A Short Synthesis And Its Application To The Preparation Of Radio Labelled Leukotriene Inhibitor Sch 37224.

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SUMMARY

A new, short synthesis of 1-(1,2-dihydro-4-hydroxy-1-phenyl-2-oxo-1,8-naphthyridin-3-yl)-pyrrolidinium hydroxide, inner salt, **1**, was achieved by condensing methyl 2-phenylamino-3-pyridine carboxylate **2** with ethyl 1-pyrrolidine acetate **4**. This gave highly pure product in 60% yield. This synthesis was applied to the preparation of ^{14}C labelled **1**. Radiolabelled **1** was synthesized from u-[^{14}C]-aniline in three steps at 97% radiochemical purity and 27.3% radiochemical yield.

Key Words: Radio Labeled 1,8-naphthyridine-2(1H)ones , Leukotriene Inhibitor, Sch 37224, New Synthesis, 1-(1,2-Dihydro-4-hydroxy-1-phenyl-2-oxo-1,8-naphthyridin-3-yl)-pyrrolidinium, inner salt.

INTRODUCTION

Sch 37224, **1**, is an efficient leukotriene release inhibiton (1). Two syntheses of this compound have been reported (2,3). Both use methyl 2-phenylamino-3-pyridine carboxylate, **2**, as the starting material. Although the latter synthesis is efficient and has been used for a large scale preparation of **1**, we sought a new synthesis of **1** which would be more practical for the preparation of radiolabeled Sch 37224, which was needed to study the drug's absorption, distribution, metabolism, and excretion.

RESULTS AND DISCUSSION

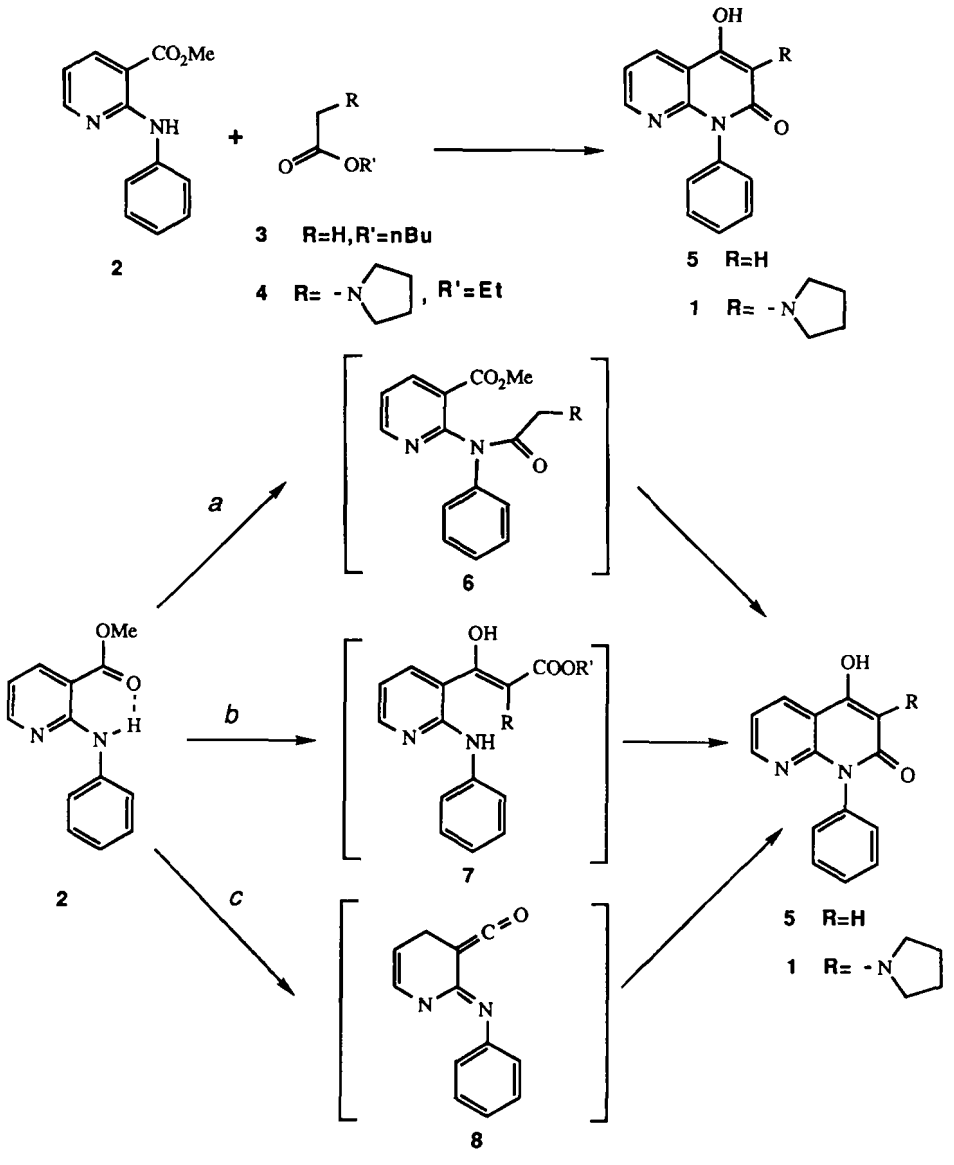
The condensation of **2** with a large excess of n-butyl acetate, **3**, in the presence of potassium-*t*-butoxide under vigorous conditions leads to the formation of naphthyridinone **5** (2,4,5). If compound **4** could be used in place of **3** **[Scheme 1]** for its condensation with **2**, a short conversion of **2** to **1** could be realized (6). Based on the mechanistic considerations described below, it was anticipated that more vigorous reaction conditions would be required for the above conversion compared to the conditions needed for the condensation of **2** with **3**. In fact, it was noticed that under the reaction conditions that gave an excellent yield of **5** from the condensation of **2** with **3** (2,4,5), only a trace of reaction between **2** and **4** was seen. However, with the use of refluxing xylenes,K-O-*t*-Bu and a large excess of **4**, a 30% yield of **1** was obtained. For the synthesis of **1**, a large excess of **4** would be cost prohibitive. Hence we sought to optimize the above synthesis where the yield was improved *and* the excess of **4** was minimized.

A logical way to optimize the above synthesis would involve an understanding of the reaction mechanism(s), which can then be utilized to manipulate the outcome of the above reaction. Three

0362–4803/91/060651–06$05.00

Received 14 November, 1990
Revised 15 January, 1991

Scheme 1



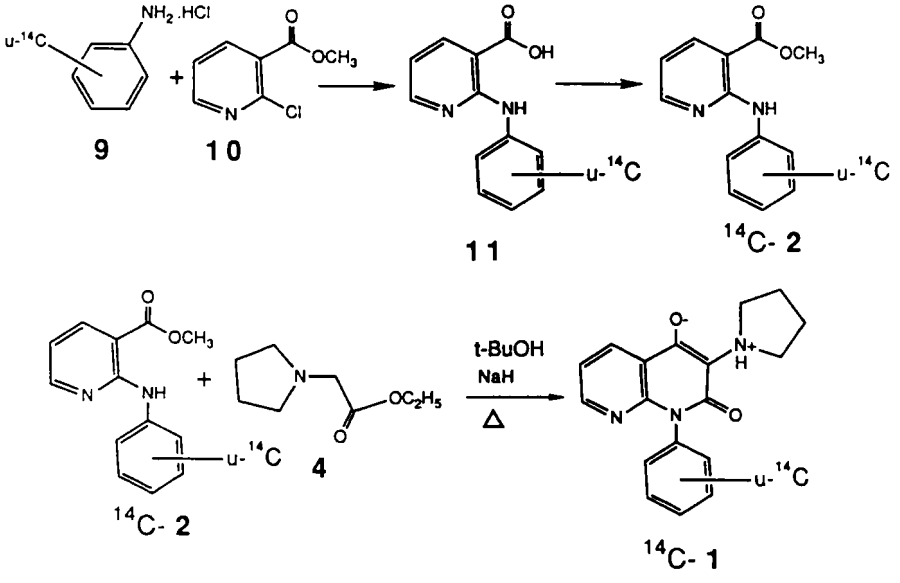
mechanisms for the synthesis of naphthyridinone **5** or **1** from the condensation of **2** with **3** or **4**, respectively, are possible **[Scheme 1]**. They are: (*a*) addition of the anion of **2** to **3** or **4** to form **6** which then cyclizes to **5** or **1**, (*b*) addition of anion of **3** or **4** to **2** to form **7**, (which could exist in the keto form as shown in the scheme, or in its enol form, or as a mixture of both forms), which can cyclize to **5** or **1**; or (*c*) formation of ketene **8** (either via thermal elimination of methanol or via the anion of **2**) which then condenses with the anion of **3** or **4**, to form **5** or **1**.

Attempts to isolate/detect/identify any of the proposed intermediates were unsuccessful. This is probably due to the fact that in the case of mechanism *a* and *b* the first step is an intermolecular condensation. Since compound **2** exists as a stable intramolecular hydrogen bonded six-membered

structure (3), forming its anion or, adding an anion to it necessitates high energy conditions. The second step in either case is intra molecular, which is expected to be more facile, making the intermediates **6** and **7** short lived. In fact, **6** (R=pyrrolidine) has been synthesized (3). This α-amido amine was efficiently cyclized under mild conditions to obtain **1**. This fact lends support to the argument that the second step is very facile. Similarly, due to the stability of **2**, the formation of ketene **8** would require high energy conditions. Under these conditions the anion of **3** probably forms readily. Since ketenes are very reactive species, they are consumed quickly. Compared to **2**, the methylene hydrogens of **4** are less acidic, and thus require more vigorous conditions to form the anion. Finally, it is possible that under the vigorous conditions, all three mechanisms are operative.

Under the vigorous reaction conditions ester **4** probably underwent a Claisen condensation (7). This side reaction competed with the desired reaction, and thus required a large excess of **4**. During the course of our study, and based on the yields of the isolated product **1**, it was established that Na-bases were more efficient than the K-bases for the conversion of **2** to **1**, whereas Li-bases were the least efficient (8). Thus, if the conditions were so modified that the condensation of **2** with **4** was favored over the Claisen condensation of **4**, a more practical synthesis of **1** could materialize. This was accomplished by slowly adding **4** over a long period of time to a rapidly stirred, preheated mixture of **2** and a Na-base (e.g. NaH) in xylenes with a cosolvent. These conditions maintained a relatively high concentration of **2** in the reaction mixture with respect to **4** thereby improving the condensation of **2** with **4** over Claisen condensation of **4**. Thus, using approximately four to five equivalents of **4**, a 60% yield of **1** was obtained. These conditions are described in the Experimental Section. This process minimizes the handling of materials and intermediates compared to the previously known processes (2,3), and it gives highly pure Sch 37224 in good yields, and hence it was considered the process of choice for the preparation of radiolabeled **1**. The actual radiosynthesis was done in three steps as outlined in **Scheme 2**. First, u-[^{14}C]-aniline hydrochloride, **9**, was condensed with 2-chloronicotinic acid, **10**. This acid was

Scheme 2



esterified using methylsulfate to obtain radiolabelled **2**. The conversion of **2** to **1** was carried out in refluxing xylene with NaH. Sodium-*t*-butoxide was generated *in situ* by dropwise addition of *t*-butanol to this mixture. Next,a four fold excess of ethyl-1-pyrrolidineacetate, **4**, was added dropwise over an hour. The product was collected by filtration and recrystallized from trifluroethanol. The procedures and the yields for the preparation of the ^{14}C labeled Sch 37224 are detailed in the Experimental Section.

In summary, a new, short synthesis of a potent leukotriene release inhibitor Sch 37224 has been developed. This synthesis was used for the preparation of radiolabeled product.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian FT-80 or Varian XL 300. Chemical shifts are expressed in parts per million downfield from Me_4Si. The infrared spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. The electro impact (EI) mass spectra were recorded on a Varian MAT CH-5 spectrometer at 70 ev. Elemental microanalyses were conducted by Schering Analytical Research Services. Melting points were recorded on a Mel-Temp® apparatus. Methyl 2-phenylamino-3-pyridine carboxylate, **2**, was synthesized from 2-chloronicotinic acid as described previously (2,5), ethyl 1-pyrrolidine acetate was purchased from Aldrich Chemical Company and was used without further purification. For the synthesis of radiolabeled **1**, ^{14}C-aniline hydrochloride was purchased from New England Nuclear/Dupont as an ethanol solution. It had a specific activity of 6.0 mCi/mmol. A Bioscan 2000 linear analyser was used to integrate radioactive peaks on TLC. Whatman LK6DF TLC plates were used for normal phase and LKC18F plates were used for reversed phase thin layer chromatography (TLC).

Radiolabeled intermediates and product were identified by comparison with authentic cold materials in the chromatographic systems listed, and were found identical.

1-(1,2-Dihydro-4-hydroxy-1-phenyl-2-oxo-1,8-naphthyridin-3-yl)-pyrrolidinium hydroxide, inner salt (1): To a solution of 1.5g (6.5 mM) methyl 2-phenylaminonicotinate in dry xylenes at room temperature was added 0.69g (14.54M) of sodium hydride (50 percent oil emulsion) followed by a small amount of N, N-dimethylformamide (DMF). The reaction mixture was heated to a temperature of 85-95°C, and 1.05 mL (6.5 mM) of ethyl l-pyrrolidineacetate in xylenes was slowly added over a period of 10 minutes. The reaction mixture was heated for 1 to 3 hours prior to the addition of portions of 0.32g NaH followed by 1.05mL of ethyl 1-pyrrolidineacetate as described above (total 3 portions). Following addition of the portions, the reaction mixture was cooled to 0°C and quenched with a slow addition of glacial acetic acid, and then water was added. The product was filtered and washed with water, acetone, methylene chloride, and acetone. The solid thus obtained was dried in vacuo to give 1.20g (60% yield) of title compound, a white solid, identical in all respect to the one made via alternative syntheses (2,3).

Radiolabelled 1:

Methyl 2-[u-^{14}C]-phenylamino-3-pyridine carboxylate (2): p-Toluenesulfonic acid monohydrate was added to an ethanolic solution of [u-^{14}C]-aniline hydrochloride (50 mCi, 1.080g, 8.37mM).

The solution was evaporated to a powder under reduced pressure. The powder was added to a reaction vessel containing 2-chloronicotinic acid (1.319g, 8.37mM) and 10mL of N, N-dimethylaniline. The reaction vessel was fitted with a condenser and attached to two traps, each containing dilute sulfuric acid. The reaction was stirred under an inert atmosphere at 130°C for 2.5 h. After cooling to room temperature, the reaction mixture was partitioned between Et_2O (50 mL) and 10% (w/v) aqueous NaOH (50mL). The aqueous layer was then acidified with HCl and reextracted with 2 X 50mL of CH_2Cl_2. The combined CH_2Cl_2 solution contained 29.5mCi of 2-[u-^{14}C]-phenylamino-3-pyridine carboxylic acid (60% radiochemical yield) at 97% radiochemical purity by TLC scanning. (TLC system: n-BuCl: MeOH::92:8. Product rf:0.45).

2[u-^{14}C]-phenylamino-3-pyridine carboxylic acid (1.400g, 6.54mM, 29.5mCi) was dissolved in DMF (45mL). Cs_2CO_3 (2.125g, 6.52mM) was added followed by $(CH_3)_2SO_4$ (0.824g 6.54 mM). The reaction was stirred at room temperature for 1h. The reaction mixture was then added to H_2O (100mL) and extracted with 3 X 50mL of CH_2Cl_2. The CH_2Cl_2 layers were combined and evaporated to give 27.5mCi of **2** (93% yield). The radiochemical purity was measured by TLC scanning in the following systems:

MeOH: MeCN: 0.2 N NH_4OAc:: 70:15:20 on C-18 plates- 91% rf:0.25

n-BuCl: MeOH: HOAc:: 82:18: 1 on silica plates- 92% rf:0.78

1-(1,2-dihydro-4-hydroxy-1-[u-^{14}C]-phenyl-2-oxo-1,8-naphtyridin-3-yl)-pyrrolidinium hydroxide, inner salt (1): Methyl 2-[u-^{14}C]-phenylamino-pyridine-3-carboxylate,**2**, (23.9mCi, 3.98mM) was dissolved in dry xylenes (15mL). NaH (0.768g, 4.0mM) was added and the reaction was heated to 138°C and stirred under N_2. A solution of ethyl 1-pyrrolidineacetate (3.13g, 20mM) and *t*-BuOH (1.0mL) in 15mL of xylenes is added dropwise over a period of 1h. A slow reflux was maintained as the ethanol and methanol byproducts were collected in a dean-stark trap. After 3h, the reaction mixture was cooled to room temperature and quenched with acetic acid (4mL). A precipitate formed which was collected by filtration, washed with toluene and dried *in vacuo*. The crude product was purified by recrystallization, as follows: The precipitate (3.1g) was dissolved in 15mL CF_3CH_2OH by sonication. This solution was added to 150mL H_2O. The precipitate which formed was collected and washed with H_2O. Repeating the process afforded 11.60mCi (49% radiochemical yield) of [^{14}C]-Sch 37224. Radiochemical purity by TLC/plate scanning:

CF_3CH_2OH on silica- 97% rf:0.52

This batch was combined with cold Sch 37224 and recrystallized to give a final specific activity of 10.2uCi/mg (3.13mCi/mmol).

Acknowledgement: We thank Drs. A. Ganguly, M. Green, and M. Steinman for their interest and candid discussions during this work.

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