Summary

A series of twenty-one diacylureas derived from branched chain aliphatic acids has been prepared by the reaction of an acid chloride with a monoacylurea. The chemical characteristics of these compounds are similar to the analogous derivatives of the normal acids with the exception that the more highly branched compounds are very slightly more stable to alkali. These substances were found to have hypnotic properties, and their relative activity has been evaluated.

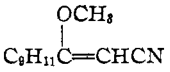
NASHVILLE, TENNESSEE RECEIVED NOVEMBER 25, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Benzoylmesitylacetylene[1]

BY REYNOLD C. FUSON, G. E. ULLYOT AND J. L. HICKSON

Among the products obtained by treating the enol methyl ethers (I) of 2,4,6-trimethylbenzoylacetonitrile with phenylmagnesium bromide there were found varying amounts of a ketone whose identity was for a long time in doubt and whose origin is still not entirely clear.[2] The present paper reports a study of the reactions of this unusual compound. The results showed it to be benzoylmesitylacetylene (II)—a conclusion which has been confirmed by an independent synthesis of the compound in question.



$C_9H_{11}C(OCH_3){=}CHCN$

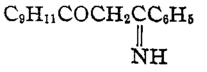
I

$C_9H_{11}C{\equiv}CCOC_6H_5$

II

Actually the acetylenic compound was not obtained directly by the interaction of the enol ethers (I) with phenylmagnesium bromide. A yellow amorphous solid appeared to be its precursor; this solid contained nitrogen and halogen, but was not obtained in pure form. When it was dissolved in boiling 95% alcohol the acetylenic ketone was formed. Boiling glacial acetic acid converted the precursor into the imino ketone (IV), showing that the skeletal structure is $C_9H_{11}C{-}C{-}CC_6H_5$.

The presence of an unhindered carbonyl group in the acetylenic ketone was shown by the formation of a semicarbazone and by the reaction with phenylmagnesium bromide. The latter reagent converted the ketone to the corresponding carbinol (VI). The latter absorbed three moles of hydrogen in the presence of Raney nickel. Ozonization of the acetylenic ketone gave β-isodurylic acid, benzoic acid and a small amount of mesityl phenyl diketone.

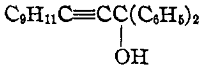


$C_9H_{11}COCH_2C({=}NH)C_6H_5$

IV

$C_9H_{11}COCH_2COC_6H_5$

V



$C_9H_{11}C{\equiv}CC(OH)(C_6H_5)_2$

VI

It was this information which suggested that the ketone might be benzoylmesitylacetylene. Mesityl phenyl triketone would be expected as a product of the action of ozone, and the diketone is known to be a decomposition product of the triketone.[3]

$$C_9H_{11}C{\equiv}CCOC_6H_5 \xrightarrow{O_3} C_9H_{11}COCOCOC_6H_5 \xrightarrow{-CO} C_9H_{11}COCOC_6H_5$$

Further evidence in favor of the acetylenic structure for the unsaturated ketone is its conversion into 2,4,6-trimethyldibenzoylmethane (V) by the action of sulfuric acid. Nef[4] used this method to prove the structure of benzoylphenylacetylene.

Reduction of the ketone (II) with hydrogen in the presence of Raney nickel gave benzoylmesitylethane, the structure of which was confirmed by synthesis of the compound from β-chloropropiophenone and mesitylene by the Friedel–Crafts method.

A more satisfactory synthesis[5] of the ethane was developed by use of α-chloroisodurene made by the method of Nauta and Dienske.[6] This chloride condensed with the sodium derivative of ethyl benzoylacetate to give a solid which was presumably ethyl α-isodurylbenzoylacetate. The latter was subjected to hydrolysis without purification. Decarboxylation of the resulting acid gave the desired ethane.

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[1] Original manuscript received June 18, 1938.

[2] Fuson, Ullyot, Stedman, Gehrt and Tawney, THIS JOURNAL, **60**, 1447 (1938).

[3] Fuson, Weinstock and Ullyot, *ibid.*, **57**, 1803 (1935).

[4] Nef, *Ann.*, **308**, 277 (1899).

[5] This synthesis was carried out by Mr. J. J. Denton.

[6] Nauta and Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).

The structure of the acetylenic ketone was finally established by synthesis. Mesitylacetylene, prepared by the method of Vaughn and Nieuwland[7], was converted into its sodium derivative. The latter reacted with benzoyl chloride to give benzoylmesitylacetylene.

Experimental Part

The precursor of benzoylmesitylacetylene was obtained by treating the enol methyl ether of 2,4,6-trimethylbenzoylacetonitrile with phenylmagnesium bromide and decomposing the reaction mixture with dilute sulfuric acid.[2] It separated as a yellow, amorphous compound, insoluble in water, benzene, carbon tetrachloride, ligroin and ethyl acetate.

It was dissolved in boiling glacial acetic acid and the solution was boiled a few moments. By dilution of this solution with water the imino ketone (IV) was obtained.

Benzoylmesitylacetylene (II) formed when the precursor was dissolved in boiling 95% alcohol. Nearly colorless needles were obtained melting at 72° (from alcohol).

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.87, 86.95, 87.12; H, 6.67, 6.67, 6.67.

The semicarbazone was prepared and crystallized from high-boiling ligroin; m. p. 171–172°.

Anal. Calcd. for $C_{18}H_{19}ON_3$: C, 74.73; H, 6.26; N, 13.76. Found: C, 75.00, 74.62; H, 6.46, 6.42; N, 14.32, 13.65.

Ozonization of Benzoylmesitylacetylene (II).—One gram was dissolved in carbon tetrachloride and ozonized oxygen was passed in for five hours. The ozonide precipitated and was treated with water and a few cubic centimeters of 3% hydrogen peroxide. The aqueous layer was made alkaline with sodium hydroxide and the carbon tetrachloride layer was separated. By acidification of the aqueous solution 0.3 g. of a colorless solid was obtained. This was separated into benzoic acid and β-isodurylic acid by extraction with hot water. Evaporation of the carbon tetrachloride solution left a small amount of yellow solid. This was crystallized from methyl alcohol; m. p. 130–133°. A mixed melting point with 2,4,6-trimethylbenzil was 130–134°.

1-Benzoyl-2-mesitylethane.—Five grams of benzoylmesitylacetylene dissolved in 150 cc. of alcohol was reduced in an Adams reduction apparatus, using 1 g. of Raney nickel catalyst.[8] The initial pressure of hydrogen was forty pounds (2.67 atm.). Four grams of colorless needles was isolated after concentration of the alcohol solution; m. p. 84–85°. One crystallization of the compound from methyl alcohol raised the melting point to 85–85.5°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.66; H, 8.00. Found: C, 85.45, 85.64; H, 8.40, 8.30.

The product was identical with that obtained by causing β-chloropropiophenone to react with mesitylene in the presence of aluminum chloride in a carbon disulfide solution.[8] A solution of 16.8 g. of β-chloropropiophenone in 100 cc. of carefully purified carbon disulfide was added to a well-stirred mixture of 120 g. of mesitylene, 20 g. of aluminum chloride and 100 cc. of carbon disulfide. The reaction mixture was stirred for two hours at room temperature and then refluxed for four hours. After decomposition of the reaction mixture with ice and hydrochloric acid the carbon disulfide layer was separated, washed with water, dried over calcium chloride and evaporated under diminished pressure. The oil so obtained was distilled *in vacuo*. Seven grams of mesitylene (b. p. 38–41° at 5 mm.) was recovered. The residue was crystallized from methyl alcohol. Benzoylmesitylethane and β-chloropropiophenone crystallized; the latter was almost entirely removed by washing the solid on a filter with methyl alcohol. The remaining solid was crystallized from methyl alcohol: yield, 1 g.; m. p. 79–83°. Repeated crystallization of the compound raised the melting point to 84–84.5°. A mixture of this sample with that from benzoylmesitylacetylene melted at 84.5–85.5°.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.66; H, 8.00. Found: C, 85.74; H, 8.00.

A more convenient synthesis of the ethane is the following. A mixture of 10 g. of ethyl benzoylacetate, 115 cc. of dry benzene and 1.2 g. of sodium was refluxed for twenty-four hours. Nine grams of α-chloroisodurene was added over a period of one hour and the mixture was refluxed for an additional eight hours. It was then cooled to room temperature, and 15 g. of cracked ice added. After being shaken thoroughly the benzene layer was separated, washed with 5% sodium bicarbonate solution, and dried with sodium sulfate. The residue remaining after distillation of the solvent was fractionally distilled under diminished pressure. After a fore-run, the fraction boiling at 225–230° (23 mm.) (partial decomposition) was collected. The crude ethyl α-isodurylbenzoylacetate thus obtained was a slightly yellow oil which solidified on standing overnight; yield, 3.7 g.

To a boiling solution of the ester in absolute alcohol was added a solution of 1.9 g. of potassium hydroxide in 100 cc. of water. When the resulting mixture was cooled to room temperature, a brownish oil separated; it solidified on standing in an ice chest overnight. The solid was isolated and, after several recrystallizations from methyl alcohol, the pure benzoylmesitylethane was obtained as fine, white needles; m. p. 85–85.5°; yield, 1.3 g. A mixed melting point with the hydrogenation product showed no lowering.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.66; H, 8.00. Found: C, 85.67; H, 8.06.

Action of Phenylmagnesium Bromide on Benzoylmesitylacetylene and Reduction of the Resulting Product.—Phenylmagnesium bromide prepared from 0.48 g. of magnesium and 3.14 g. of bromobenzene was allowed to react with 2.48 g. of the acetylenic compound. The reaction mixture was refluxed four hours and worked up in the usual manner. The product obtained by evaporation of the ether layer was crystallized from high-boiling ligroin. The yield was 2.3 g.; m. p. 93–97.5°. One treatment with Norite and several crystallizations raised the melting point to 97.5–98.5°.

Anal. Calcd. for $C_{24}H_{22}O$: C, 88.32; H, 6.80. Found: C, 88.13, 88.18; H, 7.17, 7.15.

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[7] Vaughn and Nieuwland, THIS JOURNAL, **56**, 1207 (1934).

[8] Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

[9] This synthesis was carried out by Mr. R. V. Lindsey, Jr.

The product was reduced quantitatively in a semimicro reduction apparatus using Adams, Voorhees and Shriner's platinum catalyst.[10] The reductions were carried out at a pressure slightly greater than atmospheric. Fifty cubic centimeters of acetic acid was used as a solvent. The amount of catalyst was 0.2 g.

	Sample, g.	Hydrogen abs. calcd. to standard cond., cc.	Mol. equiv. of abs. hydrogen	Time, min.
1	0.1984	39.3	2.88	60
2	.2005	41.7	3.04	160

Action of Sulfuric Acid on the Acetylenic Ketone.—A solution of 1 g. of the acetylenic ketone in 15 cc. of concentrated sulfuric acid was allowed to stand at room temperature for three hours. A deep red color developed. The solution was poured into a beaker of ice and the resulting mixture was extracted with ether. Three-tenths of a gram of colorless crystals was obtained by evaporating the ether and crystallizing the residue from methyl alcohol; m. p. 74–77°. This was identified as 2,4,6-trimethyldibenzoylmethane by a mixed melting point determination.

Benzoylmesitylacetylene.—A solution of 7.2 g. of mesitylacetylene in 25 cc. of absolute ether was added to 1.5 g. of sodium and the mixture refluxed for thirty minutes. The contents of the flask were cooled to −15° and 18 g. of benzoyl chloride in 20 cc. of absolute ether was added all at once. The mixture was refluxed for one hour and again cooled. Enough 15% glacial acetic acid in absolute ether was added to dissolve the unchanged sodium. The resulting mixture was poured into 50 cc. of water; the ether layer was separated and shaken with 75 cc. of 10% sodium hydroxide solution for eight hours.

The ether solution was dried and divided into two portions. One of these was heated to drive off the ether and the residual oil was treated with semicarbazide. The **semicarbazone** melted at 170–172°. A mixed melting point with the semicarbazone of the original ketone (II) showed no lowering.

The second portion of the ether solution was evaporated to dryness and the residue recrystallized from alcohol. The benzoylmesitylacetylene obtained in this way melted at 68–70°. A mixture with II showed no lowering of the melting point.

Summary

Among the secondary products obtained by the interaction of phenylmagnesium bromide and β-methoxy-β-mesitylacrylonitrile is found a small amount of benzoylmesitylacetylene. Its structure has been established by degradation and by synthesis.

URBANA, ILLINOIS RECEIVED DECEMBER 22, 1938

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[10] Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, 1932, p. 452.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Synthesis of Mixed Benzoins[1]

BY REYNOLD C. FUSON, WILLIAM S. EMERSON[2] AND H. H. WEINSTOCK, JR.

There is considerable evidence to suggest that the hindrance provided by ortho substituents favors the tendency of a benzoin to exist as an enediol.[3] To gain a more definite notion of the influence of hindrance on the properties of benzoins we have extended these studies to other highly hindered benzoins. The successful synthesis of hexamethylbenzoin by condensing mesitylglyoxal with mesitylene[1] suggested that mixed benzoins of this type might be made generally available. The present paper is a report of attempts to prepare these substances.

Mesitylglyoxal was first condensed with the series benzene, toluene, *m*-xylene and mesitylene in order to study the general synthesis under conditions of increasing hindrance. Carbon disulfide was used as the solvent in order to obtain a standard set of conditions and to lessen the formation of diarylaroylmethanes. The time of the reaction was found to be very important. For benzene the reaction required twenty hours, for toluene six to ten and for *m*-xylene four to six hours. With shorter periods mesitylglyoxal hydrate was recovered, and with longer ones the product would not crystallize. The benzoins were identified by oxidation to the benzils either with sodium methylate and iodine in methyl alcohol[4] or copper sulfate and pyridine.[5]

The yields of benzoins from benzene, toluene and *m*-xylene were 57, 24 and 17%, respectively. Mesitylene gave a 40% yield and the reaction was complete in one to one and one-half hours.

In the case of *m*-xylene 34% of 2,4,6-trimethylbenzoyldi-(2,4-dimethylphenyl)-methane was also obtained. Here the use of the carbon disulfide

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[1] This is the third paper in this series. For the preceding paper see Arnold and Fuson, THIS JOURNAL, **58**, 1295 (1936).

[2] Du Pont Post-Doctorate Fellow, 1937–1938.

[3] Weinstock and Fuson, THIS JOURNAL, **58**, 1986 (1936).

[4] Corson and McAllister, *ibid.*, **51**, 2822 (1929).

[5] Clarke and Dreger, "Org. Syntheses," Coll. Vol. I, 1932, p. 80.