THIAZOLOISOQUINOLINES

I. THE SYNTHESIS OF THIAZOLO[4,5-*c*]ISOQUINOLINE[1]

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ABSTRACT

Thiazolo[4,5-*c*]isoquinoline (I), a new heterocyclic ring system, has been synthesized from 3-aminoisoquinoline (II) in four steps by reaction with potassium thiocyanate and bromine to give 3-amino-4-thiocyanoisoquinoline (VII), cyclization with hydrochloric acid to yield 2-aminothiazolo[4,5-*c*]isoquinoline (VIII), Sandmeyer reaction to give 2-chlorothiazolo-[4,5-*c*]isoquinoline (IX), and finally reduction with hydrogen iodide and red phosphorus to yield I. The attempted preparation of I via 3-amino-4-bromoisoquinoline was unsuccessful. Various 2-substituted derivatives of I were prepared by nucleophilic displacement of the chlorine atom in 2-chlorothiazolo[4,5-*c*]isoquinoline. The nuclear magnetic resonance and ultraviolet spectra of I and some of its derivatives were studied.

INTRODUCTION

Although all four isomers of thiazolopyridines (1–8) and many of the isomers of thiazoloquinolines (9–16) are known, thiazoloisoquinolines, of which eight isomers are possible, have remained an unknown class of heteroaromatic compounds, even in the form of derivatives. However, some thiazoloisoquinolinium compounds are known (17, 18). The synthesis of various isomers of thiazoloisoquinolines was undertaken to study the chemical, physical, and spectral properties of this new class of compounds. The first isomer chosen was thiazolo[4,5-*c*]isoquinoline (I).

RESULTS AND DISCUSSION

The preparation of thiazolopyridines and thiazoloquinolines is usually accomplished by reaction of the appropriate *o*-aminoarylthiol with carboxylic acids or their derivatives, such as the acid chlorides or the anhydrides (2, 5, 8, 10–12). The cyclization of *o*-thiocyanoarylamines to yield 2-aminothiazolo compounds has also been used (1, 13, 14). The former method was first chosen for the synthesis of thiazolo[4,5-*c*]isoquinoline (I), but difficulties were encountered in the attempted preparation of the intermediate 3-aminoisoquinoline-4-thiol (III).

The preparation of III was attempted with 3-amino-4-bromoisoquinoline as an intermediate. The method of Johnson and Nasutavicus (19) was used to prepare 3-aminoisoquinoline (II) from 2-cyanobenzyl cyanide. Bromination of II with bromine in carbon tetrachloride gave a 73% yield of 3-amino-4-bromoisoquinoline (IV). The bromine atom was proven to be in the 4-position in IV by infrared and nuclear magnetic resonance (n.m.r.) spectral evidence. In the infrared, a strong band at 750 cm^{-1}, indicative of an *o*-disubstituted benzene ring, showed that the bromine atom was in the heterocyclic ring. Since the resulting compound was different from the known 3-amino-1-bromoisoquinoline (19), it must be 3-amino-4-bromoisoquinoline. Comparison of the n.m.r. spectrum of IV

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with that of 3-aminoisoquinoline confirmed this assignment (Figs. 1A and 1B). 3-Aminoisoquinoline (II) shows a singlet at 1.15 τ for proton 1, a complex multiplet at 2.16 to 2.95 τ for the four protons on the carboxylic ring (H-5, H-6, H-7, and H-8), a singlet at 3.31 τ for the proton ortho to the amino group (H-4), and a broad singlet at 5.65 τ for the amino group protons. 3-Amino-4-bromoisoquinoline (IV) has a singlet at 1.38 τ for proton 1, a multiplet at 2.18 to 3.00 τ for the carboxylic ring protons, and a broad singlet at 5.00 τ for the amino group protons. Loss of the singlet at 3.31 τ, corresponding to proton 4 in II, proves that the bromine atom must be in the 4-position in IV.

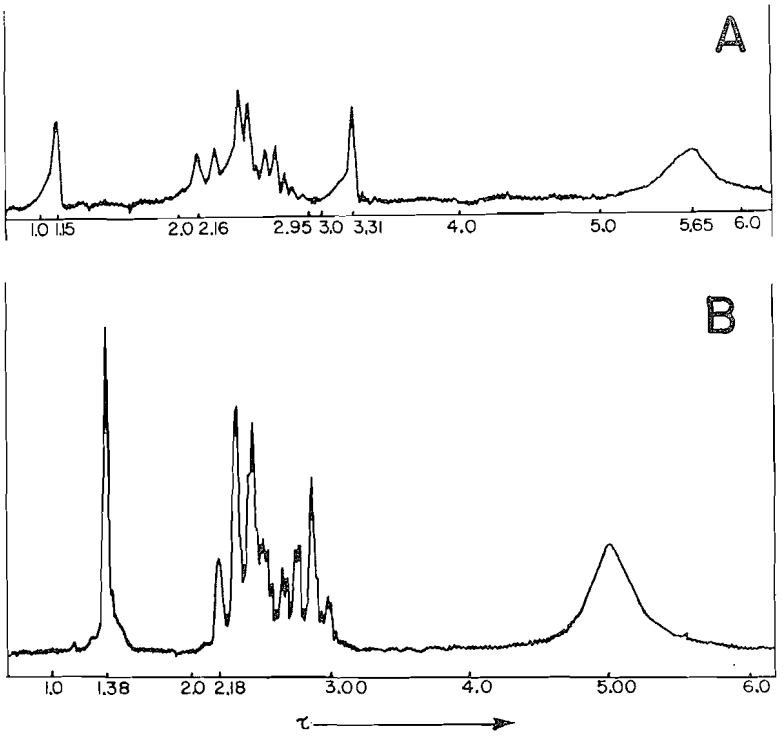


FIG. 1. The n.m.r. spectra (in $DCCl_3$) of (A) 3-aminoisoquinoline and (B) 3-amino-4-bromoisoquinoline.

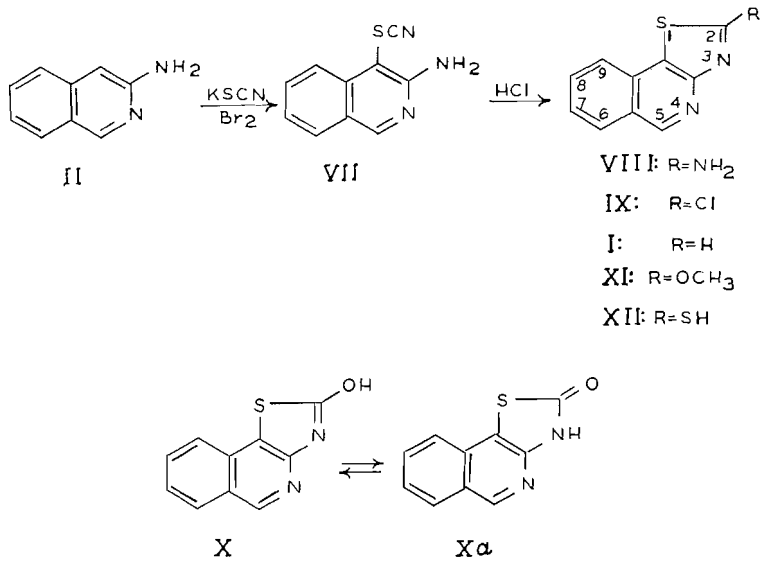
Acetylation of 3-amino-4-bromoisoquinoline with acetic anhydride in the presence of pyridine gave a mixture of 3-monoacetamido-4-bromoisoquinoline (V) and 3-*N*,*N*-diacetylamino-4-bromoisoquinoline (VI). The infrared spectrum of V showed a strong band at 1 663 cm^{-1} (C=O stretching) and a medium-intensity band at 3 240 cm^{-1} (N—H stretching). Its n.m.r. spectrum (in a $CDCl_3$ and $(CD_3)_2SO$ mixture) exhibited a singlet at 1.04 τ for H-1, a multiplet at 1.88 to 2.61 τ for the four aromatic protons of the benzenoid ring plus the proton on the acetamido nitrogen, and a singlet at 7.60 τ for the methyl protons. After exchange with deuterium oxide, one proton was lost from the aromatic region (1.88 to 2.61 τ), thus confirming that the amide proton absorbed in this region.

The attempted reaction of 3-acetamido-4-bromoisoquinoline (V) with thiourea to obtain 3-acetamidoisoquinoline-4-thiol was unsuccessful.

The infrared spectrum of 3-*N*,*N*-diacetylamino-4-bromoisoquinoline (VI) had a strong doublet at 1 705 and 1 725 cm^{-1} in the solid state (KBr pellet), but only a single strong

band at 1 725 cm^{-1} in either carbon tetrachloride or carbon disulfide solution. The n.m.r. spectrum of VI (in $CDCl_3$) exhibited a singlet at 0.94 τ for H-1, a complex multiplet at 1.80 to 2.43 τ for the four remaining aromatic protons, and a sharp singlet at 7.78 τ for the six methyl protons.

The synthesis of thiazolo[4,5-*c*]isoquinoline (I) was successfully accomplished via 3-amino-4-thiocyanoisoquinoline (VIII) (Reaction Scheme 1). The latter was obtained by the reaction of 3-aminoisoquinoline with potassium thiocyanate and bromine (20). The structure of VII was proven by infrared and n.m.r. spectroscopy. Thus, its infrared spectrum showed a strong band at 753 cm^{-1} characteristic of an *o*-disubstituted benzene ring, as well as a band at 2 143 cm^{-1} for the thiocyano group (21) and bands at 3 433 and 3 270 cm^{-1} for the amino group. In the n.m.r. spectrum of 3-amino-4-thiocyanoisoquinoline (VII) (in chloroform-*d* solution), a singlet at 1.29 τ was assigned to proton 1, a complex multiplet at 2.03 to 2.96 τ to the four benzenoid ring protons, and a broad singlet at 4.65 τ to the amino group protons.



REACTION SCHEME 1.

The cyclization of the thiocyano and amino groups in compound VII was achieved by refluxing VII in aqueous ethanolic hydrochloric acid. The resulting 2-aminothiazolo-[4,5-*c*]isoquinoline (VIII) was obtained in a 73% yield. Diazotization of VIII followed by reaction with cuprous chloride gave 2-chlorothiazolo[4,5-*c*]isoquinoline (IX). Reduction of IX with hydriodic acid and red phosphorus produced the parent compound of this series, thiazolo[4,5-*c*]isoquinoline (I). The n.m.r. spectrum of I (Fig. 2) exhibits a doublet at 0.87 and 0.92 τ with an area corresponding to two protons (assigned to H-2 and H-5), and a complex ABCD pattern of bands at 1.93 to 2.64 τ with an area corresponding to four protons of the benzenoid ring. It is not possible to state definitely whether H-2 absorbs at lower field than H-5, or vice versa. It was noted that, in the n.m.r. spectrum of I recorded in an acetone solution, the band for one of these protons moves downfield more than the other (two peaks at 0.44 and 0.60 τ).

The preparation of other 2-substituted derivatives of thiazolo[4,5-*c*]isoquinoline was accomplished by displacement of the chlorine atom of IX with various nucleophilic

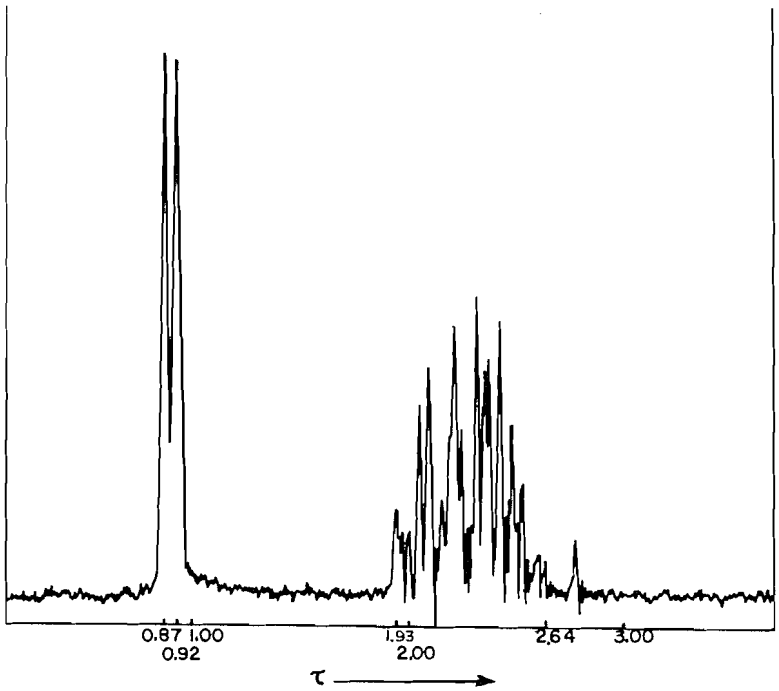


FIG. 2. The n.m.r. spectrum of thiazolo[4,5-*c*]isoquinoline (in $DCCl_3$).

reagents. For example, reaction of IX with sodium hydroxide gave the 2-hydroxy derivative X, and reaction of IX with sodium methoxide gave the 2-methoxy derivative XI. Reaction of IX with thiourea yielded the 2-mercapto derivative XII. The 2-hydroxythiazolo[4,5-*c*]isoquinoline (X) was shown, by infrared and other evidence (which will be the subject of a future publication in this series), to exist mainly in the lactam form X*a* rather than the hydroxy form. By analogy, 2-mercaptothiazolo[4,5-*c*]isoquinoline (XII) also probably exists as the thiolactam.

The chemical shifts of the protons of I and some of its derivatives are summarized in Table I. In all the compounds studied, the proton on the carbon atom adjacent to the heterocyclic nitrogen atom absorbs at lower field than the benzenoid protons. This is in agreement with the observations of other workers (22).

TABLE I

Proton chemical shifts of thiazolo[4,5-*c*]isoquinoline and some 2-substituted derivatives

Compound	Solvent	Chemical shift (τ)			
		H-2	H-5	H-6, H-7, H-8, H-9	Other
Thiazolo[4,5-*c*]-isoquinoline	$CDCl_3$	0.87 or 0.92	0.87 or 0.92	1.93 to 2.64	—
Thiazolo[4,5-*c*]-isoquinoline	Acetone	0.44 or 0.60	0.44 or 0.60	1.48 to 2.37	—
Derivatives					
2-Chloro	$CDCl_3$	—	0.73	1.81 to 2.38	—
2-Chloro	CH_3SOCH_3	—	0.50	1.46 to 2.22	—
2-Amino	CH_3SOCH_3	—	0.83	1.73 to 2.46	NH_2*
2-Hydroxy	CD_3SOCD_3	—	1.05	1.95 to 2.64	−2.58 (NH)
2-Methoxy	$CDCl_3$	—	0.78	1.80 to 2.59	5.62 (OCH_3)

*Superimposed upon the H-5, H-6, H-7, and H-8 bands.

The ultraviolet spectra of thiazolo[4,5-*c*]isoquinoline and its 2-substituted derivatives (Table II) generally show three groups of absorption bands, which are classified as the α-, *p*-, and β-bands (23). All the bands of I occur at longer wavelengths than do the corresponding bands of isoquinoline (α-band, 319 mμ and 308 mμ; *p*-band, 268 mμ; β-band, 220 mμ (24)). Annealing the thiazole ring to benzene, quinoline, and naphthalene similarly results in a bathochromic displacement of the bands from those of the parent compounds (25, 26). Electron-donating substituents, such as chlorine, give rise to bathochromic displacements of all the bands of the parent compound (I), as expected.

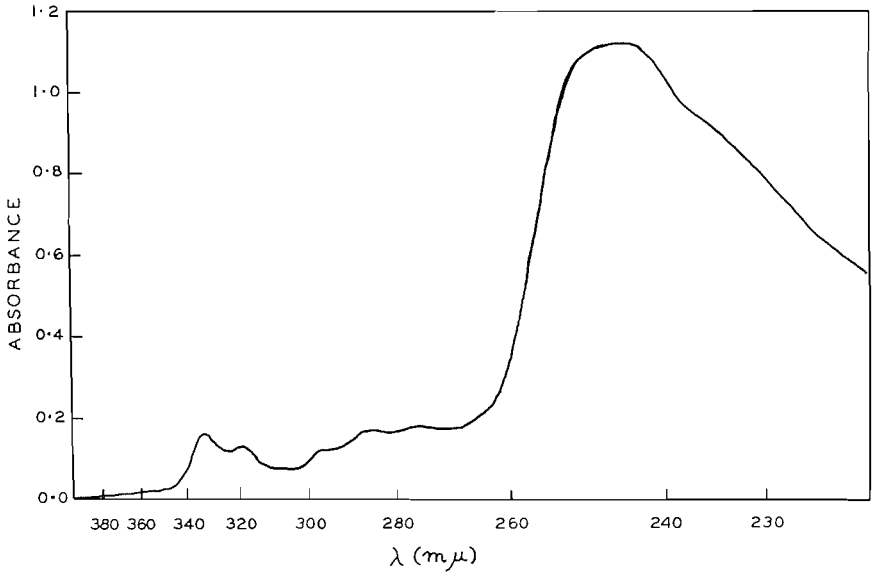


FIG. 3. The ultraviolet spectrum of thiazolo[4,5-*c*]isoquinoline (in ethanol).

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin–Elmer model 421 grating spectrophotometer in KBr disks. Ultraviolet spectra were obtained on a Perkin–Elmer model 350 spectrophotometer with absolute ethanol as solvent. Nuclear magnetic resonance spectra were determined on Varian high-resolution n.m.r. spectrometers, model HR-60 or model A60. Solvents used for the n.m.r. work were chloroform-*d*, dimethyl sulfoxide, and dimethyl sulfoxide-d_6; tetramethylsilane was used as an internal reference. Elemental analyses were carried out by Dr. C. Daesslé, Montreal, and by A. Bernhardt, Mülheim, Germany.

Preparation of 3-Amino-4-bromoisoquinoline (IV)

3-Aminoisoquinoline (2.90 g, 0.02 mole) was dissolved in 100 ml of glacial acetic acid in a 500 ml three-necked flask equipped with an air condenser, a dropping funnel, and a mechanical stirrer. To this stirred solution was added dropwise, over 45 min, 210 ml of 0.1 *M* bromine solution in carbon tetrachloride.

The reaction mixture was stirred for an additional 5 min and then poured into 500 ml of a sodium acetate solution. The organic layer was separated and the aqueous layer extracted once with carbon tetrachloride. The organic extract was dried over sodium sulfate and filtered, and the solvent was evaporated, leaving 4.46 g of a black solid. Crystallization from hexane gave 3.25 g (73% yield) of 3-amino-4-bromoisoquinoline (IV) as yellow needles, m.p. 120.5–122°.

Anal. Calcd. for $C_9H_7BrN_2$: C, 48.46; H, 3.16; Br, 35.83; N, 12.55. Found: C, 48.24; H, 3.01; Br, 35.71; N, 12.61.

Acetylation of 3-Amino-4-bromoisoquinoline

3-Amino-4-bromoisoquinoline (2.32 g, 0.01 mole) was dissolved in a mixture of 32 ml of acetic anhydride and 16 ml of pyridine, and the resulting solution was heated at 90–95° for 4 h. It was cooled to room temperature and poured into an excess of dilute ammonium hydroxide solution, whereupon a crystalline substance

TABLE II

Positions of the ultraviolet absorption maxima and corresponding log ϵ values of thiazolo[4,5-*c*]isoquinoline and its derivatives (solvent, ethanol)

Compound	α-Band		p-Band		β-Band	
	mμ	log ϵ	mμ	log ϵ	mμ	log ϵ
Thiazolo[4,5-*c*]-isoquinoline	334 320	3.56 3.52	298 286 276	3.54 3.69 3.70	245 237 sh	4.45 4.37
Derivatives						
2-Amino	360	3.48	311 299 288 sh	3.98 3.90 3.66	259	4.57
2-Acetamido	343	3.81	311 302 290 sh	4.01 3.97 3.86	266 258	4.44 4.42
2-Chloro	337 324	3.70 3.63	304 292 282 sh	3.72 3.77 3.72	249 232 sh	4.51 4.39
2-Hydroxy	350	3.66	301 288 278	3.55 3.60 3.56	246.5 235 sh	4.45 4.36
2-Methoxy	345 335	3.61 3.61	301 289 278	3.73 3.79 3.71	247	4.63
2-Thiol*	344	—	290 283	— —	249	—

*Because of very low solubility, log ϵ could not be calculated.

precipitated. This was filtered off to yield 1.33 g (43% yield) of tan needles, m.p. 105–108°. Recrystallization from hexane gave colorless needles of the diacetyl derivative VI, m.p. 107–108.5°.

Anal. Calcd. for $C_{13}H_{11}BrN_2O_2$: C, 50.83; H, 3.61; N, 9.12. Found: C, 50.57, 50.73; H, 3.15, 3.33; N, 9.48, 9.41.

Evaporation of most of the filtrate from the crude reaction product above yielded 1.22 g (46% yield) of the monoacetyl derivative V as colorless needles, m.p. 166–168° (crystallized from ethanol).

Anal. Calcd. for $C_{11}H_9BrN_2O$: C, 49.83; H, 3.42; N, 10.57. Found: C, 49.83, 49.74; H, 3.11, 3.35; N, 10.80, 10.60.

Attempted Reaction of 3-Acetamido-4-bromoisoquinoline (V) with Thiourea

3-Acetamido-4-bromoisoquinoline (0.50 g, 0.0019 mole) was refluxed with 0.17 g (0.0022 mole) of thiourea in 15 ml of absolute ethanol for 7 h. Evaporation of the solvent and recrystallization of the residue from ethanol gave colorless needles, m.p. 165–168°, the infrared spectrum of which was identical with that of the starting 3-acetamido-4-bromoisoquinoline.

Preparation of 3-Amino-4-thiocyanoisoquinoline (VII)

3-Aminoisoquinoline (12.9 g, 0.09 mole) and potassium thiocyanate (34.8 g, 0.36 mole) were dissolved in 165 ml of 95% acetic acid in a 500 ml three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. The resulting solution was cooled to −5 to −10°, and bromine (5.10 ml, 0.09 mole) in 25 ml of 95% acetic acid was added dropwise to the stirred solution over a period of 35 min. After the reaction mixture was stirred for a further 15 min, it was poured into 1 500 ml of water. The resulting precipitate was filtered off and recrystallized from ethanol to give 11.74 g (65% yield) of 3-amino-4-thiocyanoisoquinoline as yellow needles, m.p. 158.5–160.5°. Two more recrystallizations from ethanol gave pale-yellow needles, m.p. 163–164°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.84; H, 3.67; N, 20.77.

When the original reaction mixture was allowed to stand overnight at room temperature, no cyclization of 3-amino-4-thiocyanoisoquinoline to 2-aminothiazolo[4,5-*c*]isoquinoline (VIII) was observed.

Preparation of 2-Aminothiazolo[4,5-c]isoquinoline (VIII)

3-Amino-4-thiocyanoisoquinoline (11.8 g, 0.06 mole) was dissolved in 900 ml of boiling ethanol, and 510 ml of 15% hydrochloric acid was added. The resulting solution was refluxed for 6 h. It was cooled to room temperature, diluted with 1 500 ml of water, and basified with solid sodium carbonate. The resulting precipitate was filtered off, dried, and washed with benzene to yield 8.57 g (73% yield) of yellow needles. Recrystallization from a large volume of benzene gave VIII as colorless needles, m.p. 240–242°.

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.87; H, 3.54; N, 20.76.

The acetyl derivative of VIII was prepared by refluxing VIII (1.00 g, 0.005 mole) in a mixture of 16 ml of acetic anhydride and 8 ml of pyridine for 5 h. The starting material did not appear to dissolve, but a new insoluble product was formed. Filtration of the cooled reaction mixture gave 0.85 g (75% yield) of tan needles, m.p. 326.7°. Recrystallization from absolute ethanol gave pale-tan needles of the monoacetyl derivative of VIII, m.p. 327–328°.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.34; H, 3.51; N, 17.53; S, 13.03.

Preparation of 2-Chlorothiazolo[4,5-c]isoquinoline (IX)

Cuprous chloride was prepared in the usual manner from 1.32 g of sodium chloride, 6.00 g of hydrated cupric sulfate, 1.08 g of sodium bisulfite, and 0.72 g of sodium hydroxide, and was dissolved in 10 ml of concentrated hydrochloric acid.

2-Aminothiazolo[4,5-*c*]isoquinoline (2.40 g, 0.012 mole) was dissolved in a mixture of 80 ml of 85% phosphoric acid and 20 ml of 70% nitric acid, and then cooled to 0–5°. Sodium nitrite (0.88 g, 0.013 mole) in 8 ml of water was added over a 15 min period to the cooled stirred solution. The reaction mixture was stirred for another 20 min at 0–5°. The cold diazonium solution was then added over 20 min, with stirring, to the cuprous chloride solution at 0–5°. A vigorous reaction occurred during the addition. The reaction mixture was stirred for 1 h longer at room temperature. It was then basified with 10% sodium hydroxide solution, with cooling, and the basic mixture extracted with three 200 ml portions of ether. The organic extract was dried over sodium sulfate and the solvent evaporated, leaving 1.53 g of an oily brown solid. Extraction of this solid with boiling hexane gave 1.20 g (45% yield) of pale-yellow 2-chlorothiazolo[4,5-*c*]isoquinoline (IX), m.p. 114–117°. Recrystallization from hexane followed by vacuum sublimation gave colorless crystals of IX, m.p. 116.5–118°.

Anal. Calcd. for $C_{10}H_5ClN_2S$: C, 54.42; H, 2.28; Cl, 16.07; N, 12.70. Found: C, 54.36; H, 2.13; Cl, 15.97; N, 12.59.

Preparation of Thiazolo[4,5-c]isoquinoline (I)

2-Chlorothiazolo[4,5-*c*]isoquinoline (0.51 g, 2.3 mmoles) was dissolved in a mixture of 8 ml of 47% hydriodic acid, 4 ml of water, and 4 ml of acetic acid, and 0.28 g of red phosphorus was added. The resulting mixture was refluxed for 3½ h. It was cooled to room temperature, diluted with 250 ml of water, and filtered. The filtrate was basified with solid sodium carbonate and extracted with two 200 ml portions of ether. After the extract was dried over sodium sulfate, the ether was evaporated, leaving 0.39 g (91% yield) of a tan solid. Chromatography of 0.21 g of this material on 10 g of alumina (Woelm, activity 1) with benzene–ether (1:1) as eluent gave 0.18 g of a colorless solid. Recrystallization from hexane gave colorless needles of thiazolo-[4,5-*c*]isoquinoline (I), m.p. 117–118°.

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.49; H, 3.25; N, 15.05. Found: C, 64.68; H, 3.50; N, 15.08.

2-Hydroxy[4,5-c]isoquinoline (X)

2-Chlorothiazolo[4,5-*c*]isoquinoline (0.16 g, 0.7 mmole) was refluxed in 30 ml of 0.1 *N* sodium hydroxide solution for 5 h. The resulting solution was filtered while hot, cooled to room temperature, and acidified with dilute acetic acid. The flocculent precipitate was filtered off, washed with water, and dried to give 0.11 g (79% yield) of a tan solid, m.p. 285–285.5°. Recrystallization from ethanol–water gave pale-yellow needles of 2-hydroxythiazolo[4,5-*c*]isoquinoline (X), m.p. 286.7°.

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.38; H, 2.99; N, 13.85; S, 15.86. Found: C, 59.34; H, 3.20; N, 13.87; S, 15.79.

2-Methoxy[4,5-c]isoquinoline (XI)

2-Chlorothiazolo[4,5-*c*]isoquinoline (0.20 g, 0.9 mmole) was dissolved in 15 ml of absolute methanol, and a solution of 0.05 g (1.2 mmoles) of sodium in 5 ml of absolute methanol was added. After the mixture was stirred at room temperature for 1 h, the clear-yellow solution was neutralized with dilute acetic acid, diluted with water, and dried to give 0.15 g (79% yield) of 2-methoxythiazolo[4,5-*c*]isoquinoline, m.p. 147–148.5°. Recrystallization from methanol gave pale-yellow needles, m.p. 149.5–150.5°.

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.96; S, 14.83. Found: C, 61.04; H, 3.51; N, 13.11; S, 14.76.

Thiazolo[4,5-c]isoquinoline-2-thiol (XII)

A solution of 2-chlorothiazolo[4,5-*c*]isoquinoline (0.20 g, 0.9 mmole) and thiourea (0.10 g, 1.3 mmoles) in 10 ml of ethanol was refluxed for 1 h. The reaction mixture was cooled to room temperature and filtered.

The crystalline precipitate was dissolved in 40 ml of 1 *N* sodium hydroxide solution and filtered. Acidification of the filtrate with acetic acid gave a flocculent precipitate, which was filtered off, washed with water, and dried to give 0.14 g (70% yield) of pale-yellow thiazolo[4,5-*c*]isoquinoline-2-thiol, m.p. 323–326°. After this compound was dissolved in sodium hydroxide again and reprecipitated with acetic acid, the melting point was 324–326°.

Anal. Calcd. for $C_{10}H_6N_2S_2$: C, 55.03; H, 2.77; N, 12.84. Found: C, 55.05; H, 2.75; N, 12.80.

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