[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Cinnolines. I. A Synthesis of 3-Nitro- and 3-Aminocinnolines

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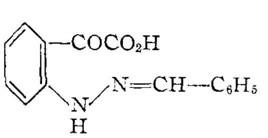
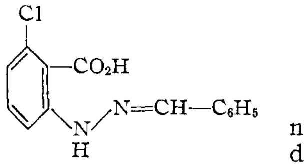
Diazotized *o*-aminobenzaldehyde has been coupled with nitromethane in dilute solution to give nitroformaldehyde *o*-formylphenylhydrazone (Va). Cyclization of the latter yielded 3-nitrocinnoline. By a similar sequence *o*-aminoacetophenone was converted into 4-methyl-3-nitrocinnoline, but attempts to prepare 4-hydroxy-3-nitrocinnoline from anthranilic acid by the same route were unsuccessful. Reduction of the 3-nitrocinnolines with stannous chloride and hydrochloric acid gave 3-aminocinnoline and 3-amino-4-methylcinnoline, respectively.

The various methods utilized for the synthesis of cinnoline and its derivatives have been reviewed recently in several places.[2-4] Apparently only seven procedures have been reported which are sufficiently different to be called distinct syntheses.[5] Two of these seven methods have utilized the cyclization of *o*-carbonyl(or carboxyl)-phenylhydrazones to form the cinnoline nucleus. Stolle and Becker[6] reported the synthesis of 4-carboxy-3-phenylcinnoline, apparently by the ring closure of benzaldehyde *o*-glyoxalylphenylhydrazone (I) (formed from the action of hot alkali on N-benzylideneisatin), while Pfannstiehl and Janecke[7] reported the synthesis of 5-chloro-4-hydroxy-3-phenylcinnoline by ring closure of benzaldehyde 2-carboxy-3-chlorophenylhydrazone (II). The yield from the former synthesis was not reported and from the latter was said to be very small. Both of these syntheses were discovered in the course of work toward other objectives and have not been investigated further by the discoverers. Indeed, an attempt by Leonard, Boyd and Herbrandson[8] to extend the Pfannstiehl–Janecke synthesis to other Bz-chlorocinnolines was not successful.[9]



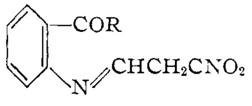
I



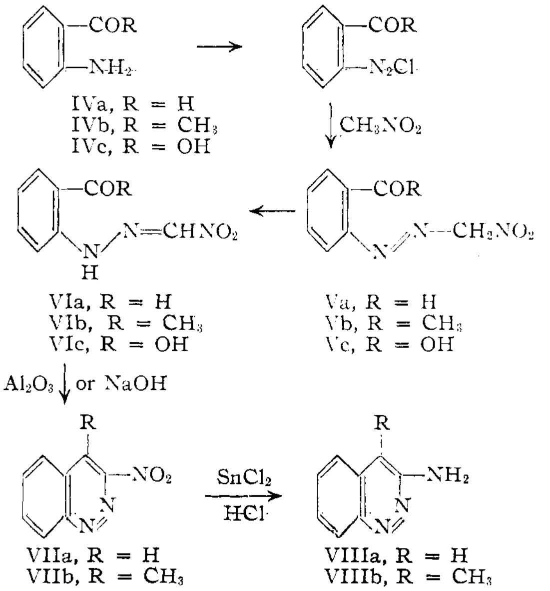
II

This communication reports the first applications of a new synthesis of 3-substituted-cinnolines.

The new synthesis, outlined in the flow sheet, will be seen to belong to the same general class of cinnoline syntheses as the two older methods described above. However, despite the apparent similarity to these procedures, the new method was first suggested to us by the work of Bachman, Welton, Jenkins and Christian[10,11] on the synthesis of 4-hydroxy-3-nitroquinoline by cyclization of N-(β-nitroethylidene)-anthranilic acid (IIIa) and by the first of an excellent series of papers by Schofield and Theobald[12] on the synthesis of various 3-nitrolepidines by cyclization of N-(β-nitroethylidene)-*o*-aminoacetophenones (IIIb). It seemed possible that the nitrogen analogs, nitroformaldehyde *o*-acetylphenylhydrazone (VIb) and *o*-carboxyphenylhydrazone (VIc) (or their azo tautomers, Vb and Vc), of IIIa and IIIb might cyclize to 4-hydroxy-3-nitrocinnoline and 4-methyl-3-nitrocinnoline (VIIb), respectively, under conditions similar to those used for the quinoline derivatives and that VIb and VIc might be prepared by the coupling of diazotized anthranilic acid (IVc) and



IIIa, R = OH
IIIb, R = CH₃



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[1] Samuel Avery Fellow, 1951–1953.

[2] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 512 (1945).

[3] N. J. Leonard, *Chem. Revs.*, **37**, 269 (1945).

[4] J. C. E. Simpson, "Heterocyclic Compounds, Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953.

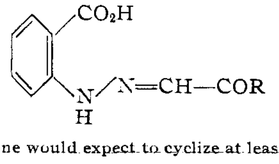
[5] This count includes the recent elaboration by E. J. Alford and K. Schofield (*J. Chem. Soc.*, 2102 (1952)) of the inaccessible and almost neglected syntheses of Bossel, Inaug.-Diss., Tubingen, May, 1925, p. 31 (*cf.*, P. W. Neber, G. Knoller, K. Herbst and A. Trissler, *Ann.*, **471**, 113 (1929)).

[6] R. Stolle and W. Becker, *Ber.*, **57**, 1123 (1924).

[7] K. Pfannstiehl and J. Janecke, *ibid.*, **75B**, 1096 (1942).

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

[9] Leonard, Boyd and Herbrandson attempted the cyclization of compounds of the type



XI

which *a priori* one would expect to cyclize at least as readily as II.

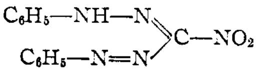
[10] G. B. Bachman, D. E. Welton, G. L. Jenkins and J. E. Christian, THIS JOURNAL, **69**, 365 (1947).

[11] See ref. 12 for a complete citation of other published work in this field.

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

o-aminoacetophenone (IVb) with nitromethane. The study was later expanded to include the cyclization of nitroformaldehyde *o*-formylphenylhydrazone (IVa) to 3-nitrocinnoline (VIIa).

The reaction of benzenediazonium halides with nitromethane has been said to give more than a dozen different products.[13] Under normal coupling conditions (cold, mildly alkaline) the principal product is said to be the dicoupled nitroformazyl (IX) although the monocoupled product, nitroformaldehyde phenylhydrazone (X), may be obtained in reasonable amount by following the excellent directions of Bamberger,[14] confirmed by us as a prelude to the preparation of V. The ultraviolet spectra of IX and X were determined and found to be, as expected, quite different and to be valuable adjuncts for the characterization of crude mixtures of mono- and/or dicoupled products obtained from the reaction of diazonium salts with nitromethane. The spectrum of X was quite similar in shape to those of other phenylhydrazones,[15a] resembling fairly closely the spectrum of *p*-nitrobenzaldehyde phenylhydrazone but shifted about 40 mμ away from the visible. The spectrum of IX was similar in shape to a number of curves obtained by Grammaticakis[15b] for formazans, $C_6H_5—N{=}N—C(R){=}N—NH—C_6H_5$, and especially to bis-phenylazophenylhydrazonomethane, $(C_6H_5—N{=}N)_2C{=}N—NH—C_6H_5$ (λ_{max} 450 (4.38), 338 (4.23) and 254 mμ (4.13) and λ_{min} 361 (4.17) and 288 mμ (3.79)), as may be seen by reference to Table I.



$$C_6H_5—NH—N{=}C(—NO_2)—N{=}N—C_6H_5$$

IX

$$C_6H_5—NH—N{=}CH—NO_2$$

X

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA IN 95% ETHANOL

Compound	λ_{max}, mμ	log ϵ_{max}	λ_{min}, mμ	log $\epsilon_{min.}$
IX[a]	446	4.35	363	3.80
	321	4.03	277	3.61
	256	3.83		
X[b]	390	4.21	300	3.18
	237	4.11		
VIa	392	4.05	294	3.36
	258	4.22	240	4.14
	232	4.19		
VIb	395	4.16	296	3.26
	230	4.26		
VIc	396	4.20	327	3.34
	257	4.04	243	3.93

[a] M.p. 154–155° (lit.[14] m.p. 152°). [b] M.p. 73–74° (lit.[14] m.p. 74.5–75.5°).

In dilute, neutral or weakly alkaline solution the coupling of diazotized IVc (or its methyl ester) gave yields of as high as 88% (95% for the ester) of a crude product which appeared to be largely VIc. This assignment of structure was based on elementary analysis and comparison of the ultraviolet spectrum of the product with that of X. A slight bathochromic shift in the maximum at 390 mμ (to 396 mμ) may be attributed to the carboxyl group of VIc.

In more concentrated solutions the coupling reaction gave rubbery, red, intractable solids, from which VIc could be isolated only with difficulty. In even weakly acidic solutions the yield of coupling product fell off considerably.

Although the diazotization of *o*-aminoacetophenone is followed by intramolecular cyclization to 4-hydroxycinnoline[2,16,17] (the Borsche synthesis), the latter is a relatively slow reaction. The intermolecular coupling of diazotized IVb with nitromethane proceeded rapidly to yield crude VIb in up to 98% yields. The characterization of VIb was based on its elementary analysis and its ultraviolet spectrum, which differed little from those of X or VIc.

Although the diazotization of *o*-aminobenzaldehyde (IVa)[18] and of 2-aminopiperonal[19] have been reported, neither of the procedures described in the literature gave satisfactory yields of VIa in the subsequent coupling step. The procedure of Schoutissen,[20] successful with *p*-aminobenzaldehyde, was not satisfactory for IVa. In our hands the most satisfactory yields of VIa (53–67%) were obtained when IVa was diazotized by the "nitrite paste" procedure of Erban and Mebus[21] and then coupled with nitromethane in the usual manner. The product was characterized as described above for VIb and VIc.

In the preparations of VIa, VIb and VIc only the monocoupled product was isolated in subsequent purification steps. Moreover, the ultraviolet spectra of the crude products, subjected only to air drying, differed very little from those of the analytically pure materials. There was little or no suggestion of a peak at or near 446 mμ which might indicate the presence of the nitroformazyl in the crude product. One explanation for the apparent preferential monocoupling in these experiments is that the *ortho* substituent in the products VI sterically inhibits the approach of a second diazotate ion. Such inhibition would be aided by dilution and by absence of an excess of the diazotate ion. In this connection it may be noted that Hubbard and Scott[22] have prepared a number of nitroformazyls with both electron-attracting and electron-releasing substituents on the phenyl rings. The only compound examined by them which failed to give the nitroformazyl was IVc. However, *o*-toluidine, the only other *ortho*-substituted aniline studied (and with a somewhat smaller *ortho* substituent), *did* give a nitroformazyl. This point is being studied further.

A considerable number of attempts were made to cyclize VIc (or its methyl ester) by treatment at various temperatures with acetic anhydride and

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[13] K. H. Saunders, "The Aromatic Diazo Compounds," Edward Arnold and Co., London, 1949, p. 217.

[14] E. Bamberger, O. Schmidt and H. Levenstein, *Ber.*, **33**, 2059 (1900); *cf.* E. C. S. Jones and J. Kenner, *J. Chem. Soc.*, 919 (1930).

[15] (a) P. Grammaticakis, *Bull. soc. chim. France*, 438 (1947); 965 (1951); (b) P. Grammaticakis, *Compt. rend.*, **225**, 684 (1947).

[16] W. Borsche and A. Herbert, *Ann.*, **546**, 293 (1941).

[17] N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, **11**, 419 (1946).

[18] T. S. Patterson, *J. Chem. Soc.*, **69**, 1002 (1896).

[19] A. Rilliet and L. Kreitmann, *Helv. Chim. Acta*, **4**, 588 (1921).

[20] H. A. J. Schoutissen, *Rec. trav. chim.*, **54**, 9 (1935).

[21] F. Erban and A. Mebus, *Chem. Z.*, **31**, 1101 (1907).

[22] D. M. Hubbard and E. W. Scott, THIS JOURNAL, **65**, 2390 (1943).

sodium or potassium acetate.[23] No cinnoline derivative has been isolated from among the several products obtained in small yields in these attempts.[24] Part of the failure of the reaction may be attributed to the decomposition of VIc in the reaction mixture (as evidenced by evolution of oxides of nitrogen) at temperatures well below those commonly used for the cyclization of IIIa.

When the methyl ester of VIc was dissolved in warm, dilute sodium hydroxide solution, it was rapidly hydrolyzed to VIc. Although this procedure proved to be the most satisfactory method for preparing VIc, no cinnoline was obtained in the reaction. Sodium methoxide in methanol likewise failed to cause the cyclization of the methyl ester of VIc.

When VIa was dissolved in dilute, aqueous sodium hydroxide and allowed to stand at room temperature, VIIa slowly precipitated from solution in 39% yield. Schofield and Theobald[12] have pointed out that the cyclization of IIIb competes with the hydrolytic cleavage of the molecule. As a means of reducing losses due to hydrolysis, Schofield and Theobald used activated aluminum oxide in acetone solution as a cyclizing agent. Application of this technique to VIa gave VIIa in 43% yield. Reduction of VIIa with stannous chloride and hydrochloric acid gave 3-aminocinnoline (VIIIa)[25] in 31% yield. The properties of VIIIa (including its ultraviolet spectrum) prepared in this way were essentially identical with those reported recently by Alford and Schofield[26] for VIIIa prepared by ammonolysis of 3-bromocinnoline.[27]

Cyclization of VIb by dissolution in dilute sodium hydroxide gave only a trace of VIIb. Cyclization in acetone solution over activated aluminum oxide yielded 59% of VIIb. Reduction of VIIb with stannous chloride in hydrochloric acid gave 4-methyl-3-aminocinnoline (VIIIb)[25] in 76% yield. Several attempts to hydrogenate VIIb over Raney nickel catalyst at room temperature yielded no VIIIb.

The success of the present cinnoline synthesis suggests that a re-examination of the ingenious but unsuccessful synthetic route of Leonard, Boyd and Herbrandson[8] (possibly with replacement of the carboxyl group in XI with formyl or acetyl) might be profitable. This re-examination as well as other apparent extensions of the method described here are under investigation.

Experimental

Nitroformaldehyde *o*-Formylphenylhydrazone (VIa).—A mixture of 4.3 g. (0.036 mole) of finely ground *o*-aminobenzaldehyde[28] and 2.45 g. (0.036 mole) of sodium nitrite was made into a slurry with a small amount of water. The slurry was added to a mixture of 6.25 ml. (0.075 mole) of concentrated hydrochloric acid and 10 g. of ice with vigorous stirring at 0°. Some orange resinous material separated during the diazotization. This was removed by suction filtration of the solution onto 15 g. of cracked ice. The resultant pale pink solution was poured into a solution of sodium isonitromethane which had been prepared by adding a solution of 2.17 g. (0.036 mole) of nitromethane in 5 ml. of ethanol to a mixture of 1.44 g. (0.036 mole) of sodium hydroxide, 20 ml. of water and 100 g. of cracked ice. A bright yellow-orange solid separated immediately from the reaction mixture. The air-dried crude material melted at 152–157°. The crude material was recrystallized from 50 ml. of acetone with very gentle warming on the steam-bath, giving 3 g. (57%) of fine orange needles, m.p. 160–160.5°, soluble in dioxane, pyridine and dilute alkali, less so in ethanol, acetone, insoluble in benzene and petroleum ether.

Anal. Calcd. for $C_8H_7N_3O_3$: C, 49.74; H, 3.66; N, 21.85. Found: C, 49.53; H, 3.80; N, 21.75.

In other experiments the yield varied from 53–63%. With much larger quantities than those indicated (up to 0.2 mole), diazotization of *o*-aminobenzaldehyde was carried out in a Waring blender or in several small portions which were combined after filtration. If the diazotization was carried out in the blender, the moist *o*-aminobenzaldehyde[28] obtained in the reduction of *o*-nitrobenzaldehyde could be used directly without drying. By this procedure the yield of nitroformaldehyde *o*-formylphenylhydrazone was 39–48%, *based on o-nitrobenzaldehyde.*

3-Nitrocinnoline (VIIa). (a).—To a solution of 0.59 g. (0.0122 mole) of sodium hydroxide in 30 ml. of water was added 2.35 g. of finely ground nitroformaldehyde *o*-formylphenylhydrazone. The solid dissolved giving a dark red solution which slowly deposited a pale tan solid. After the solution had stood two hours at room temperature, the product was collected by suction filtration, washed well with cold water and air dried. The yield of crude material was 0.94 g. (44%). The crude product was recrystallized from methanol (about 80 ml.), giving 0.83 g. (39%) of 3-nitrocinnoline as long, cream-colored needles, m.p. 205.5–206.5°.

(b).—To a solution of 3 g. of the crude nitroformaldehyde *o*-formylphenylhydrazone in 200 ml. of acetone was added 30 g. of activated aluminum oxide (Merck, chromatographic grade). The mixture was allowed to stand at room temperature for 36 hours. The alumina was removed by filtration and shaken with 200 ml. of acetone in several portions. The combined acetone solutions were evaporated under reduced pressure to a volume of about 75 ml. The solution was treated with a small amount of charcoal and filtered. The volume of the filtrate was reduced to about 20 ml. with gentle warming on the steam-bath. As the solution cooled, long, cream-colored needles separated, which were collected and washed with a small amount of cold ether. The yield of pure 3-nitrocinnoline, m.p. 205–205.5°, was 1.1 g. (43%).

Anal. Calcd. for $C_8H_5N_3O_2$: C, 54.86; H, 2.88; N, 23.99. Found: C, 55.09; H, 3.44; N, 24.43.

Use of ordinary untreated "ignited aluminum oxide" yielded only a trace of the 3-nitrocinnoline.

3-Aminocinnoline (VIIIa).—A solution of 4.3 g. (0.019 mole) of stannous chloride dihydrate in 4.5 ml. of concentrated hydrochloric acid was added to a suspension of 0.80 g. of 3-nitrocinnoline in 18 ml. of 6 *N* hydrochloric acid. The amine dissolved rapidly. The solution was heated for 15 minutes on the steam-bath, cooled in ice, and made alkaline with a cold solution of 20 g. of potassium hydroxide in 20 ml. of water. The mixture was filtered and both the solid and the filtrate were extracted with ether until the

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[23] Leonard, Boyd and Herbrandson[8] used heat or sulfuric acid plus heat in their attempted cyclizations of XI. The report of Bachman, *et al.*,[9] that the anhydride–acetate combination appears to be essential for the cyclization of IV seems to us to be quite logical and to be applicable also to VIc (and possibly to XI). Although Bachman cited no explanation for the requirement, it appears to us that the function of the anhydride is to convert the less reactive carboxyl group (with respect to the carbonyl portion of that group) into the more reactive mixed anhydride and that the function of the acetate is to promote the requisite ionization of the carbon atom alpha to the nitro group. That this combination is not invariably successful, however, is indicated not only by our own results but also by those of G. B. Bachman and D. E. Weldon (*J. Org. Chem.*, **12**, 208 (1947)), who were unable to cyclize 1-(N-*o*-carboxyphenylamino)-2-nitroalkanes with sodium acetate–acetic anhydride.

[24] As indicated in the Experimental section, one product may have been 1,2-diacetylindazolone, formed by cleavage of the phenylhydrazone, cyclization of the resultant *o*-carbomethoxyphenylhydrazine into indazolone and acetylation.

[25] The representation of VIIIa and VIIIb by the structural formulas in the flow sheet is not intended to indicate the fine structure of the 3-substituent.[26]

[26] E. J. Alford and K. Schofield, *J. Chem. Soc.*, 1811 (1953).

[27] The infrared spectrum also supports the assigned structure. This spectrum and the infrared spectra of other cinnoline derivatives will be reported later.

[28] L. I. Smith and J. W. Opie, *Org. Syntheses*, **28**, 11 (1948).

extracts were colorless. The ether was dried over potassium carbonate, filtered and evaporated to dryness under reduced pressure. The orange residue (0.49 g.) was recrystallized twice from benzene (using a small amount of charcoal), giving 0.20 g. (31%) of 3-aminocinnoline, m.p. 165–166° (lit.[26] m.p., 166–166.5°), as lustrous, bright yellow needles. A 1.00×10^{-5} *M* solution in 95% ethanol showed absorption maxima at 237 mμ (log ϵ_{max} 4.65) and 384 mμ (log ϵ_{max} 3.56), reported[26] maxima, 237 mμ (log ϵ_{max} 4.59) and 385 mμ (log ϵ_{max} 3.43). The considerable loss on recrystallization was due to the presence in the crude product of other reduction products or by-products which were removed in some experiments only by repeated recrystallization from benzene. In other experiments the yield of pure amine varied from 20–31%.

Nitroformaldehyde *o*-Acetylphenylhydrazone (VIb).—To a mixture of 4.2 ml. (0.05 mole) of concentrated hydrochloric acid, 10 ml. of water and 10 g. of ice cooled to 0° was added 8.76 g. (0.050 mole) of *o*-aminoacetophenone hydrochloride.[29] A solution of 3.50 g. of sodium nitrite in a minimum quantity of water was added to the solution dropwise with rapid stirring. Cracked ice was added as necessary to keep the temperature below 5°.

Meanwhile a solution of 3.06 g. (0.05 mole) of nitromethane in 10 ml. of ethanol was added to a solution of 2 g. (0.05 mole) of sodium hydroxide in 500 ml. of water and 200 g. of cracked ice. The diazonium solution was poured into the sodium isonitrosomethane solution and a yellow-orange solid began to precipitate immediately. The mixture was stirred for one hour and was filtered with suction. The product was washed well with water and allowed to air-dry. The crude condensation product, 10.2 g. (98%), melted at 145–154°. Five grams of the crude material was dissolved in 200 ml. of acetone with a minimum of warming on the steam-bath and filtered. From the cooled solution orange crystals of nitroformaldehyde *o*-acetylphenylhydrazone were collected, m.p. 169.5–170°.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.26; H, 4.87; N, 20.25.

In other experiments the yield of crude product varied from 74 to 98%, average yield, 90%. It was not necessary to purify the product before proceeding to the next step.

4-Methyl-3-nitrocinnoline (VIIb). (a).—To a solution of 1.0 g. (0.025 mole) of sodium hydroxide in 40 ml. of water was added with mechanical stirring 2.07 g. (0.01 mole) of finely pulverized, crude nitroformaldehyde *o*-acetylphenylhydrazone. The solid slowly dissolved giving a dark red solution, which was stirred at room temperature for two hours during which time the solution turned brown and a solid slowly separated from solution. The product was collected by suction filtration and was washed well with water. After air drying the crude brown material (0.85 g.) was extracted with ethanol (using charcoal), giving only a trace of 4-methyl-3-nitrocinnoline, m.p. 188–189°. The crude brown solid was not soluble in acetone, dilute hydrochloric acid or dilute sodium hydroxide. The nature of this material has not been determined.

(b).—To a solution of 16.8 g. (0.08 mole) of the crude nitroformaldehyde *o*-acetylphenylhydrazone in 1 l. of acetone was added 168 g. of activated aluminum oxide (Merck, chromatographic grade). The mixture was allowed to stand at room temperature for 60 hours. The alumina was removed by filtration and was shaken with ten 100-ml. portions of acetone. The combined acetone solutions were evaporated under diminished pressure at room temperature. The tan solid residue was recrystallized from ethanol (using charcoal), giving 9.0 g. (59%) of 4-methyl-3-nitrocinnoline, m.p. 188–189°, as lustrous brown needles, soluble in ethanol, acetone, ether and dilute acid but insoluble in water, dilute base and petroleum ether.

Anal. Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.22. Found: C, 57.37, 57.52; H, 4.29, 3.92; N, 21.65, 22.09.

3-Amino-4-methylcinnoline (VIIIb).—To a stirred suspension of 4.6 g. (0.025 mole) of 4-methyl-3-nitrocinnoline and 144 ml. of 6 *N* hydrochloric acid was added a solution of 24 g. (0.11 mole) of stannous chloride dihydrate in 24 ml. of concentrated hydrochloric acid. After addition was complete, the mixture, which had warmed spontaneously, was heated under reflux on the steam-bath for one hour. The cooled (in ice) reaction mixture was made strongly alkaline with 50% potassium hydroxide solution and was stirred until most of the tin salts had dissolved. The solid material was separated by filtration and both the solid and the filtrate were extracted with 100-ml. portions of ether until the ether was no longer colored. The combined extracts were dried over magnesium sulfate, the latter was removed by filtration and the ether was evaporated under reduced pressure. The residue (2.8 g. (76%), m.p. 158–159°) was recrystallized from benzene (in which it dissolves rather slowly) with little loss, giving pure 3-amino-4-methylcinnoline as bright yellow needles, m.p. 159.5–160°.

Anal. Calcd. for $C_9H_9N_3$: C, 67.92; H, 5.70; N, 26.40. Found: C, 67.99; H, 6.02; N, 26.29.

A 1×10^{-5} *M* solution of the product in 95% ethanol showed absorption maxima at 237 mμ (log ϵ_{max} 4.65) and 382 mμ (log ϵ_{max} 3.51).

Nitroformaldehyde *o*-Carboxyphenylhydrazone (VIc). (a) **From Anthranilic Acid.**—To a solution of 83 ml. (1.0 mole) of concentrated hydrochloric acid in 100 ml. of water was added 68.5 g. (0.5 mole) of anthranilic acid. The mixture was warmed on the steam-bath to ensure conversion of all of the anthranilic acid to the hydrochloride. The slurry was cooled to 0° and a solution of 35 g. (0.5 mole) of sodium nitrite in the minimum amount of water was added dropwise with stirring. Cracked ice was added as necessary to keep the temperature below 3°. The diazonium salt solution was added slowly, with stirring, to a mixture prepared by adding 30.5 g. (0.5 mole) of nitromethane in 50 ml. of ethanol to a solution of 20 g. (0.5 mole) of sodium hydroxide in 1 l. of water and 1 kg. of cracked ice. After addition was complete the mixture was stirred an additional hour. The orange precipitate was collected by filtration and air-dried overnight, giving 76 g. (73%) of crude nitroformaldehyde *o*-carboxyphenylhydrazone, m.p. 164–173° dec. Recrystallization of the crude material from ethylene dichloride gave a product melting at 177–178.5° dec. Although this material had ultraviolet and infrared spectra identical with those of the product described in (b) below, its melting point was not significantly raised on repeated recrystallization.

(b) **From Methyl Anthranilate.**—The procedure described in (a) was followed exactly except for the substitue tion of 71.5 g. (0.5 mole) of methyl anthranilate for the anthranilic acid. After air drying, 100 g. (95%) of crude orange-yellow **nitroformaldehyde *o*-carbomethoxyphenylhydrazone**, m.p. 95–102°, was obtained. After recrystallization from methanol, the product melted at 111–112°. The ultraviolet spectrum of the crude product was virtually identical with that of VIc (Table I).

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.07; N, 18.83. Found: C, 47.95; H, 3.81; N, 19.12.

The compound was dissolved in 2 *N* sodium hydroxide (a slight excess over the theoretical amount). Addition of 6 *N* hydrochloric acid (to congo red) precipitated a bright yellow solid, nitroformaldehyde *o*-carboxyphenylhydrazone, which was collected by filtration and air dried. The recovery was essentially quantitative. Recrystallization from ethylene dichloride several times gave bright yellow needles, m.p. 181.5° dec., recovery about 80%.

Anal. Calcd. for $C_8H_7N_3O_4$: C, 45.94; H, 3.98; N, 20.09. Found: C, 46.09, 45.69; H, 4.04, 3.96; N, 20.06.

Atempted Cyclization of Nitroformaldehyde *o*-Carbomethoxyphenylhydrazone. (a).—Crude nitroformaldehyde *o*-carbomethoxyphenylhydrazone (4.18 g., 0.02 mole) and 100 ml. of acetic anhydride were warmed with stirring to 60° and treated with 2 g. (0.02 mole) of fused potassium acetate. The solution, which became dark and warmed spontaneously to 78°, was kept at 80° for 1.5 hours. Most of the solvent was removed by distillation at reduced pressure. The residue was poured into approximately 150 ml. of water and warmed on the steam-bath until hydrolysis of the acetic anhydride was complete. After cooling, 3.45 g. of brown solid was isolated. The crude material was dissolved in ethanol, treated with charcoal and filtered. Water was added to incipient precipitation and the product was allowed to crystallize, giving 1.7 g. of soft white needles, m.p. 112.5–113.5°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.22, 60.56; H, 4.79, 4.81; N, 12.66.

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[29] G. T. Morgan and J. E. Moss, *J. Soc. Chem. Ind.*, **42**, 462T (1923).

The elementary analysis indicated that the product might be 1,2-diacetylindazolone; however, the latter has been reported[7] to melt at 135° (this m.p. was not supported by analytical or other data) and the N-acetyl value (calcd. for two N-acetyl units, 39.49; found,[30] 46.25) of the present compound deviated unsatisfactorily from the theoretical value.

(b).—Nitroformaldehyde *o*-carbomethoxyphenylhydrazone (2.23 g., 0.01 mole) and 50 ml. of acetic anhydride were warmed, with stirring, to 50° and treated with 1 g. (0.01 mole) of fused potassium acetate. The solution, which warmed slightly, was heated at 80° for two hours. Most of the solvent was removed by distillation under reduced pressure, the residue was poured into 50 ml. of water and the mixture was warmed on the steam-bath until hydrolysis of the acetic anhydride was complete. As the solution cooled, a brown solid separated (0.8 g.). The crude product was recrystallized twice from ethanol–water (using charcoal), giving 0.6 g. of a pale tan solid, m.p. 83.5–85°. The product was not soluble in dilute sodium hydroxide.

Anal.[31] Calcd. for $C_{10}H_8N_4O_4$: C, 48.39; H, 3.25; N, 22.58. Found: C, 48.51; H, 3.00; N, 22.66.

The compound had a rather complicated spectrum (in nujol mull), the principal peaks above 1250 cm.$^{-1}$ being: 3158 (m), 1738 (s), 1607 (m), 1587 (w), 1540 (s), 1500 (w), 1485 (m), 1443 (s), 1359 (s), 1301 (s), 1271 (s). The spectrum in carbon tetrachloride solution differed little from that in the nujol mull.[31] The nature of this compound was not determined, but it was not likely that it was the sought after 3-nitro-4-hydroxycinnoline.

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[30] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

[31] We are indebted to Prof. C. W. Rook for the determination of these spectra.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Terpenes. II. The Reactions of Carvone and Dihydrocarvone with Methanol in the Presence of Sulfuric Acid

BY G. BÜCHI AND ROBERT E. ERICKSON

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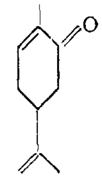
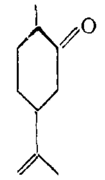
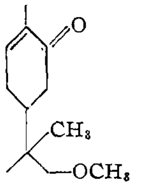
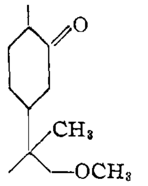
The reactions of carvone and dihydrocarvone with methanol in the presence of sulfuric acid have been reported to yield compounds III and IV, respectively. In the present investigation carvone has been shown to give V and VI. Similarly dihydrocarvone gives VII and VIII. No abnormal additions to the isopropenyl system are involved in these reactions.

The reactions of carvone (I) and dihydrocarvone (II) with methanol and sulfuric acid have been reported[1] to yield compounds III and IV, respectively. The present investigation was undertaken to clarify this novel addition of the elements of dimethyl ether to the isopropenyl double bond and to determine whether the reaction might be generally applicable. A repetition of the reactions reported by Treibs[1] yielded in both cases a mixture of compounds, none of which had properties in agreement with structures III and IV.

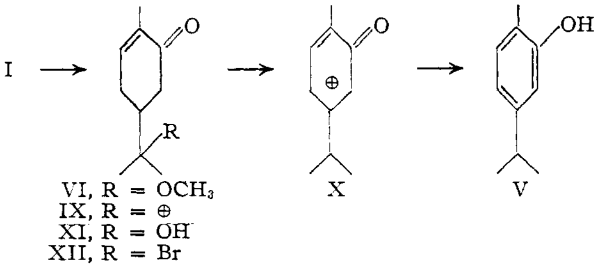

I


II

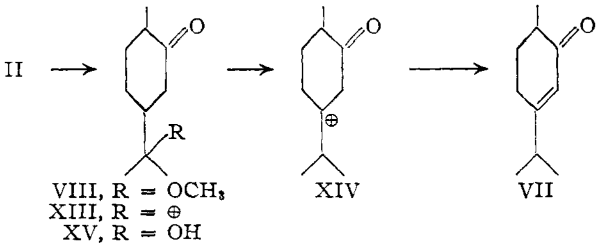

III


IV

The products from the reaction of carvone (I) with methanol were found to be carvacrol (V) and a methoxycarvotanacetone to which we have assigned structure VI. When dihydrocarvone (II) was allowed to react with methanol and sulfuric acid, carvenone (VII) and a methoxycarvomenthone (VIII) were formed. The following sequence of reactions appears to account satisfactorily for formation of the products found.



VI, R = OCH_3
IX, R = ⊕
XI, R = OH
XII, R = Br
X
V



VIII, R = OCH_3
XIII, R = ⊕
XV, R = OH
XIV
VII

The carbonium ion intermediate IX readily can rearrange to a new ion X as demonstrated by the ready isomerization of carvone (I) to carvacrol (V) under acidic conditions.[2,3] Either IX or X can react with methanol to yield the corresponding methyl ether. In view of the great tendency of X to lose a proton to form an aromatic ring the reaction of IX with methanol to give 8-methoxycarvotanacetone (VI) seems more probable. The optical activity of the product actually isolated provides further evidence for structure VI, because the corresponding compound derived from X should be optically inactive.

Analogous reactions of carvone with reagents other than methanol are known. The hydration of carvone (I) with dilute sulfuric acid has been

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[1] W. Treibs, *Ber.*, **70**, 384 (1937).

[2] H. Goldschmidt and E. Kisser, *ibid.*, **20**, 486 (1887).

[3] O. Wallach, *Ann.*, **305**, 237 (1899).