

## Synthesis of some 3-Methyl-11*H*-indolo[3,2-*c*][1,8]naphthyridines. A New Heterocyclic Ring System

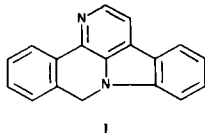
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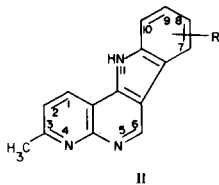
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Some derivatives of 11*H*-indolo[3,2-*c*][1,8]naphthyridine, a new heterocyclic system, have been prepared using the Fischer indole synthesis on the appropriately phenylhydrazones. The preparation of some substituted 5,6-dihydro-11*H*-indolo[3,2-*c*][1,8]naphthyridines is also described.

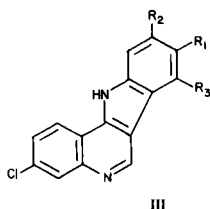
Some alkaloids with high pharmacological interest contain the indole nucleus as a part of a polycyclic system see e.g., lysergic acid, reserpine, the *Vinca* alkaloids, etc. In a previous paper one of us described some compounds in which the nucleus of 9*H*-benzo[*h*]indolo[3,2,1-*d,e*][1,5]-naphthyridine was present (I) (1).



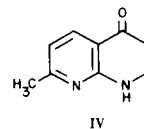
We continued our investigation in this field by preparing some substituted 11*H*-indolo[3,2-*c*][1,8]naphthyridines (II), which represent a new heterocyclic ring structure.



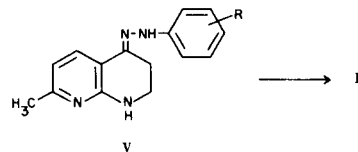
Compounds of this type appear to be potentially important because of their structural relationship to amodiaquine, one of the most widely used antimalarial drugs. Recent studies have shown that the increased planar area of amodiaquine as in III increased the activity (2). Besides compounds II are quasi-steroidal heterocycles (3).



The preparation of 7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)one (IV) was recently described (4).



We have now prepared the title compounds using the Fischer indole synthesis on the appropriately phenylhydrazones of IV (V) (see Table I).



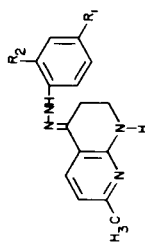
The naphthyridinoindoles II were obtained in 36-70% yield by treating V with dilute sulfuric acid or with polyphosphoric acid. In this reaction indolization is followed by spontaneous dehydrogenation. This atmospheric oxidation to the fully aromatic type is well known (2,3,5).

The phenylhydrazones Vg,h,i could not be cyclized, owing to the deactivating effect of the substituents on the benzene nucleus. The substances II, thus obtained, are very high melting crystalline solids (m.p. above 320°), slightly soluble in all usual organic solvents.

The most soluble product was 3-methyl-10-chloro-11*H*-indolo[3,2-*c*][1,8]naphthyridine (II*f*). The structure of this compound has been confirmed by nmr spectral data (DMSO-*d*<sub>6</sub>, 110°). In fact, the nmr spectrum of II*f* shows a singlet at 2.78 δ (three protons) assigned to CH<sub>3</sub>, a singlet at 9.9 δ assigned to H<sub>6</sub>, a singlet (broad) at 13.0 δ assigned to NH, two proton signals at 9.35 δ and 7.50 δ due to H<sub>1</sub> and H<sub>2</sub> respectively (*J* = 8.0 cps). The absorption range for phenyl protons is 8.4 δ to 7.58 δ. It was impossible to obtain nmr spectra of IIa-e because of their insolubility. The molecular weight of IIa (233) was determined by mass spectrum.

Table I

## 7-Methyl-2,3-dihydro-1,8-naphthyridin-4-(1H)one Phenylhydrazones (V)

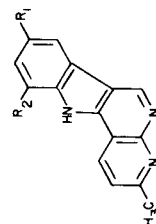


Compound	R <sub>1</sub>	R <sub>2</sub>	Yield %	M.p., °C	Crystallization Solvent	Empirical Formula	Elemental Analyses				
							Calcd., %	Found, %	N		
Va	H	H	87	172-174	95% ethanol	C <sub>15</sub> H <sub>16</sub> N <sub>4</sub>	6.35	22.22	71.50	6.15	22.00
Vb	Br	H	92	127-129	benzene	C <sub>15</sub> H <sub>15</sub> BrN <sub>4</sub>	4.53	16.92	54.59	4.30	16.62
Vc	F	H	98	119-121	benzene	C <sub>15</sub> H <sub>15</sub> FN <sub>4</sub>	5.55	20.74	66.41	5.48	20.73
Vd	Cl	H	87	210-213	95% ethanol	C <sub>15</sub> H <sub>15</sub> ClN <sub>4</sub>	5.23	19.54	62.71	5.17	19.33
Ve	OCH <sub>3</sub>	H	96	142-145	(a)	C <sub>16</sub> H <sub>18</sub> N <sub>4</sub> O	6.38	19.86	67.95	6.34	19.78
Vf	H	Cl	95	198-200	95% ethanol	C <sub>15</sub> H <sub>15</sub> ClN <sub>4</sub>	5.23	19.54	62.72	5.22	19.38
Vg	NO <sub>2</sub>	H	90	260-261	DMFA	C <sub>15</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub>	5.05	23.57	60.45	5.15	23.48
Vh	H	COOH	95	303-305	DMFA	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	5.40	18.92	64.60	5.36	18.69
Vi	NO <sub>2</sub>	NO <sub>2</sub>	91	308-310	DMFA-water	C <sub>15</sub> H <sub>14</sub> N <sub>6</sub> O <sub>4</sub>	4.09	24.56	52.35	3.99	24.45

(a) Recrystallization is not possible because this compound decomposes to a black tar.

Table II

## 3-Methyl-11H-indolo[3,2-c][1,8]naphthyridines (II)

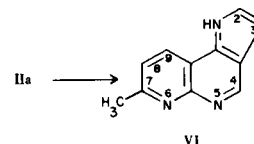
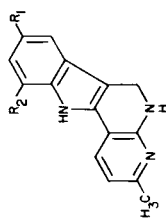


Compound	R <sub>1</sub>	R <sub>2</sub>	Yield %		Recrystallization Solvent	Empirical Formula	Elemental Analyses			Ultraviolet absorption spectra λ max. mμ (log ε)					
			Method a	Method b			Calcd., %	Found, %	N						
IIa	H	H	70	70	DMFA	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub>	77.25	4.72	18.02	77.34	4.56	18.15	234 (4.627)	257 (4.230) (a)	280 (4.730)
IIb	Br	H	68	65	DMFA	C <sub>15</sub> H <sub>10</sub> BrN <sub>3</sub>	57.69	3.20	13.46	57.91	3.10	13.73	244 (4.683)	260 (4.214) (a)	282 (4.720)
IIc	F	H	61	61	DMFA	C <sub>15</sub> H <sub>10</sub> FN <sub>3</sub>	71.71	3.98	16.73	71.45	3.78	16.43	230 (4.612)	258 (4.220) (a)	280 (4.707)
IId	Cl	H	60	58	DMFA	C <sub>15</sub> H <sub>10</sub> ClN <sub>3</sub>	67.29	3.74	15.70	67.05	3.85	15.48	242 (4.679)	260 (4.176) (a)	281 (4.698)
IIe	OCH <sub>3</sub>	H	36	36	DMFA	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O	73.00	4.94	15.97	72.98	4.98	15.96	236 (4.679)	264 (4.437)	286 (4.597)
IIf	H	Cl	66	63	95% ethanol	C <sub>15</sub> H <sub>10</sub> ClN <sub>3</sub>	67.29	3.74	15.70	67.25	3.86	15.40	238 (4.643)	256 (4.214) (a)	278 (4.709)

(a) Inflection.

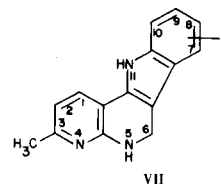
Table III  
3-Methyl-5,6-dihydro-1*H*-indolo[3,2-*c*][1,8]naphthyridines (VII)

Compound	R <sub>1</sub>	R <sub>2</sub>	Yield %	Empirical Formula	Calcd., %			Found, %			Ultraviolet absorption spectra		
					C	H	N	C	H	N	λ max, mμ	(log ε)	
VIIa	H	H	74	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub>	76.59	5.53	17.87	76.62	5.31	17.79	218 (4.602)	268 (4.049)	374 (4.296)
VIIb	Br	H	67	C <sub>15</sub> H <sub>12</sub> BrN <sub>3</sub>	57.32	3.82	13.37	57.22	3.57	13.45	222 (4.621)	270 (4.120)	379 (4.326)
VIIc	F	H	76	C <sub>15</sub> H <sub>12</sub> FN <sub>3</sub>	71.15	4.74	16.60	71.21	4.72	16.31	215 (4.551)	270 (4.079)	376 (4.305)
VII d	Cl	H	72	C <sub>15</sub> H <sub>12</sub> ClN <sub>3</sub>	66.79	4.45	15.58	66.60	4.56	15.38	222 (4.610)	268 (4.086)	378 (4.309)
VIIe	OCH <sub>3</sub>	H	75	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O	72.45	5.66	15.84	72.19	5.52	15.56	220 (4.579)	270 (4.017)	376 (4.301)
VII f	H	Cl	50	C <sub>15</sub> H <sub>12</sub> ClN <sub>3</sub>	66.79	4.45	15.58	66.52	4.63	15.36	220 (4.549)	274 (3.763) (a)	374 (4.296)



Only several 4-aryl derivatives of 1*H*-pyrrolo[3,2-*c*][1,8]naphthyridine were previously described (9).

When the ketone IV and the required phenylhydrazine were heated in ethanol with concentrated hydrochloric acid, the indolization reaction proceeds without aromatization with the formation of the dihydroderivatives VII (yield from 50% to 76%, see Table III).



Compounds VII are very stable in the solid state (m.p. above 320°), instead in solution, very rapidly on heating, gave quantitatively the fully aromatic type II. The fluorescence of the solutions of VII, even when very dilute, in Wood's light, disappears because of the aromatization. Additional support for the above structure VII was obtained by the ir spectra (nujol) which show two NH bands at 3450 and 3250 cm<sup>-1</sup>.

The uv spectra of VII show a behaviour closely similar among them, but they are different to those of II (see Table III). Nmr spectra were not recorded because the

(a) Inflection.

dehydrogenation of compounds VII to II in concentrated solution takes place.

#### EXPERIMENTAL

All melting points were determined on a Kofler apparatus and are 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 ethanol. The nmr spectra were obtained on a Jeol Model C 60 HL spectrometer.

General Procedure for the Preparation of 7-Methyl-2,3-dihydro-1,8-naphthyridin-4(1H)one Phenylhydrazones (Va-i).

A mixture of 3.0 g. of IV, 60 ml. of ethanol and slight excess of the required phenylhydrazine hydrochloride was refluxed for 15 minutes. After cooling, a yellow-orange precipitate formed, which was collected, suspended in water and alkalized with 2*N* aqueous sodium hydroxide, collected again and washed with water. The crystallization solvent, yield, melting point and analytical data for compounds Va-i, prepared by this general procedure, are given in Table I.

3-Methyl-11*H*-indolo[3,2-*c*][1,8]naphthyridines (IIa-f).

Method a: Phenylhydrazone hydrochloride (1.0 g.) was mixed with 10 ml. of 20% sulfuric acid and heated in the water bath for 25-30 minutes. The mixture was cooled and the crude yellow product was collected and treated with 2*N* aqueous sodium hydroxide. The solid was filtered, washed with water and dried. The crystallization solvent, yield and analytical data for compounds IIa-f prepared by this general procedure, are given in Table II.

Method b: Phenylhydrazone hydrochloride (1.0 g.) was added to an excess of polyphosphoric acid (6-8 g.) and the mixture was heated in oil bath at 100°, with stirring. The internal temperature was raised to 110° and maintained at 130° for 10 minutes. The mixture was allowed to cool somewhat, poured on ice and 10% aqueous sodium hydroxide. The solid was collected and washed with water. The yield is similar to that obtained under the conditions described in Method a.

7-Methyl-1*H*-pyrrolo[3,2-*c*][1,8]naphthyridine (VI).

3-Methyl-11*H*-indolo[3,2-*c*][1,8]naphthyridine (IIa) (2.33 g., 0.01 mole) was added slowly, with stirring, to concentrated sulfuric acid (17.5 ml.). During the addition, the temperature rose to ~40°. Chromium(VI) oxide (3.0 g., 0.03 mole) was added to the stirred solution in small portions. When necessary, the mixture was cooled to keep the temperature below 70°. After the addition was complete, the mixture was stirred until the temperature dropped to 35°, then it was cooled to room temperature and poured onto

crushed ice. The precipitated solid was filtered off, washed with water, and treated with 10% aqueous sodium hydroxide. The filtrate was acidified with dilute hydrochloric acid and the precipitate was collected, washed with water and dried (1.35 g.), m.p. >320°. A mixture of this crude product, copper chromite (0.2 g.) and 50.0 ml. of quinoline was refluxed for three hours. The mixture was filtered, the filtrate was evaporated to 6-7 ml. at reduced pressure and the residue was diluted with petroleum ether. The precipitated solid was collected, washed with 10% aqueous sodium hydroxide and heated *in vacuo* (2-3 mm.) at 320°. This was obtained a small amount of VI. The analytical sample was obtained by crystallization from ethanol, m.p. 276-278° dec.

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.35; H, 5.00; N, 22.68.

3-Methyl-5,6-dihydro-11*H*-indolo[3,2-*c*][1,8]naphthyridines (VIIa-f).

To a solution of 1.62 g. (0.01 moles) of IV and 0.011 moles of the required phenylhydrazine hydrochloride in 20 ml. of ethanol, 5 ml. of concentrated hydrochloric acid was added and the mixture was refluxed for 18 hours. The yellow-orange precipitate was collected and treated with 10% aqueous sodium hydroxide. The solid was filtered, washed with water and dried. Recrystallization is not possible, because the aromatization of compounds VII to II takes place. Yield and analytical data are given in Table III.

Acknowledgment.

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