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A General Synthetic Method Suitable for the Introduction of Deuterium or Tritium in Buspirone Type Anxiolytic Agents

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SUMMARY

In recent years, a number of putative non-benzodiazepine anxiolytic agents incorporating the 4- aminobutylimide or sulfonamide-imide linkage have been reported and at least two of these, buspirone and gepirone, have been shown to have anxiolytic activity in man. In order to study the metabolism, body distribution and binding affinities of this class of compound, it was of interest to devise a precursor which could be specifically labelled with tritium to high specific activity. We have devised a synthetic route to the corresponding but-2-ynyl and but-2-enyl analogs of gepirone and have converted the latter to dideuterogepirone as an example of the methodology. Thus the method chosen has been found to be practical and is believed to be of sufficient generality to enable the synthesis of a variety of derivatives of this type containing either two or four atoms of label. Furthermore, by appropriate choice of reagents, incorporation of ^{14}C into these compounds may be achieved.

Key words: 4-Aminobutylimides, Anxiolytics, ^{3}H or D, Gepirone.

INTRODUCTION

In recent years, a number of new pharmacological agents in which a 4-pyrimidinylpiperazine group is linked to an imide- (1 - 3) or sulfonamide-imide (4) moiety by a saturated, four-carbon linker have been found to possess pharmacological properties indicative of anxiolytic activity in man distinct from the activities of classical benzodiazepine anxiolytics. These properties, including freedom from benzodiazepine-related side effects, such as abuse potential and interactions with alcohol, have engendered much research into the mechanism of action of such agents and to the clinical investigation of a number of related derivatives(5, 6). To this end, syntheses of specifically labelled ^{14}C- and ^{15}N-buspirone (7) , tetradeuterated buspirone (8) and tritiated ipsapirone (9) have been reported. In the process of similar studies in our laboratories, it became of interest to study the receptor binding properties of compounds of this type and thus to synthesize agents specifically labelled with tritium at a known site for this purpose. It was also of interest to devise a synthetic methodology of general utility which could be utilized for the synthesis of analogous compounds. Finally, we hoped to incorporate more than one atom of label into such molecules so that high specific activity could be achieved. Reduction of an olefin (or an acetylene) with tritium provides a convenient, high yield method for accomplishing these objectives and can often be

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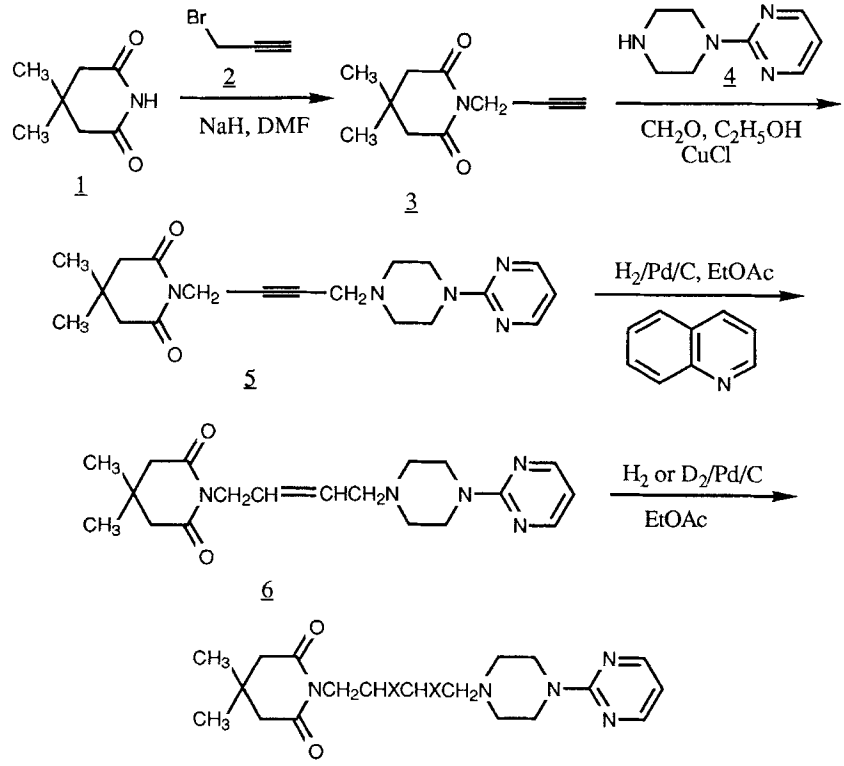
performed at the last step of a synthesis thereby avoiding the necessity for excessive handling of highly radioactive species. The two central methylene groups of the butyl chain found in buspirone and related compounds appeared to be a convenient location for the label and thus the following synthesis was undertaken.

It has been known for some time that the condensation of prop-2-ynyl imides with formaldehyde and a secondary amine in the presence of CuCl leads to the corresponding N-(4-disubstituted amino-2-butynyl) substituted imides(10). Such compounds have also been reduced to the corresponding saturated derivatives under mild conditions (11) and there is ample precedent for the synthesis of the corresponding alkene derivatives by partial reduction (12). These alkene derivatives appeared to be highly desirable as substrates for tritiation, since reduction with tritium would lead to the incorporation of two atoms of label thus meeting our goals of high specific activity and incorporation in a known location. Reduction of the alkyne directly with tritium would result in the $^3H_4$ species if this level of incorporation should be desired. Synthesis of a model species, 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione (MJ-13805, gepirone) according to the procedures illustrated in Scheme I was undertaken in order to demonstrate the feasibility of this method.



SCHEME I

RESULTS AND DISCUSSION

N- prop-2-ynyl-4,4-dimethylglutarimide **3** was prepared by alkylation of the coresponding imide **1** with propargyl bromide in a standard way (13). Condensation of this compound with formaldehyde and the free base of 1-(2-pyrimidinyl)piperazine **4** gave the acetylenic derivative **5** in moderate but acceptable yield. Partial reduction of this compound proved to be more difficult than anticipated in that Lindlar catalyst gave complete reduction to the hydrocarbon **7** under all conditions tried. This problem was overcome by further poisoning the Lindlar catalyst with quinoline (12) which led to almost complete conversion of the substrate **5** to the olefin **6** without a detectable amount of **7** being formed. Over- reduction of this type of acetylenic derivative with Lindlar catalyst has been seen in other derivatives of this type in our laboratories but in every instance the quinoline-poisioned Lindlar catalyst has been capable of achieving the partial reduction required.

As expected, compound **6** was found to be readily reduced with a standard palladium catalyst under mild conditions. Thus, hydrogenation gave compound **7** which was identical in all respects with a sample of gepirone prepared by the published procedure (14). Reduction with deuterium gave the dideuterated derivative **8** , identical to **7** except for the aliphatic protons missing in the 300 MHz proton NMR spectrum and the anticipated mass differences in certain fragments of the electron impact mass spectrum.

In conclusion, the procedure presented herein offers a general entry into tritiated aminobutylimide anxiolytic agents of the buspirone type. It could be readily adapted to the synthesis of tetradeuterated or tetratritiated analogs by reduction of the corresponding alkynes or for the preparation of ^{14}C labelled compounds of this type by substitution of labelled formaldehyde in the Mannich step followed by catalytic reduction. Finally, since the Mannich procedure has been utilized for the synthesis of unrelated medicinal agents and derivatives thereof from other acetylenic derivatives(10), the opportunity to utilize this procedure in other areas may arise.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^1H NMR spectra were recorded on a Varian XL-300 spectrometer with internal deuterium lock. IR spectra were determined with a Perkin-Elmer Model 21 spectrometer. EI mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. Analytical results as presented agreed with theoretical within ± 0.4%.

Preparation of 4,4-Dimethyl-N-prop-2-ynylglutarimide **3**. Dry DMF (50 mL) was added to 1.32 g of pentane-washed NaH in a flame-dried 3-necked flask under N_2 and the suspension was cooled to 5-10° C in an ice bath. A solution of 7.05 g (50.0 mmol) of 4,4-dimethylglutarimide **1** in 50 mL of dry DMF was added dropwise over 20 min. Some foaming occurred. After stirring for 20 min at 5° C, a solution of propargyl bromide **2** in 10 mL of DMF was added dropwise. The resulting

solution was allowed to warm to ambient temperature and stir overnight. The reaction mixture was poured into cold water and extracted three times with EtOAc. The combined extracts were washed with brine and dried with $MgSO_4$. Treatment with decolorizing carbon and evaporation of the solvent gave an essentially quantitative yield of the desired product which was of adequate purity to be used in the next step of the synthesis. A 300 mg lot of the material was purified by chromatography on silica gel, eluting with 5:1 hexane/EtOAc to give the analytical sample as a pale yellow oil. NMR ($CDCL_3$) ∂ 1.06 (6 H, s), 2.09 (1 H, t, J = 3), 2.52 (4 H, s), 4.50 (2 H, d, J = 3). Anal: C, H, N.

Preparation of 4,4-Dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-2-butynyl]-2,6-piperidinedione **5.** The free base of 1-(2-pyrimidinyl)piperazine **4** was prepared by dissolving 4.74 g (20.0 mmol) of dihydrochloride in 5 mL of water and basifying with 50% NaOH solution. This mixture was extracted three times with MIBK and the combined extracts were dried over Na_2SO_4, filtered and most of the solvent was evaporated on a rotary evaporator. This oil was dissolved in 100 mL of absolute ethanol to which was added 1.68 mL (0.62 g, 20.0 mmol) of 47% aqueous formaldehyde solution. The reaction mixture was heated to about 40° C and 2.69 g (20.0 mmol) of CuCl was added followed by 3.58 g (20.0 mmol) of compound **3** dissolved in 100 mL of EtOH. This mixture was stirred under dry N_2 over the weekend. The solids were then filtered and washed with EtOH. Solvent was evaporated from the filtrate and the residues were taken up with EtOAc and water . The product was extracted into EtOAc, dried ($MgSO_4$) and evaporated to give crude material which was chromatographed on 100 g of silica gel using EtOAc as eluent to give the desired product which crystallized on standing. The yield was 2.94 g (41%), m.p. 62-64° C. A sample of the material was converted to the HCl salt and recrystallized from isopropanol for the analytical sample, m.p. 195.5-197.0° C. NMR ($CDCL_3$) ∂ 1.04 (6 H, s), 2.48 (4 H, s), 2.53 (4 H, t, J = 3), 3.28 (2 H, s), 3.80 (4 H, t, J = 3), 4.51 (2 H, s), 6.44 (1 H, t, J = 5), 8.27 (2 H, d, J = 5). Anal: C, H, N.

Preparation of 4,4-Dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]-2-butenyl]-2,6-piperidinedione **6.** A solution of 550 mg (1.55 mmol) of compound **5** in 30 mL of EtOAc was treated with 200 mg of Lindlar catalyst and 8 drops of quinoline. This mixture was hydrogenated at 1 atm until 1.1 theoretical equivalents of H_2 had been absorbed (about 20 min). TLC analysis of the reaction mixture showed, in addition to quinoline, a trace of compound **5** and a more polar product. This mixture was filtered and the solvent was evaporated. The residues were chromatographed on 25 g of silica gel, eluting with 9:1 EtOAc/MeOH , to give 376 mg (68%) of the pure product. An analytical sample was prepared by addition of a solution of HCl gas in ether to a solution of the compound in acetone, m.p. 243-244° C. NMR ($CDCL_3$) ∂ 1.04 (6 H, s), 2.47 (4 H, s), 2.53 (4 H, t, J = 3), 3.22 (2 H, d, J = 7), 3.84 (4 H, t, J = 3), 4.41 (2 H, d, J = 7), 5.47 (1 H, m), 5.61 (1 H, m), 6.42 (1 H, t, J = 5), 8.24 (2 H, d, J = 5). Anal: C, H, N.

Preparation of 4,4-Dimethyl-1-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione **7.** A solution of 500 mg (1.41 mmol) of compound **5** in 30 mL of EtOAc was treated with 100 mg of 5% Pd/C and hydrogenated at 1 atm. After two equivalents of H_2 had been absorbed, the catalyst was removed by filtration and the solvent was evaporated. The residue crystallized from ether to

give 341 mg (67%) of the desired product identical in all respects to an authentic sample of gepirone prepared by the published method (14). The melting point of this product and the mixed m.p. with authentic gepirone was 105-106° C . NMR ($CDCl_3$) ∂ 1.05 (6 H, s), 1.54 (4 H, m), 2.40 (2 H, m), 2.48 (8 H, broadened s), 3.73 - 3.86 (6 H, m), 6.44 (1 H, t, J = 5), 8.26 (2 H, d, J = 5).

Preparation of 4,4-Dimethyl-1-[2,3-dideutero-4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,6-piperidinedione **8.** A solution of 300 mg (0.84 mmol) of compound **6** in 10 mL of EtOAc was treated with 85 mg of 5% Pd/C and reduced in an atmosphere of D_2 gas. When the reduction was complete by TLC (9:1 EtOAc/MeOH), the catalyst was filtered off and the solvent was evaporated. The residues were crystallized from ether to give the product, 238 mg (79%), as colorless crystals, m.p. 105-106° C, mixed with authentic gepirone, m.p. 105-106° C. NMR ($CDCl_3$) ∂ 1.04 (6 H, s), 1.54 (2 H, m), 2.39 (2 H, m), 2.47 (8 H, broadened s), 3.74 - 3.90 (6 H, m), 6.43 (1 H, t, J = 5), 8.25 (2 H, d, J = 5).

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