[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Chemistry of Lactones. III. Reactions of α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide[1,2,3]

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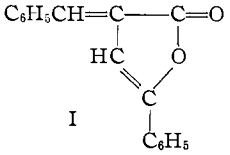
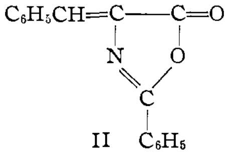
The γ-lactone, α-benzylidene-γ-phenyl-Δ,β,γ-butenolide (I), reacts with aqueous base, with methanol under both acidic and basic conditions, and with primary and secondary amines to form the ring-opened γ-ketocarboxylic acid, methyl ester and substituted amides. Analogies are drawn with the structurally similar 2-phenyl-4-benzylidene-5(4H)-oxazolone (II).

Highly conjugated γ-lactones, such as the α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (I), have been described previously[4] and a study has been made of the ultraviolet spectra of ring-substituted analogs of I.[5] However, the chemical properties of these compounds have received little attention. In contrast, there has been much research on the structurally similar azlactones,[6] such as 2-phenyl-4-benzylidene-5(4H)-oxazolone (II), which is isoelectronic with I. This emphasis may be attributed in large measure to the structural studies on penicillin[7] and because azlactones are precursors of α-amino acids.


I


II

In a continuation of our studies on unsaturated lactones,[1] we have examined the properties of I in some detail and in the present paper a number of ring-opening reactions are described.

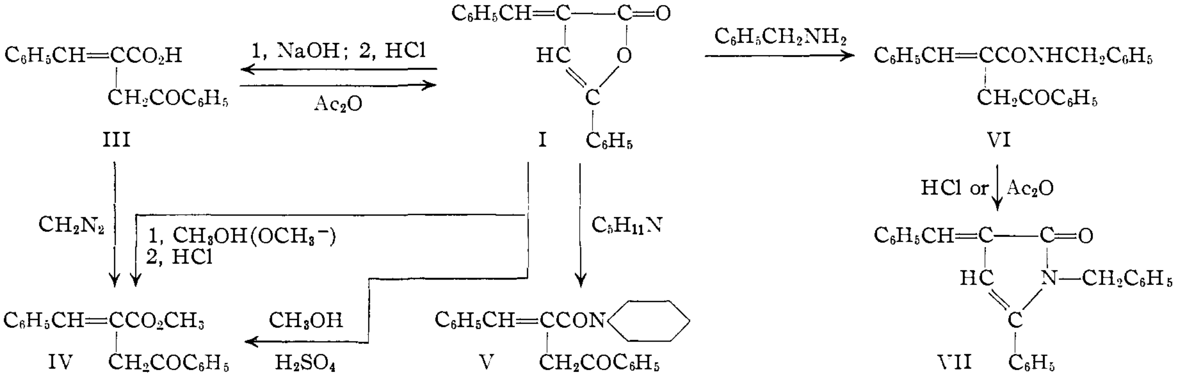
Compound I is prepared by condensation of benzaldehyde with 3-benzoylpropionic acid in the presence of acetic anhydride and sodium acetate ("Perkin" conditions) analogous to the preparation of II.[6a] Under strongly acidic or basic conditions, condensation occurs at the β-carbon to give 3-benzylidene-3-benzoylpropionic acid which readily cyclizes to a substituted naphthalene.[4a]

Previous workers[4,5] have denoted I as "α-benzylidene-γ-phenylcrotonolactone." This usage is misleading and should be replaced by the butenolide nomenclature indicated in the title or described as a γ-lactone of a γ-hydroxybutenoic acid.[8] The butenolide designation will be used throughout this and subsequent papers.

Compound I exhibits strong carbonyl absorption at 1785 cm.$^{-1}$, characteristic of β,γ-unsaturated-γ-lactones.[9] The maximum at 384 mμ is in agreement with the literature.[5a]

The reactions we have studied are summarized in Chart A.

CHART A



Hydrolysis.—At elevated temperatures, the lactone ring was opened readily by dilute aqueous sodium hydroxide and reaction was complete after an hour. On acidification, the γ-keto acid III was isolated. The structure for III is supported by analytical and spectral data, preparation of the 2,4-dinitrophenylhydrazone, reconversion to I on treatment with acetic anhydride and reaction with diazomethane to form the methyl ester IV.

Alcoholysis.—The butenolide reacted with methanol in the presence of methoxide ion to afford the methyl ester IV in 23% yield; IV was also obtained in even lower yield by acid-catalyzed methanolysis using sulfuric acid. Its structure was confirmed by independent synthesis from III (which is a better preparative method), prepara-

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[1] Part II, R. Filler and L. M. Hebron, *J. Org. Chem.*, **23**, 1815 (1958).

[2] Abstracted from the M.S. thesis of L. M. H. submitted to the Graduate School of Illinois Institute of Technology, 1958.

[3] Presented in part at the 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958.

[4] (a) W. Borsche, *Ber.*, **47**, 1107, 2718 (1914); (b) E. P. Kohler, G. A. Hill and L. A. Bigelow, THIS JOURNAL, **39**, 2417 (1917); (c) W. T. Smith, Jr., and C. Hanna, *ibid.*, **73**, 2387 (1951).

[5] (a) F. W. Schueler and C. Hanna, *ibid.*, **73**, 3528 (1951); (b) **75**, 741 (1953).

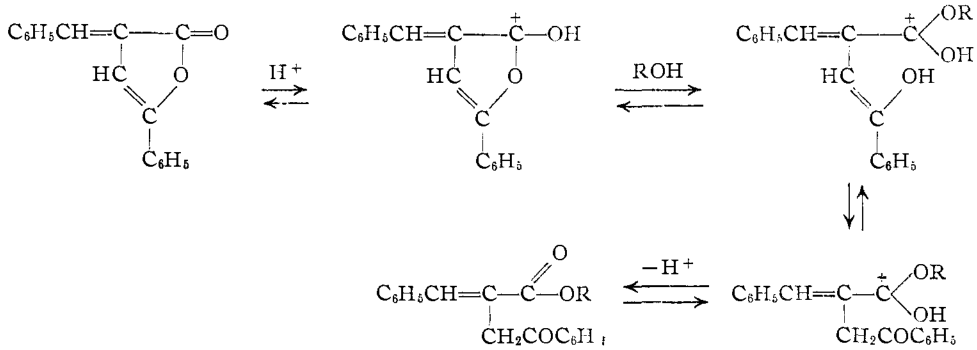
[6] (a) H. E. Carter in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 198; (b) E. Baltazzi, *Quart. Revs.*, **9**, No. 2, 150 (1955); (c) J. W. Cornforth in R. C. Elderfield, "Heterocyclic Chemistry," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 336.

[7] "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson and R. Robinson, Editors, Princeton University Press, Princeton, N. J., 1949.

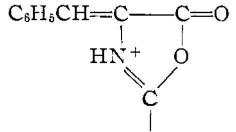
[8] This nomenclature was suggested by the late Austin M. Patterson in a private communication with R. F.

[9] J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

tion of the 2,4-dinitrophenylhydrazone, and elemental and infrared analyses. These results parallel those observed with II.[10] The acid-catalyzed alcoholysis most probably involves a carbonium ion intermediate



In the case of the oxazolone, this would involve the "oxazolonium ion" (IIa).[11]



IIa

All attempts to prepare the ethyl ester by treating I with ethanol and sodium ethoxide led to the acid as the sole product in yields of more than 70%. Apparently, the sodium salt of III was readily formed under the conditions employed.

Non-catalyzed ethanolysis (95% ethanol) of I (followed spectrophotometrically) proceeded much more slowly than with II. There was little change after one week at room temperature, whereas appreciable reaction occurred with the oxazolone[12] after several days.

Aminolysis.—Benzylamine reacted rapidly with the butenolide to form the γ-keto benzylamide VI. Ring-opening by this primary amine proceeded at a faster rate than it did during base-catalyzed alcoholysis. Due to this facile opening of lactone rings, benzylamine has been used to determine the composition of mixtures containing an azlactone.[13] On the other hand, secondary amines, such as piperidine and morpholine, reacted somewhat more slowly with I. A crystalline piperidide, V, was prepared, but we were unable to isolate its geometric isomer, as in the case of II, when excess amine was used.[14] The product obtained with morpholine did not correspond to the required analysis for the morpholide. Its infrared spectrum, however, was consistent with an N,N-disubstituted amide structure[15] and similar to that for the piperidide. Thus far, we have not determined the structure of this compound. The weakly basic secondary amine, carbazole, failed to react, nor was the lactone isomerized. The less stable geometric isomer of II was obtained when II was treated under these conditions.[14]

When the benzylamide VI was heated either with dilute hydrochloric acid, glacial acetic acid or acetic anhydride, orange needles were isolated. Analytical data and the mode of formation, as well as ultraviolet and infrared spectra, are consistent with structure VII. This compound possessed a strong band at 1675 cm.$^{-1}$, probably due to the carbonyl group in the β,γ-unsaturated-γ-lactam, though there is little data on this point[15,16]; VI exhibited an –NH– stretching band which was absent in VII.

The strong maximum at 410 mμ is attributed to the $C_6H_5CH{=}\underset{|}{C}CH{=}\underset{|}{C}C_6H_5$ chromophore.[5] There were also maxima at 305 and 258 mμ, the latter probably due to the $C_6H_5CH{=}\underset{|}{C}{-}$ partial chromophore.[17]

Isomerization.—The structures of I and II permit geometric isomerism and whereas the two isomers of several 4-alkylidene and -arylidene-5(4H) oxazolones have been isolated,[18] this has not been true for I. Under "Perkin" conditions, only one isomer is obtained. We attempted to cause isomerization of I using 48% HBr. Though this conversion was reportedly accomplished with II,[19] we were unsuccessful not only with I, but also in repeating the previous work.

Isomerization to an α,β-unsaturated-γ-lactone cannot occur when there is an exocyclic double bond on the α-carbon. When this group is saturated, such isomerization is possible and the isomers are often readily interconvertible (tautomers).[20]

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(10) R. E. Buckles, R. Filler and L. Hilfman, *J. Org. Chem.*, **17**, 233 (1952).

(11) J. L. O'Brien and C. Niemann, THIS JOURNAL, **79**, 80 (1957).

(12) E. L. Bennett and E. Hoerger, *ibid.*, **74**, 5975 (1952).

(13) This is referred to as the "azlactone equivalent" and involves the titration of excess benzylamine with standard acid; ref. 7, p. 735.

(14) D. K. Barnes, E. Campaigne and R. L. Shriner, THIS JOURNAL, **70**, 1769 (1948).

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 182.

(16) Unfused lactams show carbonyl absorption near 1700 cm.$^{-1}$ (ref. 15), but it is of interest that certain pyrimidones and hydroxypurines, having a contribution from the $-\underset{|}{N}-\underset{\underset{O}{\|}}{C}-$ structure, possess a carbonyl stretching band at a lower frequency. Thus, 6-hydroxypurine has a band at 1670 cm.$^{-1}$ and 1-methyl-2-pyrimidone at 1675 cm.$^{-1}$. See S. F. Mason in "The Chemistry and Biology of Purines," Ciba Foundation Symposium, Little, Brown, and Co., Boston, Mass., 1957, p. 63.

(17) D. A. Bassi, V. Deulofeu and F. A. F. Ortega, THIS JOURNAL, **75**, 171 (1953); see also ref. 5.

(18) (a) H. E. Carter and C. M. Stevens, *J. Biol. Chem.*, **133**, 117 (1940); (b) H. E. Carter and W. C. Risser, *ibid.*, **139**, 255 (1941).

(19) S. Tatsuoka and A. Morimoto, *J. Pharm. Soc. Japan*, **70**, 253 (1950); *C. A.*, **45**, 1541a (1951).

(20) F. Ramirez and M. B. Rubin, THIS JOURNAL, **77**, 3768 (1955).

Experimental[21]

Reaction of I with Sodium Hydroxide.—To 4.9 g. (0.02 mole) of I was added 25 ml. of 6 *N* NaOH and the mixture heated under reflux for 2 hours. On cooling, the reaction mixture was neutralized with 20% HCl, the solution evaporated to dryness and the residue washed with water. After crystallization from C_6H_6–CCl_4 (1:1), the product weighed 4.2 g. (79%), m.p. 171–173°; λ_{max}^{EtOH} 248 mμ; infrared 1680 (s) cm.$^{-1}$ (>C=O), 2600 (m) cm.$^{-1}$ (–OH in–COOH).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30; mol. wt., 266.3. Found: C, 76.53; H, 5.30; mol. wt., 265 (neut. equiv.).

2,4-Dinitrophenylhydrazone, orange crystals, m.p. 229–230°, λ_{max}^{EtOH} 256, 372 mμ.

Anal. Calcd. for $C_{23}H_{18}N_4O_6$: N, 12.55. Found: N, 12.75.

Reaction of I with Ethanol and Sodium Ethoxide.—To a solution of 0.69 g. (0.03 g. atom) of sodium in 50 ml. of absolute ethanol was added a suspension of 7.4 g. (0.03 mole) of I in 200 ml. of absolute ethanol. The mixture was heated under reflux for 6 hours and then allowed to cool to room temperature; HCl (20%) was added until the mixture was acid to litmus. After standing overnight, an amorphous material was obtained. On crystallization from a 1:1 mixture of C_6H_6–CCl_4, 5.8 g. of a white crystalline substance, m.p. 173–174°, was obtained. This material gave no depression when admixed with the product obtained by reaction of I with NaOH; yield 73.4%. This reaction also was run using less sodium and by keeping the temperature lower. In all cases, only the acid III was isolated.

Reaction of I with Methanol and Sodium Methoxide.—When this reaction was carried out in a manner similar to that described using ethanol, only the acid III was obtained. However, under the following conditions, the methyl ester IV was isolated.

To a solution of 0.46 g. (0.02 g. atom) of sodium in 30 ml. of absolute methanol was added with stirring a suspension of 4.9 g. (0.02 mole) of I in 100 ml. of dry benzene. The reaction mixture was maintained at 0–5° during the addition and then allowed to warm to room temperature. The mixture was acidified with 10% HCl, the benzene layer washed with water, dried over anhydrous sodium sulfate and the volume of solvent reduced *in vacuo*. On standing overnight, an amorphous material was obtained. Crystallization from 95% ethanol gave 1.3 g. (23%) of a white crystalline product, m.p. 76–77°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.24; H, 5.64.

2,4-Dinitrophenylhydrazone, orange-red needles, m.p. 178–179°.

Anal. Calcd. for $C_{24}H_{20}N_4O_6$: N, 12.16. Found: N, 12.18.

Reaction of I with Methanol and Sulfuric Acid.—A mixture of 2.5 g. (0.01 mole) of I, 3 ml. of concentrated sulfuric acid and 20 ml. of methanol was heated on a steam-bath until solution was effected. The mixture was cooled and water added. The crude ester was crystallized from 95% ethanol to give 0.5 g. (18%) of IV, m.p. 76–77° with no depression when admixed with the product obtained using sodium methoxide.

Compound I reacted with methanol and the 2,4-dinitrophenylhydrazine reagent to give the 2,4-dinitrophenylhydrazone of IV, m.p. 178–179°.

Reaction of III with Diazomethane.—A suspension of 2.5 g. (0.0094 mole) of III in 10 ml. of methanol was treated with an ether solution of diazomethane obtained by treating 2.2 g. of N-methyl-N-nitroso-*p*-toluenesulfonamide in ether with excess potassium hydroxide in Carbitol.[22] On removal of solvent, the crude methyl ester was obtained, which on crystallization from 95% ethanol, gave 2.1 g. (80%) of IV, m.p. 76–77°, with no depression when mixed with a sample obtained by the ring-opening of I.

Reaction of III with Acetic Anhydride.—One gram of III was heated on a steam-bath for an hour with 5 ml. of acetic anhydride. After cooling, water was added to the yellow solution and the mixture cooled overnight. The crude yellow solid which precipitated was crystallized from 95% ethanol to give 0.7 g. of a bright yellow product, m.p. 152–154°, which did not depress the m.p. of an authentic sample of I.

Reaction of I with Piperidine.—To 6.15 g. (0.024 mole) of I suspended in 25 ml. of dry benzene in a 125-ml. erlenmeyer flask fitted with a reflux condenser, was added 2.12 g. (0.024 mole) of freshly distilled piperidine. The reaction mixture warmed spontaneously and then was heated for 1 hour on a steam-bath, during which time the mixture became homogeneous. Approximately two-thirds of the solvent was removed under reduced pressure. On standing overnight, an amorphous material precipitated. This was washed with petroleum ether and crystallized from 95% ethanol to give a faintly yellow crystalline substance, m.p. 107–108°. The crude yield was 4.12 g. (65%), λ_{max}^{EtOH} 247 mμ (ε 2700). When excess piperidine was used, no product could be isolated, nor was the starting material recovered.

Anal. Calcd. for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.21; H, 7.07; N, 4.24.

Reaction of I with Morpholine.—Compound I was treated similarly with morpholine. After standing in the refrigerator for several days, crystals were observed. These were collected, washed with ether, and recrystallized from 95% ethanol, m.p. 184–185°.

Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 68.58, 68.85; H, 6.61, 6.43; N, 5.95, 5.86.

Carbazole failed to react with I and the lactone was recovered unchanged.

Reaction of I with Benzylamine.—A mixture of 4.44 g. (0.02 mole) of I in 50 ml. of dry benzene and 3.21 g. (0.03 mole) of benzylamine was heated under reflux for 30 minutes. On cooling, white crystals separated, which were washed with petroleum ether and recrystallized from 95% ethanol to give 5.7 g. (80%) of VI, m. p. 173–174°; infrared ($CHCl_3$), 3230 (w) cm.$^{-1}$ (–NH–); 1670 (s) cm.$^{-1}$ (ketone >C=O); 1645 (s) cm.$^{-1}$ (amide >C=O).

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.09; H, 5.95; N, 3.94. Found: C, 81.06; H, 5.86; N, 3.71.

Lactamization of VI.—A suspension of 1.0 g. (0.0028 mole) of VI in 50 ml. of 6*N* HCl was heated under reflux for 1.5 hours. The solid turned yellow, then orange. On cooling, the solid was collected, washed with water and crystallized from 95% ethanol to give 0.75 g. (80%) of VII, fine orange needles, m.p. 142–143°; λ_{max}^{EtOH} 410, 305, 258 mμ; infrared 1675 (s) cm.$^{-1}$ (probably lactam >C=O). The same results were obtained when VI was heated with acetic anhydride or glacial acetic acid.

Anal. Calcd. for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.39; H, 6.63; N, 4.09.

Attempted Isomerization of I.—Compound I (1 g.) was treated with 15 ml. of 48% HBr, the mixture allowed to stand overnight in the refrigerator, poured on ice-water and filtered. The yellow solid was washed with water and dried, m.p. 152–154°. There was no m.p. depression when this material was mixed with an authentic sample of I.

The azlactone II was treated similarly but no isomeric lactone could be isolated.[19] Only unchanged II was obtained.

Spectral Measurements and Analyses.—Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer and Perkin-Elmer Infracord. The samples were examined either in CCl_4 or $CHCl_3$ solution or as Nujol mulls. Ultraviolet spectra were measured in 95% ethanol using a Beckman DK-2 spectrophotometer. Microanalyses were conducted by Micro-Tech Laboratories, Skokie, Ill.

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[21] All m.p.'s were determined on a Fisher–Johns block and are uncorrected.

[22] T. J. DeBoer and H. J. Backer, *Org. Syntheses*, **36**, 16 (1956).