After cooling, the contents of the tube were evaporated to dryness under reduced pressure, and the solid residue boiled with 20 ml. of ethanol, which failed to dissolve all the material. This very low solubility in ethanol is in contrast with the properties of the starting methobromide. The flask was cooled overnight in the ice-box, and the solid filtered off, giving 55 mg. of crystals of high decomposition point. These could be recrystallized in long needles, by dissolving in 30 ml. of ethanol containing 2 ml. of water, and removing most of the water by repeated boiling with benzene. The product melted at 270° with rapid heating, if inserted in the melting-point block at 250°. It gave an X-ray powder photograph which was quite distinct from that of the starting material, yield 92%.

Anal. Calcd. for $C_7H_{15}Br_2NS$: C, 27.55; H, 4.96; N, 4.59; S, 10.51; ionic Br, 52.40. Found: C, 28.05; H, 5.10; N, 4.60; S, 10.91; ionic Br, 52.58.

This reaction was carried out also at room temperature, by allowing 70 mg. of 4-(2-bromoethyl)-thiamorpholine N-methobromide in 5 ml. of 40% hydrobromic acid to stand for 172 days. The reaction mixture was worked up as before, yielding 67 mg. (96%) of 4-azabicyclo(2,2,2)octane-1-thionium bromide methobromide, which was identified by its X-ray powder photograph.

(2) From 4-(2-Hydroxyethyl)-thiamorpholine N-Methobromide.—A solution of 150 mg. of 4-(2-hydroxyethyl)-thiamorpholine N-methobromide in 3 ml. of 42% hydrobromic acid was heated at 100° in a sealed tube for 285 hours. The product was worked up as in the previous preparation yielding 40 mg. of small prismatic crystals of high decomposition point. The X-ray powder photograph of this substance was identical to that given by the product of the previous run; yield 26%.

Anal. Calcd. for $C_7H_{15}Br_2NS$: C, 27.55; H, 4.96; Br, 52.40. Found: C, 27.77; H, 5.22; Br, 52.32.

Concentration of the alcoholic mother liquors yielded 95 mg. of starting material.

OTTAWA, ONTARIO

[CONTRIBUTION FROM THE CHEMOTHERAPY DEPARTMENT, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

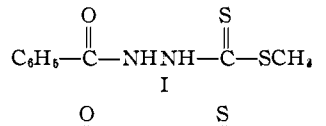
The Cyclization of 3-Acyldithiocarbazate Esters[1]

BY RICHARD W. YOUNG AND KATHRYN H. WOOD

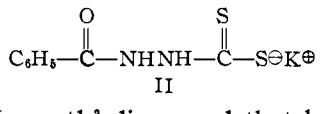
RECEIVED JULY 7, 1954

Acid-catalyzed cyclodehydration of 3-acyldithiocarbazic acid esters has been shown to produce 2-substituted 5-sulfido-1,3,4-thiadiazoles. The mechanism for this reaction as well as for the formation of 1,3,4-oxadiazoles in alkaline cyclizations is discussed. A series of 2-substituted-5-mercapto-1,3,4-oxadiazoles and 2-substituted-5-benzylmercapto-1,3,4-thiadiazoles has been prepared.

In the course of an investigation of the stereochemistry of hydrazones, Busch and Starke[2] prepared methyl-3-benzoyldithiocarbazate (I) by methylation of the salt formed from benzoic acid hydrazide and carbon disulfide in alcoholic potassium hydroxide. Although no evidence was put forth, the salt was assigned the structure II.



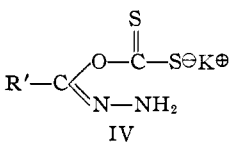
I



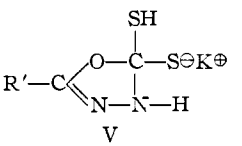
II

Recently Hoggarth[3] discovered that both the salt and the ester could be converted to 2-phenyl-5-mercapto-1,3,4-oxadiazole (III) by boiling in pyridine solution. In our own work, we found that the salt need not be isolated; merely refluxing of the alcoholic alkaline solution containing the hydrazide and carbon disulfide results in evolution of hydrogen sulfide and an excellent yield of III is obtained. (The same oxadiazole was obtained by refluxing the ester (I) with sodium ethylate in ethanol.) Other 2-substituted oxadiazoles were prepared from the corresponding hydrazides in the same manner (Table I).

The mechanism of the formation of oxadiazoles under these conditions is interesting, in view of the structures proposed for I and II. Instead of the formation of II as the initial product of the reaction, the first logical intermediate should be formed by a nucleophilic attack of the enolate ion of the hydrazide on carbon disulfide forming a "xanthate-type" salt IV.[4] By intramolecular acylation of the neighboring amino function the oxadiazole would be produced with concomitant loss of hydrogen sulfide or, alternatively, IV might rearrange to II *via* an intermediate oxadiazoline V



IV



V

analogous to the intermediate suggested[5] for the N → O and O → N acyl migrations of amino alcohols. Furthermore, V would be involved in formation of the oxadiazoles under these conditions whether derived from II or IV. The fact that alkylation of the salt produced I does not constitute structural evidence for the salt in view of the possibility for rearrangement after alkylation.[6]

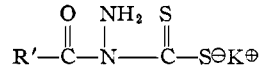
By analogy with the amino alcohol systems, an attempt was made to effect the N → O migration of I to the ester corresponding to IV, by dissolving I in concentrated sulfuric acid for a few minutes.

(1) Presented in part before the Division of Organic Chemistry of the American Chemical Society, New York, N. Y., September, 1954.

(2) M. Busch and M. Starke, *J. prakt. Chem.*, [2] **93**, 49 (1916).

(3) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(4) The possibility for the formation of the other carbazate salt is recognized but is not considered, in view of the necessity for prior rearrangement to either II or IV in order to produce the observed products.

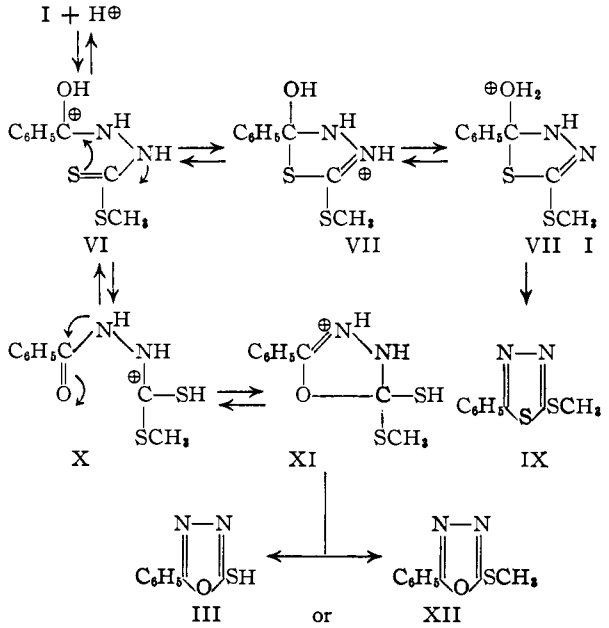


(5) (a) M. Bergmann, E. Brand and F. Weinmann, *Z. physiol. Chem.*, **131**, 1 (1923); (b) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).

(6) The infrared spectrum of the dry salt in Nujol mull did not permit a decision between the alternative structures, although the low amide absorption (1615 cm.$^{-1}$) tends to favor IV.

Dilution of the solution with water produced, instead, a high yield of 2-phenyl-5-methylmercapto-1,3,4-thiadiazole (IX) as the only product. The structure of IX was demonstrated by analysis, by oxidation to the sulfone, and by comparison with the product made by alkylation of the mercapto thiadiazole formed by the reaction of carbon disulfide and thiobenzoic acid hydrazide in alcoholic potassium hydroxide.[7]

This product must have arisen from protonization of the amide carbonyl followed by internal attack of this carbonium ion by the sterically favorable thiono group forming a thiadiazolinium ion VII from which the product is derived by acid-catalyzed dehydration (VI → IX)



It is possible that an equilibrium exists between VII and XI or at least between the corresponding protonated straight chain precursors VI and X, the position of which could be influenced by the relative nucleophilic character of oxygen *vs.* sulfur or by steric hindrance around the carbonyl carbon.[8] In the two examples in which the equilibrium might be shifted by steric factors, the *ortho*-substituted benzyl-3-benzoyldithiocarbazates, no oxadiazoles could be isolated, although the possibility that small quantities were formed cannot be excluded. Both 2-phenyl-5-mercapto- and 2-phenyl-5-benzylmercapto-1,3,4-oxadiazole can be recovered from concentrated sulfuric acid unchanged; so, if formed, oxadiazoles should be isolable.

The cyclization employing concentrated sulfuric acid has been applied to a series of benzyl-3-acyldithiocarbazates[9] (Table III) and illustrates a convenient synthesis of the thiadiazole ring which circumvents the tedious preparation of thiohydrazides.[10]

This reaction has been effected with other acids, *e.g.*, polyphosphoric and *p*-toluenesulfonic. In two cases, the 3-acyldithiocarbazate was not isolated. Heating benzyldithiocarbazate in refluxing formic acid produced 2-benzylmercapto-1,3,4-thiadiazole directly and heating benzyldithiocarbazate with trifluoroacetic anhydride produced 2-trifluoromethyl-5-benzylmercapto-1,3,4-thiadiazole.

The previous method[2,3] for the preparation of the requisite 3-acyldithiocarbazate esters started with the hydrazide. It was found convenient in this work to prepare acylcarbazates by the reaction of an acid chloride or anhydride with a dithiocarbazic acid ester, thus avoiding the preparation of hydrazides. The identity of the acyl esters prepared by these two methods also serves to confirm the structure originally assigned to them by Busch.[2]

Acknowledgment.—The analyses were performed by the staff of the Microanalytical Laboratory under the direction of Dr. J. A. Kuck.

Experimental[11]

Preparation of 2-Substituted-5-mercapto-1,3,4-oxadiazoles (Table I).—To a solution containing 200 cc. of 95% ethanol and 0.05 mole of potassium hydroxide (dissolved in 10 cc. of water) there was added 0.05 mole of the hydrazide. After solution occurred, slightly more than one equivalent of carbon disulfide was added and the mixture was held at reflux for 2–3 hours or until most of the hydrogen sulfide had been evolved. Occasionally a solid appeared upon the addition of carbon disulfide, but this usually dissolved on heating. After concentration of the solution to a small volume, the residue was dissolved in water. A precipitate was obtained by adding the solution to ice containing hydrochloric acid. The solid was filtered off and dried. These compounds were recrystallized from alcohol or purified by redissolving in alkali and reprecipitating with acid.

In addition to the standard procedure above, **2-phenyl-5-mercapto-1,3,4-oxadiazole (III)** was prepared by refluxing for 2 hours a solution of 1.01 g. (0.0033 mole) of benzyl-3-benzoyldithiocarbazate in 15 cc. of ethanol containing 0.08 g. of sodium. Concentration of the solution and isolation as before gave an 86% yield.

Preparation of Benzyl 3-Acyldithiocarbazates (Table II).—To a solution of 0.1 mole of benzyl dithiocarbazate[12] in 100 cc. of pyridine there was added 0.1 mole of acyl chloride, causing the temperature to rise to 60–70°. The solution was held at 80–90° on the steam-bath for one hour after which time it was poured onto about 700 cc. of ice containing 75 cc. of concentrated sulfuric acid. The resulting product (usually a sticky solid) was extracted into ethyl acetate, the latter being washed with two 100-cc. portions of water. After being dried over sodium sulfate and concentrated almost to dryness the resultant solid was triturated with ether. This product was usually satisfactory for the next step. The compounds were recrystallized from benzene for analysis.

Preparation of 2-Substituted-5-benzylmercapto-1,3,4-thiadiazoles (Table III).—The benzyl-3-acyldithiocarbazate

(7) J. Sandström [*Arkiv Kemi*, **4**, 297 (1952)] reported the isolation of 2-phenyl-5-mercapto-1,3,4-thiadiazole as one of the products of the reaction of potassium thiobenzoylthioglycolate with ethyl dithiocarbazate.

(8) A referee suggested that the formation of IX was favored by the greater ease of acid-catalyzed elimination of water (from VII) rather than of methyl mercaptan or hydrogen sulfide (from XI).

(9) Benzylmercaptothiadiazoles were desired as intermediates for the preparation of sulfonyl chlorides and sulfonamides according to the chlorinative oxidation procedure reported first by T. Zincke and O. Kruger, *Ber.*, **45**, 3468 (1912). The exploitation of this reaction for the preparation of heterocyclic sulfonamides will be reported in a later paper.

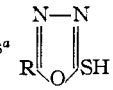
(10) The cyclization conditions parallel those used by Hoggarth [*J. Chem. Soc.*, 1163 (1949)] for the conversion of 1-benzoylthiosemicarbazides to 2-substituted-5-amino-1,3,4-thiadiazoles. In addition to the possibility for thiadiazole and oxadiazole formation, the reactions of acylthiosemicarbazides are complicated further by the possibility for triazole formation.

(11) All melting points are corrected and were taken on a Fisher–Johns block.

(12) Benzyl dithiocarbazate was prepared according to the procedure of Busch and Starke[2] except that the crude product could be purified by triturating with anhydrous ether giving material m.p. 126–127°. The crude product may also be recrystallized from toluene, but fairly large quantities are required.

TABLE I

2-SUBSTITUTED-5-MERCAPTO-1,3,4-OXADIAZOLES[a]

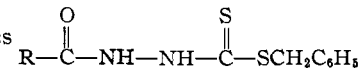


R	M.p., °C. (cor.)	Yield,[b] %	Analyses, % Calcd. C	H	N	Found C	H	N
C_6H_5[c]	219–220	69	53.9	3.39	15.7	54.0	3.40	15.8
p-ClC_6H_4[d]	176.5–178	66	45.2	2.37	13.2	45.6	2.54	13.2
2-Thiazolyl-	193–195	40	32.4	1.63	22.7	32.3	1.72	22.5
2-Furyl-	177–179.5	65	42.8	2.40	16.7	43.1	2.64	16.6
4-Pyridyl-	272–272.5	49	46.9	2.81	23.4	46.9	2.90	23.1

[a] These compounds are expressed as mercapto oxadiazoles rather than as thiono oxadiazolines for simplicity, although it is recognized that they probably exist as thiono derivatives, in the solid state at least. [b] Yields refer to recrystallized product. [c] Literature m.p. 218–220° (ref. 3). [d] Literature m.p. 175–176° (ref. 3).

TABLE II

BENZYL-3-ACYLDITHIOCARBAZATES

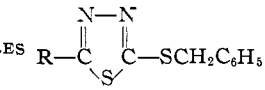


R	Empirical formula	M.p., °C. (cor.)	Yield, %	Analyses, % Calcd. C	H	Found C	H
H	$C_9H_{10}N_2OS_2$	129–130	50[a]	47.8	4.45	47.8	4.56
CH_3	$C_{10}H_{12}N_2OS_2$	142.5–145	72[b]	50.0	5.04	50.2	5.17
$C_6H_5CH_2$	$C_{16}H_{16}N_2OS_2$	115–116	69	60.7	5.10	60.9	5.22
C_6H_5	$C_{15}H_{14}N_2OS_2$	156.5–158	66	59.6	4.67	59.4	4.71
2-IC_6H_4	$C_{15}H_{13}IN_2OS_2$	132–134	32	42.1	3.06	41.8	3.01
2-ClC_6H_4	$C_{15}H_{13}ClN_2OS_2$	138–140	72	53.5	3.89	53.3	4.07
4-ClC_6H_4	$C_{15}H_{13}ClN_2OS_2$	152–154.5	49	53.5	3.89	53.0	3.95
3,4-$Cl_2C_6H_3$	$C_{15}H_{12}Cl_2N_2OS_2$	158–159	51	48.5	3.26	48.5	3.10
4-$NO_2C_6H_4$	$C_{15}H_{13}N_3O_3S_2$	188–190	54	51.9	3.77	52.0	3.73

[a] This was prepared by the cautious addition of formic–acetic anhydride to benzyl dithiocarbazate slurried in cold ether. About 30–40% of the thiadiazole was isolated. [b] A 44% yield was obtained when benzyl dithiocarbazate was warmed for 5 minutes with acetic anhydride.

TABLE III

2-SUBSTITUTED-5-BENZYLMERCAPTO-1,3,4-THIADIAZOLES



R	Empirical formula	M.p., °C. (cor.)	Yield, %	Analyses, % Calcd. C	H	Found C	H
H	$C_9H_8N_2S_2$	60.5–62	83[a]	51.9	3.87	52.2	3.82
CH_3	$C_{10}H_{10}N_2S_2$	63–64	59	54.0	4.53	53.8	4.64
CF_3	$C_{10}H_7F_3N_2S_2$	45.5–46	92[b]	43.5	2.55	43.3	2.65
$C_6H_5CH_2$	$C_{10}H_{14}N_2S_2$	36–36.3	82	64.4	4.73	64.1	4.81
C_6H_5	$C_{15}H_{12}N_2S_2$	111.5–112.5	81	63.3	4.26	63.6	4.48
2-IC_6H_4	$C_{15}H_{11}IN_2S_2$	61–61.8	60	43.9	2.70	44.1	2.65
2-ClC_6H_4	$C_{15}H_{11}ClN_2S_2$	85.5–86	88	56.5	3.48	56.4	3.45
4-ClC_6H_4	$C_{15}H_{11}ClN_2S_2$	134.5–136	68	56.5	3.48	56.6	3.06
3,4-$Cl_2C_6H_3$	$C_{15}H_{10}Cl_2N_2S_2$	130–131	78	51.0	2.85	51.3	3.05
4-$NO_2C_6H_4$	$C_{15}H_{11}N_3O_2S_2$	187–189	78	54.7	3.37	54.8	3.48

[a] Prepared from benzyl ditliiocarbazate and formic acid–acetic anhydride. Yields of 80–90% were obtained by heating a formic acid solution of benzyl dithiocarbazate. [b] Prepared by heating benzyl dithiocarbazate and trifluoroacetic anhydride.

was dissolved in a minimum of concentrated sulfuric acid (5–10 cc./g. of compound) at room temperature. Usually the temperature rose to 40–50°. After solution was complete (about 3 minutes), the reaction mixture was poured on to ice (about 50 cc./g. of compound) with external cooling. The resultant precipitate was filtered off and recrystallized from alcohol.

2-Benzylsulfonyl-1,3,4-thiadiazole.—Oxidation of a solution of 1.13 g. of 2-benzylmercapto-1,3,4-thiadiazole in 20 cc. of glacial acetic acid at 60° with 120 cc. of a 3% aqueous solution of potassium permanganate gave a brown suspension which was decolorized with sulfur dioxide. Upon cooling, a colorless oil separated, which solidified and was filtered off, washed and dried. A yield of 1.1 g. (79%), m.p. 110–112°, of **2-benzylsulfonyl-1,3,4-thiadiazole** was obtained. Recrystallization from hot water gave 0.89 g. (64%), m.p. 112–113°.

Anal. Calcd. for $C_9H_8N_2O_2S_2$: C, 45.0; H, 3.34; N, 11.7. Found: C, 44.7; H, 3.37; N, 11.9.

2-Phenyl-5-methylmercapto-1,3,4-thiadiazole (IX).—The cyclization of methyl 3-benzoyldithiocarbazate (I) proceeded in 85% yield when conducted in sulfuric acid according to the general procedure. When I was warmed for 18 hours at 85° in commercial polyphosphoric acid a 69% yield was isolated. Refluxing a 4% solution of I in benzene containing 0.4% of *p*-toluenesulfonic acid monohydrate gave a 74% yield of IX. This material may be conveniently crystallized by dissolving in petroleum ether and cooling to −40°. The crystalline solid has m.p. 56.5–57°.

Anal. Calcd. for $C_9H_8N_2S_2$: C, 51.9; H, 3.9; N, 13.5. Found: C, 51.6; H, 3.9; N, 13.3.

2-Phenyl-5-mercapto-1,3,4-thiadiazole.—This compound was prepared in 75% yield, m.p. 215–217°, from thiobenzoic

acid hydrazide[13] by the procedure used for the corresponding oxadiazole.

Anal. Calcd. for $C_8H_6N_2S_2$: C, 49.5; H, 3.11; N, 14.4. Found: C, 49.5; H, 3.31; N, 14.2.

An ethanolic solution of 2-phenyl-5-mercapto-1,3,4-thiadiazole containing one equivalent of sodium ethylate was methylated with methyl iodide giving IX, m.p. 56.5–57° after crystallization from aqueous methanol. It was identical in m.p. and mixed m.p. and in infrared spectrum with IX prepared from benzyl-3-benzoyldithiocarbazate.

2-Phenyl-5-methylsulfonyl-1,3,4-thiadiazole.—A solution of 5.3 g. of IX in 300 cc. of 50% acetic acid was cooled to 10° during the 30-minute addition of chlorine gas. A solid precipitated from the solution, m.p. 130–150°, which rose to 159–160° after crystallization from ethyl acetate–petroleum ether.

Anal. Calcd. for $C_9H_8N_2O_2S_2$: C, 45.0; H, 3.36; N, 11.7. Found: C, 44.9; H, 3.30; N, 11.5.

STAMFORD, CONNECTICUT

(13) B. Holmberg, *Arkiv Kemi Mineral Geol.*, **17A**, 1 (1944).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF ARTS AND SCIENCES, UNIVERSITY OF LOUISVILLE]

2-Pyrones. XII. γ-Keto-β-methylglutaconic Anhydride Arylhydrazones and Their Conversion to 1-Aryl-3-carboxy-4-methyl-6-pyridazones

BY RICHARD H. WILEY AND C. H. JARBOE, JR.[1]

RECEIVED JULY 6, 1954

Eleven aryldiazonium salts have been coupled with β-methylglutaconic anhydride to give products for which several tautomeric structures may be written. These products are intensely colored with characteristic absorption spectra. The γ-keto-β-methylglutaconic anhydride arylhydrazone structure II is indicated by ultraviolet and infrared absorption data. On hydrolysis with dilute alkali or acid, these hydrazones are converted to 1-aryl-3-carboxy-4-methyl-6-pyridazones (IV). The structure of 1-phenyl-3-carboxy-4-methyl-6-pyridazone has been established by its decarboxylation to the known 1-phenyl-4-methyl-6-pyridazone.

In previous papers, we have described[2,3] condensation reactions of β-methylglutaconic anhydride with a series of aldehydes and with several acid anhydrides. We wish to report the results of a continuing study of such reactions in which we have condensed a variety of aryldiazonium salts with this anhydride to form eleven previously uncharacterized products. There are apparently only two references in the literature reporting coupling reactions of this type. These include the reaction of benzenediazonium chloride with β-carboxyglutaconic anhydride (*trans*-aconitic anhydride)[4] and with β-chloroglutaconic anhydride.[5] The products of these reactions were assigned phenylhydrazone structures on the basis of negative ferric chloride enol tests.

The data characterizing eleven new products obtained by coupling the aryldiazonium salt with β-methylglutaconic anhydride are given in Table I. These products precipitated on adding a cold, alkaline solution of the anhydride to the diazotized amine and were recrystallized from carbon tetrachloride or ethyl acetate. Dinitroaniline was diazotized in concd. sulfuric acid and the sulfanilic acid product was precipitated at −20°. Benzidine and its 3,3′-methoxy derivative gave uncharacterizable solids. The colors varied from yellow to blue.

The ultraviolet absorption data for three of these coupling products and some related compounds are given in Table II. All three of these products are characterized by absorption maxima in the 225–240 mμ region and in the 365–400 mμ region. In addition, the phenyl and diethylaminophenyl compounds show intermediate maxima. None show a maximum at 340 mμ. Comparison of these data with the absorption data for reference compounds permits the following structural correlations. The absorption in the 225–240 mμ region is observed also with β-methylglutaconic anhydride and is attributable to the carbonyl group present in all of these compounds. The absorption in the 350–400 mμ region is characteristic of phenylhydrazones.[6] Both the wave length and intensity of the absorption band for the dinitrophenyl compound are comparable to those associated with many varieties of 2,4-dinitrophenylhydrazones. The absorption observed at 370 mμ with the unsubstituted phenyl derivative is attributable to the phenylhydrazone linkage and the absorption at 400 mμ observed with the diethylamino derivative is attributable to hydrazone absorption shifted to longer wave lengths under the influence of the diethylamino groups. The only appearance of an absorption band at frequencies characteristic of the azo linkage is that at 325 mμ (log ε 4.19) for the diethylamino derivative. However, this absorption maximum corresponds to that at 285 mμ in the curve for the unsubstituted phenyl analog, shifted to longer wave lengths under the influence of the diethylamino group. The absence of absorption at 340 mμ, as well as negative ferric chloride enol tests, is indicative of the absence of the enolic hydroxyl. Such enolic absorption is observed with β-methylglutaconic anhydride but is weak and, as with the dialkyl glutaconates,[7] does not obey Beer's law, is stronger in dilute alkali

(1) The authors wish to acknowledge support of this research through a grant (NSF-G55) from the National Science Foundation. For the previous paper in this series see R. H. Wiley and A. N. Moyer, THIS JOURNAL, **76**, 5706 (1954).

(2) R. H. Wiley, E. L. DeYoung and N. R. Smith, *ibid.*, **76**, 1675 (1954).

(3) R. H. Wiley and N. R. Smith, *ibid.*, **74**, 3893 (1952).

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