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Derivatives of Dihydroeugenol and Certain Pharmacological Properties of Some of the Compounds[1]

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The therapeutic properties of eugenol, thymol and guaiacol are fairly well known. Employing alcoholic solutions of these three phenols, Courmont, Morel and Bay[2] have shown that eugenol has the strongest sterilizing properties of the three compounds, the tests being conducted on homogeneous cultures of tuberculosis bacilli.

Due to the similarity in structure of eugenol and dihydroeugenol and since dihydroeugenol has been investigated only to a minor extent, this research was undertaken in order to study the properties of this compound, some of its derivatives and to study further certain pharmacological properties of some of these compounds.

The formation of dihydroeugenol from eugenol involves the reduction of the allyl group. In this investigation dihydroeugenol was prepared by catalytic reduction, using platinum oxide as the catalyst. By nitration of dihydroeugenol, a 5-nitro derivative was obtained, the nitro group entering ortho to the hydroxyl. By the reduction of 5-nitrodihydroeugenol, 5-aminodihydroeugenol was formed which was identical with the compound formed by direct reduction of 5-nitroeugenol. 5-Nitroeugenol was prepared by a modification of the method employed by Weselsky and Benedict[3] and Klemenc.[4]

Several other derivatives of dihydroeugenol and 5-aminodihydroeugenol were prepared: the acetate, the benzoate, the glycolic acid derivative and the sodium salt from dihydroeugenol; the 5-aminodihydroeugenol was acetylated, benzoylated, diazotized and coupled with several intermediates and it was condensed with *p*-nitrobenzaldehyde to the Schiff base.

It has been found that the saturation of the allyl group in eugenol alters the pharmacological properties of the resulting compound considerably.

Experimental Part

The eugenol used in this investigation was Merck U. S. P. X. This was carefully fractionated, and the portion which distilled at 135–136° under 15 mm. pressure was used throughout the investigation. It is a colorless distillate, sp. gr. 1.0630 at 18.5°. The eugenol was kept in amber colored bottles and was fractionated prior to its use in the various syntheses.

Dihydroeugenol.—Twenty-five grams of eugenol was dissolved in 150 cc. of alcohol and placed in a thick wall reduction bottle; 0.3 g. of platinum oxide, prepared according

(1) Abstracted from a thesis presented by David E. Levin to the Graduate School in partial fulfilment of the requirements for the Ph.D. degree.

(2) Courmont, Morel and Bay, *Compt. rend. soc. biol.*, **98**, 318 (1928).

(3) Weselsky and Benedict, *Monatsh.*, **3**, 386 (1883).

(4) Klemenc, *ibid.*, **33**, 378 (1912).

to the directions given in "Organic Syntheses,"[5] was used as a catalyst. The reduction was performed in a Parr catalytic hydrogenation machine; fifteen minutes was required for the reduction. The resulting solution was filtered, the alcohol distilled, the oil dissolved in ether and dried over sodium sulfate. The ether solution was filtered, the sodium sulfate washed with ether and the ether distilled; yield, 24 g.

The boiling points of dihydroeugenol as determined in this investigation under various pressures are as follows: 1 mm., 94–95°; 3 mm., 103–104°; 5 mm., 112–113°; 10 mm., 119–121°; 15 mm., 126–127°; 17 mm., 131–132°; 18 mm., 133–134°; 25 mm., 138–139°.

Sodium Salt of Dihydroeugenol.—Five grams of dihydroeugenol was shaken with 4 cc. of an aqueous solution (25%) of sodium hydroxide. The precipitate was filtered by suction, washed with anhydrous ether and dried *in vacuo*.

Anal. Calcd. for $C_{10}H_{13}O_2Na$: Na, 12.23. Found: Na, 12.20, 12.08.

5-Nitrodihydroeugenol.—Twenty grams of dihydroeugenol was dissolved in 250 cc. of ethyl ether. This mixture was placed in a 1-liter flask, fitted with a condenser, mechanical agitator, thermometer and dropping funnel. The flask was placed in a water-bath and the contents stirred vigorously until the mixture was at a temperature between 20 and 23°; 10 cc. of fuming nitric acid (sp. gr. 1.5) was added at such a rate (twenty-five minutes) below the surface of the mixture, the contents of the flask being stirred violently, so that the temperature of the reaction mixture did not rise above 26°. The solution changes from colorless to deep red. Rapid stirring was continued for ten hours, the temperature being maintained at 23 to 25°. The mixture was neutralized with alcoholic potassium hydroxide solution, using brom thymol blue and Congo red as indicators. The precipitated potassium nitrate was filtered, washed with ether and the filtrate dried over anhydrous sodium sulfate. The solution was filtered, the solvent removed, the product vacuum distilled and the portion boiling at 133–135° (2 mm.) was collected. The oil, on cooling with carbon dioxide snow, solidified. The product was recrystallized twice from alcohol and once from ligroin; yellow-orange crystals, m. p. 33.8–34.2°; yield, 12 g.

Anal. Calcd. for $C_{10}H_{13}O_4N$: N, 6.63; OCH_3, 14.68. Found: N, 6.47, 6.68; OCH_3, 14.97, 14.22.

Potassium Salt of 5-Nitrodihydroeugenol.—To 2 g. of 5-nitrodihydroeugenol dissolved in 25 cc. of ether was added 19 cc. of alcoholic potassium hydroxide solution (2.8%). A red crystalline precipitate separated. This compound was recrystallized from alcohol, filtered, washed with ether and dried *in vacuo;* yield, 1.8 g.

Anal. Calcd. for $C_{10}H_{12}O_4NK$: K, 15.66. Found: K, 15.55, 15.33.

5-Nitroeugenol.—The nitration of eugenol was carried out using essentially the same procedure employed for the nitration of dihydroeugenol. To 20 g. of eugenol in 250 cc. of ether at 25° was added 10 cc. of nitric acid (sp. gr. 1.5) at such a rate (fifteen minutes) that the temperature of the reaction mixture did not rise above 33°. The mixture was stirred for ten hours. After neutralizing the excess of nitrating acid, filtering off the potassium nitrate, drying and removing the solvent, the product was vacuum distilled and the portion boiling at 140° (2 mm.) was collected. The deep orange-colored nitro compound, obtained in the form of a viscous oil, solidified upon cooling in carbon dioxide snow. The compound was recrystallized from alcohol until there was no further increase in melting point; yellow-orange needles; m. p. 42.8–43.4°; yield, 11 g. Weselsky and Benedict, and Klemenc reported 43–44° for this compound.

Anal. Calcd. for $C_{10}H_{11}O_4N$: N, 6.69. Found: N, 6.47, 6.51.

(5) Adams, Voorhees and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

Potassium Salt of 5-Nitroeugenol.—This compound was prepared in the same manner as the above-mentioned potassium salt of 5-nitrodihydroeugenol.

Anal. Calcd. for $C_{10}H_{10}O_4NK$: K, 15.78. Found: K, 15.43, 15.41.

Acetyldihydroeugenol.—Acetyl chloride (1.9 g.) was added drop by drop with stirring to 4.15 g. of dihydroeugenol in 2.0 g. of pyridine and 2.5 g. of acetic anhydride. After fifteen minutes, water was added and a pale yellow oil separated. This was washed repeatedly with 0.5 *N* sulfuric acid and then with water. The oil was extracted with ether and dried over sodium sulfate. The oil was purified by vacuum distillation; b. p. 115° (2 mm.); yield, 3 g. The colorless oil differs in properties from acetylcoerulignol reported by Pastrovich.[6]

Anal. For acetic acid after hydrolysis. Calcd. for $C_{12}H_{16}O_3$: CH_3COOH, 28.84. Found: CH_3COOH, 28.98, 29.02.

Benzoyldihydroeugenol.—To 4 g. of dihydroeugenol in 2.0 g. of pyridine, 3.5 g. of benzoyl chloride was added drop by drop with stirring. The solution became warm. It was then heated for ten minutes at 70° and cooled in an ice–salt bath. On stirring, white crystals separated in a solid mass. The product was filtered, washed with 0.5 *N* sulfuric acid, dilute sodium carbonate solution and several portions of water and recrystallized from alcohol three times; m. p. 73°; yield, 3.0 g.

Anal. Calcd. for $C_{17}H_{18}O_3$: OCH_3, 11.47. Found: OCH_3, 11.50, 11.69.

Dihydroeugenol Glycolic Acid.—Monochloroacetic acid (18.9 g.) dissolved in 38 cc. of a 22.7% potassium hydroxide solution was added to 16.6 g. of dihydroeugenol in 38 cc. of a 40% potassium hydroxide solution. The mixture was refluxed for six hours, allowed to cool and an excess of hydrochloric acid added. The resultant fine white needles were washed free from acid, dried and recrystallized three times from glacial acetic acid and three times from ether; m. p. 104°; yield, 21 g.

Anal. Calcd. for $C_6H_3(C_3H_7)(OCH_3)OCH_2COOH$: neutral equivalent (mol. wt.), 224. Found: 221.76, 221.76.

5-Aminodihydroeugenol.—(1) Catalytic reduction of 5-nitrodihydroeugenol: 10 g. of 5-nitrodihydroeugenol was dissolved in 150 cc. of alcohol, 0.2 g. of platinum oxide added and the reduction carried out in the hydrogenation machine as previously described. The reduction was completed in thirty minutes. The resulting solution was filtered, 800 cc. of water added with rapid stirring and the amine precipitated. The silvery white flaky precipitate was filtered, washed several times with water and dried in a desiccator; yield, 8 g.; m. p. 83–84°. The compound was purified by dissolving in alcohol and precipitated with water.

Anal. Calcd. for $C_{10}H_{15}O_2N$: N, 7.73. Found: N, 7.79, 7.73.

(2) Catalytic reduction of 5-nitroeugenol: 10 g. of the nitro compound was dissolved in 150 cc. of alcohol, 0.3 g. of platinum oxide added and the reduction carried out as in the above procedure. About one hour was required for the reduction. The compound was purified as above, m. p. 83–84°; yield, 8 g.; mixed m. p. of amine prepared by (1) and (2) 83–84°.

Anal. Calcd. for $C_{10}H_{15}O_2N$: OCH_3, 17.12. Found: OCH_3, 16.78, 17.30.

5-Aminodihydroeugenol Hydrochloride.—Dry hydrogen chloride gas was passed into 1 g. of 5-aminodihydroeugenol dissolved in 20 cc. of anhydrous ethyl acetate. The compound precipitated as a pink-white crystalline body. It was filtered, washed with anhydrous ethyl acetate and dried *in vacuo*. It decomposed between 191–192°.

Anal. Calcd. for $C_{10}H_{15}O_2N \cdot HCl$: HCl, 16.76. Found: HCl, 16.32, 17.14.

Dihydroeugenol-azo-β-naphthol.—3.3 g. of 5-aminodihydroeugenol dissolved in 100 cc. of 4.5% hydrochloric acid at 0° was diazotized with 16 cc. of 7.8% sodium nitrite

(6) Pastrovich, *Monatsh.*, **4**, 188 (1883).

solution. The temperature did not rise above 7°; 3 g. of β-naphthol in 100 cc. of 10% sodium hydroxide was cooled to 5° and the diazotized product was added with stirring. A red precipitate formed at once. The suspension was stirred for five hours, allowed to stand overnight, filtered and washed with water. This was purified by dissolving in alcohol, adding dilute hydrochloric acid and precipitating with water. It was purified three times by dissolving in alcohol and reprecipitating with water; yield, 4.1 g.

Anal. Calcd. for $C_{20}H_{20}O_3N_2$: N, 8.33. Found: N, 8.37, 8.50.

The dyes listed in Table I were prepared by essentially the same procedure.

TABLE I

Name, dihydroeugenol-azo-	Color	Formula	Analysis, N, % Calcd.	Found
1,8-Aminonaphthol-3,6-disulfonic acid	Deep purple	$C_{20}H_{21}O_9N_3S_2$	8.21	8.13 7.99
2-Hydroxy-3-naphthanilide	Deep blue	$C_{27}H_{25}O_4N_3$	9.23	8.97 8.89
1-Naphthol-4-sulfonic acid	Purple	$C_{20}H_{20}O_6N_2S$	6.73	6.40 6.20

Qualitative couplings were carried out with the following compounds: salicylic acid—dark brown; resorcinol—purple-brown; 1,8-dihydroxynaphthalene-3,6-disulfonic acid—deep purple.

5-Benzoylamino-1-propyl-3-methoxy-4-benzoxybenzene.—Benzoyl chloride (4.21 g.) was added drop by drop while stirring to 2.93 g. of 5-aminodihydroeugenol in 10 cc. of chloroform and 3 cc. of pyridine. The reaction mixture became warm. The solution was heated gently for fifteen minutes and then cooled in an ice–salt bath. The product was washed with water, filtered, washed with several portions of 0.5 *N* sulfuric acid, water, dilute sodium carbonate solution and finally with water. It was recrystallized three times from alcohol, a white crystalline body resulting; m. p. 162°; yield, 4.9 g.

Anal. Calcd. for $C_{24}H_{23}O_4N$: N, 3.59. Found: N, 3.50, 3.69.

1-Propyl-3-methoxy-4-hydroxy-5-(*p*-nitrobenzal)-aniline.—To 2.715 g. of 5-aminodihydroeugenol in 25 cc. of alcohol was added 1.51 g. of *p*-nitrobenzaldehyde dissolved in 25 cc. of hot alcohol. The mixture was refluxed for one hour. The compound separated in fine yellow silky needle-shaped crystals. It was filtered, recrystallized from alcohol twice and dried *in vacuo;* m. p. 133–134°; yield, 2.7 g.

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: N, 8.91. Found: N, 8.95, 9.00.

5-Acetylamino-1-propyl-3-methoxy-4-acetoxybenzene.—Acetic anhydride (5 g.) was added to 5-aminodihydroeugenol (4.55 g.) in 10 cc. of anhydrous chloroform and 4 g. of pyridine. The solution was then treated with 4 g. of acetyl chloride, added drop by drop with constant stirring. The reaction mixture became warm. The solution was heated for fifteen minutes at 50°. It was cooled to 0° and a yellowish-white product precipitated. This was filtered, washed with 0.5 *N* sulfuric acid, water, dilute sodium carbonate solution and water. The product was recrystallized twice from alcohol, giving a white crystalline body; m. p. 155°; yield, 4 g.

Anal. For acetic acid after hydrolysis. Calcd. for $C_{14}H_{19}O_4N$: CH_3COOH, 45.28. Found: CH_3COOH, 45.40, 45.50.

Pharmacological Tests.[7]—Some of the compounds were studied pharmacologically and a brief outline is summarized as follows.

Eugenol and dihydroeugenol when injected subcutaneously into the guinea pig have a minimum lethal dose per kilogram body weight of 0.93 g.

(7) These compounds are being studied pharmacologically by Dr. Edward C. Reif, Professor of Materia Medica and Physiology, College of Pharmacy, University of Pittsburgh. The authors wish to express their indebtedness to him.

and 3.95 g., respectively. Dihydroeugenol did not produce the deep narcosis observed with eugenol.

Skin tests: Eugenol, irritation; dihydroeugenol, no irritation.

Local action on mucous membrane: eugenol, blanching of tissue in five minutes; dihydroeugenol, slight blanching of tissue in forty-five minutes.

Local action on cardiac muscle: eugenol, blanching of tissue in five minutes; dihydroeugenol, no blanching of tissue in sixty minutes.

Local action on turtle heart *in situ:* sodium salt of eugenol, caused complete stoppage of auricle and ventricle for three and one-half minutes; sodium salt of dihydroeugenol, lessened the amplitude and force of the contraction, but did not cause complete stoppage.

Effect on blood pressure: sodium salt of eugenol, caused a slight rise in doses of 0.01 and 0.05 g.; sodium salt of dihydroeugenol, caused a slight rise followed by a drop in doses of 0.01 and 0.05 g.; 5-aminodihydroeugenol hydrochloride, caused a slight rise in doses of 0.01, 0.05 and 0.1 g.; 5-benzoylamino-1-propyl-3-methoxy-4-benzoxybenzene, caused a slight drop in pressure in doses of 0.01 g.

Effect on respiration: sodium salt of eugenol, no perceptible change in doses of 0.01 and 0.05 g.; sodium salt of dihydroeugenol, no perceptible change in doses of 0.01 and 0.05 g.; 5-aminodihydroeugenol hydrochloride, no perceptible change in doses of 0.01 and 0.05 g.; 5-benzoylamino-1-propyl-3-methoxy-4-benzoxybenzene, caused a perceptible change in the rate and rhythm.

The last four compounds mentioned above when injected intravenously in dogs caused no salivation, nausea, vomiting, defecation, diarrhea or urination.

The blood pressure and respiration experiments were performed on dogs and the skin tests on human subjects. The mucous membrane and cardiac muscle experiments were performed on turtles.

Summary

1. Dihydroeugenol has been prepared by catalytic reduction using Adams platinum oxide as the catalyst. The following derivatives of dihydroeugenol have been prepared: (a) acetyldihydroeugenol; (b) dihydroeugenol glycolic acid; (c) 5-nitrodihydroeugenol; (d) potassium salt of 5-nitrodihydroeugenol; (e) sodium salt of dihydroeugenol; (f) 5-aminodihydroeugenol; (g) 5-aminodihydroeugenol hydrochloride; (h) dihydroeugenol-azo-β-naphthol; (i) dihydroeugenol-azo-1-hydroxynaphthalene-4-sulfonic acid; (j) dihydroeugenol-azo-1,8-aminonaphthol-3,6-sulfonic acid; (k) dihydroeugenol-azo-2-hydroxy-3-naphthanilide; (l) 1-propyl-3-methoxy-4-hydroxy-5-(*p*-nitrobenzal)-aniline; (m) 5-benzoylamino-1-propyl-3-methoxy-4-benzoxybenzene; (n) 5-acetylamino-1-propyl-3-methoxy-4-acetoxybenzene.

2. Certain pharmacological properties of dihydroeugenol, eugenol and some of their derivatives have been studied.

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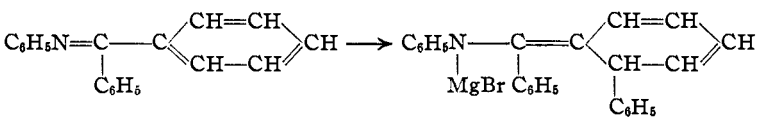
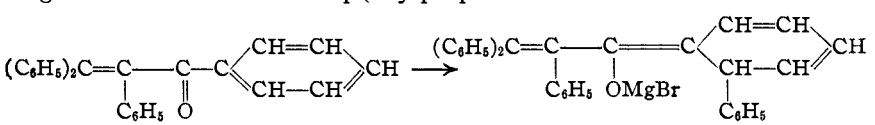
Ring–Chain Conjugation in the Quinoline Series

BY ARNOLD HOFFMAN, MARK W. FARLOW AND REYNOLD C. FUSON

There are many types of evidence which indicate that conjugation occurs between aromatic rings and their unsaturated side-chains containing suitably placed multiple linkages. The most convincing evidence of conjugation in this type of molecule is that in certain cases 1,4-addition of the Grignard reagent has been observed. This type of addition is characteristic of systems of conjugated double bonds in which a terminal position is occupied by an electronegative atom such as oxygen or nitrogen. It has recently been shown to take place even when one of the double bonds is situated in a benzene ring. Gilman, Kirby and Kinney[1] have found that phenylmagnesium bromide adds to benzophenone anil

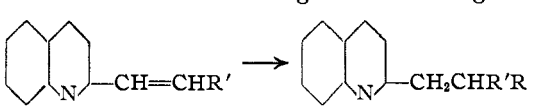


and similarly, Kohler and Nygaard[2] have observed the addition of phenylmagnesium bromide to tetraphenylpropenone



In both of these cases the ethylenic double bond involved in the addition reaction is situated in a benzene ring. The present paper deals with a similar case of ring–chain conjugation in which, however, the ethylenic double bond is in the side-chain and is conjugated with a nitrogen–carbon double bond situated in an aromatic ring.

The compounds which have been studied are benzalquinaldines and with RMgX they have been found to undergo the following transformation



Benzalquinaldine when treated with a solution of phenylmagnesium

(1) Gilman, Kirby and Kinney, THIS JOURNAL, **51**, 2252 (1929).
(2) Kohler and Nygaard, *ibid.*, **52**, 4128 (1930).