.* 60°.[12,13]

In *N*-benzylideneiminoacetate ion (I), however, a considerable increase of methylene acidity by the adjacent benzylideneimino group is expected. The acidity of I may be close to that of phenylacetonitrile ($pK_a < 24$) in view of the rate constant for the condensation of glycine with benzaldehyde, which is *ca.* $^1/_6$ of that of phenylacetonitrile, while acidity of I is lower than that of acetophenone ($pK_a = 19$),[6] which can easily condense with benzaldehyde.[14] It is higher than that of acetic acid ($pK_a = 24$)[6] which does not condense with benzaldehyde. Hence, the pK_a value of I may be 20–23.

A probable mechanism involving the Schiff base (I) is as follows.



If the concentrations of VI, I, and VII are low, the steady-state approximation leads to the following rate equation, where k and K are rate and equilibrium constants of subscripted steps, respectively.

$$v = \frac{d[IX]}{dt} = k_4[VII][IV] = \frac{k_1k_2k_3k_4[IV]^2[V][B^-]}{(k_{-1} + k_2)k_3k_4[IV][B^-] + (k_{-3}[BH] + k_4[IV])k_{-1}k_{-2}[H_2O]}$$

As an extreme case, if $k_{-1} \gg k_2$ and $k_{-3}[BH] \gg k_4 \cdot [IV]$, the equation is simplified to

$$v = \frac{K_1k_2K_3k_4\frac{K_{BH}}{[H^+]}}{K_3k_4\frac{K_{BH}}{[H^+]}[IV] + k_{-2}[H_2O]}[IV]^2[V]$$

(11) E. Imoto, presented at the 19th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1959.

(12) V. I. Minkin, Yu. A. Zhdanov, E. A. Medyantzeva, and Yu. A. Ostroumov, *Tetrahedron*, **23**, 3651 (1967).

(13) E. Haselbach and E. Heilbronner, *Helv. Chim. Acta*, **51**, 16 (1968).

(14) E. Coombs and D. P. Evans, *J. Chem. Soc.*, 1295 (1940).

where $K_1 = k_1/k_{-1}$, $K_3 = k_3/k_{-3}$, and $K_{BH} = [H^+] \cdot [B^-]/[BH]$. This assumption seems to be rational, since the dehydration (eq 5) is a slower step than the condensation (eq 4) under alkaline conditions in the Schiff base formation,[15] and generally the protonation of carbanion (reverse of eq 6, k_{-3}) is very rapid compared with the carbonyl addition (eq 7).[6]

The dissociation constant or K_3K_{BH} of benzylideneiminoacetate ion may be small ($\lesssim 10^{-20}$), then $K_3k_4(K_{BH}/[H^+])[IV] \ll k_{-2}[H_2O]$; hence the rate equation is expressed as

$$v = K_1K_2K_3k_4\frac{[B^-]}{[BH][H_2O]}[IV]^2[V]$$

Here $K_2 = k_2/k_{-2}$. This is consistent with our observation.[16]

Experimental Section

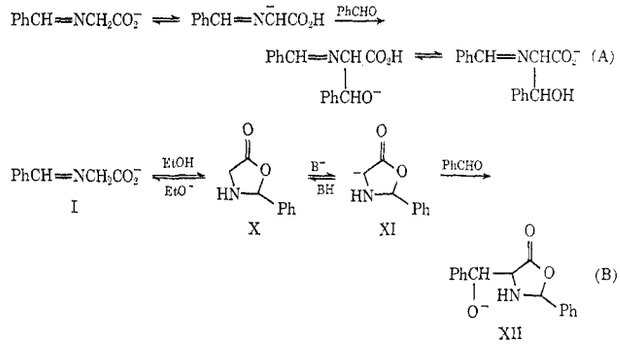
Materials.—Commercial benzaldehyde was distilled under reduced N_2 flow. Glycine was of commercial guaranteed grade and used without further purification. Methoxyacetic acid[17] and its ethyl ester,[17] *N*-methylglycine,[18] ethyl glycinate,[19] phenylacetonitrile,[20] and phenylacetic acid[20] were prepared according to the literature.

Kinetics.—Absolute ethanol was used as a solvent. Glycine in ethanolic potassium hydroxide and benzaldehyde in ethanol (each 10 ml) were mixed after a thermal equilibrium had been attained. Aliquots were taken out and diluted with a 0.1 *N* HCl solution in 50% (v/v) aqueous methanol to hydrolyze the Schiff base of phenylserine, and the absorbance of benzaldehyde at 248 mμ in the solution was determined. The decrease of absorbance is ascribed to the phenylserine formation. The apparent second-

(15) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

(16) As a referee pointed out, the literature [K. F. Bonhoeffer, K. H. Gerib, and O. Reitz, *J. Chem. Phys.*, **7**, 664 (1939)] shows that the CH_3 group of the acid molecule may ionize 10^4 times as fast as that of the negatively charged acetate ion. However, the observed condensation of glycine or its ester with *p*-nitrobenzaldehyde to *p*-nitrophenylserine without base [E. D. Bergmann, H. Bendas, and W. Taub, *J. Chem. Soc.*, 2673 (1951); G. Ehrhart, *Ber.*, 483 (1953)], in spite of no condensation of unsubstituted acetic acid, should be ascribed to the enhancement of deprotonation by introducing the *p*-$NO_2C_6H_4CH{=}N$ group to acetate ion. Hence, the existence of VII in the presence of base may be probable.

Alternative schemes (A and B) suggested by the referee are considered.



The rate equation derived from scheme A does not show the first-order dependence on the excess concentration of KOH, which is not the case.

Scheme B agrees with the rate equation and is not distinguishable from our mechanism (eq 4–8). However, the methylene in X does not seem to be active enough to effect the condensation, since (1) ethyl methoxyacetate of an acidity similar to that of X did not react with benzaldehyde, and (2) the carbanion formation from X may be suppressed by the neighboring electron-releasing NH group, which is contrasted to the PhCH=N group. No detection of X and also the facile reaction of benzaldehyde with ethyl *N*-benzylideneglycinate, probably in which cyclic X forms with difficulty, are unfavorable to scheme B.

(17) R. C. Fuson and B. H. Wojcik, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 260.

(18) W. Cocker and A. Lapworth, *J. Chem. Soc.*, 1894 (1931).

(19) G. Hillman, *Z. Naturforsch*, **1**, 682 (1946).

(20) R. Adams and A. F. Thal, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, pp 107, 436.

order rate coefficient was calculated according to the following stoichiometry.

$$2PhCHO + NH_2CH_2CO_2^- \longrightarrow PhCH(OH)-CH(N{=}CHPh)CO_2^- + H_2O$$

A blank reaction under the reaction conditions without glycine shows a decrease in benzaldehyde below 4% in 2.5 hr which is negligibly small compared with the phenylserine formation (over 70% conversion in 2.5 hr). Phenylserine was isolated from the reaction solution in a yield of 44%: mp 187–189° (lit. mp 192–194°); ν_{max} (KBr) 3500–2500 (NH_3^+, OH), 1630 (CO_2^-), 760 and 710 cm^{-1} (monosubstituted phenyl).

Formation of the Schiff Base.—Condensation of ethyl glycinate with benzaldehyde in benzene containing anhydrous $MgSO_4$ as a dehydrating agent at room temperature gives *N*-benzylideneglycine ethyl ester almost quantitatively. This product was confirmed by ir and nmr: ν_{max} (KBr) 1740 (C=O), 1640 (C=N), 1180 [CC(=O)O)], 750 and 686 cm^{-1} (monosubstituted phenyl); τ (CCl_4) 1.81 (s, CH=N, 1 H), 2.27–2.63 (m, aromatic H, 5 H), 5.73 [s, (C=N)CH_2–, 2 H], 5.85 [q, –$CH_2(CH_3)$] 2 H], 8.75 (t, CH_3, 3 H).

Condensation of glycine with benzaldehyde in benzene or ethanol containing anhydrous $MgSO_4$ gives *N*-benzylidenemethylamine and *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, but *N*-benzylideneglycine could not be isolated. The infrared spectrum of the former was consistent with that of the authentic sample and the latter was identified by ir and nmr: mp 106–108°; ν_{max} (KBr) 3350–3000 (NH, OH), 1650 (C=N), 750 and 690 cm^{-1} (monosubstituted phenyl); τ (DMSO) 1.74 (s, CH=N, 1 H), 2.24–2.57 (m, aromatic H, 10 H), 4.59 (b, OH, 1 H), 5.06 (q, CH, 1 H), 6.20 (d, CH_2, 2 H).

The infrared spectrum of the ethanolic mixture of benzaldehyde, glycine, and potassium hydroxide at an early stage of reaction had C=N absorption at 1640 cm^{-1}.

Reaction of Ethyl *N*-Benzylideneglycinate.—To a solution of KOH (5.61 g, 0.1 mol) and ethyl *N*-benzylideneglycinate (9.56 g, 0.05 mol) in absolute ethanol (75 ml), there was added a solution of benzaldehyde (5.31 g, 0.05 mol) in absolute ethanol (25 ml). The mixture was allowed to stand at room temperature. A crystalline product was separated. Ethanol was decanted and the residual crystals were dissolved in a mixture of 2 *N* hydrochloric acid (20 ml) and benzene (20 ml). The solution was concentrated under vacuum until all ethanol was removed. After neutralization with concentrated ammonia, crystalline phenylserine (2.52 g, 27%) was obtained, which was identified by ir and melting point with the authentic specimen. Phenylserine ethyl ester was separated from ethanol solution by means of tlc: ν_{max} (KBr) 3450–3300 (NH_2, OH), 1730 (C=O), 1210–1190 [CC(=O)O], 750 and 700 cm^{-1} (monosubstituted phenyl); τ ($CDCl_3$) 2.70 (m, aromatic H), 4.97 (s, OH, 1 H), 5.35 (d, CH, 1 H), 5.73 (d, CH, 1 H), 6.06 (q, CH_2, 2 H), 7.24 (s, NH_2, 2 H), 9.24 (t, CH_3, 3 H).

Registry No.—Glycine, 56-40-6; benzaldehyde, 100-52-7; phenylserine, 1078-17-7; ethyl glycinate, 459-73-4; *N*-benzylideneglycine ethyl ester, 40682-54-0; *N*-benzylidenemethylamine, 622-29-7; *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, 25558-12-7; phenylserine ethyl ester, 40682-56-2.

Amino Group Protection in Peptide Synthesis. The 4,5-Diphenyl-4-oxazolin-2-one Group[1]

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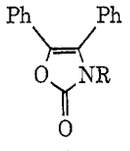
The preparation and properties of 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives (1) of amino acids are described and these derivatives evaluated as protected intermediates in peptide synthesis. The Ox group—one of the few protecting groups which mask both hydrogens of a primary amino function—is unreactive under the usual conditions used to remove protecting groups, but may be cleaved under mild reductive or oxidative conditions. The use of Ox protection for the ε-amino group of lysine is described.

The previously described properties of the 4,5-diphenyl-4-oxazolin-2-ones[2] (1) have indicated the



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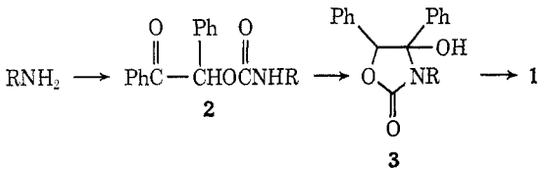
potential of this heterocyclic system[3] as a protecting group for primary amines, one of the few protecting groups which mask both hydrogens of a primary amine function.

Compounds of this type are extremely stable and unreactive under a variety of rigorous conditions. Methods existed for the preparation of this cyclic system through the easily prepared benzoin urethanes. The oxazolinones are highly crystalline, yet reasonably soluble in organic solvents; because of the *cis*-stilbene moiety present in the system, they are also highly fluorescent. Finally, possibilities existed for the removal of the protecting group under mild oxidative or reductive conditions.

The proposed preparation of the 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives involved a two-step reaction sequence: the preparation of benzoin urethanes, followed by cyclization and simultaneous dehydration of the urethanes to oxazolinones in an acid medium.



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In contrast to the usual methods of preparing urethanes, a novel method is available for the preparation of the benzoin urethanes. Treatment of benzoin with phosgene in the presence of *N*,*N*-dimethylaniline, followed by thermal cyclization of the intermediate, unstable chloroformate affords a cyclic unsaturated carbonate (4) in good yield.[4] Treatment of this

(1) Dedicated to Professor Dr. Theodor Wieland on the occasion of his 60th birthday, June 5, 1973.

(2) J. C. Sheehan and F. Guziec, Jr., *J. Amer. Chem. Soc.*, **94**, 6561 (1972).

(3) Reviewed by R. Filler, "Advances in Heterocyclic Chemistry," Vol. IV, Academic Press, New York, N. Y., 1965, p 103.

(4) A minor by-product is desyl chloride, formed in a reaction analogous to the thionyl chloride–pyridine chlorination of alcohols. This compound becomes the major product of the reaction unless *N*,*N*-dimethylaniline hydrochloride is removed prior to the chloroformate cyclization.