green-brown oil, 300 ml. eluent, (*3*) 1.36 g., red semi-solid, 650 ml. eluant. Fraction *1* was composed principally of product (1.1 g., 5% as 1-phenyl-2-bromonaphthalene, n_D^{25} 1.6763–1.6768) boiling at 143°/0.45 mm.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 67.86; H, 3.92. Found: C, 68.06; H, 4.22.

Fraction *3* was recrystallized from chloroform-methanol to give 0.154 g. of red needles melting at 197–207°. The melting point of this product, or of one component of the product, was raised to 216–217.3° by subsequent recrystallization.

Anal. Calcd. for $C_{31}H_{22}$: C, 94.38; H, 5.62; mol. wt., 394.5. For $C_{16}H_{10}$: C, 95.01; H, 4.98; mol. wt., 202. Found: C, 94.15, 94.45; H, 5.61, 5.62; mol. wt. (benzene), 199.

2-Carbethoxyindene. Ethyl α-formylhydrocinnamate (41.6 g., 0.202 mole, b.p. 96–98°/0.9 mm., n_D^{25} 1.5142–1.5156, prepared in 22% yield by the method of von Auwers[26]) was added to a warm (70°) solution prepared from phosphorus pentoxide (426 g.) and phosphoric acid (85%, 426 g.). The resulting mixture was stirred vigorously and maintained at 70° for 30 min. The resulting red mixture was poured onto an excess of ice, and the viscous oil was stirred vigorously until the red color disappeared. The hydrolysis mixture was extracted four times with ether and the ether extracts were washed with dilute sodium hydroxide. The basic aqueous wash was extracted once with ether. The combined ether extract was dried, filtered, and distilled to remove solvent. The red oily residue (33.7 g.) was dissolved in the minimum amount of petroleum ether (b.p. 60–68°), absorbed on a column of alumina, and eluted with petroleum ether (b.p. 60–68°). Evaporation of the first eluant fraction (475 ml.) afforded 17.3 g. of product which crystallized from petroleum ether (b.p. 30–60°) as small white needles (16.8 g., 44% yield, m.p. 46.5–49°). Two additional recrystallizations of this product afforded 13.6 g. of 2-carbethoxyindene, m.p. 48.8–50° (reported melting point is 50°).[27]

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.92; H, 6.73.

Reaction of 2-carbethoxyindene, chloroform and potassium t-butoxide. Benzene was removed (at room temperature) from the brilliant blue mixture obtained from 2-carbethoxyindene (13.60 g., 0.0723 mole), potassium *t*-butoxide (0.031 mole), chloroform (2.87 g., 0.024 mole), and benzene (16 ml.). A portion (16.9 g.) of the bluish black residue (21.1 g.) was dissolved in benzene (7 ml.) and chromatographed on alumina (200 g.), using petroleum ether (60–68°) as developer and eluant. A viscous clear blue oil (6.22 g.) was obtained from the first 600 ml. of eluant. This oil was chromatographed again and the crystalline and oily products were processed by recrystallization from petroleum ether; three white crystalline products were isolated in low yield: (A) unchanged 2-carbethoxyindene (m.p. 48–50°), (B) solid B (less soluble in petroleum ether than C), m.p. 95–96°, (C) solid C, m.p. 80–81°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.61; H, 6.43; mol. wt., 188. Found: Solid B; C, 76.72; H, 6.43; mol. wt., (benzene) 254, 218. Solid C; C, 77.18; H, 6.30; mol. wt. (benzene) 300.

MINNEAPOLIS, MINN.

(26) K. von Auwers, *Ann.*, **415**, 99 (1918).

(27) J. Bougault, *Compt. rend.*, **159**, 745 (1914); *Chem. Abstr.*, **9**, 614 (1915).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

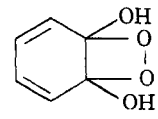
On the Mechanism of Oxidation of *o*-Quinone by Hydrogen Peroxide[1,2]

ARTHUR A. PATCHETT[3] AND BERNHARD WITKOP

Received July 9, 1957

For the hydroperoxide, formed by the action of anhydrous ethereal hydrogen peroxide on *o*-quinone in chloroform solution, structure VIII is suggested which makes it a derivative of *o*-quinone dimer (IV). The latter has been crystallized and its structure proven by rearrangement to the catechol V, which was characterized by its phenazine derivative VI. The products arising from acid- and base-catalyzed rearrangements and by hydrogenation of the hydroperoxide VIII were studied chromatographically (Fig. 1 and 2), electrophoretically (Fig. 3) and chemically (Chart I). A major product, obtained in the base-catalyzed rearrangement of VIII and in the oxidative cleavage of *o*-quinone dimer (IV) by hydrogen peroxide, is also present in the mother liquors of VIII; it is 2,3,6-tricarboxy-4-cyclohexeneacrylic acid X which was converted by partial hydrogenation and oxidation to an epimer (presumably XVa or b) of cyclohexane-1,2,3,4-tetracarboxylic acid. By reduction of the hydroperoxide VIII with Lindlar catalyst a phenolic (or diosphenolic, *cf.* IX) compound $C_{12}H_{12}O_6$ was obtained which could be converted *via* its hexahydro derivative XII to 2,3,6-tricarboxycyclohexanepropionic acid (XI), the hydrogenation product of X.

The mechanism of the enzymatic oxidation of catechol to *cis,cis*-muconic acid (III) by pyrocatechase,[4] has been discussed in terms of an intermediate peroxide II or its cyclic tautomer XVII.[5] The enzymatic intermediate, be it II or XVII, was directly derived from catechol and oxygen, thus rul-



XVII

(1) This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

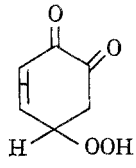
(2) Oxidation Mechanisms. XX. Preceding papers in this series, *cf.* ref. 5 and *J. Am. Chem. Soc.*, **79**, 3191 (1957).

(3) Present address, Research Department, Merck Sharp and Dohme, Rahway, N. J.

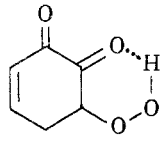
(4) O. Hayaishi, M. Katagiri, and S. Rothberg, *J. Am. Chem. Soc.*, **77**, 5450 (1955).

(5) O. Hayaishi, A. A. Patchett, and B. Witkop, *Ann.*, **608**, 158 (1957). Corrections should be made for some typographical error in the experimental part, p. 166, as follows: line 18: molecular weight of peroxide $(142.1)_2$; lines 20 and 36: Tetracarbonsäure $C_{12}H_{12}O_8$; line 31: Tetracarbonsäure $C_{12}H_{16}O_8$.

ing out an alternate pathway proceeding *via* *o*-quinone (I). Attempting the synthesis of such intermediate peroxides derived from *o*-quinone, we studied the action of hydrogen peroxide on *o*-quinone in the absence of catalytic agents. Peracids oxidize *o*-quinone to *cis,cis*-muconic acid, whose transformation products, rather than precursors, have been observed in this reaction.[6] An intermediate such as the hydroxyhydroperoxyketone II has so far not been noticed. We investigated the action of hydrogen peroxide in dry organic solvents. This reagent is capable of adding to carbonyl groups in ketones and aldehydes to yield a variety of peroxidic substances.[7] Whereas the simplest addition product of H_2O_2 to a ketone, the peroxyhydrate > C(OH)OOH is apparently not observed, a few cases are known where α,β-diketones add ethereal H_2O_2 to give compounds which have been formulated as hydroxyhydroperoxides derived, *e.g.*, from alloxan[8] and dimethyl diketosuccinate.[9] The system *o*-quinone and hydrogen peroxide theoretically might undergo 1,4- or, less likely, 1,6-Michael addition of hydrogen peroxide to give the intermediate hydroperoxides XVIII and XIX, analogous to similar additions in *o*-quinone chemistry.[10] 4,5-Double addition has been reported with ethyleneimine.[11]



XVIII



XIX

Special conditions for the oxidation had to be observed: a 1.5 molar quantity of dry ethereal hydrogen peroxide[7] at 0° was added to a large quantity of chloroform containing one mole of *o*-quinone. Since hydrogen peroxide is not particularly soluble in chloroform a dispersion of what we assume to be fine droplets of concentrated hydrogen peroxide resulted when the ethereal hydrogen peroxide and the chloroform were mixed. The oxidation was allowed to proceed at −5° for about fifteen hours. An insoluble crystalline hydroperoxide (15%) was then collected and the reaction mixture was further worked up, as described previously,[5] to yield *cis,cis*-muconic acid (5–15%) and a tetracarboxylic acid, $C_{12}H_{12}O_8$ (20–25%) with a total balance of isolated products of 40–50%.

When it was discovered that the hydroperoxide could not be converted to *cis,cis*-muconic acid, either by enzymatic or by chemical means, the purely chemical and structural aspects eclipsed the biochemical problem.

Structures XVIII and XIX (expected λ_{max} 255, *cf.* quinone dimer IV), resulting from Michael addition could be ruled out for the hydroperoxide (λ_{max} 230, ϵ 8300). Furthermore, such structures could have gone to the corresponding hydroxyquinones, *e.g.*, to hydroxy-*p*-quinone (from XVIII), a precursor of humic acid,[12] or 3-hydroxy-*o*-quinone (from XIX), a precursor of purpurogallin,[13] neither of which was observed. Various mild hydrolytic and reductive conditions, led to C_{12}-compounds, among them the tetracarboxylic acid, $C_{12}H_{12}O_8$, which is also isolable from the mother liquors of the peroxide. Assuming, in the simplest case, that the hydroperoxide itself was a C_{12}-compound, we suspected dimerization (or polymerization) of *o*-quinone to antecede oxidation by hydrogen peroxide.

In his classical investigations of *o*-quinone, Willstätter[14] had isolated a yellow decomposition product of *o*-quinone which he believed to be dimeric, although no molecular weight was reported. Later workers have occasionally encountered it[15] but gave no proof for its molecular weight and structure. We prepared some of the material in very small yield by refluxing a dry ethereal solution of *o*-quinone and recrystallizing the insoluble precipitate from acetone. The compound formed bright yellow crystals, m.p. 194–196°, and gave a molecular weight of 218 (Rast, calculated 216). In analogy to the structure of a number of dimeric substituted *o*-quinones[16] and *o*-quinonedibenzimides,[17] *o*-quinone dimer may be formulated as IV. The spectral data are in agreement with this structure.

The ultraviolet absorption at 254 mμ (ϵ 7500) compares favorably with a value of 252 (log ϵ 3.95) for the analogous dimer of 4,5-dimethyl-*o*-quinone.[18] In support of the Diels-Alder structure for the *o*-quinone dimer was its mild acid-catalyzed rear-

(6) J. Böeseken, *Proc. Acad. Sci. Amsterdam*, **35**, 750 (1932); J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer, and D. B. Pattison, *J. Chem. Soc.*, 2228 (1950).

(7) A. V. Tobolsky and R. B. Mesrobian, *Organic Peroxides*, Interscience, New York, 1954, p. 44; R. Criegee, in Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, Vol. 8, 1952, p. 44.

(8) B. Witkop, S. Goodwin, and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5813 (1954).

(9) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5599 (1954).

(10) L. Horner and K. Sturm, *Ann.*, **597**, 1 (1956); R. Willstätter and H. E. Müller, *Ber.*, **44**, 2187 (1911); C. L. Jackson and W. Koch, *Ber.*, **31**, 1458 (1898); *Am. Chem. J.*, **26**, 21 (1901). *Cf.* H. Jackson and C. P. Kendall, *Biochem. J.*, **44**, 477 (1949).

(11) L. Horner and H. Lang, *Ber.*, **89**, 2773 (1956).

(12) J. M. Nelson and C. R. Dawson, *Advances in Enzymol.*, **4**, 114 (1944).

(13) A. Critchlow, R. D. Haworth, and P. L. Pauson, *J. Chem. Soc.*, 1318 (1951).

(14) R. Willstätter and H. E. Müller, *Ber.*, **44**, 2187 (1911).

(15) J. L. E. Erickson and J. M. Dechary, *J. Am. Chem. Soc.*, **74**, 2644 (1952).

(16) L. Horner and K. Sturm, *Ann.*, **597**, 1 (1955); H. J. Teuber, *Angew. Chem.*, **68**, 420 (1956); H. J. Teuber and G. Staiger, *Ber.*, **88**, 802 (1953); E. Adler, *Angew. Chem.*, **69**, 272 (1957).

(17) R. Adams and J. W. Way, *J. Am. Chem. Soc.*, **76**, 2763 (1954).

(18) L. Horner and K. Sturm, *Ann.*, **597**, 1 (1955).

rangement to a catechol (V) and the preparation of a phenazine (VI) which gave a positive ferric chloride test.

By oxidation of *o*-quinone dimer (IV) with hydrogen peroxide in chloroform at −5° for one week a good yield (~80%) of the tetracarboxylic acid $C_{12}H_{12}O_8$ was obtained. Unfortunately, *o*-quinone dimer (IV) was very insoluble in this mixture, and the reaction had to be continued for a much longer time than for *o*-quinone itself. Hydroxyhydroperoxy intermediates, which hardly could have survived these extended conditions, could not be isolated. The structure which we propose for the hydroperoxide has to rest, therefore, on indirect evidence rather than on a direct synthesis.

The $C_{12}H_{12}O_8$ acid is a tetracarboxylic acid which shows only end absorption in the ultraviolet. It was characterized as its tetrabenzhydryl ester and by conversion to a tetrahydro derivative whose chromatographic behavior is shown in Fig. 1, column 1. The derivation of this acid from *o*-quinone dimer and the available data permit its structural assignment as X.

Fig. 2 summarizes the chromatographic data which we obtained in an attempted conversion of

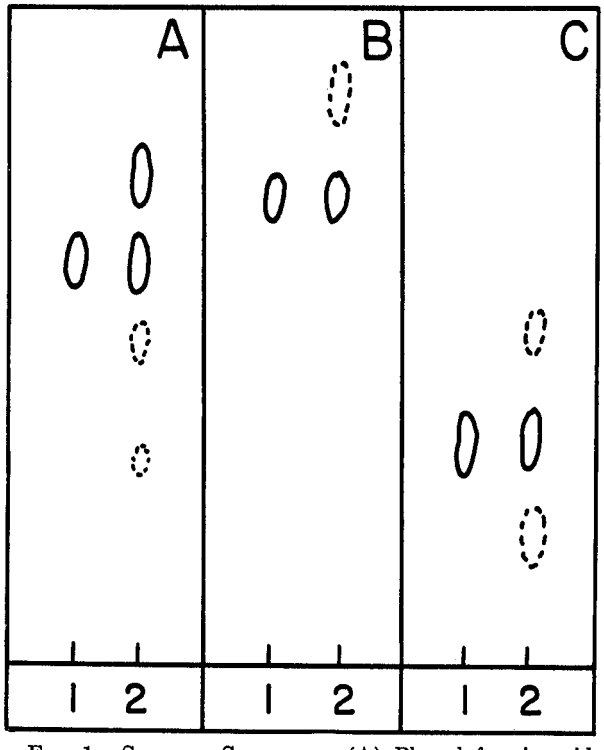


FIG. 1. SOLVENT SYSTEMS: (A) Phenol formic acid-water (120 g: 1.6 cc: 40 cc.), R_F value of 0.6; (B) *sec*-butanol-formic acid-water (75:15:10), R_F 0.7; (C) 99% of a mixture of 2 pts. of methanol, 1 part of benzene, 1 part of *n*-butanol and 1 part of water, and 1% of a 15% aqueous ammonia solution, R_F value 0.3.

1. Analytically pure tetrahydro tetracarboxylic acid XI, m.p. 211–213°; 2. Oxidation mixture from dimethyl ester of XII with periodic and peracetic acid followed by hydrolysis. The spot in solvent system A, in a separate experiment not recorded here, was eluted and rechromatographed in systems B and C to give spots identical with XI.

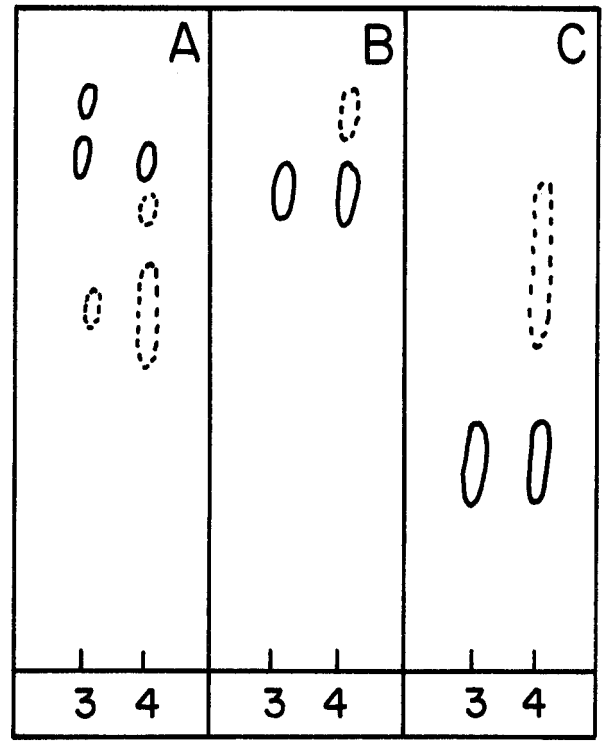
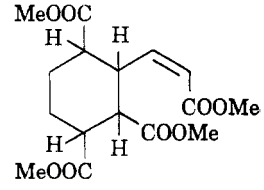


FIG. 2. THE SOLVENT SYSTEMS A, B, C, ARE THE SAME AS IN 1. The products obtained by acid hydrolysis of the tetramethyl ester of XVa are shown under 3, the oxidation products resulting from nitric acid oxidation of the partial hydrogenation product from X are shown under 4.

the acid X to a known cyclohexane-1,2,3,4-tetracarboxylic acid. In order to increase the differential reactivity of the double bonds for the purpose of partial hydrogenation, acid X was converted to its oily tetramethyl ester. The reduction of this ester was stopped after the uptake of one mole of hydrogen. Presumably a considerable quantity of the dihydroester XXI was then in hand. Vigorous oxidation of this ester with refluxing nitric acid, followed by partial purification *via* the (mono) anhydride, led to an acid mixture, one of whose R_f values was identical with one of the two acids derived by acid hydrolysis of authentic tetramethyl *trans-cis-trans*-cyclohexane-1,2,3,4-tetracarboxylate, (XVa, m.p.

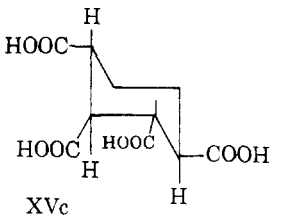


XXI

(19) We are greatly obliged to Professor Kurt Alder for his kind donation of samples of this ester as well as of the all-*cis*-acid XIV, and for information on the epimerization of XVa to the *all-trans*-acid by acid. The acid (XIV) has been described: K. Alder and H. Vagt, *Ann.*, **571**, 153 (1950) and E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 899 (1929). The acid XVa and its epimers are described in Dipl. Arbeit of R. Reeber, Cologne 1949; Diss. Cologne 1951.

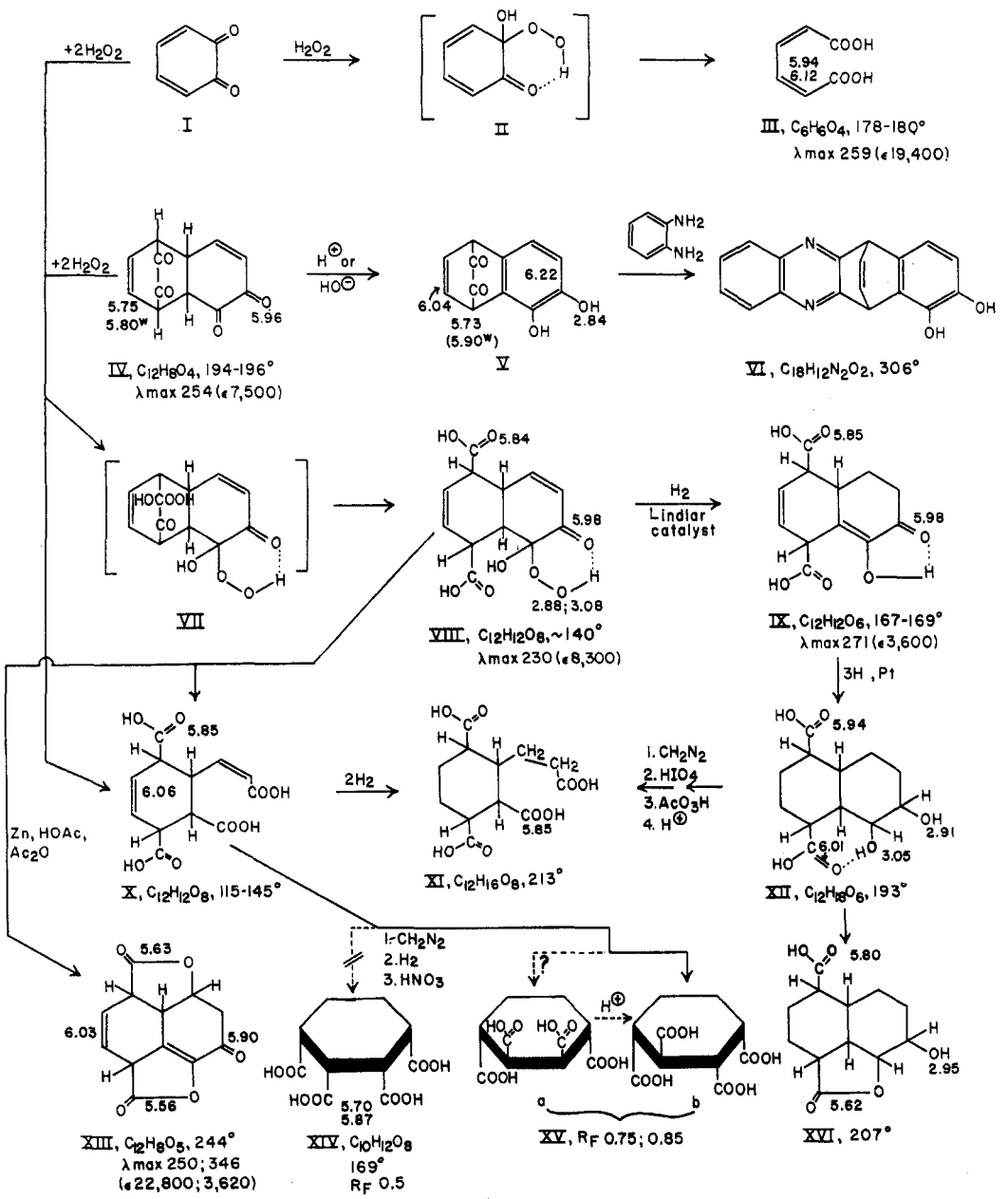
71°).[19] This identity of one of the degradation products with a cyclohexane-1,2,3,4-tetracarboxylic acid is a welcome confirmation for the proposed structure X. No stereochemical assignments for X are made at this point in view of the appearance of *two* spots in the chromatogram of the hydrolyzate of the tetramethylester of XVa.

It was unfortunate that the acid hydrolyzate of authentic tetramethyl *trans-cis-trans*-cyclohexane-1,2,3,4-tetracarboxylate gave two spots. We feel that the conditions were sufficient to effect complete hydrolysis and conclude that epimerizations in this series vitiate steric correlations. The epimerization of the *trans-cis-trans* cyclohexane-1,2,3,-4-carboxylic acid (XVa, preferred constellation 2 equatorial, 2 axial substituents) to the *all-trans-epimer* (XVc, 4 equatorial carboxyls) by the action of strong acid is known.[19] It would be expected to lead through XVb (3e, 1a carboxyl).



XVc

With a knowledge of structure X for the $C_{12}H_{12}O_8$ acid, structure VIII for the hydroperoxide may be envisaged. The spectral data (Chart I) for the hydroperoxide are in agreement with such a structure. Recrystallization of the hydroperoxide was not possible, but the analytical values for the crude



material were close to those calculated for $(C_6H_6O_4)_2$. Titration with base furnished a neutralization equivalent of 136 (theor. 142). The peroxidic nature was evidenced by the liberation of I_2 from acidified KI, by the liberation of oxygen with lead tetraacetate, and by decomposition by mechanical force or by heat. One of the infrared bands coincides with the —OOH band at 2.88.[20] An iodometric determination of the active oxygen content gave a value of 5.7% (theor. 5.6%). An alternative dihydroperoxide formulation VII for the peroxide VIII was also considered. It necessitates the assumption that the hydroperoxide function, derived from the bicyclic diketone system, rearranges rapidly to a diacid in the course of the determination of both neutralization equivalent and active oxygen content. We prefer the simpler explanation that the hydroperoxide as isolated is indeed VIII, and VII its labile nonisolable precursor. The 5.84 μ band in the hydroperoxide, which belongs to the carboxyls, is about twice as intense as the conjugated ketone band at 5.98 μ, as might be expected for structure VIII.

Attempted rearrangement of the hydroxyhydroperoxide VIII under various solvolytic conditions has been briefly studied. Under *acidic conditions* overnight there is little change in the neutralization equivalent and in the active oxygen titer; however, a *new* phenolic substance (m.p. 192–194°), not identical with IX (m.p. 169°), is formed, although the latter gives a major spot on the pherogram (Fig. 3) in an identical position. On the other hand, dilute aqueous *base* at room temperature, led to a pronounced decrease in the neutralization equivalent of such solutions. After twenty-four hours, the active oxygen content had dropped to virtually zero and the increased alkali consumption corresponded very closely to that expected for the formation of two additional carboxyls. Electrophoretic analysis with the Wieland-Pfleiderer pherograph[21] (Fig. 3) showed that the product was the tetracarboxylic acid X unaccompanied by the acid formed under acidic conditions. Acid- and base-catalyzed oxidative cleavages of diketones by hydrogen peroxide are well-known reactions. Anhydride formation has been observed under acid catalysis.[22] Authentic X, as pure as it can be obtained by repeated recrystallization, shows a contaminant, presumably the C2-epimer or the geometric *trans*-isomer of the acrylic acid group.

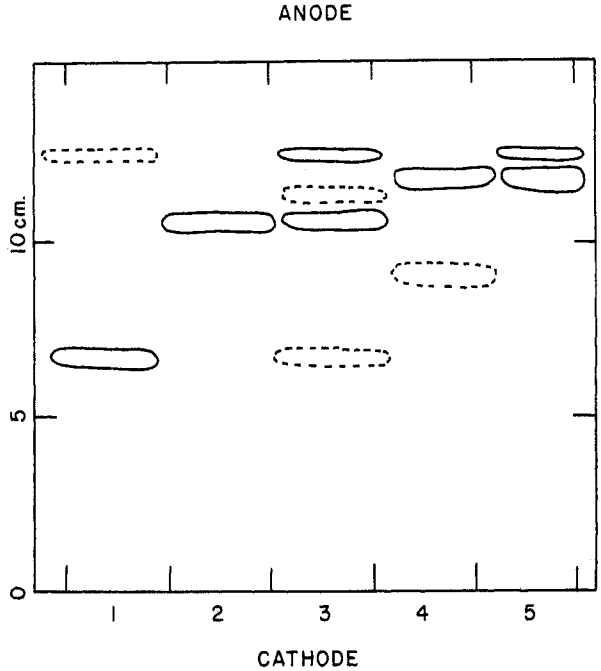
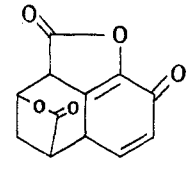


FIG. 3. SEPARATION OF THE HYDROPEROXIDE VIII AND ITS TRANSFORMATION PRODUCTS IN AN ELECTRIC FIELD OF APPROXIMATELY 50 VOLTS PER CM., OVER A PERIOD OF 65 MINUTES IN BUFFER pH 6.5 (PYRIDINE ACETIC ACID WATER 100:10:890) IN A PHEROGRAPH ACCORDING TO WIELAND AND PFLEIDERER. The spraying agent was ammoniacal bromophenol blue. 1. Hydroperoxide VIII in aqueous solution. 2. Hydroperoxide in 5 N hydrochloric acid after twelve hours at 5°. 3. Dicarboxylic acid $C_{12}H_{12}O_6$ (IX). 4. Hydroperoxide, after standing in 1 *N* sodium hydroxide for 12 hours at 5°. 5. Tetracarboxylic acid $C_{12}H_{12}O_8$(X).

Two further substances were obtained in reductions of the hydroperoxide VIII. One is a dilactone formed by the action of zinc in glacial acetic acid on the hydroperoxide. It is isolated in very poor yield by sublimation after the crude reduction product has been treated with acetic anhydride and sodium acetate. On the basis of its composition ($C_{12}H_8O_5$) molecular weight (235, theor. 232), ultraviolet [λ_{max} 250 mμ (ϵ 22,800) and 346 mμ (ϵ 3620)] and infrared bands [at 5.56, 5.63, 5.90, and 6.03 (w) μ] and its neutral character, structures XIII or XXII are considered not unreasonable suggestions.



XXII

A second substance obtained in modest yield in the reduction of the hydroperoxide using Lindlar[23] catalyst has the composition $C_{12}H_{12}O_6$. The material is a dibasic acid with a neutralization equivalent 129 (theor. 126), molecular weight 259 (theor. 252) and major infrared bands at 2.95, 5.86, 5.97, and 6.04 (w) μ (Nujol). There was no absorption in the aromatic region between 6.04 and 6.85 μ. Its ultraviolet spectrum showed λ_{max} 271 mμ (ϵ 3600), shifted by base to 318 mμ (ϵ 2540). This acid on paper responded to several sprays: it reduced ammoniacal silver solution at room temperature,

(20) O. D. Shreve, M. R. Heether, H. B. Knight, and D. Swern, *Anal. Chem.*, **23**, 282 (1951).

(21) Th. Wieland and G. Pfleiderer, *Angew. Chem.*, **67**, 257 (1955).

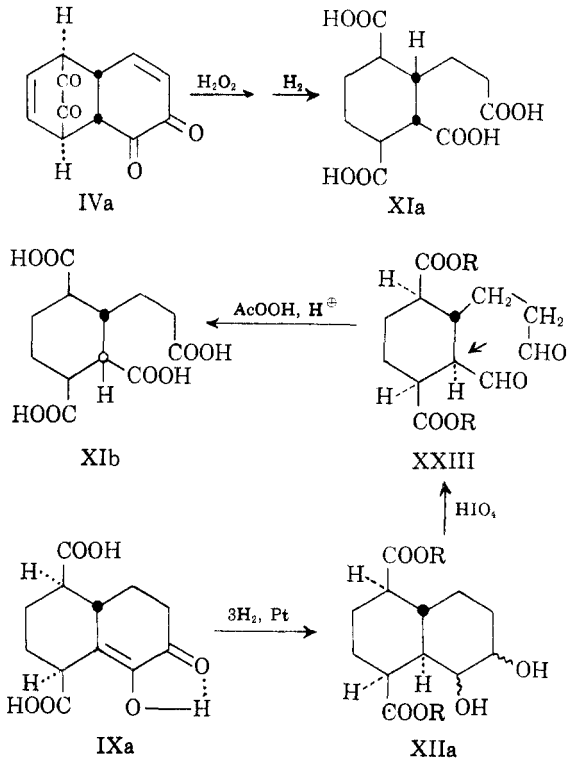
(22) J. E. Leffler, *J. Org. Chem.*, **16**, 1785 (1951).

(23) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

gave a weak greyish purple color with 1% $FeCl_3$ in 0.1*N* HCl, showed a greenish-grey color on treatment with phosphomolybdic acid followed by ammonia gas, and yielded an orange spot with diazotized sulfanilic acid. No phenazine could be prepared, but an oily red precipitate resulted after about ten minutes from the reaction (room temperature) with ethanolic 2,4-dinitrophenylhydrazine in the presence of sulfuric acid. The enolic properties of this compound seem to be best explained by the diosphenol structure IX because of the chemical and infrared evidence for carbonyls in the substance other than those belonging to the carboxyls. The shift of the ultraviolet absorption by base to higher wave lengths but lower intensity is also generally taken to be evidence for a diosphenol chromophore.[24,25] However, the low intensity[25] of the 271-mμ band is more like that of a phenol than that of a diosphenol. In addition, we were unable to find precedent for the reduction of the hydroperoxide VIII to yield a diosphenol such as IX. The substance was further characterized by its dibenzhydryl ester which gave a positive $FeCl_3$ test. The infrared bands of this ester were at 2.91, 5.76, 5.95, and 6.01 (w) μ.

A correlation with the tetracarboxylic acid X was achieved by reduction of the $C_{12}H_{12}O_6$ acid to its hexahydro derivative $C_{12}H_{18}O_6$ XII of unspecified configuration. This substance gave no $FeCl_3$ test. On treatment with hydrobromic in glacial acetic acid it formed a lactone XVI. The oily dimethyl ester was oxidized by periodic acid at 80° for ten hours, followed by peracetic acid oxidation at 80° for one hour and hydrolysis of the ester groups with 5*N* hydrochloric acid. Chromatography of the ether-soluble acidic fraction gave material showing R_f values in three different solvent systems (Fig. 1) identical with those of the tetrahydro acid XI obtained from X.

Stereochemical considerations. If one applies the "*endo*-rule"[22] for Diels-Alder reactions of cyclic dienes the configuration of *o*-quinone dimer IV should be expressed by IVa. Accordingly, the tetrahydrotetracarboxylic acid XI would be XIa. On the other hand, acid XI was also identified by paper chromatography to result from XII by a number of steps whose steric course is not certain. For instance, the uptake of hydrogen by IXa from the less hindered side may lead to XIIa. The glycol XIIa, on the other hand, may, at the stage of the dialdehyde (XXIII), epimerize again (arrow). The position of the 2-carboxy group in XIb (open circle) must be left open. The same uncertainty attaches to the conversion of the dehydro precursor of XIa to XVa or XVb.



EXPERIMENTAL[27]

Acid- and base-catalyzed rearrangements of o-quinone-dimer hydroperoxide (VIII). *A. Neutral conditions.* The hydroperoxide VIII[5] (20.3 mg.), containing 5.7% active oxygen (calcd. 5.62%), was dissolved in 10 cc. of water and titrated with 0.0321*N* NaOH to the phenolphthalein end point. The found neutralization equivalent was 127 (other determination on fresher hydroperoxide sampler gave 136, calcd. 142). After standing overnight (17 hr.) there was added to this neutral solution excess potassium iodide and 4 cc. of 3.6*N* H_2SO_4. The iodine was liberated slowly; the reaction mixture was titrated after standing for 10 min. The total volume of 0.0228*N* $Na_2S_2O_3$ solution was 5.6 cc., equivalent to 5.04% active oxygen.

B. Basic conditions. The hydroperoxide VIII (22.6 mg.) was dissolved in 10 cc. of water and neutralized as before (needed 5.64 cc. of 0.321 NaOH). Then was added 1.28 cc. of base (0.0321*N* NaOH) and left standing for 24 hr. Back titration with HCl to a phenolphthalein end point required 9.9 cc. of 0.0207*N* HCl. Considering this and the amount of excess alkali added, it is evident that 0.57 mmole of alkali was consumed after the initial neutralizations. The sample represented 0.079 mmole (22.6/286), hence each mole consumed two additional moles of alkali to form the sodium salt of the tetracarboxylic acid. The pherogram (Fig. 3) of an alkaline solution of the hydroperoxide was made in the same way: after neutralization and evaporation to dryness the rearrangement product was taken up in buffer *p*H 6 (pyridine-water-HOAc) and chromatographed as indicated in Fig. 3. The major product was at the same spot as the tetracarboxylic acid X.

C. Acid catalysis. The hydroperoxide VIII (23.2 mg.) was dissolved in 10 cc. of water and left overnight with 10 cc. of 0.0207*N* HCl. The titration of 0.0227*N* NaOH to the phenolphthalein end point gave a neutralization equivalent of 145. The active oxygen content of this solution amounted to 3.1% of the sample weight. The pherograph showed only one single spot (Fig. 3) at the same place where the di-

(24) D. Lavie, *Chemistry & Industry*, 466 (1956).
(25) D. H. R. Barton and J. F. Eastham, *J. Chem. Soc.*, 424 (1953).
(26) M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948).
(27) All melting points are corrected.

carboxylic acid IX has a major spot. Since IX could not possibly be formed in this rearrangement, the rearrangement was done on a preparative scale by evaporating the solution of 20 mg. of the hydroperoxide in 4 cc. of 4*N* HCl slowly in a desiccator and isolating the solid residue which could be washed and freed of colored impurities by repeated extraction with cold ether to yield a colorless crystalline powder, m.p. 192–194° (sintering 188°, clear, slightly yellow melt with bubbles at 200°). λ_{max}^{EtOH} 290 mμ (ε 2210); λ_{max}^{Nujol} 5.63, 5.84 μ; no bands between 6.0–6.85 μ. This compound gave a poor ferric chloride test (lactone involving one phenolic hydroxyl?); the ether washings gave a distinct green color with $FeCl_3$.

Dilactone (XIII or XXII) *by the reduction of the hydroperoxide* VIII *with zinc dust.* Glacial acetic acid (15 ml.) was stirred at 60–70° and to this was added in small portions during 5 min. a finely ground mixture of 1.00 g. of the peroxide and 6.00 g. of zinc dust. Fifteen min. after the addition was complete, the solution was filtered and concentrated to dryness. Acetic anhydride (7.5 ml.) and 0.75 g. of fused sodium acetate was added and this acetylating mixture was heated on the steam bath for 3 hr. with the exclusion of moisture. Much of the excess acetic anhydride was removed *in vacuo* and the residue was treated with 0.5*N* HCl and extracted with ethyl acetate. The dried solution left a reddish brown oil which was extracted with 15 ml. of hot benzene. The benzene solution on cooling deposited 0.22 g. of an orange powder. This material sublimed very slowly in high vacuum at 200° to yield a colorless oil and a bright yellow powder. The latter could be recrystallized from methanol to yield 0.018 g. of yellow, cotton-like crystals, m.p. 244°. The major infrared bands were at 5.56, 5.63, 5.90, and 6.03 μ (KBr pellet) and in the ultraviolet λ_{max} 250 mμ (ε 22,800) and 346 mμ (ε 3620) in ethanol, shifted by base to λ_{max} 248 mμ (ε 18,400), 305 mμ (ε 1980) and 345 mμ (ε 2160). A Rast determination in camphor gave a molecular weight of 235, calculated 232.

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.07; H, 3.47. Found: C, 61.79; H, 3.09.

o-Quinone dimer (IV). 1.0 g. *o*-Quinone[28] was refluxed in 400 ml. of dry ether with anhydrous magnesium sulfate for 8 hr. At the end of this time the magnesium sulfate and precipitated material was filtered off and extracted with a total of about 250 ml. of hot acetone. This filtered yellow acetone solution was concentrated until crystals of *o*-quinone dimer appeared. The yield was 0.061 g. of shining yellow plates of m.p. 192–193°. A sample recrystallized from acetone showed m.p. 194–196°. The ultraviolet spectrum was characterized by λ_{max} 254 (7500) and in the infrared bands were at 5.68 (w), 5.75, 5.80 (w), 5.96, and 6.17 (w) μ. Its molecular weight by the Rast method was 218.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.54; H, 4.00.

Rearrangement by acid. When this material was warmed with ethanolic HCl for several minutes on the steam bath and then taken to dryness, the prominent infrared bands were 2.84, 5.73, 5.90 (w), 6.04 (w), and 6.22 (w).

Phenazine derivative VI *of rearranged o-quinone dimer* (V). *o*-Quinone dimer (0.020 g.) was heated on the steam bath with 0.5 ml. of acetic acid and 0.005 g. of anhydrous sodium acetate for 5 min. *o*-Phenylenediamine (0.015 mg.) was then added in 0.5 ml. of methanol. Gentle heating was continued for 30 min. with occasional replenishment of the methanol. Crystallization occurred during this period and was allowed to proceed at room temperature for 3 hr. The crude phenazine weighed 0.019 g. and was of m.p. 304–306° (dec.). With anhydrous $FeCl_3$ in diethylene glycol dimethyl ether (diglyme)[29] it gave a greenish black color changing to deep blue on the addition of a small amount of pyridine. The infrared showed no carbonyl absorption.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.10; H, 4.50; N, 9.31.

Tetracarboxylic acid X *by the oxidation of o-quinone dimer.* *o*-Quinone dimer (IV, 0.100 g.) was added to a suspension of ethereal H_2O_2 (1.5 × theoretical for 2 moles) in 10 ml. of chloroform. The dimer would not dissolve in this mixture and, therefore, the reaction had to be conducted at −5° for 1 week before it had gone to completion. At the end of this time, the chloroform was decanted and evaporated to dryness leaving 0.024 g. of an oil which was shown by paper chromatography to be a mixture of the tetracarboxylic acid X and a second as yet unidentified acid. Left behind in the original flask after the chloroform had been decanted was an oil which dissolved completely in ether. Evaporation of the ether left a foam weighing 0.102 g. and on crystallization from ether and chloroform an acid was obtained in good yield of m.p. 137–148° which was identical with X by infrared comparison. The identity was confirmed by paper chromatography in three solvent systems: phenol:water:formic acid 75:25:1; 1-butanol:formic acid:water 10:2:15; 1-butanol:benzyl alcohol:water:formic acid 45:45:9:1.

Diacid $C_{12}H_{12}O_6$ (IX, *m.p. 167–169°*) *by the reduction of the hydroperoxide* VIII *with Lindlar's catalyst.* One g. of Lindlar catalyst[23] was prereduced in 150 ml. of ethyl acetate. A fine powder of the hydroperoxide (2.00 g.) was added and the reduction was allowed to go to completion. The uptake of hydrogen was 255 ml. (74% of theory for one —OOH group per molecular weight 142). Evaporation of the ethyl acetate left a foam which was submitted to partition chromatography. The supporting phase was 200 g. of silicic acid moistened with 100 ml. of water. The elution mixture consisted of ether and chloroform (1:1) saturated with water; 175-ml. fractions were collected. A dark colored oil came out in the first two fractions. From the 3rd to the 7th fraction an oil appeared which was recrystallized from ether and cyclohexane. This acidic material weighed 0.410 g. (23%) and had m.p. 160–163°. An analytical sample crystallized from the same solvent mixture showed m.p. 167–169°, molecular weight 259 (Rast) and neutralization equivalent 129. The ultraviolet spectrum showed λ_{max} 271 mμ (ε 3600) in ethanol and 318 mμ (ε 2540) in ethanol with base added. The infrared spectrum showed bands at 2.95, 5.86, 5.97, and 6.04 (w). The substance liberated carbon dioxide from $NaHCO_3$ solution, it gave a black-brown color with $FeCl_3$ in diethylene glycol dimethyl ether[29] with added pyridine[29] and it yielded an oily 2,4-dinitrophenylhydrazone after 5 to 10 min. with 2,4-dinitrophenylhydrazine in ethanol with H_2SO_4 as a catalyst. On paper it became visible by spraying with ammoniacal silver nitrate solution which was reduced instantaneously without warming. A 1% solution of $FeCl_3$ in 0.1*N* HCl produced a weak greyish purple color. A greenish grey color with phosphomolybdic acid developed in an atmosphere of ammonia gas. No crystalline phenazine could be prepared when the acid was heated with *o*-phenylenediamine in acetic acid and methanol in the usual manner. Bismuth oxide in hot acetic acid was reduced to a black precipitate.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.07; H, 4.75.

Dibenzhydryl ester. Diphenyldiazomethane in slight excess of 2 moles yielded a dibenzhydryl derivative. The reaction was conducted overnight in a small amount of methanol and ether. Two crystallizations of the crude product from ethyl acetate gave the benzhydryl ester m.p. 182–184° with infrared absorption at 2.91, 5.76, 5.95, and 6.01 μ. The substance gave the same $FeCl_3$ color reaction as the parent acid.

Anal. Calcd. for $C_{38}H_{32}O_6$: C, 78.06; H, 5.52. Found: C, 77.88; H, 5.76.

Hexahydrodicarboxylic acid (XII). Platinum oxide (0.1 g.) was prereduced in 95% ethanol and to this was added 0.100 g. of the dicarboxylic acid (IX) which had been prepared by reduction of the hydroperoxide VIII in the pres-

(28) S. Goldschmidt and F. Graef, *Ber.*, 61, 1868 (1928).

(29) S. Soloway and S. H. Wilen, *Ann. Chem.*, 24, 979 (1952).

ence of Lindlar's catalyst. The hydrogenation was allowed to go to completion. The uptake was 24 cc. (2.5 moles) of hydrogen. After completion of the hydrogenation the solution was filtered and evaporated to dryness and the residual oil was dissolved in ethyl acetate. Addition of chloroform precipitated 0.02 g. of amorphous material. The mother liquor was then crystallized from ethyl acetate and petroleum ether (b.p. 65°) to yield 0.047 g. of the hexahydrocarboxylic acid (XII) as colorless prisms of m.p. 168–170°. The substance showed no ferric chloride test. One more crystallization from the same solvent mixture gave the analytical sample, m.p. 192–194°.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.51; H, 7.04.

Lactonization (XVI). A solution of XII in glacial acetic acid containing a drop of concentrated hydrobromic acid (48%) left on evaporation in the desiccator at 20° fine feathery crystals, m.p. 205–207°, at 180° sublimation and transformation to stubby cubes. Although the analysis (found: C, 57.89; H, 6.62) indicated incomplete lactonization or retention of $^1/_2$ mole of water (dried at 100° *in vacuo*), the infrared spectrum (KBr pellet) showed a strong saturated lactone band at 5.62 μ in addition to a band for COOH at 5.80 μ.

Conversion of the hexahydrodicarboxylic acid (XII, *m.p. 194°*) *to the 2,3,6-tricarboxycyclohexanepropionic acid* (XI). A solution of 70 mg. of the hexahydrodicarboxylic acid XII in 5 cc. of absolute ether was reacted at room temperature with 4 cc. of a 0.2*N* ethereal solution of diazomethane. After completion of the reaction and evaporation to dryness the oily dimethyl ester was taken up in 10 cc. of 50% aqueous dioxane. Three equal portions of this solution were mixed with 3 cc. of an aqueous solution of periodic acid containing 6.8 g. of H_5IO_6 in 100 cc. of water. One portion was kept at 80° for 10 hr. Then 0.5 cc. of glacial acetic acid containing 0.5 cc. of 30% H_2O_2 was added and the reaction mixture was kept at 80° for 1 hr. After evaporation to dryness in a vacuum desiccator the residue was taken up in 3 cc. of 50% aqueous dioxane and heated on the steam bath with an equal volume of 5*N* hydrochloric acid. After evaporation to dryness the residual lacquer was extracted with ether. The ether-soluble material was chromatographed in the following three solvent systems: (*A*) phenol-formic acid-water (120 g.:1.6 cc.:40 cc.), R_f value 0.6; (*B*) 2-butanol-formic acid-water (75:15:10), R_f 0.7; (*C*) 99% of a mixture of 2 parts of methanol, 1 part of benzene, 1 part of 1-butanol, and 1 part of water, and 1% of a 15% aqueous ammonia solution, R_f value 0.3. The spraying reagent used was a weakly ammoniacal solution of 0.5 g. of brom phenol blue in 100 cc. of 95% ethanol. The R_f values of authentic XI were identical (see Fig. 1) in every respect.

Conversion of the tetracarboxylic acid X *to one of the hydrolysis products of tetramethyl trans-cis-trans-cyclohexane-1,2,3,4-tetracarboxylate* (XVa). In order to increase the differential reactivity between the conjugated and the unconjugated double bonds in X the tetramethylester (0.586 g.), obtained as a colorless oil by methylation with excess diazomethane in ethereal solution, was hydrogenated in ethyl acetate using 10% palladium-on-carbon as a catalyst. Within 12 min. 39 cc. of hydrogen (1 mole) had been taken up. There was no clear indication of a break in the rate of hydrogen uptake. The hydrogenation was therefore discontinued at this point. The reaction mixture, after evaporation of the solvent, left 0.6 g. of a colorless oil which was heated with 10 cc. of concentrated nitric acid (d = 1.4) at 150° (oil bath) for 2 hr. until the lively evolution of nitrous gases had subsided. After evaporation to dryness the noncrystalline residue was refluxed in 5 cc. of acetyl chloride for 5 hr. and, after evaporation to dryness, separated into a chloroform-soluble part, containing 124 mg. of a light-colored oil, and a chloroform-insoluble part, soluble in ether, consisting of 165 mg. of a brown oil. The infrared spectrum of the chloroform-soluble fraction showed, in chloroform solution, a hydroxyl band at 2.90μ, anhydride bands at 5.36 and 5.58 μ, and a doublet at 5.79–5.82 μ, indicative of free carboxyls. This material, presumably largely the monoanhydride of a tetracarboxylic acid, was reconverted into the free acid by refluxing in water for 2 hr. After evaporation to dryness the brown residue was extracted with ether. This ether extract was used for chromatographic analysis in three different solvent systems (see above and Fig. 2). One of the two spots in the chromatogram of the hydrolyzate of authentic tetramethylester of XVa was identical with that of the major oxidation product from X. Fractionation of the ether-soluble brown residue using chloroform and ethyl acetate gave a small amount of crystalline material showing a characteristic crystalline transformation into colorless long daggers at 160–180°, m.p. 185–186°, depressed to 181° on admixture with a crystalline product (m.p. 195–197°) obtained by hydrolysis of the tetramethyl ester of XVa by refluxing in dioxane 5*N* hydrochloric acid (1:1) for 6 hr.

Acknowledgment. We are greatly indebted to Dr. K. Freter for generous assistance with the preparation and paper chromatographic analysis of compounds, and to Dr. W. A. Alford for titrations and analyses.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Quinuclidines. I. 4-Phenylquinuclidines as Potential Analgesics*

T. D. PERRINE

Received June 13, 1957

This paper presents the synthesis and structure proof of 4-phenylquinuclidine, the first 4-arylquinuclidine to be reported. The physical and physiological properties are briefly discussed, and several related substances are described.

With few exceptions, substances which are potent analgesics[1] have the common partial structure exemplified in I.

4-Phenylquinuclidine (II) has such a structure. We have been intrigued by the symmetry of II, and felt that examination of it and related compounds might lead to substances of pharmacological interest. Physiological activity in the quinuclidine

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.