ester bond at the secondary, rather than the primary, carbon atom.[43]

The conversion of A-5′-P to A-3′:5′-P by the action of DCC in anhydrous tri-*n*-butylamine–pyridine is a reaction of some interest. The first step in the reaction is the formation of P^1,P^2-diadenosine-5′-pyrophosphoric acid[44] (AppA). At room temperature this is the end-product. Only on heating the reaction mixture for extended periods is A-3′:5′-P obtained. It is unlikely that the DCC is involved directly in the conversion of AppA to A-3′:5′-P. This conversion is probably catalyzed by the organic bases, since it has been found that P^1,P^2-dithymidine-5′-pyrophosphoric acid is converted to T-3′:5′-P by heating in pyridine solution.[14] The formation of A-3′:5′-P is believed to be, therefore, another example of intramolecular phosphorylation,[21] like the conversion of ATP to A-3′:5′-P by means of barium hydroxide.[5] There is no evidence that the formation of A-3′:5′-P from A-5′-P plus DCC involves the formation of a neutral pyrophosphate ester as an intermediate, a reaction mechanism which has been suggested for the conversion of 4-hydroxybutylphosphoric acid to butane-1,4-diolphosphoric acid by means of DCC.[21]

It has been known for many years that O-glycosides are very rapidly decomposed by liquid, anhydrous hydrogen fluoride, while ordinary ethers are stable toward this reagent.[45] Under strictly anhydrous conditions glycosyl fluoride is the principal product of the reaction, but by varying conditions the sugar itself may be obtained. It was found that the N-glycosidic bond in nucleosides and nucleotides also is broken by the action of liquid, anhydrous hydrogen fluoride at room temperature. In the purine compounds the reaction appears to be as rapid as with O-glycosides. However, not only is the glycosidic bond attacked by liquid, anhydrous hydrogen fluoride, but with nucleotides rapid dephosphorylation also takes place.

Acknowledgment.—This investigation was supported in part by research grant C-3870 from the National Cancer Institute, Public Health Service. Partial support also was provided by the United States Atomic Energy Commission.

(43) This similarity in behavior of A-3′:5′-P, T-3′:5′-P and α-methyl-D-glucoside-4:6-phosphoric acid may indicate a similarity in conformation. It is presumed that, like in the latter, the 3′-hydroxyl group and the CH_2OH are equatorial in both A-3′:5′-P and T-3′:5′-P. The X-ray data of Furberg[39] are in agreement with this presumption. However, the alkaline hydrolysis of β-methyl-D-galactoside-4:6-phosphoric acid also yields the 4- and 6-phosphate esters in a ratio of 5:1.[41]

(44) M. Smith and H. G. Khorana, THIS JOURNAL, **80**, 1141 (1958).

(45) K. Wiechert in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, 1958, pp. 346–349.

ST. LOUIS 5, MO.

[CONTRIBUTION FROM RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL CO.]

π-Complexes of the Transition Metals. X. Acetylenic π-Complexes of Chromium in Organic Synthesis[1]

BY W. HERWIG, W. METLESICS AND H. ZEISS

RECEIVED JUNE 1, 1959

Disubstituted acetylenes are cyclically condensed by triaryl- and trialkyl-chromium compounds to benzene derivatives, to polynuclear aromatic hydrocarbons and to aromatic π-complexes. These condensations are considered to proceed *via* acetylenic π-complexes of chromium and are useful as a general synthetic method.

The isolation of triphenylchromium(III) in the form of its tetrahydrofuranate and its rearrangement to aromatic π-complexes of chromium have been described in detail.[2] This compound and its congeners are now found to have broad potentialities in organic synthesis. Their ability to promote cyclic condensation of acetylenes is reported as the first part of our investigation in this area.

The existence of triphenylchromium as a fully coördinated chromium(III) compound, *e.g.*, $(C_6H_5)_3$-Cr·3 THF, allows the assumption that its molecular geometry is that of the octahedron such as obtains in the coördinated chromium(III) salts and also in chromium hexacarbonyl, *i.e.*, d^2sp^3 bonding to chromium. Using this geometrical representation, the reaction of phenylmagnesium bromide and chromic trichloride may be described by Fig. 1, which summarizes the literature bearing on this reaction (*cf.* paper VII, footnotes 2, 3, 4, and 5).[3]

The formation of triphenylchromium is not observed when phenylmagnesium bromide and chromic trichloride are allowed to react in diethyl ether; but in tetrahydrofuran, a solvent which is considerably more basic than ether,[4] the triarylchromium is stable and isolable. The stabilizing effect of tetrahydrofuran in the hexacoördinated organochromium compound is clearly demonstrated by the irreversible rearrangement of triphenylchromium to the π-complex structure when its crystalline tetrahydrofuranate is washed with diethyl ether. The instability of the diethyl etherate of triphenylchromium provides an explanation for past failures in isolating this substance from atttempted preparations in the latter solvent. The unstable etherate appears also to be the ephemeral intermediate in the solution of reacting phenylmagnesium bromide–chromic trichloride which Job and Cassal treated with carbon monoxide to obtain the zero valent chromium hexacarbonyl.[3,5]

(1) Preliminarily communicated to THIS JOURNAL, **80**, 2913 (1958).

(2) W. Herwig and H. Zeiss, paper VIII in this series, *ibid.*, **81**, 4798 (1959); paper IX, G. N. Schrauzer, *ibid.*, **81**, 5307 (1959).

(3) M. Tsutsui and H. Zeiss, *ibid.*, **81**, 1367 (1959).

(4) H. C. Brown and R. M. Adams, *ibid.*, **64**, 2557 (1942).

(5) The Job–Cassal reaction also leads to organic carbonyl derivatives and is a forerunner of new methods of synthesis now being ex-

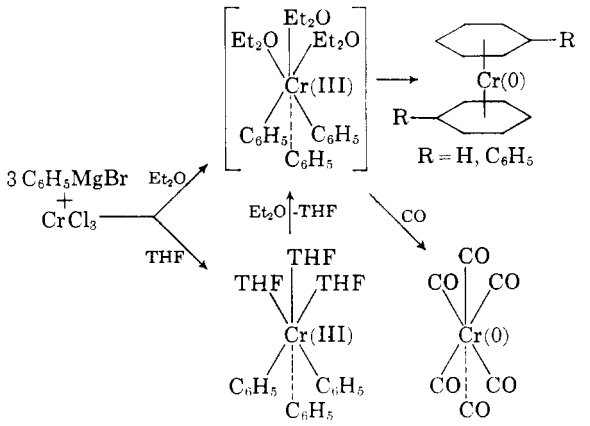

Fig. 1.

The concept of a hexacoördinated organochromium(III) compound containing replaceable tetrahydrofuran molecules has led to experiments with π-electron systems which would not only serve as the replacing ligands on chromium but which would also be expected to react further within the confines of the hexacoördinated complex. Thus, an acetylenic π-electron system has been used to displace the tetrahydrofuran, after which the acetylene molecules, now positioned favorably within the octahedral complex, may condense into cyclic arrangements. By analogy with the interpretation of the Job–Cassal reaction, it was anticipated that a new synthesis of zero valent chromium bis-arene π-complexes as well as of aromatic rings from the acetylenes could be devised.

Triphenylchromium is stable in tetrahydrofuran solution maintained at room temperature under nitrogen and free from moisture. If, however, either acetylene or a monosubstituted acetylene is added to the solution, the triarylchromium is rapidly decomposed by acetylenic hydrogen and the acetylene is polymerized. The sensitivity of organochromium compounds toward acidic hydrogen is, therefore, similar to that of the Grignard reagents. Disubstituted alkyl- or aryl-acetylenes, however, react quite smoothly with the organochromium compounds along reaction paths which may be varied by stoichiometric control.

Addition of 2-butyne to solid triphenylchromium produces an exothermic reaction which is completed within several minutes. If the reaction is performed in tetrahydrofuran, the interaction is considerably less rapid and is characterized by induction periods which are dependent on the reactant ratios: *i.e.*, the larger the relative amount of 2-butyne employed, the shorter the induction period. Product dependence on reactant ratio is most significant. For example, limitation of 2-butyne concentration to four mole equivalents or less per mole of triphenylchromium produces **1,2,3,4-tetramethylnaphthalene and its chromium π-complex,** which is either bis-1,2,3,4-tetramethylnaphthalene-chromium or 1,2,3,4-tetramethylnaphthalene-biphenylchromium. Only when quantities of 2-butyne exceeding four mole equivalents are used does triphenylchromium promote the formation of hexamethylbenzene in appreciable amounts. At a six-mole equivalent level, 2-butyne is cyclically condensed by triphenylchromium to a 38–40% yield of the naphthalene and a 50–55% yield of the benzene. When 2-butyne is employed in large excess, *e.g.*, twenty mole equivalents, the π-complexes of hexamethylbenzene and 1,2,3,4-tetramethylnaphthalene are formed also. This latter result permits the conclusion that the bis-aromatic π-complexes are not intermediates in the synthesis of the aromatic hydrocarbons, although they may be easily decomposed to them.

ploited using metal carbonyls. The reaction is the subject of a paper now in preparation.

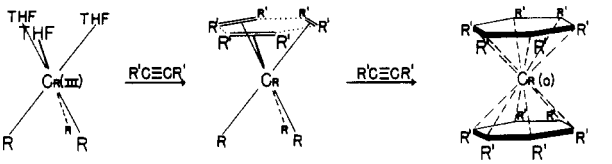

Fig. 2.

The course of reaction between 2-butyne and triphenylchromium is indicated by the dependence of product on stoichiometry. Stepwise replacement of the coördinating tetrahydrofuran molecules and participation of the phenyl groups on chromium in intramolecular reaction is supported by this variation in product.[6] The synthesis of 1,2,3,4-tetramethylnaphthalene requires a transition assembly composed of one phenyl group and two moles of 2-butyne which is expressed in the reaction diagram as a tetramethylcyclobutadiene intermediate. The fact that this naphthalene is *always* produced by the reaction, regardless of the amount of 2-butyne used, supports but of course does not prove this formulation of a highly reactive intermediate. There is also evidence indicating that the chromium atom is responsible for the abstraction of *ortho*-hydrogen from the phenyl group, facilitating ring closure at that position to the naphthalene structure.[7] When sufficient 2-

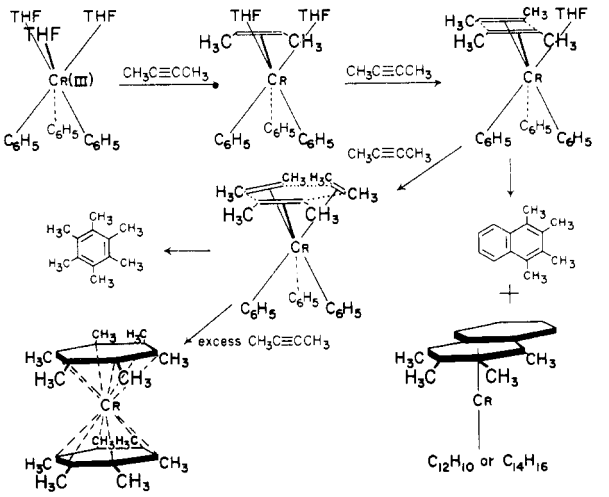

Fig. 3.

(6) Intramolecular reaction of the first intermediate in the diagram just above involving addition of one or two phenyl groups to an acetylenic bond and consequent formation of a substituted styrene or stilbene has been realized and is the subject of a separate communication: W. Metlesics and H. Zeiss, THIS JOURNAL, **81**, 4117 (1959).

(7) M. Tsutsui and H. Zeiss, *ibid.*, in press.

butyne is present it is supposed that this intermediate may either lose its remaining tetrahydrofuran in favor of a third mole of the acetylene or undergo a Diels–Alder addition with 2-butyne to produce the hexamethylbenzene. Saturation of the reaction system with 2-butyne is favorable to further reaction of the third intermediate to yield the bis-arene π-complexes *via* the mechanism proposed for the Job–Cassal reaction.[5]

The condensation of 2-butyne by triethylchromium, prepared in tetrahydrofuran in the same way as triphenylchromium, leads to hexamethylbenzene in somewhat higher yield than that obtained using triphenylchromium. Hexamethylbenzene again is the only condensation product isolated when a triarylchromium having blocked *o*-positions, *e.g.*, trimesitylchromium, is used as the cyclizing agent.[7]

Diphenylacetylene is condensed by triphenylchromium to hexaphenylbenzene and 1,2,3,4-tetraphenylnaphthalene.[8] The generality of these

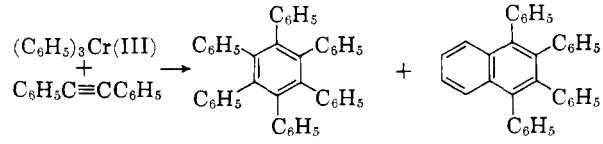

Fig. 4.

reactions is illustrated further by the preparation of tri-α-naphthylchromium in tetrahydrofuran and its ability to condense 2-butyne to **1,2,3,4-tetramethylphenanthrene** and hexamethylbenzene. The condensation of this acetylene with tri-β-naphthylchromium also was performed for the purpose of detecting any unusual directive influences during the ring closure. However, both **1,2,3,4-tetramethylanthracene** and 1,2,3,4-tetramethylphenanthrene were formed, the latter in the greater amount.

The effectiveness of triphenyl- and triethylchromium in promoting condensations of alkyl and aryl disubstituted acetylenes is not dependent on the isolation of the organochromium reagents prior to the condensation reactions. It is found, for example, that the cyclization of 2-butyne proceeds spontaneously when it is added to a mixture of magnesium powder, bromobenzene and chromium trichloride tetrahydrofuranate.[9] As a synthetic method, therefore, it is comparable to the Grignard procedure in operational detail.

Experimental[10]

Reaction of Triphenylchromium with 2-Butyne. (a) In Mole Ratio of 1:20.—A solution of 800 ml. of tetrahydrofuran containing 67.2 mmoles of triphenylchromium, prepared by the previously published method,[11] was magnetically stirred at room temperature under nitrogen in a three-necked flask. To this solution was added rapidly 105 ml. (72.8 g.,

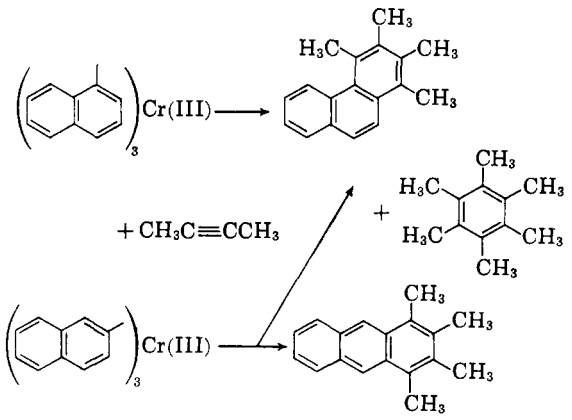

Fig. 5.

1.35 moles) of pure 2-butyne, b.p. 27°, in one portion. After 15 minutes reaction occurred accompanied by a temperature rise to 50° and a color change in the mixture from red-brown to brown-black. Three days later, two-thirds of the solvent was distilled from the dark, turbid solution *in vacuo* at 30°. The residual liquor was hydrolyzed with 600 ml. of water and then filtered. A dark brown solid remained on the filter, and the yellow-orange filtrate was put aside for further treatment.

The solid isolated on the filter was now triturated with 2 *N* sulfuric acid and then extracted with ether. On concentration of the green ether extract to small volume, 10.93 g. of a crude crystallizate was obtained. This solid was next dissolved in hot ethanol in high concentration and then mixed with a cold, saturated ethanolic solution of 16 g. of picric acid to form 23.4 g. of a precipitated orange picrate. Stepwise concentration of a warm ethanolic solution of this picrate was employed to separate seven crystalline fractions. The head fraction consisted of the orange-red needles of pure **1,2,3,4-tetramethylnaphthalene picrate**, m.p. 183.5–184.5° (lit. 182–183°).

Anal.[12] Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63; N, 10.17. Found: C, 58.13; H, 4.34; N, 10.55.

Cleavage of this picrate with aqueous ammonia yielded pure **1,2,3,4-tetramethylnaphthalene**, m.p. 107–108.5°, previously prepared from prehnitene by a five-step synthesis (m.p. 106.5–107°). Comparison of ultraviolet and infrared spectra of the two preparations confirmed their identity.[13]

The tail fraction from the picrate crystallizations consisted mainly of **hexamethylbenzene picrate** which was purified by recrystallization, m.p. 175–176° (lit. 176–177°). Cleavage of this substance with aqueous ammonia gave **hexamethylbenzene**, m.p. 165–167° (lit. 165–167°), mixed m.p. 165–167°.

By careful fractional crystallization procedure, the middle picrate fractions could be separated into the tetramethylnaphthalene and hexamethylbenzene components almost quantitatively. Total yields, based on triphenylchromium, were 4.70 g. (25.5 mmoles, 38%) of 1,2,3,4-tetramethylnaphthalene and 5.32 g. (32.8 mmoles) of hexamethylbenzene plus an additional 0.7 g. of the benzene derivative from the mother liquor as described below, bringing the yield of the latter product to 55% and an over-all yield of 93%.

An aqueous solution of sodium tetraphenylboron was added to the yellow-orange filtrate which had been put aside above. This caused the precipitation of 1.5 g. of a salt which proved to be mostly bis-hexamethylbenzene-chromium(I) tetraphenylboron. Efforts to recrystallize the salt from acetone, however, resulted in decomposition of the salt with formation of chromium hydroxide and hexamethylbenzene, m.p. 158–160°. The latter product contained less then 5% of 1,2,3,4-tetramethylnaphthalene according to infrared analysis. A sample of bis-hexamethylbenzene-chromium (I) tetraphenylboron prepared by the Fischer–Hafner

(8) We are indebted to Professor G. Wittig, Heidelberg, for a sample and infrared spectrum of this hydrocarbon which had been prepared *via* a Diels–Alder addition of tetracyclone to benzyne followed by loss of carbon monoxide; *cf.* ref. 17.

(9) It is noted, however, that none of these three reagents, either singly or in pairs, has a similar effect on the acetylene.

(10) All melting points are corrected. The microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. G.E. lamp-grade nitrogen was used in all experiments requiring the exclusion of air and moisture.

(11) W. Herwig and H. Zeiss, *J. Org. Chem.*, **23**, 1404 (1958).

(12) This analysis was performed by Galbraith Microanalytical Laboratory, Knoxville, Tenn.

(13) M. C. Kloetzel, R. P. Dayton and H. L. Herzog, THIS JOURNAL, **72**, 273 (1950). We wish to thank Professor Kloetzel for a copy of the infrared spectrum of his sample.

method[14] showed the same instability, decomposing in acetone to pure hexamethylbenzene quite rapidly.

(b) **In Mole Ratio 1:3.**—The amount of triphenylchromium and the procedure described in (a) again were employed with the exception that only 15.7 ml. (10.9 g., 202 mmoles) of 2-butyne was added. In this experiment, exothermic reaction and consequent color change were not observed until after 90 minutes had elapsed. Concentration and hydrolysis of the reaction mixture gave—as in (a)—an orange water solution and an insoluble hydrocarbon residue. Addition of an aqueous sodium tetraphenylboron solution to the colored filtrate produced a precipitate of a chromium complex of 1,2,3,4-tetramethylnaphthalene which decomposed rapidly when dissolved in acetone and deposited chromium hydroxide. The remaining, nearly colorless acetone solution was concentrated, the acetone replaced with ethanol and then treated with picric acid. The picrate of the tetramethylnaphthalene, 0.28 g., m.p. 182–184°, was precipitated which, on cleavage with aqueous ammonia, gave pure 1,2,3,4-tetramethylnaphthalene.

The insoluble material left on the filter above was treated as described in (a) except that the crude material was fractionally crystallized from ethanol without the addition of picric acid. The first fraction consisted of 4.7 g. of crude 1,2,3,4-tetramethylnaphthalene which when recrystallized once from ethanol gave 4.5 g. of substance, m.p. 105–107.5°. The second fraction, 2.10 g., consisted of the naphthalene contaminated with biphenyl which was removed by crystallizing 1.12 g. of the picrate of the tetramethylnaphthalene from ethanolic solution. The mother liquor from the picrate precipitation was diluted with aqueous ammonia, and the colorless precipitate so obtained was purified by sublimation and identified as biphenyl, 1.4 g., m.p. 69.5–70°. Total yields were 27.1 mmoles (40%) of the tetramethylnaphthalene and 9.1 mmoles of biphenyl. No hexamethylbenzene was detected.

(c) **Dependence of Product on Reacting Ratios of Triphenylchromium and 2-Butyne.**—The triphenylchromium–tetrahydrofuran solutions used in these runs were withdrawn from the same source as those employed in (a) and (b).

Mole ratio of $(C_6H_5)_3$-Cr:2-butyne	1:1	1:2	1:3	1:5	1:20
Start of exothermic reaction, min.	330	280	90	50	15
Yield of $(CH_3)_6C_6$, %	...	...	..	25	55
Yield of 1,2,3,4-tetramethylnaphthalene, %	13	31	40	36	38

Reaction of Triethylchromium with 2-Butyne.—Chromium trichloride tri-tetrahydrofuranate (10.1 g., 27 mmoles) was magnetically stirred into 100 ml. of tetrahydrofuran under nitrogen and then treated dropwise at −20° with 80 mmoles of ethylmagnesium bromide prepared from 9.8 g. of ethyl bromide (90 mmoles, 6.71 ml.) and 3 g. of magnesium in 300 ml. of tetrahydrofuran. The reaction started immediately, accompanied by the development of brown color in the solution, and after one hour the reaction was completed. The clear organochromium solution was maintained at −20° while 45 ml. (31.2 g., 0.58 mole) of 2-butyne was added. This mixture was kept at room temperature for three days and then freed of solvent *in vacuo* at 30°. The brown residue was triturated with a mixture of 2 *N* sulfuric acid and ether. The green ether layer was concentrated, diluted with ethanol and then cooled to 0° yielding 2.40 g. of almost pure hexamethylbenzene, m.p. 155–161°. Removal of ether and alcohol from the mother liquor and then distillation of the residue at 0.1 mm. gave an additional 0.25 g. of the benzene derivative, 1.8 g. of a green oil, and a pot residue consisting of 1.8 g. of a black solid. The latter fractions were not identified. The total yield of hexamethylbenzene came to 2.65 g. (16.3 mmoles, 60%) which was recrystallized almost quantitatively from ethanol to purity, m.p. 163–164°.

Reaction of Tri-α-naphthylchromium with 2-Butyne.—At −40° 3.72 g. of chromium trichloride tri-tetrahydrofuranate (9.9 mmoles) was magnetically stirred under nitrogen into 60 ml. of tetrahydrofuran and then treated dropwise with 66 ml. (29.7 mmoles) of α-naphthylmagnesium bromide solution (0.45 *N*) prepared from 10.35 g. (50 mmoles) of α-bromonaphthalene, 2.4 g. of magnesium and 95 ml. of tetrahydrofuran.[15] Reaction started immediately with color change to green, then to green-brown and finally after 30 minutes to an intense wine-red. On warming to −10°, the solution became quite clear, and after three days at this temperature its bright color remained unchanged.

To this solution of tri-α-naphthylchromium now was added 2.34 ml. (1.62 g., 30 mmoles) of 2-butyne with stirring at room temperature under nitrogen. Exothermic reaction commenced at once and was controlled by ice-bath cooling. The red color of the original solution turned to brown. After three days standing, the mixture was hydrolyzed with ice-water and then extracted with ether. This ether extract was concentrated, diluted with ethanol, and then boiled to remove most of the ether. At 0°, 1.01 g. of a crystallizate was obtained from the solution, which after sublimation at 80° (20 mm.) gave 0.68 g. of naphthalene as sublimate and 0.33 g. of 1,2,3,4-tetramethylphenanthrene as residue, m.p. 85–86°; picrate, m.p. 139–141°.

The ethanolic mother liquor from the crystallizate obtained above was treated with a saturated ethanolic solution of picric acid to give 1.37 g. of 1,2,3,4-tetramethylphenanthrene picrate which after recrystallization from ethanol melted at 141–143°.

Anal. Calcd. for $C_{24}H_{21}O_7N_3$: C, 62.20; H, 4.57; N, 9.07. Found: C, 62.55; H, 4.73; N, 9.21.

The mother liquor from the picrate precipitation yielded, after dilution with aqueous ammonia, about 2 g. of black tar. Only 0.72 g. of naphthalene was obtained from this residue by sublimation.

Cleavage of the picrate with aqueous ammonia gave the corresponding hydrocarbon which when combined with that obtained above and recrystallized from ethanol yielded 1.02 g. (4.35 mmoles, 44%) of colorless flakes of 1,2,3,4-tetramethylphenanthrene, m.p. 87–89°; infrared and ultraviolet spectra of this substance were recorded.

Anal. Calcd. for $C_{18}H_{18}$: C, 92.26; H, 7.74; mol. wt., 234. Found: C, 92.27; H, 7.90; mol. wt., 225.

Reaction of Tri-β-naphthylchromium with 2-Butyne.—A solution of β-naphthylmagnesium bromide (0.087 mole) was prepared from 20 g. (0.096 mole) of 2-bromonaphthalene and 3 g. of magnesium in 150 ml. of tetrahydrofuran and then added under nitrogen at −20° to 4.6 g. (0.029 mole) of chromium trichloride suspended in 150 ml. of the same solvent. After two hours, precipitation of the brick-red, insoluble tri-β-naphthylchromium was observed which, after warming to room temperature in the reaction mixture, was treated with 8 ml. (0.1 mole) of 2-butyne. Reaction was very sluggish for, after 24 hours standing, no change was observed either in the color of the precipitate or the solution. However, following 30 minutes of refluxing, the solution turned black, and the precipitate had disappeared. The solvent next was removed, and the residue was steam distilled to remove naphthalene together with a minute amount of hexamethylbenzene. The residue from the steam distillation was extracted with ether, and the insoluble β,β-binaphthyl was removed by filtration. The extract was freed of ether, and the residue was distilled in a ball tube at 0.2 mm. and a bath temperature ranging from 120–220°. The oily distillate in methanol gave yellow needles of **1,2,3,4-tetramethylanthracene** which after two recrystallizations from the same solvent melted at 138–140° and showed infrared and ultraviolet spectra characteristic of the anthracenes.[16]

Anal. Calcd. for $C_{18}H_{18}$: C, 92.3; H, 7.74. Found: C, 91.83; H, 7.86.

A picrate was prepared from this hydrocarbon in acetic acid and crystallized from this solvent as dark red needles, m.p. 169–171°.

Anal. Calcd. for $C_{24}H_{21}O_7N_3$: C, 62.2; H, 4.57; N, 9.07. Found: C, 62.22; H, 4.81; N, 8.91.

The methanolic mother liquor remaining after the isolation of the anthracene derivative was now concentrated and cooled to yield white leaflets of **1,2,3,4-tetramethylphenanthrene** which after several recrystallizations from acetic acid melted at 89–91° alone and when mixed with the sample of

(14) E. O. Fischer and W. Hafner, *Z. anorg. Chem.*, **286**, 146 (1956).

(15) This Grignard solution is supersaturated at room temperature but can be handled without crystallization for 2–3 hours after preparation.

(16) C. L. Hewett, *J. Chem. Soc.*, 293 (1940), reports a m.p. of 135.5–136.5° for this tetramethylanthracene and 165–166° for its picrate.

the tetramethylphenanthrene prepared earlier from 2-butyne and tri-α-naphthylchromium.

Reaction of Triphenylchromium with Tolane.—A solution of phenylmagnesium bromide (0.88 mole) in 100 ml. of tetrahydrofuran was added under nitrogen to 5 g. (0.032 mole) of chromium trichloride suspended in 250 ml. of the same solvent. To this dark red solution containing *ca.* 0.03 mole of triphenylchromium was now added 5.2 g. (0.029 mole) of tolane dissolved in 20 ml. of tetrahydrofuran without a noticeable temperature effect. After refluxing this reaction mixture for 3 hours, the black solution was left overnight before removal of the solvent *in vacuo* and hydrolysis with ice-water. The solid reaction product was collected on a filter and extracted with ether. The insoluble residue consisted of green chromium salt and a small amount of **hexaphenylbenzene.** The yellow ether extract was freed of solvent and then distilled in a ball tube at 0.4 mm. and separated into several fractions. At a bath temperature up to 150°, a fraction consisting of 1 g. of white crystalline material was obtained whose composition according to vapor phase chromatographic analysis was 90% biphenyl, 8% *stilbene*, 1% unreacted tolane and 1% unidentified volatile substance. Between 150–200° 3.4 g. of a yellow glass was collected, leaving 2.3 g. of a brown glass, containing *ca.* 0.01 g. of hexaphenylbenzene as residue. Hexaphenylbenzene was identified in both instances here by infrared spectral comparisons with authentic sample of the benzene prepared from tetraphenylcyclopentadienone and tolane.

The yellow and brown glasses together yielded 2.3 g. of crude **1,2,3,4-tetraphenylnaphthalene** when crystallized from ether–ethanol. Chromatography of the mother liquor on basic alumina with isoöctane yielded another 0.5 g., bringing the total yield to 45% based on tolane. Repeated recrystallization from ether, alcohol and acetic acid gave tetraphenylnaphthalene with unchanged m.p. at 195–198°. However, after melting and resolidifying, the m.p. rose to 201–203°. A sample of 1,2,3,4-tetraphenylnaphthalene prepared by another method[17] showed the same behavior and melted undepressed when mixed with the above sample. Their infrared spectra were also identical in all respects.

Anal. Calcd. for $C_{34}H_{24}$: C, 94.41; H, 5.59. Found: C, 94.85; H, 5.55.

(17) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).

DAYTON 7, OHIO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NOVOCOL CHEMICAL MFG. CO., INC.]

Alkoxyphenyl N-Substituted Aminopropanols

BY ELIAS EPSTEIN

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Several 1-alkoxyphenyl 3-N-substituted aminopropanols-2 were prepared. They were screened on laboratory animals for anesthetic potency, toxicity and for irritation. The anesthetic efficiencies of some of these compounds were sufficiently high to warrant clinical study.

Although two *p*-methoxyphenyl N-substituted aminopropanols were prepared near the beginning of the nineteenth century,[1] there was little to indicate in the literature that these compounds had a pronounced local anesthetic effect. Fernald, in 1953,[2] disclosed that ethoxynaphthyl N-substituted aminopropanols were potent topical anesthetics. On testing these compounds of Fernald, we found that although the topical potency was high and the toxicity on white mice low, they were highly irritating when applied to the eye of the rabbit. To determine whether substitution of the phenyl for the naphthyl group would reduce the irritating qualities of this type of compound, we prepared a series of N-substituted derivatives of methoxy-, ethoxy-, propoxy-, butoxy- and isoamyloxyphenylaminopropanols. These compounds were screened on laboratory animals for possible value as local anesthetics.

The general method of preparation was to treat the alkoxyphenylmagnesium bromide with epichlorohydrin in a Grignard reaction. The resulting chloropropanols were treated with an excess of the appropriate amine to form the anesthetic base. The anesthetic compounds were isolated as their hydrochloride salts and purified by recrystallization from isopropyl alcohol or some other suitable solvent.

The yields of the Grignard reaction ranged from 25 to 60% of theoretical. As discussed in a review by Gaylord and Becker,[3] the reaction proceeded to give two main products in varying yields:

$$ROC_6H_5MgBr + CH_2(O)CHCH_2Cl \longrightarrow ROC_6H_5CH_2CHOHCH_2Cl + BrCH_2CHOHCH_2Cl$$

(1) M. Daufresne, *Compt. rend.*, **145**, 875 (1907).

(2) M. C. Fernald, U. S. Patent 2,629,738 (1953).

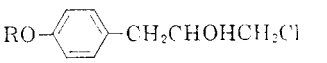
(3) N. G. Gaylord and E. I. Becker, *Chem. Revs.*, **49**, 413 (1951).

Attempts to improve the yield substantially by varying the conditions of the reaction were unsuccessful. The use of the Grignard chloride resulted in a very small or no yield, even when higher boiling solvents such as diisopropyl and dibutyl ether were used.

Table I lists the alkoxyphenyl chloropropanols with their boiling points, refractive indexes and analyses. Table II lists the boiling points of the bases as well as the melting points and analyses of the hydrochlorides of the alkoxyphenylaminopropanols.

TABLE I

ALKOXYPHENYLCHLOROPROPANOLS



R	Position	B.p., °C.	μ	$n^{20}D$	Formula	Chlorine, % Calcd.	Found
CH_3	*o*	99–101	30	1.5458	$C_{10}H_{13}O_2Cl$	17.68	16.92
CH_3	*p*	103–105	40[a]	1.5421	$C_{10}H_{13}O_2Cl$	17.68	17.42
C_2H_5	*o*	86–89	20	1.5231[b]	$C_{11}H_{15}O_2Cl$	16.53	16.99
C_2H_5	*p*	106–108	35	1.5369	$C_{11}H_{15}O_2Cl$	16.53	16.23
C_3H_7	*p*	120–124	60	1.5330	$C_{12}H_{17}O_2Cl$	15.52	15.48
C_4H_9	*m*	121–124	35	1.5270	$C_{13}H_{19}O_2Cl$	14.63	14.43
C_4H_9	*p*	112–115	20	1.5258	$C_{13}H_{19}O_2Cl$	14.63	14.32
i-C_5H_{11}	*m*	125–130	25	1.5210	$C_{14}H_{21}O_2Cl$	13.82	13.77
i-C_5H_{11}	*p*	123–128	30	1.5325	$C_{14}H_{21}O_2Cl$	13.82	14.05

[a] Reported[4] b.p. 188–190° (24 mm.). [b] At 40°.

Pharmacology.—A pharmacological investigation of these compounds was conducted to evaluate their potential use as local anesthetics. The anesthetic potency, toxicity and irritation were determined and compared with cocaine and procaine. The intraperitoneal and subcutaneous toxicities were determined on a Swiss strain of male white mice. An average of twenty mice was used to ob-

(4) E. Fourneau and M. Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1227 (1908).