The reaction can be pictured as (1) a bimolecular reaction between diazonium ion and cuprous complex to give products directly or (2) the formation of an intermediate diazonium–cuprous complex which then slowly decomposes to products or reactive fragments leading to products. These two processes are kinetically indistinguishable.[21,22] In either case there arises a question concerning the electronic requirements of this transfer. There are several schools of thought on this point[5,23] none of which have been satisfactorily demonstrated. We have designed experiments to distinguish among these possibilities.

Acknowledgment.—I would like to thank Dr. J. Kumamoto and Dr. E. Kosower for many helpful suggestions and discussions.

(21) See, however, G. Ropp and V. Raaen, THIS JOURNAL, **76**, 4484 (1954).

(22) Although we have not conclusively eliminated the possibility of a radical chain process for either the Sandmeyer reaction, Meerwein reaction or the inhibition of both by oxygen, we believe that these reactions have a common mechanistic path through the cuprous catalyst. The absence of vinyl polymers and recent experiments by O. Vogl and C. Rondestvedt, THIS JOURNAL, **77**, 3067 (1955), indicate that free radicals in the usual sense are not responsible for the Meerwein reaction.

The selectivity of the reactions (nitrile > Meerwein > Sandmeyer) under various conditions involving halide, cyanide and olefin, present alone or acting in combination, leads us to believe that the group (halide, cyanide or alkyl) which replaces the diazonium group is attached to the cuprous catalyst as a complex. The rate of formation of each product will then depend on the equilibrium constant controlling the concentration of each catalytic cuprous complex species and the rate at which these complexes react with diazonium ion. The factors which influence this latter rate must be scrutinized in greater detail.

(23) H. Meerwein, E. Buchner and K. VanEmster, *J. prakt. Chem.*, **152**, 237 (1939); C. Koelsch and V. Boekelheide, THIS JOURNAL, **66**, 412 (1944); E. Muller, *Angew. Chem.*, **61**, 179 (1949); W. Brunner and J. Kustascher, *Monatsh.*, **82**, 100 (1951); J. Rai and K. Mathur, *J. Indian Chem. Soc.*, **24**, 413 (1947), earlier and later papers.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

A Study of an Oxidative-amination Method for the Synthesis of Aminoquinones[1]

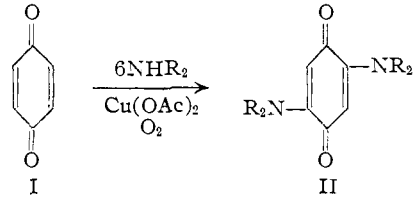
BY ALAN H. CROSBY[2] AND ROBERT E. LUTZ

RECEIVED JULY 28, 1955

The oxidative-amination of 1,4-benzoquinones, and the amine displacements of alkoxyls from 2,5-dialkoxyquinones, to give 2,5-bis-(dialkylamino)-benzoquinones, are shown to be limited to active amines. The failure of diisopropylamine to react in these ways is attributed to its relatively weak basicity with respect to the Lewis acid quinone. The oxidative-amination method has been shown to be applicable to 1,4-naphthoquinone also.

Amines of many types, including even tertiary amines,[3] react with quinones,[4–10] but the usual method for the synthesis of aminoquinones (using the quinone itself as oxidant) is often very unsatisfactory. Since a series of aminoquinones was desired for testing as possible antimalarials or tumor-necrotizing agents,[1a] it was of interest to study the applicability of the elegant method developed by Baltzly and Lorz[9] for the preparation of 2,5-bis-(dimethylamino)-benzoquinone (II, R = CH_3).

This oxidative-amination reaction or a suitable modification of it was successfully applied to the direct synthesis from benzoquinone of seven 2,5-bis-



I II

(dialkylamino)-1,4-benzoquinones which are listed and described in Table I. The secondary amines used in this study were chosen so as to investigate any limitations of the reaction occasioned by steric relations within the amine component. Such a limitation was found when diisopropylamine, in contrast with di-*n*-propyl-, methylisopropyl- and benzylmethylamines, did not yield an aminobenzoquinone. The method has not been successful with primary amines.[9] In the naphthoquinone series, 1,2-naphthoquinone did not give a piperidyl derivative under conditions which converted 1,4-naphthoquinone into 2-(1-piperidyl)-1,4-naphthoquinone. It thus appears that this oxidative amination method is limited to 1,4-quinones and to relatively unbranched secondary amines.

The limitation of the reaction with respect to the branching of the chains of the secondary amines can be explained by a mechanism which postulates that quinone functions as a Lewis acid and undergoes nucleophilic attack by the amine as the first step in the reaction sequence leading to the aminoquinones; and, therefore, if the amine is of insufficient base strength with respect to quinone as a Lewis acid (because of steric hindrances such as B

(1) (a) This investigation was supported in part by a grant from the National Institutes of Health under recommendation by the National Cancer Institute. It was initiated under an earlier N.I.H. antimalarial grant for the purpose of ascertaining whether dialkylaminoquinones would possess greater activity than the dialkylaminodibenzoylethylenes and related compounds [R. E. Lutz, T. A. Martin, *et al.*, *J. Org. Chem.*, **14**, 982 (1949)]. (b) Abstracted in part from the dissertation of A. H. Crosby submitted to the Graduate Faculty of the University of Virginia in partial fulfillment of the requirement for the degree of Doctor of Philosophy.

(2) National Cancer Institute Pre-doctoral Fellow, 1949–1950. Northwestern State College, Natchitoches, La.

(3) O. Diels and R. Kassebart, *Ann.*, **530**, 51 (1937).

(4) H. Suida and W. Suida, *ibid.*, **416**, 113 (1918).

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TABLE I

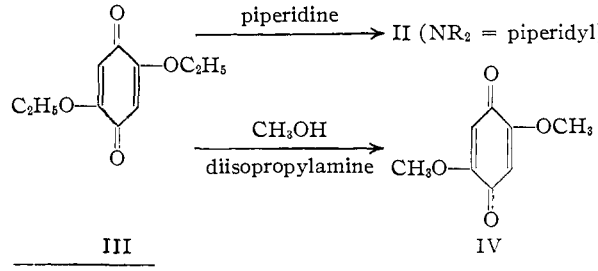
2,5-DIAMINOQUINONES AND THEIR HYDROQUINONE DIACETATES

$-NR_2$	Color and form	M.p., °C. (cor.)	Yield, %	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
N-Substituted 2,5-diaminoquinones								
$-N(C_2H_5)_2$	Red needles	112–114[a,b]	44	$C_{14}H_{22}N_2O_2$[p]	67.16	67.32	8.86	8.67
-Morpholinyl[k,n]	Red needles	232–238[c,g,h]	96	$C_{14}H_{18}N_2O_4$[q]	60.42	60.24	6.52	6.52
-Piperidyl[l]	Purple-red cubes	179–180[b,g]	89					
$-N(CH_3)CH(CH_3)_2$	Red needles	111–113[a,b]	48	$C_{14}H_{22}N_2O_2$	67.16	67.30	8.86	8.96
$-N(CH_2CH_2CH_3)_2$	Red clusters	55–57[a]	45	$C_{18}H_{30}N_2O_2$	70.55	70.52	9.87	9.86
$-N(CH_2CH_2CH_2CH_3)_2$	Red, waxy	45–47[a]	55	$C_{22}H_{38}N_2O_2$	72.88	73.18	10.56	10.58
$-N(CH_3)CH_2C_6H_5$	Red blades[i]	176–178[b,c,g]	86	$C_{22}H_{22}N_2O_2$	76.27	76.50	6.40	6.17
2,5-Diaminohydroquinone diacetates[m]								
$-N(C_2H_5)_2$	Blades	48–50[a]	40	$C_{18}H_{28}N_2O_4$	64.26	64.62	8.39	8.50
-Morpholinyl	....	242–243[d,e,g,i]	58	$C_{18}H_{24}N_2O_6$	59.33	59.30	6.64	6.57
-Piperidyl	Tabular	166–167[f]	90	$C_{20}H_{28}N_2O_4$	66.64	66.87	7.83	8.00
$-N(CH_3)CH(CH_3)_2$	Plates	117–119[a,f]	77	$C_{18}H_{28}N_2O_4$	64.26	64.35	8.39	8.43
$-N(CH_2CH_2CH_3)_2$	Plates	71–72[a]	35	$C_{22}H_{36}N_2O_4$	67.31	67.55	9.25	9.43
$-N(CH_2CH_2CH_2CH_3)_2$	Clusters	50–51[a]	32	$C_{26}H_{44}N_2O_4$	69.60	69.73	9.89	10.01
$-N(CH_3)CH_2C_6H_5$	Prisms	153–155[e,f]	80	$C_{26}H_{28}N_2O_4$[r]	72.20	72.26	6.52	6.48

Recrystallized from: [a] isoöctane; [b] ethanol; [c] dioxane; [d] butanone; [e] *t*-butyl alcohol; [f] ethyl acetate. [g] Melts with decomposition, heated at 2° per minute. [h] Ref. 10 reports m.p. 248–249°. [i] Ref. 10 report m.p. 226.5–229.5. [j] Became pink on drying. [k] This compound[10] was also prepared by heating 2,5-dimethoxybenzoquinone in excess morpholine. [l] This compound[5] was also prepared from 2,5-diethoxybenzoquinone by displacement of the alkoxyls using the conditions described below for the formation of dimethoxybenzoquinone from diethoxybenzoquinone. [m] Colorless. [n] It is interesting to note that morpholine, the weakest of the bases used relative to the hydrogen acids, gave the best yield of product. [p] Calcd. N, 11.19. Found: N, 10.99. [q] Calcd.: N, 10.07; Found: N, 9.93. [r] Calcd.: N, 6.48. Found: N, 6.58.

and F strain) the initial reaction step would not occur to any great extent and competing reactions, for example oxidation,[9] might account for the destruction of the quinone before any detectable amount of aminoquinone could be formed. Since methylisopropylamine and benzylmethylamine gave aminoquinones whereas diisopropylamine did not, it appears that the line of demarcation in terms of reactivity (or basicity) with respect to quinone falls between secondary amines with one branched chain and secondary amines with two branched chains. These results are consistent with the observation by Brown and Pearsall that diisopropylamine is a far weaker base than di-*n*-propylamine with respect to the Lewis acid trimethylboron.[11]

Further evidence for the low reactivity of diisopropylamine is the fact that in refluxing *t*-butyl alcohol it does not react appreciably with 2,5-diethoxyquinone (III) in three days whereas the more reactive base piperidine displaces the ethoxyls readily to give dipiperidylquinone (II, NR_2 = piperidyl). If the diethoxyquinone is treated with diisopropylamine in refluxing methyl alcohol, however, the diethoxyquinone is not recovered nor is an aminoquinone formed, but, instead, a nearly quantitative yield of dimethoxyquinone (IV) is obtained within one hour. Since methoxyl does not displace ethoxyl under similar conditions in the absence of diisopropylamine, this rapid displacement of ethoxyl by methoxyl is presumably brought about by the presence of an appreciable concentration of methoxide ion produced from methanol by the proton-accepting action of diisopropylamine. Thus it appears that diisopropylamine acts as a much stronger base with respect to methyl alcohol as a proton donor than it does with respect to the quinone as a Lewis acid.



III IV

The 2,5-diaminobenzoquinones listed in Table I, as well as the 2-(1-piperidyl)-1,4-naphthoquinone, were characterized by reductive acetylation to the corresponding aminohydroquinone diacetates. The 2,5-structure assigned to the aminobenzoquinones was proven for three of them by the hydrolysis of each to 2,5-dihydroxybenzoquinone using base catalysis in one case and the seemingly superior acid catalysis in the other two cases. The product from each hydrolysis reaction was identified as 2,5-dihydroxybenzoquinone by reductive acetylation to 1,2,4,5-tetraacetoxybenzene because the melting point of 2,5-dihydroxybenzoquinone is too indefinite to serve for positive identification. A few other derivatives of dihydroxyquinone were made and they too were identical with authentic samples or had the melting points reported in the literature.

Experimental

The **2,5-bis-dialkylaminobenzoquinones** were prepared essentially by the procedure and apparatus of Baltzly and Lorz.[9] A mixture of 20 g. (0.1 mole) of finely-powdered cupric acetate monohydrate, 0.6 mole of the secondary amine and 300 ml. of methanol was stirred and warmed to facilitate solution of the copper acetate (in those cases where a whitish precipitate formed it was disregarded). After flushing with oxygen, a solution of 10.8 g. (0.1 mole) of benzoquinone in 200 ml. of methanol was added cautiously (because of lag in the strongly exothermic oxygen absorption) at such a rate that the temperature could be held between

(11) H. C. Brown and H. Pearsall, THIS JOURNAL, **67**, 1765 (1945).

20–30° by ice-water cooling. After oxygen absorption had ceased (usually 30–60 min.), the mixture was cooled to 10°. If a sparingly soluble product (2, 3 and 7 of Table I) had formed it was filtered. But, if the product (1, 4, 5 and 6 of Table I) did not precipitate, the solvent was completely evaporated under reduced pressure at room temperature and to the residue was added 300 ml. of ether and then a cold solution of 22 ml. of 96% sulfuric acid in 500 ml. of water. The ether layer was separated after brief shaking and several more extractions with ether were carried out as rapidly as possible. The ether (about 1500 ml.) was evaporated and the residue was extracted with portions of hot isoöctane until no more colored material was removed. Evaporation of the isoöctane in an air stream gave successive crops of crystals.

Reductive Acetylation Procedure. 2,5-Bis-dialkylaminohydroquinone Diacetates.—A solution of the quinone in a minimum of redistilled acetic anhydride was treated with several ml. of dry triethylamine and excess zinc dust. This suspension was warmed and stirred until the color disappeared and then it was filtered hot. In the case of 2,5-di-(1-piperidyl)-hydroquinone diacetate, the product crystallized directly on cooling to −20°. Usually the solution was cooled to room temperature and poured into water. If a precipitate appeared (2, 4 and 7 of Table I) after hydrolysis of the acetic anhydride, it was filtered; otherwise (1, 5 and 6 of Table I), the resulting solution was extracted with ether, the ether was evaporated, and the residual oil was crystallized from isoöctane.

Attempted Synthesis of 2,5-Bis-(diisopropylamino)-benzoquinone.—A solution of 1.0 g. (0.005 mole) of 2,5-diethoxybenzoquinone[12] and 4.0 g. (0.04 mole) of diisopropylamine in 100 ml. of *t*-butyl alcohol was refluxed for three days. Evaporation of the solvent gave 0.8 g. of a brown residue, m.p. 180–188°. One recrystallization from 20 ml. of ethanol gave 0.4 g. of 2,5-diethoxybenzoquinone, m.p. 186–188°, identified by mixture m.p. and by comparison of its hydroquinone diacetate with an authentic sample.

The Formation of 2,5-Dimethoxybenzoquinone (IV) from 2,5-Diethoxybenzoquinone (III).—The red-brown solution of 2.0 g. (0.01 mole) of 2,5-diethoxybenzoquinone[12] and 4.0 g. (0.04 mole) of diisopropylamine in 100 ml. of methanol was refluxed for one hour (a precipitate had appeared after a few minutes heating). The precipitate was filtered and identified as 2,5-dimethoxybenzoquinone (IV), yield 1.5 g. (88%), by reductive acetylation to 2,5-dimethoxyhydroquinone diacetate, m.p. 186–188°, alone or in admixture with the sample prepared below. Under similar conditions in the absence of diisopropylamine, no precipitate appeared and diethoxyquinone, m.p. 186–188°, was quantitatively recovered by evaporation of the methanol.

2,5-Dimethoxyhydroquinone diacetate was obtained in 47% yield from finely-powdered, crude 2,5-dimethoxyquinone[12] by the reductive acetylation procedure using effective stirring, heating at 90° and crystallizing directly after filtering. It was crystallized from acetic anhydride, methyl alcohol, and isopropyl alcohol, and was identified by analysis and m.p. 186–188° (reference 13 reports 187–188°).

2,5-Dihydroxybenzoquinone.—Acid hydrolysis of 5.5 g. (0.02 mole) of finely-powdered 2,5-di-(1-piperidyl)-benzoquinone was effected by heating with 30 ml. of 96% sulfuric acid in 120 ml. of water at 50–55° for one-half hour. The suspension was continuously extracted with ether until the ether layer was practically colorless. Evaporation of the ether extract gave a purple residue which was fractionally crystallized and recrystallized slowly from a minimum of hot dioxane; 1.4 g. (50%) light-yellow crystals which slowly became yellow-orange on standing.[14]

2,5-Bis-(N-methylisopropylamino)-benzoquinone was hydrolyzed in a similar manner with similar results.

Alkaline hydrolysis of 2,5-bis-(diethylamino)-benzoquinone was effected by suspending 1.0 g. in 80 ml. of boiling 2 *N* sodium hydroxide, adding sufficient dioxane to dissolve the quinone, and refluxing for one hour. Cooling, acidification, extraction with ether, evaporation, extraction of the residue with hot benzene and evaporation of the benzene gave a small amount of the same 2,5-dihydroxyquinone.

Conversion of 2,5-Dihydroxybenzoquinone into 2,5-Diethoxybenzoquinone.—A solution of 0.7 g. (0.005 mole) of 2,5-dihydroxybenzoquinone in 50 ml. of absolute ethanol was treated with one ml. of boron trifluoride etherate, was allowed to stand five hours, and then was distilled until crystals appeared. Cooling to room temperature and recrystallizing the precipitate gave 0.3 g. (30%), m.p. 188–189° (lit.[12] m.p. 183°).

Conversion into 2,5-Diacetoxybenzoquinone.—By gentle warming, 1.4 g. (0.01 mole) of 2,5-dihydroxybenzoquinone was dissolved in a solution consisting of 20 ml. of acetic anhydride and 3 ml. of boron trifluoride etherate. After standing five minutes, the solution was poured into water and the 2,5-diacetoxybenzoquinone[15] was filtered, giving 1.0 g. (45%), m.p. 150–155° dec. (lit.[15] m.p. 150–152°); canary-yellow plates from benzene. Reductive acetylation by the above procedure gave 1,2,4,5-tetraacetoxybenzene.

Conversion into 1,2,4,5-Tetraacetoxybenzene.—Using 1.4 g. of dihydroxybenzoquinone, 30 ml. of acetic anhydride and 15 ml. of triethylamine in the reductive acetylation procedure, there was obtained, on cooling from 90 to −20°, 1.0 g. (32%) of 1,2,4,5-tetraacetoxybenzene,[16] m.p. 228–230° (lit.[16] m.p. 226°). This product was converted into **1,2,4,5-tetramethoxybenzene**, m.p. 101–102° (lit.[17] m.p. 102.5°) by methanolic hydrochloric acid deacylation followed by methylation with dimethyl sulfate.

2-(1-Piperidyl)-1,4-naphthoquinone was prepared using the above procedure for aminobenzoquinones modified as follows: To a solution of 10 g. (0.05 mole) of cupric acetate monohydrate, 21.3 g. (0.25 mole) of piperidine and 150 ml. of methanol, there was added a solution of 7.9 g. (0.05 mole) of 1,4-naphthoquinone in 400 ml. of methanol; and, after evaporation of the methanol, a solution of 8 ml. of 96% sulfuric acid in 250 ml. of water was added. The solid obtained from the isoöctane crystallized from 25 ml. of methanol giving 10.5 g. (87%), m.p. 92–95°; after several recrystallizations from isoöctane, m.p. 94–96°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27. Found: C, 75.01; H, 6.37.

An attempt to synthesize 4-(1-piperidyl)-1,2-naphthoquinone in a similar manner was unsuccessful.

2-(1-Piperidyl)-1,4-naphthoquinone diacetate, prepared by the reductive acetylation procedure above, crystallized on cooling the acetic anhydride solution to −20°; yield 78%, m.p. 120–130°; recrystallized from ethyl acetate, m.p. 130–131° (not changed by subsequent recrystallizations from ethyl acetate and isoöctane).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47. Found: C, 70.00; H, 6.73.

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