Synthesis of some 3-Substituted [1,8]Naphthyrido[3,2-*c*][1,8]naphthyridines A New Heterocyclic Ring System

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Some 3-substituted-5,6-dihydro[1,8]naphthyrido[3,2-*c*][1,8]naphthyridines (V) were obtained by the condensation of 7-substituted-2,3-dihydro-1,8-naphthyridin-4-(1*H*)ones (IV) with 2-aminonicotinaldehyde. All of the 5,6-dihydro derivatives V were transformed into the fully aromatic compounds VI by refluxing with nitrobenzene.

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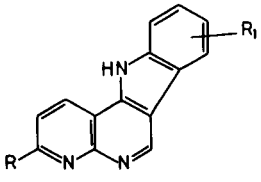
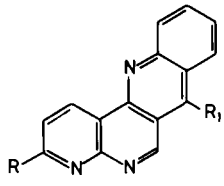
Previously, we described the synthesis and pharmacological activity of some 11*H*-indolo[3,2-*c*][1,8]-naphthyridines I (1a-c).

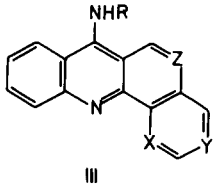


I



II

Recently we prepared several 3- and 3,7-substituted quino[3,2-*c*][1,8]naphthyridines II (2a,b), because of their structural relationship to the compounds III, which exhibited good antiamebic activity (3a-c).

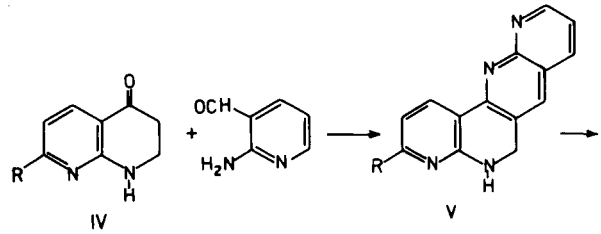


a: X=N, Y=Z=CH
b: Y=N, X=Z=CH
c: Z=N, X=Y=CH

III

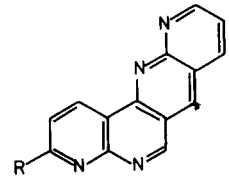
The quinonaphthyridines II were obtained by treating the appropriate ketones IV (1c,2b,4) in acid or alkaline solution with *o*-aminobenzaldehyde, *o*-aminoacetophenone or *o*-aminobenzophenone.

In the present work, the synthesis and properties of some 3-substituted [1,8]naphthyrido[3,2-*c*][1,8]naphthyridines V are reported. The route employed for the synthesis of V, which represents a new heterocyclic ring structure, was essentially the same as described for the preparation of compounds II (2a,b). Therefore, 2-aminonicotinaldehyde, prepared by sulfamation of nicotinamide with ammonium sulfamate followed by hydrolysis of the reaction mixture in hydrochloric acid (5), was condensed with ketones IV (1c,2b,4) to give derivatives V (see Table I).



IV V

a): R = CH_3
b): R = Br
c): R = Cl
d): R = OC_2H_5
e): R = SH



VI

Thus, when 7-methyl-2,3-dihydro-1,8-naphthyridin-4-(1*H*)one (IVa) and 2-aminonicotinaldehyde were allowed to stand at room temperature for one day in an anhydrous ethanolic solution of hydrogen chloride, the expected 3-methyl-5,6-dihydro[1,8]naphthyrido[3,2-c][1,8]naphthyridine (Va) was obtained in 71.9% yield.

Similar treatment of ketones IVc and IVd with 2-aminonicotinaldehyde and hydrogen chloride in ethanolic solution gave the reaction product Vc and Vd, respectively. In order to prevent a possible substitution of bromine atom (in the 3 position) with chlorine, the ketone IVb was condensed to give 3-bromo-5,6-dihydro[1,8]naphthyrido[3,2-c][1,8]naphthyridine Vb in an anhydrous ethanolic solution of hydrogen bromide. In previous work (2b), this substitution was described for analogous compounds when the reaction was carried out with hydrogen chloride. Compounds V were then converted in satisfactory yield to the fully aromatic naphthyridonaphthyridines VI, by refluxing with nitrobenzene (see Table II).

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Table I

3-Substituted 5,6-Dihydro[1,8]naphthyrido[3,2-*c*][1,8]naphthyridines (V)

Compound No.	Starting Material	Reaction Acid	Reaction Time (days)	Yield %	Mp °C	Recrystallization solvent	Empirical formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
Va	IVa	hydrogen chloride	1	71.9	230-235 dec	DMF	$C_{15}H_{12}N_4$	72.58	4.84	22.58	72.78	4.71	22.78
Vb	IVb	hydrogen bromide	3	78.7	> 320	DMF	$C_{14}H_9BrN_4$	53.67	2.87	17.89	53.88	2.89	17.68
Vc	IVc	hydrogen chloride	5	88.3	> 320	DMF	$C_{14}H_9ClN_4$	62.57	3.35	20.86	62.63	3.46	20.59
Vd	IVd	hydrogen chloride	3	78.7	179-182	ethanol	$C_{16}H_{14}N_4O$	69.06	5.05	20.14	69.16	5.17	20.04

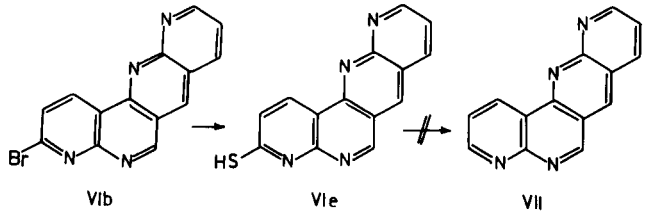
Table II

3-Substituted[1,8]Naphthyrido[3,2-*c*][1,8]naphthyridines (VI)

Compound No.	Yield %	M.p. °C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd. % C	H	N	S	Found % C	H	N	S
VIa	78.6	280-283 dec	toluene	$C_{15}H_{10}N_4$	73.17	4.06	22.76	-	73.00	4.23	22.51	-
VIb	90.0	> 320	DMF	$C_{14}H_7BrN_4$	54.02	2.25	18.01	-	54.24	2.46	18.00	-
VIc	80.6	> 320	DMF	$C_{14}H_7ClN_4$	63.04	2.63	21.01	-	62.90	2.85	20.75	-
VId	70.5	253-255	DMF	$C_{16}H_{12}N_4O$	69.56	4.35	20.29	-	69.88	4.19	20.51	-
VIe	42.8	> 320	-	$C_{14}H_8N_4S$	63.64	3.03	21.21	12.12	63.39	3.27	21.01	12.36

The structure of these compounds (Va-d, VIa-d) were confirmed by nmr spectral data (trifluoroacetic acid; see Table III). For example we report the more characteristic signals of the nmr spectrum of Va and VIa. The nmr spectrum of Va shows two doublets at δ 9.35 and δ 7.22 (1H each) due to H_1 and H_2, respectively, and two singlets at δ 5.50 (2H) and δ 8.76 (1H) assigned to H_6 and H_7, respectively. By contrast, the nmr spectrum of the fully aromatic compound VIa exhibits two doublets at δ 10.42 and δ 8.60 and one singlet at δ 10.37 (2H) due to H_1, H_2 and H_6, H_7, respectively.

It was also interesting to prepare the thio derivatives Ve and VIe for the synthesis of the parent nucleus which has not been reported in the literature. Attempts to obtain 3-mercapto-5,6-dihydro[1,8]naphthyrido[3,2-c][1,8]-napthyridine (Ve) by condensation of ketone IVe with 2-aminonicotinaldehyde in acid or alkaline solution were unsuccessful. However, 3-mercapto[1,8]naphthyrido[3,2-c]-[1,8]naphthyridine (VIe) was prepared in 42.8% yield by treating VIb with thiourea in absolute ethanolic solution (6).



VIb VIe VII

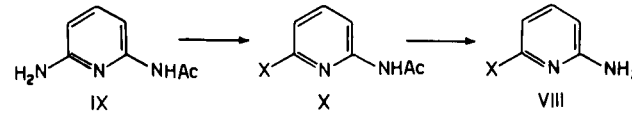
Elemental analysis and nmr spectrum are consistent with the assigned structure VIe. Because of the instability of VIe in trifluoroacetic acid, its nmr spectrum was recorded in sodium deuterioxide solution (see Table III).

Attempts to obtain [1,8]naphthyrido[3,2-*c*][1,8]naphthyridine (VII) by catalytic reduction of bromo derivative VIb or by oxidation of the methyl group of VIa (potassium permanganate or potassium dichromate) and decarboxylation failed. In previous papers, we reported the use of Raney nickel for desulfurizations of Ia (R = SH, R_1 = H) and IIa (R = SH, R_1 = H) (1c, 2a). In contrast, under the same conditions, Raney nickel failed to effect desulfurization of the thio derivative VIe.

The already known 2-amino-6-halopyridines VIII, starting materials for the synthesis of ketones IVb,c, were prepared by different methods from those previously described in the literature (7,8).

Compound VIIIb was obtained under the same conditions as used with VIIIa, in contrast with results reported by Johnson and co-workers (7). 2-Amino-6-chloropyridine VIIIb was obtained in 42.1% yield by reaction of 3-hydroxyglutaronitrile with anhydrous hydrogen chloride, as mentioned in our previous paper (2b) (see Experimental).

Moreover, an alternative synthesis of VIII was carried out in the following way.

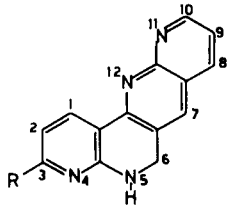


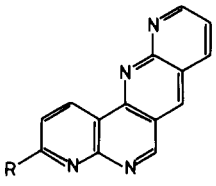
IX X VIII

a) X=Br ; b) X=Cl

Table III

^{1}H Nmr Spectral Data of V and VI (δ Values; Observed Chemical Shifts, Temperature 25°)





Compound No.	R	H_1	H_2	H_6	H_7	H_9	$H_{8,10}$		$J_{1,2}$
Va	CH_3	9.35 (d)	7.22 (d)	5.50 (2H, s)	8.76 (s)	8.40 (dd)	9.47 (m)	CH_3 = 2.75 (s)	8.25
Vb	Br	9.05 (d)	7.42 (d)	5.50 (2H, s)	8.72 (s)	8.35 (dd)	9.27 (m)	-	8.25
Vc	Cl	9.10 (d)	7.15 (d)	5.42 (2H, s)	8.57 (s)	8.22 (dd)	9.20 (m)	-	8.25
Vd	OC_2H_5	9.32 (d)	6.75 (d)	5.50 (2H, s)	8.75 (s)	8.37 (dd)	9.34 (m)	CH_3 = 1.67 (t); CH_2 = 4.7 (q)	9.00
VIa	CH_3	10.42 (d)	8.60 (d)	10.37 (s)	10.37 (s)	8.70 (dd)	9.95 (m)	CH = 3.37 (s)	9.00
VIb	Br	9.82 (d)	8.65 (d)	10.75 (s)	10.60 (s)	8.70 (dd)	9.95 (m)	-	9.00
VIc	Cl	9.95 (d)	8.45 (d)	10.79 (s)	10.62 (s)	8.72 (dd)	10.00 (m)	-	9.00
VId	OC_2H_5	9.87 (d)	7.95 (d)	10.32 (s)	10.30 (s)	8.60 (dd)	9.80 (m)	CH_3 = 1.75 (t); CH_2 = 4.97 (q)	9.75
VIe	SH	6.76 (d)	6.50 (d)	8.01 (s)	7.32 (s)	6.75 (dd)	7.20 (m) 8.26 (m)	-	8.50

Diazotization of 2-acetamido-6-aminopyridine (IX) (9) in hydrochloric acid gave directly 2-acetamido-6-chloropyridine (Xb), in 59.4% yield, without recourse to a copper catalyst. If the same reaction was performed in hydrobromic acid, 2-acetamido-6-bromopyridine (Xa) (10) was prepared, but in only 13.3% yield. These results are in accord with the behaviour observed with 2-aminopyridines and 2-aminoquinolines (11). Compounds X were then converted in good yield to VIII by hydrolysis with sulfuric acid.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus. Ir spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer in Nujol mulls. ^{1}H nmr spectra were obtained in trifluoroacetic acid with a JEOL Model C 60 HL spectrometer with TMS as an internal standard. The ^{1}H nmr spectrum of compound VIe was determined for a sodium deuterioxid solution on a Varian CFT-20 spectrometer working in FT mode at 80 M Hz, with DDS as an internal standard.

General Procedure for the Preparation of 3-Substituted-5,6-dihydro[1,8]-naphthyrido[3,2-*c*][1,8]naphthyridines (Va-d).

An ice cooled suspension of 3.0 mmoles of ketones IVa-d and 3.6 mmoles of 2-aminonicotinaldehyde in 40 ml of dry ethanol was saturated with anhydrous hydrogen halide. After standing at room temperature some days the solution was concentrated *in vacuo* to a small volume and treated with 10% aqueous sodium hydroxide. The separated solid was then collected by filtration and washed with water (see Table I).

General Procedure for the Preparation of 3-Substituted [1,8]Napthyrido-[3,2-*c*][1,8]naphthyridines (VIa-d).

A solution of Va-d (1.0 g) in nitrobenzene (10 ml) was refluxed for 30 minutes. After cooling, compounds VIa-d were obtained by addition of light petroleum to the reaction mixture (see Table II).

3-Mercapto[1,8]naphthyrido[3,2-c][1,8]naphthyridine (VIe).

A mixture of 0.88 g of VIb, 6.0 g of thiourea and 100 ml of absolute ethanol was refluxed for 24 hours. The solvent was then evaporated at reduced pressure to a small volum. To the obtained suspension 80 ml of water were added and the mixture was heated on a boiling steam bath for 30 minutes. After cooling, the crude product was collected and treated with 50 ml of 10% sodium hydroxide solution on a boiling steam bath for 15 minutes. After cooling, the solid was filtered and washed with water. The filtrate was acidified with dilute hydrochloric acid and the precipitate was collected, washed with water and dried to give 0.32 g of practically pure VIe.

2-Acetamido-6-chloropyridine (Xb).

To a stirred and cooled (*ca* - 10°) suspension of 20.0 g of 2-acetamido-6-aminopyridine (IX) in 100 ml of 36% hydrochloric acid, 20 ml of 40% aqueous sodium nitrite solution were added dropwise over a period of 90 minutes. After the addition, the solution obtained was stirred for 30 minutes and treated with concentrated ammonia. The solid was collected and crystallized from light petroleum (60-80°) to give 13.4 g (59.4%) of Xb, mp 145-148°.

Anal. Calcd. for $C_7H_7ClN_2O$: C, 49.27; H, 4.10; N, 16.42. Found: C, 49.50; H, 4.26; N, 16.57.

2-Acetamido-6-bromopyridine (Xa).

To a stirred and cooled (*ca* - 5°) suspension of 1.0 g of 2-acetamido-6-aminopyridine (IX) in 8 ml of 36% hydrobromic acid, 2.0 ml of 40% aqueous sodium nitrite solution were added dropwise. After the addition, the solution obtained was stirred for 1 hour and treated with concentrated ammonia. The solid was collected and crystallized from light petroleum (60-80°) to give 0.16 g (13.2%) of Xa, mp 154-156°.

From the alkaline mother liquors, extracted with chloroform, 0.15 g of starting material IX was recovered.

2-Amino-6-chloropyridine (VIIIb).

A) From 3-Hydroxyglutaronitrile.

A suspension of 30.0 g of 3-hydroxyglutaronitrile in 300 ml of dry ether was cooled in an ice bath. Dry hydrogen chloride was then bubbled through the mixture until the precipitation of the hydrogen chloride salt appeared complete. The reaction mixture was poured into an excess of sodium hydrogen carbonate solution and the organic phase was separated; the aqueous solution was extracted with ether three times.

The combined extracts were washed with a small amount of water, dried over magnesium sulfate and evaporated to dryness to give 14.8 g (42.1%) of VIIIb, which was crystallized from light petroleum (60-80°), mp 71-72°.

B) From Xb.

A solution of 13.0 g of Xb in 130 ml of 10% sulfuric acid was heated on a boiling steam bath for 30 minutes. After cooling, the solution was made alkaline with concentrated ammonium hydroxide. The mixture was extracted several times with chloroform and the combined extracts were evaporated to dryness *in vacuo* to give 6.8 g (69.4%) of VIIIb.

2-Amino-6-bromopyridine (VIIIa).

This compound was obtained by hydrolysis from Xa in a manner similar to that used for the preparation of VIIIb, and was crystallized from light petroleum (60-80°), yield 80.0%, mp 88-90°.

Acknowledgement.

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