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Synthesis and structure-activity relationships of a new highly selective rodenticide - brominated *n*-piperidine dibenzocycloheptoid

F. Chen, Ch. Qu, J. Wang, L. Liu, Sh. Ning

Department of Chemistry, College of science ,Northeastern University, Shenyang City, People's Republic of China

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With the widespread use of anticoagulant rodenticides, drug-resistant rats appeared, thus new types of rodenticides being needed. N-piperidine-10,11-dihydro dibenzo[a,d]cyclohepten (R) is a highly selective rodenticide but because of its low toxicity, it is not widely used. By adding bromine to the rodenticide molecule, the toxicity dramatically improves by keeping its high selectivity. Five different new brominated N-piperidine dibenzocycloheptoid rodenticides were synthesized in the present work. Toxicology experiments showed that the new rodenticides have excellent palatability and selectivity. Death time and death number relation graphs show that the distribution is moderate and is concentrated in 1 to 2.5 h. Brominated N-piperidine dibenzocycloheptoid is an excellent rodenticide.

Key words: Highly selective rodenticide, N-piperidine dibencycloheptanone, Bromo-substitution, *Rattus norvegicus*, Toxicity

INTRODUCTION

Rodents are widely distributed, endangering agriculture and spreading diseases [1-3]. The efficient control of the rodents has been a major subject [4-8]. Rodenticides have already become an important part of pesticides [9]. With the widespread use of first- and second-generation anticoagulant rodenticides, drug-resistant mouse populations emerged [10-12]. N-piperidine-10,11-dihydro-5H-dibenzo [a, d] cyclohepten is the most selective known rodenticide. But the toxicity of this compound is relatively lower in comparison with other rodenticides, which limits its use. Bromine is an effective toxic agent [13-15]. Connecting bromine atoms to this rodenticide could enhance the toxicity. The molecular formulas of the rodenticides R,R_1,R_2,R_3,R_4 are shown in Fig. 1. Synthesis routes of these substances are shown in Fig. 2.

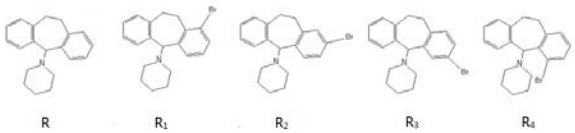

Fig. 1. Structural formulas of compounds R_1,R_2,R_3,R_4

EXPERIMENTAL

Materials and analytical methods

Equipment and reagents

The main reagents required are: phthalic anhydride, phenylacetic acid, sodium acetate, sodium borohydride, bromine water, thionyl chloride, piperidine, sodium sulfite, aluminum chloride.

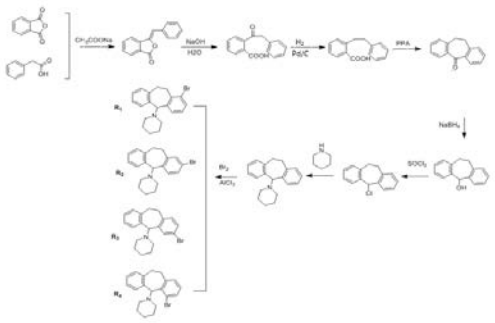

Fig. 2. Synthesis road of compound R

The IR spectra were recorded by FT-IR spectroscopy on a Spectrum One spectrometer. The solid samples were analyzed by the KBr tabletting method. The NMR data were acquired on an ARX 300 nuclear magnetic resonance (1H-NMR) spectrometer using TMS as internal standard, $CDCl_3$ and DMSO as solvents.

Synthesis of dibenzosuberone

10.00 g (67.56 mmol) of phthalic anhydride, 8.70 g (63.95 mmol) of phenylacetic acid and 0.43 g (5.24 mmol) of anhydrous sodium acetate were added into a three-neck flask and the mixture was heated at 120-130°C for 6 h, cooled and filtered. Recrystallization gave 9.94 g product.

10 g of synthetic benzylidenephthalide, 6 ml of water and 16 ml of 30% sodium hydroxide solution were added into a the three-neck flask and the mixture was heated at 38°C and stirred for 8.5 h. The pH was adjusted to 7.0 by hydrochloric acid. The reaction gave 2-phenylacetylbenzoic acid. The product was not separated and the next reaction directly followed.

*To whom all correspondence should be sent:
E-mail: E-mail:1600209@stu.neu.edu.cn

1.00 g of 5% Pd/C was added to the above system and the reaction was carried out at 95°C and 2 MPa under nitrogen for 8 h. After the end of the reaction, hydrochloric acid was added to the solution to adjust the pH at 3. Filtration and recrystallization gave 9.15 g of 2-phenylethyl) benzoic acid.

20.00 g (88.40 mmol) of 2-phenethylbenzoic acid and 20.00 g (59.20 mmol) of polyphosphoric acid were added to a 250 mL three-neck flask. The mixture was heated at 120°C under stirring and refluxed for 5 h. The organic phase was extracted and evaporated to dryness to give 16.36 g of a pale yellow solid.

Synthesis of R_1, R_2, R_3 and R_4

25.01 g (120.00 mmol) of dibenzocyclo-heptanone were added into a 250 mL three-neck flask. Sodium borohydride was added slowly. The mixture was stirred at room temperature for 4 h and allowed to stay overnight. Then concentrated hydrochloric acid was added to adjust to pH 3. The product after filtration was 22.58 g.

To 20.02 g (95 mmol) of the prepared dibenzoheptol in a 250 mL three-neck flask, 50.00 mL of thionyl chloride was added dropwise at 80°C and reacted for 4 h. After completion of the reaction, unreacted sodium sulfoxide was removed at 50°C under a vacuum of 0.035 MP. The obtained product was reddish brown.

90.00 mL of piperidine were added to a 250 mL three-neck flask and were stirred at 0°C. Then 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*] [7] annulene was slowly added. The mixture was stirred at room temperature till no gas was produced. 70 ml of water were added to the organic phase. The solvent was evaporated to dryness giving 18.86 g of a light brown solid.

The conditions of the chromatographic separation were as follows: stationary phase silica gel 75 ~ 45μm; column height 20 cm (wet packing); eluent - a mixture of n-hexane and ethyl acetate (30 ∶1, M / M).

R_1: 2.05 g, recovery 11.76%, melting point 163.2℃,^{1}H NMR ($CDCl_3$, 300Hz,δ) 5.19 (s,1H,-CR_1R2N-H), 7.19 (m，1H,Ph-H), 2.87~2.90 (m，4H，CH_2), 2.25(m，4H，CH_2), 1.59(m，6H，CH_2)，7.10~7.20 (m，3H，Ph-H)，7.09~7.12 (s，1H，Ph-H).

R_2: 3.56 g, recovery 20.35%， melting point 175.4 °C, ^{1}H NMR ($CDCl_3$，300Hz，δ) 5.18 (s，1H，-CR_1R_2N-H)，7.17 (s，1H，Ph-H)，7.13 (m，1H，Ph-H), 2.87~2.91 (m，4H，CH_2)，2.25 (m，4H，CH_2)，1.59 (m，6H，CH_2)，7.10~7.21 (m，3H，Ph-H)，7.09~7.12 (s，2H，Ph-H).

R_3: 0.95 g, recovery 5.38％， melting point 178.1 °C; ^{1}H NMR ($CDCl_3$，300Hz，δ) 5.18 (s，1H，CR_1R_2N-H)，7.73 (d，1H，Ph-H)，7.33 (m，1H，Ph-H), 2.87~2.91 (m，4H，CH_2)，2.25 (m，4H，CH_2)，1.59 (m，6H，CH_2)，7.05~7.21 (m，3H，Ph-H)，7.09~7.12 (m，2H，Ph-H).

R_4: 0.25 g， recovery 1.46％，melting point 185.7 °C, ^{1}H NMR ($CDCl_3$，300Hz，δ) 5.19 (s，1H，CR_1R_2N-H) 7.13 (d，1H，Ph-H)，2.87~2.91 (m，4H，CH_2)，2.23~2.25 (m，4H，CH_2)，1.59 (m，6H，CH_2)，7.04~7.21 (d，3H，Ph-H)，7.06~7.12 (m，3H，Ph-H).

R_5: 16.23 g， recovery 72.56%， melting point 175.2 °C, ^{1}H NMR ($CDCl_3$，300Hz，δ) 5.18 (s，2H，CR_1R_2N-H)，7.44 (s，2H，Ph-H)，7.79 (d，2H，Ph-H), 7.12 (d，2H，CH_2)，2.45 (m，4H，CH_2)，1.39~1.50 (m，6H，CH_2)，2.86~2.90 (m，4H，Ph-H).

Determination of feeding coefficient

Feeding coefficient is an index that shows the palatability of rodenticides [31-32]. The captured experimental rats were of the kind *rattus norvegicus* in Shenyang and were reared in the laboratory. The rats were 150 ~ 300 d old, weighing 150 ~ 200 g, half male and female (females not pregnant).

Determination of LD_{50}

Experimental animals were mice (*mus musculus*) belonging to Kunming closed group, aged 28 ~ 30 d, weight 18 ~ 22 g, half male and female (female not pregnant). Experimental animals *rattus norvegicus* were caught in Shenyang and were reared in the laboratory, age 150 ~ 300 d, weight 150 ~ 200 g, half male and female (females not pregnant).

RESULTS AND DISCUSSION

The experimental results for R_1, R_2, R_3, R_4, R_5 selectivity are 0.9, 0.87, 0.71 and 0.68, respectively.

The LD_{50} of R, R_1,R_2 ,R_3 ,R_4 and R_5 of *rattus norvegicus* and the mice were calculated by the Karber method [16-17].

The results are shown in Table 1. Table 2 shows that the reduction ratio of LD_{50} percentage for *rattus norvegicus* is larger than that for mice for all R_1,R_2,R_3,R_4 and R_5,which means that the rate of increase in the toxicity of such rodenticides against *rattus norvegicus* is greater than against mice. The newly synthesized rodenticide enhances the selectivity. The toxicity of brominated compounds has been strengthened while retaining the high selectivity of the original drug.

Table 1 Toxicity comparison of each rodenticide against *rattus norvegicus*

Product	Rodenticide				
	R	R_1	R_2	R_3	R_4
LD50 (mg/kg)	8.85	6.79	5.65	7.55	9.16
LD50 reduction (mg/kg)	-	2.06	3.20	1.30	-0.31
LD50 reduction percentage (%)	-	23.28	36.16	14.69	-3.15

Table 2 Toxicity comparison of each rodenticide against *mus musculus*

Project	Rodenticide				
	R	R_1	R_2	R_3	R_4
LD50 (mg/kg)	939.72	882.67	855.07	883.08	970.05
LD50 reduction (mg/kg)	-	57.05	84.65	56.64	-30.33
LD50 reduction percentage (%)	-	6.07	9.01	6.03	-3.23

The toxicity of the rodenticides changes with the substitution position of bromine on the benzene ring. R_4 was the most toxic, and R_2 was the least toxic. The toxicity mechanism of the rodenticides is related to the biological activity of the nitrogen atom which contained in there. In the body of *rattus norvegicus*, the nitrogen-containing organics first combine with the substance and then exert toxic effects. It is a bimolecular process [18]. The reason for the difference in toxicity of the newly synthesized drugs is related to the extent of steric hindrance. Because bromine in R_4 is closer to the nitrogen, it hinders the contact between the nitrogen atom in the compound and the biological active group of the organism, which affects the toxicity. Thus the toxicity of R_4 is small. On the contrary, the bromine atom in the R_1 and R_2 molecules is far away from the nitrogen atom. So the steric hindrance is small and the toxicity is strong.

It can be seen from the experimental data that brominated N-piperidine dibenzocycloheptoid, especially the 2- brominated compound, is the best rodenticide in the examined group. It has strong toxicity and good selectivity.

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