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One-Step Synthesis of 6*H*-Indolo[2,3-*b*][1,8]naphthyridines. A New Heterocyclic Ring System

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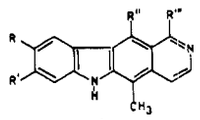
The photolysis of 4-phenyltetrazolo[1,5-*a*][1,8]naphthyridines (**11**) in trifluoroacetic acid produces in high yield the corresponding 6*H*-indolo[2,3-*b*][1,8]naphthyridines (**2**). Compounds **2**, belonging to a hitherto unknown ring system, are interesting because of their structural resemblance to ellipticine and olivacine, two alkaloids which exhibit antitumor properties. Also the preparation of the parent nucleus **2g** is described.

Several alkaloids containing the indole nucleus as a part of a polycyclic system are very useful as curvative agents (see, e.g., reserpine, lysergic acid derivatives, the *Vinca* alkaloids, etc.). More recently the disclosure of potentially useful tumor inhibitory properties of certain 6*H*-pyrido[4,3-*b*]carbazoles such as ellipticine (**1a**), 9-methoxyellipticine (**1b**), and olivacine (**1c**) has prompted considerable interest[1] and several

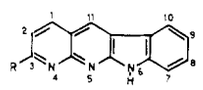


a : R = R' = R''' = H , R'' = CH_3
b : R = OCH_3 , R' = R''' = H , R'' = CH_3
c : R = R' = R'' = H , R''' = CH_3

1

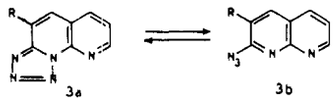
syntheses have been elaborated in attempts to make the above compounds and related substances available for evaluation as chemotherapeutic agents.[2]

Because of our interest in substances which might exhibit similar antitumor properties, we wish now to report on the one-step synthesis that was used to readily prepare some substituted 6*H*-indolo[2,3-*b*][1,8]naphthyridines (**2**), analogues and isosteres of the 6*H*-pyrido[4,3-*b*]carbazoles.



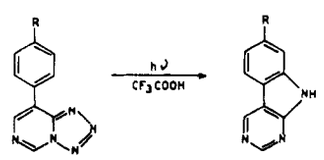
2

In the course of our studies on tetrazole derivatives of 1,8-naphthyridines, evidence was presented to demonstrate that the tetrazole ring structure **3a** is the dominant species in the solid state and in alkaline solution, while the open-chain azido form **3b** dominates in acidic solution.[3] Several tetrazole



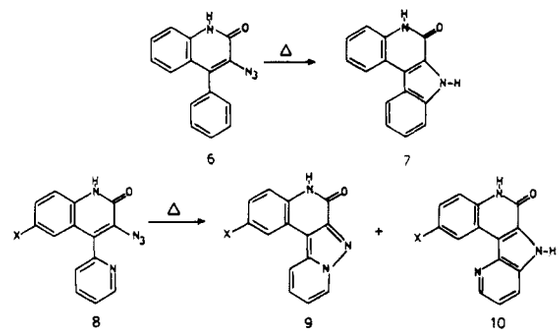
3a 3b

derivatives of 1,8-naphthyridine with a phenyl group in an adjacent position to the tetrazole nucleus were described.[3] Besides, it is well known that the photolysis of substituted 8-phenyltetrazole[1,5-*c*]pyrimidines (**4**) in trifluoroacetic acid produces in high yield the corresponding 9*H*-pyrimido[4,5-*b*]indoles (**5**).[4]



4 5

There has also been described the preparation in good yield of indolo[2,3-*c*]quinolone (**7**) by pyrolysis of 3-azido-4-phenylcarbostyril (**6**);[5] the pyrolysis of 3-azido-4-(2-pyridyl)carbostyrils (**8**) affords mixtures of the isomeric tetracyclic

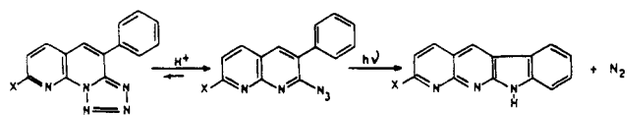


6 7 8 9 10

products **9** and **10**, resulting from nitrenoid cyclization reactions.[6]

The above researches suggested that similar processes might be of synthetic utility in yielding a number of compounds to evaluate for antitumor activity because of their structural resemblance to the pyridocarbazole system found in ellipticine.

We wish to report here an one-step, high-yield synthesis and the characterization of some 6*H*-indolo[2,3-*b*][1,8]naphthyridine derivatives (**2**), which represent a new heterocyclic ring structure. The title compounds **2** were prepared by photolysis of some 4-phenyltetrazolo[1,5-*a*][1,8]naphthyridines (**11**) in trifluoroacetic acid, yields ranging between 84 and 97%.



11a , X = NH_2
b , X = OH
c , X = Cl
d , X = OCH_3
e , X = OC_2H_5

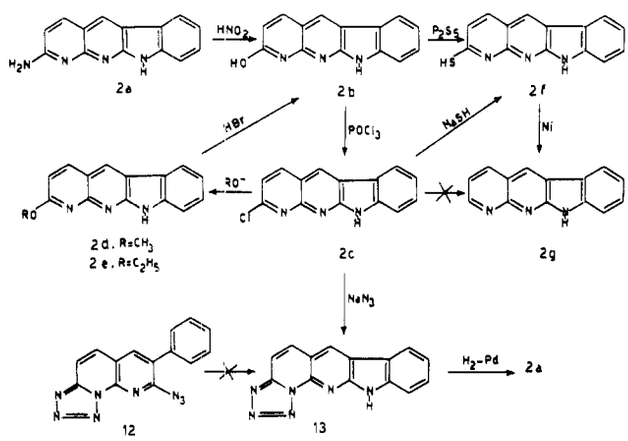
11'

2a , X = NH_2
b , X = OH
c , X = Cl
d , X = OCH_3
e , X = OC_2H_5

The tetrazolonaphthyridines **11** were previously described,[3] except **11d**, which was prepared in the same manner as **11e**. The naphthyridinoindoles **2** are very high melting, crystalline, yellow to yellow-brown solids (mp above 320 °C), slightly soluble in many usual organic solvents. The most soluble product was 3-amino-6*H*-indolo[2,3-*b*][1,8]naphthyridine (**2a**). The structure of this compound was proved by analytical and NMR spectral data. In fact, the NMR spectrum

(Me_2SO-d_6, 25 °C) of **2a** shows two singlets at δ 7.02 (two protons) and at δ 12.35, that disappear on exchange with deuterium oxide: the first can be attributed to NH_2 and the other is broader and corresponds to NH proton. A singlet at δ 8.81 is due to H_{11} and two-proton signals at δ 8.19 and 6.92 are due to H_1 and H_2, respectively (J = 8.0 Hz). The absorption range for phenyl protons is δ 7.95–7.14. It was impossible to obtain NMR spectra of **2b–e** because of their insolubility. The structures of these compounds were assigned based upon analytical data and chemical evidence. Compounds **2b–e** were synthesized besides as described above (**11** → **2**), also using the amino derivative **2a** as starting material. The 3-chloro compound **2c** was prepared by treatment of **2a** with nitrous acid to give hydroxy derivative **2b,** followed by the reaction with phosphorus oxychloride. Treatment of chloronaphthyridineindole **2c** with sodium methoxide or sodium ethoxide produced the compounds **2d** and **2e,** respectively, from which hydroxy derivative **2b** was again obtained by refluxing in 48% hydrobromic acid (see Scheme I). The structures of the above

Scheme I



compounds were also confirmed by UV spectra, which show a behavior analogous among them and to that of olivacine and of 10*H*-pyrido[3,4-*b*]carbazole[7] (see Table II).

It was also of interest to prepare the pentacyclic 11*H*-tetrazolo[1,5-*a*]indolo[3,2-*g*][1,8]naphthyridine (**13**), which represents another unknown heterocyclic ring system. We first tried to synthesize the model compound by photolysis of **12** in trifluoroacetic acid solution, but the reaction did not afford definite products. Instead compound **13** was obtained in 87.7% yield from the chloro derivative **2c,** by reaction with sodium azide in *N,N*-dimethylformamide (DMF). Its structure was assigned based upon analytical data, as well as upon IR spectrum in Nujol mulls, that shows absorption indicative of the tetrazole nucleus in the region between 1110 and 1000 cm^{-1}. Instead the IR spectrum in trifluoroacetic acid shows strong azide absorption at 2140 cm^{-1}, and nearly complete absence of the tetrazole absorption. This effect of acid on the azidoazomethine–tetrazole equilibrium has been previously reported for several heterocyclic systems.[3,4,8] The catalytic reduction of **13** in acetic acid solution reduced the tetrazole nucleus and produced the amino derivative **2a** in 44.4% yield.

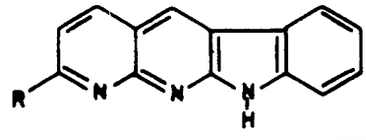
A matter of particular interest was the preparation of the unknown parent nucleus: 6*H*-indolo[2,3-*b*][1,8]naphthyridine (**2g**). None of the attempts to obtain **2g** by catalytic reduction of chloro compound **2c** were successful. However, direct substitution of oxygen by sulfur using phosphorus pentasulfide as the thiating agent has been widely applied to heterocyclic systems when the hydroxyl structure is tautomeric with the cyclic amidelike or lactamic structure.[9] The replacement of sulfur by hydrogen in sulfurated organic compounds using Raney nickel is well known.[9e,10] We have applied these methods treating hydroxy compound **2b** with phosphorus pentasulfide in pyridine. The thio derivative **2f** was obtained in satisfactory yield (78%). Also the chloronaphthyridinoindole **2c** was converted with sodium hydrosulfide in ethanol[10b] into the same mercapto derivative **2f** in 77.7% yield. Elemental analysis and IR and NMR spectra are all consistent with the assigned structure **2f.** Its NMR spectrum shows two proton signals at δ 8.01 and 7.03 due to H_1 and H_2, respectively (J = 8.0 Hz) and a singlet at δ 8.9 due to H_{11}. The absorption range for phenyl protons is δ 8.40–7.44.

The mercapto derivative **2f** was then desulfurized to the parent nucleus **2g,** by means of sponge nickel catalyst. It was impossible to determine the NMR spectrum of **2g** because of its insolubility, but the elemental analysis and the molecular weight (219) determination by mass spectrum were consistent with the assigned structure. UV spectrum in ethanol of **2g** shows a behavior analogous to those of other naphthyridinoindoles **2** and to that of olivacine (see Table II).

Conclusions

The present research has demonstrated that the photolysis of tetrazole derivatives of 1,8-naphthyridine in acid media is a high-yield route to the 6*H*-indolo[2,3-*b*][1,8]naphthyridines, a new heterocyclic ring system, interesting because of the structural resemblance with the pyridocarbazole system found in ellipticine and olivacine, two tumor inhibitory alkaloids.[1,2] The reaction involves a shift of the tetrazole–azidoazomethine equilibrium in the acid media to the azide form (tautomer) and its subsequent photolysis (Scheme II). The previously

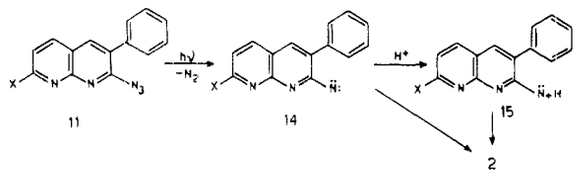
Table I. 6*H*-Indolo[2,3-*b*][1,8]naphthyridine Derivatives



Registry no.	Compd	R	Yield, %	Crystn solvent[a]	Formula[b]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
61634-73-9	**2a**	NH_2	97.0	95% ethanol	$C_{14}H_{10}N_4$	71.79	4.27	23.93	71.50	4.27	23.64
61634-74-0	**2b**	OH	84.5	Me_2SO	$C_{14}H_9N_3O$	71.49	3.83	17.87	71.27	4.10	17.72
61634-75-1	**2c**	Cl	90.8	DMF	$C_{14}H_8ClN_3$	66.27	3.15	16.57	66.18	3.17	16.68
61634-76-2	**2d**	OCH_3	85.6	DMF	$C_{15}H_{11}N_3O$	72.29	4.42	16.87	71.99	4.31	17.15
61634-77-3	**2e**	OC_2H_5	96.0	DMF	$C_{16}H_{13}N_3O$	73.00	4.94	15.97	73.29	5.04	16.24
61634-78-4	**2f**	SH	78.0	DMF	$C_{14}H_9N_3S$	66.93	3.58	16.73	67.21	3.78	16.68
61634-79-5	**2g**	H	47.7	DMF	$C_{14}H_9N_3$	76.71	4.11	19.18	76.46	4.39	18.89

[a] All compounds melt above 320 °C. [b] Satisfactory analytical data (±0.3% for C, H, N) were found for all new compounds listed in the table.

Scheme II



proposed mechanism of the transformation **4** → **5**[4] that involves the hypothetical intermediates **14** and **15** appears to be effective also in this case and satisfactorily rationalizes the formation of indolonaphthyridines **2** from the corresponding tetrazolonaphthyridines **11**.

A wide-range screening was carried out with the compounds **2a–e** in collaboration with the Bristol Myers Laboratories, Syracuse, N.Y., in order to assay the microbiological, pharmacological, and tumor inhibitory properties, but compounds prepared exhibited no activity.

Experimental Section

Melting points were determined on a Kofler apparatus and were uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer in Nujol mulls. Ultraviolet spectra were recorded on a Zeiss Model PMQ II spectrophotometer in 95% ethanol. NMR spectra were obtained in a JEOL Model C60 HL spectrometer in Me_2SO-d_6 with tetramethylsilane as internal standard. All photolyses were performed with a 70-W high-pressure mercury lamp (Hanau, Model TQ 81), equipped with an immersion well system.

8-Methoxy-4-phenyltetrazolo[1,5-*a*][1,8]naphthyridine (11d). A. To a solution containing 0.2 g (8.69 mmol) of sodium metal in 50 mL of absolute methanol was added 0.5 g (1.73 mmol) of **12**; the mixture was heated under reflux for 24 h. The solution was concentrated; the obtained solid was collected, washed with water, and dried to give 0.35 g (72.8%) of **11d**. An analytical sample was obtained by crystallization from ethanol: mp 217–220 °C; IR (Nujol) 1625, 1600, 1295, 1085, 1010, 785 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_5O$: C, 64.98; H, 3.97; N, 25.27. Found: C, 64.70; H, 3.71; N, 25.12.

B. To a solution containing 0.3 g (13 mmol) of sodium metal in 20 mL of absolute methanol was added 1.0 g (3.55 mmol) of **11c**. The mixture was refluxed for 1 h; after cooling the solid was collected by filtration, washed with water, and dried (0.85 g, 86.4%).

General Procedure for Photochemical Cyclization of 8-Substituted 4-Phenyltetrazolo[1,5-*a*][1,8]naphthyridines (11a–e). The following procedure is typical of compounds **2a–e** reported in Table I. A solution of 3.0 g of **11a–e** in 100 mL of trifluoroacetic acid was irradiated until evolution of nitrogen ceased (24 h). The trifluoroacetic acid was removed in vacuo; the residue was treated with water and neutralized (pH 6–7) with 10% NaOH solution. The obtained solid was washed with water and dried. Yields, crystallization solvents, melting points, and IR and UV spectral data for **2a–e** are reported in Tables I and II.

3-Hydroxy-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2b). A. By Diazotization of 2a. To an ice-cooled solution of 0.1 g (0.42 mmol) of **2a** in 2 mL of concentrated H_2SO_4 was added 0.033 g (0.47 mmol) of $NaNO_2$ in small amounts. After standing at room temperature for 2 h the mixture was poured onto crushed ice. The obtained solid was collected by filtration, treated with 10% NaOH solution, and neutralized (pH 6–7) to give 0.09 g (89.6%) of **2b**.

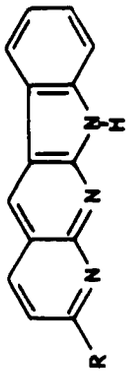
B. By Hydrolysis of 2d. A solution of 0.15 g of **2d** in 1 mL of acetic acid and 1 mL of 48% HBr was refluxed for 4 h. After cooling, the obtained solid was collected, treated with 10% NaOH solution, and neutralized (pH 6–7) to give 0.1 g (70.6%) of **2b**.

C. By Hydrolysis of 2e. Under conditions similar to those described in B, 0.15 g of **2e** gave 0.05 g (82.1%) of **2b**.

3-Chloro-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2c). A mixture of 0.15 g of **2b** and 1.5 mL of $POCl_3$ was refluxed for 15 min. After cooling the solution was poured onto a mixture of ice and excess aqueous NH_3. The formed precipitate was collected, washed with water, and dried to give 0.1 g (61.8%) of **2c**.

3-Methoxy-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2d). To a solution containing 0.04 g (1.73 mmol) of sodium metal in 50 mL of absolute methanol was added 0.075 g (0.29 mmol) of **2c**; the mixture was refluxed for 24 h and, after cooling, filtered obtaining 0.05 g of

Table II. IR and UV Spectral Data of 6-*H*-Indolo[2,3-*b*][1,8]naphthyridine Derivatives



Compd	R	Infrared, cm^{-1}	UV λ_{max}, nm (ϵ_{max})			
2a	NH_2	3480, 3340, 1615, 1245, 915, 800	230 (33 000)	261 (28 000)	275 (27 100)	284 (27 100)	382 (30 000)
2b	OH	1655, 1600, 1240, 960, 830, 780	219 (41 500)	279 (25 700)			376 (29 900)
2c	Cl	1580, 1130, 995, 910, 795, 735	227 (30 500)	270 (36 000)		291 (19 500)	336 (15 600)
2d	OCH_3	1615, 1345, 1240, 1045, 915, 800	226 (39 500)	260 (31 500)		286 (26 250)	340 (16 200)
2e	OC_2H_5	1615, 1345, 1250, 1050, 800, 745	222 (34 500)	261 (34 500)		281 (33 000)	342 (15 900)	365 (15 500)
2f	SH	1615, 1320, 1245, 1110, 785, 712	228 (30 000)	259 (19 000)		282 (28 500)	
2g	H	1615, 1580, 1245, 910, 790, 735	224 (34 000)	269 (36 200)		290 (14 500)	328 (14 300)

starting material; the filtrate was evaporated to dryness under reduced pressure. The residue was treated with water and collected to give 0.015 g (61%) of **2d.**

3-Ethoxy-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2e). To a solution containing 0.04 g (1.73 mmol) of sodium metal in 50 mL of absolute ethanol was added 0.075 g (0.29 mmol) of **2c;** the mixture was refluxed for 24 h. The obtained solution was evaporated to dryness, and the residue was treated with water, collected, and dried to give 0.05 g (64.3%) of **2e.**

11*H*-Tetrazolo[1,5-*a*]indolo[3,2-*g*][1,8]naphthyridine (13). A suspension of 0.15 g (0.59 mmol) of **2c** in 16 mL of DMF and 0.1 g (1.53 mmol) of NaN_3 was refluxed for 30 min. After cooling, the mixture was poured into water, and the precipitate was collected, washed with water, and dried to give 0.135 g (87.7%) of **13.** An analytical sample was prepared by crystallization from DMF: mp >320 °C; IR (Nujol) 3340, 1600, 1260, 1090, 790, 755 cm^{-1}.

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.07; N, 32.31. Found: C, 64.90; H, 3.35; N, 32.21.

3-Amino-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2a). A solution of 0.1 g of **13** in 120 mL of acetic acid was hydrogenated in the presence of 0.05 g of 10% Pd/C catalyst at 3 atm for 46 h at room temperature. After separation of the catalyst, the acetic solution was evaporated to dryness, and the obtained residue was treated with 10% NaOH solution, washed with water, and dried to give 0.04 g (44.4%) of **2a.**

3-Mercapto-6*H*-indolo[2,3-*b*][1,8]naphthyridine (2f). A. By Hydroxy Derivative 2b. A mixture of 0.3 g (1.27 mmol) of **2b** and 0.3 g (1.35 mmol) of P_2S_5 in 30 mL of anhydrous pyridine was refluxed for 2 h. The resulting warm solution was filtered and diluted with 300 mL of water. The obtained crude product was collected and purified by extraction with boiling CS_2 to remove a small quantity of sulfur and crystallized from DMF to give 0.25 g (78%) of **2f.**

B. By Chloro Derivative 2c. A sodium hydrosulfide–ethanol solution was prepared by passing H_2S for 30 min through 260 mL of absolute ethanol in which 0.16 g (6.95 mmol) of sodium metal had previously been dissolved. To this solution was added 0.260 g (1.02 mmol) of **2c** and the suspension was refluxed for 48 h. The resulting solution was reduced to half volume and, after cooling, filtered; addition of 10 mL of water and a few drops of concentrated HCl resulted in the precipitation of yellow solid, which was washed with water and collected to give 0.2 g (77.7%) of **2f.**

6*H*-Indolo[2,3-*b*][1,8]naphthyridine (2g). A suspension of 0.36 g of **2f** and 3 g of Raney nickel catalyst was refluxed and stirred for 8 h. The catalyst was separated by filtration and extracted several times with boiling ethanol. The combined extracts and solution were evaporated to small volume to give 0.15 g (47.7%) of **2g.** An analytical sample was obtained by crystallization from DMF, mp >320 °C.

Acknowledgment. This work was supported by a grant from the Consiglio Nazionale delle Ricerche.

Registry No.—**11a,** 30167-89-6; **11b,** 30167-59-0; **11c,** 30167-85-2; **11d,** 61634-80-8; **11e,** 30167-60-3; **12,** 30167-81-8; **13,** 61634-81-9.

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Synthesis and Reactivity of *anti,exo,exo*- and *anti,exo,endo*-Tetracyclo[5.4.0.$0^{2,5}$.$0^{8,11}$]undeca-3,9-dien-6-yl Tosylates. A Conformationally Restricted Bicyclo[3.2.0]hept-6-en-2-yl System

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Synthesis of *anti,exo,exo*- and *anti,exo,endo*-tetracyclo[5.4.0.$0^{2,5}$.$0^{8,11}$]undeca-3,9-dien-6-yl tosylates (**11**-OTs and **10**-OTs, respectively) was carried out to investigate conformational effects on the reactivity and products of the bicyclo[3.2.0]heptenyl derivatives. The acetolysis rate of **11**-OTs indicates a rate enhancement of 65 (25 °C) when compared to that of *exo*-bicyclo[3.2.0]hept-6-en-2-yl tosylate (**12**-OTs) in spite of the fact that a similar transition state should be expected in their reactions. An exo/endo rate ratio of this rigid tetracyclic system (**11**-OTs/**10**-OTs = 12) is lower than that of the conformationally changed bicyclic system (**12**-OTs/**13**-OTs = 3500) by a factor of 290. Both **10**-OTs and **11**-OTs undergo acetolysis with stereospecific rearrangement to *exo,exo,syn*-tetracyclo[4.4.$1^{2,5}$.0.$0^{7,10}$]undeca-3,8-dien-11-yl acetate (**15**-OAc). Further, the *p*-nitrobenzoate (**15**-OPNB), obtained from **15**-OAc, possesses a solvolytic reactivity ca. 100 times as great as that of the *anti*-7-norbornenyl derivative (**19**). From the above results, the importance of conformational factors associated with Pitzer and *F* strains and of homoallylic and cyclobutyl participations is discussed in detail.

Interrelation of 7-norbornenyl **1** and tricyclo[2.2.1.-$0^{2,7}$]hept-3-yl **2** cations has provided many interesting aspects regarding the study of carbonium ion structure and reactivity.[1] Most recently, bicyclo[3.2.0]hept-6-en-2-yl carbonium ion **3**[2-7] has received a considerable amount of attention for an alternate route to the nonclassical carbonium ion (**5**) by way of