Quinazolines. XXV*
The Synthesis of 8-Chloro-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine Hydrochloride (8-Chloroprazosin Hydrochloride)

Wilfred L. F. Armarego[A] *and Phillip A. Reece*[B]

[A] John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra City, A.C.T. 2601.
[B] Department of Clinical Pharmacology, The Queen Elizabeth Hospital, Woodville, S.A. 5011.

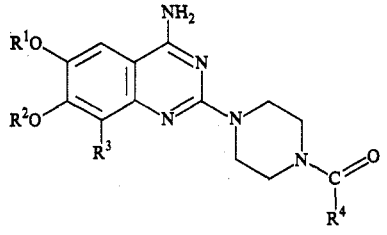
Abstract

A twelve-step synthesis of 8-chloroprazosin (3) hydrochloride starting from vanillin has been achieved in 16% overall yield (59% w/w yield). The hydrochloride is a useful internal standard for the quantitative estimation of the drug prazosin in human plasma.

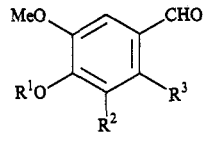
Prazosin, 2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (1), hydrochloride is an antihypertensive drug that is used clinically,[1] and is dispensed under the trade names Minipress, Hypovase and Sinetens.[2] Nanogram quantities of this drug are found in human plasma after oral administration and can be determined by high performance liquid chromatography (h.p.l.c.) with fluorescence detection, after a suitable extraction procedure.[3,4] For the accurate quantitative estimation of the drug in tissues an appropriate internal standard is necessary. A good internal standard needs to be readily available, stable, and should have a chemical structure which is similar to that of the drug so that it can be similarly isolated from tissue fluid. It should also possess a retention time on an h.p.l.c. column which will allow it to be separated completely from the drug and other substances extractable from the fluid. Compound (2) was used as internal standard in a reported h.p.l.c. assay[4] but was unsatisfactory because it did not sufficiently resemble prazosin in structure.[3] In looking for an alternative standard we have adopted a synthesis which can be used to prepare a variety of quinazolines related to prazosin (1) in which the general structure (1) is retained but with various R^2 and R^3 groups. The synthesis is straightforward and follows a route which is similar to the one reported by Althuis and Hess.[5] However, we are describing here in some detail the synthesis of one related compound, the 8-chloro derivative (3), so that it can be readily prepared by anyone contemplating its use. We have found that 8-chloroprazosin hydrochloride possesses the desired properties for the internal standard that we were seeking.

* Part XXIV, *Aust. J. Chem.*, 1979, **32**, 1805.

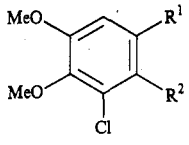
[1] Stokes, G. S., and Weber, M. A., *Br. Med. J.*, 1974, **2**, 298; Graham, R. M., Thornell, I. R., Gain, J. M., Bagnoli, C., Oates, H. F., and Stokes, G. S., *Br. Med. J.*, 1976, **2**, 1293.
[2] Treleaven, G. K., (Ed.) 'Prescription Proprietaries Guide' Aust. Pharm. Publ. Co., Suppl. No. 4, 1979, p. 108.
[3] Reece, P. A., *J. Chromatogr.*, 1980, **221**, 188.
[4] Twomey, T. M., and Hobbs, D. C., *J. Pharm. Sci.*, 1978, **67**, 1468.
[5] Althuis, T. H., and Hess, H.-J., *J. Med. Chem.*, 1977, **20**, 146.



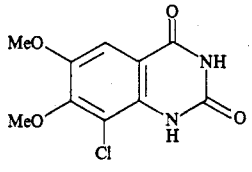
	R^1	R^2	R^3	R^4
(1)	Me	Me	H	2-furyl
(2)	Me	Me	OMe	$OCH_2C(Me)=CH_2$
(3)	Me	Me	Cl	2-furyl



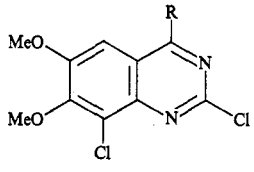
	R^1	R^2	R^3
(4)	H	Cl	H
(5)	Me	Cl	H
(6)	Me	Cl	NO_2



	R^1	R^2
(7)	CO_2H	NO_2
(8)	H	NO_2
(9)	COCl	NO_2
(10)	$CONH_2$	NO_2
(11)	$CONH_2$	NH_2
(12)	$CONH_2$	$NHCONH_2$



(13)



(14) R = Cl
(15) R = NH_2

Chlorination of vanillin by a modification of Menke and Bentley's method[6] gave high yields (>90%) of 5-chlorovanillin (4). Methylation of the latter proved troublesome and was finally achieved by using excess of dimethyl sulfate, sodium hydrogen carbonate and potassium carbonate at 70°, and adjusting the pH of the solution to 8. This gave 5-chloroveratraldehyde (5) in over 80% yields. Attempts to alkylate with diazomethane or to use the phase transfer catalysis method[7] failed, most probably because of steric hindrance from the two *ortho* substituents. Nitration of the aldehyde (5) with fuming nitric acid according to the general method of Raiford and Floyd[8] gave a 52% yield of 5-chloro-3,4-dimethoxy-6-nitrobenzaldehyde (6). The crude nitration product contained much acidic material which was removed by recrystallization from acetic acid, and the ^1H n.m.r. spectrum indicated partial demethylation and oxidation. The nitro aldehyde (6) was oxidized to the corresponding 5-chloro-3,4-dimethoxy-6-nitrobenzoic acid (7) by the method of Althuis and Hess[5] (10% aqueous $KMnO_4$–acetone) and, less conveniently, by the general method

[6] Menke, A. E., and Bentley, W. E., *J. Am. Chem. Soc.*, 1898, **20**, 316; Raiford, L. C., and Lichty, J. G., *J. Am. Chem. Soc.*, 1930, **52**, 4576.
[7] McKillop, A., Fiand, D. E., and Hug, R. P., *Tetrahedron*, 1970, **30**, 1752.
[8] Raiford, L. C., and Floyd, D. E., *J. Org. Chem.*, 1943, **8**, 358.

described by Raiford and Floyd[8] (5% aqueous $KMnO_4$–pyridine). In both cases the oxidation was incomplete, even with excess of oxidant, but the starting material can be extracted out of an alkaline solution and recycled satisfactorily.

The above nitrobenzoic acid (7) obtained by both methods melted 16° higher than the acid reported,[8] and this fact casts some doubts on its structure and those of its precursors. Comparison of the melting points of the intermediates (4) and (5) with the isomeric chlorovanillins and chloroveratraldehydes was uninformative because some of the isomers had values which were close to each other. The aromatic protons in the ^1H n.m.r. spectra of compounds (4) and (5) appeared as two doublets in each case with coupling constants of 1·4 (±0·3) Hz and 1·6 (±0·2) Hz respectively. Unfortunately these *J* values are on the borderline of the *para* (0·2 to 1·5 Hz) and the *meta* (1·2 to 3·1 Hz) range of coupling constants.[9] The constitution of the acid (7) was established by decarboxylation in boiling quinoline containing a trace of copper bronze, which gave a small amount of 2-chloro-3,4-dimethoxy-1-nitrobenzene (8). This had a ^1H n.m.r. spectrum which showed two *ortho* aromatic protons with *J* values of 8·0 Hz (the range for *ortho* aromatic protons is 6·0 to 9·4 Hz).[9] Also, catalytic reduction of the acid (7) with 50% palladium-on-charcoal gave 3,4-dimethoxyanthranilic acid with a ^1H n.m.r. spectrum that showed two *para* aromatic protons with *J* values less than 0·6 Hz, i.e. unresolved.

The acid (7) was converted into the acid chloride (9) which reacted with liquid ammonia to produce 5-chloro-3,4-dimethoxy-6-nitrobenzamide (10) in 98% overall yield. Reduction of the amide with iron and acetic acid gave the anthranilamide (11). Attempts to convert this amide into 8-chloro-6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione (13) by heating with urea in pyridine (method of Althuis and Hess) failed and all the starting material was recovered.[5] On the other hand, the amide (11) reacted with sodium cyanate (method of Curd, Landquist and Rose)[10] to form 5-chloro-3,4-dimethoxy-6-ureidobenzamide (12) almost quantitatively. The latter liberated ammonia in 2 N sodium hydroxide and formed the quinazolinedione (13) on final acidification. Chlorination of the dione (13) with phosphoryl chloride gave 2,4,8-trichloro-6,7-dimethoxyquinazoline (14) which reacted with ammonia to form 2,8-dichloro-6,7-dimethoxyquinazolin-4-amine (15). This amine condensed with 1-(2-furoyl)piperazine in boiling isopentyl alcohol to give 8-chloro-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (3) hydrochloride. The yields of all the steps except for the nitration reaction (52%) are better than 73%. The overall yield is 15·8%, and because there is a considerable increase in weight (the molecular weights of vanillin and the hydrochloride of (3) are 152 and 565 respectively) the w/w yield (58·7%) is very favourable. With slight modification of this synthesis it should be possible to prepare a variety of quinazolines related to (1) having different R^2 groups, e.g. by altering the alkylating agent in the second step, and the halogen atom can be removed at a later stage or not be introduced in the first place, or a different halogen atom may be introduced.

Under the chromatographic conditions recently described for the assay of prazosin,[2] compounds (1), (2) and (3) had retention times of 350, 1270 and 625 s

[9] Jackman, L. M., and Sternhell, S., 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' 2nd Edn, p. 306 (Pergamon: Oxford 1969).
[10] Curd, F. H. S., Landquist, J. K., and Rose, F. L., *J. Chem. Soc.*, 1948, 1759.

respectively. The shorter retention time of compound (3) made it a more convenient internal standard than the allylic ester (2). There were no interferences by plasma components of other drugs and their metabolites with either compounds (1) or (3) in the modified assay.[3]

Experimental

Microanalyses were carried out by the Australian National University Analytical Services Unit. I.r. spectra (KBr discs) were measured on a Unicam SP 1050 spectrometer, and only the bands that were tentatively assigned were reported. ^{1}H n.m.r. spectra were measured on a Varian T60A instrument (chemical shifts in δ and coupling constants in Hz) in $(CD_3)_2SO$ and locked on Me_4Si ($\delta = 0$) unless otherwise stated.

5-Chloro-3,4-dimethoxybenzaldehyde (*5*)

5-Chlorovanillin (20 g, m.p. 169–170°) [prepared by bubbling chlorine through a solution of vanillin in chloroform,[6] and recrystallizing from acetic acid (lit.[6] 164–165°); it had ν_{max} 3320 (OH br), 2860 (aldehyde CH), 1685 (C=O), 680 (C–Cl) cm^{-1}; and ^{1}H n.m.r. 3·97 (s, 3-MeO, 4-MeO), 7·47 (d, H2, *J* 1·4), 7·63 (d, H6, *J* 1·4), 9·83 (s, CHO)] in water (100 ml) containing sodium hydrogen carbonate (80 g) and potassium carbonate (10 g) was stirred at 70–80°. Dimethyl sulfate (20 ml) was added, and after stirring for 20 min a further quantity of dimethyl sulfate (10 ml) was added and this was repeated three times. As the solution became acidic solid potassium carbonate was added to maintain the pH to *c.* 8. Frothing was moderated by dropwise addition of ether. The solution was cooled to 10° and the solid (15 g) was collected and dried. A further quantity (2·4 g, 81% total yield) was obtained by stirring the filtrate at 70–80° with dimethyl sulfate (10 ml) for 1 h and adjusting the pH to 8 by addition of potassium carbonate. The crude aldehyde had m.p. 52–55° (lit.[11] 54–55°) and ν_{max} 2950 (methoxy CH), 2840 (aldehyde CH), 1700 (C=O), 670 (C–Cl) cm^{-1}; and ^{1}H n.m.r. 3·88 (s, 3-MeO), 3·95 (s, 4-MeO), 7·52 (d, H2, *J* 1·6), 7·67 (d, H6, *J* 1·6), 9·93 (s, CHO); and was suitable for the next step.

5-Chloro-3,4-dimethoxy-6-nitrobenzaldehyde (*6*)

The aldehyde (5) (17 g) was added slowly to fuming nitric acid (70 g, *d* 1·5) at 0–10° (mostly at 8°) with stirring because a solid started to separate after about 12 g of aldehyde was added. The solution was stirred for 15 min, poured onto crushed ice (210 g), and the yellow solid was collected, washed with water and dried to give the crude nitro derivative (15·7 g). The solid was dissolved in hot acetic acid (25 ml), filtered (quartz wool), and gave large plates of pure nitrobenzaldehyde (5) (10·8 g, 52%), m.p. 122–123° [lit.[8] 122–123° (from dilute acetic acid; we found that this solvent gave impure product)]; ν_{max} 3100 and 2960 (methoxy CH), 2860 (aldehyde CH), 1710 (C=O), 1542 and 1320 (NO_2), 620 (C–Cl) cm^{-1}; ^{1}H n.m.r. 3·93 (s, 3-MeO), 4·00 (s, 4-MeO), 7·70 (s, H2), 9·67 (s, CHO).

5-Chloro-3,4-dimethoxy-6-nitrobenzoic Acid (*7*)

The nitro aldehyde (6) (10 g) in acetone (180 ml) was added dropwise to a hot (*c.* 60°) aqueous solution of 10% potassium permanganate (120 ml) under a reflux condenser (*c.* 40 min). The solution was stirred at reflux temperature until the colour was discharged (40–60 min), and the black solid (MnO_2) was filtered off (Celite). The residue was washed with hot acetone (100 ml) and hot water (2 × 100 ml). The combined filtrates were evaporated to remove acetone and the pH of the residual solution was adjusted to 11–12 with a few drops of 2 N sodium hydroxide and extracted with chloroform (3 × 50 ml). The dried extract (Na_2SO_4) was evaporated and gave the starting material (1·73 g, 17·3%). The aqueous solution was acidified with hydrochloric acid and the white solid was collected, washed with water, and dried first at 70° then at 100° to give pure nitrobenzoic acid (8·1 g, 92%), m.p. 206–207° (lit.[8] 190–191°), which crystallized from hot ethanol diluted with six volumes of water (Found: C, 41·2; H, 3·3; Cl, 13·7; N, 5·2. $C_9H_8ClNO_6$ requires C, 41·3; H, 3·1; Cl, 13·6; N, 5·4%). ν_{max} 3000 (OH br), 1710 (CO_2H), 1550 and 1330 (NO_2), 700 (C–Cl) cm^{-1}; ^{1}H n.m.r. 3·82 (s, 3-MeO), 3·90 (s, 4-MeO), 7·37 (s, H2).

[11] Wittmer, F. B., and Raiford, L. C., *J. Org. Chem.*, 1945, **10**, 527.

5-Chloro-3,4-dimethoxy-6-nitrobenzamide (*10*)

The preceding acid (7) (8 g) in thionyl chloride (80 ml) was boiled under reflux overnight and excess of solvent was removed in a vacuum. The residual solid was cooled in liquid nitrogen and liquid ammonia (100 ml) was added carefully to it. The ammonia was evaporated off, the residue was suspended in water (50 ml), collected, dried at 100°, and crystallized from ethanol to give the *amide* (7·83 g, 98%), m.p. 205–206° (mixed m.p. with the acid (7) was 180–185°) (Found: C, 41·6; H, 3·5; Cl, 13·8; N, 10·6. $C_9H_9ClN_2O_5$ requires C, 41·5; H, 3·5; Cl, 13·6; N, 10·7%). ν_{max} 3420 and 3200 (NH), 3012 and 2950 (CH), 1675 (C=O), 1540 and 1358 (NO_2), 640 (C–Cl) cm^{-1}; ^1H n.m.r. 3·87 (s, 3-MeO), 4·00 (s, 4-MeO), 7·45 (s, H2), 7·57 (br s, NH), 8·23 (br s, NH).

6-Amino-5-chloro-3,4-dimethoxybenzamide (*11*)

The nitrobenzamide (10) (6·4 g) in acetic acid (150 ml) was heated to 90°, and iron powder (3·7 g) was added with stirring during 20 min and the temperature was allowed to rise to 105°. After further heating for 15 min the mixture was filtered and the solid was washed with hot acetic acid (30 ml). The combined filtrates were poured into ice-cold water (600 ml) and a colourless solid crystallized out on stirring. The solid, m.p. 172–173°, was collected, dried and recrystallized from methanol to give the *amino amide* (4·8 g, 85%) m.p. 174–175° (Found: C, 47·0; H, 4·9; Cl, 15·7; N, 12·0. $C_9H_{11}N_2O_3$ requires C, 46·9; H, 4·8; Cl, 15·4; N, 12·1%). ν_{max} 3488 and 3420 (NH_2), 3375 and 3200 (amide NH_2), 2955 and 2845 (methoxy CH), 1650 (C=O), 710 (C–Cl) cm^{-1}; ^1H n.m.r. 3·73 (s, 3-MeO, 4-MeO), 6·37 (br s, NH_2), 7·20 (s, H2), 7·37 (br s, $CONH_2$).

5-Chloro-3,4-dimethoxy-6-ureidobenzamide (*12*)

The above amide (11) (3·76 g) in acetic acid (56 ml) was treated with a solution of sodium cyanate (2·1 g) in water (18 ml). The mixture was clear, but after 3–4 min a white solid crystallized out. When crystallization was complete (*c.* 15 min) the mixture was diluted with water (50 ml) and the solid was collected, washed with water and dried at 100° to give the pure *ureido amide* (4·4 g, 99%), m.p. 222–223° (effervescence) (Found: C, 43·9; H, 4·5; Cl, 13·0. N, 15·1. $C_{10}H_{12}ClN_3O_4$ requires C, 43·9; H, 4·4; Cl, 13·0; N, 15·4%). ν_{max} 3440 and 3320 (NH), 2950 (CH), 1665 and 1600 (C=O), 640 (C–Cl) cm^{-1}; ^1H n.m.r. 3·77 (s, 3-MeO), 3·85 (s, 4-MeO), 6·08 (s, urea NH_2), 7·17 (s, H2), 7·47 (s, amide NH), 7·70 (s, amide NH), 7·98 (s, urea NH).

8-Chloro-6,7-dimethoxyquinazoline-2,4(1H,3H)-dione (*13*)

The urea (12) (5·3 g) in 2 N sodium hydroxide (150 ml) was heated on a steam bath until evolution of ammonia ceased (30 min). Although the solution did not become clear, the nature of the solid had altered during the reaction. The mixture was diluted with water (300 ml) and the pH of the stirred solution was adjusted to 1·0 with hydrochloric acid. The solid was collected, washed thoroughly with water and dried at 100° to give pure *quinazolinedione* (4·76 g, 95%), m.p. 240–241° (effervescence) (Found: C, 46·5; H, 3·6; Cl, 13·7; N, 10·9. $C_{10}H_9ClN_2O_4$ requires C, 46·8; H, 3·5; Cl, 13·8; N, 10·9%). ν_{max} 3190 and 3060 (NH), 2840 (CH), 1750 (C=O), 645 (C–Cl) cm^{-1}; ^1H n.m.r. 3·88 (s, 6-MeO, 7-MeO), 7·47 (s, H5), 10·27 (br s, H1), and 11·23 (br s, H3).

2,4,8-Trichloro-6,7-dimethoxyquinazoline (*14*)

The quinazolinedione (13) (4·7 g) and diethylaniline (5·7 g) in phosphoryl chloride (60 ml) was boiled under reflux for 4 h, stirred overnight at 20° and evaporated in a vacuum. The residue was treated with water, collected and dried in a vacuum to give the *trichloroquinazoline* (5·33 g, 99%), m.p. 172–173°, which was used directly in the next step. Recrystallization from benzene/light petroleum, b.p. 40–60°, did not alter the m.p. (Found: C, 41·1; H, 2·3; Cl, 36·2; N, 9·7. $C_{10}H_7Cl_3N_2O_2$ requires C, 40·9; H, 2·4; Cl, 36·2; N, 9·5%). ν_{max} 2960 (CH), 1605 (C=N), 800 and 778 (C–Cl) cm^{-1}; ^1H n.m.r. ($CDCl_3$) 4·03 (s, 6-MeO, 7-MeO), 7·30 (s, H5).

2,8-Dichloro-6,7-dimethoxyquinazolin-4-amine (*15*)

Dry ammonia was bubbled through a solution of the above trichloroquinazoline (5·3 g) in tetrahydrofuran (120 ml) at 0° for 30 min and set aside overnight. The solid was collected, washed with water and dried at 100° for 2 h to give the *quinazolinamine* (3·8 g, 77%), m.p. 258–259° (effervescence) after recrystallization from methanol (Found: C, 43·8; H, 3·3; Cl, 25·6; N, 15·0.

$C_{10}H_9Cl_2N_3O_2$ requires C, 43·8; H, 3·3; Cl, 25·9; N, 15·3%). ν_{max} 3520 and 3130 (NH_2 br), 2960 (CH), 1655 (C=N), 778 and 710 (C–Cl) cm^{-1}; ^1H n.m.r. 3·87 (s, 6-MeO), 3·93 (s, 7-MeO), 7·70 (s, H 5), 8·23 (br s, NH_2).

8-Chloro-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine Hydrochloride (8-Chloroprazosin Hydrochloride)

1-(2-Furoyl)piperazine (1·36 g, 1·1 mol equiv., m.p. 66–67°, prepared from 2-furoyl chloride and piperazine monohydrobromide)[5] and 2,8-dichloro-6,7-dimethoxyquinazolin-4-amine (1·88 g, 1 mol equiv.) in isopentyl alcohol (90 ml) were boiled for 2·5 h (all the solid appeared to have separated after *c.* 1·5 h). The solution was cooled and filtered. The *hydrochloride* (2·81 g, 73%) was collected, washed with ether and dried at 100°, and had m.p. 205–206° (effervescence). After recrystallization by dissolving in methanol (300 ml) and adding 8 M methanolic hydrogen chloride (1 ml) followed by ether until crystallization was complete, the salt had m.p. 207–208° (effervescence) (Found: C, 49·6; H, 4·5; Cl, 15·2; N, 14·8. $C_{19}H_{20}ClN_5O_4HCl,0·5H_2O$ requires C, 49·6; H, 4·8; Cl, 15·3; N, 15·1%). ν_{max} 3440 and 3120 (NH_2 br), 1630 (C=O), 1590 (C=N), 766 (C–Cl) cm^{-1}; ^1H n.m.r. (90 MHz) 3·87 (s, 6-MeO), 3·91 (s, piperazine H 2′,3′,5′,6′), 3·92 (s, 7-MeO), 6·62 (q, *J* 1·7, 3·4, furan H 4″), 7·05 (q, *J* 0·7, 3·4, furan H 3″), 7·83 (q, *J* 0·7, 1·7, furan H 5″), 7·98 (s, quinazoline H 5), 9·02 (br s, NH_2).

Acknowledgment

We thank Pfizer Pty Ltd, West Ryde, Australia, for a grant to assist with these studies.

Manuscript received 30 January 1981