water, and used for paper chromatography and radioactivity assay.

For the large-scale production of the urinary metabolites (in non-radioactive form), three rats were placed in metabolism cages and injected at 48-hour intervals with 1 ml. of vitamin A acetate (2.5 mg.) emulsion. Urine was collected under toluene and frozen daily. After 3 weeks, the collected urine was lyophilized and extracted with anhydrous butanol. The extract was reduced in volume and applied to the base-line of a 3-MM Whatman chromatographic paper. The bands were developed with butanol (Table IV). The marginal portion of the sheets was cut off and sprayed with dinitrophenylhydrazine reagent to locate the band of the metabolite (Table V). This band was then cut out, the metabolite eluted with water, ether-soluble material removed by ether extraction and the dinitrophenylhydrazone derivative prepared. After extraction into toluene, it was crystallized from ethanol. An aliquot of a solution of the *radioactive* dinitrophenylhydrazone of WS was added (15,868 counts per minute) prior to the first crystallization and recrystallization was carried out to constant specific activity. About one-half of the activity added (8,625 c./min.) remained in the mother liquor. The rest was crystallized, yielding a dark red solid, m.p. 182–186° (specific activity, 55 c./min./mg.); yield 108.8 mg.

Anal. Calcd. for $C_{17}H_{18}O_7N_4$: C, 52.4; H, 4.6; N, 14.4. Found: C, 53.0; H, 4.8; N, 14.5.

Upon saponification of this dinitrophenylhydrazone derivative, an acidic compound was obtained, soluble in alkali, insoluble in water, acid, ether and alcohol.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Reactions of Naphthoquinones with Malonic Ester and its Analogs. III. 1-Substituted Phthaloyl- and Phthaloylbenzopyrrocolines[1]

BY ERNEST F. PRATT, RIP G. RICE AND RAYMOND W. LUCKENBAUGH[2]

RECEIVED AUGUST 20, 1956

A variety of 1-substituted 2,3-phthaloylpyrrocolines (II to VI) have been prepared by the extension to other active methylene compounds of the previously reported condensation of acetoacetic ester with pyridine and 2,3-dichloro-1,4-naphthoquinone. The carbethoxy-, acetyl- and cyanopyrrocolines have been interrelated by conversion to the same acid or amide. Similarly substituted 2,3-phthaloyl-7,8-benzopyrrocolines (XIII to XXI) have been smoothly prepared by using isoquinoline in place of pyridine. The pyrrocoline structures have been confirmed by practical new syntheses of 1-acetyl- and 1-benzoyl-2,3-phthaloylpyrrocolines (II and III) from 2-acetonyl- or 2-phenacylpyridine and 2,3-dichloro-1,4-naphthoquinone. In the same way 1-acetyl-2,3-phthaloyl-5,6-benzopyrrocoline (XXIII) has been obtained from 2-acetonylquinoline.

In the preceding study of this series[3] it was found that acetoacetic ester reacted with 2,3-dichloro-1,4-naphthoquinone and pyridine to give a product for which the structure 1-carbethoxy-2,3-phthaloylpyrrocoline (I) was proposed. This reaction has now been extended to a number of analogs of acetoacetic ester. The active methylene compounds employed, the formulas of the products and the yields were as follows: acetylacetone, II, 58%; benzoylacetone, III, 10%; ethyl cyanoacetate, IV, 53%; methyl cyanoacetate, IV, 50%; phenylacetone, V, 17%; benzyl ethyl ketone, V, 1%; and nitroethane, VI, 23%. Compounds II,[4] IV[5] and V[5] were also obtained, in somewhat lower yields, from unsubstituted 1,4-naphthoquinone.

A 74% yield of the above cyanopyrrocoline (IV) resulted upon the treatment of ethyl (2-chloro-1,4-naphthoquinonyl-3)-cyanoacetate[6] with pyridine.[7] A by-product formulated as X on the basis of the results of ultimate analysis and the formation of a precipitate with aqueous silver nitrate was also isolated. Both this synthesis of the pyrrocoline and the formation of the by-product are consistent with the route of reaction previously proposed.[3] The same by-product was isolated in the synthesis of the cyanopyrrocoline from ethyl cyanoacetate and the dichloroquinone.

The hydroquinone diacetates of the cyano- and phenylpyrrocolines (IV and V) were readily prepared. By the Rast method, using camphor, the molecular weights of the acetylpyrrocoline (II) and the hydroquinone diacetate of IV were found to be 296 and 365 as compared to the calculated values of 289 and 358. The infrared absorption spectrum of the cyanopyrrocoline (IV) showed a peak at 2227 cm.$^{-1}$ indicating a cyano group conjugated with a carbon–carbon double bond.[8,9]

Upon treatment of this nitrile IV with sulfuric acid the amide VII was obtained. This crystallized as an allotropic form of the amide previously prepared[3] from the carbethoxypyrrocoline (I) *via* the acid (VIII), and the same acid was obtained from the acetyl analog II *via* the pyridinium iodide (IX).[10]

Compounds which on the basis of their melting points, elementary composition and color are identical with the carbethoxy- and acetylpyrrocolines (I and II) have been prepared in another laboratory from the dichloroquinone by essentially the same method, but the structures proposed in the initial independent reports were those of the ionic compounds Ia and IIa.[11] The results of quantitative analysis for hydrogen furnish significant support for the pyrrocoline structure since they contain two

(1) From the Ph.D. thesis of R. W. Luckenbaugh, May, 1952, and Rip G. Rice to be submitted in May, 1957.

(2) Research Corporation Fellow 1950–1951 and National Institutes of Health Fellow 1951–1952.

(3) E. F. Pratt, R. W. Luckenbaugh and R. L. Erickson, *J. Org. Chem.*, **19**, 176 (1954).

(4) It is a pleasure to acknowledge our indebtedness to Mr. Raymond L. Erickson, who carried out this experiment.

(5) It is a pleasure to acknowledge our indebtedness to Mr. Robert W. Storherr who carried out this experiment.

(6) Prepared by the method of C. Liebermann, *Ber.*, **32**, 916 (1899).

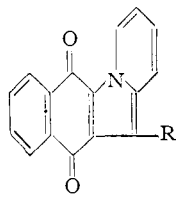
(7) Subsequent to the completion of this synthesis (ref. 12) closely related reactions were reported in ref. 11.

(8) R. E. Kitson and N. E. Griffith, *Anal. Chem.*, **24**, 334 (1952).

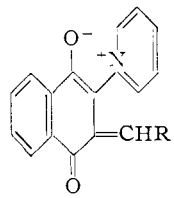
(9) We wish to thank Dr. Robert Spurr and his staff for the determination of the infrared absorption spectra.

(10) L. King, THIS JOURNAL, **66**, 894 (1944).

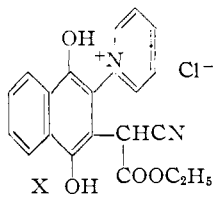
(11) B. Suryanarayana and B. D. Tilak, *Current Sci. (India)*, **22**, 171 (1953); *C. A.*, **48**, 14212 (1954); *Proc. Indian Acad. Sci.*, **39A**, 185 (1954); *C. A.*, **49**, 12411 (1955).



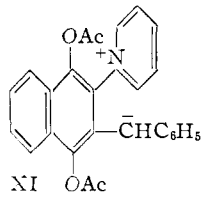
I, R = $COOC_2H_5$
II, R = $COCH_3$
III, R = COC_6H_5
IV, R = CN
V, R = C_6H_5
VI, R = CH_3
VII, R = $CONH_2$
VIII, R = COOH
IX, R = $COCH_2N^+C_5H_5I^-$



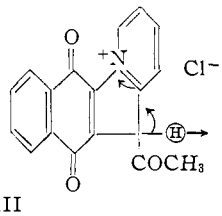
Ia, R = $COOC_2H_5$
IIa, R = $COCH_3$
Va, R = C_6H_5



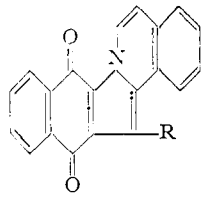
X



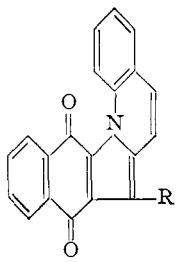
XI



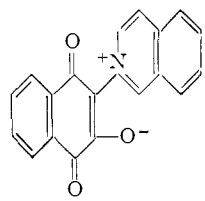
XII



XIII, R = $COOC_2H_5$
XIV, R = $COOCH_3$
XV, R = $COCH_3$
XVI, R = COC_6H_5
XVII, R = CN
XVIII, R = C_6H_5
XIX, R = CH_3
XX, R = H
XXI, R = C_2H_5



XXIII, R = $COCH_3$
XXIV, R = COOH
XXV, R = H



XXII

less hydrogen atoms and the total hydrogen content is unusually low. The products of reductive acetylation are readily formulated as diacetates of the pyrrocoline hydroquinones,[3,12] but a reasonable formulation on the basis of the ionic structures is often impossible; on this basis, for example, the product from the phenyl analog Va would be XI which contains a free carbanion. The ionic formulations recently have been withdrawn in favor of our pyrrocoline structures primarily on the basis that the product of decarboxylation of the acid (VIII) was identical with that isolated in about 1% yield from the reaction of 2,3-dichloro-1,4-naphthoquinone with a large excess of α-picoline.[13]

Further confirmation of the pyrrocoline structures has now been obtained by preparation of the acetyl and benzoyl analogs (II and III) from 2-acetonyl- and 2-phenacylpyridine with 2,3-dichloro-1,4-naphthoquinone. The results of melting point and mixture melting point determinations showed that identical products were obtained by the two routes. Since the yields were 40% or better the alternative route is of preparative value. It is suggested that an intermediate such as XII is formed by a route closely analogous to that proposed for the first steps of the earlier synthesis[3]; loss of the highly activated hydrogen as a proton followed by electron shifts as indicated in XII would give the acetylpyrrocoline (II).

When isoquinoline is used in place of pyridine together with 2,3-dichloro-1,4-naphthoquinone and an active methylene compound, the corresponding 1-substituted 2,3-phthaloyl-7,8-benzopyrrocolines are obtained.[14] The yields are in general superior to those obtained with pyridine and are especially satisfactory when it is considered that at least five successive reactions appear to be involved.[3] The active methylene compounds used, the formulas of the products and the yields were as follows: ethyl acetoacetate (XIII), 64%; ethyl benzoylacetate (XIII), 61%; methyl acetoacetate (XIV), 64%; acetylacetone (XV), 72%; benzoylacetone (XVI), 43%; ethyl cyanoacetate (XVII), 80%; methyl cyanoacetate (XVII), 72%; benzoylacetonitrile (XVII), 68%; phenylacetone (XVIII), 19%; nitroethane (XIX), 26%; and nitromethane (XX), 9%.

The results of mixture melting point determinations showed that the two carboalkoxyl analogs XIII and XIV were identical with those previously obtained from coal tar "quinoline" and which had been, therefore, formulated as 5,6-benzopyrrocolines.[3] Since it has now been found that synthetic quinoline gives no crystalline products under these conditions while synthetic isoquinoline does give the products in good yield, it is apparent that the isoquinoline impurity in the large excess of coal tar quinoline is the actual reactant and that the products should, therefore, be formulated as 1-carboalkoxy-7,8-benzopyrrocolines (XIII and XIV).

Most of the isoquinoline derivatives (XIII through XX) were also obtained in fair yields from coal tar "quinoline" and the reaction may well prove useful for removing isoquinoline from the coal tar product. With 1-nitropropane and coal tar "quinoline" a 29% yield of the ethylbenzopyrrocoline (XXI) was obtained while with isoquinoline a difficultly separable mixture of this product and the ionic by-product XXII apparently resulted. The only crystalline product isolated from the attempted reaction of dimethyl malonate, ethyl benzyl ketone or acetonitrile with the dichloroquinone and isoquinoline had the carbon, hydrogen and nitrogen content of the ionic by-product XXII, and the same compound was made directly from isoquinoline and the dichloroquinone in 77% yield. The pyridine analog is well known.[3,15]

The parent 2,3-phthaloyl-7,8-benzopyrrocoline

(12) R. W. Luckenbaugh, Ph.D. Thesis, Univ. of Maryland, May, 1952, pp. 34–44.

(13) R. V. Acharya, B. Suryanarayana and B. D. Tilak, *J. Sci. Indust. Res. (India)*, **14B**, 394 (1955); *C. A.*, **50**, 12971 (1956). The preparation of III from acetophenone or dibenzoylmethane is also described in this paper.

(14) The ordinarily safe assumption that the reaction occurs at the 1 and 2 rather than the 2 and 3 positions of the isoquinoline is made here.

(15) F. Ullman and M. Ettisch, *Ber.*, **54**, 259 (1921).

(XX) prepared from nitromethane as described above was obtained in better yield by decarbethoxylation of XIII. Reductive acetylation of both the phenyl- and the methylbenzopyrrocolines (XVIII and XIX) proceeded satisfactorily.

Pyrrocolines have now been prepared from thirteen active methylene compounds, and for ten of these there is general agreement on which of the two substituents on the active methylene group attracts electrons more strongly.[16] It is noteworthy that the results with methyl and ethyl cyanoacetates were exceptions to the otherwise consistently fulfilled expectation that the substituent which attracts electrons more strongly is cleaved from the active methylene group. It is also of interest that only the unsubstituted 2,3-phthaloyl-7,8-benzopyrrocoline (XX) was isolated from the reaction of nitromethane, although the 1-nitro analog would appear to have been an equally probable product.

Although, as already mentioned, quinoline did not react to give the 5,6-benzopyrrocolines, a compound which had the carbon, hydrogen and nitrogen content of the acetyl analog XXIII was obtained in 47% yield by an extension to 2-acetonylquinoline of the above described reaction of 2-acetonylpyridine. The acid (XXIV) was smoothly prepared *via* the pyridinium iodide[10] and decarboxylated to the parent 5,6-benzopyrrocoline (XXV).

Modification of a previously published synthesis of isoquinoline has significantly increased the yield.

Experimental[17]

1-Acetyl- and 1-Benzoyl-2,3-phthaloylpyrrocolines (II and III).—To a mixture of 0.5 g. of 2,3-dichloro-1,4-naphthoquinone and 4 ml. of acetylacetone in 25 ml. of absolute alcohol was added 7 ml. of pyridine. The resultant blue solution was heated under reflux for 4 hr. during which time it turned red-brown. Recrystallization from glacial acetic acid of the precipitate obtained upon cooling the reaction mixture in an ice-bath gave a 58% yield of red needles of **1-acetyl-2,3-phthaloylpyrrocoline** (II) which melted at 205–206°. *Anal.* Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.20; H, 3.86; N, 4.89.

Compound II also was obtained when a solution of 0.40 g. of 1,4-naphthoquinone, 6 ml. of pyridine and 2 drops of 6 *N* hydrochloric acid was treated at 45–50° with 1.2 ml. of acetylacetone.[4] The mixture was allowed to stand overnight in the refrigerator whereupon 0.22 g. of a red solid precipitated. Recrystallization from absolute alcohol and from dry benzene gave II as a red powder which melted at 205–206° both alone and when mixed with the product described in the preceding paragraph.

For the preparation of the acid VIII a mixture of 0.90 g. of II, 0.90 g. of iodine and 15 ml. of pyridine was heated on a water-bath for 1 hr. and allowed to stand overnight at room temperature.[10] The remaining pyridine was removed by distillation and the residue filtered off, washed with water, with ethanol and finally with ether. A 69% yield of the pyridinium salt intermediate IX was obtained as orange plates which melted at 258–259.5° dec. To this solid was added 30 ml. of water and 1.10 g. of sodium hydroxide, and the mixture was heated 2 hr. on the water-bath. The precipitate was filtered off and digested with glacial acetic acid. Recrystallization of the resultant solid from nitrobenzene followed by washing with alcohol and ether and drying under reduced pressure for 10 hr. at 118° gave 0.18 g. (27%) of **1-carboxy-2,3-phthaloylpyrrocoline** (VIII) as glistening maroon needles. These melted at 313.5–314.5° dec. both alone and when mixed with the acid previously obtained from the carbethoxy compound (I).[3] *Anal.* Calcd. for $C_{17}H_9NO_4$: C, 70.10; H, 3.12; N, 4.81. Found: C, 69.86; H, 3.56; N, 4.90.

When 0.70 g. of the solid benzoylacetone replaced the 4 ml. of acetylacetone in the above-described reaction with 2,3-dichloro-1,4-naphthoquinone, the desired **1-benzoyl-2,3-phthaloylpyrrocoline** (III) was obtained.[13] Recrystallization from glacial acetic acid gave a 10% yield of maroon needles which melted at 256–257.5° dec. *Anal.* Calcd. for $C_{23}H_{13}NO_3$: C, 78.62; H, 3.73; N, 3.99. Found: C, 78.30; H, 3.88; N, 4.17.

1-Cyano-2,3-phthaloylpyrrocoline (IV).—This compound was prepared from 2,3-dichloro-1,4-naphthoquinone exactly as described in the first paragraph of this Experimental except that 4 ml. of ethyl cyanoacetate replaced the 4 ml. of acetylacetone. Upon recrystallization from nitrobenzene a 53% yield of **1-cyano-2,3-phthaloylpyrrocoline** (IV) was obtained as orange needles which melted at 307.5–308.5°.

Concentration of the solution from which the crude solid cyanopyrrocoline (IV) had been filtered resulted in the separation of yellow crystals (0.22 g.) which were filtered off and washed with ether. The solid which showed some discoloration on standing melted at 278–279° dec. The results of elementary analysis indicated it was the hydroquinone X. *Anal.* Calcd. for $C_{20}H_{17}N_2O_4Cl$: C, 62.42; H, 4.45; N, 7.28; Cl, 9.21. Found: C, 62.59; H, 4.50; N, 7.39; Cl, 9.36. Upon recrystallization from glacial acetic acid one molecule of solvent per molecule of hydroquinone apparently entered the crystal, but the melting point was unchanged. *Anal.* Calcd. for $C_{20}H_{17}N_2O_4Cl \cdot C_2H_4O_2$: C, 59.39; H, 4.77; N, 6.30; Cl, 7.97. Found: C, 59.53; H, 4.66; N, 6.43; Cl, 7.96.

When 4 ml. of methyl cyanoacetate replaced the 4 ml. of ethyl cyanoacetate in the foregoing procedure, a 50% yield of the same product (IV) was obtained. It melted at 307.5–308.5° both alone and when mixed with the product previously obtained.

This cyanopyrrocoline (IV) also was obtained from the unsubstituted 1,4-naphthoquinone.[5] Three grams of the quinone was dissolved in 15 ml. of pyridine with gentle warming and 5.0 ml. of ethyl cyanoacetate was added. After several days at room temperature the precipitate was filtered off and recrystallized from pyridine. A 23% yield of orange needles (IV), which melted at 307.5–308.5° both alone and when mixed with the product described in the preceding paragraph, was obtained. *Anal.* Calcd. for $C_{17}H_8N_2O_2$: C, 74.99; H, 2.96; N, 10.29. Found: C, 75.00; H, 3.17; N, 10.47.

For the preparation of the amide VII a solution of 0.39 g. of the nitrile IV in 7 ml. of concentrated sulfuric acid was heated for 3 hr. at 130°. The red precipitate obtained upon pouring the violet solution onto cracked ice was filtered off, washed with water and with ethanol, treated with decolorizing carbon and recrystallized twice from 75 ml. of nitrobenzene. Fine, light orange needles of **1-carboxamido-2,3-phthaloylpyrrocoline** (VII), which melted at 313.5–314.5°, were obtained in 36% yield. A mixture with the lower melting amide (302°) previously obtained[3] from the carbethoxy compound I melted at 308–310°. *Anal.* Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.40; H, 3.61; N, 10.17.

When 0.30 g. of the high melting amide was heated at about 250° for 1 hr., it turned dark red. Recrystallization from 15 ml. of nitrobenzene gave 0.19 g. of maroon needles which melted at 302–303° both alone and when mixed with the low melting amide obtained from the carbethoxypyrrocoline (I) as previously described.[3] Upon recrystallization of this low melting amide from glacial acetic acid, light orange needles were obtained which melted at 313.5–314.5° both alone and when mixed with the high melting amide obtained as described in the preceding paragraph. The infrared[9] and ultraviolet absorption spectra of the low and high melting crystals were essentially identical.

Oxidation of the cyanopyrrocoline (IV) with nitric acid gave phthalic anhydride as previously described[3] for the carbethoxy analog I.

For the reductive acetylation a mixture of 0.50 g. of the nitrile IV and 20 ml. of 1:1 pyridine:acetic anhydride was heated to boiling to effect solution. One gram of zinc dust was added gradually over 0.5 hr., and refluxing was continued for an additional 0.5 hr. The yellow precipitate obtained upon pouring the solution into ice-water was

(16) E. F. Pratt and E. Werble, THIS JOURNAL, **72**, 4638 (1950); S. Hünig and O. Boes, *Ann.*, **579**, 41 (1953).

(17) All melting points are corrected. We are indebted to Professor Mary Aldridge and Miss Katherine Gerdeman for the analyses. Most of the analytical data are averages of duplicates.

filtered off, dried and extracted in a Soxhlet with absolute ethanol until the extract was a pale yellow. This extract was discarded and the extraction continued with 200 ml. of toluene until solution was complete. The precipitate which formed when the toluene solution was allowed to stand overnight was filtered off, washed with ethanol and dried. Upon dissolving the product in toluene, decolorizing with carbon and cooling 0.23 g. (35%) of the hydroquinone diacetate of IV was obtained. The yellow needles melted at 268–269° with sintering at 235°. *Anal.* Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.20; H, 4.09; N, 7.49.

When 0.30 g. of ethyl (2-chloro-1,4-naphthoquinonyl-3)-cyanoacetate,[6] 7 ml. of dry pyridine and 25 ml. of absolute ethanol was heated under reflux for 4 hr., 0.20 g. of the cyanopyrrocoline (IV) was obtained.[7] It melted at 307.5–308.5°, both alone and when mixed with the product obtained from the dichloroquinone as described above. Concentration of the filtrate gave 0.09 g. of yellow crystals which melted at 278–279° dec. both alone and when mixed with the hydroquinone by-product X previously obtained.

1-Phenyl-2,3-phthaloylpyrrocoline (V).—This was prepared as described in the first paragraph of this Experimental except that 4 ml. of phenylacetone replaced the acetylacetone and the reaction mixture was stirred during the refluxing. The mixture of deep red and light orange solids obtained (0.30 g.) was extracted in a Soxhlet with boiling water for 2 hr. Extraction of the residue with boiling absolute ethanol for 55 hr. and concentration of this extract gave 0.10 g. of deep red needles of the **1-phenyl-2,3-phthaloylpyrrocoline (V)** which melted at 244.5–245.5°. *Anal.* Calcd. for $C_{22}H_{13}NO_2$: C, 81.72; H, 4.05; N, 4.33. Found: C, 81.92; H, 4.02; N, 4.58. An additional 0.02 g. of V was obtained by extraction of the residue in the Soxhlet with acetone for 13 hr. Upon cooling the above aqueous extract, 0.09 g. (14%) of the hydrate of the pyridine analog of XXII was obtained. This was identified on the basis of its melting point and mixture melting point with the material previously obtained.[3]

When 4 ml. of benzyl ethyl ketone[18] was used in place of phenylacetone in the procedure of the preceding paragraph, the chief product was the pyridine analog of XXII which was obtained in a total yield of 67%. Addition of water to the filtrates which contained both petroleum ether and ethanol gave, after standing one week in the refrigerator, an estimated 0.01 g. of deep red needles which melted at 242–244° both alone and when mixed with the phenylpyrrocoline (V) prepared as above from phenylacetone.

This pyrrocoline (V) also was obtained from the unsubstituted 1,4-naphthoquinone.[5] A mixture of 1.0 g. of this quinone and 8 ml. of technical pyridine was warmed to 45°; 2 ml. of phenylacetone was then added with stirring, and the solution was allowed to stand at room temperature for one week. Fine red needles (0.25 g.) which melted at 243.5–244.5° both alone and when mixed with the above described product (V) from the dichloroquinone and phenylacetone were obtained.

For the reductive acetylation a solution of 0.30 g. of the phenylpyrrocoline (V) in 20 ml. of 1:1 pyridine:acetic anhydride was heated to boiling and 1.0 g. of zinc dust was added gradually over 15 minutes. After an additional 30 minutes of refluxing the mixture was poured into 200 ml. of water. The resulting red solid was filtered off, washed with water and recrystallized six times from absolute ethanol. A 29% yield (0.11 g.) of deep red prisms of the hydroquinone diacetate of V was obtained. They melted at 229–231° with previous softening. *Anal.* Calcd. for $C_{26}H_{19}NO_4$: C, 76.27; H, 4.68. Found: C, 76.41; H, 4.71.

1-Methyl-2,3-phthaloylpyrrocoline (VI).—When 7 ml. of pyridine replaced the isoquinoline in the procedure described in the following paragraph and nitroethane was the active methylene compound 0.44 g. of a mixture of orange and red needles was obtained. The residue remaining after extraction for 24 hr. in the Soxhlet with water was crystallized from ethyl acetate. A 23% yield (0.13 g.) of brilliant red needles (VI) which melted at 245.5–246.0° was obtained. *Anal.* Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.13; H, 4.22; N, 5.42. Evaporation of the aqueous extracts afforded a 43% yield of the pyridine analog of XXII.

(18) Prepared by method of H. B. Hass, A. G. Susie and R. L. Heider, *J. Org. Chem.*, **15**, 10 (1950).

Synthesis of 1-Substituted 2,3-Phthaloyl-7,8-benzopyrrocolines (XIII through XXI).—Unless otherwise noted the following procedure was used for the preparation of all the 7,8-benzopyrrocolines. To a mixture of 0.5 g. of 2,3-dichloro-1,4-naphthoquinone, 4 ml. of active methylene compound and 25 ml. of commercial absolute ethanol was added 7 ml. of isoquinoline. The mixture was heated under reflux 4 hr. while stirring magnetically. After cooling overnight in a refrigerator the solid was filtered off, washed with a little absolute ethanol, then with ether and recrystallized from the designated solvent. In all cases in which it is indicated below that a given pyrrocoline was obtained from coal tar isoquinoline or from coal tar "quinoline," as well as from synthetic isoquinoline, mixture melting points with material from the synthetic isoquinoline showed no depression.

Ethyl acetoacetate with synthetic isoquinoline gave, upon one recrystallization of the crude solid from 1-nitropropane, a 52% yield of **1-carbethoxy-2,3-phthaloyl-7,8-benzopyrrocoline (XIII)** which melted at 239.0–239.5°. Coal tar isoquinoline gave a 64% yield, m.p. 240.5–241.5°. The coal tar isoquinoline used here and elsewhere was Eastman Kodak Co. best grade which had been redistilled. With ethyl benzoylacetate and coal tar isoquinoline, the results of melting point and mixture melting point determinations showed that XIII was again obtained. The results of ultimate analyses of this and the following compound (XIV) were previously reported.[3]

Methyl acetoacetate and synthetic isoquinoline gave a 54% yield of **1-carbomethoxy-2,3-phthaloyl-7,8-benzopyrrocoline (XIV)** upon recrystallization of the crude material from 1-nitropropane, m.p. 246.5–247.5°. A 64% yield of XIV was similarly obtained from coal tar isoquinoline.

With acetylacetone and synthetic isoquinoline, there was obtained upon recrystallization of the crude solid from pyridine a 55% yield of **1-acetyl-2,3-phthaloyl-7,8-benzopyrrocoline (XV)** as orange needles which melted at 281–282°. With coal tar isoquinoline a 72% yield was obtained while coal tar "quinoline," with the same procedure except that stirring was omitted, gave a 57% yield of XV. The coal tar "quinoline" used here and elsewhere was redistilled Matheson best grade. *Anal.* Calcd. for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 78.05; H, 3.87; N, 4.12.

The yield of orange needles of **1-benzoyl-2,3-phthaloyl-7,8-benzopyrrocoline (XVI)** obtained upon one recrystallization from 1-nitropropane of the crude product from benzoylacetone and synthetic isoquinoline was 38%, m.p. 307.5–308.5°. With coal tar isoquinoline the yield was 43%. Since benzoylacetone is a solid, only 1.0 g. was used in place of the 4 ml. of liquid active methylene compound called for in the above standard procedure. *Anal.* Calcd. for $C_{27}H_{15}NO_3$: C, 80.78; H, 3.77; N, 3.49. Found: C, 80.61; H, 3.98; N, 3.72.

When ethyl cyanoacetate and coal tar isoquinoline were employed the yield of yellow needles of **1-cyano-2,3-phthaloyl-7,8-benzopyrrocoline (XVII)** was 80%. This material which was recrystallized from 9:1 1-nitropropane:nitrobenzene melted at 350.0–350.5°. According to the results of melting point and mixture melting point determinations, the same product (XVII) was obtained from methyl cyanoacetate, in 72% yield, and from benzoylacetonitrile in 68% yield. Only 1.0 g. of the solid benzoylacetonitrile was used under conditions otherwise standard. With coal tar "quinoline" (and no stirring) a 40% yield of XVII was obtained from ethyl cyanoacetate and a 27% yield from methyl cyanoacetate. *Anal.* Calcd. for $C_{21}H_{10}NO_2$: C, 78.25; H, 3.13; N, 8.68. Found: C, 77.85; H, 3.13; N, 8.80.

When the reaction with phenylacetone and coal tar isoquinoline was carried out in the standard fashion, the solid obtained was a mixture of orange needles and a deep yellow powder. This was extracted 50 hr. in a Soxhlet with 125 ml. of 95% ethanol. Upon chilling the extract 0.09 g. of solid was obtained which when added to the 0.01 g. of residue in the thimble and recrystallized from 1-nitropropane gave a 19% yield of **1-phenyl-2,3-phthaloyl-7,8-benzopyrrocoline (XVIII)** as red-orange needles which melted at 314.5–315.5°. *Anal.* Calcd. for $C_{26}H_{15}NO_2$: C, 83.63; H, 4.05; N, 3.75. Found: C, 83.80; H, 4.22; N, 4.02. From synthetic isoquinoline a 7% yield of XVIII was obtained while the yield from coal tar "quinoline" was 15%.

The 95% ethanol solution from which the above 0.09 g. of solid was filtered gave, upon evaporation to dryness, a solid

which was recrystallized three times from 1-nitropropane. The 0.12 g. of orange needles melted at 315.5–316.5°, and apparently they are a lower melting or slightly impure form of the ionic by-product XXII. Thus when mixed with XVIII the melting range was 291–303°, while a mixture with XXII (m.p. 323.0–323.5°), prepared as described below, melted at 316–323°.

The phenylbenzopyrrocoline (XVIII) was reductively acetylated to the corresponding hydroquinone diacetate exactly as described above for the phenylpyrrocline (V). From 0.30 g. of XVIII there was obtained after recrystallization from benzene a 51% yield of diacetate as yellow needles which melted at 256.0–257.5° dec. *Anal.* Calcd. for $C_{30}H_{21}NO_4$: C, 78.41; H, 4.61. Found: C, 78.30; H, 4.82.

When the reaction of nitroethane and coal tar isoquinoline was carried out in the standard fashion, a mixture of the desired pyrrocoline XIX and the by-product XXII was filtered from the chilled reaction mixture. This was extracted in a Soxhlet for 12 hr. with 95% ethanol. The small amount of red needles, obtained upon chilling the ethanol extract, was combined with undissolved material in the thimble and recrystallized from 1-nitropropane. A 26% yield of 1-**methyl-2,3-phthaloyl-7,8-benzopyrrocoline** (**XIX**) which melted at 292.5–293.0° was obtained. Evaporation of the ethanol filtrate gave a 36% yield of crude XXII. In the same way a 13% yield of XIX was obtained from synthetic isoquinoline. The best yield (45%) of this pyrrocoline (XIX) was obtained from coal tar "quinoline" and none of the by-product XXII was found. *Anal.* Calcd. for $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50. Found: C, 80.79; H, 4.24; N, 4.30.

For the reductive acetylation a solution of 0.26 g. of the methylpyrrocoline (XIX) in 20 ml. of 1:1 pyridine:acetic anhydride was heated to boiling; 1 g. of zinc dust was added over a period of 5 minutes. After an additional hour of refluxing, the reaction mixture was poured onto ice and water and the solid filtered off, washed well with water and recrystallized three times from ethyl acetate. A 6% yield of yellow needles which melted to a red liquid at 265.0–266.5° was obtained. *Anal.* Calcd. for $C_{25}H_{19}NO_4$: C, 75.55; H, 4.82; N, 3.53. Found: C, 75.43; H, 4.76; N, 3.69.

From 1-nitropropane and coal tar "quinoline" there was obtained, upon recrystallization from 1-nitropropane, a 29% yield of 1-**ethyl-2,3-phthaloyl-7,8-benzopyrrocoline** (**XXI**) as bright red needles which melted at 238.5–240.5°. Recrystallization from glacial acetic acid raised the melting point to 240.0–240.5°. *Anal.* Calcd. for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.43; H, 4.63; N, 4.16. With coal tar isoquinoline apparently a mixture of the ethylpyrrocoline (XXI) and the by-product XXII was obtained which did not separate satisfactorily when subjected to the Soxhlet extraction procedure.

When nitromethane was used with coal tar isoquinoline under the standard conditions, a mixture of crystals of the desired pyrrocoline (XX) and the by-product XXII was obtained. Upon digesting this 10 minutes with 20 ml. of 1:1 1-nitropropane:ethanol and cooling and filtering 0.06 g. (9%) of brick-red microneedles of **2,3-phthaloyl-7,8-benzopyrrocoline** (**XX**) was obtained. Further recrystallization from 1-nitropropane, then from pyridine and then from *p*-cymene raised the melting point from 293.5–294.5° to 295–296°. *Anal.* Calcd. for $C_{20}H_{11}NO_2$: C, 80.80; H, 3.73; N, 4.71. Found: C, 81.03; H, 3.75; N, 5.02.

When alkaline hydrolysis of the carbethoxy compound XIII was attempted, decarboxylation apparently occurred spontaneously to give the parent pyrrocoline (XX). A suspension of 1.16 g. of XIII in 65 ml. of boiling 95% ethanol was treated with a solution of 1 g. of sodium hydroxide in 30 ml. of 75% ethanol, and the mixture was heated to boiling for 10 minutes. Since no reaction was apparent, a solution of sodium ethoxide prepared from 40 ml. of absolute alcohol and 0.80 g. of sodium was added and the mixture heated under reflux for 5.5 hr. The solid obtained upon cooling and filtering the mixture was extracted with glacial acetic acid for 19 hr. in a Soxhlet. Upon cooling the extracts, 0.56 g. (60%) of compound XX which melted at 289.5–291.5° was obtained. Recrystallization three times from 1-nitropropane afforded 0.33 g. (36%) of brick-red needles which melted at 296–297° both alone and when mixed with compound XX prepared from nitromethane as described just above.

The by-product XXII encountered in several cases, as noted above, was also prepared under the standard conditions described for the 7,8-benzopyrrocolines except that the active methylene compound was omitted. From the coal tar isoquinoline there was obtained after recrystallization from 1-nitropropane a 77% yield of XXII. The orange needles melted at 323.0–323.5° dec. *Anal.* Calcd. for $C_{19}H_{11}NO_3$: C, 75.07; H, 3.62; N, 4.57. Found: C, 75.31; H, 3.82; N, 4.45.

Pyrrocolines (II, III and XV) from 2-Pyridyl and 2-Quinolinyl Ketones.—To a solution of sodium ethoxide prepared from 0.06 g. of sodium and 25 ml. of absolute alcohol was added, with stirring, 0.34 g. (1 mole) of 2-acetonylpyridine.[19] When solution was complete 0.57 g. (1 mole) of 2,3-dichloro-1,4-naphthoquinone was added, and the mixture was heated under reflux about 15 hr. with continued stirring. The solid obtained upon cooling and filtering the reaction mixture was washed with a little absolute alcohol and with ether. To remove sodium chloride the solid was heated with 1-nitropropane and the mixture filtered while hot. **The 1-acetyl-2,3-phthaloylpyrrocoline** (II), which was obtained as red crystals in 40% yield upon slow cooling of the filtrate, melted at 206–207° both alone and when mixed with the product obtained from acetylacetone as described above.

When 2-phenacylpyridine[20] replaced the 2-acetonylpyridine in the foregoing procedure, under conditions otherwise identical, 1-**benzoyl-2,3-phthaloylpyrrocoline** (III) was obtained. Recrystallization, as above, from 1-nitropropane gave a 44% yield of red needles which melted at 257.0–257.5° both alone and when mixed with the product III obtained from benzoylacetone as previously described.

Application of the foregoing procedure to 0.46 g. of 2-acetonylquinoline[20] except that 0.12 g. of sodium was used in place of the 0.06 g. gave upon filtration of the reaction mixture a solid which was freed from sodium chloride by dissolving in hot pyridine and filtering. Upon slow cooling 0.40 g. (47%) of 1-**acetyl-2,3-phthaloyl-5,6-benzopyrrocoline** (**XXIII**) was obtained as orange-red needles which melted at 278.5–279.0°. A mixture of this and the isomeric compound XV (m.p. 280°) melted at 245–258°. *Anal.* Calcd. for $C_{22}H_{13}NO_3$: C, 77.87; H, 3.86; N, 4.13. Found: C, 77.82; H, 3.75; N, 4.33.

For conversion to the acid XXIV, 0.50 g. of the acetyl compound XXIII, 20 ml. of pyridine and 0.50 g. of iodine was stirred and refluxed 1 hr.[10] The pyridine was removed under reduced pressure and the residue washed with a little 95% ethanol, then with water and finally with ether. The solid pyridinium salt intermediate weighed 1.01 g. and melted at 238–240° dec. A mixture of this with 1.20 g. of sodium hydroxide and 30 ml. of water was heated under reflux for 1.5 hr. The solid obtained upon cooling and filtering the mixture was heated with 25 ml. of glacial acetic acid on the steam-bath for 1 hr. and the solution poured onto ice-water. Upon filtering off the resulting solid and recrystallizing it from nitrobenzene, there was obtained 0.44 g. (87%) of 1-**carboxy-2,3-phthaloyl-5,6-benzopyrrocoline** (**XXIV**) as purple-brown needles which melted at 305.0–307.0°. Two recrystallizations from nitrobenzene raised the melting point to 310.5–311.5° and lowered the yield to 0.36 g. (72%). *Anal.* Calcd. for $C_{21}H_{11}NO_4$: C, 73.89; H, 3.25; N, 4.10. Found: C, 73.73; H, 3.18; N, 4.40.

When a mixture of 0.25 g. of this acid XXIV, 5 ml. of coal tar quinoline which had been purified *via* the zinc chloride double salt and 0.10 g. of precipitated copper[21] was boiled gently for 1 hr. and poured into 50 ml. of 6 *N* hydrochloric acid, decarboxylation occurred. Recrystallization from 1-nitropropane of the solid filtered from the cold reaction mixture gave 0.11 g. (51%) of **2,3-phthaloyl-5,6-benzopyrrocoline** (**XXV**), as reddish-brown needles which melted at 240.5–241.5°. *Anal.* Calcd. for $C_{20}H_{11}NO_2$: C, 80.80; H, 3.73; N, 4.71. Found: C, 80.90; H, 3.85; N, 5.04.

Improved Preparation of Isoquinoline.—The *N*-formyl derivative from 30.3 g. (0.25 mole) of β-phenylethylamine was prepared as per Decker[22] and without isolation stirred

(19) Prepared by method of N. N. Goldberg, L. B. Barkley and R. Levine, THIS JOURNAL, **73**, 4303 (1951).

(20) Prepared by the method of N. N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

(21) Prepared by the method of R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 446.

(22) H. Decker, *Ann.*, **395**, 286 (1913).

and heated 2 hr. at 160–180° with 175 g. of polyphosphoric acid.[23] Upon decomposition of the acid and isolation of the product as previously described,[24] except that retreatment of the acid-insoluble neutral component with more polyphosphoric acid was omitted, there was obtained 26.0 g. (79% over-all) of crude 3,4-dihydroisoquinoline which distilled at 64–67° (0.60 mm.), $n^{25}D$ 1.5793. A 31% yield of picrate was previously obtained with the polyphosphoric acid treatment at a somewhat lower temperature.[24]

The 26.0 g. of 3,4-dihydroisoquinoline was heated under reflux with 5.2 g. of 5% palladium–charcoal for 12 hr. The catalyst was filtered off, washed with ether, the ether volatilized from the filtrate and the residue distilled. A 72% yield (57% over-all, 18.35 g.) of crude isoquinoline was collected at 62–67° (0.85 mm.), $n^{25}D$ 1.6174. A similar yield was reported previously using equal weights of 3,4-dihydroisoquinoline and palladium dust.[25] Purification of the 18.35 g. of crude isoquinoline was accomplished by precipitation of the picrate from benzene solution, digestion of the solid with 4 l. of butanol and liberation of the free amine with 20% aqueous sodium hydroxide followed by distillation. A 32% over-all yield (10.43 g.) of pure isoquinoline with $n^{25}D$ 1.6208 (lit.[26] $n^{25}D$ 1.6208) was collected at 57–58° (0.60 mm.).

(23) Victor Chemical Works, Chicago, Ill.

(24) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2964 (1950).

(25) E. Späth, F. Berger and W. Kuntara, *Ber.*, **63**, 135 (1930).

(26) H. Frieser and N. L. Glowacki, THIS JOURNAL, **71**, 514 (1949).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Alkaloid Studies. XVI.[1] Alkaloids of *Rauwolfia tetraphylla* L. The Structures of Tetraphylline and Tetraphyllicine[2,3]

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From the root bark of the West Indian tree *Rauwolfia tetraphylla* L. there have been isolated the following alkaloids: reserpine, ajmaline, serpentinine, ψ-yohimbine, tetraphylline and tetraphyllicine. The last two alkaloids are new and evidence is presented for the structure assignment of these substances. Tetraphylline (I) is a stereoisomer of reserpinine and isoreserpinine and must differ from these two members of the ajmalicine group in the configuration of one or more of three centers (positions 15, 19 and 20) since destruction of the asymmetric center at C-3 does not yield identical derivatives. The structure of tetraphyllicine (X) follows from its conversion to desoxyajmaline upon hydrogenation and the isolation of acetaldehyde by ozonolysis, and it represents an interesting biogenetic intermediate in this class of alkaloids. Tetraphyllicine is identical with the hydrolysis product of rauvomitine thus proving the latter's constitution as tetraphyllicine trimethoxybenzoate (XI). A possible structure for ajmalidine (XII), an alkaloid isolated in trace amounts from *R. sellowii*, is presented. Some observations on serpentinine are also recorded in the Experimental portion of this paper.

In spite of the great number of *Rauwolfia* species growing on the American continent, relatively few have been studied chemically[4] and at the time that this investigation was initiated, the alkaloid composition of only one American *Rauwolfia* species, *R. heterophylla* Roem. and Schult. (synonymous[5] with *R. hirsuta* Jacq.) had been recorded.[6,7] Through the kind coöperation of Dr. Murrell P. Morris and Mr. Bartolome Cancel of the U. S. Department of Agriculture Experiment Station in Mayaguez, Puerto Rico, a considerable quantity of root bark of the West Indian *R. tetraphylla* L.[5] was secured and this was processed for alkaloids by substantially the scheme outlined earlier by Hochstein and collaborators.[7]

Reserpine was separated by virtue of the chloroform or benzene solubility of its acetate and could be isolated in *ca.* 0.09% yield by direct crystallization. Preliminary experiments indicated that fractionation[7] of the remaining alkaloids into medium and strong bases was of no advantage in this particular case and the total, reserpine-depleted bases were separated by a combination of chromatographic and counter-current distribution techniques. As described in detail in the Experimental portion of this paper, the principal alkaloids encountered were serpentinine (0.033%)[8] and two new bases which we named tetraphylline (0.024%) and tetraphyllicine (0.023%); trace quantities of ajmaline and ψ-yohimbine also were noted. The relevant experiments leading to the structure elucidation of these two alkaloids are described below.

Elementary analysis indicated the composition $C_{22}H_{28}N_2O_4$ for tetraphylline and this was confirmed by analysis of its nitrate and perchlorate salts. The presence of one C-methyl and two methoxyl groups was demonstrated by appropriate functional group analysis and since the infrared spectrum exhibited the typical bands at 5.92 and 6.17 μ of the —C—O—C=C—$COOCH_3$ grouping,[9] the nature of all four oxygen atoms is accounted for. The ultraviolet absorption spectrum[2a] of tetraphylline is completely superimposable upon that

(1) Paper XV, C. Djerassi, J. Herran, H. N. Khastgir, B. Riniker and J. Romo, *J. Org. Chem.*, **21**, 1510 (1956).

(2) Portions of this work have been reported in two preliminary communications: (a) C. Djerassi and J. Fishman, *Chemistry & Industry*, 627 (1955); (b) C. Djerassi, M. Gorman, S. C. Pakrashi and R. B. Woodward, THIS JOURNAL, **78**, 1259 (1956).

(3) Generous fellowship support was provided by grants from Chas. Pfizer and Co. (Brooklyn, N. Y.) and from the American Heart Association.

(4) These are listed by W. B. Mors, P. Zaltzman, J. J. Beereboom, S. C. Pakrashi and C. Djerassi, *Chemistry & Industry*, 173 (1956).

(5) R. E. Woodson, Jr., *North American Flora*, **29**, part 2 (1938).

(6) C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso, THIS JOURNAL, **76**, 4463 (1954).

(7) F. A. Hochstein, K. Murai and W. H. Boegemann, *ibid.*, **77**, 3551 (1955).

(8) *Cf.* E. Schlittler, H. U. Huber, F. E. Bader and H. Zahnd, *Helv. Chim. Acta*, **37**, 1912 (1954). For additional observations on serpentinine, see Experimental portion of present paper.

(9) *Cf.* F. E. Bader, *ibid.*, **36**, 215 (1953); M. M. Janot, R. Goutarel and J. Massonneau, *Compt. rend.*, **234**, 850 (1952).