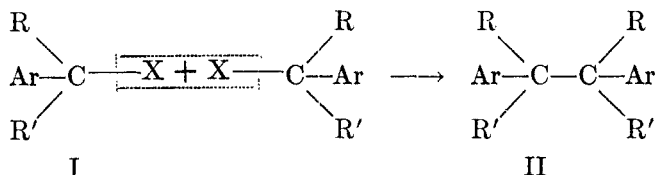


THE REACTION OF α -HALOGENATED ARYLALKANES WITH
METAL POWDERS IN HYDROXYLATED MEDIA¹

NG. PH. BUU-HOÏ² AND NG. HOÃN

Received March 7, 1949

One problem most frequently encountered in preparative organic chemistry is the removal of the halogen atom from α -halogenated arylalkanes with coupling of the remaining radical, resulting in the formation of symmetrical diarylalkanes (I) according to the following scheme:



Two important methods have hitherto been devised to meet this problem: 1. The use of alkali or earth-alkali metals in anhydrous media (especially ethyl ether) as was originated by Wurtz and Fittig, some modifications being introduced later by different authors (1) who recommended the use of various metals (Al, Mg, Zn) or alloys (such as the liquid alloy of potassium and sodium); 2. The excellent method of Kharasch and his co-workers (2) based upon the reduction of Grignard compounds by cobaltous chloride with subsequent dimerization of the free radicals thus liberated.

Although these methods have proven to be of the greatest value for various syntheses, they both require the use of anhydrous solvents, with all the inconveniences inherent in that technique. The second method necessitates also the intervention of very low temperatures, while yields obtained by the former are generally low in the case of arylalkanes bearing halogens adjacent to a secondary or tertiary carbon; these lose a molecule of halogen acid easily in the presence of strong electropositive metals under anhydrous conditions.

A few years ago, Ogata, Turuta, and Oda (3) found that benzyl and benzal chlorides could be reacted in aqueous medium with iron powder to give dibenzyl and stilbene. Although it has no special significance for the preparation of the substances cited, this observation prompted us to investigate the possibility of using iron, as well as other more or less active metal and alloy powders in aqueous or other hydroxylated media for the synthesis of symmetrical diarylalkanes and diarylethylenes not readily prepared through routine methods. Since our work began, Sisido and Nozaki (4) have reported the preparation with low yields (ranging from 5 to 15%) of 2,3-diphenylbutane, 3,4-dianisylhexane, and two

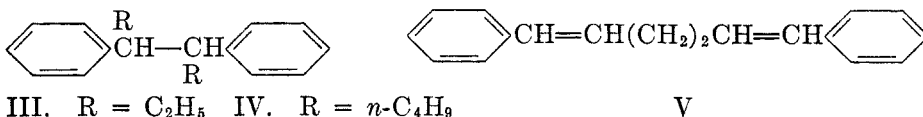
¹ This paper is part of a more general investigation into estrogenic substances. For earlier reports, see (25).

² Full postal address, 26, Rue d'Ulm, Paris (V*), France.

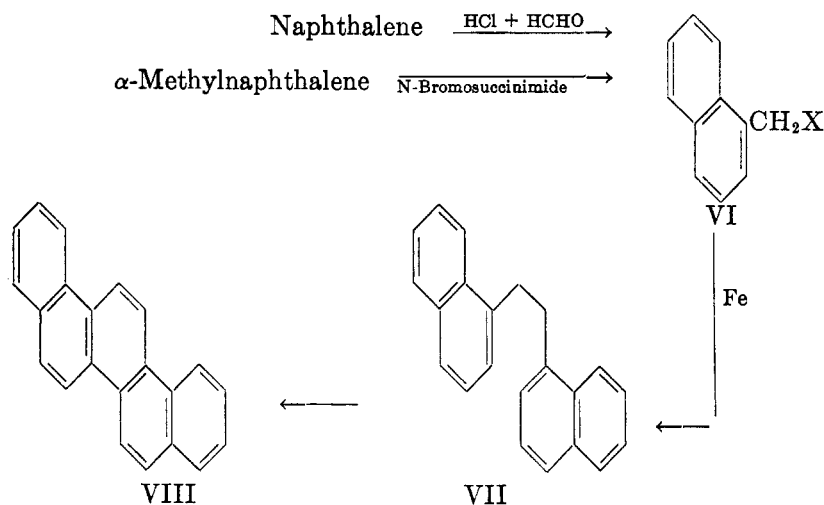
analogous compounds by treatment of the appropriate α -chloro- or α -bromo-arylalkanes with iron powder in hot water.

The present work records the results we have obtained in numerous syntheses of symmetrical diarylalkanes (II), using a great variety of chloro- and bromo-compounds of type (I), and many metal or alloy powders, some of which were even superior to the initial iron powder. In some standard cases, the influence of temperature, solvents, and catalysts has also been ascertained. It was found that upon the choice of the metal and quality of samples used, and of the experimental conditions, depend not only the yields but also the nature of the reaction-products. All the substances, the syntheses of which are reported here, and many of which were hitherto unknown, have to a greater or lesser degree some biological interest, either on account of their own physiological activity, or of their connection with natural products.

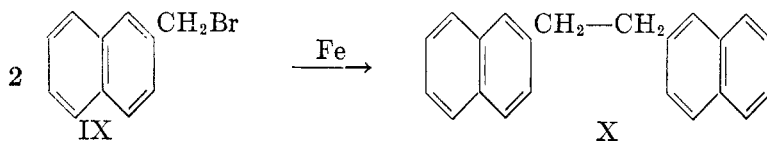
Synthesis of hydrocarbons. *meso*-3,4-Diphenylhexane (III), a key substance in the chemistry of synthetic hormonal compounds, and weakly estrogenic itself (5), was readily obtained along with its racemic isomer, by the coupling of α -chloropropylbenzene ($C_6H_5CHClCH_2CH_3$), under the influence of hydrogen-reduced iron powder. α -Chloroamylbenzene ($C_6H_5CHCl(CH_2)_3CH_3$), gave under the same conditions a mixture of a liquid 5,6-diphenyldecane (which we assume to be the racemic compound), with a solid isomer, presumably *meso*-5,6-diphenyldecane (IV). Coupling of cinnamyl chloride was also achieved, giving a complex mixture of many hydrocarbons, from which small quantities of dicinnamyl (V) could be isolated in a pure state. It may be observed that the foregoing substance has recently been identified as the *trans,trans*-derivative by Koch (6), who obtained it by treatment of cinnamyl chloride with magnesium.



In the naphthalene series, 1,2-di-(α, α' -naphthyl)ethane (VII) was easily made either from α -chloromethylnaphthalene (VI, X = Cl) [readily obtainable from naphthalene and formaldehyde in 60% yield, following routine methods (7)], or even better from α -bromomethylnaphthalene (VI, X = Br) [readily prepared by side-chain bromination of α -methylnaphthalene according to Buu-Hoï and Lecocq (8)]. As 1,2-di-(α, α' -naphthyl)ethane is easily convertible into picene under the dehydrogenating influence of aluminum chloride, following the Ruzicka-Hösli reaction (9), these observations offer a convenient three-step synthesis of picene (VIII) from naphthalene or α -methylnaphthalene in at least 10% over-all yield. As it is known that dimethylnaphthalenes are very readily converted into side-chain monobromo compounds (8, 10), our synthesis provides a means of preparing various dimethylpicenes, some of them being of biological significance through their connection with the triterpenes and with the carcinogenesis problem. This modification of the Ruzicka picene synthesis represents an important simplification over the original procedure which started from α -tetralone and β -1-naphthylethanol (11).

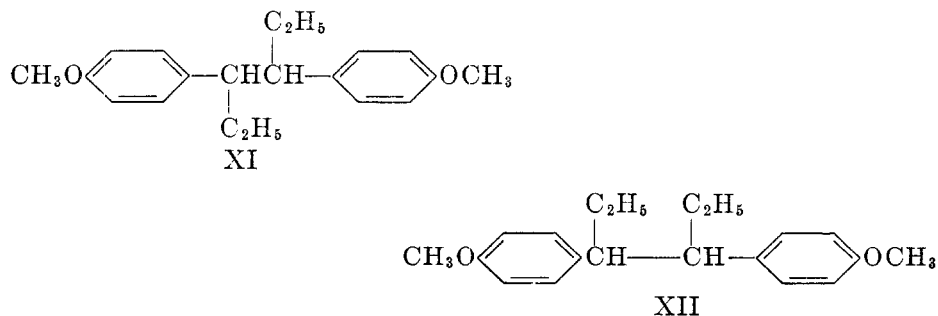


Also in the naphthalene series, we obtained with satisfactory yield 1,2-di-(β, β' -naphthyl)ethane (X) from β -bromomethylnaphthalene (IX), prepared by side-chain bromination of β -methylnaphthalene with N-bromosuccinimide (12).



1,2-di-(β, β' -naphthyl)ethane could be expected to yield 3,4,5,6-dibenzo-phenanthrene, a slightly carcinogenic, rare hydrocarbon (13), upon treatment with aluminum chloride, but no conclusive results have yet been obtained in that respect.

Synthesis of dl- and meso-3,4-dianisylhexane. Sisido and Nozaki (4) reported a 10% yield of *meso*-3,4-dianisylhexane (XI) on treatment of anethole hydrochloride with iron powder in a mixture of ligroin and hot water, and a 15% yield of the same product when anethole hydrobromide was used. No mention of racemic 3,4-dianisylhexane was made on this occasion. We have found that by



using very fine, hydrogen-reduced iron and introducing slight modifications

into the technique of the Japanese workers, we nearly doubled the yield of *meso*-3,4-dianisylhexane from anethole hydrochloride, and that amounts of the *dl*-isomer (generally obtained in an oily state, which is due to the presence of the dissolved *meso*-form) roughly equivalent to those of the *meso*-compound were always encountered when iron was the reagent, so that a 40% conversion of anethole into 3,4-dianisylhexanes could thus be achieved in aqueous medium. This latter point is of practical importance considering the possibility of stereomutation of XII into XI under the influence of certain catalysts, such as hydrogen sulfide or iodine (14) or ultraviolet irradiation.

Replacement of reduced iron by Raney alloy enhanced the yield of each isomer to about 21%, and if Raney nickel was used, 25% of the *meso*-compound was reached, at the expense of the *dl*-form. Addition to iron powder of iodine as a catalyst produced a slightly favorable effect, while other substances such as cobalt or nickel chloride had apparently no such effect.

A remarkable feature of this coupling reaction is that the *dl-meso* ratio could be augmented by the replacement of the foregoing active metals or alloys by relatively "weak" ones. For instance, the yields of *meso* registered with Devarda's alloy, zinc, and magnesium powder were considerably lower than those of the racemic form, and even in the case of hydrogen-reduced copper powder, no traces of the crystalline *meso* could be isolated, whereas the *dl*-compound was obtained in high yield and in spontaneous crystalline condition. The favorable effect of copper upon the formation of *dl*-3,4-dianisylhexane was also perceptible when the zinc-copper couple was used, the amount of *meso* obtained being smaller than in the case of pure zinc powder. It may be mentioned that addition to water of other hydroxylated solvents, such as alcohols, did not give any interesting results.

Methylmagnesium iodide has been recommended by Sisido and Nozaki (4) for the demethylation of *meso*-3,4-dianisylhexane, but we have found for that purpose a most convenient device in the use of pyridine hydrochloride.

Recent investigations suggest that the activity of stilbestrol and other estrogenic substances for the control of prostatic cancer does not run strictly parallel to their estrogenic potency as measured by the Allen-Doisy test (15). This led us to a quest for substances with structures closely related to stilbestrol or hexestrol, but with little or no estrogenic properties. The preparation of a series of new ethers of hexestrol listed in Table I was part of that scheme of research. They are now under clinical investigation by Professor Lacassagne and Dr. Corre, especially in cancer of the lung. Unlike the stilbestrol series, in which many ethers are known, only a few ethers of hexestrol have hitherto been prepared and tested for estrogenic potency (16).

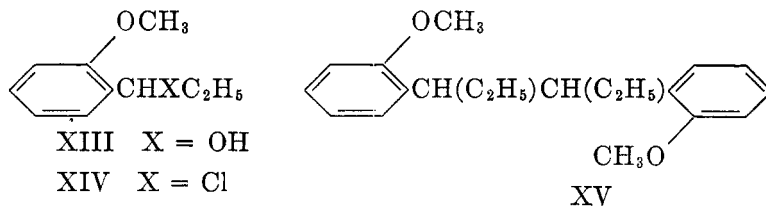
Synthesis of isomers and homologs of the 3,4-dianisylhexanes. Coupling of α -chloroaryllkanes by metal powders in aqueous medium was found to be a convenient way to obtain a series of isomers and homologs of *dl*- and *meso*-dianisylhexane, which were intermediates in the synthesis of isomers and homologs of hexestrol. These latter were required for biological investigation in the line of medical research indicated in the preceding section.

o-(α -Hydroxypropyl)anisole (XIII), obtained from *o*-methoxybenzaldehyd and ethylmagnesium bromide, was converted by dry hydrogen chloride into *o*-(α -chloropropyl)anisole (XIV), and this underwent the usual coupling reaction with iron powder or Raney nickel to give a mixture of a *liquid* and a *solid* 3,4-di-(*o*-methoxyphenyl)hexane (XV). By analogy with the *para*-isomers, we assign

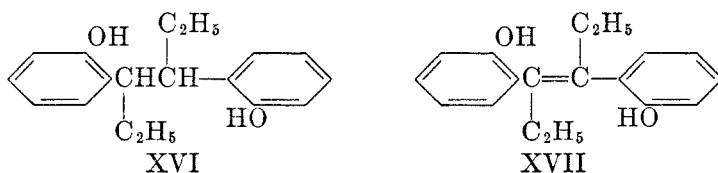
TABLE I
NEW DIETHERS OF HEXESTROL
 p - $\text{ROC}_6\text{H}_4\text{CH}(\text{C}_2\text{H}_5)\text{CH}(\text{C}_2\text{H}_5)\text{C}_6\text{H}_4\text{OR}-p$

R	FORMULA	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
Ethyl.....	$\text{C}_{22}\text{H}_{30}\text{O}_2$	133	80.9	9.2	81.1	9.3
<i>n</i> -Propyl.....	$\text{C}_{24}\text{H}_{34}\text{O}_2$	110	81.3	9.6	81.2	9.6
Isopropyl.....	$\text{C}_{24}\text{H}_{34}\text{O}_2$	115	81.3	9.6	81.2	9.8
Isobutyl.....	$\text{C}_{26}\text{H}_{38}\text{O}_2$	109	81.6	9.9	81.6	10.1
Isoamyl.....	$\text{C}_{28}\text{H}_{42}\text{O}_2$	83	81.9	10.2	81.8	10.1
<i>n</i> -Hexyl.....	$\text{C}_{30}\text{H}_{46}\text{O}_2$	73	82.2	10.5	82.1	10.6
<i>n</i> -Octyl.....	$\text{C}_{34}\text{H}_{54}\text{O}_2$	66	82.5	10.9	82.4	10.8
<i>n</i> -Decyl.....	$\text{C}_{38}\text{H}_{62}\text{O}_2$	57	82.8	11.4	82.4	11.2
<i>n</i> -Dodecyl.....	$\text{C}_{42}\text{H}_{70}\text{O}_2$	79	83.1	11.6	83.3	11.6
<i>n</i> -Tetradecyl.....	$\text{C}_{46}\text{H}_{78}\text{O}_2$	65	83.3	11.7	83.2	11.7
<i>n</i> -Hexadecyl.....	$\text{C}_{50}\text{H}_{86}\text{O}_2$	72	83.5	12.0	83.3	12.2
<i>n</i> -Octadecyl.....	$\text{C}_{54}\text{H}_{94}\text{O}_2$	92	83.6	12.2	83.6	12.3
Benzyl.....	$\text{C}_{32}\text{H}_{34}\text{O}_2$	219	85.3	7.5	85.2	7.6
<i>p</i> -Chlorobenzyl.....	$\text{C}_{32}\text{H}_{32}\text{Cl}_2\text{O}_2$	194	73.9	6.1	73.6	6.2
2,5-Dimethylbenzyl.....	$\text{C}_{36}\text{H}_{42}\text{O}_2$	198	85.4	8.3	85.8	8.6
β -Phenylethyl.....	$\text{C}_{34}\text{H}_{38}\text{O}_2$	119	85.3	8.0	85.6	8.0
γ -Phenylpropyl.....	$\text{C}_{36}\text{H}_{42}\text{O}_2$	157	85.4	8.3	85.6	7.2
α -Naphthylmethyl.....	$\text{C}_{40}\text{H}_{38}\text{O}_2$	233	87.2	6.9	87.0	7.0
Cinnamyl.....	$\text{C}_{36}\text{H}_{38}\text{O}_2$	180	86.0	7.8	86.2	7.9

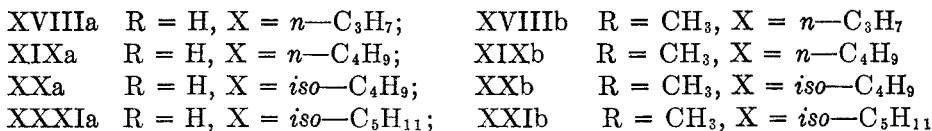
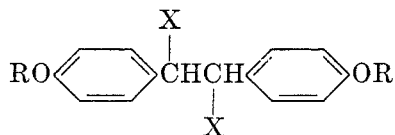
the racemic structure to the liquid, and the *meso*-structure to the solid. De-



methylation of the latter with pyridine hydrochloride readily yielded *meso*-3,4-di-(*o*-hydroxyphenyl)hexane (XVI), ("Orthohexestrol"). It may be recalled in that respect that the analog of this compound in the stilbestrol series, 2,2'-dihydroxy- α,β -diethylstilbene (XVIII), already prepared by Dodds, *et al.* (17), is considerably less estrogenic than the *para*-isomer.

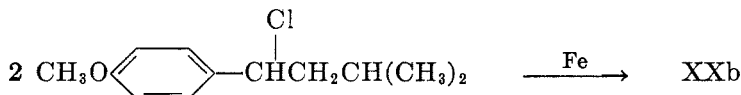


A drop in potency has also been recorded by the preceding authors when the two ethyl groups in hexestrol are replaced by *n*-propyl groups, resulting in *meso*-4,5-di-(*p*-hydroxyphenyl)octane (XVIIIa). This substance was prepared with great difficulty by hydriodic acid demethylation of the solid dimethyl ether (XVIIIb) obtained in the catalytic hydrogenation of 4,4'-dimethoxy- α,β -di-*n*-propylstilbene, along with a liquid isomer. We prepared (XVIIIb) much more conveniently from *p*-(α -hydroxybutyl)anisole following the normal sequence of reactions, and its demethylation with pyridine hydrochloride gave (XVIIIa)



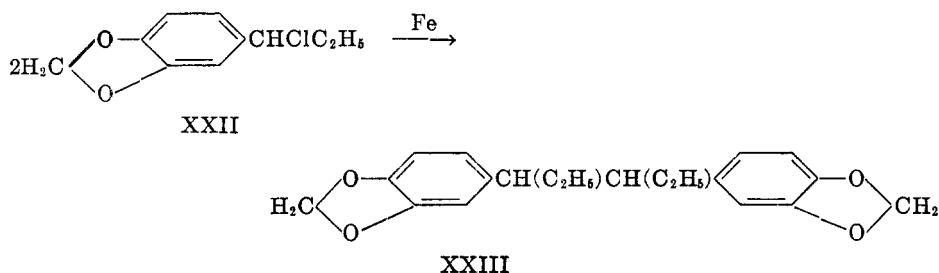
in very high yield. A liquid isomer, apparently identical with that of Dodds, *et al.* was also encountered during the preparation of (XVIIIb), and its demethylation gave the *liquid* 4,5-di-(*p*-hydroxyphenyl)octane mentioned by the above authors.

Following a similar procedure, and starting from *p*-(α -chloroamyl)anisole by saturating with hydrogen chloride either 4-methoxy- β -*n*-propylstyrene or *p*-(α -hydroxyamyl)anisole (both obtained from anisaldehyde and *n*-butylmagnesium bromide), we prepared a *solid* 5,6-di-(*p*-hydroxyphenyl)decane, believed to be the *meso*-form (XIXa), *via* a *solid* 5,6-dianisyldecane (XIXb). The latter was accompanied by a high proportion of a *liquid* isomer, which was demethylated to a *liquid* 5,6-di-(*p*-methoxyphenyl)decane. It is remarkable that coupling of *p*-(α -chloroisoamyl)anisole [prepared from anisaldehyde and isobutylmagnesium bromide and subsequent hydrogen chloride treatment either of the carbinol itself or of its dehydration product, 4-methoxy- β -isopropylstyrene *p*-CH₃OC₆H₄—CH=CHCH(CH₃)₂] yielded an unusually high proportion of a *solid* 2,7-dimethyl-4,5-dianisyldecane, probably (XXb), with only minute quantities of the *liquid* isomer expected. This is probably a steric effect due to the branching of the two molecules of *p*-(α -chloroisoamyl)anisole to be coupled, the *meso*-configuration being thus favored at the expense of the sterically hindered racemic form.



Also consistent with this view is our failure to obtain any significant amount of coupling product from *p*-(α -chloroisobutyl)anisole $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CHClCH}(\text{CH}_3)_2$. On the contrary, *p*-(α -chlorohexyl)anisole [prepared by addition of hydrogen chloride to 4-methoxy- β -isoamylstyrene $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}=\text{CH}(\text{CH}_2)_2\text{CH}(\text{CH}_3)_2$] gave good yields of a coupling product, which could not be resolved into a *meso*- (XXIb) and a *dl*-isomer, although demethylation produced a solid diphenol, probably *meso*-2,9-dimethyl-5,6-di-(*p*-hydroxyphenyl)decane (XXIa). *p*-(α -Chlorohexyl)anisole $p\text{-CH}_3\text{C}_6\text{H}_4\text{CHCl}(\text{CH}_2)_4\text{CH}_3$ also gave high yields of a liquid coupling product, probably a mixture of *dl*- and *meso*-6,7-dianisyldecane.

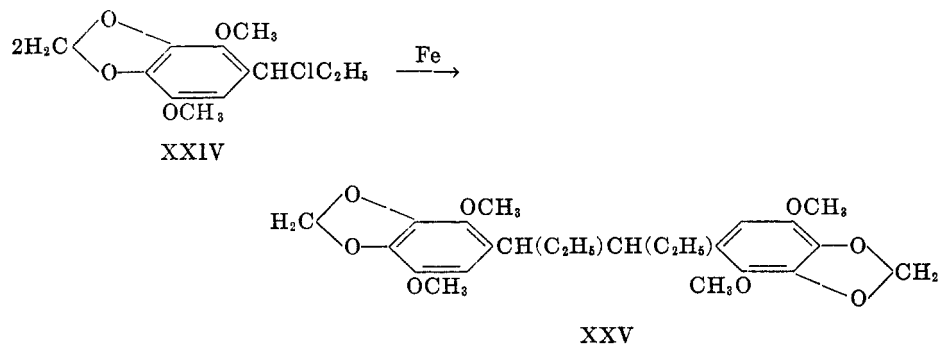
Coupling of chloro derivatives of polyphenol ethers. The coupling reaction of α -chloroarylkanes by metal powders in aqueous medium can be extended to the syntheses of complicated molecules such as those bearing fragile ether groups.



The adduct (XXII) of one molecule of hydrochloric acid to isosafrole was thus readily converted into a mixture of a liquid and a solid 2,3-di-(*m*,*p*-methylenedioxyphenyl)hexane (XXIII). For reasons of analogy, we assign the *meso*-structure to the solid isomer, which could thereby be related to the 3,4-(*m*,*p*-dihydroxyphenyl)hexane m.p. 231–232°, already prepared by Short (18).

The adduct (XXIV) of hydrochloric acid and isoapiole similarly underwent a coupling reaction, giving a mixture of 2,3-di-(2,5-dimethoxy-3,4-methylenedioxyphenyl)hexanes (XXV), from which a small amount of a *solid* substance believed to be the *meso*-form could be isolated.

The results of the biological investigations undertaken by Professor A. Lacasagne and Dr. I. Corre upon the substances described in this paper will be published elsewhere.



EXPERIMENTAL

Coupling of α -chloropropylbenzene. This substance (120 g.) was obtained in 98% yield by saturating ethylphenylcarbinol with dry hydrogen chloride at room temperature; the organic layer was decanted from the water formed, and washed thoroughly three times with iced-water. It was then added in small portions to a well-stirred mixture of pure hydrogen-reduced iron powder (60 g.) (purchased from Rhône-Poulenc, and obtained from the pure oxide by reduction with hydrogen at low temperature), and water heated to about 90–95° (250 ml.). A lively reaction set in accompanied by coloration of the water to pale green; following the addition, the mixture was boiled for thirty minutes. After cooling, the iron powder in excess was filtered off, washed with benzene, and the two-layer filtrate thoroughly extracted with the same solvent. The solvent was removed, and the residue vacuum-distilled. The forerun (50 g.) consisted mainly of propenylbenzene (bromine-test) and unchanged α -chloropropylbenzene, and was followed by 22 g. of the coupling product, b.p. 170–176°/13 mm. This partly solidified in the refrigerator, giving 6 g. of *meso*-3,4-diphenylhexane, crystallizing from methanol in colorless, shiny rods, m.p. 88–89° [the melting points recorded in the literature vary from 83–84° (19) to 93° (20)]. After some time in the refrigerator, the filtrate again deposited 1.5 g. of that compound; the remaining liquid was then rectified, giving 12 g. of a colorless oil, b.p. 170–172°/13 mm., considered to be the *dl*-isomer. The yields of 3,4-diphenylhexanes were slightly higher when α -bromopropylbenzene (prepared by bubbling dry hydrobromic acid into ice-cooled ethylphenylcarbinol) was used for coupling.

Coupling of α -chloroamylbenzene. Butylphenylcarbinol (120 g.) was saturated with dry hydrogen chloride, and the α -chloroamylbenzene thus obtained was treated with iron powder (55 g.) in hot water as above. The reaction was much less perceptible than for the lower homolog. Yield, 6 g. of coupling product, b.p. 200–205°/15 mm., which yielded 2 g. of a solid after prolonged standing at –10° in methanol. After recrystallization from acetone, long colorless, shiny needles, m.p. 77°, probably *meso*-diphenyldecane, were obtained.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.8; H, 10.2.

Found: C, 89.7; H, 10.4.

The liquid isomer (3.5 g.) was a colorless, rather fluid oil, b.p. 200–203°/15 mm.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.8; H, 10.2.

Found: C, 89.8; H, 10.5.

Redistillation of the forerun obtained in this experiment gave 100 g. of pure α -chloroamylbenzene in the form of a mobile, colorless liquid, b.p. 130–135°/15 mm.; decomposing on boiling at ordinary pressure.

Anal. Calc'd for $C_{11}H_{15}Cl$: C, 72.3; H, 8.2.

Found: C, 72.1; H, 8.1.

Coupling of cinnamyl chloride. When 125 g. of the chloride, b.p. 225–228°/17 mm., was treated in the usual way with 60 g. of iron powder in hot water (200 ml.) there was little apparent reaction. After working up the mixture in the usual manner, 35 g. of a higher-boiling fraction was obtained in the form of a very viscous, brown-yellow oil, b.p. 205–220°/10 mm., which crystallized partially; the solid was recrystallized from alcohol, giving *trans-trans*-dicinnamyl in the form of glistening, colorless leaflets, m.p. 81–82°. After a prolonged stay in the refrigerator, the mother liquors yielded a further crop of the same compound (yield, 6 g.). No attempts were made to isolate pure isodicinnamyl.

1,2-Di-(α,α' -naphthyl)ethane (VII). (a) α -Chloromethylnaphthalene (26 g.) was treated with a great excess of iron powder (20 g.) in boiling water (100 ml.) for two hours. The reaction product was taken up in benzene, and gave, after the usual treatment, 17 g. of unchanged α -chloromethylnaphthalene (b.p. 158–160°/13 mm.) and 5 g. of 1,2-di-(α,α' -naphthyl)ethane, b.p. 275–278°/13 mm., crystallizing from a mixture of alcohol and benzene in colorless prisms, m.p. 161–162° [Bamberger and Lodter (21) described this compound as yellow-green plates, m.p. 160°].

(b) α -Bromomethylnaphthalene (10 g.) was prepared from α -methylnaphthalene and N-bromosuccinimide in the presence of some benzoyl peroxide and in carbon tetrachloride solution (yield, over 75%); treated as above with iron powder, it gave 4 g. of 1,2-di-(α,α' -

naphthyl)ethane. Similar results were obtained when Raney nickel was substituted for iron powder.

A solution of 10 g. of the latter compound in 50 ml. of carbon disulfide was boiled for two hours on the water-bath with 20 g. of finely powdered aluminum chloride. The mixture obtained was poured on to ice, and the semi-solid material formed was extracted with chloroform; the organic layer was dried over sodium sulfate, the solvents removed, and the residue crystallized from xylene, giving *picene* in the form of needles, m.p. 365°. The mother liquors from this operation gave on vacuum-distillation some unchanged dinaphthylethane and then a further quantity of *picene* (total yield, 4 g.).

1,2-Di-(β,β' -naphthyl)ethane (X). β -Bromomethylnaphthalene (10 g., prepared from β -methylnaphthalene and N-bromosuccinimide as for the α -isomer), treated as above with 10 g. of iron powder, yielded 5 g. of 1,2-di-(β,β' -naphthyl)ethane, crystallizing from benzene in colorless prisms, m.p. 255° [Bamberger and Lodter (21) gave m.p. 253°]. After treatment with aluminum chloride in carbon disulfide solution for two hours, this compound was partly changed into a mixture of many high-boiling hydrocarbons, the constitution of which is being investigated.

COUPLING OF *p*- α -CHLOROPROPYLANISOLE

This compound was prepared in almost quantitative yield by saturating ice-cooled ethyl-anisylcarbinol mixed with some petroleum ether (b.p. 50–90°) with dry hydrochloric acid; the addition of hydrogen chloride to anethole is nevertheless a more convenient method, although the yields of *p*- α -chloropropylanisole are substantially lower. The yield of the addition could be increased by certain catalysts such as stannous chloride.

(a) *By hydrogen-reduced iron powder*. An ice-cooled mixture of 200 g. of crystallized anethole and 40 ml. of petroleum ether was saturated with dry hydrogen chloride and the dark colored liquid obtained was thoroughly washed with iced water, which produced decoloration into pale pink. The liquid was added in small portions (10 ml.) to a well-stirred mixture of 80 g. of hydrogen-reduced iron powder and 1,000 ml. of water previously heated at 75–80°; a lively reaction was noticeable after each addition, most of the petroleum ether being allowed to distil off. After the addition, the reaction mixture was boiled for 30 minutes and then left overnight at 2°. The upper organic layer had by then partly solidified; the *meso*-2,3-dianisylhexane and the iron powder in excess were filtered off and XI separated by extraction with benzene; evaporation of the solvent and crystallization of the residue from methanol gave 17 g. of the *meso*-compound, m.p. 147–148°. The filtrate was extracted with benzene, the solvent removed, and the remaining oil vacuum-distilled. After the forerun (50 g. of anethole, b.p. 232°, containing some propylanisole, b.p. 212–218°), 62 g. of an oil was obtained, b.p. 222–235°/13 mm., which partly solidified, giving a further crop of XI; the remaining oil was dissolved in methanol, and the mixture kept some time in the refrigerator, yielding a third crop of XI (total yield, 36 g.). The filtrate from this operation was distilled, and 41 g. of the racemic compound, b.p. 225–230°/13 mm. was thus obtained. Attempts to increase the yields by addition of cobalt or nickel chloride (1 g.) did not succeed, nor did the addition of alcohol or dioxane. Addition of iodine (0.5 g.) or substitution of anethole hydrobromide for α -chloropropylanisole raised the yield to about 45% of a mixture of roughly equal amounts of the two forms.

In the following experiments, the weight of reagents is the same as above. As in the case of iron, the dispersion grade and the quality of the metal or alloy powder has an important influence upon the yields. Unless otherwise stated, the *dl*-form referred to was not quite pure and therefore remained in the liquid state.

(b) *By aluminum powder*: the reaction was very energetic, but the mixture of isomers obtained (35 g.) yielded little of the *meso*-form.

(c) *By Raney alloy*: yield, 41 g. of the *meso*-form (m.p. 148°) and 42 g. of the *dl*-form; 35 g. of anethole recovered.

(d) *By Raney nickel catalyst*: yield, 50 g. of the *meso*-form and 16 g. of the *dl*-form.

(e) *By Devarda's alloy*: yield, 19.5 g. of the *meso*-form, and 40 g. of the *dl*-form.

(f) *By magnesium powder*: the reaction was extremely violent, and yielded 83 g. of an oil consisting mainly of the *dl*-form.

(g) *By zinc powder*: the reaction was hardly noticeable at 80°, and the mixture of reagents was therefore boiled for two hours; yield, 15 g. of the *meso*-form and 20 g. of the *dl*-form.

(h) *By zinc-copper couple* (zinc powder + copper sulfate): the reaction was violent, and yielded 31 g. of the *meso*-form and 48 g. of the *dl*-form. Very little anethole (8 g.) was recovered.

(i) *By hydrogen-reduced copper powder*: the reaction was a considerably weaker one and yielded an oil which rapidly solidified in the refrigerator. After recrystallizations from methanol or ligroin, the solid *dl*-form (50 g.) was obtained in colorless prisms, m.p. 49–53° [Dodds, *et al.* (17) gave m.p. 56–57° for a sample prepared by methylation of *dl*-3,4-dianisylhexane (m.p. 128°)]; 105 g. of anethole was recovered.

Demethylation of meso-3,4-dianisylhexane. A mixture of 300 g. of anhydrous pyridine hydrochloride and 100 g. of *meso*-3,4-dianisylhexane was gently refluxed until the supernatant layer had disappeared. Heating was continued for ten minutes, and the hot reaction product was poured into 1 l. of well-stirred iced-water. The almost colorless solid thus obtained was filtered, thoroughly dried, and crystallized from benzene, giving *meso*-3,4-di-(*p*-hydroxyphenyl)hexane, m.p. 187° [the literature (17) gives m.p. 184–185°, in 92% yield.

Preparation of diethers of hexestrol. The diethyl ether was prepared by adding the calculated amount of diethyl sulfate (2 mol.) to a solution of hexestrol in a slight excess of 20% aqueous NaOH. The precipitate obtained was recrystallized from ethanol. The other diethers were prepared by refluxing for two to four hours a mixture of the alkyl or arylalkyl bromide involved and hexestrol, dissolved in a slight excess of 20% alcoholic potassium hydroxide. The reaction product was poured into an excess of slightly alkaline water, and the precipitate recrystallized from ethanol for the dialkyl ethers, and from toluene for the diarylalkyl ethers, which are generally scarcely soluble in ethanol. In all cases, colorless prisms were obtained in at least 90% yield. A solid diether was also obtained from *N*-diethylaminoethyl chloride by the same procedure.

Synthesis of "orthohexestrol". Ethyl-*o*-anisylcarbinol was prepared in 82% yield from *o*-methoxybenzaldehyde and ethylmagnesium bromide in the usual way. The carbinol (100 g.) was mixed with 100 ml. of petroleum ether and saturated at –5° with dry hydrogen chloride. The coupling of 1- α -chloropropyl-2-methoxybenzene was effected with iron powder (50 g.) according to the usual procedure. Yield, 17 g. of an oil, b.p. 196–202°/13 mm., which partly solidified in the refrigerator, yielding 3.5 g. of a substance believed to be *meso*-3,4-di-(*o*-methoxyphenyl)hexane. This crystallized from methanol in fine, colorless needles m.p. 102°; the filtrates yielded after some standing at 0° a further crop of the same compound (0.5 g.).

Anal. Calc'd for C₂₀H₂₆O₂: C, 80.5; H, 8.7.

Found: C, 80.3; H, 8.8.

The remaining oil was rectified, giving 12 g. of a pale yellow viscous liquid, b.p. 195–202°/13 mm., believed to be *dl*-3,4-di-(*o*-methoxyphenyl)hexane.

Anal. Calc'd for C₂₀H₂₆O₂: C, 80.5; H, 8.7.

Found: C, 80.4; H, 8.9.

Demethylation of meso-3,4-di-(o-methoxyphenyl)hexane. The solid isomer (3 g.) and 10 g. of pyridine hydrochloride were refluxed for two hours, and the reaction product worked up as for hexestrol. After recrystallization from benzene, tufts of colorless shiny needles, m.p. 155°, extremely soluble in alcohol, more soluble in benzene than hexestrol, and readily sublimable around the m.p., were obtained. Yield, 96%.

Anal. Calc'd for C₁₃H₂₂O₂: C, 80.0; H, 8.2.

Found: C, 79.9; H, 8.4.

This compound should be structurally related to the 2,2'-dihydroxy- α,β -diethylstilbene, m.p. 152–153° prepared by Dodds, *et al.* (17).

SYNTHESES OF HIGHER HOMOLOGS OF HEXESTROL

4,5-Di-(p-hydroxyphenyl)octanes. *p*-(α -Hydroxybutyl)anisole, a pale yellow oil, b.p. 145–146°/13 mm., was obtained in 80% yield from benzaldehyde and *n*-propylmagnesium

bromide in ether. It was transformed by dry hydrogen chloride at -5° into *p*-butenylanisole prepared according to Klages (22). The coupling reaction was performed with iron powder, and the product worked up in the usual way, giving 20 g. of a mixture of 3,5-dianisyl octanes. From the mixture, 8 g. of the solid *meso*-isomer crystallizing from ethanol in shiny colorless prisms m.p. 123° , was obtained [the literature (17) gave m.p. 121 – 122° , for a specimen prepared by hydrogenation of the corresponding stilbene]. Demethylation of this substance (5 g.) by pyridine hydrochloride (20 g.) gave a 98% yield of *meso*-4,5-di-(*p*-hydroxyphenyl)octane, crystallizing from toluene in long colorless needles, m.p. 168° (literature m.p. 165°). The residue from the separation of *meso*-4,5-dianisyl octane was rectified, affording *dl*-4,5-dianisyl octane in the form of a pale yellow, viscous oil b.p. 235 – $236^\circ/13$ mm. (yield, 11 g.), which was demethylated by pyridine hydrochloride to the oily *dl*-4,5-di-(*p*-hydroxyphenyl)octane, which did not solidify even after many months (yield, 10 g.).

Coupling of p-(α -chloroamyl)anisole. The reaction of *n*-butylmagnesium bromide upon anisaldehyde in ether gave a mixture of *n*-amylanisylcarbinol (pale yellow liquid b.p. 266 – 270°) and its dehydration product 4-methoxy- β -*n*-propylstyrene (pale yellow, rather mobile liquid, b.p. 254 – 258° , with a pleasant aromatic odor). The mixture of both substances (70 g.) was saturated at -5° with dry hydrogen chloride, and the resulting *p*-(α -chloroamyl)anisole treated with iron powder as usual. Yield, 33 g. of a coupling product, b.p. 245 – $246^\circ/13$ mm.; this gave, after a long standing in the refrigerator, a small amount of a solid, believed to be pure *meso*-5,6-dianisyldecane (XIXb), which crystallized from ethanol in beautiful shiny tablets, m.p. 84° , easily soluble in hot ethanol.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.0; H, 9.7.

Demethylation of the foregoing compound gave in 98% yield *meso*-5,6-di-(*p*-hydroxyphenyl)decane (XIXa), crystallizing from benzene in fine, dull colorless needles, m.p. 167 – 168° .

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.9; H, 9.2.

Found: C, 80.7; H, 9.5.

Because of the great solubility of *meso*-5,6-dianisyldecane in its *dl*-isomer, no attempt was made to isolate the latter substance in a satisfactorily pure state.

Coupling of p-(α -chloroisoamyl)anisole. The reaction of isobutylmagnesium bromide upon anisaldehyde in the usual way yielded a mixture of isoamylanisylcarbinol and its dehydration product 4-methoxy- β -isopropylstyrene (b.p. 245 – 252°) [the latter substance has already been prepared in another way by Puxeddu (23), who gave b.p. 248 – 252°]. On coupling, *p*-(α -chloroisoamyl)anisole obtained from that mixture (60 g.) yielded 21 g., of a product b.p. 234 – $235^\circ/13$ mm. which readily solidified; after recrystallization from methanol, 18 g. of *meso*-2,7-dimethyl-4,5-dianisyl octane (XXb) was obtained in the form of clusters of colorless plates, m.p. 127 – 128° , closely resembling silver nitrate.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.2; H, 9.8.

Demethylation of this compound (15 g.) by pyridine hydrochloride (80 g.) resulted, in usual yield, in *meso*-2,7-dimethyl-4,5-di-(*p*-hydroxyphenyl)octane (XXa), crystallizing from benzene in long, silky colorless needles, m.p. 206 – 207° (sublimation above 180°).

Anal. Calc'd for $C_{22}H_{30}O_2$: C, 80.9; H, 9.2.

Found: C, 80.6; H, 9.2.

In the mother liquors from the crystallization of (XXb), a small quantity of a resinous material was found. This probably contained the *dl*-isomer.

Coupling of p-(α -chloroisoheptyl)anisole. The reaction of isoamylmagnesium bromide with anisaldehyde gave a product which, after repeated distillation, resulted in pure 4-methoxy- β -isobutylstyrene, a pale yellow, rather mobile oil, b.p. 264 – 265° , with an aromatic wood odor (yield, 70%).

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.1; H, 9.4.

Found: C, 82.2; H, 9.7.

After addition of hydrogen chloride to the foregoing compound (70 g.) and coupling with

iron powder, there was obtained 30 g. of a *dl-meso*-mixture in the form of a pale yellow, viscous oil b.p. 246°/13 mm., which did not solidify at 0° even after one year.

Anal. Calc'd for $C_{26}H_{38}O_2$: C, 81.6; H, 9.9.

Found: C, 81.4; H, 10.2.

Pyridine-demethylation of that oil resulted in small amounts of a solid compound (along with much resinous material) believed to be *meso-2,9-dimethyl-5,β-di-(p-hydroxyphenyl)-decane* (XXIa), crystallizing from benzene in large colorless prisms, m.p. 119–120°, extremely soluble in methanol.

Anal. Calc'd for $C_{24}H_{34}O_2$: C, 81.3; H, 9.6.

Found: C, 81.0; H, 9.6.

Attempts towards the synthesis of 2,5-dimethyl-3,4-dianisylhexanes. The reaction of isopropylmagnesium bromide upon anisaldehyde gave a mixture (b.p. 230–245°) of isopropylanisylcarbinol and 4-methoxy- β,β -dimethylstyrene. This mixture was dissolved in petroleum ether and saturated at -5° with dry hydrogen chloride, and the resulting product treated with iron powder as usual. A lively reaction was observed, but no coupling could be detected.

COUPLING OF CHLORO DERIVATIVES OF POLYPHENOL ETHERS

Coupling of the hydrogen chloride-adduct of isosafrole. Isosafrole (85 g.) prepared from safrole by treatment with a solution of sodium in isoamyl alcohol (24), was mixed with petroleum ether (50 ml.) and saturated at -5° with dry hydrogen chloride. The resulting α -chlorodihydrosafrole was treated in the usual way with 40 g. of iron powder and 250 ml. of water previously heated at 90°, and the mixture was subsequently boiled for thirty minutes. The reaction was a moderate one, and gave 32 g. of the coupling product in the form of an extremely viscous yellow oil, b.p. 255–268°/13 mm.; this solidified on trituration with ethanol. After several recrystallizations from a mixture of ethanol and benzene, fine colorless prisms, m.p. 175° were obtained. A lower-melting isomer was present in the mother liquors, but could not be completely purified. The higher-melting substance is assumed to be *meso-2,3-di-(m,p-methylenedioxyphenyl)hexane*.

Anal. Calc'd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.7.

Found: C, 73.5; H, 6.8.

Coupling of the hydrogen chloride-adduct of isoapiole. Isoapiole (75 g.), prepared by heating apiole with a solution of potassium hydroxide in ethanol, was dissolved in petroleum ether (150 ml.) and saturated at -5° with dry hydrogen chloride. The coupling reaction was performed as usual, giving 42 g. of a product, b.p. 296–304°/13 mm., in the form of an extremely viscous pale yellow oil. On prolonged standing of its acetone solution this gave a solid (3 g.) which was recrystallized from ethanol, and from acetone. Fine silky, colorless needles m.p. 157° were thus obtained, and this substance is believed to be *meso-2,3-di-(2,5-dimethoxy-3,4-methylenedioxyphenyl)hexane*.

Anal. Calc'd for $C_{24}H_{30}O_8$: C, 64.6; H, 6.7.

Found: C, 64.5; H, 6.8.

In the mother liquors from the crystallization of the supposed *meso*-form, there remained a great quantity of a thick oil which gave after rectification the presumed *dl*-form, b.p. 298–300°/13 mm., which did not solidify even after prolonged standing in the refrigerator.

Anal. Calc'd for $C_{24}H_{30}O_8$: C, 64.6; H, 6.9.

Found: C, 64.3; H, 6.9.

Both isomers charred on prolonged heating with pyridine hydrochloride.

SUMMARY

1. The reaction of different metal and alloy powders upon α -halogenated arylalkanes in hydroxylated media has been examined with a view of developing it into an instrument for various organic syntheses.

2. The preparation by this reaction of a number of substances bearing a biological interest and of intermediates for the syntheses of such compounds is described; in particular, a convenient device is elaborated for the technical preparation of hexestrol.

PARIS V^e, FRANCE

REFERENCES

- (1) SHORT, *Chemistry & Industry*, **59**, 703 (1940); PEAK AND SHORT, *J. Chem. Soc.*, 232 (1943); DOCKEN AND SPIELMAN, *J. Am. Chem. Soc.*, **62**, 2163 (1940); BERNSTEIN AND WALLIS, *J. Am. Chem. Soc.*, **62**, 2871 (1940).
- (2) KHARASCH AND KLEIMAN, *J. Am. Chem. Soc.*, **65**, 491 (1943).
- (3) OGATA, TURUTA, AND ODA, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **21**, 616 (1942).
- (4) SISIDO AND NOZAKI, *J. Am. Chem. Soc.*, **70**, 778 (1948).
- (5) ROSS, *J. Chem. Soc.*, 536 (1945).
- (6) KOCH, *J. Chem. Soc.*, 1111 (1948).
- (7) CAMBRON, *Can. J. Research*, **B17**, 10 (1939).
- (8) BUU-HOÏ AND LECOCQ, *J. Chem. Soc.*, 830 (1946).
- (9) RUZICKA AND HÖSLI, *Helv. Chim. Acta*, **17**, 470 (1934).
- (10) BUU-HOÏ AND LECOCQ, *Compt. rend.*, **224**, 658 (1947); *Compt. rend.*, **226**, 87 (1948).
- (11) RUZICKA AND HOFMANN, *Helv. Chim. Acta*, **20**, 1155 (1937); RUZICKA AND MORGELI, *Helv. Chim. Acta.*, **19**, 377 (1936).
- (12) BUU-HOÏ, *Ann.*, **556**, 1 (1944).
- (13) BARRY, *et al.*, *Proc. Roy. Soc. (London)*, **B117**, 318 (1935).
- (14) PEAK AND SHORT, British Patent 556,601 (October 12, 1943).
- (15) BERGER AND BUU-HOÏ, *Lancet*, II, **172** (1947).
- (16) GESCHICKER AND BYRNES, *J. Clin. Endocrinol.*, **2**, 19 (1942); KERSCHBAUM, KLEEDORFER, PRILLINGER, WESSELY, AND ZAJIK, *Naturwissenschaften*, **27**, 131 (1939); SCHMELKES, U. S. Patent 2,385,472 (September 25, 1945); [*Chem. Abstr.*, **40**, 176 (1946)].
- (17) DODDS, GOLDBERG, GRÜNFELD, LAWSON, SAFFER, AND ROBINSON, *Proc. Roy. Soc. (London)*, **B132**, 83 (1944).
- (18) SHORT, British Patent 523,320 [*Chem. Abstr.*, **35**, 5910 (1941)].
- (19) BROWNLEE, COPP, DUFFIN, AND TONKIN, *Biochem. J.*, **37**, 575 (1943).
- (20) SPÄTH, *Monatsh.*, **34**, 2009 (1913).
- (21) BAMBERGER AND LODTER, *Ber.*, **21**, 54 (1888).
- (22) KLAGES, *Ber.*, **37**, 3998 (1904).
- (23) PUXEDDU, *Gazz. chim. ital.*, **50** (I), 153 (1920).
- (24) GASSMANN, *Compt. rend.*, **124**, 40 (1902).
- (25) LACASSAGNE, BUU-HOÏ, CORRE, LECOCQ, AND ROYER, *Experientia*, **2**, 70 (1946); BUU-HOÏ AND LECOCQ, *J. Chem. Soc.*, 641 (1947).