Synthesis of ^{14}C-labelled 4-(2-hydroxy-3-isopropylamino-propoxy)-2-methyl-indole (mepindolol).

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Summary: Mepindolol, a potent ß-adrenoceptor blocking agent, was labelled with ^{14}C by two different routes yielding the 2-[^{14}C]methyl and [2-^{14}C] products. While the first alternative was abandoned because of low overall yield, the latter route provided mepindolol with a specific activity of 2.06 GBq/mmole (55.8 mCi/mmole) and in a radiochemical yield of 40% starting from $Ba^{14}CO_3$.

Key words: Synthesis, mepindolol, carbon-14.

Introduction and Discussion

ß-adrenergic antagonists with their antihypertensive mode of action have been the subject of extensive research throughout the past years. In the course of our chemical and pharmacological studies on mepindolol we required an efficient chemical synthesis and a ^{14}C labelling procedure as well. There is a report of carbon-14 synthesis of pindolol, an analogue of mepindolol lacking the 2-methyl group. Radioactivity was introduced into the aliphatic side chain by reaction of epoxide (6 without 2-methyl) with 2-amino [2-^{14}C] propane[1]. Due to the possible biological instability of this label we looked for a different approach. Sundberg[2]

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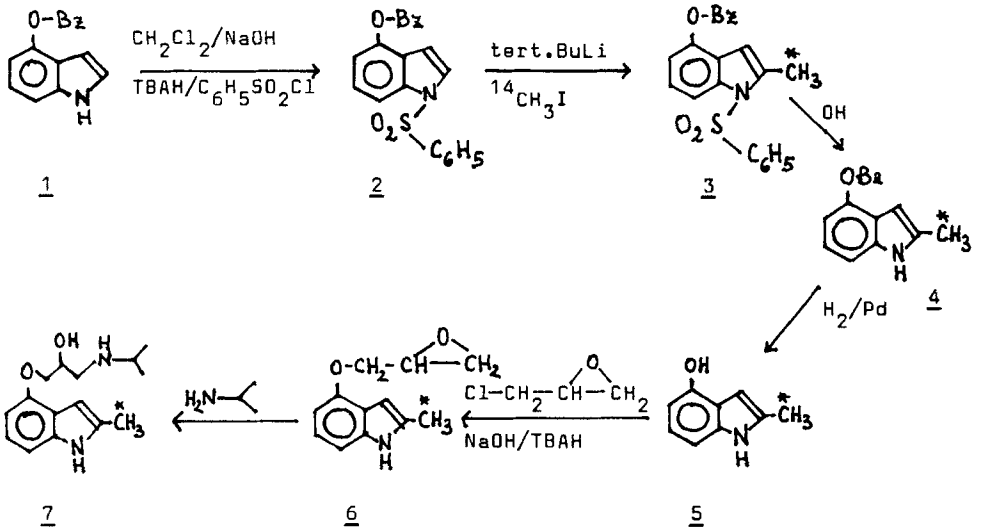
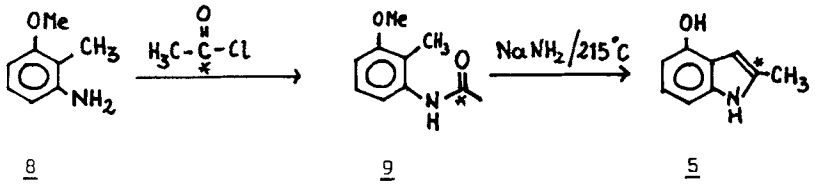
has described selective lithiation of N-protected indoles at carbon 2 with tert.-butyllithium and subsequent reaction of this anion with methyl iodide. This approach looked promising, and we carried out the synthesis as outlined in scheme 1.

Scheme 1



The crucial step turned out to be the lithiation of (2) and the following reaction with $^{14}CH_3I$ (prepared from $Ba^{14}CO_3$ by common procedures). Incorporation of radioactivity never exceeded 20%, which was in contrast to the rather good yields reported. Although we finished the synthesis this way, we were looking for a more suitable procedure and developed a method based on Madelungs indole synthesis (scheme 2). It could be employed also for bulk chemical synthesis.

Scheme 2



The synthesis outlined proceeds with a minimum of steps and uses [1-^{14}C] acetyl chloride as starting material, which is conveniently prepared from $Ba^{14}CO_3$. Conversion of 3-methoxy-2-methyl-aniline (8) to the acetate (9), followed by cyclization and ether cleavage, gave 4-hydroxy-2-methyl-[2-^{14}C] indole (5) in an excellent yield. Because of its sensitivity to light and temperature, we modified the reaction of (5) with epichlorohydrin by working under phase transfer catalytic (PTC) conditions using tetrabutylammonium hydrogensulfate (TBAH) as catalyst. Thus 4-(2,3-epoxypropoxy)-2-methyl-[2-^{14}C] indole (6) could be prepared within one hour at room temp. in a 69% yield. The final product (7) was stored as its sulfate in EtOH at -20°C. In three months decomposition products amounted to 15%. Mepindolol was successfully purified using HPLC.

Experimental

3-Methoxy-2-methyl-[1-^{14}C] acetanilide (9): [1-^{14}C] Acetyl chloride (prepared from 3.7 GBq/100 mCi $Ba^{14}CO_3$) was transferred in vacuo to a solution of 3-methoxy-2-methyl-aniline (1.8 mmole) in dichloromethane (3 ml) and pyridine (160 µl). After stirring for one hour at room temperature, it was poured into ice water and extracted with CH_2Cl_2. The product was purified on 7.5 g of silica gel. Elution with CH_2Cl_2: acetone (8:2) gave 2.59 GBq/70 mCi of (9), TLC showing a single spot in $CHCl_3$: MeOH (95:5), R_f 0.4.

4-Hydroxy-2-methyl-[2-^{14}C] indole (5): 3-methoxy-2-methyl-[1-^{14}C] acetanilide (9) (0.925 GBq/25 mCi) was dissolved in N,N-diethylaniline (2 ml), which was degassed with N_2 prior to use. Under nitrogen $NaNH_2$ (250 mg) was added and the temperature raised within 45 min. to 215°C. The mixture was stirred at this temperature for 30 min., cooled to

90°C, and decomposed with water. The aqueous phase was extracted with ether acidified with HCl and then again extracted with ether. The yield was 0.8658 GBq/23.4 mCi of (5), which was used for the next step without purification.

4-(2,3-Epoxy-propoxy)-2-methyl-[2-^{14}C]indole (6): the above yield of (5), epichlorohydrin (2 ml), 1N NaOH (2 ml) and TBAH (170 mg) were vigorously stirred for one hour at room temp. After extraction with dichloromethane, the product was chromatographed on silica gel (5 g) with CH_2Cl_2 to yield 0.599 GBq/16.2 mCi of pure (6). TLC in ethyl acetate:isopropanol:ammonia (9:1:1), R_f 0,6.

4-(2-Hydroxy-3-isopropylamino-propoxy)-2-methyl-[2-^{14}C] indole-sulfate (7):

The preceding product (6) (0.599 GBq/16.2 mCi) was refluxed with isopropylamine (4 ml) under nitogen for 52 hours. The excess base was evaporated, the residue taken up in ethyl acetate and then extracted five times with tartaric acid (10%). The combined extracts were made alkaline with NaOH and then extracted with chloroform. The organic phase was washed with water and after evaporation gave 0.54 GBq/14.6 mCi mepindolol. The radiochemical purity was 97.9% by inverse dilution analysis. Mepindolol base was dissolved in EtOH (1 ml) and, after addition of a few drops of water, it was titrated with 0.2N H_2SO_4 (pH 6.3). Total activity 0.531 GBq/ 14.36 mCi at a specific activity of 2.06 GBq(55.8 mCi)/mmole.

TLC systems: benzene:EtOH:ammonia (84:15:1)
ethyl acetate: isopropanol: ammonia (9:1:1), R_f 0.56.
benzene: AcOH:ethyl acetate:MeOH (6:4:4:3)
n-pentane:MeOH:CH_2Cl_2:isopropanol:ammonia (60:20:10:10:0.5).

Radioscans of all four chromatograms showed a purity of 99%.

Throughout the synthesis all TLC was carried out on HPTLC plates silica gel 60 F 254 (Merck). Radioscans were performed on a Berthold LB 2722-2 radioscanner. Radioactive disintegrations were measured on a Berthold BF 5003 A liquid scintillation counter.

HPLC: Knauer high-pressure liquid chromatography system 52.00, LiChrosorb RP 18 analytical column. Gradient elution H_2O (500 ml + 0.5 ml ammonia):MeOH, methanol concentration changing from 20% to 90% within 10 minutes at a flow rate of 4 ml/min. Retention times: mepindolol 2 min., impurity 2.8 min. Monitored with a 254 µm Knauer UV detector.

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