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

Synthesis of Muconyldimalonates

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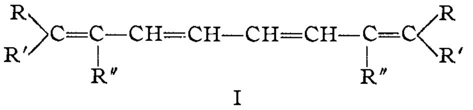
Some muconyldimalonates have been synthesized and their properties including their infrared and ultraviolet spectra determined. It has been found that even in the solid state these compounds exist entirely in the enolic form. They easily form stable enolates and in the case of the tetracarboxylic ethyl ester the dienol dipotassium salt has been found to have weak but definite antibiotic properties. An attempt to prepare 3,5-octadiene-dione-2,7 from the muconyldimalonates has not been successful since most of the hydrolytic agents tried caused cleavage with the formation of muconic acid or its salts.

The preparation of dimalonates from dicarboxylic acid chlorides and sodium diethylmalonate already has been described.[2,3] Since sodium diethylmalonate is known to add across the conjugated system of diethyl muconate,[4] the muconyldimalonates were prepared by making use of the method originally proposed by Lund[5a] and subsequently utilized by other investigators.[5b-g]

The present investigation was directed to the preparation of muconyldimalonates from muconyl chloride[6] and ethoxymagnesium malonates for the purpose of obtaining 3,5-octadiene-dione-2,7 an important intermediate in the synthesis of β-carotene.[7]

Muconyldimalonates exist entirely in the enolic form even in the solid state and behave as octatetraene tetracarbethoxy esters having the general formula I. They dissolve in cold sodium carbonate solution and give strong positive tests with ferric chloride. They also exhibit strong characteristic ultraviolet absorption spectra which are plotted in Fig. 1.



$$\begin{matrix}R \\ R'\end{matrix}\!\!>C{=}\underset{\displaystyle R''}{\underset{|}{C}}{-}CH{=}CH{-}CH{=}CH{-}\underset{\displaystyle R''}{\underset{|}{C}}{=}C\!\!<\!\!\begin{matrix}R \\ R'\end{matrix}$$

I

I, R = R′ = C_2H_5OOC–, R″ = –OH

II, R = C_2H_5OOC–, R′ = $(CH_3)_3COOC$–, R″ = –OH

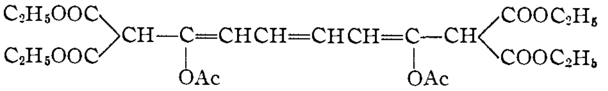
III, R = C_2H_5OOC–, R′ = H, R″ = –OH

IV, R = R′ = C_2H_5OOC–, R″ = CH_3COO–

V, R = R′ = C_2H_5OOC–, R″ = CH_3O–

VI, R = R′ = C_2H_5OC–, R″ = –OK

VII, R = R′ = C_2H_5OC–, R″ = –NH_2



$$\begin{matrix}C_2H_5OOC \\ C_2H_5OOC\end{matrix}\!\!>CH{-}\underset{\displaystyle OAc}{\underset{|}{C}}{=}CHCH{=}CHCH{=}\underset{\displaystyle OAc}{\underset{|}{C}}{-}CH\!\!<\!\!\begin{matrix}COOC_2H_5 \\ COOC_2H_5\end{matrix}$$

VIII

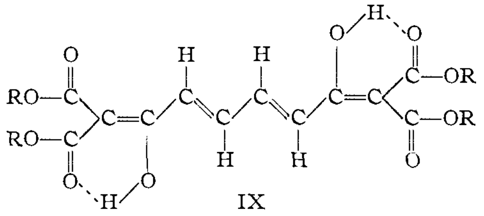
The infrared spectra of muconyldimalonates show bands at 1630–1640 cm.$^{-1}$ which indicate strong conjugate chelation[8] between the ester carbonyl and the enolic hydroxyl. The same spectra also confirm the *trans-trans* relationship of the central double bonds originally present in the *trans-trans*-muconic acid. Weaker bands which appear between 670–700 cm.$^{-1}$ may be ascribed to the presence of the *cis*-configuration of the double bonds of the chelates although the presence of these bands in the spectrum of compound V is not easily understood at present. Table I shows some of the characteristic infrared bands of this group of compounds as compared with those of the *trans-trans*-3,5-octadienedione-2,7.[9] The general structure IX is therefore proposed to account for the spectroscopic data as well as the chemical behavior of these compounds.

TABLE I

CHARACTERISTIC BANDS[a] OF INFRARED SPECTRA OF MUCONYLDIMALONATES AND RELATED COMPOUNDS

Compound	Solvent	Chelate band, cm.$^{-1}$	*trans*-$\vert^{=}$ band, cm.$^{-1}$	*cis*-$\vert^{=}$ band, cm.$^{-1}$
trans-trans-3,5-Octadiene-dione-3,7	$CHCl_3$	1640W	963S	Absent
I (solid)	KBr	1630S	983S	685W
I	$CHCl_3$	1630S	993S	690W
II	$CHCl_3$	1630S	993S	683W
III	$CHCl_3$	1640S	992S,945S	688W
IV	$CHCl_3$	Absent	985S	Absent
V	$CHCl_3$	Absent	998S,963S	685W(?)
VI	Nujol mull	1640	970S	670W
VIII	$CHCl_3$	Absent	970S	Absent

[a] S = strong, W = weak.



IX

Although muconyldimalonates exist in the enolic form, under certain conditions they also exhibit ketonic properties. For example, the tetracarboxylic ethyl ester forms both the mono- and the di-2,4-dinitrophenylhydrazones.

Aqueous as well as alcoholic alkalies caused a cleavage of muconyldimalonates to form nearly quantitative yields of the corresponding alkali salts of muconic acid. However, under controlled con-

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(2) J. Schreiber, *Ber.*, **42**, 1318 (1909).

(3) W. Borsche and U. Wannagat, *Chem. Ber.*, **85**, 193 (1952).

(4) E. H. Farmer and T. N. Mehta, *J. Chem. Soc.*, 1962 (1931).

(5) (a) H. Lund, *Ber.*, **67**, 935 (1934); (b) D. S. Breslow, E. Baumgartner and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944); (c) N. A. Milas, U. S. Pat., 2,369,158 (Feb. 13, 1945); (d) B. Riegel and W. M. Lilienfeld, THIS JOURNAL, **67**, 1273 (1945); (e) H. Walker and C. R. Hauser, *ibid.*, **68**, 1386 (1946); (f) R. E. Bowman, *J. Chem. Soc.*, 322, 325 (1950); (g) R. E. Bowman and W. D. Fordham, *ibid.*, 3945 (1952).

(6) E. E. Mange, B.S. Thesis, M.I.T., 1948; D. S. Bailey and J. M. Ross, THIS JOURNAL, **71**, 2370 (1949).

(7) N. A. Milas, P. Davis, I. Belič and D. Fleš, *ibid.*, **72**, 4844 (1950).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 157.

(9) G. Teckakumpuch, B.S. Thesis, M.I.T., May, 1953.

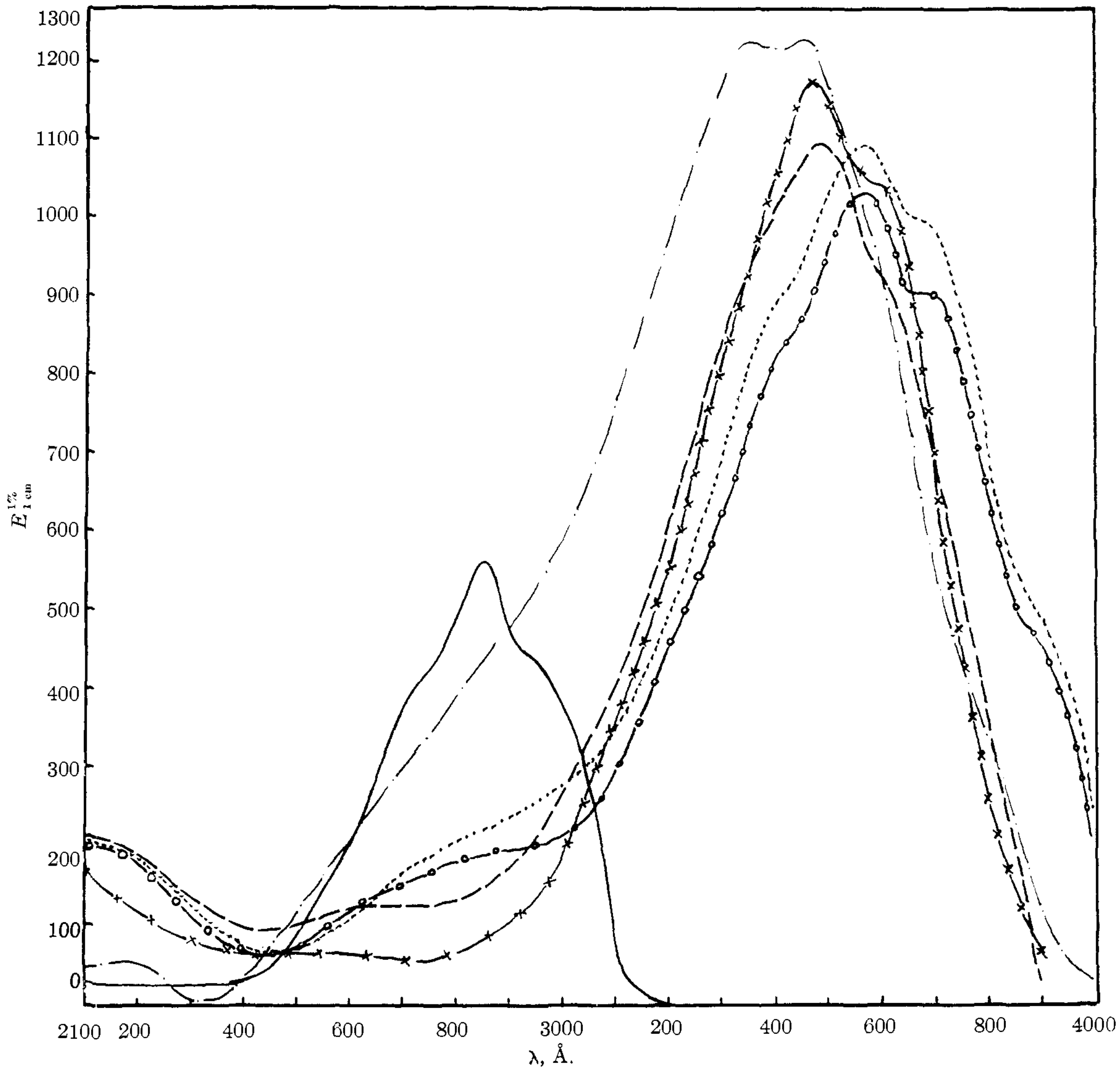

Fig. 1.—Ultraviolet absorption spectra of muconyldimalonates, etc.: (I) o-o-o-, tetracarboxylic ethyl ester; (II) . . . . . . dicarboxylic ethyl dicarboxylic *t*-butyl ester; (III) - - - · - - ·, dicarboxylic ethyl ester; (IV), -x-x-x-, dienol diacetate; (V), - - - - - -, dienol dimethyl ether; (VIII) ———, diacetate VIII.

ditions, the tetracarboxylic ethyl ester I was converted with alcoholic potassium hydroxide to the dipotassium salt VI which was found to have weak but definite antibiotic activity against *Bacillus cereus*. The dienol diacetate IV was easily prepared from the dipotassium salt when the latter was treated with acetic anhydride.

Diazomethane is known to form cyclic products with diethyl muconate[10] and dibenzoylbutadiene.[11] The tetracarboxylic ethyl ester I, on the other hand, formed the normal dienol dimethyl ether V when it was treated with a large excess of diazomethane.

While aqueous ammonium hydroxide caused a cleavage of muconyldimalonates to give the ammonium salts of muconic acid, anhydrous alcoholic ammonia yielded the diamide of muconic acid. However, when the dienol dimethyl ether V was treated with alcoholic ammonia the diaminotetracarboxylic ethyl ester VII was formed. A similar reaction with ethoxymethylenemalonic ester was described previously by Claisen.[12]

Hydrazine hydrate and isonicotinyl hydrazide also caused a cleavage of muconyldimalonates. With the tetracarboxylic ethyl ester I the corresponding dihydrazide and diisonicotinyl hydrazide of muconic acid were formed, respectively.

An attempt to hydrolyze the tetracarboxylic ethyl ester with mineral acids also led to a complete cleavage and the formation of muconic acid. To avoid this cleavage the mixed ethyl *t*-butyl malonic ester[5b] was used for the synthesis of *cis*-1,7-*trans*-3,5-octatetraen-diol-2,7-dicarboxylic ethyl-1,8-dicarboxylic-*t*-butyl ester-1,8 (II) which was then hydrolyzed to the dicarbethoxy ester III. Attempts to prepare the desired 3,5-octadienedione-2,7 from the dicarbethoxy ester III were also unsuccessful. A further attempt was made to prepare the tetracarboxylic *t*-butyl ester, which might yield the desired ketone, but this too led to

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[10] P. C. Guha and D. K. Sankaran, *Ber.*, **70**, 2109 (1937).

[11] D. S. Bailey and J. M. Ross, THIS JOURNAL, **71**, 2370 (1949).

[12] L. Claisen, *Ann.*, **297**, 77 (1897).

inconclusive results and this line of investigation was therefore discontinued.

It is of interest to mention here some experiments on the selective reduction of muconyldimalonates. Catalytic hydrogenation of either the tetracarboxylic ethyl ester I or the dienol diacetate IV using palladium on various supports with or without the use of quinoline was not selective. However, reduction of the dienol diacetate with either aluminum amalgam in moist ether or with zinc in glacial acetic acid was fully selective with 1,8-addition of hydrogen to form the new dienol diacetate VIII.

Experimental

Muconyl Chloride.—Muconyl chloride was prepared from *trans*-muconic acid (20 g.)[13,14] and thionyl chloride (120 cc.) following the method of Mange.[6] At the end of the reaction the excess thionyl chloride was removed under reduced pressure and the crude muconyl chloride recrystallized from acetyl chloride into long needles, m.p. 98–99°; yield 18 g. (72%).

Anal. Calcd. for $C_6H_4O_2Cl_2$: Cl, 39.62. Found: Cl, 39.46.

***cis*-1,7-*trans*-3,5-Octatetraen-diol-2,7-tetracarboxylic Ethyl Ester-1,1,8,8 (I).**—A mixture of 60 cc. of absolute ethanol, 4.86 g. of magnesium turnings and 0.5 cc. of carbon tetrachloride was allowed to react; the reaction was strongly exothermic. When the reaction subsided 75 cc. of anhydrous ether was added followed by a dropwise addition of 32 g. (0.2 mole) of diethyl malonate with vigorous stirring and external cooling. Finally another portion of anhydrous ether (100 cc.) was added and the mixture gently refluxed for two hours. A solution of muconyl chloride (9 g., 0.1 mole) in 200 cc. of anhydrous ether was then added dropwise with vigorous stirring. A yellow precipitate was immediately formed. Stirring was continued for four hours, then the mixture allowed to stand overnight at room temperature. The product was then poured into a mixture of 150 cc. of water containing 150 g. of ice and 40 g. of tartaric acid. A yellow precipitate which formed was removed by filtration and the two layers of the filtrate separated. The aqueous layer was extracted once with 50 cc. of benzene and the benzene extract combined with the non-aqueous layer, dried over magnesium sulfate and the solvent removed. The crystalline residue dried in a vacuum desiccator and recrystallized from a mixture of (1:2) of benzene and petroleum ether into canary yellow needles, m.p. 147–148°; yield 24 g. (85%).

Anal. Calcd. for $C_{20}H_{26}O_{10}$: C, 56.33; H, 6.15; unsaturation, 4 $|^{=}$; active hydrogen, 2. Found: C, 56.44; H, 6.25; unsaturation, 4.45 $|^{=}$ (Pt, in g.a. acid); active hydrogen, 1.93 ($LiAlH_4$ in pyridine).

The ultraviolet spectrum of this compound is plotted in Fig. 1 (curve 1) and the characteristic bands of the infrared spectrum are listed in Table I. In addition this product gives a strong ferric chloride reaction but fails to react normally with methylmagnesium iodide (Zerewitinoff). However, with lithium aluminum hydride in dry pyridine it gives normal active hydrogen.

Catalytic Reduction of (I).—The tetracarboxylic ethyl ester (I, 1.28 g.) was reduced in benzene with hydrogen using platinum oxide (100 mg.) as catalyst. The reaction was stopped after four moles of hydrogen had been absorbed; the mixture filtered and the benzene evaporated. The viscous residue (1.2 g.) was further purified by precipitation from benzene with petroleum ether at −10°. Attempts to crystallize the final product were not successful.

Anal. Calcd. for $C_{20}H_{34}O_{10}$: C, 55.29; H, 7.89; active hydrogen, 2.0. Found: C, 55.35; H, 7.30; active hydrogen (Zer.), 1.81.

An attempt to selectively hydrogenate double bonds 1 and 7 was not successful. Hydrogenation in glacial acetic acid led to a considerable hydrogenolysis and the products isolated were not definitely characterized.

Dipotassium Salt VI.—Aqueous alkalies cause quantitative cleavage of muconyldimalonates to the corresponding alkali salts of muconic acid. However, under the following conditions the dipotassium salt of I has been prepared in good yields. To a cold solution of 50 cc. of absolute ethanol containing 0.56 g. of potassium hydroxide was added 2.13 g. of the tetracarboxylic ethyl ester I. The reaction is strongly exothermic and the mixture should not be allowed to heat excessively. After a few minutes a yellow crystalline product separated. Ether (400 cc.) was then added and the mixture cooled to −10° for two hours. The yellow crystalline product was removed by filtration and washed with 100 cc. of anhydrous ether and dried under reduced pressure; yield 2.24 g. (89.3%).

Anal. Calcd. for $C_{20}H_{24}O_{10}K_2$: K, 15.57. Found: K, 15.38.

The characteristic bands of the infrared spectrum of this salt are listed in Table I. This salt has been tested for antibiotic activity against *Bacillus cereus* by the National Dairy Research Laboratories. They reported that "in a concentration of 10,000 micrograms per cc. it had an activity equivalent to 0.5 micrograms of Streptomycin and 2 micrograms of Terramycin or Aureomycin."

Dienol Diacetate IV.—The dipotassium salt (1 g.) described in the previous section was dissolved in 40 cc. of acetic anhydride and the solution boiled on a hot plate for ten minutes. The dark yellow solution was then poured on ice and left there for one hour. After decanting the water layer the semi-crystalline residue was extracted with ether and the ethereal solution washed several times with 5% solution of sodium bicarbonate, dried over magnesium stsulfate and the ether removed. The residue was recryallized from ethanol into large shining plates, m.p. 144–145°; yield 0.3 g. (30%).

Anal. Calcd. for $C_{24}H_{30}O_{12}$: C, 56.46; H, 5.92. Found: C, 56.26; H, 6.04.

The ultraviolet spectrum of this compound is plotted in Fig. 1 (curve IV) and the characteristic infrared bands are listed in Table I. In glacial acetic acid and in the presence of platinum oxide as catalyst the dienol diacetate absorbed 5.6 moles of hydrogen showing considerable hydrogenolysis. Hydrogenation in ethanol using palladium on calcium carbonate and in the presence of quinoline failed to show any selectivity.

Partial Reduction of the Dienol Diacetate IV with Aluminum Amalgam—Preparation of the Diacetate VIII.—To 300 cc. of moist ether was added 900 mg. of the dienol diacetate IV and the mixture shaken for two hours with aluminum amalgam freshly prepared from 10 g. of aluminum sheet. The ethereal solution was then filtered, dried over magnesium sulfate and the ether evaporated. The residue was recrystallized from ethanol, m.p. 111°; yield 700 mg. (78%).

Anal. Calcd. for $C_{24}H_{32}O_{12}$: C, 56.24; H, 6.29; unsaturation, 3 $|^{=}$. Found: C, 56.37; H, 6.43; unsaturation, 3.02 $|^{=}$[Pd($CaCO_3$) + quinoline], 4.54 $|^{=}$(Pt in g.a. acid).

The catalytic hydrogenation in glacial acetic acid showed definite hydrogenolysis. The ultraviolet spectrum of this compound is plotted in Fig. 1 (curve VIII) and the characteristic infrared bands are listed in Table I. It appears from these results that with aluminum amalgam the hydrogen added 1:8 rather than 1:2.

The diacetate VIII was also obtained in 70% yield when the dienol diacetate IV was reduced with zinc dust in glacial acetic acid, m.p. 111°, mixed m.p. with the product obtained with aluminum amalgam showed no depression.

Dienol Dimethyl Ether V.—An ethereal solution (150 cc.) containing 2.13 g. of the tetracarboxylic ethyl ester I was treated at 0° with diazomethane freshly prepared from 6 g. of nitrosomethylurea and the mixture allowed to stand overnight at the same temperature. The small amount of precipitate which formed during the night was discarded and the ethereal solution evaporated to dryness. The residual red oil (2.33 g.) which solidified on standing was recrystallized from absolute ethanol into long yellow needles, m.p. 77–78.5°; yield 1.5 g. (66%).

Anal. Calcd. for $C_{22}H_{30}O_{10}$: C, 58.14; H, 6.65. Found: C, 58.20; H, 6.63.

The ultraviolet spectrum of the dimethyl ether V is plotted in Fig. 1 (curve V) and the characteristic infrared bands are listed in Table I.

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[13] R. Behrend, *Ber.*, **49**, 999 (1916); R. Behrend and G. Heyer, *Ann.*, **418**, 294 (1919).

[14] P. C. Guha and D. K. Sankaran, *Org. Syntheses*, **26**, 57 (1946).

1,3,5,7-Octatetraen-diamino-2,7-tetracarboxylic Ethyl Ester-1,1,8,8 (VII).—A solution of absolute ethanol containing 0.5 g. of the dimethyl ether V was cooled to 0°, saturated with dry ammonia and allowed to stand in the refrigerator overnight. The mixture which had turned deep red was then subjected to vacuum distillation to remove the solvent. A yellowish crystalline residue (450 mg.) was obtained. This was recrystallized from absolute ethanol; m.p. 184–185°; yield 350 mg. It was recrystallized once again from a mixture of benzene–petroleum ether and again from absolute ethanol, m.p. 185–186° or 190–191° (Kofler microscopic method).

Anal. Calcd. for $C_{20}H_{28}O_8N_2$: C, 56.59; H, 6.65; N, 6.60. Found: C, 56.43; H, 6.72; N, 6.50.

Mono-2,4-dinitrophenylhydrazone of I.—When I was allowed to react with excess 2,4-dinitrophenylhydrazine reagent in ethanolic solution and heated on the water-bath only long enough to dissolve it, a yellowish-orange product was formed which after several crystallizations from ethanol melted at 126°.

Anal. Calcd. for $C_{26}H_{30}O_{13}N_4$: C, 51.48; H, 4.98; N, 9.24. Found: C, 51.45; H, 4.85; N, 9.36.

Di-(2,4-dinitrophenylhydrazone) of I.—When I was heated on the water-bath for 15 minutes with a large excess of 2,4-dinitrophenylhydrazine reagent in ethanol an orange precipitate was formed which was extracted several times with hot ethanol to remove the mono-2,4-dinitrophenylhydrazone. A deep red precipitate which remains was insoluble in most of the common organic solvents. It was finally recrystallized from a large volume of xylene. This product decomposes at 219° without melting.

Anal. Calcd. for $C_{21}H_{34}O_{16}N_8$: C, 48.85; H, 4.36; N, 14.25. Found: C, 49.27; H, 4.42; N, 14.96.

Muconyldiamide.—A solution of the tetracarboxylic ethyl ester (1 g.) in 100 cc. of absolute ethanol was saturated at 0° with dry ammonia. At the beginning of the reaction the solution became deeply red but after a few minutes the color disappeared and a white precipitate was formed. The mixture was allowed to stand overnight at room temperature then the solvent removed under reduced pressure. The yellowish residue was triturated with cold water and the insoluble portion (280 mg.) was crystallized first from a mixture of alcohol and water then from boiling water and finally sublimed at 240–250° (0.0002 mm.), darkens at 276° but melts at 292° (cor.).

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.36; H, 5.91; N, 20.07.

An authentic sample of muconyldiamide prepared in benzene from muconyl chloride and dry ammonia was identical with the above product.

Muconyl Dihydrazide.—A solution of 300 mg. of tetracarboxylic ethyl ester in 25 cc. of absolute ethanol was treated with 2 cc. of hydrazine hydrate. The red color which formed disappeared in a few minutes and a crystalline product precipitated. The mixture was allowed to stand at room temperature for four hours then filtered and the crystals washed with water and dried, m.p. 274° (cor.); yield 113 mg. (93%). A sample was sublimed for analysis at 255–260° (0.001 mm.) in the form of colorless plates.

Anal. Calcd. for $C_6H_{10}O_4N_4$: C, 42.82; H, 5.92; N, 32.93. Found: C, 42.57; H, 6.06; N, 32.79.

An authentic sample of muconyl dihydrazide prepared in benzene from diethyl muconate and hydrazine hydrate was identical with the above product.

Muconyl Diisonicotinylhydrazide.—To a mixture of 639 mg. of tetracarboxylic ethyl ester in 25 cc. of absolute ethanol was added 411 mg. of isonicotinyl hydrazide and the mixture refluxed for 48 hours. A yellow precipitate was formed which was removed by filtration and dried; yield 80 mg. This solid was insoluble in all common solvents but dissolved in dilute hydrochloric acid (5%). To remove the color the solution was treated with charcoal, filtered and the water removed under reduced pressure. The residue failed to crystallize. It was then dissolved in 20 cc. of methanol containing 1 cc. of dilute hydrochloric acid and precipitated with ether; the precipitate separated and dried *in vacuo* at 80° for 24 hours.

Anal. Calcd. for $C_{18}H_{16}N_6 \cdot 2HCl$: C, 47.69; H, 4.00; N, 18.43. Found: C, 47.91; H, 4.31; N, 17.82.

***cis*-1,7-*trans*-3,5-Octatetraen-diol-2,7-dicarboxylic Ethyl-1,8-dicarboxylic-*t*-butyl Ester-1,8 (II).**—A mixture of 2.1 cc. of absolute ethanol, 2.4 g. of freshly turned magnesium shavings and 0.5 cc. of carbon tetrachloride was allowed to react; the reaction was strongly exothermic. After the reaction ceased 70 cc. of dry ether was added, followed by a dropwise addition with stirring of a mixture of 8.6 cc. of absolute ethanol and 18.3 g. of ethyl *t*-butyl malonate.[5b] The reaction mixture was then refluxed for two hours, then 4.66 g. of muconyl chloride dissolved in 150 cc. of ether was added dropwise in the course of 15 minutes. A pale yellow precipitate was formed immediately. Stirring was continued for four hours then the mixture allowed to stand overnight at room temperature. The final product was then hydrolyzed with 20 g. of tartaric acid dissolved in 150 cc. of water and 150 g. of ice. The ethereal layer was separated, dried over magnesium sulfate and the ether removed under reduced pressure. The yellowish crystalline residue was recrystallized from a benzene–petroleum ether mixture into long, yellow needles, m.p. 149–150°; yield 7 g. (62%).

Anal. Calcd. for $C_{24}H_{34}O_{10}$: C, 59.74; H, 7.10. Found: C, 59.79; H, 7.03.

The ultraviolet spectrum of this compound is plotted in Fig. 1 (curve II) and the characteristic infrared bands are listed in Table I.

***cis*-1,7-*trans*-3,5-Octatetraen-diol-2,7-dicarboxylic Ethyl Ester-1,8 (III).**—A solution of 15 cc. of benzene containing 1.2 g. of dicarboxylic ethyl dicarboxylic-*t*-butyl ester II was refluxed with 60 mg. of *p*-toluenesulfonic acid for 45 minutes. The vigorous gas evolution, which occurred in the beginning of the reaction, ceased after 30 minutes. The benzene solution was then extracted three times with 20 cc. of 5% sodium bicarbonate solution, followed by water, dried over magnesium sulfate, filtered and the benzene removed under reduced pressure. The pale yellow residue, 0.54 g. (77%), was recrystallized from a 50–50 mixture of benzene–petroleum ether; m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.56; H, 6.51.

The ultraviolet spectrum of this ester is plotted in Fig. 1 (curve III) and the characteristic infrared bands are listed in Table I.

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