mixture was refluxed for 1 hr, cooled to room temperature, filtered to remove precipitated salt, and concentrated *in vacuo*. Chilling and scratching with a glass rod caused the oil to crystallize and a 77% yield, mp 51–54° from methanol (lit.[13b] mp 52°), of methyl (S-carbomethoxymethyl)thiosalicylate was obtained.

The crystals were redissolved in 18 ml of methanol containing 0.60 g of sodium methoxide and refluxed for 10 hr. Cold water was added dropwise and the organic precipitate filtered off, washed with cold water, and recrystallized from methanol. A 76% yield of white needles, mp 106.5–108° (lit.[17] mp 107–108°), was obtained. Mixture melting point and infrared spectrum were identical with those of the ammonolysis product.

Attempted Piperidine Catalysis of Cyclization of 6a.—To 0.029 moles of **6a** was added a solution of 0.029 moles of piperidine in 100 ml of methanol. The mixture was refluxed for 1 hr and became progressively more yellow and a white precipitate appeared. The solid was filtered off and recrystallized from N,N-dimethylformamide. After several recrystallizations, the melting range, 170–220° dec, of the crystals (30% yield) was still not precisely defined. Although the material was of insufficient solubility to obtain an nmr spectrum, the infrared spectrum revealed intense carbonyl absorptions centered at 1710 cm^{-1}. The crystals did not appear to contain nitrogen and analyzed for the approximate loss of one molecule of methanol from the adduct **6a**.

Anal. Calcd for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62. Found: C, 56.19; H, 4.05.

Concentration of the mother liquors from the original reaction precipitate a highly soluble, pinkish white compound, mp 85–88° from methanol, in 18% yield. The elemental and nmr analyses were consistent with an assignment as dimethyl α-(1-piperidinyl)-α′-(2-carbomethoxyphenylthio)succinate.

Anal. Calcd for $C_{19}H_{25}NO_6S$: C, 57.70; H, 6.37. Found: C, 57.67; H, 6.40.

The nmr spectrum displayed proton complexes characteristic of piperidine moieties centered at 2.50 ppm (four protons adjacent to nitrogen) and at 1.41 ppm (six protons of C-3 and C-4). Two mutually coupled doublets at 4.30 and 3.52 ppm (one proton each) were assigned to the methines. Three ester methyls at 3.65, 3.69, and 3.86 ppm and an aromatic complex at 7.0–8.0 ppm (four protons) were also in agreement with the assignment.

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Registry No.—**4**, 13134-72-0; **6a** maleate, 13134-73-1; **6a** fumarate, 13134-74-2; **6b** fumarate, 13134-75-3; **6c** fumarate, 13127-30-5; **6d** fumarate, 13127-31-6; **6e** fumarate, 13127-32-7; **7a**, 13134-76-4; **7b**, 13134-77-5; **7c**, 13134-78-6; dimethyl α-(1-piperidinyl)-α′-(2-carbomethoxyphenylthio)succinate, 13134-79-7.

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One-Step Synthesis of Fused Pyrimidinethiones from *o*-Aminonitriles and Thioamides

JOHN A. ZOLTEWICZ AND THOMAS W. SHARPLESS

Department of Chemistry, University of Florida, Gainesville, Florida 32601

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Substituted quinazoline-4(3H)-thiones were prepared in one step from 2-aminobenzonitriles and aliphatic or aromatic thioamides in acetic acid–hydrogen bromide or N,N-dimethylformamide–hydrogen bromide solvent. Competing reaction between aminobenzonitrile and solvent leads to the formation of quinazolin-4(3H)-one side products. Cyclization of aminonitrile to quinazolinone is the major reaction in the acidic solvents in the absence of thioamide. Alcoholic solutions of quinazolinethiones spontaneously form diquinazolinyl disulfides.

Quinazoline-4(3H)-thiones, examples of fused-ring pyrimidinethiones, frequently have been prepared by multistage syntheses which often involve drastic conditions.[1] Among the more convenient preparations, however, are four one-step routes; each of these starts with a 2-aminobenzonitrile. The first of these is the most general preparation in that a variety of 2-substituted quinazoline-4(3H)-thiones may be synthesized when a mixture of an inorganic sulfide and an acid anhydride are employed as additional reactants.[2] Since the anhydride is encorporated into the 2 position of the heterocyclic ring during the cyclization, a change in the structure of this reactant provides a method for the preparation of a variety of substituted compounds. This method, however, is limited by the accessibility of the acid anhydrides. In a second approach, a thiol acid is employed to introduce sulfur into the aminonitrile and to act as the cyclizing agent.[2] A third synthesis utilizes ethyl orthoformate and inorganic sulfide to effect cyclization to quinazoline-4(3H)-thione unsubstituted at position 2.[3] When pyridine and carbon disulfide are employed in a fourth method of cyclizing 2-aminobenzonitriles, quinazoline-2,4(1H,3H)-dithiones are prepared.[4]

Our report deals with a new, one-step synthesis of quinazoline-4(3H)-thiones from 2-aminobenzonitriles.[5] This simple, convenient method may be employed for the preparation of quinazoline-4(3H)-thiones having a hydrogen, an aliphatic, or an aromatic group at C-2. Thioamides are employed to effect cyclization of the aminonitrile. In the preparation, reactants are heated in a strongly acidic solution and then concentrated; the residue is taken up in aqueous alkali and quinazolinethione is precipitated on acidification, Scheme I. The 2-aminobenzonitrile reactants employed in this study include those with a methoxyl group at C-4 (R_3) and a methoxyl, methyl, or nitro group at C-5 (R_2).

(1) For reviews of reactions, see (a) T. A. Williamson in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 369–372; (b) W. L. F. Armarego, *Advan. Heterocyclic Chem.*, **1**, 253 (1963); (c) H. M. Blatter and H. Lukaszewski, *Tetrahedron Letters*, 855 (1964); (d) H. M. Blatter, H. Lukaszewski, and G. de Stevens, *J. Org. Chem.*, **30**, 1020 (1965).

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(4) E. C. Taylor, A. McKillop, and R. N. Warrener, *ibid.*, **23**, 891 (1967).

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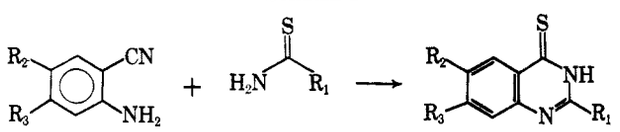
TABLE I

SUBSTITUTED QUINAZOLINE-4(3H)-THIONES PREPARED FROM 2-AMINOBENZONITRILES AND THIOAMIDES

Compd	Substituent R1	Substituent R2	Substituent R3	Mp, °C	Reaction solvent	Reaction time, hr	Method of prepn	Yield,[a] %
1	H	H	H	320–322[b]	DMF	2.5	C	70
2	C_6H_5	H	H	221–221.5	DMF	3	C	50
3	H	NO_2	H	255.5–256.5[c] dec	HOAc	1	B	60[d]
					DMF	10	C	28
4	CH_3	NO_2	H	255–256 dec	DMF	2	C	38[d,e]
5	C_6H_5	NO_2	H	247–248	DMF	11	C	45
6	H	H	CH_3O	253.5–254 dec	HOAc	0.5	A	42[f]
7	CH_3	H	CH_3O	274–276 dec	HOAc	4	B	47[g]
8	C_6H_5	H	CH_3O	196–198	HOAc	2	B	17[h]
					DMF	4	C	32
9	H	CH_3O	H	323–324 dec	HOAc	2	A	34[i]
					DMF	7	C	43
10	CH_3	CH_3O	H	286.5–287.5 dec	HOAc	3	A	42
11	C_6H_5	CH_3O	H	226–227.5 dec	HOAc	3	B	1
					DMF	11	C	6
12	H	CH_3	H	322–323 dec	HOAc	1	B	25[g]
13	CH_3	CH_3	H	258–259 dec	HOAc	2	B	30
14	C_6H_5	CH_3	H	240–241	HOAc	2	B	5[g]
					EtOH	4.5	D	21

[a] Average of several determinations. [b] N. J. Leonard and D. Y. Curtain, *J. Org. Chem.*, 11, 349 (1946). [c] E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *ibid.*, 82, 6058 (1960). [d] Recrystallized from water. [e] Reaction mixture diluted with equal parts of ethanol and ether to aid precipitation. [f] Purified by reprecipitation on neutralization of an alkaline solution. [g] Recrystallized from ethanol–water. [h] Purified by subliming. [i] Residue was recrystallized from ethanol–water after the solvent was removed under reduced pressure.

SCHEME I



Results and Discussion

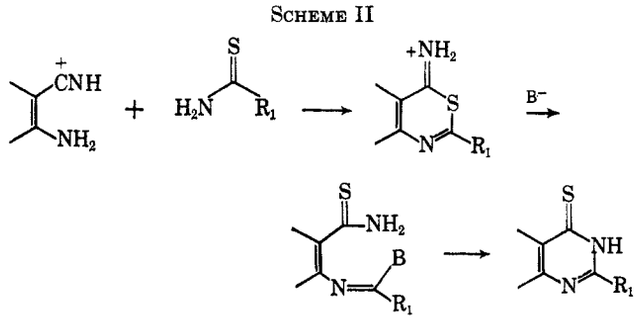
That the products from the reaction of 2-aminobenzonitriles with thioamides are quinazoline-4(3H)-thiones was proven by comparison with known compounds. Table I summarizes the work. It is evident from these data that a variety of aminonitriles and thioamides enter into the cyclization reaction. Although the synthesis is characterized by its simplicity, the yields of pure, cyclic product, as reported in Table I, range from moderate to low. Crude yields were much higher, but the presence of several components in the raw product leads to considerable loss of material on purification.

Thioamide Reactivity.—Aliphatic and aromatic thioamides participate in the cyclization reaction. Little difference in reactivity was observed between thioacetamide and thioacetanilide or between thiobenzamide and thiobenzanilide. The primary thioamides, however, generally gave cleaner products. Both thioformanilide and thioacetamide are noticeably more reactive than thiobenzamide. When thiobenzamide was employed, reaction time had to be extended in order to increase the yield of product. Although excess thioamide was used, the extent of the excess seemed to be without noticeable effect on the yield of quinazolinethione. The cyclization reaction could not be extended to include thiourea, acetyl-, or phenylthiourea. Nitrile reactants were recovered unchanged in each instance.

Selection of Solvent.—The acid-catalyzed cyclization is conveniently effected at steam-bath temperature in a variety of nonaqueous solvents saturated with hydrogen bromide. Suitable solvents include N,N-dimethylformamide (DMF–HBr), glacial acetic acid (HOAc–HBr), or ethanol (EtOH–HBr). The choice of solvent is largely dictated by the solubility of the aminonitrile hydrobromide which forms on addition of the aminonitrile to the acid medium. The cyclization reaction is inconveniently slow when this salt is suspended in the medium. Insolubility and incomplete reaction frequently are encountered when EtOH–HBr are employed. Although aminonitrile hydrobromide is soluble in DMF–HBr or HOAc–HBr, aminonitrile substrate may react with these carbonyl-containing solvents to give side products.

Reaction Mechanism.—A rational for product formation was suggested in an earlier publication[5] and is summarized in Scheme II. Thioamide reacts with protonated aminonitrile to give a fused 4(3H)-imino-*m*-thiazine which then ring opens by C–S bond breaking;

SCHEME II



quinazolinethione results when the open-chain species cyclizes. Repeated, unsuccessful attempts were made to isolate the proposed unrearranged intermediate. The ring-opening, ring-closure sequence could take place in the acidic reaction medium or during the work-up in alkali. Rearrangements in heterocyclic systems

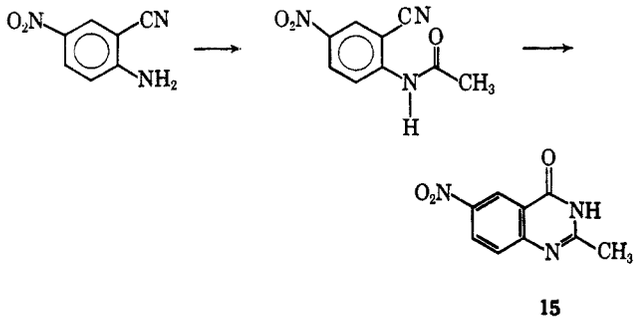
which proceed by this type of opening–closing sequence can be very rapid reactions.[6-8]

Side Reactions.—Several types of fused-ring side products were isolated from reaction mixtures employed to prepare quinazolinethione. These side products are formed by a reaction between solvent and aminonitrile or a derivative of the aminonitrile which is formed during the course of the reaction. When 5-methoxy-2-aminobenzonitrile and thioformanilide were allowed to react in HOAc–HBr, the isolated products included not only 6-methoxyquinazoline-4(3H)-thione but also a small quantity of 2-methyl-6-methoxyquinazoline-4(3H)-thione. One possible route to this latter product commences with a hydrogen sulfide exchange reaction between aminonitrile and thioamide to form aminothioamide which then is acetylated by the solvent.[9] Cyclization of the acetylaminothioamide leads to the observed product.

Several sulfur-free fused-ring side products were also isolated. 6-Nitroquinazolin-4(3H)-one[10] (57%) was recovered from a mixture of 5-nitro-2-aminobenzonitrile and thioformanilide in EtOH–DMF–HBr. The C-2 portion of this quinazolinone comes from the DMF solvent probably by means of a formylation reaction.

2-Methyl-6-nitroquinazolin-4(3H)-one[11] (**15**) was obtained (48% yield) from a mixture of thioacetamide and 5-nitro-2-aminobenzonitrile in HOAc–HBr. No quinazolinethione was recovered. This quinazolinone could arise by several pathways. Acetylation of the aminonitrile to give an acetylaminonitrile followed by cyclization to observed product is one possible route, Scheme III. The cyclization of 2-acetylaminobenzonitrile to 2-methylquinazolin-4(3H)-one in glacial acetic acid has long been known.[12] From a separate experiment conducted in the absence of thioamide, quinzolinone **15** was recovered in 43% yield. To demonstrate further that quinazolin-4(3H)-one can arise from aminonitrile in the absence of thioamide, 2-methyl-7-methoxyquinazolin-4(3H)-one[13] was prepared from a mixture of 4-methoxy-2-aminobenzonitrile and HOAc–HBr.

SCHEME III



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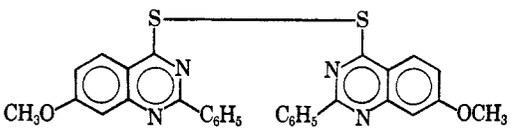
Ultraviolet absorption spectra were used to provide a quick preliminary indication of whether the acidic product obtained under conditions leading to cyclization of aminonitrile was a quinazoline-4(3H)-thione or a quinazolin-4(3H)-one. The spectra of alkaline solutions of the former class of compounds generally exhibit an absorption maximum >320 mμ; solutions of the latter materials are transparent in this region.

Disulfide Formation.—Solutions of the quinazolinethiones in 95% ethanol showed time-dependent ultraviolet absorption spectra. Spectral changes ceased after the solutions stood at room temperature for about 3 days. In several instances a solid was isolated from the alcohol solution; this material has a melting point different from quinazolinethione starting material. That quinazolinethione was being oxidized to a diquinazolinyl disulfide was proven in the case of 2-phenyl-7-methoxyquinazoline-4(3H)-thione by an independent synthesis of the disulfide **16**. An alkaline



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solution of the thione when oxidized by iodine gave a solid which was identical with the material obtained from the ethanolic solution. Curiously, few such spontaneous disulfide formation reactions have been reported in the pyrimidinethione[14] or fused pyrimidinethione series; examples seem to be confined to those compounds in which sulfur exists in the thiol form.

This and earlier[9] work clearly indicates that a wide variety of *o*-aminonitriles and thioamides enter into the cyclization reaction to yield fused pyrimidinethiones bearing an array of substituents at position 2. The characteristic of this synthesis is its preparative simplicity.

Experimental Section

All melting points are uncorrected and were obtained with a Thomas–Hoover apparatus. Ultraviolet spectra were recorded with a Cary 14 spectrophotometer. Analyses were by International Chemical and Nuclear Corp., City of Industry, Calif. Analyses for quinazoline-4-(3H)-thiones are given in Table II; melting points of the analytical samples are in Table I.

Chemicals.—Reagents prepared by methods in the literature include 5-methoxy-2-aminobenzonitrile,[15,16] 5-nitro-2-aminobenzonitrile,[17] 5-methyl-2-aminobenzonitrile,[17] 4-methoxy-2-aminobenzonitrile,[18] 5-nitroisatoxime,[19] 5-methylisatoxime,[20] thiobenzamide,[21] and thioformanilide.[22] Commercially available materials employed include thioacetamide, thioacetanilide, thiobenzanilide, 15% HBr in glacial acetic acid, *p*-anisidine, 4-methoxy-2-nitroaniline, 2-aminobenzonitrile, 5-nitroisatin, and 5-methylisatin.

(6) (a) D. D. Perrin and I. H. Pitman, *Australian J. Chem.*, **18**, 471 (1965); (b) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 5542 (1965), and references cited therein.

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TABLE II

MICROANALYSES AND ULTRAVIOLET ABSORPTION SPECTRA OF SOME QUINAZOLINE-4(3H)-THIONES

Compd	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\lambda_{max}^{0.1\ N\ NaOH}$, mμ[a]	ε × 10⁻⁴
2	70.58	4.23	11.76	70.71	4.22	11.89	250, (278), 366[b]	1.35, (0.51), 0.575
3	46.38	2.43	20.29	46.56	2.19	20.53	231.5, 248.5, 278.5, 350.5	1.81, 1.61, 1.14, 0.78
4	48.87	3.19	19.00	48.87	3.31	18.87	231, (248.5), 283, 350	1.93 (1.57), 1.31, 0.81
5	59.36	3.20	14.84	59.45	3.38	14.80	231, (259), 305, (351.5), 402	2.24, (1.60), 2.16, (0.88), 0.71
6	56.25	4.20	14.58	56.43	4.24	14.86	229, 271, 343.5	3.06, 1.12, 1.50
7	58.25	4.89	13.58	58.37	5.19	13.79	233.5, 267.5, 341.5	3.02, 0.92, 1.41
8	67.15	4.51	10.44	67.39	4.38	...	257.5, 278, 349.5	3.39, 2.58, 1.33
9	56.25	4.20	14.58	56.28	4.30	14.58	224, 239, 299, 356.5	3.14, 1.70, 0.49, 1.18
10	58.25	4.89	13.58	58.08	4.68	...	223.5, 242, 295.5, 360.5	3.55, 1.84, 0.54, 1.13
11	67.15	4.51	10.44	67.07	4.62	10.60	256.5, 292.5, 361.5	2.10, 1.11, 0.74
12	61.36	4.58	15.90	61.27	4.73	16.09	234, 298.5, 351.5	1.78, 0.44, 1.27
13	63.15	5.30	14.73	63.33	5.48	14.83	235.5, 299, 350.5	2.12, 0.54, 0.76
14	71.40	4.79	11.10	71.38	4.96	11.30	256, (284.5), 356	3.28, 1.50, 1.21

[a] Shoulders are indicated in parentheses. [b] In ethanol.

Reaction of 2-Aminobenzonitriles with Thioamides. General Procedure. A. 2-Methyl-6-methoxyquinazoline-4(3H)-thione (10).—A mixture of 1.0 g (6.8 mmoles) of 5-methoxy-2-aminobenzonitrile,[15] 2.0 g (27 mmoles) of thioacetamide, and 20 ml of glacial acetic acid saturated with hydrogen bromide[23] was heated with stirring over a steam bath for 3 hr. A light-colored precipitate formed and dissolved and then a second precipitate began to appear after 15 min. The reaction mixture was cooled, filtered, and the residue was washed successively with 1 ml of glacial acetic acid and with 10 ml of anhydrous ether. The crude product was recrystallized from a small amount of dimethylformamide–water. A first crop of 0.53 g (42% yield) of pure 2-methyl-6-methoxyquinazoline-4(3H)-thione, mp 284–286° dec, was obtained as yellow needles. A second crop consisting of 0.1 g of impure products was obtained following the addition of water to the mother liquor.

Reaction of 2-Aminobenzonitriles with Thioamides. General Procedure. B. 6-Methoxyquinazoline-4(3H)-thione (9).—A solution of 0.30 g (2.0 mmoles) of 5-methoxy-2-aminobenzonitrile[15] and 0.30 g (2.2 mmoles) of thioformanilide[22] in a minimum amount of glacial acetic acid was saturated with hydrogen bromide without cooling. The solution was then heated over a steam bath for 1 hr. A precipitate began to form after the first 5 min of heating. The volume of solvent was reduced by evaporation under reduced pressure and the residue was dissolved in dilute aqueous sodium hydroxide. The basic solution was chilled, filtered, and then acidified with glacial acetic acid to effect precipitation. After the yellow precipitate was recrystallized from aqueous dimethylformamide, 0.16 g (41% yield) of yellow needles of 6-methoxyquinazoline-4(3H)-thione, mp 312–314° dec, was obtained. The second crop from the concentrated mother liquor was mostly 2-methyl-6-methoxyquinazoline-4(3H)-thione which was sublimed to pure material, mp 284–287° dec.

Reaction of 2-Aminobenzonitriles with Thioamides. General Procedure C. 2-Phenyl-7-methoxyquinazoline-4(3H)-thione (8).—A stirred solution of 0.5 g (3.4 mmoles) of 4-methoxy-2-aminobenzonitrile[18] and 0.65 g (4.7 mmoles) of thiobenzamide[21] in 8 ml of dimethylformamide was saturated with hydrogen bromide without external cooling. The mixture was then heated over a steam bath for 4 hr. The solvent was partially removed under reduced pressure after the addition of 10 ml of ethanol and 10 ml of water. A slurry of the residue was made pH 2–5 by the careful addition of dilute aqueous potassium hydroxide and then was filtered. The solid residue was recrystallized from absolute ethanol; 0.19 g (32% yield) of golden crystals of 2-phenyl-7-methoxyquinazoline-4(3H)-thione, mp 195–197°, was obtained.

Reaction of 2-Aminobenzonitriles with Thioamides. General Procedure. D. 2-Phenyl-6-methylquinazoline-4(3H)-thione (14).—A solution of 0.50 g (3.8 mmoles) of 5-methyl-2-aminobenzonitrile[17] and 1.0 g (7.3 mmoles) of thiobenzamide[21] in 10 ml of absolute ethanol was saturated with hydrogen bromide and then gently refluxed for 4.5 hr. The reaction mixture was chilled in ice and the resulting precipitate was collected. The solid was dissolved in dilute aqueous potassium hydroxide and then reprecipitated by the addition of glacial acetic acid. The product was filtered from the acidic solution and one recrystallization from 50% ethanolic dimethylformamide gave 0.20 g (21% yield) of yellow needles of 2-phenyl-6-methylquinazoline-4(3H)-thione, mp 239–240°.

6-Nitroquinazolin-4(3H)-one.—A mixture of 0.50 g (3.1 mmoles) of 5-nitro-2-aminobenzonitrile[17] and 0.6 g (4.4 mmoles) of thioformanilide[22] in 10 ml of 50% ethanol–dimethylformamide was saturated with hydrogen bromide without external cooling. After the mixture was heated in an oil bath at 74° for 13 hr, the resulting precipitate was removed, dissolved in dilute aqueous alkali, and reprecipitated by the addition of acetic acid. The yellow solid was recrystallized from ethanol–dimethylformamide and 0.33 g (57% yield) of 6-nitroquinazolin-4(3H)-one, mp 282–283° (lit.[24] mp 286–287°), was obtained.

2-Methyl-6-nitroquinazolin-4(3H)-one (15).—A solution of 0.50 g (3.1 mmoles) of 5-nitro-2-aminobenzonitrile[17] in 15 ml of glacial acetic acid saturated with hydrogen bromide was heated on a steam bath for 4.5 hr. The cooled mixture was filtered and the solid was taken up in hot, dilute aqueous alkali. Following acidification with glacial acetic acid, 0.25 g (43% yield) of 2-methyl-6-nitroquinazolin-4(3H)-one, mp 298.5–299 dec (lit.[10,11] mp 299°), was recovered. From the filtrate of the reaction mixture, 0.15 g (36% yield) of 5-nitroanthranilic acid, mp 272–273° with sublimation (lit.[23] mp 278° dec), was obtained following evaporation of the solvent, dissolution of the residue in aqueous alkali, and reprecipitation with acetic acid.

2-Methyl-7-methoxyquinazolin-4(3H)-one.—A solution of 0.30 g (2.0 mmoles) of 4-methoxy-2-aminobenzonitrile[18] in 10 ml of glacial acetic acid was saturated with hydrogen bromide and then heated at 100° for 6.5 hr. The cold mixture was filtered and the collected solid was recrystallized from ethanol–water. There was obtained 0.09 g (23% yield) of 2-methyl-7-methoxyquinazolin-4(3H)-one, mp 270–272° (lit.[13] mp 272°), as white needles.

Di-(7-methoxy-2-phenylquinazolinyl) Disulfide (16).—To a stirred solution of 0.50 g (1.9 mmoles) of 7-methoxy-2-phenylquinazoline-4(3H)-thione in 5 ml of dilute NaOH was added a solution of 0.3 g (1.2 mmoles) of iodine in ethanol. A white solid began to form and after 1 hr at room temperature the ma-

(23) When commercially available 15% HBr in glacial acetic acid was employed, the precipitation of the hydrobromide was less complete. Addition of ether to the reaction mixture or concentration of the mixture under reduced pressure was employed prior to the work-up.

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terial was collected, washed with ethanol, and recrystallized from pyridine–water to give product: mp 229–232°; $\lambda_{max}^{dioxane}$ 265, 325, 339 mμ (ε × 10^{-4} 9.23, 1.62, 1.68).

Anal. Calcd for $C_{30}H_{22}N_4O_2S_2$: C, 67.41; H, 4.15; N, 10.48. Found: C, 67.42; H, 3.99; N, 10.20.

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Registry No.—**2**, 6483-99-4; **3**, 13116-83-1; **4**, 13116-84-2; **5**, 13116-85-3; **6**, 13116-86-4; **7**, 13116-87-5; **8**, 13135-41-6; **9**, 13116-88-6; **10**, 13116-89-7; **11**, 13116-90-0; **12**, 13116-91-1; **13**, 13116-92-2; **14**, 13116-93-3; **16**, 13116-94-4.

Acylation and Other Reactions of 2- and 4-Pyridylacetonitriles[1]

C. DAVID GUTSCHE AND HEINZ-WERNER VOGES[2]

Department of Chemistry, Washington University, St. Louis, Missouri 63130

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A study of the acylation reactions of 2- and 4-pyridylacetonitriles has shown that (a) the product from cold or hot acetic anhydride and 2-pyridylacetonitrile is the C-acetyl derivative **3**, (b) the product from cold acetic anhydride and 4-pyridylacetonitrile is the N-acetyl derivative **9**, (c) the product from hot acetic anhydride and 4-pyridylacetonitrile is the C,N-diacetyl derivative **10**, and (d) the C,N-diacetyl derivative **10** is convertible to the C-acetyl derivative **11** by alcoholysis. Alkylation of the C-acetyl compounds yields the O-alkyl derivative from **3** and the N-methyl derivative from **11**. In addition to the acylation reactions, the dimerization reaction and Knoevenagel reaction were carried out with 2-pyridylacetonitrile and the structures of the products were established.

As part of a program directed to a study of the intramolecular catalysis of α-carbanion formation some of the reactions of 2-pyridylacetonitrile and 4-pyridylacetonitrile have been investigated. Although these reactions failed to yield the desired catalysts they are, nevertheless, of some general interest.

2-Pyridylacetonitrile (**1**), which has been described previously,[3-9] was prepared by the action of cyanide on 2-chloromethylpyridine.[4,5,7-9] Although its structure appeared to be secure, a further confirmation was prompted by the recent observation[10] that 2-chloromethyl-3-benzylimidazole undergoes an SN2′ reaction with cyanide to yield 2-methyl-3-benzyl-4-cyanoimidazole. Evidence that the assigned structure is correct has been provided by an nmr spectrum which is in complete accord with 2-pyridylacetonitrile and by hydrolysis to 2-pyridylacetamide, a compound whose structure has been well established.[4,6,11] 4-Pyridylacetonitrile (**8**), also previously described,[4,7,9,12] was prepared by dehydration of 4-pyridylacetamide[13] or by the action of cyanide on 4-chloromethylpyridine.[7,9,12]

Reactions of 2-Pyridylacetonitrile.—When 2-pyridylacetonitrile (**1**) is heated with ethanolic sodium ethoxide it is converted to a solid material which possesses an elemental analysis identical with that of the starting material, a molecular weight twice that of the starting material, and spectral characteristics that are best accommodated by a dimer of structure **2** (presumably **2B** is the tautomer present in larger amount). The infrared spectrum of this compound contains bands characteristic for a nonhydrogen-bonded N–H as well as a hydrogen-bonded N–H,[14a] a band characteristic for a conjugated nitrile,[14b] and a band associated with an olefinic moiety;[14c] the nmr spectrum shows a two-proton singlet for the PyCH_2C group,[15a] a six-proton multiplet for the pyridine H_3, H_4, and H_5, a two-proton multiplet for the pyridine H_6,[15b] and resonances at 3.33 and 3.5–3.8 ppm corresponding to almost two protons and possibly arising from N–H;[15c] the ultraviolet spectrum has the longest wavelength band at 320–324 mμ commensurate with a β-(2-pyridyl)vinylamine structure.[16]

Treatment of 2-pyridylacetonitrile with acetic anhydride–acetic acid yields a $C_9H_8N_2O$ compound as a pale yellow solid which is soluble in dilute acid and base.

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(15) (a) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery ("NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962–1963) report that PyCN_2CONH_2 (Spectrum No. 159) has a resonance at 3.72 ppm. (b) Bhacca, *et al.*,[15a] report that the spectra of pyridine (No. 96), 2-vinylpyridine (No. 154), and 2-pyridylacetamide (No. 159) show that the pyridine H_3 resonance occurs at 7.0–7.3 ppm, the pyridine H_4 resonance at 7.55–7.65 ppm, the pyridine H_5 resonance at 7.0–7.2 ppm, and the pyridine H_6 resonance at 8.5–8.6 ppm. (c) N–H resonances show a wide variation with respect to position and sharpness; a compound with certain structural similarities to **2B** is $NH_2C(CH_3)H{=}CHCO_2CH_3$ (ref 15a, No. 442), which possesses an extremely broad and barely discernible N–H resonance at *ca.* 6 ppm. (d) Bhacca, *et al.*,[15a] report that $CH_3COCH_2CONHC_6H_5$ (No. 256) has a resonance at 2.17 ppm, and $CH_3C(=C)OCOCH_3$ (No. 175) has a resonance at 1.98 ppm. (e) Bhacca, *et al.*,[15a] report that CH_3COCl (index) has a resonance at 2.67 ppm. (f) The chelated H in acetylacetone has a resonance near 15.5 ppm (L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 70).

(16) 1,2-Dihydronaphthalene absorbs at 259 mμ (ε 9449) and 3-methoxy-1,2-dihydronaphthalene absorbs at 272 mμ (ε 26,300) (W. Hückel, E. Vevera, and U. Wörffel, *Chem. Ber.*, **90**, 901 (1957)). A qualitatively similar and possibly quantitatively greater difference might be anticipated between 2-vinylpyridine which absorbs at 282 mμ (ε 7150) and a β-aminovinylpyridine (*e.g.* **2B**, that absorbs at 324 mμ (ε 18,100)).