[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Studies in Mixed Ester Condensations. IV. Acylations with Methyl Dimethoxyacetate[1]

BY E. EARL ROYALS AND A. G. ROBINSON, III[2]

RECEIVED MARCH 2, 1956

A study has been made of the Claisen acylation of active hydrogen compounds by means of methyl dimethoxyacetate in the presence of sodium methoxide. A convenient synthesis of methyl dimethoxyacetate is reported. A series of six aliphatic methyl esters was subjected to mixed ester condensation with methyl dimethoxyacetate to give the mixed condensation products in yields of 50–85%. Basic cleavage of the mixed condensation products gave α-ketoacetals in yields of 73–90%. Acidic cleavage of the α-ketoacetals gave easily polymerized α-ketoaldehydes in yields of 18–39%. Claisen condensation of a series of seven ketones with methyl dimethoxyacetate gave α,γ-diketoacetals in yields of 30–60%. These α,γ-diketoacetals could not be successfully converted to α,γ-diketoaldehydes; only unworkable tars, presumably resulting from aldol condensation of the cleavage products, resulted. Methyl dimethoxyacetate underwent Claisen condensation with butyronitrile to give α-(dimethoxyaceto)-butyronitrile in 61% yield. Condensation of methyl dimethoxyacetate with fluorene gave 9-(dimethoxyaceto)-fluorene in 32% yield; acid hydrolysis gave 9-fluorenylglyoxal in 42% yield.

In continuation of studies[1] in mixed ester condensations, the use of dialkoxyacetates as acylating esters appeared attractive because of the expected high carbonyl reactivity of such esters and the interesting polyfunctional nature of the condensation products. Because of the inherent advantages in the use of sodium methoxide as condensation agent,[1] methyl dimethoxyacetate (methyl glyoxylate dimethylacetal) was chosen as the particular such ester for study. Relatively few Claisen condensations involving dialkoxyacetic esters have been reported in the literature, but the isolated observations available supported the expectation that such esters are quite reactive acylating agents. Dakin and Dudley reported[3] the acylation of ethyl acetate with ethyl diethoxyacetate in the presence of sodium wire to give ethyl γ,γ-diethoxyacetoacetate in 71% yield. This β-ketoester was alkylated with a number of alkyl halides, and the resulting condensation products were cleaved with dilute base to give α-ketoacetals. Johnson and Cretcher reported[4] the condensation of ethyl diethoxyacetate with ethyl acetate, but did not isolate the ketoester. Johnson and Mikeska[5] condensed ethyl diethoxyacetate with ethyl propionate and obtained ethyl α-methyl-γ,γ-diethoxyacetoacetate in 70% yield. Rugeley and Johnson[6] reported the acylation of diethyl succinate by means of ethyl diethoxyacetate in 48% yield. Henze and Carroll[7] condensed ethyl dimethoxyacetate with ethyl acetate in 76% yield. Even fewer acylations of ketones with dialkoxyacetic esters have been reported. Helferich and Russe[8] acylated methyl ethyl ketone with ethyl diethoxyacetate and with ethyl dimethoxyacetate in the presence of sodium ethoxide to give the 1,1-dialkoxy-2,4-hexanediones in 33 and 42% yields. Ethyl diethoxyacetate has also been used[9] to acylate acetone and methoxyacetone in 70 and 40% yields, respectively; acylation of acetone with ethyl dimethoxyacetate gave a 55% yield of 1,1-dimethoxy-2,4-pentadione. Other types of active hydrogen compounds appear not to have been acylated by means of dialkoxyacetic esters.

Methyl dimethoxyacetate for use in our condensations was prepared by a method first used by Helferich and Russe[8] and patterned after an earlier synthesis of ethyl diethoxyacetate by Wohl and Lange.[10] The method involves the reactions

$$\mathrm{Cl_2CHCO_2H + 3NaOCH_3 \longrightarrow (CH_3O)_2CHCO_2Na + 2NaCl + CH_3OH} \quad (1)$$

$$\mathrm{(CH_3O)_2CHCO_2Na + HCl + CH_3OH \xrightarrow{H^+} (CH_3O)_2CHCO_2CH_3 + NaCl + H_2O} \quad (2)$$

Although Helferich and Russe originally reported a yield of 62% of methyl dimethoxyacetate, later workers reported[11] much lower yields of the order of 40–45%. By a study of variables of this reaction, we have developed a procedure (Experimental Section) for the preparation of methyl dimethoxyacetate in 62% yield; by reworking recovered sodium dimethoxyacetate, the over-all yield could be raised to 65–70%.[12] The principal factors leading to satisfactory yields from this process would appear to be allowing sufficient time for the rather slow reactions, particularly the esterification step, and the use of a full equivalent of hydrogen chloride in step (2) in addition to the equivalent necessary for neutralization of the sodium dimethoxyacetate.

A series of six aliphatic methyl esters was subjected to mixed ester condensation with methyl dimethoxyacetate in the presence of a benzene suspension of sodium methoxide, using in all cases equivalent quantities of the two esters. Methyl α-alkyl-γ,γ-dimethoxyacetoacetates were formed according to the reaction

$$\mathrm{R\text{-}CH_2\text{-}CO_2CH_3 + (CH_3O)_2CH\text{-}CO_2CH_3 \xrightarrow{NaOCH_3} (CH_3O)_2CH\text{-}CO\text{-}CHR\text{-}CO_2CH_3 + CH_3OH}$$

---

[1] For the previous paper in this series, see E. E. Royals and D. G. Turpin, THIS JOURNAL, **76**, 5452 (1954).

[2] Abstracted from a thesis presented by A. G. Robinson, III, to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1955.

[3] H. D. Dakin and H. W. Dudley, *J. Chem. Soc.*, **105**, 2453 (1914).

[4] T. B. Johnson and L. H. Cretcher, *J. Biol. Chem.*, **26**, 106 (1944).

[5] T. B. Johnson and L. A. Mikeska, THIS JOURNAL, **42**, 2349 (1920).

[6] E. W. Rugeley and T. B. Johnson, *ibid.*, **47**, 2997 (1925).

[7] H. R. Henze and D. W. Carroll, *ibid.*, **76**, 4580 (1954).

[8] B. Helferich and A. Russe, *Ber.*, **56B**, 759 (1923).

[9] W. Braker, E. W. Pribyl, J. T. Sheehan, E. R. Spitzmiller and W. A. Lott, THIS JOURNAL, **69**, 3072 (1947).

[10] A. Wohl and M. Lange, *Ber.*, **41**, 3612 (1908).

[11] A. C. Cope, THIS JOURNAL, **58**, 570 (1936); S. M. McElvain, S. B. Mirviss and C. L. Stevens, *ibid.*, **73**, 3807 (1951).

[12] After completion of our work there appeared a published procedure very similar to ours for the preparation of ethyl diethoxyacetate in 45–50% yield; R. B. Moffett, *Org. Syntheses*, **35**, 59 (1955).

TABLE I

SYNTHESIS OF METHYL α-ALKYL-γ,γ-DIMETHOXYACETOACETATES $(CH_3O)_2CH{-}CO{-}CHR{-}CO_2CH_3$, BY CONDENSATION OF METHYL DIMETHOXYACETATE WITH ALIPHATIC METHYL ESTERS

R-group	Method	Yield, %	B.p., °C. (5 mm.)	$n^{25}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$-H$	A	52	76	1.4266	47.72	47.94	6.88	6.93
$-CH_3$	A	74	88	1.4278	50.54	50.29	7.43	7.51
$-CH_3$	B	81	88	1.4278				
$-C_2H_5$	A	76	96	1.4290	52.92	52.98	7.91	8.08
$-C_2H_5$	B	81	96	1.4290				
$-n$-C_3H_7	A	70	109	1.4301	55.02	54.79	8.33	8.19
$-n$-C_3H_7	B	74	109	1.4301				
$-n$-C_4H_9	A	61	118	1.4316	56.87	56.69	8.69	8.80
$-n$-C_4H_9	B	70	118	1.4316				
$-n$-C_7H_{15}	A	39	142	1.4340	61.28	61.24	9.57	9.39
$-n$-C_7H_{15}	B	57	142	1.4340				

TABLE II

PREPARATION OF α-KETOACETALS $(CH_3O)_2CH{-}CO{-}R$, BY CLEAVAGE OF METHYL α-ALKYL-γ,γ-DIMETHOXYACETOACETATES

R-group	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$-CH_3$	84	141	760	1.4102	50.83	50.61	8.53	8.40
$-C_2H_5$	88	49	13	1.4139	54.53	54.29	9.16	8.99
$-n$-C_3H_7	81	66	14	1.4150	57.51	57.40	9.65	9.33
$-n$-C_4H_9	90	73	10	1.4177	59.97	59.83	10.07	9.93
$-n$-C_5H_{11}	84	98	5	1.4218	62.04	61.83	10.41	10.29
$-n$-C_8H_{17}	73	128	8	1.4270	66.63	66.41	11.18	10.79

The results of these condensations are summarized in Table I. The condensations were run under simple equilibration conditions and under forcing conditions. The forcing conditions consisted in stirring the reaction mixtures at reflux under a simple fractionation column while the benzene–methanol azeotrope was removed. Reaction was considered to be complete when distillation of the azeotrope ceased. The high reactivity of methyl dimethoxyacetate as an acylating ester is indicated by the facts that in no case was an excess of the self-condensable ester necessary for good yields of the mixed condensation product and that, except in the case of the methyl pelargonate condensation, forcing conditions resulted in only small improvements in the yields of condensation products.

Each of the methyl α-alkyl-γ,γ-dimethoxyacetoacetates was cleaved by means of dilute aqueous potassium hydroxide to the corresponding α-ketoacetal which was subsequently hydrolyzed by means of dilute aqueous sulfuric acid to the α-ketoaldehyde.

$$(CH_3O)_2CHCO{-}CHR{-}CO_2CH_3 \xrightarrow{\text{dil. KOH}} (CH_3O)_2CH{-}CO{-}CH_2R \xrightarrow{\text{dil. } H_2SO_4} HCO{-}CO{-}CH_2R$$

Good yields of α-ketoacetals were obtained, but only poor to fair yields of α-ketoaldehydes were obtained because of easy polymerization of these substances on attempted distillation. The distilled samples of α-ketoaldehydes polymerized to glasses on standing for a few days at room temperature. The results of these cleavage reactions are summarized in Tables II and III.

TABLE III

PREPARATION OF α-KETOALDEHYDES, R–CO–CHO, BY CLEAVAGE OF α-KETOACETALS

R-group	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	Derivative, m.p.
$-CH_3$	18	75	760	1.3974	Disemicarbazone, 255–257[a]
$-C_2H_5$	22	90	760	1.4006	Phenylosazone, 114–115[b]
$-n$-C_3H_7	20	112	760	1.4034	Phenylosazone, 102.5–104[c]
$-n$-C_4H_9	34	48	12	1.4101	*p*-Nitrophenylosazone, 266–268[d]
$-n$-C_5H_{11}	39	59	10	1.4154	*p*-Nitrophenylosazone, 177–179[e]
$-n$-C_8H_{17}	31	108	12	1.4209	*p*-Nitrophenylosazone, 308[f]

[a] Reported,[3] m.p. 254°. [b] Reported, personal communication from R. R. Seiler, m.p. 116°. [c] Reported, E. B. Reid, R. B. Fortenbaugh and H. P. Patterson, *J. Org. Chem.*, **15**, 572 (1950), m.p. 105°. [d] *Anal.* Calcd. for $C_{18}H_{17}O_4N_6$: C, 56.69; H, 4.49; N, 22.04. Found: C, 56.53; H, 4.41; N, 22.98. [e] Reported, A. Kirrman, P. Chancel, M. Vignalou and P. Federlin, *Bull. soc. chim. (France)*, **17**, 707 (1950), m.p. 177°. [f] *Anal.* Calcd. for $C_{32}H_{27}O_4N_6$: C, 68.68; H, 4.86; N, 15.02. Found: C, 68.62; H, 4.82; N, 14.99.

A series of seven aliphatic and alicyclic ketones was subjected to acylation by means of methyl dimethoxyacetate in the presence of sodium methoxide under reaction conditions similar to those used for ester acylation; α,γ-diketoacetals were obtained in yields ranging from 26 to 62%.

$$R{-}CH_2{-}CO{-}CH_2{-}R + (CH_3O)_2CH{-}CO_2C_2H_5 \xrightarrow{NaOCH_3} (CH_3O)_2CH{-}CO{-}CHR{-}CO{-}CH_2R + 2CH_3OH$$

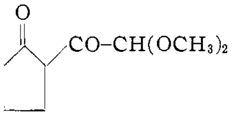
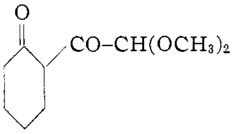
The ketones for this study were so chosen that the problem of methyl *vs.* methylene condensation did not arise. The results of the condensations are summarized in Table IV. In accord with general experience in ester–ketone condensations,[13] higher yields of α,γ-diketoacetals were obtained from condensations involving a methyl group than from those involving a methylene group. Use of a low reaction temperature led to an improved yield from

---

(13) See C. R. Hauser, F. W. Swamer and J. T. Adams in R. Adams "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 65.

TABLE IV

PREPARATION OF α,γ-DIKETOACETALS BY CONDENSATION OF KETONES WITH METHYL DIMETHOXYACETATE

α,γ-Diketoacetal	Cond. method	Yield, %	B.p., °C. (5 mm.)	$n^{25}D$	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
$CH_3-CO-CH_2-CO-CH(OCH_3)_2$	A[a]	39	73	1.4518	52.52	52.48	7.50	7.31
	C[b]	50	73	1.4518				
$CH_2CH_2-CO-CH(CH_3)-CO-CH(OCH_3)_2$	A	32	100	1.4556	57.43	57.41	8.57	8.38
	B[c]	46	100	1.4556				
	C	35	100	1.4556				
$CH_3(CH_2)_2-CO-CH(C_2H_5)-CO-CH(OCH_3)_2$	A	32	131	1.4556	61.09	60.81	9.32	9.09
	B	44	131	1.4556				
$(CH_3)_2CH-CO-CH_2-CO-CH(OCH_3)_2$	A	51	96	1.4560	57.43	57.32	8.57	8.29
	B	60	96	1.4560				
$(CH_3)_2CHCH_2-CO-CH_2-CO-CH(OCH_3)_2$	A	54	108	1.4576	59.39	59.27	8.97	8.88
	B	62	108	1.4576				
	A	32	127	1.4590	58.05	57.86	7.58	7.43
	B	40	127	1.4590				
	A	26	139	1.4598	59.98	59.91	8.06	7.88
	B	38	139	1.4598				

[a] Reaction run at reflux under non-forcing conditions. [b] Reaction run at a temperature of 10°. Reaction run at reflux under forcing conditions.

the condensation of methyl dimethoxyacetate with acetone. The use of forcing conditions gave improved yields of α,γ-diketoacetals from all of the condensations studied, the effect being somewhat greater for those condensations occurring at a methylene group.

All attempts to hydrolyze the α,γ-diketoacetals to α,γ-diketoaldehydes failed. Conditions which led to facile hydrolysis of α-ketoacetals gave only tars when applied to the hydrolysis of α,γ-diketoacetals, presumably because of easy aldol condensation of the α,γ-diketoaldehydes. From a few hydrolysis experiments, traces of ketones were isolated, indicating the occurrence of some cleavage of the β-diketone function.

Condensation of methyl dimethoxyacetate with phenylacetonitrile under forcing conditions led to the formation of 50% of the theoretical quantity of methanol. On attempted distillation of the crude reaction product under reduced pressure extensive resinification occurred, and no homogeneous product could be isolated. Similar results were obtained when the condensation reaction was effected at room temperature. Apparently the condensation product decomposes at the temperature necessary for distillation even at reduced pressure; attempts to crystallize the crude reaction product without distillation were fruitless. Butyronitrile, however, condensed readily with methyl dimethoxyacetate under forcing conditions to give α-ethyl-γ,γ-dimethoxyacetoacetonitrile in 61% yield.

Condensation of methyl dimethoxyacetate with fluorene under forcing conditions gave 9-dimethoxyacetylfluorene[14] in 32% yield. The low yield was probably due to rather extensive decomposition which occurred on distillation of the crude reaction product (b.p. 187° (1 mm.)). During the condensation reaction 65% of the theoretical quantity of methanol was formed. Acid hydrolysis of 9-dimethoxyfluorene gave 9-fluorenylglyoxal in 42% yield.

On attempted condensation of methyl dimethoxyacetate with nitromethane under forcing conditions, 50% of the theoretical amount of methanol was formed, and on working up the reaction mixture 95% of the starting materials were recovered unreacted. Apparently nitromethane was completely converted to its anion by sodium methoxide (giving 1 mole of methanol), but the nitromethane anion failed completely to react with the ester even under the forcing conditions used.

Experimental[15]

Preparation of Methyl Dimethoxyacetate.—Sodium methoxide, 162 g. (3.0 moles), was dissolved in 500 ml. of absolute methanol, and 130 g. of dichloroacetic acid was added slowly to the stirred solution at gentle reflux. Fifty minutes was required for the addition; reflux was continued for 12 hours. The reaction mixture was cooled to 10°, and a solution of 72 g. (2.0 moles) of hydrogen chloride in absolute methanol was added to the stirred mixture at such a rate as to produce no appreciable temperature rise. The mixture was then stirred at room temperature for 18 hours. The mixture was neutralized to litmus using methanolic sodium methoxide, and the precipitated salts were removed from the filtrate by distillation under diminished pressure. The residue was mixed with an equal volume of benzene, and the benzene-immiscible layer was separated. Removal of the benzene and distillation of the residue under vacuum gave 83 g. (62%) of methyl dimethoxyacetate, b.p. 54° (5 mm.), $n^{25}D$ 1.4047.

The above benzene-immiscible layer was covered with 200 ml. of absolute methanol, and the mixture was saturated

---

(14) This compound proved to be a strong skin irritant, and should be handled with care.

(15) Melting and boiling points reported are uncorrected. All analyses reported in this section and in the Tables were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England.

with dry hydrogen chloride. The precipitated salt was removed and the mixture allowed to stand at room temperature overnight, after which it was worked up as described above to give an additional 18 g. of methyl dimethoxyacetate (over-all yield 70%).

General Procedures for Ester Condensations.—The following general procedures were used for condensations of methyl dimethoxyacetate with esters. Data on the individual products are given in Table I.

Method A. Non-forcing Conditions.—A mixture of 0.5 mole of methyl dimethoxyacetate and 0.5 mole of the second ester component was added dropwise to a suspension of 0.5 mole of sodium methoxide in 200 ml. of dry benzene. The resulting mixture was stirred at reflux temperature for 4 hours. The reaction mixture was cooled to below 10° and poured with stirring into an ice cold solution of 50 ml. of glacial acetic acid in an equal volume of water. After all solid material had disappeared, the organic layer was separated, and the aqueous layer was extracted 4 times with 50-ml. portions of ether. The ether extracts were combined with the organic layer and the combined solutions were washed with water, with saturated sodium bicarbonate solution until acid-free, and again with water. The ether solution was dried first over anhydrous sodium sulfate, then over Drierite. After removal of ether by distillation, the residue was distilled through a Claisen head under diminished pressure. Analytical samples were obtained by redistillation through the same apparatus and taking a middle cut of constant boiling point.

Method B. Forcing Conditions.—A mixture of 0.5 mole of methyl dimethoxyacetate and 0.5 mole of the second ester component was added to a suspension of 0.5 mole of sodium methoxide in 200 ml. of benzene under a 24-inch, total condensation, partial takeoff column packed with glass helices. The reaction mixture was heated under total reflux until the head temperature became constant. The benzene–methanol azeotrope was then slowly taken off (b.p. 55–63°) until reaction was complete; the theoretical volume of azeotrope for a run of this size is 84 ml. The forced reactions required reaction times of 2–3 hours. Products were isolated as described above under method A.

General Procedure for Preparation of α-Ketoaldehydes.—The α-alkyl-γ,γ-dimethoxyacetate, 0.2 mole, was dissolved in 75 ml. of methanol and mixed with 130 ml. of 2 *N* potassium hydroxide. The mixture was refluxed for 1 hour. The reaction mixture was cooled and poured into 500 ml. of ice-water. The aqueous system was extracted with ten 25-ml. portions of ether, the extracts were dried over anhydrous sodium sulfate, and the ether was removed by distillation. Distillation of the residues gave α-ketoacetals, the properties of which are recorded in Table II.

The α-ketoacetal, 0.1 mole, was refluxed for 30 minutes with 100 ml. of 5% aqueous sulfuric acid. After cooling, the reaction mixture was extracted with five 25-ml. portions of ether, the extracts were combined, washed to neutrality with saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Removal of the ether and distillation of the residues gave α-ketoaldehydes, the properties of which are recorded in Table III. Extensive polymerization occurred in the still pot during distillation of the α-ketoaldehydes; the purified α-ketoaldehydes changed to semi-solid polymers on standing.

General Procedures for Condensations of Methyl Dimethoxyacetate with Ketones.—The majority of these condensations were run exactly as described above under methods A and B for ester condensations. In certain cases, a third procedure C, described below, was used.

A mixture of 0.5 mole of ketone and 0.5 mole of methyl dimethoxyacetate was added to a stirred slurry of 0.5 mole of sodium methoxide in 200 ml. of benzene cooled in an ice-bath at such rate that the temperature was maintained below 10°. After addition was complete, stirring was continued for 1 hour at 10°, and the reaction mixture was allowed to stand in the refrigerator for 18 hours. The reaction mixture was then worked up as described above under method A for ester condensations.

The properties of the products of these condensations are recorded in Table IV.

Condensation of Methyl Dimethoxyacetate with *n*-Butyronitrile.—A mixture of 30 g. (0.5 mole) of *n*-butyronitrile and 67 g. (0.5 mole) of methyl dimethoxyacetate was added to a slurry of 27 g. (0.5 mole) of sodium methoxide in 200 ml. of benzene, and the condensation was run as described under method B for ester condensations. The volume of distillate collected was 86% of the theoretical. Distillation of the crude product through a Claisen still gave 51 g. (61%) of α-(dimethoxyaceto)-butyronitrile, b.p. 105° (2 mm.), $n^{25}\mathrm{D}$ 1.4330. *Anal.* Calcd. for $C_8H_{13}O_3N$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.07; H, 7.40; N, 7.95.

Condensation of Methyl Dimethoxyacetate with Fluorene.—Fluorene, 83 g. (0.5 mole), and 67 g. (0.5 mole) of methyl dimethoxyacetate were added to a slurry of 27 g. (0.5 mole) of sodium methoxide in 200 ml. of benzene, and the condensation was run under forcing conditions as described under method B above. The reaction mixture, after cooling, was mixed with 500 ml. of ice-water, the organic layer was separated, and the aqueous layer was twice extracted with 50-ml. portions of ether. The aqueous layer was then carefully neutralized to litmus with 50% aqueous acetic acid, and the condensation product was isolated as described above under method A for ester condensations. Distillation of the crude reaction product gave 40 g. (32%) of 9-methoxyacetylfluorene, b.p. 187° (1 mm.), $n^{25}\mathrm{D}$ 1.5812. *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.06; H, 5.77. Extensive resinification occurred during distillation of this material. The pure product had a strongly irritating skin action.

Preparation of 9-Fluorenylglyoxal.—9-Methoxyacetylfluorene, 26 g. (0.1 mole), was covered with 100 ml. of 5% aqueous sulfuric acid and left at room temperature for 18 hr. Filtration of the resulting solid mass of crystals and crystallization from aqueous methanol gave a light yellow powder which readily gave positive Fehling and Tollens tests. Recrystallization from aqueous methanol gave 9 g. (42%) of 9-fluorenylglyoxal, m.p. 81°. *Anal.* Calcd. for $C_{13}H_{10}O_2$: C, 81.06; H, 4.54. Found: C, 80.94; H, 4.26. This material gradually turned light red on standing for 3 weeks.

EMORY UNIVERSITY, GEORGIA