by the method outlined by Beckmann[12] showed no depression, m.p. 108–108.5°.

Acknowledgments: The authors wish to thank Professor R. K. Hill of Princeton University for his many comments and suggestions in connection with these investigations and Canisius College for a Faculty Research Grant to R.T.C. to aid in the preparation of this communication.

(12) E. Beckmann, *Ber.*, **22**, 1589 (1889).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Substituted γ-Lactones. II. Some Electrophilic Substitution Reactions of α-Benzylidene-γ-butyrolactone

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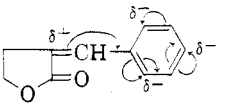
In electrophilic substitution reactions, α-benzylidene-γ-butyrolactone (I) is similar to cinnamic acid. It can be nitrated predominantly in the para position. With chlorosulfonic acid it gives the *p*-chlorosulfonyl derivative (VIII). The structures of the substitution products have been verified by oxidative degradation. The reduction of the three isomeric α-nitrobenzylidene-γ-butyrolactones and the preparation of several derivatives of the α-aminobenzylidene-γ-butyrolactones obtained is described.

In a previous paper[2] the condensation of several aldehydes with butyrolactone was described. It has been found that this reaction did not proceed well with nitrobenzaldehydes or with *p*-acetamidobenzaldehyde, which compounds gave small yields or substantially no yields at all. However, nitro- and amino-substituted α-benzylidene- γ-butyrolactones and some of their derivatives were desired in order to investigate their pharmacological properties; therefore, a nitration of the readily available[3] α-benzylidene-γ-butyrolactone (I) was attempted. The nitration products obtainable from this reaction could serve as intermediates in the preparation of the corresponding amino compounds and derivatives thereof. We also were interested in sulfonic acid derivatives of I and hence ran a sulfochlorination of I.

Reaction of I with potassium nitrate in concentrated sulfuric acid at low temperature[4] furnished a 60% yield of α-(*p*-nitrobenzylidene)-γ-butyrolacrone (II) and a lesser amount of the *o*-isomer (III). The structures of the compounds obtained were proven by oxidative degradation to the corresponding nitrobenzoic acids, and, in the case of II, by comparison with an authentic sample, obtained by a condensation between *p*-nitrobenzaldehyde and butyrolactone.[2] In one experiment which was carried out with an excess of potassium nitrate, a small yield of a dinitro product, presumably α-(2,4-dinitrobenzylidene)-γ-butyrolactone (IV), was obtained.

These experiments show that in I electrophilic substitution occurs in the *p*- and *o*-positions. This can be explained by assuming that during the attack of the nitrating agent a time-variable electromeric electron shift occurs similarly to that observed in the nitration of cinnamic acid,[5] thus, activating the ortho and para positions towards an electrophilic attack: The ratio of the yields of II



and III is about 3.3:1. Underwood and Kochmann,[5b] in the nitration of cinnamic acid, observed a para: ortho ratio of about 2.5:1. The greater tendency of I towards para-substitution can be explained by the appreciable amount of steric hindrance imposed by the lactone ring on the ortho positions. Accordingly the sulfochlorination of I gave predominantly the *p*-chlorosulfonyl derivative (VIII). The corresponding ortho derivative could not be isolated. Probably due to increased steric hindrance, its formation might occur only to a minor extent, if any.

Reduction of II, III, and of α-(*m*-nitrobenzylidene)-γ-butyrolactone (V)[2] with stannous chloride and concentrated hydrochloric aicd gave solid complexes which on treatment with aqueous ammonia and subsequent extraction with an organic solvent such as chloroform or tetrahydrofuran gave the corresponding amino derivatives in high

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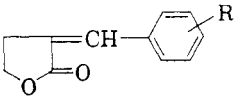
(2) H. Zimmer and J. Rothe, *J. Org. Chem.*, **24**, 28 (1959).

(3) W. Reppe and co-workers, *Ann.*, 596, 158 (1955).

(4) *e.g.*, W. Borsche, K. Diacont, and H. Hanau, *Ber.*, **67**, 675 (1934); T. Kariyone and T. Fukui, *J. Pharm. Soc. Japan*, **68**, 276 (1948); *Chem. Abstr.*, **45**, 9520i (1951).

(5) (a) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1954, p. 439. (b) H. W. Underwood Jr. and E. L. Kochmann, *J. Am. Chem. Soc.*, **48**, 254 (1926).

TABLE I



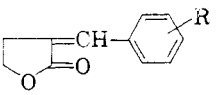
SUBSTITUTED α-BENZYLIDENE-γ-BUTYROLACTONES

R	Formula	M.P., °C.	[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
m-Acetamido-	$C_{13}H_{13}NO_3$	181.5–182	M					6.06	6.21
p-Acetamido	$C_{13}H_{13}NO_3$	200–201[b]	M						
m-Benzenesulfonamido	$C_{17}H_{15}NO_4S$	157–158	M	61.99	62.10	4.59	4.73		
p-Benzenesulfonamido	$C_{17}H_{15}NO_4S$	226–228d.	E	61.99	61.76	4.59	5.14	4.25	3.90
m-(*p*-Nitrobenzenesulfonamido)	$C_{17}H_{14}N_2O_6S.H_2O$	238–239d.	M	52.03	51.87	4.11	4.58		
p-(*p*-Nitrobenzenesulfonamido)	$C_{17}H_{14}N_2O_6S.H_2O$[c]	212–214d.	M	52.03	51.53	4.11	4.48		
m-(*p*-Acetamidobenzenesulfonamido)	$C_{19}H_{18}N_2O_5S.H_2O$	251–252.5d.	W[d]	56.42	56.07	4.95	5.19		
p-(*p*-Acetamidobenzenesulfonamido)	$C_{19}H_{18}N_2O_5S.H_2O$	253–253.5d.	X	56.42	56.71	4.95	4.90		

[a] Solvent for recrystallization: M = methanol, E = ethanol, W = water, X = purified by extracting with dioxane-ethanol. [b] Mixed m.p. with an authentic[2] sample: 200–201°. [c] Found after drying at 50° (high vacuum): C, 54.32; H, 4.21. Calcd. for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77. [d] Analytical sample from dimethylformamide-ether.

yields. The *m*-(VI) and *p*-compounds (VII) could be hydrogenated[2] to the corresponding α-aminobenzylbutyrolactones. α-(*o*-Aminobenzylidene)-γ-butyrolactone appears to be somewhat unstable in solution, and its hydrogenation does not seem to follow the normal path. Further work on this compound is in progress.

Some acyl and sulfonyl derivatives of VI and VII were also prepared (see Table I). VIII on standing with concentrated ammonia gave the sulfonamide IX. IX was oxidized to *p*-sulfonamidobenzoic acid thus verifying the structure of VIII. Treatment of VIII with hydrazine and aniline, respectively, gave the expected derivatives. Some



I. R = H
II. R = *p*-NO_2
III. R = *o*-NO_2
IV. R = x,y-$(NO_2)_2$
V. R = *m*-NO_2
VI. R = *m*-NH_2
VII. R = *p*-NH_2
VIII. R = *p*-SO_2Cl
IX. R = *p*-SO_2NH_2

of the compounds showed interesting pharmacological properties. The results will be published elsewhere.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

Nitration of α-benzylidene-γ-butyrolactone (I). A solution of 52.2 g. (0.3 mole) of I in 180 cc. of conc. sulfuric acid was cooled by means of an ice-salt bath. While being stirred, a solution of 33 g. (0.33 mole) of potassium nitrate in 140 cc. of conc. sulfuric acid was added dropwise within 1 hr.; the internal temperature during the addition was held between 0 and +5°. The mixture was kept for 3 more hours in the ice-bath, then poured on ice. A slightly yellow precipitate occurred which was filtered by suction, thoroughly washed with water until the washings were neutral, then washed with cold methanol. This crude product was treated briefly with 250 cc. of hot methanol and filtered hot; *α-p-nitrobenzylidene)-γ-butyrolactone (II)* which remained undissolved was washed with hot and cold methanol, then with ether. The product was sufficiently pure for reduction, yield 40.0 g. (61%), m.p. 201–202°.

An analytical sample, after 3 recrystallizations from tetrahydrofuran, had the same m.p.; yellowish needles.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14. Found: C, 60.02; H, 3.92.

A mixed m.p. with an authentical sample (m.p. 202–203°) obtained by condensation of *p*-nitrobenzaldehyde with butyrolactone[2] was 201–203°. II is rather insoluble in cold common solvents except in acetic acid. It is soluble in warm dioxane, acetone, and ethyl acetate.

The methanolic filtrates of I precipitated on concentration the isomeric *α-(o-nitrobenzylidene)-γ-butyrolactone (III)*; after one recrystallization from methanol, 11.9 g. (18%), m.p. 96–97°, were obtained. After two more recrystallizations from methanol, the m.p. of the yellowish leaflets was 96–97.5°.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.15; H, 4.03; N, 6.58.

Formation of α-(x,y-dinitrobenzylidene)-γ-butyrolactone (IV). A solution of 17.4 g. (0.1 mole) of I in 60 cc. of sulfuric acid was prepared. With external cooling (ice) and stirring, a solution of 22 g. (0.22 mole) of potassium nitrate in 100 cc. of sulfuric acid was added gradually within 15 min. during which the internal temperature was kept at 22–25°. Stirring was continued for 2 more hours at 20–30°, then the mixture was poured on ice. A resinous precipitate occurred which was filtered, washed, and recrystallized from 50 cc. of methanol and 3.9 g. (15%) of crude material, m.p. *ca.* 131–136° (not clear until 180°), were obtained.

Not less than 250 cc. of methanol were required for the recrystallization of the crude product; on cooling, two different kinds of crystals appeared which were filtered and separated manually: octahedra (m.p. 131.5–132.5°, 2.8 g.) and fine needles (m.p. 185–190°, 0.3 g., probably II).

The octahedra were again recrystallized from 100 cc, of methanol yielding yellowish cubes, m.p. 134–137°, and a small amount of a brownish powder, m.p. 159–190°. The cubes were separated manually and recrystallized 3 more times from methanol to give the pure *α-(x,y-dinitrobenzylidene)-γ-butyrolactone* (*IV*) m.p. 136.5–137.5°.

Anal. Calcd. for $C_{11}H_{18}N_2O_6$: C, 50.01; H, 3.05; N, 10.60. Found: C, 50.07; H, 3.04; N, 10.72.

Various crystalline fractions were obtained from the aqueous and the first methanolic filtrates, indicating that some II and III had been formed during the reaction. Because of the abundant resinous by-products, however, they were not investigated further.

Verification of the structures of II and III. Boiling of II for 10 hr. with an excess of potassium permanganate in sodium carbonate solution, removal of manganese dioxide, and acidification gave *p*-nitrobenzoic acid (m.p. 239–243°; mixed m.p. with an authentic sample: 239–242°).

Similarly, a small amount of *o*-nitrobenzoic acid (m.p. 138–140°) was obtained from III. Mixed m.p. with an authentic sample (m.p. 145.5–148°): 142–144°.

Oxidation of IV with permanganate led to an acid (m.p. 145–150° dec.) the amount of which was too small for further purification. Mixed m.p. with an authentic sample of 2.4-dinitrobenzoic acid (m.p. 181–182°): 165–168° dec.

Reduction of II, III, and V to α-aminobenzylidene-γ-butyrolactones. Ninety grams of tin (II) chloride dihydrate (0.4 mole) were dissolved in 225 cc. of conc. hydrochloric acid and 14.8 g. (0.0675 mole) of V[2] (m.p. 142–145°) were added. Nearly the entire amount went into solution. After a few minutes a moderately exothermic reaction occurred and the mixture solidified. After 24 hours' standing at room temperature, the precipitate was filtered by suction, (still wet) immediately added to 300 cc. of a conc. aqueous solution of ammonia, and stirred for several hours at room temperature. The residue was filtered, washed thoroughly with water, and dried carefully. The brown-yellowish powder was then extracted with chloroform in a Soxhlet apparatus for about 24 hr. until the residue did not contain any more organic material.

The chloroform solution in which the amine VI partly had precipitated was evaporated to dryness and the yellow residue recrystallized from methanol, yielding 9.3 g of yellow leaflets, m.p. 164–165.5°. From the mother liquor, a second fraction (1.4 g., m.p. 161.5–162.5°) was obtained. Total yield: 10.7 g. (84%) of *α-(m-aminobenzylidene)-γ-butyrolactone* (*VI*).

An analytical sample melted at 163°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: C, 69.73; H, 6.05.

The *hydrochloride*, after several recrystallizations from 95% ethanol, decomposed between 237 and 240°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.36; N, 6.21. Found: C, 58.11; H, 5.45; N, 5.93.

Similarly, from 40.2 g. of II, a yield of 32.3 g. (93%) of *α-(p-aminobenzylidene)-γ-butyrolactone* (*VII*), m.p. 189–192°, was obtained. The analytical sample melted at 194–195.5°, yellow-brownish needles from 95% ethanol.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.18.

Hydrochloride, m.p. 224–225.5° (from 10% aq. hydrochloric acid).

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.72. Found: Cl, 15.55.

Similarly, from 3.0 g. of III, 2.1 g. (81%) of *α-(o-aminobenzylidene)-γ-butyrolactone* (*VIII*), m.p. 147–149°, were obtained. The analytical sample, yellow plates from methanol, melted at 149–150°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.47.

Hydrochloride, m.p. 198–199° dec. (from 10% aq. hydrochloric acid).

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.72. Found: Cl, 15.72.

Hydrogenations of VI and VII. The hydrogenations were performed in methanol with platinum oxide as catalyst in a Parr apparatus as described earlier.[2] Since the uptake of hydrogen was rather slow, some heating was applied. In both cases, the reaction product solidified after evaporation of the methanol and was recrystallized from methanol-ether; from the mother liquors a second fraction was obtained.

Four grams of VI yielded thus 2.0 g. of a first fraction, m.p. 73–75°, and 0.3 g. of a second fraction, m.p. 69–73°, totaling 57% of *α-(m-aminobenzyl)-γ-butyrolactone*. The analytical sample melted at 73.5–75°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.53.

Similarly, an 81% yield of *α-(p-aminobenzyl)-γ-butyrolactone* was obtained from VII, m.p. 84.5–85.5° after 4 recrystallizations from methanol and methanol-ether, respectively.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.44.

Amides of VI and VII (*cf. Table I*). The following derivatives have been prepared according to standard procedures[6] in high yields.

Reaction of I with chlorosulfonic acid. A solution containing 20 g. (0.115 mole) of I in 50 cc. of chloroform was prepared and cooled by means of an ice-salt mixture. No attention was paid to the partial reprecipitation of I that occurred. Chlorosulfonic acid (100 cc.) was added gradually with shaking and the mixture was kept in a stoppered bottle for 2 days at room temperature. It was then poured on ice. The resulting precipitate was filtered with suction and washed with large amounts of water until the washings were neutral. The crude product, after drying, weighed 20.5 g. and melted at 160–165° (157° sint.). The two layers of the filtrate were separated, the chloroform layer washed with water, and the solvent evaporated. A greyish residue remained which after putting on a clay plate and recrystallization from a small amount of dioxane gave additional 0.5 g. of material, m.p. 164–165.5°. Total yield: 21.0 g. of crude material (67%). Several recrystallizations from dioxane-ether raised the m.p. of the *α-(p-chlorosulfonylbenzylidene)-γ-butyrolactone* (*VIII*) to 171–172°. Small white leaflets.

Anal. Calcd. for $C_{11}H_9ClO_4S$: C, 48.45; H, 3.33; Cl, 13.00; S, 11.76. Found: C, 48.75; H, 3.43; Cl, 12.79; S, 11.76.

The compound can also, less satisfactorily, be recrystallized from ethyl acetate.

Reaction of VIII with ammonia. Five g. of VIII were kept for 48 hr. at room temperature with 100 cc. of conc. aqueous ammonia. The crystals dissolved slowly. On evaporation in an open porcelain dish (no heat), white crystals precipitated. These were filtered and washed with water, then with methanol and with ether; 0.6 g., m.p. 209–210.5°. The filtrate was evaporated to dryness, the residue treated with 5 cc. of water, filtered, and washed as above; 1.7 g., m.p. 210–211°. Total yield: 2.3 g. (49%). After several recrystallizations from methanol, the analytical sample of *α-(p-sulfonamidobenzylidene)-γ-butyrolactone* (*IX*) melted at 210–211°.

Anal. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.04; H, 4.36; N, 5.33; S, 12.36.

Oxidation of IX by 4 hr. refluxing with an aqueous solution of potassium permanganate gave *p*-sulfonamidobenzoic acid, dec. at 279° after one recrystallization from water (lit.[7]: dec. 280°).

Reaction of VIII with hydrazine. With stirring, 2.6 g. of VIII were added to a mixture of 5 cc. of 85% hydrazine hydrate and 5 cc. of water. The slightly exothermic reaction did not start until the reaction mixture was gently warmed on a water bath (40°) for a few minutes. After cooling with ice-water, a voluminous white precipitate was obtained which was filtered and washed with a small amount of water;

(6) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 103. 226.

(7) C. Palmer, *Am. Chem. J.*, **4**, 164 (1882).

1.5 g., m.p. 134–135° (dec.). Only oily substances which were discarded resulted on evaporation of the filtrate. After three recrystallizations from methanol (considerable loss of material:), *α-(p-hydrazidosulfonylbenzylidene)-γ-butyrolactone* decomposed at 159–160°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.59. Found: C, 49.19;H, 5.23.

Reaction of VIII with aniline. α-(p-Phenylamidosulfonylbenzylidene)-γ-butyrolactone was prepared according to standard procedures[6] and recrystallized from methanol-ether. M.p. 173–173.5° dec.

Anal. Calcd. for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59. Found: C, 61.41, H, 4.85.

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