

cooled to 5°. Morpholine (49 g.) was added very slowly to 38 g. of formalin cooled to 5°. The  $\beta$ -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  $\alpha$ -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  $C_{16}H_{19}O_2NCl$ : 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*-aminobenzoate 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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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF RALPH L. EVANS ASSOCIATES]

## Quinaldil, Quinaldoin and Diquinolylhydantoin

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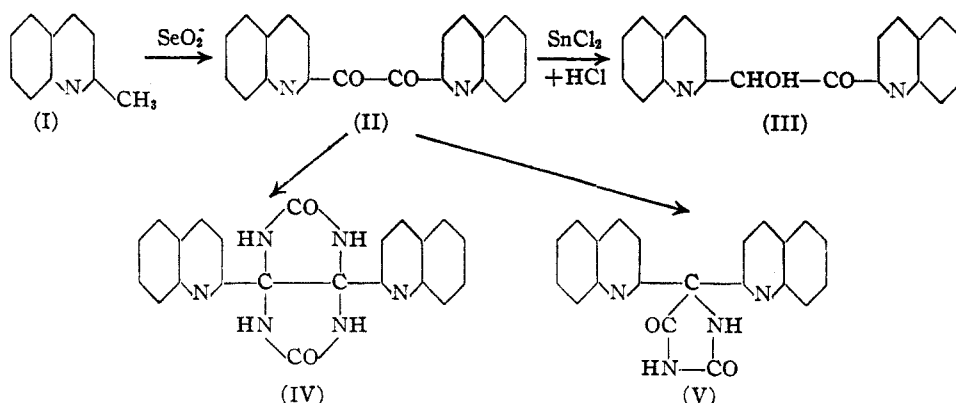
The sodium salt of diphenylhydantoin introduced into medicine a few years ago as Dilantin Sodium has already proved one of the most valuable anti-convulsants and has won official recognition by being included in the U.S. Pharmacopoeia XII. We felt justified, therefore, in studying certain heterocyclic 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 Kaplan<sup>1</sup> we obtained only quinaldil (II) from this

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



oxidation, whereas that author claimed that his product was quinaldoin (III). We made the latter compound from our quinaldil by reduction with stannous chloride in hydrochloric acid. So prepared, quinaldoin gives a green coloration with ferric chloride solution, reduces Fehling solution, and forms acyl derivatives, whereas the oxidation product originally obtained—quinaldil—fails to give any of these characteristic benzoin-type reactions. Also it was found impossible to oxidize this original reaction product by either nitric acid or air in alkaline medium, thus definitely proving its  $\alpha,\beta$ -diketone structure. As expected, quinaldil condensed with urea in alcoholic solution in the presence of sodium ethoxide, yielding 3a,6a-di- $\alpha$ -quinolyglycoluril (IV) and 5,5'-di- $\alpha$ -quinolyhydantoin (V) in complete analogy to the behavior of benzil.

### Experimental

**Quinaldil (II).**—In a 1-liter three-necked flask equipped with thermometer, mechanical stirrer, and reflux condenser, 54 g. of selenium dioxide (commercial product, not sublimed<sup>2</sup>) was dissolved in 480 cc. of dioxane and 20 cc. of water with mild warming (45°).

To this solution was added in portions with stirring during fifteen minutes, a solution of 60 g. of quinaldine (redistilled) in 100 cc. of dioxane. During the addition the flask was heated on a steam-bath until the mixture started to reflux, and then maintained at this temperature for one hour. The selenium precipitate was filtered from the hot reaction mixture. The dioxane and water were distilled from the filtrate under reduced pressure, leaving a semi-solid residue. This was distilled with steam to remove some quinoline  $\alpha$ -aldehyde, and the non-volatile solid was dried in a desiccator; yield 60 g. (91%). When recrystallized from dioxane and water, this formed brown needles; m. p. 175°. The base was fairly soluble in ethanol, benzene, and concentrated mineral acids; insoluble in ligroin, water and dilute mineral acids.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{12}\text{O}_2\text{N}_2$ : C, 76.92; H, 3.85. Found: C, 76.91; H, 4.04.

**Quinaldoin (III).**—To a solution of 5 g. of crude quinaldil in concentrated hydrochloric acid was added 5.3 g. of crystalline stannous chloride with mechanical agitation

while the temperature was kept below 70°. The reaction mixture was then heated at the maximum temperature of a steam-bath for thirty minutes with stirring and finally cooled overnight. Some solid was removed by filtration, the filtrate was diluted to 750 cc., and filtered again. The tin salts were completely precipitated by a current of hydrogen sulfide. The filtrate from these tin sulfides was then evaporated to dryness on a steam-bath, yielding 1.9 g. of a red crystalline residue. When recrystallized from dioxane this formed light brown needles, m. p. 135°, which were soluble in alcohol and benzene, but insoluble in water and dilute mineral acids.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{14}\text{O}_2\text{N}_2$ : C, 76.43; H, 4.46. Found: C, 76.64; H, 4.27.

**3a,6a-Di- $\alpha$ -quinolyglycoluril (IV).**—To a boiling solution of 0.4 g. of metallic sodium in 48 cc. of absolute ethanol was added 1 g. of urea and, when this had dissolved, 3 g. of crude quinaldil. The mixture was refluxed on a steam-bath for thirty minutes, then evaporated to half of its volume, cooled somewhat, and a solution of 4 g. of sodium acetate in 160 cc. of water was added. After standing overnight, 0.9 g. of the glycoluril (IV) was removed by filtration and recrystallized from a mixture of chloroform and ligroin. It formed in clusters of very fine brown needles, m. p. 185° (dec.), soluble in most organic solvents, insoluble in water and ligroin.

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{16}\text{O}_2\text{N}_4$ : C, 66.67; H, 4.04. Found: C, 66.92; H, 4.09.

**5,5'-Di- $\alpha$ -quinolyhydantoin (V).**—The filtrate from the glycoluril (IV) was saturated with carbon dioxide and 0.2 g. of precipitate was collected. This was recrystallized from chloroform-ligroin, yielding fine brown needles (m. p., 230° dec.), soluble in alcohol and dioxane; insoluble in water, ether, acetone.

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{14}\text{O}_2\text{N}_4$ : C, 71.19; H, 3.95. Found: C, 71.21; H, 4.15.

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### Summary

Quinaldil was obtained by oxidizing quinaldine with selenium dioxide. It was reduced to quinaldoin by stannous chloride.

Quinaldil yielded two condensation products with urea: 3a,6a-di- $\alpha$ -quinolyglycoluril, and 5,5'-di- $\alpha$ -quinolyhydantoin.

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(2) This selenium dioxide had been imported from Germany before the war; therefore it was at least seven years old at the time it was used.