and subsequent papers and for permission to publish the results.

Summary

1. The composition of the di-, tri- and tetra-isopropylbenzene fractions, obtained by the action of propene on benzene in presence of sulfuric acid or aluminum chloride, has been determined.

2. In presence of aluminum chloride, 1,2,4-triisopropylbenzene is converted to the 1,3,5-isomer with simultaneous formation of higher and lower homologs.

3. Two di-, two tri- and one tetra-isopropylbenzene have been isolated in a state of high purity and their physical properties determined.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Some 5,5-Disubstituted Hydantoins

BY HENRY R. HENZE, LOREN M. LONG,[1] ROBERT J. SPEER[2] AND THOMAS R. THOMPSON[3]

Under the title "Some New 5,5-Disubstituted Hydantoins," Marsh and Lazzell[4] recently reported brief data for six hydantoins obtained by the Bucherer[5] method. Apparently, they were unaware of the fact that the synthesis by this method of one of these hydantoins had previously been reported.[6] Of course the mere question of priority of synthesis of 5-methyl-5-styrylhydantoin is of but little moment, but we have to offer other comments concerning their note. In the course of an extended study of the synthesis of hydantoins,[7] we had occasion to attempt the conversion of about one hundred and fifty aldehydes and ketones into the corresponding hydantoins; hence, we have investigated very nearly every common example of these two types of carbonyl compounds. Where we had tried to prepare the hydantoins listed by Marsh and Lazzell,[4] our results were not wholly corroborative of those cited. Our data suggest that Marsh and Lazzell in most cases did not succeed in their desire to obtain a pure sample of each hydantoin, and in certain instances may not have obtained the anticipated product.

We had not prepared a hydantoin from *p*-aminoacetophenone at the time of the appearance of the note by Marsh and Lazzell. However, the melting point of 100–101°, recorded by these investigators for 5-methyl-5-(*p*-aminophenyl) hydantoin seemed to us as highly improbable since it was lower than that of any hydantoin derivative which we had synthesized and, indeed, about seventy degrees below the melting point reported for a hydantoin derived from any other phenyl ketone. In our Laboratory this hydantoin has been prepared and found to melt at 186–188° (cor.).

The report of the preparation of a hydantoin, again of unexpectedly low melting point, from Michler's ketone was of particular interest to us because of the difficulty which we had in securing other than mere traces of this compound by means of the usual Bucherer procedure, in all probability because of the limited solubility of this ketone. However, using our new modification[8] of the Bucherer method we were able to synthesize the hydantoin in 38% yield. It is to be noted that we record a melting point of 276–280° (cor.) for our *white*-colored hydantoin, whereas Marsh and Lazzell reported a melting point of 136–137° for a product of *yellow* color.

Although we had not converted cyclohexyl methyl ketone into 5-cyclohexyl-5-methylhydantoin, the latter was prepared by catalytic hydrogenation of an authentic sample of 5-methyl-5-phenylhydantoin. The melting point of our crude reaction product is close to that listed by Marsh and Lazzell, but that of our purified hydantoin is significantly higher.

Considerable difficulty was encountered in our attempts[9] to obtain 5-methyl-5-(2-methylpropenyl) hydantoin in good yield from mesityl oxide, since

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(4) Marsh and Lazzell, THIS JOURNAL, **62**, 1306 (1940).

(5) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(6) Before the Division of Medicinal Chemistry of the American Chemical Society at Baltimore, Md., April 9, 1939; see Henze and Long, THIS JOURNAL, **63**, 1936 (1941).

(7) Henze and Speer, *ibid.*, **64**, 522 (1942); see also American Documentation Institute Document No. 1603, American Documentation Institute, 2101 Constitution Avenue, Washington, D. C.

(8) Henze and Long, *ibid.*, **63**, 1939, 1941 (1941).

(9) Henze, Thompson and Speer, *J. Org. Chem.*, in press.

both the yield and the identity of the products formed varied markedly with changes in the period during which the reactants were warmed. This result is not too surprising since the Bucherer process involves use of potassium cyanide and ammonium carbonate, and it is rather well known that mesityl oxide can react with ammonia[10] to form diacetoneamine, and with potassium cyanide[11] to yield mesitonitrilecyanohydrin; hence, an excellent yield of hydantoin would be more unexpected than a low yield. We have obtained the desired hydantoin but its melting point is definitely (15°) lower than that reported by Marsh and Lazzell. The identity of our sample of 5-methyl-5-(2-methylpropenyl) hydantoin was confirmed by conversion, through catalytic hydrogenation, into 5-isobutyl-5-methylhydantoin, the latter being compared with an authentic sample of this compound prepared from isobutyl methyl ketone.[7] From the reaction mixtures in our experiments we have been able also to isolate 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone,[12] the melting point of which happens to be the same as that recorded by Marsh and Lazzell[4] for their hydantoin. This pyrrolidone derivative was converted into α-hydroxy-α,γ-dimethyl-γ-valerolactone[13] for purposes of characterization. It is of some interest to note that the substituted pyrrolidine can be obtained also by interaction of an aqueous solution of potassium cyanide and diacetoneamine.

Again, in the preparation of a hydantoin from diacetone alcohol we have found[9] that variations in time and temperature conditions seemingly occasion differences in the identity of the products isolated from the reaction mixture. Here, too, α-hydroxy-α,γ-dimethyl-γ-valerolactone was identified. In addition, we obtained 5,5-dimethylhydantoin, the latter arising, in all probability, from dissociation of the diacetone alcohol into acetone. Obtained from our experiments[9] 5-methyl-5-(2-hydroxy-2-methylpropyl) hydantoin melts at 147° (cor.), whereas Marsh and Lazzell noted 180–181° (cor.) for their preparation. Finally, we have isolated another product of molecular formula $C_8H_{13}NO_4$ with melting point of 209–210°. While the structure of the latter is still somewhat in doubt, it certainly is not that of a hydantoin derivative and in all probability the product is correctly formulated as α,γ-dimethyl-α-ureido-γ-valerolactone.

(10) Sokoloff and Latschinoff, *Ber.*, **7**, 1387, 1777 (1874).
(11) Lapworth, *J. Chem. Soc.*, **85**, 1217 (1904).
(12) Weil, *Ann.*, **232**, 208 (1886).
(13) Kohn, *Monatsh.*, **30**, 403 (1909); Tafel, *Ber.*, **32**, 1864 (1889).

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Experimental

5-Cyclohexyl-5-methylhydantoin.—The 5-methyl-5-phenylhydantoin used was prepared from acetophenone by means of the Bucherer[5] method and melted at 198.5° (cor.).[7] Eight and seven-tenths grams of this hydantoin dissolved in ethyl alcohol was diluted with four equivalents of hydrochloric acid and exposed to reaction with hydrogen in the presence of the Adams catalyst for seven hours. After removal of the catalyst by filtration, the reduction product was obtained by concentration of the solution; weight 7.5 g. (86% yield); m. p. 206–210°. After two recrystallizations from water the m. p. of the cyclohexylmethylhydantoin was 214.6–215.8° (cor.).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: mol. wt., 196.24; C, 61.19; H, 8.21; N, 14.27. Found: mol. wt. (boiling point elevation of acetone), 202; C, 61.00; H, 8.17; N, 14.14.

5-Methyl-5-(*p*-aminophenyl)-hydantoin.—After dissolving 13.5 g. of *p*-aminoacetophenone in 100 cc. of 50% alcohol, 9 g. of potassium cyanide and 28.8 g. of ammonium carbonate cubes were added and the reaction mixture was warmed at 57–60° for eighteen hours. The mixture was neutralized with hydrochloric acid and filtered; the solid thus obtained was treated with 200 cc. of 5% of sodium hydroxide solution and, upon filtration, there was recovered 3 g. of unreacted ketone. From the filtrate the hydantoin separated upon exact neutralization with hydrochloric acid. Dried, the product weighed 13 g. (81% yield) and melted at 184°; after recrystallization from 20% alcohol, m. p. 186–188° (cor.).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: mol. wt., 205.21; C, 58.52; H, 5.40; N, 20.48. Found: mol. wt. (b. p. elevation of acetone), 212; C, 58.56; H, 5.51; N, 20.72.

Bis-[5-(*p*-dimethylaminophenyl)]-hydantoin.—Attempts to prepare this hydantoin in other than mere traces by the Bucherer[5] method having failed, the synthesis succeeded when 13.4 g. of fused acetamide[8] and 4.5 g. of potassium cyanide were mixed and stirred until completely dissolved, 14.4 g. of ammonium carbonate cubes was added and the bomb was closed. After being heated in an oven at 140° for fourteen hours, the bomb was cooled to room temperature, opened and the contents stirred with 500 cc. of water and neutralized (Hood!) with hydrochloric acid. The insoluble material was filtered, extracted with 5% sodium hydroxide solution, again filtered and the hydantoin was precipitated from the filtrate by exact neutralization with acid. It was recrystallized from acetone yielding a *white* crystalline solid, melting at 276–280° (cor.), which weighed 6.4 g. (38% yield).

Anal. Calcd. for $C_{19}H_{22}N_4O_2$: mol. wt., 338.40; C, 67.43; H, 6.55; N, 16.56. Found: mol. wt. (b. p. elevation of acetone), 352; C, 67.00; H, 6.70; N, 16.51.

Summary

A study has been made of the preparation of

hydantoins, by means of the Bucherer method, from methyl styryl ketone, methyl cyclohexyl ketone, *p*-aminophenyl methyl ketone, Michler's ketone, diacetone alcohol and mesityl oxide, respectively.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Oxidative Degradation of *i*-Stigmasteryl Methyl Ether

BY BYRON RIEGEL, EDWIN W. MEYER AND JOHN BEISWANGER

In an endeavor to make more readily available certain *bisnor*-cholenic acids for the synthesis of steroidal hormones, an investigation of the oxidative degradation of *i*-stigmasteryl methyl ether has been made. The classical method of ozonizing 5,6-dibromostigmasteryl acetate is not entirely satisfactory. The bromination of the 5–6 double bond of stigmasteryl acetate in preference to the 22–23 double bond may not be too selective and thus lead to a lower yield of 3-acetoxy-5-*bisnor*-cholenic acid. A truly selective method for the protection of the 5–6 double bond is based upon the formation of the so-called *i*-ether and furthermore this structure involves the simultaneous protection of the 3-hydroxyl group. The *i*-ether configuration which is sufficiently stable for many reactions, yet labile enough to be converted to desired structures, presents an unique arrangement for the oxidative degradation of the stigmasterol side-chain.

Crystalline *i*-stigmasteryl methyl ether[1] (I) can be prepared from pure stigmasterol in about a 77% over-all yield. Ozonolysis of this ether gave 6-methoxy-*i*-*bisnor*-cholenic acid (II) which crystallized with a molecule of water of hydration, melted at 174.8–176.3° and had a specific rotation of +17°. Because of the difficulty in obtaining the crystalline acid in good yield, conversion to other derivatives was investigated. All attempts to convert the *i*-ether configuration of the free acid to the normal configuration were only partly successful, hence attention was centered upon the methyl ester (III). Although all efforts to crystallize the methyl ester (III) prepared by oxidative degradation were unsuccessful, it underwent conversion to the normal configuration smoothly. The characteristic ease of rearrangement of *i*-methyl ethers to normal methyl ethers[2] upon treatment with methanol containing a trace of acid, receives added confirmation with the rearrangement of methyl 6-methoxy-*i*-*bisnor*-cholenate (III) to methyl 3-methoxy-5-*bisnor*-cholenate (IV). The normal methyl ether (IV) melted at 117–118° and had a specific rotation of −63.3°. Saponification of the ester (IV) gave 3-methoxy-5-*bisnor*-cholenic acid (VIII).

The *i*-ether-ester (III) was prepared by an unequivocal method for a comparison of its behavior with that of the ester obtained from the degradation of *i*-stigmasteryl methyl ether. A convenient starting material was 3-acetoxy-5-*bisnor*-cholenic acid. Saponification and esterification yielded the known methyl 3-hydroxy-5-*bisnor*-cholenate (VI). When treated with *p*-toluenesulfonyl chloride in pyridine, this ester (VI) gave methyl 3-*p*-toluenesulfonoxy-5-*bisnor*-cholenate (VII) melting at 139.8–140.5°. The *i*-ether-ester (III) was obtained by refluxing a methanol solution of the *p*-toluenesulfonate (VII) containing potassium acetate. The ester (III) prepared by this method did not crystallize readily; however, under proper conditions, it was obtained in the crystalline form. This ester (III) melted at 72.0–72.8° and possessed a specific rotation of +37.3°. The free acid obtained by saponification of the ester (III) melted at 168–171° and gave a specific rotation of +33°. A mixed melting point with the acid (II) prepared from *i*-stigmasteryl methyl ether gave a slight depression. By their methods of formation and their reactions these acids should be identical. The acids proved difficult to purify. This discrepancy in physical properties is being investigated. The *i*-ether-ester (III) prepared from the *p*-toluenesulfonate (VII) was easily converted either to the normal methyl ether (IV) or to the 3-acetoxy derivative (V). As a further check, the acid (II) prepared by saponification of the ester (III) was reconverted to the normal methyl ether-ester (IV). The identity of these derivatives and the corresponding ones above lends strong support to the assigned structures. Methyl 3-methoxy-5-*bisnor*-cholenate (IV)

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