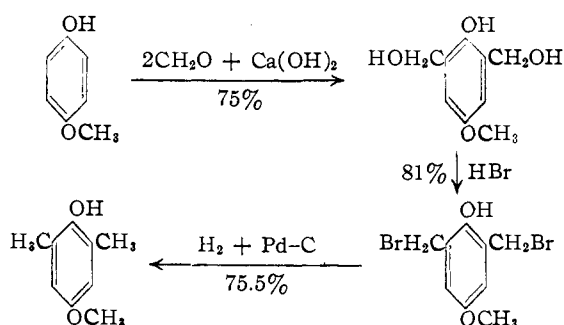


[CONTRIBUTION FROM NATIONAL DAIRY RESEARCH LABORATORIES, INC.]

Nuclear Methylation of Some Phenolic Compounds¹BY WILLIAM J. MORAN, ERIC C. SCHREIBER,^{2a} ERIC ENGEL, DONALD C. BEHN^{2b} AND J. L. YAMINS

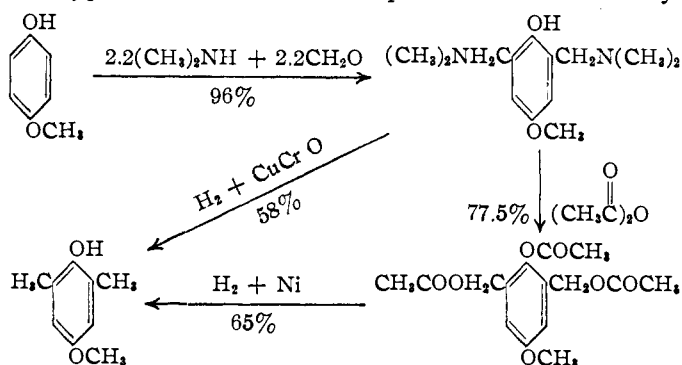
The Lederer-Manasse reaction has been utilized for the introduction of hydroxymethylene groups into the nucleus of 2,4-dimethylphenol and hydroquinone monomethyl ether. Conversion of the hydroxymethylene to methyl was accomplished by hydrogenolysis of the corresponding halogen methylene compound. Mono and di-Mannich bases of hydroquinone monomethyl ether were prepared by reaction with formaldehyde and dimethylamine. Hydrogenolysis of the bases or the corresponding acetoxy methyl compounds yielded 4-methoxy-*o*-cresol and 4-methoxy-2,6-xyleneol. 2-Bromo-4-methoxy phenol on treatment with butyllithium followed by methyl iodide yielded after acidification 4-methoxy-*o*-cresol.

Some ring-methylated phenols have been synthesized by subjecting 2,4-dimethylphenol and hydroquinone monomethyl ether to the Lederer-Manasse reaction, converting the resulting hydroxymethyl phenols to the corresponding halogen methyl phenols and replacing the halogen by hydrogen. A typical reaction sequence is shown below.



Utilizing the procedure of Alexander and Underhill³ mono- and di-Mannich bases of hydroquinone monomethyl ether were prepared. 4-Methoxy-*o*-cresol (I) and 4-methoxy-2,6-xyleneol (II) were obtained by hydrogenolysis of the Mannich bases over copper chromite, or the corresponding acetoxy methyl acetates over Raney nickel in ethanol. 4-Methoxy-*o*-cresyl acetate (III) was obtained by hydrogenolysis of α^2 -acetoxy methyl-4-methoxy-*o*-cresyl acetate (IV) in dioxane over Raney nickel.

A typical Mannich reaction sequence is



4-Methoxy-*o*-cresol (I) was synthesized by reaction of methyl iodide with the corresponding 2-lithium derivative prepared by the method of

Gilman and Arntzen⁴ from the 2-bromo-4-methoxyphenol.

3,5-Dimethyl saligenin (V) prepared by the method of Manasse,⁵ was converted by the procedure of Ziegler, *et al.*,⁶ to α^6 -chloromesitol (VI) which was transformed by hydrogen over palladium-charcoal to mesitol.

Hydroquinone monomethyl ether has been reported by Helfer⁷ to yield 5-methoxysaligenin together with a small amount of α^2, α^6 -dihydroxy-4-methoxy-2,6-xyleneol (VII). In this study, this latter compound was prepared in 75% yield. VII on treatment with hydrogen bromide yielded α^2, α^6 -dibromomethyl-4-methoxy-2,6-xyleneol (VIII) which was converted to 4-methoxy-2,6-xyleneol (II) by hydrogenation over palladium charcoal catalyst. VII was readily methylated with methyl iodide to give α^2, α^6 -dihydroxy-2,6-xylhydroquinone dimethyl ether (IX). 2,6-Xylhydroquinone dimethyl ether was prepared from IX following the same sequence of reactions for the synthesis of II.

α^2 -Dimethylamino-4-methoxy-*o*-cresol (XI) was prepared by the method of Decombe.⁸ α^2, α^6 -Di-(dimethylamino)-4-methoxy-2,6-xyleneol (XII) was prepared in 96% yield from hydroquinone monomethyl ether. Reeve and Sadle^{9a, b} reported a 77% yield of this compound. XI and XII were transformed by the method of Bruson and MacMullen¹⁰ into α^2 -acetoxy-4-methoxy-*o*-cresyl acetate (IV) and α^2, α^6 -diacetoxy-4-methoxy-2,6-xyleneol acetate (XIII), respectively. Hydrogenolysis of these compounds in ethanol over Raney nickel produced the corresponding methylated phenols I and II.

2-Bromohydroquinone was treated with butyllithium following the procedures of Gilman, *et al.*¹¹ This solution was treated with methyl iodide to produce I in 50% yield.

The data in connection with the above compounds is presented in Tables I and II.

Experimental^{12, 13}

Method A. α^2, α^6 -Dihydroxy-4-methoxy-2,6-xyleneol.—To a suspension of 62.0 g. (0.5 mole) of hydroquinone monomethyl ether in 400 ml. of water was added 90.0 g. (1.2 mole) of 40% formaldehyde solution. To this mixture, in an atmosphere of

(4) H. Gilman and C. F. Arntzen, *ibid.*, **69**, 1537 (1947).(5) O. Manasse, *Ber.*, **35**, 3894 (1902).(6) E. Ziegler, H. Meralla and J. Simmler, *ibid.*, **76**, 669 (1943).(7) L. Helfer, *Helv. Chim. Acta*, **7**, 955 (1924).(8) J. Decombe, *Compt. rend.*, **197**, 258 (1933).(9) (a) W. Reeve and A. Sadle, *THIS JOURNAL*, **72**, 3252 (1950).

(b) This publication appeared after completion of our work.

(10) H. A. Bruson and C. W. MacMullen, *THIS JOURNAL*, **63**, 270 (1941).(11) H. Gilman, *et al.*, *ibid.*, **71**, 1499 (1949).

(12) All melting points taken on Fisher-Johns block.

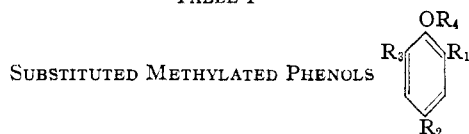
(13) Analytical data by Messrs. Robert Radford and John Horsey.

(1) Presented before the Meeting-in-Miniature of the Metropolitan Long Island Group of the New York Section of the American Chemical Society, March 17, 1950, and before the Division of Organic Chemistry, 118th Meeting of the American Chemical Society, Chicago, Illinois, September 3-8, 1950.

(2) (a) Charles Pfizer and Co., Brooklyn, N. Y.; (b) Dept. of Chemistry, Washington State University, Pullman, Washington.

(3) E. R. Alexander and E. J. Underhill, *THIS JOURNAL*, **71**, 4014 (1949).

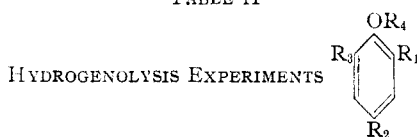
TABLE I



	R ₁	R ₂	R ₃	R ₄	Yield, %	M.p., °C.	Analyses, %				Halogen		Pro- cedure		
							Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found		Calcd.	Found
V	CH ₃	CH ₃	CH ₂ OH	H	66	56-57									
VI	CH ₃	CH ₃	CH ₂ Cl	H	90	58									Ref. 4
	CH ₃	CH ₃	CH ₃	H	100	70									
VII	CH ₂ OH	OCH ₃	CH ₂ OH	H	79.1	124-126									Method A
VIII	CH ₂ Br	OCH ₃	CH ₂ Br	H	81.0	113-114	34.87	35.05	3.25	3.35		51.56	51.50		Method B
II	CH ₃	OCH ₃	CH ₃	H	75.5	77									Method C
IX	CH ₂ OH	OCH ₃	CH ₂ OH	OCH ₃	69.0	112	60.59	60.5	7.12	7.2					
	CH ₂ Br	OCH ₃	CH ₂ Br	OCH ₃	69.0	98.5	37.06	36.9	3.73	3.4		49.33	49.5		Method B
X	CH ₃	OCH ₃	CH ₃	OCH ₃	86 ^a		72.26	72.6	8.49	8.65					Method C
XI	CH ₂ N(CH ₃) ₂	OCH ₃	H	H	82	49									Ref. 6
XII	CH ₂ N(CH ₃) ₂	OCH ₃	CH ₂ N(CH ₃) ₂	H	96 ^b		65.51	65.2	9.30	9.3	11.76	11.4			
IV	CH ₃ COOCH ₂	OCH ₃	H	CH ₃ CO	92 ^c		60.50	60.58	5.92	6.01					Ref. 8
XIII	CH ₃ COOCH ₂	OCH ₃	CH ₃ COOCH ₂	CH ₃ CO	77.5	75	58.06	57.8	5.85	5.8					Ref. 8

^a B.p. 103° (10 mm.). ^b B.p. 115° (0.5 mm.). ^c B.p. 128° (0.7 mm.).

TABLE II



	R ₁	R ₂	R ₃	R ₄	Yield, %	M.p., °C.	°C.	B.p. Mm.	Empirical formula	Starting compound	Catalyst	Solvent
	CH ₃	OCH ₃	CH ₃	H	75.5	77			C ₉ H ₁₂ O ₂	^a	Pd-C	ETOH
I	CH ₃	OCH ₃	H	H	93	72			C ₈ H ₁₀ O ₂	XI	Cu CrO	ETOH
II	CH ₃	OCH ₃	CH ₃	H	58	77			C ₉ H ₁₂ O ₂	XII	Cu CrO	ETOH
	CH ₃	OCH ₃	CH ₃	H	65	77			C ₉ H ₁₂ O ₂	XIII	Ni	ETOH
	CH ₃	OCH ₃	H	CO-CH ₃	94		70-71	0.3	C ₁₀ H ₁₂ O ₂ ^b	IV	Ni	Dioxane

^a α²-Dimethylamino-4-methoxy-*o*-cresol. ^b Anal. Calcd.: C, 66.65; H, 6.72. Found: C, 66.53; H, 6.79.

nitrogen, was added 15.6 g. (0.24 mole) of Baker calcium oxide (86% pure). The flask was tightly stoppered and shaken in a mechanical shaking apparatus until the calcium oxide dissolved. This solution was then allowed to stand in the closed flask in the dark for three days. At the end of this time, a large quantity of bright yellow calcium salt of the product had precipitated. This mixture was acidified with 40 ml. of glacial acetic acid and heated with stirring until the solid dissolved. The solution was treated with Norite, filtered hot, allowed to cool, and finally was cooled in an ice-box for three hours. The solid was filtered off and washed with a small amount of cold water. The product was air dried at room temperature; yield 73.0 g.; 79.1%, m.p. 124-126°.

This product was recrystallized from the minimum amount of boiling ethyl acetate. A yield of 64.0 g. of first crop material melting at 127-128° was obtained. Helfer⁷ reports 126-127°.

The procedure described below is a general procedure for the bromomethyl compounds.

Method B. α²,α⁶-Dibromo-4-methoxy-2,6-xyleneol.—A solution of 21.2 g. of hydrogen bromide (0.263 mole) in 100 ml. of glacial acetic acid was cooled to 10-12°. To this solution was added all at once with stirring 20.0 g. (0.108 mole) of α²,α⁶-dihydroxy-4-methoxy-2,6-xyleneol. In about two minutes the solid had completely dissolved and about 30 seconds later a rapid crystallization of the brominated compound occurred. The temperature rose to 18° and stirring of the thick paste ceased except in the vicinity of the stirrer. After keeping at 15-20° for a half-hour, the product was filtered on a sintered glass funnel, pressed free of excess mother liquor, and washed twice with 10 ml. of cold glacial acetic acid, followed by 10-ml. portions of petroleum ether. The crude product on drying weighed 23.7 g. (71% yield). A second crop of 3.4 g. was obtained from the mother liquor making a total yield of 81.0%. The product was purified by recrystallization from cyclohexane and melted at 113-114°.

Hydrogenolysis of the halogen methyl compounds were accomplished by the procedure in Method C.

Method C. 4-Methoxy-2,6-xyleneol.—Into a solution of 6.2 g. (0.02 mole) of α²,α⁶-dibromo-4-methoxy-2,6-xyleneol in 170 ml. of absolute ethanol was added 1.0 g. of 10% palladium-on-charcoal catalyst. This mixture was shaken on a Parr low-pressure hydrogenator at room temperature under an initial hydrogen pressure of 40 lb. The theoretical quantity of hydrogen was absorbed in two hours. The catalyst was removed by filtration and solid sodium bicarbonate was added to the filtrate until it was neutral. The salts were separated by filtration, and the filtrate was concentrated in reduced pressure to an oil. The oil was dissolved in ether and the ether solution was washed with water and saturated sodium bicarbonate solution. This solution was dried over anhydrous magnesium sulfate, and after removal of the drying agent, the ether solution was evaporated to an oil which crystallized in long needles; yield 3.2 g.; m.p. 69-73°.

This material was recrystallized from petroleum ether using Norite to decolorize the hot solution. A first crop yield of 1.7 g. melting at 76-77° was obtained. An additional 0.6 g. of product melting at 76-77° was isolated from the mother liquor; total yields 2.3 g. 75.5%.

Bamberger¹⁴ reports a melting point of 77°.

α²,α⁶-Di-(dimethylamino)-4-methoxy-2,6-xyleneol.—A solution of dimethylaminomethanol was prepared from 400 g. of 25% aqueous dimethylamine and 200 g. of 35% aqueous formaldehyde solutions in 500 ml. of 95% ethanol according to the procedure of Alexander and Underhill.³ After standing at room temperature for 16 hours, 124 g. (1.0 mole) of hydroquinone monomethyl ether was dissolved in this solution and the mixture was refluxed for three hours. At the end of this time, the alcohol was distilled off in reduced pressure and the aqueous mixture was cooled and acidified with 20% hydrochloric acid. Acid insoluble material was removed by extraction with ether. The oil which separated from the aqueous layer, on neutralizing with 28% ammonia water, was extracted completely with chloroform. The

(14) E. Bamberger, *Ber.*, **36**, 2040 (1903).

combined chloroform extracts were washed with 75 ml. of 10% sodium bisulfite solution followed by 75 ml. of water. After drying over anhydrous magnesium sulfate, the chloroform was distilled off in reduced pressure. The oily residue was distilled at 115° (0.5 mm.). Reeve and Sadle¹⁴ report 143 to 150° at 0.3 and 0.36 mm. The distillate was light yellow; yield 229.6 g., 96%.

A typical procedure for hydrogenolysis of Mannich bases is described in Method D.

Method D. 4-Methoxy-*o*-cresol by Hydrogenolysis of α^2 -Dimethylamino-4-methoxy-*o*-cresol.—A solution of 18.1 g. (0.1 mole) of α^2 -dimethylamino-4-methoxy-*o*-cresol in 150.0 ml. of absolute ethanol and 2.0 g. of copper chromite catalyst was reduced at 175° and an initial pressure of 1800 lb. for six hours. The catalyst was filtered off and the filtrate was concentrated to about 50 ml. This solution was diluted with 200 ml. of water and acidified with 10% hydrochloric acid. The oil which separated was extracted completely with ether. The combined ether extracts were washed with water until neutral and then dried over calcium chloride. Evaporation of the ether on a steam-bath yielded 13.8 g. of tan solid melting at 66–69°. Recrystallization of this material from petroleum ether gave a white crystalline solid melting at 71–72°. Bamberger¹⁵ reports a melting point of 71.5°; yield 12.9 g., 93%.

A general procedure for hydrogenolysis of acetoxymethyl acetate to phenols is described below.

Method E. 4-Methoxy-2,6-xyleneol by Hydrogenolysis of α^2, α^6 -Diacetoxy-4-methoxy-2,6-xyleneol Acetate.—A solution of 22 g. (0.071 mole) of α^2, α^6 -diacetoxy-4-methoxy-2,6-xyleneol acetate¹⁰ in 200 ml. of absolute ethanol and about 1.0 g. of Raney nickel¹⁶ was placed in a hydrogenation bomb and rocked for 24 hours at 165° and 100 atmospheres pressure. After filtration of the catalyst, the alcohol was concentrated in vacuum to about 40 ml. This solution was diluted with 200 ml. of water and then extracted with ether. The combined ether extracts were washed with sodium bicarbonate and dried over magnesium sulfate. After separation of the drying agent, the ether was distilled off in vacuum. The oily residue was distilled at 91–92° (0.4

mm.). The colorless distillate rapidly solidified in the receiver; yield 8.9 g., 65%; m.p. 76–77°.

4-Methoxy-*o*-cresol.—Ten and two-tenths grams (0.05 mole) of 2-bromohydroquinone monomethyl ether (prepared by method of Irvine and Smith¹⁷) was dissolved in 50 ml. of anhydrous ethyl ether. Into this solution was added slowly over a period of 45 minutes in an atmosphere of nitrogen 210 ml. of 0.715 *N* butyllithium in ether solution. The reaction mixture warmed up to reflux temperature during the early stages of the addition. This mixture was then allowed to stand for three hours before adding, dropwise, a solution of 21.3 g. of methyl iodide in 50 ml. of anhydrous ether. The mixture was then refluxed for two hours and allowed to stand overnight. The next day, the mixture was poured into 250 ml. of ice-water and acidified with 20% hydrochloric acid. The ether layer was separated and the aqueous portion was extracted completely with ether. The combined ether extracts were washed with water before drying over sodium sulfate. The ether was distilled off in vacuum leaving a brown oil. This oil was dissolved in boiling petroleum ether and after slight cooling, a brown oil settled on the bottom of the flask. The solvent was decanted and after cooling in an ice-box for several hours, white needle crystals separated. This procedure was repeated several times on the brown oil. The crystals from the combined extracts were filtered off and air-dried; yield 3.5 g.; 50.5%, m.p. 70–71°.

4-Methoxy-*o*-cresyl Acetate.— α^2 -Acetoxy-4-methoxy-*o*-cresyl acetate¹⁰ was reduced in dioxane by Method E in 94% yield. Saponification of a sample of the distilled 4-methoxy-*o*-cresyl acetate with 10% sodium hydroxide solution produced the known 4-methoxy-*o*-cresol in 90% yield.

A mixed melting point of the material with a sample of 4-methoxy-*o*-cresol obtained from hydrogenolysis of α^2 -dimethylamino-4-methoxy-*o*-cresol showed no depression.

Acknowledgment.—The authors wish to thank Henry Walton for suggestions relating to this work.

(17) F. M. Irvine and J. C. Smith, *J. Chem. Soc.*, 47 (1947).

OKDALE, LONG ISLAND, NEW YORK

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(15) E. Bamberger, *Ann.*, **390**, 174 (1912).

(16) A. A. Pavlic and H. Adkins, *This Journal*, **68**, 1471 (1946).

[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Cyclic Quaternary Immonium Compounds Derived from 2,2-Diphenyl-4-pentenoic Acid¹

BY PAUL N. CRAIG

A mechanism is proposed for the lactonization of 2,2-diphenyl-4-pentenoic acid and its methyl ester with bromine or sulfuric acid. Evidence for the proposed mechanism is given by showing that amides and dialkylamides of the above acid cyclize in an analogous manner to give cyclic quaternary immonium ethers. The structures assigned to these cyclic ethers are substantiated by their properties and conversion to the corresponding lactones and, in one case, to an aminolactone.

A study of the lactonizations of 2,2-diphenyl-4-pentenoic and 2,2-diphenyl-4-methyl-4-pentenoic acids² led to the observation that the latter acid was lactonized more readily than the former by both bromine and sulfuric acid. Consideration of the reaction mechanism proposed by Tarbell and Bartlett³ for the formation of halolactones from 1,2-dimethylfumaric and 1,2-dimethylmaleic acids leads to the proposed reaction scheme given.

In the present case the reaction can proceed to completion due to the availability of the covalent-bonded electron pair joining the hydrogen and oxygen atoms for participation in the reaction sequence as shown. This is in contrast with the reactions studied by Tarbell and Bartlett, where the

ring is closed by an electron pair present on the negatively charged carboxyl anion.

When R is methyl (e.g., 2,2-diphenyl-4-methyl-4-pentenoic acid) the methyl group may act by hyperconjugation to favor transformations which may be considered to involve an intermediate carbonium ion.⁴ In accordance with this factor, 2,2-diphenyl-4-methyl-4-pentenoic acid lactonizes more readily with bromine or sulfuric acid than does the 2,2-diphenyl-4-pentenoic acid.²

Consideration of the course in the reaction which might follow the formation of such a carbonium ion intermediate indicates that a group which is in position to close a five or six-membered ring can attack the carbonium carbon atom, providing that the electron release from the attacking group (in this case the oxygen atom of the carboxyl group) may be compensated for by subsequent electron

(1) Allyldiphenylacetic acid obtained from General Mills, Inc., Minneapolis, Minnesota.

(2) P. N. Craig and I. H. Witt, *This Journal*, **72**, 4925 (1950).

(3) D. S. Tarbell and P. D. Bartlett, *ibid.*, **59**, 407 (1937).

(4) J. W. Baker, *Trans. Faraday Soc.*, **37**, 632 (1941).