

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

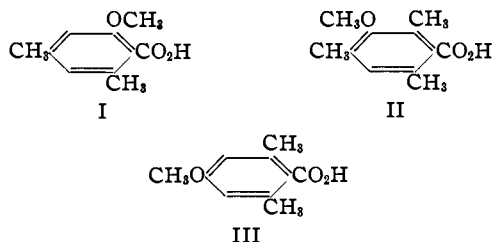
Eneidiols. VIII.¹ Methoxystilbenediols

BY REYNOLD C. FUSON, JOSEPH CORSE AND P. B. WELLDON

The remarkable permanence of the enediol group in the stilbenediols derived from mesitoic, 2,4,6-triethylbenzoic, 2,4,6-triisopropylbenzoic and 2,6-xylic acids appears to be closely related to the so-called ortho effect. It is possible also that the aromatic character of the rings has a profound influence on the behavior of these enediols. This suggestion might be evaluated by a study of a purely aliphatic or alicyclic analog in which the enediol group is joined to radicals that are known to exert hindrance. This project is now under way, but experimental difficulties make progress slow. In the meantime, it seemed feasible to gain a clue to the answer by a study of an enediol from an aromatic acid in which the ring carried a substituent which is known to alter greatly the character of the nucleus.

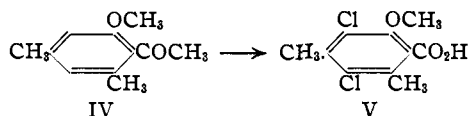
The methoxyl group was selected for reasons of expedience and because it is known to change the nature of the benzene ring to a remarkable degree. The problem attacked was to determine whether there was a corresponding variation in the character of the related stilbenediol. The plan was to synthesize diols having the methoxyl group ortho, meta or para to the enediol group and to be otherwise as closely similar as possible to that from mesitol.

The first problem was the preparation of suitably substituted benzoic acids. For various reasons the choice fell on 6-methoxy-2,4-xylic (I), 3-methoxymesitoic (II) and 2,6-dimethylanisic (III) acids.



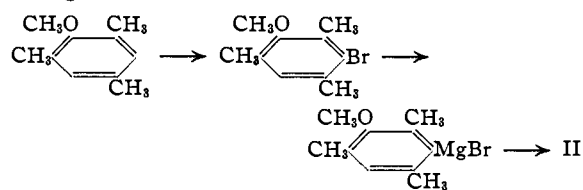
An attempt to prepare the ether of the 6-hydroxy-2,4-xylic acid was made by subjecting the corresponding acetophenone (IV) to the action of sodium hypochlorite. Unfortunately for our purpose, the degradation was accompanied by nu-

clear chlorination; the product was 6-methoxy-3,5-dichloro-2,4-xylic acid (V).



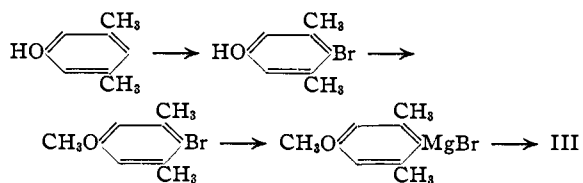
The phenolic acid was obtained from 3,5-xyleneol by the Kolbe method and gave the desired methoxy derivative (I) when methylated. However, the yield by this method was unsatisfactory. No attempt was made to carry the synthesis through to the enediol.

The mesitoic acid was made from the methyl ether of mesitol by the following sequence of changes.

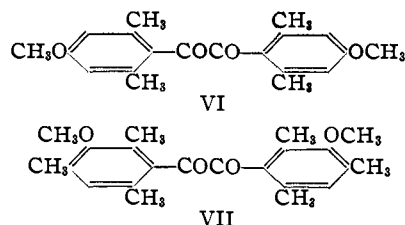


The yield in the bromination was 87%; replacement of the bromine atom by the carboxyl group took place in yields of 43%.

The anisic acid (III) was obtained from 3,5-xyleneol by the following transformations.



The bromination, methylation and carbonation gave yields of 63, 84 and 69%, respectively. By the action of the binary mixture, Mg + MgI₂,² on the corresponding acid chloride this substance was converted to the desired benzil, 2,2',6,6'-tetramethylanisil (VI). The corresponding enediol

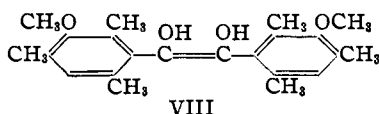


(1) For the preceding article in this series, see Fuson, Scott and Lindsey, *THIS JOURNAL*, **63**, 1679 (1941).

(2) Gomberg and Bachmann, *ibid.*, **49**, 236 (1927).

could not be isolated as a product of the coupling reaction. From the catalytic hydrogenation of the benzil (VI) there was obtained a solid compound which was undoubtedly an enediol, since it gave the characteristic test with sodium 2,6-dichlorobenzeneoneindophenol. This enediol was the most unstable of any of the stilbenediols yet isolated; it was oxidized to the diketone (VI) immediately upon exposure to air. Its extreme instability may be attributed to the effect of the methoxyl groups in the para positions. Replacement of the para hydrogen atoms by bromine in the case of 2,6-xylyl caused a similar decrease in the stability of the resulting enediols.¹

3,3'-Dimethoxymesityl (VII) proved to be the most readily accessible of the three benzils originally sought and, as a consequence, the investigation resolved itself into a study of this diketone. Actually, when it was prepared by treating 3-methoxymesityl chloride with the binary mixture, Mg-MgI₂, the chief product was an enediol (VIII). In one experiment the yield of this enediol was 55% while that of the diketone was only 26%.



The enediol obtained in this way melted at 138.5–139.5° and probably has the *cis*-configuration. Hydrogenation of the benzil gave a second enediol—presumably the *trans*-isomer—which melted at 232–233°. These enediols possess the same remarkable properties observed in stilbenediols which contain no methoxyl groups. The *cis*-enediol was appreciably oxidized by twenty minutes of exposure to the air. The *trans* form remained colorless after two weeks of contact with the air. Neither form showed any tendency to ketonize spontaneously.

Experimental

6-Methoxy-3,5-dichloro-2,4-xylic Acid.—To a solution consisting of 34.5 g. of sodium hypochlorite and 7 g. of sodium hydroxide, dissolved in 400 cc. of water and 100 cc. of pyridine, was added 8 g. of 2,4-dimethyl-6-methoxyacetophenone. The mixture was stirred vigorously for seventy-two hours. It was then extracted with ether, and the ether extract, in turn, was extracted with 10% potassium hydroxide solution. The original aqueous layer was combined with the basic extract, diluted with 500 cc. of water, and carefully acidified. The solid acid thus precipitated was purified by solution in dilute potassium bicarbonate solution, filtration and reprecipitation. It weighed 4.5

g. and, after recrystallization from aqueous methanol, melted at 120–121°.

*Anal.*³ Calcd. for C₁₀H₁₀O₃Cl₂: C, 48.21; H, 4.05; neutral equivalent, 249.1. Found: C, 48.34; H, 4.11; neutral equivalent, 248.6.

6-Methoxy-2,4-xylic Acid.—Eighty grams of dry sodium 3,5-dimethylphenoxide was placed in a 500-cc. glass-lined bomb in layers with dry-ice. The bomb was sealed as quickly as possible and heated to 110° for nine hours. The contents were removed and suspended in water. The *sym-m*-xylenol was collected on a filter. The filtrate was acidified; the precipitate formed was purified by solution in 10% potassium bicarbonate solution and reprecipitation. After recrystallization from ether–low-boiling petroleum ether, the 6-hydroxy-2,4-xylic acid melted at 164–165°. The yield was 12 g. (10% of the theoretical amount).

The hydroxy acid was methylated with 10% sodium hydroxide solution and methyl sulfate. The crude ester (10 g.) thus obtained was dissolved in 100 cc. of ethanol; 10 cc. of water and 20 g. of potassium hydroxide were added, and the solution was refluxed for sixty hours. Acidification gave 7 g. of 3-methoxy-2,4-xylic acid melting at 166.5–167° (53% yield, based on the hydroxy acid).⁵

3-Methoxybromomesitylene.—The procedure was that described for the preparation of bromomesitylene in "Organic Syntheses."⁶ Seventy-five grams of mesityl methyl ether gave 100 g. of the bromo compound; yield, 87%; b. p. 132–135° (17 mm.); m. p. 8°; *n*²⁰_D 1.5472; *d*²⁰₄ 1.3420.

Anal. Calcd. for C₁₀H₁₀OBr: C, 52.40; H, 5.72; Br, 34.89. Found: C, 52.49; H, 5.88; Br, 34.85.

3-Methoxymesitylic Acid.—The procedure described by Fuson and Corse⁷ for the preparation of 2,4,6-triethylbenzoic acid was employed to convert the bromo compound to the acid through the corresponding Grignard reagent. Forty grams of 3-methoxybromomesitylene gave 14.5 g. of 3-methoxymesitylic acid; yield, 43%. The acid melted at 104.5–105.5°. Neutral equivalent calculated for C₁₁H₁₄O₃, 194; found, 192, 193.

The acid was converted to the acid chloride in 82% yield by means of thionyl chloride, using the procedure of Fuson, Corse and McKeever⁸ for the preparation of 2,4,6-triethylbenzoyl chloride. The acid chloride boiled at 138–139° (15 mm.).

3-Methoxymesitylamide was prepared by the reaction of the acid chloride with liquid ammonia. After the crude solid product had been extracted with hot, dilute sodium hydroxide solution to remove traces of acid and recrystallized from benzene–high-boiling petroleum ether, it was obtained in 50% yield as white needles, m. p. 169°.

Anal. Calcd. for C₁₁H₁₄O₂N: C, 68.35; H, 7.83; N, 7.25. Found: C, 68.24; H, 7.74; N, 7.31.

(3) The analyses reported in this paper are microanalyses. They were carried out by Mr. L. G. Fauble and Miss Mary S. Kreger.

(4) German Patent 254,122; Friedländer, 11, 232; Chem. Zentr. 84, 1, 133 (1913).

(5) Auwers and Sauerwein, Ber., 55, 2380 (1922).

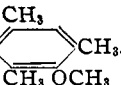
(6) Org. Syntheses, 11, 24 (1931).

(7) Fuson and Corse, THIS JOURNAL, 60, 2063 (1938).

(8) Fuson, Corse and McKeever, *ibid.*, 61, 2010 (1939).

TABLE I

Compound	M. p., °C.	Solvent	Analyses, %			
			Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$\begin{array}{c} \text{OH} \quad \text{OH}^a \\ \quad \\ \text{RC}=\text{CR} \\ \quad \\ \text{RCOCOR} \end{array}$	138.5–139.5 ^b	Ether–low-boiling petroleum ether	74.11	74.24	7.92	8.17
	78–79	Methanol	74.53	74.68	7.40	7.46
$\begin{array}{c} \text{OH} \\ \\ \text{RC}=\text{CR}^c \\ \\ \text{OH} \end{array}$	232–233 ^b	Benzene–low-boiling petroleum ether	74.11	73.92	7.92	7.94
$\begin{array}{c} \text{CH}_3\text{COO} \\ \\ \text{RC}=\text{CR}^d \\ \\ \text{OCOCH}_3 \end{array}$	192–193	Methanol	70.87	70.73	7.33	7.19
$\begin{array}{c} \text{CH}_3\text{COO} \quad \text{OCOCH}_3^e \\ \quad \\ \text{RC}=\text{CR} \end{array}$	134–135	Low-boiling petroleum ether	70.87	70.97	7.33	7.41

^a R = . ^b Determined in a nitrogen-filled capillary tube. ^c Prepared by the hydrogenation of the

benzil in methanol in the presence of a trace of piperidine; cf. Fuson, Scott, Horning and McKeever, *ibid.*, **62**, 2091 (1940). ^d Prepared by the action of acetic anhydride on the *trans*-enediol.⁸ ^e Prepared by reduction of the benzil in acetic anhydride; cf. Thompson, *ibid.*, **61**, 1281 (1939).

4-Bromo-3,5-dimethylphenol.—The procedure was that described by Auwers, Borsche and Steinich⁹ for the bromination of *sym-m*-xylenol. From 122 g. of the phenol there was obtained 112 g. of the bromophenol, melting at 112–114°; yield, 63%.

4-Bromo-3,5-dimethylanisole.¹⁰—The methylation of 4-bromo-3,5-dimethylphenol was accomplished by means of dilute sodium hydroxide solution and methyl sulfate. From 118 g. of the phenol there was obtained 106 g. of the anisole, boiling at 131–134° (14–15 mm.); yield, 84%.

2,6-Dimethylanisic Acid.—The Grignard reagent was prepared by the slow addition of a solution of 106 g. of 4-bromo-3,5-dimethylanisole in 300 cc. of dry ether to 12.5 g. of magnesium turnings in 200 cc. of dry ether. After addition was finished, the mixture was stirred and refluxed for five hours, and then poured on 200 g. of dry-ice. The carbonation product was isolated and purified in the usual manner.⁷ A yield of 59 g. (69%) of the crude acid melting at 141–143° was obtained. After recrystallization from benzene–petroleum ether, the acid melted at 144.5–145°.

Anal. Calcd. for C₁₀H₁₂O₂: C, 66.65; H, 6.71. Found: C, 66.73; H, 6.77.

2,2',6,6'-Tetramethylanisil.—Fifteen grams of 2,6-dimethylanisic acid was added to 40 cc. of thionyl chloride and the mixture allowed to stand overnight. The excess thionyl chloride was then removed by reduced pressure and heating up to 50°. The residual acid chloride was diluted with 25 cc. of benzene and then coupled in the usual fashion¹¹ using the binary mixture, Mg + MgI₂.² The ether–benzene solution of the product was evaporated on the steam-bath; the residue was taken up in 50 cc. of methanol, and the solution was cooled. The diketone which precipitated weighed 5.1 g. (38%); after several recrystallizations from benzene–petroleum ether, it melted at 197–198.5°.

(9) Auwers, Borsche and Steinich, *Ber.*, **48**, 1698 (1915).

(10) Auwers and Schuette, *Ann.*, **421**, 63 (1920).

(11) Fuson, McKeever and Corse, *THIS JOURNAL*, **62**, 600 (1940).

Anal. Calcd. for C₂₀H₂₂O₄: C, 73.60; H, 6.79. Found: C, 73.75; H, 6.75.

Catalytic Reduction of 2,2',6,6'-Tetramethylanisil.—The usual procedure for catalytic hydrogenation of benzils using platinum oxide and 1.5 atmospheres pressure of hydrogen did not effect any reduction of 2,2',6,6'-tetramethylanisil. This reduction was accomplished using Raney nickel and 40 pounds pressure of hydrogen on a solution of the benzil in either methanol or cyclohexane. When the latter solvent was employed, a white precipitate was obtained which decolorized sodium 2,6-dichlorobenzeneoneindophenol. Attempts to separate this enediol from the catalyst by solution in ether, filtration, and reprecipitation with petroleum ether yielded only the yellow diketone. Solutions containing the enediol were oxidized immediately upon exposure to air, and the white solid itself gave evidence of oxidation after one minute.

Action of the Binary Mixture on 3-Methoxymesityl Chloride.—The usual procedure¹¹ for the reductive coupling reaction was employed. From 15 g. of 3-methoxymesityl chloride there was obtained 7 g. (55%) of *cis*-2,2',4,4',6,6'-hexamethyl-3,3'-methoxystilbenediol and 3.3 g. (26%) of the corresponding benzil. If no effort was made to isolate the unstable enediol, a 62% yield of the benzil could be obtained.¹² The melting point and analytical data for the benzil and its derivatives are given in Table I.

Summary

The peculiar properties observed in enediols from other hindered benzils persist undiminished in the dimethoxy analogs.

3-Methoxymesityl chloride has been synthe-

(12) In two experiments a compound was isolated in small amounts which had the composition of 3,3'-dimethoxydimesitylacetylene. A similar observation was made earlier in the isodurene series [Fuson and Kelton, *ibid.*, **68**, 1500 (1941)].

sized and coupled to 3,3'-dimethoxymesitol and the corresponding *cis*-enediol. The *trans*-enediol has been obtained by hydrogenation of the benzil.

The corresponding enediol with methoxyl groups

in the para positions, 2,2',6,6'-tetramethyl-4,4'-dimethoxystilbenediol, has been shown to exist but is exceedingly sensitive to oxidation by the air.

URBANA, ILLINOIS

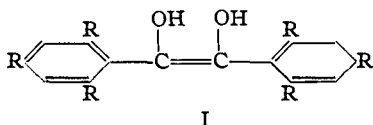
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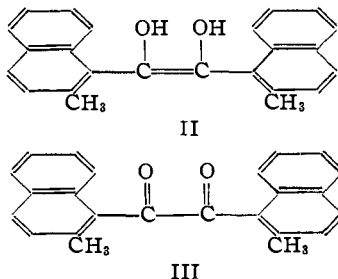
Enediols. IX.¹ Enediols in the Naphthalene Series

BY REYNOLD C. FUSON, C. H. MCKEEVER² AND LYELL C. BEHR

Enediols of type I have been prepared in which R = CH₃, C₂H₅ or (CH₃)₂CH. The evidence at hand with respect to these compounds suggests that their peculiar character is closely related to the aromatic nature of the rings involved. This point of view raises the question as to whether the benzene ring might not be replaced by some other aromatic nucleus. In the present work it has been shown that the naphthalene ring will serve.

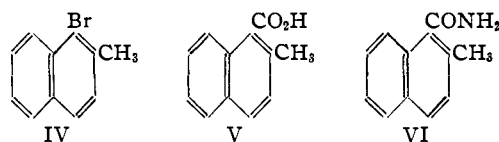


The enediols which have been made are the *cis* and *trans* di-(2-methyl-1-naphthyl)-acetylene glycols (II).



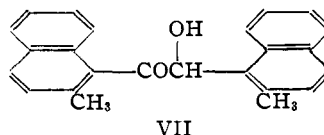
The starting point in the synthesis was 2-methyl-naphthalene. Bromination of this hydrocarbon produced 2-methyl-1-bromonaphthalene³ (IV). 2-Methyl-1-naphthoic acid (V) was made from the bromo compound by carbonation of the corresponding Grignard reagent. Several methods of carbonation were tried. The best of these involved addition of well-crushed dry-ice to the Grignard solution.⁸ One of the methods studied consisted in making the nitrile from the bromo compound by the procedure of Newman.⁴ The

nitrile was obtained in good yield but the hydrolysis gave only traces of the desired acid. 2-Methyl-1-naphthamide (VI) was always the chief product.



Treatment of 2-methyl-1-naphthoyl chloride with the binary mixture, Mg + MgI₂,⁵ gave a mixture of *cis*-di-(2-methyl-1-naphthyl)-acetylene glycol (II) and 2,2'-dimethyl-1,1'-naphthil (III). The diol was colorless and the diketone was orange-red. The use of a nitrogen atmosphere increased the quantity of the enediol at the expense of the naphthil. Hydrogenation of the naphthil could be used to obtain either the *cis* or *trans* enediol merely by changing the solvent. In methanol the *cis* compound was produced whereas in petroleum ether the *trans* isomer was the product.

The enediols could be transformed into the corresponding diacetates by heating with acetic anhydride. The keto form, 2,2'-dimethyl-1,1'-naphthoin (VII), was obtained by heating the *trans* compound with a mixture of methanol and hydrochloric acid. This change has not been observed to take place spontaneously.



No satisfactory method has yet been discovered for determining the stability of enediols toward the air. It appears that the new enediols are about as stable as the hexaethylstilbenediols, less stable than the hexaisopropyl analogs and more stable than the enediols of the mesitylene series.

(1) For the preceding communication in this series see Fuson, Corse and Weldon, *THIS JOURNAL*, **63**, 2645 (1941).

(2) Röhm and Haas Research Assistant, 1938-1940.

(3) McGrew, Ph.D. Thesis, University of Illinois, 1938.

(4) Newman, *THIS JOURNAL*, **59**, 2472 (1937).

(5) Gomberg and Bachmann, *ibid.*, **49**, 236 (1927).