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SYNTHESIS OF SOME LOW MOLECULAR WEIGHT DERIVATIVES OF PROCAINAMIDE

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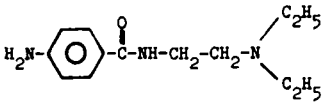
ABSTRACT

Low molecular weight derivatives of procainamide, with a terminal functional group have been prepared. The synthesis and characterization of the succinic half-amide respectively of N-(ω-amino alkanoyl)derivatives of the parent drug are reported.

INTRODUCTION

In the past decades there has been an increasing interest in optimizing the efficiency of existing drugs through chemical transformation of the parent drug into so-called prodrugs, defined as drug derivatives, from which upon administration the parent compound is being liberated. Prodrugs can be low molecular weight as well as macromolecular derivatives. The latter can be obtained either by converting the drug into a polymerizable derivative or by binding the drug or a derivative thereoff onto an existing polymer. As part of a current researchproject on polymeric drugs we have been interested in the preparation of various derivatives of procainamide (I), a cardiac depressant.



Procainamide (I)

A number of low molecular weight derivatives have been prepared, mainly as intermediates used for subsequent transformation into macromolecular substances. The synthesis and biological evaluation of some polymerizable derivatives of procainamide have been discussed in previous papers[1-3]. In the present paper we wish to report the synthesis and characterization of a series of non-polymerizable derivatives. These derivatives were prepared in order to change the functionality of the drug as a means to enhance the coupling possibilities with various polymers suitable as drug carriers. So the aniline function of the drug was substituted with groups having a terminal carboxylic, or primary amino function. These modifications allow binding with polymers having amino, hydroxyl, aldehyde or carboxylic side groups.

EXPERIMENTAL PART

1. Preparation of procainamide free base

A concentrated aqueous solution of the commercially available procainamide hydrochloride (Siegfried, CH-Zofingen) is added dropwise to a 5% sodium hydroxide solution. The turbid mixture is extracted with chloroform and the organic layer is dried over calcium sulphate. On concentrating the chloroform solution, procainamide starts precipitating as colourless needles. The uncorrected melting point was 73.5°C.

2. Preparation of the succinic half-amide of procainamide

To a stirred solution of 3 g (0.013 mole) procainamide base, dissolved in 100 ml of an anhydrous 50/50 mixture of N,N-dimethylformamide and methylene chloride, is added 2.6 g (0.025 mole) succinic anhydride. After 30 minutes a white product starts to precipitate. The reaction mixture is stirred at room-temperature for about 20 h. The white precipitate is isolated by filtration, washed with small portions of methylene chloride and further purified by redissolving in ethanol/water (90/10) and precipitating in diethylether. The yield is 3.6 g (85 %).

3. Preparation of N-chloroacetyl procainamide

A solution of 10 g (0.043 mole) procainamide base in 100 ml anhydrous chloroform is added dropwise to an ice-cooled solution of 5.5 g (0.049 mole) chloroacetyl chloride (Aldrich-Europe, Beerse) in 50 ml chloroform. The reaction mixture is stirred for 16 h. after which 100 ml of dry ether is added. The precipitate is isolated, washed with small portions of ether and dried under vacuum. The yield is 13 g (95 %).

4. Preparation of N-glycylprocainamide

5 g of the chloroacetyl derivative is dissolved in 25 ml of an ethanol/water mixture (90/10). The solution is saturated with ammonia and transferred into a 100 ml thick-walled glass tube which is subsequently sealed and placed in a waterbath thermostatted at 60°C. After 24 h. the reaction mixture is cooled to room temperature and the tube is opened. The solvent is removed on a rotary evaporator and the residue is dissolved in 25 ml anhydrous ethanol. Hydrogen chloride gas is passed through the solution. The resulting precipitate is isolated and recrystallised twice from anhydrous ethanol. The yield after purification is 2.2 g (45 %).

5. Preparation of N-(ω-aminoalkanoyl)procainamide.

For the preparation of N-(4-amino butanoyl), respectively N-(6-amino hexanoyl) and N-(11-amino undecanoyl)procainamide the same reaction procedure was followed. The synthesis of N-(6-aminohexanoyl)procainamide is given as an example.

a) Preparation of N-(tert-butoxycarbonyl)-6-aminohexanoic acid :

To a solution of 5 g (0.038 mole) 6-aminohexanoic acid (Aldrich-Europe, B-Beerse) in 40 ml water/tert.butanol (50/50) is added 10 g (0.045 mole) of di-tert.butyl dicarbonate (Aldrich). The reaction mixture is stirred during 20 h. at room-temperature. Subsequently the solvent is evaporated at reduced pressure. The product is redissolved in water, sodium hydroxide is added and the solution is extracted with ethyl acetate. The water layer is collected and acidified with hydrochloric acid and again extracted with ethyl acetate. The organic layer is collected and the solvent is evaporated. An oily product is obtained which slowly crystallizes on standing. The yield is 8 g (90 %).

b) Preparation of N-[6-(N'-t.butoxycarbonyl aminohexanoyl]procainamide :

To a solution of 5 g (0.022 mole) of the previous product in dry methylene chloride is added 5.7 g (0.024 mole) procainamide free base and 0.7 g (0.006 mole) dimethylaminopyridine. The solution is cooled in an ice-bath and 6.8 g (0.033 mole) N,N'-dicyclohexylcarbodiimide is added. The solution is stirred during 2 h. at 0°C and then for 20 h. at room-temperature. The precipitated dicyclohexylureum is removed by filtration. The solution is extracted (3x) with hydrochloric acid solution (10^{-3} N). The water layer is adjusted to pH 10 with sodium hydroxide and then extracted with ethylacetate. The solvent is removed by evaporation. The oily residue is used directly for the next reaction step.

c) Preparation of N-(6-aminohexanoyl)procainamide :

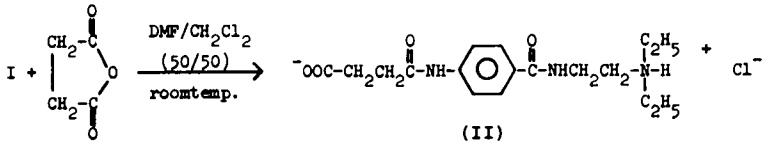
The previous product is dissolved in acetic acid. Hydrochloric acid gas is slowly passed through the solution during 30 minutes. Stirring is continued for 2 h. The solvent is removed on a rotary evaporator. From the residue the reaction product is isolated by preparative column chromatography on silicagel. Initially a 0.5 % solution of ammonia in ethanol is used as eluens. After elution of all procainamide, the concentration of ammonia is increased to 1.25 %. The composition of the eluting solvent is monitored by means of thin layer chromatography on silica plates (Merck). Ethanol, containing 1.25 % ammonia, is used as solvent system. The RF-values for procainamide, respectively the desired reaction product are 0.65, resp. 0.30. All fractions containing only the desired reaction product are collected. The solvent is evaporated at reduced pressure. A white solid is obtained (yield : 3.3 g, 43 %).

RESULTS AND DISCUSSION

A carboxyl-terminated derivative of procainamide was prepared by succinylation of the aniline function of the drug.
Reaction of the drug with chloroacetyl chloride led to the corresponding chloroacetyldrug derivative. Treatment of the latter with ammonia yields the N-glycine derivative. Other amino terminated derivatives were prepared starting from ω-amino carboxylic acids and the parent drug. The synthesis and characterization of the above mentioned procainamide derivatives will now be discussed in detail.

1. Synthesis of the succinic half-amide of procainamide

Procainamide (free base) reacts smoothly with succinic anhydride with formation of the corresponding half-amide (N-(3-carboxypropionyl)procainamide, II).

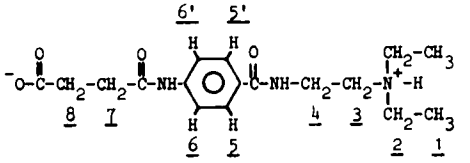


(II)

The structure of the reaction product was characterized by means of 360 MHz ^1H NMR spectroscopy. The NMR data are summarized in Table 1.

Table 1

NMR Parameters[M)] of the succinic half-amide of procainamide.



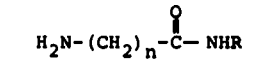
Proton	ν (ppm)	J (Hz)
H-1	1.37	$^3J(1,2)$: 7.2
H-2	3.30	
H-3	3.39	$^3J(3,4)$: 6.2
H-4	3.74	
H-5,5'	7.75	$^3J(5,6)$: 8.5
H-6,6'	7.54	$^4J(5,5')$, $^5J(5,6')$: 1.5
H-7	2.66	$^3J(7,8)$: 6.9
H-8	2.54	

M) Solvent D_2O.

The pattern of the NMR signals for the siccinyl methylene protons is strongly influenced by lowering the pH. Upon addition of deuterium chloride, the two triplets for the methylene protons 3 and 4 are replaced by one singlet appearing at 2.75 ppm.

2. Synthesis of N-(ω-amino alkanoyl)procainamide derivatives

A number of amino terminated alkanoyl groups of varying length have been substituted on the procainamide aniline group. There general structure can be presented as follows :



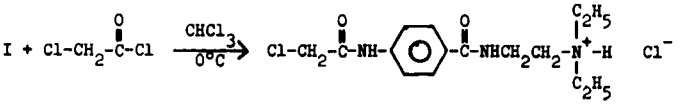
where $R-NH_2$ represents procainamide.

n	1	3	5	10
product	IV	V	VI	VII

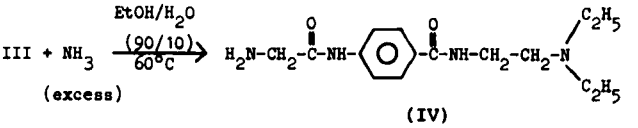
As pointed out before the objective of the preparation of the presently described derivatives is to obtain procainamide derivatives able to be covalently linked to suitable polymers. The introduced substituents will also function as a spacer group in between the drug moiety and the macromolecular carrier. The length of this group may greatly influence the biological activity of the final product[4,5].

a) N-glycyl procainamide (n = 1) :

The N-glycyl procainamide (IV) was prepared by reaction of procainamide with chloroacetylchloride and subsequent treatment of the formed chloroacetyl procainamide (III) with an excess ammonia :



(III)

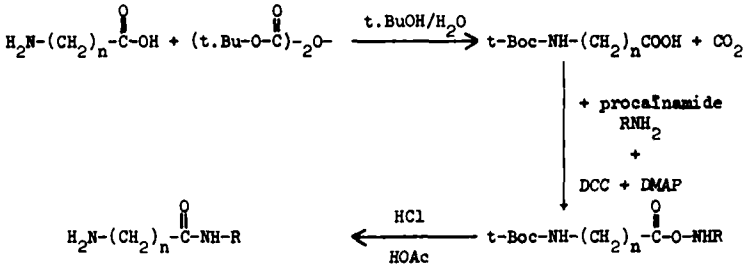


(IV)

The structure of the reaction products was confirmed by NMR. The methylene protons in α-position of the chlorine (product III) appear as a singulet at 4.2 ppm (D_2O). The integration accounts for 2 protons per procainamide residue, proving the purity of the reaction product. In case of the glycyl derivative these methylene protons for the free base form, respectively the fully protonated form show up at 3.45 ppm ($CDCl_3$), resp. 4.03 ppm (D_2O).

b) N-(ω-aminoalkanoyl)procainamide derivatives (n > 1) :

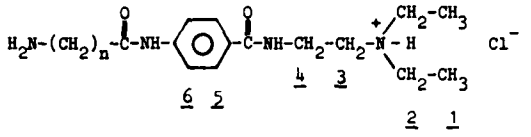
The other amino-terminated derivatives (V-VII) were prepared starting from procainamide and the appropriate ω-amino carboxylic acid according to the reactionscheme given below :



In the first step of the reaction sequence the amino group was protected using di-tert-butyl dicarbonate. Coupling of the carboxylic acid with the aniline group of procainamide was performed in methylene chloride using dicyclohexyl carbodiimide (DCC) as coupling agent. To improve the yield of this reaction 4-(N,N-dimethylamino)pyridine (DMAP) was added. The protective t-butoxy carbonyl group (t-Boc) was removed under mild conditions. The resulting reaction products were purified via preparative adsorption chromatography on silica gel. The structure of the intermediates as well as the end products was characterized by means of NMR spectroscopy. The NMR parameters of the ω-amino alkanoyl derivatives are summarized in Table 2.

TABLE 2

NMR-Parameters*) of the N-(ω-amino alkanoyl)procainamides



n = 1 | R = $H_2N\underline{C}H_2$- (III)

n = 3 | $H_2N\underline{C}H_2-\underline{C}H_2-\underline{C}H_2$- (IV)

n = 5 | $H_2N\underline{C}H_2-\underline{C}H_2-\underline{C}H_2-\underline{C}H_2-\underline{C}H_2$- (V)

n = 10 | $H_2N\underline{C}H_2-\underline{C}H_2-(\underline{C}H_2)_6-\underline{C}H_2-\underline{C}H_2$- (VI)

Product	ν (ppm) :						J (Hz) :
	H-1	H-2	H-3	H-4	H-5	H-6	
III-VII	1.31	3.31	3.43	3.78	7.80	7.60	$^3J(1,2)$: 7.2; $^3J(3,4)$: 6.2; $^3J(5,6)$: 8.5
	H-7	H-8	H-9	H-10	H-11		
III	4.02	-	-	-	-		
IV	2.51	2.04	3.05	-	-		$^3J(7,8)$: 7.5; $^3J(8,9)$: 7.7
V	2.46	1.71	1.45	1.71	3.03		$^3J(7,8)$: 7.3; $^3J(8,9)$: 7.0; $^3J(9,10)$: 7.0
VI	2.39	1.58	1.2	1.58	2.97		$^3J(7,8)$: 7.2; $^3J(10,11)$: 7.5. $^3J(10,11)$: 7.5.

*) Performed with 360 MHz ^1H NMR, in D_2O

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