

EXPERIMENTAL

(All m.p.'s are uncorrected.)

Tetraethyl 1,5-diphenyl-1,1,5,5-pentanetetracarboxylate (I). A two-liter, three-necked, round-bottomed flask was fitted with a reflux condenser with calcium chloride drying tube attached, a mechanical stirrer with a strong variable motor, and nitrogen inlet tube. The system was dried by heating with a free flame while passing dry nitrogen through it, and then flushing with nitrogen for about 2 hr. Anhydrous *t*-butanol (750 ml.), previously dried by refluxing over sodium and distilling, was introduced into the flask, followed by the careful addition, in portions, of freshly-cut potassium metal (49 g., 1.25 moles). The mixture was heated under gentle reflux for about 2 hr., was allowed to cool, and redistilled diethyl phenylmalonate (295 g., 1.25 moles) was added in a steady stream with stirring. When the addition was about a third complete, a voluminous white solid precipitated, rendering stirring difficult. The mixture was diluted with 250 ml. of anhydrous *t*-butanol, and the rate of stirring was increased. After all the malonate had been added, the mixture was rapidly stirred and heated under reflux for about 30 min. Freshly distilled 1,3-dibromopropane (101 g., 0.5 mole) was then added dropwise over a period of 45 min. The resulting mixture was stirred and heated under reflux overnight.

After allowing the mixture to cool, most of the excess *t*-butanol was removed by distillation, and, with stirring, 500 ml. of a 2% aqueous sulfuric acid solution was added, causing the salt to dissolve and producing two layers. The organic layer was diluted with diethyl ether, was separated, and was washed well with water. The aqueous layer was extracted with three 250-ml. portions of diethyl ether, the ether extracts were combined with the organic layer, and the ethereal solution was dried over anhydrous magnesium sulfate. The solvent was removed from the dried solution by distillation, and the resulting viscous, red liquid was distilled through a small heated Vigreux column under reduced pressure. There was obtained 196.6 g. (76.5% of theory, based on 1,3-dibromopropane) of orange-colored liquid, b.p. 210–220°/0.2–0.3 mm., n_D^{20} 1.5190. A small sample was redistilled, b.p. 164°/0.07 mm., n_D^{20} 1.5178.

Anal. Calcd. for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 68.04; H, 7.39.

When this condensation of malonic ester with 1,3-dibromopropane was carried out under the usual conditions with sodium ethoxide, the yields were less than 40%.

α,α' -Diphenylpimelic acid (II). In a three-liter, three-necked, round-bottomed flask, fitted with a mechanical stirrer (Hershberg) and modified Dean-Stark trap, was placed 350 g. (0.683 mole) of tetraethyl 1,5-diphenyl-1,1,5,5-pentanetetracarboxylate. Hydriodic acid (47%; 1120 g.; 4.1 moles of acid) was added, and the mixture was stirred and heated under reflux until no more ethyl iodide was collected (almost 5 days). During this time 204.1 g. (1.3 moles) of ethyl iodide was collected. The mixture was allowed to cool, and enough 25% aqueous sodium hydroxide was added to render the mixture basic to litmus. The red-colored basic solution was extracted with two 500-ml. portions of diethyl ether, and was acidified with cold, concentrated sulfuric acid. Ethyl acetate was added to dissolve the red oil obtained, and the aqueous layer was separated. The organic solution was washed well with aqueous sodium thiosulfate to remove the red color, and was dried over anhydrous magnesium sulfate. The dried solution was concentrated to about 750 ml. and petroleum ether (b.p. 30–60°) was added until the hot solution became cloudy. Enough ethyl acetate was added to render the solution clear, and, upon cooling,

there was obtained 54.3 g. of a white solid, m.p. 150–155°. Concentration of the mother liquor resulted in the isolation of 103 g. or more of crude di-acid. A third crop of crystals was obtained by evaporating the remaining solution to dryness and crystallizing the resultant oil from benzene–low-boiling petroleum ether. The yellow-colored solid obtained weighed 64.9 g. and had m.p. 150–160°. Total yield of crude acid was 222.2 g. A small sample was purified further by recrystallization from benzene–low-boiling petroleum ether three times to yield a white, crystalline solid, m.p. 136–138°. Infrared analysis⁸ was in agreement with the structure of the di-acid.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.90; H, 6.72.

Because of difficulties in crystallization, this crude acid was not purified further.

2,6-Diphenylheptandiol-1,7 (III). In a two-liter, three-necked, round-bottomed flask fitted with reflux condenser, mechanical stirrer, and dropping funnel was placed a slurry of finely-powdered lithium aluminum hydride (7.6 g., 0.2 mole) in 700 ml. of dry diethyl ether. α,α' -Diphenylpimelic acid (16.0 g.; 0.051 mole), dissolved in 300 ml. of dry diethyl ether, was added dropwise by means of the dropping funnel with stirring at such a rate so as to maintain gentle reflux. When the addition was complete, stirring and heating were continued overnight.

After allowing the mixture to cool, 50 ml. of water was cautiously added with stirring while the flask was cooled in an ice water bath; this was followed by the addition of 150 ml. of 10% aqueous sulfuric acid, again while the flask was cooled in an ice water bath. When it was certain that the excess lithium aluminum hydride had been decomposed, the mixture was transferred to a separatory funnel, and the aqueous layer was separated. The organic layer was washed with 150 ml. of 10% aqueous sodium carbonate and then with 150 ml. of water. The aqueous layer was extracted with diethyl ether, and the extract was washed, first with 10% aqueous sodium carbonate and then with water. The combined ether solutions were dried overnight over anhydrous magnesium sulfate.

The solvent was removed from the dried solution by distillation under reduced pressure, yielding 14.5 g. (98% yield) of a clear viscous oil, which crystallized upon cooling. This waxy solid was purified by recrystallization from methanol. An accurate melting point could not be obtained on the resulting waxy solid. Analytical data, however, were in agreement with the structure of 2,6-diphenylheptandiol-1,7.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 80.20; H, 8.51. Found: C, 79.95; H, 8.71.

2,6-Diphenyl-1,7-diacetoxyheptane (IV). In a 300-ml., three-necked, round-bottomed flask, fitted with reflux condenser with calcium chloride drying tube attached, stirrer, and dropping funnel, was placed a solution of 2,6-diphenylheptandiol-1,7 (19.3 g.; 0.067 mole) in 100 ml. of anhydrous ether. With stirring, acetyl chloride (20.4 g.; 0.26 mole) was added dropwise at room temperature. When the addition was complete (15 min.), the mixture was stirred and heated under gentle reflux overnight.

The solvent and excess acetyl chloride were removed by distillation under reduced pressure, and the viscous liquid obtained was distilled under vacuum. There was obtained 22.9 g. (93% yield) of a clear, viscous liquid, b.p. 172–176°/0.08 mm., n_D^{20} 1.5273.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.05; H, 7.67.

Pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane. The various pyrolyses were carried out in the following way: The liquid diacetate was dropped at the rate of about 50 drops/min. through a vertical, 20 × 250 cm. Vycor glass combustion tube packed with 1/16 inch glass helices. The tube was con-

(7) The microanalyses were performed by Mr. Jozsef Nemeth, Mrs. F. Ju, Miss Claire Higham, and Miss Jane Liu, University of Illinois.

(8) The infrared spectra were determined by Mr. P. E. McMahon and Miss Mary DeMott, University of Illinois.

tinuously swept out with dry, oxygen-free nitrogen, and was heated externally at temperatures varying between 540 and 560° with a 12-inch Hoskins electric furnace.

A typical pyrolysis was as follows: At the rate given above, 145 g. (0.394 mole) of 2,6-diphenyl-1,7-diacetoxyheptane was dropped through the column, heated to 555–560°. The pyrolysate was collected in a receiver immersed in a Dry Ice-acetone bath. At the completion of the pyrolysis, the pyrolyzate was diluted with diethyl ether, and was washed well with 10% aqueous sodium carbonate and then with water. After drying over anhydrous sodium sulfate, the solvent was removed from the solution by distillation under reduced pressure, and the red-colored liquid residue was distilled through an 8-inch Vigreux column under reduced pressure. The water-white liquid (30.8 g.) boiling between 60 and 75°/17 mm. was collected. The residue from this distillation was allowed to cool and was subjected to pyrolysis once again at 555–565°. After the usual work-up and distillation, there was obtained 21.8 g. more of colorless liquid, b.p. 60–80°/19–20 mm.

In the manner described above 344 g. (0.934 mole) of diacetate was pyrolyzed to give 125.1 g. of colorless liquid, b.p. 60–80°/17–20 mm. After two distillations of this liquid (inhibited with 1,3,5-trinitrobenzene) in a dry nitrogen atmosphere there was obtained 43.7 g. of colorless liquid, b.p. 70°/26 mm., n_D^{25} 1.5360. The infrared and nuclear magnetic resonance spectra⁹ of this liquid were identical with those of an authentic sample of α -methylstyrene. A vapor-phase chromatogram obtained from a 1:1 mixture of this distillate with pure α -methylstyrene showed only one peak. In addition to this pure fraction, there was obtained a slightly lower-boiling fraction (14.4 g.), b.p. 65–68°/26 mm., n_D^{25} 1.5350, which was shown by vapor phase chromatography to be largely α -methylstyrene contaminated with a small amount of lower-boiling liquid.

1,4-Diphenyl-4-vinylcyclohexene (2-phenylbutadiene dimer) (VIII). The pot residues from the distillations which gave α -methylstyrene as described above were combined and heated at 160° in an oil bath for 1 hr. The mixture was then distilled under vacuum to give 21.7 g. of a yellow oil, b.p. 140–175°/1.0–1.5 mm. This oil was dissolved in enough boiling methanol to render it completely soluble, and, after cooling overnight, there was obtained from this solution 14.1 g. of a white crystalline solid, m.p. 59.5–61.0°. (Alder⁴ reports the melting point of 2-phenylbutadiene dimer as 60°.) A small sample of this solid was recrystallized twice from methanol to give colorless needles, m.p. 63.5–64.0°. Infrared analysis was in agreement with the structure of 1,4-diphenyl-4-vinylcyclohexene (the structure of the dimer as reported by Alder⁴).

Anal. Calcd. for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 92.35; H, 8.00.

Dehydrogenation of 2-phenylbutadiene dimer. The pure dimer (3.0 g.) was mixed thoroughly with 2.0 g. of 10% palladium on charcoal catalyst in a 50-ml., round-bottomed flask. The mixture was heated by means of a Wood's metal bath to 320° for 16 hr. in a dry nitrogen atmosphere. After cooling, the mixture was extracted several times with hot ethyl acetate. From this solution was isolated 0.61 g. of shiny leaflets, m.p. 211–212.5°. (Lit.¹⁰ m.p. of *p*-terphenyl, 209°.)

2,6-Diphenylheptadiene-1,6 (V). 1,3-Dibenzoylpropane was prepared without difficulty from glutaryl chloride and benzene in 86% yield by following a procedure analogous to that for the preparation of 1,4-dibenzoylbutane.¹¹

Methyl triphenylphosphonium bromide was typically prepared in the following manner: Triphenylphosphine

(65.6 g.; 0.25 mole) dissolved in benzene (150 ml.) was combined with methyl bromide (40 g.; 0.42 mole) in a one-liter centrifuge bottle cooled in a Dry Ice-acetone bath. The bottle was stoppered while cold by wiring a rubber stopper in the opening, and the mixture was allowed to stand at room temperature for 2 days. At the end of this time the bottle was cooled in an ice bath, and was carefully opened. The white crystalline salt was isolated by filtration on a Büchner funnel, and was washed well with benzene. The amount of dried salt obtained was 87.5 g. (98%); m.p. 229–230°. (Wittig⁵ reports m.p. 227–229°.)

The phosphonium salt (121 g.; 0.338 mole) was dispersed in 500 ml. of anhydrous ethylene glycol dimethyl ether contained in a two-liter, three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, reflux condenser, and nitrogen inlet tube. The system was swept with dry nitrogen while a solution of 0.37 mole of phenyllithium in diethyl ether was added over a period of approximately 45 min. Practically all of the solid dissolved, giving a red-colored solution. A solution of 40 g. (0.158 mole) of 1,3-dibenzoylpropane in 200 ml. of dry ethylene glycol dimethyl ether was then added dropwise to the stirred mixture over a period of about 1 hr., and the mixture was stirred and heated under gentle reflux for 19 hr. The solvents were then evaporated to near dryness, and about 700 ml. of dry diethyl ether was added. The dark red oil which formed was thoroughly shaken with the solvent, and the ethereal solution was decanted into a three-liter separatory funnel. After washing well with water, the ether solution was dried over anhydrous sodium sulfate overnight, and the solvent was then removed under vacuum, leaving 43.0 g. of dark red oil. This oil, inhibited with a small amount of 4-*t*-butylpyrocatechol, was distilled under vacuum by means of a small Vigreux column to give 18.3 g. (46.7%) of water-white liquid, b.p. 113–117°/0.02–0.04 mm. Hg, n_D^{25} 1.5795. The infrared spectrum of a chloroform solution showed absorption peaks at 890 cm^{-1} ($CR_1R_2=CH_2$), 1490 and 1595 cm^{-1} (C_6H_5), 1570 cm^{-1} (conjugated C_6H_5-), and 1625 cm^{-1} (C_6H_5- conjugated $-C=C-$).

Anal. Calcd. for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 91.71; H, 8.32.

We are indebted to Dr. N. Field for permission to use his method for the synthesis of this hydrocarbon.

Pyrolysis of 2,6-diphenylheptadiene-1,6. By means of the apparatus and in an analogous manner to that described above for the pyrolysis of 2,6-diphenyl-1,7-diacetoxyheptane, 10.0 g. (0.04 mole) of 2,6-diphenylheptadiene-1,6 was pyrolyzed at 540–550°. At the completion of the pyrolysis, the column was washed with diethyl ether, and the washings were combined with the pyrolyzate. After the solvent was removed under vacuum, the red-colored liquid residue (8 g.), inhibited with a small amount of hydroquinone, was distilled under reduced pressure by means of a 10-inch spinning-band column. There were collected three fractions: I, 0.66 g., b.p. 45–50°/12 mm., n_D^{25} 1.5324; II, 2.19 g., b.p. 49–50°/11 mm., n_D^{25} 1.5369; III, 0.31 g., b.p. 54–58°/11 mm., n_D^{25} 1.5438. The infrared spectra of fractions I and II in carbon tetrachloride were identical with the spectrum of an authentic sample of α -methylstyrene in the same solvent. The spectrum of III was that to be expected of 2-phenyl-1,3-butadiene, slightly contaminated with α -methylstyrene. This spectrum showed the following important absorption maxima: 895 cm^{-1} ($CR_1R_2=CH_2$), 915 cm^{-1} (CH_2 out-of-plane deformation of the $-CH=CH_2$ grouping), 990 cm^{-1} (CH out-of-plane deformation of the $-CH=CH_2$ grouping), 1497 and 1595 cm^{-1} (C_6H_5-), 1630 (C_6H_5- conjugated $-C=C-$), in addition to a weak absorption at 1375 cm^{-1} ($C-CH_3$).

The residue from the above distillation was heated under reflux at 150–160° for about 2 hr. It was then distilled under vacuum to yield 1.6 g. of an orange oil, b.p. 130–140°/0.02

(9) The nuclear magnetic resonance spectrum was determined by Mr. B. A. Shoulders, University of Illinois.

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mm. It was not possible to crystallize this oil from methanol, even after attempted purification of an *n*-pentane solution on an activated alumina column. The infrared spectrum of this oil dissolved in chloroform, however, was consistent with that to be expected of the impure dimer of

2-phenyl-1,3-butadiene. A broad absorption maximum in the region of 900 cm.^{-1} ($\text{CR}_1\text{R}_2=\text{CH}_2$) seems to indicate that dimerization was not complete.

URBANA, ILL.

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH DIVISION, DIRECTORATE OF RESEARCH, USA CHEMICAL WARFARE LABORATORIES]

Synthesis of Some Hydroxamic Acids. Reactivity with Isopropyl Methylphosphonofluoridate (GB)

G. F. ENDRES¹ AND JOSEPH EPSTEIN²

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Eight hydroxamic acids, of which five are new compounds, were synthesized and tested for reactivity with the nerve gas GB, isopropyl methylphosphonofluoridate. The compounds were designed to sterically increase the reactivity of hydroxamic acids with GB. The reactivity however, was found to be not appreciably different from that predicted from well-established relationships of pK_a and reaction rate with other hydroxamic acids.

Several papers³⁻⁵ have appeared since the publication of Hackley *et al.*⁶ reporting on various aspects of the reaction between hydroxamic acids and the nerve gas GB (isopropyl methylphosphonofluoridate). In connection with our program to find non-protein substances which react more rapidly with GB in aqueous solution at neutral pH than the compounds studied in the previous publications, we have synthesized and tested several hydroxamic acids. Table I contains data on the dissociation constants, rate constants for their reaction with GB and the moles of hydrogen ion released per mole of GB at infinite time for hexanehydroxamic acid, gluconohydroxamic acid, three long-chain hydroxamic acids derived from sebacic acid and three carboxyhydroxamic acids. The results of our kinetic studies indicate that none of the compounds is significantly more or less active than would be predicted from the relationship of the reactivity with the basic strength of the hydroxamic acid anion reported in previous publications^{4,5} (*e.g.* see Fig. 1) and hence offer no clues as to the means of increasing the reactivity between hydroxamic acids and GB.

The hydroxamic acids reported herein represent an unsuccessful attempt to increase the reactivity of these materials by steric effects. Some success has been achieved by pursuing this line of approach with the hydroxylated benzenes,^{7,8} and ortho substituted hydroxybenzyl amines.⁹

(1) Present address, General Electric, Schenectady, N. Y.

(2) To whom requests for reprints should be addressed.

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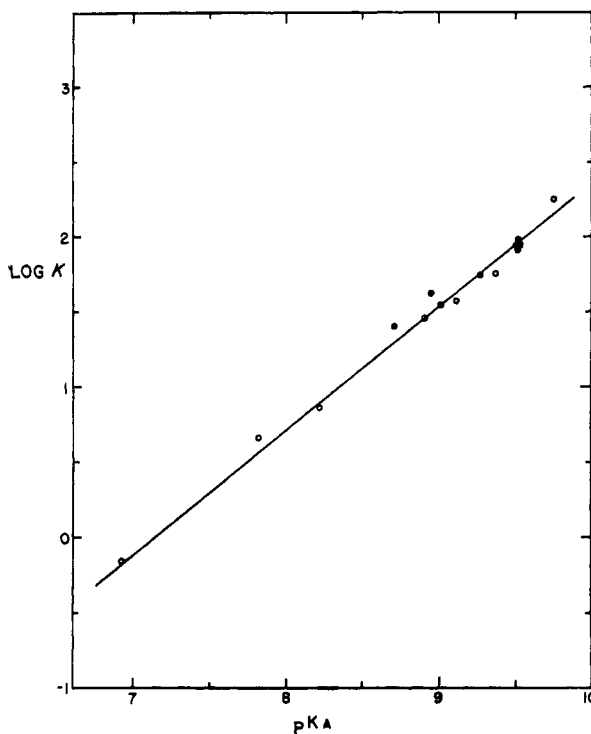


Fig. 1. Relationship between $\log k$ (second order rate constant $1\text{ mole}^{-1}\text{ sec.}^{-1}$) and pK_a of various hydroxamic acids. ● Data of present publication. ○, Data of Swidler *et al.* (see ref. no. 7 of ref. 4)

In the design of the hydroxamic acids sterically capable of polyfunctional attack, it was assumed that (a) the reaction is mediated through a simultaneous nucleophilic and electrophilic attack of the hydroxamic acid anion on the phosphorus and

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