[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF COLUMBIA UNIVERSITY]

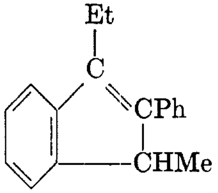
THE SYNTHESIS OF SOME INDENE AND DIHYDRONAPHTHALENE DERIVATIVES RELATED TO STILBESTROL

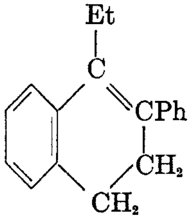
MILTON SILVERMAN AND MARSTON TAYLOR BOGERT

Received July 18, 1944

In April, 1941, Plentl and Bogert (1) published an article on the synthesis of tricyclic hydrocarbons related to stilbestrol, in which they described how compounds (I) and (II) were prepared from ethyl phenylcyanacetate and *alpha*- or *beta*-phenylethyl bromide, and mentioned the fact that experiments were already under way in these laboratories for the synthesis, by similar reactions, of the more important corresponding alkoxy and hydroxy (III, IV) derivatives.

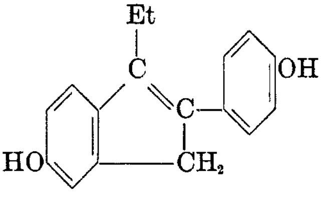
(I)

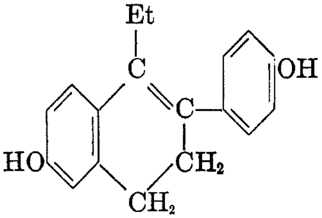




(II)

(III)

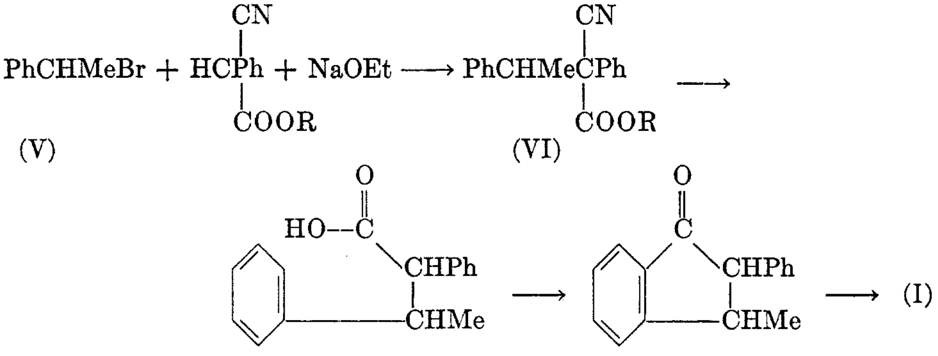




(IV)

Unfortunately, both authors of the present communication were compelled, by various war duties, to interrupt these experiments temporarily and, before the resumed work could be completed, the articles by Salzer (2, 3) and by Solmssen (4) appeared, anticipating some of our own results, as explained beyond.

The Plentl and Bogert synthesis can be summarized as follows:

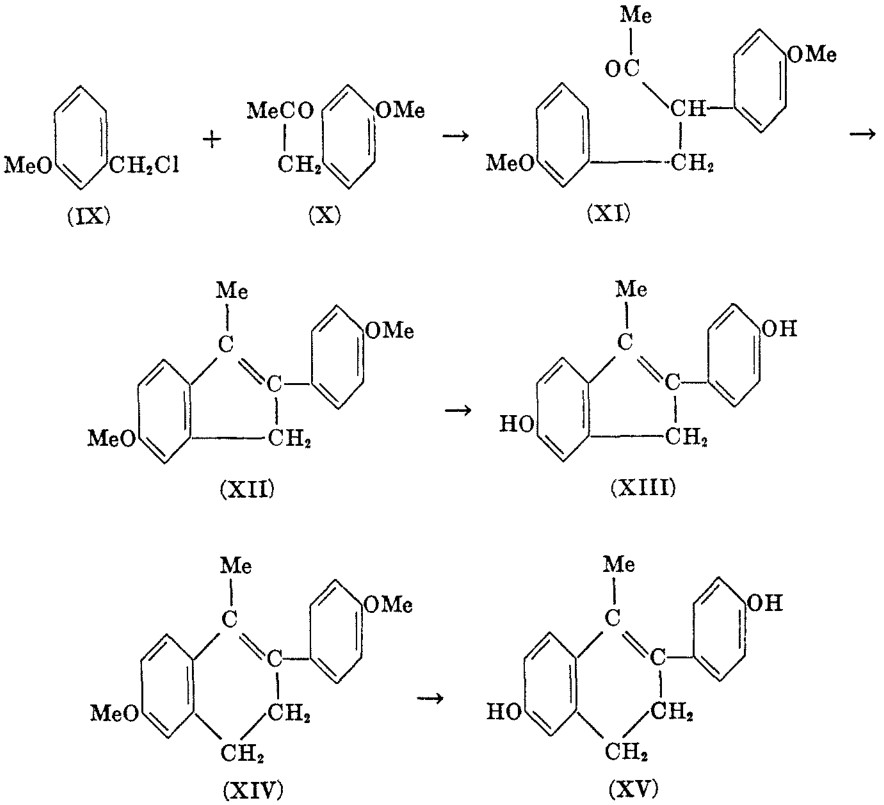


$$\text{PhCHMeBr} + \text{H}\underset{\text{COOR}}{\overset{\text{CN}}{\text{C}}}\text{Ph} + \text{NaOEt} \longrightarrow \text{PhCHMe}\underset{\text{COOR}}{\overset{\text{CN}}{\text{C}}}\text{Ph} \longrightarrow$$

(V) (VI)

(VII) (VIII) → (I)

FLOW SHEET 1



(IX) (X) (XI) (XII) (XIII) (XIV) (XV)

When the isomeric $PhCH_2CH_2Br$ was used instead of (V), the product was the corresponding dihydronaphthalene derivative (II).

The method employed by Salzer (2, 3) for the synthesis of the indene derivative (XIII) is shown in Flow Sheet 1.

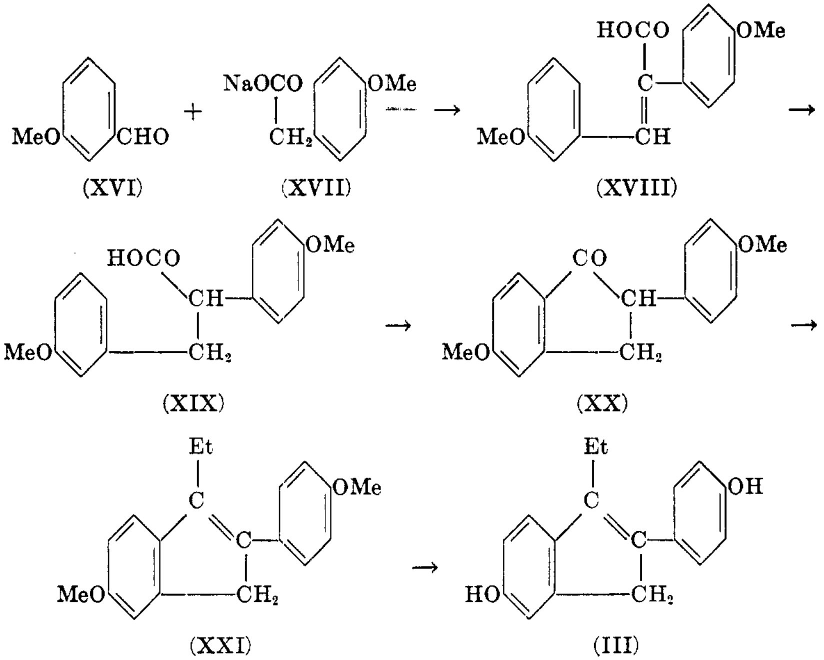
When the homologous (*m*) $MeOC_6H_4CH_2CH_2Br$ was used in place of (IX), the analogous dihydronaphthalene derivatives (XIV and XV) were formed.

Salzer failed to record the yield of several of his compounds and his final product (XIII) was obtained as an impure oil, which he identified by preparation of a crystalline diacetate (m.p. 131°) and by remethylation to (XII). He found it impossible to prepare any homologs of (XIII) or (XIV), with other substituents in position 3 of the indene, or position 1 of the dihydronaphthalene, since cyclization occurred only in the case cited.

He also concluded, without any apparent experimental proof, that ring closure of (XI) to (XII) occurred *para* to the methoxyl group, as shown in Flow Sheet 1, although his patent (3) indicates clearly that this may take place also *ortho* to the -OMe group in the formation of the indene cycle.

Solmssen (4) followed still another procedure in his synthesis of the indene derivatives:

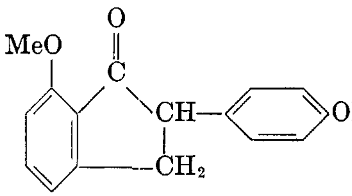
FLOW SHEET 2



In its general plan, this process differs from that of Plentl and Bogert (1), and in that pursued by us (Flow Sheet 3), only in the way in which the substituted hydrocinnamic acid (XIX) is prepared.

By hydrolysis of the dimethyl ether (XXI) with hydrobromic in glacial acetic acid, followed by a tedious chromatographic adsorption, he secured an impure dihydroxy derivative (III), from which he prepared a diacetate, but attempted purification through various esters proved unsatisfactory.

In the cyclization of the acid (XIX), he noted the formation of two isomeric indanones (m.p. 96° and 172°). Because the higher-melting form proved unreactive to the Grignard reagent, he ascribed to it the following formula:



(m.p. 172°)

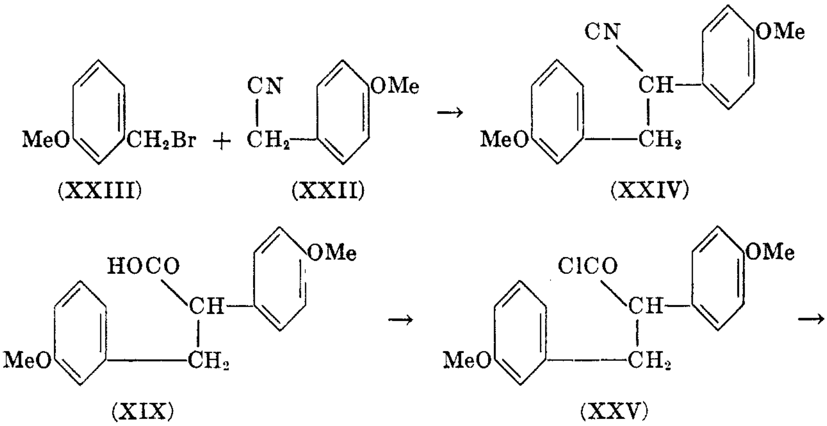
Further experimental work in this field, it seemed to us, should include additional proof of the constitution of these indanones, the preparation of the dihydroxy compound (III) in higher purity and better yield from its dimethyl ether (XXI), and corroborative identification of some of Salzer's products.

In continuing our own experimental work in this field, with the object of obtaining the desired alkoxy and hydroxy derivatives (III, IV), homoanisonitrile

(XXII) was selected as initial material. This was prepared from *p*-nitrobenzylcyanide in excellent over-all yield, as follows (5, 6): *p*-$O_2NC_6H_4CH_2CN$ → $H_2NC_6H_4CH_2CN$ → $HOC_6H_4CH_2CN$ → $MeOC_6H_4CH_2CN$ (XXII). The *m*-$MeOC_6H_4CH_2Br$ (XXIII) with which it was condensed was prepared from *m*-methoxybenzaldehyde by these steps: HOC_6H_4CHO → $MeOC_6H_4CHO$ → $MeOC_6H_4CH_2OH$ → $MeOC_6H_4CH_2Br$.

We synthesized the indene derivative (III) as shown in Flow Sheet 3.

Flow Sheet 3



(XX) → (XXXI) → III (as in Flow Sheet 2).

For the synthesis of the corresponding dihydronaphthalene derivatives, *m*-$MeOC_6H_4CH_2CH_2Br$ was substituted for (XXIII) in the initial reaction above. This bromide was obtained by the following series of reactions:

m-$H_2NC_6H_4Br$ → HOC_6H_4Br → $MeOC_6H_4Br$ → $MeOC_6H_4CH_2CH_2OH$ → $MeOC_6H_4CH_2CH_2Br$ (XXX).

The *m*-bromoanisole was prepared by the process of Koelsch (10), and then converted into the alcohol and bromide as described by Bachmann and Thomas (8).

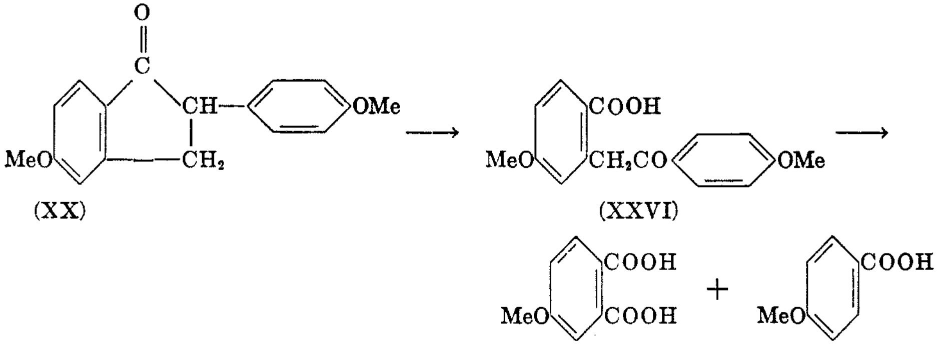
The sodium derivative of the homoanisic nitrile (XXII) was formed by reaction with a molar equivalent of sodamide in liquid ammonia, adding benzene and driving off the excess of ammonia. The sodamide was prepared fresh by the method of Vaughn, Vogt, and Nieuwland (7).

This sodium derivative was condensed with the bromide (XXIII) in dry benzene, and the resulting nitrile (XXIV) saponified by dilute alcoholic alkali to the acid (XIX).

The cyclization of this acid to the indanone (XX) was accomplished by the addition of stannic chloride to a benzene solution of the acyl halide (XXV), in much the same way as Bachmann and Thomas (8) prepared 6-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. An excellent yield of the lower-melting isomer (m.p. 96–97°) was obtained as the sole product.

This product, on oxidation with chromic acid in dilute sulfuric acid solution, gave 2-(4′-methoxyphenacyl)anisic acid (XXVI). Oxidation of this acid by

30% hydrogen peroxide in alkali solution, yielded anisic and 4-methoxyphthalic acids:



These results on the indanone (XX) support the structures (XXI and III) assigned by Solmssen (4) to his products.

We have also verified the correctness of Salzer's (2, 3) constitutional formula (XII) for the cyclization product of the ketone (XI), since we have obtained the same compound (m.p. 110–111°) by our process.

The conversion of the indanone (XX) into the indene derivative (XXI) was accomplished by refluxing it with ethylmagnesium iodide in toluene solution, the carbinol first formed undergoing dehydration at that temperature. In this way, not only the 2-ethyl (XXI), but also the 2-methyl, 2-phenyl, and 2-cyclohexyl derivatives were obtained.

In common with other investigators (2, 4, 9), we experienced great difficulty in demethylating these ethers, and we failed to isolate appreciable amounts of the pure dihydroxyindene by treatment with any of the following chemicals:

(a) Potassium hydroxide in alcohol, ethylene or propylene glycol, at 200°, 250°, or 300°, for 24 or 48 hours.

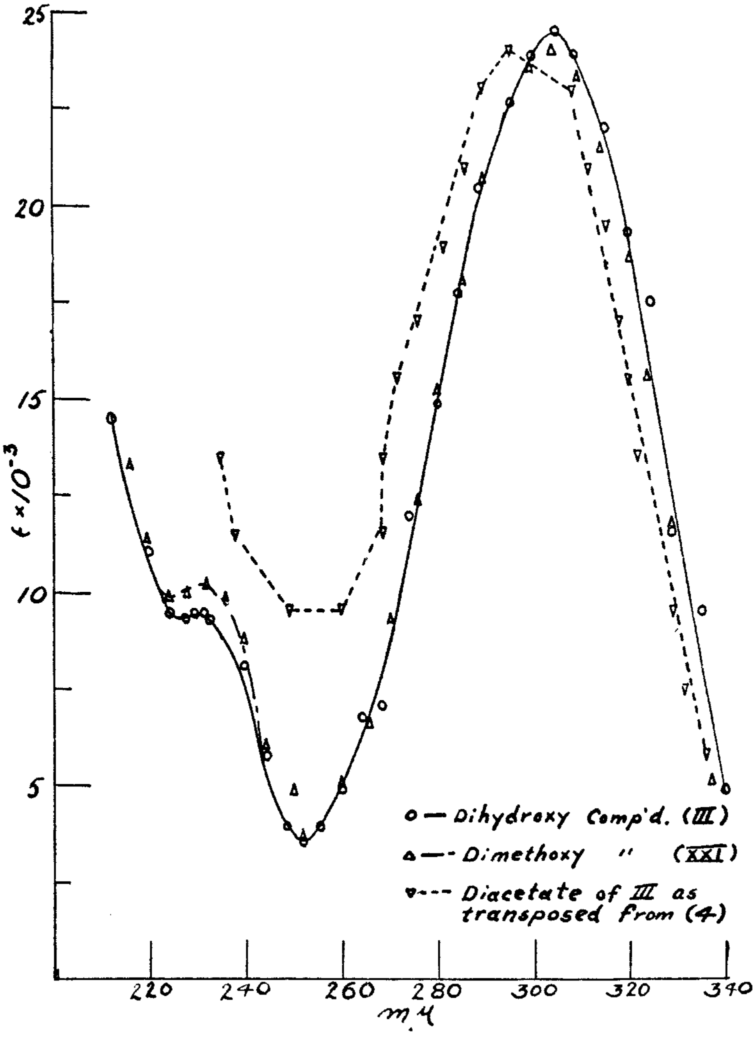
(b) Aluminum chloride in carbon disulfide, benzene, or chlorobenzene.

(c) The Grignard reagent, or aniline hydrochloride (alone, or in boiling tetralin).

Compound (III) was finally obtained by refluxing with a mixture of concentrated (48%) hydrobromic acid in glacial acetic acid, in an atmosphere of carbon dioxide, essentially as described by Solmssen (4), the proportion of reagents used being governed by the solubility of (III) in the acid mixture.

By treatment with suitable solvents, an anlytically pure product was secured, in small colorless needles, m.p. 176–177°, and the chromatographic adsorption used by Solmssen proved unnecessary. His product formed "slightly colored crystals," m.p. 136°, and gave analytical figures for carbon indicative of the presence of some impurity. The higher m.p. of our product may indicate that the compound is dimorphic. The diacetate prepared by us agreed closely with the one described by him. The pure diphenol (III), after standing for a few days in a sample bottle, darkened and apparently underwent some decomposition.

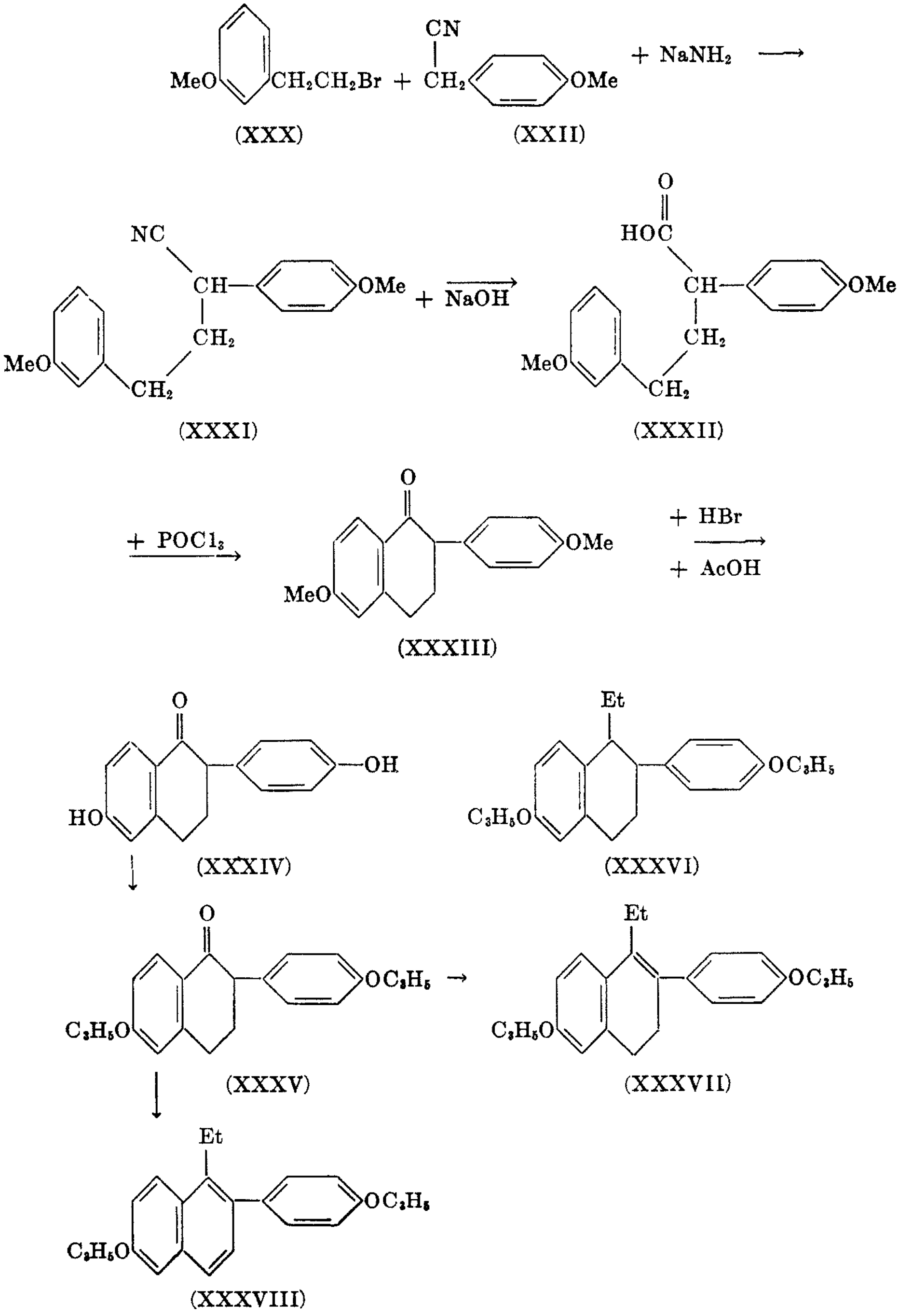
As a further check upon the identity and purity of our product (III), we have compared its ultraviolet absorption spectrum, and that of its dimethyl ether (XXI), with that of the diacetate as recorded by Solmssen (4), and found the curves for all three compounds very similar, with a maximum at 305 mμ and a minimum at 252 mμ for (XXI) and (III), as compared with a maximum of 295 mμ and a minimum of about 255 mμ for the diacetate (4). The peak at 232 mμ has not hitherto been reported.



We owe these ultraviolet absorption curves to the skill and courtesy of Professor Erwin Brand of the Columbia University College of Physicians and Surgeons, to whom we wish to express our sincere thanks.

In some preliminary experiments seeking a more direct synthesis of (XXI), a Reformatsky reaction was attempted upon *p*-methoxypropiophenone with *alpha*-chlorohomoanisonitrile in benzene solution, but the only product isolated was the di-*p*-anisylsuccinonitrile (XXIX): $(p\text{-})\text{MeOC}_6\text{H}_4\text{COEt} + \text{ClCH(CN)}$

Flow Sheet 4


MeO
CH₂CH₂Br
CN
CH₂
OMe
+ NaNH₂
(XXX)
(XXII)
NC
CH
OMe
CH₂
MeO
CH₂
+ NaOH
(XXXI)
O
HOC
CH
OMe
CH₂
MeO
CH₂
(XXXII)
+ POCl₃
O
OMe
MeO
(XXXIII)
+ HBr
+ AcOH
O
OH
HO
(XXXIV)
Et
OC₃H₅
C₃H₅O
(XXXVI)
O
OC₃H₅
C₃H₅O
(XXXV)
Et
OC₃H₅
C₃H₅O
(XXXVII)
Et
OC₃H₅
C₃H₅O
(XXXVIII)

$C_6H_4OMe(p)$(XXVIII) → $(p\text{-})MeOC_6H_4CH(CN)CH(CN)C_6H_4OMe(p\text{-})$(XXIX), obviously the result of the coupling of two molecules of (XXVIII).

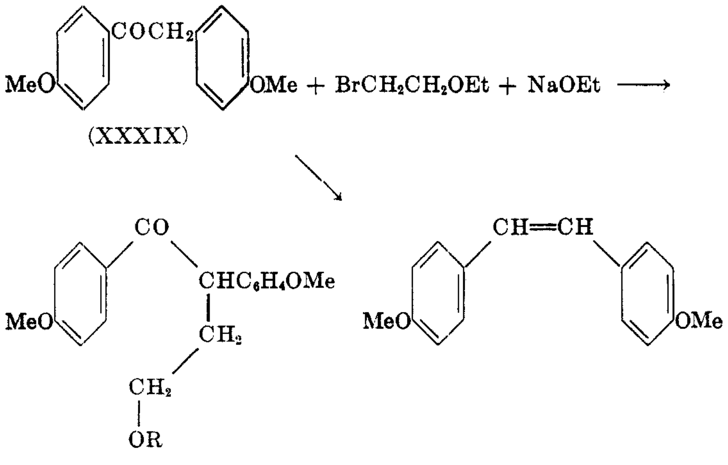
In the dihydronaphthalene series, the sodium derivative of homoanisic nitrile (XXII) was brought into reaction with *beta*-(*m*-anisyl)ethyl bromide (XXX), as mentioned above, and the substituted butyronitrile (XXXI) then saponified (XXXII) by alkali.

The cyclization to the tetralone was accomplished by means of phosphorus oxychloride, as described by Dodds *et al.* (9).

To avoid the troublesome problem of demethylating the dimethyl ether of (IV), a different line of approach was explored.

The diphenolic ketone (XXXIV), obtained from (XXXIII) by the action of concentrated hydrobromic acid in glacial acetic acid solution, was dissolved in anisole and treated with a slight excess of ethylmagnesium iodide. The interaction of the two phenolic groups with the Grignard reagent, however, precipitated the compound, so that the carbonyl group was not attacked and, upon working up the reaction mixture in the usual way, the initial compound was recovered.

An attempt was then made to take advantage of the observation of Luttringhaus and Saaf (11) that phenylallyl ethers are easily split by organometallic compounds at low temperatures. The diallyl ether (XXXV) was prepared by the Claisen method (12) and subjected to the action of ethylmagnesium iodide in benzene solution. From the reaction mixture, there were isolated the naphthalene derivative (XXXVIII), and either the di-(XXXVII) or tetrahydro (XXXVI) compound. It is suggested that compounds (XXXVI) and (XXXVIII) resulted from disproportionation of (XXXVII), although the evidence for the presence of the dihydro compound (XXXVII) was too incomplete to differentiate it satisfactorily from the tetrahydro derivative (XXXVI). No cleavage of (XXXVII) (or XXXVIII) resulted when it was subjected to the action of phenyllithium in ether at 50°.



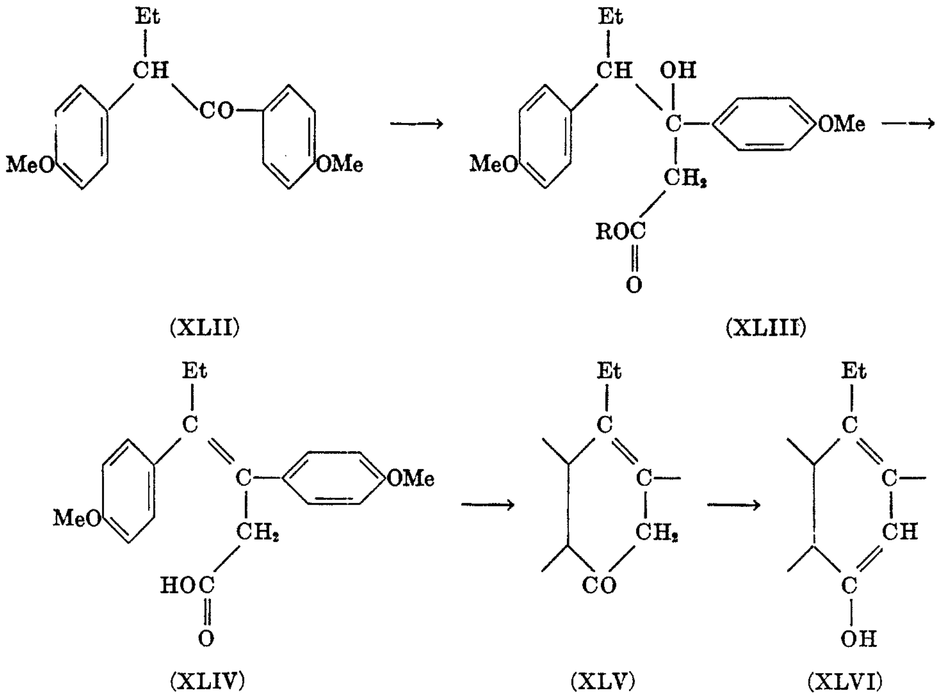
(XXXIX)

(XL)

(XLI)

Experiments were also conducted for the condensation of *beta*-bromodiethyl ether with desoxyanisoin (XXXIX), in the presence of sodium ethoxide in benzene solution, to obtain the ether (XL), in the hope that this could be hydrolyzed to the corresponding alcohol, and the latter subjected to a cyclodehydration (13). The compound actually isolated, however, proved to be the di-anisal, (4,4′-dimethoxystilbene)(XLI), presumably formed by reduction of carbonyl to the secondary alcohol group, followed by dehydration. Whether this was the *cis* or *trans* form was not determined.

Some preliminary experiments were carried out in a different direction, involving the application of the Reformatsky reaction to *alpha*-ethyldesoxyanisoin (XLII), but these had to be interrupted before completion, because of the transfer of the junior author to other important work. The reactions completed included the condensation of ethyl bromoacetate with the ethyldesoxyanisoin to the expected hydroxy ester (XLIII), dehydration of the latter to the unsaturated ester, followed by saponification to the corresponding acid (XLIV).



(XLII) (XLIII)

(XLIV) (XLV) (XLVI)

Cyclization of (XLIV) should yield first the ketodihydro compound (XLV), which probably would rearrange promptly to the tautomeric *alpha*-naphthol derivative (XLVI), but it is uncertain when these experiments can be completed.

Acknowledgments. We are indebted to the General Aniline Co. of New York for a generous supply of *m*-hydroxybenzaldehyde. To Mr. Saul Gottlieb and Miss Frances Marx, we are under obligations for the analyses reported.

EXPERIMENTAL

All melting points reported are corrected for exposed stem.

m-Bromanisole. *m*-Bromaniline was diazotized according to the method of Koelsch (10). The bromophenol, b.p. 124–127°/22 mm., (lit. b.p. 125–130°/25 mm.) (10), was methylated by the procedure of Buck (14), who prepared veratric aldehyde from vanillin. The over-all yield was 65–70%, b.p. 108–110°/22 mm., [lit. b.p. 105°/16 mm. (15)].

beta-m-Anisylethyl bromide (XXX). The directions of Bachmann and Thomas (8) were followed, except that the Grignard reagent was prepared from *m*-bromoanisole instead of the corresponding iodo derivative. We were unable to obtain the excellent yield of the alcohol reported by these workers from the reaction between the Grignard reagent and ethylene oxide. The yield of alcohol obtained for conversion to the bromide was 59%, b.p. 110–115°/5 mm., [lit. 105–110°/1 mm. (16)]. The yield of bromide, based upon the alcohol used was 61%, b.p. 137–139°/13 mm. [lit. b.p. 138°/12 mm. (17)].

p-Methoxybenzyl cyanide (homoanisonitrile) (XXII). Koessler and Hanke (5) prepared *p*-hydroxybenzyl cyanide by the reduction of *p*-nitrobenzyl cyanide followed by diazotization. Their directions are based upon the earlier work of Pschorr, Wolfes, and Buckow (6). The yield of crude product was 71%, m.p. 65–70° (lit. m.p. 67–71°).

The methylation was carried out by the method of Meisenheimer and Weibezahn (18). The yield, based upon crude *p*-hydroxybenzyl cyanide, was 88%, b.p. 153–154°/15 mm. (lit. b.p. 152°/16 mm.).

m-Methoxybenzyl bromide (XXIII). This compound was prepared as directed by Woodward (19), except that the hydroxybenzaldehyde was methylated by the method of Buck (14). The carbinol was prepared by hydrogenation of *m*-methoxybenzaldehyde using the Adams catalyst in the presence of ferrous ions. The conversion to the bromide was easily carried out by passing hydrogen bromide into a benzene solution of the alcohol. The over-all yield of bromide was 85–90%; b.p. 127–129°/18 mm. [lit. b.p. 127°/16 mm. (20)].

alpha-(p-Anisyl)-beta-(m-anisyl)propionitrile (XXIV). A solution of sodamide was prepared by adding 4.25 g. of sodium in small pieces to 75 cc. of liquid ammonia containing 0.1 g. of ferric nitrate hexahydrate. As soon as all of the sodium had reacted, 27.2 g. of homoanisonitrile was added slowly to the well-stirred solution. A suspension of the sodium enolate formed immediately and the solution turned deep yellow in color. After standing for fifteen minutes, 200 cc. of benzene was carefully added and the mixture refluxed on the steam-bath for three hours. A solution of 37 g. of *m*-methoxybenzyl bromide in 50 cc. of benzene was added through the dropping-funnel. After refluxing for six hours, the benzene solution, containing a precipitate of sodium bromide, was cooled, washed with dilute hydrochloric acid and several times with water, then separated and dried over anhydrous sodium sulfate. The solvent was evaporated, after the solution had been filtered, and the dark brown oil was taken up in hot alcohol. On cooling, a copious precipitate came down which was recrystallized from alcohol. The glistening platelets melted at 93–94°; yield, 71%.

Anal. Calc'd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4.
Found: C, 76.5; H, 6.4.

alpha-(p-Anisyl)-beta-(m-anisyl)propionic acid (XIX). Hydrolysis was accomplished by refluxing a mixture of 29.0 g. of the nitrile (XXIV) dissolved in 110.0 cc. of alcohol and 58.0 g. of sodium hydroxide dissolved in 58.0 cc. of water on the steam-bath for thirty hours. After diluting with water, the alcohol was evaporated. The cold solution was filtered and acidified with dilute hydrochloric acid. The yellow oil which separated soon solidified. It was filtered, washed, and redissolved in dilute sodium carbonate solution. The insoluble material was filtered off, and the solution was then acidified with hydrochloric acid. The white solid was crystallized from alcohol, m.p. 105–106°; yield, 85%.

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3.
Found: C, 71.5; H, 6.4.

Solmssen (4) recently prepared this compound by the catalytic hydrogenation of *m*-methoxy-*alpha*-(*p*-anisyl)cinnamic acid. He records the m.p. 106°.

2-(p-Anisyl)-6-methoxyindanone-3 (XX). Cyclization was carried out in a manner analogous to that of Bachmann and Thomas (8) in their preparation of 6-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene. The acid (XIX) (11.9 g.) was suspended in 50 cc. of dry ether containing two drops of pyridine. Thionyl chloride (5.5 g.)was added dropwise to the stirred suspension. The acyl chloride formed immediately and the reaction was ended by refluxing on the steam-bath for a few minutes. The ether was removed under reduced pressure, 10 cc. of benzene added, and this solvent also removed. The addition of benzene and its removal was repeated twice more. The oil was taken up in 100 cc. of benzene in a flask equipped with a dropping-funnel, stirrer, and reflux condenser. The solution was cooled to 5° and 12 g. of stannic chloride dissolved in 10 cc. of benzene was added dropwise. The insoluble complex separated as a dark brown oil which appeared to soldify as the mixture was stirrėd for ninety minutes at room temperature. This mixture was decomposed in the usual manner and the benzene layer separated, washed with water, dilute sodium carbonate solution, and finally with water again. After drying over anhydrous sodium sulfate, the solution was filtered and the solvent evaporated. The oil soon solidified and was crystallized from alcohol; m.p. 96–97°; yield, 82%.

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0
Found: C, 76.0; H, 6.0.

We were unable to obtain this indanone (XX) by the action of phosphorus oxychloride upon the acid (XIX), because the decomposition was so great that no pure product could be isolated. The use of sulfuric acid, dilute or concentrated, resulted always in products containing much alkali-soluble material. Attempts to effect ring closure by the action of aluminum chloride upon the acyl chloride in carbon disulfide, gave erratic results.

In the literature (4) this compound was obtained along with the isomeric 2-(*p*-anisyl)-4-indanone-3 by cyclizing (XIX) with phosphorus pentoxide in benzene. The m.p. is given as 96°.

Oxidative degradation of (XX). *2-(4'-Methoxyphenacyl)anisic acid* (XXVI). The ketone (XX) (1.65 g.) was oxidized with 70 cc. of a solution containing 10 g. of chromic acid and 10 cc. of sulfuric acid in 100 cc. of water. The reaction mixture was heated on the steam-bath for ninety minutes with frequent shaking. After cooling and filtering, the precipitate was washed with water and dissolved in dilute sodium carbonate solution. The liquid was filtered and acidified with 50% sulfuric acid until acid to Congo red paper. The solid was filtered off, washed with water and recrystallized twice from an alcohol-water mixture (1:1) yielding 0.67 g. of white hair-like needles melting at 181–183°.

Anal. Calc'd for $C_{17}H_{16}O_5$: C, 68.0; H, 5.3.
Found: C, 68.2; H, 5.5.

In another run, 2.0 g. of (XX) was oxidized by chromic acid as outlined above. After the filtered product was freed of chromic salts, it was dissolved in 25 cc. of 10% sodium hydroxide solution and slowly treated with 30 cc. of 30% hydrogen peroxide on the steam-bath. As soon as the excess peroxide had been decomposed (15 min.) the reaction mixture was cooled and acidified to Congo red paper. The precipitate which formed was filtered and twice recrystallized from water, yieldong 0.5 g. of colorless needles identified as anisic acid.

The filtrate, obtained after acidification of the peroxide-free solution, was evaporated to dryness and the residue extracted several times with ether. The solvent was removed and the solid material sublimed at 1/2 mm. (Wood's metal bath at 190–200°). The sublimate was recrystallized twice from glacial acetic acid to which a few drops of water were added, yielding 0.1 g. of white crystals melting at 95–96°. The compound was identified as 4-methoxyphthalic anhydride by analysis and by a mixed melting point with a specimen prepared from *m*-methoxybenzoic acid by the method of Chakravarti and Perkin (21); mixed m.p. 95–96°. [Lit. 95° (21)].

Anal. Calc'd for $C_9H_6O_4$: C, 60.7; H, 3.4.
Found: C, 60.7; H, 3.5.

3-Methyl-2-(p-anisyl)-6-methoxyindene (XII). The ketone (XX) (2.68 g.) was dissolved in 25.0 cc. of toluene. This solution was added dropwise to a Grignard reagent made from 0.24 g. of magnesium and 1.42 g. of methyl iodide in 25.0 cc. of ether. The solution became warm and turned orange in color. The ether was distilled off and the mixture refluxed for one hour at 105–110°. It was decomposed in the usual way with 20% iced sulfuric acid. The toluene extract was separated, washed, and dried over anhydrous sodium sulfate. The solvent was evaporated and the red oil soon solidified. It was crystallized from alcohol; m.p. 110–111.5°; yield, 60%.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8.
Found: C, 81.1; H, 6.7.

Salzer (2) has also prepared this substance by cyclizing 1-(*p*-anisyl)-1-(*m*-methoxybenzyl)acetone with concentrated sulfuric acid. The melting point 110° is in good agreement with that recorded above.

3-Ethyl-2-(p-anisyl-6-methoxyindene) (XXI). This compound was prepared from 2.68 g. of the ketone (XX) in 25.0 cc. of toluene and the required amount of ethylmagnesium bromide. The reaction mixture was refluxed for one hour and the decomposition and isolation was carried out as described above. The compound was recrystallized from alcohol; m.p. 87–88°; yield, 61%.

Anal. Calc'd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1.
Found: C, 81.4; H, 7.3.

In the literature (4) this compound was obtained by treating the indanone with ethylmagnesium iodide in benzene followed by dehydration with dilute sulfuric acid. It was purified by chromatographic adsorption on alumina and recrystallized from methanol. The m.p. is given as 87–88°.

2-(p-Hydroxyphenyl)-3-ethyl-6-hydroxyindene (II). One gram of the dimethyl ether (XXI) was refluxed for 70 minutes in a mixture containing 3.0 cc. of hydrobromic acid (48%) and 15 cc. of glacial acetic acid under carbon dioxide. The solution was made alkaline and the isoluble material removed by extraction with ether. The water layer was separated and acidified with hydrochloric acid. The precipitate was extracted with ether. The organic layer was washed several times with water, dried over sodium sulfate, and filtered. After evaporating the solvent, the oil remaining was taken up in benzene. The benzene solution was treated with Norit and filtered. After concentrating the solution to approximately 5 cc., 2–3 drops of alcohol were added and upon cooling a white crystalline material was filtered off. This was recrystallized once more from the benzene-alcohol mixture. The substance crystallized in clusters of small colorless, fibrous needles; m.p. 176–177°; yield, 2–3%.

Anal. The substance contained no methoxyl. Calc'd for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4.
Found: C, 80.6, 80.4; H, 6.4, 6.5.

This substance has previously been prepared by Solmssen (4) who records the melting point 136° for "slightly colored crystals." The analyses for the compound as given in his paper were: C, 79.8, 79.5; H, 6.5, 6.5.

The diacetate crystallized from dilute alcohol in small glistening platelets of m.p. 121–122° [lit. m.p. 118–120° (4)].

Anal. Calc'd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0.
Found: C, 75.0; H, 6.1

3-Cyclohexyl-2-(p-anisyl)-6-methoxyindene. This compound was prepared from 2.68 g. of the ketone (XX) in 25.0 cc. of toluene and the required amount of cyclohexylmagnesium bromide. After refluxing at 110° for two and one-half hours, the complex was decomposed. The organic layer was dried and the solvent removed. The straw colored oil was crystallized from alcohol. The long white fibrous needles melted at 137–139°; yield, 55%.

Anal. Calc'd for $C_{23}H_{26}O_2$: C, 82.6; H, 7.8.
Found: C, 82.2; H, 7.8.

3-Phenyl-2-(p-anisyl)-6-methoxyindene. This compound was prepared as described above by addition of the ketone (XX) dissolved in toluene, to the Grignard reagent and decomposed in the usual manner. The solid, after removal of the solvent, was crystallized from alcohol. The long white fibrous needles, which turn pink on standing, melted at 115–117°; yield, 45%.

Anal. Calc'd for $C_{23}H_{20}O_2$: C, 84.2; H, 6.1.
Found: C, 84.0; H, 6.1.

alpha-(p-Anisyl)-gamma-(m-anisyl)-n-butyronitrile (XXXI). Sodium (3.13 g.) was added in small clean pieces to 100 cc. of liquid ammonia and 0.1 g. of ferric nitrate hexahydrate contained in a 500-cc. round-bottom flask. The deep blue color of the solution disappeared as soon as all of the sodium had reacted. To the mixture of sodamide was added, through the dropping-funnel, 20 g. of homoanisonitrile. A deep yellow color developed as the sodium salt was allowed to form during fifteen minutes. One hundred cubic centimeters of dry benzene was slowy added and the mixture refluxed on the steam-bath for three hours. The benzene was dark red in color and contained a suspension of the enolate. A solution of 29.2 g. of *m*-anisylethyl bromide in 50.0 cc. of benzene was added dropwise and the mixture refluxed for twenty hours. After washing with dilute hydrochloric acid, water, and drying over anhydrous sodium sulfate, the solvent was evaporated. The dark brown viscous oil was distilled and the fraction which boiled at 155–180°/.01 mm. was collected. The material was redistilled under vacuum and a very viscous lemon-colored oil came over at 198–203°/1 mm. The analytical sample was taken off at 199°/1 mm. and appeared colorless. The yield was 55%.

Anal. Calc'd for $C_{18}H_{19}NO_2$: C, 76.9; H, 6.8.
Found: C, 77.2; H, 6.9.

This compound has just recently been prepared by Mentzer and Urbain (23) who report the b.p. 205–210°/3 mm., but no yield.

alpha-(p-Anisyl)-gamma-(m-anisyl)butyric acid (XXXII). Thirty-one grams of the nitrile (XXXI) was dissolved in 125.0 cc. of alcohol. A solution of 62.0 g. of sodium hydroxide in 62.0 cc. of water was added. Two layers formed immediately and the mixture was refluxed for twenty-four hours. After dilution, the alcohol was evaporated and the cold solution acidified with dilute hydrochloric acid. The solid was filtered off and dissolved in dilute sodium carbonate solution. The latter was filtered from any undissolved material. The acid was precipitated and allowed to dry. It was crystallized from Skellysolve "D", m.p. 100–101°. Yield, 82%.

Anal. Calc'd for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7.
Found: C, 71.8; H, 6.7.

Dodds *et al.* (9) first prepared this compound by reducing *alpha*-(*p*-anisyl)-*beta*-(*m*-anisoyl)propionic acid *via* the Clemmensen procedure. They recorded the m.p. 98–99°.

2-(p-Anisyl)-6-methoxytetralone-1 (XXXIII). This compound was prepared from the acid (XXXII) in accordance with the direction of Dodds *et al.* (9); m.p. 124–126°. [Lit. 124–126° (9)]; yield, 80%.

2-(p-Hydroxyphenyl)-6-hydroxytetralone-1 (XXXIV). Demethylation of (XXXIII) was accomplished by dissolving 3.4 g. of the dimethoxy ketone in 75 cc. of glacial actic acid containing 75 cc. of concentrated hydrobromic acid (*d.* 1.49). The solution was refluxed for six hours, cooled and diuted with water. The granular precipitate was filtered off, washed with water and recrystallized from an alcohol-water mixture. The material melted at 266–271° with decomposition after darkening at 230°; yield, 73%.

Anal. Calc'd for $C_{16}H_{14}O_3$: C, 75.6; H, 5.5.
Found: C, 75.4; H, 5.8.

2-(p-Allyloxyphenyl)-6-allyloxytetralone-1 (XXXV). Two and one-half grams of XXXIV, 3.2 g. of allyl bromide, and 6 g. of anhydrous potassium carbonate were added to 25.0 cc. of dry acetone The mixture was refluxed on the steam-bath for eight hours and diluted with water. The acetone was boiled off; the residual oil taken up in ethyl acetate and dried over anhydrous sodium sulfate. After the solvent had been evaporated, the light yellow oil was dissoved in alcohol and refrigerated overnight. The colorless crystals melted at 69–70°; yield, 80%.

Anal. Calc'd for $C_{22}H_{22}O_3$: C, 78.6; H, 6.6.
Found: C, 78.5; H, 6.7.

1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxynaphthalene (XXXVIII). One gram of the diallyloxyketone (XXXV) was dissolved in 10 cc. of dry benzene and added through a dropping-funnel to a Grignard reagent prepared from 0.072 g. of magnesium and 0.33 g. of ethyl bromide in ether. The solution turned yellow and a precipitate began to form immediately. The ether was distilled off and the mixture refluxed for three hours. It was decomposed in the usual way with ice cold 20% sulfuric acid. The benzene layer was separated, washed. and dried over anhydrous sodium sulfate. After evaporating the solvent, the light brown oil was taken up in alcohol and cooled The precipitate was filtered and recrystallized from alcohol The white platelets melted at 130–32°. Yield, 1–2%

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.6; H, 7.0.
Found: C, 83.2; H, 6.9.

1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxy-1,2,3,4-tetrahydronaphthalene (XXXVI) or *1-Ethyl-2-(p-allyloxyphenyl)-6-allyloxy-3, 4-dihydronaphthalene* (XXXVII). After removal of the naphthalene derivative the alcohol solution was concentrated and refrigerated overnight. A second crop of crystals was obtained and these were also recrystallized from alcohol; m.p. 67–78°. Yield, 1–2%.

Anal. Calc'd for $C_{24}H_{26}O_2$: C, 83.2; H, 7.5.
Found: C, 83.0; H, 7.6.

Attempt to use alpha-chlorohomoanisonitrile in the Reformatsky reaction. A mixture of 3.04 g. of *p*-methoxypropiophenone, 3.62 g. of *alpha*-chlorohomoanisonitrile, 1.57 g. of zinc, and 15.0 cc. of dry benzene was refluxed on the steam-bath for one hour. The solution was separated from unreacted zinc and added to a cold dilute sulfuric acid solution. The benzene layer was separated, washed with water and finally dried over sodium sulfate. The solution was filtered and the solvent evaporated. The remaining oil was dissolved in alcohol and a solid precipitated on cooling. By recrystallization from alcohol a crop of fine colorless needles was obtained, melting at 230–230.5°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: C, 74.0; H, 5.5.
Found: C, 74.1; H, 5.7.

The substance therefore appears to be *alpha,beta*-di-(*p*-anisyl)succinonitrile (XXIX).

Attempt to alkylate desoxyanisoin with beta-bromodiethyl ether. Sodium (0.9 g.) was dissolved in 20 cc. of absolute alcohol. Five grams of desoxyanisoin was added followed by 30.0 cc. of dry benzene. The mixture was distilled on the steam-bath until the temperature read 82°, the original volume being maintained by frequent addition of benzene. Six and two-tenths grams of *beta*-bromodiethyl ether was added all at once and the mixture refluxed until neutral to litmus. The reaction mixture was washed with water and the benzene layer separated and dried. After removal of the solvent the oil was taken up in hot acetic acid, from which glistening platelets precipitated on cooling. Upon recrystallization from this latter solvent the crystals melted at 211.5–212°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.6.
Found: C, 79.7; H, 6.6.

These constants agree with those in the literature for di-anisal (4,4′-dimethoxystilbene, XLI) (22).

Ethyl-beta-hydroxy-beta-(p-anisyl)-gamma-ethyl-gamma-(p-anisyl)butyrate (XLIII). A mixture of 5 g. of *alpha*-ethyldesoxyanisoin (XLII), 3.5 g. of ethyl bromoacetate, 1.3 g. of zinc, and 25 cc. of benzene was refluxed on the steam-bath for two hours. When most of the zinc had gone into solution, the reaction mixture was filtered and treated with 20% iced sulfuric acid until the solid matter which first appeared redissolved. The benzene layer was separated, washed with water, dried over sodium sulfate, and filtered. After the solvent had been removed, the oil was taken up in alcohol and cooled. The crystals were filtered and recrystallized from alcohol. Yield, 45%; m.p. 82–83°.

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 71.0; H, 7.5.
Found: C, 70.9; H, 7.5.

beta-(p-Anisyl)-gamma-ethyl-gamma-(p-anisyl)-beta-butenoic acid (XLIV). Five-tenths gram of (XLIII) was added in small portions to 5 cc. of cold concentrated sulfuric acid. A deep red solution resulted immediately and stirring was continued for fifteen minutes in the cold and for an equal length of time at room temperature. The solution was poured into ice-water, and the gum which separated extracted with ether. The ether solution was washed, dried, filtered, and the solvent evaporated. The resulting glass was refluxed for thirty minutes with 20% sodium hydroxide solution followed by filtration and acidification to Congo red paper. The precipitate was extracted with ether and the organic layer washed with water. It was dried and the solvent evaporated. The oil soon solidified and was recrystallized from alcohol yielding colorless crystals of m.p. 145–146°.

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8.
Found: C, 73.2; H, 6.8.

SUMMARY

1. The synthesis of indene and dihydronaphthalene derivatives, structurally related to stilbestrol, is described.

2. The path followed is that originally blazed by Plentl and Bogert for the synthesis of the corresponding tricyclic hydrocarbons. The processes used, and the products obtained, are compared with the recent work of Salzer, and of Solmssen, in this same field.

3. Experimental proof is supplied as to the structure of the indanones obtained by cyclization of the *beta*-(*m*-anisyl)propionic acids.

4. The 3-ethyl-2-(*p*-hydroxyphenyl)-6-hydroxyindene has been prepared analytically pure.

5. Corroborative identification of some of Salzer's products is reported.

6. The action of zinc upon a benzene solution of *p*-methoxypropiophenone and *alpha*-chlorohomoanisonitrile, results in the formation of di-(*p*-anisyl)succinonitrile.

7. Allyl ethers of 1-ethyl-2-(*p*-hydroxyphenyl)-6-hydroxy-3,4-dihydro-(or 1,2,3,4-tetrahydro-) naphthalene, are not split by phenyllithium in ether solution.

8. Desoxyanisoin, subjected to the action of *beta*-bromodiethyl ether, in the presence of sodium ethoxide, yields di-anisal.

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