[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEW MEXICO]

Cinnoline Chemistry. VII. 4-Cinnolinecarboxaldehyde[1,2]

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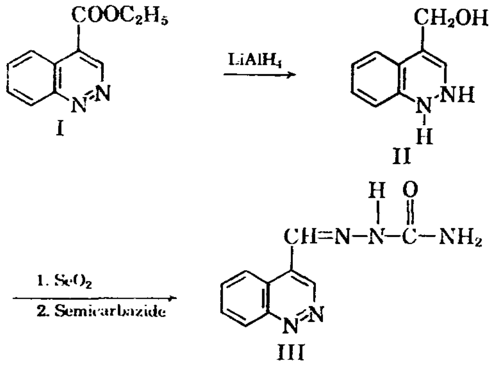
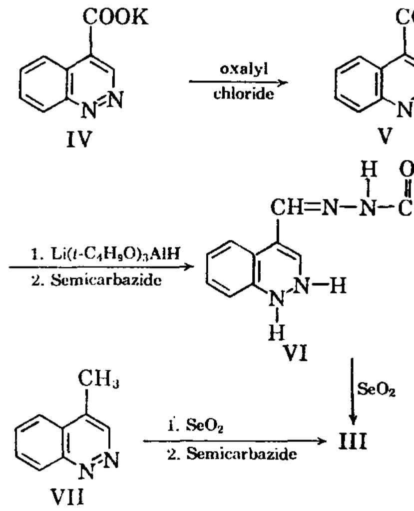
4-Cinnolinecarboxaldehyde has been prepared in good yield. It has also been prepared in the form of derivatives by two additional methods. The ease of reduction of the cinnoline ring with lithium aluminum hydride and lithium tri-*t*-butoxyaluminohydride has been studied.

The first approach to the synthesis of 4-cinnolinecarboxaldehyde was the reduction of ethyl 4-cinnolinecarboxylate (I) with lithium aluminum hydride in dry ether to obtain what was supposed to be 4-hydroxymethylcinnoline, but which was in reality 4-hydroxymethyl-1,2-dihydrocinnoline (II) in 57% yield. Perhaps the facile reduction of the ring to the unstable 1,2-dihydro compound II is not surprising in view of the work of Busch and Rast[4] who converted 4-chlorocinnoline into 1,2-dihydrocinnoline with iron and 15% sulfuric acid solution. Selenium dioxide oxidation of II in dioxane solution followed by treatment with semicarbazide hydrochloride produced 4-cinnolinecarboxaldehyde semicarbazone (III) in 58% yield.



Brown and McFarlin[5] discovered that acid chlorides could be converted into aldehydes in good yield by selective reduction with lithium tri-*t*-butoxyaluminohydride. 4-Cinnolinecarbonyl chloride (V) was prepared from the potassium salt of the acid (IV) by a method previously described.[1] The acid chloride (V) in bis-2-ethoxyethyl ether solution was allowed to react with lithium tri-*t*-butoxyaluminohydride. The reduction product was isolated as the semicarbazone in 32% yield. This compound proved to be 1,2-dihydro-4-cinnolinecarboxaldehyde semicarbazone (VI). Oxidation of VI with selenium dioxide in pyridine produced III.



The success in converting II to III prompted an additional attempt to oxidize 4-methylcinnoline (VII) directly to 4-cinnolinecarboxaldehyde with selenium dioxide with subsequent isolation as the semicarbazone (III). This was accomplished in 7% yield.[6]

The method used by Giner-Sorolla *et al.* for the synthesis of purine-6-carboxaldehyde[7] was adapted to the preparation of 4-cinnolinecarboxaldehyde. 4-Methylcinnoline (VII) was converted into 4-cinnolylmethylpyridinium iodide (VIII) in 70% yield by refluxing with iodine and pyridine. Heating a suspension of VIII with *p*-nitrosodimethylaniline in water, followed by treatment with sodium hydroxide, gave *N*,*N*-dimethyl-*N'*-(4-cinnolylmethylene)-*p*-phenylenediamine *N'*-oxide (IX) in 92% yield. Cleavage of IX with 2*N* hydrochloric acid and treatment of the acid solution with hydrazine

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(1) For paper VI in this series see R. N. Castle and M. Onda, *J. Org. Chem.*, **26**, 2374 (1961).

(2) The authors are grateful to Dr. K. Abe of the Tanabe Seiyaku Company, Ltd., Tokyo, Japan for the carbon, hydrogen, and nitrogen analyses.

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(4) M. Busch and A. Rast, *Ber.*, **30**, 521 (1897).

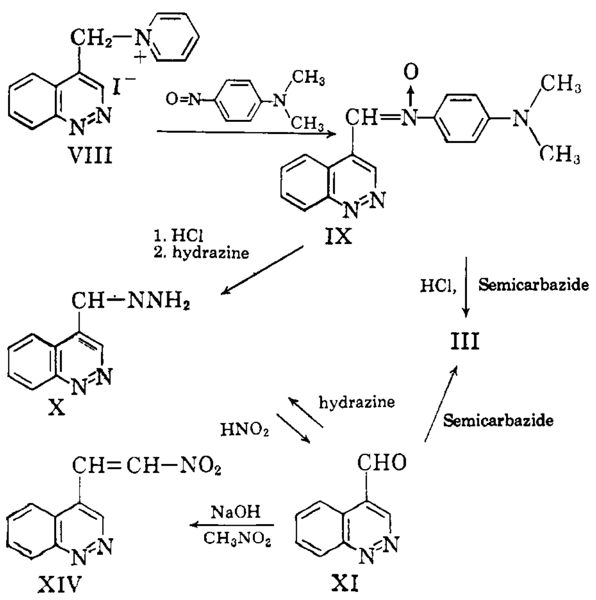
(5) H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **80**, 5372 (1958).

(6) Previous attempts to prepare 4-cinnolinecarboxaldehyde by direct oxidation of 4-methylcinnoline with selenium dioxide in several solvents (ethanol-dioxane mixtures and aqueous methanol) produced only intractable tars. 4-Methylcinnoline ethiodide when allowed to react with selenium dioxide in aqueous solution also produced tars. D. B. Cox, dissertation, University of New Mexico, May, 1953.

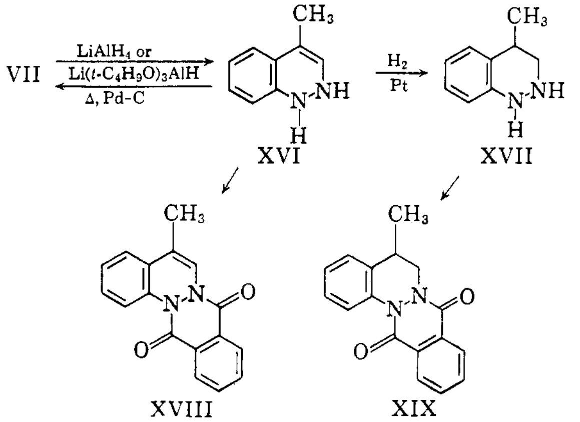
(7) A. Giner-Sorolla, I. Zimmerman, and A. Bendich, *J. Am. Chem. Soc.*, **81**, 2515 (1959).

produced 4-cinnolinecarboxaldehyde hydrazone (X) in 93% yield. When the acid solution of IX was treated with semicarbazide and potassium acetate, a quantitative yield of III was obtained. When 4-cinnolinecarboxaldehyde hydrazone (X) was treated with a hydrochloric acid solution of sodium nitrite, it was cleaved and 4-cinnolinecarboxaldehyde (XI) was obtained in 66% yield. For identification of the aldehyde it was converted into X and III by treatment with hydrazine and semicarbazide hydrochloride, respectively, and these two derivatives were compared by mixed melting points with X and III prepared as previously described. The 2,4-dinitrophenylhydrazone (XII) and the oxime (XIII) were prepared as additional derivatives of XI.

The action of nitromethane and alkali on XI gave 4-(2-nitroethenyl)cinnoline (XIV) in quantitative yield. Attempts to convert XIV into 4-(2-aminoethyl)cinnoline (XV) were not successful, presumably due to the formation of the unstable 1,2-dihydrocinnoline intermediate. Attempts to dehydrogenate these dark red syrups with palladium on charcoal were unsuccessful.



In order to be certain that lithium aluminum hydride and lithium tri-*t*-butoxyaluminohydride were producing 1,2-dihydrocinnolines, the reduction of 4-methylcinnoline (VII) was studied. When VII was allowed to react with either lithium aluminum hydride in dry ether or with lithium tri-*t*-butoxyaluminohydride in bis-2-ethoxyethyl ether 4-methyl-1,2-dihydrocinnoline (XVI) was obtained. This was established by conversion of XVI into 4-methyl-1,2,3,4-tetrahydrocinnoline (XVII) with hydrogen and platinum in acetic acid solution and by conversion of XVI into 5-methyl-8,13-dihydrophthalazino[2,3-*a*]cinnoline-8,13-dione (XVIII) by treatment of XVI with phthalic anhydride in pyridine solution. Further evidence that XVI is the 1,2-dihydro derivative comes from the conversion of XVII into 5-methyl-5,6,8,13-tetrahydrophthalazino[2,3-*a*]cinnoline-8,13-dione (XIX) by treatment of XVII with phthalic anhydride in pyridine solution. That XVIII and XIX are not identical can be observed by examining the experimental details. Thus, it is clear that lithium aluminum hydride and lithium tri-*t*-butoxyaluminohydride readily reduce the cinnoline ring to the corresponding 1,2-dihydrocinnolines. Furthermore, when XVI was heated with palladium on charcoal in benzene solution, VII was obtained. It can now be stated with certainty that II is 4-hydroxymethyl-1,2-dihydrocinnoline even though it was not possible to analyze or characterize this compound due to instability.



EXPERIMENTAL[8]

4-Cinnolinecarboxaldehyde semicarbazone (III). To a stirred and cooled solution of 0.42 g. of lithium aluminum hydride in 42 ml. of ether was added a solution containing 3.0 g. of ethyl 4-cinnolinecarboxylate in 10 ml. of ether. The mixture was stirred and heated for 2 hr. The excess lithium aluminum hydride was destroyed with moist ether and ethanol and the solution filtered. On working up the residue a light yellow syrup was obtained (1.4 g., 59% yield) boiling at 150–155° at 0.05 mm. This compound, which was shown to be 4-hydroxymethyl-1,2-dihydrocinnoline, is very unstable in air, darkening rapidly within a few minutes.

To 1.4 g. of the above syrup in 20 ml. of dioxane was added 0.7 g. of selenium dioxide. The mixture was heated with stirring at 80° for 4 hr. The mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in 20 ml. of ethanol and a solution containing 1.0 g. of semicarbazide hydrochloride and 1.0 g. of potassium acetate in 1.0 ml. of water was added and the reactants were heated for 1 hr. on the steam bath. After concentration of the reaction mixture water was added and the semicarbazone separated. A yield of 1.1 g. (58%) of the semicarbazone was obtained, m.p. 230–232° dec. The product was recrystallized from ethanol giving yellow granules, m.p. 234–235° dec. The infrared spectrum shows absorption peaks at 3450(m) cm.$^{-1}$, 3140(m), 1695(s), 1585(m), 1555(m), 1410(s) in the range from 4000 cm.$^{-1}$ to 1300 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.81; H, 4.21. Found: C, 55.81; H, 4.43.

1,2-Dihydro-4-cinnolinecarboxaldehyde semicarbazone (VI). To a suspension of 2.0 g. of potassium 4-cinnolinecarboxylate

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[8] All melting points are uncorrected. The infrared spectra were determined on a Perkin-Elmer Infracord. All were determined as Nujol mulls, except where noted.

in 20 ml. of bis-2-ethoxyethyl ether was added a solution of 1.3 g. of oxalyl chloride in 5 ml. of bis-2-ethoxyethyl ether while cooled in an ice bath. After the mixture was stirred for 15 min. while in an ice bath, it was then stirred 30 min. at room temperature and finally refluxed on the steam bath for 1 hr. The mixture was then stored in a Dry Ice–trichloroethylene mixture for 1 hr. during which time the lithium tri-*t*-butoxyaluminohydride was prepared.

To a suspension of 0.38 g. of lithium aluminum hydride in 10 ml. of bis-2-ethoxyethyl ether was added 2.2 g. of *t*-butyl alcohol over a period of 40 min. at room temperature. This lithium tri-*t*-butoxyaluminohydride solution was added to the cold acid chloride solution over a period of 1 hr., while stirring was maintained. It was stirred for an additional 1 hr. at room temperature. Wet benzene and ethanol were added to destroy the excess lithium tri-*t*-butoxyaluminohydride. The reaction mixture was filtered and evaporated to dryness *in vacuo*. The residue was heated with 30 ml. of water and treated with charcoal and filtered. To the aqueous solution was added 1.0 g. of semicarbazide hydrochloride and 1.0 g. of potassium acetate and this solution was heated on the steam bath for 1 hr. There was obtained 0.63 g. (32%) of the semicarbazone, m.p. 227–229° dec. Upon recrystallization from ethanol, yellow, silky crystals were obtained, m.p. 228–229° dec. The infrared spectrum shows absorption peaks at 3450(m) cm.$^{-1}$, 3150(m) shoulder, 1725(s), 1670(m), 1610(m), 1595(m), 1555(m) in the range from 4000 cm.$^{-1}$ to 1300 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{11}N_5O \cdot {}^1/_2H_2O$: C, 53.08; H, 4.90. Found: C, 53.11; H, 5.05.

Oxidation of 1,2-dihydro-4-cinnolinecarboxaldehyde semicarbazone. A mixture of 0.15 g. of 1,2-dihydro-4-cinnolinecarboxaldehyde semicarbazone and 0.1 g. of selenium dioxide in 15 ml. of pyridine was heated to 100° for 3 hr. with stirring. The selenium was removed by filtration, the solvent evaporated *in vacuo* and the residue recrystallized from ethanol. There was obtained 0.08 g. of yellow granules, m.p. 233–234° dec. A mixed melting point with a sample of this compound prepared by the previously described method showed no depression. The infrared spectrum was identical with that for III described above.

Oxidation of 4-methylcinnoline with selenium dioxide. A mixture of 1.0 g. of 4-methylcinnoline and 1.8 g. of selenium dioxide in 15 ml. of dioxane was refluxed with stirring for 10.5 hr. The reaction mixture was diluted with ether, filtered and evaporated *in vacuo*. The residue was dissolved in 10 ml. of ethanol, treated with charcoal and filtered. To this ethanolic solution was added a solution containing 0.8 g. of semicarbazide hydrochloride, 0.8 g. of potassium acetate and 1 ml. of water in 5 ml. of ethanol and the mixture refluxed for 10 min. The hot solution was treated with charcoal, filtered, concentrated, and water added. There was obtained 0.1 g. (7%) of yellow crystals, m.p. 233° dec., of 4-cinnolinecarboxaldehyde semicarbazone identical in all respects with the other samples of this compound prepared by the two previous methods.

4-Methyl-1,2-dihydrocinnoline. (XVI). (*a*) *By reduction with lithium aluminum hydride.* To a suspension of 0.76 g. of lithium aluminum hydride in 76 ml. of ether was added 1.4 g. of 4-methylcinnoline. The mixture was refluxed with stirring for 2 hr. Wet ether and methanol were added, the mixture filtered, evaporated, and the residue distilled under reduced pressure. There was obtained 1.2 g. of pale yellow distillate, boiling at 94–99° at 0.2 mm., m.p. 58–62°. Upon recrystallization from petroleum ether (b.p. 60–90°) 0.98 g. of colorless needles, m.p. 64–65°, of 4-methyl-1,2-dihydrocinnoline was obtained. The infrared spectrum shows absorption peaks at 3340(m) cm.$^{-1}$, 1625(w), 1585(m), 1340(m), 1295(m), 1260(m), 1245(m), 1190(w), 1150(w), 1080(m), 1055(w), 1040(m), 1020(w), 988(w), 943(w), 875(w), 847(m), 795(w), 752(s).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.96; H, 6.90; N, 19.15. Found: C, 74.12; H, 7.20; N, 18.82.

The picrate, m.p. 165–168°, was formed in brown granules from ethanol.

Anal. Calcd. for $C_{15}H_{13}N_5O_7$: C, 48.00; H, 3.49; N, 18.66. Found: C, 48.01; H, 3.69; N, 18.62.

5-Methyl-8,13-dihydrophthalazino[2,3-a]cinnoline-8,13-dione. (XVIII). In order to establish further the identity of 4-methyl-1,2-dihydrocinnoline, a solution of 0.14 g. of XVI and 0.15 g. of phthalic anhydride in 1 ml. of pyridine was refluxed for 4 hr. The reaction mixture was diluted with benzene and washed first with dilute hydrochloric acid solution and then with dilute sodium carbonate solution. After evaporation of the solvent, 0.2 g. of an orange solid was obtained, m.p. 183–184°. Recrystallization from a benzene-ether mixture gave yellowish orange needles, m.p. 185–186°. The infrared spectrum shows absorption peaks at 1665 (v.s.) cm.$^{-1}$, 1610(m), 1580(w), 1490(w), 1450(s), 1390(w), 1335(s), 1305(w), 1290(s) 1275(m), 1235(m), 1145(w), 1105 (w), 812(m), 795(s), 753(s), 744(m), 725(w), 708(s), 680(m).

Anal. Calcd. for $C_{17}H_{21}N_2O_2$: C, 73.89; H, 4.38; N, 10.14. Found: C, 74.01; H, 4.36; N, 10.17.

(*b*) *Reduction of 4-methylcinnoline with lithium tri-t-butoxyaluminohydride.* To a suspension of 0.38 g. of lithium aluminum hydride in 15 ml. of bis-2-ethoxyethyl ether was added 2.2 g. of *t*-butyl alcohol and the reaction mixture was stirred at room temperature for 0.5 hr. It was then cooled in a Dry Ice–trichloroethylene bath for 1 hr. A solution of 1.4 g. of 4-methylcinnoline in 10 ml. of bis-2-ethoxyethyl ether was added to the cold solution of the hydride over a period of 30 min. This mixture was then stirred at room temperature for 1 hr. Ethanol and moist ether were added, the mixture was treated with charcoal, and filtered. There was obtained 1.2 g. of a semisolid substance boiling at 108–121° at 0.1 mm. The distillate was dissolved in 10 ml. of ether and cooled in a Dry Ice bath whereupon a solid separated. This solid proved to be 0.6 g. of 4-methylcinnoline and was removed by filtration. The filtrate was concentrated to about 0.5 g. of a syrup. This was added to 0.5 g. of phthalic anhydride in 5 ml. of pyridine and the mixture heated at 140° for 4 hr. The product was worked up as described above giving 0.6 g. of a neutral compound, m.p. 182–184°. On admixture with XVIII, there was no depression of the melting point and the infrared spectrum was the same.

Oxidation of 4-methyl-1,2-dihydrocinnoline (XVI) *to 4-methylcinnoline* (VII). A mixture of 0.2 g. of 4-methyl-1,2-dihydrocinnoline and 0.2 g. of 5% palladium on charcoal in 5 ml. of benzene was refluxed for 8 hr. After filtration and evaporation a syrup was obtained, which upon treatment with picric acid formed 0.37 g. of a picrate, m.p. about 165°. The picrate was recrystallized twice from ethanol (charcoal treatment) to give 0.21 g. of yellow crystals, m.p. 177–179°. On admixture with an authentic specimen of 4-methylcinnoline picrate,[9] there was no depression of the melting point and the infrared spectrum was identical with that of authentic 4-methylcinnoline picrate. The infrared spectrum shows absorption peaks at 1640(m) cm.$^{-1}$, 1625(m), 1575(m), 1560(m), 1510(m) shoulder, 1385(m), 1340(m), 1315(m), 1275(m), 1240(m), 1160(m), 1080(m), 1035(m), 943(m), 927(m), 915(m), 885(m), 815(m), 790(m), 780(m), 747(m), 724(m), 710(m).

4-Methyl-1,2,3,4-tetrahydrocinnoline (XVII). A solution of 0.65 g. of 4-methyl-1,2-dihydrocinnoline in 10 ml. of glacial acetic acid was reduced at atmospheric pressure in the presence of 0.1 g. of Adams' catalyst. One molar equivalent of hydrogen was absorbed during 2.5 hr. The mixture was filtered, washed with water and made alkaline with sodium hydroxide. The oily precipitate was taken up in ether. There was obtained 0.48 g. of a syrup boiling at 84–85° at 0.02 mm. A picrate was prepared from a portion of this residue, yellowish brown granules from ethanol-ether mixture, m.p. 109–110° dec. The infrared spectrum shows absorption peaks at 3280(m) cm.$^{-1}$, 2950(m), 1610(m), 1585(m),

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(9) C. M. Atkinson and J. C. E. Simpson, *J. Chem. Soc.* 811 (1947).

1490(s), 1450(s), 1370(w), 1320(m), 1300(m), 1260(m), 1180(w), 1160(w), 1135(w), 1075(w), 1035(w), 1010(w), 950(w), 753(s). This spectrum was determined on the liquid without Nujol.

Anal. Calcd. for $C_{15}H_{15}N_5O_7$: C, 47.75; H, 4.00; N, 18.56. Found: C, 47.89; H, 4.35; N, 18.28.

5-Methyl-5,6,8,13-tetrahydrophthalazino[2,3-a]cinnoline-8,13-dione. (XIX). The procedure for the preparation of this compound was the same as that described for XVIII. There was obtained 0.27 g. of a neutral compound, m.p. 108–110° from 0.2 g. of XVII. The yellow granules had a m.p. of 110–111° when recrystallized from ether. The infrared spectrum was different from that of XVIII. The infrared spectrum shows absorption peaks at 1670(w) cm.$^{-1}$, 1640(m), 1605(w), 1590(w), 1410(m), 1350(m), 1335(m), 1315(m), 1280(m), 1240(m), 1175(w), 1135(m), 1030(w), 975(w), 795(m), 760(m), 755(w), 740(w), 717(w), 693(m).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.06. Found: C, 73.24; H, 5.12; N, 9.96.

4-Cinnolylmethylpyridinium iodide (VIII). A solution of 28.8 g. of 4-methylcinnoline and 56 g. of iodine in 300 ml. of pyridine was refluxed with stirring for 3 hr. during which time the dark red solution turned green. After cooling the solution 800 ml. of benzene was added and the slurry stirred for 5 min. The product was removed by filtration and washed with benzene. The green solid was added to 300 ml. of boiling water, treated with charcoal, and the charcoal removed by filtration. The charcoal was washed with 100 ml. of hot water and the filtrate and washings combined and reduced to a volume of 200 ml. *in vacuo*. On standing overnight in the refrigerator, there was obtained 48.9 g. (70%) of light green crystals, m.p. 185–186° dec. When recrystallized from ethanol, pale yellow prisms, m.p. 186–187° dec., were obtained. The infrared spectrum shows absorption peaks at 1630(w) cm.$^{-1}$, 1575(w), 1420(m), 1320(m), 1215(w), 1185(m), 1150(m), 1080(w), 970(w), 935(w), 900(w), 875(w), 850(w), 825(w), 770(s), 725(s), 677(s).

Anal. Calcd. for $C_{14}H_{21}N_3I \cdot {}^1/_4H_2O$: C, 47.53; H, 3.56; N, 11.88. Found: C, 47.47; H, 3.26; N, 11.95.

N,N-Dimethyl-N′-(4-cinnolylmethylene)-p-phenylenediamine N′-oxide (IX). A suspension of 45.4 g. of VIII and 19.5 g. of *p*-nitrosodimethylaniline in 500 ml. of water was heated with stirring until a clear solution was obtained; then a solution of 10.4 g. of sodium hydroxide in 100 ml. of water was added with stirring, whereupon the dark green solution turned brown. The solution was stirred for an additional 30 min. After cooling the reaction mixture, the separated solid was removed by filtration, washed with water, and dried at 100°. There was obtained 34.9 g. (92%) of a brown powder, m.p. 184–185° dec. Brown needles, m.p. 191–192° dec., were obtained after crystallization from ethanol. The infrared spectrum shows absorption peaks at 1610(m) cm.$^{-1}$, 1540(m), 1515(m), 1395(w), 1290(w), 1235(w), 1180(m), 1165(m), 1115(w), 1090(w), 1075(w), 950(w), 923(w), 907(w), 890(w), 840(w), 815(w), 795(w), 780(m), 728(w).

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.20. Found: C, 69.50; H, 5.56; N, 19.76.

4-Cinnolinecarboxaldehyde hydrazone (X). To a stirred suspension of 2.0 g. of IX in 25 ml. of water was added 25 ml. of 2*N* hydrochloric acid solution, whereupon the solution became red. After the solution was stirred for 30 min., 20% hydrazine solution was added until the *p*H of the solution was 7. The precipitate was filtered and washed with water and ethanol. There was obtained 1.1 g. (93%) of a green solid, m.p. 292–294° dec. Upon recrystallization from dimethylformamide, yellow needles, m.p. 297° dec., were obtained. The infrared spectrum shows absorption peaks at 1620(w) cm.$^{-1}$, 1570(w), 1410(w), 1335(w), 1260(w), 1185(w), 1175(w), 1130(w), 1100(w), 1040(w), 965(m), 925(w), 830(w), 795(w), 790(w), 767(s).

Anal. Calcd. for $C_9H_8N_4$: C, 62.77; H, 4.68; Found: C, 62.85; H, 5.21.

4-Cinnolinecarboxaldehyde semicarbazone (III). To a suspension of 1.6 g. of IX in 20 ml. of water was added 20 ml. of 2*N* hydrochloric acid solution and this mixture was stirred for 30 min. A mixture of 0.8 g. of semicarbazide hydrochloride and 4.8 g. of potassium acetate was added to the acid solution and the mixture heated on the steam bath for 5 min. The precipitate was collected by suction filtration and successively washed with dilute sodium carbonate solution, water, and then ethanol. There was obtained 1.1 g. (quantitative yield) of yellow crystals, m.p. 233–234° dec. When admixed with previous samples of III no depression in melting point was observed and the infrared spectrum was identical.

4-Cinnolinecarboxaldehyde (XI). To a stirred solution of 8.7 g. of X in 76 ml. of 4*N* hydrochloric acid solution, to which 20 ml. of ether was added to prevent foaming, was added a solution containing 6.8 g. of sodium nitrite in 15 ml. of water at 0–2° over a period of 1 hr. The mixture was stirred at about 5° for an additional 1 hr. The solution was treated with charcoal, filtered and the filtrate evaporated to a volume of 20 ml. while kept below 50° *in vacuo*. The concentrated solution was made alkaline with potassium carbonate and extracted with benzene. The benzene solution was evaporated to dryness *in vacuo* while kept below 40°. There was obtained 5.25 g. (66%) of yellow crystals, m.p. 145–147°. Upon recrystallization from benzene–petroleum ether (30–60°), yellow needles, m.p. 147–149°, were obtained. The aldehyde is not stable on standing. The infrared spectrum shows absorption peaks at 1695(s) cm.$^{-1}$, 1620(w), 1570(w), 1525(w), 1510(m), 1380(w), 1245(w), 1190(w), 1165(s), 1090(w), 1050(m), 935(w), 920(w), 825(w), 762(s), 720(m).

Anal. Calcd. for $C_9H_6N_2O$: C, 68.34; H, 3.82. Found: C, 68.70; H, 4.12.

The semicarbazone and the hydrazone were both prepared from 4-cinnolinecarboxaldehyde in the usual manner. Both of these compounds, when mixed with the respective authentic samples as described above, did not depress the melting point. The infrared spectrum of each was identical with those described above for each of these compounds.

4-Cinnolinecarboxaldehyde 2,4-dinitrophenylhydrazone (XII). To 10 ml. of ethanol were added 0.1 g. of XI, 0.14 g 2,4-dinitrophenylhydrazine, and 0.4 ml. of 50% acetic acid and the mixture was refluxed for 10 min. After cooling the reaction mixture there was obtained 0.19 g. of orange crystals, m.p. 316–317° dec. Recrystallization from dimethylformamide gave orange needles, m.p. 316–317° dec. The infrared spectrum shows absorption peaks at 3300(m) cm.$^{-1}$, 1620(m), 1600(m), 1590(s), 1550(m), 1515(m), 1495(s), 1410(m), 1330(s), 1310(s), 1290(m), 1265(s), 1220(s), 1185(w), 1165(w), 1145(s), 1110(w), 1090(w), 1060(w), 935(m), 918(m), 846(m), 837(w), 773(s), 740(m), 720(m), 685(w).

Anal. Calcd. for $C_{15}H_{10}N_6O_4$: C, 53.25; H, 2.98. Found: C, 53.51; H, 2.89.

4-Cinnolinecarboxaldehyde oxime (XIII). To 2 ml. of ethanol were added 0.06 g. of hydroxylamine sulfate, 0.05 g. of potassium carbonate in 0.5 ml. of water and the solution was filtered. To this filtered solution 0.1 g. of XI was added and the mixture refluxed for 10 min. After concentration of the solution, water was added to precipitate 0.1 g. of the oxime, m.p. 221–222° dec. Orange needles, m.p. 223° dec., were obtained by recrystallization from ethanol. The infrared spectrum shows absorption peaks at 1625(w) cm.$^{-1}$, 1565(m), 1550(m), 1520(m), 1335(m), 1280(m), 1260(w), 1175(m), 1140(m), 1115(m), 1060(m), 1005(s), 975(m), 925(m), 825(m), 795(m), 775(s).

Anal. Calcd. for $C_9H_7N_3O$: C, 62.41; H, 4.07. Found: C, 62.31; H, 3.87.

4-(2-Nitroethenyl)cinnoline (XIV). To a solution of 2.4 g. of XI and 1.0 g. of nitromethane in 7.5 ml. of ethanol was added 0.72 g. of sodium hydroxide in 3.5 ml. of water at 5°. The reaction mixture was stirred at 5° for 20 min. and then 1.0 g. of acetic acid in 20 ml. of water was added. The yellowish brown precipitate which was collected was washed with water and amounted to 3.4 g. (quantitative yield), m.p. 141° dec. Recrystallization from ethanol gave yellowish-brown granules, m.p. 141° dec. The infrared spectrum shows absorption peaks at 1635(w) cm.$^{-1}$, 1580(m), 1550(s), 1510(m), 1420(m), 1325(s), 1250(m), 1165(m), 1140(m), 1100(m), 935(w), 918(w), 895(w), 830(m), 795(w), 770(s), 723(m), 700(m).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.69; H, 3.50. Found: C, 59.62; H, 3.31.

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[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

7-Substituted 7*H*-Purines[1]

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A general method for the preparation of 7-substituted 7*H*-purines has been developed. The key steps in this synthesis are the alkylation of *N*-(4-amino-5-pyrimidinyl)formamides in *N*,*N*-dimethylformamide followed by ring closure in this medium.

Although the syntheses of a number of 7-substituted 7*H*-purines have appeared in the literature, none of the methods employed is generally applicable to the preparation of this type of compound. For example, a variety of 2,6-disubstituted 7-methyl-7*H*-purines have been prepared from 2,6-dichloro-7-methyl-7*H*-purine[2–4] which in turn is obtained by the phosphorus oxychloride chlorination of theobromine.[5] Thus these compounds come from a natural product and are limited to 7-*methyl*-7*H*-purines. Another method of preparation of 7-methylpurines[6,7] depends on the cyclization of *N*,*N'*-dimethyloxamide to 1-methyl-5-chloroimidazole.[8] In addition to being lengthy, this method is also confined to 7-*methyl*-7*H*-purines. Other 7-substituted 7*H*-purines have been prepared by the *N*-alkylation of purines.[9] In the case of theophylline, and closely related compounds,[10] a variety of 7-substituted derivatives have been prepared in good yield, but in most cases the directive influence of the pyrimidine substituents give rise to a mixture of 7- and 9-isomers, with the 9-isomer predominating.[7,11] In these cases, although the 9-isomer can usually be obtained pure, the 7-isomer usually cannot be[11] and, therefore, this approach, with one or two exceptions,[9,11] is not applicable as a practical method of preparation of 7-substituted 7*H*-purines.

We have now developed a synthesis of this type of compound that seems to have wide potential application. This method depends upon the alkylation of *N*-(4-amino-5-pyrimidinyl)formamides (V–VIII) with an alkyl halide and potassium carbonate in *N*,*N*-dimethylformamide, a solvent which has proven its utility in many other alkylations.[11,12] This reaction was first applied to *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]formamide (V)[13] and α-chlorotoluene and was carried out at room temperature giving a good yield of *N*-[4-amino-6-(benzylthio)-5-pyrimidinyl]-*N*-benzylformamide (IX). Cyclization of this compound to 7-benzyl-6-(benzylthio)-7*H*-purine (XVII)[12] was accomplished by heating it in formamide. Although the reaction solution discolored badly, a good yield of the purine was isolated.

In order to extend this reaction to chloropyrimidines, it was necessary to prepare the requisite 5-pyrimidinylformamides (VII and VIII). Since it is known that the chlorine atoms of these pyrimidines

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