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by

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Synthesis of some Derivatives of Cyclopentadienone and related Compounds*

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Derivatives of p-dimethylamino group substituted tetraphenylcyclopentadienones have been synthesized, condensing benzil or p-dimethylamino group substituted benzil and dibenzylketone or p-dimethylamino group substituted dibenzylketone. A new method has been found to synthesize p-dimethylamino group substituted benzil. p-Dimethylamino group substituted dibenzylketone and its intermediate compounds have been synthesized.

INTRODUCTION

Tetraphenylcyclopentadiene has been synthesized by Wislicenus and Carpenter, starting from desoxybenzoin and formaldehyde [1]. Two moles of desoxybenzoin were condensed with one mole of formaldehyde, in basic conditions, to form methylene-bis-desoxybenzoin. Zinc powder, in presence of acetic acid reduced this compound dimolecularly to 3,4-dihydroxy-1, 2, 3, 4-tetrahydrotetraphenylcyclopentane, then concentrated sulfuric acid abstracted two moles of water from this compound to give tetraphenylcyclopentadiene.

Ziegler and Schnell have oxidized tetraphenylcyclopentadiene to tetraphenylcyclopentadienone with p-nitrosodimethylaniline *via* an "anil" compound [2]. Using the same method Cl, CH₃, OCH₃ and N(CH₂)₃ substituted derivatives of tetraphenylcyclopentadienone on the benzene ring have been synthesized by Becker et al. [3].

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Synthetic route indicated above is long and in the case of aliphatic substituents on the benzene ring some complications might take place and desirable products may not be obtained. Dilthey and Quint introduced a new method to synthesize tetraphenylcyclopentadienone and its derivatives starting from benzil and dibenzylketone. This method consists of condensing benzil and dibenzylketone in basic alcoholic solution [4]. The mechanism of this one step reaction may be considered in two steps: 1° An aldol condensation between benzil and dibenzylketone, 2° Removal of two moles of water from "diol" so formed. Using this method, Dilthey at al., [5], Becker and his coworkers [6], [7], [8] have synthesized a number of substituted tetraphenylcyclopentadienones and study their absorption spectra.

Later, Dilthey and Quint's method has modified by Johnson and Grummit and become simpler and more practical [9]. These authors named tetraphenylcyclopentadienone as "tetracyclone".

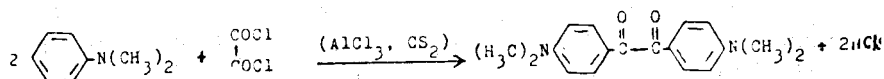
In this work, tetracyclones having *p*-dimethylamino group on benzene ring, 2,5-diphenyl-3,4-bis-(*p*-dimethylaminophenyl)cyclopentadienone (I), 2,5-bis-(*p*-dimethylaminophenyl)cyclopentadienone (II) and tetra-(*p*-dimethylaminophenyl)cyclopentadienone (III) were synthesized and some properties studied.

In order to synthesize these compounds according to Dilthey and Quint's method, following compounds are necessary: 1, 4,4-Bis-dimethylamino benzil, 2, 4,4-Bis-dimethylaminodibenzyl ketone, 3. Benzil, 4. Dibenzyl ketone.

1. 4,4'-Bis-dimethylamino benzil. This compound has been synthesized by Staudinger and Stockmann from the reaction between oxalyl chloride and dimethylaniline in a sealed tube under 300 atm. carbon monoxide pressure at 100°C for 3-4 days [10]. Because of the considerable side reactions, yield was very low and purification of the material was difficult.

According to Thomas "Anhydrous aluminum chloride has been little used in condensation of aromatic amines with acyl halide. It is not needed in replacement of N-hydrogen with acyl and attempts to use the catalyst in introduction of an acyl group

into the ring of N-acyl amines have not met with great success of formation of complex products" [11]. In spite of this experience, a Friedel-Crafts reaction between oxalyl chloride and dimethylaniline, anhydrous aluminum chloride as catalyst, gave small amount of 4,4'-bis-dimethylamino benzil. Then, using carbondisulfide as solvent and excess of aluminum chloride, 60 per cent yield has been obtained.



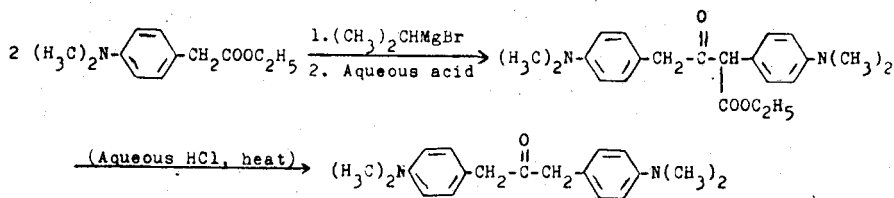
4,4'-Bis-dimethylamino benzil found to be inactive against most of chemical reactions. For example, it did not give a quinoxaline with o-phenylenediamine nor benzilic acid rearrangement with alcoholic potassium hydroxide, although these reactions are characteristic for benzils.

Dilthey and his coworkers have tried to condense 4,4'-bis-dimethylamino benzil with dibenzyl ketone to obtain tetracyclone (I), but it failed [5]. Using a modified method, this tetracyclone was synthesized.

2. 4,4'-Bis-dimethylaminodibenzyl ketone. This substance has made as a new compound. In order to synthesize this compound a number of reaction series were followed.

Conant and Blatt have found that, ethylphenylacetate (or its substituted derivatives on the benzene ring) did not give an expected addition product with isopropylmagnesium bromide. Instead of this reaction, Claisen ester condensation took place and ethyl-1,3-diphenylacetoate obtained. Ketone cleavage of this ester (boiling with an aqueous acid) gave dibenzylketone [2].

Using the same reaction but starting from ethyl-p-dimethylaminophenylacetate, ethyl- α, γ -di (p-dimethylaminophenyl) acetoacetate was obtained as a viscous and uncrystallizable oil. Boiling of this oil aqueous acid gave 4,4'-bis-dimethylaminodibenzylketone:



p-Dimethylaminophenylacetic acid and its ethyl ester were made as new compounds. General procedure of synthesizing phenylacetic acid and its substituted derivatives on the benzene ring has been given in a German patent. According to this procedure, an aromatic hydrocarbon or its derivatives heated up to 180°C with chloroacetic acid for 4–5 days [13]. p-Dimethylaminoacetic acid has been mentioned on the patent but none of its physical constants has been given. Trying of this method for p-dimethylaminophenylacetic acid was unsuccessful. Synthesis of this compounds was accomplished in two different ways 1° Hydrolysis of p-dimethylaminophenylacetthiomorpholide, 2° Reductive hydrolysis of p-dimethylaminobenzaldehyde cyanohydrin.

1° *Hydrolysis of p-dimethylaminophenylacetthiomorpholide.* This compound has been made by Barret [14]. Acidic hydrolysis of this compound gave p-dimethylaminophenylacetic acid. This is an amphoteric compound, soluble in bases, in acids. Furthermore, it is highly soluble in water and also soluble in organic solvents, so it is difficult to isolate from hydrolyzed solutions. In order to carry out isolation of this compound from aqueous solutions, two equal volumes of solution containing exactly the same amount of compounds, one is anion other is cation form, were mixed together and liberated compound extracted with chloroform.

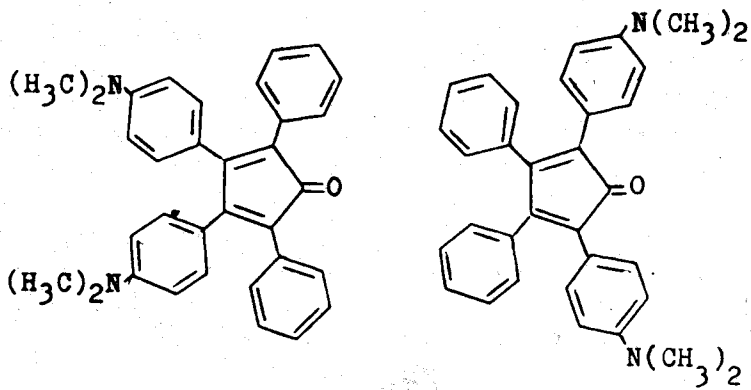
2° *Reductive hydrolysis of p-dimethylaminobenzaldehyde cyanohydrin.* Levine, Eble and Fischbach have found a method to convert benzaldehyde cyanohydrin or its substituted derivatives on the benzene ring to phenylacetic acid or its derivatives. This method consists of heating cyanohydrins with stannous chloride dissolved in hydrochloric acid in presence of small amount

of hydroiodic acid [15]. This method was successfully applied to synthesize p-dimethylaminophenylacetic acid.

Fischer's general esterification methods was used to esterify p-dimethylamino-phenylacetic acid [16].

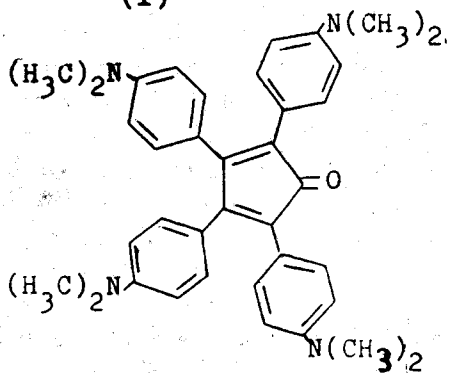
3. *Benzil* and 4. *Dibenzylketone* are well known compound and available commercially.

p-Dimethylamino group substituted tetracyclones. Following compounds were synthesized: 2,5-Diphenyl-3,4-bis- (p-dimethylaminophenyl) cyclopentadinone (I), 2,5-bis- dimethylaminophenyl)-3,4-diphenylcyclopentadiennone. Tetra - p-(dimethylaminophenyl) cyclopentadienone found to be unstable.



(I)

(II)



(III)

Dilthey and his coworkers have tried to synthesize tetracyclone (I), but all experiments were failed [5]. Aubry, using a modified Dilthey and Quint's method has accomplished the synthesis of (I). Aubry has used 25 % alcoholic KOH instead of a few percents of alcoholic KOH, run the reaction much longer, 150 hours, instead of 15 minutes, and at room temperature, instead of at 70–80°C [17]. This reaction has been verified.

Tetracyclone (II) was made as a new compound, condensing 4,4'-bis-dimethylaminodibenzylketone with benzil, according to Dilthey and Quint's method. This is a black crystalline compound, melting at 223–4°C (uncorrected).

In order to make tetracyclone (III), Dilthey and Quint's and Aubrey's method were unsuccessful. 4,4'-Bis-p-dimethylamino benzil which is highly inactive against most of chemical reactions did not condense with 4,4'-bis-pdimethylaminodibenzylketone to give tetracyclone (III). However, some reaction mixtures chromatographed on alumina and a violet coloration was observed on the column which is characteristic for tetracyclones. Eluation of this material gave a violet solution, but it changed to light yellow in a few minutes. The conclusion from this phenomenon is: This tetracyclone is an unstable compound, even if is formed, will decompose spontaneously.

EXPERIMENTAL*

4,4'-Bis-dimethylamino. benzil. In a 500 ml three neck flask, fitted a mechanical stirrer, a reflux condenser and a dropping funnel, were introduced 33 g (0.24 moles) of anhydrous aluminum chloride and 50 ml of carbondisulfide. Flask was cooled in an ice bath and 45 g (0.36 moles) of dimethylaniline was added slowly. Then temperature of the flask was reduced down to -5°C using an ice-salt mixture, 7.6 g (0.06 moles) of oxalylechloride in 150 ml of carbondisulfide was introduced into dropping funnel and mechanical stirrer started. Oxalylechloride solution was dropped into the reaction flask in a moderate rate. (Apparatus was set up in a darkish hood and dropping funnel wrapped with a black

* All melting and boiling points are uncorrected.

paper). After ending of oxalylehlaride addition, stirring continued for an half hours more. About 25 g of ice was added into the flask and carbondisulfide removed by steam distillation. Residue was filtered on a Büchner funnel and washed twice with water. 12.5 g of green colored impure material (m.p. 195–200°C) was obtained. This was dissolved in 200 ml of chloroform, shaken with three times 3 % hydrogenperoxide (basified, 25 ml each). Green color of solution was turned to pale yellow. Chloroform layer separeted, solvent removed by distilation and residue recrystallized from acetone to give 10.8 g (37 mmloes, 62%, based on oxalychloride) of light yellow crystalline material, melted at 200–201°C. No melting point depression was observed mixing this compound with 4,4-bis-dimethylamino benzil.

p-Dimethylaminophenylacetic acid.

1. *From hydrolysis of p-dimethylaminophenylacetthiomorpholide.* In a one liter round bottom flask fitted with reflux condenser, was introduced 100 g (0.38 moles) of p-dimethylaminophenylacetthiomorpholide (m.p. 140–142°) [14], 500 ml of 1:1 (v:v) diluted hydrochloric acid and heated on a water bath for three hours and let stand over night. Next day excess of hydrochloric acid removed by distillation (or into *vacuo*) as well as possible. 200 ml of water was added into the flask and basified adding sufficient amount of 5N NaOH (about 100 g), heated, treated with charcoal (4 g) and filtered. Pale yellow solution was cooled down, a few drops of phenolphthalein added and neutralized with 2N HCl until pink color of solution disappeared, then a few drops of 2N NaOH added to get pink color back. The clear solution was divided exatly in two equal portions, a few drops of methy-lorange added into one of this solution and 2N HCl added to get an orange color. Pink and orange solutions were mixed and stirred well, extracted three times with chloroform (100 ml eeach), solvent removed, 55 g (0.30 moles, 80 %) of brown crude product obtained, m.p. 105–110°C. This crude product may be esterify dirctly. Analytical sample was prepared several crystallization from ligroin and benzene, m.p. 114–5°C, colourless microcrystals.

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82,
Found: C, 66.94; H, 7.41; N, 7.79.

2. *From reductive hydrolysis of p-dimethylaminobenzaldehyde cyanohydrin.* In a 50 ml round bottom flask fitted with reflux condenser, were introduced 10 g of crystalline stannous chloride, 20 ml of conc. hydrochloric acid 2 ml of hydroiodic acid (d, 1.7) and warmed up to get a clear solution, then 0.6 g (34 mmoles) of p-dimethylaminobenzaldehyde cyanohydrin [18] (m.p. 109-112 °C) added and heated on a water bath for three hours. Some stannic salts were precipitated during the reaction. Reaction mixture was cooled, filtered through a fritted glass funnel, filtrate basified adding 5N NaOH then worked up as described above, 3.8 g (23 mmoles, 68 %) of brown crude product (m.p. 95-105 °) obtained. Several recrystallization from ligroin and benzene raised melting point to 114-115 °C. No depression in melting point observed with the mixture of previously obtained compound.

p-Dimethylaminophenylacetic acid is a colourless microcrystalline compound, highly soluble in water, aqueous acids and bases, methanol, ethanol, chloroform, carbon tetrachloride. Moderately soluble in ether, cyclohexane less soluble in hexane, petroleum ether and ligroin.

Ethyl-p-dimethylaminophenylacetate. In a 500 ml two neck round bottom flask, fitted with reflux condenser (protected with a CaCl₂ tube at the top) and a glass inlet tubing, were introduced 54 g (0.30 moles) of p-dimethylaminophenylacetic acid (crude product, m.p. 105-110 °C) and 250 ml of absolute alcohol. Dry HCl gas was bubbled in the solution at room temperature to saturation, then refluxed for two hours while bubbling HCl and let stand overnight. Next two third of alcohol was removed by distillation under diminished pressure, residue transferred in a 2 liter beaker, 500 ml of water added, basified adding 10 % sodium carbonate solution carefully, extracted three times with ether (150 ml each), ether layer washed with 10 ml of saturated sodium chloride solution, dried over sodium sulfate, solvent removed, residue distilled under reduced pressure. 48 g (0.23 moles, 77 %) of slightly yellow oil collected at 105-6 °C /1 mm Hg. This compound is soluble in aqueous acids and organic solvents, insoluble in water and aqueous bases. Density: 1.0483 g/cm³ at 25 °C, refraction index $n_{25}^{25} = 1.5339$.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.28; N, 6.76,
 Found: C, 69.41; H, 8.12; N, 6.84.

p-Dimethylaminophenylacetamide. In a glass stoppered 50 ml bottle were put 2.0 g (10 mmoles) of ethyl-p-dimethylaminophenylacetate and 10 ml of ammonium hydroxide (28%). Mixture let stand at room temperature for 24 hours, shaking frequently in daytime. Oil phase disappeared and white solid was formed. This was filtered, washed with water and recrystallized from alcohol. 1.2 (7 mmoles, 70 %) of colourless crystalline product was obtained, m.p. 175.5–176°C.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72.
 Found: C, 67.36; H, 7.76; N, 15.73.

p-Dimethylaminophenylacetmorpholide. In a 50 ml round bottom flask were introduced 2.6 g (10 mmols) of p-dimethylaminophenylacetthiomorpholide and 10 ml of alcoholic KOH (10 %) and was refluxed for 15 minutes, acidified with 5 % hydrochloric acid, transferred into a 50 ml beaker, treated with charcoal, filtered, dilute ammonia added, precipitate collected on a Büchner funnel. Recrystallization of this crude product from alcohol gave 1.1 g (4.5 mmoles, 45%) of colourless compound, m.p. 101–101.5°C. This compound is soluble in aqueous acids and organic solvents, insoluble in aqueous bases and water.
 Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.36,

Found: C, 67.81; H, 7.99; N, 11.37.

4,4'-Bis-dimethylaminodibenzylketone. In a 500 ml three neck round bottom flask (previously dried well) fitted a dropping funnel, a mechanical stirrer and a reflux condenser (having a $CaCl_2$ tube at the top), were introduced 5.5 g (0.23 atomgram) of magnesium turnures and 50 ml of absolute ether, inside of flask swept out with dry nitrogen. 29 g (0.23 moles) of isopropylbromide in 100 ml of absolute ether was put in the dropping funnel and a Grignard reagent prepared as the known manner. This was cooled in an ice bath, 31.6 g (0.15 moles) of ethyl-p-dimethylaminophenylacetate in 50 ml of absolute ether put into the dropping funnel and added by dropwise while stirring the Grignard reagent. Let stand overnight at room temperature.

Next day, reaction mixture was refluxed for 1/2 hours, cooled with an ice bath, about 15 g of ice and 50 ml of saturated ammonium chloride solution was added. After vigorous reaction ceased, reaction mixture refluxed for about 15 minutes to dissolve most of solids (a few pieces of magnesium left). This was cooled, ether layer separated, aqueous layer extracted once with 50 ml of ether, ether solution combined, dried with anhydrous sodium sulfate transferred in a 500 ml round bottom preweighed flask, ether removed by distillation on a water bath, traces in vacuo and 28 g of uncrystallizable brown oily residue remained (ethyl- α , β -bis-(p-dimethylaminophenylacetoacetate). Into the flask a mixture of 50 ml conc. hydrochloric acid and 40 ml of water was added and refluxed vigorously for two hours, cooled, basified adding 5N NaOH, An oil was separated first, then solidified as a yellow material. This was filtered, washed with ether, 21 g of crude product (m.p. 90–96 °C) was obtained. Twice recrystallization from cyclohexane afforded 17 g (60 mmoles, 75 %) of 4,4'-Bis-dimethylaminodibenzylketone, m. p. 104–6 °C. This is pure enough for the next step. Analytical sample was prepared by several recrystallization from cyclohexane and ethanol, this was slightly yellow needles having melting point 108.2–109 °C.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45,

Found: C, 76.83; H, 8.19; N, 9.57.

Phenyldrazone of 4,4'-bis-dimethylaminodibenzylketone.

1.5 g (5.0 mmoles) of 4,4'-bis-dimethylaminodibenzylketone, 1.5 g of phenylhydrazine and 15 ml of ethanol was refluxed for 20 minutes, let stand too cool, separated solid filtered, washed with alcohol. Recrystallization twice from ethanol gave 1.1 g (3.0 mmoles, 60 %) colourless needles, m.p. 120–2 °C (decomposed).

Anal. calcd. for $C_{25}H_{30}N_4$: N, 14.50, found: 14.32.

2,5-Bis-p-dimethylaminophenyl-3,4-diphenylcycloptadienone.

In a 100 ml round bottom flask, fitted with reflux condenser, were introduced 2.1 g (10 mmoles) of benzil. 3.0 g (10 mmoles) of 4,4'-bis-dimethylaminodibenzylketone and 40 ml of absolute alcohol. Mixture was brought just below to boiling point of ethanol, and 2 ml of alcoholic potassium hydroxide (25 %) was

added through the condenser, refluxed for 15 minutes and let stand to cool. Separated dark solid was filtered, washed with methanol. Recrystallization from benzene-ethanol mixture (1:1, v:v) gave 2.8 g (6.0 mmoles, 60 %) of dark crystalline compound, m.p. 223–4°C.

Anal. Calcd. for $C_{33}H_{30}N_2O$: C, 84.22; H, 6.43; N, 5.95,
Found: C, 84.03; H, 6.39; N, 6.24.

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Ö Z E T

Benzil veya p-dimetilamino süstitüe benzil ve dibenzil keton veya p-dimetilamino süstitüe dibenzil ketonların kodensasyonuyla, p-dimetilamino süstitüe tetrafenilsiklopentadienonlar elde edilmiştir. p-Dimetilamino süstitüe benzilin elde edilmesi için yeni bir metod geliştirilmiş, p-dimetilamino süstitüe dibenzil keton ve bu bileşiğin elde edilmesi için gerekli olan bazı ara basamak ürünleri yeni bileşikler olarak elde edilmiştir.

AVIS IMPORTANT

La Revue "Communications de la Faculté des Sciences de l'Université d'Ankara" sera publiée dorénavant sous forme de fascicules à l'arrivée de chaque article. Le tome 13 de la série B', continuant par ce fascicule, sera complété par le dernier fascicule à paraître avant le 31 décembre 1966.

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