made accessible, mixed acetals can be prepared.

A mechanism for the exchange reaction has been proposed.

A procedure for the preparation of pure monobenzal- and pure dibenzalpentaerythritol is described.

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

The Preparation of Synthetic Estrogens. V.[1] New Routes to 3,3-Bis-(*p*-hydroxyphenyl)-4-hexanone and the Allied Substances

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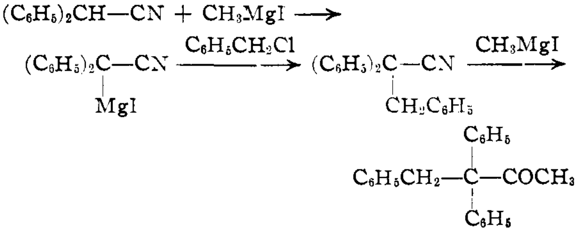
3,3-Bis-(*p*-hydroxyphenyl)-4-hexanone and its derivatives, *viz.*, ethers and esters, have been used as key intermediates in the synthesis of diethylstilbestrol.[2,3,4] In the first paper of this series[4] we described a preparation of the ketone by a pinacolone rearrangement of 3,4-di-*p*-anisyl-3,4-hexanediol as well as the succeeding conversion of the product to diethylstilbestrol. In the course of subsequent investigations we have developed new methods for the preparation of the pinacolone derivatives.

The first one consists in an adaptation of the condensation between phenol and biacetyl that we had reported in the previous paper.[1] Condensation of phenol with bipropionyl in place of biacetyl by the action of sulfuric acid resulted in the formation of the desired 3,3-bis-(*p*-hydroxyphenyl)-4-hexanone. Since the ketone formed a viscous oil, it was converted into the crystalline diacetate[2] for the identification.

It is of interest to note the structural resemblance between the pinacolone and analgesic aminoketones of the "amidone" (methadon) series. Amidone and the allied substances may be regarded as mixed pinacolones, since in these ketone derivatives two phenyl radicals and a β-amino-substituted alkyl group are attached to a quaternary carbon atom adjacent to a carbonyl group. Accordingly, methods[5] for synthesizing the analgesics may also be applicable to the preparation of estrogenic stilbestrol derivatives. This constitutes another approach to the pinacolone.

Di-*p*-anisylacetonitrile was ethylated in the presence of sodium amide and the resulting α,α-di-*p*-anisyl-*n*-butyronitrile, a new compound, was treated with ethylmagnesium bromide. Hydrolysis of the reaction product with hydrochloric acid yielded 3,3-di-*p*-anisyl-4-hexanone. In the course of this Grignard reaction, when the dianisylbutyronitrile was mixed with 5 moles of ethylmagnesium bromide and was heated at 130–170° for two and a half hours, there took place, besides the Grignard condensation, demethylation in the anisyl groups; acetylation of the resulting product gave 3,3-bis-(*p*-acetoxyphenyl)-4-hexanone, which did not depress the m. p. of the specimen obtained in the condensation of phenol with bipropionyl.

The third method for the pinacolone synthesis is a modification of this process in which a Grignard reagent is used instead of sodium amide as a condensing agent. We have discovered that treatment of a reaction mixture obtained from diphenylacetonitrile and methylmagnesium iodide with benzyl chloride, followed by heating at 60–110° during eight hours, gave 1,2,2-triphenyl-3-butanone in a 64% yield based on the diphenylacetonitrile. If this reaction was interrupted after a three-hour heating at 50–65°, α,α,β-triphenylpropionitrile was obtained in a 67% yield. Undoubtedly the first step of this reaction consists in a replacement of the active hydrogen of the diphenylacetonitrile with a halomagnesium residue of the Grignard reagent. The halomagnesium residue thus attached to the nitrile is then substituted with benzyl radical. In this reaction, when there is an excess of the Grignard reagent, it adds to the nitrile group in the usual way yielding a mixed pinacolone, 1,2,2-triphenyl-3-butanone.



$$(C_6H_5)_2CH{-}CN + CH_3MgI \longrightarrow \underset{\substack{| \\ MgI}}{(C_6H_5)_2C{-}CN} \xrightarrow{C_6H_5CH_2Cl} \underset{\substack{| \\ CH_2C_6H_5}}{(C_6H_5)_2C{-}CN} \xrightarrow{CH_3MgI} C_6H_5CH_2{-}\overset{\substack{C_6H_5 \\ |}}{\underset{\substack{| \\ C_6H_5}}{C}}{-}COCH_3$$

Similar reactions of a Grignard reagent have been observed recently by Hauser, Saperstein and Shivers,[6] by Stanley and Wawzonek[7] as well as by Fuson and Porter.[8]

Unfortunately lower yields of the pinacolone derivatives were obtained in the reactions of diphenyl- and of di-*p*-anisylacetonitriles with methyl or ethyl iodide in the presence of appropriate Grignard reagents. There resulted also unalkyl

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[1] Previous paper: Sisido, Nozaki and Iwako, THIS JOURNAL, **71**, 2037 (1949).

[2] Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

[3] Adler, Gie and von Euler, Swedish Patent 115,816, Feb. 12, 1946; *C. A.*, **41**, 486 (1947); U. S. Patent 2,421,401, June 3, 1947.

[4] Sisido and Nozaki, THIS JOURNAL, **70**, 776 (1948).

[5] See for example: Schultz, Robb and Sprague, *ibid.*, **69**, 2454 (1947).

[6] Hauser, Saperstein and Shivers, *ibid.*, **70**, 606 (1948).

[7] Stanley and Wawzonek, *ibid.*, **68**, 1157 (1946).

[8] Fuson and Porter, *ibid.*, **70**, 895 (1948).

ated by-products formed by the ordinary Grignard reaction, *i. e.*, 1,1-diarylacetones and 1,1-diaryl-2-butanones, respectively. We have succeeded, however, in preparing by this process 2,2-diphenyl-3-butanone, 2,2-di-*p*-anisyl-3-butanone and 3,3-di-*p*-anisyl-4-hexanone in 24, 34 and 24% yields, respectively. The latter pinacolone was converted into *trans*-3,4-di-*p*-anisyl-3-hexene according to the previous method.[4]

It is a matter for further investigation to test the possibility of adapting the reaction abovementioned to the synthesis of the analgesic pinacolones. The experiments along this line are in progress in our Laboratory.

Experimental[9]

Condensation of Phenol with Bipropionyl.—Bipropionyl was prepared from propionoin[10] according to the method of Wegmann and Dahn.[11] To an ice-cooled solution of 19 g. of phenol and 10 g. of the α-diketone in 45 cc. of glacial acetic acid 20 g. of 98% sulfuric acid was added dropwise with stirring. After heating at 30–45° for three hours the mixture was allowed to stand overnight. The product was poured onto 200 g. of crushed ice and the whole was subjected to steam distillation. The residue was extracted with ether and this ether extract was shaken out with 10% potassium hydroxide solution. After acidification with sulfuric acid the aqueous layer was extracted with ether and the ether solution was washed with water, dried and evaporated. The residue formed a brown viscous oil weighing about 20 g.

The condensation product was acetylated with 30 g. of acetic anhydride and several drops of pyridine. Upon distillation of the product 9 g. of a yellow sirup came over at 250–265° under 9 mm. Recrystallizations of the distillate from methanol gave 6 g. (19%) of colorless prisms, m.p. 88–88.5°. Wessely, *et al.*,[2] recorded the m.p. of 3,3-bis-(*p*-acetoxyphenyl)-4-hexanone as 91.5° with sintering at 88°.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.41; H, 6.33.

α,α-Di-*p*-anisyl-*n*-butyronitrile.—A mixture of 12.6 g. of di-*p*-anisylacetonitrile,[12] 3 g. of sodium amide and 100 cc. of benzene was refluxed with stirring for one and a half hours. To the cooled mixture was added 11 g. of ethyl iodide and the whole refluxed for fifteen hours. After treating the reaction product with ice-water, the benzene layer was separated, washed with water, dried and evaporated. Distillation of the residual liquor yielded a fraction, b.p. 235–240° at 11 mm., which weighed 11 g. Upon recrystallization from methanol 8 g. of the desired nitrile in colorless plates melting at 37–38° was obtained.

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81. Found: C, 76.40; H, 6.77.

From the less soluble portion there was isolated, as a by-product, 2 g. of 4,4′-dimethoxybenzophenone, m.p. and mixed m.p. 143°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.31; H, 5.84.

3,3-Di-*p*-anisyl-4-hexanone.—A solution of 12.5 g. of α,α-di-*p*-anisyl-*n*-butyronitrile in 50 cc. of ether was added dropwise to a Grignard reagent prepared from 15 g. of ethyl bromide, 3.4 g. of magnesium and 30 cc. of ether. After refluxing the mixture for eight hours the product was hydrolyzed with ice-water and 30 g. of concentrated hydrochloric acid was added. The resulting mixture was refluxed for four hours, extracted with benzene and the benzene solution was washed with water and 5% sodium carbonate solution, dried and distilled to yield 10 g. of a yellowish oil,[4] b.p. 245–250° at 10 mm. In order to identify the compound, it was converted into dimethyl ether of diethylstilbestrol. Reduction of 10 g. of the oily pinacolone, followed by the retro-pinacolone rearrangement, according to the procedure reported in the first paper of this series,[4] yielded 2.6 g. of *trans*-3,4-di-*p*-anisyl-3-hexene, m.p. and mixed m.p. 123–124°. Overall yield of the crystalline 3-hexene derivative based on the α,α-di-*p*-anisyl-*n*-butyronitrile amounted to 20%.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.05; H, 8.38.

3,3-Bis-(*p*-acetoxyphenyl)-4-hexanone.—To a Grignard reagent prepared from 16 g. of ethyl iodide, 2.4 g. of magnesium and 60 cc. of ether was added a solution of 5 g. of α,α-di-*p*-anisyl-*n*-butyronitrile in 50 cc. of xylene. After refluxing the resulting mixture for thirteen hours the solvents were removed and the residue was heated at 130–170° for two and a half hours. The product was poured onto 120 g. of crushed ice acidified with 25 g. of concentrated hydrochloric acid. The whole was refluxed for one and a half hours and after cooling was extracted with ether. The ether solution was washed successively with water, 5% sodium thiosulfate solution and water. The phenolic product dissolved in the ether was extracted with 10% sodium hydroxide solution and the aqueous layer was separated, acidified and a dark brown oil which separated was extracted with ether. This ether solution was washed with water, dried and evaporated. The residual oil weighed 4 g. Acetylation of 4 g. of the oily product with acetic anhydride and pyridine, followed by distillation, gave a fraction, b.p. 250–260° at 10 mm., weighing 1.8 g. Upon recrystallizations from methanol there was obtained 0.3 g. of colorless prisms, m.p. 88–88.5°, which did not depress the m.p. of the specimen prepared in the abovementioned condensation of phenol with bipropionyl.

α,α,β-Triphenylpropionitrile.—A solution of 9.7 g. of diphenylacetonitrile[5,13] in 40 cc. of toluene was added dropwise to a Grignard reagent obtained from 21.4 g. of methyl iodide, 3.7 g. of magnesium and 30 cc. of ether and the mixture was heated at 50–65°. During this procedure an evolution of a gas, presumably methane, was observed. After refluxing for two hours, 6.7 g. of benzyl chloride was added dropwise. The resulting mixture was heated at 50–65° for an additional three hours and poured onto iced hydrochloric acid. The toluene was removed by steam distillation and the residue was extracted with benzene. The benzene solution was washed with water, dried and evaporated. Recrystallization of the residue from alcohol gave 9.5 g. (67%) of colorless needles melting at 126°.[14]

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.01; H, 6.05. Found: C, 89.15; H, 5.77.

1,2,2-Triphenyl-3-butanone.—A Grignard reagent prepared from 42.6 g. of methyl iodide, 7 g. of magnesium and 100 cc. of ether was treated with a solution of 15 g. of diphenylacetonitrile in 50 cc. of toluene in the same way as above and 12 g. of benzyl chloride was added. The resulting mixture was heated at 60–75° for three hours and, after removal of the ether, the heating was continued at 110° for an additional five hours. The product was poured onto iced hydrochloric acid and the toluene was removed by steam distillation. After refluxing the residual liquor for two and a half hours the product was extracted with benzene. The benzene solution was washed with water, dried and distilled. There was obtained a sirup boiling at 255–260° under 15 mm. which weighed 17 g. Recrystallization of the distillate from methanol yielded 15 g. of colorless needles, m.p. 63–64°[15]; yield, 64%.

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[9] Microanalyses by Miss Kenko Ogawa of our Laboratory.

[10] Snell and McElvain, "Org. Syntheses," Coll. Vol. II, 1946, p. 114.

[11] Wegmann and Dahn, *Helv. Chim. Acta*, **29**, 113 (1946); *C. A.*, **40**, 2820 (1946); *cf.* also Rüggli and Zeller, *Helv. Chim. Acta*, **28**, 741 (1945); *C. A.*, **40**, 1819 (1946). Since the original papers were not available to us, we followed the recipe of the abstracts.

[12] Péteri, *J. Chem. Soc.*, 833 (1940).

[13] Robb and Schultz, *Org. Syntheses*, **28**, 55 (1948); Ginsberg and Baizer, THIS JOURNAL, **71**, 2254 (1949).

[14] Neure, *Ann.*, **250**, 140 (1889).

[15] Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **33**, 759 (1923).

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.64; H, 7.06.

2,2-Diphenyl-3-butanone.—A solution of 10 g. of diphenylacetonitrile in 50 cc. of toluene was added dropwise to a Grignard reagent prepared from 28.4 g. of methyl iodide, 5 g. of magnesium and 70 cc. of ether. After refluxing for two and a half hours 8 g. of methyl iodide was added slowly with stirring and the resulting mixture was refluxed for an additional ten hours. The reaction product was poured onto ice-cold hydrochloric acid and was subjected to steam distillation to remove the toluene. The residual liquor was boiled under reflux for three hours. The cooled product was extracted with benzene and the benzene solution was washed with water, dried and the solvent was distilled off. Distillation of the residue yielded 7.7 g. of an oil, b.p. 168–172° at 11 mm., which proved to be a mixture of 2,2-diphenyl-3-butanone and a by-product, 1,1-diphenylacetone. When a solution of 7 g. of the distillate, hydroxylamine hydrochloride and sodium acetate in aqueous alcohol was allowed to stand overnight at room temperature, oxime of the diphenylacetone,[16] m. p. 164°, separated out. On further standing of the mother liquor at room temperature for four weeks, another crop of crystals was obtained. Recrystallization of the latter from methanol gave 3 g. of colorless plates, m. p. and mixed m. p. with an authentic specimen of 2,2-diphenyl-3-butanone[4] oxime[17] 151.5°. The yield based on the starting nitrile is 24%.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16. Found: C, 79.93; H, 7.25.

2,2-Di-*p*-anisyl-3-butanone.—To the methylmagnesium iodide solution prepared in the same quantity as above was added a solution of 10 g. of di-*p*-anisylacetonitrile in 200 cc. of toluene. After refluxing the mixture for two and a half hours 6 g. of methyl iodide was added and the heating was continued for an additional fifteen hours at the boiling point of the mixture. Hydrolysis of the product in a usual way followed by distillation yielded 9.2 g. of a viscous oil, b. p. 225–230° at 5 mm., which also proved to be a mixture of 2,2-di-*p*-anisyl-3-butanone and 1,1-di-*p*-anisylacetone. Upon refluxing a solution of 9.2 g. of the distillate, hydroxylamine hydrochloride and sodium acetate in aqueous alcohol during four hours 9 g. of colorless prisms, m. p. 155–159°, was obtained. Repeated recrystallizations from methanol yielded 4.0 g. of 2,2-di-*p*-anisyl-3-butanone oxime, m. p. and mixed m. p. with a known sample[4] 185–186°. The yield based on the nitrile is 34%. Although Price and Mueller[18] reported the m. p. of the oxime as 192–194°, our specimen changed no more the m. p. upon further recrystallizations.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 72.02; H, 7.41.

From the mother liquor 1,1-di-*p*-anisylacetone oxime,[19] m. p. 125°, was isolated.

3,3-Di-*p*-anisyl-4-hexanone.—To a Grignard reagent prepared from 50 g. of ethyl iodide, 7.7 g. of magnesium and 100 cc. of ether 20 g. of di-*p*-anisylacetonitrile was added in small portions. After addition of 200 cc. of xylene the resulting mixture was refluxed for two hours. To this mixture 20 g. of ethyl iodide was added dropwise and the whole was heated at 60–65° for fifteen hours. The reaction product was treated as usual. Upon distillation there was obtained 18.4 g. of a sirup, b. p. 225–230° at 5 mm. Recrystallization of this product from alcohol gave 10.1 g. of crystals, m. p. 57–58°, which was found to be 1,1-di-*p*-anisyl-2-butanone.[12,19] The oily portion was treated with hydroxylamine in aqueous alcohol in order to remove the last trace of the dianisylbutanone by converting it into the corresponding oxime,[19] m. p. 98–99°. The mother liquor of the oxime was poured into water, extracted with benzene and the benzene solution was washed with sodium carbonate solution, dried and evaporated. Distillation of the residue gave 6 g. (24%) of crude 3,3-di-*p*-anisyl-4-hexanone,[20] b. p. 225–233° at 4 mm. Reduction of 6 g. of the product and the following retro-pinacolone rearrangement gave 1 g. of *trans*-3,4-di-*p*-anisyl-3-hexene, m. p. and mixed m. p. 123–124°.

Summary

Condensation of phenol with bipropionyl, followed by acetylation, gave 3,3-bis-(*p*-acetoxyphenyl)-4-hexanone.

Di-*p*-anisylacetonitrile was ethylated in the presence of sodium amide with ethyl iodide. The resulting α,α-di-*p*-anisyl-*n*-butyronitrile was subjected to Grignard reaction to yield 3,3-di-*p*-anisyl-4-hexanone. When the reaction was carried out with excess of the Grignard reagent at higher temperature, there was obtained 3,3-bis-(*p*-hydroxyphenyl)-4-hexanone.

A Grignard reagent was found to be effective in this reaction as a condensation agent in place of sodium amide. The following compounds were prepared from diarylacetonitriles by the action of organic halides in the presence of appropriate Grignard reagents: α,α,β-triphenylpropionitrile 1,2,2-triphenyl-3-butanone, 2,2-diphenyl-3-butanone, 2,2-di-*p*-anisyl-3-butanone and 3,3-di-*p*-anisyl-4-hexanone. Diethylstilbestrol dimethyl ether was prepared from the latter pinacolone.

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[16] Stoermer, *Ber.*, **39**, 2303 (1906).

[17] Chu and Chu, *J. Chinese Chem. Soc.*, **9**, 190 (1942); *C. A.*, **37**, 6643 (1943).

[18] Price and Mueller, THIS JOURNAL, **66**, 634 (1944).

[19] Weill, *Bull. soc. chim.*, [4] **49**, 1811 (1931).

[20] This ketone forms no oxime; see ref. 4.