Corporation in defraying a part of the cost of this study.

Summary

The absorption spectra of six *p*-substituted acetophenone azines and of 2-thienyl methyl ketazine were determined. The results of this study lead to the interpretation of the hypsochromic effects of alpha alkyl groups on the absorption spectrum of benzalazine in terms of a hyperconjugation phenomenon. The spectral behavior of sulfur containing azines strongly supports the belief in the expansion of the octet of the sulfur atom in the excited state.

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[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

3-(Alkoxyphenoxy)-1,2-propanediols

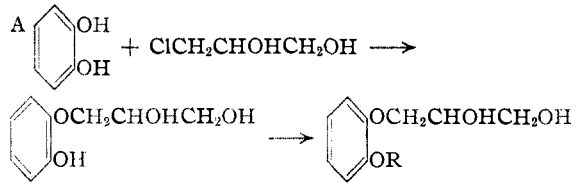
BY ROBERT I. MELTZER AND JOHN DOCZI

The search for improved muscle-relaxing drugs led to the preparation of a number of 3-(alkoxyphenoxy)-1,2-propanediols in these laboratories. Launoy[1] observed that 3-phenoxy-1,2-propanediol inhibited certain muscular contractions and Berger and Bradley[2] reported that many glyceryl ethers have such activity. The use of the best of these drugs, 3-(2′-methylphenoxy)-1,2-propanediol, is limited, however, by certain of its pharmacological properties as well as by low water solubility.

Guaiamar, 3-(2′-methoxyphenoxy)-1,2-propanediol, has a lower but similar activity[3] to 3-(2′-methylphenoxy)-1,2-propanediol and is much more soluble. The investigation in these laboratories included the study of the effect of the introduction into 3-phenoxy-1,2-propanediol of more than one methoxyl group and also of an alkoxyl group higher than methoxyl. Accordingly, there were prepared the six isomeric 3-(dimethoxyphenoxy)-propanediols and the three isomeric 3-(ethoxyphenoxy)-propanediols.

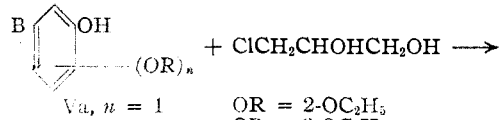
Compounds of desirable solubility were obtained among the dimethoxyl compounds. These compounds were unsatisfactory, however, as motor depressants.[3] Among the ethoxyl compounds, only the ortho-substituted compound had good solubility and appeared of interest pharmacologically.[3] This prompted the preparation of compounds in which the ethyl group of 3-(2′-ethoxyphenoxy)-1,2-propanediol was replaced by *n*-propyl, isopropyl, *n*-butyl and isobutyl. The solubilities of these compounds are low. The pharmacological investigation of all these compounds will be reported elsewhere.

All the phenoxypropanediols were prepared according to one of two general methods. In Method A, catechol was condensed with glycerol chlorohydrin to give 3-(2′-hydroxyphenoxy)-1,2-propanediol. The phenolic hydroxyl was then etherified by the appropriate alkyl bromide using sodium ethylate as condensing agent.

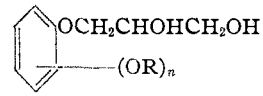


I, R = $CH_2CH_2CH_3$ III, R = $CH_2CH_2CH_2CH_3$
II, R = $CH(CH_3)_2$ IV, R = $CH_2CH(CH_3)_2$

According to Method B, the appropriate alkoxyphenol in the form of its sodium salt was condensed with glycerol chlorohydrin in absolute ethanol.



Va, n = 1	OR = 2-OC_2H_5
VIa, n = 1	OR = 3-OC_2H_5
VIIa, n = 1	OR = 4-OC_2H_5
VIIIa, n = 2	OR = 2,6-$(OCH_3)_2$
IXa, n = 2	OR = 3,5-$(OCH_3)_2$
Xa, n = 2	OR = 2,5-$(OCH_3)_2$
XIa, n = 2	OR = 3,4-$(OCH_3)_2$
XIIa, n = 2	OR = 2,4-$(OCH_3)_2$
XIIIa, n = 2	OR = 2,3-$(OCH_3)_2$



V, n = 1	OR = 2-OC_2H_5
VI, n = 1	OR = 3-OC_2H_5
VII, n = 1	OR = 4-OC_2H_5
VIII, n = 2	OR = 2,6-$(OCH_3)_2$
IX, n = 2	OR = 3,5-$(OCH_3)_2$
X, n = 2	OR = 2,5-$(OCH_3)_2$
XI, n = 2	OR = 3,4-$(OCH_3)_2$
XII, n = 2	OR = 2,4-$(OCH_3)_2$
XIII, n = 2	OR = 2,3-$(OCH_3)_2$

Three of the requisite phenols were prepared by peracetic acid oxidation of the corresponding benzaldehyde. These three phenols, the 2,3-, the 2,4- and the 3,4-dimethoxyphenols, were prepared by a modification of the Wacek and Bezard[4] oxidation of veratraldehyde to 3,4-dimethoxyphenol.

For the preparation of 2,6-dimethoxyphenol, gallic acid was completely methylated and then

(1) Launoy, *Compt. rend. soc. biol.*, **69**, 191 (1910).
(2) Berger and Bradley, *Brit. J. Pharmacol.*, **1**, 265 (1946).
(3) Communication from the Pharmacology Department of this Institute.
(4) Wacek and Bezard, *Ber.*, **74**, 845 (1941).

TABLE I

R—$OCH_2CHOHCH_2OH$[d]

No.	R	B. p., °C.	Mm.	M. p., °C.[a]	Recrystn. solvent[b]	Yield, %	Sol.[c] in water, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	2-$CH_3CH_2CH_2OC_6H_4$	153–154	0.5	69–71	Sc	58	< 2	63.69	63.97	8.02	8.36
II	2-$(CH_3)_2CHOC_6H_4$	148	0.35	57–58.5	Sc	53	< 5	63.69	63.63	8.02	7.95
III	2-$CH_3CH_2CH_2CH_2OC_6H_4$	154–155	0.2	71.5–72.5	Sc	24	< 0.5	64.98	65.07	8.39	8.55
IV	2-$(CH_3)_2CHCH_2OC_6H_4$	143–149	0.7	68.5–70	Sc	35	< 0.5	64.98	64.74	8.39	8.45
V	2-$C_2H_5OC_6H_4$	153–154	1.0	65–66	Sb	60	>50	62.24	62.28	7.60	7.63
VI	3-$C_2H_5OC_6H_4$	170–173	1.4	57.5–59.5	Aq–Et	58	< 2	62.24	62.24	7.60	7.55
VII	4-$C_2H_5OC_6H_4$	174	1.1	91–92	Aq–Et	73	< 2	62.24	62.31	7.60	7.90
VIII	2,6-$(CH_3O)_2C_6H_3$	165–167	0.6			81	>50	57.89	57.91	7.07	7.15
IX	3,5-$(CH_3O)_2C_6H_3$	197	1.1	70.5–71.5	Aq–Et	70	< 3	57.89	58.05	7.07	6.96
X	2,5-$(CH_3O)_2C_6H_3$	183–185	0.5	57.5–58.5	Aq	58	5	57.89	57.86	7.07	7.16
XI	3,4-$(CH_3O)_2C_6H_3$	195–197	0.8	40–41	Sb	38	>50	57.89	57.51	7.07	7.19
XII	2,4-$(CH_3O)_2C_6H_3$	178–181	0.5	62–62.5	Sb	56	>50	57.89	57.70	7.07	7.10
XIII	2,3-$(CH_3O)_2C_6H_3$	182–184	1.1	87.5–89	Sb	80	23	57.89	58.02	7.07	7.16

[a] Uncorrected. [b] Legend: Aq–Et = aqueous alcohol; Aq = water; Sb = Skellysolve B; Sc = Skellysolve C. [c] Weight/volume, at 25°. [d] Analyses by Mr. L. Dorfman and Mrs. B. Kent, of these laboratories.

partially demethylated to give syringic acid. It was found that the decarboxylation of this acid to the desired phenol proceeded faster and at lower temperature in the presence of dimethylaniline. Previous preparations called for straight thermal decomposition.[5,6]

We prepared 2,5-dimethoxyphenol by oxidation of the Grignard reagent from bromodimethylhydroquinone. This method is mentioned but not described in the literature.[7] The other phenols were prepared according to procedures described in the literature.

Acknowledgment.—The authors wish to express thanks for the interest and help of Drs. H. M. Wuest and John A. King. The pharmacological investigation of the substances herein reported was carried out in the Pharmacology Department of this Institute, under the direction of Dr. N. Ercoli.

Experimental[8]

Ethoxyphenols (Va, VIa and VIIa).—The *o*- and *m*-ethoxyphenols were prepared by diazotization of *o*-phenetidine,[9] and by ethyl bromide monoethylation of resorcinol,[10] respectively. The *p*-isomer was obtained from Eastman Kodak Co. and was used after one recrystallization.

2,6-Dimethoxyphenol (VIIIa).—Gallic acid was methylated to trimethoxybenzoic acid.[11] This was demethylated at the 4-position by hydrobromic[5] or sulfuric[6] acid to syringic acid. In our hands the procedure using sulfuric acid proved more satisfactory. Hahn and Wassmuth[6] decarboxylated the syringic acid to the desired phenol by heating the acid alone to 250–295° for thirty hours. We carried out the decarboxylation by heat alone and also by heating in the presence of an equal weight of dimethylaniline. We obtained similar yields (50%) in both ways and found that the latter procedure required only 210–245° for ten hours. The procedure with dimethylaniline is very probably capable of better yields.

3,5-Dimethoxyphenol (IXa).—This was prepared according to the procedure of Pratt and Robinson[12] from phloroglucinol and methanol in the presence of hydrogen chloride.

Bromodimethylhydroquinone.—To a solution of 220 g. (2 moles) of hydroquinone in 500 ml. of chloroform and 2900 ml. of ether, was added dropwise with stirring 320 g. (2 moles) of bromine in 400 ml. of chloroform. The flask was kept cold in an ice-bath. The addition took five hours. The solvent was then distilled off and replaced by 1.2 l. (9 moles) of 30% sodium hydroxide. The temperature within the flask was kept at 30–40° while 400 ml. (4.3 moles) of dimethyl sulfate was added dropwise with stirring. An additional 120 g. (3 moles) of sodium hydroxide and 160 ml. (1.7 moles) of dimethyl sulfate were then added in the same way. An additional 80 g. (2 moles) of sodium hydroxide was added and the reaction product was distilled with steam until solid began to form in the condenser. The distillate was allowed to remain overnight and the oil was then separated from the aqueous phase and distilled. Redistillation gave 310 g., b. p. 160–164° (40 mm.). The yields varied from 70–80%, compared with the 30% of Gilman and van Ess.[7]

2,5-Dimethoxyphenol (Xa).—Gilman and van Ess[7] prepared this phenol by allowing magnesium to react with bromodimethylhydroquinone and with *n*-butyl bromide. The resulting Grignard compounds were then oxidized by oxygen. No details of procedure were given.

Grignard compounds were prepared from 40 g. of magnesium, 280 g. of bromodimethylhydroquinone and 44 g. of *n*-butyl bromide in 1400 ml. of ether. The reaction mixture was placed in an ice-bath and oxygen was passed over the solution while vigorous stirring was carried on. The temperature of the reaction mixture was kept under 30°. After about thirty minutes a negative Michler ketone test for Grignard reagent was obtained. The reaction with oxygen was permitted to continue for an additional ten minutes. The reaction mixture was decomposed with 4 *N* hydrochloric acid. The aqueous layer was extracted with ether and the organic layers were then extracted with 5 *N* sodium hydroxide. The alkaline extract was acidified and extracted with ether. The ether extract was dried and distilled. Redistillation gave a fraction boiling at 245–255°. Yields varied from 20 to 25% compared to the 43% reported by Gilman and van Ess.[7]

Dakin Oxidations.—The peracetic acid used was prepared according to the procedure of Findley, Swern and Scanlan,[13] and was titrated before and during the reaction by a method based on that suggested by Buffalo

(5) Hunter and Levine, THIS JOURNAL, **48**, 1610 (1926).
(6) Hahn and Wassmuth, *Ber.*, **67**, 701 (1934).
(7) Gilman and van Ess, THIS JOURNAL, **61**, 1365 (1939).
(8) All melting points and boiling points are uncorrected.
(9) Titherley and Hudson, U. S. Patent, 1,878,061; *C. A.*, **27**, 312 (1933).
(10) Klarman, Gatyas and Shternov, THIS JOURNAL, **53**, 3397 (1931).
(11) Mauthner, "Organic Syntheses," Coll. Vol. I, p. 537 (1941).
(12) Pratt and Robinson, *J. Chem. Soc.*, **125**, 193 (1924).
(13) Findley, Swern and Scanlan, THIS JOURNAL, **67**, 412 (1945).

Electro-Chemical Company.[14] The commercial product is satisfactory provided the sulfuric acid present is first neutralized by sodium acetate.

One milliliter of the acid in a volumetric flask was diluted to 100 ml. with distilled water at 0–5°. A 20.0-ml. portion of this solution was added to 200 ml. of 1 *N* sulfuric acid containing enough ice so that some should be left at the end of the titrations. After addition of 3 drops of saturated manganese sulfate solution, the solution was titrated with 0.1 *N* potassium permanganate to a pink color lasting ten seconds. The hydrogen peroxide was thus eliminated. Only about 0.1 ml. of permanganate solution was required. There was immediately added 10 ml. of 10% potassium iodide and the solution was titrated with 0.100 *N* sodium thiosulfate using starch indicator.

Titrations of the reaction mixtures were carried out using 2.0 ml. of reaction mixture in place of the 20.0 ml. of aqueous solution used in the titration of the peracetic acid.

3,4-Dimethoxyphenol (XIa).—This was prepared according to modification of the procedures of Wacek and Bezard[4] and of Böeseken and Greup.[15]

To a 245-ml. solution of 40 g. (0.240 mole) of veratraldehyde in glacial acetic acid was added 195 ml. of acetic acid containing 0.488 equivalent of peracetic acid. The addition was carried out over a period of fifteen minutes. The temperature rose and was kept at 40–45° by cooling. At the end of fifty minutes, a 2.0-ml. sample was titrated. This showed that about 91% of the peracetic acid had been consumed. At the end of ten hours over 99% of the peracetic acid had been consumed.

The reaction mixture was concentrated to about 60 ml. under 20 mm. pressure, taken up in ether, and washed twice with 50-ml. portions of water. The ether layer was dried over sodium sulfate and distilled. There was obtained 35.4 g. (81%) of material boiling at 146° (13 mm.)–165° (16 mm.) (reported[4] for formate of 3,4-dimethoxyphenol 130–145° (12 mm.)).

This product was hydrolyzed by refluxing with 10% potassium hydroxide in 80% alcohol. The reaction mixture was concentrated *in vacuo* to almost dryness, taken up in water, and made acid with sulfuric acid. The phenol was extracted with ether and dried. Distillation gave 25 g. (67%) of product boiling at 155–166° (14 mm.).

This product solidified and was recrystallized from carbon tetrachloride to give 20 g. (55%) of purified product, m. p. 78–80° (reported 80–81°[16]).

2,4-Dimethoxyphenol (XIIa).—To a 220-ml. solution of 35.85 (0.216 mole) of 2,4-dimethoxybenzaldehyde[17] in glacial acetic acid, was added 170 ml. of acetic acid containing 0.425 equivalent of peracetic acid over a period of twenty-five minutes. The temperature was kept at 40–45° by cooling. After two hours about 96% of the peracetic acid had been consumed. At the end of twenty hours over 99% had been consumed.

This reaction mixture was worked up as in the case of 3,4-dimethoxybenzaldehyde. There was obtained 35.6 g. (90%) of formate, b. p. 150–156° (3 mm.), which on hydrolysis gave 27.8 g. (84%) of phenol after two distillations; b. p. 129° (10 mm.). The benzoate melted at 89° (reported 90°[18]).

2,3-Dimethoxyphenol (XIIIa).—To a 245-ml. solution of 40 g. (0.240 mole) of 2,3-dimethoxybenzaldehyde in glacial acetic acid, was added 195 ml. of acetic acid containing 0.488 equivalent of peracetic acid over a period of ten minutes. The temperature rose to 36° in about three and a half hours. The solution turned red in color. After four hours 81% of the peracetic acid had been consumed and after twenty hours about 98% had been consumed.

This reaction mixture was worked up as in the case of 3,4-dimethoxybenzaldehyde. There was obtained 29.2 g. (67%) of formate, b. p. 126–136° (13 mm.). The phenol was freed from its sodium salt by carbon dioxide instead of by sulfuric acid. The product was distilled under vacuum and then at atmospheric pressure; b. p. 230–240° (reported value 230–240°[19]). The yield was 17.1 g. (46%).

The methods for preparing the final glyceryl ethers are illustrated by the following preparations:

3-(2′-Hydroxyphenoxy)-1,2-propanediol (Method A).—This was prepared according to the procedure of Read and Miller.[20] Our product distilled at 249–259° (20 mm.) and was redistilled at 190–192° (0.6 mm.). The distillate, recrystallized from benzene, melted at 87.5–88°. The compound is reported as an oil, b. p. 245–255° (18 mm.).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.77; H, 6.50.

The etherification of 3-(2′-hydroxyphenoxy)-1,2-propanediol by *n*-propyl, isopropyl, *n*-butyl and isobutyl bromides is illustrated by the preparation of 3-(2′-isopropoxyphenoxy)-1,2-propanediol.

3-(2′-Isopropoxyphenoxy)-1,2-propanediol (II).—To 6 g. (0.26 mole) of sodium in 200 ml. of absolute ethanol was added 45.5 g. (0.25 mole) of 3-(2′-hydroxyphenoxy)-1,2-propanediol in 100 ml. of absolute ethanol. After the resulting mixture was refluxed for fifteen minutes, 42 g. (0.34 mole) of isopropyl bromide in 150 ml. of absolute ethanol was added. Refluxing was continued for two hours. After addition of 150 ml. of water, refluxing was continued for another two hours. The solution was evaporated to dryness. The residue was extracted with absolute ethanol and the extract distilled and redistilled. The fraction, b. p. 148° (0.25 mm.), was recrystallized from Skellysolve C to give a product having a m. p. 57–58.5°. The yield was 30 g. (53.5%).

3-(2,6-Dimethoxyphenoxy)-1,2-propanediol (VIII) (Method B).—To a solution of 8 g. (0.35 mole) of sodium in 175 ml. of absolute ethanol, was added 53 g. (0.35 mole) of 2,6-dimethoxyphenol in 100 ml. of absolute ethanol. The resulting suspension was treated with 50 g. (0.45 mole) of glycerol monochlorohydrin in five portions at about five-minute intervals. The reaction mixture was refluxed for two hours and filtered. There was collected 11 g. (95%) of sodium chloride. The filtrate was distilled. The fraction boiling at 165–167° (0.6 mm.) was redistilled to give 64 g. (81%) of product with $n^{26}D$ 1.5340.

Summary

As part of a study of muscle-relaxing drugs, a series of 3-aryloxy-1,2-propanediols has been prepared. There is described the preparation of the six isomeric 3-(dimethoxyphenoxy)-1,2-propanediols, the three isomeric 3-(ethoxyphenoxy)-1,2-propanediols, and the 3-phenoxy-1,2-propanediol substituted in an ortho position by a propoxy, an isopropoxy, a butoxy or an isobutoxy group.

NEW YORK 11, N. Y. RECEIVED APRIL 7, 1950

(14) Buffalo Electro-Chemical Company, Data Sheet No. 1 on Peracetic Acid.

(15) Böeseken and Greup, *Rec. trav. chim.*, **58**, 528 (1939).

(16) Baker and Evans, *J. Chem. Soc.*, 372 (1938).

(17) Prepared from dimethylresorcinol according to Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).

(18) Spaeth, Paller and Gergely, *Ber.*, **73**, 935 (1940).

(19) Baker and Smith, *J. Chem. Soc.*, 2542 (1931).

(20) Read and Miller, THIS JOURNAL, **54**, 1192 (1932).