3-Amino-1-(3,4-dichloro-α-methyl-benzyl)-2-pyrazolin-5-one (Bay g 2821), a potent diuretic from a new substance class

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Summary. Chemistry, salidiuretic activity and mechanism of action of 3-amino-1-(3,4-dichloro-α-methyl-benzyl)-2-pyrazolin-5-one (Bay g 2821), a new diuretic, are described. Owing to the initial rapid onset of activity, the reserve in capacity and the additional long duration of activity, this substance represents a potent diuretic and antihypertensive agent.

The diuretics in use at the present time may be classified according to their intensity of activity into compounds with high ceiling activity and those with low ceiling activity. Diuretics with low ceiling activity, to which all thiazides[2,3] and related compounds such as chlorthalidone[4,5], clopamide[6,7] and mefruside[8,9] belong, have a dose effect curve with a plateau in the therapeutic dosage range. Their maximum effect, above which no increase in activity is possible, is mostly weak. A great advantage of these compounds is the normally protracted duration of action.

In contrast to this, diuretics with high ceiling activity such as etacrynic acid[10,11], furosemide[12,13] and bumetanide[14,15] exhibit an almost linear dose effect curve without a plateau in the well-tolerated dosage range. An increase in dosage leads accordingly to an increase in action. This effect is called a reserve in capacity. Their disadvantage is a short duration of action. Furthermore, after the activity has subsided, the excretion rate sinks temporarily below control values (the rebound phenomenon).

Our research target was a substance having both a reserve in capacity and a protracted duration of activity. While it did not seem to be very promising to seek compounds with the desired activity-profile within known substance classes, such as uracils, organomercury compounds, aryloxyacetic acid derivatives and sulphonamides, we concentrated on the search for new active classes. In this, certain properties such as amphoteric character and structural features – for example amidine groupings – served as guide lines.

A few years ago, in the course of this work program, we found a new class of compounds which was strongly diuretic in rats and dogs: the 3-amino-2-pyrazolin-5-ones[16]. No pharmacological activities had previously been reported for this class. In animal experiments, one of the most active derivatives was found to be 3-amino-1-(3,4-dichloro-α-methyl-benzyl)-2-pyrazolin-5-one[17] (Bay g 2821) and this was selected for clinical studies. The chemistry, salidiuretic activity and mechanism of action of Bay g 2821 are discussed in the following.

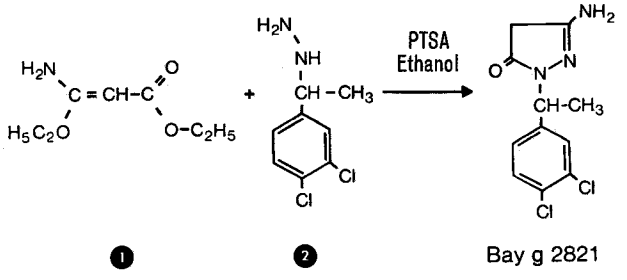

Fig. 1. Synthesis of Bay g 2821.

Chemistry: The synthesis of Bay g 2821 (**3**) was carried out according to a known method[18] by reaction of α-methyl-3,4-dichloro-benzyl-hydrazine (**2**) with ethyl β-amino-β-ethoxy-acrylate (**1**) (figure 1). The substance

Chemical and physical properties of Bay g 2821

Molecular formula	$C_{11}H_{11}Cl_2N_3O \cdot {}^1/_2\ H_2O$				
Molecular weight	281.1 with $^1/_2\ H_2O$ 272.2 without $^1/_2\ H_2O$				
Elemental analysis	C	H	N	Cl	O
calculated	46.99	4.30	14.95	25.22	8.54
found	46.8	4.4	14.9	25.1	8.2
pK (lost)	9.3				
log P (octanol/water)	2.29				

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crystallises as a hemihydrate. The most important chemical and physical properties of Bay g 2821 are summarized in the table. A noteworthy characteristic of this new diuretic is its amphoteric character. Bay g 2821 has 5 possible tautomeric forms but exists predominantly in the 2-pyrazolin-5-one form ('CH-form') in non-polar solvents. This tautomer is the only one found by NMR-spectroscopy in chloroform solution. In protic solvents, a mixture of the 5-hydroxy-pyrazole form ('OH-form') and the 3-pyrazolin-5-one form ('NH-form') is found. By X-ray structure analysis, it has been shown that Bay g 2821 exists in the 2-pyrazolin-5-one form in the crystal lattice[19]. In comparison to furosemide, Bay g 2821 has a higher pK value and is characterized by more lipophilic properties.

Salidiuretic activity: The threshold dose of Bay g 2821 in the dog is 0.1 mg/kg p.o. With increasing dosage, the action increases almost linearly. The chloride and sodium excretion rates are influenced most strongly; potassium to a lesser extent. Bicarbonate excretion is practically unaffected. Bay g 2821 is more active than furosemide in the dog[20]. In addition to the high ceiling activity, Bay g 2821 also has a long duration of action. In figure 3 the action/time relationship for Bay g 2821 in the dog is shown. Here the volume losses due to saluresis were replaced by an infusion carefully matched to the excretion rate.

Dose effect curve (dog)

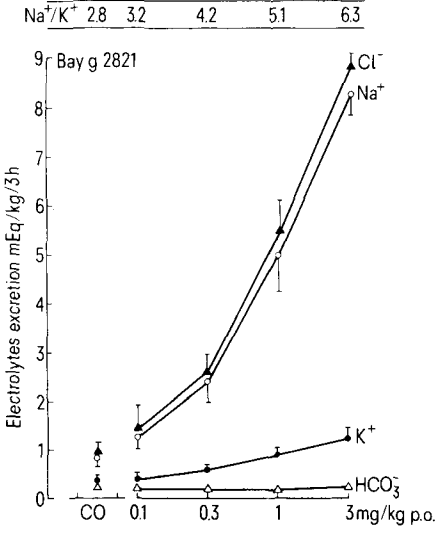

Fig. 2. Salidiuretic activity of Bay g 2821; dose effect curve in dog.

The graph shows that the action of Bay g 2821 is of rapid onset and subsides only slowly. The initial value is not regained even after 180 min. In comparison the action of furosemide has subsided after 90 min, under the same experimental conditions.

Mechanism of action: Studies on the intrarenal haemodynamics have shown that Bay g 2821 works via an inhibition of tubular reabsorption and not by increased filtration[21]. The inulin clearance remains unaffected by Bay g 2821, the PAH clearance is increased. In order to ascertain the site of action of Bay g 2821, the net flow-back of osmotically free water (TC_{H_2O}) was studied (figure 4). Under osmotic diuresis with increasing volume of mannitol, TC_{H_2O} remains almost unchanged. After i.v. injection of 1 mg/kg Bay g 2821, the urine/min volume increases more rapidly than C_{osmol}. Here TC_{H_2O} becomes smaller and U/P_{osmol} almost 1. This means that the increase in diuresis caused by Bay g 2821 is isotonic. From this may be deduced that Bay g 2821, like etacrynic acid and furosemide, inhibits the sodium transport at the medullary section of the ascending limb of the Henle's loop.

Time-response curve with volume substitution (dog)

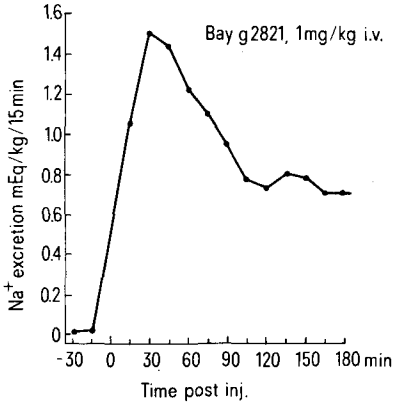

Fig. 3. Time-response curve with volume substitution (dog) for Bay g 2821.

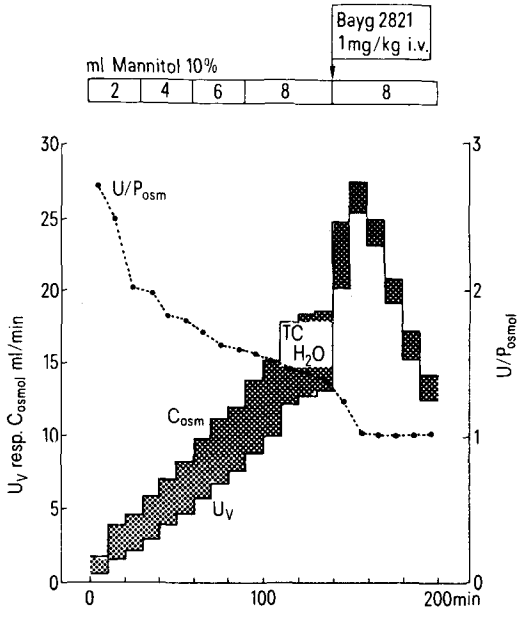

Fig. 4. Mechanism of action of Bay g 2821.

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