

TABLE II

AMIDES			
Amide R = cyclohexyl	M. p., °C.	Nitrogen, %	
		Calcd.	Exptl.
R—CH ₂ —CO—NH ₂ ^a	170		
R—(CH ₂) ₂ —CO—NH ₂ ^b	120		
R—(CH ₂) ₃ —CO—NH ₂	111	8.28	8.36
R—(CH ₂) ₄ —CO—NH ₂ ^c	124		
R—(CH ₂) ₅ —CO—NH ₂	117	7.10	7.37

^a Wallach, *Ann.*, **353**, 297 (1907), gives the m. p. as 168°.

^b Sabatier and Murat, *Compt. rend.*, **156**, 753 (1913), give the m. p. as 123°. ^c Katsnel'son and Dubinin, *Compt. rend. acad. sci. (U. R. S. S.) (N. S.)*, **4**, 405 (1936), give the m. p. as 123°.

TABLE III

NITRILES							
Nitrile R = cyclohexyl	Yield, %	B. p., °C. Mm.	<i>d</i> ₂₀ ⁴	<i>n</i> _D ²⁰	Chlorine, %		
					Calcd.	Exptl.	
R—CH ₂ —CN ^a	70.0	57 1	0.9180	1.4575			
R—(CH ₂) ₂ —CN	80.0	71 1	.9107	1.4602	10.20	10.42	
R—(CH ₂) ₃ —CN	83.0	82 1	.9056	1.4607	9.26	9.40	
R—(CH ₂) ₄ —CN	85.0	93 1	.8950	1.4618	8.48	8.76	
R—(CH ₂) ₅ —CN	86.0	112 1	.8979	1.4637	7.80	7.90	

^a Wallach, *Ann.*, **359**, 311 (1908), reports *n*_D¹⁸ 1.4575 and *n*_D²⁰ 0.913.

TABLE IV

KETIMINES								
Ketimine R = cyclohexyl, R ₂ = <i>s</i> -butyl	Yield, %	B. p., °C. Mm.	<i>d</i> ₂₀ ⁴	<i>n</i> _D ²⁰	Nitrogen, %			
					Calcd.	Exptl.		
R—(CH ₂) ₂ —C(=NH)—R ₂	56.0	101 2	0.8680	1.4689	7.17	7.00		
R—(CH ₂) ₃ —C(=NH)—R ₂	43.0	107 1	.8611	1.4699	6.68	6.57		
R—(CH ₂) ₄ —C(=NH)—R ₂	45.0	121 1	.8754	1.4700	6.11	6.00		
R—(CH ₂) ₅ —C(=NH)—R ₂	60.0	130 1	.8808	1.4719	5.90	5.65		

in the manner previously described.³ The only product obtained with ω -cyclohexylacetone nitrile was a tarry material which could not be purified. Similar tars were obtained in varying amounts from the other nitriles. It was assumed that these tars were iminonitriles of the type indicated by Hauser.⁷

(7) C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950).

Experimental

Acid Chlorides.—The acid chlorides were prepared by the method described in "Organic Syntheses."⁸ Analyses were obtained by refluxing samples of the acid halides with standard sodium hydroxide and back-titrating the excess alkali with standard hydrochloric acid. The end-point arbitrarily set at pH 8.0, was determined by a Beckman pH meter. Physical constants and analyses are given in Table I.

Amides.—The acid chlorides were added slowly to well-stirred ice-cold ammonium hydroxide. The amides were filtered, washed with water and recrystallized from methanol-water. All yields were above 80%. Melting points and analytical data are given in Table II.

Nitriles.—The amides were dehydrated with an excess of phosphorus oxychloride and the nitriles purified by distillation. Yields, physical constants and analyses are given in Table III.

Ketimines.—The procedure of Pickard and Vaughan¹ was followed using 0.25 mole of *s*-butyl bromide and 0.20 mole of nitrile. The yields, physical properties and analyses are given in Table IV.

Summary

- Five acid chlorides, two not previously described, have been prepared and characterized.
- Five amides, two not previously reported, have been prepared.

3. Five nitriles, four not previously described, have been prepared and characterized.

4. Four new ketimines have been prepared and characterized.

(8) "Organic Syntheses," Collective Volume I, John Wiley and Sons, New York, N. Y., 1946, p. 147.

NORMAN, OKLAHOMA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

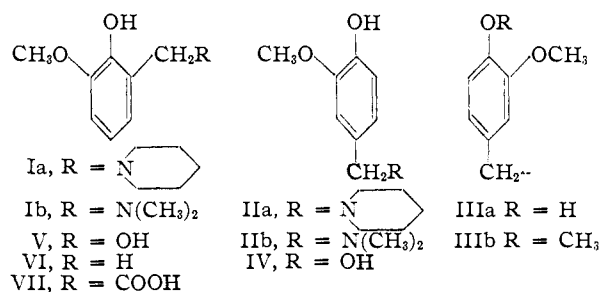
The Structure of the Guaiacol "Mannich Bases"

BY ERNEST L. ELIEL

The recent finding¹ that certain "Mannich Bases" derived from phenols² can be used as carbon alkylation agents suggested an investigation of corresponding reactions of dialkylaminomethylguaiacols (I or II), in view of the fact that the 3-methoxy-4-hydroxybenzyl (IIIa) and especially the 3,4-dimethoxybenzyl (IIIb) system are of frequent occurrence in products of natural origin. It seemed possible that guaiacol Mannich bases might be convenient intermediates in the synthesis of some of these natural products and that they might even play a part in their biosynthesis.

(1) (a) Salzer and Andersag, U. S. Patent 2,315,661 (1943); *C. A.*, **37**, 5418 (1943). (b) J. H. Brewster, Ph.D. Dissertation, University of Illinois, Urbana, Ill., 1948.

(2) (a) Blicke in Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303; (b) Carlin and Landerl, *This Journal*, **72**, 2762 (1950).



The product of the reaction of guaiacol with formaldehyde and piperidine was first described by Auwers and Dombrowski.³ These authors assumed

(3) Auwers and Dombrowski, *Ann.*, **344**, 283 (1905). The name "Mannich Base" as applied to the dialkylaminoalkylphenols is obviously a misnomer but is used in this paper in agreement with established custom.

that substitution took place in the para position (formula IIa) but did not prove the structure of their product. Madinaveitia⁴ synthesized dimethylaminomethylguaiacol in a similar fashion and purportedly proved that his product was the para-substituted isomer (IIb) by treating it with refluxing acetic anhydride and isolating from the reaction what he describes as the diacetate of vanillyl alcohol (IV). Décombe⁵ repeated the reaction of guaiacol with formaldehyde and dimethylamine, but, apparently disregarding Madinaveitia's results, assigned the ortho-substituted structure (Ib) to the product on the basis of analogy with other phenolic Mannich bases.

Before proceeding further, it seemed necessary to prove the structures of the products mentioned above in an incontrovertible fashion. Repetition of the acetic anhydride treatment⁴ of dimethylaminomethylguaiacol gave a product which had the correct boiling point⁶ for the diacetate of vanillyl alcohol (IV) but melted about 25° too low. This product was shown to be the diacetate of *o*-vanillyl alcohol (V) by an unequivocal synthesis from *o*-vanillin by catalytic reduction followed by acetylation. Therefore, the original Mannich base had structure Ib rather than IIb. This was further confirmed by catalytic reduction to the known *o*-creosol⁷ (VI). The piperidinomethylguaiacol³ was similarly shown to have structure Ia, for upon treatment with acetic anhydride, it, also, was converted to *o*-vanillyl diacetate. Moreover, the piperidino compound (Ia) was obtained when the dimethylamino compound (Ib) was refluxed with piperidine. Hence the structures proposed by Auwers³ and Madinaveitia⁴ are in error and that assumed by Décombe⁵ is correct. This is especially remarkable since the reaction of guaiacol with formaldehyde in the presence of mineral base yields mainly vanillyl alcohol⁸ (IV), thus confirming once more^{2a,9} that this alcohol is not an intermediate in the formation of the Mannich base.

Only two-carbon alkylation reactions of the 6-dimethylaminomethylguaiacol (Ib) were studied, not only because this compound is evidently unsuitable for the synthesis of substances which contain the desirable *p*-substituted groups IIIa and IIIb, but also because it proved to be a very poor alkylation agent. From a reaction of Ib with sodium cyanide in aqueous ethylene glycol, only a very small amount of 2-hydroxy-3-methoxyphenylacetic acid (VII) could be isolated. Reaction of Ib with ethyl cyanoacetate gave N,N-dimethylcyanoacetamide as the only crystalline product. In both cases large amounts of resins also resulted.

Experimental¹⁰

6-Dimethylaminomethylguaiacol (Ib).—To 62 g. (0.5 mole) of guaiacol (Fisher Scientific Co., synthetic, redis-

(4) Madinaveitia, *Anales soc. espan. fis. quim.*, **19**, 259 (1921); *C. A.*, **16**, 1230 (1922).

(5) Décombe, *Compt. rend.*, **197**, 258 (1933).

(6) Vavon, *Ann. chim.*, [9] **1**, 160 (1914).

(7) Majima and Okazaki, *Ber.*, **49**, 1488 (1916).

(8) (a) Manasse, *ibid.*, **27**, 2409 (1894); Bayer and Co., German Patent 85,588 (1896); *Frdl.*, **4**, 95 (1899); (b) Goethals, *Naturw. Tijdschr.*, **18**, 249 (1936); *C. A.*, **30**, 7556 (1936).

(9) Lieberman and Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

(10) All melting points and boiling points are uncorrected. Microanalyses by Microtech Laboratories, Skokie, Ill. High-pressure hydrogenation by Mr. Erwin Kohn and Mr. John Falvey.

tilled, b.p. 91–92° (11 mm.), m.p. 15–22°), dissolved in 225 ml. of absolute ethanol, was added 111 g. (0.5 mole) of a 40% aqueous solution of dimethylamine followed by 37.5 ml. (0.5 mole) of a 40% aqueous solution of formaldehyde. When the solution was homogenized by gentle swirling, a slightly exothermic reaction ensued. After about 24 hours at room temperature, the alcohol was removed *in vacuo*, about 50 ml. of water was added, and the oily residue was dissolved in 200 ml. of ether. The aqueous layer was again extracted with 100 ml. of ether and the combined ether layers were dried over sodium sulfate and concentrated. The residue was distilled at a pressure of 0.8 mm. with the aid of an eight-inch fractionating column which contained a glass spiral. Three fractions were collected: No. 1, b.p. to 98°, 19.5 g.; No. 2, b.p. 100–106°, 42.6 g.; No. 3, b.p. 106–125°, 5.5 g. A gummy residue weighing about 10 g. was left in the still. Fraction no. 1 was partitioned between ether and dilute hydrochloric acid. From the non-basic fraction, 10.3 g. (16.6%) of guaiacol, b.p. 90–92° (13 mm.) (identified by its picrate, m.p. and mixed m.p. with an authentic specimen 87.5–89.5°) was recovered. Treatment of the acidic solution with sodium carbonate followed by ether extraction yielded only about 1 g. of basic material.

Fraction no. 2 crystallized in part. It was chilled and then freed of adhering oil by vacuum filtration followed by washing with ice-cold petroleum ether (b.p. 30–60°). There was thus obtained 35.6 g. of crystalline material. Recrystallization from petroleum ether (b.p. 30–60°) gave 31.5 g. (35%) of white material melting at 50–51° (lit.³ 46–47°). The picrate, upon recrystallization from ethanol, melted at 200.5–202.5° (lit.⁴ 202°).

Anal. Calcd. for C₁₆H₁₈N₂O₉: C, 46.82; H, 4.42. Found: C, 46.87; H, 4.58.

Attempts to purify fraction no. 3 by redistillation in high vacuum resulted in decomposition; this fraction was not further investigated.

6-Piperidinomethylguaiacol (Ia).—This compound, synthesized in the same manner as the dimethylamino analog, boiled at 132–142° (0.3 mm.) and melted at 98.5–100.5° (lit.³ 99.5–100.5) after recrystallization from aqueous ethanol. The picrate, crystallized from ethanol, melted at 176–177.5°.

Anal. Calcd. for C₁₉H₂₂N₂O₉: C, 50.66; H, 4.92. Found: C, 50.56; H, 4.85.

Conversion of 6-Dimethylaminomethylguaiacol (Ib) to the Piperidino Compound (Ia).—Five grams of the dimethylamino compound (Ib) and 15 ml. of piperidine were refluxed for 24 hours. A basic gas was evolved. The excess piperidine was removed *in vacuo*, and the oily residue was crystallized from petroleum ether (b.p. 30–60°). There was thus obtained 5.7 g. (93%) of the piperidino compound (Ia) melting at 97.5–99.5°. Recrystallization from dilute ethanol raised the melting point to 98.5–100.5° and there was no depression on admixture of a specimen obtained directly from guaiacol.

***o*-Vanillyl Alcohol (V).**—A solution of 45.6 g. of *o*-vanillin (Eastman Kodak Co. practical grade, recrystallized from aqueous ethanol) in 65 ml. of absolute ethanol was reduced at 2000 p.s.i. at 55–65° in the presence of ca. 3 g. of Raney nickel. The theoretical amount of hydrogen was taken up in about ninety minutes. The solution was filtered and concentrated, petroleum ether (b.p. 30–60°) added, the mixture cooled and the precipitate filtered. Evaporation of the mother liquor to dryness and crystallization from petroleum ether yielded additional material; the total yield of material melting at 59–62° was 40 g. (86.5%). Recrystallization from benzene raised the melting point¹¹ to 61–62°.

Anal. Calcd. for C₈H₁₀O₃: C, 62.33; H, 6.53. Found: C, 62.35; H, 6.44.

Diacetate of *o*-Vanillyl Alcohol from Vanillyl Alcohol.—A solution of 5 g. of *o*-vanillyl alcohol in 20 ml. of acetic anhydride was refluxed for two hours, then stirred with 250 ml. of water for ten minutes and extracted twice with 100-ml. portions of ether. The extracts were washed with saturated aqueous sodium bicarbonate solution followed by water, dried over sodium sulfate and concentrated. The

(11) Mauthner, *J. prakt. Chem.*, **158**, 321 (1941), reports *o*-vanillyl alcohol as a liquid, b. p. 162° (12 mm.). In the present investigation it was found to boil at 117–127° (0.2 mm.) with extensive decomposition.

product boiled at 112–114° (0.1 mm.); yield 5.6 g. (72%); m.p. 22–24° after recrystallization from aqueous ethanol.

From 6-Dimethylaminomethylguaiacol (Ib).—A solution of 18.1 g. (0.1 mole) of Ib in 50 ml. of acetic anhydride was refluxed for six hours and then poured into 300 ml. of water. The product, isolated as described above, boiled at 110–112° (0.05 mm.) and weighed 20.7 g. (87%). When recrystallized from aqueous ethanol and redistilled for analysis it melted at 23–25° and did not depress the melting point of the authentic specimen described above.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92; sapn. equiv., 119. Found: C, 60.33; H, 6.10; sapn. equiv., 120.

From 6-Piperidinomethylguaiacol (Ia).—When 6.6 g. of Ia and 15 ml. of acetic anhydride were refluxed for four hours and the reaction mixture was worked up as described before, 4.1 g. (58%) of material melting at 22–24° was obtained. The mixed melting point of this material with *o*-vanillyl diacetate (above) was not depressed.

Catalytic Reduction of 6-Dimethylaminomethylguaiacol (Ib).—Nine grams of Ib, dissolved in 50 ml. of dioxane, was reduced at 150–175° and an initial pressure of 2600 p.s.i. in the presence of 5 g. of copper chromite.^{2b,12} The catalyst was removed by filtration and the solution concentrated *in vacuo*. The residue was steam distilled and the oil in the distillate was extracted with two 100-ml. portions of ether. The solution was dried over sodium sulfate, concentrated and the residue distilled at 11 mm. The *o*-creosol, collected at 93–94°, weighed 4.2 g. (61%) and melted at 41–42° (lit.⁷ 41–42°). The compound gave a reddish-brown color with ferric chloride as reported.⁷

2-Hydroxy-3-methoxyphenylacetic Acid (VII).—A solution of 18.1 g. (0.1 mole) of 6-dimethylaminomethylguaiacol (Ib) and 12.5 g. of sodium cyanide in 125 ml. of ethylene glycol and 12.5 ml. of water was refluxed for two hours in an atmosphere of nitrogen. The mixture was then diluted with 400 ml. of water and solid carbon dioxide was added until the aqueous solution was faintly acidic. An amorphous precipitate formed and was removed by filtration. The filtrate was acidified with hydrochloric acid, extracted twice with 200 ml. of ether, the extracts washed twice with water, combined, dried over sodium sulfate and concentrated. When the viscous brown sirup was subjected to dis-

(12) (a) Caldwell and Thompson, *THIS JOURNAL*, **61**, 765 (1939); (b) Bruson and Covert, U. S. Patent 2,194,215 (1940); *C. A.*, **34**, 4742 (1940); (c) Reeve and Sadle, *THIS JOURNAL*, **72**, 3252 (1950).

tillation at 0.5 mm. pressure, a small amount of distillate was collected at 130–155°. The distillate crystallized in part and on recrystallization from benzene-petroleum ether (b.p. 30–60°) yielded 0.71 g. (3.9%) of waxy solid. After a second recrystallization this material (0.23 g.) melted at 119.5–122.5° and gave a green color with ferric chloride in ethanol. The melting point was not changed by recrystallization from ethyl acetate-petroleum ether. Mosimann and Tambor¹³ report a melting point of 124° for 2-hydroxy-3-methoxyphenylacetic acid and also mention that this material gives a green ferric chloride test.

Anal. Calcd.: neut. equiv., 182. Found: neut. equiv., 188.

The lactone¹³ melted at 78–79° after recrystallization from petroleum ether (lit.¹³ 80°).

Reaction of 6-Dimethylaminomethylguaiacol Ib with Ethyl Cyanoacetate.—A solution of 9 g. of Ib in 25 ml. of ethyl cyanoacetate was heated at 190° under nitrogen for three hours. Upon fractionation, 4.6 g. of distillate, b.p. 103–128° (0.2 mm.), was collected. It crystallized in the receiver to a waxy solid. After several recrystallizations from benzene, the material melted at 65–66° and the mixed melting point with an authentic sample of *N,N*-dimethylcyanoacetamide (prepared from ethyl cyanoacetate and dimethylamine in aqueous solution) was not depressed.

Anal. Calcd. for $C_8H_8N_2O$: C, 53.56; H, 7.18; N, 24.99. Found: C, 53.70; H, 7.07; N, 24.25.

Hydrolysis of the product with 10% aqueous sodium hydroxide yielded basic gases and malonic acid (m.p. 132.5–134° dec., not depressed by admixture of an authentic sample; neut. equiv. calcd., 52.0; found, 52.6).

Summary

1. The reaction of guaiacol with formaldehyde and dimethylamine or piperidine results in substitution ortho to the phenol function.

2. 6-Dimethylaminomethylguaiacol alkylates sodium cyanide in very low yield; it does not alkylate ethyl cyanoacetate.

3. Convenient syntheses of *o*-vanillyl alcohol and its diacetate are described.

(13) Mosimann and Tambor, *Ber.*, **49**, 1258 (1916).

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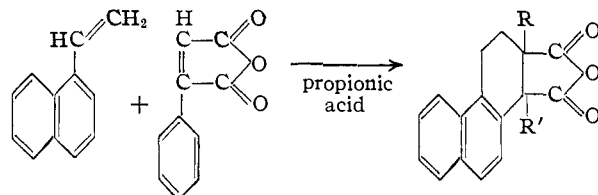
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Phenylmaleic Anhydride as a Diene in the Diels-Alder Reaction

BY LEONARD E. MILLER AND D. J. MANN²

It has been reported³ that phenylmaleic anhydride participates in the Diels-Alder reaction as a dienophile when such dienes as 1,3-butadiene, 2-methyl-1,3-butadiene, 2-ethyl-1,3-butadiene, 2-isopropyl-1,3-butadiene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene and anthracene are employed.

Since 1-vinylnaphthalene behaves as a diene on reaction with maleic anhydride or citraconic anhydride⁴ in boiling propionic acid to give derivatives of tetrahydrophenanthrene, it was thought that a similar reaction might occur with phenylmaleic anhydride as



Ia, R = H, R' = C_6H_5
Ib, R = C_6H_5 , R' = H

Contrary to this expected result, when freshly prepared 1-vinylnaphthalene was treated with phenylmaleic anhydride and trace of *p-t*-butylcatechol in boiling propionic acid for 48 hours, the chief product isolated (II) proved to be a derivative of 1,1'-binaphthyl. The formation of II can most reasonably be explained if one considers that phenylmaleic anhydride has participated as a

(1) Presented before the Division of Organic Chemistry of the American Chemical Society, Philadelphia, April 10, 1950.

(2) Atlantic Research Corporation, 812 N. Fairfax Street, Alexandria, Virginia.

(3) L. E. Miller and D. J. Mann, *THIS JOURNAL*, **72**, 1484 (1950).

(4) W. E. Bachmann and L. B. Scott, *ibid.*, **70**, 1462 (1948).