THE STRUCTURE OF MUSK KETONE AND MUSK TIBETENE¹

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Chloromethylation of 5-*t*-butyl-1,3-dimethylbenzene (I) yields a single product which was identified by Carpenter (1) as 2-*t*-butyl-4,6-dimethylbenzyl chloride (II). The symmetrical structure (III), however, was assigned to this compound by Fuson, Denton, and Kneisley (2) and by Buu-Hoi and Cagniant (3). The evidence favored the unsymmetrical structure, since the hydrocarbon obtained by reduction had been prepared by treatment of pseudocumene with



t-butyl chloride in the presence of aluminum chloride (4). Admittedly this is not strong evidence, since rearrangement of groups may have occurred in the presence of aluminum chloride. Moreover, the yields were low.

Carpenter's conclusion derived further support by analogy with the acetylation of the butylxylene by the Friedel-Crafts method; the acetylation product, mother substance of musk ketone, was believed to possess the unsymmetrical structure, IV (6, 10).

In a search for additional evidence relative to the structure of the chloromethylation product and the acetyl compound, we have carried out numerous experiments, many of which consisted in attempts to check earlier reports. The results have convinced us that these compounds have the symmetrical (III and V) rather than the unsymmetrical structures (II and IV). From this conclusion it follows that the structures hitherto assigned to musk ketone and Musk Tibetene are to be revised also and are correctly represented by formulas

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VI and VII, respectively. The conclusion with reference to musk ketone corroborates that of Chichibabin (9).



The primary reference compound in our work was the mononitration product. (m.p. 85°) (VIII). Its structure was established by Baur (7, 10) by an unequivocal method and has never been questioned. We have converted it to the corresponding bromo derivative (X) by way of the amine (IX). The amine was made by reducing the nitro compound and was transformed to the bromo compound by the Sandmeyer method. The product, a solid of melting point 51° , is the same as that obtained by direct bromination of the hydrocarbon (8) or by heating the N,N-dibromo derivative of 4-*t*-butyl-2,6-dimethylbenzamide (9).



The bromo compound, the structure of which was thus made certain, was employed as the reference substance in the determination of the structure of the chloromethyl derivative. Treatment with zinc dust and water converted the chloromethyl compound to 5-t-butylhemimellitene (XI) (m.p. 32°), the structure of which was established by showing that the compound could be made also by the action of methyl sulfate on the Grignard reagent prepared from the bromo compound (X). The two samples of the butylhemimellitene were nitrated separately. The nitration products (m.p. 136°) proved to be identical and are undoubtedly Musk Tibetene (VII).

The bromo compound served also to establish the structure of musk ketone. Carbonation of the Grignard reagent made from the bromo derivative yielded an acid (XII), the acid chloride of which reacted with dimethylcadmium to yield a ketone (m.p. $46-47^{\circ}$) identical with that which is formed by the Friedel-Crafts method.



Its structure is, therefore, correctly represented by Formula V and that o^{f} musk ketone by Formula VI.

Although the foregoing proofs of structure for the chloromethyl compound (III) and for the acetyl derivative (V) involve only reactions which are known to proceed normally, the importance of the problem seemed to warrant additional confirmation. It has been found possible to relate the two key compounds through the hydrocarbon, 4-t-butyl-2,6-dimethylethylbenzene (XIII). It was obtained from the ketone by a Clemmensen reduction and by the action of dimethyl sulfate on the Grignard reagent derived from the chloromethyl compound. The two samples of the ethyl compound yielded the same dinitro derivative (m.p. 129°).



It remained to discover if possible the error in the original structure proof of Baur (10) which led him to assign the unsymmetrical structure to the methyl aryl ketone. The symmetrical nitrile (XV) appears to be the key compound in his proof. It has been prepared from the amine by the Sandmeyer method (10, 11) and was reported to melt at 88° (10). In one report (11) this melting point, possibly by a misprint, was given as 83° . We have prepared it from the amine by the Sandmeyer method and from the bromo compound by the Rosenmund-von Braun method. The two products had the same melting point (64.5-65.5°) and proved to be identical. We were able to relate this nitrile to the acid (and hence to the methyl ketone) through the aldehyde (XIV) obtained by reduction of the acid chloride. It may be mentioned in passing that a plan for preparing the aldehyde from the methyl ketone by an oxidative process was not carried beyond the glyoxal. Dehydration of the oxime of the aldehyde yielded a sample of the nitrile which was the same as the others.



The method for converting the aldehyde to the nitrile was that employed by Baur. Our aldehyde had the same melting point (60°) as his. Likewise the dinitro derivative of our sample had the melting point (111°) reported by Baur. Yet the nitrile which we obtained melted at $64.5-66.5^{\circ}$ instead of 70° , the melting point reported by Baur. Thus we have made the nitrile in three different ways without observing either of the compounds reported by Baur. From these results it seems certain that musk cyanide (10, 11) and musk aldehyde (12)possess the symmetrical structures XVI and XVII, respectively. Chichibabin also came to the conclusion that musk aldehyde had the symmetrical structure (9).



EXPERIMENTAL

Nitration of 5-t-butyl-1,3-dimethylbenzene. The reaction, first reported by Baur (7), was carried out according to a procedure similar to that of Powell and Johnson for nitromesitylene (13). The symmetrical product, 4-t-butyl-2,6-dimethylnitrobenzene, was obtained in 66% yield; m.p. 84-85°. The liquid isomer, 6-t-butyl-2,4-dimethylnitrobenzene, was isolated from the filtrates in a yield of 29%; b.p. 109-110.5° (4 mm.); n_{D}^{20} 1.5145 d_{20}^{20} 1.0373. Molecular refractivity; Calc'd for C₁₂H₁₇NO₂: 60.23. Found: 60.18.

The solid mononitro compound was converted to the corresponding trinitro compound (musk sylene) by the following procedure. Four milliliters of fuming nitric acid was added, dropwise with stirring, to a mixture of 1 g. of the nitro compound and 6 ml. of fuming sulfuric acid. The reaction mixture was warmed for fifteen minutes on a steam-bath and poured on cracked ice. The product crystallized from 95% ethanol in white platelets; m.p. 112-113°.

Anal. Calc'd for C12H15N3O6: C, 48.48; H, 5.05; N, 14.14.

Found: C, 48.61; H, 5.14; N, 14.23.

Nitration of the liquid mononitro compound by a similar procedure yielded a product

melting at 109-111°. A mixture of the two nitration products melted at 110-111.5°. Baur (7) reported the trinitro derivative to melt at 110°.

4-t-Butyl-2,6-dimethylacetanilide. A mixture of 91 g. of 4-t-butyl-2,6-dimethylnitrobenzene, 400 ml. of water, 5 ml. of concerntrated hydrochloric acid, and 110 g. of iron powder was heated under reflux, with stirring, for five and one-half hours. The solution was made basic by the addition of 10 g. of sodium carbonate, and the precipitate removed by suction filtration. The precipitate was washed with five 100-ml. portions of ether. The ether washings were then used to extract the amine from the aqueous filtrate. Three extractions of this ether solution were made, using 100-ml. portions of dilute hydrochloric acid. The amine hydrochloride was removed by filtration and washed well with ether; yield 94%.

One gram of the amine hydrochloride was treated with 12 ml. of 20% potassium hydroxide solution and 5 ml. of acetic anhydride. The white amide was recrystallized from an ethanol-water mixture; m.p. 162.5-163°.

Anal. Cale'd for C14H21NO: C, 76.66; H, 9.65.

Found: C, 76.96; H, 9.85.

Chichibabin (9) gave the melting point of the acetanilide as 159° and Baur (10) as 81°. Because of this discrepancy the corresponding benzoyl derivative was made. It was found to melt at 229-231° when heated rapidly on the Macquenne block. The melting point reported by Baur (10) for this derivative is 233°.

6-t-Butyl-2,4-dimethylacetanilide. By use of a procedure similar to that just outlined for the symmetrical isomer, 6-t-butyl-2,4-dimethylaniline was obtained in 75% yield. The acetanilide, after recrystallization from an ethanol-water mixture, melted at 188-189°.

Anal. Calc'd for C14H21NO: C, 76.66; H, 9.65.

Found: C, 76.66; H, 9.59.

The benzoyl derivative melted at 206-207°. Baur (10) reported the value 206°.

4-t-Butyl-2,6-dimethylbromobenzene. A. From 4-t-butyl-2,6-dimethylaniline. The amine was converted into the bromide by use of the Sandmeyer method. From 5 g. of the amine was obtained 4.5 g. of bromide, which separated from ethanol in white platelets melting at 50-51°.

B. From 5-t-butyl-1,3-dimethylbenzene. The hydrocarbon was brominated by a procedure similar to that employed by Smith (24) for bromomesitylene. The product, obtained in 93% yield, melted at 48-50° and did not depress the melting point when mixed with the sample described under A. The value given in the literature for the melting point is 45° (8, 9).

Attempts to chloromethylate the bromo compound were unsuccessful.

5-t-Butylhemimellitene. By use of the procedure of Fuson, Denton, and Kneisley (2) 4-t-butyl-2,6-dimethylbenzyl chloride was converted to the hydrocarbon in 89.5% yield. The hydrocarbon was made also from 4-t-butyl-2,6-dimethylbromobenzene. To a Grignard reagent, prepared from 5 g. of magnesium, 51 g. of the bromo compound, and 750 ml. of dry ether, and cooled to 10°, was added dropwise 104 g. of freshly distilled dimethyl sulfate in 500 ml. of dry ether. After the mixture had stood overnight, the product was isolated according to conventional methods. The butylhemimellitene (12 g.) distilled at 88-90° (4 mm.) and crystallized in the receiver. After one recrystallization from ethanol, it melted at 31-32°. It was shown by the mixed melting point method to be identical with the sample prepared from the chloromethyl compound. The two samples of hydrocarbon yielded the same dinitro derivative (m.p. 134.5-136°).

4-Bromo-5-t-butylhemimellitene. This compound was made by bromination of 5-t-butylhemimellitene. A solution of 8.3 g. of bromine in 15 ml. of carbon tetrachloride was added over a period of three hours, with vigorous stirring, to a mixture of 8.8 g. of 5-t-butylhemimellitene, 25 ml. of carbon tetrachloride, and 0.4 g. of iron powder. The mixture was cooled in an ice-bath during the addition and for three hours afterward. It was then kept, for eight hours, with continued stirring, at room temperature. The bromide, isolated by the usual procedure, was purified by distillation followed by three recrystallizations from ethanol; m.p. 50-51°. A mixture of this compound with an authentic sample of 4-*t*-butyl-2,6-dimethylbromobenzene (m.p. 49.5-51°) melted at 30-33°.

Anal. Cale'd for C₁₃H₁₉Br: C, 61.18; H, 7.50.

Found: C, 60.83; H, 7.56.

4-t-Butyl-2,6-dimethylacetophenone. A. From 5-t-butyl-1,3-dimethylbenzene. Anhydrous aluminum chloride (141 g.) was added, with vigorous stirring and over a period of ninety minutes, to a mixture of 75 g. of the hydrocarbon, 195 g. of freshly distilled acetyl chloride, and 350 ml. of carbon disulfide. The mixture was allowed to stand for one hour. The ketone, isolated by conventional procedures, boiled at 107-110° (2.5 mm.) and melted at 45.5-46.5°. It crystallized from methanol in large glistening plates. Baur (5, 10) reported the melting point 48° for the unsymmetrical isomer.

Anal. Calc'd for C14H20O: C, 82.30; H, 9.87.

Found: C, 82.27; H, 9.97.

The dinitro derivative, prepared by nitration with yellow fuming nitric acid, was recrystallized from methanol; m.p. 135.5-136°.

Anal. Calc'd for C14H18N2O5: C, 57.13; H, 6.16.

Found: C, 57.27; H, 6.34.

B. From 4-t-butyl-2,6-dimethylbromobenzene. 4-t-Butyl-2,6-dimethylbenzoic acid was prepared in 61% yield by a procedure similar to that of Barnes for mesitoic acid (14). The melting point was 167-168°. The value reported by Baur (5, 10) for the unsymmetrical isomer was 168°.

Anal. Calc'd for C₁₃H₁₈O₂: C, 75.69; H, 8.79.

Found: C, 75.59; H, 8.82.

The dinitro derivative, after repeated recrystallization from methanol, melted at 233–235° when heated rapidly on an aluminum block. Baur (5, 10) gives 236° as the melting point of the unsymmetrical isomer.

Anal. Calc'd for C13H16N2O6: C, 52.70; H, 5.44.

Found: C, 52.22; H, 5.27.

The acid chloride, purified by recrystallization from high-boiling petroleum ether, was found to melt at 59-61°; the value recorded (25) is 62° . The acid chloride was converted to 4-t-butyl-2,6-dimethylacetophenone by treatment with dimethylcadmium prepared by the method of Gilman and Nelson (15). One gram of the acid chloride in 10 ml. of dry ether was added gradually to a solution containing approximately a seven-fold excess of dimethylcadmium. The mixture was then heated under reflux, with stirring, for three hours and decomposed by the addition of cracked ice. The ketone, isolated by conventional procedures, was recrystallized from methanol; m.p. $46-47^{\circ}$; yield 34%. A mixture with the sample prepared by method A melted at $45.5-47^{\circ}$.

4-t-Butyl-2,6-dimethylethylbenzene. A. From 4-t-butyl-2,6-dimethylacetophenone. The ketone was reduced by a method similar to that employed by Smith and Kiess (16). The yield of redistilled hydrocarbon was 47%; b.p. 125-127° (20 mm.); n_{D}^{∞} 1.5050. Fuson, Denton, and Kneisley (2) gave the following constants; b.p. 125° (20 mm.); n_{D}^{∞} 1.5044.

Two grams of the hydrocarbon was dropped slowly, with stirring, into 60 ml. of yellow fuming nitric acid maintained below 5°. The mixture was allowed to stand at this temperature for one hour. The dinitro compound was removed by filtration and recrystallized eight times from methanol; m.p. 128-129°. The melting point recorded in the literature is 128.5-129° (2).

Anal. Calc'd for C14H20N2O4: C, 59.98; H, 7.19; N, 10.00.

Found: C, 59.98; H, 7.36; N, 9.99.

B. From 4-t-butyl-2,6-dimethylbenzylmagnesium chloride and methyl sulfate. The method was similar to that used by Gilman and Catlin (17) in the preparation of n-propylbenzene. The yield was 34.6%; b.p. $81-84^{\circ}$ (4 mm.); n_D^{∞} 1.5043. The coupling product, 1,2-di-(2,6-dimethyl-4-t-butylphenyl)ethane (m.p. 216-217°), was obtained as a by-product.

The nitration product of the ethyl compound melted at 127-128°. A mixture with the sample described under method A melted at 126-128°.

4-t-Butyl-2,6-dimethylbenzonitrile. A. From 4-t-butyl-2,6-dimethylbromobenzene. The bromo compound was converted to the nitrile by a procedure patterned after that of Newman for 1-naphthonitrile (18). The product was purified by distillation; b.p. 104-107° (5 mm.); m.p. 64-66°; yield 67.4%. The analytical sample, after being recrystallized from ethanol, melted at 64.5-65.5°. Baur (10) reported the melting point to be 88°.

Anal. Calc'd for C₁₈H₁₇N: C, 82.93; H, 9.63.

Found: C, 82.93; H, 9.42.

The dinitro derivative was prepared by adding one gram of the nitrile, with stirring, to a mixture of 8 ml. of 15% fuming sulfuric acid and 4 ml. of yellow fuming nitric acid (sp. gr. 1.49-1.50) at 3°. The mixture was allowed to stand for one hour at 27° and poured on ice. The yield was 0.8 g.; m.p. 105-108°. The analytical sample was recrystallized five times from 95% ethanol; m.p. 108-109°. The accepted value is 110° (10).

Anal. Calc'd for C13H15N8O4: C, 56.31; H, 5.45; N, 15.16.

Found: C, 56.20; H, 5.66; N, 15.02.

B. From 4-t-butyl-2,6-dimethylbenzaldehyde. The aldehyde was obtained from the acid chloride in 77% yield by following closely the procedure of Barnes for 2,4,6-trimethylbenzaldehyde (19). The product was distilled at 100-103° (3 mm.) and solidified immediately in the receiver; m.p. 59-60°.

Anal. Calc'd for C13H18O: C, 82.06; H, 9.53.

Found: C, 80.85; H, 9.60.

The dinitro derivative of the aldehyde, after repeated recrystallization from 50% ethanol, melted at 110-111°. The value found in the literature is 110° (12).

Anal. Calc'd for C12H16N2O5: C, 55.71; H, 5.75.

Found: C, 55.45; H, 5.75.

The 2,4-dinitrophenylhydrazone of the dinitro aldehyde separated from ethyl acetate in canary yellow crystals; m.p. 245-246° (slow heating on an aluminum block).

Anal. Calc'd for C18H20N6O8: C, 49.56; H, 4.38.

Found: C, 49.78; H, 4.54.

The 2,4-dinitrophenylhydrazone of 4-t-butyl-2,6-dimethylbenzaldehyde was recrystallized first from chloroform, then from ethyl acetate; m.p. 217-218°.

Anal. Calc'd for C₁₉H₂₂N₄O₄: C, 61.61; H, 5.99.

Found: C, 61.81; H, 6.11.

The oxime of 4-t-butyl-2,6-dimethylbenzaldehyde was purified by repeated recrystallization from 50% ethanol followed by recrystallization from low-boiling petroleum ether; m.p. 107-108°. The literature records the melting point 97-98° for the unsymmetrical isomer.

Anal. Calc'd for C₁₃H₁₉NO: C, 76.05; H, 9.33.

Found: C, 76.20; H, 9.29.

A mixture of 1 g. of the oxime and 10 ml. of acetic anhydride was heated under reflux for 20 minutes, cooled, and poured into 100 ml. of cold water. After one hour the solid nitrile was removed by filtration and recrystallized from 95% ethanol; m.p. 65.5-66.5°. A mixture with the sample described under method A melted at 66.0-66.5°.

The dinitro derivative prepared from the nitrile made from the oxime melted at 107-108°. A mixture with the sample described under method A melted at 107.5-108.5°.

C. From 4-t-butyl-2,6-dimethylaniline. The amine was converted to the nitrile by a procedure closely similar to that of Clarke and Read for the preparation of o-tolunitrile (20). From 16 g. of the amine there was obtained 3.1 g. of nitrile. The nitrile was purified by recrystallization from alcohol and from high-boiling petroleum ether; m.p. 64-65.5°. It did not depress the melting point of the sample made by the Rosenmund-von Braun method.

Similarly, the dinitro derivative (m.p. 106-108°) did not depress the melting point of the sample which was analyzed.

4-t-Butyl-2,6-dimethylglyozal. 4-t-Butyl-2,6-dimethylacetophenone was oxidized by a method similar to that employed by Fuson and Gray (21) for the preparation of mesitylglyoxal from acetomesitylene. From 10.2 g. of the methyl ketone was obtained 8.9 g. of glyoxal boiling at 122-127° (7 mm.); yield 81.5%. The glyoxal set to a yellow solid, but difficulty was encountered in obtaining a reproducible melting point. The white crystalline hydrate, formed by mixing the glyoxal with boiling water, melted at 81-84°. The *semicarbazone* was purified by recrystallization from 25% ethanol. It formed white plates melting at 187-188°.

Anal. Calc'd for C₁₅H₂₁N₃O₂: C, 65.43; H, 7.69.

Found: C, 65.19; H, 7.86.

The 2, 4-dinitrophenylhydrazone was recrystallized from a mixture consisting of two parts of benzene and five parts of ethanol. It formed yellow platelets melting at 162–163°.

Anal. Calc'd for C20H22N4O5: C, 60.29; H, 5.57.

Found: C, 60.07; H, 5..55.

4-t-Butyl-2,6-dimethylbenzophenone. This compound, prepared according to the method of Noelting (22), melted at 106-107.5°; yield 48%.

Anal. Calc'd for C₁₉H₂₂O: C, 85.67; H, 8.33.

Found: C, 85.74; H, 8.60.

Noelting believed it had the unsymmetrical structure. However, by analogy with our results with the corresponding acetyl compound we considered the symmetrical structure more probable. In confirmation of this opinion it was found possible to prepare this ketone by the action of phenylmagnesium bromide on 4-t-butyl-2,6-dimethylbenzoyl chloride. The procedure was patterned after that employed by Whitmore and Heyd (23) for the synthesis of t-butyl neopentyl ketone. A solution of phenylmagnesium bromide, prepared from 3.14 g. of bromobenzene, 0.5 g. of magnesium, and 25 ml. of dry ether, was filtered and added gradually over a period of forty minutes to a solution of 2.25 g. of 4-t-butyl-2,6-dimethylbenzoyl chloride in 30 ml. of ether. The product, isolated by conventional procedures, was recrystallized from methanol. It formed glistening platelets melting at 108-109°. A mixed melting point with the sample made by the Friedel-Crafts method was 108-109°. Noelting reported the melting point of the unsymmetrical isomer as 105° (22).

SUMMARY

Musk Tibetene has been proved to be 5-t-butyl-4,6-dinitrohemimellitene and not 6-t-butyl-3,5-dinitropseudocumene as previously reported. Similarly, musk ketone has been shown to be 4-t-butyl-3,5-dinitro-2,6-dimethylacetophenone instead of 6-t-butyl-3,5-dinitro-2,4-dimethylacetophenone, the structure assigned long ago by Baur.

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