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The Synthesis of Pyrido[2, 1-b]-3, 4-dihydro-4-iminothiazole Derivatives. A New Meso-ionic Heterocyclic System[1,2]

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The action of acyl chlorides on 2-pyridylthioacetonitrile and related compounds gives the corresponding *N*-acylated pyrido[2, 1-b]-3, 4-dihydro-4-iminothiazoles and related compounds.

In the preceding paper of this series,[1] the formation of pyrido[2, 1-b]-3, 4-dihydro-4-oxothiazole (I) by a new mode of formation was reported. Although a considerable amount of work has been reported on this ring system, the corresponding imino derivatives (e. g., II) were not known when this investigation was completed.[3] An attempt to prepare this compound by the reaction of (2-pyridylthio)acetamide and acetyl chloride gave the oxo derivative I, as we have reported.[1] In the present communication, we will report the successful preparation of *N*-acyl-pyrido[2, 1-b]-3, 4-dihydro-4-iminothiazoles (II) and related compounds.

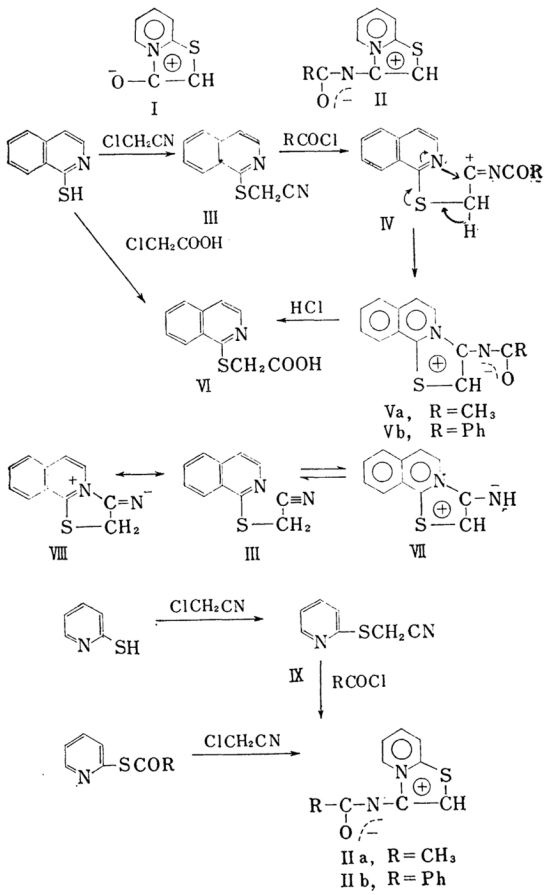
Results and Discussion

The reaction of 1-mercaptoisoquinoline and chloroacetonitrile gave 1-isoquinolylthioacetonitrile

1) Studies on Meso-ionic Compounds. Part XXV. Part XXIV: H. Kato, K. Tanaka and M. Ohta, This Bulletin, **39**, 1248 (1966).

2) For a preliminary communication, see H. Kato, K. Tanaka and M. Ohta, ibid., **35**, 1901 (1962).

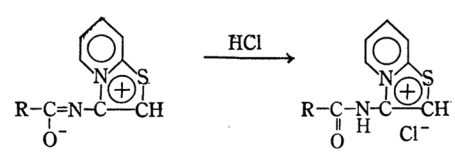
3) As a result of our preliminary communication,[2] a number of condensed and uncondensed compounds of this type have been prepared in this laboratory: H. Chosho, K. Ichimura and M. Ohta, This Bulletin, **37**, 1670 (1964); K. Ichimura and M. Ohta, ibid., **38**, 707 (1965).



(III). The presence of a nitrile group was revealed by an infrared absorption at 2240 cm^{-1}. No ring closure took place when it was treated with hydrogen chloride[4] or acetic anhydride. Successful ring closures with these reagents to give meso-ionic compounds have been reported in the case of *N*-nitroso-*N*-phenylglycinonitrile (with hydrogen chloride)[5] and *N*-benzyl-2-pyridylaminoacetonitrile (with acetic anhydride).[6] On heating a benzene solution of 1-isoquinolylthioacetonitrile with acetyl chloride, a hydrochloride was formed, which gave a free base with the empirical formula $C_{13}H_{12}ON_2S$ on treatment with alkali. A similar reaction occurred with benzoyl chloride to give a free base, $C_{18}H_{12}ON_2S$. The infrared absorption at 2240 cm^{-1} has disappeared in these compounds, suggesting that the nitrile group has participated in the reaction. From the above results and known analogous ring formation reactions, it may safely be deduced that the reaction products are *N*-acetyl and *N*-benzoyl-isoquinolo[1, 2-b]-3, 4-dihydro-4-iminothiazole (Va and Vb). The formation of this compound can reasonably be explained by considering the attack of an acyl cation on the nitrile group to give the intermediate cation IV, followed by ring formation and a proton removal to give the products V shown in the above chart. Since the ring nitrogen atom is by far the more basic than the nitrile nitrogen atom, a strong acid such as hydrogen chloride preferably would add to the ring nitrogen atom rather than to the nitrile nitrogen atom to facilitate the polarization, thus resulting in the loss of the nucleophilic aptitude of the ring nitrogen atom. Such is evidently not the case with *N*-nitroso-*N*-substituted glycinonitrile, which gives a sydnone-imine derivative when treated with hydrogen chloride. The failure of ring formation with acetic anhydride is probably due to its poor acylating power in forming the intermediate IV. The fact that it does not give the product with acetic anhydride and the presence of the infrared absorption of III at 2240 cm^{-1} further show the absence of an equilibrium between the open-chain (III) and cyclic (VII) isomers, and even the absence of an intramolecular interaction such as III↔VIII, which is sometimes to be found in structurally similar systems.[7]

This meso-ionic system seems rather stable, and when the *N*-benzoyl derivative Vb was treated with phenylhydrazine, aniline, chromic acid or zinc powder in acetic or hydrochloric acid, or when heated in acetic acid, no reaction took place and the starting material was recovered unchanged. Sydnone-imines which are structurally similar to compound V are quite stable to strong acidic conditions, but the hydrolysis of the *N*-benzoyl derivative Vb by hydrochloric acid caused a cleavage of the ring to give benzoic acid and (1-isoquinolylthio)acetic acid (VI). The structure of the reaction product was established by preparing the compound independently from 1-mercaptoisoquinoline and chloroacetic acid.

The treatment of 2-mercaptopyridine with chloroacetonitrile gave 2-pyridylthioacetonitrile (IX), which, by the action of acetyl and benzoyl chloride, gave *N*-acetyl- and *N*-benzoyl-pyrido-[2, 1-b]-3, 4-dihydro-4-iminothiazole (IIa and IIb) respectively. The same compounds, IIa and IIb, were obtained by the action of 2-acetylthio- and 2-benzoylthio-pyridine and chloroacetonitrile, albeit in lower yields. The mode of formation



X

4) It was later found[3] that an uncondensed ring system could be prepared by the action of hydrogen chloride.

5) H. Kato, M. Hashimoto and M. Ohta, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zassi*), **78**, 707 (1957).

6) N. W. Bristow, P. T. Charlton, D. A. Peak and W. F. Short, *J. Chem. Soc.*, **1954**, 616.

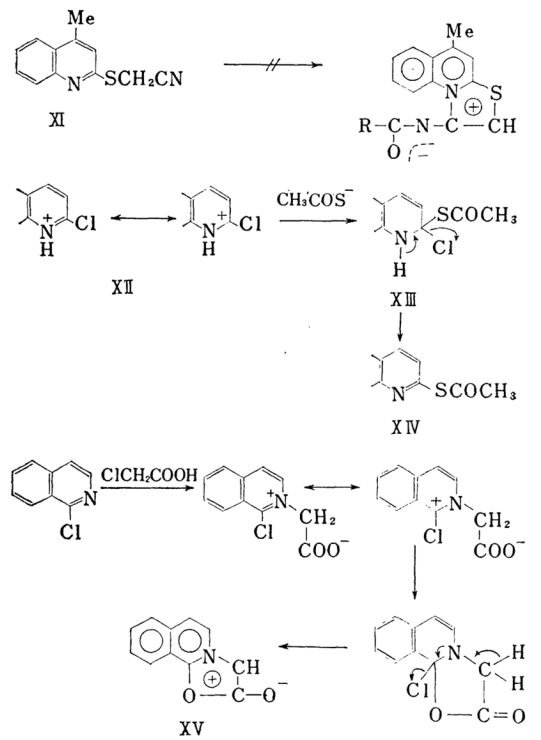
7) See, e.g., M. Ohta and H. Kato, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **86**, 661 (1965).

in the latter case would be essentially the same as that of the formation of the corresponding oxo compound I from 2-acylthiopyridine and chloroacetic acid.

Mention should be made of the infrared spectra of these compounds. Neither of the *N*-acetyl free bases, IIa or Va, shows any absorption in the normal amide carbonyl region. This is in marked contrast to the corresponding oxo ring system (e. g., I), which shows an alsmost normal carbonyl absorption at 1675 cm^{-1}, suggesting that the carbonyl groups of II and V are very strongly polarized; it supports further the rather superficial similarity of the oxo and imino-type meso-ionic compounds, as has been discussed elsewhere in the case of sydnones and sydnone-imines.[7,8] In contrast to the common idea, these "amides," II and V, are soluble in dilute hydrochloric acid and form stable hydrochlorides. The infrared absorption of IIa hydrochloride shows a strong absorption due to an amide group at 1702 cm^{-1}. This fact, and the absorption centered at 3180 cm^{-1} show that the proton is attached neither to the ring nitrogen atom nor to the polarized carbonyl oxygen, but to the exocyclic "amide" nitrogen atom, to give a tropylium salt-like structure, X.

A similar treatment of 2-mercapto-4-lepidine with chloroacetonitrile gave 4-lepidly-2-thioacetonitrile (XI), this, however, did not give the expected corresponding imino derivative by the action of acyl chlorides. Since the basicity of this compound is considered to lie between, or to be nearly equal to, those of the pyridyl and isoquinolyl derivatives, this anomalous behavior is certainly not related to the basicity of this compound. (The pK_a's of 2-methylthiopyridine, 2-methylthioquinoline and 1-methylthioisoquinoline are reported to be 3.62, 3.71 and 3.93 respectively.[9]) This result may most reasonably be explained by considering a steric hindrance between the *N*-acyl group and the hydrogen atom of the 8-position of the quinoline nucleus. A similar effect has been observed in an attempted synthesis of the oxo analogue; though (2-quinolylthio)-acetic acid gave the corresponding oxo-compound, when the 8-position of the quinoline ring was substituted, no ring formation took place.[10] In the present case, a study of a model indicates that even a small atom like hydrogen at that position is bulky enough to interact with relatively bulky acyl groups.

It was found that the chlorine atoms of 1-chloroisoquinoline and 2-chloro-4-lepidine are active enough to give, on brief heating with mercaptoacetic acid, almost a quantitative yield of the corresponding mercapto derivatives which are required as the starting materials in this study. This phenomenon can reasonably be explained by considering an attack of the acetothioxy anion on protonated azines XII to give XIII, followed by the removal of a molecule of hydrogen chloride to give XIV, which later gives the mercapto derivatives by hydrolysis or thioacetolysis. This fact led us to try to prepare a new meso-ionic compound, XV, by the following sequence of reactions. When 1-chloroisoquinoline and chloroacetic acid were heated in benzene, the reaction product was isocarbostyril, showing that the attack of chloroacetic acid at the 1-position of the isoquinoline ring precedes the formation of the quaternary salt formation.



Experimental

All melting points were determined on a micro hot stage and are corrected. Boiling points are uncorrected. The infrared spectra were taken on a Nippon Bunko Infrared Spectrometer, Model S, equipped with an NaCl prism on KBr tablets.

1-Isoquinolylthioacetonitrile (III).—To a solution of 1.24 g. of sodium hydroxide and 5 g. of 1-mercaptoisoquinoline in 50 ml. of ethanol, a solution of 2.35 g. of chloroacetonitrile in 10 ml. of ethanol was added; the mixture was then warmed on a water bath for twenty minutes. The precipitate which separated out was filtered off, the filtrate was concentrated under reduced pressure, and the pale yellow plates which separated out on cooling were collected (4 g., m. p. 95.0—95.5°C) and recrystallized from ethanol to give white plates, m. p. 95.5°C. IR, 2240 cm^{-1}.

8) F. H. C. Stewart, *Chem. Revs.*, **64**, 129 (1964).
9) A. Albert and G. B. Barlin, *J. Chem. Soc.*, **1959**, 2384.
10) G. F. Duffin and J. D. Kendall, ibid., **1951**, 734.

Found: C, 65.91; H, 3.84; N, 14.27. Calcd. for $C_{11}H_8NS_2$: C, 65.99; H, 4.03; N, 13.99%.

***N*-Acetyl-isoquinolo[1, 2-b]-3, 4-dihydro-4-iminothiazole (Va).**—To a solution of 1 g. of 1-isoquinolylthioacetonitrile in 6 ml. of benzene, a solution of 0.4 g. of acetyl chloride in 4 ml. of benzene was added; the mixture was then refluxed on a water bath for one hour. The pale yellow precipitate was collected (1.2 g., m. p. 255—256°C) and dissolved in water. The aqueous solution was made alkaline with sodium bicarbonate and was extracted with chloroform. The chloroform extract was dried over sodium sulfate and concentrated, and the yellow fine needles which separated out were collected (0.4 g., m. p. 210—212°C). Recrystallization from benzene afforded 0.2 g. of yellow prisms, melting at 215°C. This substance is soluble in dilute hydrochloric acid. IR: no absorption around 2240 cm^{-1}.

Found: C, 64.25; H, 4.40; N, 11.59. Calcd. for $C_{13}H_{10}ON_2S$: C, 64.46; H, 4.16; N, 11.59%.

***N*-Benzoyl-isoquinolo[1,2-b]-4,3-dihydro-4-iminothiazole (Vb).**—To a solution of 1 g. of 1-isoquinolylthioacetonitrile in 10 ml. of benzene 0.7 g. of benzoyl chloride was added. The mixture was then refluxed on a water bath for ten minutes. The benzene was evaporated, and the residue was warmed on the water bath for another two hours. The dark mass which formed was tritulated with 5 ml. of ethanol, and the solid was collected by filtration to afford 1.25 g. of a brown powder (m. p. 255—260°C). This was dissolved in water, the solution was made alkaline with sodium bicarbonate, and the precipitate which formed was collected to give 1.13 g. of a yellow powder, melting at 271°C. One recrystallization from *n*-butanol gave 0.88 g. of yellow leaflets melting at 273°C. This substance is soluble in 10% hydrochloric acid.

Found: C, 71.30; H, 3.81; N, 9.49. Calcd. for $C_{18}H_{12}ON_2S$: C, 71.04; H, 3.98; N, 9.21%.

The Acid Hydrolysis of the *N*-Benzoyl Compound Vb.—A solution of 1 g. of *N*-benzoyl-isoquinolo[1, 2-b]-3, 4-dihydro-4-iminothiazole in 50 ml. of 10% hydrochloric acid was heated on a water bath for one hour. After cooling, the crystals (portion A) which separated out were collected, and the filtrate was concentrated under reduced pressure. The residue was washed with aqueous sodium bicarbonate and recrystallized from ethanol-ligroin to give 0.25 g. of silky white needles melting at 96°C. The melting point of this substance was not depressed on admixture with a sample of (1-isoquinolylthio)acetic acid prepared by the method to be described below.

Found: N, 6.62. Calcd. for $C_{11}H_9O_2NS$: N, 6.39%.

The sodium bicarbonate washings were acidified with hydrochloric acid, and the crystals which separated out were added to portion A and recrystallized from water to give 0.35 g. of colorless needles; these needles were identified as benzoic acid by their melting point (122°C) and mixed melting point with an authentic sample of benzoic acid.

(1-Isoquinolylthio)acetic Acid (VI).—Into a solution of 0.8 g. of 1-mercaptoisoquinoline and 0.4 g. of sodium hydroxide in a mixture of 20 ml. of ethanol and 2 ml. of water, 0.5 g. of chloroacetic acid was stirred. After two hours, the precipitate of sodium chloride was filtered off; the new crystals which separated out on cooling were collected and dissolved in water, and the aqueous solution was acidified with acetic acid. The crystals which separated out were recrystallized from ethanol-ligroin to give 0.5 g. of silky white needles melting at 98°C.

Found: N, 6.53. Calcd. for $C_{11}H_9O_2NS$: N, 6.39%.

2-Pyridylthio acetonitrile (IX).—Into a solution of 9.3 g. of 2-mercaptopyridine and 5.3 g. of sodium hydroxide in 50 ml. of ethanol, 6.3 g. of chloroacetonitrile was stirred while the solution was being cooled. The precipitate of sodium chloride was removed by filtration, and the filtrate was concentrated and distilled under reduced pressure to give 9.5 g. of a yellow liquid boiling at 118—120°C/3 mmHg.

Found: C, 55.03; H, 3.90; N, 18.26. Calcd. for $C_7H_6N_2S$: C, 56.00; H, 4.03; N, 18.66%.

This substance darkened quite rapidly, and no good analytical agreement was obtained on several repeated analyses.

***N*-Acetyl-pyrido[2, 1-b]-3, 4-dihydro-4-iminothiazole (IIa).**—a) A solution of 2 g. of 2-pyridylthioacetonitrile and 0.95 ml. of acetyl chloride in 10 ml. of benzene was refluxed on a water bath for one hour. The precipitate which formed was then collected to give 3.0 g. of a yellow powder. Recrystallization from ethanol afforded 2.1 g. of yellow prisms melting at 250°C. IR: 1702 cm^{-1}.

Found: N, 12.04. Calcd. for $C_9H_9ON_2SCl$: N, 12.25%.

This substance was dissolved in water, made alkaline with potassium carbonate, and extracted with chloroform. The chloroform extracts were concentrated, and the residue was recrystallized from benzene to give 1.3 g. of yellow needles, melting at 73—74°C.

Found: C, 51.52; H, 5.06; N, 13.58. Calcd. for $C_9H_8ON_2S+H_2O$: C, 51.42; H, 4.80; N, 13.33%.

After being dried at 60°C under a vacuum for a day:

Found: N, 14.02. Calcd. for $C_9H_8ON_2S$: N, 14.58%. This substance is soluble in dilute hydrochloric acid. IR: no strong absorption between 1700—1600 cm^{-1}.

b) A solution of 1 g. of 2-acetylthiopyridine and 0.5 g. of chloroacetonitrile in 3 ml. of benzene was refluxed on a water bath for one hour. The crystals which separated out were collected to give 0.9 g. of a dark yellow powder, which was then recrystallized from ethanol to give 0.45 g. of orange needles, m. p. 252—254°C (decomp.).

Found: N, 12.03. Calcd. for $C_9H_9ON_2SCl$: N, 12.25%.

***N*-Benzoyl-pyrido[2, 1-b]-3, 4-dihydro-4-iminothiazole (IIb).**—a) A solution of 2 g. of 2-pyridylthioacetonitrile and 1.54 ml. of benzoyl chloride in 10 ml. of benzene was refluxed for one hour on a water bath. The benzene was then evaporated, and the residue was warmed on a water bath for another thirty minutes. The crystals which separated out on cooling were collected to give 3 g. of a pale yellow powder. This substance was suspended in water and made basic with sodium bicarbonate. The resultant solid was collected to give 2.35 g. of a brown powder, which was recrystallized from ethanol to give 1.75 g. of yellow needles with a green fluorescence, m. p. 206°C.

Found: C, 66.14; H, 3.75; N, 10.76. Calcd. for $C_{14}H_{10}ON_2S$: C, 66.13; H, 3.96; N, 11.02%.

b) A solution of 2 g. of 2-benzoylthiopyridine and 0.7 g. of chloroacetonitrile was refluxed on a water

bath for twelve hours. After cooling, the yellow precipitate was collected to give 0.25 g. of yellow crystals, which were basified with sodium bicarbonate and recrystallized from ethanol to give 0.1 g. of yellow needles, m. p. 206°C, undepressed on admixture with a sample prepared by Method a).

4-Lepidyl-2-thioacetonitrile (XI).—Into a solution of 3.2 g. of 2-mercapto-4-lepidine and 0.74 g. of sodium hydroxide in 30 ml. of ethanol, 1.4 g. of chloroacetonitrile was added dropwise with cooling and stirring. The precipitate of sodium chloride was filtered off, and the filtrate was concentrated to give 4.1 g. of pale yellow needles melting at 64—65°C. Recrystallization from ethanol afforded colorless needles melting at 65°C.

Found: C, 67.28; H, 4.71; N, 13.09. Calcd. for $C_{12}H_{10}ON_2S$: C, 67.28; H, 4.71; N, 13.08%.

The Attempted Preparation of *N*-Acyl-4-lepido-[2, 1-b]-3, 4-dihydro-4-iminothiazole.—A solution of 1.3 g. of 4-lepidyl-2-thioacetonitrile and 0.58 g. of acetyl chloride in 5 ml. of benzene was refluxed for one hour on a water bath. The precipitate which separated out was collected (0.8 g.) and recrystallized from ethanol to give yellow needles. It was suspended on water, made alkaline with potassium carbonate, and extracted with chloroform. The chloroform extract was then concentrated under reduced pressure, and the residue was recrystallized from ligroin to give colorless needles melting at 65—66°C, undepressed on admixture with 4-lepidyl-2-thioacetonitrile.

When 4-lepidyl-2-thioacetonitrile was treated with benzoyl chloride in benzene, the starting material was recovered unchanged after it had been heated on a water bath for five hours.

1-Mercaptoisoquinoline.—a) To a suspension of 2 g. of isoquinoline in 5 ml. of water, 0.94 g. of thioacetic acid was added, and the mixture was warmed for thirty minutes on a water bath. The crystals which separated out were collected to give 1.75 g. of yellow prisms melting at 171°C. One recrystallization from ethanol gave yellow prisms, m. p. 171°C.

b) An exothermic reaction occurred when 2 g. of 1-chloroisoquinoline was mixed with 2 ml. of thioacetic acid. After it had been warmed on a water bath for ten minutes, the mixture was cooled and the pale yellow prisms which separated out were collected (1.8 g., m. p. 166°C) and recrystallized from ethanol to give 1.65 g. of yellow prisms, m. p. 170°C.

2-Mercapto-4-lepidine.—a) To a suspension of 0.5 g. of 2-chloro-4-lepidine in 10 ml. of water, 0.22 g. of thioacetic acid was added and the mixture was warmed on a water bath for thirty minutes. The crystals which separated out were collected to give 0.45 g. of yellow needles, melting at 260°C.

b) A mixture of 0.5 g. of 2-chloro-4-lepidine and 1 ml. of thioacetic acid was warmed on a water bath for thirty minutes. The mixture was concentrated under reduced pressure, and the residue was washed with water to give 0.5 g. of yellow needles, melting at 261°C.

The Reaction of 1-Chloroisoquinoline and Chloroacetic Acid.—A solution of 1 g. of 1-chloroisoquinoline and 0.6 g. of chloroacetic acid in 10 ml. of benzene was refluxed on a water bath for two hours. Benzene was distilled off under reduced pressure, and the residue which solidified was recrystallized from ethanol to afford 0.3 g. of pale yellow needles, m. p. 210—211°C, undepressed on admixture with an authentic specimen of isocarbostyrile.

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