

78–86°, $[\alpha]_D -24^\circ$, $\lambda_{\text{max}}^{\text{EtOH}}$ 222 m μ , $\log \epsilon$ 3.78²⁷; orange-yellow color with tetranitromethane.

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.33; H, 8.70; O, 13.62.

The wide melting point range indicated that the product was not pure,²⁸ but the presence of the double bond was demonstrated by quantitative microhydrogenation in ethanol solution with 10% palladized charcoal which resulted in the consumption of 1.08 equivalents of hydrogen. Recrystallization from aqueous ethanol afforded crystals,

(27) The ultraviolet absorption spectrum appears to be compatible with the unsaturated cyclopropane formulation XIV as indicated by the few relevant data listed in the literature (ref. 21).

(28) For possible side reactions see ref. 21.

m.p. 54–76°, which presumably represent a contaminated²⁸ sample of the saturated cyclopropane derivative XV.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46. Found: C, 76.15; H, 9.78.

The unsaturated alcohol Xb was converted to the mesylate Xd in the conventional manner, but the product could only be obtained as an amorphous powder in spite of repeated attempts at crystallization. When this mesylate Xd was treated with sodium iodide in acetone solution as described above for the dimesylate Vf, there were obtained colorless crystals (m.p. 59–78°) of the supposed unsaturated cyclopropane XIV, whose infrared spectrum was identical with that of the solid isolated in the dimesylate-sodium iodide reaction.

DETROIT, MICHIGAN

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

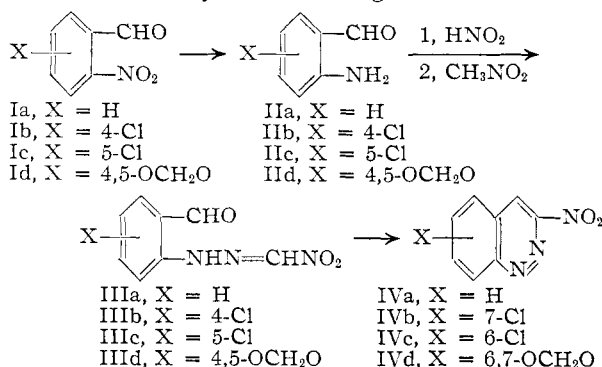
Cinnolines. III. Synthesis of bz-Substituted 3-Nitro- and 3-Aminocinnolines^{1,2}

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The synthesis of three new bz-substituted 3-nitrocinnolines by the cyclization of nitroformaldehyde *o*-formylphenylhydrazones (III) is described as well as an alternative route for proceeding from the usual starting material, an *o*-nitrobenzaldehyde, to the cinnoline. Two of the 3-nitrocinnolines have been reduced to the corresponding 3-aminocinnolines.

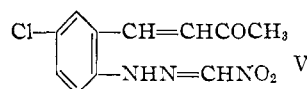
Of the ten to twelve syntheses of the cinnoline ring described in the literature, only three procedures (the Richter, Widman-Stoermer and Borsche syntheses) appear to be of established generality.³ In the first paper of this series⁴ a new synthesis (I \rightarrow IV) of cinnolines was described involving cyclization of nitroformaldehyde *o*-acylphenylhydrazones (such as III) to 3-nitrocinnolines. The present communication describes our further exploration of the generality of this synthesis as applied to *o*-nitrobenzaldehydes as starting materials.



For the present work three of the more accessible *o*-nitrobenzaldehydes, 4-chloro-2-nitrobenzaldehyde (Ib), 5-chloro-2-nitrobenzaldehyde (Ic) and 6-nitropiperonal (Id), were employed. The *o*-nitrobenzaldehydes were reduced to the corresponding *o*-aminobenzaldehydes (II). Without purification

the *o*-aminobenzaldehydes were diazotized and coupled with nitromethane to give the nitroformaldehyde *o*-formylphenylhydrazones (III), and the latter were cyclized by treatment with dilute aqueous potassium hydroxide without intermediate purification, giving 7-chloro-3-nitrocinnoline (IVb), 6-chloro-3-nitrocinnoline (IVc) and 6,7-methylenedioxy-3-nitrocinnoline (IVd) in 10–15, 12–17 and 10% yields, respectively, based on I.

Only in the case of IVb was there any deviation from the expected behavior. In all experiments at the 0.04-mole level, IVb was obtained in 10–15% yield. However, in several experiments at the 0.20-mole level, using various concentrations of base, times of reaction and temperatures, the reaction was erratic and little IVb was formed. On recrystallizing the crude apparent product from acetone the only material isolated in quantity (about 10–26%) appeared to be nitroformaldehyde 5-chloro-2-(3-oxo-1-butenyl)-phenylhydrazone (V),



based on its analysis and infrared spectrum. This material apparently arose from the reaction of the uncyclized intermediate IIIb with acetone during the recrystallization. Thus, the use of acetone as a solvent during the cyclization or purification steps appears to be contraindicated.

The principal apparent limitation to the generality of the present synthesis is the relative inaccessibility of derivatives of II.⁵ Various de-

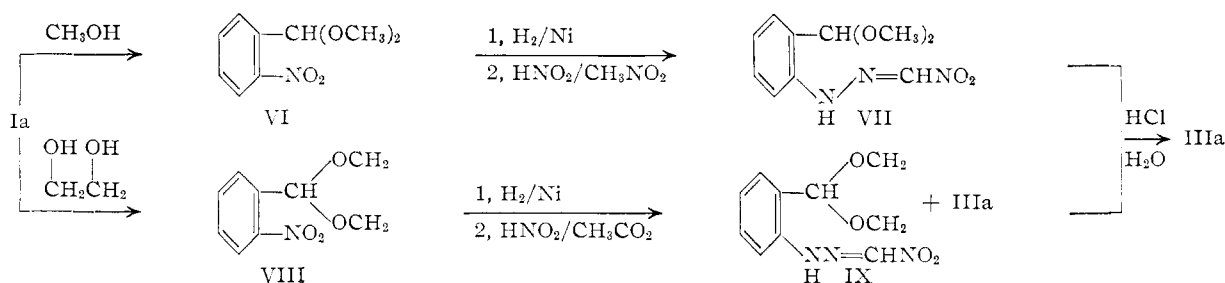
(1) This work was supported in part by grant G-1090 of the National Science Foundation.

(2) Paper II, *THIS JOURNAL*, **77**, 5109 (1955).

(3) The cyclization of *o*-hydrazinomandelic acids (Neber-Bossel synthesis, E. J. Alford and K. Schofield, *J. Chem. Soc.*, 2102 (1952)) appears to be a potentially general synthesis also; however, as will be borne out by results to be reported shortly from this Laboratory, the use of presently published procedures may lead to the isomeric N-aminodioxindoles rather than cinnoline derivatives.

(4) H. E. Baumgarten and M. R. DeBrunner, *THIS JOURNAL*, **76**, 3489 (1954).

(5) According to our count (D. L. Pedersen, M.S. thesis, University of Nebraska, June, 1956) at least 30 monosubstituted and 80 di- and trisubstituted *o*-nitrobenzaldehydes (I) are mentioned in the literature but only approximately 8 monosubstituted and 14 di- and trisubstituted *o*-aminobenzaldehydes have been described. The disparity in these figures is to some extent a measure of the difficulty of reduction of I and its derivatives and the instability of II and its derivatives.



VICES have been developed through necessity in heterocyclic synthesis to avoid the use of II.^{6,7} One scheme devised for this purpose in connection with the present synthesis is outlined in the sequences Ia \rightarrow VII \rightarrow IIIa and Ia \rightarrow IX \rightarrow IIIa.

Conversion of Ia into its dimethyl acetal VI was accomplished in 87–88% yield using several different procedures, the most interesting of which employed the ion exchange resin, Amberlite IR-120 (nuclear sulfonic acid type), as the catalyst for the reaction. Hydrogenation of VI gave the corresponding amino compound, which was not isolated but was diazotized and coupled with nitromethane to give the dimethyl acetal VII of IIIa in 49–71% yield, the structural assignment being based on analysis and the infrared spectrum. Treatment of VII with warm, dilute hydrochloric acid gave IIIa in 86–93% yield. The attempted direct cyclization of VII (without prior hydrolysis of the acetal group) was not effective. The range of over-all yields of IIIa by this process was 37–58% (based on Ia) compared with 39–48% for the sequence Ia \rightarrow IIa \rightarrow IIIa.⁴

By a similar sequence of reactions Ia was converted into the ethylene acetal in 78–94% yield and the latter was hydrogenated and the resultant amine diazotized and coupled with nitromethane. The product in this instance was a roughly 1:1 mixture of the ethylene acetal IX of IIIa and IIIa itself in 91–92% combined yield. Hydrolysis of the acetal gave IIIa in 94% yield. The over-all yield of IIIa by this process was 69–84%, a very substantial improvement over any prior sequence. Although exact reason for the superiority of the ethylene acetal over the dimethyl acetal is not yet clear, we have inferred that the former gives a more stable product during and immediately after the hydrogenation step.

Thus far, two techniques have been used for the cyclization of IIIa and its derivatives: treatment with dilute aqueous potassium hydroxide, applicable only to III and its derivatives, and treatment with aluminum oxide in acetone, applicable not only to IIIa but also to nitroformaldehyde *o*-acetylphenylhydrazone.⁴ The latter procedure was based upon the very successful use of this combination by Schofield and Theobald⁸ in the cyclization of *N*-(β -nitroethylidene)-*o*-aminoacetophenones. Now, however, this combination appears to have

several disadvantages for the ring closure at hand: (1) as noted above III may react with acetone to form V under the conditions of the closure, (2) a possible competitive reaction, hydrolysis of III, may be aided by the water formed when the relatively large quantity of acetone remains in contact with the aluminum oxide,⁹ (3) some difficulty is encountered in separating the product from the aluminum oxides in some instances and (4) the process is quite slow. An attractive alternative to the above two techniques is the use of the anion exchange resin, Amberlite IRA-400, in tetrahydrofuran solution.¹⁰ The maximum yield of IVa (55%, based on IIIa, or 46%, based on Ia and using VIII as an intermediate) resulted when the reaction was run at 60° for about 20 hours. This yield is considerably better than that obtained using dilute aqueous potassium hydroxide for the cyclization step. In a limited series of experiments, the resin, Amberlite IR-4B, appeared to be ineffective as a cyclizing agent.

In the earlier paper⁴ the reduction with stannous chloride of IVa to 3-aminocinnoline in 31% yield accompanied by by-products of unknown structure was described. The use of iron and acetic acid for the reduction has given yields of 70–83% of 3-aminocinnoline in numerous experiments with little or no by-product formation. Similarly, the reductions of IVb and IVc with iron and acetic acid have given 7-chloro-3-aminocinnoline and 6-chloro-3-aminocinnoline in 70–74% and 74–90% yields, respectively.

Experimental¹¹

7-Chloro-3-nitrocinnoline (IVb).—2-Amino-4-chlorobenzaldehyde was prepared from 7.5-g. (0.04-mole) batches of 4-chloro-2-nitrobenzaldehyde¹² following the procedure¹³ described for the reduction of *o*-nitrobenzaldehyde with no significant deviation. The crude, moist product (usually about 7 g.) was used without further purification. The present procedure was more convenient than that described by Sachs and Sichel.¹⁴

To a mixture of 7 g. (ca. 0.04 mole) of crude, moist 2-amino-4-chlorobenzaldehyde, 2.9 g. (0.042 mole) of sodium nitrite and 75 g. of crushed ice, made into a slurry in a Waring blender, a mixture of 9 ml. (0.11 mole) of concentrated hydrochloric acid and 50 g. of crushed ice was added

(6) An example is the Borsche modification of the Friedlander synthesis.

(7) Cf. H. E. Baumgarten and K. E. Cook, *J. Org. Chem.*, **22**, 138 (1957) for leading references in which II is replaced by *o*-aminobenzaldehyde. Several attempts to use the latter substance in this synthesis were unsuccessful.

(8) K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 395 (1950).

(9) J. A. Riddick and E. E. Toops, Jr., in A. Weissberger's "Technique of Organic Chemistry," Vol. VII, "Organic Solvents," Interscience Publishers, Inc., New York, N. Y., 1955, p. 382.

(10) An acyclic analogy is the recently reported condensation of carbonyl compounds with nitroparaffins using ion exchange resins as catalysts (M. J. Astle and F. P. Abbott, *J. Org. Chem.*, **21**, 1228 (1956)).

(11) Melting points are corrected; boiling points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(12) D. P. Spalding, G. W. Moersch, H. S. Mosher and F. C. Whitmore, *THIS JOURNAL*, **68**, 1596 (1946).

(13) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 56.

(14) F. Sachs and E. Sichel, *Ber.*, **37**, 1862 (1904).

in one portion. The mixture was blended for about 5 minutes until a clear solution was obtained. Small amounts of crushed ice were added periodically during the blending to keep the temperature low. The solution was filtered through a chilled funnel onto a small amount of crushed ice.

Meanwhile a solution of 4.3 ml. (0.08 mole) of nitromethane in 5 ml. of ethanol was added slowly with stirring to a solution of 5.7 g. (0.1 mole) of potassium hydroxide in 3.5 l. of ice-water. After the nitromethane had dissolved, 3.3 g. (0.04 mole) of sodium acetate was added to the solution. The diazonium solution was poured slowly into the solution of potassium *aci*-nitromethane. A yellow precipitate formed immediately. The mixture was allowed to stand for 20 minutes. The crude nitroformaldehyde 5-chloro-2-formylphenylhydrazone was collected by filtration and transferred to the Waring blender without further purification. A solution of 1.3 g. of potassium hydroxide in 50 ml. of water was added to the solid in the blender. A blood-red color developed immediately. The mixture was blended until the red color faded into a chocolate brown (about 5–10 minutes). The mixture was poured into a beaker, allowed to stand for 2.5 hr. and filtered. The resultant brown solid was dried overnight in the vacuum desiccator. The crude material, 1.51 g., was recrystallized from acetone or, preferably, ethyl acetate, giving 1.1 g. (13%, based on 4-chloro-2-nitrobenzaldehyde) of 7-chloro-3-nitrocinnoline as pale yellow needles, m.p. 165.5–166°. In eight other experiments yields of 10–15% were obtained.

Anal. Calcd. for $C_9H_6ClN_3O_2$: C, 45.84; H, 1.92; N, 20.05; Cl, 16.92. Found: C, 46.30; H, 2.08; N, 19.56; Cl, 16.70.

Nitroformaldehyde 5-Chloro-2-(3-oxo-1-butenyl)-phenylhydrazone (V).—The procedure described above for the preparation of 7-chloro-3-nitrocinnoline was followed exactly except for the following deviations: a fourfold larger quantity of each reagent was used; however, 3.5 l. of ice-water was used in the preparation of the potassium *aci*-nitromethane solution. The crude, yellow nitroformaldehyde 5-chloro-2-formylphenylhydrazone was blended with a solution of 5.2 g. of potassium hydroxide in 200 ml. of water. The blood-red color developed as usual and was displaced by the brown color in about 10 minutes. The mixture was allowed to stand 2.5 hours and was filtered. The brown solid, after drying, was refluxed with 300 ml. of acetone for 2 hr. The resultant solution was filtered, treated with charcoal and refiltered. The volume of the filtrate was reduced to about 75 ml. On cooling orange needles separated, which were collected (6.1 g.) and recrystallized from acetone as yellow-orange needles, m.p. 234–235°. In three experiments at the 0.20-mole level the yields of 5-chloro-2-(3-oxo-1-butenyl)-phenylhydrazone varied from 5.5 to 14.0 g. (10–26%) in spite of variations introduced into the procedure in the hope of avoiding the formation of this substance.

Anal. Calcd. for $C_{11}H_{10}N_3O_3Cl$: C, 49.40; H, 3.77; N, 15.70; Cl, 13.26. Found: C, 49.89, 49.91; H, 3.77, 3.93; N, 15.30; Cl, 13.24.

6-Chloro-3-nitrocinnoline (IVc).—In a 5-l., three-necked flask equipped with a dropping funnel, stirrer and a Kjeldahl trap leading to an efficient condenser a solution of 180 g. of ferrous sulfate heptahydrate in 600 ml. of water was heated to 90°. To the hot solution was added a hot solution of 15.6 g. (0.084 mole) of 5-chloro-2-nitrobenzaldehyde¹⁵ in 360 ml. of ethanol. To the resultant mixture 600 ml. of concentrated ammonium hydroxide was added slowly over a period of 10 minutes. Immediately after the addition was complete, the dropping funnel was replaced by a steam inlet tube, and the mixture was steam distilled. The first 300–500 ml. of distillate collected contained mostly ethanol and ammonium hydroxide, and none of the desired product could be obtained from this portion. An additional 2 l. of distillate was collected, cooled to 5° and saturated with sodium chloride. The product was collected by filtration, yielding 6.5–7.0 g. of crude, moist 2-amino-5-chlorobenzaldehyde, which was used without further purification. In one experiment the crude aldehyde was air-dried to constant weight, giving 43% of crude 2-amino-5-chlorobenzaldehyde, m.p. 73.5–74.5°. ¹⁶

(15) E. J. Alford and K. Schofield, *J. Chem. Soc.*, 2102 (1952).

(16) The yield in this reduction appears to be about half of that obtained in the reduction of Ib. The lower yield may have been due to isomeric contaminants in the Ic.

From this point the procedure described above for the preparation of 7-chloro-3-nitrocinnoline was followed substituting the 7.0 g. of moist 2-amino-5-chlorobenzaldehyde for the same amount of 2-amino-4-chlorobenzaldehyde. The crude, brown product, 5.1 g., was recrystallized from ethyl acetate, giving 2.8 g. (16%, based on 5-chloro-2-nitrobenzaldehyde) of 6-chloro-3-nitrocinnoline as pale yellow plates, m.p. 227–228°. In four other experiments the yields varied from 10–17%.

Anal. Calcd. for $C_9H_6ClN_3O_2$: C, 45.84; H, 1.92; N, 20.05. Found: C, 45.92; H, 2.06; N, 20.36.

6,7-Methylenedioxy-3-nitrocinnoline (IVd).—Nitroformaldehyde 4,5-methylenedioxy-2-formylphenylhydrazone was prepared from 9.0 g. (0.054 mole) of 6-aminopiperonal¹⁷ (from 15 g. (0.075 mole) of 6-nitropiperonal) and other reagents in proportion as outlined above in the preparation of 7-chloro-3-nitrocinnoline. The crude, deep red solid was cyclized according to that procedure, giving 1.96 g. (12%) of crude 6,7-methylenedioxy-3-nitrocinnoline. Repeated recrystallization from ethyl acetate gave cream-colored needles, 1.6 g. (10%), which sublimed with no clearly defined m.p. in the interval 255–310°, on the Kofler hot-stage. In the Hershberg melting point bath the crystals blackened at 250° but did not appear to melt.

Anal. Calcd. for $C_9H_8N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.27; H, 2.43; N, 19.12.

3-Aminocinnoline.—To a hot suspension of 13.8 g. (0.079 mole) of 3-nitrocinnoline⁴ in a solution of 110 ml. of acetic acid and 55 ml. of water was added over about 5 minutes 11 g. (0.20 mole) of iron powder (Baker reduced). The mixture was shaken vigorously during the addition and until a vigorous reaction began. The mixture was heated under reflux on the steam-bath for 1 hr. and then poured into 300 g. of ice-cold 33% potassium hydroxide solution. The mixture was allowed to stand overnight to settle the iron oxides. The supernatant liquid was filtered through a layer of Celite and then the iron oxides were washed onto the filter mat. The filter cake was washed well with water. The entire moist cake was suspended in 150 ml. of absolute ethanol and the suspension was heated to boiling. The mixture was filtered and the solids were again extracted with 150-ml. and 100-ml. portions of absolute ethanol. The combined filtrates were treated with charcoal, filtered and evaporated to dryness under reduced pressure. The crude 3-aminocinnoline was recrystallized from 250 ml. of benzene, giving 8.0 g. (70%) of pure 3-aminocinnoline, m.p. 165–166°. Concentration of the filtrate to 40 ml. yielded another 1.1 g. of product, making the total yield 79%. In other experiments the total yield varied from 70–83%. In this preparation it was often advantageous to extract the aqueous, alkaline solution with ether and to combine the ether and ethanol extracts before evaporation and recrystallization of the product from benzene.

3-Amino-7-chlorocinnoline.—The reduction of 3.0 g. (0.014 mole) of 7-chloro-3-nitrocinnoline as described above for the reduction of 3-nitrocinnoline gave 2.2 g. (85%) of 3-amino-7-chlorocinnoline as bright yellow plates, m.p. 202° dec.

Anal. Calcd. for $C_9H_6ClN_3$: C, 53.49; H, 3.37; N, 23.40. Found: C, 53.53; H, 3.29; N, 23.93.

3-Amino-6-chlorocinnoline.—The reduction of 3.0 g. (0.014 mole) of 6-chloro-3-nitrocinnoline as described above for the reduction of 3-nitrocinnoline gave 1.91 g. (74%) of 3-amino-6-chlorocinnoline as bright yellow needles, m.p. 215° dec.

Anal. Calcd. for $C_9H_6ClN_3$: C, 53.49; H, 3.37; N, 23.40. Found: C, 53.49; H, 3.53; N, 23.20.

***o*-Nitrobenzaldehyde Dimethyl Acetal (VI).** (a).—To a solution of 10 g. (0.066 mole) of *o*-nitrobenzaldehyde in 50 ml. of absolute methanol two drops of concentrated hydrochloric acid and 0.75 g. of calcium chloride were added, and the mixture was allowed to stand for six days in a desiccator over calcium chloride. The solution was filtered and neutralized with methanolic sodium methoxide until it was just alkaline to moist litmus. After removing the methanol by distillation, the oily residue was distilled under reduced pressure, giving 11.4 g. (88%) of pale yellow *o*-nitrobenzal-

(17) K. N. Campbell, P. F. Hopper and B. K. Campbell, *J. Org. Chem.*, **16**, 1736 (1951).

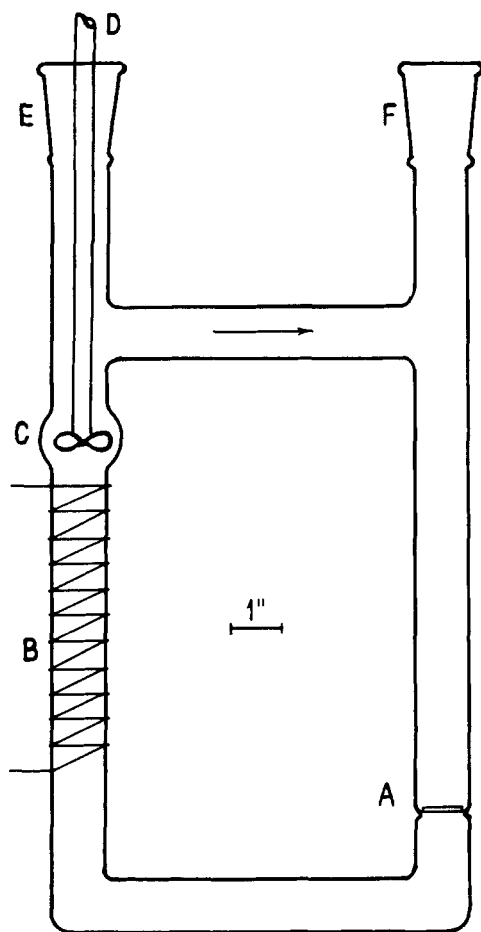


Fig. 1.—Reaction apparatus.

dehyde dimethyl acetal, b.p. 146–149° (27 mm.) (lit.¹⁸ b.p. 141–144° (15 mm.)), n_D^{20} 1.5265.

(b).—To a solution of 100 g. (0.66 mole) of *o*-nitrobenzaldehyde in 750 ml. of benzene and 50 ml. of absolute methanol in a reflux set-up equipped with a modified Dean and Stark water separator¹⁹ was added 2 g. of *p*-toluenesulfonic acid and the mixture was heated under reflux for 28 hr. After removing 500 ml. of the solution by distillation the remainder of the solution was neutralized with methanolic sodium methoxide and worked up as described in (a) above, giving 116 g. (87%) of *o*-nitrobenzaldehyde dimethyl acetal.

(c).—To a solution of 15 g. of *o*-nitrobenzaldehyde in 250 ml. of benzene and 35 ml. of absolute methanol in the reflux set-up described in (b) was added 2 g. of Amberlite resin IR-120 which had been washed thoroughly with absolute methanol, and the mixture was heated under reflux for 35 hr. The resin was removed by filtration, the methanol by distillation and the residue was distilled under reduced pressure, giving 18.4 g. (87%) of *o*-nitrobenzaldehyde dimethyl acetal.

***o*-Nitrobenzaldehyde Ethylene Acetal (VIII).** (a).—To a solution of 10 g. (0.066 mole) of *o*-nitrobenzaldehyde in 250 ml. of benzene and 25 ml. of ethylene glycol 0.25 g. of *p*-toluenesulfonic acid was added and the mixture was heated under reflux for 30 hours in the set-up described under *o*-nitrobenzaldehyde dimethyl acetal (b). Water was removed periodically. About 150 ml. of solution was removed by distillation, the remaining solution was made alkaline to moist litmus with sodium methoxide and the mixture was fractionally distilled. Fractions were removed at 27° (70 mm.) and 105° (37 mm.) before the *o*-nitrobenzaldehyde ethylene acetal distilled at 120.7° (0.7 mm.) as a pale yellow oil, 10.3 g. (78%), n_D^{20} 1.5487.

(18) W. Cocker, J. O. Harris and J. V. Loach, *J. Chem. Soc.*, 751 (1938).

(19) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 382.

Anal. Calcd. for $C_8H_9NO_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.42; H, 4.35; N, 7.36.

(b).—To a solution of 15 g. of *o*-nitrobenzaldehyde in 250 ml. of benzene and 10 ml. of ethylene glycol in the reflux set-up described under *o*-nitrobenzaldehyde dimethyl acetal (b) was added 2 g. of Amberlite resin IR-120 (washed with absolute methanol and dried) and the mixture was refluxed for 30 hours, removing water from the moisture trap when necessary. The resin was filtered from the solution and washed with a small amount of hot benzene. The solution was distilled as in (a) above, giving 18.4 g. (94%) of *o*-nitrobenzaldehyde ethylene acetal, b.p. 120° (0.7 mm.). It is noteworthy that the reaction mixture after filtering off the resin, was not acidic.

Nitroformaldehyde *o*-Formylphenylhydrazone Dimethyl Acetal (VII).—A mixture of 5.0 g. (0.025 mole) of *o*-nitrobenzaldehyde dimethyl acetal, 100 ml. of absolute methanol and about 1 g. of Raney nickel was shaken with hydrogen in the usual fashion under 45 p.s.i. pressure.²⁰ Hydrogenation usually required about one hour. After filtering the catalyst from the solution, the filtrate, 50 ml. of water, 3.5 g. (0.05 mole) of sodium nitrite and 300 g. of crushed ice were made into a slurry in the Waring blender. To the slurry 25 ml. of 6 *N* hydrochloric acid was added and the mixture was blended for 20 minutes (adding ice periodically). Meanwhile, a solution of 3.0 g. (0.05 mole) of nitromethane in 10 ml. of ethanol was added slowly with stirring to a solution of 5.7 g. (0.1 mole) of potassium hydroxide in 400 ml. of water. The diazonium solution was then added dropwise with stirring to the potassium *aci*-nitromethane solution over about 20 minutes. The bright orange precipitate was collected and recrystallized from 1:3 acetone:water, giving 4.3 g. (71%) of nitroformaldehyde *o*-formylphenylhydrazone dimethyl acetal as bright orange needles, m.p. 80–81°. In two other runs the yields were 49 and 51%.

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.61; H, 5.33; N, 17.19.

Nitroformaldehyde *o*-Formylphenylhydrazone Ethylene Acetal (IX).—Following the procedure described for the dimethyl acetal, a mixture of 4.3 g. (0.022 mole) of *o*-nitrobenzaldehyde ethylene acetal, 50 ml. of absolute methanol and approximately 0.5 g. of Raney nickel was hydrogenated, the catalyst removed by filtration and the filtrate diazotized in the blender with 3 g. (0.044 mole) of sodium nitrite, 100 ml. of water, 300 g. of ice and 22 ml. of 6 *N* hydrochloric acid. The diazonium solution was added to a solution of potassium *aci*-nitromethane prepared from 4 g. (0.066 mole) of nitromethane, 10 ml. of ethanol, 7.5 g. (0.118 mole) of potassium hydroxide in 400 ml. of ice-water. Dilute hydrochloric acid (1%) was added to the mixture until the pH was 3. Golden crystals formed immediately. The mixture was stirred for 20 min. (at 5°) and filtered. The product, 2.5 g., m.p. 78–85°, was recrystallized from acetone-water giving 2.3 g. (47%) of nitroformaldehyde *o*-formylphenylhydrazone ethylene acetal as golden yellow plates, m.p. 83.7–85°.

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.94; H, 5.06; N, 18.08.

The filtrate was allowed to warm to room temperature and was extracted with ether. Removal of the ether on the steam-bath gave 1.8 g. (44%) of nitroformaldehyde *o*-formylphenylhydrazone, m.p. 156–158°. One other experiment gave 49% of ethylene acetal and 43% of the free aldehyde.

Nitroformaldehyde *o*-Formylphenylhydrazone (IIIa). (a) **From the Dimethyl Acetal.**—To a solution of 3 ml. of concentrated hydrochloric acid in 200 ml. of water heated to 95° in the Waring blender (preheated to 80°) was added 0.87 g. (0.0037 mole) of nitroformaldehyde *o*-formylphenylhydrazone dimethyl acetal. The solution was blended for 0.5 hr., cooled to 10° and extracted with ether. The ether was evaporated and the yellow product was recrystallized from 3:1 water-acetone giving 0.66 g. (91%) of nitroformal-

(20) This hydrogenation is definitely exothermic and caution should be exercised when larger quantities of the acetal are reduced. Use of the minimal amount of catalyst appeared to slow the reaction somewhat. Stopping the reaction occasionally to cool the bottle or reaction vessel may be advisable with very active catalysts. In those reductions of VI in which the temperature rose substantially, the yield of VII appeared to be much lower.

dehyde *o*-formylphenylhydrazone, m.p. 157–158°. Other experiments gave yields varying from 86 to 93%.

(b) **From the Ethylene Acetal.**—Following the procedure described in (a) 0.65 g. (0.0028 mole) of nitroformaldehyde *o*-formylphenylhydrazone ethylene acetal was hydrolyzed with 2 ml. of concentrated hydrochloric acid in 150 ml. of hot water, giving, after extraction and recrystallization, 0.49 g. (94%) of nitroformaldehyde *o*-formylphenylhydrazone, m.p. 157–158°.

3-Nitrocinnoline (IVa).—A Witt plate of the appropriate diameter was placed on the wall indentations (A) of the apparatus shown in the scale drawing (Fig. 1). The plate provided a platform for 6 g. of dry ion exchange resin, Amberlite IRA-400.¹⁰ With heating to 55° by means of the Nichrome coil (B), a solution of 2.0 g. (0.01 mole) of nitroformaldehyde *o*-formylphenylhydrazone in 300 ml. of tetrahydrofuran was circulated through the apparatus for 18 hr. by means of the propeller stirring rod (C).²¹ The two

(21) A spiral impeller, such as described by H. E. Drechsel (*Anal. Chem.*, **29**, 659 (1957)), might be preferable.

outlets (E) and (F) were fitted with a ball-joint stirrer sleeve²² and a reflux condenser, respectively. The solution was filtered and the solvent was removed by distillation on the steam-bath. The light tan solid was recrystallized from dilute acetone (charcoal), giving 1.0 g. (55%) of 3-nitrocinnoline, m.p. 204–205°.

In several experiments the solution was refluxed over the resin in the usual reflux set-up using either tetrahydrofuran or dimethoxyethane as the solvent for periods varying from 10 to 20 hr. The reflux procedure gave yields about 10% lower and the resin underwent partial decomposition. When the quantity of resin used was lowered to 3 g., only a trace of 3-nitrocinnoline could be isolated. Raising the quantity of resin used did not effect any increase in the yield.

(22) *Organic Chemical Bulletin* (Eastman Kodak Co.), **24**, no. 3 (1952).

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. IV. Synthesis of 3-Acetyl- and 3-Carbethoxycinnolines^{1,2}

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Diazotization of *o*-aminobenzaldehyde and coupling of the diazonium salt with acetoacetic acid gave the unstable pyruvaldehyde 1-(*o*-formylphenylhydrazone) (VIa), which cyclized spontaneously to form 3-acetylcinnoline. Coupling of the diazonium salt with ethyl hydrogen malonate and spontaneous cyclization of the unstable ethyl glyoxylate *o*-formylphenylhydrazone (VIIIa) gave 3-carbethoxycinnoline. In a somewhat similar fashion 2-amino-4-chloro- and 2-amino-5-chlorobenzaldehydes gave the corresponding 3-acetyl-7-chloro- and 3-acetyl-6-chlorocinnoline and the 3-carbethoxy-7-chloro- and 3-carbethoxy-6-chlorocinnoline, respectively, although the cyclization step was not always both spontaneous and complete in these examples.

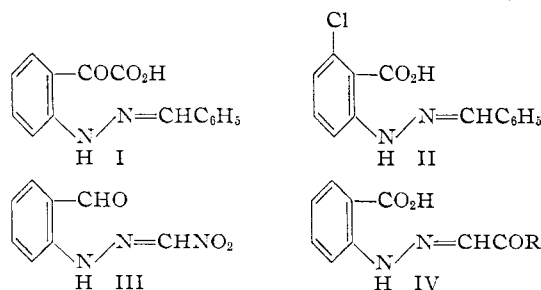
Three related syntheses of the cinnoline ring system have employed the cyclization of an *o*-acyl- or *o*-carboxyphenylhydrazone (I–III) in the terminal step: the Stolle–Becker³ synthesis (I), the Pfannstiehl–Janecke⁴ synthesis (II) and that (III) reported from this Laboratory.^{1,5} Each of the first two of these procedures is known by a single example, and an attempt by Leonard, Boyd and Herbrandson⁶ to extend the Pfannstiehl–Janecke synthesis to phenylhydrazones of the type IV was not successful. In the first paper⁵ of this series it was suggested that the cyclization of derivatives of IV in which the carboxyl group was replaced by formyl or acetyl might be more satisfactory than the cyclization of IV itself. This possibility has

now been realized in part and is the subject of this communication.

When *o*-aminobenzaldehyde (Va)⁷ was diazotized and coupled with acetoacetic acid, the expected pyruvaldehyde 1-(*o*-formylphenylhydrazone) (VIa) appeared to form, but purification of the product yielded only the cyclized 3-acetylcinnoline (VIIa) in 16–22% yield. Although cyclization may have occurred in some experiments during the recrystallization of the product, in others examination of the crude material indicated that cyclization had occurred at some earlier stage, and thus far no authentic sample of VIa has been obtained. The identity of VIIa was established by analysis, comparison of its infrared spectrum with that of the presumably analogous 3-acetylquinoline and conversion of VIIa into the known 3-aminocinnoline⁸ by application of the Schmidt reaction.

When Va was diazotized and coupled with ethyl hydrogen malonate, the product was a tarry material from which only 3-carbethoxycinnoline (IXa) could be isolated in 8–12% yield. The assignment of structure was based upon analysis and the infrared spectrum. Again none of the intermediate ethyl glyoxylate *o*-formylphenylhydrazone (VIIIa) has been isolated.

Extension of the above operations to 2-amino-4-chlorobenzaldehyde⁷ (Vb) and to 2-amino-5-chlorobenzaldehyde⁷ (Vc) gave somewhat different re-



(1) Paper III, *THIS JOURNAL*, **80**, 1977 (1958).

(2) This work was supported in part by grant G-1090 of the National Science Foundation.

(3) R. Stolle and W. Becker, *Ber.*, **57**, 1123 (1924).

(4) K. Pfannstiehl and J. Janecke, *ibid.*, **75B**, 1096 (1942).

(5) H. E. Baumgarten and M. R. DeBrunner, *THIS JOURNAL*, **76**, 3489 (1954).

(6) N. J. Leonard, S. N. Boyd, Jr., and H. F. Herbrandson, *J. Org. Chem.*, **12**, 47 (1947).

(7) The *o*-aminobenzaldehydes used in this study were prepared from the corresponding *o*-nitrobenzaldehydes as described previously^{1,4} and were crude materials. Over-all yields are based, therefore, on the *o*-nitrobenzaldehyde.