Synthesis of 1,8-Naphthyridine Derivatives. Potential Antihypertensive Agents. 1

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Reaction of substituted 7-chloro-1,8-naphthyridines with *N*-carbethoxypiperazine gave in good yields the corresponding 7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridines V as potential antihypertensive agents.

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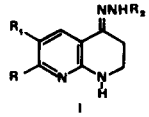
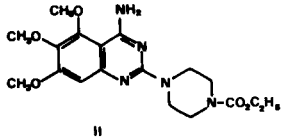
It has been reported that many compounds having the quinazoline [1-5], quinoline [4], isoquinoline [4] or 1,8-naphthyridine [6,7] ring system, possess antihypertensive or hypotensive activity.

Recently we prepared and pharmacologically investigated several 1,8-naphthyridine derivatives I. Two of these compounds exhibited a significant antihypertensive activity at doses of about 3 mg/Kg p. o. [8].

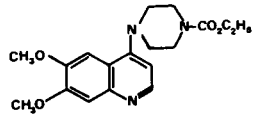
We have now continued our studies in this field by preparing and testing some substituted 1,8-naphthyridines having in 2-position a piperazine ring, present in a variety of hypotensive or antihypertensive agents [1-5], for example as in the compounds II [5] and III [4].



I



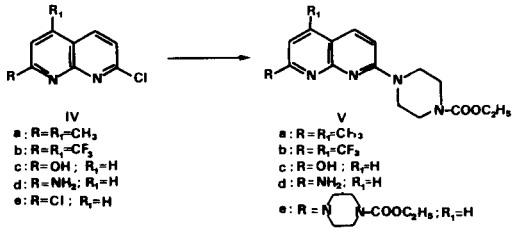
II



III

Treatment of IVa [9], IVb,c [10] and IVe [11] with carbethoxypiperazine (CEP) in toluene under reflux conditions, gave the required carbethoxypiperazine derivatives Va-c,e. Under the same conditions acetamidonaphthyridine VI [12] afforded 2-amino-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine hydrochloride (Vd·HCl) in 55% yield and 2-acetamido-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (VII) in 26% yield (Scheme I). The same compound Vd was isolated in 47% yield when a mixture of 2-amino-7-chloro-1,8-naphthyridine (IVd) [10] and CEP was refluxed in toluene (Scheme II).

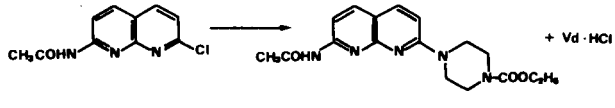
Scheme I



IV
a: R=R$_1$=CH$_3$
b: R=R$_1$=CF$_3$
c: R=OH; R$_1$=H
d: R=NH$_2$; R$_1$=H
e: R=Cl; R$_1$=H

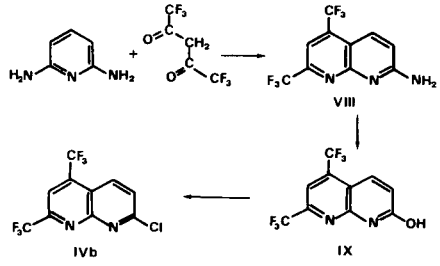
V
a: R=R$_1$=CH$_3$
b: R=R$_1$=CF$_3$
c: R=OH; R$_1$=H
d: R=NH$_2$; R$_1$=H
e: R=N(4-COOC$_2$H$_5$); R$_1$=H

Scheme II



Diazotization of 2-amino-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Vd) in sulfuric acid gave 2-hydroxy-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Vc) in good yield. The synthesis of the di(trifluoromethyl)-7-chloro-1,8-naphthyridine (IVb) is outlined in Scheme III.

Scheme III



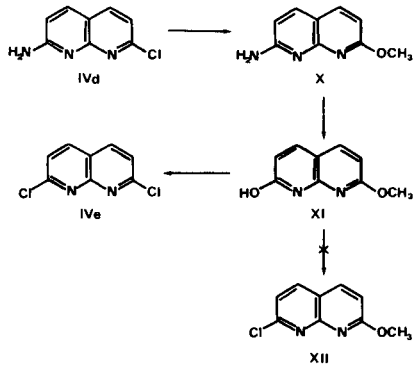
Cyclization of 2,6-diaminopyridine with 1,1,1,5,5,5-hexafluoroacetylacetone in phosphoric acid at 90° provided derivative VIII [13] in good yield. Diazotization of this 1,8-naphthyridine followed by treatment of the resulting compound IX [13] with phosphoryl chloride gave the chloroderivative IVb.

It was also of interest to attempt the preparation of 2-methoxy-7-(4-carbomethoxypiperazin-1-yl)-1,8-naphthyridine (XIV).

A possible starting material for the synthesis of this compound, could have been 2-amino-7-chloro-1,8-naphthyridine (Vd) [10], but this route was unsuccessful. Thus, treatment of chloroderivative IVd with sodium methoxide afforded the methoxy derivative X. Diazotization of X in

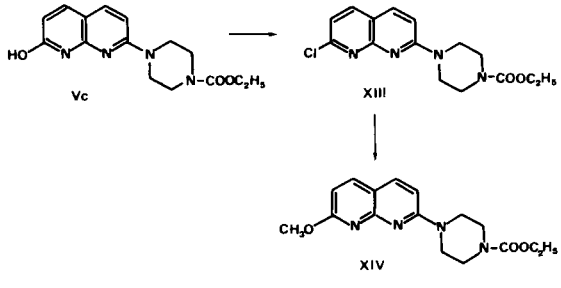
concentrated sulfuric acid afforded in good yield the corresponding compound XI. This compound, when allowed to react with phosphoryl chloride in order to obtain the desired 2-methoxy-7-chloro-1,8-naphthyridine (XII), gave instead 2,7-dichloro-1,8-naphthyridine (IVe) [11] (Scheme IV).

Scheme IV



Therefore an alternative profitable procedure was chosen: Vc was transformed into 2-methoxy-7-(4-carbomethoxypiperazin-1-yl)-1,8-naphthyridine (XIV) via chloro derivative XIII (Scheme V).

Scheme V



All the synthetized compounds were characterized by elemental analysis, ir and nmr spectra (Table I).

The antihypertensive activity of some of the above compounds have been assayed; the results will be reported in another paper.

EXPERIMENTAL

All compounds were routinely checked for their structure by ir and ^1H nmr spectroscopy. Melting-points were determined on a Kofler hotstage and are uncorrected. The ir spectra, in nujol mulls, were measured with a Perkin-Elmer infrared spectrophotometer model 1310. The ^1H nmr spectra of compounds VIII, IX (DMSO-d_6) and IV, V, VII, X, XI, XIII, XIV (deuteriochloroform) were determined on a Varian EM 360 A spectrometer. TMS was used as internal standard.

7-Chloro-2,4-di(trifluoromethyl)-1,8-naphthyridine (IVb).

A mixture of 1.0 g of IX and 10 ml of phosphoryl chloride was refluxed for 1 hour. The cooled solution was poured into crushed ice and the mixture made basic with concentrated ammonium hydroxide. The resulting precipitate was collected, washed with water and crystallized from 2-propanol/water (1:1) to give 1.1 g (84%) of IVb, mp 90-91°.

Anal. Calcd. for $C_{10}H_3ClF_6N_2$: C, 39.95; H, 1.00; N, 9.31; Cl, 11.79. Found: C, 40.30; H, 0.82; N, 9.20; Cl, 11.93.

2,7-Dichloro-1,8-naphthyridine (IVe).

A mixture of 0.50 g of XI and 5 ml of phosphoryl chloride was heated at 70° for 10 minutes. After cooling the solution was poured into crushed ice and the mixture made basic with concentrated ammonium hydroxide. The precipitate was collected and washed with water to give 0.50 g (89%) of practically pure IVe, identical with an authentic sample [11].

2,4-Dimethyl-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Va).

A mixture of 0.30 g (1.56 mmoles) of IVa [9], 0.54 g (3.41 mmoles) of carbethoxypiperazine (CEP) and 15 ml of toluene, was refluxed for 3 hours. After cooling, the solid was filtered off and the solution was evaporated to dryness *in vacuo* to give an oily residue, which was treated with water. The separated solid was collected by filtration and crystallized from petroleum ether 100-140°, to give 0.42 g (86%) of Va, mp 75-76°.

Anal. Calcd. for $C_{17}H_{22}N_4O_2$: C, 64.94; H, 7.05; N, 17.82. Found: C, 65.05; H, 7.16; N, 17.97.

2,4-Di(trifluoromethyl)-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Vb).

A mixture of 1.1 g (3.66 mmoles) of IVb, 1.5 g (9.48 mmoles) of CEP and 10 ml of toluene was refluxed for 3 hours. After cooling, the solid was filtered off and the solution was evaporated to dryness *in vacuo*. The residue was crystallized from ethanol/water (4:1) to give 1.3 g (84%) of Vb, mp 129-131°.

Table I

^1H NMR Chemical Shifts (δ) and IR Data (cm^{-1})

Compound	Aromatic	Piperazine	CH_3CH_2	Others	cm^{-1}
IVb	7.90 (d), 8.26 (s), 8.70 (m)				1600, 1280, 1210, 1130, 1110
Va	6.88 (d), 6.92 (d), 8.05 (d)	3.70 (m)	1.30 (t), 4.16 (q)	2.53 (s), 2.63 (s) (2,4-CH_3)	1680, 1265, 1230, 1220,
Vb	7.33 (d), 7.76 (s), 8.26 (m)	3.80 (m)	1.35 (t), 4.23 (q)		1700, 1260, 1240, 1220
Vc	6.40 (d), 6.51 (d), 7.63 (d), 7.65 (d)	3.63 (m)	1.30 (t), 4.20 (q)	10.46 (OH)	1700, 1250, 1230, 1220, 1210
Vd	6.45 (d), 6.64 (d), 7.60 (d), 7.65 (d)	3.68 (m)	1.30 (t), 4.16 (q)	5.00 (NH_2)	3340, 3150, 1280, 1260, 1230
Ve	6.45 (d), 6.55 (d), 7.70 (d), 7.76 (d)	3.75 (m)	1.30 (t), 4.18 (q)		1680, 1280, 1240, 1220
VII	6.90 (d), 7.83 (d), 7.90 (d), 8.20 (d)	3.75 (m)	1.30 (t), 4.20 (q)	8.90 (NH)	3240, 1660, 1270, 1250, 1220
VIII	7.36 (d), 7.90 (s), 8.33 (m)			7.75 (NH_2)	3450, 3300, 1640, 1020, 790
IX	7.28 (d), 7.83 (s), 8.26 (m)			6.53 (OH)	3450, 3340, 3200, 1640, 1280
X	6.62 (d), 6.73 (d), 7.82 (d)			5.16 (NH_2), 4.10 (s) (CH_3O)	3450, 3300, 1640, 1320, 1020
XI	6.57 (d), 6.60 (d), 7.66 (d), 7.75 (d)			4.00 (s) (CH_3O)	3450, 1650, 1270, 840
XIII	7.03 (d), 7.20 (d), 7.92 (m)	3.76 (m)	1.30 (t), 4.23 (q)		1700, 1260, 1240, 1220
XIV	6.69 (d), 6.85 (d), 7.80 (d), 7.85 (d)	3.73 (m)		4.13 (s) (CH_3O), 3.73 (s) (CH_3)	1700, 1260, 1240, 1220, 1210

Anal. Calcd. for $C_{17}H_{16}F_6N_4O_2$: C, 48.34; H, 3.81; N, 13.26. Found: C, 48.02; H, 3.63; N, 13.11.

2-Hydroxy-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Vc).

a) A mixture of 0.36 g (2.0 mmoles) of IVc [10], 0.70 g (4.4 mmoles) of CEP and 25 ml of toluene was refluxed for 3 hours. After cooling, the separated solid was collected by filtration and washed with water. On crystallization from water 0.51 g (85%) of Vc was obtained, mp 218-219°.

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.29; H, 6.12; N, 18.38.

b) To a cooled (0°) solution of 5.0 g of Vd in 10 ml of concentrated sulfuric acid, 2.5 g of sodium nitrite in small amounts was added. After standing at room temperature for 2 hours the mixture was poured into crushed ice and made basic with concentrated ammonium hydroxide. The precipitate was collected giving 4.2 g (94%) of practically pure Vc.

2-Amino-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Vd).

a) A mixture of 0.18 g (1.0 mmoles) of IVd [10], 0.35 g (2.2 mmoles) of CEP and 10 ml of toluene was refluxed for 3 hours. After cooling, the separated solid was collected by filtration, suspended in concentrated ammonium hydroxide, again collected and washed with water. On crystallization from water 0.14 g (47%) of Vd was obtained, mp 115-116°.

Anal. Calcd. for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.36; N, 23.24. Found: C, 59.73; H, 6.65; N, 23.07.

b) A solution of 0.30 g of VII in 3 ml of 10% sulfuric acid was refluxed for 30 minutes. The cooled solution was made basic with concentrated ammonium hydroxide; there was obtained 0.22 g (84%) of Vd.

2-Amino-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine hydrochloride (Vd·HCl) and 2-Acetamido-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (VII).

A mixture of 2.0 g (9.02 mmoles) of VI [12], 3.14 g (19.8 mmoles) of CEP and 80 ml of toluene was refluxed for 3 hours. After cooling, the separated solid was collected by filtration and was treated with water. The solid residue was crystallized from DMF to give 1.8 g (55%) of Vd·HCl, mp 270-271°.

Anal. Calcd. for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73; Cl, 10.49. Found: C, 53.63; H, 6.12; N, 20.86; Cl, 10.83.

The toluene mother liquors were evaporated to dryness *in vacuo* to obtain an oily residue, which was treated with water. The compound VII separated as solid which was collected by filtration and crystallized from benzene, 0.86 g (26%), mp 188-190°.

Anal. Calcd. for $C_{17}H_{21}N_5O_3$: C, 59.46; H, 6.16; N, 20.40. Found: C, 59.15; H, 6.14; N, 20.14.

2,7-Di(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (Ve).

A mixture of 2.5 g (12.5 mmoles) of IVe, 8.3 g (55.3 mmoles) of CEP and 50 ml of toluene was refluxed for 3 hours. After cooling, the solid was filtered off and the solution was evaporated to dryness *in vacuo*. The oily residue was diluted with water and extracted with chloroform. The combined extracts were dried (magnesium sulfate) and evaporated under reduced pressure. The product crystallized from petroleum ether 100-140° gave 1.4 g (25%) of Ve, mp 121-122°.

Anal. Calcd. for $C_{22}H_{30}N_6O_4$: C, 59.71; H, 6.83; N, 18.99. Found: C, 61.10; H, 6.62; N, 18.73.

7-Amino-2,4-di(trifluoromethyl)-1,8-naphthyridine (VIII).

A mixture of 1.09 g (10 mmoles) of 2,6-diaminopyridine, 2.5 g (12 mmoles) of 1,1,1,5,5,5-hexafluoroacetylacetone and 5 ml of 85% phosphoric acid was stirred and heated in a sealed tube at 60° for 12 hours. The cooled mixture was poured into crushed ice and made basic with concentrated ammonium hydroxide. The resulting precipitate was collected, washed with water and crystallized from methanol/water (2:1) to give 2.6 g (95%) of VIII, mp 214-215° [13].

7-Hydroxy-2,4-di(trifluoromethyl)-1,8-naphthyridine (IX).

To a cooled (0°) solution of 0.60 g of VIII in 6 ml of concentrated sulfuric acid was added 0.60 g of sodium nitrite in small amounts. After standing at room temperature for 12 hours, the mixture was poured into crushed ice, heated on a boiling steam bath for 30 minutes and made basic with concentrated ammonium hydroxide. The product was collected, washed with water and crystallized from 2-propanol/water (1:4); 0.5 g (83%) of IX, mp 190-191° [13].

2-Amino-7-methoxy-1,8-naphthyridine (X).

To a solution of 50 ml absolute methanol, in which 0.5 g (21.7 mmoles) of sodium metal was dissolved, 0.5 g (2.7 mmoles) of IVd [10] was added and the mixture was refluxed for 1 hour. The solvent was then removed by evaporation under reduced pressure, water was added and the product collected by filtration. Crystallization from water gave 0.60 g (61%)of X, mp 150-151°.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.94; H, 5.16; N, 23.86.

2-Hydroxy-7-methoxy-1,8-naphthyridine (XI).

To a cooled (0°) solution of 0.5 g of X in 5 ml of concentrated sulfuric acid, was added 0.5 g of sodium nitrite in small amounts. After standing at room temperature for 12 hours the mixture was poured into crushed ice and made basic (*p*H 9) with concentrated ammonium hydroxide. The product was collected, washed with water to give 0.45 g (91%) of pure XI, mp 171-172°.

Anal. Calcd. for$C_9H_9N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.56; H, 4.58; N, 15.90.

2-Chloro-7-(4-carbethoxypiperazin-1-yl)-1,8-naphthyridine (XIII).

A mixture of 1.0 g of Vc and 10 ml of phosphoryl chloride was refluxed for 1 hour. The cooled solution was poured into crushed ice and the mixture made basic with ammonium hydroxide. The resulting precipitate was collected, washed with water and crystallized from 2-propanol/water (1:3), to give 0.80 g (75%) of XIII, mp 126-130°.

Anal. Calcd. for $C_{15}H_{17}ClN_4O_2$: C, 56.16; H, 5.34; N, 17.46; Cl, 11.05. Found: C, 56.15; H, 5.34; N, 17.46; Cl, 11.24.

2-Methoxy-7-(4-carbomethoxypiperazin-1-yl)-1,8-naphthyridine (XIV).

To a solution of 100 ml of absolute methanol, in which 3.5 g (152.1 mmoles) of sodium metal was dissolved, 3.5 g (10.91 mmoles) of XIII was added and the mixture was refluxed for 1 hour. The solvent was removed by evaporation under reduced pressure; the oily residue was diluted with water and then extracted with chloroform. The combined extracts were dried (magnesium sulfate) and evaporated to dryness *in vacuo*. The oily residue was crystallized from petroleum ether 100-140°, to give 2.64 g (80%) of XIV, mp 126-128°.

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.32; H, 6.17; N, 18.88.

Acknowledgement.

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