Preparation of [^{3}H]-Prazosin

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Summary

The synthesis of the bromoprazosin, in which bromination and acylation of furoic acid were completed by means of very simple method was described. The reductive catalyzed debromination with tritium gas afforded the [^{3}H]-prazosin. Its specific activity and radiochemical purity were 22.6 Ci/mmol and 98% respectively.

Key words: Synthesis, Bromination, Tritium Labelling, Reductive Catalyzed Debromination, Tritiated Prazosin.

Introduction

The adrenoreceptor, which is divided into α_1 and α_2 type was put forward by Lander[1] in 1974, since then it has been widely studied. [^{3}H]-prazosin is a $\alpha_1$adreno-radioligand. For the preparation of [^{3}H]-prazosin the corresponding bromoprazosin should be used as starting material. In 1978, Dietriech[2] reported the catalytic dehalogenation for preparation of prazosin, in which synthesis of bromoprazosin was also simple reported, but he did not report the bromination and acylation of furoic acid, which were not described in literature. We described here the details of synthesis of bromoprazosin, especialy for the bromination and acylation of furoic acid. The preparation of furoic acid[3] and 2-chloro-4-amino-6,7-

0362-4803/87/111307-06$05.00

Received January 21, 1987

dimethoxyquinzolin[4] was not described here. The catalytic halogen replacement was utilized to prepare [^{3}H]-prazosin, with a high specific activity of 22.6 Ci/mmol and high radiochemical purity of 98%. Our method is shown in Figure 1.

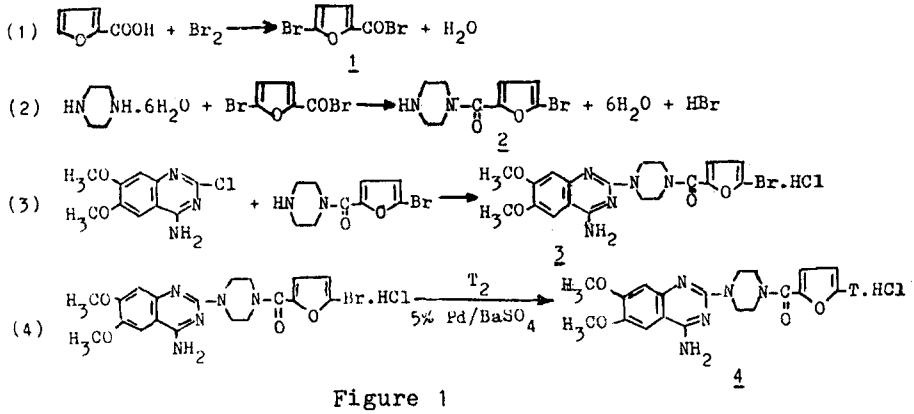

Figure 1

Experimental

Some chemicals used were as obtained from manufactures and others were prepared by ourselves. Melting points were determined on microscopic melting point apparatus. Ultraviolet spectra were obtained on the UV-210 spectrameter using ethanol as solvent. Radiochemical purity was determined using thin layer radioscanner Model RTLS-A. tritium was counted using a Packard liquid scintillation counter, Model FJ-353G. Element analysis was determined on the Elementary

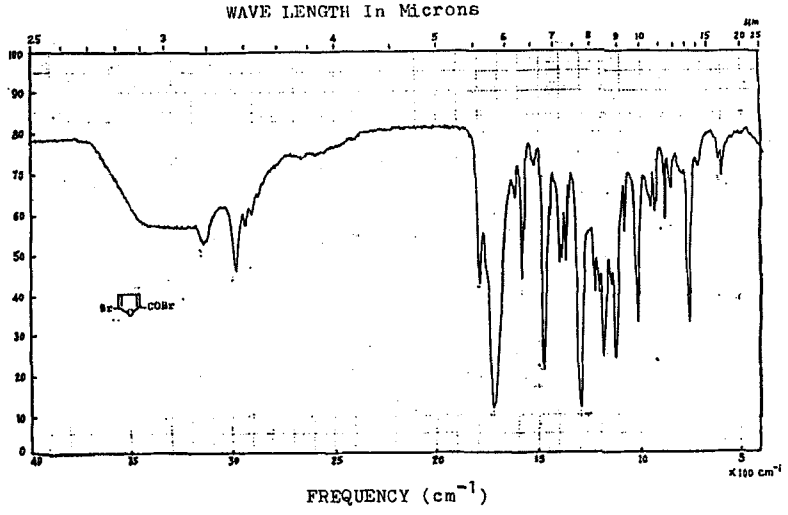

Figure 2 IR spectrum of 5-bromo-2-furoyl bromide

Analyzer Model 1106. IR spectrum was recorded on Specord 75 IR Spectrophotometer. NMR spectrum was recorded on Model Bruker WP 80SY.

(1) Preparation of the 5-Bromo-2-furoyl Bromide 1

To 14 ml of chloroform were added 1.2 g(9.19 mmol) of furoic acid and 1.2 ml(46 mmol) of bromine. The mixture was refluxed for 384 hours. Then it was chilled to 5°C. The resident solid in the reaction was filtered and the extra bromine and chloroform were removed, leaving a pale yellow liquid of the 5-bromo-2-furoyl bromide. Its infrared spectrum was shown in Fifure 2. Analysis, Calculated for $C_5H_2O_2Br_2$, C,23.62; H,0.79; Br,62.99. Found, C,23.18; H,o.84; Br,63.40.

(2) Synthesis of 5-Bromo-2-furoyl Piperazine 2

2.3 g(11.8 mmol) of piperazine hexahydrate was dissolved in 11.4 ml of absolute alcohol by stirring, then 1.2 ml ≥40% hydrobromic acid solution was added dropwise, maintaining a temperature of 40-50°C. The resultant solution was stirred at 45°C, 0.6 ml of 5-bromo-2-furoyl bromide was added dropwise over 5 minutes period. The slurry was stirred at 80°C for 1.5 hours and then chilled to room temperature and filtered. The pale yellow filtrate was concentrated in vacuo and dissolved in 3 ml H_2O. The aqueous mixture was extracted with dichloromethane. The CH_2Cl_2 extracts were dried over anhydrous Na_2CO_3 and then concentrated in vacuo to yield crystals on cooling. The crude product was taken up in ethyl acetate and the solution stirred at room temperature as hexane was added to the cloud point. An additional hexane was added slowly as the product crystallized. The product was filtered and washed with hexane to yield pale yellow 5-bromo-2-furoyl piperazine. M.P. 114-116°C. Analysis: Calculated for $C_9H_{11}O_2N_2Br$ C,41.72; H,4.28; N,10.81; Br, 30.84; Found C,41.38; H,4.48; N,10.41; Br,31.17.

(3) Synthesis of bromoprazosin 3

To 12 ml of isoamyl alcohol was added 0.2 g(0.77 mmol) of 5-bromo-2-furoyl piperazine and 0.25 g(1.08 mmol) of 2-chloro-4-amino-6,7-dimethoxyquinozoline. The mixture was refluxed for 4 hours, and stirred with rapidly cooling to room temperature. After standing for half an hour at ambient temperature, the reaction product was filtered. The product was washed with acetone and isoamyl alcohol three times, yielding pale yellow large rod-like crystal of bromoprazosin. M.P. 275-279°C, Analysis: Calc'd. for $C_{19}H_{20}N_5O_5Br.HCl$, C,45.7; H,4.2; N,14.04; Br,16.05. Found, C,45.92; H,4.54; N,13.61; Br,16.51.

(4) Preparation of [^{3}H]-Prazosin 4

To 20 ml of reaction flask were added 2.5 mg of bromoprazosin and 1.5 ml of N,N-dimethylformamide as well as 9.5 mg of 5% Pd/$BaSO_4$ catalyst. After the reaction flask was cooled by liquid nitrogen it was evacuated to 1 x 10^{-3}mm Hg. The tritiation facility was charged with ca. 400 Ci of carrier-free T_2(generated from urinium tritide) and was maintained at 660 mm Hg before the sample thawed, the mixture of bromoprazosin and T_2 was stirred for 4 hours over 5% Pd/$BaSO_4$. The reaction flask was refrozed with liquid nitrogen, waste T_2 was removed to a T_2 storge tank. The catalyst was removed by filtration and the labile tritium was removed by the repeated addition of ethanol followed by evaporation. Dissolved in the solution of 0.01N HCl:ethanol=1.1(v/v) afforded the product of [^{3}H]-prazosin. Its specific activity and radiovhemical purity were 22.6 Ci/mmol and 98% respectively.

Results and Discussion

Preparation of 5-bromo-2-furoyl bromide. Our results have shown that 5-bromo-2-furoyl bromide is readily prepared. The bromination and acylation of furoic acid can be finished in one step, it need not to be esterified[5] before bromination of furoic acid and deesterified is also not used before it acylate with SO_2Cl_2. However bromination reaction was longer than the acylation, so in order to complete bromination and acylation reaction, longer time and extra bromine were needed. The infrared spectrum and elemental analysis have shown that the bromination and acylation was complete.

Synthesis of 5-Bromo-2-furoyl Piperazine. In our experiment, instead of anhydrours piperazine and nitrogen, we used piperazine hexahydrate and air to synthesize 5-bromo-2-furoyl piperazine. This differs from the procedure described in literature[6], while the same good product is obtained.

Synthesis of Bromoprazosin. The result has shown that the temperature of reflux was controled above 150°C, the yielding product must be a α-form that was demanded. When reaction was ended it was rapidly chilled to room temperature to get larger crystals, so that residue on the surface of product could be removed easly. The product NMR spectrum has shown that the 5th position of H(7.9ppm) in the furan ring at Br-H spectrum, the 7.9 ppm of H peak was disapeared and indicate that the hydrogen atom was replaced by bromine in the 5th position of furan ring.

Preparation of [^{3}H]-Prazosin. The catalytic reductive debromination with T_2 needed longer reaction time and high tritium pressure, that was shown in Table 1 and 2, the former result indicated that the tritiodebromination does not react in two hours, it begins to react in three hours.

Table 1 Relation of reaction time with yield

Reaction time (Hr.)	Temperature (°C)	Yield (mCi)	Specific Activity (Ci/mmol)
1	15-20	0	0
2	"	"	"
3	"	51	20
4	"	64	22
5	"	68	22

Table 2 relation of tritium pressure with yield

Tritium Pressure (mm Hg)	Temperature (°C)	Yield (mCi)	Specific Activity (Ci/mmol)
480	15-20	27	6.6
560	"	53	15
660	"	68	22

so 4 hours reaction time was optimium in our reaction condition. The latter result showed that the yield increased with high tritium pressure. However if the tritium pressure was too high it would cause the radiated product increased. So 660 mm Hg tritium pressure was more

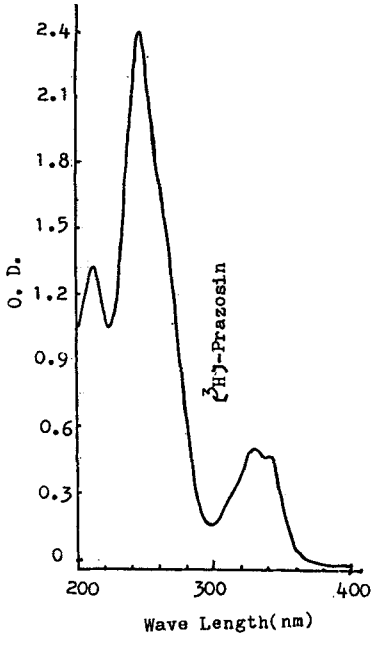

Figure 3 spectrum of [^{3}H]-prazosin

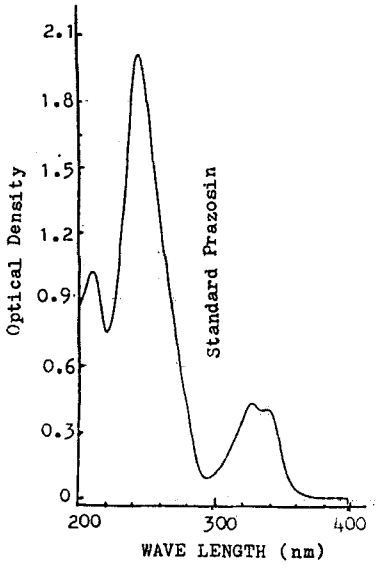

Figure 4 spectrum of standarnd prazosin

fitted in our condition. On the other hand the significant characteristic in our experiment is that the final product needs not be purified, but its radiochemical purity is very high (98%), the ultravailet spectrum of (^{3}H)-prazosin is same as standard prazosin (see Figure 3,4). It has been further proved that bromoprazosin synthesis in this laboratory is very stable in radiation and not decomposed in tritiation.

Acknowledgement

The authers thank Dang Shuqin for the recording of NMR spectrum of bromoprazosin.

Referance

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