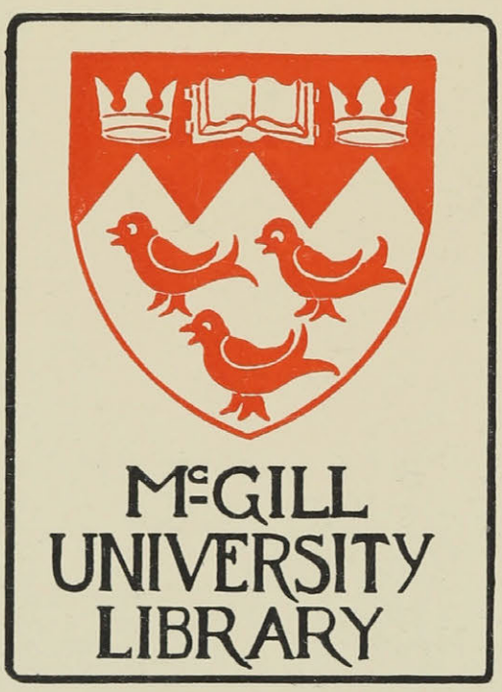
ACTION OF THE GRIGNARD REAGENT ON POLYNUCLEAR KETONES



ACTION OF THE GRIGNARD REAGENT ON POLYNUCLEAR KETONES

A Thesis

by

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Presented to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

McGill University

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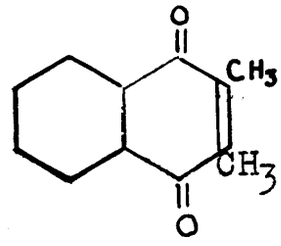
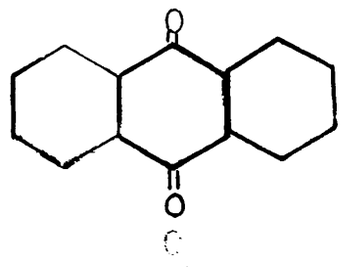
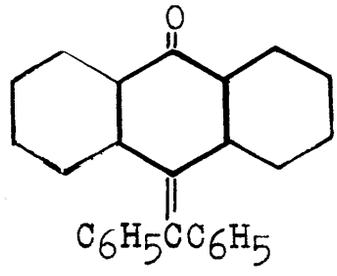
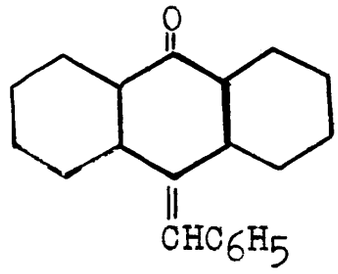
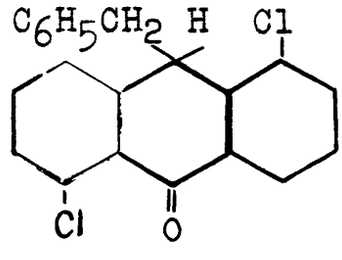
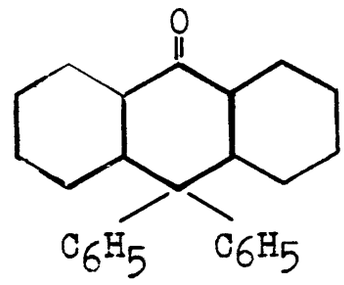
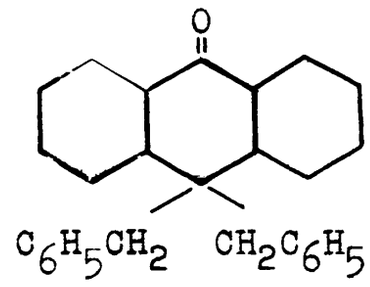
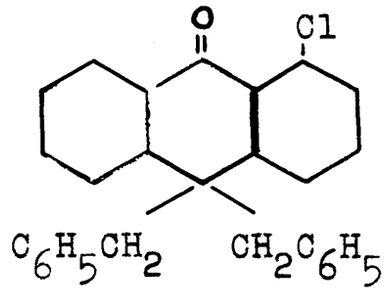
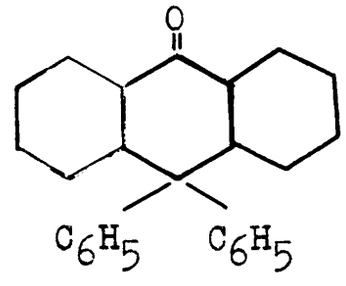
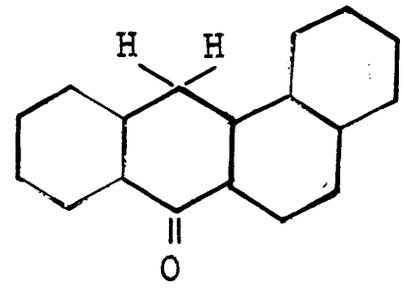
I. HISTORICAL AND INTRODUCTION

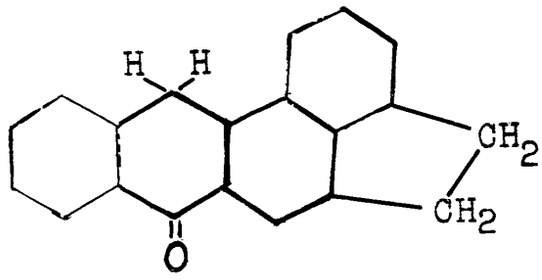
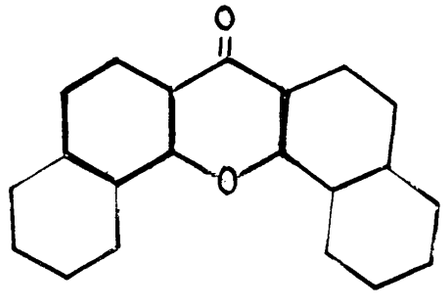
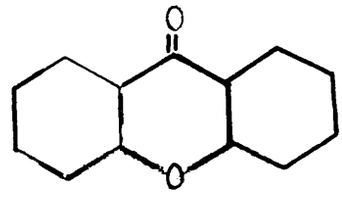
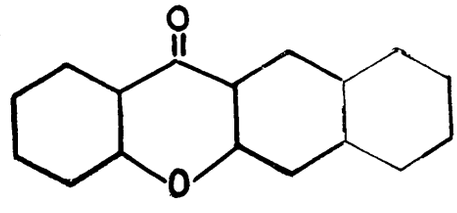
Outline of the Work

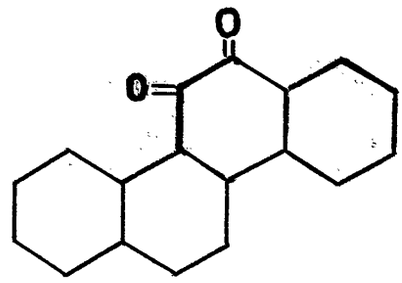
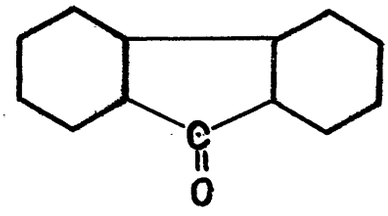
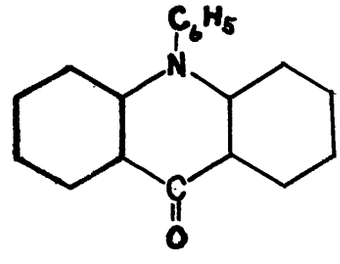
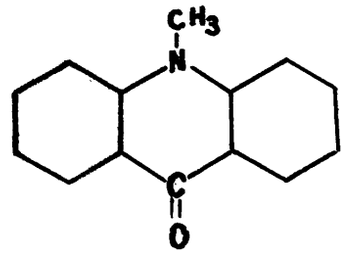
It has been known for some time that Grignard reagents may give both 1,2- and 1,4- addition to α,β - unsaturated ketones(58). More recently it has been shown that, when there is a sufficient amount of substitution, an aromatic ring might provide the α,β - unsaturation for such a 1,4- addition(43),(59). Some quinones are like α,β - unsaturated ketones but have been found to give 1,2- addition with Grignard reagents in most cases. A partial list of the quinones that have been investigated is given in Table I. This list is only intended to bring up to date and supplement a similar one incorporated in a previous thesis presented at this University(60).

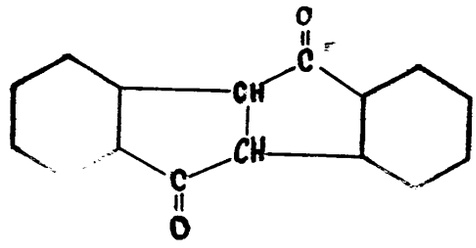
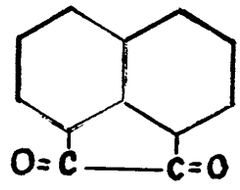
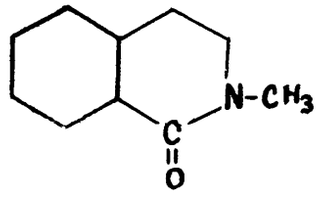
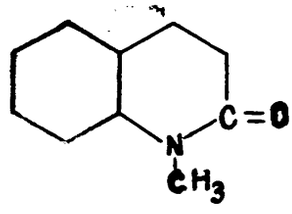
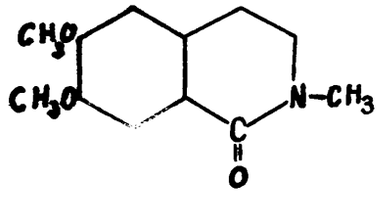
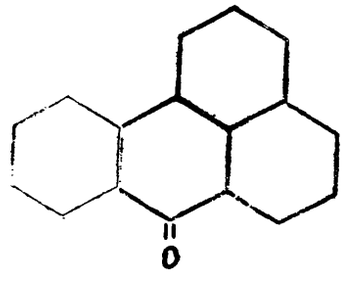
TABLE I.

Name of compound	Formula	R in RMgX	Addition	Reference
2,3-dimethyl-1,4-naphthoquinone (I)		phenyl	1,2 and 1,4	(40)
anthraquinone (II)		o-phenyl-phenyl	1,2	(47)
		o-phenoxy-phenyl	1,2	(47)
anthrafuchsone (III)		methyl	1,2	(41)
		phenyl	1,2	(41)
benzalanthrone (IVa)		methyl	1,2	(42)
1,5-di-chloro-9-benzylanthrone (IVb)		phenyl	1,2	(44)
		benzyl	1,2	(44)

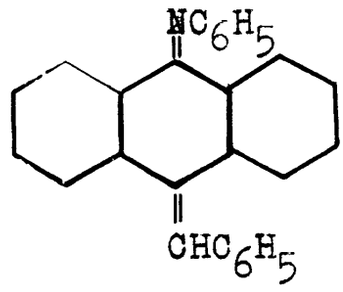
9,9-diphenyl-anthrone (V)		methyl	1,2	(44)
		benzyl	1,2	(44)
9,9-dibenzyl-anthrone (VI)		methyl	1,2	(44)
		phenyl	1,2	(44)
		benzyl	1,2	(44)
1-chloro-10, 10-dibenzylan-throne (VII)		phenyl	1,2	(44)
9,9-diphenyl-anthrone (VIII)		o-phenyl-phenyl	1,2	(47)
		o-phenoxy-phenyl	1,2	(47)
1,2-benz-10-anthrone (IX)		benzyl	1,2	(45)

acenaphth-anthrone (X)		benzyl	1,2	(45)
cis-di-benz-ox-anthrone (XI)		phenyl	1,2	(46)
oxanthrone (XII)		o-phenyl-phenyl	1,2	(47)
		o-phenoxy-phenyl	1,2	(47)
		o-benzyl-phenyl	1,2	(47)
		o-(diphenyl-methyl)-phenyl	1,2	(47)
2,3-benzox-anthrone (XIII)		phenyl	1,2	(48)

5,6-chrysene-quinone (XIV)		phenyl	1,2	(49)
fluorene-one (XV)		o-phenyl-phenyl	1,2	(47)
		o-phenoxy-phenyl	1,2	(47)
		o-(p-methyl-phenoxy)-phenyl	1,2	(47)
		o-benzyl-phenyl	1,2	(47)
		o-(diphenyl-methyl)-phenyl	1,2	(47)
N-phenyl acridone (XVI)		phenyl	1,2	(50)
N-methyl acridone (XVII)		benzyl	1,2	(53)

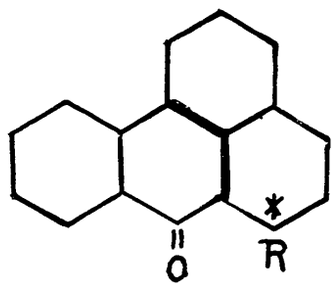
diphenyl succindone (XVIII)		phenyl	1,2	(51)
		p-tolyl	1,2	(51)
acenaphthene quinone (XIX)		phenyl	1,2	(52)
		o-phenyl-phenyl	1,2	(47)
N-methyl-iso-quinoline-one (XX)		benzyl	1,2	(53)
N-methyl-quin-oline-one (XXI)		benzyl	1,2	(53)
dimethoxy-N-methyl-isoquin-oline-one (XXII)		benzyl	1,2	(53)
benzanthrone (XXIII)		t-butyl	1,2	(54)
		phenyl	1,4	(54)
		n-heptyl	1,4	(54)
		cyclo-hexyl	1,4	(54)
		benzyl	1,4	(54)

benzalanthrone anil (XXIV)

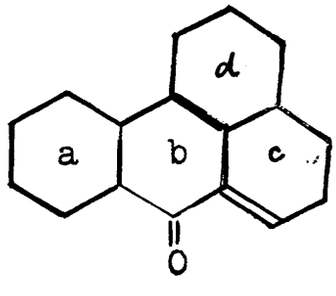


phenyl 1,4 (55

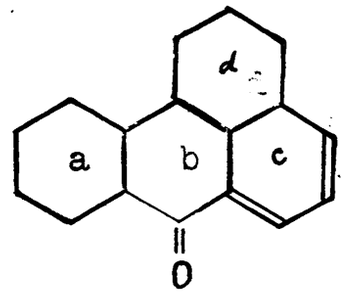
Quite recently it was found that benzanthrone reacts with several Grignard reagents to give 1,4-addition products(54). This reaction provides a method of locating double bonds in polynuclear compounds, for, in order to obtain a substance in which the position indicated (XXV) is occupied by the group R, a double bond must have existed as shown in XXVIa. In no other reasonable way could the formation of 4-phenyl-benzanthrone be explained. Furthermore, locating one double



(XXV)



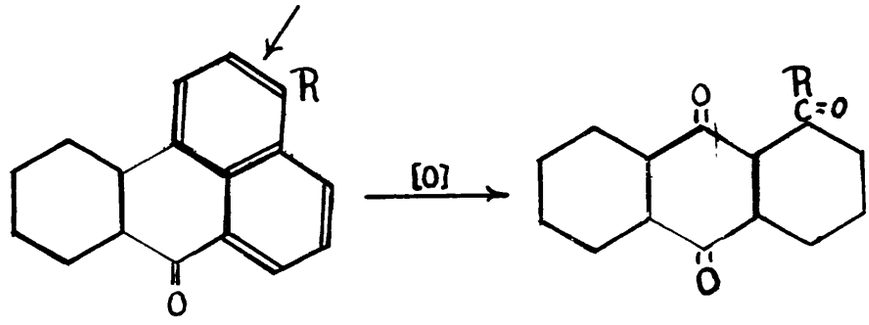
(XXVIa)



(XXVIb)

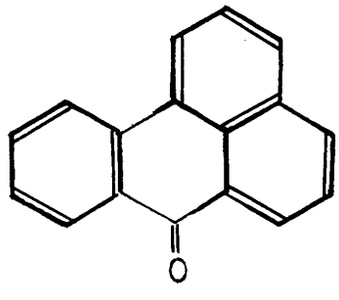
bond in the ring "c" establishes the position of a second double bond as shown in XXVIb.

The bonds in the benz ring are probably arranged as in XXVIIa, since oxidation of homologs substituted in the benz-1 position always gives alpha keto-anthraquinones (XXVIIb); this would seem to indicate that the oxidizing agent had attacked the double bonds as marked in XXVIIa.



(XXVIIa) (XXVIIb)

The position of the bonds in ring "a" (Figure XXVI) is unknown, although the arrangement in XXVIII seems more probable than the alternative configuration, because no product has yet been isolated showing a phenyl group on the 5-position. This problem is being studied by a fellow student.



(XXVIII)

It should be pointed out that certain assumptions are implied in the foregoing proof. First, it is assumed that benzanthrone has a "frozen" formula in which the bonds are stationary in rings "c" and "d" at least. This may be attributed to the carbonyl oxygen, which, like any substituent group, is generally believed to act in such a way as to maintain one bond arrangement. Second, it is assumed that the bond arrangement is not altered by the approach of the reacting molecule, so that, for example, when chromic acid oxidizes off the benz ring, there is no change in the position of the double linkages.

At first sight it seemed possible that the use of the Grignard reagent,as outlined above, could be extended to other ring systems, using ketones having the carbonyl group in the side chain. This could be accomplished by selecting ketones such that hindrance to ordinary 1,2-addition would be greatly hindered or even prevented by the nature of the R group in the side chain. From Conant and Blatt's work(61) it is known that in t-butyl ketones addition to the carbonyl group is slowed down so much that other reactions, usually unnoticed in simple compounds, appear as the main reactions. Mesityl ketones also show none of the normal 1,2-addition; when "forced", the Grignard reagent adds 1,4- involving a conjugated system to which such addition will not ordinarily take place(62).

$$(C_6H_5)_2C{=}CHCC_6H_2(CH_3)_3 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CCH_2CC_6H_2(CH_3)_3$$
(O) (O)

(XXIX)

The use of the mesityl ketones of polynuclear ring compounds, even of a simple one such as naphthalene, would entail so many difficulties in determining structures of reaction products that it was not considered. On the other hand, it is relatively easy to introduce the pivalyl group (- $COC(CH_3)_3$) into hydrocarbons by the Friedel-Crafts reaction. The position taken can be determined by analogy with known Freidel-Crafts reactions and confirmed by degradation using sodamide(63).

$$RCOC(CH_3)_3 \xrightarrow[NaNH_2]{110^\circ} RCONH_2 + (CH_3)_3CH$$

(XXX)

Three pivalyl aryl ketones have been described in the literature; phenyl-t-butyl ketone(64), α-naphthyl-t-butyl ketone(63), and β-naphthyl-t-butyl ketone(63) The first has been shown to yield a carbinol(XXXI) (1, 2-addition to the carbonyl group) when treated with Grignard reagents

$C_6H_5CRC(CH_3)_3$
|
OH

(XXXI)

(65, 66, 67), indicating that the hindrance was not so great as would be expected by comparison with the analogous aliphatic ketones(61). Just a few months ago it was shown that this ketone formed other carbonyl derivatives; e.g., a dinitro-phenyl-hydrazone(68). These reactions indicate that a pivalyl group alone would not offer sufficient hindrance for our purpose. In the case of the naphthyl ketones, however, the alpha form has an additional hindrance owing to the second ring in the ortho position (Although an oxime is mentioned(63), it was prepared only with difficulty and with very poor yield.) and might be expected to behave in a different manner.

A study of the substance revealed several new features. First, α-naphthyl-t-butyl ketone is volatile with steam, so can be separated from reaction mixtures readily. Steam distillation was found, in fact, to be the best method of preparing a crystalline product from the crude. Second, the compound does not react with phenylmagnesium bromide or methylmagnesium iodide even under forced conditions, hence was useless for our purpose. Third, the formation of the ketones by the Friedel-Crafts reaction requires only a trace of aluminum chloride, and the latter is, therefore, truly catalytic; the t-butyl group is apparently a

sufficient hindrance to prevent formation of Perrier double compounds.

Thus it appears, that it is not practicable to use polynuclear ketones having the carbonyl group in the side chain to determine the location of annular double bonds by 1,4-addition of Grignard. One is reduced, therefore, to the use of mono- or di- ketones where the carbonyl group is part of a ring. This at once limits the usefulness of the method, because, obviously, the linkages are determinable in only two rings at most. However, it is of value to learn even that much of the "finer structure" in many instances.

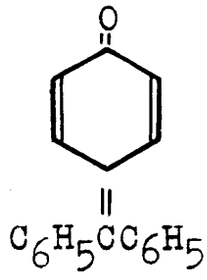
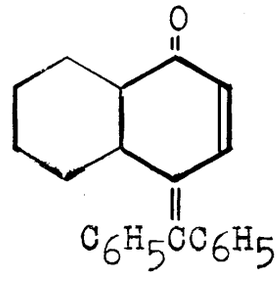
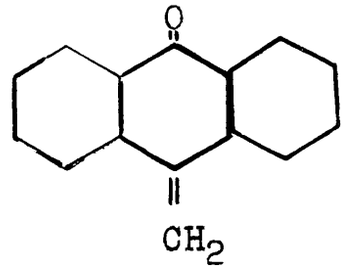
In the case of diketones, moreover, the substances are always quinones; this introduces further complications, owing to the oxidizing properties of this latter class of compounds(69). Simple quinones (e.g., p-benzoquinones, duroquinone, 2,3-dimethyl-1,4-naphthoquinone) give complex mixtures of products(40), while para- quinones having rings on each side of the ring containing the carbonyl group give carbinols (1,2-addition) in by far the greatest number of cases. (Table I)

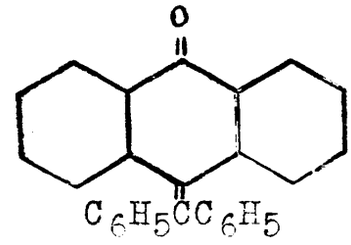
Relatively little has been done with the ortho-quinones, but again, the 1,2-diones seem to give 1,2-addition in all cases reported. (Table I) We have investigated only one ortho-quinone, 5,6-chrysenequinone, and found that

it forms a diol; this confirms Cook's results(49).

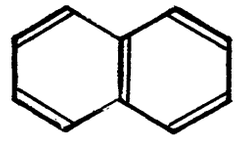
In discussing the addition of Grignard reagents to ketones in which the carbonyl group is part of a ring, reference must be made to Julian's work which shows that Grignards add 1,6 to fuchsone, naphthafuchsone, and methylene anthrone(41, 56, 57). Surprisingly enough, anthrafuchsone adds Grignard reagents to give carbinols(41).

TABLE II

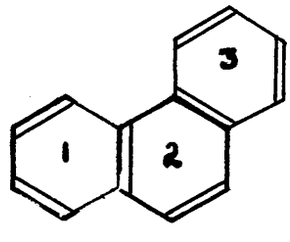
fuchsone (XXXII)		methyl	1,6	(41)
naphtha-fuchsone (XXXIII)		methyl	1.6	(41)
methylene anthrone (XXXIV)		methyl	1,6	(57)
		ethyl	1,6	(57)
		phenyl	1,6	(57)

anthra-		methyl	1,2 (41)
fuchsone		phenyl	1,2 (41)
(XXXV)			

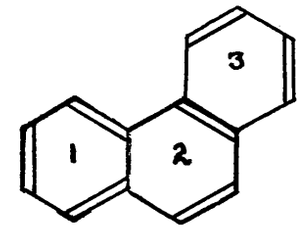
Benzanthrone was the first polynuclear ketone discovered to give 1,4-addition with Grignard reagent. It was obviously of interest to ascertain if possible which, if any, of the uninvestigated quinones would be likely to give similar 1,4-addition. The work of Fries(70) and Fieser(71,72) has been helpful in this connection. Apparently, the normal bond arrangement in naphthalene is as shown in XXXVI. Furthermore, the bond arrangement in polynuclear compounds tends to be such that as many naphthalene units are present as possible. For example, phenanthrene will be as shown in XXXVIIa rather than as in XXXVIIb, because, in the former, rings 1 and 2 constitute a naphthalene unit and rings 2 and 3 do likewise. In XXXVIIb there are no naphthalene units.



(XXXVI)



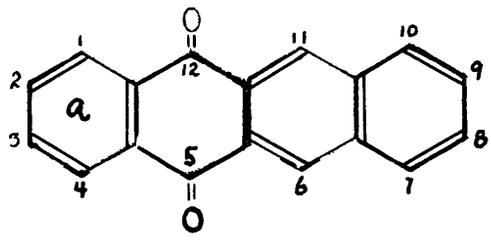
(a)



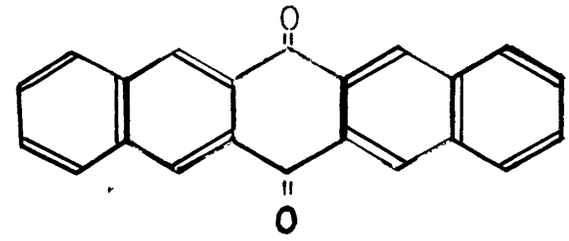
(b)

(XXXVII)

In the same way, one would predict formulas XXXVIIIa and XXXVIIIb for naphthacenequinone and pentacenequinone respectively.



(a)

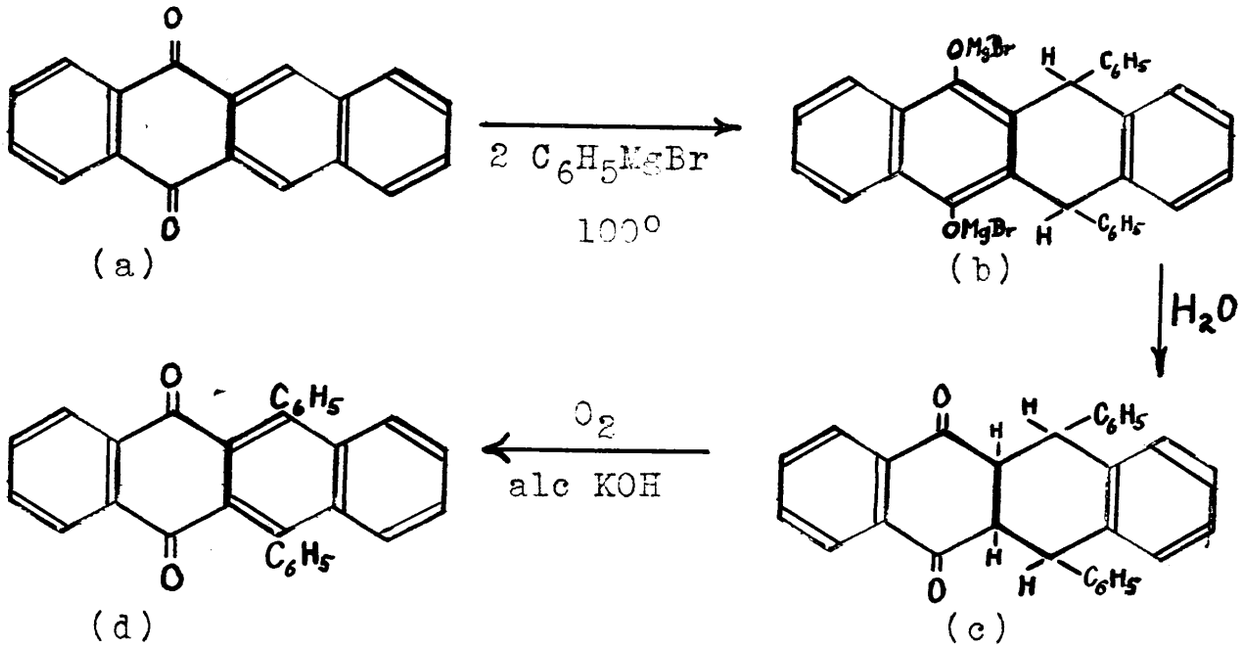


(b)

(XXXVIII)

The arrangement of bonds in these compounds is thus predicted to be such that 1,4-addition is at least possible.

In this connection, the reactions of naphthacenequinone have been determined and are recorded in this thesis. It has been shown that 1,4- addition actually does take place with phenylmagnesium bromide under forced conditions. Two moles of the reagent add per mole of quinone, the phenyl groups appearing on positions 6 and 11. The course of the reaction is shown below.



(XXXIX)

The magnesium complex (b) was not isolated, of course, but two compounds, both yellow, one melting at 224° and the other at 293-7°, corresponding to two possible stereo-isomeric forms of c, were obtained. This corresponds to the formation of saturated ketones from unsaturated ketones by 1,4-addition of Grignard.

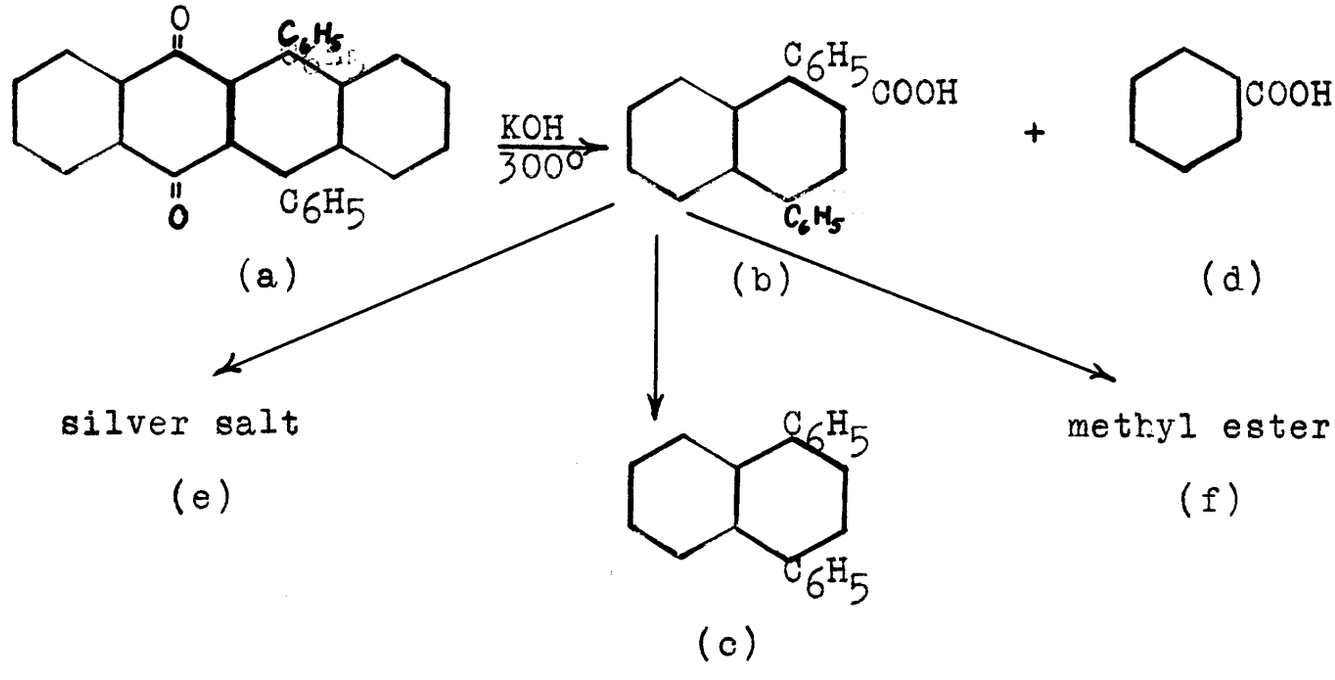
$$C_6H_5CH{=}CHCC_6H_5 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH{=}CC_6H_5 \xrightarrow{H^+} (C_6H_5)_2CHCH_2CC_6H_5$$
(O; OMgBr; O)

Both dissolved in alcoholic potassium hydroxide, giving deep blue solutions and precipitating yellow, crystalline 6,11-diphenyl-5,12-naphthacenequinone upon air oxidation.

The 1,4-addition of Grignards to quinones follows, therefore, the same mechanism as the 1,4-addition of Grignards to α,β-unsaturated ketones of the aliphatic series.

The isolation of the intermediate hydro compounds was possible in the case of naphthacenequinone when not possible in the case of benzanthrone(54) because compound c(XXXIX) is a tetrahydrobenzene derivative while the corresponding intermediate in the case of benzanthrone is a dihydrobenzene and, accordingly, is easily dehydrogenated on account of the marked tendency of dihydrobenzene derivatives to go to the aromatic state.

The structure of the 6,11-diphenyl-5,12-naphthacenequinone was proved by alkaline fusion and identification of the degradation products.

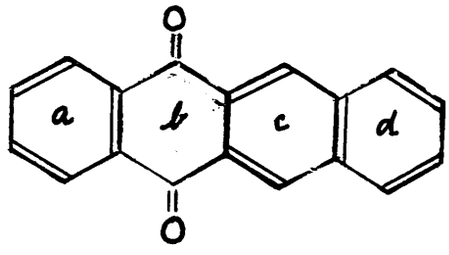


(XL)

1,4-Diphenyl-2-naphthoic acid (XLb), its methyl ester (XLf), and 1,4-diphenyl-naphthalene (XLc) were identified by their melting points, all of which agreed with those given in the

literature(73). 1,4-Diphenyl-2-naphthoic acid was further identified by analysis of its silver salt. Benzoic acid (XLd) was recognized by its melting point and a mixed melting point.

The 1,4- addition of Grignard reagent to naphthacenequinone is strong evidence for Fieser's formula (XLI.



(XLI)

Although, from theoretical considerations based on physicochemical evidence, Fieser believes the ring "a" to be arranged as shown, no conclusive evidence was advanced(71). The addition of phenylmagnesium bromide to diphenylnaphthacenequinone(XLa) was therefore attempted. There was no reaction, even under forced conditions. The absence of 1,2-addition may be explained by hindrance (for example, 1,4- or 1,5- disubstituted anthraquinones are not reduced by alkaline hydrosulfite(87), and we found that 6,11-diphenyl-5,12-naphthacenequinone was not reduced by this reagent even under conditions which were effective with naphthacenequinone(71)), but the absence of 1,4-addition can be explained only by a bond arrangement of ring "a" as shown in XLI and previously surmised by Fieser. If the alternative arrangement were present, there is no reason why a tetraphenylnaphthacenequinone would not be formed.

Our work, in conjunction with that of Fries and Fieser (loc. cit.) therefore affords strong evidence in favor of the structure XLI for naphthacenequinone.

The empirical formula of diphenylnaphthacene-quinone is $C_{30}H_{18}O_2$. It was interesting to observe that the carbinol that would have resulted from 1,2-addition of phenylmagnesium to both the carbonyl groups of diphenyl-naphthacenequinone would have an empirical formula of $C_{42}H_{30}O_2$ the same as that of dihydroxy-rubrene. The structure of rubrene and its derivatives has been one of the puzzling problems of the last decade; synthesis of a rubrene derivative, by a reaction of known mechanism, would be a definite contribution to the solution of this problem.

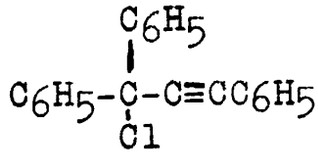
Recently, two independent reports of ready peroxide formation by anthracene derivatives appeared in the literature (86, 87). Since ease of peroxide formation is one of the unusual properties of rubrene(76), it seemed quite possible that rubrene could be a naphthacene derivative. When, some months later, Dufraisse announced the detection of dihydroxy-rubrene following the action of phenylmagnesium bromide upon a naphthacene derivative(84), it seemed worth while for us to undertake a structure proof of these compounds, using our previously prepared 6,11-diphenyl-5,12-naphthacenequinone as starting material and proceeding by established reactions,

the course of which was well known.

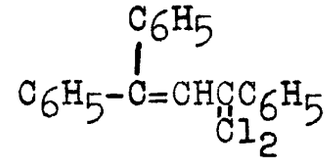
II. RUBRENE

About ten years ago the discovery of a hydrocarbon colored deep red was announced(74). This compound, named rubrene, possessed several unusual properties. In the first place, its color alone would arouse interest. In the second place, rubrene was found to be reversibly oxidizable to a peroxide(75). Peroxide formation proceeded readily in the presence of air, solvent, and light, but was entirely stopped by the absence of any one of these. The peroxide so formed, a colorless compound containing solvent of crystallization, readily regenerated rubrene, oxygen, solvent, and even light when warmed. Within the limits of experimental error, the reaction seemed to be quantitative both ways, and could be repeated an indefinite number of times. The similarity of this compound to haemoglobin was a point of considerable interest.

Rubrene was originally prepared by warming phenyl-(di-phenyl-chloro-methyl)-acetylene (XLII) (74), but has since been prepared from β -phenyl-benzalacetophenone through a keto-chloride (XLIII) (76) or from similar compounds, two

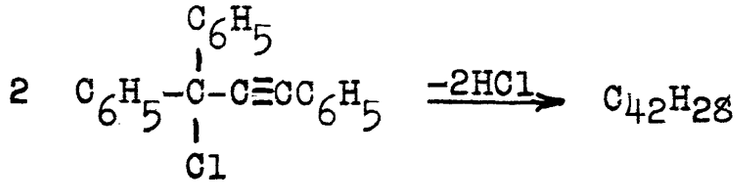


(XLII)



(XLIII)

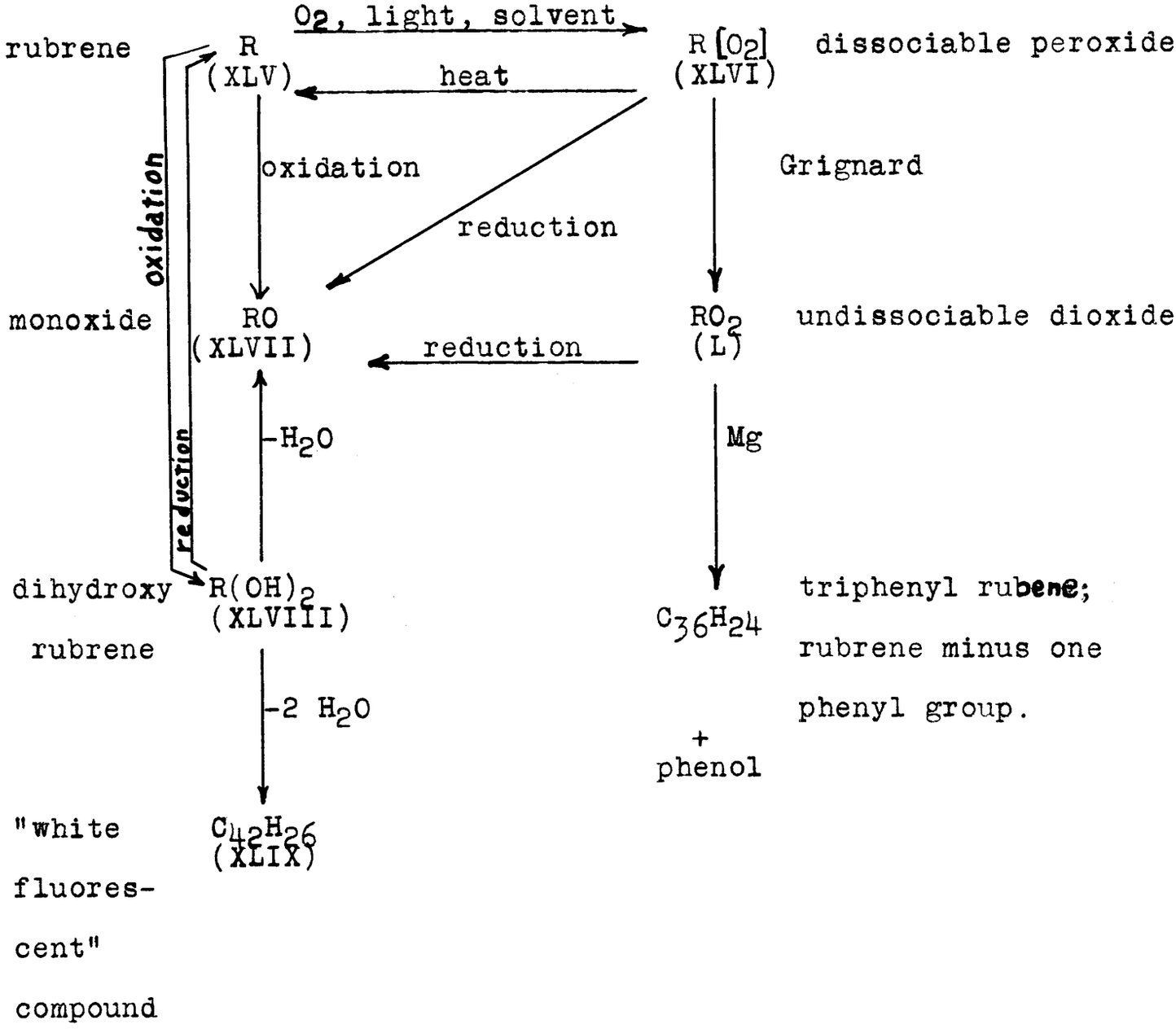
molecules of halogen compound doubling up with the loss of two molecules of hydrogen chloride to give one molecule of rubrene, $C_{42}H_{28}$.



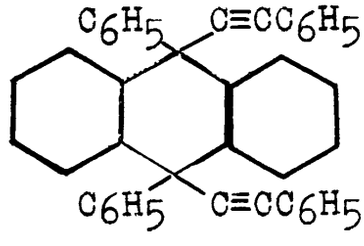
(XLIV)

A summary of the reactions of rubrene is shown by the flowsheet, in which R stands for the hydrocarbon rubrene.

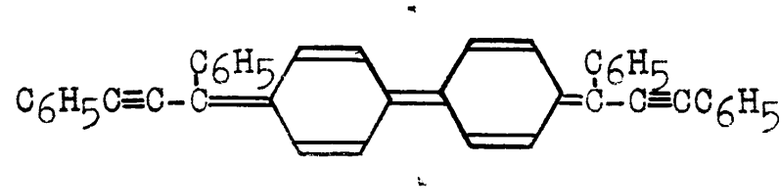
By a recent change in nomenclature, "rub-ene" is the name given the hydrocarbon residue characteristic of these compounds. The name "rubrene" is reserved for the compound known as tetraphenylrub-ene according to this newer nomenclature



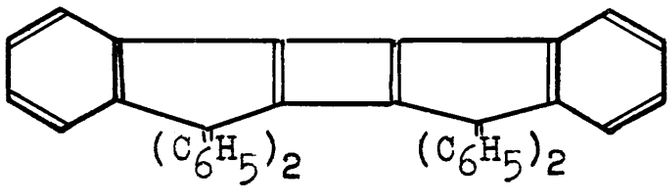
The following structures have been suggested for rubrene:



(LI)(78)

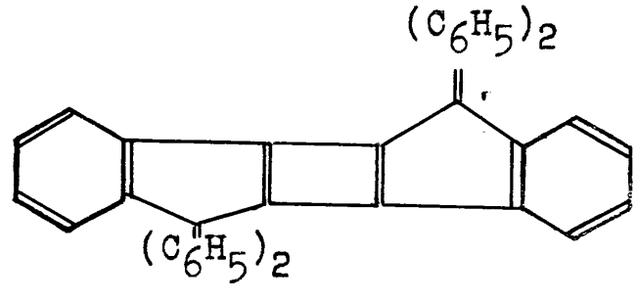


(LII)(78)

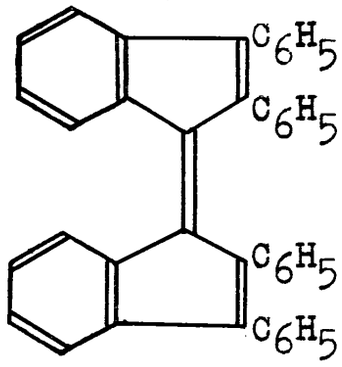


(LIIIa)(78)

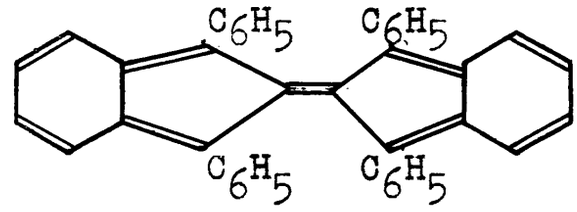
or



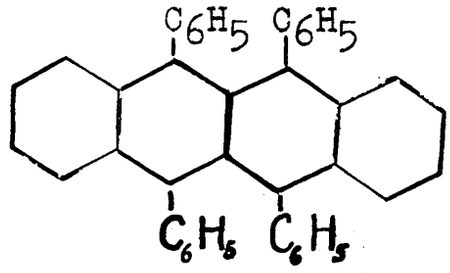
(LIIIb)(78)



(LIV)(79)



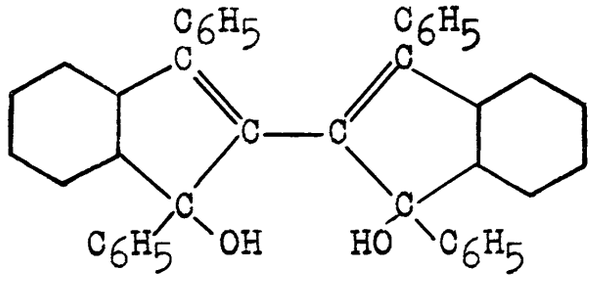
(LV)(77,80)



(LVI)(81)

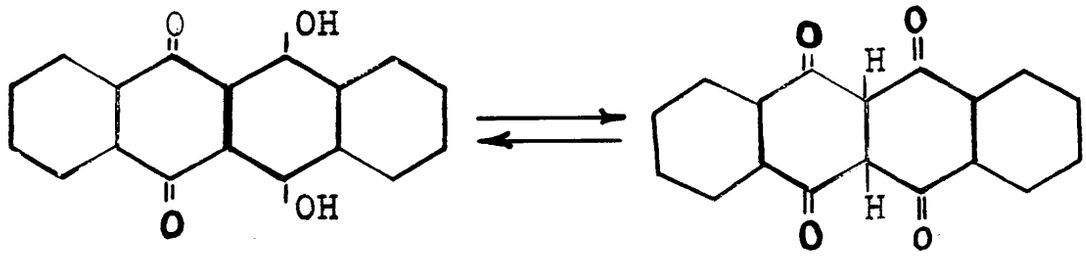
When it was learned that rubrene, upon oxidation with chromic acid, gave o-dibenzoylbenzene(77), formulas LII, LIIIa, LIIIb, and LIV were all ruled out. Formula LI never had received much credence because it did not account for the color of the compound, and no evidence for the presence of acetylenic bonds could be found(78). The di-indene formula LV has, therefore, been generally accepted up to the present(76, 77, 80).

In October, 1935, Marvel showed, by synthesis, that bis 2,2'-(1,3-diphenylindenol-3)(LVII) was not dihydroxyrubrene(XLVIII) nor was it convertible to rubrene(82). He had already eliminated another possible bis-(diphenylindene) structure for rubrene by a previous synthesis(83). Koelsch reported similar findings the same month(88).



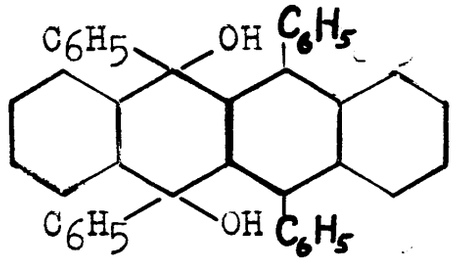
(LVII)

About the same time, Dufraisse announced, without giving any reasons, that he believed rubrene to be 5,6,11,12-tetraphenylnaphthacene(LVI)(81), but in two subsequent papers (89, 90) he still used the old di-indene formula. Some months later, he announced a preparation of rubrene, starting from 5,12-dihydroxy-6,11-naphthacenequinone(LVIII)(84). By a reaction, the mechanism of which is not made clear as



(LVIII)

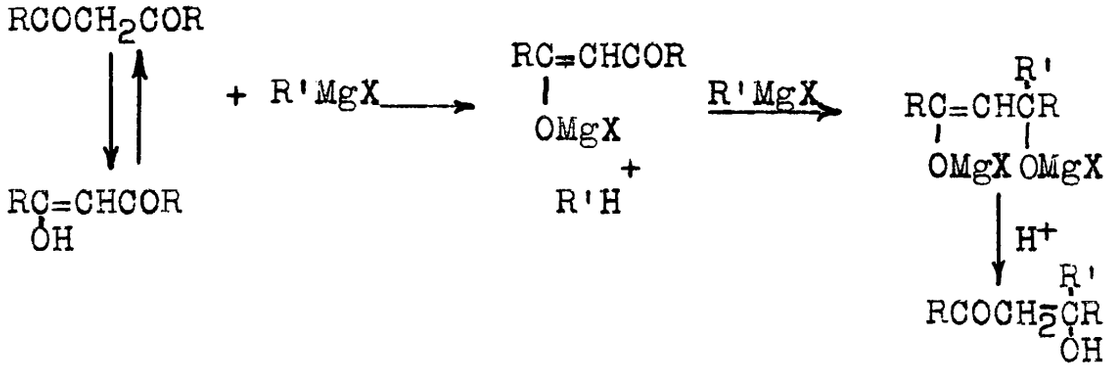
no experimental details are given, he prepared dihydroxyrubrene(XLVIII) to which he ascribed formula LIX. Since dihydroxyrubrene was only one of several compounds isolated



(LIX)

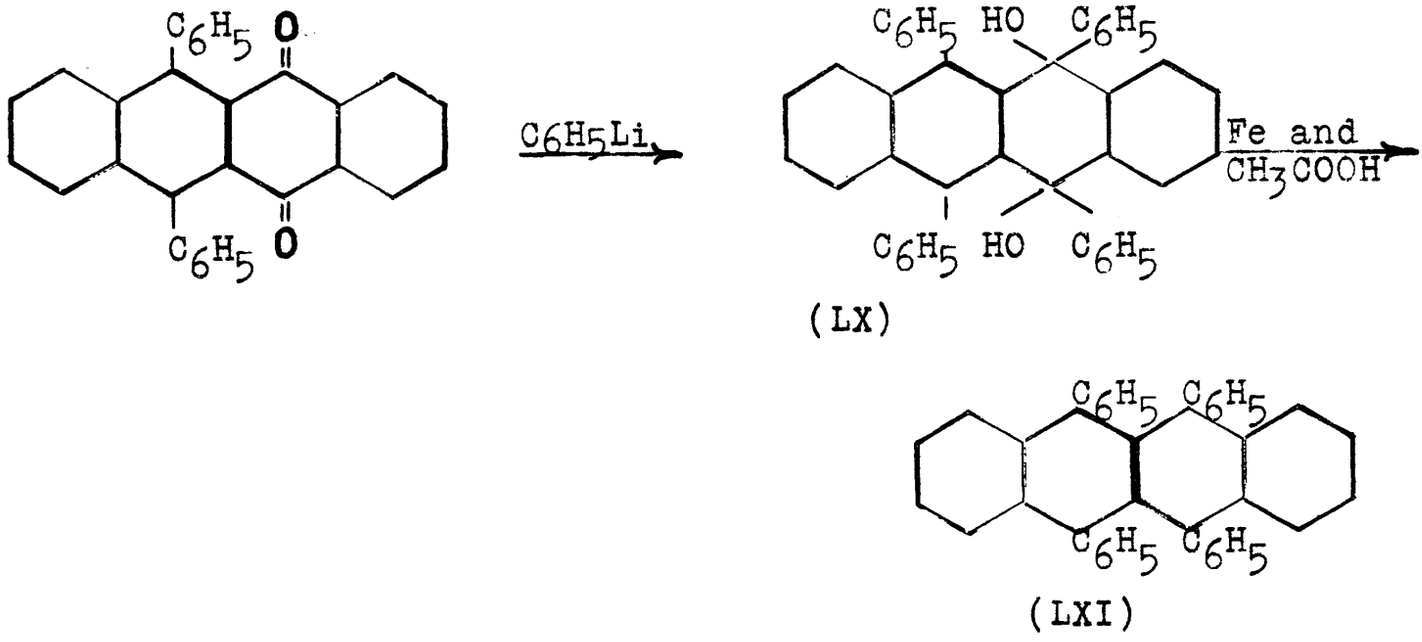
from the reaction mixture, the synthesis did not prove that the dihydroxyrubrene formed was 5,11-dihydroxy-5,6,11,12-tetraphenyl-naphthacene.

Furthermore, the starting material(LVIII) is a β-diketone and is enolized. This acidic property is so pronounced that the discoverers were puzzled and could not agree on the true structure(91). Now it is well known that two moles of Grignard reagent are needed to introduce one R group. Accordingly, the production of a diol is not



strictly analogous.

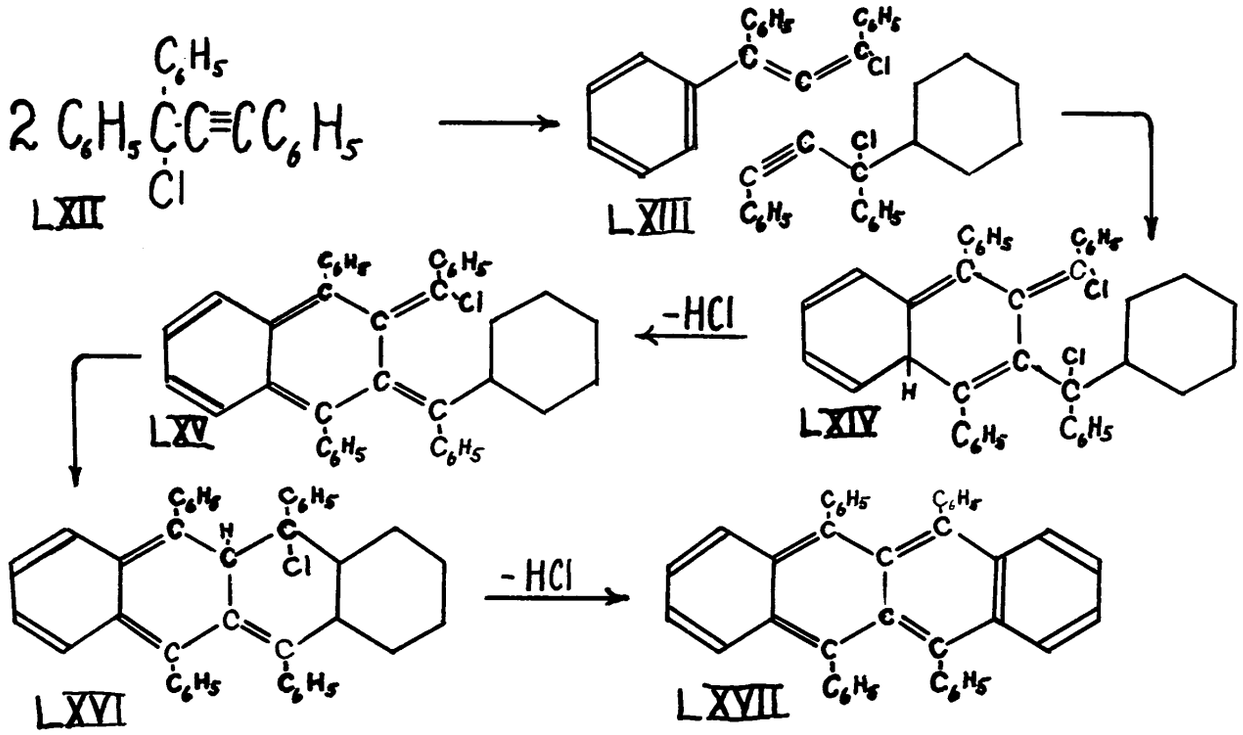
Therefore, to secure unequivocal evidence on the subject, a synthesis of the diol was undertaken. This, and a reduction to rubrene, were accomplished by two, clear-cut steps. We used lithiumphenyl rather than phenylmagnesium



bromide for the preparation of the carbinol LX because the former is known to give only 1,2- addition to α,β - unsaturated ketones. Subsequently it was found that phenylmagnesium bromide did not add to diphenylnaphthacenequinone at all. The dihydroxytetraphenyldihydronaphthacene derivative isolated(LX) proved to be identical with dihydroxyrubrene. Its melting point agreed with that for dihydroxyrubrene, action of dehydrating agents yielded a compound of the same properties as the "white fluorescent compound"(XLIX) in the literature(85), and reduction gave rubrene. This last compound was identified by its reversible peroxide formation and by its absorption spectra, as well as by its color and that of its solutions.

Accordingly, this synthesis establishes definitely that rubrene is 5,6,11,12- tetraphenylnaphthacene(LXI).

The transformation of a propyne into a naphthacene derivative, in the original synthesis of rubrene(XLIV), seems quite surprising at first sight, especially as the reaction proceeds readily at so low a temperature as 120°C(74) and will even proceed at room temperature in the course of several weeks(76). The following series of reactions are suggested as a probable mechanism.



The change of one molecule from the acetylenic to the allenic bond structure in the first step is an ordinary 1,3-shift of a halogen atom, and is facilitated by the looseness with which the chlorine atom is bound in LXII. A chlorine atom attached to a carbon bearing two phenyl groups and an acetylenic chain is comparable to the chlorine atom in

triphenylmethyl chloride. The shift involved is an example of the now common anionotropy.

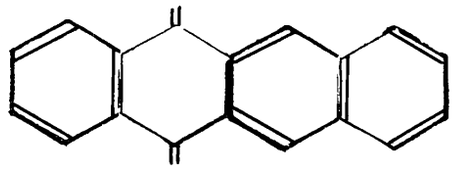
The closure effected in going from LXIII to LXIV is a Diels-Alder diene synthesis; it is the addition of an acetylenic bond to conjugated double bonds, part of which are in an aromatic nucleus. This is the key step in this mechanism and is believed to account for the ease with which rubrene is formed from phenyl-(diphenyl-chloro-methyl)-acetylene. When such a diene synthesis does go, it usually proceeds with great ease.

The change from LXIV to LXV is the 1,4-elimination of hydrogen chloride to form a pair of conjugated double bonds in place of one double bond and is facilitated by the presence of two phenyl groups on the carbon atom to which chlorine is attached.

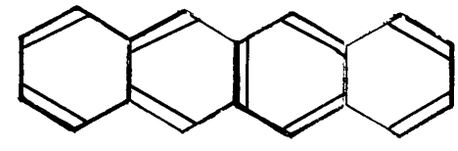
The ring closure in forming LXVI gives the intermediate monochloride with an active chlorine atom as reported and isolated by Robin(92). The final elimination of hydrogen chloride to form an aromatic ring from a dihydrobenzene structure would be expected.

With the structure of rubrene and dihydroxyrubrene definitely established, many of the reactions of this compound are easily explained. In the first place, the great reactivity of the pair of meso carbons is characteristic of naphthacene. Fieser's researches have shown that only the

derivatives of dihydronaphthacene are stable, derivatives of naphthacene itself showing a pronounced tendency to oxidize, rearrange, or even disproportionate in order to go over to the dihydro form(71, 72). Apparently this is because two of the aromatic rings in dihydro-naphthacene can form a naphthalene nucleus, and the third can assume a benzene structure(LXVIII), while, in derivatives of naphthacene, two rings can assume the naphthalene arrangement, but the remaining two can neither be naphthalenic nor benzenoid in structure(LXIX).

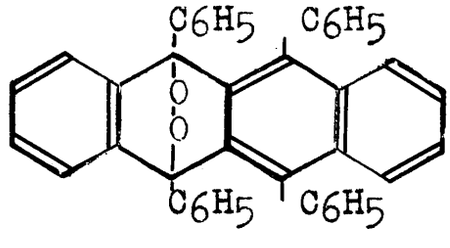


(LXVIII)



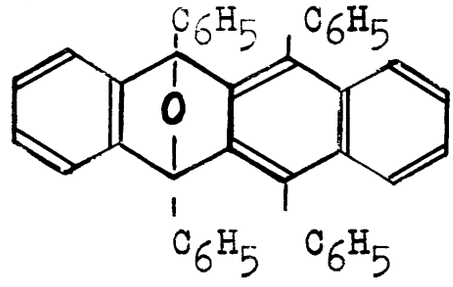
(LXIX)

The dissociable peroxide(XLVI in Flowsheet) probably, then, has the structure LXX. Its ease of formation is explained by the considerations in the preceding paragraph. The ready reversibility of the reaction is in accord with our knowledge of organic peroxides which usually lose oxygen upon being warmed.



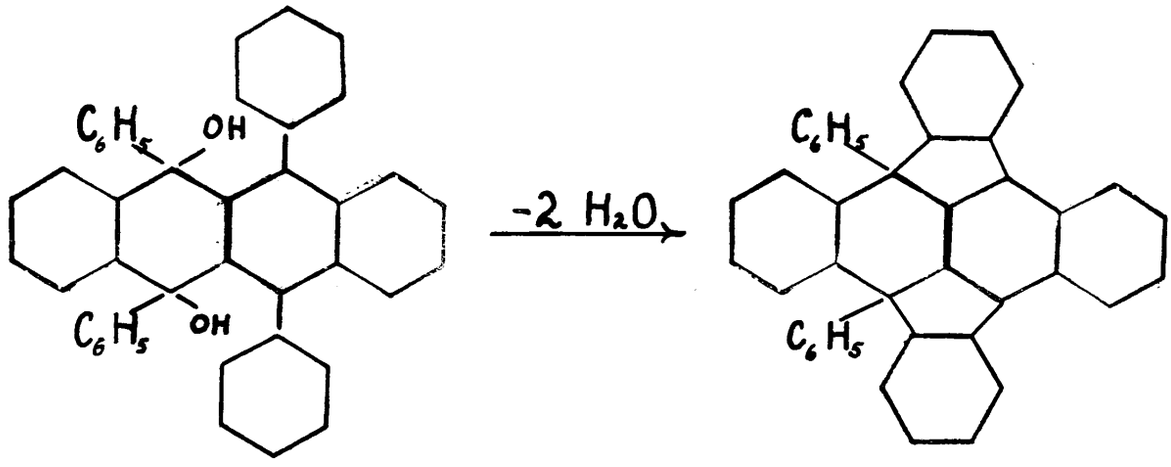
(LXX)

Similar considerations lead to formulating rubrene monoxide(XLVI in Flowsheet) as LXXI. If our formula for rubrene peroxide(LXX) is correct, additional evidence for LXXI as the structure of rubrene monoxide exists in the formation of the latter by reduction of the former (see Flowsheet). Furthermore, such a structure is supported by the preparation of rubrene monoxide from dihydroxy-rubrene (LX) by the loss of one molecule of water(76).



(LXXI)

The "white fluorescent" compound(XLIX Flowsheet) in all likelihood is as Dufraisse has suggested(LXXII) and is formed from dihydroxy-rubrene(LX) by the loss of two molecules of water.



LX LXXII

III. EXPERIMENTAL

o- (Tetroyl-2) - benzoic acid:

This compound was prepared according to Fieser's directions(71). We can only add that it was found advisable to introduce the aluminum chloride in portions rather than all at once, in order to avoid too vigorous a reaction. Further, no decantation of benzene was possible at the end of the coupling reaction. The yields were from 85% to 90% of the theoretical.

1,2- and 2,3- Tetralanthraquinone mixture:

The preparation of a mixture of 1,2- and 2,3-tetralanthraquinones and their subsequent separation followed in general the directions of Schroeter(92) as modified by Fieser(71). Twelve 30g. portions and one 15g. portion were made of 375g. of finely powdered o-(tetroyl-2)-benzoic acid. Each 30g. portion was added to 75ccs. of fuming sulfuric acid (10-15% excess SO_3) in a 300cc. Erlenmeyer flask over a period of 5 minutes. External cooling was applied when necessary to keep the temperature below 30°C. After warming 10 minutes on the steam bath, the mixture was run into boiling water during the course of another 5 minutes.

Although each 30g. portion of acid was treated separately, as detailed in the preceding paragraph, all

were run into the same flask of water. For this purpose, 3.25 l. of water was brought to boiling in a 5-l. flask equipped with a mechanical stirrer. The sulfuric acid solutions were added through a dropping funnel while the water was stirred vigorously.

Immediately after the addition of the last portion of sulfuric acid solution, the hot aqueous mixture was filtered with suction, using two thicknesses of filter paper. The black residue was washed repeatedly with water until it became tan in color and the washings had become almost colorless. The organic material was then made into a slurry with dilute sodium carbonate solution. If the previous washings had not been thorough, excessive frothing hindered the work at this point. The insoluble material was filtered, washed with water, and dried; the residue weighed 255g. (73% yield).

2,3- Tetralanthraquinone:

The 255g. of mixed tetralanthraquinones, prepared as above, was dissolved in 1785 ccs. of benzene. After the addtion of 10 g. of animal charcoal, the solution was filtered hot. Crystals of 1,2-tetralanthraquinone separated out upon cooling to room temperature. On recrystallization from 500 ccs. of constant boiling chloroform-methyl alcohol mixture (4:1), 57 g of a product melting at 208-11° was obtained. A second crop of 24 g., also melting at

208-11°, was secured by adding methyl alcohol to the boiling filtrate until a precipitate just formed and cooling to room temperature.

5,12-Naphthacenequinone(XXXIXa):

A few details may be added to Fieser's directions for the preparation of naphthacenequinone from 2,3-tetralanthraquinone(71). It was found advisable to distill all the solvent from the dehydrogenation mixture rather than to attempt to transfer a syrupy solution from one flask to another. The dry mixture was readily broken out of the first flask and, after powdering, could easily be introduced into the second.

Attempts to purify the quinone by recrystallization omitting distillation were useless. Apparently a pure product can be secured only after at least two distillations. The most satisfactory apparatus for this procedure was found to be a pyrex retort with a Claisen flask as receiver. The side tube of an ordinary distilling flask quickly became clogged with sublimed quinone. A retort of 125 ccs. capacity and a 250 cc. Claisen flask as receiver would just about accommodate the product obtained from 50 g. of 2,3-tetralanthraquinone.

Two recrystallizations of redistilled quinone, using 6 ccs. of tetrachloroethane per 1 g. of quinone each time, gave a 62% yield (31 g.) of product melting at 283-4°.

6,11-Diphenyl-5,12-naphthacenequinone (XXXIXd):

In a 1-l. three neck flask, equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel, were placed 45 g. of magnesium turnings (1.86 moles = 6 equivalents) and 400 ccs. of dry ether. The stirrer was started, and 292 g. of bromobenzene (1.86 moles = 6 equivalents) was added through the dropping funnel at such a rate that strong refluxing was maintained. When the boiling ceased, the solution was refluxed an additional 30 minutes, and 150 ccs. of ether was then removed by distillation. The Grignard solution was drawn through glass wool by suction into a second 1-l. three neck flask also fitted with a mechanical stirrer and a reflux condenser. About 200 ccs. of dry n-butyl ether was added. Over a period of five minutes, 40 g. (0.155 moles) of 5,12-naphthacenequinone, m.p. 283-4° was introduced in portions. Moderate ebullition accompanied each addition. The mixture was heated on the steam bath for two hours with continuous stirring; the internal temperature during this time was 85-90°. Excess Grignard reagent was present at the end of this two hours as evidenced by a positive Gilman test. The mixture was decomposed with ice and acetic acid and was steam distilled; this took about 20 hours at the rate of a drop a minute. This operation served to remove 7-8 g. diphenyl as well as the solvent. The brownish resinous sub-

stance remaining weighed 69 g. It was triturated, first with a 100 cc. and then a 50 cc. portion of ether, followed by 20 cc. of cold acetone; 15 g. of a greenish-yellow residue was thus obtained. This is a mixture of the stereoisomeric tetrahydroquinones (XXXIXb), the separation of which (described below) is unnecessary for the next step.

A portion (9.2 g.) of this residue was mixed with 150 cc. of alcoholic potash; it became dark blue almost immediately, and yellow crystals slowly separated. After 3 days the blue color had disappeared, so the solid was filtered from the alkaline solution, dissolved in chloroform, and a small amount of gray insoluble material filtered. On evaporation of the solvent, 8 g. (20.4 per cent) of bright yellow prisms remained. The best solvent for recrystallization was found to be a 1 : 1 mixture of p-cymene and o-dichlorobenzene. Recrystallized three times from this mixture, 5.7 g. of material remained (14.6 per cent), melting at 284°. An admixture with naphthacenequinone (which melts at 283-4°) melted at 255-60°.

Anal. Calcd. for $C_{30}H_{18}O_2$: C, 87.8; H, 4.4. Found C, 87.5; H 4.8

The Tetrahydrodiphenylnaphthacenequinones (XXXIXb):

The greenish-yellow material above, isolated by washing the reaction product from phenylmagnesium bromide and naphthacenequinone with ether and acetone, was shown to

be a mixture of at least two compounds. A portion (4 g.) of this material was refluxed a half hour with 60 cc. of glacial acetic acid and filtered hot. About 0.4 g. of a crystalline yellow product remained on the filter. When this was recrystallized once from 10 cc. of chlorobenzene and once from chloroform, it formed exceedingly fine needles melting at 293-7°. No further attempts were made to purify this compound on account of the small amount obtained and the advisability of showing its relation to diphenylnaphthacenequinone by atmospheric oxidation.

Upon cooling, the hot acetic acid filtrate above deposited yellow needles melting 215-20°. These were dissolved in a minimum of boiling chloroform. Methyl alcohol was added at the boiling point until crystals began to appear. The solution was cooled to -5° and the crystals removed by filtration. They were then dissolved in about twice the minimum amount of boiling dioxane, and boiling n-propyl alcohol was added until just a faint turbidity existed. Dioxane was added dropwise until the solution became clear. The crystals that separated upon cooling were finally recrystallized from a minimum of boiling acetic acid. The melting point was 224-5.5° and was unaffected by further recrystallizations.

Alkali Fusion of 6,11-Diphenyl-5,12-naphthacenequinone:

A finely ground mixture of 2 g. of the diphenylquinone and 12 g. of potassium hydroxide was heated by means of a metal bath at 310° for 10 minutes and at 290° for a further 10 minutes. The cold melt was dissolved in water and extracted with chloroform; this removed 0.65 g. of 1,4-diphenylnaphthalene (XLc) m.p. 134-6° after one recrystallization from dilute alcohol. The literature gives 135-7°(73).

The aqueous alkaline solution was poured into dilute hydrochloric acid, digested on the steam bath for several hours and filtered; from the cooled filtrate, benzoic acid was isolated by ether extraction and identified in the usual manner (m.p. and mixed m.p., 122°).

The insoluble acid removed by filtration weighed 0.15 g.; repeated recrystallizations from dilute alcohol yielded a product, m.p. 218-223°. Since the literature gave 223-5° as the melting point of 1,4-diphenyl-2-naphthoic acid (XLb), the silver salt was prepared and analyzed, and the methyl ester was prepared.

About 0.05 g. of the crude 1,4-diphenyl-2-naphthoic acid (m.p. 205-20°) was dissolved as completely as possible in an excess of dilute ammonium hydroxide and filtered to remove a small amount of insoluble residue. The filtrate was warmed on the steam bath until the vapors in

the beaker no longer affected red litmus paper. Upon the addition of 0.1 g. of silver nitrate dissolved in 10 cc. of distilled water, a heavy white precipitate formed. The solution was filtered, and the residue washed several times with distilled water and several times with alcohol. The silver salt was dried for 2 hours at 110° without discoloration.

Anal. Calcd. for $C_{23}H_{15}O_2Ag$: Ag, 25.0 Found: 25.4

To prepare the methyl ester of 1,4-diphenyl-2-naphthoic acid (XLf), 0.1 g. of crude acid, m.p. 205-20°, was dissolved in 50 cc. of absolute methyl alcohol, and hydrogen chloride gas was passed over the solution for two hours. It was necessary to cool the flask in an ice bath to prevent marked heating. The solution stood for three days at room temperature, protected from atmospheric moisture by a drying tube, and was then poured into an excess of sodium carbonate dissolved in 300 cc. of water. The solution became turbid at once, and the product settled out as a granular material after standing three days at 35°. This product was refluxed gently for 1 hour with 7 cc. of absolute methyl alcohol plus 1 cc. of benzene, and the solution was filtered hot to remove a small amount of insoluble residue. Cooled to 10°, the solution deposited white crystals which, recrystallized again from benzene-methyl alcohol mixture, melted at 163-5°, agreeing with the melting point given in the literature(73).

Properties of 6,11-Diphenyl-5,12-naphthacenequinone:

The quinone dissolved readily in concentrated sulfuric acid giving a deep red color very much like that given by 5,12-naphthacenequinone itself only slightly more violet. When alcoholic potassium hydroxide and aqueous sodium hydrosulfite were added to an alcoholic suspension of the diphenylquinone, the solution became blood red immediately and almost at once became a pale blue. The intensities of the colors were much less than resulted from treating 5,12-naphthacenequinone in a similar manner, and were so slight that it was considered a negative test for a vat dye.

Treated with phenylmagnesium bromide in a mixture of diethyl and di-n-butyl ether for two and a half hours at 98°only unchanged diphenylnaphthacenequinone was recovered upon working up the mixture, as described under the preparation of 6,11-diphenyl-5,12-naphthacenequinone.

5,6,11,12-Tetraphenyl-5,12-naphthacenediol (LX) (Dihydroxyrubrene):

In a 500 cc. three neck flask, equipped with a mechanical stirrer and a reflux condenser, was placed 200 cc. of dry ether. Through the third neck, dry nitrogen was introduced at a slow rate. Metallic lithium was hammered into prisms approximately 2x4x8 mm. and 0.83 g. (0.0615 moles) and was cut into shreds with scissors, the shreds being allowed to fall directly into the flask through

one of the necks which was opened temporarily. It was desired to use a twelve molar excess of lithiumphenyl, and the quantity of lithium calculated was then increased by 40 per cent in anticipation of no more than a moderate yield of organometallic compound. When all the lithium had been added, 9.7 g. of bromobenzene (0.0615 moles) was added slowly through a dropping funnel in the condenser. The reaction started almost at once upon a little warming. When all the bromobenzene had been added, an additional 30 minutes was allowed for completion of the reaction, and then 1.5 g. of 6,11-diphenyl-5,12-naphthacenequinone (0.00366 moles) m.p. 283-4° was added. The mixture was refluxed 13 hours and gave a positive test for lithiumphenyl at this time. The solution, which had been a blue gray color after the preparation of lithiumphenyl was complete, had become brown at the end of 4 hours refluxing. No further changes were visible. All during the preparation of the lithiumphenyl and the reaction with the diphenylquinone, stirring had been continuous, and a constant flow of dry nitrogen had been maintained through the system.

When cool, the solution was decomposed by the cautious addition of small pieces of ice. Finally, enough water was added to make a total aqueous solution of about 200 cc. The ether was distilled away, leaving a clear aqueous solution and orange lumps. The latter were removed

by filtration, dissolved in chloroform for convenience in handling, and steam distilled to remove diphenyl. The organic residue was dissolved in chloroform, filtered from a small amount of insoluble gray material, and the solvent was evaporated. The salmon-pink product was then dissolved in 10 cc. of dioxane on a steam bath, and, while still keeping the solution hot, 60 cc. ligroin (b.p. 90-100°) was added. After cooling to room temperature, white crystals, melting at 288-300° were obtained. These were dissolved in a minimum of boiling n-propyl alcohol and consecutive crops of white 5,6,11,12-tetraphenyl-5,12-naphthacenediol(LX) secured, all melting at 308-10°. This substance is dihydroxyrubrene for which a melting point of 307-8° (bloc Maquenne) is given(93).

An additional amount of the carbinol was obtained by evaporation of the dioxane-ligroin filtrate to dryness, recrystallizing the resin so formed from n-propyl alcohol, and washing the product with acetone, in which dihydroxyrubrene is insoluble. The total yield of carbinol melting 308-10° was 0.7 g., a 34 per cent yield.

The literature(76) states that rubrene monoxide (XLVIII) is formed by the "moderate heating" of dihydroxyrubrene. Nevertheless, samples prepared as above were heated under carbon dioxide at 150° for two hours and then under carbon dioxide at 220° for two hours without any change.

"White Fluorescent Compound": the hydrocarbon $C_{42}H_{26}$(85,93)(LXII)

According to the literature(85,93), dehydrating agents act upon dihydroxyrubrene to give a white compound, melting at 430° and characterized by low solubility in all solvents; the very dilute solutions, however, show a strong violet fluorescence. A small amount (approximately 0.05 g.) of dihydroxyrubrene prepared as given above, dissolved readily in 20 cc. of acetyl chloride. Evaporation to dryness gave a white compound that failed to melt below 360°, and was very insoluble, but the solutions showed a very strong violet fluorescence. This is very probably the "white fluorescent compound" recorded in rubrene chemistry.

5,6,11,12-Tetraphenylnaphthacene (LXI) (Rubrene):

An intimate mixture of 0.1 g. of the diol, m.p. 308-10°, was suspended in 12.5 cc. of glacial acetic acid and the whole refluxed one hour. The mixture was diluted with 125 cc. of distilled water and filtered. The filtrate was extracted twice with benzene, giving pink extracts. The residue was extracted with 10 cc. portions of benzene until the extracts were colorless. Evaporation of the combined benzene solutions gave a red resin.

This resin was dissolved in a minimum of carbon disulfide and transferred to a large test tube. The solvent was removed by passing a slow current of air over the solution. The air in the test tube was then replaced by

carbon dioxide, and the tube was evacuated by means of the water pump. The system was kept for two hours at 140° under 10 mm. pressure; the compound gradually became much darker in color as the dioxide present dissociated. The temperature was then raised to 200°, and the compound was kept thus at 10 mm. pressure for 44 hours. During this time, the rubrene gradually sublimed to the cooler part of the tube and deposited as a ruby red resin.

Benzene or carbon disulfide solutions of rubrene prepared from the above were orange if at all concentrated and pink when diluted. All showed an orange fluorescence were stable to light in the absence of air, or to air in the absence of light, but decolorized rapidly in the presence of both air and light, Low temperature evaporation of such a decolorized solution gave the white peroxide which, warmed at 120°, quite rapidly regenerated the red rubrene.

A benzene solution gave an absorption spectra indistinguishable from a benzene solution of similar concentration containing authentic rubrene*. The maxima at 5300 Å and 4950 Å were clearly marked (see photo), although the solutions were too concentrated to show the

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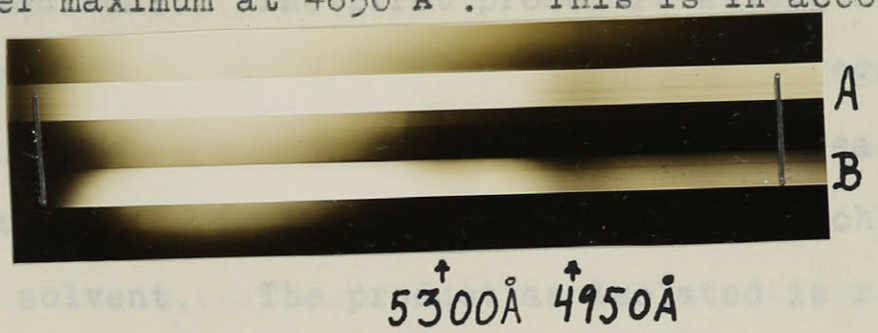
* We acknowledge our indebtedness to Professor C. S. Marvel of the University of Illinois who supplied us with a very pure sample of rubrene.

much fainter maximum at 4650 A*. This is in accord with



Absorption Spectra of Rubrene (benzene solution)

A-Our specimen

B-Sample submitted by
Prof. C. S. Marvel

the results recorded in the literature(76). There was a slight difference in concentration between the solutions compared, resulting in a very slight difference in intensities as recorded on the plate. Unfortunately, the printing magnified these differences several fold, with the result that an apparently large discrepancy was observed. However, even in the prints, the identical location of the maxima is evident.

o-(α-Naphthoyl)-benzoic Acid:

Our interest in o-(α-naphthoyl)-benzoic acid resulted from the report(95) that this compound, fused with a mixture of aluminum chloride and sodium chloride, gave

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* These were examined by Dr. J. S. Foster, Physics Department, McGill University, to whom we render our thanks.

naphthacenequinone. The first procedure attempted for the preparation of the requisite acid was that of Groggins and Newton(94). Their method was a Friedel-Crafts reaction using naphthalene and phthalic anhydride in o-dichlorobenzene as solvent. The product as isolated is reported to be practically pure. Several attempts gave us only impure acid that could not be satisfactorily purified even by successive recrystallizations from both acetic acid and dilute alcohol. Dissolving in either ammonium hydroxide or sodium hydroxide and reprecipitating by running into cold, dilute hydrochloric acid was no more effective.

The preparation of o-(α-naphthoyl)-benzoic acid by the action of α-naphthylmagnesium bromide on phthalic anhydride has also been reported(95). Following the directions as given, only a product badly contaminated with phthalic acid could be secured.

A ring closure with the object of obtaining naphthacenequinone was tried, using o-(α-naphthoyl)-benzoic acid prepared by the first method mentioned and recrystallized several times. After being finely powdered, 20 g. of aluminum chloride and 4 g. of sodium chloride were mixed together thoroughly and heated in a flask to 170°. The mixture became almost totally molten. To this, at room temperature, was added 2 g. of well ground acid melting 155-160°. The whole was heated at 140° for 1 hour with

frequent shaking. Hydrogen chloride was evolved for about the first forty-five minutes. When the mixture had cooled to room temperature, ice was added in small portions until decomposition was complete. The residue was filtered, washed with sodium carbonate solution, and recrystallized from diethyl carbinol. A product was finally secured, after several recrystallizations, that melted at 265-275°. However, since this material failed to give the slightest red coloration with concentrated sulfuric acid, it was believed to contain no naphthacenequinone.

5,6-Chrysenequinone:

5,6-Chrysenequinone was prepared according to the directions in the literature(108). Trichlorobenzene was found to be the best solvent for recrystallization. The quinone also is slowly soluble in hot p-cymene and is moderately soluble in hot n-butyl ether.

5,6-dihydroxy-5,6-diphenyl-5,6-dihydrochrysene:

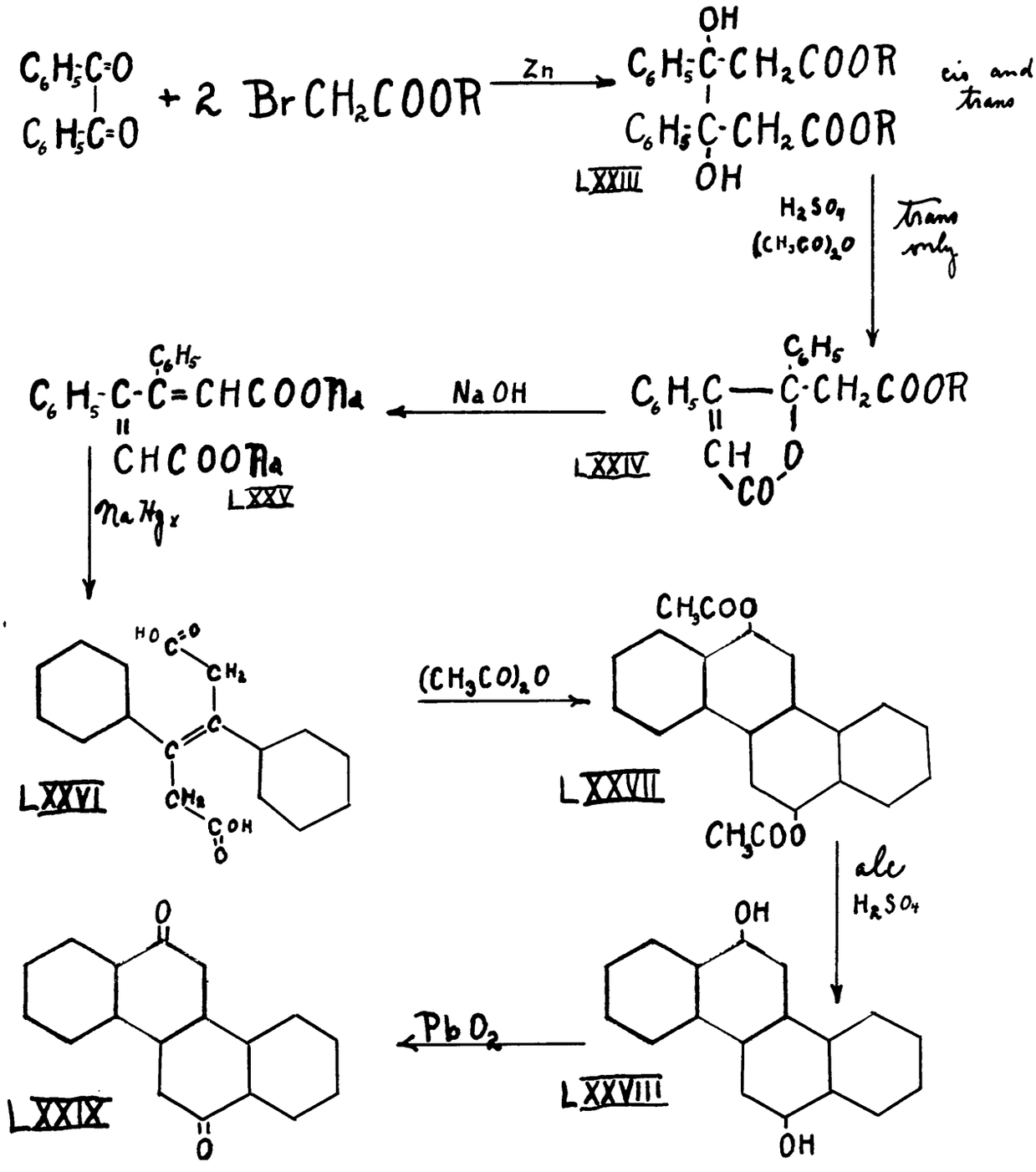
Phenylmagnesium bromide was prepared in the usual manner from 3 g. magnesium (0.125 moles; 12.5 equivalents) and 20 g. of bromobenzene (0.125 moles; 12.5 equivalents) in 30 cc. of ether. To this was added 35 cc. of n-butyl ether and 2.5 g. of 5,6-chrysenequinone (0.01 moles). The mixture was heated an hour and a half on the steam bath, allowing the diethyl ether to distill out. Excess Grignard

was present as evidenced by a positive Gilman test. Water and hydrochloric acid were added and the mixture was steam distilled until the removal of solvent and diphenyl was complete. The brownish, brittle residue remaining was insoluble in alcohols but very soluble in chloroform, acetone or benzene. Extraction with petroleum ether (b.p. 60-8°) removed much oil, leaving a yellowish solid. This could be recrystallized from t-amyl alcohol but the method was troublesome, and better results were obtained by dissolving in chloroform, adding an equal volume of i-propyl alcohol, and allowing the solution to stand. On recrystallizing to a constant melting point, white prisms were obtained, m.p. 201-2°. Cook reported a melting point of 219-20°, using benzene and ligroin (b.p. 90-100°) as solvent(96). Recrystallization of our material from these solvents gave no change from 201-2°. The yield was 1.8 g., 60 per cent as compared with 50 percent reported by Cook. Dehydration by Cook's method gave an oxide with the same melting point that he recorded. A mixed melting point with the starting material was depressed to 180°.

The action of Grignard reagent on chrysenequinone, using toluene, left at least five-sixths of the quinone unchanged, although a small amount of diol was isolated.

Amphi- or 2,8-chrysenequinone(LXXIX):

Amphi-chrysenequinone was prepared by Beschke's method(97), as outlinedin the flowsheet.



The principal difficulty was encountered in the first operation, the Reformatsky reaction. It was discovered that

the reaction could be made to start in a few minutes instead of several hours by introducing a few particles of amalgamated zinc. The separation of the desired ester in a solid state was the troublesome and unsatisfactory step; emulsions formed and caused much difficulty in isolating crystalline material. Eventually, the material was allowed to accumulate, by whatever means it could be separated and was not further purified. The details of operation follow.

Reformatsky reaction: In a 2-l. three neck flask on a steam bath, fitted with a stirrer, a dropping funnel, and three reflux condensers, were placed 44 g. of zinc turnings (freshly cut from Merck's C.P. sticks), 180 cc. of dry benzene, and 100 g. of dry ethyl bromacetate. Both of the liquids had been dried by distilling and discarding the first 10 percent, using the residue directly. A few pieces of zinc, amalgamated by touching quickly to mercury wet with sulfuric acid, were introduced and the mixture was heated and stirred until reaction set in; this was within a few minutes of the time boiling started. The heat was removed at once and the reaction allowed to proceed by itself until signs of slackening became evident (about 15 minutes), whereupon heating was resumed and continued for another 45 minutes. Small pieces of unused zinc were always found. On account of the difficulty of separating layers in a

separatory funnel as directed, the brown solution was added to ice and sulfuric acid in a beaker, stirred well and allowed to stand overnight.

From preliminary runs it was learned that it was necessary to use iced acid for the decomposition to get any solid at all; the oily residues yielded nothing of value. The use of magnesium instead of zinc gave oil only, but the result is inconclusive since the trial was made before optimum conditions were established.

Dehydration and Hydrolysis: A mixture of 16 g. of the crude ester(LXXIII), 50 cc. of acetic anhydride, and 3 cc. of concentrated sulfuric acid was stirred with external cooling until all the solid was dissolved, and the greenish yellow solution was decomposed by iced sodium carbonate in the usual manner. The gummy mass was washed by decantation and at once hydrolyzed by boiling with strong aqueous sodium hydroxide, using just enough of the latter to give a clear solution; after addition of animal charcoal and further boiling for 5-10 minutes, the solution was filtered by suction and poured into an excess of dilute hydrochloric acid. The buff-colored precipitate was filtered, washed, and air-dried.

Reduction: Sodium amalgam (3.1 g.) was prepared according to the procedure outlined in Organic Syntheses(98), using 300 g. (22 cc.) of mercury and 10 g. of sodium; this

represented a 300 percent excess over that calculated for 21 g. of the acid above. The accumulated acid from all hydrolyses was dissolved in a minimum of sodium hydroxide, made up to approximately 225 cc., and placed in a 500 cc. flask with the amalgam. The visible action was slight, indicating a good reduction; the next day the flask and contents were warmed on the steam bath to complete the reduction and use up all the amalgam; hydrogen was visibly evolved. The aqueous solution was decanted and filtered into an excess of dilute hydrochloric acid, using an ordinary funnel without suction. A white acid precipitated. In a capillary tube this shrank at about 190°, and nearly all had liquified at 240°, indicating that the reduction had proceeded satisfactorily. This material was digested a half hour on the steam bath with an amount of alcohol insufficient for solution. Filtration gave an acid(LXXVI) that was white and clean. The yield, unfortunately, cannot be over 50 percent, the remainder going to the cis isomer.

Ring Closure: To 10 g. of the acid(LXXVI) suspended in 40 cc. of acetic anhydride and cooled in a cold water bath, was added 5 cc. of sulfuric acid dropwise. Contrary to the literature, complete solution did not result, but, after all the acid had been added, the mixture became tan in color and very mushy. There was no further change upon the addition of 15 cc. more of acetic anhydride. The

mixture was filted after 2 hours and was washed with acetic acid, ethyl alcohol, and ether. The product(LXXVII) was in the form of rods, melting 210-215°.

Hydrolysis: To a suspension of 2 g. of the diacetate(LXXVII) in 80 cc. of 95 percent ethyl alcohol, was added 10 cc. of concentrated sulfuric acid, and the mixture was stirred and refluxed for 2 hours. The product (LXXVIII) formed diamond-shaped plates; it was filtered and washed with hot acetic acid, giving a 1.5 g. yield. The filtrate was used as solvent for another run. In a succeeding run, 11.2 g. of acid gave 7 g. in the first crop, 0.8 g. in the second crop, and another 2 g. upon addition of water to the filtrate. This material gave a lemon-yellow color with acqueous sodium hydroxide, rapidly turning bluish due to atmospheric oxidation; this behaviour agreed with that described in the literature.

Oxidation: This step did not proceed as expected. The literature directions were vague, so that it was impossible to know what conditions were necessary. Actually, under varied conditions, a new (?) red quinone resulted from all attempts, and the desired amphi-quinone was only obtained by accident. Thus, 0.5 g. of diol and 0.5 g. of lead dioxide. suspended in 40 cc. of acetic acid turned orange after five minutes heating just below the boiling point. There was no apparent change on adding a further 0.5 g. of the

dioxide, so the solid was filtered at once. The first crystals that separated were the desired amphiquinone; they had a melting point of 296-7°, which was unchanged after recrystallization from acetic acid and/or p-cymene, and very rapidly liberated iodine from acidified potassium iodide solution (the change was most marked if a starch solution was added).

The filtrate deposited a red solid, which was usually the only product found after the oxidation. It is suspected that the secret is to heat for a very short time--a half hour gave only the red substance.

The new substance crystallizes in fine, long, scarlet plates, best from p-cymene, and melts at 235°. It gives a magenta color with concentrated sulfuric acid. It is insoluble in alcohol or ether but is moderately soluble in acetic acid. The compound must be a 1,2-diketone, since it gave a quinoxaline in a few minutes when o-phenylenediamine was added to a solution of the substance in hot acetic acid; the red color at once became brown and, in 5 minutes, greenish. Lemon-yellow needles were formed. These gave a.m.p. 207°, unchanged by recrystallization from a mixture of ethyl acetate and ethyl alcohol. The quinoxaline is very soluble in the former but insoluble in the latter of these two solvents.

This 1,2-quinone is not the ordinary 5,6-chrysene-

quinone which has the same color and melts at 235°, because a mixed melting point of the two was depressed to 195-8°. The crystalline form as well as the color in sulfuric acid is also different. This quinone gives a magenta color with sulfuric acid, while 5,6-chrysenequinone gives a pure blue. Neither is the compound 1,2-hydroxychrysenequinone, which has no melting point, nor the acetate of the latter (m. p. 252°); a sample of this acetate, synthesized by Beschke's method(97), not only differed in color (deep yellow) but depressed a mixed melting point to 215-25°.

Anal. Calcd. for $C_{26}H_{18}O_5$: C,76.1; H,4,4; M.W.410
Found: C,76.1, 76.1; H,4,6,4.4; M.W. (Rast) 416.

The analytical figures correspond to $C_{26}H_{18}O_5$, or a hydroxyquinone. This would confirm our surmise that the oxidation had proceeded too far. The reaction is under independent investigation.

Pivalyl Chloride (Trimethylacetyl Chloride):

A 250 cc. Claisen flask was set at such an angle that liquid condensing in the delivery tube would run back into the flask, and the end of the tube was tightly stoppered. A reflux condenser was set in the side neck of the flask, and a dropping funnel was fitted into the remaining neck with the stem of the funnel projecting as far as possible into the flask. This is so that refluxing thionyl chloride

will keep the funnel stem warm and prevent the acid's freezing and clogging the flow. All joints were made tight and the top of the condenser was provided with a tube leading to a gas trap. An excess of thionyl chloride (120 g., 1.0 moles) was run into the flask and brought to a gentle boil. After being warmed to 60°, 51 g. (0.5 moles) of trimethylacetic acid was added dropwise at such a rate that gentle refluxing was maintained. The solution was refluxed an additional 4 hours and was then fractionally distilled, taking fractions at 80°, 80-90°, 90-99°, and 99-105°. After refractionating twice, 47 g. of product boiling above 99° was obtained, a yield of 78 percent.

Pivalyl Naphthalenes (α-and β-naphthyl-t-butyl ketones):

In a three neck flask fitted with a reflux condenser, a mechanical stirrer, and a dropping funnel was placed 49 g. (0.38 moles) naphthalene, 150 cc. of carbon disulfide, and 5 g. (0.037 moles) of aluminum chloride. This amount of aluminum chloride was sufficient to maintain the reaction at a good rate, and gave quite as good a yield as the usual 1.1 equivalents. The mixture was cooled to 5°, and 48 g. (0.40 moles) of pivalyl chloride was run in with constant stirring. The addition took one hour and was accompanied by a copious evolution of hydrogen chloride. The temperature was kept at 5° during this time and for an additional three hours. The mixture was decomposed with

ice, the organic layer separated and dried with calcium chloride, and filtered into a 250 cc. Claisen flask. After removing the solvent, the residue was distilled at 15 mm. pressure, the small amount of naphthalene that came over first being collected separately. The yield of yellow oil coming over between 125° and 190° at 15 mm. weighed 30 g., a 35 percent yield of mixed ketones.

Picrate Purification: The mixture obtained above was expected to contain approximately 65 percent α-naphthyl-t-butyl ketone and 35 percent of the beta isomer(109). Only the beta compound has been reported to give a picrate(63).

The following procedure was planned to remove the beta isomer as well as any naphthalene still present. To 5 g. of picric acid dissolved in 80 cc. of absolute alcohol was added 10 g. of the mixed ketones from above. The solution was boiled several minutes and then cooled to 10°. The yellow crystals that formed were removed by filtering and were washed with 10 cc. of petroleum ether (b.p. 60-80°). This crystalline material melted at 135-150°; since naphthalene picrate melts at 150° sharply, this was believed to be impure naphthalene picrate, probably containing the picrate of β-naphthyl-t-butyl ketone. No further investigation was made of this crystalline mixture. The filtrate and the washings were combined and were heated on the steam bath several hours to remove as much solvent as possible. The oil was taken

up in ether and thoroughly extracted with 10 percent sodium hydroxide solution. Evaporation of the ether left 6 g. of ketone.

Steam Distillation: When the product that was recovered by evaporation of the ether was subjected to steam distillation, about one-third of the material came over as an oil. Thereafter, a white, crystalline solid distilled, m.p. 71-3°. Mixed with naphthalene, the melting point was depressed to 50-65°. The melting point reported for α-naphthyl-t-butyl ketone is 73-4°.

Attempted Grignard Additions: α-Naphthyl-t-butyl ketone was added to a three molar excess of phenylmagnesium bromide in ether and refluxed one hour. The ether was removed as completely as possible with the aid of suction at a temperature of 100°. The residue was refluxed three hours with dry benzene, the internal temperature being 98°. Decomposed with ice and steam distilled, a considerable amount of diphenyl was collected. Later a white crystalline solid came over that melted at 71-3° and melted from 50-60° when mixed with diphenyl. The melting point was undepressed upon mixing with starting material.

α-Naphthyl-t-butyl ketone gave no addition when treated in the usual manner in the Grignard Machine. A second attempt was made, this time heating the reaction flask to 150° for three hours. The addition of water showed no

Grignard remained. Since two and a half molar excess Grignard was present deducting the amount consumed by "active hydrogen", it was believed that the high temperature had destroyed the reagent The heating had been conducted away from the machine, so the resulting gas was not collected Steam distillation of the residue gave back 70 percent of the original ketone with unchanged melting point, and unchanged when mixed with starting material.

SUMMARY

Phenylmagnesium bromide reacted with 5,12-naphthacenequinone to give two diphenyltetrahydronaphthacenequinones, both of which were readily oxidized to 6,11-diphenyl-5,12-naphthacenequinone This latter compound reacted with lithiumphenyl to form 5,6,11,12-tetraphenyl-5,12-naphthacenediol, which was shown to be dihydroxyrubrene Reduction of this diol gave the hydrocarbon rubrene

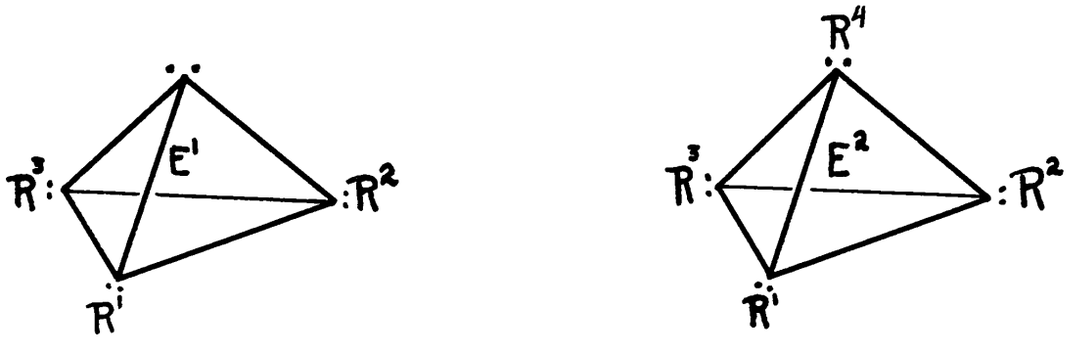
ASYMMETRIC TRIVALENT ARSENIC

I. HISTORICAL

LeBel and van't Hoff pointed out that four different objects can be placed at the points of a tetrahedron in two different ways, one arrangement the mirror image of the other. Applied to the stereochemistry of carbon, this explained the structure of optically active molecules. Such views predicted that optical activity was not specifically a property of the carbon atom, but that any molecule containing an atom surrounded by four different atoms or groups could exist in optically active forms. The subsequent resolution of compounds of several tetravalent elements demonstrated the accuracy of such a prediction. That this type of isomerism was first discovered in organic compounds was probably due to the fact that not only one, but two or more atoms, each surrounded by four different groups, occur frequently in the compounds of carbon.

With the development of the Octet Theory of electron arrangements, it became evident that tetravalency of an atom was not a necessary condition for the existence of an asymmetric tetrahedral grouping about that atom. A compound $(R^1,R^2,R^3)E^1$ of the trivalent element E^1 might be arranged as shown in Figure A, wherein the fourth point of the tetrahedron is occupied by a pair of electrons rather than by a fourth group as in the compound

$(R^1,R^2,R^3,R^4)E^2$ of the tetravalent element E^2, shown in Figure B.

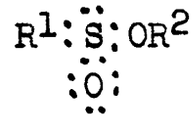


A B

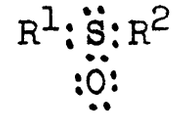
The question arises immediately whether or not a compound existing in form A would actually be optically active. In such a molecule, the asymmetry might be too slight to affect the passage of polarized light; or the rigidity of the molecule might be so low that the enantiomorphorous forms might pass one into the other in the course of normal intra-molecular vibrations. Either of these possibilities could render the molecule optically inactive. Investigations have shown, however, that certain molecules, at least of the type A, are both sufficiently asymmetric and sufficiently stable to be isolated in optically active forms.

For example, sulfinic esters(3) and suitably substituted sulfoxides(4) have been resolved into optically active forms. These two classes of compounds are represented electronically as in C and D respectively, in each of which two groups occupy two of the points of a tetra-

hedron, an oxygen atom occupies a third, and the fourth is filled by a lone pair of electrons.



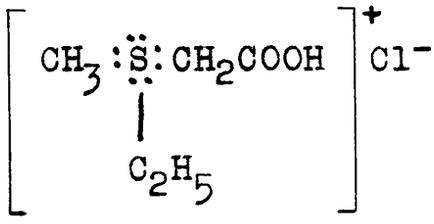
C



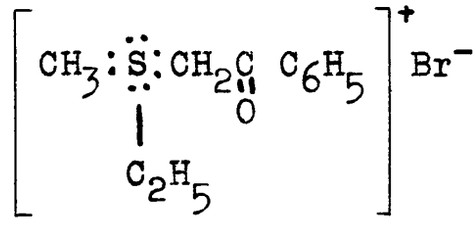
D

This same arrangement occurs in several other slightly different types of sulfur compounds and again results in stable isomeric forms(5).

The sulfonium ion has been shown to exist in enantiomorphic forms. Methyl-ethyl-thetine chloride, E, and methyl-ethyl-phenacyl sulfonium bromide, F, have both been resolved (6, 7). These are represented electronically as shown.



E

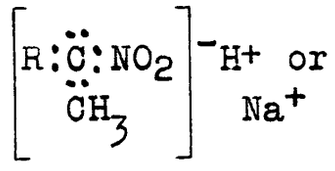


F

These examples differ from the sulfinic esters and sulfoxides in that the sulfur atom in both the latter is neutral, while in sulfonium compounds it bears a positive charge of 1 electron.

2-Nitro-butane and 2-nitro-octane have been resolved into optically active forms. The most surprising feature of these compounds is that aqueous solutions of the

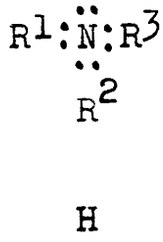
corresponding sodium or potassium salts are also optically active. When all the properties of these compounds are considered, it appears that they must be constituted as shown in Figure G(8,9). In this case we find a lone pair



G

of electrons attached to an atom carrying a negative charge of 1 electron.

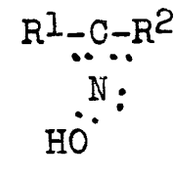
Because of the frequent occurrence of trivalent nitrogen in organic compounds, the question of corresponding optical activity has been one arousing keen interest. Electronically, a nitrogen compound $(R^1,R^2,R^3)N$ probably is as indicated in Figure H, entirely comparable with the



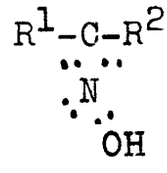
H

sulfinic esters and the sulfoxides. We have cited instances in which lone pairs of electrons are part of a stable configuration in neutral atoms, atoms positively charged, and atoms negatively charged; therefore, there is no reason to believe that the arrangement shown in H is necessarily unstable. We can cite the same examples to prove that, when such a configuration does exist, sufficient asymmetry is created to result in optical activity.

There is reason to believe that trivalent nitrogen compounds do exist in a tetrahedral form(10). For example, both ammonia and tertiary amines, in which all three groups attached to nitrogen are the same, show a dipole moment(1, 2, 11). Further, the existence of oximes in stable isomeric forms (Ia and Ib) shows that a lone pair of electrons on a nitrogen atom does not of itself, at least, lead to structural instability.

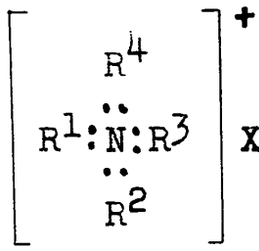


Ia

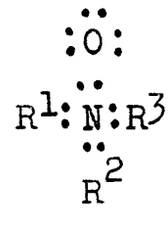


Ib

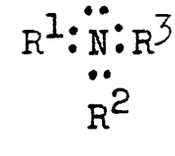
With all the evidence apparently pointing to a successful outcome, many attempts have been made to resolve trivalent nitrogen compounds in which the three substituents were all different. The resolution of numerous quaternary ammonium ions(12, 13, 14, 15) and amine oxides(16) also seemed to support the view that properly substituted amines would be resolvable, although neither of the former types of compound is strictly analogous to the free amines. Ja, Jb, and Jc show the arrangement of each of these three classes of compounds.



Ja



Jb



Jc

Nevertheless, in spite of apparently good reason to hope otherwise, all attempts to prepare substances owing their optical activity to asymmetrically substituted trivalent nitrogen have been unsuccessful. Numerous claims for the preparation of such compounds have appeared in the literature, but all have been disproved in the course of time.

The failure to isolate isomeric forms of compounds of the type $(R^1,R^2,R^3)N$ is generally believed to be due to the great ease with which they racemize(2, 11). We know that the isolated dextro and laevo forms of quaternary ammonium ions racemize very rapidly(2). But then, how shall we explain the stability of the same configuration in sulfinic esters and sulfoxides? Mills(11) states that the difference in the two is due to a positive residual charge of something less than 1 electron on the sulfur atom in a sulfoxide, resulting in the atoms having a firmer hold on its circulating electrons, while in an amine the nitrogen atom has a residual negative charge, also something less than 1 electron, 0.3 electrons to be exact, which acts to

decrease the firmness with which that atom holds a similar pair of electrons. If this explanation were valid, however, optically active ions of nitroparaffines would be unthinkable, because in the latter (see Figure G) a pair of isolated electrons is held with remarkably little tendency to racemize(9) by a central atom carrying a negative charge of 1 electron - more than three times that ascribed to the nitrogen atom of a tertiary amine.

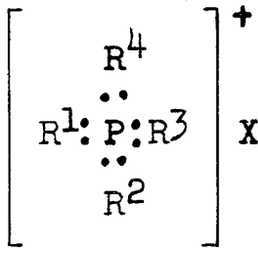
So we are left without an entirely satisfactory explanation of the apparent non-resolvability of tertiary amines, since, if we accept the ease of racemization explanation, we cannot say why the dextro and laevo forms of these compounds pass one into the other with such ease while the alkaline solutions of optically active nitro-paraffines show no pronounced decrease in rotation at the end of twenty-four hours(9).

Mention must be made of recent work by Mumm and Ludwig(17) in which it is claimed that a certain type of cis and trans isomers of a dihydroquinoline derivative has been found. Should the compounds have the constitution claimed for them by these authors, a stable configuration like that diagrammed in Figure H would exist. A final evaluation of this work must await confirmation. Similar claims have been made so often in the past, only to be disproven ultimately, that one is much inclined to expect that

this too will prove to be isomerism due to some other cause than that to which it is ascribed by its discoverers.

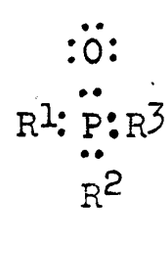
The unexpected results encountered in studying the stereochemistry of nitrogen have undoubtedly done much to provoke investigation of the optical properties of the other elements in Group V of the Periodic Table.

Attempts to prepare optically active phosphonium compounds, analogous to the previously isolated optically active ammonium compounds, have been unsuccessful(18), but numerous phosphine oxides, phosphorous analogs of the amine oxides, have been resolved(20, 21). At least one derivative of ortho-phosphoric acid has been shown to be optically active(19). In the absence of derivatives of ortho-nitric acid, no such compound is possible in the nitrogen series. These compounds are illustrated in Figures Ka, Kb, and Kc.



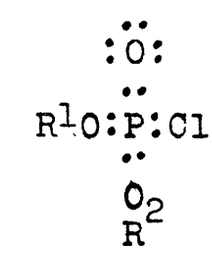
Phosphonium salts

Ka



Phosphine oxides

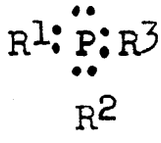
Kb



Ester of ortho-phosphoric acid chloride

Kc

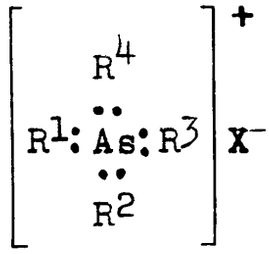
The additional shell of electrons in the phosphorous atom should make the enantiomorphic forms of its trivalent derivatives more stable than those of nitrogen. These compounds would be the phosphorous analogs of the



amines as shown in Figure L. Investigation of the phosphines in this respect has been found to be very difficult, however, because of the great ease with which these compounds are oxidized by air to the pentavalent state.

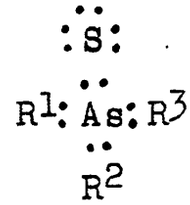
The stereochemistry of arsenic has attracted the attention of quite a number of investigators, because here two additional shells of electrons should give even greater stability, and the tendency to oxidize, although present, is much less pronounced than in phosphines. The earlier workers were unsuccessful in their attempts to resolve arsonium compounds (22,23), but more recently phenyl-α-naphthyl-benzyl-methyl arsonium bromide(26) and ethyl-n-propyl-p-tolyl-benzyl arsonium iodide(27) have both been isolated as optically active arsonium salts. Strangely enough, no arsine oxides have yet been resolved(26, 28, 29), although an arsine sulfide(30) has been successfully worked with. Trivalent arsenic compounds have been less investigated. A number of derivatives have yielded negative results(1,31), and one claim of resolution has been advanced(32). Unfortunately this latter is not entirely free of certain factors that allow other interpretations of the optical activity observed. Figures Ma, Mb, and Mc show the electronic arrangements of these three types of arsenic compounds. Their similarity

with nitrogen derivatives will be obvious. Table I summarizes the work done to date on the stereochemistry of arsenic. Only the compounds that formed crystalline products with resolving agents are listed.



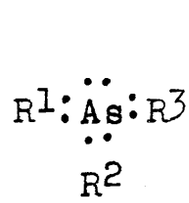
Arsonium salts

Ma



Arsine sulfide

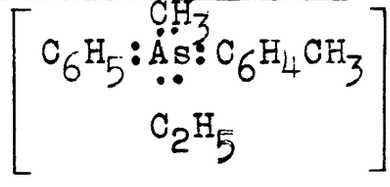
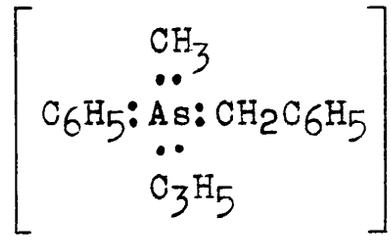
Mb

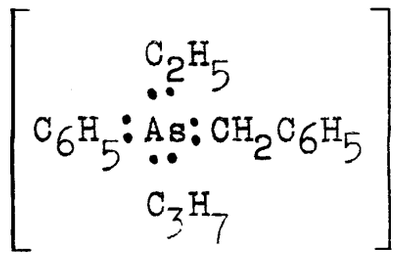


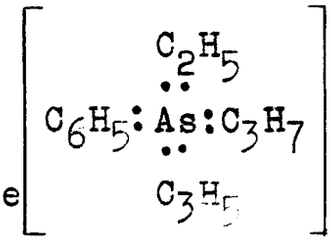
Arsines

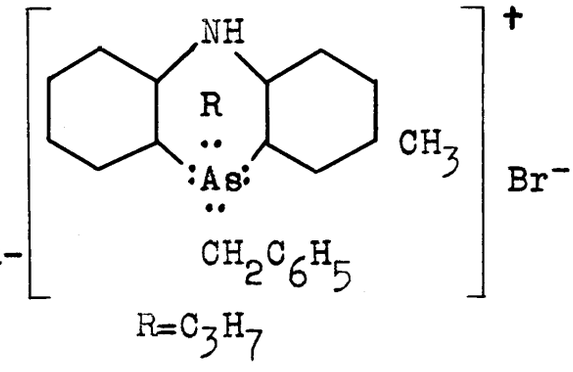
Mc

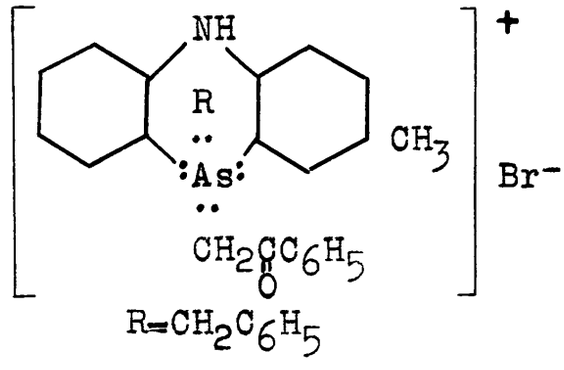
TABLE I

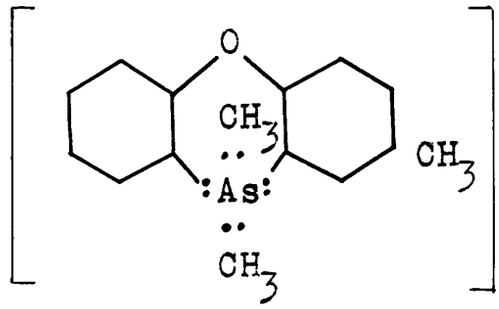
Name of Compound	Formula	Result	Reference
Arsonium Compounds			
(1) phenyl-p-tolyl-ethyl-methyl arsonium iodide		no resolution	(22)
(2) phenyl-benzyl-methyl-allyl arsonium iodide		"	(23)

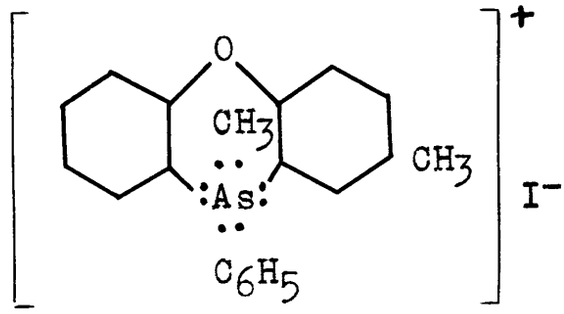
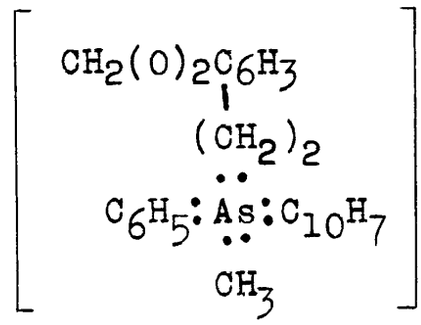
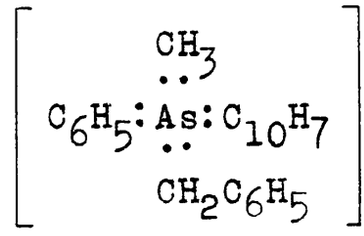
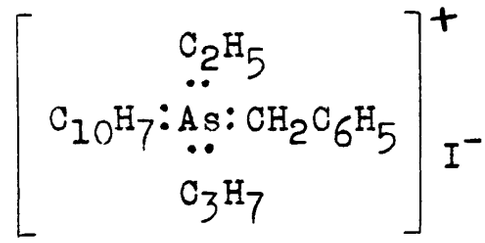
(3) phenyl-benzyl-ethyl-n-propyl arsonium iodide  no resolution (23)

(4) phenyl-ethyl-n-propyl-allyl arsonium bromide  " (23)

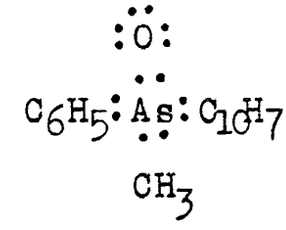
(5) 2-methyl-10-benzyl-10-n-propyl-5,10-dihydrophenarsazonium bromide  " (25)

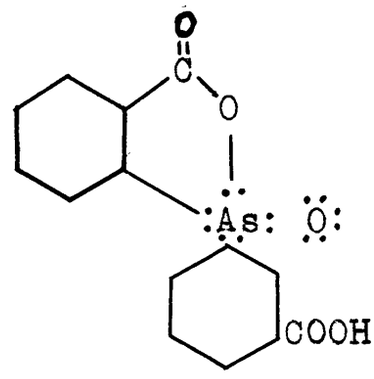
(6) 2-methyl-10-benzyl-10-phenacyl-5,10-dihydrophenarsazonium bromide  " (25)

(7) 2,10-dimethyl phenoxarsine methiodide  " (33)

(8) 2-methyl-10-phenyl phenoxarsine methiodide		no resolution	(33)
(9) homo-piperonyl-phenyl-α-naphthyl-methyl arsonium bromide		inconclusive	(26)
(10) phenyl-α-naphthyl-benzyl-methyl arsonium bromide		resolved	(26)
(11) ethyl-n-propyl-α-naphthyl-benzyl arsonium iodide		"	(27)

Arsine Oxides

(12) phenyl-α-naphthyl-methyl arsine oxide		no resolution	(26)

(13)	O, O'-dicarboxy-diphenyl arsinic acid anhydride		no re-solution	(28)
(14)	phenyl-(o-carboxyphenyl)-methyl arsine oxide	$C_6H_5{:}As(:O:)(CH_3){:}C_6H_4COOH$	"	(29)

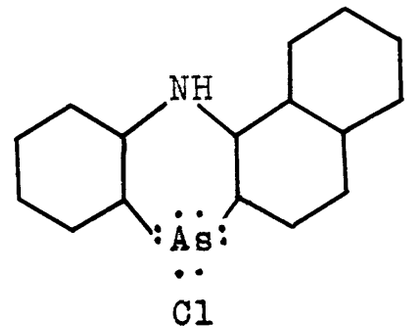
Arsine Sulfides

(15)	(p-carboxyphenyl)-methyl-ethyl arsine sulfide	$C_2H_5{:}As(:S:)(CH_3){:}C_6H_4COOH$	resolved	(30)

Trivalent Arsenic Compounds

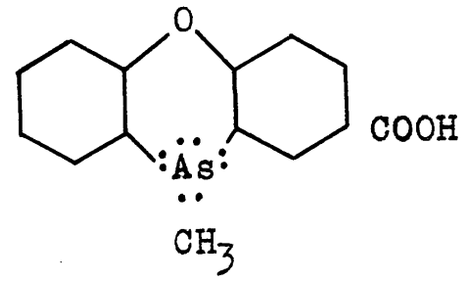
(16)	(p-carboxyphenyl)-ethyl-n-propyl-arsine	$C_2H_5{:}As(C_3H_7){:}C_6H_4COOH$	no re-solution	(1)
(17)	(p-carboxyphenyl)-phenyl-methyl arsine	$C_6H_5{:}As(CH_3){:}C_6H_4COOH$	"	(31)

(18) 7-chloro-7,12-dihydro-δ-benzophenarsazine



resolved (32)

(19) 10-methyl-phenoxarsine carboxylic acid



(34)

These compounds, especially the last two, will be discussed in the next section.

II. THE THEORETICAL CONSIDERATIONS INVOLVED

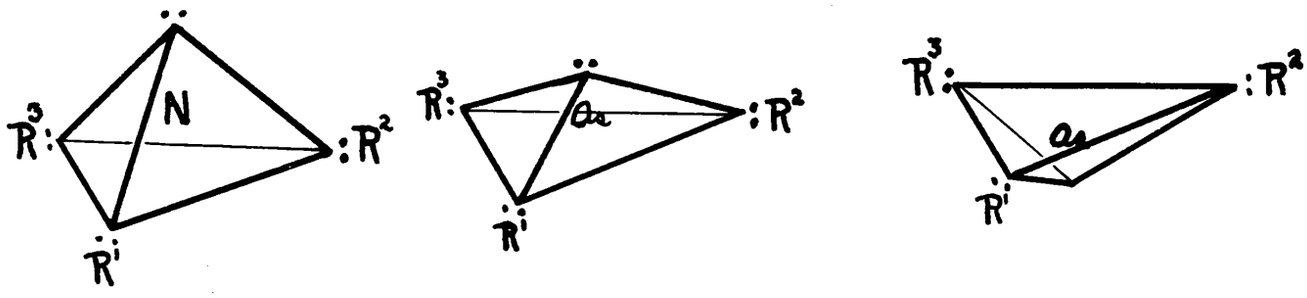
Since the attempts to resolve trivalent arsenic compounds were undertaken largely because derivatives of trivalent nitrogen could not be separated into enantiomorphous forms, we must consider whether or not the former offers any greater prospect of success than the latter. It would be useless to work with a class of compounds promising greater difficulties than another class already found to be unrewarding of work.

Against the probability of resolving arsine derivatives when derivatives of ammonia have resisted such separation is the observation that the optically active arsonium ions that

have been prepared racemize even more readily than do optically active ammonium ions(11,26). The relationship of properties of arsonium and ammonium compounds, however, are not necessarily a guide to the relationship of the properties of derivatives of arsine to those of the derivatives of ammonia. The greater firmness with which ammonia, as compared with arsine, holds groups in salt formation is well known. If, as is entirely possible, the greater ease of racemization of arsonium compounds is due to a greater tendency of groups to separate momentarily from the arsenic atom, resulting, upon recombination, in partial racemization, than for groups to withdraw momentarily from the nitrogen atom in ammonium compounds, it can be seen that this greater ease of racemization of arsonium ions is no criterion of the rate of racemization of an arsine derivative as compared with one of ammonia. The relative strengths of salt formation may account for the relative rates of racemization of arsonium and ammonium compounds, but would not affect the relative rates of racemization of arsine and ammonia derivatives.

Possibly a more valid reason for expecting arsine derivatives to racemize more readily than those of ammonia is the fact that arsine has a weaker dipole moment than ammonia(1). Accordingly, the groups about a trivalent arsenic atom must lie in a plane that approaches the nucleus of the central atom more closely than would be the case if the same groups were placed

about a nitrogen atom - condition Nb as compared with condition Na.



N a N b N c

In the case of Nb as compared with the case of Na, a lesser molecular vibration would suffice to bring the three R's and the lone pair of electrons into one plane, from which position the groups, with equal ease, could either revert to condition Nb or proceed to configuration Nc, which latter course would constitute racemization.

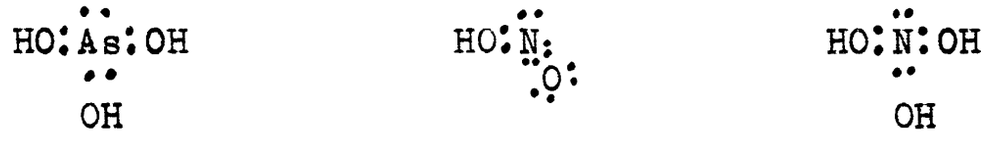
But the proximity of the plane of the three R groups to the nucleus of the central atom may not be the most important factor in the racemization of such compounds. The nitrogen nucleus being smaller than that of the arsenic atom, the groups about it may be crowded, resulting in a condition of strain causing frequent exchange of position between an R group and the lone pair of electrons. Crowding three groups closely about the nucleus might increase enormously the chance of two groups simultaneously imparting vibrational energy to the third in sufficient quantity to bring about the displacement necessary to effect racemization

by the mechanism just mentioned. In that case, the greater size of the arsenic atom and the corresponding decrease in crowding of attached groups would probably increase the configurational stability sufficiently to make the lower dipole moment unimportant.

Finally it should be pointed out again that we do not know that ease of racemization accounts for the non-resolution of amines, and both of the above objections to a study of arsines as compared with amines are based on the assumption that greater ease of racemization of arsines than amines would necessarily render the trivalent arsenic compounds unresolvable.

The preceding arguments are inconclusive. They do not leave us with definite reason to expect either greater or lesser ease of preparation of optically active isomers in the trivalent arsenic series than in the nitrogen analogs. The probable effect of substituting arsenic for nitrogen is unpredictable. Under such circumstances there is little to do but try the experiment in the laboratory and find out what that effect appears to be. We do know that the chemistry of arsenic shows certain differences in kind from that of nitrogen as well as the differences in degree that we expect as we progress from the first member of a Periodic Group to the lower ones. One such difference, for example, is the absence of a nitrogen acid corresponding to ortho-arsenous acid, H_3AsO_3, Figure 0a. The only known trivalent

nitrogen acid is the meta-nitrous acid, Figure Ob, a dehydrated form of the hypothetical ortho-nitrous acid, Figure Oc, corresponding to ortho-arsenous acid.



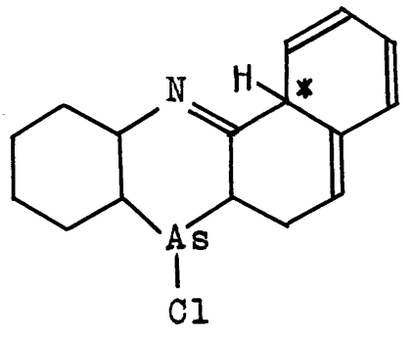
Oa Ob Oc

There is reason to believe that some difference in the arsenic atom as compared with the nitrogen atom might render arsines more readily resolved than amines, just as some difference in these atoms renders the existence of ortho-arsenous acid common but that of ortho-nitrous acid unknown.

III. DISCUSSION OF THIS WORK

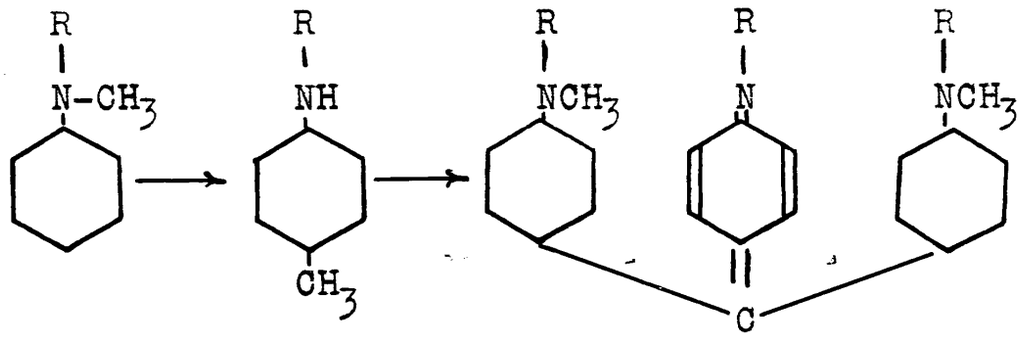
N-Methyl-7-chloro-7,12-dihydro-γ-benzophenarsazine:

It was recognized at the time of publication that, although 7-chloro-7,12-dihydro-γ-benzophenarsazine was resolvable, the center of optical activity might not be the arsenic atom. The shift of a hydrogen atom could give a molecule in which there existed an asymmetric carbon atom (32), Figure P. To eliminate such a possibility, it was



P

desired to prepare the corresponding N-methyl derivative and determine whether or not optical properties were still present. 7-chloro-7,12-dihydro-γ-benzophenarsazine (P) was prepared by heating phenyl-α-naphthyl amine with arsenic trichloride. When the same procedure was tried with methyl-phenyl-α-naphthyl amine, a small amount 7-chloro-7, 12-dihydro-γ-benzophenarsazine was formed along with a large amount of a blue dye, but none of the N-methyl arsenic compound was found. Apparently part of the methyl-phenyl-α--naphthyl amine, a substituted methyl aniline, had undergone a rearrangement in the presence of heat and an acid reagent to give p-tolyl-α-naphthyl amine. This compound then reacted with unchanged tertiary amine to give a dye of the triphenyl methane type. These are both well known reactions and are known to proceed under such conditions. They are given in Figure Q, in which R = α-naphthyl.



Q

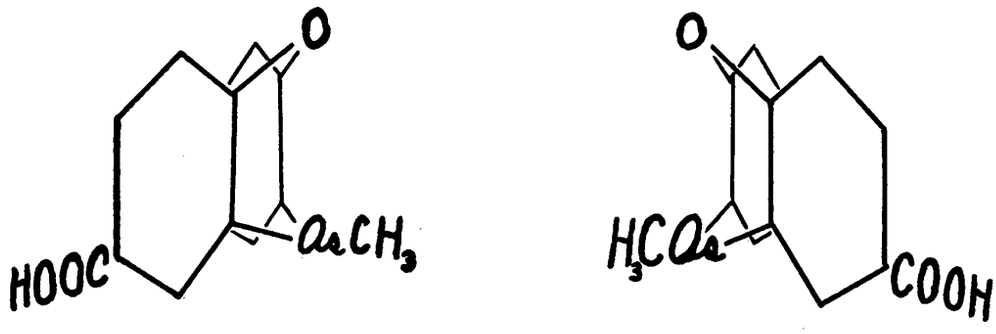
Wieland reports a similar blue dye from the action of arsenic trichloride on methyl-diphenyl amine under the same conditions(35).

The formation of 7-chloro-7,12-dihydro-γ-benzophenarsazine was due to the action of arsenic trichloride on demethylated methyl-phenyl-α-naphthyl amine in which rearrangement had not followed demethylation.

Further work in this series was not conducted, because it was decided that more conclusive results could be obtained from a slightly different type of compound.

2-Nitro-5-chloro-dibenzoarsenole:

Not long after publication of the resolution of 7-chloro-7,12-dihydro-γ-benzophenarsazine(32), Lesslie and Turner announced the resolution of 10-methyl-phenoxarsine carboxylic acid (19 in Table I). They expressed themselves as being of the opinion that the optical activity both of their compound and of 7-chloro-7,12-dihydro-γ-phenoxarsazine was due to the existence of a non-planar molecule, and stated that they did not consider either compound to owe its optical properties to the presence of an asymmetric arsenic atom. They represented the two enantiomorphous forms of their compound as shown in Figure R.



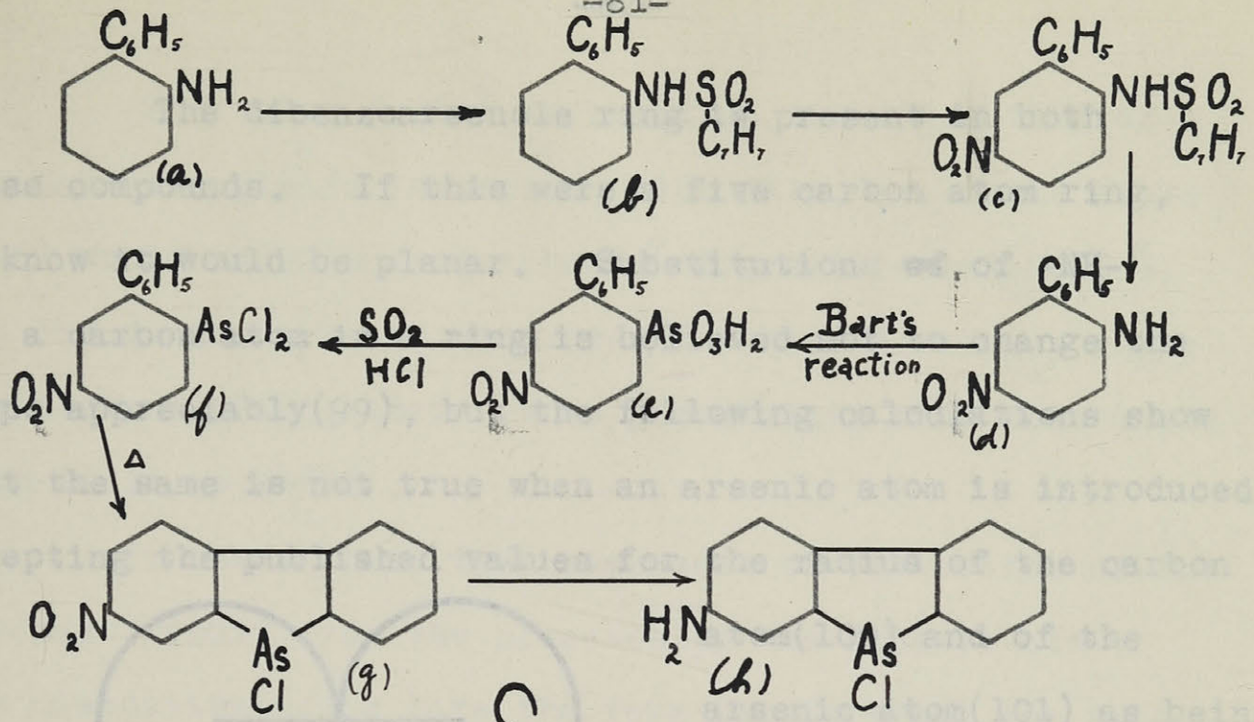
(R)

7-Chloro-7,12-dihydro-γ-phenoxarsazine would be represented similarly.

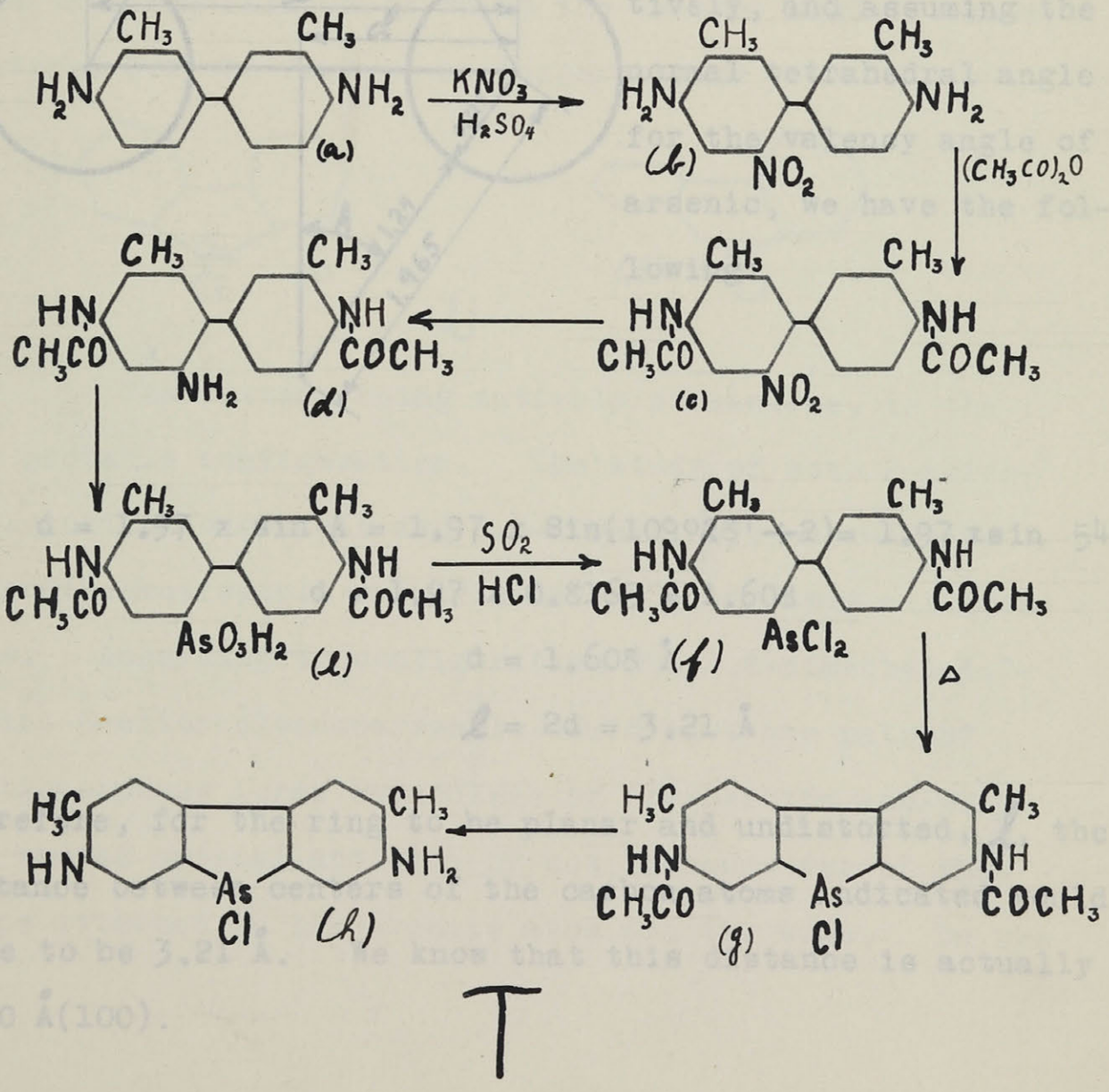
Uncertainty as to the value of valency angles and atomic radii and, further, the lack of evidence that either of these is constant from one compound to the next makes it impossible to either prove or disprove the contentions advanced by Lesslie and Turner. It may be surmised that if

both the non-carbon atoms making up the central ring have approximately the atomic radii and valency angles of carbon, the compounds would, like anthracene and ang-benzanthracene, be planar. If, however, either of those atoms has a normal valency angle (the normal valency angle being that assumed by the atom when no distorting forces are being exerted) very different from the angle of carbon it seems probable that the molecule would take a folded form to relieve the resulting strain. The same form would probably result if the difference in atomic radii of the two non-carbon atoms was more than very slight. Otherwise a strain would exist in all the valency angles of the middle ring. These valency angles are known not to be constant from compound to compound(11,24), but it seems most probable that there exists some one value for each atom from which that atom will not deviate when so simple a mechanism as folding the molecule is a possible alternative.

As long as the possibility of asymmetry of the molecule could not be definitely excluded upon theoretical grounds, it was decided to synthesize and study two compounds, 2-amino- 5-chloro- dibenzoarsenole (Sh) and 2,8-dimethyl-3,7-diamino-5-chlorodibenzoarsenole (T h), according to the flow sheet.

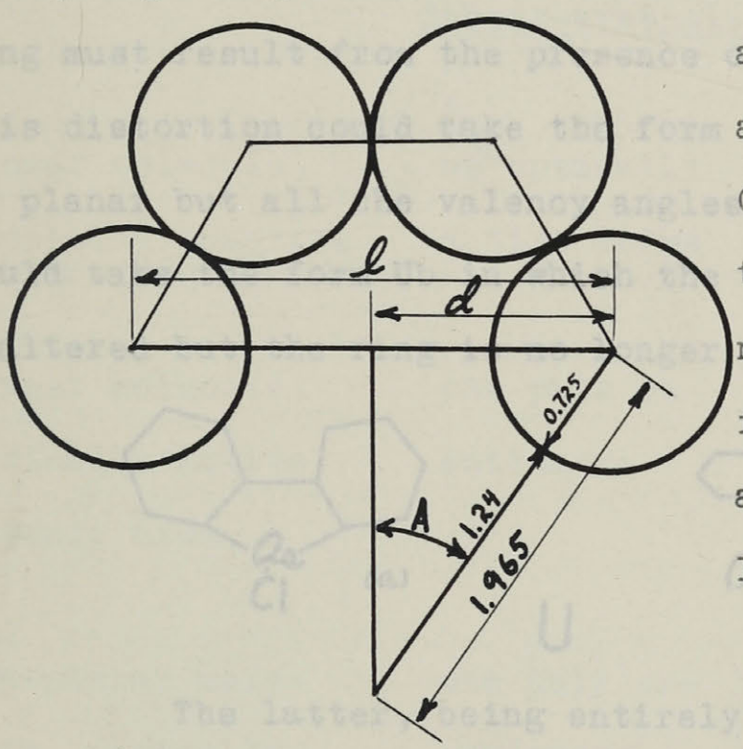

C6H5
NH2
(a)
NHSO2C7H7
(b)
O2N
(c)
Bart's reaction
(d)
SO2
HCl
AsO3H2
(e)
AsCl2
(f)
Δ
(g)
(h)
Cl

S


CH3
H2N
NH2
(a)
KNO3
H2SO4
NO2
(b)
(CH3CO)2O
HN
CH3CO
NH
COCH3
(c)
(d)
AsO3H2
(e)
SO2
HCl
AsCl2
(f)
Δ
(g)
Cl
(h)

T

The dibenzoarsenole ring is present in both these compounds. If this were a five carbon atom ring, we know it would be planar. Substitution of -NH- for a carbon atom in a ring is believed not to change the shape appreciably(99), but the following calculations show that the same is not true when an arsenic atom is introduced. Accepting the published values for the radius of the carbon atom(100) and of the arsenic atom(101) as being 0.725 Å and 1.24 Å respectively, and assuming the normal tetrahedral angle for the valency angle of arsenic, we have the following:



$$d = 1.97 \times \sin A = 1.97 \times \sin(109°28' \div 2) = 1.97 \times \sin 54°44'$$

$$d = 1.97 \times 0.8165 = 1.608$$

$$d = 1.608 \text{ Å}$$

$$l = 2d = 3.21 \text{ Å}$$

Therefore, for the ring to be planar and undistorted, l, the distance between centers of the carbon atoms indicated would have to be 3.21 Å. We know that this distance is actually 2.90 Å(100).

The value 3.21 Å is based on the assumption of a tetrahedral angle for arsenic. Actually, any angle above 94°46' would require a distance ℓ of greater than 2.90 Å. Even though the arsenic atom does not have a valency angle of exactly 109°28', there is no probability that that angle is as small as 94°46'.

It seems then, that some sort of distortion of the ring must result from the presence of the arsenic atom. This distortion could take the form Ua, in which the ring is planar but all the valency angles are increased, or it could take the form Ub in which the valency angles remain unaltered but the ring is no longer planar.

U

The latter, being entirely strainless, is the more probable configuration. The study of both 2-amino-5-chlorodibenzoarsenole and 2,8-dimethyl-3,7-diamino-5-chlorodibenzoarsenole was intended to clear away all questions. According to configuration Ub, 2,8-dimethyl-3,7-diamino-5-chlorodibenzoarsenole would have one pair of enantiomorphous forms regardless of whether the arsenic atom showed optical activity or not, because two of the groups attached to the arsenic atom are the same. On the

other hand, 2-amino-5-chlorodibenzoarsenole would have one pair of mirror images if the arsenic atom was optically inactive, but two pairs if asymmetry existed in that atom. The various possibilities and the corresponding results to be expected with the two compounds are listed below:

	2-amino-5-chloro-dibenzoarsenole	2,8-dimethyl-3,7-diamino-5-chloro-dibenzoarsenole
planar molecule, optically inactive arsenic atom	no optically active forms	no optically active forms
planar molecule, optically active arsenic atom	one pair enantiomers	no optically active forms
non-planar molecule, optically inactive arsenic atom	one pair enantiomers	one pair enantiomers
non-planar molecule, optically active arsenic atom	two pairs enantiomers	one pair enantiomers

A complete study of these compounds, then, would have gone far toward answering questions concerning not only the arsenic atom involved but also the question of planarity in the dibenzoarsenole ring.

Actually, the work was not carried beyond the synthesis of 2-nitro-5-chloro-dibenzoarsenole (Sg) in the one series and 2-amino-4,4'-diacetylamino-5,5'-dimethylbiphenyl (T d) in the other. If the molecule had two sources of optical activity, 2-nitro-5-chlorodibenzoarsenole (Sg) should have existed in two diastereo-isomeric forms. No evidence for such was found. Since the existence of a non-planar molecule was expected, this indicated no optical activity on the part of the arsenic atom, and our interest in the compound was, accordingly, much lessened. In view of the experimental difficulties involved and the exceedingly low yields encountered at each step, the problem was eventually discontinued.

IV. EXPERIMENTAL

Attempted Preparation of N-Methyl-7-chloro-7,12-dihydro-γ-benzophenarsazine:

Freshly distilled methyl-phenyl-α-naphthylamine*

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*We are indebted to the E.I.du Pont de Nemours Company for a sample of this technical product.

was used in this experiment, taking the clear, yellow fraction boiling at 192-4° at 19 mm. In a test tube, fitted with a reflux condenser and protected from atmospheric moisture, were placed 3 g. (0.0128 moles) of redistilled methyl-phenyl-α-naphthylamine and 2.6 g. (0.0143 moles) of freshly redistilled arsenic trichloride. The solution was heated at 175-200° for two hours. When cool, the residue was rinsed out with dry benzene, and the insoluble material was extracted repeatedly with more benzene hot. The resulting greenish crystals were finally recrystallized from p-cymene. The melting point was 218-9°, unchanged when mixed with authentic 7- chloro-7,12-dihydro-δ-benzophenarsazine. The washings were all dark blue and contained the dye for which the structure Q is suggested.

2-Aminodiphenyl (Sa):

In a 2-l. round bottom flask was placed 199 g. (1 mole) of technical 2-nitrodiphenyl (m. p.31-3°) and 350 cc. (4.24 moles) of concentrated hydrochloric acid. The mixture was warmed to 50° and stirred mechanically until an emulsion resulted. To this was added in fast drops 337 g. (1.5 moles) of stannous chloride dihydrate dissolved in 250 cc. (3.0 moles) of concentrated hydrochloric acid. The mixture was cooled as necessary to keep the temperature below 60°. After the addition of the last of the stannous chloride, the reaction temperature was

allowed to rise to 90°, and stirring was continued an extra hour after the reaction seemed to have subsided. A solution of 750 g. (18.7 moles) of sodium hydroxide in 750 cc. of water was added in portions with stirring. The whole was transferred to a larger container, diluted with an additional 600 cc. of water, and extracted once with 300 cc. of benzene and twice more with 200 cc. each time. The benzene extracts were washed with water, filtered to remove a small amount of insoluble material, and evaporated to one-third volume. Hydrogen chloride gas was now run in until precipitation appeared to be complete and the solution showed no more tendency to heat. The brown amine hydrochloride was filtered out, washed with benzene until the washings were clear, washed once with ether, and was air dried. The dry hydrochloride weighed 156 g., a 76 per cent yield. This was used in subsequent steps without further purification.

Recrystallized once from alcohol, the free amine, melting 47.5-9°, was recovered rather than the hydrochloride.

2-Amino-5-nitrodiphenyl (S d):

The preparation of this compound followed, in general, the directions given by Bell(102). A mixture of 276 g. (1.34 moles) of 2-aminodiphenyl hydrochloride as separated above, 276 g. (1.45 moles) of p-toluenesulfonyl chloride, 200 g. (3.78 equivalents) of sodium carbonate,

and 500 cc. of water was heated in a three neck flask on the steam bath for 8 hours with vigorous stirring. Without separating the amine derivative (S c), the solution was diluted with an additional liter of water and made acid to Congo Red paper with sulfuric acid. To this was added 140 cc. (2.2 moles) of concentrated nitric acid (sp. gr. 1.42). This made the solution 1.47 N. with nitric acid. The mixture was again heated on the steam bath with vigorous stirring, and, at the end of one hour, 21.2 cc. (0.335 moles) of concentrated nitric acid was added. The product began solidifying about the end of the second hour, so the mixture was cooled to 70° and 300 cc. of benzene was added and a reflux condenser was attached. Thereafter, heating had to be more gentle to prevent excessive refluxing. At the end of the third hour and again at the end of the sixth, additional 21.2 cc. portions of concentrated nitric acid were introduced. The reaction ran a total of 9 hours. When cool, the acid layer was poured off. An excess of sodium carbonate in 200 cc. of water was added and the mixture was agitated with warming. When cool, the aqueous layer was decanted, and the remaining oil was poured into 800 cc. of concentrated sulfuric acid. The hydrolysis was accompanied by a rise in temperature, but the solution was kept down to 35°. After standing for an hour, the mixture was poured onto 3000 g. of ice. The black mass of crude 2-amino-5-

nitrodiphenyl (S d) that formed was recrystallized once from benzene and once from ethyl alcohol. The resulting material was used directly in the following steps.

2-Phenyl-4-nitrobenzenearsonic acid (S e):

The Bart's reaction was run following quite closely the procedure of Johnson and Adams(103). The nitroamine was ground very fine and passed through a 60 mesh screen. To 42 cc. (0.5 moles) of concentrated hydrochloric acid in 58 cc. of water was added 21.4 g. (0.1 moles) of sifted 2-amino-5-nitrodiphenyl. With constant stirring, 6.9 g. (0.1 moles) of finely ground sodium nitrite was added in small portions over a period of 7 hours. Undissolved material was removed by filtration, and 600 g. of ice was added. This was followed at once by 75 cc. of arsenite solution, prepared according to the directions of Johnson and Adams (loc. cit.), and 20 cc. of 20 per cent copper sulfate solution, 6 cc. of 5 N. hydrochloric acid and 8 g. of sodium hydroxide dissolved in 100 cc. of water. (According to Johnson and Adams, 0.1 moles more sodium hydroxide should have been added at this time, but the addition of 8 g. rather than 12 g. gave a better yield). It was necessary to add ethyl acetate to keep down the foam. After standing 15 minutes, another 4 g. of sodium hydroxide in solution was poured in. The mixture stood another two hours, was warmed to 40°, and was filtered after the addition of a considerable

amount of animal charcoal. The solution was made acid to litmus with acetic acid and was filtered again. Finally, the solution was made acid to Congo Red with hydrochloric acid. The arsonic acid (S e) precipitated out, slowly at first. After being filtered and dried for 8 hours at 95°, the yield was 6.8 g., 21 per cent. The melting point was indefinite.

The arsonic acid was recrystallized from methyl alcohol, using 3 cc. of solvent per gram of acid. Upon cooling to 0°, seventy-five per cent of the crude acid was recovered as a white product melting above 310°.

2-Phenyl-4-nitrophenylarsine Dichloride (S f):

To 300 cc. of glacial acetic acid was added 21 g. of the arsonic acid and 70 cc. of concentrated hydrochloric acid. The mixture was warmed to 80°, and sulfur dioxide was passed through with continuous stirring for 6 hours. Almost everything was in solution at this time, and filtering at 100° removed 0.75 g. of insoluble residue. As soon as it cooled, the filtrate began precipitating small oily drops. The material was caused to separate in a crystalline state by slow cooling and scratching. After cooling to 20°, 21 g. (94 per cent) of the arsine dichloride (S f) was filtered out. Dissolved in 200 cc. of petroleum ether (b.p. 60-8°) to which 50 cc. of chloroform had been added, 16.1 g. of pale yellow crystals were recovered, m.p. 104-6°.

That this product was a dichloride was shown by the following tests: it dissolved in dilute sodium hydroxide; arsine chlorides are soluble even in dilute alkali, while arsine oxides are only soluble in strong alkali. Acidification of the alkaline solution gave a white powder that did not melt below 360°. This white powder was dissolved in equal volumes of glacial acetic acid and hydrochloric acid, was heated 15 minutes on the steam bath, and was diluted with more hydrochloric acid. Yellow crystals were precipitated which showed by their melting point and a mixed melting point that they were starting material again. The white powder, apparently, had been the corresponding arsine oxide, which was formed by the action of alkali upon the dichloride and which was acted upon by hydrochloric acid to give the dichloride again.

Ring Closure:

In a thoroughly dried flask were placed 8.5 g. of p-dichlorobenzene and 1 g. of 2-phenyl-4-nitrophenylarsine dichloride. The mixture was refluxed 28 hours, after which the dichlorobenzene was removed by vacuum distillation. Recrystallization from mixtures of petroleum ether (b.p. 60-8°) and chloroform failed to separate the two products that seemed to be present. Since these might be diastereoisomers, the mixture was analyzed for chlorine. Calculated for

$C_{12}H_7O_2NClAs$ (2-nitro-5-chlorodibenzoarsenole (S g)):Cl, 11,6%; Found: 8,6, 8.2.

A few crystals were separated in one recrystallization that melted sharply at 197°, but not enough could be obtained to be investigated.

m-Nitro-o-tolidine (T b):

Following the directions given by Löwenherz(104), 42,4 g. (0.2 moles) of o-tolidine (T a) was dissolved in 294 g. of concentrated sulfuric acid and cooled to 0°. To this with constant stirring, was added 20.2 g. of finely powdered potassium nitrate in small portions. When the solution had warmed up to room temperature, it was poured into 600 cc. of water and the amine sulfate was filtered out. This was stirred into a warm solution of an excess of sodium carbonate, liberating the free amine. Separation of the di- from the mono-nitro compound was accomplished by boiling with dilute hydrochloric acid, in which the mono-nitro derivative is soluble but the di-nitro compound remains undissolved. The amine was again liberated with sodium carbonate and was then recrystallized from mixtures of benzene and ligroin (b.p. 90-100°). The yield of bright red crystals melting at 153-5° was 8.5 g., 17 per cent, as compared with the 30 per cent claimed in the literature.

Diacetyl m-Nitro-o-tolidine (T c):

A one hundred per cent molar excess of acetic anhydride was poured over finely powdered m-nitro-o-tolidine. Considerable heat was evolved almost at once, and the reaction was complete in about a minute. One recrystallization from glacial acetic acid gave pale yellow crystals melting at 290-2°.

The preparation of several other compounds was studied as preliminary to preparing certain phenoxarsines. The results of these investigations are given below.

2,5-Dichloronitrobenzene:

Following, in general, the directions in the literature(105, 106), 426 g. (2.9 moles) of p-dichlorobenzene (m.p. 52-3°) was placed in a 2-l. flask equipped with a mechanical stirrer and was warmed to 60°. The mixed acid, prepared by adding 220 cc. of sulfuric acid (sp. gr. 1.84) to 198 cc. (4.14 moles) fuming nitric acid (sp. gr. 1.52), was run in slowly with constant stirring over about 1 hour. The temperature of the reaction mixture was maintained at 60° by external cooling. When all the acid had been added and the temperature no longer tended to rise, a water bath at 80-90° was applied for an hour longer. The reaction mixture was allowed to cool to about 60° and was then poured into a mixture of 1 l. of water and 1 kg. of ice. The nitro compound was stirred vigorously until it solidified. When

completely cool, the product was filtered off and air dried for ten hours. After recrystallization from a mixture of 200 cc. of acetone and 100 cc. of methyl alcohol, the yield of 2,5-dichloronitrobenzene (m.p. 54.5°) was 508 g., or 91 per cent. By partial evaporation of the solvent residues, a second crop was obtained, raising the yield to 94 per cent.

2-Nitro-4-chlorodiphenyl ether:

Using the proportions of reagents suggested by Henley(107), 305 g. (4.2 moles) of molten phenol was poured into a 2-l. three neck flask fitted with a stirrer and a reflux condenser. To this was added 180 g. (3.2 moles) of potassium hydroxide and 4 cc. of water. The whole was refluxed until the hydroxide had dissolved, stirring was started, and 481 g. (2.5 moles) of 2,5-dichloronitrobenzene was added in portions as rapidly as possible without causing too violent a reaction. The mixture was then refluxed 8 hours with continuous stirring.

After the addition of 500 cc. of water, the mixture was steam distilled, vigorous stirring being maintained all the while. When no more organic material was removed with the steam, the product was separated from the water and dissolved in benzene. After being dried with calcium chloride, the benzene was removed under the vacuum of a water pump, and the residue was vacuum distilled at 8 mm. 2-Nitro-

4-chlorodiphenyl ether boils at 185-7° at 8 mm. and 214-16° at 26 mm. The yield of product boiling at 185-7° at 8 mm. was 395 g., or 63 per cent. The material did not crystallize even upon long standing.

2-Amino-4-chlorodiphenyl Ether:

In a 1-l. flask was placed 330 g. (1.46 moles) of stannous chloride dihydrate, and 360 cc. (4.36 moles) of concentrated hydrochloric acid was added with stirring. Warmed to 85°, the crystals dissolved, giving a clear solution. To this, 120 g. (0.485 moles) of 2-nitro-4-chlorodiphenyl ether was added dropwise at such a rate that the temperature remained at 80-85° without either external warming or cooling. Vigorous stirring was maintained throughout. When the last of the 2-nitro-4-chlorodiphenyl ether had been added, the mixture was warmed in boiling water ten minutes. Stirring was stopped, and, on cooling, a brown gum precipitated. The aqueous layer was decanted and discarded. The gummy product was a stannic chloride double salt of 2-amino-4-chlorodiphenyl ether.

The amine double salt was dissolved in a minimum of 10 per cent sodium hydroxide solution to which a small amount of sodium bisulfite had been added to reduce oxidation. This solution was extracted three times, using 10 cc. of benzene each time for each 100 cc. of aqueous solution. All the benzene extracts were combined, washed with

water until free of scum, and were concentrated on the steam bath. When reduced to about one-third of its original volume, the benzene solution was allowed to evaporate to dryness at room temperature. There remained 48 g. of crystalline but crude product, a 45 per cent yield. Recrystallized once from 40 cc. of ligroin (b.p. 90-100°) and once from 24 cc. of methyl alcohol, 48 g. of crude product gave 35 g. of 2-amino-4-chlorodiphenyl ether melting at 42-3°, a 72 per cent recovery of pure compound from the crude.

In some instances, no stannic chloride double salt separated at the completion of the reduction. In these cases, the separation and purification of the amine were conducted as above, except that no decantation of the aqueous layer was possible, and a correspondingly larger volume of sodium hydroxide solution had to be used because of the excess acid present.

Attempts to reduce 2-nitro-4-chlorodiphenyl ether to 2-amino-4-chlorodiphenyl ether using any of the following were unsuccessful: tin and hydrochloric acid, zinc and hydrochloric acid, aluminum and hydrochloric acid, zinc and acetic acid, iron filings and water.

2-Amino-4-chlorodiphenyl Ether Hydrochloride:

2-Amino-4-chlorodiphenyl ether dissolves in concentrated hydrochloric acid upon heating. The white

crystals that separate upon cooling are the amine hydrochloride, m.p. 192°.

Purification of technical 2,4-Dinitrochlorobenzene:

The technical 2,4-dinitrochlorobenzene available melted over an 8° range and was therefore dissolved in boiling methyl alcohol, 50cc. of solvent for each 100 g. of dinitrochlorobenzene. Cooling to room temperature gave an 85 per cent yield of yellow crystals melting at 50-2°.

2,4-Dinitrodiphenyl Ether:

In a 2-l. three neck flask equipped with a mechanical stirrer was placed 336 g. (1.5 moles) of 2,4-dinitrochlorobenzene (m.p. 50-2°), and the whole was warmed to 55°. When the dinitrochlorobenzene was all melted, one half of a mixture consisting of 226 g. (2.4 moles) of phenol, 112 g. (2.0 moles) of potassium hydroxide, and 200 cc. of water was added. The mixture was warmed to 95° and stirred vigorously for 10 minutes, the other half of the phenol-potassium hydroxide-water mixture was added, and the whole was refluxed for an hour and a half. This was then cooled until the product solidified, the aqueous layer was decanted, and the diphenyl ether was washed by stirring vigorously with 200 cc. of 10 per cent sodium hydroxide solution at 80° for 15 minutes. When this alkaline layer had been decanted, the product was recrystallized once from

200 cc. of methyl alcohol to which 200 cc. of acetone had been added and once from 200 cc. of methyl alcohol to which 40 cc. of acetone had been added. There was recovered 340 g. of 2,4-dinitrodiphenyl ether, m.p. 67-8.5°, an 87 per cent yield.

2-Amino-4-nitrodiphenyl Ether:

In a 2-l. flask fitted with a mechanical stirrer, 80 g. (0.31 moles) of 2,4-dinitrodiphenyl ether was dissolved in 800 cc. of methyl alcohol with warming and stirring. This solution was cooled to 40°, causing partial precipitation of the nitro compound, but this went back into solution during the reduction. To this was added 208 g. (0.92 moles) of stannous chloride dihydrate dissolved in 200 cc. (2.42 moles) of concentrated hydrochloric acid. The rate of addition was adjusted so that the temperature remained below 42° without external cooling. The addition required 3-4 hours. A solution of 320 g. (8 moles) of sodium hydroxide in a minimum of water at 30° was added with stirring, and the temperature was kept below 40° by cooling as necessary. The solution was filtered and the filtrate was discarded. The residue was extracted once with 400 cc. of benzene and once with 200 cc. of benzene and was then discarded. The combined extracts were washed twice with 100 cc. of 10 per cent aqueous sodium hydroxide each time and were filtered to remove a small amount of residue. Dry hydrogen chloride

was passed into the benzene solution until there was no more tendency to heat, about one and a half to two hours being required with a good stream of gas. The solid was filtered out and washed twice with boiling benzene. The remaining 2-amino-4-nitrodiphenyl ether hydrochloride weighed 37 g. when dry, a 45 per cent yield.

The free amine was prepared by warming the gray hydrochloride with aqueous sodium carbonate and recrystallizing the product. 2-Amino-4-nitrodiphenyl ether so prepared recrystallized from alcohol in dark red needles, melting at 107-8°.

SUMMARY

2-Nitro-5-chlorodibenzoarsenole was found to show no evidence of existing in diastereoisomeric forms.

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