The mixture was heated under reflux with stirring for 16 hr., filtered and the filter cake washed well with acetone. The acetone was removed by distillation, and the dark-brown residue was distilled through a 15-cm. Vigreux column; yield 5.17 g. (31%), b.p. 79–105° (0.2–0.5 mm.), $n^{25}\text{D}$ 1.4422–1.4435.

A sample of semicarbazone of this substance was prepared in a 48% yield, m.p. 174.5–175.5°, and when admixed with a sample of semicarbazone as derived above (III→IV), no depression in melting point was observed.

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PULLMAN, WASHINGTON

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Preparations of Synthetic Estrogens. VIII.[1a] New Syntheses of 1,1,2-Tri-*p*-anisylethylene and Diethylstilbestrol

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1,1,2-Tri-*p*-anisylethylene (VI) has been obtained by the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride. A similar condensation of α-chloroacetophenone (VII) with 2 moles of anisole gave 1,2-di-*p*-anisyl-1-phenylethylene (VIII). When these condensations were carried out with sulfuric acid or aluminum chloride as a catalyst, 1,1,1,2- and 1,1,2,2-tetra-*p*-anisylethanes as well as 1,1-di-*p*-anisylethylene were obtained instead of triarylethylenes. 2,3-Di-*p*-anisylbutene-2 (X) and diethylstilbestrol dimethyl ether (XII) were prepared by the condensation of 3-chlorobutanone (IX) and 4-chlorohexanone-3 (XI) with 2 moles of anisole in the presence of titanium tetrachloride.

In the previous paper[1a] it was reported that the treatment of *p*-methoxy-α,α-di-*p*-anisylacetophenone with phosphorus pentachloride effected simultaneous chlorination and dehydrochlorination giving 1,1,2-tri-*p*-anisyl-2-chloroethylene. The usual preparation[2] of 1,1,2-tri-*p*-anisyl-2-chloroethylene is the chlorination of tri-*p*-anisylethylene (VI) with chlorine in carbon tetrachloride. Recent studies in this Laboratory have given a new preparation of the key intermediate, tri-*p*-anisylethylene (VI), using a Grignard reaction between α-chloro-*p*-methoxyacetophenone (I) and *p*-anisylmagnesium bromide.[1] It has now been discovered that the condensation of α-chloro-*p*-methoxyacetophenone (I) with 2 moles of anisole in the presence of titanium tetrachloride gives tri-*p*-anisylethylene (VI) in a 53% yield. This method, in which the use of a Grignard reaction is avoided, seems to be suitable for large scale preparation.

The condensation of α-haloketones with phenol in the presence of an acidic catalyst has been studied by Lippmann.[3] Zaheer, *et al.*,[4] have reported recently that the reaction between chloroacetone and phenol or its ether in the presence of sulfuric acid or aluminum chloride as a catalyst gives 4,4′-dihydroxy- or -dialkoxy-α-methylstilbene, respectively. They have reported further that the similar condensation of 4-chlorohexanone-3 (XI) with anisole gives 3,3,4-tri-*p*-anisylhexane in addition to 1,1-di-*p*-anisyl-2-ethylbutene-1, and that phenol reacts with 1,3-dichloroacetone only at its carbonyl group to give 1,3-dichloro-2,2-di-*p*-hydroxyphenylpropane.[5] It was observed in the present experiments, in which sulfuric acid or aluminum chloride was used, that anisole reacted with α-chloro-*p*-methoxyacetophenone (I) to give various condensation products, among which, however, the desired tri-*p*-anisylethylene (VI) could not be found. The treatment of the chloroketone I with 2 moles of anisole in the presence of concentrated sulfuric acid in glacial acetic acid solution resulted in almost quantitative recovery of the starting materials. Essentially the same result was obtained in a reaction without the solvent, but further experiments in which the chloroketone I was dissolved in a large excess of anisole gave 1,1,1,2-tetra-*p*-anisylethane (III) and 1,1,2,2-tetra-*p*-anisylethane (IV).

$$\underset{\text{I}}{\text{ClCH}_2\text{COC}_6\text{H}_4\text{OCH}_3\text{-}p} + \underset{\text{II}}{3\text{C}_6\text{H}_5\text{OCH}_3} \xrightarrow{\text{concd. H}_2\text{SO}_4}$$

$$\underset{\text{III}}{p\text{-CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{C(C}_6\text{H}_4\text{OCH}_3\text{-}p)_3} +$$

$$\underset{\text{IV}}{(p\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{CHCH(C}_6\text{H}_4\text{OCH}_3\text{-}p)_2}$$

As to the mechanism of the initial step of the condensation of chloroketone with phenol, Zaheer, *et al.*, postulated either a Friedel–Crafts type removal of the chlorine atom involving combination of phenol at that position,[4a] or an addition of one mole of phenol at the carbonyl group and a subsequent rearrangement involving a dehydrochlorina-

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[1] (a) Previous paper: K. Sisido, K. Okano, T. Isida and H. Nozaki, THIS JOURNAL, **77**, 6580 (1955). (b) Department of Chemistry, Cornell University, Ithaca, N. Y.

[2] R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, THIS JOURNAL, **75**, 5491 (1953).

[3] E. Lippmann, *Ber.*, **45**, 2489 (1912).

[4] (a) P. M. Bhargava and S. H. Zaheer, *Nature*, **171**, 746 (1953); (b) V. D. N. Sastri, N. S. Rao and S. H. Zaheer, *Current Sci.* (*India*), **22**, 338 (1953); *C. A.*, **48**, 6984h (1954); (c) S. H. Zaheer, V. Singh, B. Bhushan, P. M. Bhargava, I. K. Kacker, K. Ramachandran, V. D. N. Sastri and N. S. Rao, *J. Chem. Soc.*, 3360 (1954).

[5] S. H. Zaheer, B. Singh, B. Bhushan, I. K. Kacker, K. Ramachandran and N. S. Rao, *ibid.*, 1706 (1955).

tion and a migration of an aromatic nucleus.[4b] The latter mechanism seems to be more plausible, as they suggested,[4c] since in the chloroketone the chlorine atom is attached firmly by the effect of the electron-attracting carbonyl group and the Friedel–Crafts type reaction, in which the chlorine atom must be taken off as an anion, would not be expected to occur.

In either route, however, desoxyanisoin may be formed at the first step of this reaction, being followed by attacks of second and third molecules of anisole to give 1,1,1,2-tetra-*p*-anisylethane (III) *via* 1,1,2-tri-*p*-anisylethanol. The unsymmetrical tetraanisylethane may partly be isomerized to the symmetrical one because of excessive crowding in III.

When the chloroketone I was treated with a large excess of anisole in the presence of aluminum chloride as a catalyst, 1.1-di-*p*-anisylethylene (V) and a resinous product were obtained. The mechanism of the production of this material is presumed to involve the removal of the chlorine atom by means of the reducing action of aluminum chloride at the first step and the subsequent addition of one mole of anisole at the carbonyl group followed by a dehydration. Similar removal of the chlorine atom has been observed in the reaction of acetyl chloride and cyclohexene in the presence of aluminum chloride.[6] It seems that 1-acetyl-2-chlorocyclohexane is formed at the first step of the reaction but is reduced to acetylcyclohexane by means of aluminum chloride.

$$\mathrm{I + II \xrightarrow{AlCl_3} CH_2{=}C(C_6H_4OCH_3\text{-}\mathit{p})_2}$$

$$\mathrm{I + II \xrightarrow{TiCl_4} \mathit{p}\text{-}CH_3OC_6H_4CH{=}C(C_6H_4OCH_3\text{-}\mathit{p})_2}$$

$$\mathrm{\underset{VII}{ClCH_2COC_6H_5} + II \xrightarrow{TiCl_4}}$$

$$\mathrm{\underset{VIII}{\mathit{p}\text{-}CH_3OC_6H_4CH{=}C(C_6H_5)C_6H_4OCH_3\text{-}\mathit{p}}}$$

This specificity of catalytic action of individual Lewis acids in this condensation stimulated the trial of titanium tetrachloride, which was reported[7] recently to be an advantageous catalyst in Friedel–Crafts reactions. When the chloroketone I was treated with a large excess of anisole in the presence of 2 moles[7a] of titanium tetrachloride at 35–37°, 1,1,2-tri-*p*-anisylethylene (VI) was obtained in a 53% yield. Higher reaction temperature decreased the yield of VI, *i.e.*, 35% at 50° and only resinous product resulted above 60°. Treatment of the reaction mixture at 0–35° gave 1,1,1,2-tetra-*p*-anisylethane (III) besides a small quantity of 1,1,2-tri-*p*-anisylethylene (VI). If carbon disulfide was used as a solvent instead of an excess of anisole, only starting materials were recovered, and if chloroacetyl chloride was used as a reactant instead of I, 1,1,2-tri-*p*-anisylethylene (VI) and I were obtained in very poor yield.

It was found furthermore that the condensation of α-chloroacetophenone (VII) with 2 moles of anisole in the presence of titanium tetrachloride at 0° gave two forms of 1,2-di-*p*-anisyl-1-phenylethylene (VIII), m.p. 105.5–107° and 92–94°[8] in 61% yield. Prolonged reaction time decreased the yield of VIII and phenyl-tri-*p*-anisylethane was obtained as a by-product.

Attempted condensations with stannic chloride or polyphosphoric acid failed. Thus treatment of the α-chloro-*p*-methoxyacetophenone (I) with anisole in the presence of these Lewis acids afforded only a non-crystallizable resin.

In addition to these reactions, it was also discovered that the condensations of 3-chlorobutanone (IX) and 4-chlorohexanone-3 (XI) with 2 moles of anisole in the presence of titanium tetrachloride at 0° gave 2,3-di-*p*-anisylbutene-2 (X) and 3,4-di-*p*-anisylhexene-3 (XII), so-called diethylstilbestrol dimethyl ether, in 32 and 19% yields, respectively. As described above, Zaheer, *et al.*,[5] were unable to prepare 3,4-di-*p*-anisylhexene-3 (XII) by the condensation of 4-chlorohexanone-3 (XI) with anisole in the presence of sulfuric acid or aluminum chloride. It was found that the reaction with titanium tetrachloride gave an oil, presumably the *cis* form of 3,4-di-*p*-anisylhexene-3 (XII), in a 51% yield, and that when the oil was treated with iodine in chloroform solution[9] the stilbestrol ether (XII) was obtained in crystalline form.

$$\mathrm{\underset{IX}{CH_3COCHClCH_3} + \underset{II}{2CH_3OC_6H_5} \xrightarrow{TiCl_4}}$$

$$\mathrm{\underset{X}{\mathit{p}\text{-}CH_3OC_6H_4C(CH_3){=}C(CH_3)C_6H_4OCH_3\text{-}\mathit{p}}}$$

$$\mathrm{\underset{XI}{C_2H_5COCHClC_2H_5} + \underset{II}{2CH_3OC_6H_5} \xrightarrow{TiCl_4}}$$

$$\mathrm{\underset{XII}{\mathit{p}\text{-}CH_3OC_6H_4C(C_2H_5){=}C(C_2H_5)C_6H_4OCH_3\text{-}\mathit{p}}}$$

An attempted condensation of 4-chlorohexanone-3 (XI) with phenol under the same conditions, however. failed to afford 3,4-di-*p*-hydroxyphenylhexene-3. A considerable quantity of starting materials besides a small amount of tar was recovered.

Experimental[10]

Tetra-*p*-anisylethane (III and IV).—To a solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II), 100 g. of concentrated sulfuric acid was added dropwise with stirring. The addition required about 40 minutes, during which the temperature was maintained below 0°. The stirring was continued for an additional six hours at 20° and the mixture was allowed to stand overnight. Ice-cold water was then added and the product was extracted with benzene. The benzene solution was washed with dilute sodium hydroxide solution and water. After distilling off the solvent the residue was subjected to steam distillation in order to remove excess anisole. The residue was taken up in benzene. dried over anhydrous sodium sulfate. the solvent was removed on a water-bath. and the residue was recrystallized from ethanol. Distillation of the crystals gave 2.4 g. of unchanged chloroketone I and 1.9 g. of 1.1.2.2-tetra-*p*-anisylethane (IV) boiling at 265–272° (3 mm.). which melted at 190°[11] after a single recrystallization from glacial acetic acid.

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[6] C. D. Nenitzescu and E. Ciorănescu. *Ber.*, **69**. 1820 (1936).

[7] (a) N. M. Cullinane, S. J. Chard and D. M. Leyshon. *J. Chem. Soc.*, 376 (1952); (b) 4106 (1952); (c) B. M. Cullinane and D. M. Leyshon, *ibid.*, 2942 (1954).

[8] E. C. Dodds. L. Goldberg. W. Lawson and R. Robinson. *Proc. Roy. Soc.* (London). **B127**, 140 (1939). reported m.p. of 105–106° and 92–93°. respectively.

[9] F. v. Wessely. E. Kerschbaum. A. Kleedorfer. F. Prillinger and E. Zajic. *Monatsh.*, **73**, 127 (1940).

[10] All temperatures are uncorrected.

[11] E. Bergmann and S. Fujise. *Ann.*, **483**. 65 (1930). reported a m.p. of 189°.

Anal. Calcd. for $C_{30}H_{30}O_4$: C. 79.27; H, 6.65. Found: C, 79.14; H, 6.78.

On the other hand, distillation of the mother liquor of the recrystallization gave 1.3 g. of I and 1.8 g. of 1,1,1,2-tetra-*p*-anisylethane (III) boiling at 265–275° (3 mm.) which melted at 149–150°[12] after several recrystallizations from glacial acetic acid.

Anal. Calcd. for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65. Found: C, 79.15; H, 6.52.

1,1-Di-*p*-anisylethylene (V).—To a solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II), 14.6 g. (0.109 mole) of anhydrous aluminum chloride was added below 10° in small portions, and the mixture was heated at 92–94° for five hours, during which time a vigorous evolution of hydrogen chloride was observed. After cooling, the reaction mixture was poured into ice-cold dilute hydrochloric acid. The product was taken up as usual and the distillation gave 1 g. of 1,1-di-*p*-anisylethylene (V) boiling at 167–180° (4 mm.) and 3 g. of a brown resinous product boiling at 261–263° (4 mm.). The former product melted at 139–141° after several recrystallizations from ethanol and showed no depression when admixed with an authentic specimen.[13] The latter fraction could not be crystallized.

1,1,2-Tri-*p*-anisylethylene (VI).—A solution of 10.0 g. (0.054 mole) of α-chloro-*p*-methoxyacetophenone (I) in 150 g. of anisole (II) was cooled with an ice–salt-bath and 20.9 g. (0.110 mole) of titanium tetrachloride was added dropwise with stirring at a rate sufficient to maintain the temperature at about −3°. After the addition was completed, the mixture was heated at 35–37° for five hours. An evolution of hydrogen chloride took place in the initial stage of the reaction. The dark-brown sticky product was poured into a mixture of 200 g. of crushed ice and 20 ml. of concentrated hydrochloric acid and the precipitated oil was extracted with benzene. The benzene solution was washed with dilute sodium hydroxide solution and water. After distilling off the solvent the residue was subjected to steam distillation. The residue was taken up in benzene and dried over calcium chloride. After removing the solvent, distillation of the residue gave 2.5 g. of unchanged chloroketone I followed by the product boiling at 245–260° (4 mm.) which was crystallized from glacial acetic acid. A single recrystallization from glacial acetic acid gave 10.0 g. (53%) of 1,1,2-tri-*p*-anisylethylene (VI), m.p. 97–99°,[14] which showed no depression when admixed with the product prepared by the Grignard reaction in the previous paper.[1]

When this reaction mixture was treated at 0–35° for 6 hours, the evolution of hydrogen chloride was not vigorous and 2.0 g. of 1,1,1,2-tetra-*p*-anisylethane (III) boiling at 260–275° (4 mm.) was obtained, which melted at 149° after a single recrystallization from glacial acetic acid. In addition 0.8 g. of 1,1,2-tri-*p*-anisylethylene (VI) also was isolated from the mother liquor of the recrystallization.

1,2-Di-*p*-anisyl-1-phenylethylene (VIII).—To a solution of 10.0 g. (0.065 mole) of α-chloroacetophenone (VII) in 150 g. of anisole (II), 24.7 g. (0.130 mole) of titanium tetrachloride was added dropwise below 0°. The addition required about 40 minutes, after which time the mixture was immediately poured into ice-cold dilute hydrochloric acid. The product was taken up as usual, and the distillation gave 15.5 g. of a resinous product boiling at 235–243° (4 mm.), which was crystallized to yield 12.4 g. (61%) of 1,2-di-*p*-anisyl-1-phenylethylene (VIII) by the treatment with ethanol. Fractional recrystallization from ethanol gave nearly the same quantity of two crystalline products which were considered to be *cis* and *trans* isomers. The less soluble one melted at 105.5–107° (VIIIa), while the substance isolated from the mother liquor melted at 92–94° (VIIIb).[8] Each mixed melting point with the products prepared by the use of the Grignard reaction between α-chloroacetophenone (VII) and *p*-anisylmagnesium bromide showed no depression.

When the stirring was continued for an additional 2.5 hr. at 0° after the addition was completed, 8.2 g. (40%) of 1,2-di-*p*-anisyl-1-phenylethylene (VIII) boiling at 230–240° (5 mm.) and 4.0 g. of 1,1,2-tri-*p*-anisyl-1- or -2-phenylethane boiling at 245–260° (5 mm.), which melted at 113–114° after a single recrystallization from ethanol, were obtained.

Anal. Calcd. for $C_{29}H_{28}O_3$: C, 82.05; H, 6.65. Found: C, 82.23; H, 6.64.

2,3-Di-*p*-anisylbutene-2 (X).—To a stirred mixture of 5.3 g. (0.050 mole) of 3-chlorobutanone (IX)[15] and 10.8 g. (0.100 mole) of anisole (II), 19.0 g. (0.100 mole) of titanium tetrachloride was added dropwise during 1.5 hr. at 0–5°, and the mixture was allowed to stand for five hours at the same temperature. The product was poured into ice-cold hydrochloric acid and was extracted with ether. The extract was washed with dilute sodium hydroxide solution and water and dried over anhydrous sodium sulfate. Distillation gave 4.3 g. (32%) of 2,3-di-*p*-anisylbutene-2 (X) boiling at 180–200° (5 mm.), which melted at 129–130° after a single recrystallization from methanol and the mixed m.p. with an authentic sample[16] showed no depression.

3,4-Di-*p*-anisylhexene-3 (XII).—To a mixture of 17.5 g. (0.15 mole) of propionoin and 18.0 g. (0.15 mole) of dimethylaniline, 18.3 g. (0.15 mole) of thionyl chloride was added at 0–5° with vigorous stirring. The addition required about 1.5 hr., during which the mixture almost solidified. The mixture was slightly heated until the semi-solid was dissolved, poured into water and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. Distillation gave 8.0 g. (39%) of 4-chlorohexanone-3 (XI) boiling at 42–43° (8 mm.).

A mixture of 8.0 g. of (0.059 mole) of 4-chlorohexanone-3 (XI) and 12.8 g. (0.118 mole) of anisole (II) was treated with 22.6 g. (0.119 mole) of titanium tetrachloride below 0° in the manner described above and the product was worked up as usual. Distillation gave 9.0 g. (51%) of yellow viscous oil boiling at 196–200° (8 mm.) which could not be crystallized. When the oil was treated with 1.0 g. of iodine in 190 ml. of chloroform,[9] 3.3 g. (19%, based on XI) of 3,4-di-*p*-anisylhexene-3 (XII) was obtained. A single recrystallization from petroleum ether gave colorless plates melting 123–124°, which showed no depression when admixed with an authentic specimen.[16]

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[12] E. Ziegler and K. Gitschthaler, *Österr. Chem.-Ztg.*, **53**, 208 (1952); *C. A.*, **48**, 6404c (1954), reported a m.p. of 151°.

[13] Prepared according to L. Gattermann, *Ber.*, **22**, 1129 (1889), who reported a m.p. of 140°.

[14] The recorded m.p. is 97–98.5° (ref. 1).

[15] The compound prepared by the method of G. Korschun, *Ber.*, **38**, 1125 (1905), was used.

[16] K. Sisido and H. Nozaki, This Journal, **70**, 776 (1948).