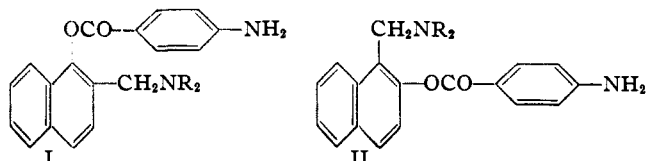


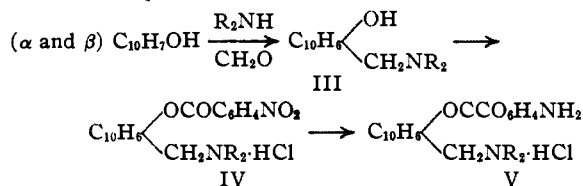
[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS]

***p*-Aminobenzoates of Piperidino- and Morpholinomethylnaphthols**BY R. L. SHRINER, G. F. GRILLOT AND W. O. TEETERS¹

The present report describes the synthesis of the monohydrochlorides of the *p*-aminobenzoates derived from piperidinomethyl- and morpholinomethyl- α - and β -naphthols represented by the

(where $-\text{NR}_2$ are piperidino and morpholino groups)

formulas I and II. These compounds were desired in order to explore the pharmacological behavior of these isomers. The first step in their preparation involved carrying out the Mannich² reaction on α - and β -naphthols using formaldehyde and piperidine and morpholine, respectively. The substituted aminomethylnaphthols (III) were treated with *p*-nitrobenzoyl chloride to produce the monohydrochlorides of the *p*-nitrobenzoic



esters (IV) which were catalytically reduced to the monohydrochlorides of the *p*-aminobenzoates (V).

The pharmacological action of these compounds has been reported by Fellows, Cunningham and Livingston.³ The hydrochloride salts of the *p*-aminobenzoic esters of 2-piperidinomethyl-1-naphthol, 2-morpholinomethyl-1-naphthol and 1-morpholinomethyl-2-naphthol produced anesthesia of poor depth and variable duration. The hydrochloride salt of the *p*-aminobenzoic ester of 1-piperidinomethyl-2-naphthol produced marked anesthesia and had low toxicity. All these compounds were inferior to procaine or cocaine.

Experimental

1-Piperidinomethyl-2-naphthol.—A mixture of 85 g. of piperidine and 75 g. of formalin was chilled to 5°. A solution of 115 g. of β -naphthol in 450 ml. of 95% alcohol was chilled to 5°, and then added in three portions to the above mixture with mechanical stirring. The product crystallized in a short time and was collected by filtration and

washed with a small amount of alcohol. Crystallization from 95% alcohol gave colorless crystals which melted at 94.5–95.5°. The yield amounted to 198 g. (82%).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{ON}$: N, 5.81. Found: N, 5.69.

1-Piperidinomethyl-2-naphthyl *p*-Nitrobenzoate Hydrochloride.—Fifteen grams of the above naphthol base was dissolved in 100 ml. of warm dry toluene and was added to 11.5 g. of *p*-nitrobenzoyl chloride which had previously been dissolved in 100 ml. of dry toluene. The mixture was warmed on a steam cone for five hours. It was then cooled and filtered. The solid was recrystallized from 95% alcohol and melted at 184–191°. A yield of 21 g. or 80% of the theoretical was obtained. Upon recrystallization from 95% alcohol, the compound melted at 190–191°. It formed beautiful light yellow needles.

Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_4\text{N}_2\text{Cl}$: N, 6.56; Cl, 8.32. Found: N, 6.25, 6.22; Cl, 8.21, 8.29.

1-Piperidinomethyl-2-naphthyl *p*-Aminobenzoate Hydrochloride.—Ten grams of the purified 1-piperidinomethyl-2-naphthyl *p*-nitrobenzoate hydrochloride was suspended in 250 ml. of 95% alcohol and 0.2 g. of platinum oxide catalyst was added. Reduction was completed in fifteen minutes at 25° and 40 lb. per sq. in. pressure of hydrogen. The platinum was removed by filtration and most of the alcohol was evaporated. The amine salt separated as buff-colored crystals. A yield of 7.5–7.8 g. (80–85%) was obtained. It was recrystallized several times from alcohol using Darco. Prisms which were almost colorless were obtained which decomposed at 151–152°.

Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_2\text{N}_2\text{Cl}$: N, 7.06; Cl, 8.95. Found: N, 6.70; Cl, 9.08.

2-Piperidinomethyl-1-naphthol.—The procedure described above for 1-piperidinomethyl-2-naphthol was applied to α -naphthol. The product formed long colorless needles melting at 133.5–134.5° which checked the value reported by Auwers and Dombrowski.³ The yield was 190 g. (75%).

2-Piperidinomethyl-1-naphthyl *p*-Nitrobenzoate Hydrochloride.—Fifteen grams of 2-piperidinomethyl-1-naphthol was dissolved in 100 ml. of warm dry toluene and this was added to 11.5 g. of *p*-nitrobenzoyl chloride which was dissolved in 100 ml. of toluene. The mixture was warmed on a steam cone for five hours. It was then cooled and filtered. The solid was recrystallized from 95% alcohol. Light yellow prisms decomposing at 203.5–205.5° were obtained. The yield amounted to 23 g. or 85% of the theoretical.

Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_4\text{N}_2\text{Cl}$: N, 6.56; Cl, 8.32. Found: N, 6.49; Cl, 8.40.

2-Piperidinomethyl-1-naphthyl *p*-Aminobenzoate Hydrochloride.—Five grams of the 2-piperidinomethyl-1-naphthyl *p*-nitrobenzoate hydrochloride was dissolved in 300 ml. of 95% alcohol. Two-tenths gram of platinum oxide catalyst was added and the compound was hydrogenated at 25° and 40 lb. per sq. in. pressure in thirty minutes. Most of the alcohol was evaporated and the resulting compound was permitted to crystallize. Small crystals which had a slight buff color were obtained. The yield amounted to 3 g. or 60% of the theoretical. This compound was only slightly soluble in water: (about 0.1 g. in 100 ml. of water). It decomposed at 230.5–232.5°.

Anal. Calcd. for $\text{C}_{23}\text{H}_{26}\text{O}_2\text{N}_2\text{Cl}$: N, 7.06; Cl, 8.95. Found: N, 6.86; Cl, 9.15.

1-Morpholinomethyl-2-naphthol.—A solution of 68 g. of β -naphthol was dissolved in 450 ml. of 95% alcohol and

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(2) Auwers and Dombrowski, *Ann.*, **344**, 284 (1906); Decombe, *Compt. rend.*, **197**, 258 (1933); Blicke, "Organic Reactions," Vol. I, 303 (1942).

(3) Fellows, Cunningham and Livingston, *J. Pharmacol.*, **78**, 27–32 (1941).

cooled to 5°. Morpholine (49 g.) was added very slowly to 38 g. of formalin cooled to 5°. The β -naphthol solution was added in three portions while the reactants were stirred. A flaky crystalline precipitate began to form at once and the precipitation was soon complete. This was filtered, dried and recrystallized from 95% alcohol. Colorless flat plates were formed. The yield amounted to 86 g. or 75% of the theoretical. These plates melted at 115–116°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: N, 5.76. Found: N, 5.60.

1-Morpholinomethyl-2-naphthyl *p*-Nitrobenzoate Hydrochloride.—Fifteen grams of 1-morpholinomethyl-2-naphthol dissolved in 100 ml. of hot dry toluene, was added to 11.5 g. of *p*-nitrobenzoyl chloride also dissolved in 100 ml. of dry toluene. The reaction mixture was heated on the steam cone for five hours. The mixture was filtered and the solid product was recrystallized from 95% alcohol. Small pale-yellow needles were formed which decomposed at 168–169°. A yield of 21 g. or 80% of the theoretical was obtained.

Anal. Calcd. for $C_{22}H_{21}O_3N_2Cl$: N, 6.53; Cl, 8.28. Found: N, 6.26; Cl, 8.21.

1-Morpholinomethyl-2-naphthyl *p*-Aminobenzoate Hydrochloride.—Five grams of the 1-morpholinomethyl-2-naphthyl *p*-nitrobenzoate was suspended in 250 ml. of 95% alcohol and 0.2 g. of platinum oxide catalyst was added. This compound was hydrogenated at 25° and 40 lb. per sq. in. pressure in forty-five minutes. The platinum was removed by filtration. The alcohol was partly evaporated to a volume of about 50 ml. in an inert atmosphere of nitrogen. Some solid material was separated by filtration and the compound then caused to crystallize by chilling in a refrigerator. The yield amounted to 2 g. or 40%. Almost colorless small crystals were obtained which decomposed at 181–182°. About 2 g. dissolved in 100 ml. of water.

Anal. Calcd. for $C_{22}H_{23}O_3N_2Cl$: N, 7.02; Cl, 8.91. Found: N, 6.85; Cl, 8.82.

2-Morpholinomethyl-1-naphthol.—The procedure was similar to that described for 1-morpholinomethyl-2-naphthol except that α -naphthol was used. The product separated as an oil which was permitted to stand for two hours in an ice-bath after which time it solidified. In order to purify this compound, the crude base was added to a solution of alcoholic hydrogen chloride. This mixture was warmed until solution was complete. On cooling, white crystals of 2-morpholinomethyl-1-naphthol hydrochloride separated. It decomposed at 172–173°.

Anal. Calcd. for $C_{16}H_{18}O_2NCl$: N, 5.31; Cl, 13.47. Found: N, 5.46; Cl, 13.22.

Twenty-five grams of the 2-morpholinomethyl-1-naphthol hydrochloride was dissolved in 100 ml. of water, filtered, and sodium bicarbonate solution was added until the solution was just alkaline to litmus. An oily precipitate formed which on standing for about three hours became solid and could be filtered. When properly dried it was a buff amorphous powder. A yield of 20 g. was obtained. On recrystallization from 95% alcohol, an almost colorless crystalline precipitate was obtained which was dried. It melted at 71.5–72.5°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: N, 5.76. Found: N, 5.89.

2-Morpholinomethyl-1-naphthyl *p*-Nitrobenzoate Hydrochloride.—Eleven and a half grams of *p*-nitrobenzoyl chloride dissolved in 100 ml. of warm dry benzene was added to 15 g. of the 2-morpholinomethyl-1-naphthol (crude) dissolved in 100 ml. of warm benzene. The reaction mixture was heated for five hours on the steam cone. It was then cooled, the precipitate filtered and recrystallized from 95% alcohol. Pale yellow needles were obtained that decomposed at 181–184°. The yield amounted to 19 g. or 75%.

Anal. Calcd. for $C_{22}H_{21}O_3N_2Cl$: N, 6.53; Cl, 8.28. Found: N, 6.64; Cl, 8.39.

2-Morpholinomethyl-1-naphthyl *p*-Aminobenzoate Hydrochloride.—Five grams of the 2-morpholinomethyl-1-naphthyl *p*-nitrobenzoate hydrochloride was suspended in 250 ml. of 95% alcohol. To this was added 0.2 g. of platinum oxide catalyst and 0.038 mole of hydrogen (at 40 lb. per sq. in.) was absorbed in about forty-five minutes. The platinum was removed by filtration and most of the alcohol was evaporated. On placing the solution in the ice box for twenty-four hours a pale yellow precipitate formed. The yield amounted to 3 g. or 60% of the theoretical. It decomposed at 174–176°. Solubility tests indicated that about 20 g. of this substance was soluble in 100 ml. of distilled water.

Anal. Calcd. for $C_{22}H_{23}O_3N_2Cl$: N, 7.02; Cl, 8.91. Found: N, 7.05; Cl, 8.83.

Summary

The syntheses of the *p*-nitrobenzoyl and *p*-aminobenzoyl esters of 1-piperidinomethyl-2-naphthol, 2-piperidinomethyl-1-naphthol, 1-morpholinomethyl-2-naphthol and 2-morpholinomethyl-1-naphthol are described.

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BLOOMINGTON, IND.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF RALPH L. EVANS ASSOCIATES]

Quinaldil, Quinaldoin and Diquinolylhydantoin

BY FRED LINSKER AND RALPH L. EVANS

The sodium salt of diphenylhydantoin introduced into medicine a few years ago as Dilantin Sodium has already proved one of the most valuable anti-convulsants and has won official recognition by being included in the U.S. Pharmacopoeia XII. We felt justified, therefore, in studying certain heterocyclic analogs of diphenylhydantoin with the view to possibly improving the effectiveness and counteracting the toxic side reactions of the drug.

Replacing the phenyl groups by quinolyl radicals would necessarily increase the basicity of the

compound, making it possible to prepare soluble salts with mineral acids, and thus avoid the alkalinity of a hydantoin sodium salt. Still more interesting observations were to be expected from a comparison of the physiological action of the new, fully heterocyclic, compound with the well known effects of its diphenyl analog.

Starting from quinaldine (I) we obtained a fair yield of quinaldil by oxidation with selenium dioxide in dioxane. Following the procedure of Kaplan¹ we obtained only quinaldil (II) from this

(1) Kaplan, *THIS JOURNAL*, **68**, 2654 (1941).