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Iodotrimethylpivalophenones and Iodotetramethylpivalophenones. Preparation and Properties[1]

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Synopsis. Three isomeric iodotrimethylpivalophenones and iodotetramethylpivalophenones have been prepared from the corresponding polymethylbenzenes by using the Perrier procedure of the Friedel-Crafts acylation, followed by the iodination of the resulting ketones with iodine-periodic acid dihydrate. Attempts to convert some of these hindered iodoketones to bis(pivaloyl)polymethylbenzenes *via* the Grignard reagent have failed.

In the course of our work on the non-conventional electrophilic substitution of polyalkylaromatics, some bis(pivaloyl)polymethylbenzenes are required. Several hindered aromatic ketones such as acetomesitylene, acetodurene, and acetoisodurene have been known to allow further acylation due to the lack of the coplanarity between acyl group and aromatic ring.[2] Similar attempts to convert hindered polymethylpivalophenones to bis(pivaloyl)polymethylbenzenes, however, did not afford the desired diketones but led to the extensive deacylation, giving the complicated mixture of hydrocarbons and polymeric substances. No evidence has been obtained of the diketone formation.

As an alternative approach to the diketones, the reaction of the Grignard reagent from bromopolymethylpivalophenones with pivaloyl chloride appeared to be attractive, since 3-bromo-2,4,6-trimethylpivalophenone had been reported by Pinkus and coworkers to yield the Grignard reagent with a keto carbonyl function intact.[3] We repeated their work and found the reaction to be slow and incomplete. Consequently, it was thought desirable to replace the bromo compound by the iodo one for the preparation of the Grignard reagent. This note describes the preparation and some properties of iodotrimethylpivalophenones and iodotetramethylpivalophenones.

Direct nuclear iodination of alkyl aryl ketones has apparently not been described to date probably because of the high propensity of the alkyl ketone moiety to react with attacking species as well as the deactivating effect of acyl group upon the aromatic ring. Iodine-periodic acid dihydrate as an iodinating agent was found to provide a simple direct route to some iodopolymethylacylophenones.[4] Trimethylpivalophenones were readily iodinated with the above reagent to give the monoiodo derivatives in an average isolated yield of over

TABLE 1. PHYSICAL PROPERTIES OF SOME MONOIODOTRIMETHYLPIVALOPHENONES AND MONOIODOTETRAMETHYLPIVALOPHENONES

Compound	Mp (°C)	Yield (%)	^{1}H NMR spectra (δ)		IR spectra[b] (cm^{-1})	Elementary analysis (%)			
			CH_3[a]	Aromatic H		Found		Calcd	
						C	H	C	H
5-Iodo-2,3,4-trimethylpivalophenone	107—109	83	1.24 (3) 2.08 (1) 2.29 (1) 2.49 (1)	7.45	978, 1092, 1205, 1283, 1693,	50.63	5.81	50.92	5.80
3-Iodo-2,4,5-trimethylpivalophenone	85—86	89	1.24 (3) 2.30 (1) 2.35 (1) 2.48 (1)	6.85	891, 1092, 1178, 1274, 1697	51.10	5.83	50.92	5.80
3-Iodo-2,4,6-trimethylpivalophenone	52—53	88	1.23 (3) 2.14 (1) 2.32 (1) 2.44 (1)	6.93	932, 1160, 1696	50.71	5.82	50.92	5.80
6-Iodo-2,3,4,5-tetramethylpivalophenone	114—116	85	1.34 (3) 2.15 (1) 2.17 (1) 2.32 (1) 2.49 (1)	—	888, 933, 1689	52.08	6.23	52.34	6.15
5-Iodo-2,3,4,6-tetramethylpivalophenone	92—94	94	1.23 (3) 2.08 (1) 2.31 (2) 2.57 (2)	—	907, 1086, 1198, 1695	52.20	6.36	52.34	6.15
4-Iodo-2,3,5,6-tetramethylpivalophenone	133—134	93	1.23 (3) 2.16 (2) 2.49 (2)	—	960, 1091, 1680	51.93	6.15	52.34	6.15

a) Numerals in parentheses refer to the number of methyl groups. b) Principal peaks in the region, 650—1300 and 1500—2000 cm^{-1}.

80%, with the ease of iodination decreasing in the order 2,4,6->2,3,4->2,4,5-. 2,3,4-Trimethylpivalophenone gave 5-iodo-2,3,4-trimethylpivalophenone, and 2,4,5-trimethylpivalophenone gave 3-iodo-2,4,5-trimethylpivalophenone as the only product. As expectedly, the *meta* position to the acyl group was preferred to *ortho* position. The position occupied by iodine atom in these systems was established by the comparison of their ^{1}H NMR spectra with those of the parent ketones.

Iodination of tetramethylpivalophenones proceeded with much ease. Of three isomeric ketones, 2,3,4,6-tetramethylpivalophenone was the most reactive, followed by 2,3,5,6-tetramethylpivalophenone and 2,3,4,5-tetramethylpivalophenone. Infrared and ^{1}H NMR spectral inspection of the crude reaction product had no indication of displacement of acyl group by iodine atom nor substitution on alkyl side-chain.

All the iodotrimethylpivalophenones and iodotetramethylpivalophenones obtained are well crystallized solids melting between 85 and 134 °C. They are moderately or readily soluble in light petroleum, benzene, carbon tetrachloride, chloroform, and hot ethanol, and are only slightly soluble in cold methanol. Yields, physical constants, and analytical data are given in Table 1.

The Grignard reagents were prepared from 5-iodo-2,3,4,6-tetramethylpivalophenone and 4-iodo-2,3,5,6-tetramethylpivalophenone, respectively, and treated with an excess of pivaloyl chloride. Ordinary work-up followed by chromatography on alumina, however, gave the parent tetramethylpivalophenones as the major product. Thick-layer chromatography of the product mixture gave some amounts of two other products, and none of these proved to be the expected bis(pivaloyl)-tetramethylbenzenes.

Experimental

All mp's are uncorrected. ^{1}H NMR measurements were made with a Varian T-60 spectrometer in deuteriochloroform solutions against internal TMS. Infrared spectra were determined in Nujol mulls on a Hitachi 215 spectrophotometer. Trimethylpivalophenones and tetramethylpivalophenones were prepared from the corresponding polymethylbenzenes by using the Perrier procedure of the Friedel-Crafts acylation.[5]

Procedure for the Preparation of Iodopolymethylpivalophenones. The general procedure is illustrated below by the reaction of 2,3,4,6-tetramethylpivalophenone.[6]

5-Iodo-2,3,4,6-tetramethylpivalophenone. A mixture of 2,3,4,6-tetramethylpivalophenone (6.45 g), iodine (3.0 g), periodic acid dihydrate (1.35 g), and 80% acetic acid (40 ml) containing several drops of concentrated sulfuric acid was kept with stirring at 70—80 °C for about 1 hr until the color of iodine disappeared. After cooling water was added, and the crystalline deposit was collected by filtration and passed over a short alumina column with light petroleum. From the eluate the iodo compound was obtained as colorless prisms, mp 92—94 °C (from methanol). Yield, 9.52 g (94%).

Attempted Conversion of Iodotetramethylpivalophenones to Bis-(pivaloyl)tetramethylbenzenes. To a solution of 5-iodo-2,3,-4,6-tetramethylpivalophenone or 4-iodo-2,3,5,6-tetramethylpivalophenone (3.38 g) in dry ether (50 ml) were added magnesium powder (0.24 g) and a small crystal of iodine, and the mixture was stirred magnetically in a tightly stoppered vessel placed in a polythene bag containing silica gel desiccant until the metal had almost disappeared. This required several days. The Grignard reagent was then added at one time to a solution of fresh pivaloyl chloride (6.0 g) in the same solvent (20 ml). After mild reaction had ceased, the mixture was hydrolyzed by pouring it into a slurry of crushed ice and hydrochloric acid. The ether layer was separated and washed with aqueous sodium hydrogencarbonate and water. The ethereal solution was dried over anhydrous sodium sulfate and evaporated to leave a light yellow oil, which on standing partly solidified to a crystalline mass. The solid product (*ca.* 1.4 g) was identified as the parent tetramethylpivalophenone by comparison with the authentic sample. Preparative thick-layer chromatography of the oily part gave three minor components. They were found to be unchanged starting material, aliphatic ketone, and alcohol of yet unidentified structure, respectively. None of the expected diketones could be isolated.

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6) New compound. Mp 35—38 °C; bp 133—135 °C/6 mmHg. ^{1}H NMR: δ 1.23 (s, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 2.24 (s, 3H), and 6.84 ppm (s, aromatic H). Prolonged, slow pivaloylation of isodurene leads to the formation of appreciable amounts of 2,3,5,6-tetramethylpivalophenone.