A Facile Synthesis of 2-Aminothiazolo[5,4-*b*]- and 2-Aminothiazolo[4,5-c]pyridines

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The hydrochlorides of the title compounds are obtained in moderate yields by refluxing 2-chloro-3-aminopyridine or 3-amino-4-chloropyridine, respectively, with an alkyl-, aralkyl-, or aryl isothiocyanate in absolute ethanol solution. A proof is presented that the 2-aminothiazolopyridine hydrochloride and not the isomeric *o*-chloropyridylthiourea is the product of this reaction. The free-bases may be obtained from the hydrochlorides with aqueous sodium bicarbonate. A mechanism for the formation of the thiazole ring is briefly considered. The interactions of 2-chloro-3-aminopyridine with 1-substituted-5-mercapto-1*H*-tetrazoles are also described.

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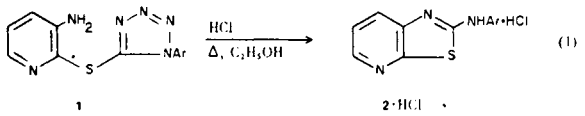
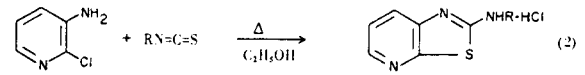
Attempted acid-promoted Smiles rearrangements of 2-tetrazolylthio-3-aminopyridines **1** that contained aryl groups on the tetrazole moiety resulted in the elimination of hydrazoic acid to give the corresponding 2-anilinothiazolo[5,4-*b*]pyridines **2** (reaction 1) (1). This approach, however, to 2-aminothiazolo[5,4-*b*]pyridines is



(1)

1 2·HCl

unsatisfactory for two reasons. The preparation of **1** requires three discrete reaction steps and only 2-anilinothiazolo[5,4-*b*]pyridines are accessible by this route (1). We have developed a one-step synthesis of 2-anilino-, 2-aralkylamino-, and 2-alkylaminothiazolo[5,4-*b*]pyridines by refluxing the commercially available 2-chloro-3-aminopyridine with the appropriately substituted isothiocyanate (reaction 2). A recently reported similar synthesis of 2-aminothiazolo[5,4-*b*]pyridines (2) has prompted us to



(2)

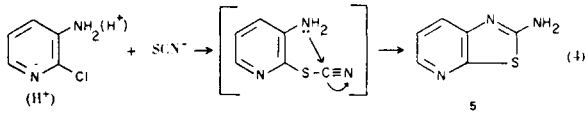
publish our results since many of our thiazolopyridines are new and we have extended this synthesis to the preparation of 2-aminothiazolo[4,5-c]pyridines **3** (reaction 3). We have also shown, utilizing ^{13}C nmr spectroscopy,

(3)

4 3·HCl

that the 2-aminothiazolo[5,4-*b*]pyridine hydrochlorides and not the isomeric 3-(2-chloropyridyl)thioureas are formed in reaction 2.

In principle, protonation of the amino group (or the pyridyl nitrogen) of 2-chloro-3-aminopyridine should enable the facile nucleophilic displacement of the 2-chloro group by the thiocyanate ion. The amino group should then add to the nitrile group in the thiocyanate function to form a thiazole ring (reaction 4). This prediction was



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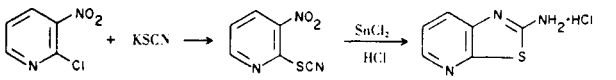
confirmed when 2-chloro-3-aminopyridine was refluxed with two equivalents of potassium thiocyanate in ethanol to which concentrated hydrochloric acid had been added. The heterocycle, 2-aminothiazolo[5,4-*b*]pyridine (**5**) was isolated in 27% yield. This thiazolopyridine has also been prepared independently (reaction 5) (3).

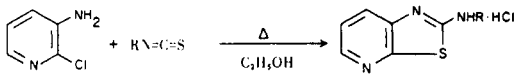


(5)

Work was then undertaken to extend reaction 4 to the preparation of various 2-substituted aminothiazolo[5,4-*b*]-pyridines. An obvious first step was to reflux 2-chloro-3-aminopyridine with the appropriately substituted isothiocyanate in ethanolic hydrochloric acid. When this trans-

Table I

Properties of 2-Aminothiazolo[5,4-*b*]pyridine Hydrochlorides

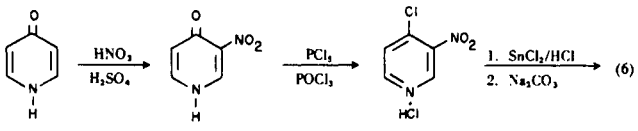


Compound	R	Yield, % (a)	M.p. °C	*Anal.* Calcd.: Found.:
I	CH_3	60	264-265	C, 41.7; H, 4.0; N, 20.8 C, 41.3; H, 4.0; N, 20.7
II	C_2H_5	35 (b)	215-216	C, 44.5; H, 4.6; N, 19.4 C, 44.4; H, 4.7; N, 19.3
III	n-C_4H_9	33	207	C, 49.3; H, 5.7; N, 17.2 C, 49.7; H, 5.8; N, 17.4
IV	CH_2=$CHCH_2$	53 (b)	193-194	C, 47.4; H, 4.4; N, 18.4 C, 47.4; H, 4.4; N, 18.5
V	$C_6H_5CH_2$	61	236-238	C, 56.2; H, 4.3; N, 15.1 C, 56.5; H, 4.1; N, 15.1
VI	$C_6H_5CH_2CH_2$	30	216 (c)	C, 57.6; H, 4.8; N, 14.4 C, 57.8; H, 4.7; N, 14.6
VII	C_6H_5	57	284-285	C, 54.6; H, 3.8; N, 15.9 C, 55.0; H, 3.7; N, 16.0
VIII	3-$NO_2C_6H_4$	60 (d)	275-277 dec.	C, 52.9; H, 2.9; N, 20.6 C, 52.6; H, 3.1; N, 20.5
IX	4-FC_6H_4	62	273-274 (e)	C, 51.1; H, 3.2; N, 14.9 C, 51.2; H, 3.0; N, 15.1
X	1-Naphthyl	54	207	C, 61.2; H, 3.8; N, 13.4 C, 61.3; H, 3.7; N, 13.4

(a) Isolated yield from the chilled alcohol mixture. (b) Ethyl ether was added to the alcohol suspension before chilling. (c) Lit. (2) m.p. 221-223°. (d) Separated as the free-base. (e) Lit. (2) m.p. 284°.

formation was attempted with methyl isothiocyanate and 2-chloro-3-aminopyridine, no change took place. When, however, these reactants were refluxed in absolute ethanol *without* acid, 2-methylaminothiazolo[5,4-*b*]-pyridine hydrochloride was isolated in 60% yield. This transformation was then attempted with various alkyl-, aralkyl-, and aryl isothiocyanates and the results are summarized in Table I. Thus, 2-chloro-3-aminopyridine was refluxed with one equivalent of the desired isothiocyanate for 18 hours in alcohol solution. The corresponding 2-aminothiazolo[5,4-*b*]pyridine hydrachloride usually separated from the chilled alcohol solution as a colorless or pale yellow crystalline solid. In certain cases. more of the salt was obtained by adding ethyl ether to the cooled ethanol mixture. In other instances, the salt separated during the refluxing operation. The salts in all cases were analytically pure. The free-bases were liberated from most of these hydrochlorides with aqueous sodium bicarbonate. The solids obtained were then characterized after purifying by crystallization (Table II).

The generality of this thiazolopyridine synthesis was extended by the preparation of three 2-aminothiazolo-[4,5-c]-pyridines **3** (reaction 3). Unfortunately, 3-amino-4-chloropyridine (**4**) was not commercially available and had to be prepared by a rather cumbersome procedure (reaction 6) (4-6). Pyridine **4** was refluxed with an alkyl-,



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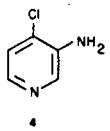

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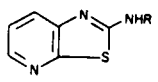
aralkyl-, or an aryl isothiocyanate in absolute ethanol for 18 hours, and the thiazolopyridine hydrochloride was then precipitated by adding ethyl ether to the cooled alcohol mixture. The free-base was obtained by treating

Table II

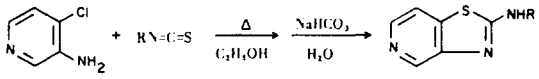
Properties of 2-Aminothiazolo[5,4-*b*]pyridines



Compound	R	M.p. °C	Crystallization Solvent	Crystal Form	*Anal.* Calcd.: Found.:
I	CH_3	154-155	Ether	colorless prisms	C, 50.9; H, 4.2; N, 25.4 C, 51.0; H, 4.0; N, 25.2
II	C_2H_5	174-175	Ethyl acetate/ether	colorless needles	C, 53.6; H, 5.0; N, 23.4 C, 53.6; H, 5.0; N, 23.5
III	n-C_4H_9	109-110	Ethyl acetate/ether	colorless plates	C, 57.9; H, 6.3; N, 20.3 C, 57.8; H, 6.5; N, 20.5
IV	CH_2=$CHCH_2$	162-163	Ethyl acetate/ether	colorless plates	C, 56.5; H, 4.8; N, 22.0 C, 56.3; H, 4.5; N, 22.1
V	$C_6H_5CH_2$	126-127	Ethyl acetate/ethanol	colorless prisms	C, 64.7; H, 4.6; N, 17.4 C, 64.3; H, 4.8; N, 17.6
VI	C_6H_5	179-180	Ethyl acetate	colorless needles	C, 63.4; H, 4.0; N, 18.5 C, 63.2; H, 3.8; N, 18.6
VII	4-FC_6H_4	209-210	Ethanol	colorless powder	C, 58.8; H, 3.3; N, 17.1 C, 58.4; H, 2.9; N, 17.2
VIII	1-Naphthyl	174-175	Ethyl acetate	pale yellow prisms	C, 69.3; H, 4.0; N, 15.2 C, 69.2; H, 4.2; N, 15.3

Table III

Analytical Values for 2-Aminothiazolo[4,5-*c*]pyridines

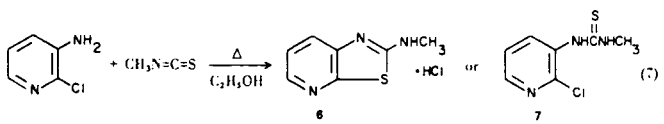


Compound	R	Yield % (a)	M.p. °C (b)	Crystallization Solvent (b)	*Anal.* Calcd.: Found:
I	C_6H_5	48	234-235	Ethanol/ethyl acetate	C, 63.4; H, 4.0; N, 18.5 C, 63.2; H, 4.1; N, 18.4
II	CH_3	63	160-161	Ethyl acetate (c)	C, 49.6; H, 4.4; N, 24.8 C, 49.5; H, 4.1; N, 25.2
III	$C_6H_5CH_2$	62	171-172	Ethyl acetate	C, 64.7; H, 4.6; N, 17.4 C, 64.5; H, 4.6; N, 17.4

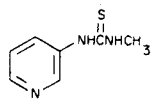
(a) Hydrochloride salt. (b) Free-base. (c) This base was hygroscopic. Calcd. for $C_7H_7N_3S \cdot 0.25\ H_2O$.

the hydrochloride with aqueous sodium bicarbonate (Table III).

Proof that thiazolopyridine hydrochloride **6**, and not the isomeric thiourea **7**, formed when methyl isothiocyanate was refluxed with 2-chloro-3-aminopyridine (reaction 7) was furnished by ^{13}C nmr spectral studies on a model compound **8** (7). Thiourea **8** was easily prepared by refluxing 3-aminopyridine with an equivalent of methyl isothiocyanate in ethanol. The thione carbon of



8 showed a ^{13}C nmr resonance at δ 181.7 ppm while the lowest resonance value for the product obtained from reaction 7 was δ 166.1 ppm. In the latter case, on



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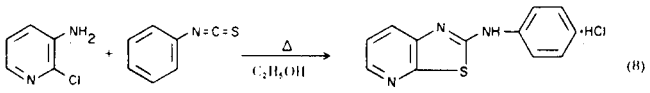
the basis of the ^{13}C nmr resonance value for the thione carbon of **8**, one would reasonably expect a lower resonance value if **7** rather than **6** were the product from reaction 7. The δ 166.1 ppm value was assigned to the thiazole carbon in **6** to which the methylamino group is attached.

Additional proof that the thiazolopyridines formed in one step was provided by the observation that 2-anilinothiazolo[5,4-*b*]pyridine hydrochloride obtained *via* reaction 8 was identical to the product (2·HCl, Ar = phenyl) obtained from reaction 1.



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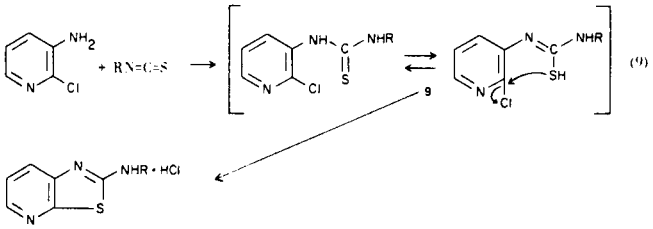
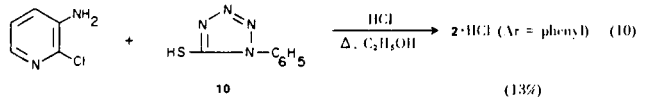
The mechanism of formation of the thiazole ring probably involves initial formation of the thiourea **9**, the thione (or tautomeric thiol) of which then spontaneously displaces the chloro group (reaction 9). In the absence of a 2-chloro substituent, the thiourea can be isolated (*vide supra*).



(9)

As an interesting extension of the concept behind reaction 4, a one-step synthesis of 2-anilinothiazolo[5,4-*b*]pyridine was achieved when 2-chloro-3-aminopyridine was refluxed with 1-phenyl-5-mercapto-1*H*-tetrazole (**10**) in ethanol that contained a few drops of concentrated hydrochloric acid (reaction 10). A nucleophilic displacement of the 2-chloro group from the protonated 2-chloro-3-aminopyridine by the mercapto group of **10** occurred to give an intermediate (1, Ar = phenyl) that eliminated hydrazoic acid to form 2·HCl (Ar = phenyl) (see reaction 1) (1). When 1-methyl-5-mercapto-1*H*-tetrazole (**11**) (8) was treated with 2-chloro-3-aminopyridine under the same reaction conditions (reaction 11), tetraazo-9,10-dihydroanthracene dihydrochloride (**12**) was unexpectedly formed. Mercaptotetrazole **11**



10 (13%)

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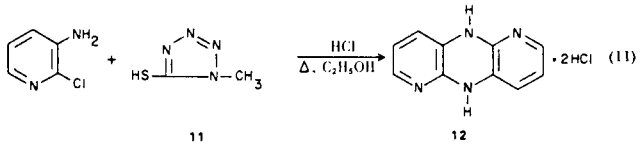

11 12

(11)

is evidently required for the formation of **12** since 2-chloro-3-aminopyridine was recovered unchanged when it was refluxed by itself in ethanolic hydrochloric acid.

Conclusions

A convenient one-step synthesis of 2-aminothiazolopyridines has been described. They are easily prepared by refluxing the appropriately substituted isothiocyanate with one equivalent of 2-chloro- or 4-chloro-3-aminopyridine in ethanol solution. The formation of the thiazolopyridine apparently proceeds by a transient pyridylthiourea intermediate that eliminates the elements of hydrogen chloride to form the thiazole ring.

EXPERIMENTAL

The following compounds are Eastman Organic Chemicals: methyl isothiocyanate, ethyl isothiocyanate, *n*-butyl isothiocyanate, allyl isothiocyanate, benzyl isothiocyanate, 2-phenethyl isothiocyanate, phenyl isothiocyanate, 3-nitrophenyl isothiocyanate, 1-naphthyl isothiocyanate, 3-aminopyridine, 1-phenyl-5-mercapto-1*H*-tetrazole and 4-1*H*-pyridone. The following were obtained from the Aldrich Chemical Company: 4-fluorophenyl isothiocyanate and 2-chloro-3-aminopyridine. Mass spectra were measured on a Hitachi-Perkin Elmer RMS-4 mass spectrometer. The ^1H nmr spectra were determined on a Varian Associates A60 or on a Perkin Elmer R-32 (90 MHz) nmr spectrometer. The ^{13}C nmr spectra were measured with a Brücker Model HX-90 (22.63 MHz) nmr spectrometer. The solvent DMSO-d_6 was used for all of the nmr spectra with TMS as the internal standard. All of the compounds in this report exhibited satisfactory mass and ^1H nmr spectra.

2-Aminothiazolo[5,4-*b*]pyridine (**5**).

To a stirred mixture of 2-chloro-3-aminopyridine (25.8 g., 0.2 mole) and potassium thiocyanate (38.9 g., 0.4 mole) in 200 ml. of absolute ethanol was added concentrated hydrochloric acid until this stirred mixture was shown to have a *p*H of *ca.* 1 (use of indicator paper). This stirred mixture was refluxed for 66 hours and the solvents were then removed under reduced pressure. The residue was partitioned between dilute ammonium hydroxide (15% ammonia) and chloroform. Undissolved solid was collected, washed with water and chloroform, and air-dried. This solid was suspended in hot ethanol and then was collected and dried under vacuum, yield, 8.1 g. (27%), m.p. 240-242° dec. The mass spectrum showed the parent peak at m/e 151 (Calcd. 151).

Anal. Calcd. for $C_6H_5N_3S$: C, 47.6; H, 3.3; N, 27.8. Found: C, 47.3; H, 3.5; N, 27.7.

Representative 2-Aminothiazolo[5,4-*b*]pyridine Synthesis Illustrated for 2-Methylaminothiazolo[5,4-*b*]pyridine.

A stirred ethanol solution (25 ml.) of 2-chloro-3-aminopyridine (5.0 g., 0.039 mole) and methyl isothiocyanate (2.8 g., 0.039 mole) was refluxed for 18 hours. After cooling, the precipitated solid was collected and dried under vacuum, yield,

4.6 g. (60%), m.p. 264-265°; ^{13}C nmr: δ (ppm) 31.111 (NCH_3), 122.287, 123.786, 141.109, 141.649, 149.442 (all five values for the pyridine ring carbons), and 166.107 (2-thiazole carbon). The mass spectrum showed the parent peak of the free-base at m/e 165 (Calcd. 165).

Anal. Calcd. for $C_7H_8ClN_3S$: C, 41.7; H, 4.0; N, 20.8. Found: C, 41.3; H, 4.0; N, 20.7.

The free-base was crystallized from ethyl ether, m.p. 154-155°. The mass spectrum showed the parent peak at m/e 165 (Calcd. 165).

Anal. Calcd. for $C_7H_7N_3S$: C, 50.9; H, 4.2; N, 25.4. Found: C, 51.0; H, 4.0; N, 25.2.

Physical characteristics of other 2-aminothiazolo[5,4-*b*]pyridines are presented in Tables I and II.

N-(3-Pyridyl)-*N'*-methylthiourea (**8**).

A stirred 3A alcohol solution (50 ml.) of 3-aminopyridine (9.4 g., 0.1 mole) and methyl isothiocyanate (7.3 g., 0.1 mole) was refluxed for 18 hours. The solvent was then removed under reduced pressure and the residual clear yellow syrup was triturated with *ca.* 1:1 v/v ethyl acetate:ethanol. The resulting solid was then crystallized from ethanol, yield, 9.5 g. (57%), m.p. 140-141° [lit. (7) 144-146°]; ^{13}C nmr: δ (ppm) 31.051 ($NHCH_3$), 123.127, 130.680, 136.315, 144.887 (pyridine ring carbons - two of these carbons exhibit identical resonance values), and 181.753 (thione carbon). The mass spectrum showed the parent peak at m/e 167 (Calcd. 167).

3-Amino-4-chloropyridine (**4**).

To a mixture of fuming nitric acid (5.7 g.) and 20% oleum (5.7 g.) was added 4-(1*H*)pyridone (5.6 g., 0.059 mole). This mixture was gently warmed and, after an initial exothermic reaction had subsided, was refluxed for one hour. The cooled mixture (a viscous yellow liquid) was cautiously poured into stirred distilled water (40 ml.) and the resulting mixture was neutralized with concentrated ammonium hydroxide. The separated yellow solid was crystallized from distilled water, yield, 3.5 g. (42%), m.p. 283.5-285° [lit. (4) 278-279°]. The mass spectrum showed the parent peak at m/e 140 (Calcd. 140). To an intimate mixture of this 3-nitro-4-(1*H*)pyridone (21.8 g., 0.16 mole) and phosphorus pentachloride (38.0 g.) was added phosphorus oxychloride (2 ml.). This mixture was gently refluxed for three hours and the phosphorus oxychloride was removed from the cooled reaction mixture under reduced pressure. The residual yellow solid was dissolved in dichloromethane and the hydrochloride of 3-nitro-4-chloropyridine was precipitated by bubbling hydrogen chloride gas through this solution. The salt was collected, washed with ether and dried under vacuum to give 18.0 g. (59%) of product. The mass spectrum showed the parent peak of the free-base at m/e 158 (Calcd. 158). Caution! This salt should be kept in a cool dry environment since it is highly susceptible to hydrolysis. To a stirred suspension of this hydrochloride (6.6 g., 0.035 mole) in ethyl ether (30 ml.) was slowly added to a concentrated hydrochloric acid solution (100 ml.) of stannous chloride dihydrate (100 g.). During this addition, the reaction became exothermic enough to evaporate the ether. This reaction mixture was cooled in an ice-bath and the orange precipitate was collected. All of this precipitate was suspended in distilled water and the mixture was made alkaline with sodium carbonate. The basic solution was extracted with two portions of chloroform and the combined chloroform extract was dried over magnesium sulfate. The solvent was removed under reduced pressure leaving a pale yellow liquid that solidified after chilling, yield, 4.1 g. (91%), m.p. 52-57° [lit. (5) 59.5-60.5°]. This 3-amino-4-chloropyridine was used for the reaction below without further purification.

Representative 2-Aminothiazolo[4,5-*c*]pyridine Synthesis Illustrated for 2-Methylaminothiazolo[4,5-*c*]pyridine.

A stirred ethanol solution (11 ml.) of 3-amino-4-chloropyridine (1.1 g., 0.0086 mole) and methyl isothiocyanate (0.7 g., 0.0096 mole) was refluxed for 18 hours. The cooled ethanol suspension was briefly chilled and then ethyl ether was added to the suspension. The salt was collected and dried under vacuum, yield, 1.1 g. (63%), m.p. 251-254°. The mass spectrum showed the parent peak of the free-base at m/e 165 (Calcd. 165).

Anal. Calcd. for $C_7H_8ClN_3S$: C, 41.7; H, 4.0; N, 20.8. Found: C, 41.6; H, 4.1; N, 21.0.

A stirred aqueous (25 ml.) mixture of sodium bicarbonate (0.8 g.) and this hydrochloride (0.8 g.) was kept at ambient temperature for two hours. The resulting brown solid was collected and dissolved in hot ethyl acetate. This solution was treated with decolorizing carbon and the clear yellow filtrate was chilled for 18 hours, yield, 0.1 g., m.p. 160-161°; ^1H nmr: δ (ppm) 3.00 (s, 3H, NCH_3), 7.78 (d, J = 6 Hz, 1H, aromatic H), 8.17 (d, J = 6 Hz, 1H, aromatic H), and 8.62 (s, 1H, aromatic H). The mass spectrum showed the parent peak at m/e 165 (Calcd. 165).

Anal. Calcd. for $C_7H_7N_3S \cdot 0.25\ H_2O$: C, 49.6; H, 4.4; N, 24.8. Found: C, 49.5; H, 4.1; N, 25.2.

Other examples may be found in Table III.

Reaction of 2-Chloro-3-aminopyridine with 1-Phenyl-5-mercapto-1*H*-tetrazole (**10**). 2-Anilinothiazolo[5,4-*b*]pyridine.

A stirred solution of 2-chloro-3-aminopyridine (6.4 g., 0.05 mole) and 1-phenyl-5-mercapto-1*H*-tetrazole (17.8 g., 0.10 mole) in ethanol (50 ml.) that contained 10 ml. of concentrated hydrochloric acid was refluxed for 66 hours. At the end of this time, a pale yellow solid (4.6 g.) separated from the dark brown solution. This solid was partitioned between dilute aqueous ammonium hydroxide (15% ammonia) and chloroform. The chloroform extract was then washed with distilled water and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residual brown solid was dissolved in ethanol, the solution treated with decolorizing carbon (Nuchar C-190-N), and the suspension filtered through an analytical filter-aid (Super Cell). The filtrate was evaporated to dryness and the residual tan solid was crystallized from ethyl acetate, yield, 1.5 g. (13%) of colorless needles (see Table II), m.p. 177-178°. The mass spectrum showed the parent peak at m/e 177-178°. The mass spectrum showed the parent peak at m/e 227 (Calcd. 227).

Reaction of 2-Chloro-3-aminopyridine with 1-Methyl-5-mercapto-1*H*-tetrazole (**11**). Tetraazo-9,10-dihydroanthracene Dihydrochloride (**12**).

A stirred solution of 2-chloro-3-aminopyridine (2.8 g., 0.022 mole) and 1-methyl-5-mercapto-1*H*-tetrazole (5.0 g., 0.043 mole) in ethanol (25 ml.) that contained 5 ml. of concentrated hydrochloric acid was refluxed for 66 hours. The yellow solid that separated was collected and dried, yield, 2.1 g. (38%); m.p. slow decomposition above 200°. The mass spectrum showed the parent peak of the free-base at m/e 184 (Calcd. 184).

Anal. Calcd. for $C_{10}H_8N_4 \cdot 2\ HCl$: C, 46.7; H, 3.9; N, 21.8. Found: C, 46.5; H, 3.9; N, 21.6.

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D. P. Maier and R. S. Gohlke determined the mass spectra,

and T. H. Regan and R. L. Young measured the nmr spectra. The elemental analyses were performed by G. N. Meyer and his staff at the Kodak Research Laboratories.

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