# Analgesics: Synthesis of 1-Dioxolanoalkylnormeperidines and 1-Dioxanoalkylnormeperidines

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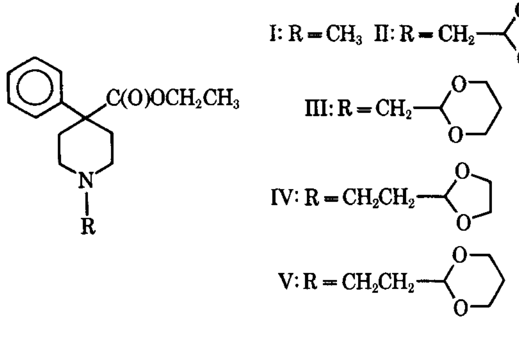
**Abstract** □ The syntheses of the maleate salts of *N*-(2-methylene-1,3-dioxolano)normeperidine (II), *N*-(2-methylene-1,3-dioxano)-normeperidine (III), *N*-(2-ethylene-1,3-dioxolano)normeperidine (IV), and *N*-(2-ethylene-1,3-dioxano)normeperidine (V) are reported. The dioxolane derivatives (II and IV) possessed analgesic activity, with II being slightly more active than meperidine. None of these compounds antagonized the analgesic effect of meperidine.

**Keyphrases** □ 1-Dioxolanoalkylnormeperidines—synthesis as possible analgesics □ 1-Dioxanoalkylnormeperidines—synthesis as possible analgesics □ Analgesics, potential—synthesis, pharmacological evaluation of 1-dioxolanoalkylnormeperidines, 1-dioxanoalkylnormeperidines



Replacement of the *N*-methyl in meperidine with heterocyclic-containing alkyls has sometimes given rise to compounds that are more potent analgesics than meperidine (I) itself (1–4). Potent analgesic derivatives of meperidine also occur when the nitrogen is substituted with groups that contain ether linkages in the chain (3–9). In the continuation of a study designed to explore the potential of substituted dioxolanes and dioxanes as medicinal agents, some *N*-dioxolanoalkylnormeperidines and *N*-dioxanoalkylnormeperidines were prepared and screened for analgesic activity (10, 11).

Alkylation of normeperidine with the appropriate 2-bromoalkyl-1,3-dioxolane or 2-bromoalkyl-1,3-dioxane in dimethylformamide at 100° or refluxing toluene gave the desired meperidine analog. The products were characterized as their maleate salts. The synthesis of ethyl 4-phenylpiperidine-4-carboxylate (normeperidine) was accomplished through *N*-tosylation, nitrile hydrolysis, and detosylation and esterification of 4-phenyl-4-cyanopiperidine according to the procedure of Thorp and Walton (12).

Following a method described by Bedoukian (13), the cyclic acetals, 2-bromomethyl-1,3-dioxolane and 2-bromomethyl-1,3-dioxane, were synthesized by adding 1,2-dibromoethyl acetate to a solution of the appropriate glycol and distilling the resulting mixture. The preparation of 2-(2-bromoethyl)-1,3-dioxolane and 2-(2-bromoethyl)-1,3-dioxane was carried out according to an established procedure that required the addition of acrolein to a cold solution of anhydrous hydrogen bromide in an appropriate glycol (14).

## PHARMACOLOGICAL RESULTS

The *N*-substituted normeperidine salts were subjected to a preliminary analgesic screen, using a modification of the Eddy and Leimbach method (15). Male and female white mice were observed for signs of pain after being placed on a metal plate floating on a circulating hot water (53°) bath. Those animals whose reaction time increased to at least twice the mean reaction time of the control animals were assumed to show significant pain relief. The test was conducted 15 min. after subcutaneous administration of the required dose. The ED$_{50}$ levels were calculated according to the method of Miller and Tainter (16). Meperidine, according to this method, had an ED$_{50}$ of 9 mg./kg., while *N*-(2-methylene-1,3-dioxolano)normeperidine and *N*-(2-ethylene-1,3-dioxolano)normeperidine had ED$_{50}$'s of 20 and 6 mg./kg., respectively. The dioxane derivatives did not possess any analgesic activity at doses of 50 mg./kg.

Using the general procedure of Harris and Pierson (17), Compounds II, III, IV, and V were assayed in rats for their ability to antagonize the normal analgesic response of meperidine. A dose of 100 mg./kg. of the test compound was administered subcutaneously 10 min. prior to a 100-mg./kg. subcutaneous dose of meperidine. Analgesia was determined using the D'Amour-Smith tail-flick method (18). Pain measurements at 30- and 60-min. intervals showed that the *N*-dioxolanoalkylnormeperidines and the *N*-dioxanoalkylnormeperidines did not reverse the analgesic effect of meperidine and possessed no narcotic antagonist effect. In fact, they potentiated the analgesic effect of meperidine; rats receiving both meperidine and the test compound were much more lethargic and unresponsive than the control animals who were given only meperidine.

## EXPERIMENTAL[1]

**2-Bromomethyl-1,3-dioxolane**—Following the procedure of Bedoukian (13), 2-bromomethyl-1,3-dioxane was isolated as colorless liquid distilling at 70–76° at 18–20 mm. [lit. (19) 63–65° at 12 mm.]; yield: 72%.

**2-Bromomethyl-1,3-dioxane**—Following the procedure of Bedoukian (13), 2-bromomethyl-1,3-dioxane was isolated as a colorless liquid distilling at 67–72° at 6 mm. [lit. (19) 80-86° at 12 mm.]; yield: 70%.

**2-(2-Bromoethyl)-1,3-dioxolane**—Following the procedure of Hill and Potter (14), 2-(2-bromoethyl)-1,3-dioxolane was isolated as a colorless oil distilling at 68–73° at 10 mm. [lit. (14) 72–73° at 10 mm.]; yield: 30%.

**2-(2-Bromoethyl)-1,3-dioxane**—Following the procedure of Hill and Potter (14), 2-(2-bromoethyl)-1,3-dioxane was isolated as a colorless oil distilling at 68–74° at 4.8 mm.

*Anal.*—Calc. for $C_6H_{11}BrO_2$: C, 36.94; H, 5.69. Found: C, 37.16; H, 5.77.

***N*-(2-Methylene-1,3-dioxolano)normeperidine Maleate**—Normeperidine (3.0 g., 0.013 mole) and 2-bromomethyl-1,3-dioxolane (4.3 g., 0.026 mole) were added to 25 ml. of toluene. Five grams of anhydous sodium carbonate was added, and the mixture was refluxed for 18 hr. After filtration, the filtrate was extracted twice with 30 ml.

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[1] Melting points were determined on a Thomas-Hoover melting apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, School of Chemistry, University of Minnesota, Minneapolis, Minn., with the exception of *N*-(2-methylene-1,3-dioxano)normeperidine maleate which was analyzed by Galbraith Laboratories, Inc., Knoxville, Tenn.

of 0.5 *N* aqueous hydrochloric acid. The aqueous layer was basified immediately with aqueous sodium carbonate, and the solution was extracted three times with ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to a yellow oil, which was distilled to yield 1 g. (24%) of a colorless oil, b.p. 134–137° at 0.2 mm. This material was dissolved in 5 ml. of anhydrous ether; to it was added maleic acid (0.38 g., 0.0032 mole) dissolved in 2 ml. of ethanol. The white crystals which formed were recrystallized from ethanol–ether; yield: 1.0 g. (74%); m.p. 116–119°.

*Anal.*—Calc. for $C_{22}H_{29}NO_8$: C, 60.88; H, 6.71. Found: C, 61.05; H, 7.05.

***N*-(2-Methylene-1,3-dioxano)normeperidine Maleate**—Normeperidine (1.0 g., 0.004 mole) in 20 ml. of dimethylformamide was treated with 2-bromomethyl-1,3-dioxane (0.8 g., 0.004 mole) and anhydrous sodium carbonate (0.6 g., 0.006 mole). The mixture was stirred at 100° for 18 hr. After cooling, it was added to 20 ml. of water and extracted three times with 20-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to 10 ml. Maleic acid (0.5 g., 0.004 mole) was dissolved in 5 ml. of ethanol, and to this was added the concentrated ether extracts. The resulting crystals were recrystallized from chloroform–ether; yield: 1.6 g. (85%); m.p. 145–148°.

*Anal.*—Calc. for $C_{23}H_{31}NO_8$: C, 61.45; H, 6.95; N, 3.12. Found: C, 61.66; H, 6.81; N, 2.94.

***N*-(2-Ethylene-1,3-dioxolano)normeperidine Maleate**—The procedure used was the same as described for *N*-(2-methylene-1,3-dioxano)normeperidine maleate, except 2-(2-bromoethyl)-1,3-dioxolane (0.85 g., 0.0047 mole) was used instead of 2-bromomethyl-1,3-dioxane; yield: 1.35 g. (70%); m.p. 162–164°.

*Anal.*—Calc. for $C_{23}H_{31}NO_8$: C, 61.45; H, 6.95. Found: C, 61.32; H, 7.16.

***N*-(2-Ethylene-1,3-dioxano)normeperidine Maleate**—The procedure used was the same as described for *N*-(2-methylene-1,3-dioxano)normeperidine maleate, except 2-(2-bromoethyl)-1,3-dioxane (0.8 g., 0.004 mole) was used instead of 2-bromomethyl-1,3-dioxane; yield: 0.8 g. (40%); m.p. 135–137°.

*Anal.*—Calc. for $C_{24}H_{33}NO_8$: C, 62.17; H, 7.18. Found: C, 62.20; H, 7.27.

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## ACKNOWLEDGMENTS AND ADDRESSES

Received January 6, 1971, from the **Department of Medicinal Chemistry, School of Pharmacy, Southwestern State College, Weatherford, OK 73096* and the †*Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455*

Accepted for publication March 26, 1971.

# Aromatic Amines Condensed with Aminothiazoles, Directly and with Isatoic Anhydride, for Schistosomiasis Treatment I

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**Abstract** ☐ Structural combination between the two moieties necessary for the biological effectiveness in both oral schistosomicidal agents, 1-(2-diethylaminoethylamino)-4-methylthiaxanthone and 1-(5-nitro-2-thiazolyl)-2-imidazolidinone, namely, the substituted aromatic amine and aminothiazole, respectively, were tried. The combination between both systems was suggested to be through amide linkage.

**Keyphrases** ☐ Aminothiazoles, condensation with aromatic amines—synthesis of oral schistosomiasis agents ☐ Aromatic amines, condensation with aminothiazoles—synthesis of oral schistosomiasis agents ☐ Schistosomiasis agents, oral—aromatic amines condensed with aminothiazoles, isatoic anhydride

The search for an oral chemotherapeutic agent for treatment of schistosomiasis led to the synthesis of 1-(2-diethylaminoethylamino)-4-methylthiaxanthone[1] (1), which was found also to be of carcinostatic value (2). Evidence has been accumulated that the structural feature necessary for the biological activity of this agent is a dialkylaminoalkylamine side chain *para* to a methyl on an aromatic ring (3–5). The drug was not ideal because of its undesirable side effects.

Recently, attention was attracted to the use of 5-nitrothiazole derivatives in the oral chemotherapy of schistosomiasis. The compound 1-(5-nitro-2-thiazolyl)-2-imidazolindinone[2] was found to exert good schistosomi-

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[1] Lucanthone or Miracil D.

[2] Coded as Ciba-32644 or Ambilhar.