DERIVATIVES OF 3-AMINOPIPERIDINE-2, 6-DIONE

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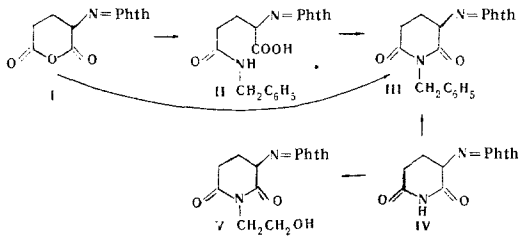
Several N-substituted 3-phthalimidopiperidine-2, 6-diones and 3-(3'-phthalimido-2', 5'-dioxopyrrolid-1'-yl)piperidine-2, 6-dione have been synthesized.

The discovery of teratogenic properties in 3-phthalimidopiperidine-2, 6-dione (thalidomide) (IV) [1] has induced a number of workers to synthesize several related compounds [2–4] in order to study their biological activity [3, 5–7].

Of substances of this type we have obtained: 1-benzyl-3-phthalimidopiperidine-2, 6-dione (III), 1-(2'-hydroxyethyl)-3-phthalimidopiperidine-2, 6-dione (V), and 3-(3'-phthalimido-2', 5'-dioxopyrrolid-1'-yl)piperidine-2, 6-dione (XII).

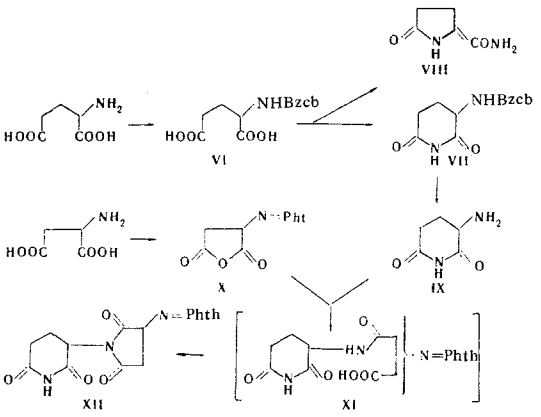


The N-benzyl derivative of thalidomide (III) was obtained by the condensation of the anhydride of N-phthaloylglutamic acid (I) with benzylamine in boiling o-xylene* [2], but this substance melted at 179–180° C rather than the 104–108° C given in the literature. Since we obtained 1-benzyl-3-phthalimidopiperidine-2, 6-dione from thalidomide (I) and benzyl chloride and also by the cyclization of α-N-phthaloyl-N'-benzylglutamine (II) [8], the melting point for III of 104–108° C given in the literature is apparently incorrect.

1-(2-Hydroxyethyl)-3-phthalimidopiperidine-2, 6-dione (V) was synthesized by the action of ethylene oxide on thalidomide (IV) under the conditions used for the hydroxyethylation of phthalimide [9]. However, probably because of the less acidic nature of the hydrogen of the imide group of thalidomide, in our case the hydroxyethylation reaction required more severe conditions (180° C instead of 170° C, 8 hr instead of 4). In the presence of even traces of alkali the reaction mixture resinified completely.

*In addition to III, N-benzylphthalimide was isolated from the reaction mixture; the formation of this substance is obviously the result of transacylation. This reaction was observed in o-xylene, pyridine, and dimethylaniline, but not in m-xylene, dioxane, and n-decane.

To obtain 3-(2', 5'-dioxo-3'-phthalimidopyrrolid-1'-yl)piperidine-2, 6-dione (XII) we used the following synthetic scheme:



3-Benzoxycarbonylaminopiperidine-2, 6-dione (VII) [10, 11] was obtained by condensing N-benzoxycarbonylglutamic acid (VI) with formamide. In addition to VII, we isolated pyrrolid-5-one-2-carboxyamide (VIII) from the reaction mixture. A cyclization of this type starting from glutamic acid or its esters or anhydride has been described previously [13, 14].

The hydrogenolysis of the benzoxycarbonylamine VII in the presence of Pd/C formed 3-aminopiperidine-2, 6-dione (IX) [10]. The condensation of the amine IX with the anhydride of N-phthaloylaspartic acid (X) [15] in pyridine with subsequent acetic anhydride treatment led to compound XII.

In the usual method for the closure of the imide ring by heating the intermediate compound XI with acetic anhydride, the reaction takes place in an unwanted direction and all the compounds formed are acidic in nature; however, by treating the reaction mixture with acetic anhydride in the cold we succeeded in obtaining the required compound.

EXPERIMENTAL

1-Benzyl-3-phthalimidopiperidine-2, 6-dione (III). A) A mixture of 19 g (73.4 mM) of the anhydride I purified by crystallization from acetic anhydride to mp 202–203° C (literature 195–196° C [8]) and 8.81 g (82 mM) of freshly-distilled benzylamine in 200 ml of dry o-xylene was boiled with a Dean and Stark trap and a reflux condenser until water ceased to separate out (4 hr) and then the solvent was distilled off in vacuum. The residual oil was dissolved in 55 ml of methylcellosolve and the hot solution was decolorized with activated carbon. The crystals that deposited (6.8 g) were separated off and washed with 250 ml of hot ether. The residue consisted of 3.7 g of unpurified III (yield 14.5%), mp 179–180° C (from methylcellosolve). Found, %: C 68.9; H 4.7; N 8.4; mol. wt. (Rast) 373. Calculated for $C_{20}H_{16}N_2O_4$, %: C 69.0; H 4.6; N 8.0; mol. wt. 348.

On cooling, the ethereal solution deposited 0.2 g of α-N-phthaloyl-N'-benzylglutamine (II), mp 200–204° C (from 70% ethanol); literature: 202–204° C [8]. Found, %: C 65.3; H 4.8; N 7.7. Calculated for $C_{20}H_{18}N_2O_5$, %: C 65.6; H 4.9; N 7.6.

Distillation of the ether yielded 2.8 g of N-benzylphthalimide, mp 115–117° C (from ethanol); literature: 116° C [16]. Found, %: C 75.9; H 4.7; N 5.9. Calculated for $C_{15}H_{11}NO_2$, %: C 76.0; H 4.7; N 5.9.

B) A suspension of 1.0 g (3.85 mM) of IV and 3 g of K_2CO_3 in 6 ml of benzyl chloride was stirred at 100° C for 14 hr. After cooling, 50 ml of petroleum ether (40–60° C) was added. The yield of III was 1.3 g (96%), mp 178–179° C (from methylcellosolve). A mixture with a sample obtained by method (A) showed no depression of the melting point.

C) A suspension of 1 g (2.73 mM) of α-N-phthaloyl-N'benzylglutamine (II) [8] in 10 ml of acetic anhydride was heated at 100° C for 2 hr. The acetic anhydride was distilled off in vacuum and the residual oil was triturated with 20 ml of dry ether. Yield 0.67 g (70.5%), mp 177–179° C (from methylcellosolve). A mixture with the samples obtained by methods (A) and (B) gave no depression of the melting point.

1-(2'-Hydroxyethyl)-3-phthalimidopiperidine-2,6-dione (V). A mixture of 5 g of thalidomide (IV) and 3 ml of ethylene oxide was heated in a sealed tube of neutral glass at 180° C for 8 hr. The oil formed was triturated with ethanol. The yield of V was 3.9 g (67%), mp 171.5–173.5° C (from ethanol). Found, %: C 59.3; H 4.7; N 9.7. Calculated for $C_{15}H_{14}N_2O_5$, %: C 59.6; H 4.7; N 9.3.

3-Benzyloxycarbonylaminopiperidine-2,6-dione (VII). A mixture of 50 g (0.18 mole) of N-benzyloxycarbonylglutamic acid (VI) [12] (mp 115–116° C) and 9.5 ml (0.24 mole) of freshly-distilled formamide was heated at 170° C in vacuum (200 mm) under a reflux air condenser for 4 hr. The reaction mixture was dissolved in 170 ml of boiling isopropanol and the solution was decolorized with activated carbon and cooled to give 10.3 g (22%) of VII, mp 130–132° C (from ethyl acetate), literature: 129–131° C [10], 122–124° C [11]. Found, %: C 59.5; H 5.3; N 11.1. Calculated for $C_{13}H_{14}N_2O_4$, %: C 59.5; H 5.4; N 10.7.

After the separation of the VII, the isopropanol solution deposited 2.5 g of pyrrolid-5-one-2-carboxyamide (VIII), mp 217–219° C (decomp., from isopropanol), literature: 220–221° C [17]. Found, %: C 47.1; H 6.3; N 21.6. Calculated for $C_5H_8N_2O_2$, %: C 46.9; H 6.3; N 21.8.

3-Aminopiperidine-2,6-dione (IX). A solution of 2.01 g (78 mM) of the 3-benzyloxycarbonylamine VII in 50 ml of absolute isopropanol was hydrogenated at room temperature and atmospheric pressure in the presence of 1 g of 5% Pd/C for 4 hr. The solution was heated and the catalyst was filtered off. After cooling, the filtrate deposited 0.79 g of the amine IX with a faint bluish color, mp 132–134° C (decomp). An additional 0.07 g of the amine was obtained from the mother solution, giving a total yield of 0.86 g (87.6%). After two recrystallizations from isopropanol the product was still colored, mp 139–140° C (literature: 142–143° C [10]). Found, %: C 46.7; H 6.2; N 22.1. Calculated for $C_5H_8N_2O_2$, %: C 46.9; H 6.3; N 21.8. **Hydrochloride.** Mp 270° C (decomp., from 80% ethanol), literature: 200° C [18], 225° C [19], 265° C [10]. Found, %: C 36.3; H 5.2; Cl 21.4; N 17.2. Calculated for $C_5H_8N_2O_2 \cdot HCl$, %: C 36.5; H 5.5; Cl 21.6; N 17.0.

Picrate. Yellow-green prisms, mp 205–207° C (from ethanol). Found, %: C 36.9; H 3.1; N 19.7. Calculated for $C_5H_8N_2O_2 \cdot C_6H_3(NO_2)_3OH$, %: C 37.0; H 3.1; N 19.6.

3-(2',5'-Dioxo-3'-phthalimidopyrrolid-1'-yl)piperidine-2,6-dione (XII). A mixture of 0.56 g (2.28 mM) of the anhydride X [15] and 0.29 g (2.27 mM) of the amine IX in 7.5 ml of dry pyridine was boiled for 2 hr, and then the pyridine was distilled off, the residue was treated with 50 ml of acetic anhydride, and the mixture was left at room temperature for a day. The oil that separated out after the acetic anhydride had been distilled off in vacuum was triturated with absolute ether, giving 0.8 g (31.5%) of XII, mp 248.5–250° C (decomp., from methylcellulose). Found, %: C 57.0; H 4.0; N 11.3. Calculated for $C_{17}H_{13}N_3O_6$, %: C 57.5; H 3.7; N 11.8.

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