[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS, OBERLIN COLLEGE, AND THE UNIVERSITY OF NORTH DAKOTA]

The Chemistry of Heterocyclic Quinones. I. The Direct Oxidation of 6-Hydroxycarbostyrils to Carbostyril-5,6-quinones

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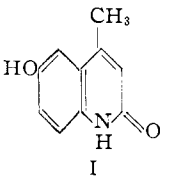
4-Methyl-6-hydroxycarbostyril is oxidized in good yield with chromic acid or lead tetraacetate to 4-methylcarbostyril-5,6-quinone. Dry hydrogen chloride adds to this substance with formation of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril. The latter forms a diacetyl derivative with acetic anhydride but a tribenzoyl derivative with benzoyl chloride in pyridine. Oxidation of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril with chromic acid leads to 4-methyl-8-chlorocarbostyril-5,6-quinone. The proof of structure of these substances by synthesis of an authentic sample of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril by an unequivocal method is described. 4-Methylcarbostyril-5,6-quinone is reduced catalytically to 4-methyl-5,6-dihydroxycarbostyril, but with aqueous sodium hydrosulfite the quinone gives water-soluble products. In contrast to β-naphthoquinone, which gives a 3-nitro derivative with concentrated nitric acid, 4-methylcarbostyril-5,6-quinone is unaffected by this reagent. The preparation of 6-hydroxycarbostyril (by a new method) and of 3-*n*-butyl-4-chloro-6-hydroxycarbostyril is described. Both of these substances are oxidized directly with chromic acid to carbostyril-5,6-quinones. The question of the correct choice between two possible tautomeric structures for the carbostyril quinones is discussed, and arguments based upon the color (bright red), infrared spectrum, and mode of addition of hydrogen chloride are presented, indicating that these substances are correctly formulated as carbostyril-5,6-quinones.

The quinoline quinones have recently become a focus of interest in the search for better antimalarial drugs. It now appears that the mechanism of action of the important 6-methoxy-8-aminoquinolines involves their *in vivo* conversion to quinoline-5,6-quinones.[2] The elegant work of Drake, *et al.*,[2a] has lent strong support to the theory[3] that it is these quinones which are responsible for the therapeutic action of the drugs.

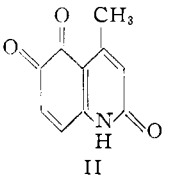
The 8-aminoquinolines, however, despite great therapeutic effectiveness, are toxic.[4] A clue as to a modification which might be made in these and similar drugs in order to lower their toxicity was supplied by the discovery[5] that rabbit liver detoxifies quinine *in vitro* by converting it into a substance which has been shown[6] to be the corresponding carbostyril.

It occurred to the present authors that the oxidative detoxication of quinine by rabbit liver far from indicating, as usually assumed,[7] the advantage of blocking[8] the 2-position of the quinoline antimalarials, might equally well be construed as an argument in favor of deliberately introducing an oxygen at this position. Specifically, it seemed possible that substances which were structurally related to the 8-aminoquinoline drugs and which were both quinoline quinones and carbostyrils might exhibit a desirable combination of low toxicity and high antimalarial activity. The present paper describes some preliminary experiments aimed at developing methods for the synthesis of such compounds.

No quinones derived from carbostyril have been reported in the literature. Indeed, very little is known of the chemistry of the simplest quinoline quinones.[9] A few examples of the direct oxidation of 6-hydroxyquinolines to 5,6-quinones have been reported,[9] but only one of them[2a] is described in sufficient detail to be of any practical value. We have found that 6-hydroxy-4-methylcarbostyril (I) may be directly oxidized to the corresponding 5,6-quinone (II) in good yield by action of either aqueous chromic acid or lead tetraacetate. The method is convenient and suitable for the preparation of the quinone in quantity.



I



II

The quinone II decomposed without melting at temperatures in the neighborhood of 180°. It was only slightly soluble in the common organic solvents, but could be recrystallized in small amounts from boiling glacial acetic acid. Prolonged boiling with this or higher boiling solvents destroyed it.

Curiously enough, the quinone was unaffected by concentrated (70%) nitric acid at room temperature. It dissolved readily and separated unchanged, in nicely crystalline condition, on diluting the solution with water. The stability of II to concentrated nitric acid is in marked contrast to the behavior of the naphthalene analog of II, 1,2-naphthoquinone (III), which[10] is rapidly attacked by concentrated nitric acid with formation of 3-nitro-1,2-naphthoquinone (IV). Apparently the formation of a positively-charged quinolinium ion in strongly acid solution effectively prevents the electrophilic attack of nitric acid on II.

Sodium hydrosulfite decolorized a suspension of

(1) Abstracted in part from the senior theses of James Conrady, James Guthrie and Robert McKay, Oberlin College, 1952.

(2) (a) N. L. Drake and Y. T. Pratt, THIS JOURNAL, **73**, 544 (1951); (b) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 198.

(3) F. Schonhofer, *Z. physiol. Chem.*, **274**, 1 (1942).

(4) L. H. Schmidt, in Wiselogle, "Survey of Antimalarial Drugs," Vol. I, Edwards Bros., Ann Arbor, Michigan, 1946, p. 106.

(5) F. E. Kelsey, E. M. K. Geiling, F. K. Oldham and E. H. Dearborn, *J. Pharmacol.*, **80**, 391 (1944).

(6) (a) J. F. Mead and J. B. Koepfli, *J. Biol. Chem.*, **154**, 507 (1944); (b) E. Ochiai, T. Okamoto and G. Kobayashi, *J. Pharm. Soc. Japan*, **68**, 109 (1948).

(7) M. M. Rapport, A. E. Senear, J. F. Mead and J. B. Koepfli, THIS JOURNAL, **68**, 2697 (1946).

(8) J. F. Mead, M. M. Rapport and J. B. Koepfli, *ibid.*, **68**, 2704 (1946); J. F. Mead, A. E. Senear and J. B. Koepfli, *ibid.*, **68**, 2708 (1946); R. F. Brown, *et al.*, *ibid.*, **68**, 2705 (1946); S. Winstein, *et al.*, *ibid.*, **68**, 2714 (1946); E. R. Buchman, *et al.*, *ibid.*, **68**, 2710 (1946); E. R. Buchman and D. R. Howton, *ibid.*, **68**, 2718 (1946).

(9) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 196.

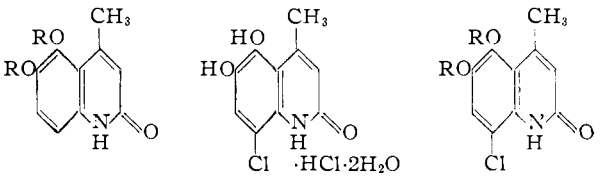
(10) Th. Zincke, *Ann.*, **268**, 260 (1892); L. F. Fieser and M. L. Ames, THIS JOURNAL, **49**, 2615 (1927).

II in aqueous alcohol at room temperature with formation of water-soluble products. This is in contrast to the behavior of 1,2-naphthoquinone, which[11] under these conditions is simply reduced to the hydroquinone. With concentrated aqueous ammonia II gave a green solution which rapidly darkened and deposited a purple solid. This behavior is reminiscent of the interesting but poorly understood phthaleoquin test[12] for quinine and certain of its derivatives. Indeed, the postulated[13] course of the phthaleoquin reaction involves intermediates of the 5,6-quinolinequinone type.

Attempts to reductively acetylate II with zinc dust and acetic anhydride led only to tars. However, an alcoholic suspension of the substance was readily hydrogenated in the presence of Adams platinum catalyst to the corresponding hydroquinone V. The latter formed an acetyl derivative VI which gave the correct analytical figures for a diacetyl derivative of V.

Hydroquinone V, with aqueous ammonia, gave the same color reactions as quinone II.

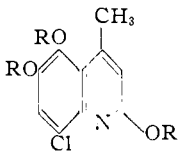
When dry hydrogen chloride was bubbled through a suspension of II in chloroform, a yellow substance, VII, was formed. This, after recrystallization from a boiling mixture of hydrochloric and acetic acids, proved to be a dihydrate of the hydrochloride of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril. Boiling water converted VII into the free base VIII, 4-methyl-5,6-dihydroxy-8-chlorocarbostyril. With hot acetic acid–acetic anhydride, VIII formed a diacetyl derivative IX; but with excess benzoyl chloride and pyridine, a tribenzoyl derivative X.



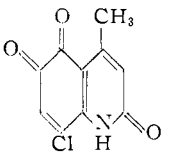
V, R = H
VI, R = CH_3CO

VII

VIII, R = H
IX, R = CH_3CO



X, R = C_6H_5CO



XI

On oxidation with chromic acid VIII gave rise to bright red crystals of 4-methyl-8-chlorocarbostyril-5,6-quinone (XI).

The structure of VIII, and therefore also the gross structure of quinones II and XI, was proven by synthesis of an authentic sample of VIII by the following unequivocal method.

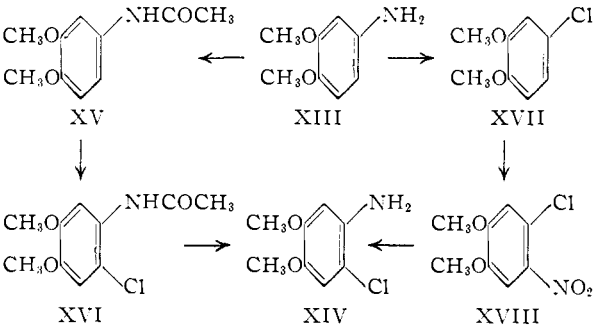
A search of the literature revealed that Seer and Karl[14] had obtained a chloroaminoveratrole melting at 72–73°, tentatively represented as 5(?)-chloro-4-aminoveratrole, by reduction of 4-nitroveratrole (XII) with tin and hydrochloric acid. No proof of structure was attempted.

Repetition of the work of Seer and Karl[14] led, in our hands, to a mixture of two amines, 4-aminoveratrole (XIII) and a chloroaminoveratrole (XIV) melting at 72–73°, presumably identical with the chloroaminoveratrole reported by Seer and Karl.

Direct chlorination of 4-acetaminoveratrole (XV) in chloroform solution at 5–10° led smoothly to 5-chloro-4-acetaminoveratrole (XVI) in over 90% yield. Hydrolysis of acetylamine XVI with boiling 10% sodium hydroxide led to a chloroaminoveratrole identical with XIV.

In order to establish unequivocally the position of the chlorine atom in XIV and XVI, 4-chloroveratrole (XVII) (prepared by diazotization of 4-aminoveratrole (XIII) and treatment of the diazonium salt with cuprous chloride) was nitrated, and the resulting nitro compound XVIII was reduced with zinc and acetic acid. The chloroaminoveratrole obtained in this way melted at 72–74° and was identical with the XIV obtained by the two methods already described.

Since the chlorine atom in the sample of XIV obtained by the last method was known to be in the 5-position; and since the amino group in the XIV obtained by the first two methods was known to be in the 4-position, it follows that XIV must be 5-chloro-4-aminoveratrole, as suggested by Seer and Karl.[14] It also follows that nitration of XVII produced 5-chloro-4-nitroveratrole (XVIII) as assumed by Bogert.[15,16]



Action of excess boiling acetoacetic ester on 5-chloro-4-aminoveratrole (XIV) gave (Limpach reaction)[17] acetoacet-(2-chloro-4,5-dimethoxy)-anilide (XIX).

When XIX was heated with concentrated sulfuric acid, in accordance with the directions usually recommended[18] for the cyclization of acetoacetanilides in the Knorr reaction, only water-soluble products resulted. Even the ten-minute heating period recommended by Michailov[19] and used

(11) L. F. Fieser and M. Fieser, THIS JOURNAL, **56**, 1575 (1934).

(12) G. W. Hargreaves, *J. Am. Pharm. Assoc.*, **15**, 100 (1926).

(13) H. Fuhner, *Arch. Pharm.*, **244**, 602 (1906); *Ber.*, **38**, 2713 (1905).

(14) C. Seer and E. Karl, *Monatsh.*, **34**, 631 (1913).

(15) C. A. Petscher and M. T. Bogert, *J. Org. Chem.*, **4**, 77 (1939).

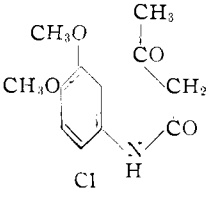
(16) Seer and Karl[14] prepared an iodochloroveratrole by diazotization of XIV and treatment of the resulting diazonium salt with potassium iodide. The iodo compound was tentatively assigned the structure 5(?)-chloro-4-iodoveratrole. From the latter a biphenyl, tentatively assigned the structure 6,6'(?)-dichloro-3,4,3',4'-tetramethoxybiphenyl, was obtained. In view of the experiments described above it is apparent that the structures assigned to these compounds were correct.

(17) L. Limpach, *Ber.*, **64**, 969 (1931).

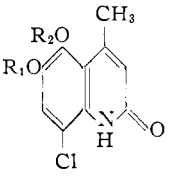
(18) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 32.

(19) G. I. Michailov, *J. Gen. Chem. (USSR)*, **6**, 511 (1936).

successfully by Bogert[20] in the cyclization of 2-nitro-3,4-dimethoxyacetoacetanilide, failed to give any of the expected 4-methyl-5,6-dimethoxy-8-chlorocarbostyril (XX). But when a solution of XIX in concentrated sulfuric acid was allowed to stand at room temperature for 36–72 hours, a mixture of the expected 4-methyl-5,6-dimethoxy-8-chlorocarbostyril (XX) and 4-methyl-5,6-dihydroxy-8-chlorocarbostyril (VIII) was formed. Curiously enough, no 5-hydroxy-6-methoxy-8-chlorocarbostyril (XXI) was found, although the crude reaction mixture was fractionally crystallized with some care.



XIX



VIII, $R_1 = R_2 = H$
XX, $R_1 = R_2 = CH_3$
XXI, $R_1 = CH_3$; $R_2 = H$

It is well-known that the methoxy group of a 5-methoxyquinoline is labile[21] but it is surprising that both 5- and 6-methoxy groups were cleaved during sulfuric acid cyclization of XIX under the relatively mild conditions (room temperature) used. Sulfuric acid cyclization of the similarly-constituted 4-methoxyacetoacetanilide under much more vigorous conditions (90–100° for four hours) gives 6-methoxycarbostyril in excellent yield,[22] with the 6-methoxy group intact.

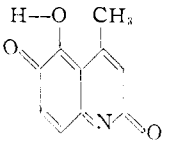
Many years ago Knorr[23] found that sulfuric acid cyclization of α-methylacetoacetanilide was best carried out at room temperature. Our experience with XIX indicates that this method of carrying out the Knorr reaction may be of some general value.

The acetyl and benzoyl derivatives of VIII prepared by cyclization of XIX were identical with the acetyl IX and benzoyl X derivatives of the VIII prepared by addition of hydrogen chloride to quinone II.

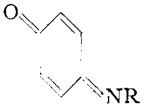
Thus the position of the chlorine atoms in VII, VIII, IX, X and XI, and the positions of the oxygen atoms in II, VII, VIII, IX, X and XI were established unequivocally.

Although the gross structure of quinone II was easily determined in this way, the choice between II and another—*a priori* equally probable—quinoid structure, IIa, tautomeric with II, was not easily made. Furthermore, the possibility of a rapid tautomeric conversion of one form to the other cannot be ignored; although in the related case involving 4-amino-1,2-naphthoquinone and its tautomer, 2-hydroxynaphthoquinoneimine,[24] Fieser has shown that the conversion of one form into the other is surprisingly difficult.

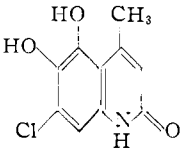
A clue to the correct formulation—II or IIa—may perhaps be found by considering the structure of VIII, the substance formed by addition of hydrogen chloride to II. Adams[25] has found that hydrogen chloride adds to quinone monoimides such as XXII with formation of chloro compounds having the chlorine atom *meta* to nitrogen, as in XXIII. Now a substance of structure IIa may be regarded as a quinone monoimide, and might then be expected, by analogy with the behavior of



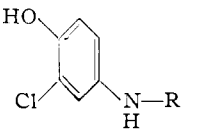
II-a



XXII



XXIV



XXIII

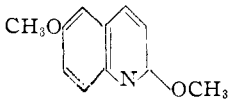
XXII,[25] to add hydrogen chloride in such a way as to produce a 7-chloroquinoline (XXIV). That VIII, rather than XXIV, is the product actually obtained is an indication—though no more than an indication—that structure II rather than IIa, is correct.

It is well-known[26] that in the naphthalene series the *o*-quinones are red and the *p*-quinones yellow. In the solid state and in solution, both II and its 8-chloro derivative XI, are red. This observation also indicates that II is the correct structure. Finally, the infrared spectrum of II showed no band in the region characteristic of the –OH group, and this observation again supports II as the tautomer best representing the structure of the quinone.

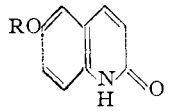
In order to explore further the direct oxidation of 6-hydroxycarbostyrils to carbostyril-5,6-quinones, 6-hydroxycarbostyril itself (XXV) was synthesized. The substance has been reported by Gattermann[27] as the product of electrolytic reduction of *o*-nitrocinnamic acid, and by Sahashi[28] and Gulland[29] as the product of decarboxylation of the corresponding 4-carboxylic acid. It was described by Sahashi as yellow needles melting at 310°, and by Gulland and Peters as white platelets melting "above 300°." In the present work the pure substance was obtained as white needles melting at 337–339° by another method, starting with the N-oxide[30] of 6-methoxyquinoline. This was converted to a mixture of 2- and 4-chloro-6-methoxyquinolines by the method of Bachman,[31] and the 2-chloro isomer with sodium methoxide in dry methanol gave rise in excellent yield to 2,6-dimethoxyquinoline (XXVI), which was selectively hydrolyzed by means of boiling 6 *N* hydrochloric acid

(20) K. C. Frisch and M. T. Bogert, *J. Org. Chem.*, **9**, 349 (1944).
(21) Reference 18, p. 6; R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).
(22) K. N. Campbell, *et al.*, *J. Org. Chem.*, **11**, 803 (1946).
(23) L. Knorr, *Ann.*, **245**, 358 (1888).
(24) L. F. Fieser and M. Fieser, THIS JOURNAL, **56**, 1565 (1934).
(25) R. Adams and J. H. Looker, *ibid.*, **73**, 1145 (1952).
(26) S. C. Hooker and A. Steyermark, *ibid.*, **58**, 1202 (1936); L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath and Co., Boston, 1944, p. 724.
(27) L. Gattermann, *Ber.*, **27**, 1936 (1894).
(28) Y. Sahashi, *Biochem. Z.*, **189**, 208 (1927); **168**, 69 (1926).
(29) J. M. Gulland, R. A. Peters, *Biochem. J.*, **23**, 1124 (1929).
(30) O. Magidson, *J. Gen. Chem. (USSR)*, **7**, 1896 (1937).
(31) G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, **9**, 302 (1944).

to 6-methoxycarbostyril (XXVII). Attempts to convert 2-chloro-6-methoxyquinoline directly to XXVII by action of hot 6 *N* hydrochloric acid were not entirely successful. A mixture of products, containing only a little XXVII, was formed.



XXVI

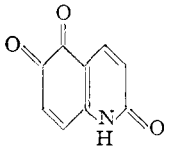


XXVII, R = CH_3
XXV, R = H

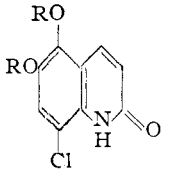
Methoxy compound XXVII was then cleaved by 48% hydrobromic acid to the desired 6-hydroxycarbostyril (XXV).

An attempt to convert the N-oxide of 6-methoxyquinoline directly to 6-methoxycarbostyril (XXVII) by action of benzoyl chloride and alkali, a method found by Henze[32] and by the present authors[33] to be effective for the conversion of quinoline-N-oxide to carbostyril, failed completely. No 6-methoxycarbostyril was obtained, but instead, a high-melting, alkali-insoluble substance (XXVIII) whose analysis corresponded to the empirical formula $C_{24}H_{19}NO_5$. A detailed account of the nature of substance XXVIII will be the subject of a future communication.

On shaking a suspension of 6-hydroxycarbostyril (XXV) in aqueous sulfuric acid with chromic acid, the substance dissolved, and after a few moments the solution began depositing red platelets of a quinone, formulated by analogy with the 4-methyl compound previously described, as carbostyril-5,6-quinone (XXIX).



XXIX



XXX, R = H
XXXI, R = CH_3CO

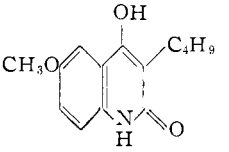
The quinone, obtained in about 50% yield, was quite insoluble and sensitive to the action of hot solvents. It was therefore difficult to recrystallize, although small amounts could be recrystallized (unsatisfactorily) from hot acetic acid, from which it separated as red platelets very similar in appearance to crystals of the 4-methyl analog, II. Like II, XXIX had no melting point, and was rapidly reduced by aqueous-alcoholic sodium hydrosulfite in the cold to colorless, soluble products.

Dry hydrogen chloride in chloroform decolorized XXIX rapidly with formation of the hydrochloride of 5,6-dihydroxy-8-chlorocarbostyril. The free base XXX, high-melting and insoluble, was liberated on treatment with water. The substance XXX formed a diacetyl derivative XXXI on treatment with acetic anhydride in acetic acid.

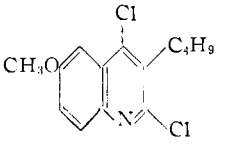
The synthesis of a more complex hydroxycarbostyril, 3-*n*-butyl-4-chloro-6-hydroxycarbostyril (XXXII), was effected starting with the thermal condensation (boiling Dowtherm A) of *n*-butylmalonic ester and *p*-anisidine, an example of the convenient synthesis of 3-substituted-4-hydroxycarbostyrils developed by Baker, Lappin and Riegel.[34] The resulting 3-*n*-butyl-4-hydroxy-6-methoxycarbostyril (XXXIII), obtained in 90% yield, was smoothly converted to 2,4-dichloro-3-*n*-butyl-6-methoxyquinoline (XXXIV) by the action of phosphorus oxychloride.

On boiling with 6 *N* hydrochloric acid compound XXXIV gave rise to 3-*n*-butyl-4-chloro-6-methoxycarbostyril (XXXV) in good yield. The selective hydrolysis of the 2-chlorine in XXXIV is of considerable interest in that it extends the observations of Lutz[35] and of Buchman and Hamilton[36] on the difference in reactivity of the chlorine atoms in 2,4-dichloroquinolines.

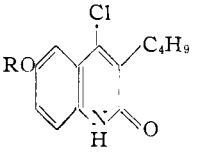
The inertness of the chlorine atom in 4-chlorocarbostyril XXXV was strikingly demonstrated by its resistance to the action of boiling 48% hydrobromic acid. Although XXXV was boiled for 48 hours with this reagent the product was 3-*n*-butyl-4-chloro-6-hydroxycarbostyril (XXXII), with the chlorine atom still intact.



XXXIII

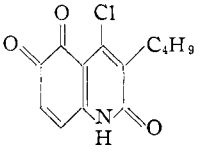


XXXIV

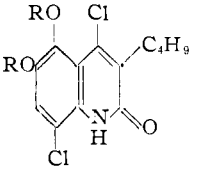


XXXV, R = CH_3
XXXII, R = H

Hydroxycarbostyril XXXII, like its analogs, was oxidized by chromic acid to a quinone XXXVI, formulated by analogy with simpler compounds previously described, as 3-*n*-butyl-4-chlorocarbostyril-5,6-quinone. The substance had no melting point, but decomposed without melting at temperatures above about 180°. It was easily reduced in the cold by aqueous alcoholic sodium hydrosulfite to colorless, soluble products, and gave the same green color reaction with ammonia as did other quinones of this type. Dry hydrogen chloride in chloroform added to XXXVI almost instantly with formation of 3-*n*-butyl-4,8-dichloro-5,6-dihydroxycarbostyril XXXVII (*via* the hydrochloride). The substance XXXVII was so high melting and difficultly soluble in all solvents that it could not be purified. Its diacetyl derivative XXXVIII, however, was readily purified by crystallization from acetic acid.



XXXVI

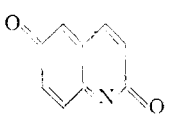


XXXVII, R = H
XXXVIII, R = CH_3CO

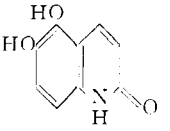
(32) M. Henze, *Ber.*, **69**, 1566 (1936).
(33) Unpublished experiments, present authors.
(34) R. H. Baker, G. R. Lappin and B. Riegel, THIS JOURNAL, **68**, 1284 (1946).
(35) R. J. Rowlett, Jr., and R. E. Lutz, *ibid.*, **68**, 1288 (1946).
(36) E. R. Buchman and C. S. Hamilton, *ibid.*, **64**, 1357 (1942).

The quinone XXXVI was somewhat more soluble than its analogs and could be recrystallized from boiling ethanol as well as from acetic acid. Prolonged action of either of these solvents, hot, resulted in destruction of the compound. The substance could also be purified by sublimation *in vacuo*.

The ease with which the above 6-hydroxycarbostyrils were oxidized to 5,6-quinones may be explained, perhaps, by the fact that the 6-hydroxycarbostyrils are "internal" acyl derivatives of *p*-aminophenol. Since Adams and co-workers[25] have shown that acyl derivatives of *p*-aminophenol may be oxidized readily to the corresponding derivatives of quinone monoimine; and since they have also shown that these quinone monoimides are reactive substances with a strong tendency to undergo 1,4-addition to the conjugated system commencing with the nitrogen atom, a plausible scheme for the conversion of XXV to XXIX (for example) may be constructed involving XXXIX and XL as intermediates.



XXXIX



XL

The present work, taken in conjunction with that of Drake[2a] on air oxidation of the 8-amino-6-hydroxyquinolines, indicates that the one-step oxidation of 6-quinolinols to 5,6-quinones may be a reaction of rather general applicability. Its importance as a source of certain carbostyril-5,6-quinones of possible significance in the chemotherapy of malaria is being explored in these laboratories.

Acknowledgment.—The authors are indebted to Dr. Roger Adams for advice and encouragement in connection with this investigation; to Miss Elizabeth Peterson for the determination and interpretation of the infrared spectra; and to Miss Emily Davis and Mrs. Katherine Pih for some of the microanalyses.

Experimental[37]

4-Methyl-6-hydroxycarbostyril (I).—A mixture of 48% hydrobromic acid (150 ml.), glacial acetic acid (100 ml.) and 4-methyl-6-methoxycarbostyril[22] (30 g., 0.16 mole) was boiled for 12 hours, and the solution was diluted with water (150 ml.). The white needles of the hydrobromide of I obtained were warmed and stirred with 5% aqueous ammonia (500 ml.) for two hours, and the free base (I) was removed. Crystallization from glacial acetic acid gave 23 g. (0.13 mole, 81%) of beautiful white blades melting at 326–330°. A portion was recrystallized from glacial acetic acid, then from dimethylformamide, and again from acetic acid. Pure I melting at 330–332° was then obtained.

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.30; H, 5.18; N, 8.04.

Oxidation of I. 4-Methylcarbostyril-5,6-quinone (II).—Attempts to oxidize I with dry lead tetraacetate in chloroform or benzene led only to dark gums from which nothing crystalline could be isolated. An attempt to oxidize it in boiling ether with freshly precipitated, dried lead dioxide[38] gave a faintly yellowish solution, but only unchanged I was isolated from the mixture.

A.—The hydroxycarbostyril I (1.5 g., 8.5 mmoles) was powdered, and shaken with a warm 1:1 mixture of acetic acid and acetic anhydride (10 ml.) containing lead tetraacetate (8.0 g., 18.0 mmoles) for half an hour. The orange solid was removed and boiled with acetic acid (10 ml.). This mixture was filtered hot and 0.75 g. (4.0 mmoles, 47%) of tiny orange-red crystals was obtained. A sample was recrystallized from hot acetic acid (only slightly soluble) and then gave bright red plates of II, decomposing at about 180° and above, without melting.

B.—The hydroxycarbostyril I (20.0 g., 0.114 mole) was suspended in a mixture of acetic acid (200 ml.) and water (100 ml.). Concentrated sulfuric acid (20 g.) was added and the mixture was warmed to bring the solid into solution. The solution was cooled to 40° and then chromium trioxide (15.0 g., 0.150 mole) in 20 ml. of water was added with vigorous shaking. The dark-colored solution was, after about two minutes, cooled rapidly in a stream of water, and then beautiful gleaming plates of the red oxidation product II separated. These (11.0 g., 0.058 mole, 51%) were removed by filtration, washed with water and acetic acid, and dried. A small sample was recrystallized from hot acetic acid.

Anal. Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.34. Found: C, 62.96; H, 3.98; N, 7.20.

The infrared spectra of this material and that obtained by oxidation in acetic acid–acetic anhydride with lead tetraacetate were identical. The spectrum showed no band in the region characteristic of the OH group.

The quinone II could not be recrystallized satisfactorily more than once. Attempts to recrystallize from acetic acid a second time led to less pure material. Higher-boiling solvents, or prolonged boiling with acetic acid, destroyed the substance completely (black tar), and it was so insoluble in the lower-boiling solvents as to make recrystallization from them impossible. A similar difficulty in attempts to purify β-naphthoquinone by recrystallization has been reported.[39]

The substance II dissolved readily in concentrated sulfuric acid in the cold, but the deep red color of the solution soon faded to yellow. On pouring the yellow solution into water, no precipitate formed. The quinone also dissolved readily in cold concentrated (70%) nitric acid. When the solution was, after a few moments, diluted with an equal volume of ice-water, and cooled, the quinone II separated in nicely crystalline condition.

Shaking a suspension of II in alcohol with aqueous sodium hydrosulfite at room temperature led to a colorless solution, from which nothing precipitated on further dilution with water. With concentrated aqueous ammonia, the quinone gave a clear, green solution which rapidly darkened in contact with air. After some time a purple, amorphous solid precipitated. Action of stannous chloride or zinc dust in acetic acid on II led to a white, insoluble powder melting with decomposition above 330°.

4-Methyl-5,6-diacetoxycarbostyril (VI).—The powdered quinone II (2.0 g., 0.011 mole) suspended in ethanol (100 ml.) was shaken at room temperature (26°) with hydrogen at atmospheric pressure (740 mm.) in the presence of 0.2 g. of Adams platinum catalyst (prereduced) until enough hydrogen (275 cc., 0.011 mole) to correspond to reduction to the hydroquinone had been absorbed (a few minutes). The mixture of white powder and black catalyst was boiled with acetic acid (100 ml.) and filtered hot. The filtrate was diluted with water (100 ml.) and allowed to stand at room temperature for 24 hours. The gray solid V obtained (1.0 g., 5.2 mmoles, 47%) was boiled for ten minutes with a mixture of acetic acid (5 ml.) and acetic anhydride (3 ml.) and then water was added dropwise until a turbidity appeared. On cooling, the solution deposited colorless blades (0.87 g., 3.1 mmoles, 60%) of VI. Four recrystallizations from acetic acid–water gave the pure substance, m.p. 283°.

Anal. Calcd. for $C_{14}H_{13}O_5N$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.02; H, 4.73; N, 4.86.

The hydroquinone V was shaken with concentrated aqueous ammonia, and a green solution was formed which quickly darkened, then deposited a purple, gelatinous solid.

(37) All melting points were obtained on a Kofler hot-stage, and are to be considered as corrected. A number of the analyses were by the Clark Microanalytical Laboratory, Urbana, Illinois.

(38) R. Kuhn and I. Hamer, *Ber.*, **83**, 413 (1950).

(39) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 232.

Addition of Hydrogen Chloride to II. 4-Methyl-5,6-dihydroxy-8-chlorocarbostyril (VIII).—Dry hydrogen chloride was bubbled through a suspension of II (5.0 g., 0.026 mole) in chloroform (50 ml.). The red crystals disappeared rapidly and a yellowish powder was formed. The powder was shaken with dilute aqueous bicarbonate and the white solid (5.1 g., 0.023 mole, 89%) was removed. It melted indistinctly and with decomposition above 380°. The substance was so insoluble in all solvents that it could not be recrystallized satisfactorily. However, a boiling mixture of concentrated hydrochloric acid (300 ml.) and glacial acetic acid (700 ml.) dissolved 4.0 g. of the original yellowish powder with formation of a yellow solution. On allowing the solution to cool undisturbed it deposited bright lemon-yellow needles (4.2 g.) of a substance VII which (air dried) analyzed for the dihydrate of the hydrochloride of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril.

Anal. Calcd. for $C_{10}H_9O_3NCl\cdot 2H_2O$: C, 40.29; H, 4.39; N, 4.70. Found: C, 40.36; H, 4.77; N, 4.79.

The hydrochloride VII was boiled with water, and the free base VIII was then obtained as a white powder melting indistinctly and with decomposition above 380°.

Anal. Calcd. for $C_{10}H_8O_3NCl$: C, 53.23; H, 3.57; N, 6.07. Found: C, 53.09; H, 3.82; N, 6.08.

Hydroquinone VIII was only very slightly soluble in all the common solvents except pyridine, in which it turned black rapidly. It also dissolved in dilute aqueous sodium hydroxide with rapid darkening. Attempts to methylate it with dimethyl sulfate and alkali were unsuccessful.

The above hydroquinone VIII (2.0 g., 8.8 mmoles) was boiled with acetic anhydride (20 ml.) containing 2 drops of sulfuric acid. The solid dissolved slowly. On cooling, the clear solution deposited rosettes of white needles (2.11 g., 6.7 mmoles, 77%) melting at 245–250°. Several recrystallizations from acetic acid–water gave the pure diacetyl derivative IX melting at 260–261°.

Anal. Calcd. for $C_{14}H_{12}O_5NCl$: C, 54.29; H, 3.91; N, 4.52. Found: C, 54.50; H, 4.12; N, 4.74.

When VIII (1.0 g., 4.4 mmoles) was boiled with a mixture of benzoyl chloride (3 g.) and pyridine (25 ml.) for 15 minutes and the solution allowed to cool slowly, a colorless solid separated from the hot mixture. This was removed and recrystallized from acetic acid, giving rise to 0.9 g. (1.7 mmoles, 39%) of the tribenzoyl derivative X. Two more crystallizations from acetic acid followed by a vacuum sublimination gave pure X melting at 240–242°.

Anal. Calcd. for $C_{31}O_6NCl$: C, 69.21; H, 3.75. Found: C, 68.94; H, 3.69.

Portions of the quinone II, which had been recrystallized from nitric acid (see above) also added hydrogen chloride to give VIII, as established by conversion of the VIII from this source to the same acetyl derivative IX, m.p. and mixed m.p. 260–261° and benzoyl derivative X, m.p. and mixed m.p. 240–242° described above.

4-Methyl-8-chlorocarbostyril-5,6-quinone (XI).—Several attempts to oxidize hydroquinone VIII with chromic acid or ferric chloride in aqueous acetic acid were unsuccessful. But when VIII (1.0 g., 4.4 mmoles) was suspended in ethyl acetate (5 ml.) and a solution of chromic oxide (0.5 g., 5.0 mmoles) in a milliliter of water was added all at once, bright red crystals of chloroquinone XI (0.95 g., 4.2 mmoles, 96%) were obtained. The substance was recrystallized by dissolving it in cold concentrated nitric acid and adding water. Brilliant red crystals of pure XI precipitated at once.

Anal. Calcd. for $C_{10}H_7O_3NCl$: C, 53.47; H, 3.14; N, 6.24. Found: C, 53.39; H, 3.18; N, 6.74.

5-Chloro-4-aminoveratrole.—A sample of 4-nitroveratrole[40] (XII) (1.6 g., 8.7 mmoles) was suspended in concentrated aqueous hydrochloric acid (20 ml.) and granulated tin (2.0 g., 0.017 atom) was added with shaking. The mixture was heated on a steam-bath for 40 minutes with frequent shaking, when all the nitro compound had dissolved. The clear, hot solution was decanted from a small amount of insoluble material and allowed to stand at room temperature for four hours. The crystalline stannichloride which had separated by this time was removed and dissolved in 25 ml. of hot 15% aqueous sodium hydroxide. From the cooled solution an oil separated, which crystallized on scratching the walls of the container. Recrystallization from hot water gave 0.5 g. (3.3 mmoles, 38%) of white plates, m.p. 86–87°. A mixed melting point with an authentic sample of 4-aminoveratrole (XIII), m.p. 87–88°, was undepressed.

The mother liquors from which the above stannichloride had separated were allowed to stand in the ice-box for 12 hours, and a second crop of crystals was obtained. This material was dissolved in 25 ml. of hot 10% aqueous sodium hydroxide, and the solution was cooled in an ice-bath. The white leaflets (0.5 g., 2.7 mmoles, 31%) of XIV which crystallized out melted at 72–73°, and the substance was presumably identical with the compound of m.p. 72–73° prepared in the same way by Seer and Karl.[14] A mixed melting point with an authentic sample of 5-chloro-4-aminoveratrole (m.p. 73–74°, see below) was undepressed.

B.—A solution of 4-acetaminoveratrole[41] (XV) (21 g., 0.11 mole) in chloroform (150 ml.) was cooled to 5–10° in an ice-bath and chlorine (8.2 g., 0.12 mole) from a chlorine generator[42] slowly bubbled through it. After all the chlorine had been added, the walls of the container were scratched and the crystalline hydrochloride of 5-chloro-4-acetaminoveratrole precipitated. This was removed and dissolved in the minimum of boiling water. On cooling, the solution deposited white needles (22.8 g., 0.099 mole, 91%) of 5-chloro-4-acetaminoveratrole (XVI) melting at 127–129°. Two recrystallizations from hot water gave material melting at 130–131°. The chlorination of XV was also carried out in acetic acid solution according to the method developed by Robinson[43] for the bromination of XV, but the yield of XVI was low and the crude product difficult to purify.

Anal. Calcd. for $C_{10}H_{12}O_3NCl$: C, 52.30; H, 5.27. Found: C, 52.64; H, 5.34.

Hydrolysis of the above acetamino compound (20 g., 0.087 mole) with boiling 10% aqueous alkali (6 hours) gave the free amine, which, on recrystallization from hot water, gave rise to material (14 g., 0.075 mole, 86%) melting at 72–73°. Several recrystallizations from water led to pure 5-chloro-4-aminoveratrole (XIV) melting at 73–74°.

Anal. Calcd. for $C_8H_{10}O_2NCl$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.41; H, 5.40; N, 7.36.

C.—Although 4-chloroveratrole (XVII) has been reported as the product of chlorination of veratrole with sulfuryl chloride,[44] it was found more convenient in the present work to prepare the compound from 4-aminoveratrole (XIII).

To a cold (0°) solution of 4-aminoveratrole (25 g., 0.16 mole) in 100 ml. of ice–water mixture and 43 ml. of concentrated hydrochloric acid was added a cold solution of sodium nitrite (11.2 g., 0.16 mole) in 40 ml. of water. The mixture was stirred for 20 minutes at 0–5° and then allowed to run slowly into a cold (0°) stirred solution of cuprous chloride[45] (0.2 mole) in concentrated hydrochloric acid (78 ml.). The mixture was allowed to warm to room temperature, then heated gradually to 60°. The dark solution was extracted with three 75-ml. portions of benzene, and the combined extracts were distilled. After the solvent had been removed, 4-chloroveratrole XVII (17 g., 0.099 mole, 62%) came over as a colorless liquid boiling at 237–240° at 739 mm. (lit.[44] b.p. 242° at 763 mm.).

The above 4-chloroveratrole (2.0 g., 11.6 mmoles) was nitrated according to the directions of Bogert[15] and 5-chloro-4-nitroveratrole (XVIII) was obtained as pale yellow needles, melting at 118° as reported. The yield, not given by Bogert, was 2.3 g. (10.5 mmoles, 91%). Action of zinc dust (1.0 g., 0.015 atom) in aqueous acetic acid (5 ml. of 50%) on XVIII (1.0 g., 4.6 mmoles) gave a clear solution which, when it was made strongly basic with 15% aqueous sodium hydroxide and chilled in ice, deposited crystals (0.3 g., 1.6 mmoles, 35%) of 5-chloro-4-aminoveratrole (XIV), m.p. 72–73°. Mixed melting points with samples of XIV obtained by the two methods previously described were undepressed.

2-Chloro-4,5-dimethoxyacetoacetanilide (XIX).—Ethyl acetoacetate (100 ml.) was heated to the boiling point (164–

(40) D. Cardwell and R. Robinson, *J. Chem. Soc.*, **107**, 256 (1915).

(41) K. Fries, H. Koch and H. Stukenbrock, *Ann.*, **468**, 170 (1928).

(42) J. S. Buck and W. S. Ide, *Org. Syntheses*, **16**, 5 (1936).

(43) T. G. N. Jones and R. Robinson, *J. Chem. Soc.*, **111**, 914 (1917).

(44) A. Peratoner, *Gazz. chim. ital.*, **28**, I, 232 (1889).

(45) C. S. Marvel and S. M. McElvain, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 170.

166°) in a 3-necked flask equipped with a mechanical stirrer and heated in a metal-bath. One neck of the flask was left open and through it was added in portions pure 5-chloro-4-aminoveratrole (XIV) (25 g., 0.134 mole). The addition was carried out gradually (40 minutes) so that the temperature of the boiling liquid, which dropped due to evolution of alcohol after each addition of the amine, was again 165° before each new addition. The solution was boiled gently for an additional 30 minutes, and then it was allowed to stand at room temperature for 24 hours. At the end of this time the white crystals of XIX (17 g., 0.063 mole, 47%) were removed and recrystallized from hot, 20% aqueous alcohol three times, then sublimed *in vacuo*. White blades of pure XIX melting at 136–137° resulted.

Anal. Calcd. for $C_{12}H_{13}O_4NCl$: C, 53.24; H, 4.84. Found: C, 53.07; H, 5.17.

Cyclization of 2-Chloro-4,5-dimethoxyacetoacetanilide (XIX).—A solution of XIX (18 g., 0.067 mole) in concentrated sulfuric acid (75 ml. of d. 1.84) was allowed to stand at room temperature for four days, and then the clear, yellow solution was poured into a stirred mixture of ice and water (700 ml.). The solid which precipitated was stirred with hot 5% aqueous sodium bicarbonate for two hours, and then, after filtration, boiled with 95% ethanol (100 ml.). The hot suspension was filtered and the filtrate diluted with hot water (75 ml.). The solution was cooled slowly, and four successive crops of crystals were removed. The first crop (1.7 g.) consisted of a mixture of a small amount of a white powder and a larger amount of colorless blades. A sample of the colorless blades picked out by hand melted at 165–167°. The white powder melted indistinctly and with decomposition above 380°. The second, third and fourth crops consisted entirely of the colorless blades melting at 165–167°. Their combined weight was 6.1 g. (0.024 mole, 36%). Three recrystallizations from the minimum of hot methanol gave pure 4-methyl-5,6-dimethoxy-8-chlorocarbostyril (XX) melting at 167–168°. The analytical sample was further purified by sublimation *in vacuo*.

Anal. Calcd. for $C_{12}H_{12}NO_3Cl$: C, 56.81; H, 4.77. Found: C, 56.52; H, 4.72.

The ethanolic mother liquors from the crystallization of XX were evaporated to dryness *in vacuo* and the residue (1.3 g.) was recrystallized twice from methanol. Slightly less pure XX (0.7 g.) melting at 163–166° resulted.

The material insoluble in hot ethanol was boiled with glacial acetic acid (50 ml.) and the hot suspension was filtered. On dilution with water the filtrate gave a small amount (0.01 g.) of the white powder decomposing at about 380°. The material VIII insoluble in hot acetic acid (6.7 g., 0.030 mole, 45%) also melted indistinctly and with decomposition above 380°.

The high-melting substance VIII when boiled briefly with acetic anhydride and acetic acid formed an acetyl derivative IX, white needles from acetic acid melting at 260–261°.

Anal. Calcd. for $C_{14}H_{12}O_5NCl$: C, 54.29; H, 3.91; N, 4.52. Found: C, 54.34; H, 3.94; N, 4.57.

A mixed melting point with the diacetyl derivative IX (m.p. 260–261°) of a sample of 4-methyl-5,6-dihydroxy-8-chlorocarbostyril VIII obtained by addition of hydrogen chloride to 4-methylcarbostyril-5,6-quinone II was undepressed.

A tribenzoyl derivative X, white needles from acetic acid, m.p. 240–242°, was formed by action of excess benzoyl chloride on a sample of the above VIII in hot pyridine.

Anal. Calcd. for $C_{31}H_{20}O_6NCl$: C, 69.21; H, 3.75. Found: C, 69.51; H, 3.90.

A mixture of the above tribenzoyl compound and the tribenzoyl derivative X (m.p. 240–242°) of the hydrogen chloride adduct of 4-methylcarbostyril-5,6-quinone (II) also melted at 240–242°.

2,6-Dimethoxyquinoline (XXVI).—2-Chloro-6-methoxyquinoline (35 g., 0.18 mole) was boiled with sodium methoxide (17 g., 0.31 mole) in dry methanol (300 ml.) for 48 hours. Hot water (500 ml.) was added, when gleaming plates of the dimethoxy compound XXVI (31 g., 0.164 mole, 91%) melting at 85–88° separated. Two recrystallizations from methanol–water gave the pure substance, m.p. 88–90°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: N, 7.40. Found: N, 7.34.

If the 2-chloro-6-methoxyquinoline was boiled with sodium methoxide solution for a shorter time (six hours) the reaction was incomplete, and a mixture of unchanged starting material and XXVI was recovered.

The dimethoxy compound XXVI had a pleasant, spicy odor, slightly reminiscent of cinnamon.

6-Methoxycarbostyril (XXVII).—The above dimethoxy compound XXVI (25 g., 0.13 mole) was boiled with 6 *N* aqueous hydrochloric acid for 48 hours, and the solid product was stirred with hot, 10% aqueous ammonia, then recrystallized from acetic acid. 6-Methoxycarbostyril (XXVII) (20.4 g., 0.116 mole, 89%) melting at 218–219° (lit.[46] m.p. 218–219°) resulted. A sample was recrystallized several times from acetic acid and then melted at 221–222°. In view of the discrepancy in melting points, and the differences in method of preparation, of XXVII as reported herein and as reported by Eichengrun and Einhorn,[16] the substance was analyzed.

Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.54; H, 5.01; N, 8.02.

In an attempt to by-pass the preparation of XXVI, 2-chloro-6-methoxyquinoline was boiled with 6 *N* hydrochloric acid for 48 hours, but a mixture of products was formed from which pure XXVII was isolated only with difficulty and in low yield.

The Action of Benzoyl Chloride and Alkali on 6-Methoxyquinoline-N-oxide. Compound XXVIII.—A hot (70°) solution of 6-methoxyquinoline-N-oxide[31] (17.3 g., 0.1 mole) in aqueous sodium hydroxide (20 g., 0.5 mole, in 500 ml. of water) was stirred mechanically and benzoyl chloride (56 g., 0.4 mole) was added dropwise over a period of two hours. The hot mixture was filtered, and the solid was stirred with hot 5% aqueous sodium hydroxide, then removed and crystallized from acetic acid. The small colorless prisms so obtained (8.3 g., 0.017 mole, 17%) melted at 212–216°. Several recrystallizations from acetic acid followed by sublimation *in vacuo* gave pure XXVIII melting at 227–229°.

Anal. Calcd. for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77. Found: C, 71.75; H, 5.15.

The substance was insoluble in strong alkali, even hot, and resisted the action (1 hour) of boiling 10% aqueous alkali. It was soluble in warm 1:1 hydrochloric acid with formation of a yellow solution.

6-Hydroxycarbostyril (XXV).—Action of boiling 48% aqueous hydrobromic acid (200 ml.) on XXVII (19 g., 0.11 mole) for 48 hours gave, on diluting the solution with water (200 ml.), white needles of the hydrobromide of XXV, decomposed by water to give the free base (15.4 g., 0.096 mole, 88%) melting at 328–332°. Three recrystallizations from acetic acid followed by sublimation *in vacuo* gave pure 6-hydroxycarbostyril (XXV) as white needles melting at 337–339°.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38. Found: C, 67.35; H, 4.53.

Carbostyril-5,6-quinone (XXIX).—The above 6-hydroxycarbostyril (1.61 g., 10.0 mmoles) was boiled with 20 ml. of 20% aqueous sulfuric acid, and then the mixture was cooled to room temperature. A solution of chromic oxide (1.33 g., 0.0133 mole) was added dropwise with vigorous shaking. All gradually dissolved and after a few moments red platelets (0.90 g., 5.1 mmoles, 51%) of the quinone XXIX began crystallizing out of the dark solution. The substance was destroyed on boiling with the higher-boiling solvents and was insoluble in almost all of the common lower-boiling ones except acetic acid. Boiling acetic acid (150 ml.) dissolved approximately 0.5 g., and on allowing the solution to stand at room temperature for several hours, red platelets of the quinone (0.3 g.) separated.

Anal. Calcd. for $C_9H_5O_3N$: C, 61.72; H, 2.88. Found: C, 61.10; H, 2.92.

It was not possible to obtain the substance analytically pure, for attempts to recrystallize the once-recrystallized material led to even less pure material. A similar difficulty was reported by Fieser[39] in attempts to recrystallize β-naphthoquinone.

A suspension of the quinone in alcohol was shaken at room temperature with aqueous sodium hydrosulfite for a short time. The resulting colorless solution was diluted with water, but no precipitate was obtained. Strong aqueous

(16) A. Eichengrun and A. Einhorn, *Ann.*, **262**, 177 (1891).

ammonia dissolved XXIX with formation of a green solution which rapidly darkened and deposited a purple, gelatinous solid.

Addition of Hydrogen Chloride to Quinone XXIX. 5,6-Dihydroxy-8-chlorocarbostyril (XXX).—Dry hydrogen chloride was bubbled through a suspension of XXIX (0.4 g., 2.3 mmoles) in chloroform (5 ml.), and the resulting yellow solid was boiled with water, then with glacial acetic acid (2 ml.), and filtered. 5,6-Dihydroxy-8-chlorocarbostyril (XXX) was obtained as a white, microcrystalline powder (0.4 g., 1.9 mmoles, 83%) melting at approximately 350° with much decomposition. The substance was so insoluble in the common solvents that it could not be recrystallized. It was soluble in aqueous alkali, and hot pyridine, but the solutions rapidly turned black.

Anal. Calcd. for $C_9H_6O_3NCl$: N, 6.62. Found: N, 6.35.

The hydroquinone XXX (0.2 g., 0.9 mmole) was boiled for ten minutes with acetic anhydride (1.0 ml.) and acetic acid (3.0 ml.). Water (4.0 ml.) was added cautiously, and the solution, on cooling, deposited white needles (0.16 g., 0.54 mmole, 60%) of the diacetyl derivative XXXI. Three recrystallizations from acetic acid–water gave pure material melting at 240–242°.

Anal. Calcd. for $C_{13}H_{10}O_5NCl$: C, 52.80; H, 3.41; N, 4.74. Found: C, 52.86; H, 3.49; N, 4.65.

3-*n*-Butyl-4-hydroxy-6-methoxycarbostyril (XXXIII).—Diethyl *n*-butylmalonate (108 g., 0.5 mole) and *p*-anisidine (62 g., 0.5 mole) were boiled (air condenser) with Dowtherm A (1 liter) for eight hours. After three hours no more ethanol distilled out of the condenser. Hot *n*-heptane (500 ml.) was added, and the cooled mixture deposited colorless plates which were removed, washed on the filter with *n*-heptane, and then recrystallized from ethanol. White plates (112 g., 0.46 mole, 91%) of XXXIII melting at 210–214° were obtained. Three recrystallizations from alcohol gave material melting at 216–218°.

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 68.00; H, 6.93; N, 5.67. Found: C, 68.31; H, 6.96; N, 5.42.

2,4-Dichloro-3-*n*-butyl-6-methoxyquinoline (XXXIV).—The carbostyril XXXIII (50 g., 0.2 mole) was refluxed with phosphorus oxychloride (150 ml.) in a dry atmosphere for 12 hours. The excess phosphorus oxychloride was removed by distillation, and the residual hot sirup was *at once* poured into a mixture of crushed ice and water (500 ml.) with vigorous mechanical stirring. The suspension was made basic with dilute ammonia, stirred for an hour and the white solid was removed. The dry material (44 g., 0.154 mole, 77%) melted at 69–73°. Recrystallization four times from 50% ethanol gave gleaming platelets of pure XXXIV melting at 75–76°.

Anal. Calcd. for $C_{14}H_{15}ONCl_2$: C, 59.17; H, 5.32; N, 4.93. Found: C, 59.26; H, 5.46; N, 5.20.

3-*n*-Butyl-4-chloro-6-methoxycarbostyril (XXXV).—The dichloro compound XXXIV (40 g., 0.14 mole) was boiled with a mixture of 6 *N* hydrochloric acid (300 ml.) and dioxane (100 ml.) for 48 hours. The cooled solution deposited white needles of the hydrochloride of XXXV. These were stirred with hot 5% sodium bicarbonate (300 ml.) for two hours, and the free base was removed. Recrystallization from chloroform and then from ethanol gave white needles (29 g., 0.109 mole, 78%) of XXXV melting at 167–169°.

Anal. Calcd. for $C_{14}H_{16}O_2NCl$: N, 5.27. Found: N, 5.44.

3-*n*-Butyl-4-chloro-6-hydroxycarbostyril (XXXII).—The methoxycarbostyril XXXV (19 g., 0.071 mole) was boiled with 48% hydrobromic acid (100 ml.) and acetic acid (50 ml.) for 24 hours. The solution was cooled, the supernatant liquid decanted from the lumpy solid, and more 48% hydrobromic acid (150 ml.) and acetic acid (50 ml.) were added. The mixture was refluxed for 24 hours; water (150 ml.) was added, and the mixture was cooled. The white crystalline solid was stirred with hot, dilute aqueous sodium bicarbonate (200 ml.), and then recrystallized from ethanol. The fine white needles (14 g., 0.057 mole, 80%) melted at 193–195°, resolidified on continued slow heating, and remelted at 213–215°. A sample recrystallized from ethanol, then ethyl acetate–cyclohexane, and finally from ethanol gave fine needles of pure XXXII which melted at 194–197°, resolidified, and then remelted at 218–221°. When the material of higher melting point was recrystallized from ethanol, the lower melting form was obtained which showed the same double melting point as before.

Anal. Calcd. for $C_{13}H_{14}O_2NCl$: C, 62.03; H, 5.61; N, 5.57. Found: C, 62.20; H, 5.83; N, 5.74.

The substance gave a deep orange-red solution instantly with lead tetraacetate in acetic acid. The methoxycarbostyril (XXXV) did not.

Oxidation of 3-*n*-Butyl-4-chloro-6-hydroxycarbostyril. 3-*n*-Butyl-4-chlorocarbostyril-5,6-quinone (XXXVI).—Two procedures for the oxidation of XXXII to XXXVI were developed. One (A) led to a high yield of crude quinone, suitable for many purposes; while the other (B) led to somewhat purer quinone, but in lower yield.

A.—Hydroxycarbostyril XXXII (5.0 g., 4.0 mmoles) was dissolved, with warming, in glacial acetic acid (80 ml.). Water (70 ml.) and concentrated sulfuric acid (40 ml.) were added and the mixture was cooled in ice until all of the crystalline sulfate had precipitated and the mixture was below room temperature. Chromic oxide (2.0 g., 20 mmoles) in water (3.0 ml.) was added dropwise (a minute or two for the addition) while the mixture was mechanically stirred. After a half-hour of stirring, all of the hydroxycarbostyril XXXII had dissolved and been replaced by tiny red crystals of XXXVI. The suspension was then poured into an equal volume of water, and allowed to stand, with occasional stirring, for about five minutes. The red crystals were separated, washed on the filter with water, then stirred with water (300 ml.) at 40°, and finally removed and dried. The yield of red, microcrystalline XXXVI, decomposing without melting at about 180°, was 4.4 g. (3.3 mmoles, 83%). Although this material was pure enough for further synthetic work, it contained a persistent impurity and attempts to purify it further were unsuccessful.

B.—Pure XXXII (5.0 g., 4.0 mmoles) was dissolved in a mixture of acetic acid (50 ml.), water (30 ml.) and sulfuric acid (2.0 g.) by warming. The solution was cooled to 40°, and chromic oxide (3.0 g., 30 mmoles) in water (6 ml.) was added, with vigorous shaking. After a few minutes, red platelets of XXXVI separated from the dark solution. These (2.7 g., 2.0 mmoles, 50%) were removed and recrystallized twice from acetic acid, once from ethanol, then again from acetic acid. A sample was sublimed (very slow process) *in vacuo*. After 7 days at 140° and 1 mm. pressure, 0.18 g. of bright red, crystalline sublimate was obtained, still not quite pure.

Anal. Calcd. for $C_{13}H_{12}O_3NCl$: C, 58.76; H, 4.55. Found: C, 59.21; H, 4.66.

Stannous chloride or zinc dust in acetic acid transformed XXXVI into a white high-melting powder. Aqueous alcoholic sodium hydrosulfite, however, dissolved it with formation of colorless, water-soluble products. With strong aqueous ammonia the quinone gave a green solution which rapidly darkened, then deposited a purple solid. The substance was not appreciably soluble in cold alcohol, but in alcohol containing isoprene, it dissolved rapidly.

Addition of Hydrogen Chloride to Quinone XXXVI. 3-*n*-Butyl-4,8-dichloro-5,6-diacetoxycarbostyril (XXXVIII).—When dry hydrogen chloride was bubbled through a suspension of XXXVI (2.0 g., 7.5 mmoles) in chloroform (20 ml.) a yellow crystalline solid (the hydrochloride of XXXVII) was produced. This, on boiling with water was converted into a white powder (2.0 g., 6.6 mmoles, 88%), 3-*n*-butyl-4,8-dichloro-5,6-dihydroxycarbostyril (XXXVII). The substance was so insoluble in all suitable solvents that it could not be recrystallized. It was soluble in aqueous alkali and hot pyridine, but the solutions blackened at once. With hot acetic acid–acetic anhydride, followed by recrystallization of the product from acetic acid, XXXVII gave a diacetyl derivative XXXVIII, fine white needles melting at 237–239°.

Anal. Calcd. for $C_{17}H_{17}O_5NCl_2$: C, 52.86; H, 4.44; N, 3.63. Found: C, 52.71; H, 4.49; N, 3.50.

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