New Practical Synthesis of Prazosin

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A new four step synthesis of prazosin, 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline, has been described. The method is also adaptable for the preparation of other substituted 4-aminoquinazolines. The yields are good in every step and the reactions are performed with ease. Prazosin hydrochloride of high purity is obtained directly in the last step.

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Prazosin, 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (I), is a new highly active antihypertensive drug, which has achieved outstanding medical use during the last few years. Several methods for preparation of prazosin have been described in the patent literature. These methods are based either on the reaction of 2-chloro-4-amino- or 2-chloro-4-substitutedamino-6,7-dimethoxyquinazoline with 1-(2-furoyl)piperazine (1,2) or on the condensation of 3,4-dimethoxy-6-aminobenzonitrile with 1-cyano-4-(2-furoyl)piperazine in the presence of a basic catalyst (3). The yield of prazosin in these methods is in general low and purification of the product is difficult.

A new practical synthesis of prazosin is described in this paper. Also, some other substituted 4-aminoquinazolines have been successfully prepared according to this method (unpublished results).

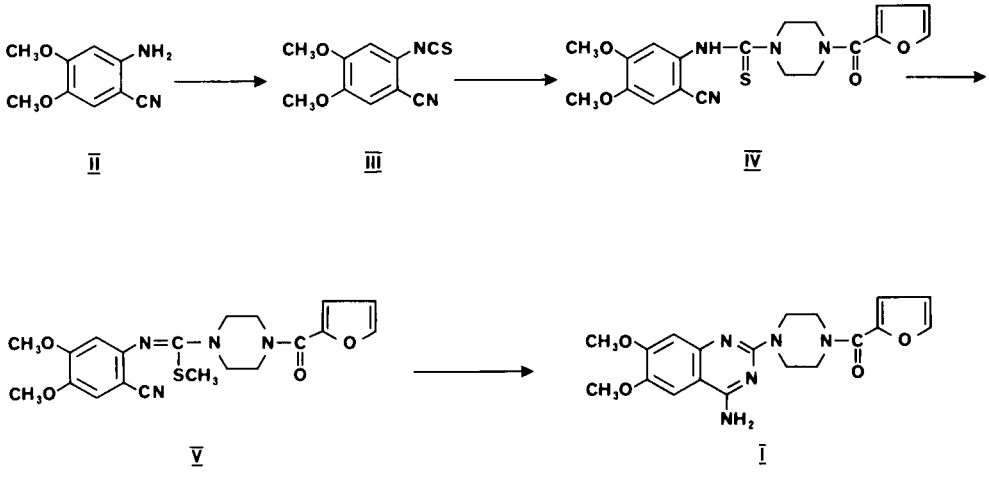
The new method used in the synthesis of prazosin is illustrated in Scheme 1. 3,4-Dimethoxy-6-isothiocyanatobenzonitrile (III) has been obtained in the usual way on treating 3,4-dimethoxy-6-aminobenzonitrile (II) with thiophosgene in a two-phase system (water-dichloromethane at 0-20°). Compound III is then allowed to react with 1-(2-furoyl)piperazine in ethyl acetate at 0-5° to give the thiourea derivative (IV). After methylation of IV with methyl iodide the free *S*-methyl isothiourea derivative (V) is liberated with a base. Product V is reacted with ammonia, ammonium chloride, urea or urea hydrochloride in formamide at 120°, whereupon intramolecular quinazoline ring formation occurs. When ammonium chloride or urea hydrochloride are used as the reacting compound, prazosine hydrochloride of high purity is obtained directly in good yield (85-86% of theoretical). When using ammonia or urea, the yield of free prazosin base is somewhat lower (65-70%).

Formamide has been found to be the solvent of choice in the last step. When DMF or other polar aprotic solvents are used the yield of prazosin is much lower and the reaction products contain several impurities. The role of formamide in this reaction remains uncertain. It is also very important to use ammonium chloride or urea hydrochloride in excess to obtain a good yield. The process allows for a problem-free, clean, large scale production of prazosin hydrochloride.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncor-

Scheme 1



II III IV V I

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rected. Elementary microanalyses were performed in Mikroanalytisches Laboratorium by Dr. Ilse Beetz, West Germany. The nmr spectra were measured on Perkin-Elmer R 12 A spectrometer using tetramethylsilane as internal standard. The mass spectra were recorded by Dr. J. Taskinen on Jeol JMS-D 100 mass spectrometer at 75 eV electron energy using a direxit inlet probe.

3,4-Dimethoxy-6-isothiocyanatobenzonitrile (III).

To a cooled (0-5°) mixture of 20.0 g. (0.2 mole) of calcium carbonate, 100 ml. of dichloromethane, 23.0 g. (0.2 mole) of thiophosgene and 200 ml. of water, was gradually added 27.0 g. (0.15 mole) of 3,4-dimethoxy-6-aminobenzonitrile in 150 ml. of dichloromethane. The mixture was stirred for 1 hour at 0-5° and thereafter 20 hours at 20°. The mixture was filtered and the organic layer separated and washed with water. The solvent was evaporated *in vacuo* and the crystalline residue was used in the next step without purification, yield 31.0 g. (94%), m.p. 126-127°; nmr (deuteriochloroform): δ 4.04 (s, 3H), 4.07 (s, 3H), 7.06 (s, 1H), 7.26 (s, 1H); ms: m/e (M^+) 220 (100%), 205 (59%), 177 (22%), 119 (27%).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72; S, 14.56. Found: C, 54.32; H, 3.75; N, 12.64; S, 14.38.

3,4-Dimethoxy-6-[4-(2-furoyl)piperazin-1-ylthiocarbamido]benzonitrile (IV).

A solution of 11.2 g. (0.051 mole) of III in 65 ml. of ethyl acetate was added gradually at 0-5° with stirring to a solution of 9.2 g. (0.051 mole) of 1-(2-furoyl)piperazine (3) in 65 ml. of ethyl acetate. The mixture was stirred for 20 hours at 0° and filtered. The crystals were washed with cold ethyl acetate and dried, yield 18.4 g. (90%), m.p. 176-180°; nmr (deuteriochloroform): δ 4.00 (s, 6H), 4.18 (s, 8H), 6.72 (dd, 1H, J_1 = 3.3 Hz, J_2 = 1.6 Hz), 7.53 (s, 1H), 7.27 (d, 1H, J_1 = 3.3 Hz), 7.53 (s, 1H), 7.78 (d, 1H, J_2 = 1.6 Hz), 8.23 (s, 1H); ms: m/e (M^+) 400 (0%), 220 (100%), 205 (57%), 180 (16%), 177 (21%), 119 (27%), 95 (81%), 85 (29%), 69 (81%), 56 (52%).

Anal. Calcd. for $C_{19}H_{20}N_4O_4S$: C, 56.99; H, 5.03; N, 13.99; S, 8.01. Found: C, 57.41; H, 5.39; N, 14.14; S, 7.68.

Methyl *N*-(3,4-Dimethoxy-6-cyanophenyl)-[4-(2-furoyl)piperazin-1-yl]thioformamidate (V).

To a stirred mixture of 20.0 g. (0.05 mole) of IV in 200 ml. of ethyl acetate, 14.2 g. (0.1 mole) of methyl iodide was added. The mixture was heated for 20 hours at 60°, cooled and treated with 80 ml. of 5% aqueous sodium hydroxide solution. The organic phase was separated, washed with water and evaporated *in vacuo* to dryness, yield 19.9 g. (95%), m.p. 105-107°; nmr (deuteriochloroform): δ 2.21 (s, 3H), 3.85 (s, 14H), 6.56 (s, 2H), 7.01 (s, 1H), 7.11 (d, 1H, J = 3.3 Hz), 7.56 (d, 1H, J = 1.6 Hz); ms: m/e (M^+) 414 (41%), 367 (31%), 340 (10%), 235 (12%), 220 (13%), 205 (10%), 179 (13%), 164 (39%), 95 (100%).

Anal. Calcd. for $C_{20}H_{22}N_4O_4S$: C, 57.96; H, 5.36; N, 13.52; S, 7.73. Found: C, 58.01; H, 5.54; N, 13.72; S, 7.53.

2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline Hydrochloride (I).

A mixture of 275 g. (0.66 mole) of V, 700 g. (13 moles) of ammonium chloride and 2750 ml. of formamide was stirred for 20 hours at 120° in a stream of nitrogen gas. The mixture was cooled to 80° and 1370 ml. of cold water was added. The precipitate was filtered, washed with water and acetone. The water of crystallization was removed by azeotropic distillation with dichloromethane and the product was dried *in vacuo*, yield 232-235 g. (85-86%), m.p. 280-282° (lit. (1,2,3) m.p. 278-280°); nmr (deuteriochloroform-DMSO-d_6): δ 3.38 (s, 14H), 6.57 (dd, 1H, J_1 = 3.3 Hz, J_2 = 1.6 Hz), 6.79 (s, 1H), 6.99 (d, 1H, J_1 = 3.3 Hz), 7.01 (s, 2H), 7.43 (s, 1H), 7.74 (d, 1H, J_2 = 1.6 Hz); ir (potassium bromide): 3319, 3226, 3077, 2857, 1634, 1597, 1481, 1468, 1425, 1280, 794, 763, 751, 721, 717, 675 cm^{-1}.

REFERENCES AND NOTES

(1) H. J. Hess, *U.S. Patent,* 3,511,836 (1970); *U.S. Patent,* 3,935,213 (1973).

(2) P. D. Hamnen, *German Patent Application* 2,725,019 (1976).

(3) N. T. Nauta, *Netherlands Patent* 7,206,067 (1972).