fluorescence. However, the fluorescence was restored by chromatographing the material on alumina and then recrystallizing from toluene. The infrared spectra of both the fluorescent and non-fluorescent materials were nearly identical to that of 3,3'-diindolyl. No 3,3'-diindolyl-2,2'-tetrasulfide was obtained from the chromatography.

[Contribution from the Noyes Chemical Laboratory, University of Illinois, Urbana, Ill.]

Thiocyanation of Indole. Some Reactions of 3-Thiocyanoindole

By M. S. Grant[1] and H. R. Snyder

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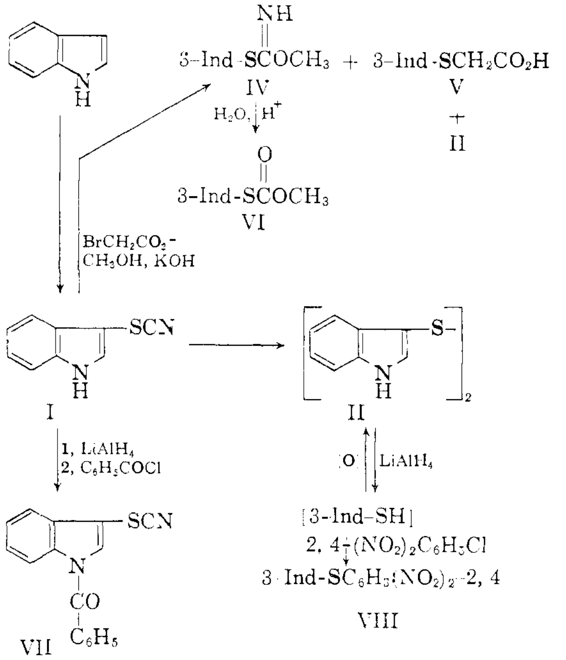
Thiocyanation of indole produces 3-thiocyanoindole in good yield. Under the influence of bases and under a variety of conditions the thiocyano compound is converted to 3,3'-indolyl disulfide, and attempts to isolate 3-mercaptoindole as an intermediate, either as such or as the S-carboxymethyl derivative, have met with little success. Neither could the mercaptan be isolated after lithium aluminum hydride reduction of the thiocyanate, but its 2,4-dinitrophenyl derivative was obtained by a similar reduction of the disulfide and treatment of the reduction mixture with 2,4-dinitrochlorobenzene. The nucleus of 3-thiocyanoindole is strongly deactivated, but the indolic nitrogen atom is attacked by some reagents.

3-Thiocyanoindole has been of interest to us as a possible source, through the procedure developed by Matteson[2] for thieno[3,2-*b*]pyrrole, of the known 4H-thieno[3,2-*b*]indole.[3] Matteson[4] found indole to be thiocyanated by the action of cupric thiocyanate to give a monothiocyanate of undetermined structure in 59% yield, along with a small amount of a high melting impurity that was not removed by sublimation. It is now shown that the major product is 3-thiocyanoindole (I), and the high-melting by-product probably was 3,3'-indolyl disulfide (II). The conversion of the former to the latter proceeds with remarkable facility; even attempts to chromatograph I on basic alumina caused the transformation to occur. The disulfide II recently has been prepared directly from indole and sulfur.[5]

In the present work thiocyanogen was generated from potassium thiocyanate and bromine in methanol at −60°, and this solution was treated with indole in methanol at −70° for one hour before being allowed to warm to room temperature. This procedure led to 3-thiocyanoindole in 89% yield. That substitution occurred in the pyrrole nucleus was shown by the infrared spectra of several of the derivatives of I, which revealed the characteristic absorption of an *o*-disubstituted benzene ring. That attack occurred in the 3-position was shown by the thiocyanation of indole-2-carboxylic acid and conversion of the product III to the same disulfide II as was obtained from I.

Attempts to alkylate the sulfur atom of I by treatment with bromoacetate and base gave mainly the disulfide II, together with some S-3-indolyl-O-methyl thioimidocarbonate (IV) and very small amounts of the originally expected S-3-indolylthioacetic acid (V), isolated as the ammonium salt. Very mild hydrolysis of the thioimidocarbonate (IV) converted it to the thiocarbonate (VI).

Since aromatic thiocyanates can be converted to thiophenols by reduction with lithium aluminum hydride,[6] the action of this reagent on I was studied.



After the reduction, benzoyl chloride was added, but the only product isolated was N-benzoyl-3-thiocyanoindole (VII, 35%). Evidently reduction was incomplete, and I is more readily benzoylated than its reduction products. When the reduction mixture was treated with bromoacetate the main product was the disulfide, with a trace of the expected thioacetic acid derivative V, isolated as the ammonium salt. Similar reductions were run on the disulfide II, but only the disulfide was obtained from efforts to isolate the mercaptan. Probably the mercaptan was formed, but was reoxidized during the isolation, for addition of 2,4-dinitrochlorobenzene to a similar reaction mixture led to the expected thioether (VIII, 37%).

Oddo and Mingoia[7] describe a compound obtained from the successive treatment of indolemagnesium bromide with sulfur and benzoyl chloride as the benzoyl derivative of 3-mercaptoindole, and they hydrolyzed the ester to a substance, regarded as 3-mercaptoindole or the tautomeric thio-

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(1) Postdoctoral Research Associate.

(2) D. S. Matteson and H. R. Snyder, *J. Org. Chem.*, **22**, 1500 (1957).

(3) P. A. S. Smith and J. H. Boyer, This Journal, **73**, 2626 (1951).

(4) D. S. Matteson, Thesis, Doctor of Philosophy, University of Illinois, 1957.

(5) W. Carpenter, M. S. Grant and H. R. Snyder, This Journal, **82**, 2739 (1960).

(6) J. Strating and H. J. Backer, *Rec. trav. chim.*, **69**, 638 (1950).

(7) B. Oddo and Q. Mingoia, *Gazz. chim. ital.*, **62**, 299 (1932).

carbonyl compound, which melted at about the same temperature as our disulfide.

3-Thiocyanoindole was not acetylated by ketene nor by isopropenyl acetate. The N-acetyl derivative was obtained by the action of refluxing acetic anhydride. The acetyl derivative IX was both desulfurized and hydrogenated by Raney nickel catalyst, the product being N-acetylindoline. Ethylmagnesium bromide and phenylmagnesium bromide converted 3-thiocyanoindole to the disulfide, and with the latter reagent the co-product, benzonitrile, was isolated in 50% yield. Adams, Bramlet and Tendrick[8] have shown that aromatic Grignard reagents cleave thiocyanates to give the aryl nitrile and a halomagnesium mercaptide as the principal products, but in the present instance the extreme ease of the formation of the disulfide appears to preclude isolation of the mercaptan.

Experimental[9]

3-Thiocyanoindole (I).—A suspension of potassium thiocyanate (100 g.) in absolute methanol (125 ml.) was vigorously stirred and cooled in a Dry Ice–acetone-bath, and a solution of bromine (80 g.) in absolute methanol (375 ml.), which had been similarly cooled, was slowly added at such a rate that the temperature did not exceed −60°. A solution of indole (58.6 g.) in absolute methanol (375 ml.) at −70° was rapidly added in one portion to the yellow thiocyanogen solution. The stirring was continued for 1 hr. and the mixture allowed to warm to room temperature. The mixture was then poured onto crushed ice (1 kg.) and after one hour the 3-thiocyanoindole was collected (78.6 g., 89.5%); m.p. 75–76°. An analytical sample was prepared by recrystallization from methylene chloride–cyclohexane; m.p. 76.5–78.0°. The infrared spectrum of a methylene chloride solution shows a sharp peak at 2160 cm.$^{-1}$, which is attributed to the thiocyanate function.

Anal. Calcd. for $C_9H_6N_2S$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.16; H, 3.60; N, 15.71%.

3,3′-Indolyl Disulfide (II).—An attempt to purify 3-thiocyanoindole by chromatography on alumina (Merck, not acid-washed) by using methylene chloride–cyclohexane eluant gave a white crystalline solid, m.p. 217–218°, identical with that obtained from the decarboxylation and hydrolysis of 3-thiocyano-2-carboxyindole (III).

Anal. Calcd. for $C_{16}H_{12}N_2S_2$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.59; H, 3.73; N, 9.36.

This disulfide was conveniently prepared by refluxing I in sodium hydroxide solution (10%) until the 3,3′-indolyl disulfide separated from the solution. It was crystallized from aqueous ethanol.

3-Thiocyano-2-carboxyindole (III).—Indole-2-carboxylic acid (8 g.), prepared as described by White,[10] in absolute methanol (40 ml.) was thiocyanated in the same way described for indole, with a thiocyanogen solution prepared from 8 g. of bromine in 40 ml. of absolute methanol and 9.7 g. of potassium thiocyanate in 15 ml. of absolute methanol. The crude product (10 g., 92%) was recrystallized twice from aqueous ethanol to give yellow needles, m.p. 195° dec. The infrared spectrum of a Nujol mull is consistent with structure III.

Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.0; H, 2.75; N, 12.85. Found: C, 55.2; H, 2.58; N, 12.64.

Attempts to decarboxylate III using copper chromite and quinoline or dimethylaniline were unsuccessful. However, when III (180 mg.) was refluxed in 10% sodium hydroxide solution for 19 hours, 100 mg. (85%) of a substance of m.p. 203–205° was obtained. This was recrystallized twice from aqueous ethanol to give II, m.p. 216.5–218°, mixed m.p. with II 215–217°. The infrared spectrum of this substance is identical with that of samples prepared as described above.

Anal. Calcd. for $C_{16}H_{12}N_2S_2$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.84; H, 3.82; N, 9.71.

Attempted Lithium Aluminum Hydride Reduction of II.—The disulfide II (10 g.) was dissolved in dry tetrahydrofuran (50 ml.) and slowly dropped into a suspension of lithium aluminum hydride (0.7 g.) in 50 ml. of the same solvent. There was a vigorous reaction. The mixture was stirred for 0.5 hr., cooled in ice, and cold 5 *N* sulfuric acid was added. The tetrahydrofuran layer was separated after salting out with solid sodium chloride, dried over sodium sulfate and evaporated to dryness. The red oil obtained, crystallized on trituration with ethanol (9 g.); m.p. 215–216°, mixed m.p. with II 215–216°. The infrared spectrum of this sample was identical with that of samples of II prepared by the methods described above.

3-(2,4-Dinitrophenylthio)-indole (VIII).—A suspension of lithium aluminum hydride (0.36 g.) in 25 ml. of dry tetrahydrofuran was stirred under an atmosphere of nitrogen and a solution of II (5 g.) in 30 ml. of tetrahydrofuran was slowly added. The reaction mixture became warm, and after stirring for a further 0.5 hr., 10 ml. of 5 *N* sodium hydroxide solution was added. A solution of 2,4-dinitrochlorobenzene (3.4 g.) in 30 ml. of tetrahydrofuran was added and the mixture refluxed on a steam-bath for 10 min. A yellow solid, infusible and insoluble in organic solvents, separated. This was removed and the filtrate evaporated to a red gum. Addition of ethanol precipitated a yellow solid which was recrystallized from ethanol as yellow needles (2 g., 37%, m.p. 175–175.5°). The elementary analysis and infrared spectrum are consistent with the structure 3-(2,4-dinitrophenylthio)-indole.

Anal. Calcd. for $C_{14}H_9N_3O_4S$: C, 53.34; H, 2.88; N, 13.33. Found: C, 53.42; H, 2.97; N, 13.15.

Evaporation of the mother liquors gave a solid, m.p. (and m.m.p. with II) 215–216°. The infrared spectrum of this substance was identical with that of II.

Attempted Preparation of 3-Benzoylthioindole.—A suspension of lithium aluminum hydride (0.61 g.) in 50 ml. of dry tetrahydrofuran was stirred under an atmosphere of nitrogen, and a solution of 3-thiocyanoindole (I) (10 g.) in 50 ml. of tetrahydrofuran was slowly added. The color of the reaction mixture changed from green to dark red during the addition. The mixture was stirred for 0.5 hr. and then 6 ml. of 10% sodium hydroxide solution was added, followed by 6.6 ml. of freshly distilled benzoyl chloride in 20 ml. of tetrahydrofuran. The filtered solution was evaporated, leaving a red gum. This crystallized on the addition of ethanol to give a white solid (5 g., m.p. 125–128°). Recrystallization from ethanol–benzene gave the pure product (35%), m.p. 131–131.5°, apparently N-benzoyl-3-thiocyanoindole (35%) (VII). The infrared spectrum is consistent with the proposed structure VII.

Anal. Calcd. for $C_{16}H_{10}N_2OS$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.75; H, 3.43; N, 9.89.

Part of VII (0.6 g.) was desulfurized by refluxing with W-2 Raney nickel (6 g.) in 50 ml. of absolute ethanol for 4 hours. The residue left after filtration and concentration of the ethanol solution was sublimed at 200° (0.1 mm.) to give a viscous oil. This crystallized on trituration with ethanol to give a white solid, m.p. 65–66°, corresponding to N-benzoylindole.[11]

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.50; H, 4.98; N, 6.33. Found: C, 81.38; H, 5.00; N, 6.29.

Attempted Preparation of 3-Indolylthioacetic Acid.—A mixture of 3-thiocyanoindole (I) (17.4 g.) and bromoacetic acid (16.7 g.) in 100 ml. of absolute methanol was vigorously stirred under a nitrogen atmosphere, and cooled below −50° in a Dry Ice–acetone-bath. A solution of potassium hydroxide (23.8 g., 85% purity) in 100 ml. of 50% methanol was added over a period of 10 minutes. The cooling bath was then removed and the stirring continued for a further 2 hr. Dry Ice was added to the mixture to adjust the *p*H to about 8, and it was then evaporated dry under vacuum on a water-bath.

Methylene chloride (80 ml.) was added and then excess ice-cold 5 *N* hydrochloric acid. A thick red oil separated,

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[8] R. Adams, H. B. Bramlet and F. H. Tendrick, THIS JOURNAL, **42**, 2372 (1920).

[9] All melting points are uncorrected. Microanalyses were performed by Mr. J. Nemeth and Miss Claire Higham. The infrared spectra were measured by Mr. Paul McMahon and his associates.

[10] E. G. White, Thesis, Doctor of Philosophy, University of Illinois, 1958.

[11] R. Weissgerber, *Ber.*, **43**, 3523 (1910), quotes the m.p. of N-benzoylindole as 67–68°.

which on treatment with sodium bicarbonate solution solidified. This was extracted with benzene–ethanol to give white needles of a substance of composition corresponding to S-3-indolyl O-methyl thioimidocarbonate (IV) (5 g., 24%, m.p. 187–188°).

Anal. Calcd. for $C_{10}H_9N_2OS$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.14; H, 4.99; N, 13.60.

Concentration of the mother liquors, followed by recrystallization from aqueous ethanol, gave a solid, m.p. 208°, not depressed on admixture with II (9.6 g., 62% yield of disulfide), whose infrared spectrum is identical with that of II.

The red methylene chloride solution was dried over magnesium sulfate, treated with charcoal, and dry ammonia gas was bubbled through it. A pink solid precipitated (1 g., 9%, m.p. 155–165°) corresponding in composition to the ammonium salt of 3-indolylacetic acid.

Anal. Cacld. for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.39; N, 12.50. Found: C, 54.18; H, 5.36; N, 11.16.

Treatment of thioimidocarbonate IV (1 g.) with a mixture of 20% acetic acid (50 ml.) and concentrated hydrochloric acid (10 ml.) at 0° for two days yielded the corresponding S-3-indolylmethylthiocarbonate (VI), m.p. 119–121° (40%). An analytical sample was recrystallized from benzene–petroleum ether; m.p. 123–124.5°.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 58.00; H, 4.35; N. 6.76. Found: C, 58.22; H, 4.26; N, 6.78.

N-Acetyl-3-thiocyanoindole (IX).—3-Thiocyanoindole (2 g.) was refluxed in 25 ml. of acetic anhydride for 3 hr. On cooling, a crystalline solid separated (2 g., 83%, m.p. 118–120°). Recrystallization from ethanol gave a sample, m.p. 122.5–123.5°, analysis of which corresponds to N-acetyl-3-thiocyanoindole. This structure is assigned on the basis of the elemental analysis, infrared spectrum, which shows no N–H stretching frequency between 3600–3100 cm.$^{-1}$ and the desulfurization product obtained below.

Anal. Calcd. for $C_{11}H_8N_2OS$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.11; H, 3.70; N, 12.81.

A portion of IX (1.8 g.) was refluxed with W-2 Raney nickel in 50 ml. absolute ethanol for 24 hr. The residue left after filtration and concentration of the solvent was recrystallized twice from ethanol to give a solid, m.p. 105°, corresponding in properties to N-acetylindoline.[12]

Anal. Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.22; H, 6.94; N, 8.56.

Reaction of 3-Thiocyanoindole with Excess Ethylmagnesium Iodide.—A solution of I (5.2 g., 0.03 mole) in 10 ml. of anhydrous ether was slowly added to the Grignard reagent prepared from 2.4 g. of magnesium and 16.2 g. of ethyl iodide (0.09 mole) in 20 ml. of anhydrous ether, the reaction being carried out under an atmosphere of nitrogen. The ether refluxed during the addition of I, and a red solid separated. Stirring was continued for 0.5 hr. and any excess Grignard reagent was decomposed with ice-cold ammonium chloride solution, an odor of hydrogen sulfide being noticed at this stage. The ether layer was separated and the aqueous phase extracted twice with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the ether gave a solid (3.3 g., 75%), m.p. 202–204° not depressed on admixture with II. The infrared spectrum was identical with that of II.

Reaction of 3-Thiocyanoindole with Excess Phenylmagnesium Bromide.—A solution of I (5.2 g., 0.03 mole) in 10 ml. of anhydrous ether was treated with the Grignard reagent prepared from 2.4 g. of magnesium and 13.5 g. of bromobenzene (0.09 mole) in 20 ml. of anhydrous ether, as described in the previous experiment. On evaporation of the ether, an oil with strong odor of bitter almonds was left. This was distilled at reduced pressure to give essentially pure benzonitrile[13] (1.4 g., 50%, b.p. 65° (13 mm.), $n^{30}D$ 1.5249). The infrared spectrum was identical with that of an authentic sample of benzonitrile.

The residue in the distillation flask solidified on cooling (m.p. 198–200°, 3 g.), and appeared from its infrared spectrum to be mainly II.

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[12] G. M. Bennett and M. M. Hafez, *J. Chem. Soc.*, 287 (1941).

[13] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, 1943, gives the b.p. as 69° (10 mm.) and $n^{20}D$ as 1.5289.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

Aromatic N-Oxides. II. The Mechanism of the Reaction of 4-Picoline N-Oxide with Acetic Anhydride[1,2]

BY VINCENT J. TRAYNELIS AND ROCCO F. MARTELLO[3]

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The reaction of 4-picoline N-oxide with acetic anhydride gives 4-pyridylmethyl acetate as the major product with some 3-acetoxy-4-methylpyridine. In addition to these esters a number of minor products are found which are best rationalized by the presence of free radicals; however, evidence is offered to exclude a radical chain mechanism. The origin of the esters is explained by an intramolecular rearrangement which proceeds through a common intermediate. Evidence is reported which favors a radical pair process for this intramolecular change.

In the previous report[1] we have confined our comments to the path of the reaction of 2-picoline N-oxide and acetic anhydride. The data collected ruled out a radical chain mechanism and favored an intramolecular rearrangement involving possibilities of a concerted process, radical pairs or ion pairs. With this communication we wish to record our observations with 4-picoline N-oxide and acetic anhydride.

Several papers have appeared defining the scope of the reaction of 4-alkylpyridine N-oxide[4-9] and 4-methylquinoline N-oxide[10] with acetic anhydride. The report by Berson and Cohen[6] described the isolation and identification of a by-product, 3-hydroxy-4-methylpyridine, in addition to the major product, 4-pyridylmethyl acetate. These authors reviewed several possible mechanisms for the origin of both substances which would be consistent with the data available. One path involves the intermediate anhydrobase II which can undergo nucleophilic attack by acetate anion at the exocyclic

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[1] For paper I in this series see, V. J. Traynelis and R. F. Martello, THIS JOURNAL, **80**, 6590 (1958).

[2] Presented at the 136th Meeting of the American Chemical Society at Atlantic City, N. J., in September, 1959.

[3] Peter C. Reilly Fellow 1957–1958. Abstracted from the Ph.D. dissertation of R. F. Martello, May, 1959.

[4] V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).

[5] O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

[6] J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).

[7] S. Furukawa, *Pharm. Bull. (Japan)*, **3**, 413 (1955); *C. A.*, **50**, 13926a (1956).

[8] T. Kato, *J. Pharm. Soc. Japan*, **75**, 1233 (1955); *C. A.*, **50**, 8664i (1956).

[9] F. Cislak, U. S. Patent 2,748,141, May 29, 1956; *C. A.*, **51**, 2878c (1957).

[10] G. Kobayashi, S. Furukawa, Y. Akimoto and T. Hoshi, *J. Pharm. Soc. Japan*, **74**, 791 (1954); *C. A.*, **49**, 11659b (1955).