[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, A'IN SHAMS UNIVERSITY]

Benzdioxazoles

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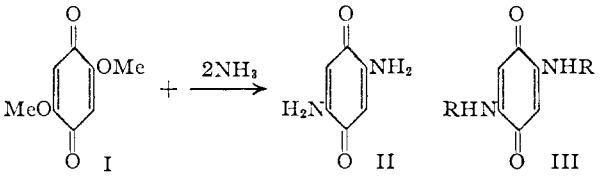
2,6-Diarylbenzdioxazoles (VI) have been prepared by the action of aromatic aldehydes on 2,5-diamino-1,4-benzoquinone (II) and its 3,6-dichloro derivative. The action of potassium methyl xanthate on 2,5-diamino-1,4-benzoquinone gave 2,6-dimercaptobenzdioxazole (IV). The 2,5-diaminoquinone required for this work was conveniently obtained by the action of alcoholic ammonia on 2,5-dimethoxyquinone whereas 2,5-dihydroxyquinone gave only the diammonium salt.

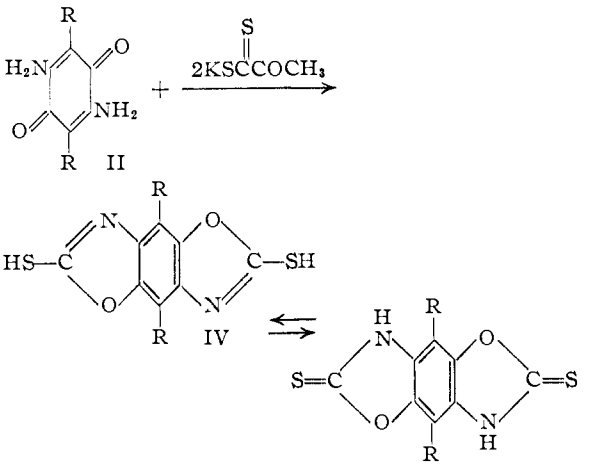
Benzoxazoles and mercaptobenzoxazoles have recently received much attention because of their marked antibacterial and antifungal activities.[1] The present investigation deals with the preparation of previously unknown benzdioxazoles and dimercaptobenzdioxazoles. Although the benzoxazoles and mercaptobenzoxazoles are well known and can be prepared easily from *o*-aminophenols, the use of the diaminodiphenols for dioxazole synthesis is difficult in practice because such compounds are very sensitive and difficult to obtain. Therefore the use of the highly stable diaminoquinones, of which 2,5-diaminobenzoquinone (II) and its 3,6-dichloro derivative were chosen as representatives, has been examined. The 2,5-diaminoquinone[2] (II) used in this investigation, was prepared after a similar procedure described by Anslow and Raistrick[3] in the case of 2,5-bis-(methylamino)-benzoquinone (III, R = CH_3). The diaminoquinone (II) resulted readily when 2,5-dimethoxybenzoquinone (I) was treated with alcoholic ammonia. This method has been extended to other aliphatic and aromatic amines with good results and it is of interest that the same course of reaction can be induced photochemically.

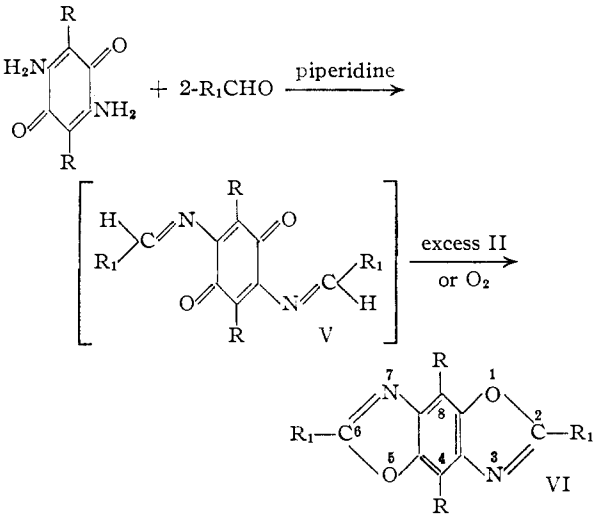


The identity of the diaminoquinone II prepared in this work and that of Kehrmann[2] was proved by mixed m.p. determinations and by the formation of derivatives such as the yellow diacetate (III, R = $COCH_3$), the orange dibenzoate (III, R = COC_6H_5) and the colorless tetraacetate resulting from reductive acetylation.

For the preparation of dimercaptobenzdioxazoles (IV), the reaction between 2,5-diaminoquinone (II, R = H) and potassium methyl xanthate gave a light yellow highly stable crystalline material, although the same reaction with 2,5-diamino-3,6-dichloroquinone (II, R = Cl) was not successful. By analogy with the work of Katz, *et al.*,[1c,1d] the reaction product has structure IV.

The 2,6-diarylbenzdioxazoles were prepared by the interaction of 2,5-diaminobenzoquinone (II, R = H) and its 3,6-dichloro derivative (II, R = Cl) with aromatic aldehydes in the presence of piperidine as a catalyst. For example, 2,5-diaminobenzoquinone reacted with benzaldehyde to give 2,6-diphenylbenzdioxazole (VI, R = H, R_1 = C_6H_5), and 2,5-diamino-3,6-dichloroquinone gave 2,6-diphenyl-4,8-dichlorobenzdioxazole (VI, R = Cl, R_1 = C_6H_5).





Scheme A

VIa, R = H; R_1 = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *o*-Cl-C_6H_4, *o*-OHC_6H_4

VIb, R = Cl; R_1 = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *o*-Cl-C_6H_4

This reaction resembles the formation of benzoxazoles from *o*-aminophenols and aldehydes[4] and can be assumed to involve intermediate products

(1) (a) French Patent 754,436, Aug. 28, 1933; (b) U. S. Patent 2,630,381, Mar. 3, 1953; (c) L. Katz, THIS JOURNAL, **75**, 712 (1953); (d) L. Katz and M. S. Cohen, *J. Org. Chem.*, **19**, 756 (1954).

(2) *Cf.* F. Kehrmann, *Ber.*, **30**, 2100 (1897).

(3) W. K. Anslow and H. Raistrick, *J. Chem. Soc.*, 1446 (1939).

(4) G. McCoy and A. R. Day, THIS JOURNAL, **65**, 1956, 2159 (1943).

TABLE I

Benzdioxazoles	Color of product	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
(a) From 2,5-diaminoquinone												
2,6-Diphenyl-	Cream-yell.	325	70	$C_{20}H_{12}O_2N_2$	76.91	76.88	3.87	3.98	8.97	9.06	...	...
2,6-Di-(*p*-tolyl)-	Colorless	325–328	75	$C_{22}H_{16}O_2N_2$	77.63	77.61	4.74	5.01	8.23	8.29	...	...
2,6-Dianisyl	Light pink	315–317	82	$C_{22}H_{16}O_4N_2$	70.96	70.72	4.33	4.51	7.52	7.57	...	...
2,6-Di-(o-chlorophenyl)-	Pale yell.	263	72	$C_{20}H_{10}O_2N_2Cl_2$	63.0	63.05	2.62	2.8	7.35	7.42	18.63	18.2
2,6-Di-(o-hydroxyphenyl)-	Colorless	340	38	$C_{20}H_{12}O_4N_2$	69.76	69.43	3.51	3.25	8.14	7.85	...	...
(b) From 2,5-diamino-3,6-dichloroquinone												
2,6-Diphenyl-4,8-dichloro-	Cream yell.	332	50	$C_{20}H_{10}O_2N_2Cl_2$	63.0	63.5	2.62	2.94	7.34	7.08	18.63	18.32
2,6-Di-(*p*-tolyl)-	Cream yell.	320	62	$C_{22}H_{14}O_2N_2Cl_2$	64.54	64.21	3.42	3.56	6.84	6.53	17.3	16.82
2,6-Dianisyl-	Cream yell.	310–312	40	$C_{22}H_{14}O_4N_2Cl_2$	59.86	59.57	3.17	3.36	6.36	6.19	16.1	15.73
2,6-Di-(o-chlorophenyl)-	Light yell.	308–310	65	$C_{20}H_8O_2N_2Cl_4$	53.33	53.13	1.77	1.52	6.22	6.01	31.55	31.12

of the type V formed by the condensation of the diaminoquinone with two molecules of the aldehyde. The intermediate products may be oxidized either by atmospheric oxygen or by excess quinone with concomitant cyclization giving the benzdioxazoles (*cf.* Scheme A). In support of this view is the fact that N-substituted diaminoquinones, for example 2,5-bis-(benzylamino)-1,4-benzoquinone (III, R = C_7H_7), did not react with benzaldehyde under the same conditions.

The resulting benzdioxazoles VI are light colored compounds which are sufficiently stable toward heat to sublime unchanged. They are insoluble in sodium hydroxide solution (50%) but dissolve in concentrated sulfuric acid with the production of blue or violet fluorescence. On dilution of the sulfuric acid solutions, the fluorescence disappeared and the compounds were reprecipitated unchanged.

Attempts to prepare benzdioxazoles from aliphatic aldehydes and the above-mentioned quinones led to uncrystallizable materials.[5] Further synthetic and biological testing are in progress.

Experimental

2,5-Diamino-1,4-benzoquinone.—A mixture of 5 g. of 2,5-dimethoxybenzoquinone and 20 ml. of ammonia was refluxed in 200 ml. alcohol for one hour. The reaction mixture was cooled and the violet crystals of 2,5-diaminobenzoquinone were collected at the pump and were pure enough for further work; yield 3.3 g. A sample was recrystallized for analysis from glacial acetic acid in glistening violet needles, m.p. 328–330° dec.

Anal. Calcd. for $C_6H_6O_2N_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.66; H, 4.47; N, 20.17.

2,5-Diaminoquinone Diacetate.—Five-tenths gram of the diaminoquinone was refluxed in 5 ml. of acetic anhydride containing 1 g. of fused sodium acetate for half an hour. The solution was cooled and the precipitated yellow diacetate was collected and crystallized from alcohol in golden yellow needles, m.p. 272° dec., yield 0.3 g.

Anal. Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.20; H, 4.39; N, 12.62.

2,5-Diaminoquinone Dibenzoate.—A mixture of five-tenths gram of the diaminoquinone, 2 g. of anhydrous potassium carbonate and few drops of benzoyl chloride was refluxed in 70 ml. of dry acetone for eight hours. The reaction mixture was filtered and the acetone was removed leaving a solid residue. This was triturated with methyl alcohol, filtered and crystallized from glacial acetic acid in pale orange needles, m.p. 258°, yield 0.25 g.

Anal. Calcd. for $C_{20}H_{14}O_4N_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.71; H, 4.26; N, 7.77.

2,5-Diaminohydroquinone Tetraacetate.—Five-tenths gram of the diaminoquinone was heated with a mixture of 10 ml. of acetic anhydride, 2 g. of zinc dust and 1 g. of fused sodium acetate for about half an hour; 10 ml. of glacial acetic acid was then added and the mixture was heated for ten minutes more to complete the reaction. The colorless product crystallized from dilute acetic acid in long needles, m.p. 263° dec., yield 0.5 g.

Anal. Calcd. for $C_{14}H_{16}O_6N_2$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.31; H, 5.13; N, 9.13.

Reaction between 2,5-Diaminoquinone and Potassium Methyl Xanthate.—A solution of potassium methyl xanthate was prepared by dissolving 1.8 g. of potassium hydroxide in a mixture of 30 ml. of methyl alcohol and 5 ml. of water. Two grams of carbon disulfide was added and the mixture was stirred so that a clear yellow solution was obtained. To this solution, 0.5 g. of the diaminoquinone was added and the mixture was heated on the water-bath for 15 hours. After treatment with charcoal, the reaction mixture was cooled and filtered. The clear filtrate was heated to boiling whereupon a small amount of acetic acid (about 5 ml.) precipitated yellowish crystalline material. This product was washed several times with water and dried. The substance was insoluble in the organic solvents and did not sublime at about 350° (2 mm.). It was purified by dissolution in a 5% alcoholic potassium hydroxide solution and reprecipitated with acetic acid. The process was repeated three times when pure sulfur-yellow needles were obtained, m.p. over 400°, yield 0.3 g.

Anal. Calcd. for $C_8H_4O_2N_2S_2$: C, 42.85; H, 1.79; N, 12.5; S, 28.57. Found: C, 43.17; H, 2.05; N, 12.25; S, 28.19.

Preparation of the Benzdioxazoles (VI).—A mixture of 2,5-diaminoquinone or its 3,6-dichloro derivative[6] (1 mole) and the aldehyde (4 moles) was refluxed in absolute alcohol containing few drops of piperidine as a catalyst for about five hours. The reaction product was collected after cooling and recrystallized from glacial acetic acid. The results are summarized in Table I. A similar experiment was carried out without piperidine, but only the unchanged quinone separated.

Action of Ammonia on 2,5-Dihydroxybenzoquinone.—An alcoholic solution of 0.5 g. of very pure 2,5-dihydroxyquinone[7] was treated with few drops of alcoholic ammonia. A red substance separated immediately and was washed several times with alcohol followed by ether. The diammonium salt was insoluble in organic solvents and decomposed on sublimation, and was analyzed without any further purification, m.p. only decomposition at 170° without melting, yield 0.25 g. The substance dissolved freely in water and was readily decomposed by alkali with the liberation of ammonia. Treatment of the aqueous solution with dilute mineral or acetic acid precipitated 2,5-dihydroxyquinone, m.p. and mixed m.p. 212–214°.

Anal. Calcd. for $C_6H_{10}O_4N_2$: N, 16.09. Found: N, 15.77.

Reaction between 2,5-Dihydroxybenzoquinone and Benzylamine.—A suspension of 0.2 g. of the quinone in 30 ml. of dry benzene was heated with few drops of benzylamine in a sealed tube at 100° for ten hours. The red precipitate of the diamine salt was filtered and dried; m.p. changes to brown at 140° and after that decomposes without melting, yield 0.18 g. The material did not dissolve in organic solvents and when treated with dilute acids liberated the di-

(5) A similar effect was observed during the preparation of chrysenoxazoles from chrysenequinoneimine and aliphatic aldehydes (W. I. Awad and A. R. Raouf, THIS JOURNAL, **77**, 1013 (1955).

(6) S. Laurent, *Ann.*, **52**, 347 (1884); H. Knapp and G. Schultz, *ibid.*, **210**, 183 (1881).

(7) G. Reuben, Jones and H. A. Schonle, THIS JOURNAL, **67**, 1034 (1945).

hydroxyquinone as identified by m.p. and mixed m.p. determinations.

Action of Amines on 2,5-Dimethoxybenzoquinone.—A mixture of 0.3 g. of the quinone and few drops of ethylamine, butylamine, benzylamine or aniline was refluxed in about 30 ml. of alcohol on the water-bath till the quinone has disappeared (about 20 minutes, except for aniline which required about 5 hours). The reaction mixture was cooled and the deposited crystals were collected and washed with alcohol. The yield was almost quantitative with all the amines.

Ethylamine gave 2,5-bis-(ethylamino)-benzoquinone, brilliant crimson crystals from benzene, m.p. 210°, undepressed with a sample prepared from benzoquinone and ethylamine.[8]

Butylamine gave bronze crystals of 2,5-bis-(butylamino)-benzoquinone, m.p. and mixed m.p. 160°.

Benzylamine gave deep red glistening plates of 2,5-bis-(benzylamino)-benzoquinone, m.p. 252°; with concentrated sulfuric acid, an orange color is produced.

Anal. Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.12; H, 5.43; N, 8.57.

With aniline the product was 2,5-bis-(anilinoamino)-quinone,[9] does not melt up to 350°.

(8) M. Martynoff and G. Tsatsas, *Bull. soc. chim., France*, 52 (1947).

Anal. Calcd. for $C_{18}H_{14}O_2N_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.05; H, 4.97; N, 9.43.

Photochemical Reaction between 2,5-Dimethoxybenzoquinone and Benzylamine.—Two-tenths gram of 2,5-dimethoxyquinone was suspended in 50 ml. of dry benzene containing a few drops of benzylamine in a closed tube filled with nitrogen. When the tube was exposed to sunlight for three days (March), the quinone gradually disappeared and a red crystalline material was formed. The product was filtered and recrystallized from glacial acetic acid in deep red shining crystals, m.p. 252°, yield 0.22 g. A mixed m.p. with 2,5-bis-(benzylamino)-benzoquinone prepared above was undepressed.

Reaction between 2,5-Bis-(benzylamino)-1,4-benzoquinone and Benzaldehyde.—Three-tenths gram of the bis-aminoquinone was refluxed with few drops of benzaldehyde in absolute alcohol and in the presence of piperidine as a catalyst. After seven hours the reaction mixture was cooled and the product was collected. It was proved to be unchanged material by m.p. and mixed m.p. determinations.

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(9) Comp. A. W. Hofmann, *J. Chem. Soc.*, 145 (1863); H. and W. Suida, *Ann.*, **416**, 113 (1918).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Biosynthesis of the Triterpene, Eburicoic Acid: The Utilization of Methyl-labeled Acetate[1,2]

BY WILLIAM G. DAUBEN, YOSHIO BAN AND JOHN H. RICHARDS[3]

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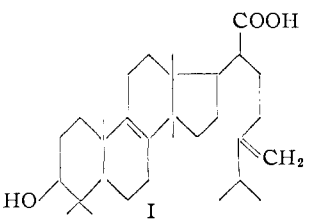
The C_{31}-triterpene, eburicoic acid, has been biosynthesized by allowing *P. sulfureus* to grow on a medium containing methyl-labeled acetate. By degradation of the acid, it has been shown that the carboxyl carbon, C_{21}, and the two methyl groups, C_{30} and C_{31}, of the *gem*-dimethyl group of ring A are derived from the methyl of acetate. Such a distribution is predicted on the basis of the squalene hypothesis of a "universal" biosynthetic mechanism leading to both the triterpenes and the sterols. It also was found that the extra carbon atom, C_{28}, found on C_{24} of the side-chain is not derived from acetate.

During the past few years, much insight has been gained into the mechanism of biosynthesis of the perhydrocyclopentanophenanthrene nucleus and one of the important results has been the establishment of the same or very similar pathway of formation of the steroids and triterpenes.[1-6]

Recently, it was shown in this Laboratory[1] that the tetracyclic triterpene eburicoic acid (I) could be obtained readily in labeled form by allowing the fungus, *P. sulfureus*, to grow on a labeled media. Using carboxyl-labeled acetate as the marked precursor, it was found that this moiety was used as a two-carbon unit, that C_4 of ring A and C_{11} and C_{12} of ring C were derived from the carboxyl of acetate and that the *gem*-dimethyl group of ring A, containing C_{30} and C_{31}, the carboxyl group, C_{21}, and the extra methylenic group, C_{28}, were not derived from the carboxyl of acetate. The location of the labeled atoms as well as the unlabeled atoms are those predicted on the basis of the squalene hypothesis.



I

Although the absence of radioactivity at certain positions in a molecule which has been derived from a carboxyl-labeled acetate strongly suggests that they are derived from the methyl of acetate, it is, indeed, worthy to establish this point by direct experiment. Accordingly, the fungus, *P. sulfureus*, was grown on a standard medium[1,7] which contained methyl-labeled acetate. After processing the dried mycelium in the usual fashion, it was found that the ether-extractable material, which is principally eburicoic acid, amounted to 53% of the dry weight of the mycelium. From this value and the specific activity of the crude extract, it can be calculated that 5.1% of the methyl-labeled acetate was incorporated into ether-extractable substances (mainly eburicoic acid). This incorporation can be compared with a value of 2.3% found with carboxyl-

(1) For the previous paper in this series, see W. G. Dauben and J. H. Richards, THIS JOURNAL, **78**, 5329 (1956).

(2) This work was supported, in part, by grant No. AT(11-1)-34, Project No. 16, U.S. Atomic Energy Commission.

(3) National Science Foundation Predoctoral Fellow, 1954-1955.

(4) For an excellent review of the pertinent work, see J. W. Cornforth, *Rev. Pure Appl. Chem.*, **4**, 286 (1954); C. Popják, *Roy. Inst. Chem.*, Lecture No. 2, 1955.

(5) R. B. Woodward and K. Bloch, THIS JOURNAL, **75**, 2023 (1953); W. G. Dauben, S. Abraham, S. Hotta, I. L. Chaikoff, H. L. Bradlow and A. H. Soloway, *ibid.*, **75**, 3038 (1953).

(6) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(7) W. G. Dauben and J. H. Richards, *Chemistry and Industry*, 94 (1955).