[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

β-Propiolactone. VI. Reactions with Phenols, Thiophenols and their Salts[1]

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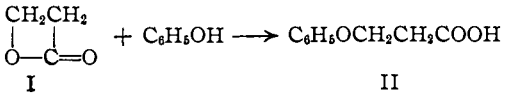
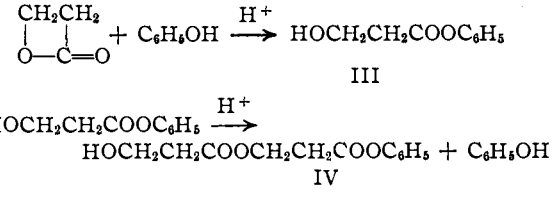
β-Propiolactone (I) and phenol react slowly at room temperature to give β-phenoxypropionic acid (II) and a small amount of a polymer of I. At higher temperatures (above 150°) the polymerization[2] becomes the major reaction. Except for the rate these results are similar to those ob-



I II

served in the reaction between alcohols[3] and I. The polymers were separated from the phenoxy acids by alkaline saponification but it was necessary to avoid an excess of alkali; otherwise the phenoxy acids were cleaved to phenol and hydracrylic acid. Nuclear substituents had marked effects on the yields of β-phenoxypropionic acids (Table II). These products result from ring opening of I at the alkyl–oxygen link.

In the presence of catalytic amounts of sulfuric acid a striking change in the reaction of I with phenol occurs. Phenyl hydracrylate (III) is formed rapidly in high yield. This product must arise from ring opening of I at the acyl–oxygen linkage and it is somewhat surprising that none of II is formed. This appears to be in direct con-



III IV

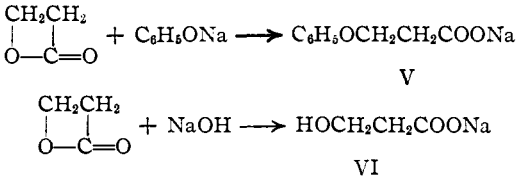
trast to the acid catalyzed reactions of I with alcohols[3] since the hydracrylate does not result from the polymers of I and phenol. The polymerization of I occurs to only a small extent.

The primary product (III) undergoes a self-alcoholysis to give phenyl β-(β-hydroxypropionoxy)-propionate (IV). This reaction continues at the expense of III beyond the few minutes required for complete reaction of I with phenol and it is possible to minimize it only to a small extent by increasing the excess of phenol or by reducing the acid catalyst concentration. The reaction also occurs to a similar extent with III and sulfuric acid in phenol solution.

Nuclear substituents have little or no effect on the yields of phenyl hydracrylates (Table I) as judged by the combined yields of phenyl hydracrylates and phenyl β-(β-hydroxypropionoxy)-propionates. The amount of self-alcoholysis tended to increase with increasing acid strength of the phenol.

The lactone and sodium phenoxide in water solution gave rise to sodium β-phenoxypropionate (V) in low yield. Hydrolysis to sodium hydracrylate (VI) accounts for most of I and variations in time, temperature, concentration and excess sodium phenoxide had only minor effects on the yields of V. In these reactions cleavage of the lactone ring occurred at the alkyl–oxygen link as in the salt reactions.[4]

Using the optimum conditions found for the reaction of I with sodium phenoxide, large variations in the yields of β-phenoxypropionates were observed with nuclear substituted phenols. The



V VI

effects of substituents (Table II) differ from those reported for similar reactions of phenoxides with alkyl halides[5] and ethylene oxide.[6]

β-Propiolactone reacts much more rapidly with thiophenol than it does with phenol and the yield of β-thiophenoxypropionic acid is higher. With aqueous sodium thiophenoxide the yield of sodium β-thiophenoxypropionate is nearly quantitative.

Experimental

Materials.—The phenols were Eastman Kodak Company chemicals or equivalent grade. They were redistilled before use. The β-propiolactone was similar to that described in the first paper[1] of this series.

Reaction of β-Propiolactone with Phenol. A. Non-Catalyzed. β-Phenoxypropionic Acid. (II).—A solution of one mole (72 g.) of β-propiolactone and three moles (282 g.) of phenol was kept at 100° for six hours with stirring. The unreacted lactone and most of the excess phenol was distilled at 20 mm. until the flask temperature was 140°. An ether solution of the distillation residue was extracted with three 300-ml. portions of saturated sodium bicarbonate solution. Evaporation of the extracted ether solution left a small residue of phenol. The combined sodium bicarbonate extract was boiled to hydrolyze the polymer until the volume was 500 ml. On cooling and acidifying with concentrated hydrochloric acid, pure β-phenoxypropionic acid was deposited. After standing overnight, the precipitate was filtered with suction, washed with water and dried at room temperature. The colorless product melted at 94–95°; yield 24.8 g., 14.8%; (18 hr. reaction time; yield 42.5 g., 24%).

(1) Presented in part at the 113th meeting of the American Chemical Society, Chicago, Illinois, April 22, 1948.

(2) Gresham, Jansen and Shaver. THIS JOURNAL, **70**, 998 (1948).

(3) Gresham, Jansen, Shaver, Gregory and Beears, *ibid.*, **70**, 1004 (1948).

(4) Gresham, Jansen, Shaver and Gregory, *ibid.*, **70**, 999 (1948).

(5) Boyd and Marle, *J. Chem. Soc.*, 2117 (1914).

(6) Goldsworthy, *ibid.*, 1234 (1926).

TABLE I

PHENYL HYDRACRYLATES

Phenol substituent	Yield,[a] %	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Sapon. equiv.[b] Calcd.	Found	Carbon, %[c] Calcd.	Found	Hydrogen, % Calcd.	Found
H	39.8	90–92	0.2	1.5200	1.1596	166.0	166.5	65.06	65.09	6.07	5.94
o-CH_3	37.8	83–84	.1	1.5170	1.1307	180.0	182	66.67	66.17	6.72	6.74
m-CH_3	41.3	84–85	.1	1.5178	1.1300	180.0	182	66.67	66.13	6.72	6.78
p-CH_3[d]	46.5	84–85	.1	1.5170	1.1315	180.0	182	66.67	66.17	6.72	6.71
o-Cl	22.4	80–82	.1	1.5283	1.2620	200.5	197	53.87	55.37	4.52	4.91
p-Cl	32.7	93–94	.1	1.5332	1.2860	200.5	208	53.87	53.54	4.52	4.63
o-OCH_3	19.0	101–105	.05	1.5220	1.1750	196.0	188	61.21	62.44	6.17	6.46
p-OCH_3[a]	35.1	104–105	.05	....	....	196.0	190	61.21	60.73	6.17	6.15

[a] Recrystallized from carbon tetrachloride, m. p. 27–28°. [b] Saponification equivalents for some compounds are in poor agreement with that calculated due to instability and interference of colored decomposition products in determining end-points. [c] Analysis for carbon is in poor agreement with that calculated, except for the unsubstituted ester, due to impurities which appear to be mostly the phenyl β-(β-hydroxypropionoxy)-propionates. Repeated attempts to purify these compounds were not successful due to the great ease with which they underwent a self-alcoholysis under distillation conditions. [d] M. p. 42–43°. [e] The yield of polymer-free residue assumed to be dimeric self-alcoholysis products were: *o*-CH_3, 31.8; *m*-CH_3, 34.2; *p*-CH_3, 38.2; *o*-OCH_3, 38.0; *p*-OCH_3, 44.8; *o*-Cl, 59.4; *p*-Cl, 51.4.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07; neut. equiv., 166. Found: C, 65.13; H, 6.14; neut. equiv., 169.5.

Stability of β-Phenoxypropionic Acid in Alkaline Solution.—A suspension of 10 g. (0.06 mole) of phenoxypropionic acid (m.p. 94–95°) in 200 ml. of water containing 2.48 g. (0.06 mole) of 97% sodium hydroxide was boiled under a reflux condenser for thirty minutes. Solution was complete at the boiling point. The solution was cooled, acidified with concentrated hydrochloric acid and after standing three hours was filtered from the β-phenoxypropionic acid. The solid acid was washed with water and dried at room temperature; wt. 9.5 g.; 95% recovery. The loss is mostly due to water solubility.

A similar experiment but using 4.96 g. (0.12 mole) of 97% sodium hydroxide gave a recovery of 7 g. (70%) of β-phenoxypropionic acid. Continued boiling of a similar solution for five hours resulted in the recovery of 0.5 g. (5%) of the phenoxy acid and 3.5 g. of phenol (62%).

B. **Acid Catalyzed. Phenyl Hydracrylate (III) and Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).**—β-Propiolactone (one mole, 72 g.) was added over a period of fifteen minutes to phenol (3 moles, 282 g.) containing 0.5 g. of sulfuric acid. The reaction was stirred and held at 46–50° by means of an ice-bath. After twenty minutes the catalyst was neutralized with an equivalent of sodium methoxide and most of the excess phenol removed at reduced pressure until the flask temperature was 100° at 1 mm. The residue was taken up in 400 ml. of ether and the solution filtered from a small amount (7 g.) of polymer, extracted with 100 ml. of saturated sodium bicarbonate, washed twice with water, dried over anhydrous sodium sulfate and evaporated. The residue was distilled at 0.2 mm. and phenyl hydracrylate (66 g., 39.8%) was collected as a colorless oil at 90–92° leaving a residue (88 g., 37%) of phenyl β-(β-hydroxypropionoxy)-propionate. Acidification of the sodium bicarbonate extract with concentrated hydrochloric acid gave no insoluble material, showing no phenoxy acid was formed. Physical and analytical data are shown in Table I.

Increase in time of reaction to six hours gave a reduction (18%) of III and an increase (15%) of IV. Doubling the number of moles of phenol in the reaction mixture gave an increase (10%) of III and a decrease (4%) of IV.

Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).—Distillation of combined residues (270 g.) from reactions carried out as in B above in a short-path still at 0.001 mm. gave 226 g. of product which was collected at a film temperature of 90–97°; $n^{20}D$ 1.5100; d^{20}_4 1.2036.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88; sapon. equiv., 119; acetyl value, 7.2; mol. wt., 238. Found: C, 61.13; H, 6.13; sapon. equiv., 122; acetyl value, 7.3; mol. wt. (cryoscopic in benzene), 230. It appears from these data that the product contained phenyl hydracrylate as an impurity.

The phenyl urethan derivative was recrystallized from chloroform from which it separated as small prisms; m. p. 97–98°.

Anal. Calcd. for $C_{19}H_{19}O_6N$: N, 3.92. Found: N, 3.85.

Self-Alcoholysis of Phenyl Hydracrylate. Phenyl β-(β-Hydroxypropionoxy)-propionate (IV).—A solution of 166 g. (1 mole) of phenyl hydracrylate, 1 g. of sulfuric acid, and 470 g. (5 moles) of phenol was stirred and held at 46° for six hours. The reaction mixture, after treatment as in B above, gave 488 g. phenol, 70 g. (42% recovery) of phenyl hydracrylate, and 44 g. (37%) of phenyl β-(β-hydroxypropionoxy)-propionate, $n^{20}D$, 1.5070. The phenyl urethan derivative melted at 97–98° after recrystallization from chloroform. The mixture melting point with the phenyl urethan above was not depressed.

The Reaction of β-Propiolactone (I) with Sodium Phenoxides. General Procedure.—β-Propiolactone (0.5 mole) was added over an eight-minute period to a solution of 0.5 mole of sodium hydroxide and 0.5 mole of the phenol in 200 ml. of water at 100° with stirring. The heat of reaction held the temperature during the addition of I and heat was then supplied to maintain the temperature for a total time of fifteen minutes. The solution was cooled to 30° with an ice-bath, and acidified with 50 ml. of concentrated hydrochloric acid. The colorless oil which separated was extracted with three 200-ml. portions of ether. The combined ether extract was shaken twice with 300-ml. portions of saturated sodium bicarbonate. The solids, which precipitated on acidification of the alkaline solution, were filtered, washed with water, dried and recrystallized from benzene–hexane. The yields, physical and analytical data for the β-phenoxypropionic acids are given in Table II.

β-Thiophenoxypropionic Acid.[7]—One mole (72 g.) of I was added dropwise (fifteen minutes) to 110 g. (1 mole) of thiophenol at 100–110° with stirring. After an additional hour the mixture was distilled at 5 mm. to give a crude fraction, b.p. 145–175°, of β-thiophenoxypropionic acid which solidified on cooling. This was crystallized from ether–petroleum ether. It formed small flat plates, m.p. 57–58°; yield 89 g. (49%).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 59.21; H, 5.56; S, 17.68.

Sodium β-Thiophenoxypropionate.—One mole (72 g.) of I was added slowly to a stirred mixture of 41.7 g. (1 mole) of 97% sodium hydroxide and 110 g. (1 mole) of thiophenol in 200 ml. of water. The temperature was held at 10° during the addition and at room temperature

(7) Krollpfeiffer and Schultze, *Ber.*, **56B**, 1821 (1923).

TABLE II

$RR'C_6H_3OCH_2CH_2COOH$

RR'	Yield, % Phenol[g]	Yield, % Sodium phenoxide[a]	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H	14.8	18.1[b]	94–95	65.06	65.13	6.07	6.14
o-CHO	..	32.0	113–114	61.85	61.87	5.19	5.27
p-CHO	..	54.8	127–128	61.85	61.84	5.19	5.24
o-NO_2[c]	0.2	32.2	117–118	51.19	51.36	4.29	4.37
m-NO_2[c]	3.7	45.1	111–112	51.19	51.33	4.29	4.38
p-NO_2[c]	0.2	51.2	114–115	51.19	51.28	4.29	4.36
o-Cl[d]	0.4	49.9	112–113	53.87	53.99	4.52	4.55
m-Cl[d]	1.5	36.2	82–83	53.87	53.95	4.52	4.55
p-Cl[d]	4.5	28.9	134–135	53.87	54.00	4.52	4.53
2,4-di-Cl	..	51.4	91–92	45.98	46.11	3.43	3.45
o-Br[e]	..	52.2	109–110	44.10	44.15	3.70	3.72
p-Br[e]	..	29.9	142–143	44.10	44.17	3.70	3.76
o-OCH_3	0.8	20.2	127–128	61.21	61.38	6.17	6.18
m-OCH_3	3.9	24.0	81–82	61.21	61.22	6.17	6.13
p-OCH_3	11.6	11.5	106–107	61.21	61.35	6.17	6.16
o-C_6H_5	..	12.5	93–94	74.36	74.47	5.83	5.95
m-C_6H_5	..	19.0	136–137	74.36	74.42	5.83	5.89
p-C_6H_5	..	3.0	168–169	74.36	74.46	5.83	5.89
o-CH_3[f]	3.3	12.9	91–92	66.65	66.69	6.71	6.73
m-CH_3[f]	4.4	16.8	104–105	66.65	66.72	6.71	6.76
p-CH_3[f]	14.4	14.7	144–145	66.65	66.64	6.71	6.74
3,5-di-CH_3	..	16.2	86–87	68.02	68.06	7.27	7.25
o-C_6H_{11}	..	3.4	89–90	72.55	72.59	8.12	8.16
p-C_6H_{11}	..	11.6	115–116	72.55	72.67	8.12	8.12
p-*t*-C_4H_9	..	12.9	93–94	70.24	70.26	8.16	8.14
p-$CH_2C_6H_5$	..	14.4	133–134	74.98	75.07	6.29	6.31
p-$OCH_2C_6H_5$	..	13.1	147–148	70.57	70.52	5.92	5.89
2-OCH_3-4-C_3H_5	..	20.8	97–98	66.08	66.08	6.83	6.79
2-*i*-C_3H_7-5-CH_3	..	4.4	93–94	70.24	70.28	8.16	8.15

[a] % yields are for purified products. [b] Less than 1 g. of β-phenoxypropionic acid was lost due to water solubility when it was carried through the work-up procedure. Other reaction conditions and results were: The yield was not changed with increased time. The yield was lower (7.8%) at 50° in one hour and with less time it was still lower. Greater dilution (300 ml. water) gave decreased yield (16.9%). Increase in the ratio of sodium phenoxide to lactone (2:1) did not change the yield. [c] *Anal.* Calcd. for $C_9H_9O_5N$: N, 6.63. Found: N, *o*-, 6.62; *m*-, 6.57; *p*-, 6.59. [d] *Anal.* Calcd. for $C_9H_9O_3Cl$: Cl, 17.67. Found: Cl, *o*-, 17.60; *m*-, 17.67; *p*-, 17.59. [e] *Anal.* Calcd. for $C_9H_9O_3Br$: Br, 32.61. Found: Br, *o*-, 32.58; *p*-, 32.73. [f] Sodium phenoxide reactions at lower temperatures (30°) for one hour gave the following % yields with the cresols: *o*-, 5.0%; *m*-, 7.0%; *p*-, 5.8%. Although the yields of β-cresoxypropionic acids are lower, the ratio of yields is similar to that at 100°. [g] A above; six hours, 100°.

for an additional hour. The crystals which separated after acidification with 100 ml. of concentrated hydrochloric acid were filtered, washed with water, dried and recrystallized from ether–petroleum ether, m.p. 57–58°; yield, 166 g. (91%). The mixture melting point with the above sample was not depressed.

Summary

β-Propiolactone reacts with phenol to give β-phenoxypropionic acid. In the presence of acid catalysts phenyl hydracrylate is formed. It reacts with sodium phenoxide to give sodium β-phenoxypropionate. The effects of nuclear substituents on these reactions are described. Thiophenol and its sodium salt react more rapidly but give similar products in higher yields.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Carbon Alkylations with 1-Methylgramine and its Methiodide[1]

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In previous papers,[3] alkylations of sodium cyanide and acetamidocyanoacetic ester with the methiodide (I) of 1-methylgramine (II) have been described. These alkylations, which proceed much more readily than corresponding reactions of quaternary salts of benzyldimethylamine,[4,5] undoubtedly occur by a substitution mechanism. However, their existence does not constitute proof that the Mannich base itself (II), as well as the quaternary ammonium salt (I), is capable of reacting by any mechanism other than the elimination-addition scheme[3a] proposed for gramine.

Further experiments have now been undertaken to elucidate this point. The alkylation reactions of the methiodide (I) have been extended to ethyl malonate, ethyl cyanoacetate, ethyl cyanomalonate, and tricarbethoxymethane, all of which were alkylated in the form of the sodium salts. The intermediate esters were not isolated but were hydrolyzed to the substituted malonic acid (III). Decarboxylation of this acid, either thermally or in refluxing pyridine,[6] yielded 1-methylindole-3(β)-propionic acid (IV). In view of the allylic rearrangement observed in the alkylation of sodium cyanide with the salt (I),[3b] an unequivocal proof of the structure of IV was considered necessary. The structure was proved by a Curtius degradation *via* the methyl ester, hydrazide, and azide of IV; the azide was subjected to rearrangement in dry xylene, and the resulting isocyanate was converted directly into N-phthalyl-1-methyltryptamine by baking it with phthalic anhydride. The phthalimide thus obtained was identical with an authentic specimen. The possibility still exists that in

(1) Presented in part before the Organic Division of the American Chemical Society at the Chicago meeting in April, 1948.

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(3) (a) Snyder and Eliel, THIS JOURNAL, **70**, 1703 (1948); (b) **70**, 1857 (1948); (c) **70**, 3855 (1948).

(4) von Meyer, *Abhandl. math.-phys. Klasse sächs. Akad. Wiss.*, **31**, 179 (1908); *Chem. Zentr.*, **80**, II, 1800 (1909).

(5) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).

(6) Grigsby, Hind, Chanley and Westheimer, *ibid.*, **64**, 2609 (1942).