_p_-Diacetylcymylenediamine.—Two grams of VII was heated with 10 ml. of acetic anhydride at 90° for five minutes. Crystallization from benzene gave m. p. 262.0–262.2°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: N, 11.28. Found: N, 11.27.

Thymoquinone.—Half a gram of finely crushed VII was shaken for five minutes with 50 ml. of 50% ferric chloride solution at room temperature. The thymoquinone was insoluble; it was filtered off and crystallized from petroleum ether; m. p. 45.6–46.0° mixed m. p. with thymoquinone[7] prepared from thymol was the same.

3-Nitro-_p_-cymene (VIII). A.—From II: 8 g. of powdered sodium nitrite was dissolved in 160 g. of sulfuric acid (sp. gr. 1.84) below 40°. Very slowly at 35–40° was added 20 g. of II to avoid the precipitation of the insoluble amine sulfate. Stirring was continued for fifteen minutes after which a drop when poured in water gave none of the colored nitroamine. To this mixture was slowly added 300 ml. of absolute ethanol with vigorous shaking; the resulting mixture was refluxed for one hour. Steam distillation gave some phenolic substance (removed by washing with dilute sodium hydroxide solution) and VIII; yield 9.7 g. (52%). VIII is a light yellow liquid of b. p. 116.7 (10 mm.), b. p. 133.5 (20 mm.), and at atmospheric pressure it is decomposed.

B.—From VI: 20 g. of VI was dissolved in 20 ml. of glacial acetic acid and diazotized exactly as in A. The product consisted mostly of a phenolic residue in the steam distillation flask. The yield of VIII was 2.3 g.

C.—Twenty grams of the mixture of isomeric nitroamines in the proportion as formed by the nitration of I was diazotized and treated as in A, with the further addition of 5 g. of freshly reduced copper as a suspension in the absolute ethanol; yield 9.8 g. (53%).

3-Amino-_p_-cymene (IX).—The VIII in A and B above, were separately reduced with iron powder and hydrochloric acid.[6] Both amines gave the same formyl derivative by refluxing with twice the volume of formic acid (90%) for two hours. **3-Formylamino-_p_-cymene** forms colorless needles from ethanol of m. p. 106.2–106.6°. There was a depression of the melting point when admixed with I.

Anal. Calcd. for $C_{11}H_{15}NO$: N, 7.90. Found: N, 7.83.

3-Amino-_p_-cymene is a colorless liquid of b. p. 105.7° (10 mm.), 122.1° (20 mm.), 240.2° (760 mm.).

Thymol.—Five grams of IX was dissolved in 50 ml. of 5% sulfuric acid and diazotized with the exact equivalent of sodium nitrite dissolved in 10 ml. of water. It was steam distilled, extracted with dilute sodium hydroxide, and acidified, giving thymol of m. p. 47–49° from petroleum ether. The m. p. was raised when mixed with synthetic thymol from *m*-cresol and isopropyl alcohol.

Summary

1. Nitration of 2-formylamino-*p*-cymene gives 70% of 2-amino-3-nitro-*p*-cymene and 30% of 2-amino-5-nitro-*p*-cymene. Nitration of 2-acetylamino-*p*-cymene gives 52 and 48%, respectively, of the above nitroamines.

2. Quantitative separation of the isomeric nitroamines can be effected by fractionation *in vacuo*.

3. The isomeric cymylenediamines can be obtained in excellent yield from the nitroamines by reduction with zinc dust and sodium hydroxide solution.

4. The nitroamine that has previously been described as 2-amino-5-nitro-*p*-cymene has been proved to be 2-amino-3-nitro-*p*-cymene.

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[7] Kremers, Wakeman, and Hixon, *Org. Syntheses*, **6**, 92 (1926).

[CONTRIBUTION NO. 181 FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE UNIVERSITY OF TEXAS]

Alkaline Hydrolysis of Condensation Products of Hydantoin with Aldehydes[1]

BY HENRY R. HENZE, WILLIAM B. WHITNEY AND MARGARET A. EPPRIGHT

The condensation of aldehydes with the methylene hydrogens in —X—CH_2—CO— has been a valuable reaction for synthetic purposes following Perkin's[2] condensation of salicylic aldehyde and sodium acetate in the presence of acetic anhydride. This reaction has since been modified and widely applied. Plöchl and Wolfrum[3] were the first to employ it in connection with condensations involving the —NH—CH_2—CO— grouping. Initially, Plöchl used glycine but later he found that hippuric acid, the benzoyl derivative of glycine, gave much better results. Erlenmeyer[4] studied the chemical behavior of these condensation products of hippuric acid and obtained alpha amino acids by their reduction and *subsequent* hydrolysis.

Wheeler and Hoffman[5] further modified the

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[1] Presented before the Division of Organic Chemistry at the 96th meeting of the American Chemical Society at Milwaukee, Wis., Sept. 5–9, 1938.

[2] Perkin, *Chem. News*, **32**, 258 (1875).

[3] Plöchl, *Ber.*, **16**, 2815 (1883); Plöchl and Wolfrum, *ibid.*, **18**, 1183 (1885).

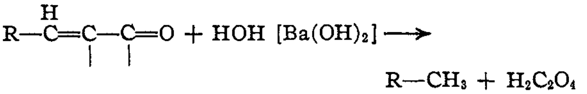
[4] Erlenmeyer, jun., *Ann.*, **271**, 137 (1892); **275**, 1 (1893); *Ber.*, **30**, 2976 (1897).

[5] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 368 (1911).

method by replacing hippuric acid with hydantoin, which contains the —NH—CH_2—CO— structure in a heterocycle. In only one instance, namely, that of anisalhydantoin, was the initial condensation product hydrolyzed by alkali *prior* to reduction, and Wheeler and Hoffman reported that "when it is boiled with alkali it gives *p*-methoxyphenylpyruvic acid." No details were recorded as to the yield and proof of identity of the latter, of the formation of by-products, or concerning the concentration and specific identity of the alkali used. Since either sodium hydroxide or barium hydroxide was utilized in hydrolyzing the reduced reaction products, it seems probable that one or the other of these bases was used in cleaving anisalhydantoin.

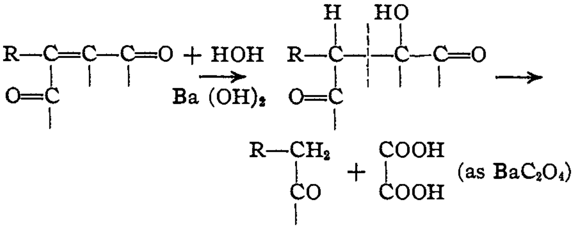
We have studied the effect of aqueous solutions of both sodium and barium hydroxide upon anisalhydantoin and believe that Wheeler and Hoffman utilized a dilute solution of barium hydroxide, for a 5% solution of sodium hydroxide liberates ammonia and forms some *p*-methoxyphenylpyruvic acid. However, some oxalic acid and *p*-methoxytoluene are formed, also. Concentrated solutions of either sodium or barium hydroxide when boiled with anisalhydantoin yield no *p*-methoxyphenylpyruvic acid; indeed, with barium hydroxide *p*-methoxytoluene and oxalate are the chief products although small amounts of anisaldehyde, anisyl alcohol and anisic acid are formed, too. It is of interest to note that concentrated solutions of either of these alkalies convert *p*-methoxyphenylpyruvic acid into oxalate and *p*-methoxytoluene.

The hydrolytic effect of barium hydroxide solution on *o*-chlorobenzalhydantoin, on *m*-nitrobenzalhydantoin, and on furfuralhydantoin has been studied. In each instance no substituted pyruvic acid was isolated; instead, the chief result was to convert the —CH= grouping into methyl.



$$\mathrm{R{-}\overset{H}{C}{=}C{-}C{=}O + HOH\ [Ba(OH)_2] \longrightarrow R{-}CH_3 + H_2C_2O_4}$$

The alkaline hydrolysis of these hydantoin condensation products is strictly analogous to the cleavage of the condensation products of hydantoin with isatin and 5-methylisatin reported by Henze and Blair[6] and for which the following mechanism had been proposed:



$$\mathrm{R{-}C{=}C{-}C{=}O \ (O{=}C) + HOH \xrightarrow[Ba(OH)_2]{} R{-}\overset{H}{C}{-}\overset{HO}{C}{-}C{=}O \ (O{=}C) \longrightarrow R{-}CH_2{-}CO + COOH{-}COOH\ (as\ BaC_2O_4)}$$

The essential steps in the mechanism of alkaline hydrolysis are: (a) the addition of a molecule of water to the ethylenic linkage in such a way that the HO— adds to the C atom of the hydantoin nucleus and the H— to the other C atom of the C=C linkage; (b) the double bond being saturated, the linkage between the two carbons breaks, either because of migration of a hydrogen atom in the reversal of enolization, or because of intermolecular change (bimolecular rather than monomolecular process).

Nicolet and Campbell,[7] as a result of a study of alkaline hydrolysis of benzalcreatinine (benzal-2-imino-1-methylhydantoin) and related compounds concluded that "It seems, however, to be well established that it is a matter of somewhat extreme difficulty to open the ring in any of the unreduced aldehyde condensation products of hydantoins by the action of alkali." That this statement is too broad is shown by the results of the present investigation.

Since *o*-chlorobenzalhydantoin and *m*-nitrobenzalhydantoin had not been synthesized previously, it was deemed desirable to reduce and hydrolyze the compounds in order to convert them into α-amino acids. By this process *o*-chlorophenylalanine and *m*-aminophenylalanine were obtained.

Experimental

Action of Sodium Hydroxide on Anisalhydantoin.—One gram of anisalhydantoin[5] was digested in 100 cc. of 5% sodium hydroxide solution for five hours at 80–90°; during this period ammonia was evolved and, in addition, the odor characteristic of *p*-methoxytoluene was detected in the reaction flask. The reaction mixture was neutralized with dilute hydrochloric acid causing the separation of a small amount of yellow solid. The latter did not contain nitrogen, and its solution in ethyl alcohol developed a fleeting blue-green color when treated with dilute, aqueous ferric chloride solution. A positive test for oxalate was obtained in the acid filtrate.

Action of Barium Hydroxide on Anisalhydantoin.—Thirty-five grams of anisalhydantoin, 300 g. of crystalline barium hydroxide and 400 cc. of water were digested under reflux in an oil-bath at 120–135° for one hundred hours.

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[6] Henze and Blair, THIS JOURNAL, **55**, 4621 (1933).

[7] Nicolet and Campbell, THIS JOURNAL, **50**, 1155 (1928).

At intervals during the hydrolysis the cooling water was withdrawn from the condenser and distillation was permitted until a total volume of 150 cc. of distillate had been collected. The distillate was saturated with potassium carbonate and the oily layer was separated and dried. Upon distillation the product (7.5 cc.) proved to be a mixture, the chief constituent being *p*-methoxytoluene, b. p. 177.5–178°; d^{20}_4 0.9735; $n^{20}_{\rm D}$ 1.5140; $M_{\rm R}$ calcd. 37.19; $M_{\rm R}$ found, 37.73; a trace of anisic aldehyde was identified.

The mixture remaining after hydrolysis was cooled and filtered, the residue and filtrate being examined independently. The residue consisted largely of barium hydroxide and carbonate, but contained oxalate, also. The filtrate was treated with ether which served to extract 1 cc. of anisyl alcohol, b. p. 259° (cor.). From the filtrate upon acidification there separated 9 g. of curdy solid which was shown to be anisic acid, m. p. 184°; neutral equivalent 149 (in alcohol), 151 (in water); m. p. of mixture with authentic sample of anisic acid 184.5°; m. p. of mixture with *p*-methoxyphenylpyruvic acid showed a depression of twenty degrees.

Anal. Calcd. for $C_8H_8O_3$: C, 63.13; H, 5.30. Found: C, 63.50; H, 5.30.

Further confirmation of the identity of anisic acid was obtained by its conversion into the ethyl ester,[8] m. p. 7° (cor.); b. p. 264.5°; $n^{20}_{\rm D}$ 1.5238.

Converson of "Anisal-azlactone" [2-Phenyl-4-(*p*-methoxyphenyl)-oxazolone] into *p*-Methoxyphenylpyruvic Acid. —Following Dakin's[9] procedure, anisaldehyde was condensed with hippuric acid to form "anisal-azlactone," m. p. 158°. Fifty grams of the "azlactone" was heated for one hour with 750 cc. of 40% sodium hydroxide solution in an oil-bath at 110–115° following the directions of Wakeman and Dakin.[10] At the close of thirty minutes it was noticed that an oil, as well as water, was refluxing in the condenser; hence, during the next half hour distillation was permitted in order to collect the oily liquid. The reaction mixture was cooled and extracted with ether, the extract being combined with that of the distillate. After drying the extract over anhydrous potassium carbonate, and removing the ether, the residual liquid boiled at 177°; d^{20}_4 0.9702; $n^{20}_{\rm D}$ 1.5120; $M_{\rm R}$ calcd. for *p*-methoxytoluene, 37.19; $M_{\rm R}$ found, 37.74.

Continuing with the procedure 13 g. of *p*-methoxyphenylpyruvic acid,[11] melting at 185°, was obtained.

Action of Barium Hydroxide on *p*-Methoxyphenylpyruvic Acid.—Four grams of *p*-methoxyphenylpyruvic acid, 13 g. of crystalline barium hydroxide and 15 cc. of water were heated in an oil-bath for fifteen hours at 115–120°. The reaction mixture was subjected to steam distillation at intervals during the period of digestion. From the distillate there was isolated 0.8 cc. of an oil sparingly soluble in water. After drying over anhydrous potassium carbonate, the oil had b. p. 176.5°; d^{20}_4 0.9705; $n^{20}_{\rm D}$ 1.5130; hence, this product was *p*-methoxytoluene. Moreover, the presence of oxalate in the reaction mixture was established.

Action of Barium Hydroxide on Furfurylhydantoin.—Thirty grams of furfuralhydantoin, 320 g. of crystalline barium hydroxide and 350 cc. of water were digested under reflux in an oil-bath at 110–120° for sixty hours. After ten hours an oil, as well as water, was noticed in the condenser; therefore, the reaction mixture was subjected intermittently to steam distillation. From a total distillate of 500 cc. there separated 8 cc. of a yellow-green colored oil, sparingly soluble in and less dense than water, and of an aromatic odor strongly suggestive of the xylenes. After drying the oil was distilled and identified as being 2-methylfuran;[12] b. p. 63.2° (cor.); d^{20}_4 0.9032; $n^{20}_{\rm D}$ 1.4310; $M_{\rm R}$ calcd., 23.71; $M_{\rm R}$ found, 23.50. No organic matter other than oxalate was identified in the material remaining after hydrolysis.

Preparation of *o*-Chlorobenzalhydantoin.—*o*-Chlorobenzaldehyde (10 g.), hydantoin (10 g.), fused sodium acetate (8.2 g.) and glacial acetic acid (59 cc. to which 1 cc. of acetic anhydride had been added) were refluxed together for one hour in an oil-bath at 145°. Upon cooling some *o*-chlorobenzalhydantoin crystallized and additional material was obtained by dilution of the solution. The total yield of crude product was 10 g. (66%). After recrystallization from acetone and ethanol the silky needles melted at 275° (cor.). This derivative is soluble in glacial acetic acid, acetone and ethanol, but is nearly insoluble in water, ether and benzene.

Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 53.94; H, 3.17; Cl, 15.92; N, 12.59. Found: C, 54.21; H, 3.36; Cl, 16.15; N, 12.87.

Action of Barium Hydroxide on *o*-Chlorobenzalhydantoin.—Ten grams of *o*-chlorobenzalhydantoin was refluxed with a mixture of 50 g. of barium hydroxide (octahydrate) and 50 cc. of water for fifty hours. The liquid refluxing in the condenser contained oily droplets; hence, the reaction mixture was steam distilled and the distillate extracted with ether. After drying and removal of the solvent, the residual liquid, by reason of the following data, was identified as being *o*-chlorotoluene: b. p. 155° (cor.); d^{20}_4 1.0890; $n^{20}_{\rm D}$ 1.5250; $M_{\rm R}$ calcd., 36.09; $M_{\rm R}$ found, 35.62.

Anal. Calcd. for C_7H_7Cl: Cl, 28.02. Found: Cl, 27.80.

Reduction of *o*-Chlorobenzalhydantoin.—Ten grams of *o*-chlorobenzalhydantoin, 45 g. of hydriodic acid (sp. gr. 1.7) and 10 cc. of glacial acetic acid were refluxed for two hours in an oil-bath at 120°. The solution was steam distilled until free from acid and cooled, thus causing the separation of 7.5 g. of white, crystalline solid material. The 5-(*o*-chlorobenzyl)-hydantoin was recrystallized from glacial acetic acid in the form of white, glistening platelets melting at 240° (cor.).

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.45; H, 4.03; Cl, 15.79; N, 12.48. Found: C, 52.64; H, 3.77; Cl, 15.78; N, 12.09.

Hydrolysis of 5-(*o*-Chlorobenzyl)-hydantoin.—Ten grams of 5-(*o*-chlorobenzyl)-hydantoin, 50 g. of barium hydroxide (octahydrate) and 50 cc. of water were refluxed for about fifty hours. Most of the barium was removed

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[8] Radcliffe and Brindley, *Perfumery Essentl. Oil Record*, **13**, 414 (1922), report m. p. 7–8°; b. p. 263°; $n^{18.5}_{\rm D}$ 1.5245.

[9] Dakin, *J. Biol. Chem.*, **8**, 18 (1910).

[10] Wakeman and Dakin, *ibid.*, **9**, 150 (1911).

[11] Wakeman and Dakin, ref. 10, report m. p. 190–192°, but Erlenmeyer and Wittenberg, *Ann.*, **337**, 294 (1904), report m. p. 186°.

[12] Paul, *Compt. rend.*, **200**, 1118 (1935).

from the solution by saturation with carbon dioxide, the remainder by exact neutralization with sulfuric acid. After filtration and concentration of the filtrate, 7.4 g. (88% yield) of white solid separated. After recrystallization from water and alcohol, *o*-**chlorophenylalanine** melts at 260–261° (cor.).

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.13; H, 5.05; Cl, 17.77; N, 7.02. Found: C, 55.14; H, 5.04; Cl, 17.30; N, 7.68.

Anhydrous hydrogen chloride was passed into an ethanol solution of *o*-chlorophenylalanine causing the separation of solid material. The latter was filtered, washed with a cold, saturated solution of hydrogen chloride in ethanol, and dried in a vacuum desiccator. The melting point of *o*-**chlorophenylalanine hydrochloride** is 255–256° (cor.).

Anal. Calcd. for $C_9H_{11}Cl_2N_2O_2$: Cl, 30.01. Found: Cl, 29.87.

Preparation of *m*-Nitrobenzalhydantoin.—Ten grams of hydantoin, 15 g. of *m*-nitrobenzaldehyde, 8.2 g. of fused sodium acetate, 60 cc. of glacial acetic acid and 2 cc. of acetic anhydride were heated together in an oil-bath at 145°; yellow solid material began to separate from solution after about three hours, but heating was continued for a total of eleven hours. Upon cooling and filtering, 14.5 g. (58% yield) of solid, with m. p. 250°, was obtained. After recrystallization from glacial acetic acid the bright yellow crystals of *m*-nitrobenzalhydantoin melted at 277° (cor.). This compound is quite sparingly soluble in all common solvents, the largest solubility being that (1.75–2 g./100 cc.) in boiling glacial acetic acid.

Anal. Calcd. for $C_{10}H_7N_3O_4$: C, 51.49; H, 3.03; N, 18.07. Found: C, 51.48; H, 3.18; N, 18.02.

Action of Barium Hydroxide on *m*-Nitrobenzalhydantoin.—Twenty grams of *m*-nitrobenzalhydantoin, 100 g. of barium hydroxide (octahydrate) and 100 cc. of water were placed in a distilling flask and heated in an oil-bath at 120° for about thirty hours. During this time a slow distillation occurred and oily droplets were collected in the receiver. After drying, the oil was identified as being *m*-nitrotoluene by its boiling point and refractive index.

The residue in the flask, to which water was added to replace that removed through distillation, was heated for an additional period of thirty hours before being examined for oxalate; the latter was present.

Reduction of *m*-Nitrobenzalhydantoin.—To 23.3 g. of *m*-nitrobenzalhydantoin were added 100 g. of tin and 500 cc. of concd. hydrochloric acid and the mixture was heated in an oil-bath for six hours at 120° while hydrogen chloride was passed into the well-stirred solution. The bright yellow crystals quickly changed to a flocculent light gray colored solid which dissolved after about five hours. The solution was concentrated, to remove much of the excess acid, diluted with water to adjust the *p*H, and saturated with hydrogen sulfide. After filtration and decolorization of the filtrate with Norite, further concentration in a vacuum desiccator over sulfuric acid caused separation of a crystalline solid. The latter was recrystallized from dilute hydrochloric acid and yielded the **hydrochloride of 5-(*m*-aminobenzyl)-hydantoin,** m. p. 270° (cor.). This salt is extremely soluble in water and alcohol, but is insoluble in acetone and ether.

Anal. Calcd. for $C_{10}H_{12}ClN_3O_2$: C, 49.68; H, 5.01; Cl, 14.67; N, 17.39. Found: C, 49.71; H, 5.27; Cl, 14.55; N, 17.11.

Action of Barium Hydroxide on 5-(*m*-Aminobenzyl)-hydantoin Hydrochloride.—The hydrolysis was accomplished in the usual manner with 17.5 g. of *m*-aminobenzylhydantoin, 87.5 g. of crystalline barium hydroxide and 87.5 cc. of water. The **dihydrochloride of *m*-aminophenylalanine,** m. p. 225° (cor.), was recrystallized from hydrochloric acid.

Anal. Calcd. for $C_9H_{14}Cl_2N_2O_2$: C, 42.69; H, 5.58; N, 11.06. Found: C, 43.02; H, 5.97; N, 11.29.

Summary

The behavior on alkaline hydrolysis of anisal-, furfural-, *o*-chlorobenzal-, and *m*-nitrobenzalhydantoin has been studied. The results are to be predicted on the basis of a mechanism advanced previously by Henze and Blair.

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