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

2-Phenylcyclobutanecarboxylic Acid[1]

ALFRED BURGER AND ALFRED HOFSTETTER

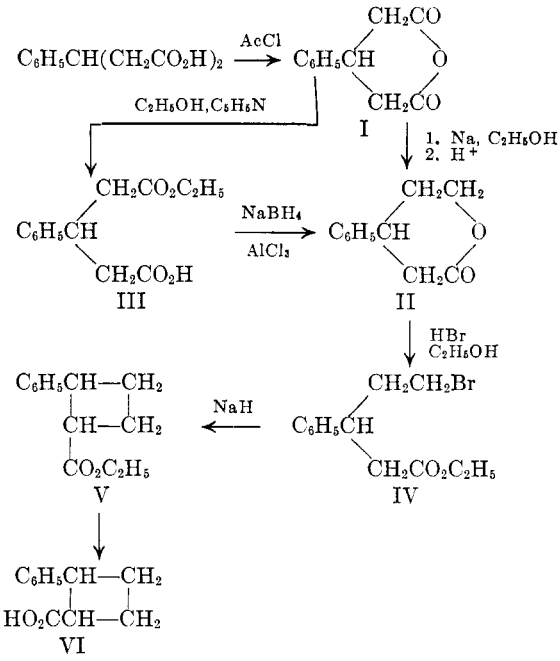
Received March 18, 1959

A six- to nine-step synthesis is recorded of 2-phenylcyclobutane-1,1-dicarboxylic acid and 2-phenylcyclobutanecarboxylic acid, starting from 3-phenylglutaric acid.

2-Phenylcyclobutanecarboxylic acid was needed as an intermediate in this laboratory. Its synthesis is described in this article.

3-Phenylglutaric acid[2] was converted to its anhydride (I) by the action of acetyl chloride instead of ketene as reported in the literature.[3] The anhydride (I) was reduced to 3-phenyl-5-valerolactone (II) by the general directions of Rydon[4] using a large excess of sodium and absolute ethanol in a vigorously conducted reaction. The structure of this lactone was supported by its infrared spectrum and by preparing from it (a) silver 5-hydroxy-3-phenylvalerate and (b) 5-hydroxy-3-phenylvaleramide with liquid ammonia under pressure. Finally, the lactone (II) could also be prepared by treating 3-phenylglutaric anhydride (I) with methanol in pyridine, and reducing the sodium salt of the resulting hydrogen methyl 3-phenylglutarate (III) with sodium borohydride in 1,5 dimethoxy-3-oxapentane (Diglyme) by the general method of Brown and Subba Rao.[5] Sodium and ethanol did not reduce the ester (III).

When the lactone (II) was treated with dry ethanolic hydrogen bromide, ethyl 5-bromo-3-phenylvalerate (IV) was obtained in excellent yield. This oily bromo ester was characterized by conversion to (a) the solid ethyl 5-iodo-3-phenylvalerate using sodium iodide in acetone solution and to (b) 3-phenyl-5-valerolactam by heating with ammonia in benzene solution. Boiling the bromo ester (IV) with sodium hydride in xylene yielded a low percentage of an oily halogen-free ester (V) which was hydrolyzed to an oily acid (VI). This material did not decolorize a bromine solution in chloroform. Although all attempts to crystallize the acid (VI) failed, even after extensive chromatography, two crystalline derivatives could be prepared which had the elementary composition expected of the respective derivatives of 2-phenylcyclobutanecarboxylic acid. The *S*-benzylisothiuronium salt melted at 150–151°, and the *p*-toluidide, prepared by way of the acid chloride and purified by chromatography, had a melting point 166–167°.



The *S*-benzylisothiuronium salt of authentic 3-phenylvaleric acid[6] was prepared for comparison. It melted at 161.5–162°; a mixture of this salt and that of acid VI melted at 146–147°.

The very low yield in the ring closure of IV to V made it necessary to increase the activity of the carbanion of IV. This was achieved by carbethoxylating the lactone (II) by means of ethyl oxalate in the presence of sodium ethoxide. When a large excess of ethyl oxalate was employed and the ethanol formed was removed continually,[7] 2-carbethoxy-3-phenyl-5-valerolactone (VIII) was formed in good yield after decarbonylating the intermediate α-keto ester (VII) by heating in a vacuum at 160–170°.

(1) This investigation was supported by Grant B-1445 from the National Institute of Neurological Diseases and Blindness, 1957–58.

(2) J. H. Paden and H. Adkins, *J. Am. Chem. Soc.*, **58**, 2498 (1907).

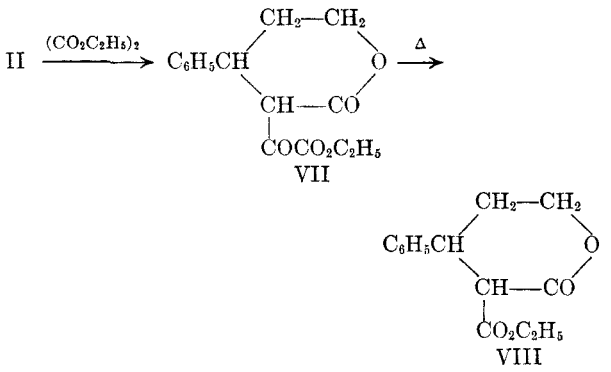
(3) A. Neuberger, *Biochem. J.*, **32**, 1452 (1938).

(4) H. N. Rydon, *J. Chem. Soc.*, 595 (1936).

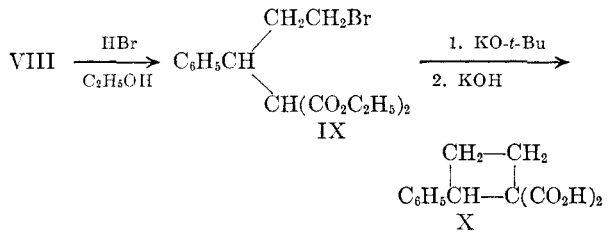
(5) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955); **78**, 2582 (1956).

(6) N. Maxim, *Ann. Chim. (France)*, (10), **9**, 55 (1928); *Chem. Zentr.*, 1928 I, 1961.

(7) D. E. Floyd and S. E. Miller, *Org. Syntheses*, **34**, 13 (1954).



An absolute ethanolic solution of the lactone ester (VIII) was saturated with dry hydrogen bromide, and diethyl (3-bromo-1-phenylpropyl)-malonate (IX) was isolated. Without purification, this bromo ester was cyclized with potassium *t*-butoxide since this strongly basic agent is sufficiently sterically hindered so that its own reaction with the carbon carrying the bromine atom of IX was minimized. A similar condensing agent (isobutoxide ion) had been used in other cyclobutane ring closures.[8] After a total of 108 hr. of refluxing, the resulting diethyl 2-phenylcyclobutane-1,1-dicarboxylate was hydrolyzed, and 2-phenylcyclobutane-1,1-dicarboxylic acid (X) was isolated in a yield of 26%. A chloroform solution of X did not decolorize bromine within 30 min.



The structure of X was supported (a) by decarboxylation to an oily acid whose *S*-benzylisothiuronium salt did not depress the melting point of the corresponding salt of the acid (VI). Moreover (b), the general features of a nuclear magnetic resonance spectrum of X[9] were consistent with a CH group which is attached to a CH_2 group in a fixed-ring situation. This CH_2 group had only a slight chemical shift from an adjacent methylene which produced many lines due to the various spin couplings and second-order effects. The structure of (2-phenylpropyl)malonic acid was ruled out due to the lack of any feature of the NMR spectrum resembling those of an ethyl group.

Attempts to decarboxylate the acid (VI) to phenylcyclobutane under a variety of conditions resulted, in our hands, in extensive decomposition.

(8) A. Campbell and H. N. Rydon, *J. Chem. Soc.*, 3002 (1953).

(9) This measurement was carried out by Varian Associates, Palo Alto, Calif., and interpreted by Dr. LeRoy Johnson.

EXPERIMENTAL

All melting points are corrected. Microanalyses by Mrs. Margaret Logan.

2-Phenylglutaric anhydride (I). Instead of preparing this material with ketene,[3] the general directions of Fieser and Martin[10] were used. A mixture of 416 g. (2 moles) of 2-phenylglutaric acid and 400 g. of acetyl chloride was refluxed for 3 hr. and allowed to crystallize overnight. The crystalline anhydride was filtered, washed with benzene which contained a little chloroform, and finally was washed with petroleum ether. The combined mother liquors were concentrated and deposited another crop of crystals. The total yield was 324 g. (82%). Recrystallization from benzene gave colorless crystals, m.p. 103–104°. The literature[3] quotes m.p. 101°.

Ethyl (and methyl) hydrogen 3-phenylglutarate (III). A solution, 30 g. of β-phenylglutaric anhydride in 30 ml. of absolute ethanol and 100 ml. of dry pyridine, was refluxed for 2 hr., poured into 300 ml. of ether, and the mixture was extracted with four 150-ml. portions of 2*N* hydrochloric acid. The ether solution was dried, evaporated, and the colorless residue digested with petroleum ether. It crystallized readily. The yield was 32 g. (86%), m.p. 59–60° after recrystallization from ether–petroleum ether.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.82. Found: C, 65.30; H, 6.88.

The corresponding methyl ester, prepared analogously, melted at 93–95°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34. Found: C, 64.49; H, 6.50.

A solution of 23.6 g. of ethyl hydrogen 3-phenylglutarate in 40 ml. of absolute ethanol was neutralized with a sodium ethoxide solution prepared from 2.3 g. (0.1 mole) of sodium and 100 ml. of absolute ethanol. The *sodium ethyl 3-phenylglutarate* was precipitated with ether and petroleum ether, filtered, and dried in a desiccator. The yield was 16 g. (62%).

3-Phenylglutarmonoamide. A solution of 20 g. of 3-phenylglutaric anhydride in 100 ml. of 28% ammonium hydroxide was heated to boiling for 10 min. Acidification precipitated crystals which, after recrystallization from ethanol, melted at 166–167°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.71; H, 6.32. Found: C, 63.72; H, 6.15.

3-Phenylglutarimide. When the ammoniacal solution from the preceding experiment was evaporated and the residue distilled at 0.1 mm. pressure, the solid distillate could be recrystallized from ethanol. It melted at 174.5–175.5°. The yield was 90%.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.87. Found: C, 69.78; H, 5.89.

3-Phenyl-5-valerolactone (II). (a) Working according to general directions for the reduction of anhydrides to lactones,[4] a 3-l. three necked flask was equipped with a long highly efficient condenser and a dropping funnel. A mixture of 200 g. of 3-phenylglutaric anhydride and 200 g. of sodium lumps was placed in the flask, and 300 ml. of absolute ethanol was added until a vigorous reaction started. More ethanol was added with occasional shaking at such a rate that the reaction was kept as vigorous as possible for 10–15 min. The mixture was then heated to reflux, and 2 l. of ethanol was added over a 3-hr. period. After refluxing overnight, some unreacted sodium was destroyed by careful addition of 80% methanol, water was added until a clear solution resulted, and the bulk of the solvents was removed in a rotating evaporator. The residue was dissolved in 500 ml. of water and made strongly acid. A brown oily mixture of lactone and hydroxy acid precipitated. It was heated for 1 hr. on a steam bath, the oil was extracted into ether, and the combined ether extracts were washed with several

(10) L. F. Fieser and E. L. Martin, *Org. Syntheses*, **Coll. Vol. II**, 560 (1943).

250-ml. portions of saturated sodium bicarbonate solution in order to remove unchanged phenylglutaric acid. After drying and evaporating the ether, the residual oil was distilled at 160–163° (1.2 mm.), 167–170° (2.5 mm.). The yield was 28%.

The oil became more viscous on standing, but viscosity decreased on warming. The substance showed a strong absorption in the infrared at 1718 cm.$^{-1}$, indicating an ester or 6-membered lactone grouping.

(b) Since cyclic anhydrides can be reduced to lactones with sodium borohydride,[5] a mixture of 200 g. of 1,5-dimethoxy-3-oxapentane (Diglyme), previously distilled over calcium hydride, and 17.4 g. (4.6 moles) of sodium borohydride was stirred at 40°, and a suspension of 59 g. (0.23 mole) of sodium ethyl 3-phenylglutarate in 200 ml. of Diglyme was added. Then a solution of 10.5 g. (0.08 mole) of anhydrous aluminum chloride in 100 ml. of Diglyme was added at such a rate that the temperature rose to 55°. After heating at 60° for 15 hr. under reflux, the mixture was cooled in ice, and excess borohydride was destroyed carefully with ice water. The solution was made alkaline with 10% sodium hydroxide solution, evaporated under reduced pressure at 90°, the dry residue was dissolved in water and heated with strong acid for 1 hr. Extraction with ether followed by working up as under (a), yielded 15.7 g. (39%) of the crude lactone.

A solution of 530 mg. of the lactone in 6 ml. of 0.5*N* ethanolic sodium hydroxide solution was evaporated, the residue dissolved in water, and mixed with a concentrated aqueous solution of 510 mg. of silver nitrate. After filtering an initial precipitate, the filtrate was concentrated to crystallization, and the crystalline silver 5-hydroxy-3-phenylvalerate (IV) was recrystallized three times from hot water. The salt decomposed at 150°.

Anal. Calcd. for $C_{11}H_{13}AgO_3$: C, 43.88; H, 4.35; Ag, 35.83. Found: C, 43.32; H, 4.28; Ag, 36.76.

5-Hydroxy-3-phenylvaleramide. A mixture of 30 g. of 3-phenyl-5-valerolactone and 150 ml. of liquid ammonia was heated in a steel autoclave at 100° for 4 hr. After cooling and evaporating excess ammonia, the oil was treated with 50 ml. of chloroform, and some insoluble material was filtered. Crystallization occurred on standing. After four recrystallizations from chloroform the compound melted at 97.5–98°. The yield was 8 g. (25%). The substance exhibited infrared absorption bands at 3333 cm.$^{-1}$ (indicating hydroxyl) and 1639 cm.$^{-1}$ (indicating amide carbonyl).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82. Found: C, 67.84; H, 7.93.

Ethyl 5-bromo-3-phenylvalerate (IV). Working according to general directions of Rydon,[11] a solution of 106 g. of 3-phenyl-5-valerolactone in 500 ml. of absolute ethanol was saturated with dry hydrogen bromide at 0°. The solution was allowed to stand overnight, poured into 1 kg. of ice, and extracted repeatedly with ether. The ether extracts were washed with water, bicarbonate solution, and again with water, dried, and distilled. The oily residue distilled as a colorless oil, b.p. 139–141° (0.6 mm.), n_D^{27} 1.5194. The yield was 160 g. (95%). The compound was characterized as the corresponding iodo and lactam derivatives.

Ethyl 5-iodo-3-phenylvalerate. A solution of 8 g. of the bromo ester (IV) and 15 g. of sodium iodide in 100 ml. of acetone was allowed to stand overnight, the precipitated sodium bromide was filtered, and the filtrate evaporated. The residue crystallized from pentane in a yield of 7 g. (75%). The colorless product melted at 36–37°.

Anal. Calcd. for $C_{13}H_{17}IO_2$: C, 47.00; H, 5.16. Found: C, 46.34; H, 4.92.

3-Phenyl-5-valerolactam. A mixture of 2 g. of ethyl 5-bromo-3-phenylvalerate and an excess of liquid ammonia in 10 ml. of benzene was heated in a sealed tube on a steam bath for 15 hr. The two layers of the reaction mixture were dissolved in 20 ml. of ethanol, ammonium bromide was filtered, and the filtrate evaporated. The oily residue was taken up in water and crystallized on scratching. It was recrystallized three times from dilute ethanol, m.p. 135–137°. The yield was 1.3 g. (100%).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.47; H, 7.35.

2-Carbethoxy-3-phenyl-5-valerolactone (VIII). In a 2-l. three necked flask equipped with thermometer, condenser, and stirrer was prepared a solution of sodium ethoxide from 11.5 g. (0.5 mole) of sodium and 250 ml. of absolute ethanol. The condenser was then set for distillation, and about 120 ml. of ethanol was removed under reduced pressure, carefully protecting the apparatus from moisture. A mixture of 88 g. (0.5 mole) of 3-phenyl-5-valerolactone and 292 g. (2 moles) of diethyl oxalate was added; the color of the solution turned dark red. Over a period of *ca.* 3 hr., and allowing the temperature to rise to 60°, all of the ethanol was removed under vacuum with stirring. The temperature was now raised to 100° in order to remove excess ethyl oxalate, 33 ml. of glacial acetic acid and then 500 ml. of water were added slowly with stirring, and after 5 min. the layers were separated. The aqueous solution was extracted with chloroform, this was added to the organic layer, and after drying the solvents were removed from the combined extracts. The dark brown oily keto ester (VII) was heated at 1 mm. and 170° for 5 to 8 hr. until gas evolution had virtually subsided, and the residue was fractionated. The fraction boiling at 162–172° (0.4–0.6 mm.) was collected, n_D^{27} 1.5221; the yield was 46 g. (37%).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.56. Found: C, 67.55; H, 6.64.

(3-Hydroxy-1-phenylpropyl)malondiamide. A sample of 2-carbethoxy-3-phenyl-5-valerolactone, dissolved in saturated absolute ethanolic ammonia was allowed to stand at 0° for several days until a crystalline solid precipitated. Recrystallization from ethanol furnished a colorless material, m.p. 175–177°.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.86. Found: C, 60.45; H, 6.99; N, 11.31.

Diethyl (3-bromo-1-phenylpropyl) malonate (IX). A solution of 46 g. (0.185 mole) of 2-carbethoxy-3-phenyl-5-valerolactone in 200 ml. of absolute ethanol was saturated with dry hydrogen bromide at 0° with stirring and allowed to stand at 0° overnight. It was poured into 800 ml. of ice water. The mixture was thoroughly extracted with ether, the ether solution washed with ice cold water and bicarbonate solution, dried over anhydrous sodium sulfate, and evaporated. The residual oil was used in the next step without further purification. The yield was 35 g. (53%).

2-Phenylcyclobutane-1,1-dicarboxylic acid (X). In a flask equipped with stirrer, condenser, dropping funnel, and gas inlet tube and carefully protected from moisture at all points, a solution of potassium-*t*-butoxide was prepared from 7 g. of potassium and 800 ml. of *t*-butyl alcohol (distilled over calcium hydride) in an atmosphere of nitrogen. A solution of 20 g. of diethyl (3-bromo-1-phenylpropyl)-malonate in 150 ml. of dry *t*-butyl alcohol was added gradually, with stirring, over a period of 48 hr. by the dilution principle. After completion of the addition, the mixture was refluxed for another 60 hr., then diluted with 200 ml. of 10% potassium hydroxide solution, and refluxed another 8 hr. Most of the solvents were removed under reduced pressure, the brown residue was diluted with 200 ml. of water, acidified, and extracted with ether. The acidic material was re-extracted from the ether into bicarbonate solution, this was cleared with charcoal, re-acidified, and again extracted with ether. The dried ether extract left, on evaporation, 9 g. of a brown oil which on standing in petroleum ether deposited 2.5 g. (26%) of crystals, m.p. 168–170°. Recrystallization from chloroform raised the melting point to 173.5–175.5°.

Anal. Calcd. for $C_{12}O_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.07; H, 5.38.

(11) H. N. Rydon, *J. Chem. Soc.*, 1341 (1937).

2-Phenylcyclobutane-1-carboxylic acid (VI). (a) To a stirred and refluxing slurry of 5 g. of sodium hydride in 200 ml. of dry xylene was added, over a period of 10 hr., a solution of 6 g. of ethyl 5-bromo-3-phenylvalerate (IV) in 100 ml. of xylene. After refluxing overnight, excess sodium hydride was destroyed with ethanol and then with water. The solvents were concentrated to a small volume, and the residual oil was refluxed with a solution of 2 g. of potassium hydroxide in 50 ml. of 75% ethanol for 4 hr. The solution was concentrated, diluted with 50 ml. of water, acidified, and extracted with ether. The oily acidic residue from the dried ether extracts weighed 1 g. It dissolved in bicarbonate solution and yielded, with benzylthiourea, an *S*-benzylsothiuronium salt, m.p. 150–151°, after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{22}N_2O_2S$: C, 66.62; H, 6.48. Found: C, 66.82; H, 6.58.

(b) A small amount of 2-phenylcyclobutane-1,1-dicarboxylic acid was heated in a molecular still at 160–180° (1 mm.) until no further gas evolution was visible, and the oily residue was distilled onto a cold-finger. It gave an *S*-benzylisothiuronium salt, m.p. 144–145°. A mixture of melting point with the salt from method (a) was 147–148°.

The *p-toluidide* was prepared by allowing 0.2 g. of the oily acid to stand in 10 ml. of benzene containing 2 ml. of thionyl chloride at 26° for 3 days, removing the solvent, and mixing the residue with a solution of 0.3 g. of *p*-toluidine in 10 ml. of benzene. Precipitated toluidine hydrochloride was filtered, the benzene solution was washed with 2*N* hydrochloric acid and bicarbonate solution, dried, and evaporated. The crystalline amide (75 mg.) melted at 159–161°. After several passages through aluminum oxide columns (10 cm. × 18 mm.) in benzene-petroleum ether solutions, the melting point became constant at 166–167°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.66; H, 7.36.

3-Phenylvaleric acid. This material was prepared from diethyl cinnamamide and ethylmagnesium bromide followed by acid hydrolysis as described by Maxim.[6] Its *S*-benzylisothiuronium salt melted at 161.5–162° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S$: C, 66.24; H, 7.03. Found: C, 66.42; H, 6.86.

A mixture melting point with *S*-benzylisothiuronium 2-phenylcyclobutanecarboxylate obtained by method (a) above (m.p. 150–151°) was 146.5–147°.

Acknowledgment. Valuable discussions concerning the synthetic procedure were held with Dr. C. L. Zirkle of Smith Kline and French Laboratories. Dr. Raymond Bennett carried out the final purification of 2-phenylcyclobutane-1,1-dicarboxylic acid.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

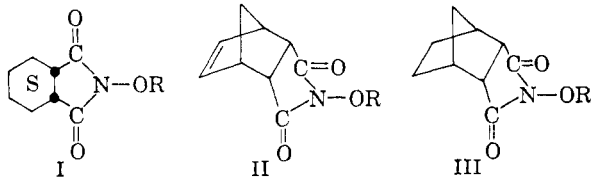
Stereospecific Lossen Rearrangements

LUDWIG BAUER AND STANLEY V. MIARKA

Received March 23, 1959

The Lossen rearrangement of several *cis*-*N*-phenylsulfonyloxy-1,2-cyclohexanedicarboximides yielded corresponding 2-aminocyclohexanecarboxylic acids whose stereochemistry remained *cis*. This method presents a facile route to 2-aminocyclohexanecarboxylic acids of known stereochemistry.

It had been shown previously that the Hofmann, Curtius, and Lossen and Wolff rearrangements at an optically active carbon atom proceeded without inversion.[1] This study was undertaken to test the stereospecificity of the Lossen rearrangement in *cis*-*N*-hydroxycyclohexanedicarboximides. For this purpose, *N*- hydroxy imides of type I, II, and III [R = H] were chosen as their stereochemistry was known.



I II III

These hydroxamic acids were synthesized from the corresponding known anhydrides and aqueous hydroxylamine as described for the preparation of *N*-hydroxyphthalimide.[2] If the hydroxamic acid was not completely precipitated, it was isolated by chloroform extraction and thus excellent yields were obtained. The hydroxamic acids were colorless and afforded colorless anions—in striking contrast to the highly colored anions derived from aromatic *N*-hydroxy imides.[3]

Acylation of the above hydroxamic acids with benzenesulfonyl chloride either in cold aqueous sodium carbonate solution or in chloroform solution in the presence of triethylamine gave the corresponding derivatives [I, II, and III; R = $SO_2C_6H_5$] which were used for this study. It was found that the benzenesulfonyl derivatives readily dis-

(1) (a) L. W. Jones and E. S. Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926). (b) E. S. Wallis and S. C. Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931). (c) E. S. Wallis and R. D. Dripps, *J. Am. Chem. Soc.*, **55**, 1701 (1933). (d) E. S. Wallis and W. W. Moyer, *J. Am. Chem. Soc.*, **55**, 2787 (1933). (e) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939). (f) J. Kenyon and D. P. Young, *J. Chem. Soc.*, 263 (1941). (g) J. F. Lane and E. S. Wallis, *J. Am. Chem. Soc.*, **63**, 1674 (1941).

(2) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

(3) L. Bauer and S. V. Miarka, *J. Am. Chem. Soc.*, **79**, 1983 (1957).