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Reductive Acetylation of Diene-Haloquinone Adducts

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Received August 15, 1958

Adducts from chloranil or 2,5-dichloroquinone with simple dienes were converted in high yields to 2-chloro- or 2,3-dichloro-5,8-dihydro-1,4-diacetoxynaphthalenes by zinc in acetic anhydride in the presence of tertiary amines. Tetrahydro and aromatic derivatives were prepared from the dihydro diacetates. Catalysis of the isomerization-acetylation of quinone-diene adducts by tertiary amines and the acid-catalyzed reaction with isopropenyl acetate are described.

An earlier paper[1] described adducts (I) obtained from dienes and chloranil or dichloroquinones and methods for the selective reductive removal of the angular chlorines to obtain 2-chloro- or 2,3-dichloro-5,8-dihydro-1,4-naphthohydroquinones. Certain disadvantages were apparent in the latter intermediates: they were sensitive to light and air and could not be handled conveniently; although the naphthoquinones could be obtained from them by oxidation *in situ* in 51–85% yields, aromatic hydroquinone derivatives were available only after several laborious steps with further reduction in yield. In addition, derivatives with lower phytotoxicities than either the hydroquinones or quinones[2] were desired for projected biological applications. This paper describes useful direct syntheses for dihydro hydroquinone diacetates which have more tractable properties and are useful intermediates.

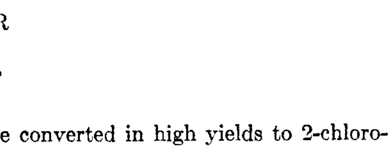
The use[1] of the zinc–acetic acid couple and similar reducing agents with diene-haloquinone adducts (I) was formally analogous to the usual methods for reducing quinones to hydroquinones. To obtain the corresponding diacetates it seemed reasonable to apply a procedure, termed "reductive acetylation," for the conversion of quinones to hydroquinone diacetates, involving zinc dust in acetic anhydride with pyridine as a catalyst.[3]

When I was treated in this manner, a much more vigorous exothermic reaction occurred than is given by quinones. The rather pure dihydro diacetate (II) was isolated in essentially quantitative yield. The reaction was extended to adducts from isoprene, 2,3-dimethylbutadiene, 2-methyl-1,3-pentadiene, and cyclopentadiene to give 6-methyl-, 5,7-, and 6,7-dimethyl-, and 5,8-methylene-derivatives of II in 74–98% yields.

I II

The structure was confirmed by hydrogenation to a tetrahydro derivative and by oxidation to the known aromatic diacetate. The oxidation of these materials with chromic acid was much superior to the use of sulfur at 230–240°. For most of these compounds, the reactions of this paper are the synthetic methods of choice.

The method was also applied successfully to adducts (III) from 2,5-dichloroquinone in 84–88% yields. In this case sulfur was used effectively in the dehydrogenation to an aromatic diacetate.



III

The function of the catalyst was investigated briefly. The cyclopentadiene-chloranil adduct (which is somewhat more labile than the adducts derived from butadienes) gave an infusible black powder and no dihydro diacetate when slowly warmed with zinc dust in acetic anhydride without pyridine. However, other tertiary amines (dimethylaniline and tri-*n*-hexylamine) could be substituted for pyridine without affecting the yield. In other reactions to which pyridine was not added until the mixture had been heated to 50–60°, it was noted that the zinc dust became agglomerated and that these aggregates were destroyed by pyridine, suggesting that reaction occurred on the surface of the zinc, coating it with the zinc salt of the hydroquinone, which did not react with acetic anhydride until the latter was activated by formation of the complex with a tertiary amine. Similar agglomeration of the zinc occurs in the reductive acetylation of quinones in the absence of an amine. The zinc salt was not noted in previous work[1] because it is destroyed by proton acids. Doubtless other active metals or even the homogeneous mixtures which were previously shown to reduce the adducts would serve as well as zinc; the mechanism of the reduction phase has been discussed.[1]

In connection with this work, the synthesis of 5,8-dihydro-1,4-diacetoxynaphthalenes (IV) from simple diene-quinone adducts has been improved.

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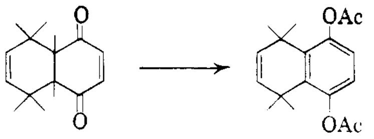
[1] R. Gaertner, *J. Am. Chem. Soc.*, **76**, 6150 (1954); also, U. S. Patents **2,750,427**, June 12, 1956, and **2,773,883**, December 11, 1956.

[2] R. J. W. Byrde and D. Woodcock, *Ann. Appl. Biol.*, **40**, 675 (1953).

[3] L. F. Fieser, W. F. Campbell, E. M. Fry, and M. D. Gates, Jr., *J. Am. Chem. Soc.*, **61**, 3216 (1939).


IV

This reaction had been carried out by simply heating the preformed adduct in acetic anhydride[4a] or by isomerizing and acetylating.[4b–d] It has now been found that both acetic anhydride and isopropenyl acetate are solvents as suitable for the adduction as the recommended acetic acid[5] and that pyridine conveniently catalyzed a rapid exothermic isomerization-acetylation[6] in acetic anhydride without the necessity of isolating the adduct. In the case of the cyclopentadiene-quinone adduct a diacetate with reasonable properties was isolated but the analysis indicated that it had not been freed of the anthrahydroquinone diacetate. The reaction mixture from isoprene and quinone in isopropenyl acetate, when treated with catalytic amounts of sulfuric acid, gave acetone and a 72.5% yield of dihydro diacetate. However, this method was limited in scope, toluquinone and butadiene or 2-methylpentadiene giving only 22–38% yields. Pyridine did not catalyze this reaction.

The synthesis of 1,4-diacetoxynaphthalenes *via* dihydro diacetates using the acetic anhydride-pyridine method, followed by oxidation with sulfur is more convenient and usually gives better yields than either the direct oxidation[5] of the adduct to the quinone followed by reductive acetylation or other less direct methods.[5]

Some reactions typical of double bonds were carried out with the chloranil-butadiene adduct (I). Addition of chlorine and bromine and epoxidation with performic acid occurred in the normal fashion at the 6,7 unsaturation.

EXPERIMENTAL[7]

Reductive acetylation of chloranil and 2,5-dichloroquinone adducts. The reaction mixture usually consisted of 0.02–0.1 mole of preformed adduct[1] with 50% excess zinc dust in fivefold excess acetic anhydride at room temperature. Stoichiometry requires anhydride:zinc:adduct mole ratios of 2:2:1 chloranil adduct and 2:1.5:1 2,5-dichloroquinone adduct. With stirring or swirling about 5 drops of pyridine was added; an exothermic reaction ensued and was controlled by cooling in an ice or water bath. Cooling was especially important with labile adducts such as those from cyclopentadiene and from 2,5-dichloroquinone. If no reaction occurred, the mixture was slowly heated to 50–60° with further dropwise addition of pyridine; if the adduct was impure and contained hydrogen chloride or quinone, additional pyridine was required. When the reaction subsided, addition of more zinc dust or pyridine had no effect and, after brief heating, the reaction was complete. Filtration to remove zinc and cautious addition of water to the warm filtrate to turbidity hydrolyzed the excess anhydride; the products crystallized from the cooled aqueous acetic acid in nearly pure form. They were not noticeably affected by light and air as the dihydro hydroquinones had been. They were recrystallized from methanol-chloroform (decolorized) and sublimed at 1 mm., in some cases, for analysis. The results are summarized in Table I.

Although the chloranil-cyclopentadiene adduct reacted exothermically at 30° in the presence of pyridine, this adduct, when heated slowly with the usual mixture of zinc and acetic anhydride, did not appear to react until, at about 100°, the solution darkened and deposited a black floc. After more of the anhydride had been added and the mixture heated to reflux for 30 min. and cooled to 60°, addition of pyridine caused no reaction. A black infusible powder was the only product.

When tri-*n*-hexylamine and dimethylaniline were added dropwise to the usual reaction mixtures of the chloranil-2,3-dimethylbutadiene adduct, exothermic reactions (rising to 110–120°) gave quantitative and 85% yields, respectively, of the dihydro diacetate, somewhat less pure than the pyridine-catalyzed product.

The application of the pyridine method to two 2,5-dichloroquinone adducts was entirely similar and the results are also listed in Table I.

TABLE I

1,4-DIACETOXY-2,3-DICHLORO-5,8-DIHYDRONAPHTHALENES

			Analyses			
			Calcd.		Found	
Substituent	Yield	M.P., °C.	C	H	C	H
	100	197–199	53.35	3.84	53.42	4.05
5,8-Methano	98	131–132	55.06	3.70	55.29	3.69
6-Methyl	95	166–167.5	54.73	4.29	54.92	4.37
5,7-Dimethyl	74	136–137.5	55.99	4.70	56.49	5.00
6,7-Dimethyl	98	239–241	55.99	4.70	56.27	5.11
2-CHLORO DERIVATIVES						
	88	138–139	59.90	4.67	60.17 60.29	4.87 4.91
6,7-Dimethyl	84	159–160	62.24	5.55	62.88	5.83

Reactions of the dihydro diacetates. Oxidation of the dihydro compounds to aromatic products was carried out by two procedures:

(*a*) A warm solution of 2,3-dichloro-5,8-dihydro-1,4-diacetoxynaphthalene (1.0 g.) in 10 ml. of acetic acid was treated dropwise with a solution of 1.0 g. of chromic acid in the minimum water with cooling to maintain 90–100°. Addition of water, filtration, and recrystallization from chloroform-alcohol gave 0.50 g. of 1,4-diacetoxy-2,3-dichloronaphthalene, identical with the product[8] (m.p. 236–238°) obtained by reductive acetylation (55% yield) of 2,3-dichloro-1,4-naphthoquinone.

(*b*) Dehydrogenation of 2-chloro-1,4-diacetoxy-5,8-dihydro-6,7-dimethylnaphthalene (3.1 g.) with 0.32 g. of roll sulfur at 230–240° for 50 min. gave, from methanol, 1.43 g.

(4a) O. Diels and K. Alder, *Ber.*, **62B**, 2337 (1929). Easily reversed adductions, *e.g.*, "monocyclopentadiene-quinone," gave mediocre yields of bismethyleneoctahydroanthrahydroquinone diacetate by reversal, bis adduction, isomerization-acetylation, and oxidation; yields of diacetates from stable adducts were seldom specified but were probably good. (b) C.-K. Chuang and C.-T. Han, *Ber.*, **68B**, 876 (1935). (c) M. L. Tamayo and J. L. Leon, *J. Chem. Soc.*, 1499 (1948). (d) H. v. Euler and H. Hasselquist, *Arkiv Kemi.*, 2, 367 (1950).

(5) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3165 (1948).

(6) This recalls the similar conversion of ketones to enol acetates by, among others, G. O. Smith, *J. Am. Chem. Soc.*, **75**, 1134 (1953).

(7) Melting points are corrected; boiling points are not. Statements of identity indicate lack of depression of mixture melting points unless other data are given.

(8) C. Graebe, *Ann.*, **149**, 14 (1869).

(47%) of 2-chloro-1,4-diacetoxy-6,7-dimethylnaphthalene; a purified sample was colorless; m.p. 141.5–142.5°.

Anal. Calcd. for $C_{16}H_{15}ClO_4$: C, 62.65; H, 4.93. Found: C, 62.79; H, 5.10.

A similar experiment with the 2,3-dichloro-6-methyl compound gave no isolable product.

Hydrogenation of these dihydro compound to tetrahydro derivatives was carried out in acetic acid in a shaker-type apparatus at 3–4 atmospheres and room temperature over Adams' platinum oxide catalyst. The products were isolated by addition of water and recrystallization from methanol: 1,4-diacetoxy-2,3-dichloro-5,6,7,8-tetrahydronaphthalene, m.p. 181–182° (*Anal.* Calcd. for $C_{14}H_{14}Cl_2O_4$: C, 53.01; H, 4.45. Found: C, 52.64; H, 4.51); the 2,3-dichloro-5,8-methylene analog, m.p. 139–140° (*Anal.* Calcd. for $C_{15}H_{14}O_4Cl_2$: C, 54.73; H, 4.29. Found: C, 54.84; H, 4.48); the 2-chloro compound, m.p. 115.5–116.5° (*Anal.* Calcd. for $C_{14}H_{15}ClO_4$: C, 59.47; H, 5.35. Found: C, 59.93; H, 5.67).

Isomerization-acetylation of diene-quinone adducts. 1. Acetic anhydride-pyridine. The preformed adduct could be used but usually it was prepared in acetic anhydride with 0.4 mole for 0.10 mole of the quinone and 0.11 mole of the diene. After standing 2–4 days in the dark at room temperature, the reaction mixture was treated with 1–4 ml. of pyridine dropwise during heating to 40–70°; an exothermic reaction occurred, the temperature rising to 110–130°. Sensitive adducts were best kept below 100° or lower by external cooling. Brief warming was followed by cautious addition of water to hydrolyze the excess anhydride and the rather pure diacetate was allowed to crystallize. Recrystallization from methanol and/or sublimation *in vacuo* was used for analytical samples. The results are tabulated below.

TABLE II

1,4-DIACETOXY-5,8-DIHYDRONAPHTHALENES

			Analyses			
			Calcd.		Found	
Substituents	Yield	M.P., °C.	C	H	C	H
None[3, 4a]	99	130.5–131.5	68.28	5.73	68.29	5.95
6-Chloro	98	107–109	59.90	4.67	60.19	4.96
2-Methyl[4b]	91	104–105.5	69.21	6.20	69.57	6.11
6-Methyl	100	104.5–106	69.21	6.20	68.80	6.10
5,8-Methano[a]	62	86–88	66.94	5.56	69.75	5.46
5,7-Dimethyl[4d,a]	57	56–59	70.05	6.61	73.14	6.42
6,7-Dimethyl[4c]	100	126–128	70.05	6.61	70.49	6.47
2,6,7-Trimethyl	97	138–139	70.81	6.99	70.36	6.63
2,6- and 2,7-Dimethyl	88	100–120				
6-Chloro-2-methyl and 7-chloro-2-methyl	83	92–100				

[a] These products doubtless contain diacetates from bisdiene adducts[3] from which they could not be freed completely by usual methods.

2. Isopropenyl acetate.[9] The adducts were prepared similarly (four days) in isopropenyl acetate, 0.75 mole for a 0.25 mole run. The most favorable case examined—that of isoprene with quinone—was studied briefly. Addition of catalytic amounts of toluenesulfonic acid and hydrochloric acid to the mixture had no effect, nor did pyridine catalyze the acetylation. Addition of a total of 2 ml. of concentrated sulfuric acid gave, on careful fractionation, 38.5 g. of acetone. Aspiration of the excess reagent gave a brown residue which solidified; it was dissolved in ether, washed with water, dried, the ether removed, and the solid recrystallized from methanol. The yield of diacetate was 72.5%, m.p. 100–102°. Similarly from isoprene and toluquinone, a 22% yield of a mixture of the 2,6- and 2,7-dimethyldihydro diacetates was isolated; m.p. 102–104°. From butadiene and toluquinone 38% of the diacetate was isolated; m.p. 99–102°. As seen from the melting points, these products were not as pure as those obtained similarly from acetic anhydride; furthermore, they contained colored impurities which were troublesome to remove. With butadiene, quinone gave only a little of the dihydronaphthohydroquinone while 2-methylpentadiene gave a dark oil. Chloroprene gave the adduct with quinone, which was recovered in part after acetylation, and with toluquinone, no identifiable product.

The 6,7-dimethyl diacetate (8.22 g.) was hydrogenated as usual giving 7.95 g. (96%) of 1,4-diacetoxy-6,7-dimethyl-5,6,7,8-tetrahydronaphthalene; m.p. 78.5–80°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.95; H, 6.98.

Aromatization was best accomplished by heating with equimolar amounts of sulfur[5]; thus, at 230–240°, a 92% yield of 1,4-diacetoxy-6-methylnaphthalene, m.p. 98–100°, was obtained. Heating at 325° with palladium-on-charcoal and oxidation with chromic acid in acetic acid at 50° were unsatisfactory.

By reductive acetylation,[3] quinones were converted to the diacetates; 1,4-diacetoxy-5,7-dimethylnaphthalene (66% yield); m.p. 105–108° (*Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.60; H, 5.93. Found: C, 70.68; H, 6.02); 1,4-diacetoxy-6-methylnaphthalene (77% yield); m.p. 102–103.5° (*Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 70.13; H, 5.67).

Addition reactions of the butadiene-chloranil adduct. Chlorine was passed into the solution of 6 g. of the adduct in 50 ml. of carbon tetrachloride containing a crystal of iodine. The temperature rose to 45° and slowly dropped to 30°. Aspiration of the solvent left an oil which with methanol crystallized after standing for a week. The dichloride (4.4 g.; 59%) formed cream-colored prisms from methanol-chloroform; m.p. 137–138.5°.

Anal. Calcd. for $C_{10}H_6Cl_6O_2$: C, 32.38; H, 1.63. Found: C, 32.66; H, 2.18.

A mixture of the adduct (4.8 g.), a crystal of iodine, 10 ml. of carbon tetrachloride, and 2.6 g. of bromine was aspirated after two days and the residue crystallized from methanol. The dibromide (0.8 g.) formed colorless flat needles; m.p. 174–176°.

Anal. Calcd. for $C_{12}H_6Cl_4Br_2O_2$: C, 26.12; H, 1.32. Found: C, 26.32; H, 1.72.

When a mixture of 6 g. of the adduct and 3 g. of 29% hydrogen peroxide in 50 ml. of 87% formic acid did not appear to react overnight, it was heated to 55–60° during 1 hr. with stirring, an additional 3-ml. portion of the peroxide added, and the solution heated to 75° briefly. Dilution with water precipitated a gummy solid (4.55 g.; 63%); m.p. 90–113°. Repeated recrystallization with loss from chloroform-methanol gave colorless diamonds; m.p. 167.5–169.5°.

Anal. Calcd. for $C_{11}H_8Cl_4O_5$: C, 38.01; H, 1.91. Found: C, 38.55; H, 2.23.

Perbenzoic acid on the adduct gave an intractable mixture which could not be purified. *N*-Bromosuccinimide and perchloromethyl mercaptan with the adduct failed to give crystalline products.

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(9) H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41,** 2920 (1949), described enol acetate interchange reactions with this reagent.