TRANSANNULAR PEROXIDES

WERNER BERGMANN AND MARGARET J. McLEAN[1]

Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut

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I. INTRODUCTION

During the years 1912 to 1913 Nelson and Wallach, working independently, made the discovery that ascaridole, the principal constituent of chenopodium oil, is a naturally occurring, liquid, organic peroxide. It is a relatively stable compound, since it can be distilled with steam or *in vacuo.* Ascaridole differed from other peroxides known at the time of its discovery principally in its structure, which was found to contain a peroxide bridge across a six-membered ring in a 1,4-position. For many years ascaridole was regarded as an oddity without an analog in organic chemistry. It was not until about twenty-five years later that other peroxides of similar constitution were discovered. The intensification of the studies on sterols, which began with the discovery of their relation

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[1] Fellow of the Jane Coffin Childs Fund for Medical Research.

to vitamin D, led to the observation by Windaus and collaborators that ergosterol and similar sterols are prone to absorb oxygen in the presence of light to form nicely crystalline peroxides. Extensive studies demonstrated convincingly that these peroxides contained a peroxide bridge across ring B of the steroid molecule in a 1,4-position. More recently it was also shown by Bergmann and Skau that an arrangement of double bonds in ring A of the steroid ring system also favored the formation of crystalline peroxides.

The occurrence of such cyclic peroxides is not restricted to alicyclic chemistry. This was first convincingly demonstrated by Dufraisse, who proved that "rubrene peroxide" was actually the peroxide of 5,6,11,12-tetraphenylnaphthacene, and that it carried a peroxide bridge across the ring at C_5 and C_{11}. In a series of investigations, Dufraisse and collaborators established the fact that the formation of such crystalline peroxides is not a peculiarity of rubrene, but that it is typical for the anthracene nucleus. Even anthracene itself can be photoöxidized in solution to give the crystalline 9,10-peroxidoanthracene.

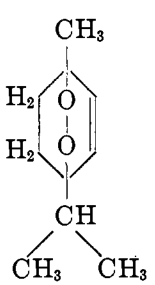
Up to the present time the peroxides mentioned in the preceding paragraph have been regarded as more or less isolated cases, and no attempt has as yet been made to organize and review them under a common denominator. These peroxides have one structural feature in common: a 1,4-peroxide bridge across a six-membered ring. All of them belong to a class of compounds which may be designated as transannular peroxides. The readiness with which many of these peroxides are formed under the influence of light and air, as well as the ease with which some of them can rearrange into more stable compounds or release oxygen, strongly suggest that they may play an important rôle in biological oxidation processes.

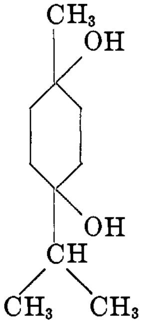
II. ASCARIDOLE

The longest known transannular peroxide is ascaridole, $C_{10}H_{16}O_2$, which was recognized in 1908 (82) as the principal anthelmintic constituent of chenopodium oil. It is an oily liquid of unpleasant odor and taste. When heated under ordinary pressure to 130–150°C., it undergoes a violent decomposition during which the temperature rises suddenly to 250°C. Combustible gases, consisting chiefly of propane, are evolved, which when ignited can lead to serious explosions. Under a reduced pressure of 4–5 mm., ascaridole distills at 83°C. without decomposition, but not without a certain amount of isomerization. Ascaridole is neutral and is indifferent to all reagents for hydroxyl and carbonyl oxygen. These properties at once indicate the peculiar character of ascaridole, which is without analog in the chemistry of ethereal oils.

The elucidation of the structure of ascaridole was mainly accomplished by Wallach (86) and Nelson (77). Formula I, proposed by Wallach in 1912, best expresses the properties and reactions of this unusual compound.

Hydrogenation of ascaridole with colloidal palladium proceeds with unusual rapidity to give *p*-menthane-1,4-diol (II) (86). Under suitable conditions the hydrogenation can be controlled to give dihydro products only. Richter and Presting (79) demonstrated that the mild reduction of ascaridole with palladium saturated with hydrogen gives rise to a mixture of compounds containing 2-*p*-menthene-1,4-diol (III). Paget (78) confirmed this observation but stated that the principal reduction product under such conditions is 1,4-peroxidomenthane (IV), which is also obtained as the sole product of the hydrogenation of ascaridole with a platinum oxide catalyst. This observation is a very surprising one, since it demonstrates that, contrary to all expectations, the double bond is hydrogenated in preference to the peroxide bridge. At present the 1,4-peroxidomenthane (IV) is the only known transannular peroxide of a completely saturated ring system.


I
Ascaridole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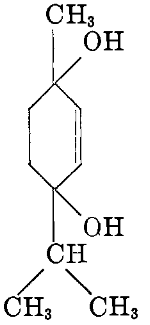
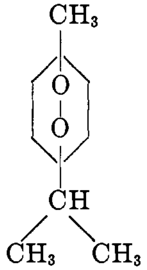
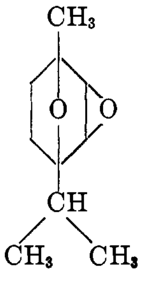
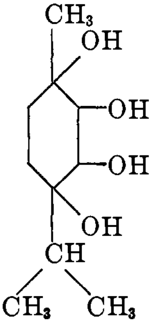
p-Menthane-1,4-diol

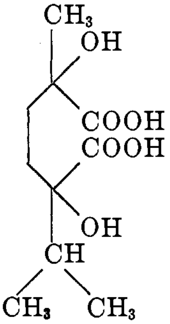

III
2-*p*-Menthene-1,4-diol

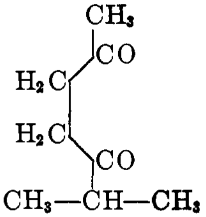

IV
1,4-Peroxidomenthane
or
dihydroascaridole

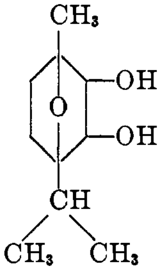
When heated in a cymene solution to 150°C., ascaridole isomerizes. One oxygen atom of the peroxide bridge splits off and adds to the double bond to give a dioxide (V) (77, 79, 85). Hydrolysis of the dioxide with dilute sulfuric acid leads to three different products, which are formed by the opening of one or the other or both of the oxide rings. The opening of both rings yields an "erythritol" (VI), the constitution of which was proven by its conversion to the dicarboxylic acid $C_{10}H_{18}O_6$ (VII) and 1,1-dimethylacetonylacetone (VIII). Hydrolysis of only the ethylene oxide ring gives rise to 1,4-oxido-*p*-menthane-2,3-diol (IX), which yields ascaric acid (X) on oxidation. Opening of the 1,4-oxygen bridge leads to the formation of 2,3-oxido-*p*-menthane-1,4-diol (XI). The constitution of this diol was established by its synthesis from 2-*p*-menthene-1,4-diol (III) and perbenzoic acid.


V


VI


VII


VIII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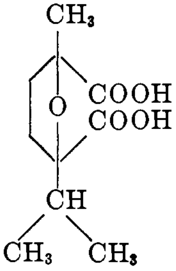
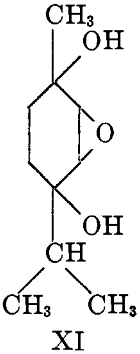
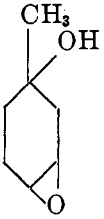
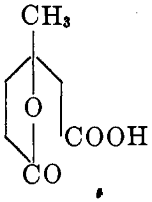
1,4-Oxido-*p*-menthane-2,3-diol


X
Ascaric acid


XI
2,3-Oxido-*p*-menthane-1,4-diol


XII
1-Methyl-3,4-oxido-1-cyclohexanol


XIII
Lactone of β-hydroxy-β-methyladipic acid

The action of an acid solution of titanous chloride on ascaridole (I) and dihydroascaridole (IV) has recently been studied by Paget (78). Ascaridole reacts with this reagent to give propane and *p*-cresol, each in a yield of about 30 per cent. The evolution of propane had already been observed by Nelson (77) during his attempts to reduce ascaridole with ferrous sulfate. The reduction of dihydroascaridole (IV) yields close to 90 per cent of propane and 1-methyl-3,4-oxido-1-cyclohexanol (XII). The formula for this new oxide is based on the observation that it gives the lactone of β-hydroxy-β-methyladipic acid (XIII) upon oxidation (78).

Ascaridole has been shown by Marvel and collaborators (80) to be an active catalyst for the reaction between sulfur dioxide and olefins of the type $RCH{=}CH_2$, and between sulfur dioxide and acetylenes of the type $RC{\equiv}CH$.

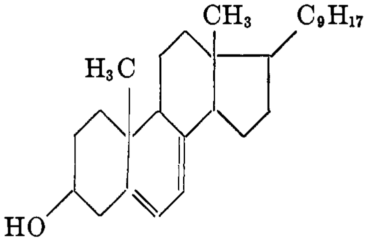
III. PEROXIDES OF STEROIDS

The discovery of the first transannular steroid peroxide was a by-product of the early work on vitamin D. During the years 1927 to 1928 Windaus and collaborators undertook a series of investigations with the object of effecting the conversion of ergosterol into vitamin D by light containing few if any ultraviolet rays. These studies were based on the working hypothesis that the "natural" formation of vitamin D from ergosterol was caused by the action of sunlight of low ultraviolet intensity with the aid of certain naturally occurring sensitizers, such as plant pigments. In the first series of experiments, alcoholic solutions of ergosterol containing small amounts of chlorophyll, carotinoid pigments, and anthocyanidin pigments were exposed in the presence or absence of air to sunlight or the light of a strong electric light bulb. When these investigations failed to give tangible results, the natural pigments were replaced by synthetic sensitizers, such as eosin and erythrosin. It was during this series of experiments that it was discovered that the irradiation of an alcoholic solution of ergosterol in the presence of eosin and air led to the formation of a stable, nicely crystalline compound of melting point 178°C. It contained two more oxygen atoms than ergosterol; since it liberated iodine from a solution of potassium iodide, it was regarded as a peroxide of ergosterol.

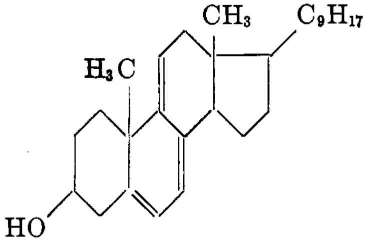
The elucidation of the structure of the new peroxide was greatly retarded by a number of conflicting and confusing observations and it was not completed until about ten years after the discovery of the peroxide. In the meantime other steroid peroxides were discovered, the structures of two of which were established without difficulty. These peroxides are dehydroergosterol peroxide and 2,4-cholestadiene peroxide, and have been shown beyond doubt to be transannular peroxides. Since the elucidation of their constitution has been instrumental in the final establishment of the structure of ergosterol peroxide, their discussion will precede that of the latter.

A. Dehydroergosterol peroxide

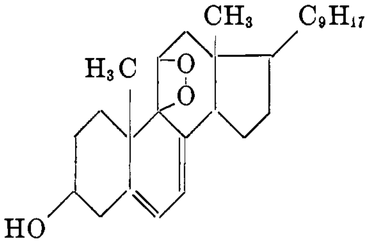
Dehydroergosterol (XV) is readily formed by the dehydrogenation of ergosterol (XIV) with mercuric acetate (97). Like ergosterol, it forms a nicely crystalline peroxide when irradiated in an alcoholic solution in the presence of eosin and oxygen (97). The peroxide shows no selective absorption in the ultraviolet above 230 mμ. This observation excludes from further consideration all structures containing a system of conjugated double bonds, since they are expected to show selective absorption between 248 and 254 mμ (76). The structures XVI and XVII for the peroxide are therefore at once eliminated. Of the remaining three possible structures, one (XVIII) can be excluded by considering the results of the catalytic hydrogenation of the peroxide. This leads to the formation of an ergostenediol which can be acetylated to a monoacetate only. This observation proves that the diol contains a tertiary hydroxyl group besides the original hydroxyl group at C_3 (76). A third hydroxyl group must have been eliminated during the hydrogenation. Since it is difficult to visualize how such a tertiary hydroxyl group could have been formed by the hy-



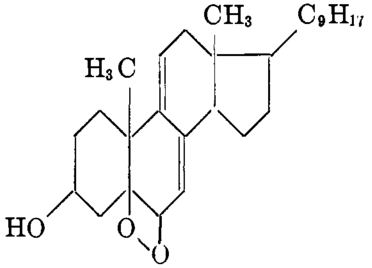
XIV
Ergosterol



XV
Dehydroergosterol

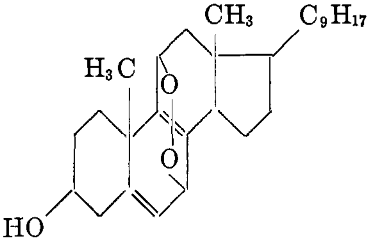


XVI

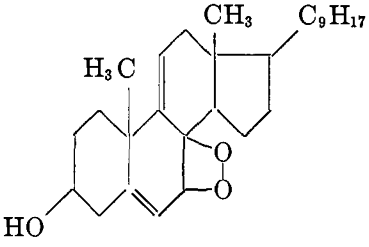


XVII

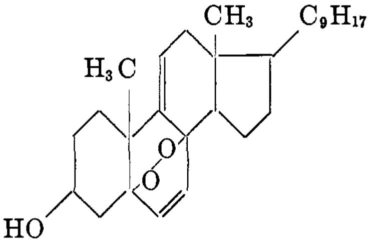
drogenation of a compound of structure XVIII, this structure can be eliminated from further consideration. Other investigations (76) on the constitution of the ergostenediol proved the presence of the tertiary hydroxyl group at C_5 and hence eliminated formula XIX. Dehydroergosterol peroxide must therefore be a transannular peroxide of the structure XX.



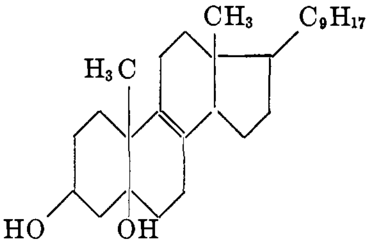
XVIII



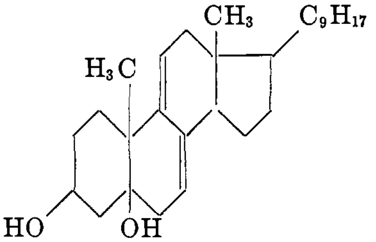
XIX



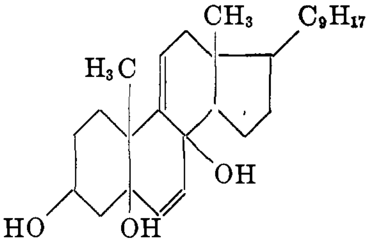
XX
Dehydroergosterol peroxide



XXI
Ergostenediol



XXII



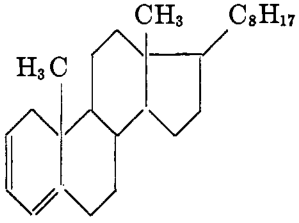
XXIII

Hydrogenation of this peroxide to ergostenediol, for which structure XXI has been established, might conceivably go by way of a 3,5,8-triol, which is immediately dehydrated to form a double bond between C_8 and C_9, which is very resistant to further hydrogenation.

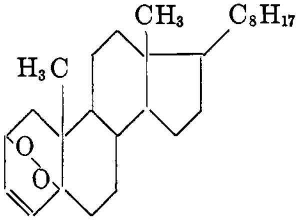
Structure XX also finds additional support in the results of the reduction of dehydroergosterol peroxide with zinc in alkali (76, 93). This leads to the formation of a compound with three double bonds, including the original double bond in the side chain, one secondary hydroxyl group at C_8, and one tertiary hydroxyl group. This trienediol shows selective absorption in the ultraviolet; hence the two ring double bonds must be conjugated. Their conjugation must extend over two rings, since the compound fails to react with maleic anhydride in the normal manner. The properties of this trienediol are best represented by formula XXII. Its formation from dehydroergosterol peroxide has probably proceeded by way of a trienetriol (XXIII), elimination of the hydroxyl group at C_8, and shifting of the ring double bonds into conjugation.

B. 2,4-Cholestadiene peroxide

The dehydration of cholesterol with alumina leads to the formation of 2,4-cholestadiene, which contains two conjugated double bonds in ring A of the steroid ring system (XXIV) (83, 84). Photoöxidation of this diene leads to one of two products, depending upon the light source (83). When a 200-watt Mazda bulb is used, a peroxide melting at 113–114°C., is obtained. When, on the other hand, the photoöxidation is carried out in the presence of sunlight, an isomeric substance melting at 172°C., is formed; this substance is not a peroxide but a ketone.



XXIV
2,4-Cholestadiene



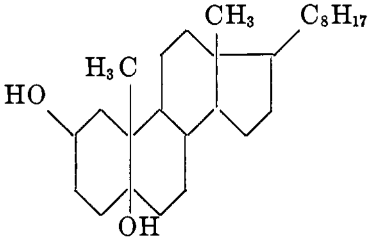
XXV
2,4-Cholestadiene peroxide

The catalytic hydrogenation of cholestadiene peroxide leads to the formation of a saturated diol, which contains a tertiary hydroxyl group since it gives a monoacetate only, and in which the hydroxyl groups cannot be in vicinal positions, since the diol fails to react with lead tetraacetate. These observations prove structure XXVI for the diol and therefore structure XXV for the peroxide. The alternative formulas for the peroxide,—namely, those of a 2,3- or 4,5-peroxide,—can be excluded from consideration, because substances of such constitution would be expected to give either a diol devoid of a tertiary hydroxyl group or a diol oxidizable with lead tetraacetate.

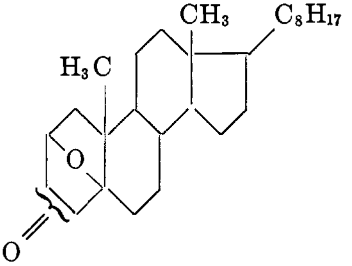
When irradiated with sunlight, 2,4-cholestadiene peroxide rearranges into the same ketone which is obtained by the photoöxidation of 2,4-cholestadiene in sunlight (7, 10). One can therefore assume that the mechanism of the photoöxidation of 2,4-cholestadiene in sunlight involves the formation of the peroxide, followed by its rearrangement into the ketone. It has been suggested that the rearrangement of the peroxide into the ketone is analogous to the isomerization of ascaridole (I) to the dioxide (V). Under the influence of sunlight, one of the oxygen atoms of the peroxide bridge of the 2,4-cholestadiene peroxide probably splits out and adds to the double bond between C_3 and C_4. The ethylene oxide may then rearrange into a C_3- or C_4-ketone (XXVII).

C. Ergosterol peroxide

The convincing proof for the transannular structure of two steroid peroxides made it logical to assume that other steroid peroxides of similar properties are of the same character. For ergosterol peroxide, however, two fundamentally different structural formulas have been proposed. On the basis of their experimental work the group of Göttingen investigators (1, 76), as well as Heilbron (59), have come to the conclusion that the peroxide bridge in ergosterol peroxide is not transannular but is attached to C_5 and C_6 (XXVIII). Fieser (59), on the other hand, has concluded that the available experimental evidence can be better interpreted in favor of a transannular formula for ergosterol peroxide (XXXIII).[2]



XXVI



XXVII

The establishment of formula XXVIII for ergosterol peroxide has been based principally on the study of ergostadienetriol (97), "triol I," which is obtained by the reduction of ergosterol peroxide with zinc in alkali. On heating with maleic anhydride, triol I isomerizes into 3,5,6-trihydroxyergostadiene, "triol II" (XXXI). This triol, whose constitution has been well established, is also the product of hydrolysis of ergosterol monoxide (XXIX) (1, 98). The ease of rearrangement of triol I into triol II seemed to prove that the two compounds were not mere position isomers but were stereoisomers of the *cis*- and *trans*-decalin type. They were assigned the structural formulas XXX and XXXI, respectively. Heilbron

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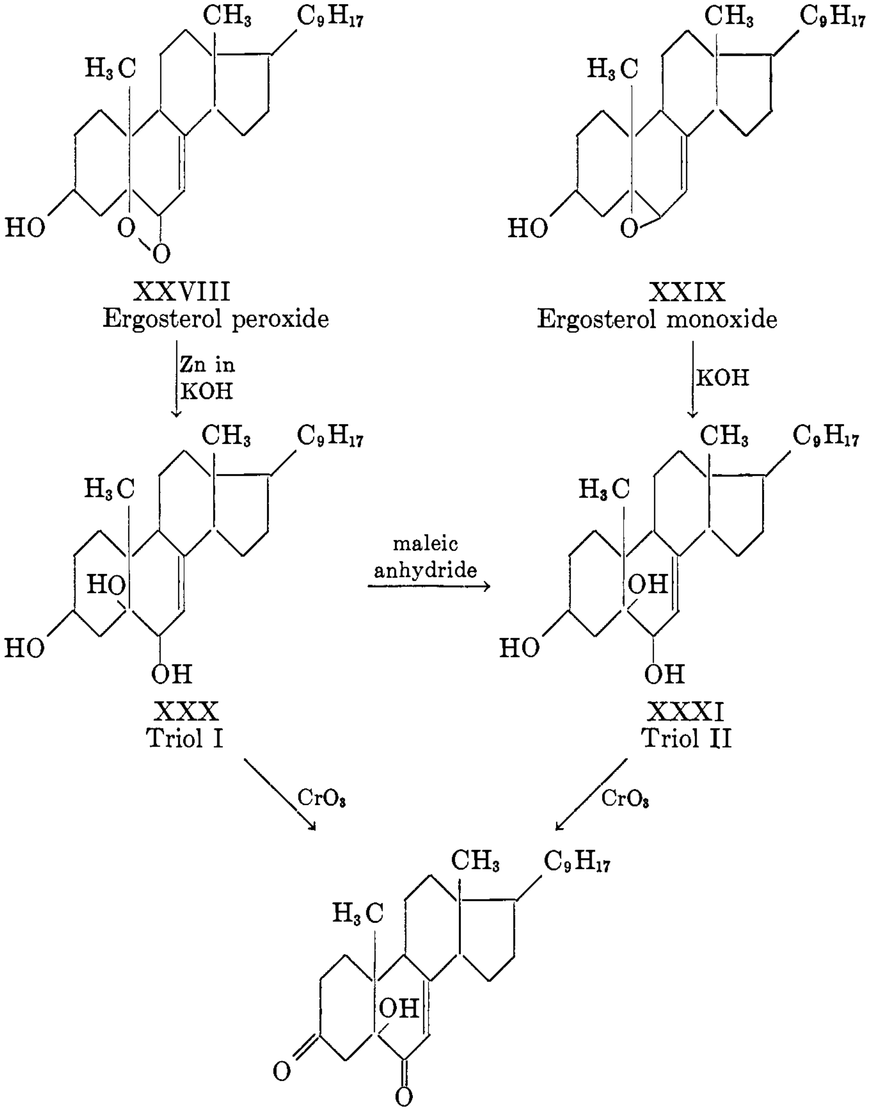
[2] A similar suggestion was made by Luttringhaus (67) in 1931.

(50) gave as additional evidence in favor of such formulations the fact that both triols render the same diketo compound (XXXII) on oxidation.



XXVIII
Ergosterol peroxide

XXIX
Ergosterol monoxide

XXX
Triol I

XXXI
Triol II

XXXII

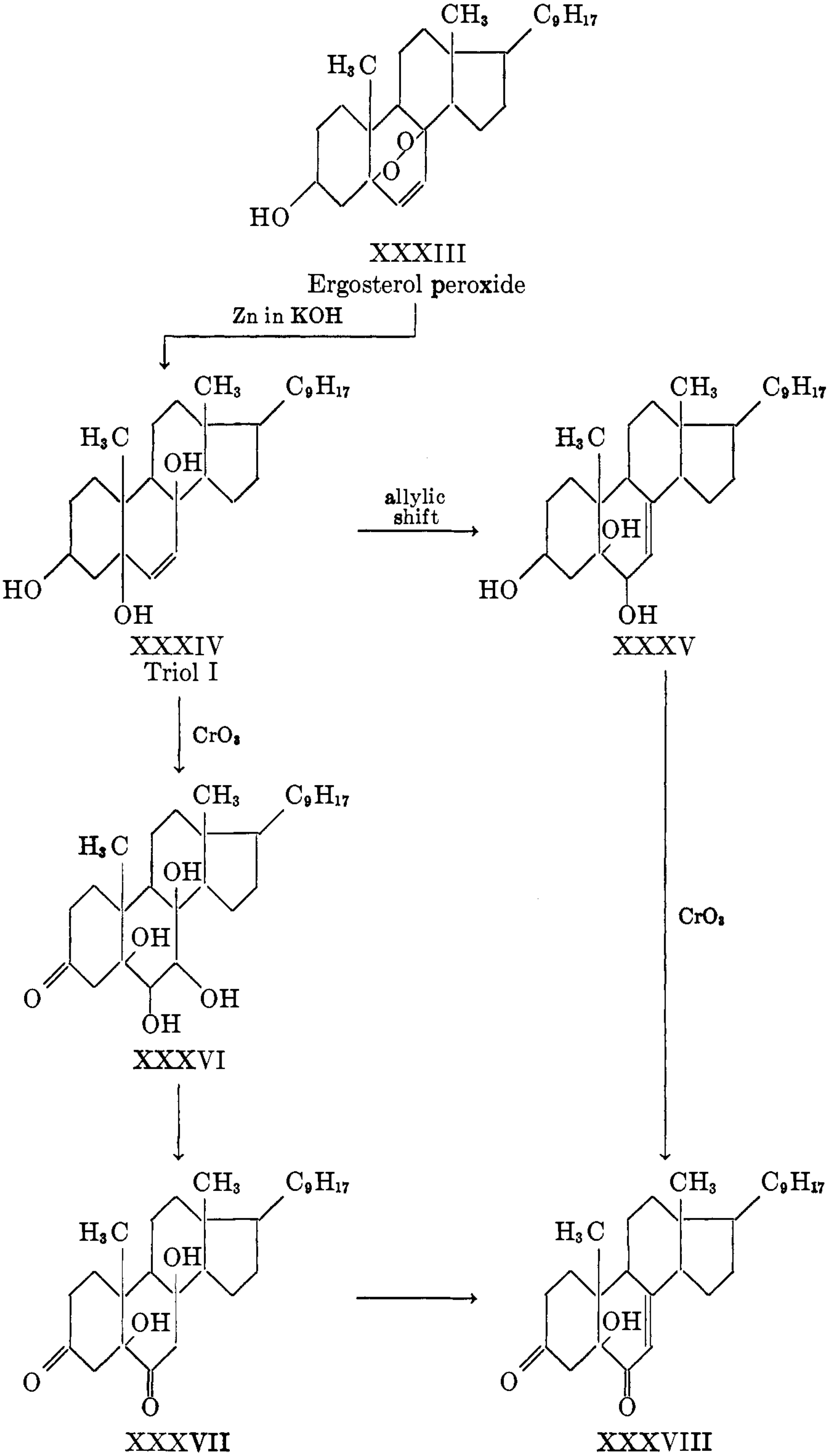
He reasoned that during the oxidation of triol I (XXX), the hydroxyl group at C_5 had undergone inversion from the *trans*- into the *cis*-position with respect to the methyl group at C_{10}. It seems more logical, however, to interpret the fact that both triols give the same diketo compounds as proof for the identical position of the hydroxyl group at C_5 (7).

Since the reactions mentioned above were thought to prove that triols I and II were stereoisomers, the conclusion was drawn that triol I had the formula XXX and that ergosterol peroxide carried a peroxide bridge at C_5 and C_6 (XXVIII). The formulation of triol I as a 3,5,6-trihydroxy compound can not, however, be readily reconciled with several of its properties. On acetylation it gives a monoacetate only (1), and on distillation *in vacuo* it loses two molecules of water to give dehydroergosterol (97) (XV). In contrast, triol II (XXXI) forms a diacetate, and can be distilled without decomposition (98). It was first pointed out by Fieser (59) that these observations strongly indicate the presence of two tertiary hydroxyl groups in triol I and favor its formulation as a 3,5,8-triol (XXXIV), which obviously must have been derived from a transannular peroxide (XXXIII). The transformation of triol I (XXXIV) into triol II (XXXV) is explained by Fieser on the basis of an allylic shift.

Fieser's formulas for ergosterol peroxide (XXXIII) and triol I (XXXIV) are the most logical expressions for all the known properties of these compounds. The fact that triols I and II form the same oxidation product does not contradict Fieser's formula for triol I. It is quite conceivable that, as the first step of oxidation of triol I (XXXIV), a 3-ketotetrahydroxy compound is formed (XXXVI), which loses, first, one molecule of water to give a diketodiol (XXXVII) and then a second molecule of water to give Heilbron's diketone (XXXVIII) (7).

Ergosterol peroxide is surprisingly stable up to 170°C., but at 185–190°C. it undergoes isomerization (67, 94). The isomer, $C_{28}H_{44}O_3$, lacks all the characteristic properties of a peroxide. Acetylation and reaction with methylmagnesium iodide show the presence of one hydroxyl group (C_3). A second oxygen atom belongs to a keto group, for the isomer gives a monoxime. The third oxygen atom, which is unreactive, is regarded as oxide oxygen.

The thermal isomerization of ergosterol peroxide is strongly reminiscent of the thermal rearrangement of ascaridole and the photorearrangement of 2,4-cholestadiene peroxide. As in the case of the isomerization of these two peroxides, the rearrangement of ergosterol peroxide is probably due to a change from a peroxide to an oxide bridge and an addition of oxygen to a double bond to form first an epoxide and then a ketone. Since ergosterol peroxide has two double bonds, the addition of oxygen may take place either at the ring double bond or at the double bond in the side chain to give compounds of the possible structures XXXIX or XL. Because of the failure of the isomer to yield 1,2-dimethylbutyraldehyde (61) upon ozonization, the latter formula is to be preferred.



XXXIII
Ergosterol peroxide

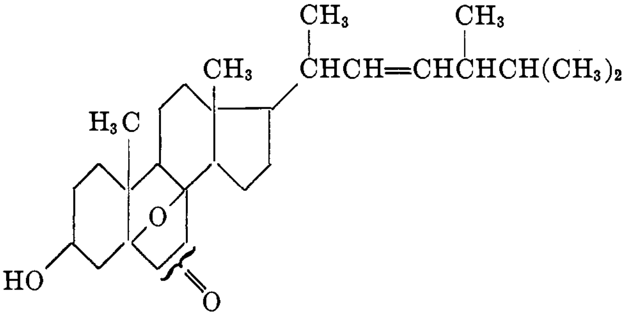
XXXIV
Triol I

XXXV

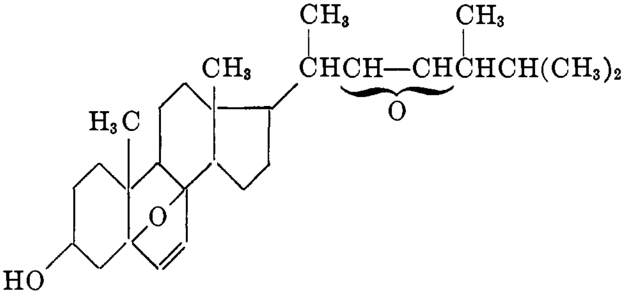
XXXVI

XXXVII

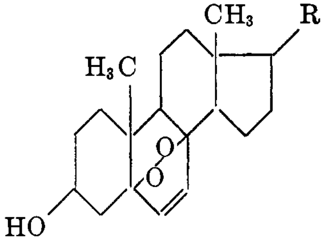
XXXVIII



XXXIX



XL



XLI

(a) R = C_9H_{19}
(b) R = C_8H_{17}
(c) R = OH

D. Other steroid peroxides

Three other steroids with a constitution similar to that of ergosterol have given crystalline peroxides upon photoöxidation in the presence of a sensitizer. They are the peroxides of 22-dihydroergosterol (96), 7-dehydrocholesterol (81), and 5,7-androstadienediol (11). Although few data have as yet appeared concerning the constitution of these peroxides, it appears logical to assume that they are of transannular character with a peroxide bridge between C_5 and C_8 (XLI, a to c).

IV. AROMATIC TRANSANNULAR PEROXIDES

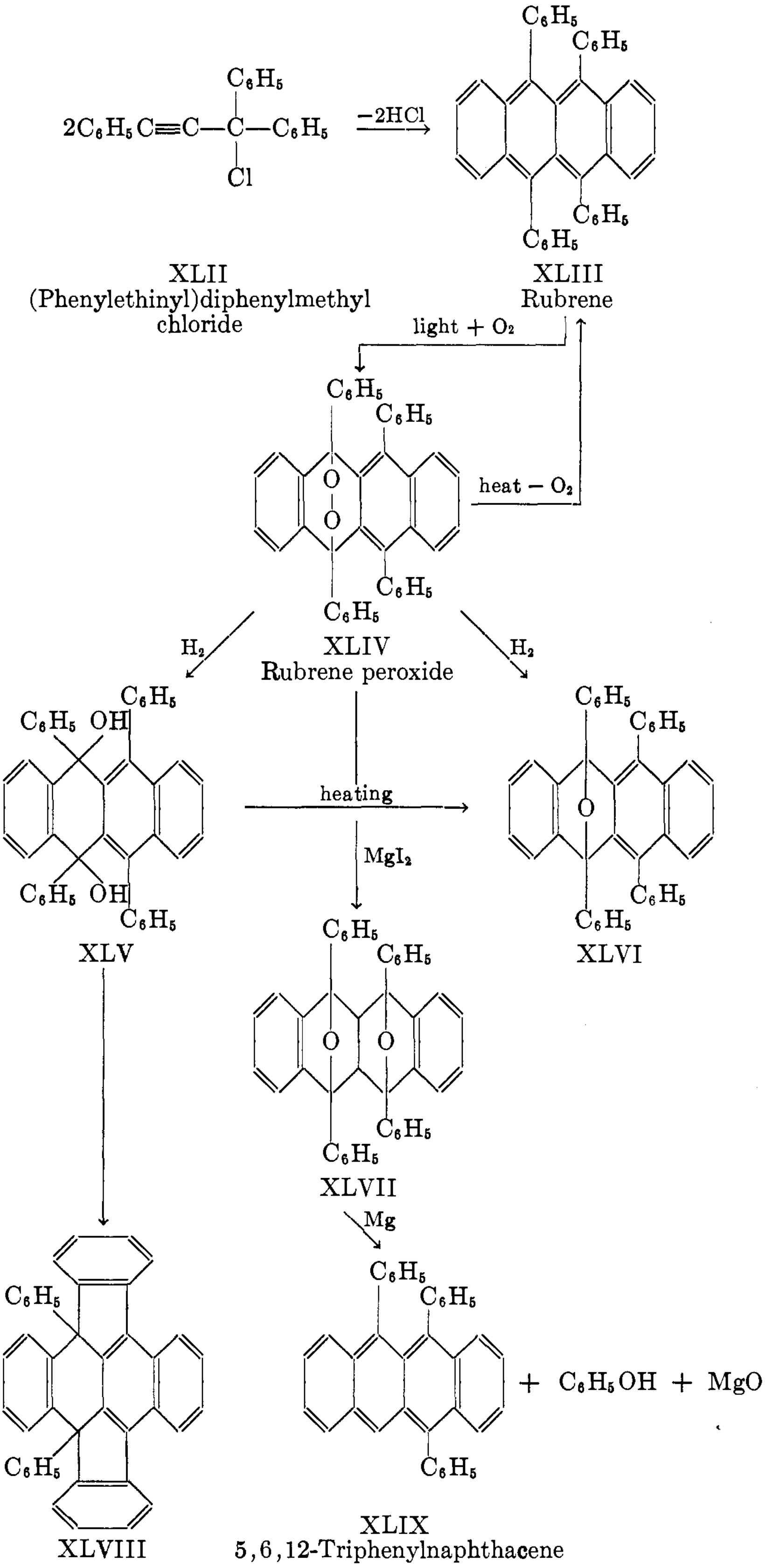
A. Preparation

Most of our present-day knowledge of the preparation, properties, and constitution of aromatic transannular peroxides is based on the results of a series of systematic studies which have been carried out under the direction of Moureu and Dufraisse. These studies began about fifteen years ago with an investigation of the properties of the hydrocarbon rubrene. This red polynuclear substance, $C_{42}H_{28}$, was first prepared in 1926 (70) by the removal of hydrochloric acid from (phenylethinyl)diphenylmethyl chloride (XLII). Moureu and collaborators (70) observed that solutions of this hydrocarbon rapidly lose their color and fluorescence when exposed to sunlight or artificial light in the presence of air. Concentration of such decolorized solutions leads to the precipitation of a compound of the formula $C_{42}H_{28}O_2$ plus solvent of crystallization (72) and possessing the properties of a peroxide.

When this compound is heated *in vacuo* a reversal of the reaction takes place; under luminescence (71) the peroxide dissociates into rubrene, solvent of crystallization, and oxygen. The dissociation is not a quantitative one, since not more than 80 per cent of the theoretical amount of oxygen is obtained. The evolution of carbon dioxide during the reaction indicates that approximately 5 per cent of the peroxide undergoes decomposition. Extension of these investigations to a number of derivatives of rubrene, the "rubenes," established the fact that the ability to add oxygen in the presence of light is a general property of this class of compounds.

Because the exact constitution of rubrene remained unknown for a number of years, the structure of rubrene peroxide was not fully established until 1936. By that time evidence had accumulated (17) which proved that rubrene is 5,6,11,12-tetraphenylnaphthacene (XLIII), and that the other hydrocarbons of the rubene series are also derivatives of naphthacene. This new formulation at once suggested that the new peroxides are either 1,2- or transannular (1,4) peroxides. Hydrogenation experiments, which will be discussed later, proved conclusively the transannular character of these peroxides and hence the correctness of formula XLIV for rubrene peroxide.

The discovery that linear polynuclear aromatic hydrocarbons are prone to undergo photoöxidation was not entirely new. As early as 1867, Fritzsche (60) made the observation that solutions of naphthacene are rapidly decolorized in the presence of light and air to give a crystalline



XLII
(Phenylethinyl)diphenylmethyl chloride

XLIII
Rubrene

XLIV
Rubrene peroxide

XLV

XLVI

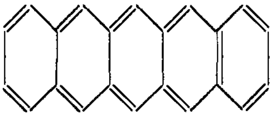
XLVII

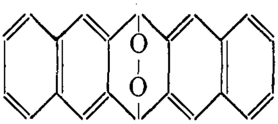
XLVIII

XLIX
5,6,12-Triphenylnaphthacene

material which regains color on fusion. In the light of the observations of Moureu and Dufraisse, it must be assumed that Fritzsche's compound was naphthacene peroxide. In 1930 Clar and John (13) found that pentacene (L) is so rapidly photoöxidized to a peroxide that they recommended that one refrain from working with solutions of this hydrocarbon in broad daylight. This tendency to undergo oxidation is even more pronounced in the case of hexacene (14). The transannular formula for pentacene peroxide (LI) suggested by Clar and John (13) appears to be justified because of its analogy to the structure of naphthacene peroxide.

On the basis of the experience gained during the study of naphthacenes, Dufraisse formulated the hypothesis that the ability of these hydrocarbons to add oxygen is intimately connected with the activity of their meso-positions. Since such meso-positions are also present in the anthracene molecule, Dufraisse decided upon an extension of his investigations to anthracene and its derivatives. He at once made the surprising discovery that not only meso-substituted anthracenes but anthracene (29, 30) itself is readily photoöxidized to give a nicely crystalline transannular peroxide (LII). Dufraisse justifiably prides himself (18) that it was his working hypothesis which led him to the discovery of this interesting reaction. It seems indeed astonishing that anthracene peroxide should have escaped the attention of so many investigators, for the photochemistry of anthracene has been extensively studied in relation to the formation of dianthracene.


L
Pentacene



LI
Pentacene peroxide

Dufraisse's discovery was greatly facilitated by his choice of carbon disulfide as a solvent in which to carry out the photoöxidation. The rate of oxidation in this solvent far exceeds that in other solvents which have so far been tested (22). Table 1 shows the comparative rates of oxidation of uniform quantities of rubrene in different solvents. The rates were measured either in terms of time required for complete decolorization of the solutions or in terms of changes in concentration in a given time. The rate of oxidation in benzene was used as standard.

The transannular peroxides of the naphthacene and anthracene series which have so far been prepared are listed in tables 2 and 3. All efforts to bring about the formation of photoperoxides in the phenanthrene, naphthalene (41), or acridine (33) series have been unsuccessful. This failure again demonstrates that the ability to form photoperoxides is dependent upon the meso additive activity of aromatic hydrocarbons and their derivatives. There exists an intimate relationship between the ability of such compounds to add maleic anhydride and to add oxygen in the presence of light. Polycyclic aromatic compounds which form transannular peroxides also form addition products with maleic anhydride. It can also be assumed that compounds which fail to give the Diels–Alder reaction will also lack the ability to form photoperoxides. 9,9-Dianthryl and 10,10-diphenyl-9,9-dianthryl (49), for example, react neither with maleic anhydride nor with oxygen in the presence of light, a fact which indicates the disappearance or great reduction of the meso activity in these compounds.

TABLE 1

Comparative rates of oxidation of rubrene in various solvents

SOLVENT	COMPARATIVE RATES OF OXIDATION
Carbon disulfide	9
Chloroform	3
Methyl iodide	1
Benzene	1
Acetone	1
Ethyl ether	0.5
Anisole	0.4
Pyridine	0.25
Nitrobenzene	0.1
75% CS_2 + 25% ether	2
50% CS_2 + 50% ether	1

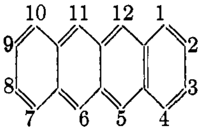
B. Photoöxidation of carcinogenic hydrocarbons

Since the most important carcinogenic hydrocarbons are substituted anthracenes, it is of considerable interest to know whether they also can undergo photoöxidation to form peroxides. It has been known for some time that solutions of a number of carcinogenic hydrocarbons are photosensitive. Moreover, it has been observed by Boyland (9) that alkaline extracts of such hydrocarbons which had been exposed to light and air arrest the activity of certain enzymes. It has also been found by Maisin and de Jonghe (68) that light accelerates the production of skin tumors in mice treated with 3,4-benzopyrene.

Independent investigations by Velluz (99), Cook (12), and the authors of this review (8) failed to find a way for the preparation of the peroxides of 1,2,5,6-dibenzanthracene and methylcholanthrene. In order to ascertain whether a small amount of peroxide is formed which might escape isolation, Velluz (99) irradiated the two hydrocarbons, dissolved in carbon disulfide, in an apparatus permitting measurements of the oxygen uptake. The reluctance of these hydrocarbons to add oxygen was indicated by the fact that no appreciable absorption had taken place even after two weeks of irradiation. In the case of 1,2-benzanthracene (12), 9,10-diphenyl-1,2-benzanthracene (101), and 1,2,3,4-tetrahydro-9,10-diphenyl-1,2-benzanthracene (101), indications of the formation of peroxides were found, but contaminations hindered their isolation. Better results were obtained with meso-dimethyl-substituted hydrocarbons. One of the most rapidly acting carcinogenic hydrocarbons now known is 9,10-dimethyl-1,2-benz-

TABLE 2

Transannular-(6,11)-peroxides of naphthacene and derivatives



Naphthacene

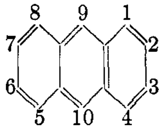
PEROXIDE OF	DISSOCIATION IN PER CENT OF OXYGEN	REFERENCES
Naphthacene	0	(31)
5,11-Diphenylnaphthacene	0	(39)
6,11-Diphenylnaphthacene	0	(32)
5,6,11-Triphenylnaphthacene	15	(21)
5,6,11,12-Tetraphenylnaphthacene (rubrene)	80	(70)
5,11-Di(*p*-tolyl)-6,12-diphenylnaphthacene*	70	(40)
5,6,11,12-Tetraphenyl-2,8-dimethylnaphthacene*	66	(37)
11-(*p*-Tolyl)-5,6,12-triphenyl-2-methylnaphthacene	64	(37)
5,11-Di(*p*-tolyl)-6,12-diphenyl-2,8-dimethylnaphthacene	74	(40)
5,11-Di(β-naphthyl)-6,12-diphenylnaphthacene	80	(76)
5,11-Di(*p*-bromophenyl)-6,12-diphenylnaphthacene*	69	(24)
5,11-Di(*p*-bromophenyl)-6,12-diphenyl-2,8-dibromonaphthacene	50	(43)
5,11,6,12-Tetra-(*p*-bromophenyl)-2,8-dibromonaphthacene	76	(44)
5,11-Di(*p*-methoxyphenyl)-6,12-diphenylnaphthacene	52	(23)
5,11-Di(*p*-carboxyphenyl)-6,12-diphenylnaphthacene	59	(25)
5,11-Diphenyl-6,12-di(biphenyl)naphthacene	70	(52)
2,6,8,12-Tetraphenyl-5,11-di(biphenyl)naphthacene	70	(51)
1,2,3,4-Tetrahydro-6,11-diphenylnaphthacene	80	(32)
5,6,12-Triphenyl-11-carbethoxynaphthacene	44	(6)
5,11-Diphenyl-6,12-dicarbethoxynaphthacene	15	(38)

* These peroxides undergo isomerization (see page 387).

anthracene. Since Bachmann (5) had shown that this hydrocarbon possesses a surprisingly high meso additive activity toward maleic anhydride, Cook (12) felt that its photoperoxide might be more readily formed. This indeed proved to be the case, and equally satisfactory

TABLE 3

Transannular-(9,10)-peroxides of anthracene and derivatives



Anthracene

PEROXIDE OF	DISSOCIATION IN PER CENT OF OXYGEN	REFERENCES
Anthracene	0	(29, 30)
9-Methylanthracene	0	(91)
9-Ethylanthracene	0	(91)
9,10-Dimethylanthracene	0	(91)
9-Methyl-10-ethylanthracene	0	(91)
9-Cyclohexylanthracene	0	(92)
9-Phenylanthracene	12	(48)
9-Phenyl-10-methylanthracene	20	(90)
9-Phenyl-10-ethylanthracene	35	(90)
9-Phenyl-10-cyclohexylanthracene	48	(92)
9,10-Diphenylanthracene	96	(27, 36)
9,10-Di(*o*-tolyl)anthracene (impure)	83	(89)
9,10-Di(*m*-tolyl)anthracene	94	(89)
9,10-Di(*p*-tolyl)anthracene	94	(89)
9,10-Di-α-naphthylanthracene	90	(88)
9,10-Di-β-naphthylanthracene	95	(88)
9,10-Diphenyl-2-bromoanthracene	91	(100)
9,10-Diphenyl-2-carboxyanthracene	91	(100)
9,10-Diphenyl-2-carbomethoxyanthracene	92	(100)
9,10-Diphenyl-1,4-dimethoxyanthracene	98	(47)
9-Phenyl-10-carbomethoxyanthracene	60	(48)
9,10-Dimethoxyanthracene	0	(42, 46)
1,2-Benzanthracene (impure)		(12)
9,10-Diphenyl-1,2-benzanthracene (impure)		(101)
9,10-Diphenyl-1,2,3,4-tetrahydro-1,2-benzanthracene (impure)		(101)
9,10-Dimethyl-1,2-benzanthracene		
5,9,10-Trimethyl-1,2-benzanthracene		(12)
6,9,10-Trimethyl-1,2-benzanthracene		(12)
5,6,9,10-Tetramethyl-1,2-benzanthracene		(12)
9,10-Dimethyl-1,2,5,6-dibenzanthracene		(12)

results were obtained with 5,9,10-trimethyl-, 6,9,10-trimethyl-, and 5,6,9,10-tetramethyl-1,2-benzanthracene and 9,10-dimethyl-1,2,5,6-dibenzanthracene. The fact that such highly carcinogenic hydrocarbons are readily photoöxidized makes untenable the assumption of Velluz (99) that the carcinogenic activity of dibenzanthracene and of methylcholanthrene is in some way related to their ability to resist photoöxidation.[3]

C. Photoöxidation of various derivatives of anthracene

Derivatives of anthracene carrying one halogen atom in a meso-position as, for example, 10-bromo- and 10-iodo-9-phenylanthracene, undergo photoöxidation (48). During the reaction, however, some halogen splits off and the peroxides can not be isolated in a pure form. Photoöxidation of 9,10-dihydroxyanthracene does not lead to the formation of a crystalline peroxide (42). The disodium salt of this compound, as was already shown by Manchot (69), autoxidizes rapidly even in the dark. Dufraisse (42) was unable to detect the presence of a peroxide during the course of this reaction. The peroxide of 9,10-dimethoxyanthracene has been made, although considerable difficulties were encountered in its preparation (42). It melts with the formation of anthraquinone, but can be sublimed *in vacuo* at 80°C. In the presence of light and air, it is rapidly oxidized to anthraquinone.

Photoöxidation of 5,11-di(*p*-carboxyphenyl)-6,12-diphenylnaphthacene gives a peroxide whose salts are water-soluble (25).

D. Reactions of the peroxides

(*1*) *Reduction.*—Upon catalytic hydrogenation the peroxides add 1 mole of hydrogen to yield the corresponding meso-dihydroxy derivatives. Thus the peroxides of anthracene, 9,10-diphenylanthracene, and rubrene give 9,10-dihydro-9,10-dihydroxyanthracene, 9,10-diphenyl-9,10-dihydroxyanthracene, and 6,11-dihydroxy-5,6,11,12-tetraphenylnaphthacene (XLV) (34). The first two hydroxides have been known for some time; the last one has more recently been prepared by the action of phenyl-

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[3] *Note added in proof:* Since this paper was submitted an article has come to the attention of the reviewers (Cook, J. W., and Martin, R. H.: J. Chem. Soc. **1940**, 1125) which contains a more detailed discussion of the peroxides of the 1,2-benzanthracene series. Cook and Martin found that an ordinary gas-filled 200-watt lamp furnishes a convenient source for the facile photoöxidation of derivatives of 1,2-benzanthracene. They also demonstrated that derivatives with only one meso-substituent (9-methyl-, 10-methyl-, and 10-isopropyl-1,2-benzanthracene) give peroxides, although less readily than the 9,10-disubstituted compounds. The peroxides are not carcinogenic, for tumors did not result from injection into mice of suspensions in sesame oil of the pure peroxide of the highly carcinogenic 9,10-dimethyl-1,2-benzanthracene.

lithium on 6,11-diphenyl-5,12-naphthacenequinone (3) and by the action of potassium permanganate on rubrene (20). The formation of the meso dihydroxides proves conclusively the transannular nature of the peroxides.

Upon moderate heating the dihydroxide (XLV) loses one molecule (20) of water to give an oxide of the probable structure XVI. The same oxide is also formed by the reduction of the peroxide XLIV (16, 74) with zinc in glacial acetic acid. The oxide is a stable compound which melts without decomposition. Upon reduction it yields rubrene and upon oxidation it forms *o*-dibenzoylbenzene.

Dehydration of the dihydroxide under the influence of strong mineral acids leads (16) to the loss of two molecules of water and cyclization to a hydrocarbon of the probable structure XLVIII.

(*2*) *Isomerization.*—Under the influence of certain reagents, such as magnesium iodide and strong mineral acids, peroxides of the naphthacene series undergo rearrangement. Addition of magnesium iodide (16, 19) to an ethereal solution of rubrene peroxide brings about an exothermic isomerization which is complete in about 5 min. The isomer no longer gives the reaction of a peroxide. It does not lose oxygen when heated; in fact, it can be distilled *in vacuo* without decomposition. Since it reacts neither with carbonyl nor with hydroxyl reagents, Dufraisse (16) regards it as a transannular 5,12,6,11-dioxide of the structure XLVII. This rearrangement of a peroxide into a dioxide is strongly reminiscent of the isomerization of ascaridole. The peroxides marked with asterisks in table 2 undergo analogous isomerization (53, 54, 57, 58).

The dioxide (XLVII) reacts with Grignard reagents (16) to give a variety of compounds, from which the monoxide (XLVI), the dihydroxide (XLV), and rubrene have been isolated. In the presence of an excess of metallic magnesium, one phenyl group is eventually split off and 5,6,12-triphenylnaphthacene (XLIX) and phenol are obtained, the latter in an almost quantitative yield (21).

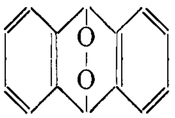
When treated with strong acids, rubrene peroxide (54) undergoes a different rearrangement, which as yet is poorly understood. The new isomer melts without decomposition and loss of oxygen and shows the presence of one hydroxyl group. Treatment with zinc in glacial acetic acid transforms this isomer into the polynuclear hydrocarbon of structure XLVIII.

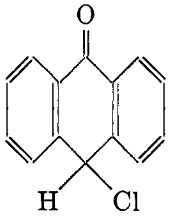
All attempts to rearrange the peroxide of 9,10-diphenylanthracene in an analogous manner have so far been unsuccessful (36). This failure may be due to the absence of a suitable "receiver" for one of the oxygen atoms in the anthracene molecule or to the instability of a transannular oxide linkage in the anthracene molecule. It has not yet been possible (21) to prepare 9,10-diphenyl-9,10-oxidoanthracene, either by partial reduction of the corresponding peroxide, by mild dehydration of the corresponding dihydroxy compound, or by oxidation of 9,10-diphenylanthracene.

(*3*) *Reactions with acids.*—Anthracene peroxide (LII) reacts (30) with hydrochloric acid to give chloroanthrone (LIII) and with hydrobromic acid to give bromoanthrone or 9,10-dibromoanthracene, depending on the concentration of the acid.

E. Dissociation of peroxides

Moureu and Dufraisse consider as one of the outstanding properties of rubrene peroxides, as well as of analogous compounds, their ability to dissociate on heating into oxygen and the parent hydrocarbon. In the case of rubrene peroxide, this dissociation is already noticeable at room temperature (73). Numerous quantitative studies on the thermal decomposition of peroxides have been carried out by the French investigators, using the following technique: A weighed amount of the peroxide is placed in a glass tube connected with a U-tube, a gas-measuring device, and a vacuum pump. After evacuation of the apparatus at room temperature, the U-tube is cooled to about −70°C., and the peroxide gently heated. The U-tube serves to condense the solvent of crystallization which is present in many peroxides. After the completion of the reaction at 220–250°C., the collected gas is analyzed for oxygen and carbon dioxide. Application of this method to almost all peroxides prepared by the French investigators brought out the fact that there exist marked differences in dissociability. The amounts of oxygen recovered from the various peroxides have been recorded in tables 2 and 3.


LII
Anthracene peroxide


LIII
Chloroanthrone

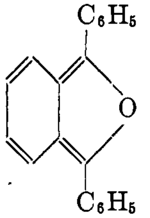
The data demonstrate that the dissociability of the peroxides is greatly influenced by the nature of the substituents in the meso-positions. Only the peroxides of 9,10-diaryl-substituted anthracenes yield an almost quantitative amount of oxygen. The dissociability of 9,10-diphenyl-1,4-dimethoxyanthracene peroxide is of unusual magnitude (47). At room temperature this compound dissociates to the extent of 25 per cent in 10 days, 55 per cent in 30 days, and 78 per cent in 40 days. Furthermore, its quantitative dissociation takes place in a few minutes at 80°C., in contrast to many other peroxides whose dissociation is barely perceptible below 100°C. Replacement of one of the aryl groups by an alkyl group or hydrogen greatly reduces the dissociability of the peroxides, and replacement of both groups leads to peroxides showing no recognizable dissociation. In all probability, complete thermal dissociation takes place in all instances. In the case of peroxides with hydrogen or alkyl substituents in the meso-position, however, this dissociation is not detectable by the technique employed, because the liberated oxygen is at once consumed in the oxidation of the molecule. Thus anthracene peroxide on heating does not decompose to give anthracene and oxygen but yields a considerable amount of anthraquinone.

Thermal dissociation of 5,6,11,12-tetraaryl-substituted naphthacene peroxides gives from 60 to 80 per cent of the theoretical amount of oxygen. This yield is low when compared with that of meso-diaryl-substituted anthracene peroxides. The reviewers believe that this is due to a partial rearrangement of the peroxide into a non-dissociable dioxide (XVIII), an isomerization which fails to take place in the case of anthracene peroxides.

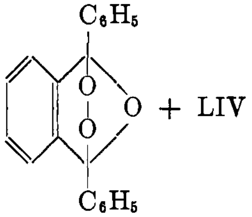
Dufraisse (16, 18) has offered elaborate discussions concerning the thermal dissociation of the peroxides and its biological implications. In the opinion of the reviewers, however, the importance of this reaction is overrated. As has been stated several times in this review, there exists an intimate parallel between the addition of maleic anhydride and the photoaddition of oxygen to polycyclic hydrocarbons. Bachmann (4) has disclosed that the addition of maleic anhydride to hydrocarbons containing the anthracene nucleus is a reversible reaction. He found, for example, that the heating of a mixture of equimolecular proportions of maleic anhydride and 3-methylcholanthrene in boiling xylene led to the formation of an adduct in a yield of 22 per cent. The identical equilibrium mixture of hydrocarbon, maleic anhydride, and adduct was obtained by heating a xylene solution of the pure adduct. It seems to the reviewers that the application of similar quantitative methods to the study of the photoöxidation of hydrocarbons containing an anthracene nucleus is very desirable. It would be more advantageous to study the reversibility of the peroxides on the basis of equilibrium mixtures than on the basis of a thermal decomposition which does not give very illuminating results. The fact that the photoöxidation of a number of hydrocarbons does not go beyond a certain yield of peroxide strongly indicates the existence of equilibrium mixtures.

F. Photoöxidation of 1,3-diphenylisobenzofuran

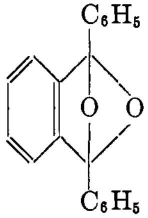
It has long been known that 1,3-diphenylisobenzofuran (LIV) is readily photoöxidized to *o*-dibenzoylbenzene (LVII). Since the furan possesses an *o*-quinonoid system and adds maleic anhydride readily in the 1,3-position (2, 87), it might be expected that the first product of photoöxidation is a transannular peroxide (LV). All attempts, however, have so far failed, either to isolate such a peroxide or to prove its presence. It is conceivable that the peroxide, immediately after its formation, gives off one atom of oxygen with the formation of an oxide bridge (LVI), and that the oxygen is added to a molecule of 1,3-diphenylisobenzofuran to form a second molecule of the dioxide. The dioxide would then rearrange into *o*-dibenzoylbenzene. This hypothesis receives support from the observation that the oxidation of 1,3-diphenylisobenzofuran to *o*-dibenzoylbenzene can be carried out with one mole of perbenzoic acid (8).



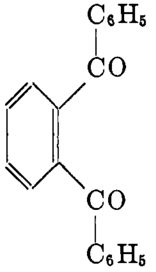
LIV
1,3-Diphenylisobenzofuran



LV



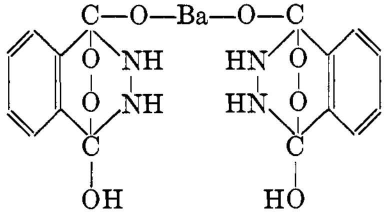
LVI



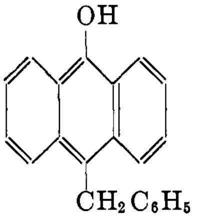
LVII
o-Dibenzoylbenzene

G. Peroxides of doubtful structure

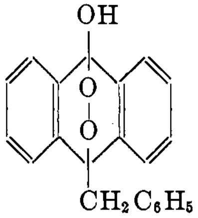
Apart from the peroxides mentioned in the preceding paragraphs, other peroxides of supposed transannular structure are now and then mentioned in the literature. These peroxides have been made almost exclusively by methods other than photoöxidation, and the transannular structure is not based on convincing evidence. Thus Drew and Garwood (15) have proposed the provisional structure LVIII for the barium salt of the peroxide of phthalaz-1,4-dione. Julian and collaborators (65, 66) observed that the passage of oxygen through a moist ethereal solution of 10-benzylanthranol (LIX) leads to the formation of a compound which they believe to be a transannular peroxide (LX). Heating of the compound resulted in the formation of anthraquinone, benzaldehyde, and benzyl alcohol. The reviewers hold, however, that the available evidence is not sufficient to prove beyond doubt the transannular character of the oxidation product of 10-benzylanthracene.



LVIII
Barium salt of phthalaz-1,4-dione



LIX
10-Benzylanthranol



LX

V. CONCLUSION

As has been shown in the preceding paragraphs, there exist a number of organic compounds which are endowed with the ability to fix oxygen in the presence of light to form peroxides of often surprising stability. In all instances the addition takes place across a ring in a 1,4-position to give transannular peroxides. In the case of ascaridole, it may be assumed that this peroxide is the result of the addition of oxygen to α-terpinene. All substances which have been found to give transannular photoperoxides possess a system of conjugated double bonds in one ring; hence they absorb ultraviolet or visible light and add maleic anhydride.

Many of the peroxides which have been described undergo rearrangement under the influence of either heat or light to give a variety of products.

The first step in this rearrangement consists in a change from the peroxide to an oxide bridge and an addition of the "free" oxygen atom to a suitable receiver, such as a double bond in the molecule. The oxides may then be rearranged to ketones. It appears probable that a number of biological oxidations may proceed by way of addition of oxygen to a cyclic diene system and subsequent rearrangement of the ensuing transannular peroxides. The formation of numerous alcohols and ketones of the terpene series from terpene hydrocarbons may be readily conceived in such a manner. In closing, it may be pointed out that a number of compounds which can be photoöxidized to give transannular peroxides also give a definite light reaction in the absence of air. Thus anthracene and 1,3-diphenylisobenzofuran are dimerized by light, and ergosterol and similar steroids are dehydrogenated to give compounds with two steroid ring systems attached to each other (63).

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