Synthesis of 4-(4-Iodophenyl)piperazine and the 1-Carboxamidino Derivative

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The previously unreported 4-(4-iodophenyl)piperazine (**2**) was synthesized in a 70% yield and characterized. The reaction of **2** with *S*-methylthiouronium sulfate gave the corresponding carboxamidino derivative **4** in a 61% yield. The tlc properties of **4** were identical with those of the radioiodinated material that had been prepared and evaluated as a potential myocardial imaging radiopharmaceutical.

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As part of our program to develop new organ specific radiopharmaceuticals we have selected compounds containing the 4-phenylpiperazine moiety as substrates for radioiodination. This choice was predicated on the observations that the moiety was incorporated into a wide variety of biologically active compounds possessing selective mechanisms of action and that the phenyl ring, being activated by the disubstituted amine, would readily undergo electrophilic substitution reactions. Upon thorough examination of the literature we found that neither the parent compound, 4-(4-iodophenyl)piperazine, nor its 1-substituted derivatives, had been previously reported. We wish to describe the facile synthesis of the parent compound, and its characterization and subsequent conversion to the 1-carboxamidino derivative, the biodistribution of which has been previously reported [1].

The typical synthetic methods for the preparation of 4-(4-substituted aryl)piperazines involve the condensation of the appropriately substituted aniline with either bis(2-haloethyl)amine hydrochloride [2,3] or bis(2-hydroxyethyl)amine in the presence of acid [4,5]. Both methods involve elevated reaction temperatures in order to ensure ring closure to form the piperazine. When the reaction of 4-iodoaniline with bis(2-chloroethyl)amine hydrochloride or bis(2-hydroxyethyl)amine hydrochloride was attempted under these conditions only very low yields (<5%) of a material corresponding to the desired product could be isolated. Indeed, the reaction was accompanied by considerable darkening of the reaction mixture and the evolution of a reddish purple vapor, possibly resulting from the loss of the iodo group on the aromatic ring. Therefore, a milder reaction milieu and, indeed, an alternative procedure were required.

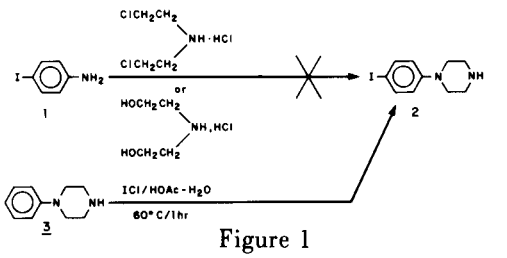

Figure 1

Because direct, stoichiometric halogenation of *N,N*-dialkylanilines had been previously reported to yield the *para*-monosubstituted product [6,7], an adaptation of this approach was employed. Using acetic acid-water (3:1) as the reaction medium, iodination of 4-phenylpiperazine with iodine monochloride at 60° for 1 hour gave good yields of the 4-(4-iodophenyl)piperazine dihydrochloride upon cooling. Alternatively neutralization of the reaction medium with aqueous sodium hydroxide followed by extraction gave the free base which was purified by recrystallization to remove the unreacted 4-phenylpiperazine. Heating at temperatures greater than 60°, *e.g.*, 90°, substantially reduced the yield of the products and resulted in more complex mixtures, while the use of lower reaction temperatures did not significantly improve the overall yield and required longer reaction times. Characterization of the isolated product confirmed substitution pattern and identity of the product.

Previously we had reported the tissue distribution of the ^{125}I-labeled derivative of 1-carboxamidino-4-phenylpiperazine which had been prepared by direct radioiodination. Although the nonlabeled material could be prepared in a similar fashion from 1-carboxamidino-4-phenylpiperazine and iodine monochloride, we wished to avoid the potentially difficult separation problems resulting from mixtures of the iodinated and noniodinated compounds. We therefore elected to react the 4-(4-iodophenyl)piperazine with the appropriate *S*-methylthiouronium salt to give the desired 1-carboxamidino-4-(4-iodophenyl)piperazine salt. The usual conditions for this reaction include heating the reactants at reflux in an alcoholic, aqueous or mixed aqueous-alcoholic medium [8-11]. Our attempts to obtain significant yields of the desired product using these conditions were unsuccessful because of the limited solubility of the reactants in the reaction solvent. Ultimately we chose dimethylsulfoxide as a solvent in which both the piperazine and *S*-methylthiouronium sulfate were soluble. Heating the reaction at 120° for 1 hour followed by cooling to ambient temperature resulted in the crystallization of the product as the sulfate salt. Characterization by ir, ^{1}H-nmr, and elemental analysis confirmed the structure assign-

ment. The radioactive material previously reported [1] co-migrated with the authentic material, establishing the structure of the radiopharmaceutical.

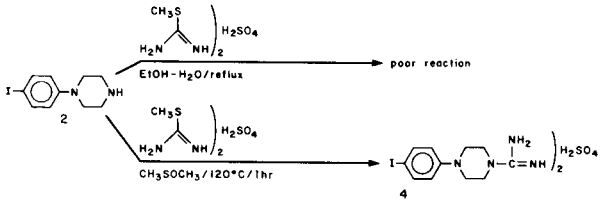

Figure 2

EXPERIMENTAL

Proton magnetic resonance spectra were obtained from a Varian T-60 spectrometer. Infrared spectra were obtained from a Perkin-Elmer Model 599 spectrophotometer. Mass spectra were obtained from a 12-90-G Nuclide mass spectrometer. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, NY. Melting points were determined using open capillaries in a Meltemp apparatus and are uncorrected.

4-(4-Iodophenyl)piperazine (**2**).

To a solution composed of 4-phenylpiperazine (4.86 g, 30 mmoles) in 7 ml of acetic acid-water (3:1) heated at 60° was added a solution of iodine monochloride (5.36 g, 33 mmoles) in 23 ml of acetic acid-water (3:1). The reaction was heated at 60° with stirring for 1 hour, then cooled to ambient temperature and stirred for an additional hour. The reaction mixture was poured over ice-water, treated with 20 ml of 1 *N* sodium thiosulfate and brought to *p*H 13 with 5 *N* sodium hydroxide. The resultant mixture was extracted with 3 × 100 ml of diethyl ether. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Crystallization from methanol-water gave 6.05 g (21 mmoles, 70%) of the product **2**, mp 122.0-124.0°; ir (potassium bromide): 2950, 2910, 2820, 1585, 1490, 1240, 830, 810 cm^{-1}; ^{1}H-nmr (deuteriochloroform-TMS): ppm 1.6 (s, 1H), 2.98 (br, s, 8H), 6.65 (d, 2H, J = 8 Hz), 7.30 (d, 2H, J = 8 Hz); ms: m/e = 288 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_2I$: C, 41.66; H, 4.51; N, 9.72. Found: C, 41.96; H, 4.73; N, 10.01.

1-Carboxamidino-4-(4-iodophenyl)piperazine Sulfate (**4**).

To a solution composed of **2** (0.576 g, 2.0 mmoles) in 30 ml of dry dimethyl sulfoxide was added *S*-methylthiouronium sulfate (0.556 g, 23 mmoles). The reaction was heated at 120° with stirring for 1 hour. Upon cooling to ambient temperature the product precipitated from the solution. The solid was collected by filtration, washed with cold water and crystallized from ethanol-water to give 0.461 g (0.61 mmoles, 61%) of **4**, mp 257-259°. The salt was converted to the free base with 5 *N* sodium hydroxide and extracted with dichloromethane. The organic layer was evaporated to dryness and the residue crystallized from ethyl acetate to give a colorless solid, mp 184-186°; ir (potassium bromide): 3020-3500 (br), 2850, 1630, 1580, 1490, 1240, 990, 820 cm^{-1}; ^{1}H-nmr (DMSO-d_6-TMS): ppm 3.13 (br, 4H), 3.27 (br, 4H), 3.80 (br, 3H), 6.70 (d, 2H, J = 8 Hz), 7.40 (d, 2H, J = 8 Hz); ms: m/e 330 (M^+).

Anal. Calcd. for $C_{22}H_{30}N_8I_2 \cdot H_2SO_4$: C, 34.83; H, 4.22; N, 14.78. Found: C, 35.17; H, 4.59; N, 14.46.

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