DRUGS IN THE SERIES OF β-PHENYLISOPROPYLAMINE DERIVATIVES.

III. PHENYLISOPROPYLAMIDES OF DIALKYLAMINOPHENYLACETIC ACIDS

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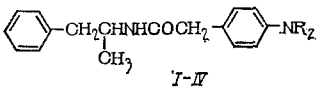
Compounds possessing adrenoblocking properties have attracted much attention lately from chemists and pharmacologists [1-3]. This paper is devoted to the synthesis of drugs based on β-phenylisopropylamine, which act on the adrenoreactive systems. The β-phenylisopropylamides of p-dialkylaminophenylacetic acids with the general formula I-IV:

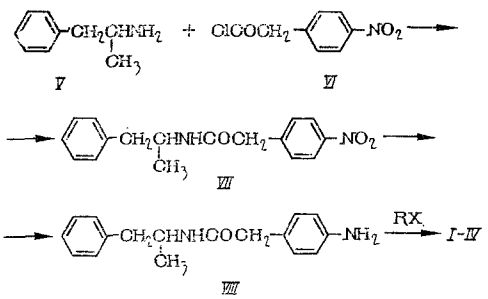


I-IV

I: R = CH_3, II: R = C_2H_5, III: R = H – C_3H_7, IV: R = H – C_4H_9

were synthesized.

The synthesis is accomplished by the following scheme:



Compounds VII and VIII have been described in the literature [4]. However, the preparation of VII in large quantities by the method reported in the literature led to the complete resinification of the product; therefore, we employed temperature controls when carrying out the reaction (see below). The reduction of the phenamide of p-nitrophenylacetic acid (VII) was also carried out by another method. Compounds I-IV were synthesized by alkylating VIII with an alkyl halide in an aqueous alcoholic solution in the presence of potassium carbonate. Both the mono- and dihydrochlorides were isolated when I-IV were reacted with an alcoholic solution of hydrogen chloride, depending on the amount (of the latter) used. Similar protonization of an amide nitrogen in certain cases has also previously been observed [5, 6].

Pharmacological experimentation has shown that all the compounds investigated are only slightly toxic and prolong the soporific action of sodium amytal, while the strength of their action increases from the methyl to the ethyl, propyl, and butyl derivatives. These compounds lengthen by 1.5 to 2 times the duration of sleep induced by chloral hydrate for white mice, and also block the adreno-receptors.

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EXPERIMENTAL

p-Nitrophenylacetic Acid β-phenylisopropylamide (VII). To 37 g of p-nitrophenylacetyl chloride (VI) in 180 ml of dry benzene while cooling with ice water and with energetic stirring was added slowly a mixture of 25 g of β-phenylisopropylamine (V) and 24 g of triethylamine in 50 ml of dry benzene. The reaction proceeds with the strong evolution of heat. After completing the addition, the reaction mixture continued to be stirred another 1 to 1.5 h and allowed to stand overnight. The precipitate was filtered off, washed several times with water on the filter, and the insoluble precipitate was recrystallized from alcohol. The yield was 83%, mp 126-127°C.

p-Aminophenylacetic Acid β-phenylisopropylamide (VIII). To a mixture of 150 g of VII, 1 liter of alcohol, and 96 g of hydrazine hydrate was carefully added 8 g of Raney nickel. The mixture warmed up; the temperature should not exceed 70°C. After the sample had ceased warming up, the flask was heated on a boiling water bath for 2 h. The solution was cooled, the catalyst was filtered off, and the alcohol was distilled off. The precipitate which had begun to crystallize was recrystallized from 50% alcohol or carbon tetrachloride. The yield was almost quantitative, mp 135-136°C.

p-Dimethylaminophenylacetic Acid β-phenylisopropylamide (I). A mixture of 13.4 g of VIII, 50 ml of methanol, 25 ml of water, 8 g of potassium carbonate, and 15 g of methyl iodide was refluxed for 1.5 h. The alcohol was distilled off, the residue was extracted with chloroform. The chloroform solution was dried with magnesium sulfate, the chloroform was distilled off, to the residue was added a small amount of methanol, and the mixture was allowed to stand in a refrigerator. The precipitate was filtered off and crystallized from methanol. The yield was 33%, mp 138-139°C. Found %: C 76.89, 77.12; H 8.15, 8.19; N 9.56. $C_{19}H_{24}N_{20}$. Calculated %: C 77.02; H 8.10; N 9.45.

p-Diethylaminophenylacetic Acid β-phenylisopropylamide (II). This compound was obtained in the same way as I. A mixture of 50 g of VIII, 170 ml of ethanol, 85 ml of water, 30 g of potassium carbonate, and 64 g of ethyl iodide was heated for 2.5 h. A total of 54.3 g (89.9%) was obtained, mp 82-84°C (from n-hexane). The yield was considerably reduced with longer heating. Found %: C 77.47, 77.22; H 8.65, 8.50; N 8.38, 8.35. $C_{21}H_{28}N_2O$. Calculated %: C 77.73; H 8.69; N 8.63.

p-(Di-n-propylamino)phenylacetic Acid β-phenylisopropylamide (III). A mixture of 13.4 g of VIII, 50 ml of propyl alcohol, 12 ml of water, 8 g of potassium carbonate, and 20 g of propyl iodide was heated on a water bath for 12 h. After two crystallizations from n-hexane, 14 g (79.5%) was obtained, mp 67-69.5°C. Found %: C 78.39, 78.31; H 9.39, 9.36; N 8.17, 8.06. $C_{23}H_{32}N_2O$. Calculated %: C 78.36; H 9.15; N 7.94.

p-(Di-n-butylamino)phenylacetic Acid β-phenylisopropylamide (IV). A mixture of 13.4 g of VIII, 50 ml of n-butanol, 15 ml of water, 8 g of potassium carbonate, and 19.5 g of butyl bromide was boiled for 24 h on a water bath. After crystallization from n-hexane, 14 g (73.7%) was obtained, mp 73-74.5°C. Found %: C 78.97, 79.09; H 9.56, 9.50; N 7.43, 7.51. $C_{25}H_{36}N_2O$. Calculated %: C 78.89; H 9.53; N 7.36.

p-Dialkylaminophenylacetic acid β-phenylisopropylamide hydrochlorides. All the hydrochlorides were prepared the same way. To 0.1 mole of the base in a minimum amount of dry acetone was added with cooling 0.11 mole of hydrogen chloride as a 20% alcoholic solution. The salt was precipitated with dry ether, the oil or deposition which precipitated out was dried in a vacuum desiccator and crystallized from the appropriate solvent. The yield was almost quantitative. Hydrochloride of I, mp 55-57°C, very hygroscopic. Found %: Cl 10.71, 10.32; N 8.76, 8.30. $C_{19}H_{24}N_2 \cdot HCl$. Calculated %: Cl 10.65; N 8.76. Hydrochloride of II, mp 154-156°C (from propyl alcohol with ether), very hygroscopic. Found %: N 7.81, 7.67. $C_{21}H_{28}N_2O \cdot HCl$. Calculated %: N 7.76. Hydrochloride of III, mp 128-130°C (from acetone with ether). Found %: Cl 9.14, 9.15; N 7.26, 7.19. $C_{23}H_{32}N_2O \cdot HCl$. Calculated %: Cl 9.12; N 7.20. Hydrochloride of IV, mp 136-137°C (from acetone with ether). Found %: Cl 8.48, 8.43; N 7.02, 7.03. $C_{25}H_{36}N_2O \cdot HCl$. Calculated %: Cl 8.49; N 6.71.

Dihydrochlorides of Compounds I-IV. These were prepared similarly to the monohydrochlorides with the only difference being that 0.22 mole of hydrogen chloride as a 20% alcoholic solution was also used used per 0.1 mole of base. The salt was crystallized from the appropriate solvent to which a small amount of hydrogen chloride was added. Dihydrochloride of I, mp 154-157°C (from acetone), hygroscopic. Found %: Cl 18.90, 18.75. $C_{19}H_{24}N_2 \cdot 2HCl$. Calculated %: Cl 19.20. Dihydrochloride of II, mp 169-170°C (from propanol with ether). Found %: Cl 17.27, 17.20, N 7.38, 7.29. $C_{21}H_{28}N_2O \cdot 2HCl$. Calculated %: Cl 17.84; N 7.05. Dihydrochloride of III, mp 165-166°C (from acetone with ether). Found %: Cl 16.31, 16.43;

N 6.65, 6.52. $C_{23}H_{32}N_2O \cdot 2HCl$. Calculated %: Cl 16.66, N 6.58. Dihydrochloride of IV, mp 142-143°C (from propanol). Found %: Cl 15.26, 15.37. $C_{25}H_{36}N_2O \cdot 2HCl$. Calculated %: Cl 15.64.

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