[Contribution from the Noyes Chemical Laboratory, University of Illinois]

A SYNTHESIS OF α-MESITYLPROPIOMESITYLENE

REYNOLD C. FUSON, NORMAN RABJOHN,[1] W. J. SHENK, Jr., and WM. E. WALLACE

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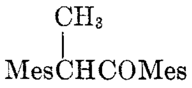
α-Mesitylpropiomesitylene (I) and a number of similar ketones (1, 2) are remarkable because their enol forms are stable. On account of the importance of these ketones, efforts have been directed to other possible synthetic routes to this type of compound. The work was planned in such a way that several of these were investigated simultaneously. Thus it came about that most of the studies were left unfinished.

An obvious approach was the methylation of the corresponding desoxybenzoins. Attempts to methylate desoxymesitoin (II), however, were unavailing. This failure made it seem probable that attachment to a mesityl radical would diminish the tendency of an active methylene group to undergo condensation reactions in general. There is evidence that this is true. It had been found earlier, for example, that the condensation of desoxymesitoin with formaldehyde took place only with difficulty (1). Ethyl mesitylacetate (III) could not be caused to react with formaldehyde or ethyl acetate. However, it did form a derivative with oxalic ester.



$MesCH(CH_3)COMes$

I

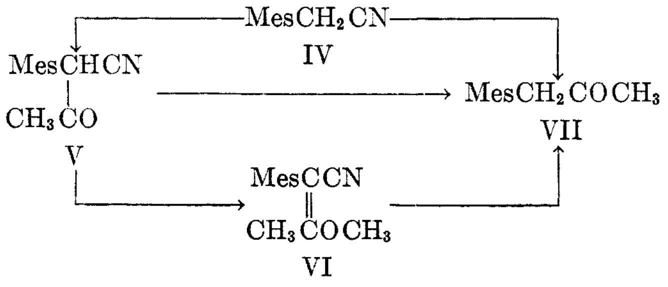
$MesCH_2COMes$

II

$MesCH_2CO_2C_2H_5$

III

Although mesitylacetonitrile (IV) failed to condense with formaldehyde, it underwent acylation normally. The formyl and acetyl (V) derivatives were obtained in satisfactory yields. It was hoped that these could be methylated and thus serve as intermediates in the synthesis of α-mesitylpropionic acid. Methylation of α-mesitylacetoacetonitrile (V), however, yielded only the O-methyl derivative (VI). This was shown by the fact that hydrolysis converted it to mesitylacetone (VII). Mesitylacetone was formed also when the keto nitrile (V) was subjected to hydrolysis. Although Holmberg (3) isolated mesitylacetone, he did not characterize it. It was found possible to make this ketone by condensation of mesitylacetonitrile with methylmagnesium iodide.



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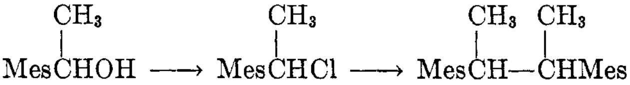
[1] Rohm and Haas Research Assistant, 1940–1942.

An attempt was made to prepare α-mesitylpropiomesitylene from mesitylmethylcarbinol (VIII) by way of the Grignard reagent. The carbinol was prepared by reduction of acetomesitylene by the method of Klages and Allendorff (4) and also by the condensation of mesitylmagnesium bromide with acetaldehyde. In a preliminary experiment, the crude chloride (IX) from the carbinol was treated with magnesium in ether and mesitoyl chloride was added. The only products that were isolated were mesitoic acid and a hydrocarbon which appeared to be 2,3-dimesitylbutane (X).

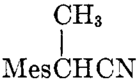


$$\mathrm{Mes\overset{\overset{CH_3}{|}}{C}HOH} \longrightarrow \mathrm{Mes\overset{\overset{CH_3}{|}}{C}HCl} \longrightarrow \mathrm{Mes\overset{\overset{CH_3}{|}}{C}H{-}\overset{\overset{CH_3}{|}}{C}HMes}$$

VIII IX X

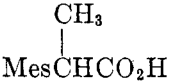
An attempt to prepare α-mesitylpropiomesitylene by condensing α-chloropropionyl chloride with mesitylene yielded only α-chloropropiomesitylene.

The synthesis which was finally successful involved methylation of mesitylacetonitrile, hydrolysis of the resulting α-mesitylpropionitrile (XI), and condensation of the chloride of the resulting acid (XII) with mesitylene.



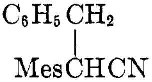
$$\mathrm{Mes\overset{\overset{CH_3}{|}}{C}HCN}$$

XI



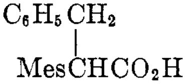
$$\mathrm{Mes\overset{\overset{CH_3}{|}}{C}HCO_2H}$$

XII



$$\mathrm{Mes\overset{\overset{C_6H_5CH_2}{|}}{C}HCN}$$

XIII



$$\mathrm{Mes\overset{\overset{C_6H_5CH_2}{|}}{C}HCO_2H}$$

XIV

It seems likely that this method of synthesis will prove to be general for ketones of the type MesCH(R)COMes. Alkylation of mesitylacetonitrile with benzyl chloride produced α-mesityl-β-phenylpropionitrile (XIII) from which the corresponding acid (XIV) was made by hydrolysis.

EXPERIMENTAL

Ethyl mesitylacetate. This ester was prepared from ethanol and the corresponding acid chloride, and by direct esterification of the acid in the presence of *p*-toluenesulfonic acid. The yields were, respectively, 95 and 70%. The ester boiled at 152–153° (22 mm.); n_D^{20} 1.5061.

Anal.[2] Calc'd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80.
Found: C, 75.97; H, 8.71.

Ethyl mesitylacetate was made in 67% yield from mesitylacetonitrile by treatment with a mixture of sulfuric acid and ethanol. A mixture of 50 cc. of ethanol, 15 cc. of sulfuric acid, and 32 g. of mesitylacetonitrile was heated under reflux for seventeen hours. In addition to the ester there was isolated a solid which, after recrystallization from benzene, melted at 236–237°.

Anal. Calc'd for $C_{22}H_{26}NO$: C, 82.45; H, 8.18; N, 4.37.
Found: C, 81.87; H, 8.89; N, 4.54.

This substance was not investigated further.

Condensation of ethyl mesitylacetate with ethyl oxalate. Three grams of sodium was dissolved in 50 cc. of absolute ethanol. A large part of the alcohol was removed by distillation under diminished pressure and the residue was diluted with 90 cc. of toluene. A mixture of 27 g. of ethyl mesitylacetate and 19 g. of ethyl oxalate was added and the mixture, heated

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[2] The microanalyses reported in this paper were carried out by Miss Mary S. Kreger, Miss Margaret McCarthy, Miss Theta Spoor, and Miss Dorothy Schneider.

by a hot water-bath, was stirred for eight hours. It was allowed to stand overnight and poured into water. After being acidified with hydrochloric acid the solution was extracted with ether. The ether solution was dried over calcium chloride and distilled. The fraction which distilled at 123–148° (3 mm.) partially solidified. The solid was recrystallized from diluted ethanol; m.p. 49–50°.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.95.
Found: C, 68.75; H, 7.91.

From its composition this ester was thought to be ethyl mesitylmalonate. An attempt to methylate it failed.

α-Mesitylacetoacetonitrile. To a solution of 18 g. of sodium in 210 cc. of absolute ethanol was added a solution of 96 g. of mesitylacetonitrile in 80 g. of ethyl acetate. The mixture was shaken thoroughly and heated under reflux for three hours. It was allowed to stand overnight and poured into water. The aqueous mixture was extracted with ether and heated to expel the dissolved ether. It was then cooled and acidified with glacial acetic acid. The mesitylacetoacetonitrile which separated was recrystallized from high-boiling petroleum ether; m.p. 117–118°; yield 48 g.

Anal. Calc'd for $C_{13}H_{15}NO$: C, 77.57; H, 7.51.
Found: C, 77.67; H, 7.83.

Methylation of α-mesitylacetoacetonitrile. To a solution of 2.3 g. of sodium in 25 cc. of absolute ethanol was added 20.1 g. of α-mesitylacetoacetonitrile. After the mixture had been heated for an hour it was cooled, and 21.3 g. of methyl iodide added. After eighteen hours of heating under reflux the mixture was allowed to cool and poured into water. The product was extracted with ether and distilled; b.p. 152–156° (3–4 mm.).

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96.
Found: C, 78.30; H, 8.14.

That this substance was the O-methyl derivative was shown by the fact that heating for five hours in a mixture of glacial acetic and sulfuric acids converted it to mesitylacetone; m.p. 60–61°.

Mesitylacetone. An impure sample of this ketone was obtained by condensing mesitylene with chloroacetone in the presence of aluminum chloride. It yielded a semicarbazone melting at 195–197°, as indicated by Holmberg (3).

Mesitylacetone was obtained also by the condensation of mesitylacetonitrile with methylmagnesium iodide[3] by the method of Shriner and Turner (5). From 21 g. of the nitrile and a five-fold excess of the Grignard reagent was obtained 6 g. of the ketone.

A third procedure for the synthesis of mesitylacetone involved the hydrolysis of α-mesitylacetoacetonitrile. A mixture of 5 g. of the nitrile, 10 cc. of concentrated sulfuric acid, and 90 cc. of glacial acetic acid was heated under reflux for ten hours and poured into water. The crude mesitylacetone was recrystallized from high-boiling petroleum ether; m.p. 60–61°.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 82.01; H, 9.30.

β-Hydroxy-α-mesitylacrylonitrile. To a warm solution of 9 g. of sodium in 105 cc. of absolute ethanol were added in succession 40 g. of mesitylacetonitrile and 30 g. of ethyl formate. The mixture was heated under reflux for two and one-half hours and poured into 1200 cc. of water. The aqueous mixture was heated to 40° and filtered to remove unchanged mesitylacetonitrile (6 g.). The filtrate, after being washed twice with ether, was acidified with acetic acid. The yellow oil which separated was dissolved in ether. Evaporation of the solvent left the hydroxymethylene compound as a solid. After being recrystallized four times from a high-boiling petroleum ether-benzene mixture, it melted at 131.5–132.5°. After the product had stood for several hours it melted at 126.5–127.5°.

Anal. Calc'd for $C_{12}H_{13}NO$: C, 76.96; H, 7.00.
Found: C, 77.18; H, 7.24.

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[3] This preparation was carried out by Dr. Quentin F. Soper.

The *anilino* derivative, β-anilino-α-mesitylacrylonitrile, was made by boiling for fifteen minutes a mixture of 2 g. of the hydroxy nitrile, 1 cc. of aniline, and 25 cc. of absolute ethanol. The derivative was recrystallized from high-boiling petroleum ether; m.p. 151.5–153°; yield, 2 g.

Anal. Calc'd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92.
Found: C, 82.59; H, 7.12.

The *benzoate* was prepared by treating the hydroxy nitrile with benzoyl chloride in the presence of pyridine. It crystallized from ethanol in beautiful, white needles; m.p. 127–128°.

Anal. Calc'd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81.
Found: C, 78.03; H, 6.07; N, 4.73.

The benzoate was unaffected by treatment with hydrogen in the presence of a platinum oxide catalyst.

Condensation of acetaldehyde with mesitylmagnesium bromide. The Grignard reagent was prepared from 50 g. of bromomesitylene and 6 g. of magnesium in 200 cc. of dry ether. This was cooled in an ice-bath while a solution of 15 g. of acetaldehyde in 100 cc. of dry ether was added slowly. After all of the aldehyde had been added, the mixture was allowed to stand overnight. The chief product was a solid which, when crystallized from alcohol, melted at 94–95°.

Anal. Calc'd for $C_{22}H_{30}O$: C, 85.10; H, 9.75.
Found: C, 84.94; H, 9.73.

The composition of this compound corresponds to that of the ether of the expected mesitylmethylcarbinol.

In another run the crude product of the condensation was treated in dry ether with hydrogen chloride. The impure chloride (b.p. 130–132°/22 mm.; n_D^{26} 1.5320) obtained in this way was treated with magnesium in an effort to form the corresponding Grignard reagent. The resulting mixture was treated with mesitoyl chloride. The only products that could be isolated were mesitoic acid and a hydrocarbon melting at 139–140°. Its composition corresponds to that calculated for 2,3-dimesitylbutane.

Anal. Calc'd for $C_{22}H_{30}$: C, 89.72; H, 10.28.
Found: C, 90.04; H, 10.17.

α-Chloropropiomesitylene.[4] Twenty grams of α-chloropropionyl chloride was added, with stirring, to a mixture of 40 g. of mesitylene, 33 g. of aluminum chloride, and 150 cc. of carbon disulfide at 5°. A large amount of hydrogen chloride was evolved. The reaction mixture was allowed to stand overnight at room temperature and poured into a mixture of 400 g. of ice and 50 cc. of concentrated hydrochloric acid. The solvent was evaporated and the α-chloropropiomesitylene was taken up in benzene. The benzene solution was washed and dried. Distillation yielded the chloro ketone; b.p. 99–100° (1.5 mm.); n_D^{20} 1.5273.

Anal. Calc'd for $C_{12}H_{15}ClO$: C, 68.38; H, 7.18.
Found: C, 69.09; H, 7.45.

This compound was unstable; in a short time it developed a brown color.

3,5-Dinitro-α-chloropropiomesitylene. One cubic centimeter of α-chloropropiomesitylene was nitrated according to the procedure of Fuson, Ross, and McKeever (6). The dinitro compound was obtained in good yield. It crystallized from ethanol in white needles; m.p. 127.5–128.5°.

Anal. Calc'd for $C_{12}H_{13}ClN_2O_5$: C, 47.92; H, 4.35; N, 9.32.
Found: C, 48.00; H, 4.38; N, 9.39.

3,5-Dinitro-β-chloropropiomesitylene. A comparison of the new chloropropiomesitylene with the known *beta* isomer showed the two to be different. Their dinitro derivatives were also unlike. One gram of β-chloropropiomesitylene (7) was added in small portions to 20 cc. of fuming nitric acid. The dinitro compound was isolated in the usual way (7). It crystallized from glacial acetic acid in white plates; m.p. 190–191.5°.

Anal. Calc'd for $C_{12}H_{13}ClN_2O_5$: C, 47.92; H, 4.35; N, 9.32.
Found: C, 48.41; H, 4.19; N, 8.87.

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[4] The experiments with the chloropropiomesitylenes were carried out by Dr. C. H. McKeever.

α-Mesitylpropionic acid. Twenty grams of sodium was added in small pieces to 500 cc. of liquid ammonia. A few crystals of ferric nitrate were used as a catalyst. The ammonia was allowed to evaporate, the last traces being removed on the water-pump. The sodium amide was suspended in 200 cc. of dry ether and to this suspension was added over a period of thirty minutes a solution of 100 g. of mesitylacetonitrile in 400 cc. of dry ether. The mixture was then heated under reflux for two hours. A solution of 92.6 g. of methyl iodide in 50 cc. of ether was added gradually over a period of two hours. After addition was complete the solution was heated under reflux for five and one-half hours longer. The mixture was cooled and decomposed by the addition of ice. The α-mesitylpropionitrile, b.p. 160–165° (35 mm.), was heated for five hours under reflux with a mixture of glacial acetic and concentrated sulfuric acids. The acid obtained in this way was purified by successive recrystallizations from 95% ethanol and dilute acetic acid; m.p. 102–103°. When this acid was mixed with that obtained by cleavage of α-mesitylpropiophenone (1) the melting point was not depressed.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.
Found: C, 74.88, 75.06; H, 8.43, 8.95.

α-Mesitylpropionamide. One gram of α-mesitylpropionitrile was heated for four hours under reflux with a solution of 1 g. of sodium hydroxide in 20 cc. of water. The mixture was poured into water and the oil which formed was allowed to crystallize. The amide was purified by recrystallization from high-boiling petroleum ether; m.p. 100–101°.

Anal. Calc'd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32.
Found: C, 75.29; H, 8.89; N, 7.33.

α-Mesitylpropiomesitylene.[5] A mixture of 10 g. of α-mesitylpropionic acid and 6.5 cc. of thionyl chloride was allowed to stand overnight. After the excess thionyl chloride had been removed under diminished pressure, 50 cc. of mesitylene was added. To this mixture was added slowly, with stirring, 6.5 g. of aluminum chloride. After the mixture had been stirred for two hours at room temperature it was heated for thirty minutes on a steam-bath. The product boiled at 160–165° (1–2 mm.) and solidified when cooled. It was recrystallized from ethanol; m.p. 74–75°.

Anal. Calc'd for $C_{21}H_{26}O$: C, 85.66; H, 8.92.
Found: C, 85.57; H, 8.98.

A mixture of this compound wth an authentic specimen of α-mesitylpropiomesitylene (1) showed no lowering of melting point.

α-Mesityl-β-phenylpropionitrile.[6] Sodium amide prepared from 8 g. of sodium in the usual way, was suspended in ether, and to the suspension was added dropwise over a period of twenty minutes a solution of 41 g. of mesitylacetonitrile in 200 cc. of absolute ether. The mixture was heated under reflux for one hour and a half. A mixture of 28.6 g. of benzyl chloride with an equal volume of absolute ether was added gradually over a period of two hours. The mixture was heated under reflux, with stirring, for an additional two hours and cooled. Ice was added and the stirring continued for twenty minutes. The ether layer was removed and washed successively with 100 cc. of 6 *N* hydrochloric acid and 50 cc. of water. When the solvent had evaporated the residual α-mesityl-β-phenylpropionitrile was purified by distillation. A fraction weighing 44 g. was collected at 173–180° (2–5 mm.). After a few days it set to a semisolid.

Anal. Calc'd for $C_{18}H_{19}N$: C, 86.70; H, 7.68.
Found: C, 86.87; H, 7.59.

α-Mesityl-β-phenylpropionic acid. A solution of 5 g. of α-mesityl-β-phenylpropionitrile in a mixture of 10 cc. of sulfuric acid and 85 cc. of acetic acid was heated under reflux for nine and one-half hours. It was allowed to cool and was then poured into 500 cc. of water. The mixture was extracted with ether. The ether solution was washed with water and extracted with dilute sodium hydroxide solution. Acidification of the latter yielded 3 g. of α-mesityl-β-phenylpropionic acid. It was recrystallized from alcohol; m.p. 136–137°.

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[5] This experiment was carried out by Mr. Sidney Melamed.

[6] This preparation was carried out by Dr. John L. Marsh.

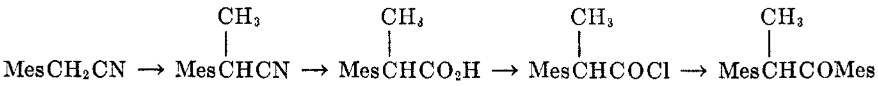
Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 81.22; H, 7.75.

From the ether solution was obtained a small amount of the amide. It was purified by recrystallization from low-boiling petroleum ether; m.p. 119–120°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92.
Found: C, 81.08; H, 7.87

SUMMARY

α-Mesitylpropiomesitylene has been synthesized by the following sequence of transformations:



$$\mathrm{MesCH_2CN} \rightarrow \mathrm{Mes}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCN} \rightarrow \mathrm{Mes}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCO_2H} \rightarrow \mathrm{Mes}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCOCl} \rightarrow \mathrm{Mes}\overset{\mathrm{CH_3}}{\overset{|}{\mathrm{C}}}\mathrm{HCOMes}$$

URBANA, ILL.

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