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Reactions of Azlactone Derivatives with Nucleophiles and Acetylenic Compounds

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Several reactions of azlactones were explored in order to find a new method for extending carbon chains utilizing the 4-position of 2-oxazolin-5-one derivatives. Treatment of 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (I) with phenylethynylmagnesium bromide (IIa) gave a ring opened product, ethyl 2-benzoylamino-5-phenyl-2-penten-4-ynoate (IIIa). The reaction of I with diethyl 3-oxoglutarate (X) in benzene in the presence of sodium hydride afforded ethyl 3-carbethoxy-5-benzoylamino-β-resorcylate (XI), whereas 3-benzoylamino-5-carbethoxy-6-carbethoxymethyl-2*H*-pyran-2-one (XII) was obtained when this reaction was carried out in methylene dichloride using triethylamine as a catalyst. Analogously, 3-benzoylamino-5-cyano-6-phenyl-2*H*-pyran-2-one (XIV) was synthesized by the reaction of I with 5-phenylisoxazole (XIII). The reaction of 2-phenyl-2-oxazolin-5-one (XVI) with benzoylacetylene (XVII) in acetic anhydride gave 3-benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII).

The chemistry of azlactones has been extensively developed as a synthetic method with amino acids along with wide studies on penicillin.[2] These reactions of azlactones have been reviewed by Carter,[3] Baltazzi[4] and Filler.[5] Among the many kinds of azlactones, 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (I) is not only a synthetic intermediate for a natural amino acid,[6] but also a historically important key compound for the synthesis of penicillin,[2] because the ethoxymethylene group of I is very reactive towards nucleophiles. Recently a German group has reported reactions of I with active methylene compounds to obtain 2*H*-pyran-2-one derivatives.[7] Considering these results, this oxazolinone (I) might prove useful as a starting matieral for a synthesis of amino acids having longer carbon chains.

At first a Grignard reagent was chosen as a nucleophile. There have been few reports concerning the Grignard reaction with azlactones. The reaction of a 2-substituted-2*H*-oxazolin-5-one with Grignard reagent gave a ring opened product arising from attack of the reagent at the 5-position.[8] Behringer, *et al.*[9] have reported the reaction of 4-chloromethylene-2-phenyl-2-oxazolin-5-one with the Grignard reagent of an indole or a pyrrole. The course of this reaction was strongly influenced by the nature of the Grignard reagent:[9,10] in the case of the N-Grignard reagent the reaction proceeded in the expected way, on the

1) Location: *2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*
2) H.T. Clarke, J.R. Johnson, and R. Robinson, "The Chemistry of Penicilline," Princeton Univ. Press, Princeton N.J., 1949.
3) H.E. Carter, "Azlactones," Organic Reactions, Vol. III, 1946, p. 198.
4) E. Baltazzi, *Quart. Rev.* (London), **9**, 150 (1955).
5) R. Filler, "Recent Advances in Oxazolone Chemistry," Vol. IV, edited by A.R. Katritzky, Academic Press, 1965, p. 75.
6) T. Kaneko, K. Oizumi, and H. Katsura, *Nippon Kagaku Zasshi*, **79**, 91 (1958).
7) H. Behringer and K. Falkenberg, *Chem. Ber.*, **96**, 1428 (1963).
8) Reference 2) p. 171, p. 452, p. 792 and p. 846; W.I. Awad and H.S. Hafez, *J. Org. Chem.*, **25**, 1180 (1960), and references cited therein; *Idem, ibid.*, **25**, 1183 (1960); W.I. Awad, H.S. Hafez, and A.E. Gadallah, *ibid.*, **27**, 1050 (1962); G. Slater and A.W. Somerville, *Tetrahedron*, **22**, 35 (1966); *Idem., ibid.*, **23**, 2823 (1967).
9) H. Behringer and H. Taul, *Chem. Ber.*, **90**, 1398 (1957).
10) L. Horner and H. Schwahn, *Ann.*, **591**, 99 (1955).

other hand, that of alkyl or aryl Grignard derivative proceeded in another, undesirable way. It was demonstrated that modification of the Grignard compound by using cadmium derivatives was effective for the desired reaction.

Treatment of I with phenylethynylmagnesium bromide (IIa) in tetrahydrofuran gave a compound, mp 119—120°, $C_{20}H_{17}O_3N$ in good yield. The nuclear magnetic resonance (NMR) spectrum exhibited typical A_2X_3 signals at 1.31 and 4.34 ppm due to an ethyl ester group, and a singlet at 6.57 ppm ascribable to an olefinic proton, together with aromatic proton peaks. From these data only two structures, IIIa, or IV, are possible for this compound. However, the infrared (IR) spectrum showed typical ester absorption bands at 1715 and 1238 cm^{-1} which excludes structure IV. The structure of IIIa was finally established by catalytic reduction and an independent synthesis. Hydrogenation of IIIa over palladium on carbon afforded a saturated amino acid derivative, mp 89—90°, which was identified as ethyl 2-benzoylamino-5-phenylpentanoate (V) by the following unambiguous independent synthesis. Cinnamaldehyde (VI) and hippuric acid (VII) were heated in acetic anhydride to yield 2-phenyl-4-(3-phenyl-2-propenyliden)-2-oxazolin-5-one (VIII),[11] which was a

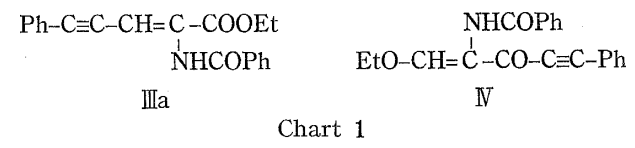


Chart 1

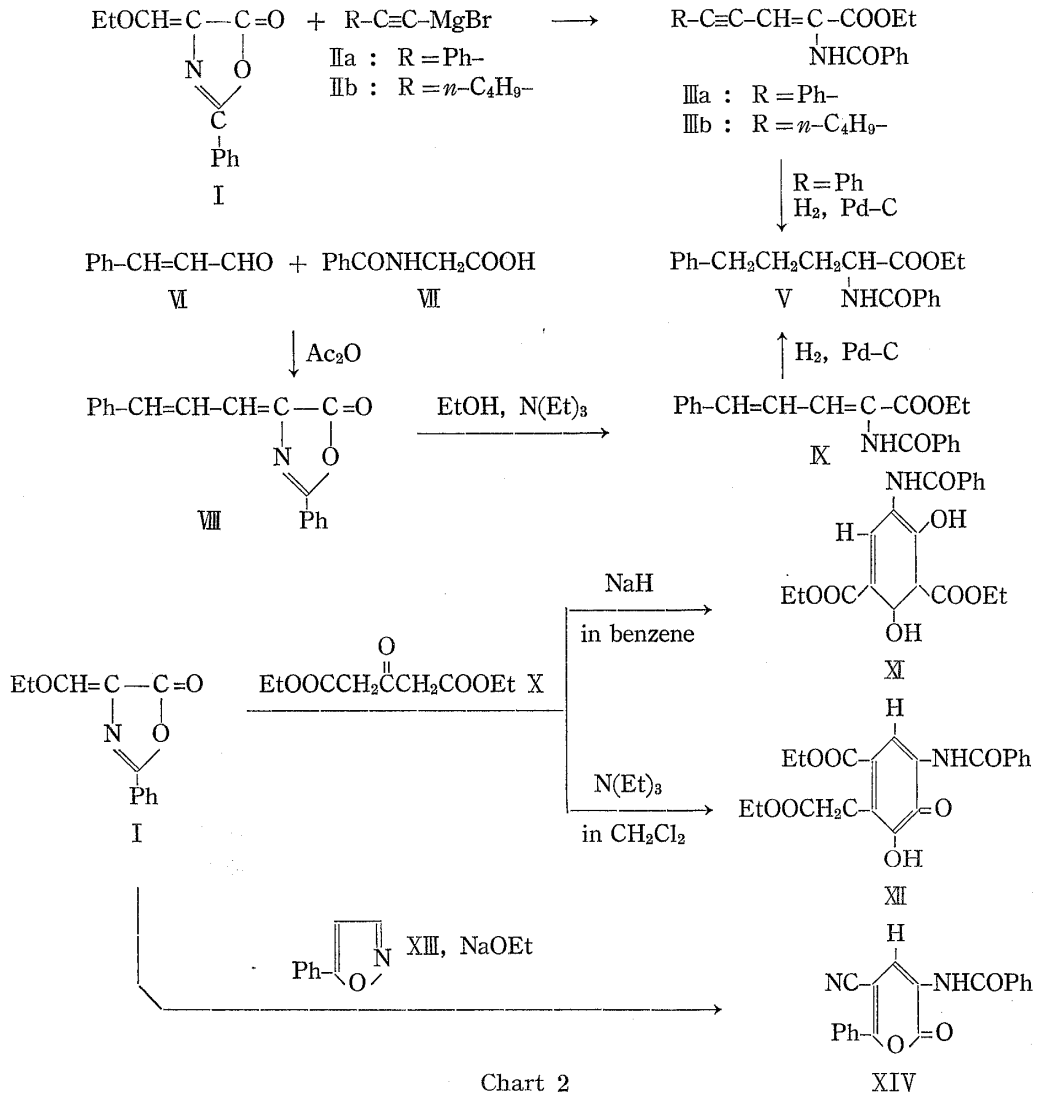


Chart 2

11) E. Matter, *Ann.*, 337, 273 (1904).

mixture of *cis* and *trans* isomers at position 4. This oxazolone (VIII), without purification, was treated with ethanol and triethylamine to give a ring opened product, ethyl 2–benzoylamino–5–phenyl–2,4–pentadienoate (IX). The oily diene (IX) (again a *cis* and *trans* mixture) was hydrogenated over palladium on charcoal to afford a compound melting at 89—90°, which was identical in all respects with V. Analogously, the reaction of 1–hexynylmagnesium bromide (IIb) with I gave ethyl 2–benzoylamino–2–nonaen–4–ynoate (IIIb), mp 64—65°.

It is not clear whether the ring opening of the oxazolone ring by ethoxide ion is intra– or intermolecular. A similar type of reaction involving a Grignard reagent in which the resultant leaving group attacks an ester moiety, has been reported by Schroll, *et al.*[12] as shown below:

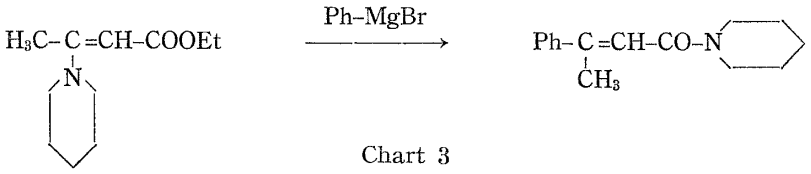
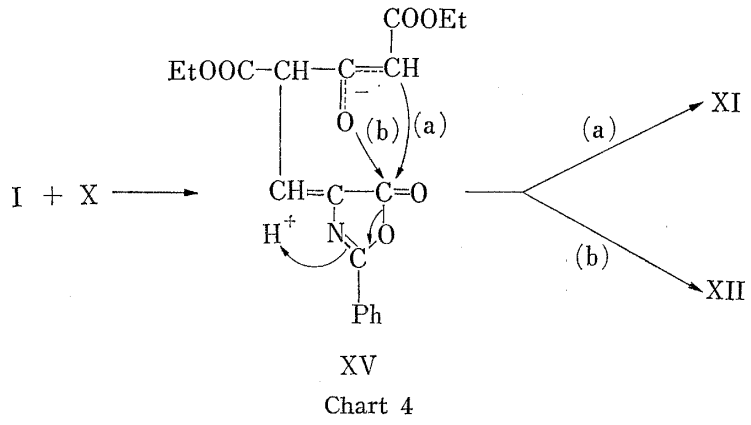


Chart 3

It is noteworthy that only acetylenic Grignard reagent gave the desired substance (IIIa) and (IIIb) in good yield. Other alkyl Grignard substances which are more strongly nucleophilic than ethynyl magnesium halide, afforded a complex mixture whose nature could not be characterized.

The reaction of I with diethyl 3–oxoglutarate (X) was found to take different courses depending on the base and solvent used. When the reaction was carried out in benzene in the presence of sodium hydride, a resorcinol derivative, mp 153—154°, was obtained in good yield. This compound was designated as ethyl 3–carbethoxy–5–benzoylamino–β–resorcylate (XI) on the following grounds: it is soluble in sodium hydroxide solution and shows a positive ferric chloride test. The NMR spectrum of XI exhibited signals at 8.40 ppm due to a secondary amide hydrogen, a singlet at 9.15 ppm assignable to an aromatic ring hydrogen, singlets at 12.47 and 13.16 ppm ascribable to two kinds of phenolic hydrogens. In addition there were two kinds of ethyl ester and aromatic hydrogen peaks.

On the other hand, the reaction of I with X in methylene dichloride using triethylamine as a catalyst afforded a α–pyrone, 3–benzoylamino–5–carbethoxy–6–carbethoxymethyl–2*H*–pyran–2–one (XII), mp 115.5—116.5°, as a major reaction product, along with a small amount of XI. The formation of XII is anlaogous to Behringer's finding.[7] Different courses for the formation of XI and XII could be explained by an intermediate enolate anion (XV), in which carbanion attack at azlactone moiety yields XI, whereas attack of the enolate oxygen would afford XII.



XV

Chart 4

Since it is known[13] that in the reaction of phenols with alkyl halides, C–alkylation is favored by heterogeneous rather than homogeneous reaction conditions whereas nonhydroxylic polar solvents appear to favor O–alkylation, our experimental results are well in agreement with these data.

12) G. Schroll, H.J. Jakobsen, and S. Lawesson, *Rec. Trav. Chim.*, **84**, 597 (1965).
13) H.O. House, "Modern Synthetic Reactions," W.A. Benjamin, Inc., New York, 1965, p. 175.

Treatment of I with 5–phenylisoxazole (XIII) in the presence of sodium ethoxide afforded 3–benzoylamino–5–cyano–6–phenyl–2*H*–pyran–2–one (XIV), mp 170—171°, which was identical in all respects with an authentic sample.[6] Since the ring opening reaction of an isoxazole having hydrogen at 3–position is well known,[14] the mechanism of the formation of XIV would be very similar to that of XII.

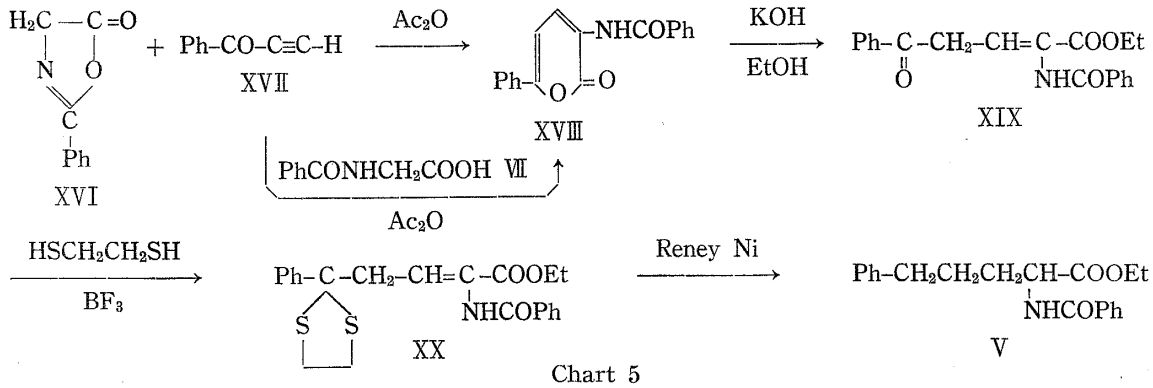


Chart 5

Secondly, 2–phenyl–2–oxazolin–5–one (XVI) was chosen as a starting material for the synthesis of an amino acid derivative. We expected a Michael type reaction of XVI with acetylenic derivatives, thus ethyl propionate, dimethyl acetylendicarboxylate, ethyl phenylpropionate and benzoylacetylene were examined as electrophiles. Among these, only benzoylacetylene was found to react with XVI.

Heating a mixture of benzoylacetylene (XVII), XVI and acetic anhydride afforded a crystalline compound, mp 200—201°, whose ultraviolet (UV) spectrum was very similar to that of XIV. The NMR spectrum of this compound showed signals at 6.80 ppm (1H, doublet, J=7.5 cps) and 8.57 ppm (1H, doublet, J=7.5 cps) ascribable to two olefinic hydrogens, in addition to those of a secondary amide hydrogen and aromatic hydrogens. These UV and NMR data indicated that the compound was 3–benzoylamino–6–phenyl–2*H*–pyran–2–one (XVIII). This deduction was confirmed by the following reactions. Treatment of XVIII with potassium hydroxide in ethanol gave a ring opened product (XIX), mp 128—129.5°, which was treated with ethylene thioglycol in the presence of boron trifluoride to afford a thioketal (XX), mp 135—136°. This thio compound (XX) was desulfurized with Raney nickel to furnish ethyl 2–benzoylamino–5–phenylpentanoate (V), mp 89—90° which was identical with the sample obtained from IIIa. Thus the structures of XVIII, XIX and XX were

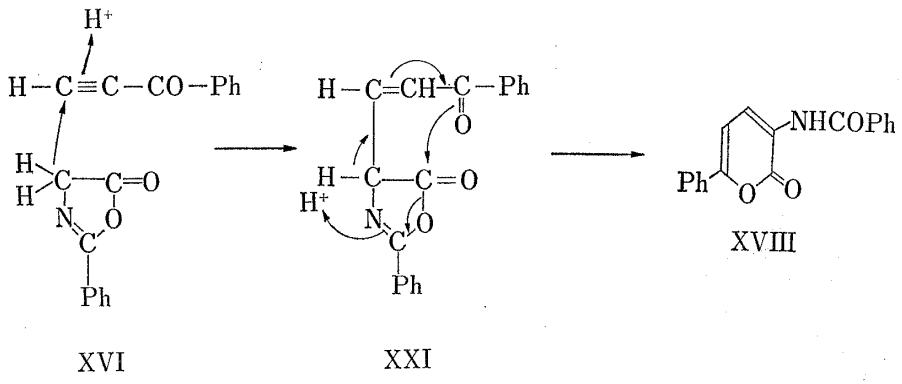


Chart 6

14) "The Chemistry of Heterocyclic Compounds. Five– and Six–membered Compounds with Nitrogen and Oxygen," edited by R.H. Wiley. A. Quilico, "Isoxazoles and Related Compounds," Interscience Publishers, New York, 1962, p. 44.

established as 3–benzoylamino–6–phenyl–2*H*–pyran–2–one, ethyl 2–benzoylamino–5–phenyl–5–oxo–2–pentenoate and ethyl 2–benzoylamino–5–phenyl–5,5–ethylendithio–2–pentenoate, respectively. The mechanism of the formation of XVIII was tentatively formulated as shown in Chart 6.

Compounds XVI and XVII react to form an adduct (XXI) which would be *trans*–formed into XVIII by ring opening of the azlactone ring.

This pyrone (XVIII) was also obtained by heating a mixture of hippuric acid (VII), benzoylacetylene (XVII) and acetic anhydride. In this reaction XVI might be an intermediate since the reaction of VII with acetic anhydride gives XVI.[15] For the synthesis of XVIII the use of hippuric acid (VII) is preferable to XVI, because the latter is known[16] to be highly sensitive to moisture and can be stored only for a short time.

Experimental[17]

Ethyl 2-Benzoylamino-5-phenyl-2-penten-4-ynoate (IIIa)——Ethylmagnesium bromide solution was prepared from Mg (243 mg, 0.01 mole), ethylbromide (1.09 g, 0.01 mole) and abs. tetrahydrofuran (4 ml) under N_2 atmospher as usual. To this solution was dropwise added phenylacetylene (1.02 g, 0.01 mole) in tetrahydrofuran (8 ml) at room temperature. Then the reaction mixture was stirred at room temperature for 2 hr. To the resulting phenylethynylmagnesium bromide solution was added 4–ethoxymethylene–2–phenyl–2–oxazolin–5–one (I) (2.17 g, 0.01 mole) in tetrahydrofuran (15 ml) all at once with ice–water cooling. The reaction mixture was stirred at room temperature overnight (16 hr). The solution was poured into 10% HCl solution (30 ml) containing ice and extracted with ether. The combined ether extracts were washed five times with saturated sodium chloride solution, dried over Na_2SO_4 and evaporated under reduced pressure to give an oil (3.0 g) which crystallized on standing. Recrystallization from EtOH gave ethyl 2–benzoylamino–5–phenyl–2–penten–4–ynoate (IIIa), mp 114—117°, with previous softening (2.38 g) (74.8% yield). One more recrystallization from the same solvent gave needles melting at 118—120° (1.62 g). The analytical sample showed mp 119—120°. *Anal.* Calcd. for $C_{20}H_{17}O_3N$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.32; H, 5.35; N, 4.47. IR ν_{max}^{Nujol} cm^{-1}: 3190 (NH), 2200 (C≡C), 1715, 1238 (ester), 1648, 1517 (amide). NMR δ ppm in $CDCl_3$: 6.57 (1H, singlet) (–C<u>H</u>=C<), 1.31 (3H, triplet, J=7.5 cps) ($COOCH_2C\underline{H}_3$), 4.34 (2H, quartet, J=7.5 cps) ($COOC\underline{H}_2CH_3$).

Ethyl 2-Benzoylamino-2-nonaen-4-ynoate (IIIb)——Ethylmagnesium bromide solution was prepared from Mg (243 mg), ethyl bromide (1.09 g) and abs. tetrahydrofuran (10 ml) as usual. To this solution was added dropwise 1–hexyne (820 mg) in abs. tetrahydrofuran (5 ml) and the reaction mixture was stirred at room temperature for 4 hr. To the resulting 1–hexynylmagnesium bromide solution was added 4–ethoxymethylene–2–phenyl–2–oxazolin–5–one (I) (2.17 g) in abs. tetrahydrofuran (10 ml) in one portion at room temperature. The solution was stirred at room temperature for 16 hr and was poured into 10% HCl solution (30 ml) containing ice and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ solution and saturated NaCl solution until neutral to litmus, dried over Na_2SO_4 and evaporated to give an oil (2.5 g). This substance was chromatographed using silica gel (90 g). Elution with *n*–hexane–benzene (1:2) and benzene gave crystalline ethyl 2–benzoylamino–2–nonaen–4–ynoate (IIIb) (1.0 g). Recrystallization from *n*–hexane–ether afforded the pure ester (IIIb), mp 64—65°. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 71.70; H, 7.04; N, 4.61. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 2225 (C≡C), 1719, 1278 (ester), 1668, 1513 (amide). NMR δ ppm in CCl_4: 0.85 (3H, triplet, J=6.5 cps) (–CH_3), 1.32 (3H, triplet, J=7.5 cps) (–$COOCH_2C\underline{H}_3$), 4.23 (2H, quartet, J=7.5 cps) (–$COOC\underline{H}_2CH_3$), 2.40 (2H, multiplet) (–$C\underline{H}_2C{\equiv}C$), 6.08 (1H, triplet, J=2.0 cps) (–C≡C–C<u>H</u>=C).

Ethyl 2-Benzoylamino-5-phenylpentanoate (V)——Ethyl 2–benzoylamino–5–phenyl–2–penten–4–ynoate (IIIa) (150 mg) in EtOH (26 ml) was shaken in H_2 atmosphere with Pd–C(5%) (150 mg) at 26°. Thirty eight milliliter of H_2 gas was absorbed (calcd., 34.6 ml). The catalyst was filtered off, washed with EtOH. Evaporation of the filtrate gave an oil, which crystallized on standing. Recrystallization from *n*–heptane gave ethyl 2–benzoylamino–5–phenylpentanoate (V), mp 89—90°, as white needles (127 mg). One more recrystallization did not alter this melting point. *Anal.* Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.15; H, 7.32; N, 4.27. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1730 (ester), 1634, 1542(amide). NMR δ ppm in $CDCl_3$: 4.87 (1H, multiplet) (>C<u>H</u>–NHCOPh), 4.22 (2H, quartet) ($COOC\underline{H}_2CH_3$) (J=7.5 cps), 1.27 (3H, triplet) ($COOCH_2C\underline{H}_3$) (J=7.5 cps).

15) H.E. Carter, J.B. Harrison, and D. Shapiro, *J. Am. Chem. Soc.*, **75**, 4705 (1953); *cf.* ref. 2) p. 778.
16) Reference 4) p. 158.
17) All melting points are uncorrected. NMR–spectra were taken using Varian A–60 spectrometer in $CDCl_3$ or CCl_4.

2-Phenyl-4-(3-phenyl-2-propenyliden)-2-oxazolin-5-one (VIII)——A mixture of cinnamaldehyde (VI) (20 g, 0.151 mole), hippuric acid (VII) (27.1 g, 0.151 mole) and acetic anhydride (43 ml) was heated on a water bath (90°) with occasional shaking for 1 hr (after 50 minutes heating the mixture became homogeneous forming a red solution). Cooling the solution resulted in a crystalline mass. This mixture was diluted with ice-water and the crystalline substance was collected by filtration, washed with H_2O. Recrystallization from benzene gave 2-phenyl-4-(3-phenyl-2-propenyliden)-2-oxazolin-5-one (VIII) as needles, mp 130—150°, which was a mixture of geometrical isomers of *cis*, *trans* derivatives. It weighed 20 g. Recrystallization from EtOH gave orange needles, mp 166—169° with previous softening (11.5 g). One more recrystallization afforded a sample melting at 167—169° (reported,[11] mp 152°). *Anal.* Calcd. for $C_{18}H_{13}O_2N$: C, 78.53; H, 4.76; N, 5.09. Found C, 78.46; H, 4.86; N, 5.22.

Ethyl 2-Benzoylamino-5-phenylpentanoate (V) from 2-Phenyl-4-(3-phenyl-2-propenyliden)-2-oxazolin-5-one (VIII)——The crude azlactone, 2-phenyl-4-(3-phenyl-2-propenyliden)-2-oxazolin-5-one (VIII) (3.5 g) obtained above (mp 130—150°, a *cis* and *trans* mixture) was suspended in absolute EtOH (70 ml), and to this suspension was added triethylamine (2 ml). Then the reaction mixture was heated under reflux for 5 hr. The solution was evaporated under reduced pressure to give crude oily ethyl 2-benzoylamino-5-phenyl-2,4-pentadienoate (IX) (*cis* and *trans* mixture) (3.7 g) which was used in the next reaction without further purification. Eight hundred and fifty miligrams of the above oil in EtOH (20 ml) was stirred in H_2 atmosphere with Pd-C(5%) (500 mg). The hydrogenation reaction stopped when 125 ml of H_2 gas was absorbed (calcd. H_2 at 26°: 130 ml). The catalyst was filtered off, washed with EtOH. The combined filtrates were evaporated under reduced pressure to give an oil which crystallized on standing. Recrystallization from *n*-heptane gave ethyl 2-benzoylamino-5-phenylpentanoate (V), mp 89—90° (619 mg). On admixture with a sample obtained from ethyl 2-benzoylamino-5-phenyl-2-penten-4-ynoate (IIIa) no depression in melting point was observed. *Anal.* Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.71; H, 7.13; N, 4.62.

Ethyl 3-Carbethoxy-5-benzoylamino-β-resorcylate (XI)——To a mixture of 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (I) (971 mg, 0.00447 mole), diethyl 3-oxoglutarate (X) (903 mg, 0.00447 mole) and benzene (8 ml) was added NaH (214 mg, 0.00447×2 mole) with ice-water cooling. After further addition of benzene (7 ml) the reaction mixture was stirred at room temperature for 16 hr. Acetic acid (535 mg, 0.51 ml) and H_2O were added, and extracted with ether and CH_2Cl_2. The combined extracts were washed three times with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a crystalline substance (1.33 g). Recrystallization from EtOH gave ethyl 3-carbethoxy-5-benzoylamino-β-resorcylate (XI) as needles, mp 152—153.5° (773 mg). One more recrystallization afforded a sample melting at 153—154°. *Anal.* Calcd. for $C_{19}H_{19}O_7N$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.83; H, 5.11; N, 3.80. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1667 (ester), 1649, 1535 (amide). UV λ_{max}^{EtOH} mμ (log ε): 230 (4.53), 250.5 (3.37) (plateau), 330 (2.84). NMR δ ppm in $CDCl_3$: 1.41 (3H, triplet, $J=7.5$ cps), 1.46 (3H, triplet, $J=7.5$ cps), 4.42 (2H, quartet, $J=7.5$ cps), 4.49 (2H, quartet, $J=7.5$ cps) (two kinds of ethyl esters), 8.40 (1H, broad singlet (NH), 9.15 (1H, singlet) (aromatic ring hydrogen), 12.47 (1H, singlet), 13.16 (1H, singlet) (two kinds of phenolic hydrogens).

3-Benzoylamino-5-carbethoxy-6-carbethoxymethyl-2*H*-pyran-2-one (XII)——To a mixture of 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (I) (570 mg, 0.00262 mole), diethyl 3-oxoglutarate (X) (530 mg, 0.00262 mole) and CH_2Cl_2 (4 ml) was added triethylamine (292 mg) and the resulting mixture was allowed to stand at room temperature overnight (18 hr). The solution was evaporated under reduced pressure leaving an oil. This oily substance was dissolved in ether and CH_2Cl_2 and washed with 10% HCl solution and with saturated NaCl solution (5 times,) dried over Na_2SO_4 and evaporated under reduced pressure to afford a red crystalline substance (957 mg). Recrystallization from EtOH afforded 3-benzoylamino-5-carbethoxy-6-carbethoxymethyl-2*H*-pyran-2-one (XII) as needles, mp 92—110° (598 mg). One more recrystallization gave needles, mp 113—115° (355 mg). Further recrystallization from EtOH afforded a sample melting at 115.5—116.5° (222 mg). All the recrystallization mother liquors were collected and evaporated under reduced pressure to give a crystalline mixture (631 mg) of ethyl 3-carbethoxy-5-benzoylamino-β-resorcylate (XI) and 3-benzoylamino-5-carbethoxy-6-carbethoxymethyl-2*H*-pyran-2-one (XII) in a ratio of 4 to 5 by NMR-analysis. *Anal.* Calcd. for $C_{19}H_{19}O_7N$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.87; H, 5.15; N, 3.77. IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH), 1733, 1708 (esters and pyron), 1674, 1535 (amide). UV λ_{max}^{EtOH} mμ (log ε): 228 (4.07), 270 (3.99), 316 (4.22). NMR δ ppm in $CDCl_3$: 1.26 (3H, triplet, $J=7.5$ cps), 1.37 (3H, triplet, $J=7.5$ cps), 4.19 (2H, quartet, $J=7.5$ cps), 4.33 (2H, quartet, $J=7.5$ cps) (two kinds of ethyl esters), 8.58 (1H, broad singlet) (NH), 8.85 (1H, singlet) (the hydrogen at 4-position of the pyrone ring), 4.07 (2H, singlet) ($-C\underline{H}_2-$).

3-Benzoylamino-5-cyano-6-phenyl-2*H*-pyran-2-one (XIV)——Sodium (128 mg, 0.00557 mole) was dissolved in EtOH (10 ml) and to this solution was added 5-phenylisoxazole (XIII) (808 mg, 0.00557 mole) in EtOH (1 ml). After stirring at room temperature for 1.5 hr 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (I) (1.21 g, 0.00557 mole) in EtOH (10 ml) was added all at once at room temperature. Then the reaction mixture was stirred at room temperature overnight. Acetic acid (334 mg, 0.318 ml) was added with ice-water cooling. The resulting mixture was evaporated under reduced pressure on a water bath (40°) to dryness. To the crystalline residue was added water and a yellow solid was collected by filtration, washed three times with water and dried (305 mg). Recrystallization from EtOH gave 3-benzoylamino-5-cyano-

2*H*-pyran-2-one (XIV), mp 171—172° (167 mg). The filtrate obtained above was acidified with 10% HCl solution and extracted with CH_2Cl_2 and ether. The combined extracts were washed with saturated sodium chloride solution (5 times), dried over Na_2SO_4, and evaporated under reduced pressure to give a crystalline substance (1.3 g). Recrystallization from EtOH gave further XIV as leaflets, mp 171—172° (805 mg). From the mother liquors further quantities of XIV, mp 170—171° was obtained, 100 mg (total yield: 61%; reported, mp 174°[6]). *Anal.* Calcd. for $C_{19}H_{12}O_3N_2$: C, 72.14; H, 3.82; N, 8.86. Found: C, 71.86; H, 3.85; N, 8.89. IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1734 (pyron), 1677, 1532 (amide), 2250 (CN). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.26), 240 (4.23), 350.5 (4.50). NMR δ ppm in $CDCl_3$: 8.66 (1H, singlet) (C=C<u>H</u>), 8.71 (1H, singlet) (NH).

3-Benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII)——A mixture of benzoylacetylene (XVII) (804 mg, 0.618 m mole), 2-phenyl-2-oxazolin-5-one (XVI) (996 mg, 0.618 m mole) and acetic anhydride (4 ml) was heated on a water bath (92—95°) for 80 minutes. On cooling a crystalline substance appeared. After addition of ice-water the mixture was stirred at room temperature for 30 minutes. Then about 10 ml of ether was added and the crystalline substance was collected by filtration, washed three times with ether, and dried to give 3-benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII), mp 198—200° (406 mg). Recrystallization from benzene yielded prisms, mp 200—201°. *Anal.* Calcd. for $C_{18}H_{13}O_3N$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.39; H, 4.60; N, 4.89. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1706 (pyron), 1669, 1530 (amide). UV λ_{max}^{EtOH} mμ (log ε): 235 (4.17), 240 (4.15) (shoulder), 355 (4.44). NMR δ ppm in $CDCl_3$: 8.57 (1H, doublet, J=7.5 cps), 6.80 (1H, doublet, J=7.5 cps).

3-Benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII) from Hippuric Acid (VII) and Benzoylacetylene (XVII)——A mixture of hippuric acid (VII) (1.79 g, 0.01 mole), benzoylacetylene (XVII) (1.30 g, 0.01 mole), sodium acetate (0.82 g, 0.01 mole) and acetic anhydride (3.1 g) was heated on a water bath (95°) for 100 minutes. To the cooled reaction mixture was added ice-water and the mixture was allowed to stand for a night in order to decompose acetic anhydride. Then, water was decanted and the resulting viscous oil was treated with ether to furnish a crystalline substance, which was collected by filtration and dried (1.12 g). Recrystallization from benzene gave fine needles of 3-benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII), mp 199—200.5° (440 mg). One more recrystallization afforded prisms, mp 200—201°. *Anal.* Calcd. for $C_{18}H_{13}O_3N$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.06; H, 4.53; N, 4.97.

Ethyl 2-Benzoylamino-5-phenyl-5-oxo-2-pentenoate (XIX)——3-Benzoylamino-6-phenyl-2*H*-pyran-2-one (XVIII) (13.5 g) was suspended in 5%-KOH-EtOH solution (190 ml) and stirred at room temperature until all crystalline substances dissolved. It took one hour to give a red homogeneous solution. Then acetic acid (10.7 g, 10.2 ml) was dropwise added with ice-water cooling. After 5 minutes a crystalline substance appeared. Water was added and the solid was collected by filtration, washed with H_2O until the filtrate became neutral to litmus and dried (12.5 g). Recrystallization from EtOH afforded ethyl 2-benzoylamino-5-phenyl-5-oxo-2-pentenoate (XIX) as needles, mp 124—126° (10.4 g). Two more recrystallization from EtOH gave a sample of mp 128—129.5°. *Anal.* Calcd. for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.10; H, 5.83; N, 4.10. IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1735 (ester), 1698 (CO), 1642, 1514 (amide). NMR δ ppm in $CDCl_3$: 1.32 (3H, triplet, J=7.5 cps) ($COOCH_2C\underline{H}_3$), 4.28 (2H, quartet, J=7.5 cps) ($COOC\underline{H}_2CH_3$), 4.02 (2H, doublet, J=7.0 cps) ($C\underline{H}_2$), 7.18 (1H, triplet, J=7.0 cps) (C<u>H</u>=), 8.17 (1H, broad singlet) (NH).

Ethyl 2-Benzoylamino-5-phenyl-5,5-ethylenedithio-2-pentenoate (XX)——To a mixture of ethyl 2-benzoylamino-5-phenyl-5-oxo-2-pentenoate (XIX) (2.0 g), acetic acid (30 ml) and ethanedithiol (2 ml) was dropwise added BF_3-etherate (4 ml) at room temperature. The reaction mixture was allowed to stand at room temperature for 6 hr. Ice-water was added and extracted with ether and $CHCl_3$. The combined extracts were washed with $NaHCO_3$ solution until all acetic acid was removed, then washed with H_2O until neutral to litmus, dried over Na_2SO_4. Evaporation of the solvent afforded an oil, which crystallized on standing. Recrystallization from EtOH afforded ethyl 2-benzoylamino-5-phenyl-5,5-ethylenedithio-2-pentenoate (XX) as needles, mp 134—136° (1.85 g). An analytical sample melted at 135—136°. *Anal.* Calcd. for $C_{22}H_{23}O_3NS_2$: C, 63.89; H, 5.61; N, 3.39; S, 15.51. Found: C, 63.75; H, 5.64; N, 3.35; S, 15.38. IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1722 (ester), 1648, 1527 (amide). NMR δ ppm in $CDCl_3$: 1.27 (3H, triplet, J=7.5 cps) ($COOCH_2C\underline{H}_3$), 4.26 (2H, quartet, J=7.5 cps) ($COOC\underline{H}_2CH_3$), 3.32 (2H, doublet, J=7.0 cps) ($C\underline{H}_2$), 6.76 (1H, triplet, J=7.0 cps) (C<u>H</u>=).

Ethyl 2-Benzoylamino-5-phenylpentanoate (V) from Ethyl 2-Benzoylamino-5-phenyl-5,5-ethylendithio-2-pentenoate (XX)——A mixture of ethyl 2-benzoylamino-5-phenyl-5,5-ethylendithio-2-pentenoate (XX) (650 mg), Raney Ni (W-2) (15 ml=0.9 g) and abs. EtOH (75 ml) was heated under reflux for 7 hr. Then, the catalyst was filtered off and washed well with EtOH. The combined filtrates were evaporated under reduced pressure to dryness to give an oil (513 mg), which was dissolved in EtOH (10 ml) and stirred with Raney Ni (W-2) (0.5 ml=300 mg) in hydrogen atmosphere. Only 16 ml of hydrogen gas was absorbed at room temperature during 4 hr stirring. The catalyst was filtered off, washed with EtOH and the filtrate was evaporated under reduced pressure to afford an oil (513 mg). This oil was purified by chromatography using silica gel (15 g). Elution with benzene—$CHCl_3$ (1:1) gave crystalline ethyl 2-benzoylamino-5-phenylpentanoate (V). Recrystallization from heptane gave needles, mp 83—86° (17 mg) (3.3% yield). One more recrystallization afforded pure V, mp 89—90°, which on admixture with the sample obtained from VIII through IX showed no depression in melting point. *Anal.* Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12;

N, 4.30. Found: C, 73.98; H, 7.03; N, 4.14. Further elution with benzene–$CHCl_3$ (1:1) and evaporation gave a crystalline substance (275 mg). Recrystallization from *n*–heptane gave ethyl 2–cyclohexylcarboxy–amino–5–phenylpentanoate (XXII) as tufts of needles, mp 76—78° (212 mg) (40.8% yield). Recrystallization from aqueous EtOH (70%) afforded needles, mp 78—79°. *Anal.* Calcd. for $C_{20}H_{29}O_3N$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.24; H, 8.79; N, 4.03. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1750 (ester), 1646, 1550 (amide). NMR δ ppm in $CDCl_3$: 1.25 (3H, triplet, $J=7$ cps) ($COOCH_2C\underline{H}_3$), 1.78 (center) (11H, broad multiplet) (cyclohexyl), 2.62 (2H, triplet, $J=6$ cps) (Ph–$C\underline{H}_2$–), 4.18 (2H, quartet, $J=7$ cps) ($COOC\underline{H}_2CH_3$), 4.63 (1H, multiplet (>CH–N$\underline{H}$–), 5.97 (1H, broad doublet, $J=8$ cps) (NH), 6.90—7.43 (5H, multiplet centered at 7.17) (aromatic hydrogens).

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