[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

CINNOLINES. III. ATTEMPTED SYNTHESES OF THE CINNOLINE NUCLEUS[1]

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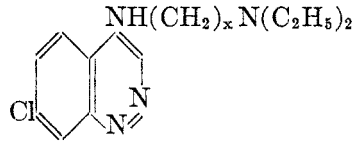
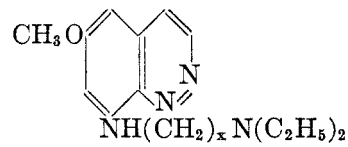
Received May 21, 1946

In the search for efficient methods of preparing potential antimalarial drugs (1, 2) of the 7-chloro-4-dialkylaminoalkylaminocinnoline (I) and 8-dialkylaminoalkylamino-6-methoxycinnoline (II) types, new methods of synthesis of the cinnoline nucleus were attempted.



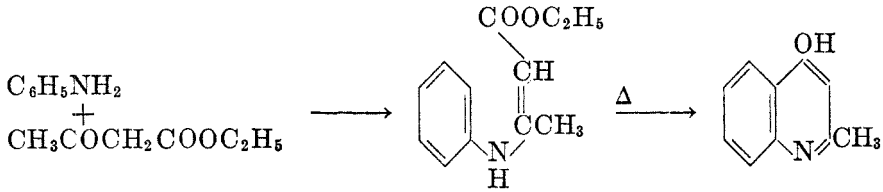
I



II

The limitations of existing methods have been reported recently (3). The development of new methods of ring closure for the cinnolines based upon cyclization procedures applied to the quinoline series appeared worthy of investigation. The results obtained indicate that in at least four different general types of ring closure, cinnolines were not formed from intermediates which were exact analogs of the precursors of quinolines.

Method A. Conrad and Limpach (4) found that aniline could be condensed with acetoacetic ester to form ethyl β-anilinocrotonate (III), which could be cyclized by various methods to form 4-hydroxyquinaldine (IV).



III IV

The same authors extended the reaction to other amines and other carbonyl compounds. In this laboratory, the scope of the reaction has been expanded

[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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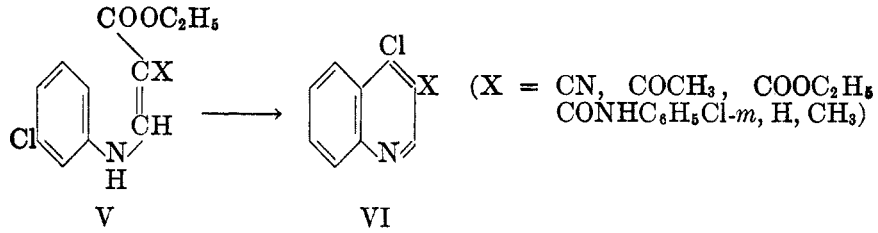
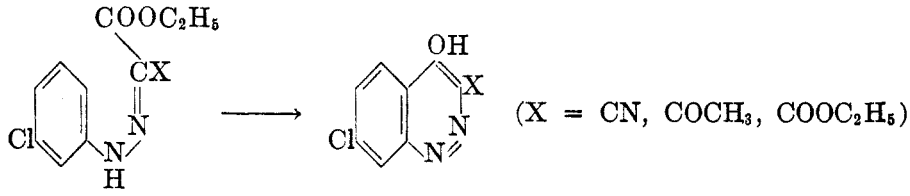
(V → VI) and it has been applied particularly to the synthesis of 7-chloro-4-hydroxyquinoline, intermediate in the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (5).



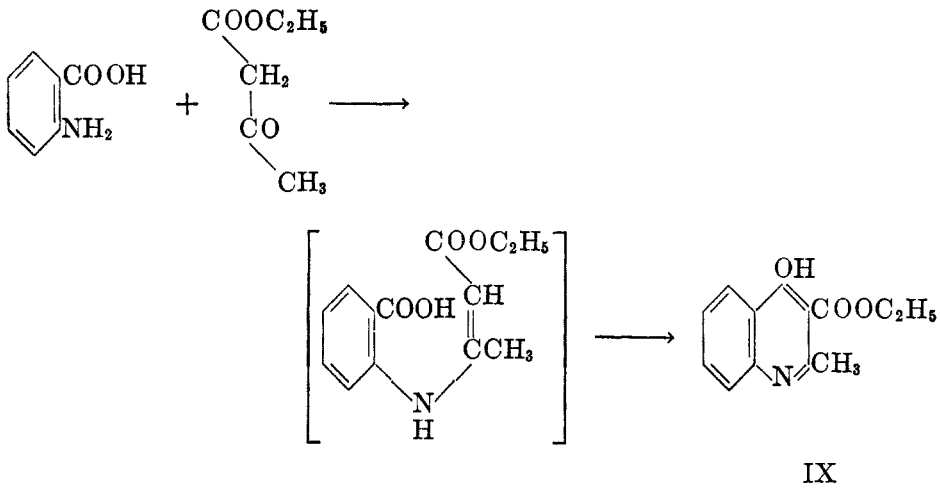
V VI



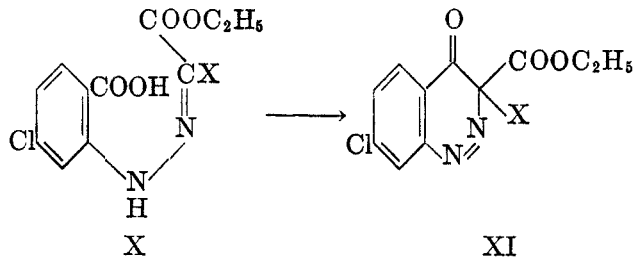
VII VIII

Similar treatment of *m*-chlorophenylhydrazones (VII) analogous to V might be expected to produce 7-chloro-4-hydroxycinnolines substituted in the 3-position (VIII). Accordingly, ethyl cyanoglyoxylate *m*-chlorophenylhydrazone (VII, X = CN), ethyl α,β-diketobutyrate α-*m*-chlorophenylhydrazone (VII, X = $COCH_3$), and diethyl mesoxalate *m*-chlorophenylhydrazone (VII, X = $COOC_2H_5$) were prepared by coupling diazotized *m*-chloroaniline with cyanoacetic ester, acetoacetic ester, and malonic ester, respectively. In an approach to compound II, diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone was prepared by coupling 4-methoxy-2-nitrobenzenediazonium chloride with malonic ester. No cinnoline formation was observed when these substituted phenylhydrazones were heated in an inert solvent. A wide range of temperature and length of heating time was employed; however, when extensive decomposition did not occur, only starting material was isolated. Since the predominating evidence favors the phenylhydrazone type of structure for these compounds rather than the tautomeric azo form (6), the coupling products are named on the basis of phenylhydrazones although no new evidence as to structure is presented at this time.

Method B. The second attempted cinnoline synthesis was suggested by the work of von Niementowski (7), who prepared substituted 4-hydroxyquinolines (IX) by the condensation of a carbonyl compound, such as acetoacetic ester, with an anthranilic acid. Thermal treatment of analogous 2-carboxy-5-chlorophenylhydrazones (X) might be expected to produce substituted 7-chlorocinnolines (XI).



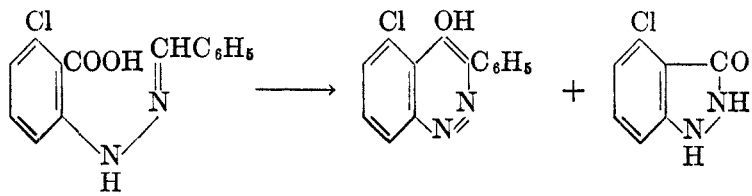
IX



X XI

(X = $COOC_2H_5$, $COCH_3$, H)

This method would be similar to that employed by Pfannstiel and Janecke (8), who heated benzaldehyde 2-carboxy-3-chlorophenylhydrazone (XII) to obtain 5-chloro-4-hydroxy-3-phenylcinnoline (XIII) in low yield, along with 4-chloro-indazolone (XIV).



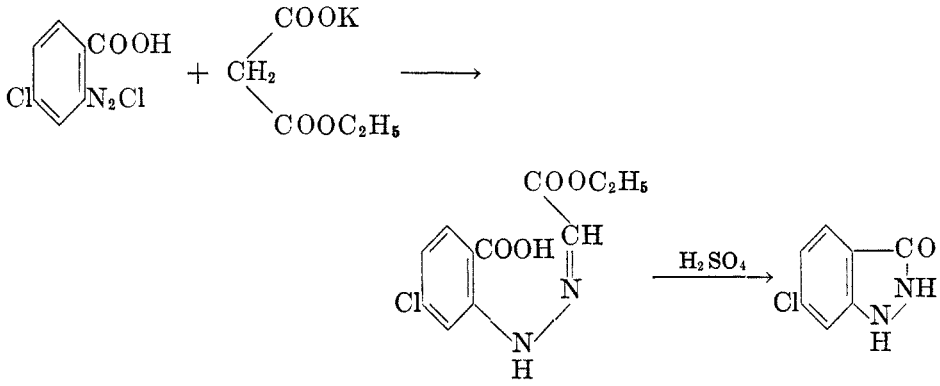
XII XIII XIV

Diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone (X, X = $COOC_2H_5$) and ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone (X, X = $COCH_3$) were prepared by coupling diazotized 2-amino-4-chlorobenzoic acid with malonic ester and acetoacetic ester. Neither compound could be induced to undergo cinnoline ring closure under thermal or acid treatment.

Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone (X, X = H) was

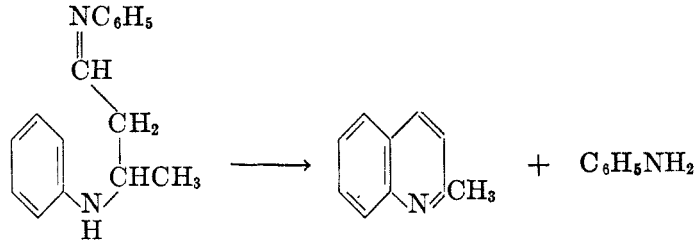
prepared by coupling diazotized 2-amino-4-chlorobenzoic acid with the monopotassium salt of ethyl hydrogen malonate. Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone was prepared in similar manner from diazotized 2-amino-5-chlorobenzoic acid. Diazotized 2-amino-3,5-diiodobenzoic acid behaved anomalously when treated with ethyl hydrogen malonate. The product isolated had the composition of 3,5-diiodobenzoic acid, and the melting point agreed with that reported by Wheeler and Liddle (9) for this diiodobenzoic acid.

When ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone and 2-carboxy-4-chlorophenylhydrazone were treated with concentrated sulfuric acid, cyclization occurred, but the products were not cinnolines. That 6-chloroindazolone (XV) and 5-chloroindazolone were the products of ring closure is indicated by the analytical data and is inferred from the course of the analogous cyclization by Pfannstiel and Janecke (8). These chloroindazolones have not been reported previously. Thermal treatment of ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone and 2-carboxy-4-chlorophenylhydrazone was ineffective in causing cyclization.



XV

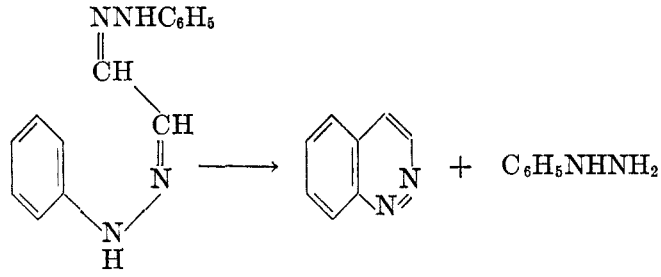
Method C. Evidence that ring closure in the Skraup reaction proceeds through elimination of a mole of aniline from the anil XVI (10) is found in the formation of quinaldine (XVII) rather than lepidine when crotonaldehyde is condensed with aniline.



XVI XVII

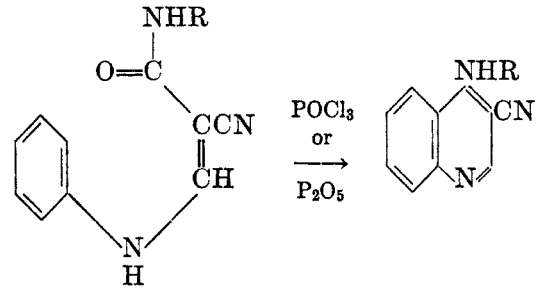
In order that a cinnoline be obtained through a reaction of this sort, it was proposed that glyoxal phenylosazone (XVIII) be used as the intermediate. Ring

closure in this case would lead directly to cinnoline (XIX) and, if successful, the reaction could be extended to appropriately substituted phenylosazones of glyoxal. The ring closures attempted with various acidic catalysts were uniformly unsuccessful. From the reactions using sulfuric acid, hydrochloric acid, and boron trifluoride diethyl etherate, the only product recovered was phenylhydrazine, identified through its explosive picrate. Only a small quantity of aniline was isolated as the picrate from the reaction of glyoxal phenylosazone with zinc chloride and hydrogen chloride in ethanol.

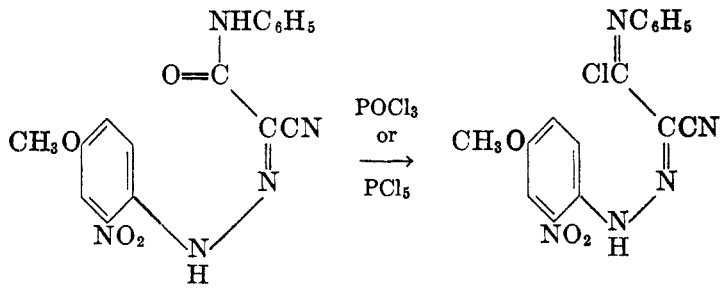


XVIII XIX

Method D. The ring closure of β-anilinoacrylamides (XX) with either phosphorus oxychloride or phosphorus pentoxide has been developed recently by Price and Boekelheide (11) as a route to the 4-aminoquinolines (XXI). α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone (XXII) was prepared readily by coupling diazotized 2-nitro-*p*-anisidine with cyanoacetanilide.



XX XXI



XXII XXIII

The attempted cyclization in benzene with phosphorus pentoxide under conditions which had been used for the preparation of the aminoquinolines furnished only tars from which about half of the unchanged amide was recovered. From refluxing phosphorus oxychloride or from refluxing benzene and phosphorus pentachloride, only the imidochloride (XXIII) could be isolated in good yield. Shah and Ichaporia (12) found that a Friedel-Crafts condensation of benzanilide imidochloride with dimethylaniline could be effected by the use of one mole of aluminum chloride. In an attempted ring closure of the 4-methoxy-2-nitrophenylhydrazone of cyanoglyoxanilide imidochloride (XXIII) with one and one-quarter moles of aluminum chloride in carbon disulfide, the imidochloride was recovered unchanged. With three moles of aluminum chloride in nitrobenzene at 73°, the imidochloride gave only resinous products.

EXPERIMENTAL[4]

Method A. m-Chlorobenzenediazonium chloride. *m*-Chloroaniline (114 g., 0.90 mole) was diazotized in the usual manner with nitrous acid in hydrochloric acid solution. Darco was added to the diazonium salt solution, which was stirred for ten minutes below 10° and filtered. The filtrate was divided into three equal portions.

Ethyl cyanoglyoxylate m-chlorophenylhydrazone. One-third of the above *m*-chlorobenzenediazonium chloride solution was added dropwise over a period of one hour to a well-stirred mixture of 33.9 g. (0.30 mole) of cyanoacetic ester in 300 cc. of water at 5–10°. Sodium carbonate (100 g.) was added in small portions to keep the reaction mixture alkaline to litmus. The reaction mixture was extracted with ether until the ether layer was no longer colored. The ether extracts were combined and dried over magnesium sulfate. The residue was recrystallized from ethanol as pale orange crystals, m.p. 89–90°, in a yield of 73 g. (97%). A sample recrystallized from ethanol for analysis melted at 91°.

Anal. Calc'd for $C_{11}H_{10}ClN_3O_2$: C, 52.49; H, 4.01.
Found: C, 52.49; H, 4.03.

Ethyl α,β-diketobutyrate α-m-chlorophenylhydrazone. This compound was prepared and isolated in the same manner as ethyl cyanoglyoxylate *m*-chlorophenylhydrazone. Thirty-nine grams (0.30 mole) of acetoacetic ester was substituted for the cyanoacetic ester. After recrystallization from ethanol, the compound formed fine yellow needles which melted at 86°. The yield was 63 g. (78.2%).

Anal. Calc'd for $C_{12}H_{13}ClN_2O_3$: C, 53.63; H, 4.88.
Found: C, 53.54; H, 4.85.

Diethyl mesoxalate m-chlorophenylhydrazone. This compound was prepared from 48 g. (0.30 mole) of malonic ester and isolated in the same manner as the above two *m*-chlorophenylhydrazones. Seventy grams (78.2%) of pale orange crystals was obtained, which melted at 56° after recrystallization from ethanol.

Anal. Calc'd for $C_{13}H_{15}ClN_2O_4$: C, 52.27; H, 5.06.
Found: C, 52.31; H, 5.20.

4-Methoxy-2-nitrobenzenediazonium chloride. A hot solution of 16.8 g. (0.1 mole) of 2-nitro-*p*-anisidine in 30 cc. of water and 21 cc. of concentrated hydrochloric acid was poured onto 30 g. of ice and cooled to 0–5°. An aqueous solution of 7.0 g. (0.1 mole) of sodium nitrite was added at once with vigorous stirring. After ten minutes the excess nitrous acid was destroyed with sulfamic acid and the solution was filtered.

Diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone. One-half of the above 4-methoxy-

[4] All melting points, unless otherwise specified, are corrected for both emergent stem and thermometer errors. Boiling points are not corrected. Microanalyses were performed by Miss Theta Spoor, Miss Lillian Hruda, and Mr. Howard Clark.

2-nitrobenzenediazonium chloride solution was added slowly with stirring to a solution of 8.0 g. (0.05 mole) of diethyl malonate and 7.0 g. of sodium acetate in 155 cc. of ethanol and 20 cc. of water. After an hour at ice-bath temperature, the suspension was allowed to come to room temperature and to stand overnight. After addition to 800 cc. of water, the coupled product was removed by filtration. The hydrazone crystallized as lustrous orange needles from benzene-petroleum ether or ethanol; m.p. 132–132.5°; yield, 8.0 g. (47%).

Anal. Calc'd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05.
Found: C, 49.94; H, 5.28.

The conditions employed for the unsuccessful thermal cyclization are summarized in Table I.

Method B. Diazotization of 2-amino-4-chlorobenzoic acid. 2-Amino-4-chlorobenzoic acid (10.9 g., 0.063 mole) was dissolved in 40 cc. of 2 *N* sodium hydroxide, and 12.7 cc. of a 5 *N* solution of sodium nitrite was added. The resulting solution was mixed thoroughly and added dropwise to a well-stirred mixture of 38 cc. of concentrated hydrochloric acid and 200 cc. of crushed ice. The system was immersed in an ice-salt bath, and the addition was carried out at such a rate that the temperature of the reaction mixture did not exceed 8°. The mixture was stirred for an additional hour below 8°. The excess nitrous acid was destroyed by the addition of urea, and the diazonium solution was divided into three equal parts.

TABLE I

ATTEMPTED CYCLIZATION OF SUBSTITUTED PHENYLHYDRAZONES
METHOD A

COMPOUND	AMOUNT, G.	SOLVENT	AMOUNT, CC.	TEMP.	TIME, HRS.
Ethyl cyanoglyoxylate *m*-chlorophenylhydrazone	15	$(C_6H_5)_2O$	500	Reflux	11[a,b]
Ethyl α,β-diketobutyrate α-*m*-chlorophenylhydrazone	10	$(C_6H_5)_2O$	50	230–240°	4
	15	$(C_6H_5)_2O$	500	Reflux	5[a]
Diethyl mesoxalate *m*-chlorophenylhydrazone	15	$(C_6H_5)_2O$	500	Reflux	11[a,b]
	15	*p*-Cymene	100	Reflux	21[a]
	10	Toluene	100	Reflux	42
	10	Tetralin	100	Reflux	22
Diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone	6	$(C_6H_5)_2O$	50	Reflux	3[a]

[a] Nitrogen stream bubbled through solution.

[b] The diphenyl ether solution was refluxed with aqueous 16% sodium hydroxide for 3 hrs. The aqueous layer was separated and rendered acid with hydrochloric acid. No precipitate resulted.

Diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone. One portion of the diazonium salt solution, which was prepared as described above, was added to a well-stirred mixture of 7 g. of malonic ester and 40 cc. of a saturated aqueous solution of sodium acetate. The mixture was stirred in an ice-bath for one and one-half hours and was then allowed to stand overnight at room temperature. The mixture was made strongly acid with concentrated hydrochloric acid. The precipitate was removed by filtration and washed with water until free from acid. The yield was 4.8 g. (67%) of fine white threads; m.p. 162–163°. A sample recyrstallized from ethanol for analysis melted at 163–164°.

Anal. Calc'd for $C_{14}H_{15}ClN_2O_6$: C, 49.06; H, 4.41; N, 8.18.
Found: C, 48.86; H, 4.69; N, 8.05.

Ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone. This compound was pre-

pared in the same manner, with the substitution of 6.0 g. of acetoacetic ester for the malonic ester. The product formed yellow threads, m.p. 228–229°, after recrystallization from ethanol; yield, 4.4 g. (67%).

Anal. Calc'd for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19; N, 8.96.
Found: C, 50.01; H, 4.34; N, 8.95.

Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone. This compound was prepared in the same manner as diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone. Seven grams of the monopotassium salt of ethyl hydrogen malonate, prepared by the method of Breslow, Baumgarten, and Hauser (13), was used in place of the malonic ester. The product separated as fine, white threads from ethanol; m.p. 212–213°; yield, 4.1 g. (72%).

Anal. Calc'd for $C_{11}H_{11}ClN_2O_4$: C, 48.81; H, 4.10; N, 10.35.
Found: C, 49.03; H, 4.02; N, 10.47.

Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone. Eight and six-tenths grams (0.05 mole) of 2-amino-5-chlorobenzoic acid (Eastman, technical grade) was diazotized in the same manner as 2-amino-4-chlorobenzoic acid. The diazonium salt solution was added to a cold solution of 13.0 g. of the monopotassium salt of ethyl hydrogen malonate and 13.0 g. of sodium acetate in 150 cc. of water, and the resulting mixture was stirred overnight. The reaction mixture was rendered distinctly acid by the addition of concentrated hydrochloric acid. The precipitate was removed by filtration and washed with water until free from acid. The product was recrystallized from ethanol as fine, white threads; m.p. 207–208°; yield, 7.0 g. (52%).

Anal. Calc'd for $C_{11}H_{11}ClN_2O_4$: C, 48.81; H, 4.10; N, 10.35.
Found: C, 49.06; H, 4.28; N, 10.36.

Attempted preparation of ethyl glyoxylate 2-carboxy-4,6-diiodophenylhydrazone. 3,5-Diiodobenzoic acid. To a solution of 19.5 g. (0.05 mole) of 2-amino-3,5-diiodobenzoic acid and 2.3 g. of sodium hydroxide in 230 cc. of water was added 10 cc. of a 5 *N* solution of sodium nitrite. The solution was kept warm to prevent precipitation of any solid and was added dropwise over a period of thirty minutes to a well-stirred mixture of 23 cc. of concentrated hydrochloric acid and ice. The temperature of the reaction mixture was maintained below 15° by an ice-salt bath. An excess of nitrous acid was maintained for one hour and then destroyed by the addition of urea. The diazonium solution was added to a cold solution of 13 g. of the monopotassium salt of ethyl hydrogen malonate and 13 g. of sodium acetate in 150 cc. of water. The reaction mixture was stirred overnight and then rendered strongly acid by the addition of hydrochloric acid. The precipitate was removed by filtration and washed with water until free from acid. After two recrystallizations from a mixture of ethanol, benzene, and petroleum ether (b.p. 90–110°), the product melted at 238° (uncor.) or 246° (cor.). The composition of the compound was suggestive of 3,5-diiodobenzoic acid, for which Wheeler and Liddle (9) have reported the melting point 235–236°. The yield was 9.0 g. (48%).

Anal. Calc'd for $C_7H_4I_2O_2$: C, 22.48; H, 1.08.
Found: C, 22.67; H, 1.38.

Action of sulfuric acid on the 2-carboxy-5-chloro- and 2-carboxy-4-chlorophenylhydrazones of ethyl glyoxylate. 6-Chloroindazolone. One gram of ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone was dissolved in 50 cc. of concentrated sulfuric acid. The resulting clear yellow solution was allowed to stand four hours at 25° and then poured onto ice. The clear aqueous solution was neutralized with ammonium hydroxide and cooled in an ice-bath. The fine, white crystals (*ca.* 0.5 g.) which separated were recrystallized from ethanol, m.p. 289°.

Anal. Calc'd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62.
Found: C, 49.87; H, 3.12; N, 16.31.

5-Chloroindazolone. This compound was obtained when ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone (1 g.) was treated in the same manner as is reported above. About 0.5 g. of fine, white needles, m.p. 275–276°, was obtained after recrystallization from ethanol.

Anal. Calc'd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62.
Found: C, 49.78; H, 3.03; N, 16.68.

Method D. α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone. A solution of 4-methoxy-2-nitrobenzenediazonium chloride from 33.6 g. (0.2 mole) of 2-nitro-*p*-anisidine was added slowly to 32 g. (0.2 mole) of cyanoacetanilide (14) in 1 liter of ethanol to which a saturated aqueous solution of 45 g. of sodium acetate had been added previously. The product of the coupling was removed by filtration, recrystallized from pyridine, and di-

TABLE II

ATTEMPTED CYCLIZATION OF SUBSTITUTED PHENYLHYDRAZONES
METHODS B, C, D

REACTANTS	SOLVENT	TIME, HRS.	TEMP., °C	PRODUCT
Method B				
Diethylmesoxalate 2-carboxy-5-chlorophenylhydrazone	H_2SO_4	12	25	No reaction
Ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone	H_2SO_4	12	25	No reaction
Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone	H_2SO_4	4	25	6-Chloroindazolone
	$(C_6H_5)_2O$	1.5	Reflux	Decomposition
	Tetralin	1.5	Reflux	No reaction
	p-Cymene	1.5	Reflux	No reaction
Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone	H_2SO_4	4	25	5-Chloroindazolone
Method C				
Glyoxal phenylosazone	H_2SO_4	24	25	Phenylhydrazine
	HCl	6	Reflux	Phenylhydrazine
	$BF_3 \cdot (C_2H_5)_2O$	3.5	Reflux	Phenylhydrazine
	$ZnCl_2$ + C_2H_5OH +HCl	1	Reflux	Aniline
Method D				
α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone + P_2O_5	C_6H_6	7	Reflux	No reaction
α-Cyanoglyoxanilide imidochloride 4-methoxy-2-nitrophenylhydrazone + AlC_3	CS_2	2	25	No reaction
	$C_6H_5NO_2$	1.5	75	Decomposition

gested with acetone to remove some of the color; yield, 38.5 g. (57%). Recrystallized from nitromethane and decolorized with activated charcoal, the compound was obtained as fine orange needles; m.p. 221–221.5°.

Anal. Calc'd for $C_{16}H_{13}N_5O_4$: C, 56.63; H, 3.86.
Found: C, 56.57; H, 4.12.

α-Cyanoglyoxanilide imidochloride 4-methoxy-2-nitrophenylhydrazone. Ten grams (0.029 mole) of the 4-methoxy-2-nitrophenylhydrazone of α-cyanoglyoxanilide and 9.3 g. (0.45 mole) of phosphorus pentachloride in 50 cc. of dry, thiophene-free benzene were refluxed for fifteen minutes, after which the evolution of hydrogen chloride ceased. The imidochloride separated from the cooled solution as orange needles and was removed by filtration

and washed well with petroleum ether (b.p. 90–110°). Nine and one-half grams (0.027 mole, 90%) of crude product melting at 178–180° was obtained. Recrystallization from nitromethane raised the melting point to 185–186°.

Anal. Calc'd for $C_{16}H_{12}ClN_5O_3$: C, 53.71; H, 3.38; Cl, 9.91; N, 19.58.
Found: C, 53.77; H, 3.51; Cl, 10.07; N, 19.31.

The imidochloride was not hydrolyzed by hot 5 *N* sodium hydroxide, but it dissolved readily in 5 *N* ethanolic sodium hydroxide solution. Acidification of the solution yielded a compound, m.p. 218–220°, which did not depress the melting point of the anilide.

SUMMARY

Substituted phenylhydrazones which were regarded as possible intermediates in the formation of cinnolines have been prepared by the coupling of diazonium salts with compounds containing an active methylene group.

Four general methods of ring closure used in quinoline formation have been applied to cinnoline formation without success. Indazolones were formed in one method.

URBANA, ILL.

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