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Thiazoloisoquinolines. IV. The Synthesis and Spectra of Thiazolo[4,5-*h*]- and Thiazolo[5,4-*f*]isoquinolines. The Ultraviolet and Proton Magnetic Resonance Spectra of Some Substituted Isoquinolines[1,2]

ALFRED TAURINS AND RICHARD KANG-CHUAN HSIA[3]

Department of Chemistry, McGill University, Montreal, Quebec

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Thiazolo[4,5-*h*]isoquinoline was synthesized from 7-aminoisoquinoline in four steps: by the reaction with potassium thiocyanate and bromine to give 7-amino-8-thiocyanoisoquinoline; cyclization of the latter with hydrochloric acid to produce 2-aminothiazolo[4,5-*h*]isoquinoline, followed by the Sandmeyer reaction to yield a 2-chloro derivative, and finally, reduction with hydriodic acid and phosphorus. Thiazolo[5,4-*f*]isoquinoline was prepared from 6-aminoisoquinoline via 6-amino-5-thiocyanoisoquinoline. The synthesis of 2,5-diaminothiazolo[5,4-*h*]isoquinoline was achieved by cyclization of 5-acetamido-8-aminoisoquinoline which was obtained from 5-aminoisoquinoline. In 5-amino-8-thiocyano- and 8-amino-5-thiocyanoisoquinolines, the thiocyano group was hydrolyzed to the thiol group with 8 *N* hydrochloric acid and ethanol (1:1).

The u.v. and p.m.r. spectra of the intermediate isoquinolines, and the i.r., u.v., and n.m.r. spectra of thiazoloisoquinolines were studied.

On a synthétisé le thiazolo[4,5-*h*]isoquinoline à partir de la 7-aminoisoquinoline en quatre étapes: par la réaction avec le thiocyanate de potassium et le brome, on obtient le 7-amino-8-thiocyanoisoquinoline; la cyclisation de ce produit avec l'acide chlorhydrique amène au 2-aminothiazolo[4,5-*h*]isoquinoline, suivi par la réaction de Sandmeyer, ce qui donne le dérivé 2-chloro dont on fait la réduction avec l'acide iodhydrique et le phosphore. On a préparé le thiazolo[5,4-*f*]isoquinoline à partir du 6-aminoisoquinoline en passant par le 6-amino-5-thiocyanoisoquinoline. On a réussi la synthèse du 2,5-diaminothiazolo-[5,4-*h*]isoquinoline qui fut obtenu à partir du 5-aminoisoquinoline. Pour les 5-amino-8-thiocyano- et le 8-amino-5-thiocyanoisoquinolines, le groupe thiocyano a été hydrolysé en thiol avec l'acide chlorhydrique 8 *N* et l'éthanol (1:1).

On a étudié les spectres ultraviolet et de r.m.p. des isoquinolines intermédiaires, de même que les spectres i.r., u.v., et r.m.n. des thiazoloisoquinolines.

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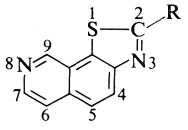
Discussion

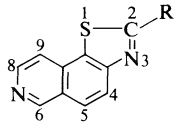
The program aimed at the synthesis of eight isomeric thiazoloisoquinolines was continued. Two representatives of this series, thiazolo[4,5-*c*]- and thiazolo[5,4-*c*]isoquinolines have been described in the previous papers (1–3). In this work, we report studies in the series of thiazolo[4,5-*h*]- (**1**), -[5,4-*f*]- (**2**), and -[5,4-*h*]isoquinoline (**3**). The general method for the preparation of the amino derivatives of **1**, **2**, and **3**, was the thiocyanation of the appropriate aminoisoquinolines, followed by the cyclization of the *o*-aminothiocyano derivatives.

The starting material for the preparation of thiazolo[4,5-*h*]isoquinoline (Scheme 1) was 7-aminoisoquinoline (**5**) which was thiocyanated in the 8-position with potassium thiocyanate and bromine in 95% acetic acid to give 7-amino-8-thiocyanoisoquinoline (**6**).

Treatment of **6** with alcoholic hydrochloric acid

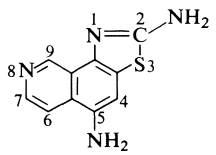


1
[4,5-*h*]

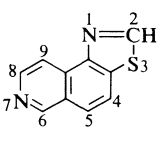


2
[5,4-*f*]

a R = NH_2
b R = Cl
c R = H



3
[5,4-*h*]

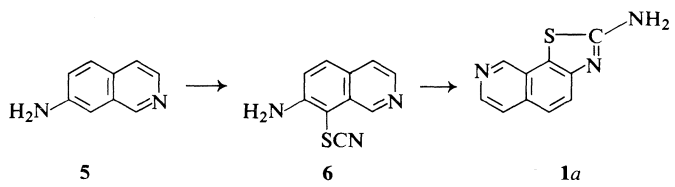


4
[4,5-*f*]

[1]For Part III, see Hall and Taurins (3).

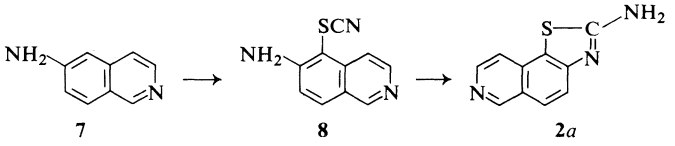
[2]This work received financial assistance from the National Research Council of Canada, Ottawa, Canada. Taken from a portion of the Ph.D. Thesis of R. K. C. Hsia.

[3]Holder of an NRCC Studentship, 1966–1969.



5 6 1*a*

SCHEME 1



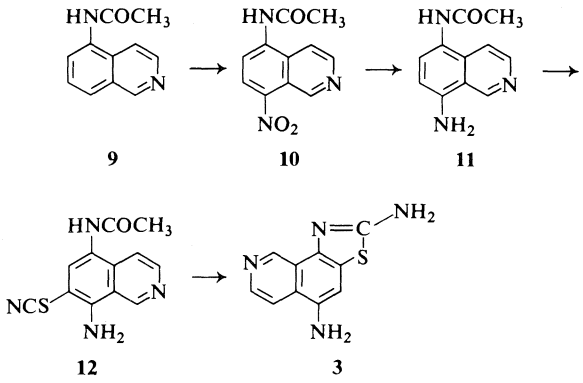
7 8 2*a*

SCHEME 2

at reflux temperature gave 2-aminothiazolo-[4,5-*h*]isoquinoline (**1***a*) in the form of a yellow crystalline substance. Diazatization of 2-amino-thiazolo[4,5-*h*]isoquinoline (**1***a*) with sodium nitrite in 70% nitric and 85% orthophosphoric acid mixture (1:4), followed by the treatment of the diazonium salt with cuprous chloride gave 2-chlorothiazolo[4,5-*h*]isoquinoline (**1***b*), which on reduction with hydriodic acid and red phosphorus gave thiazolo[4,5-*h*]isoquinoline (**1***c*). This forms colorless needles, m.p. 138–139° (*n*-hexane) and has a very low solubility in organic solvents.

In the synthesis of thiazolo[5,4-*f*]isoquinoline (**2***c*), thiocyanation of 6-aminoisoquinoline (**7**) produced the key intermediate 6-amino-5-thiocyanoisoquinoline (**8**) which was cyclized with hydrochloric acid to obtain 2-aminothiazolo-[5,4-*f*]isoquinoline (**2***a*). The further steps leading to the chloro-derivative **2***b* and the parent compound 2*c* were similar to those outlined for the [4,5-*h*] series (Scheme 2). Thiazolo[5,4-*f*]isoquinoline (**2***c*) was obtained in pure state by sublimation and recrystallization from *n*-hexane. This forms colorless needles, m.p. 170° (dec.), and has a very low solubility in organic solvents.

The preparation of 2,5-diaminothiazolo[5,4-*h*]-isoquinoline (**3***a*) is outlined in Scheme 3. To achieve the [5,4-*h*]-fusion of the thiazole and isoquinoline rings, it would be necessary to have amino and thiocyano groups in the 8- and 7-positions, respectively. To prevent the thiocyanation of the 5-position in 8-aminoisoquinoline, that position was blocked by the acetamido group. The starting material, 5-acetamidoisoquinoline (**9**), was nitrated in concentrated sulfuric acid with potassium nitrate to give 5-



9 10 11 12 3

SCHEME 3

acetamido-8-nitroisoquinoline (**10**). Catalytic hydrogenation of **10** with hydrogen and 5% palladium-on-charcoal catalyst produced 5-acetamido-8-aminoisoquinoline (**11**), which on thiocyanation yielded 5-acetamido-8-amino-7-thiocyanoisoquinoline (**12**). The compound **12** was successfully cyclized with hydrochloric acid to give 2,5-diaminothiazolo[5,4-*h*]isoquinoline (**3**), a yellow crystalline compound. Diazatization of **3**, followed by Sandmeyer reaction, failed to produce the desired 2,5-dichloro[5,4-*h*]isoquinoline.

In order to synthesize thiazolo[4,5-*f*]isoquinoline (**4**) by the same type of cyclization reactions as mentioned previously, it was desirable to obtain 5-amino-6-thiocyanoisoquinoline from 5-amino-isoquinoline. However, the only product of the thiocyanation of 5-aminoisoquinoline was 5-amino-8-thiocyanoisoquinoline (**13**). The structure of 5-amino-8-thiocyanoisoquinoline (**13**) was obvious from its inability to cyclize with 4 *N* hydrochloric acid and ethanol (1:1) under reflux (the starting material was recovered). However,

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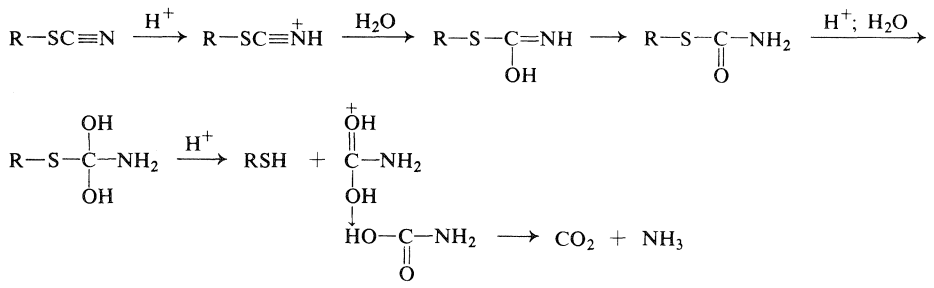
TABLE 1. The u.v. absorption maxima and log ε values of thiazolo[4,5-*h*]isoquinoline and its derivatives (in absolute ethanol)

Compound	α-Band		p-Band		β-Band	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
Thiazolo[4,5-*h*]isoquinoline	333	3.70	289	3.78	253	4.66
	319	3.64	279	3.78	227	4.36
	304	3.64			207	4.25
2-Chloro-	335	3.51	288	3.72	254	4.50
	323	3.47			228	4.14
					216 sh	3.95
2-Acetamido-	325–345	3.54	312	4.03	262 sh	4.56
			301	4.08	238	4.28
					207	4.27
2-Amino-	360	3.71	308	4.30	266	4.84
			296	4.28	228	4.41
					206	4.39
2-Hydroxy-	355	3.65	314	3.70	252	4.57
			297	3.92	216	4.40
			287	4.01		
			273	4.26		



SCHEME 4

8 *N* hydrochloric acid and ethanol (1:1) hydrolyzed **13** to give 5-amino-8-mercaptoisoquinoline (**14**).

Thiocyanation of 8-aminoisoquinoline gave only a para-substituted product, 8-amino-5-thiocyanoisoquinoline (**15**). Since no ortho-substitution occurred, 8-aminoisoquinoline could not serve as the key intermediate for the preparation of thiazolo[5,4-*h*]isoquinoline.

8-Amino-5-thiocyanoisoquinoline (**15**) was also hydrolyzed with 8 *N* hydrochloric acid and ethanol (1:1) to give 8-amino-5-mercaptoisoquinoline (**16**), a kind of reaction not reported for thiocyanates. Conversion of thiocyanates to mercaptans has been usually achieved by reduction, for example, with zinc and hydrochloric acid, lithium aluminum hydride, or sulfides (4). Riemschneider (5) found that thiocyanates are transformed into thiocarbamates by treatment with sulfuric acid at 0 to 5°, but no further change was observed.

It is believed that the acidic hydrolysis of the thiocyano group proceeds through a thiocarbamate intermediate which is hydrolyzed further to give the thiol as shown in Scheme 4.

Spectra

Ultraviolet Spectra

The u.v. absorption data of thiazolo[4,5-*h*]- and -[5,4-*f*]isoquinoline and their derivatives are presented in Tables 1 and 2. The pattern of the spectra of these compounds is characteristic of the angularly fused three-ring aromatic and hetero-aromatic systems which usually display three main types of bands arising from $\pi \rightarrow \pi^*$ transitions. (In most cases, linearly fused three-ring systems show only two bands, due to the coalescing of bands.) These bands are designated as α-, p-, and β-bands by Clar (6), or as L_b, L_a, and $B_a + B_b$ bands by Platt (7). The u.v. spectra of the angular unsubstituted thiazoloisoquinolines **1***c* and **2***c*, and also of thiazolo[4,5-*c*]- and -[5,4-*c*]-

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TABLE 2. The u.v. absorption maxima and log ε values of thiazolo[5,4-*f*]isoquinoline and its derivatives (in absolute ethanol)

Compound	α-Band		p-Band		β-Band	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
Thiazolo[5,4-*f*]isoquinoline	333	3.56	286	3.72	250 sh	4.55
	319	3.53	274	3.78	244	4.66
	306	3.45			210 sh	4.04
2-Chloro-	335	3.55	278	3.76	252	4.80
	320	3.55			227	4.53
	306	3.44				
2-Acetamido-	333	3.63	295–310	3.83	272	4.63
	319	3.87			262	4.60
					240	4.24
					229 sh	4.17
					205	4.14
2-Amino-	345 sh	3.47	320	3.80	267	4.70
					245 sh	4.21
					219 sh	4.03
					206	4.03
2-Hydroxy-	290–340	3.83	273	4.17	252	4.74
					219 sh	4.28

TABLE 3. The u.v. absorption maxima and log ε values of monosubstituted isoquinolines (in absolute ethanol)

Compound	α-Band		p-Band		β-Band	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
5-Aminoisoquinoline	335	3.64	244	4.04	208	4.26
6-Amino-	337	3.56	306	3.95	242	4.54
					206	3.88
7-Amino-	360	3.42	283	3.97	236	4.50
					214	4.16
8-Amino-	360	3.93	242	4.39	212	4.63
5-Acetamido-	320	3.86	290	3.90	220	4.62
			268	4.27		
5-Bromo-	325	3.76	286	3.82	222	4.76
			276	3.86		
5-Nitro-	330	3.72	230–235	4.02	214	4.49
	310	3.60				
6-Hydroxy-	325 sh	3.25	286	3.66	230	4.69
7-Hydroxy-	335	3.35	263	3.49	224	4.45
Isoquinoline (14)	317	3.5	266	3.6	217	4.6

isoquinoline (1, 2) are similar to those of phenanthridine (8) and benzo[*h*]isoquinoline (9).

The u.v. absorption maxima and their corresponding log ε values of the mono- and disubstituted isoquinolines, measured in ethanol, are summarized in Tables 3 and 4. The spectral data for isoquinoline (10) have been added for reference. Osburn *et al.* (11) have recorded the u.v. spectra of 2-, 3-, 4-, 5-, 6-, 7- and 8-aminoisoquinolines in neutral and strongly acidic water solutions, and determined their pK_a values. Comparison of these data with those in Table 3 shows that only 5-aminoisoquinoline has the same spectrum in water and ethanol solution, and that 6-, 7-, and 8-aminoisoquinolines in ethanol display a red shift of α- and p-bands in the order of 10 to 12 nm compared with the values obtained in water. Amino and hydroxyl groups in the 6-position produce a red shift of the β-band, as shown by the 6-amino-, 6-hydroxy-, and 6-amino-5-thio-

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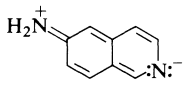
TABLE 4. The u.v. absorption spectra and log ε values of disubstituted isoquinolines (in absolute ethanol)

Compound	α-Band		p-Band		β-Band	
	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε	λ_{max} (nm)	log ε
5-Amino-8-thiocyano-isoquinoline	390	3.99	252	4.16		
	345	3.95			214	4.41
8-Amino-5-thiocyano-	370	3.88	252	4.01	214	4.06
	325	3.74				
6-Amino-5-thiocyano-	340	3.55	302	3.72	248	4.58
			292	3.80	204	3.84
5-Amino-8-mercapto-	340	3.84	254	4.06	214	4.31
8-Amino-5-mercapto-	335	3.98	244	4.40	215	4.41
8-Amino-5-bromo-	355	3.90	238	4.05	213	4.47
	325	3.85				
5-Bromo-8-nitro-	330	3.80	296	3.78	220	4.48
5-Acetamido-8-amino-	370	3.72	248	4.13	210	4.40
5-Acetamido-8-nitro-	350	3.93	230	4.32	212	4.27

cyanoisoquinoline. It is believed that this shift is due to the resonance effect which involves the 6-amino-, or 6-hydroxy group, and the ring nitrogen; for example,



The 6-amino group in isoquinolines causes also a strong red shift of the p-band. In the majority of 5,8-disubstituted isoquinolines, the p-band shows a blue shift, and a considerable red shift of the α-band, compared with the p-band of unsubstituted isoquinoline. All 5,8-disubstituted isoquinolines have the β-band very close to 216 nm, the position of the β-band in unsubstituted isoquinoline.

Nuclear Magnetic Resonance Spectra

A survey of the literature reveals that in addition to the n.m.r. spectrum of isoquinoline (12, 13) only a few spectra of substituted isoquinolines have been studied (14–16).

In this work, we recorded the n.m.r. spectra of a number of isoquinolines with one (Table 5) or two substituents (Table 6) on the benzenoid ring. When it was possible, first-order interpretation of spectra was applied and the coupling constants were measured with an accuracy of 0.2 Hz. In 5-, 6-, 7-, and 8-aminoisoquinolines, the two doublets for H-3 and -4, are well separated from other bands, but in the rest of the compounds, with the exception of 6-hydroxyisoquinoline, the H-4 is overlapping with bands from the benzenoid ring. 5-Nitroisoquinoline represents a very special case by showing a complex multiplet including also the H-3 band.

In 5-aminoisoquinoline, the protons H-6, -7, and -8 represent an ABX system, however, the spectrum of these protons is "deceptively simple", as in a quasi A_2B system, consisting of a triplet and a doublet.

6-Aminoisoquinoline displays a spectrum of the benzenoid protons from which it is possible to measure the coupling constants $J_{5,7}$ and $J_{7,8}$. However, the coupling constant $J_{5,8}$ seems to be very small, because there is no corresponding splitting between H-5 and -8. Most of the disubstituted isoquinolines (Table 6) investigated were of the 5,8-type, and the bands for H-6 and -7 showed up as two doublets, with the exception of 5-acetamido-8-nitro- and 5-bromo-8-nitroisoquinoline where H-6 and -7 formed a singlet with the intensity of two protons.

In the n.m.r. spectrum of thiazolo[4,5-*h*]isoquinoline, the two doublets at 7.78 and 8.62 δ are assigned to H-6 and -7, and the two singlets at 9.14 and 9.40 δ to H-2 and -9, respectively (Table 7). Such an assignment to H-2 and -9 is in agreement with the n.m.r. spectra of 2-substituted thiazolo-[4,5-*h*]isoquinolines in which the band at 9.14 δ is not present. The band at 9.40 δ shows also a slight coupling with both H-6 and -7. The two remaining benzenoid ring protons H-4 and -5 also display a typical AX pattern of two doublets centered at 7.82 and 8.33 δ ($J_{4,5}$ = 9.0 Hz). However, the assignment for both H-4 and -5 is not

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TABLE 5. The n.m.r. spectra of monosubstituted isoquinolines

Compound	Chemical shift (δ)*								*J* (Hz)	
	H-1	H-3	H-4	H-5	H-6	H-7	H-8	Other	$J_{3,4}$	Other
Isoquinoline†	9.22 s	8.52 s	(7.90		to	7.23)	m‖	—	6.0	
5-Acetamido-‡	9.30 s	8.55 d	m‖	—	(8.20	to	7.48) m‖	2.22 (CH_3)	6.0	
5-Amino-†	9.18 s	8.47 d	7.57 d	—	6.90 t		7.53 d	4.37 (NH_2)	6.0	
6-Amino-‡	8.94 s	8.14 d	7.38 d	6.83 d	—	7.11 q	7.79 d	5.98 (NH_2)	6.0	$J_{7,8}$ = 9.0 Hz $J_{5,7}$ = 2.4 Hz
7-Amino-‡	9.00 s	8.20 d	7.55 d	(7.77	to 7.00) m‖	—	m‖	4.10 (NH_2)	6.0	
8-Amino-‡	9.53 s	8.38 d	7.50 d	(7.60	to	6.78) m‖	—	6.05 (NH_2)	6.0	
5-Bromo-†	9.22 s	8.62 d	m‖	—	(8.00	to	7.42) m‖	—	6.0	
5-Nitro-‡	9.50 s	m‖	m‖	—	(8.80	to	7.73) m‖	—	—	
6-Hydroxy-‡§	9.22 s	8.43 d	7.70 d	m‖	—	(7.50	to 7.31) m‖	—	6.0	
7-Hydroxy-‡§	9.13 s	8.37 d	(7.97	to	7.42) m‖	—	m‖	—	6.0	

*Doublet, d; quartet, q; triplet, t.
†In $CDCl_3$ solution.
‡In DMSO-d_6 solution.
§After exchange of OH with D_2O.
‖Overlapping multiplets.

TABLE 6. The n.m.r. spectra of disubstituted isoquinolines

Compound	Chemical shift (δ)*							*J* (Hz)	
	H-1	H-3	H-4	H-6	H-7	H-8	Other	$J_{3,4}$	$J_{6,7}$
5-Acetamido-8-amino-†	9.50 s	8.39 d	7.61 d	7.44 d	6.72 d	—	3.10 (CH_3) 6.08 (NH_2)	6.0	8.5
5-Acetamido-8-nitro-†	9.90 s	8.73 d	8.30 d	8.43 s		—	3.25 (CH_3)	6.0	—
5-Amino-8-mercapto-†	9.33 s	8.43 d	8.02 d	6.71 d	7.31 d	—		6.0	8.5
8-Amino-5-mercapto-‡	9.93 s	8.30 d	8.07 d	7.70 d	6.93 d	—		6.0	8.5
5-Amino-8-thiocyano-†	9.64 s	8.66 d	8.19 d	6.97 d	7.87 d	—	6.88 (NH_2)	6.0	8.7
6-Amino-5-thiocyano-‡	9.23 s	8.53 d	8.26 d	—	7.47 d	8.16 d		6.0	‖
7-Amino-8-thiocyano-†	9.21 s	8.41 d	8.00 d	7.75 s§	—	—		6.0	—
8-Amino-5-thiocyano-†	9.64 s	8.65 d	7.95 d	7.89 d	6.60 d	—	7.10 (NH_2)	6.0	9.0
5-Bromo-8-nitro-†	10.50 s	9.58 d	8.86 d	9.00 s		—		6.0	—

*Doublet, d; singlet, s.
†In DMSO-d_6 solution.
‡In acetic acid-d_4 solution.
§Overlap with H-5.
‖$J_{7,8}$ = 9.0 Hz.

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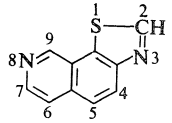
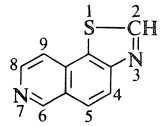
TABLE 7. The n.m.r. spectra of thiazolo[4,5-*h*]isoquinoline and its derivatives



Compound	Chemical shift (δ)*							*J* (Hz)	
	H-2	H-4	H-5	H-6	H-7	H-9	Other	$J_{4,5}$	$J_{6,7}$
Thiazolo[4,5-*f*]isoquinoline†	9.14 s	7.82 d or 8.33 d	8.33 d or 7.82 d	7.78 d	8.62 d	9.40 s	—	9.0	5.9
Acetamido-‡·§	—	Overlap at 8.21	to 8.35	8.21 d	8.91 d	9.79 s	2.61 (CH_3)	—	5.8
2-Amino-‡	—	Overlap at	7.77 7.92	to	8.47 d	9.26 s	3.39 (NH_2)	—	5.8
2-Chloro-†	—	7.76 d or 8.04 d	8.04 d or 7.76 d	7.59 d	8.67 d	9.32 s	—	9.0	5.9
2-Hydroxy-‡	—	7.51 d or 8.08 d	8.08 d or 7.51 d	7.59 d	8.55 d	9.32 s	—	9.0	5.8

*Doublet, d; singlet, s.
†In $CDCl_3$ solution.
‡In DMSO-d_6 solution.
§At 160°.

TABLE 8. The n.m.r. spectra of thiazolo[5,4-*f*]isoquinoline and its derivatives



Compound	Chemical shift (δ)							*J* (Hz)	
	H-2	H-4	H-5	H-6	H-8	H-9	Other	$J_{4,5}$	$J_{8,9}$
Thiazolo[5,4-*f*]isoquinoline*	9.19 s	7.74 d or 8.12 d	8.12 d or 7.74 d	9.38 s	8.65 d	7.82 d	—	6.0	9.0
2-Acetamido-†	—	Overlap at 8.75 d		10.01 s	9.31 d	8.58 d	3.0 (CH_3)	—	5.8
2-Amino-†	—	8.10 d	7.75 d	9.32 s	8.55 d	7.73 d	‡ (NH_2)	9.0§	5.5
2-Chloro-*	—	Overlap at 7.97 d		9.30 s	8.65 d	7.73 d		—	6.5

*In $CDCl_3$ solution.
†In DMSO-d_6 solution.
‡NH_2 absorbs in the same region as H-4 and -5.
§NH_2 bands disappear after D_2O exchange. $J_{4,5}$ value is that of the deuterated compound.

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possible from the first-order interpretation of the spectrum. The n.m.r. spectrum of thiazolo-[5,4-*f*]isoquinoline (Table 8) is analogous to that of thiazolo[4,5-*h*]isoquinoline.

Infrared Spectra

The i.r. spectra of thiazoloisoquinolines in the region 1700–400 cm^{-1} are presented in Table 9.

The strong bands starting from 1615–1602 to 1350 cm^{-1} are attributed to the aromatic and heteroaromatic double bond stretching vibrations. The bands in the region 1350–950 cm^{-1} are mostly moderate or weak, and they are assigned to C—H in-plane-deformation vibrations. Strong bands due to C—H out-of-plane bending motions occur in the region 950–650 cm^{-1}. All compounds in this series have strong bands between 835–810 cm^{-1}. In the far i.r. region, 650–400 cm^{-1} (ring deformation vibrations) (17) the band pattern is very sensitive to the nature of substituents.

The 2-aminothiazoloisoquinolines **1***a* and **2***a* are characterized by the bands 1650, 1660 and 1542, 1545 cm^{-1}, respectively (NH_2 group). The 2-hydroxythiazoloisoquinolines **1***d* and **2***d* exist actually in the lactam forms, as indicated by the strong carbonyl absorption bands at 1690 and 1680 cm^{-1}, respectively.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are corrected. The u.v. spectra were recorded on a Unicam spectrophotometer model 800. Absolute ethanol was used as the solvent. The n.m.r. spectra were taken on a Varian n.m.r. spectrometer model A-60. Solvents used were acetic acid-d_4, carbon tetrachloride, deuteriochloroform, dimethylsulfoxide-d_6, and deuterium oxide. Tetramethylsilane was used as an internal standard. The i.r. spectra were recorded on a Perkin–Elmer model 521 and model 337 spectrophotometers (on KBr pellets). Elemental analyses were carried out by C. Daessle, Montreal and A. Bernhardt, Germany. The n.m.r. spectra were recorded by Mr. Victor Yu.

2-Aminothiazolo[4,5-h]isoquinoline (1a)

7-Aminoisoquinoline (**5**) (2.88 g, 0.02 mol) and potassium thiocyanate (8 g, 0.063 mol) were dissolved in 80 ml of 95% acetic acid in a 250 ml three-neck flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel. Methanol (8 ml) was also added to the solution, which was cooled to 0–5°. Bromine (1.2 ml, 0.02 mol) in 10 ml of 95% acetic acid was added dropwise with stirring over a period of 20 min. The reaction mixture was poured into 100 ml of water after being stirred for an additional hour. The acid solution was neutralized with saturated sodium carbonate solution. The orange precipitate of 7-amino-8-thiocyanoisoquinoline (**6**) was collected and dried (yield 78%): i.r. (KBr): 2144 (SCN); 3445, 3365, 3230 cm^{-1} (NH_2).

A solution of 3.2 g of crude 7-amino-8-thiocyanoisoquinoline (**6**) in 150 ml of 4 *N* hydrochloric acid and 150 ml of ethanol was refluxed for 2 h. The hot solution was filtered and left to stand overnight. A yellow crystalline compound, 2-aminothiazolo[4,5-*h*]isoquinoline hydrochloride, precipitated. The salt was dissolved in water and neutralized with dilute sodium carbonate solution. The free base, 2-aminothiazolo[4,5-*h*]isoquinoline (**1***a*), precipitated (yield 90%); pale yellow needles, m.p. 303.5–305.5° (ethanol–water).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92. Found: C, 59.60; H, 3.67; N, 20.74; S, 16.01.

2-Chlorothiazolo[4,5-h]isoquinoline (1b)

Cuprous chloride was prepared from 3 g of copper sulfate pentahydrate, 0.66 g of sodium chloride, 0.54 g of sodium hydrogen sulfite, and 0.36 g of sodium hydroxide, and dissolved in 10 ml of concentrated hydrochloric acid. The solution was cooled while the diazotation of the amino compound **1***a* was being carried out.

2-Aminothiazolo[4,5-*h*]isoquinoline (**1***a*) (1.2 g, 6.0 mmol) was added to 40 ml of 85% phosphoric acid with mechanical stirring. It was then cooled and maintained at 5–10° and 10 ml of 70% nitric acid was added. The resulting solution was cooled to 0–5° and sodium nitrite (0.44 g, 6.5 mmol) in 4 ml of water was added, with constant stirring, over a period of 15 min. The reaction mixture was stirred for another 15 min at this temperature, and was then added over a period of 20 min to the stirred solution of cuprous chloride in concentrated hydrochloric acid at 0–5°. The reaction mixture was stirred for another hour at room temperature. It was made basic with 20% sodium hydroxide solution. The basic mixture was extracted with three 250 ml portions of diethyl ether. The ether extract was washed with water, dried over magnesium sulfate, and filtered. The ether solution was evaporated to dryness leaving a pale yellow solid. The crude 2-chlorothiazolo[4,5-*h*]isoquinoline (**1***b*) was sublimed at 2 mm (bath temperature 98°). The sublimate (0.52 g) was recrystallized from *n*-hexane to give 0.45 g of the pure colorless chloro compound, m.p. 130–131°.

Anal. Calcd. for $C_{10}H_5N_2SCl$: C, 54.42; H, 2.28; N, 12.70; S, 14.53. Found: C, 54.33; H, 2.32; N, 12.85; S, 14.57.

Thiazolo[4,5-h]isoquinoline (1c)

2-Chlorothiazolo[4,5-*h*]isoquinoline (**1***b*) (0.5 g, 2.3 mmol) was dissolved in a mixture of 8 ml of 47% hydriodic acid, 4 ml of 95% acetic acid, and 4 ml of water, and 0.28 g of red phosphorus was added. The resulting mixture was refluxed for 3 h and filtered while hot. The volume was reduced to 6 ml and allowed to cool. The orange–red crystalline precipitate was collected, dissolved in water and neutralized with dilute sodium carbonate solution. The resulting precipitate was filtered off, washed with water, and dried. Recrystallization from *n*-hexane gave colorless needles of thiazolo[4,5-*h*]isoquinoline (**1***c*) in 58% yield, m.p. 138–139°.

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.05; S, 17.21. Found: C, 64.34; H, 3.32; N, 14.93; S, 17.08.

2-Acetamidothiazolo[4,5-h]isoquinoline

2-Aminothiazolo[4,5-*h*]isoquinoline (**1***a*) (0.5 g, 2.5

TABLE 9. The i.r. spectra of thiazolo[4,5-*h*]- and -[5,4-*f*]isoquinolines

1*c*	2*c*	1*a*	2*a*	1*b*	2*b*	1*d*	2*d*
						1690 vs	1685 vs
		1650 vs	1660 vs				
	1615 s		1615 s	1610 s			1615 s
1604 m	1602 s				1603 s		
1578 m	1575 w	1590 vw	1575 m			1585 s	
			1560 s		1570 w		1570 m
1528 w		1542 vs	1545 vs				
1495 m	1498 s	1500 s	1495 s		1485 m	1503 m	1505 w
	1465 s			1464 vs	1460 s		
1452 m		1440 s	1450 s			1445 m	1455 m
1437 w	1430 s	1427 w	1425 m	1428 s	1425 s		
1409 s	1400 s		1410 m			1410 m	1402 vw
1383 m		1378 m	1390 m	1385 s	1372 s	1365 m	1388 m
1347 m	1352 s	1352 m	1350 m	1347 s	1345 s	1352 s	1360 m
1308 m	1312 w	1320 s	1315 m			1310 vw	1328 vw
1298 m	1298 w	1290 w	1290 w				
	1278 s					1270 vw	
1260 vs	1265 sh	1253 m	1250 m	1250 s	1250 s	1247 s	1265 m
1226 m	1220 w			1220 w			
1214 m							
1210 m	1208 w					1202 m	1203 w
1172 w	1176 w			1180 w		1178 m	
		1163 w	1150 w		1163 w		1170 m
1140 vw		1132 w		1140 w		1135 vw	1132 w
	1127 m	1120 w			1120 vw		
			1085 m				
			1062 vw	1060 s	1060 vs		
1048 m	1040 w		1038 m			1045 m	1045 m
1027 w		1030 vw		1028 s	1025 s		1028 m
	1010 m						
968 s	983 w	975 s		985 s	983 vs	975 m	995 m
	942 w						
	928 w						
910 w		910 vw	908 shm	910 w	910 w		
			890 vs				
865 vs	858 vs						
852 m		850 shw	854 s			845 shw	842 m
825 m	828 vs	833 vs	835 s	830 w	830 wsh	830 s	
	810 vs		810 s	816 vs	810 vs		810 s
800 w	795 w	790 vw					
	768 w			770 w	770 w		765 w
728 s					738 w		
697 s	690 s			685 w	685 shw		
680 vw	685 s		680 w	680 m	680 s		682 m
		670 w		675 w	670 s		
657 vw	652 s						640 m
		630 w				630 shm	635 wsh
		610 w					
			580 m			587 s	590 s
	573 s	565 w		575 m	570 m		570 shw
532 s	530 s	545 w				545 m	
526 s				525 w	525 w		
		512 w	510 shw	510 w	510 w		512 w
505 s			502 m	490 w	490 w	500 w	
475 s			464 m				
		450 w	440 shm				
		415 w	425 m				
	400 m				385 w		

mmol) was refluxed with a mixture of 8 ml of acetic anhydride and 4 ml of pyridine for 2 h. Filtration of the cooled reaction mixture gave 0.55 g of 2-acetamidothiazolo[4,5-*h*]isoquinoline (91% yield). Colorless crystals, m.p. > 350° (absolute ethanol).

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.08. Found: C, 59.46; H, 3.37; N, 17.29; S, 13.29.

2-Hydroxythiazolo[4,5-h]isoquinoline

2-Chlorothiazolo[4,5-*h*]isoquinoline (**1***b*) (0.3 g, 1.48 mmol) was refluxed in 30 ml of 0.5 *N* sodium hydroxide solution for 3 h. The solution was cooled and acidified with dilute acetic acid to p*H* 6. The resulting precipitate was filtered off, washed with water and dried to give a 65% yield of 2-hydroxythiazolo[4,5-*h*]isoquinoline. Pale yellow needles, m.p. 296–297.5° (ethanol).

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Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85. Found: C, 59.62; H, 2.81; N, 13.96.

*6-Amino-5-thiocyanoisoquinoline (**8**)*

6-Aminoisoquinoline (**7**) (2.88 g, 0.02 mol) and potassium thiocyanate (8.0 g, 0.063 mol) were dissolved in 100 ml of 95% acetic acid. The solution was cooled to 0–5° and bromine (1.2 ml, 0.02 mol) in 10 ml of glacial acetic acid was added dropwise. The reaction mixture was poured into 100 ml of water, and neutralized with sodium carbonate solution. The orange precipitate was collected and dried (85% yield). Recrystallization from a large volume of benzene gave yellow needles of **8**, m.p. 159.5–161°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92. Found: C, 59.59; H, 3.52; N, 20.99; S, 15.76. The i.r. (KBr): 2148 (SCN); 3382, 3316, 3162 cm^{-1} (NH_2).

*2-Aminothiazolo[5,4-f]isoquinoline (**2a**)*

A solution of 6-amino-5-thiocyanoisoquinoline (**8**) (2.0 g, 0.01 mol) in 120 ml of 4 *N* hydrochloric acid and 120 ml of ethanol was refluxed for 2 h. The acid solution was evaporated in order to remove the ethanol and was neutralized with sodium carbonate solution. The yellow precipitate was collected, washed with water, and dried to give 1.82 g (91% yield) of **2a**. Recrystallization from aqueous alcoholic solution gave yellow needles, m.p. 251–253°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.92. Found: C, 59.66; H, 3.61; N, 20.73; S, 15.80.

The i.r. (KBr): 3305, 3110 (broad) cm^{-1} (NH_2).

*2-Chlorothiazolo[5,4-f]isoquinoline (**2b**)*

2-Aminothiazolo[5,4-*f*]isoquinoline (1.2 g, 6 mmol) was transformed into 2-chlorothiazolo[5,4-*f*]isoquinoline (**2b**) by a procedure similar to that used for the preparation of **1b**. The crude 2-chlorothiazolo[5,4-*f*]isoquinoline (**2b**) was sublimed at 2 mm (bath temperature 110°). The sublimate (0.52 g, 38% yield) was recrystallized twice from *n*-hexane giving 0.45 g of colorless needles of the chloro compound, m.p. 170° (dec.).

Anal. Calcd. for $C_{10}H_5N_2SCl$: C, 54.42; H, 2.28; N, 12.70; Cl, 16.07. Found: C, 54.03; H, 2.70; N, 12.81; Cl, 16.10.

*Thiazolo[5,4-f]isoquinoline (**2c**)*

This compound was prepared from 2-chlorothiazolo-[5,4-*f*]isoquinoline (0.5 g, 2.3 mmol) by a method analogous to that applied for the preparation of **1c**. Colorless needles (55% yield) m.p. 174–175.5° (*n*-hexane).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.05; S, 17.21. Found: C, 64.76; H, 3.29; N, 14.92; S, 17.08.

2-Acetamidothiazolo[5,4-f]isoquinoline

Colorless needles (ethanol), m.p. > 350°.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.08. Found: C, 59.64; H, 3.31; N, 17.32; S, 13.33.

2-Hydroxythiazolo[5,4-f]isoquinoline

2-Chlorothiazolo[5,4-*f*]isoquinoline (**2b**) was hydrolyzed with 0.5 *N* sodium hydroxide solution and the hydroxy derivative was obtained in the form of fine yellow needles, m.p. > 350° (aqueous ethanol).

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85. Found: C, 59.41; H, 3.37; N, 13.73.

*5-Acetamido-8-aminoisoquinoline (**11**)*

5-Acetamido-8-nitroisoquinoline (**10**) (4.6 g, 0.02 mol) was reduced with hydrogen and 5% palladium-on-charcoal in absolute ethanol for 2 h. The catalyst was filtered off and the filtrate was evaporated to dryness. The resulting substance was crystallized from ethanol to give 2.4 g (85% yield) of 5-acetamido-8-aminoisoquinoline (**11**) as yellow needles, m.p. 270.5–272.5°.

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.74. Found: C, 65.77; H, 5.75; N, 20.70.

*2,5-Diaminothiazolo[5,4-h]isoquinoline (**3**)*

5-Acetamido-8-aminoisoquinoline (**11**) (3.02 g, 0.015 mol) and potassium thiocyanate (6.0 g, 0.047 mol) were dissolved in 120 ml of 95% acetic acid, and 10 ml of methanol. The resulting solution was cooled to 0–5° and bromine (0.9 ml, 0.015 mol) in 15 ml of glacial acetic acid was added dropwise over a period of 20 min. The reaction mixture was poured into 100 ml of water. The acid solution was neutralized with sodium carbonate solution. The crude orange product, 5-acetamido-8-amino-7-thiocyanoisoquinoline (**12**), weighed 3.2 g. A solution of 3 g of **12** in 150 ml of ethanol and 150 ml of 4 *N* hydrochloric acid was refluxed for 3 h. The acid solution was filtered, and the volume of the filtrate was reduced to 50 ml. The acid solution was poured onto ice and neutralized with sodium carbonate solution. The dark green precipitate was collected and recrystallized from aqueous alcoholic solution to give pale yellow needles, m.p. 274–276°. The total yield of 2,5-diaminothiazolo[5,4-*h*]isoquinoline (**3**) was 60%.

Anal. Calcd. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91. Found: C, 55.68; H, 3.77; N, 25.74.

The u.v. (ethanol): λ_{max} 227, 270, 382 nm; log ε 4.36, 4.27, 3.78; i.r. (KBr): 1652 m, 1550 vs, 1484 m, 1442 s, 1426 s, 1380 vs, 1202 m, 885 s, 847 s, 830 s, 802 m, 670 w, 580 m, 497 w, 460 w, 435 m, 420 m cm^{-1}.

2,5-Diacetamidothiazolo[5,4-h]isoquinoline

This compound was prepared from **3** using the procedure reported above for the acetamido derivative of **1c**. Fine colorless needles (dimethylformamide), m.p. > 350° (dec.).

Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 55.98; H, 4.03; N, 18.64; S, 10.68. Found: C, 55.79; H, 4.10; N, 18.78; S, 10.61.

*5-Amino-8-thiocyanoisoquinoline (**13**)*

This compound was obtained from 5-aminoisoquinoline (2.88 g, 0.02 mol) and potassium thiocyanate (8.0 g, 0.063 mol) using the procedure reported above for the preparation of **8**. The crude product (80% yield) was crystallized from a large volume of benzene to give yellow needles of **13**, m.p. 181–183°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.57; H, 3.51; N, 20.88; S, 15.94. Found: C, 59.6; H, 3.6; N, 20.9; S, 15.9.

*5-Amino-8-mercaptoisoquinoline (**14**)*

A solution of 2.0 g (0.01 mol) of 5-amino-8-thiocyanoisoquinoline (**13**) in 120 ml of 8 *N* hydrochloric acid and 120 ml of ethanol was refluxed for 4 h. The acid solution was evaporated to dryness on a water bath leaving a yellow solid, which was dissolved in 50 ml of water. Neutralization of the solution with sodium carbonate solution produced a precipitate which was filtered and

dried. Recrystallization from ethanol gave 1.5 g of **14** (87% yield), m.p. 260–262°.

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.91; S, 18.19. Found: C, 61.60; H, 4.48; N, 15.71; S, 18.11.

*8-Amino-5-thiocyanoisoquinoline (**15**)*

8-Aminoisoquinoline (3.35 g, 0.015 mol) and potassium thiocyanate (6.0 g, 0.047 mol) were dissolved in 90 ml of 95% acetic acid, and 6 ml of methanol. Bromine (0.9 ml, 0.015 mol) in 10 ml of 95% acetic acid was added dropwise, at 0–5°, followed by steps similar to the preparation of **8**. 8-Amino-5-thiocyanoisoquinoline (**15**) was obtained in a 79% yield (2.4 g). Recrystallization from benzene yielded yellow needles, m.p. 209–211°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.57; H, 3.51; N, 20.88. Found: C, 59.27; H, 3.83; N, 20.66.

*8-Amino-5-mercaptoisoquinoline (**16**)*

8-Amino-5-thiocyanoisoquinoline (**15**) was transformed into **16** by a method similar to that used for the preparation of **14**. 8-Amino-5-mercaptoisoquinoline (**16**) formed colorless needles, m.p. 244–246° (ethanol).

Anal. Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.91; S, 18.19. Found: C, 61.77; H, 4.05; N, 16.09; S, 18.13.

Starting Materials and Intermediates

7-Hydroxyisoquinoline (18), m.p. 229.5–231°; lit. 229–231°. 7-Aminoisoquinoline (**5**) (19), m.p. 203–205°; lit. 204°. 6-Methoxyisoquinoline hydrochloride (19), m.p. 216°; lit. 220°. 6-Hydroxyisoquinoline (20), m.p. 220–222°; lit. 220°. 6-Aminoisoquinoline (7), m.p. 216°; lit. 211–212° (11). 5-Nitroisoquinoline (21), m.p. 106°; lit. 106–108°. 5-Aminoisoquinoline (11), m.p. 128–131°; lit. 129–131°. 5-Acetamidoisoquinoline (**9**) (22), m.p. 161–163°; lit. 166°. 5-Bromoisoquinoline (11), m.p. 82.5–84°; lit. 82–84°. 5-Bromo-8-nitroisoquinoline (23), m.p. 128–139.5°; lit. 139–141°. 8-Aminoisoquinoline (23), m.p. 172–174°; lit. 170–172°.

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