ORGANIC REACTIONS IN AQUEOUS SOLUTION
Part-X: Effect of Sonication on the Reaction of Hexamethylenetetramine with Dibenzoylmethane in the Formation of $\alpha,\alpha,\gamma,\gamma$-Tetrabenzoylpropane

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Summary: An intensive investigation of the reaction of hexamethylenetetramine with dibenzoylmethane under varying conditions in methanol, ethanol, and their mixtures with water, and also in water alone has been carried out. The effect of sonication on these reactions has also been studied. The study has led to the development of a simple method for the synthesis of α,α,γ,γ-tetrabenzoylpropane in the theoretical yield, hitherto, not reported in the literature. Methylene-*bis*-dibenzoylmethane thus obtained turned out to be tautomeric in nature. It has not been reported in the literature so far. Its tautomeric nature has been established and is being reported for the first time.

INTRODUCTION:

Aldehydes react with dicarbonyl compounds to yield *bis*(β-diketones) and bis(β-ketoesters) [1]. Several *bis*(β-diketones) including α,α,γ,γ-tetrabenzoylpropane have been prepared by reacting an aldehyde with a β-diketo compound dissolved in organic solvents under the influence of acids or organic bases [2-5]. Hexamine is regarded as a special form of formaldehyde and is widely used in the preparation of phenolic resins [6]. Hexamine has been used as an aminomethylating agent in the preparation of certain derivatives of 1,3-diazadamantan-6-ones [7-9]. Hexamine reacts with certain β-ketoesters in presence of ammonium acetate to yield dihydropyridine derivatives possessing anti-metastatic activity [10]. Hexamine has been used as a dual source of formaldehyde and ammonia [11] in its reactions with β-ketoesters and β-dikeones in the preparation of dihydropyridine derivatives which are very useful and expensive compounds [6,10,12-15].

The present work which is a continuation of our earlier work [16], describes the synthesis of α,α,γ,γ-tetrabenzoylpropane by the reaction of hexamethylenetetramine with dibenzoylmethane in organic solvents as well as their mixtures with water at room temperature. The effect of sonication on this reaction has also been studied. Dibenzoylmethane is insoluble in water and does not react with hexamine under ordinary conditions. It, however, became reactive under the influence of ultrasound and formed methylene-*bis*-derivative. As a result of the present investigation a simple and convenient method for the preparation of α,α,γ,γ-tetrabenzoylpropane in the aqueous medium in the theoretical yield has been developed. A careful analysis has revealed that this compound is tautomeric in nature. This has been established and is being reported for the first time.

RESULTS AND DISCUSSION

The reaction of hexamethylenetetramine with dibenzoylmethane dissolved in methanol, ethanol and in their mixtures with water under acidic conditions at room and elevated temperatures, and at reflux affords α,α,γ,γ-tetrabenzoylpropane in considerably high yields (50-83%) [Table 1]. Dibenzoylmethane, owing to its insolubility in water, fails to react with hexamine under ordinary conditions. Under the influence of ultrasound, however, the reaction proceeds to afford the *bis*-compound in quantitative yield [Table 2], which has not been achieved earlier.

The ^{1}H n.m.r. of methylene-*bis*-dibenzoylmethane, m.p. 176-177 °C obtained as a result of the present and the previous work [11] signalled absorptions at 2.80 (triplet, methylene protons), 5.79 (triplet, methine protons), 7.50 (triplet, aromatic *meta* protons), 7.58 (triplet,

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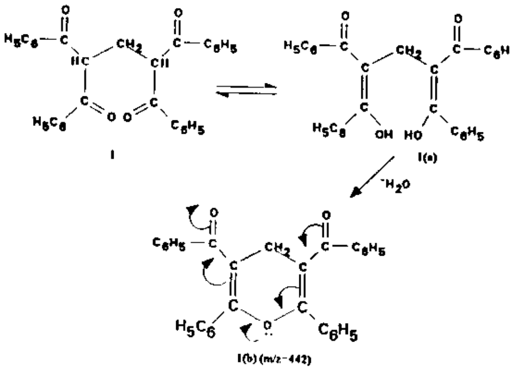
TABLE 1 α,α,γ,γ-Tetrabenzoylpropane from Hexamethylenetetramine and Dibenzoylmethane at Room Temperature (15±2 °C)

	mmol (Molar Ratio) Hexamine:Dibenzoyl-methane	Medium (37.5 mL)	pH*	Duration (days)	Yield mg. (%)
01	2.5:2.5 (1:1)	Ethanol:Water 2.5:1	5.80	3	290 (50.3)
02	"	Methanol:Water 2.5:1	5.85	"	295 (51.2)
03	"	"	"	1 **	313 (54.4)
04	"	Ethanol	5.70	3	414 (72.0)
05	"	Methanol	5.75	"	432 (75.1)
06	2.5:5.0 (1:2)	"	5.85	"	331 (57.5)
07	2.5:7.5 (1:3)	Methanol	5.65	"	213 (37.0)
08	2.5:1.25 (1:1/2)	Methanol	6.15	"	475 (82.6)
09	2.5:0.625 (1:1/4)	Methanol	6.35	"	490 (85.2)
10	2.5:0.3127 (1:1/8)	Methanol	6.45	"	425 (73.9)
11	2.5:0.625 (1:1/4)	Ethanol	5.35	"	478 (83.1)

* By the addition of 0.20-0.60 mL HCl (37% w/w), (0.20 mL for every 2.5 mmol of hexamine).

** Initial refluxing for 1 hour

aromatic *para* protons) and 8.18 PPM (duplet, *ortho* protons) in the ratio 1:1: 4:2:4 as expected of the *bis*- ketonic compound corresponding to the molecular formula $C_{31}H_{24}O_4$. However, its molecular ion signalled peak at m/z 442 (instead of 460), which corresponds to its dehydrated product. When the reaction was carefully repeated under varying conditions in water (in an ultrasonic bath at elevated temperature) as well as in different organic solvents at room temperature, the *bis*-compound thus obtained had similar melting point (175-177°C) and identical molecular ion absorption (m/z 442), which again corresponded to the dehydrated product. Its 500 MHz ^{1}H N.M.R. in $CDCl_3$ indicated a broad absorption centered at 1.594 (OH), 2.725 (triplet, methylene protons), 5.721 (triplet, methine protons), 7.470 (triplet, aromatic *meta* protons), 7.50 (triplet, *para* protons) and 8.119 PPM (doublet, *ortho* protons) (Fig.1). However, its ^{1}H N.M.R. in $CDCl_3$ with D_2O shake signalled absorptions at 2.749 (triplet, methylene protones), 4.650 (singlet, HOH), 4.909 (singlet, HOD), 5.718 (triplet, methine protons), 7.467 (triplet, aromatic m*ata* protons), 7.568 (triplet, aromatic *para* protons), and 8.155 PPM (doublet, *ortho* protons). Thus, the broad signal due to hydroxy protons at 1.594 PPM disappeared on D_2O shake. However, two additional signals appeared in the form of singlets at 4.650 and 4.909 PPM, while, all the other signals almost exactly corresponded to those indicated in Fig.1. The former singlet may be due to water present as impurity in D_2O, while the latter singlet may be attributed to HOD since, deutrated sample may exhibit an extra resonance at about 5 PPM due to HOD [17]. Hence, these N.M.R. data demonstrate the existence of tautomeric enolic form of the *bis*-compound (1a). This enolic tautomer is supposed to be in the *syn*-configuration, which can dehydrate rather smoothly to afford a stable dehydrated product (1b) due to the possibility of extension of conjugation. This might be the reason that instead of the true molecular ion (m/z 460) of the *bis*-compound it indicated only a molecular ion (m/z 442) corresponding to the molecular mass of the dehydrated product (1b). Moreover, the signal of two methylene protons indicated relative integral of 0.1194, while that of the two methine protons was 0.1107. The overall reduction of the methine signal by 0.0087 is likely due to its contribution to form the enolic tautomer (1a), which works out to 7.28% under normal circumstances. The present investigation reveals the tautomeric nature of the *bis*-compound 1(a) which is being reported for the first time.



EXPERIMENTAL

General:

Experiments were carried out in methanol, ethanol, water, and their mixtures at room temperatures (15±2 °C), at elevated temperatures (70-75 °C), and at mild reflux in Quickfit glass apparatus. Sonication was carried out in Jencons Ultrasonik 300 ultrasonic bath at 15±2–60±2 °C. The chemicals and solvents used were usually of analytical grade. Distilled water was used in all the experiments and each experiment was repeated thrice to record the average yields of the products.

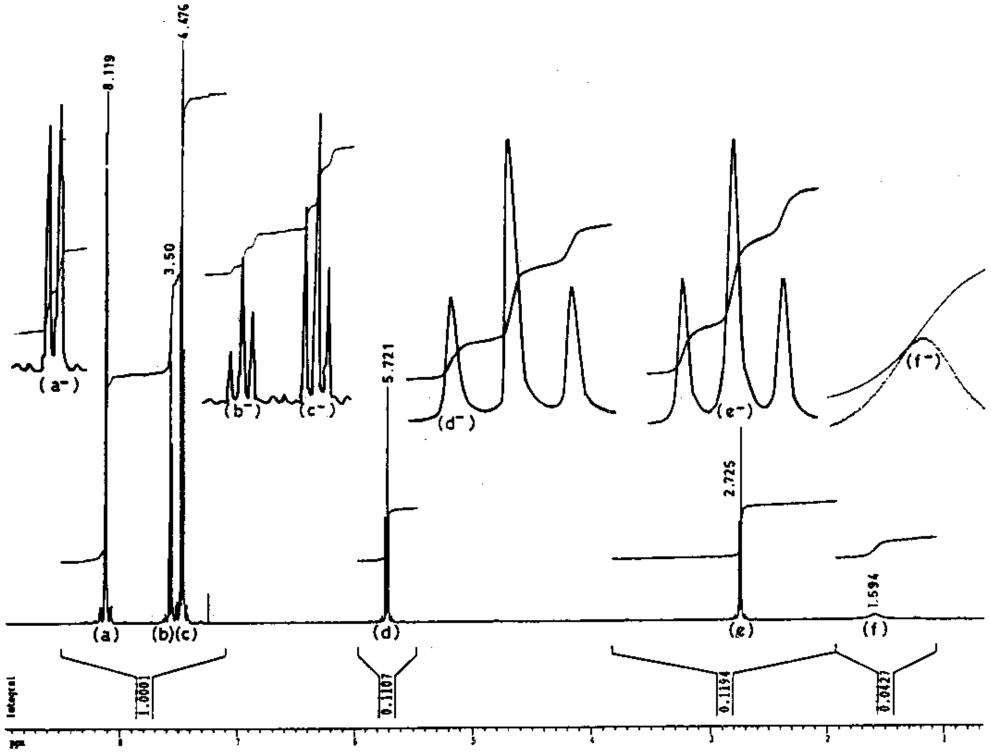


Fig. 1: ^{1}H-NMR (500 MHz) spectrum of methylene-bis-dibenzoyl methane (1 and 1a) in $CDCl_3$ and its expansion.

TABLE 2 α,α,γ,γ-tetrabenzoylpropane from Hexamethylenetetramine (0.350 g; 2.5 mmol), Dibenzoylmethane (0.560 g; 2.5 mmol), and HCl (0.20 mL ,37% w/w) by Sonication

	Medium (37.5 mL)	pH*	Temperature °C	Total Reaction Time (Sonication Time)	Yield mg (%)
01.	Water**	5.40	15±2–60±2	3 days (5 hours/day)	550 (95.6)
02.	"	"	"	8 days (5 hours/day)	575 (100)
03	Ethanol:Water 2.5:1	5.80	"	3 days (5 hours/day)	400 (69.5)
04	Methanol:Water 2.5:1	5.85	"	"	416 (72.3)
05	Ethanol	5.70	"	3 days (4 hours/day)	235 (40.8)
06	Methanol	5.75	"	"	265 (46.1)
07	"	"	"	3 days (5 hours/day)	284 (49.4)

* By the addition of 0.20 mL HCl (37% w/w)
** 40 mL

The pH's of the reaction mixtures were recorded on Hanna H 8417 Digital pH Meter. The products obtained in different reactions were isolated by filtration at mild suction by using a water-jet pump, washed several times with small portions of water, and dried in a vacuum desiccator for 2-3 days. The compounds were purified by repeated recrystallisation from ethanol and their melting points were noted on Griffin Melting Point Apparatus. These were identified by carrying out combustion analysis, infrared and mass spectroscopy. Before analysis, each specimen was finely powdered and dried at room temperature in a vacuum desiccator for 5 days. Infrared and mass spectra were run on Hitachi 270-30 Infrared Spectrometer and Hitachi-Perkin Elmer Mass Spectrometer respectively. Only a few representative methods of preparation have been described. Results are recorded in Tables 1 & 2.

Methods of Preparation:

At Room Temperature

a) Dibenzoylmethane (560 mg; 2.5 mmol) and hexamethylenetetramine (88.5 mg; 0.625

mmol), were dissolved in methanol. The mixture was acidified with 0.05 mL of hydrochloric acid (37 % w/w) and allowed to stand at room temperature with occasional shaking. After 3 days white crystals of α,α,γ,γ-tetrabenzoylpropane (490 mg; 82.5%) were obtained. Recrystallization from boiling ethanol afforded white lustrous crystals melting at 176-177 °C, lit.[2,3,11] m.p. 175-177 °C. Its melting point showed no depression when mixed with authentic sample prepared by literature methods and their i.r. spectra were identical. Its molecular ion signalled peak at m/z 442 which corresponded to its dehydrated product.

Reaction carried out in ethanol under similar conditions afforded 478 mg; 83.1% of the product.

b) Dibenzoylmetnhane (560 mg; 2.5 mmol), hexamethylenetetramine (350 mg; 2.5 mmol) and hydrochloric acid (0.2 mL; 37% w/w)were dissolved in 37.5 mL of methanol:water mixture(2.5:1) . The reaction mixture was thoroughly shaken and kept at room temperature for 3 days to obtain α,α,γ,γ–tetrabenzoylpropane (295 mg; 51.2%). Recrystallization from ethanol gave white shining granules melting at 176-177 °C, alone or mixed with the specimen prepared by the method a) as above.

Reaction in ethanol:water mixture (2.5:1; 37.5 mL) under identical conditions afforded 290 mg (50.3%) of the compound.

In Ultrasonic Bath

a) Hexamethylenetetramine (560 mg; 2.5 mmol) was dissolved in water (40 mL) in a Quick-fit conical flask. To this solution dibenzoylmethane (560 mg; 2.5 mmol) was added and shaken vigorously to get a fine suspension. The mixture was acidified with 0.20 mL of hydrochloric acid (37% w/w). It was transferred to a sonication bath , fitted with a reflux condenser, and sonicated for 5 hours. During the sonication the temperature of the reaction mixture rose from room temperature (15 ±2 °C) to 60 ±2 °C. At the end of the period the reaction mixture was taken out of the sonication bath and placed over-night at room temperature. The procedure was repeated for a further period of 7 days. The reaction mixture was finally cooled to room temperature to obtain α,α,γ,γ tetrabenzoylpropane (575 mg; 100%). Recrystallization from ethanol gave white shining crystals melting at 176-177 ° C, lit. [2,3,11] m.p.175-177 °C. Its melting point showed no depression when mixed with authentic samples prepared by literature methods and also with the specimens prepared at room temperature by the methods described above. Their i.r. spectra were also identical. (Found: C, 81.02; H, 5.26%; $C_{31}H_{24}O_4$ requires: C, 80.87; H, 5.22%). Its molecular ion also signalled peak at m/z 442 which again corresponded to its dehydrated product. The yield of the sufficiently pure compound after 3 days (sonicated for 5 hours a day) was 550 mg; 95.6%.

b) Dibenzoylmethane (560 mg; 2.5 mmol) and hexamethylenetetramine (350 mg; 2.5 mmol) were dissolved in methanol;water (2.5;1) mixture 937.5 mL) and acidified with 0.2 mL of hydrochloric acid. The mixture was placed in the sonication bath for sonication at 15±2--60±2 °C for 5 hours each day for 3 days to obtain white crystals of α,α,γ,γ-tetrabenzoylpropane (416 mg; 72.3%). Recrystallisation from ethanol yielded white crystals melting at 176-177 °C alone, or mixed with authentic samples prepared by literature methods.

The reaction when carried out in ethanol:water mixture (2.5:1; 37.5 mL) yielded 400 mg; 69.5% of the compound.

c) Dibennzoylmethane (0.50 g; 2.5 mmol), hexamethylenetetramine (350 mg; 2.5 mmol) and hydrochloric acid (0.2 mL; 37% w/w) were dissolved in 37.5 mL of methanol. The reaction mixture was placed in the sonication bath and sonicated for 3 hours. At the end of the period the reaction flask was taken out of the bath and allowed to stay at room temperature to be sonicated the next day again. After 3 days α,α,γ,γ-tetrabenzoylpropane (265 mg; 46.1%) was collected. Purification by recrystallisation from ethanol afforded white shining crystals melting at 176-177 °C.

Reaction in ethanol (37.5 mL) carried out under identical conditions yielded 235 mg; 40.8% of sufficiently pure compound.

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