Synthesis of 2-Aroylpiperazinyl-4-alkoxyquinazolines by Phase-Transfer-Catalysed Heteroaromatic Nucleophilic Substitution [1]

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A series of quinazolines, with cardiovascular activity, having 2,3-dihydroxypropoxy or 2-hydroxy-3-*t*- butylaminopropoxy groups substituted at the 4-position and chlorine or 2-aroylpiperazinyl groups at the 2-position have been synthesized. The introduction of the alkoxy substituent at C-4 was carried out under phase-transfer catalysis conditions.

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Symbiotic approaches to drug design based on the incorporation of two mutually complementary biological activities into one entity have been described [2].

In an effort to develop new antihypertensive agents we have carried out the introduction of a β-adrenergic blocking moiety [3] in a quinazoline derivative related to Prazosin [4], by heteroaromatic nucleophilic substitution (S_NHet-Ar) reactions, under phase-transfer catalysis (PTC) conditions.

The application of PTC to S_NHet-Ar employing alkoxide anions is very recent, and only a few cases have been described on 2-chloropyridine derivatives [5-7].

We now report here the substitution reactions of 2,4-dichloro-6,7-dimethoxyquinazoline (**1**) [8] with alcohols **2** [9] and **3** [10], synthons of pharmacophore moieties 2,3-dihydroxy- and 2-hydroxy-3-*tert*-butylaminopropoxy [3], under conventional liquid-liquid PTC conditions. Thus, when the reactions were carried out by stirring at room temperature of a mixture of the substrates in chlorobenzene and 20% aqueous sodium hydroxide using tetrabutylammonium bromide as catalyst the substitution products at C-4, **4** and **5** were selectively obtained in good yields. No substitution at C-2 was detected.

The reaction of **1** with the diastereoisomeric mixture **3** [10] affords the two possible diastereoisomers **5a** and **5b**, which were separated by fractional recrystallization from acetonitrile.

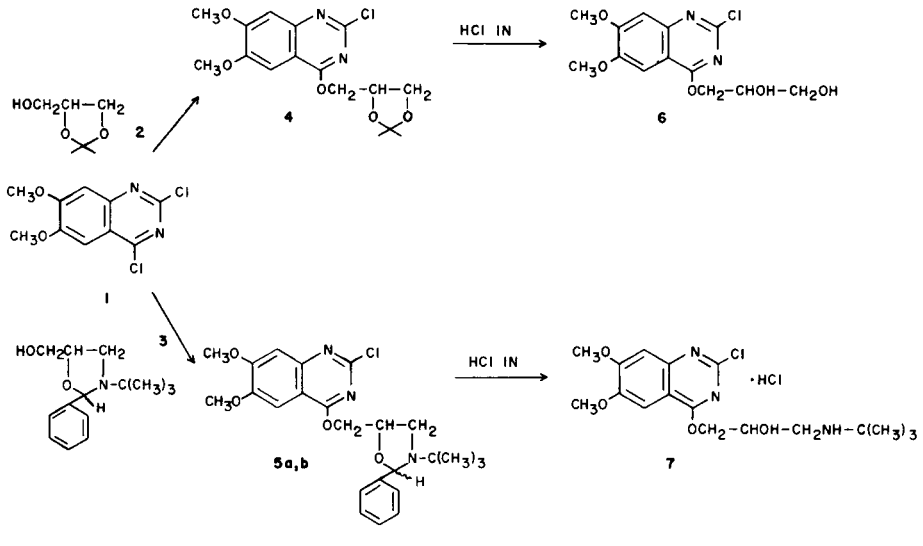
Hydrolysis of **4** and **5** with 1*N* hydrochloric acid gave hydroxy compounds **6** and **7** respectively, in good yields.

Substitution of the chlorine at C-2 in **4** and **5** was accomplished by heating with the appropriate aroylpiperazine **8a-c** [11] in isoamyl alcohol as solvent at reflux temperature. Subsequent treatment with 1*N* hydrochloric acid of the crude reaction products gave quinazolines **10a-c** as chlorhydrates and **12a-c** as dichlorhydrates in good yields (Table 1, Method A).

In the case of **4** it was also possible to isolate the corresponding reaction intermediates **9a-c**, with an intact isopropylidene group, before acid treatment (Table 1, Method B). The analogous benzylidene derivatives **11a-c** could not be isolated.

In the reactions of **4** and **5** with aroylpiperazines, **8a-c**, corresponding 2-(4-aroylpiperazin-1-yl)-4-isopentyloxy-6,7-dimethoxyquinazolines were also isolated as by-products in poor yield (5-10%). These originated by substitution at C-4 by isoamyl alcohol.

SCHEME I



SCHEME 2

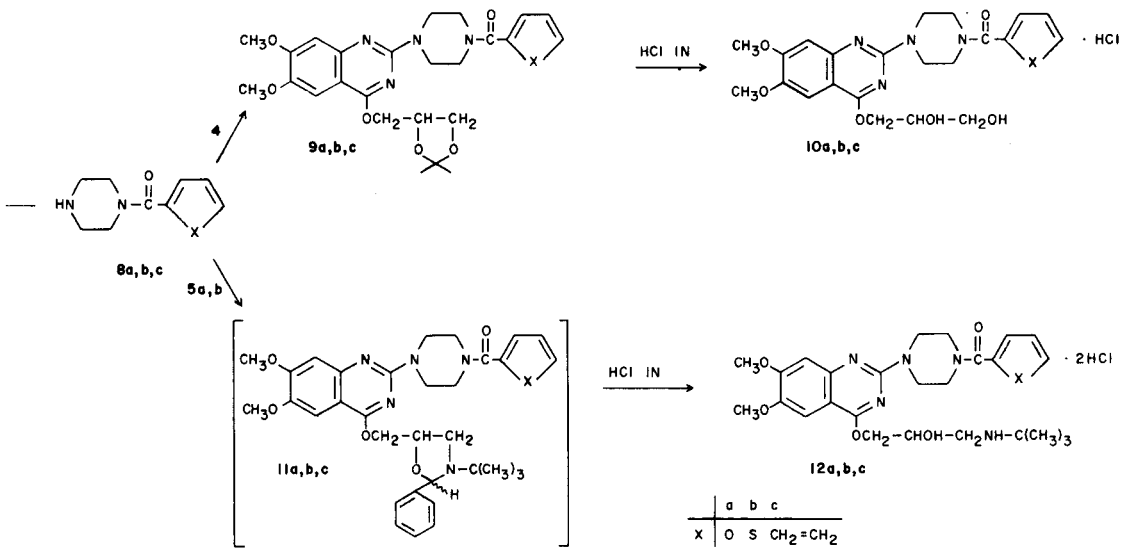


Table 1

Yields, Physical and Analytical Data of 2-Aroylpiperazinyl-4-alkoxyquinazolines **9**, **10** and **12**

Compound	Methode	Yield (%)	Mp (°C)	Formula (molecular weight)	Analysis % Calcd./Found [a] C	H	Cl	N	S
9a	B	31	165-173	$C_{25}H_{30}N_4O_7$	60.23	6.07		11.24	
				(498.5)	60.19	6.07		11.51	
9b	B	20	197-200	$C_{25}H_{30}N_4O_6S$	58.35	5.88		10.89	6.23
				(514.6)	58.26	6.03		10.85	6.07
9c	B	30	110-112	$C_{27}H_{32}N_4O_6$	63.77	6.34		11.02	
				(508.6)	63.84	6.60		10.80	
10a	A	82	197-198	$C_{22}H_{27}ClN_4O_7$	53.39	5.50	7.16	11.32	
	B	52		(494.9)	53.16	5.31	7.51	11.39	
10b	A	86	190-195	$C_{22}H_{27}ClN_4O_6S$	51.70	5.33	6.94	10.96	6.27
	B	67		(510.9)	51.42	5.02	6.82	11.05	6.15
10c	A	83	198-200	$C_{24}H_{29}ClN_4O_6$	57.09	5.79	7.02	11.10	
	B	56		(505.0)	57.06	5.75	7.03	11.11	
12a	A	61	188-192	$C_{26}H_{37}Cl_2N_5O_6$	53.24	6.37	12.09	11.94	
				(586.5)	52.96	6.09	12.44	12.06	
12b	A	56	197-199	$C_{26}H_{37}Cl_2N_5O_5S$	51.82	6.19	11.77	11.62	5.32
				(602.6)	51.63	6.47	12.16	11.66	5.70
12c	A	58	198-203	$C_{28}H_{39}Cl_2N_5O_5$	56.37	6.59	11.89	11.74	
				(596.6)	56.34	6.58	12.25	11.75	

[a] Found values were corrected for the non-stoichiometric hydration water as follows: (compound, $\%H_2O$) **10a**, 6.1%; **10b**, 4%; **10c**, 2.5%; **12a**, 7.7%; **12b**, 4.2%; **12c**, 4.4%. The corrected values were in satisfactory agreement with the calculated.

The analytical, physical and spectral data of all products (Tables 1 and 2) are consistent with the proposed structures.

Application of PTC to S_NHet-Ar using alkoxides in other heterocyclic systems such as pyridine and pyridazinone has been developed by us [7] and will be reported.

EXPERIMENTAL

Melting points (mp) were taken on a Büchi 510 capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 257 spectrophotometer. Ultraviolet (uv) spectra were taken on a Beckman DB-GD spectrophotometer. Proton magnetic resonance (^{1}H-nmr) spectra were recorded on a Varian EM-360L instrument. Chemical shifts are reported as δ units in parts per million downfield from internal tetramethylsilane.

2-Chloro-4-(*O,O*-isopropylidene-2,3-dihydroxypropoxy)-6,7-dimethoxyquinazoline (**4**).

A solution of isopropylideneglycerol [9] (**2**, 8 g, 0.06 mole) in chlorobenzene (100 ml) was added to a well-stirred mixture of 2,4-dichloro-6,7-dimethoxyquinazoline [8] (**1**, 15 g, 0.058 mole), tetrabutylammonium

Table 2

IR, ^{1}H-NMR and UV Spectral Data of Compounds **9**, **10** and **12**

Compound	IR (potassium bromide) ν max cm^{-1}	^{1}H-NMR δ (ppm) [a]	UV (ethanol) λ max nm (log ϵ)
9a	1627, 1595, 1570	(Deuteriochloroform) 7.50 (m, 1H, 5'-CH), 7.22 (s, 1H arom), 7.08 (m, 2H, 1H arom, 3'-CH), 6.48 (dd, 1H, 4'-CH), 4.9-4.3 (m, 3H, $ArOCH_2CH$), 4.3-3.6 (m, 10H, NCH_2, OCH_2), 3.97, 3.93 (2s, 6H, OCH_3), 1.50, 1.41 (2s, 6H, CH_3)	250 (4.8), 218 (4.6)
9b	1620, 1592, 1579	(Deuteriochloroform) 7.6-6.9 (m, 5H, 3'-CH, 4'-CH, 5'-CH, 2H arom), 4.8-4.3 (m, 3H, $ArOCH_2CH$), 4.3-3.6 (m, 10H, NCH_2, OCH_2), 3.98, 3.92 (2s, 6H, OCH_3), 1.50, 1.41 (2s, 6H, CH_3)	251 (5.0), 217 (4.6)
9c	1623, 1592, 1570	(Deuteriochloroform) 7.41 (s, 5H arom, Ph), 7.19, 6.92 (2s, 2H arom), 4.8-4.3 (m, 3H, $ArOCH_2CH$), 4.3-3.4 (m, 10H, NCH_2, OCH_2), 3.94, 3.90 (2s, 6H, OCH_3), 1.48, 1.41 (2s, 6H, CH_3)	251 (4.8), 217 (4.6)
10a	3400, 1640, 1605	7.88 (m, 2H, 1H arom, 5'-CH), 7.31 (s, 1H arom), 7.10 (d, 1H, 3'-CH), 6.65 (dd, 1H, 4'-CH), 5.6-3.2 (m, 15H, $ArOCH_2CHOHCH_2OH$, NCH_2), 3.91, 3.88 (2s, 6H, OCH_3)	251 (4.9), 217 (4.6)
10b	3350, 1635, 1600	7.90 (s, 1H arom), 7.80 (dd, 1H, 3'-CH), 7.53 (dd, 1H, 5'-CH), 7.32 (s, 1H arom), 7.13 (dd, 1H, 4'-CH), 5.6-3.4 (m, 15H, $ArOCH_2CHOHCH_2OH$, NCH_2), 3.90, 3.87 (2s, 6H, OCH_3)	249 (4.7), 216 (4.5)
10c	3370, 1630, 1600	7.91 (s, 1H arom), 7.50 (s, 5H arom, Ph), 7.32 (s, 1H arom), 5.4-3.3 (m, 15H, $ArOCH_2CHOHCH_2OH$, NCH_2), 3.90, 3.87 (2s, 6H, OCH_3)	248 (4.8), 215 (4.5)
12a	3410, 2770, (*NH), 1640, 1608	9.6, 8.9 (2 broad, 2H, *NH_2, exchangeable by deuterium oxide), 7.93 (broad s, 2H, 1H arom, 5'-CH), 7.47 (s, 1H arom), 7.14 (d, 1H, 3'-CH), 6.69 (dd, 1H, 4'-CH), 5.2-3.6 (m, 12H, $ArOCH_2CHOH$, NCH_2), 3.95 (s, 6H, OCH_3), 3.5-2.9 (m, 2H, NCH_2), 1.37 (broad s, 9H, $C(CH_3)_3$)	250 (4.8), 218 (4.6)
12b	3400, 2800, (*NH), 1632, 1605	9.7, 8.9 (2 broad, 2H, *NH_2, exchangeable by deuterium oxide), 7.93 (s, 1H arom), 7.83 (dd, 1H, 3'-CH), 7.53 (dd, 1H, 5'-CH), 7.41 (s, 1H arom), 7.15 (dd, 1H, 4'-CH), 5.4-3.6 (m, 12H, $ArOCH_2CHOH$, NCH_2), 3.90 (s, 6H, OCH_3), 3.5-2.9 (m, 2H, NCH_2), 1.36 (broad s, 9H, $C(CH_3)_3$)	252 (4.7), 220 (4.5)
12c	3400, 2790, (*NH), 1630, 1600	9.8, 8.8 (2 broad, 2H, *NH_2, exchangeable by deuterium oxide), 7.87 (s, 1H arom), 7.52 (s, 5H, arom, Ph), 7.43 (s, 1H arom), 5.5-3.5 (m, 12H, $ArOCH_2CHOH$, NCH_2), 3.91 (s, (s, 6H, OCH_3), 3.5-2.8 (m, 2H, NCH_2), 1.37 (broad s, 9H, $C(CH_3)_3$)	252 (4.7), 216 (4.5)

[a] Methyl sulfoxide-d_6 was used as the solvent unless otherwise noted.

bromide (0.97 g, 3 mmoles), chlorobenzene (150 ml) and 20% aqueous sodium hydroxide (60 ml). The reaction mixture was stirred for 2 hours at room temperature. Then, the layers were separated and the aqueous layer was extracted with methylene chloride (3 × 10 ml). The combined chlorobenzene and methylene chloride extracts were washed with water, dried with anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from acetone-water to give **4**, yield, 15.62 g (76%), mp 135-136°; uv (ethanol): λ max (log ϵ) 239 nm (4.7); ir (potassium bromide): ν max 1620, 1572, 1557, 1245, 1215 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.32, 7.13 (2s, 2H arom), 4.7-4.4 (m, 3H, $ArOCH_2CH$), 4.3-3.8 (m, 2H, OCH_2), 3.98 (s, 6H, OCH_3), 1.48, 1.40 ppm (2s, 6H, CH_3).

Anal. Calcd. for $C_{16}H_{19}ClN_2O_5$: C, 54.17; H, 5.40; Cl, 9.99; N, 7.90. Found: C, 54.04; H, 5.25; Cl, 10.28; N, 7.92.

2-Chloro-4-(*N,O*-benzylidene-2-hydroxy-3-*t*-butylaminopropoxy)-6,7-dimethoxyquinazolines **5a** and **5b**.

The same procedure was used as above, starting from *(S)*-2-phenyl-3-*t*-butyl-5-hydroxymethyloxazolidine [10] (**3**, 9.4 g, 0.04 mole), 2,4-dichloro-6,7-dimethoxyquinazoline (**1**, 10 g, 0.038 mole), tetrabutylammonium bromide (0.65 g, 2 mmoles), chlorobenzene (160 ml) and 20% aqueous sodium hydroxide (40 ml). After work up a mixture of **5a** and **5b** was obtained in approximate ratio 1:1 as a waxy residue. Recrystallization from acetonitrile (15 ml) gave on cooling (3°) 5.5 g (31%) of the diasterioisomer **5a**, collected by filtration; mp 177-179°; uv (ethanol): λ max (log ϵ) 238 nm (4.7); ir (potassium bromide): ν max 1620, 1571 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.8-7.1 (m, 7H arom), 5.66 (s, 1H, CH-Ph), 4.9-4.2 (m, 3H, $ArOCH_2CH$), 3.98, 3.97 (2s, 6H, OCH_3), 3.6-2.7 (m, 2H, NCH_2), 1.12 ppm (s, 9H, $C(CH_3)_3$).

Anal. Calcd. for $C_{24}H_{28}ClN_3O_4$: C, 62.95; H, 6.16; Cl, 7.74; N, 9.18. Found: C, 62.87; H, 5.88; Cl, 8.06; N, 9.43.

Then, the filtrate was cooled at −78° and the new precipitate filtered off and recrystallized from ethyl acetate-hexane to give 2.95 g (17%) of the diastereoisomer **5b**, mp 135-137°; uv (ethanol): λ max (log ϵ) 236 nm (4.7); ir (potassium bromide): ν max 1620, 1568 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.8-7.0 (m, 7H arom), 5.70 (s, 1H, CH-Ph), 4.8-4.2 (m, 3H, $ArOCH_2CH$), 3.94 (s, 6H, OCH_3), 3.8-2.6 (m, 2H, NCH_2), 1.14 ppm (s, 9H, $C(CH_3)_3$).

Anal. Calcd. for $C_{24}H_{28}ClN_3O_4$: C, 62.95; H, 6.16; Cl, 7.74; N, 9.18. Found: C, 62.76; H, 6.30; Cl, 7.87; N, 9.29.

Product **5b** may be also isolated of the mother liqueurs by evaporation of the solvent to dryness and column chromatography on silica gel using petroleum ether-ethyl acetate (3:1) as eluent.

2-Chloro-4-(2,3-dihydroxypropoxy)-6,7-dimethoxyquinazoline (**6**).

To a suspension of **4** (10 g, 0.028 mole) in 1*N* hydrochloric acid (160 ml) was added methanol (330 ml), and the mixture was stirred for 3 hours at room temperature. The precipitate was collected by filtration, dried *in vacuo* over potassium hydroxide and recrystallized from dimethylformamide-ether, yield, 7.3 g (83%), mp 231-234°; uv (ethanol): λ max (log ϵ) 238 nm (4.7); ir (potassium bromide): ν max 3400 (OH), 1620, 1585, 1563 cm^{-1}; ^{1}H-nmr (methyl sulfoxide-d_6): δ 7.40, 7.25 (2s, 2H arom), 5.1 (d, 1H, CHO*H*, interchangeable with deuterium oxide), 4.7-4.3 (m, 2H, OCH_2), 4.1-3.7 (m, 1H, C*H*OH), 3.94, 3.92 (2s, 6H, OCH_3), 3.6-3.4 ppm (m, 2H, CH_2OH).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_5$: C, 49.61; H, 4.80; Cl, 11.26; N, 8.90. Found: C, 49.34; H, 4.56; Cl, 11.55; N, 8.82.

2-Chloro-4-(2-hydroxy-3-*t*-butylaminopropoxy)-6,7-dimethoxyquinazoline Hydrochloride (**7**).

A solution of **5** (13.51 g, 0.029 mole) in 1*N* hydrochloric acid (500 ml) was magnetically stirred for 15 minutes at room temperature. The resulting precipitate was filtered off and washed with ethyl ether. The aqueous filtrate was evaporated to dryness at reduced pressure and the residue was thoroughly washed with ether. The two crops obtained were recrystallized from dimethylformamide-ether; yield: 8.87 g (74%); mp 235-237°; uv (ethanol): λ max (log ε) 255 nm (4.6); ir (potassium bromide): ν max 3400 (OH), 2550 (⁺NH), 1620, 1575 cm^{-1}; ^{1}H-nmr (methyl sulfoxide-d_6): δ 9.5, 8.8 (2 broad, 2H, NH_2^+, interchangeable with deuterium oxide), 7.57, 7.30 (2s, 2H arom), 4.7-4.3 (m, 2H, OCH_2), 4.3-3.7 (m, 1H, C*H*OH), 4.0 (s, 6H, OCH_3), 3.5-2.8 (m, 2H, NHCH_2), 1.38 ppm (s, 9H, $C(CH_3)_3$).

Anal. Calcd. for $C_{17}H_{25}Cl_2N_3O_4$: C, 50.25; H, 6.20; Cl, 17.45; N, 10.34. Found: C, 50.06; H, 5.93; Cl, 17.80; N, 10.42.

The found value was corrected for a 7.4% non-stoichiometric hydration water.

2-(4-Aroylpiperazin-1-yl)-4-alkoxy-6,7-dimethoxyquinazolines **9a-c**, **10a-c** and **12a-c**. General Procedures.

Method A.

A mixture of **4** or **5** (0.01 mole) and the corresponding 1-aroylpiperazine **8a-c** [11] (0.01 mole) was heated in isoamyl alcohol (20 ml) for 2 hours at reflux temperature with magnetic stirring and then cooled. The reaction mixture was poured into diethyl ether (100 ml) with stirring and the white precipitate was collected by filtration and washed with diethyl ether. The solid was then stirred with 1*N* hydrochloric acid (80 ml) for 30 minutes. The resulting solution or suspension was washed with diethyl ether (3 × 50 ml) and then evaporated to dryness under reduced pressure. The residue was dried *in vacuo* over potassium hydroxide and recrystallized from dimethylformamide-diethyl ether to give **10a-c** or **12a-c**.

Method B.

Following the above method, the solid obtained in the first step before treatment with hydrochloric acid was dissolved in chloroform (50 ml) and the solution washed with water (5 × 100 ml). The organic layer was dried with magnesium sulfate and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate-hexane to give **9a-c**. The aqueous layers were evaporated at reduced pressure to yield **10a-c**.

REFERENCES AND NOTES

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