which solidified upon cooling to a crystalline solid melting at 70–71°. Recrystallization from petroleum ether (b.p. 30–60°) gave colorless needles melting at 70–71°. Analytical data are given in Table II.

Acknowledgment.—The authors wish to thank Mr. Donald McDonnell for the analyses and spectra and Mr. Julian Conkey for the inhibiting concentrations reported in this paper.

APPLETON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Aromatization and Rearrangement of Cyclic Ketones. III. 2,3,5- and 3,4,5-Trimethylphenol from Isophorone[1]

BY F. MARSHALL BERINGER AND EMIL J. GEERING

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By modification of the bromination–dehydrobromination method of Knoevenagel isophorone and its enol acetate have been converted to a mixture of 2,3,5- and 3,4,5-trimethylphenol. Isophorone dibromide was investigated as a possible reaction intermediate. Related aromatizations in the literature are pointed out.

Previous studies have shown that isophorone[2] and 3-phenyl-5,5-dimethylcyclohexenone[3] could be converted to sulfonic acids, treatment of which with hot acetic anhydride yielded the acetates of 3,4,5-trimethylphenol and 3,4-dimethyl-5-phenylphenol.[4] It has since seemed of interest to see whether this oxidative rearrangement could be effected by the bromination–dehydrobromination method introduced by Knoevenagel[5] in 1893 and used in the preparation of phenol,[6,7] *m*-cresol,[5] dialkylphenols,[8–10] a trialkylphenol,[9] and phenolic esters.[6,8,11]

As in Knoevenagel's procedure,[8] bromine was added to isophorone in cold acetic acid, and the resulting solution was heated on the steam-bath and then at reflux to give a 1.2% yield of trimethylphenols. More successfully, when bromine was added to isophorone in trichlorobenzene and the solution was refluxed until the evolution of hydrogen bromide ceased, a 44–47% yield of mixed trimethylphenols[12] was obtained. Crystallization, sublimation and chromatography effected a separation of the mixture into 2,3,5-trimethylphenol[13,14] and 3,4,5-trimethylphenol[2,13,15] in the ratio of about 1:3.

In attempts to accelerate or improve the yield of the reaction several possible catalysts were tried. With hydrogen bromide continuously added, the yield was slightly higher (49%), while with benzoyl peroxide added from time to time, the yield was slightly lower (34%), possibly due to a faulty work-up. Runs with catalytic amounts of aluminum chloride or stannic chloride gave tars with only traces of phenols. Other conditions investigated are summarized in the Experimental section.

Isophorone dibromide[16] was prepared and studied as a possible intermediate in the reaction. While this material seemed stable in an evacuated desiccator, a sample in air lost in two days weight corresponding approximately to a molar equivalent of hydrogen bromide, with the residue on distillation giving 62% of isophorone. Attempts were made to convert isophorone dibromide to trimethylphenols by heating in carbon tetrachloride, 2,4-lutidine and trichlorobenzene. Only in the last case was there obtained even a trace of phenols. Two possible interpretations suggest themselves: either isophorone dibromide is not an intermediate in the reaction, or in trichlorobenzene there is formed along with isophorone dibromide a material which catalyzes the aromatization of the isophorone dibromide during the period of heating.

The enol acetate of isophorone was prepared by the method of Hagemeyer and Hull.[17] Bromination and rearrangement in the usual manner gave a 35% yield of phenols.

By aromatizations with rearrangements rather similar to that reported here, phenols were obtained by Crossley and co-workers[18,19] and by Hinkel and Williams[20] from halogenated cyclohexenones obtained by the action of phosphorus halides and

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[1] This paper, taken from a thesis submitted by Emil J. Geering in partial fulfillment of the requirements of the degree of Master of Science in Chemistry in the Graduate School of the Polytechnic Institute of Brooklyn in June, 1950, was presented in part at the 122nd meeting of the American Chemical Society, September 14 to 19, 1952, Atlantic City, N. J.

[2] W. von E. Doering and F. M. Beringer, THIS JOURNAL, **71**, 2221 (1949).

[3] F. M. Beringer and I. Kuntz, *ibid.*, **73**, 364 (1951).

[4] E. C. Horning has surveyed alicyclic-aromatic conversions in *Chem. Revs.*, **33**, 89 (1943).

[5] E. Knoevenagel, *Ber.*, **26**, 1951 (1893).

[6] A. Kötz and C. Götz, *Ann.*, **358**, 183 (1908).

[7] O. Wallach, *ibid.*, **343**, 40 (1905).

[8] E. Knoevenagel, *ibid.*, **281**, 25 (1894).

[9] J. Decombe, *Bull. soc. chim.*, **12**, 651 (1945).

[10] E. Knoevenagel, *Ann.*, **288**, 321 (1895); E. Beckmann and H. Eickelberg, *Ber.*, **29**, 418 (1896); A. D. Petrow, *ibid.*, **63**, 898 (1930).

[11] P. Rabe and F. Rahm, *Ber.*, **38**, 969 (1905); W. A. Noyes, *Am. Chem. J.*, **20**, 789 (1898).

[12] Melting point ranges for mixtures of 2,3,5- and 3,4,5-trimethylphenol were found to be: for 20% 2,3.5-trimethylphenol, 74–86°, for 40% and for 60%, 67–68°, and for 80%, 68–73°. These data are in accord with the m.p. of 66–66.5° reported for a mixture of these trimethylphenols obtained by the aromatization of dihydroisophorone with fuming sulfuric acid (ref. 2, see footnote 10).

[13] K. von Auwers and K. Saurwein, *Ber.*, **55**, 2372 (1922); G. Baddeley, *J. Chem. Soc.*, 330 (1944).

[14] O. Kruber and A. Schmitt, *Ber.*, **64**, 2270 (1931).

[15] O. Kruber and A. Marx, *ibid.*, **73B**, 1175 (1940).

[16] J. C. Baker, *J. Chem. Soc.*, 663 (1926).

[17] H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

[18] A. W. Crossley and H. R. LeSueur, *J. Chem. Soc.*, **81**, 821 and 1533 (1902); *ibid.*, **83**, 110 (1903); A. W. Crossley, *ibid.*, **85**, 264 (1904).

[19] A. W. Crossley and N. Renouf, *ibid.*, **105**, 165 (1914).

[20] L. E. Hinkel and W. D. Williams, *ibid.*, **121**, 2498 (1922); L. E. Hinkel, *ibid.*, **125**, 1847 (1924).

halogens on dimedone.[21] Especially striking is the thermal conversion of 2,3-dibromo-5,5-dimethylcyclohexenone to a mixture of 2,3- and 3,4-dimethyl-5-bromophenol.[19]

Experimental[22]

Preparation of 2,3,5- and 3,4,5-Trimethylphenol from Isophorone.—Bromine (24 cc., 0.47 mole) was added over 30 minutes to a stirred solution of 75 cc. (0.5 mole) of isophorone in 300 cc. of 1,2,4-trichlorobenzene at 5–10°, with this temperature maintained for an additional 30 minutes.

The reaction mixture was heated (brisk ebullition) for three hours and then distilled until a residue of about 50 cc. remained. The residue, which contained the greater part of the phenols, was distilled at 0.01 mm.

The phenols were separated from the trichlorobenzene in the distillates by extraction with 50% potassium hydroxide and with 10% potassium hydroxide (six times). Washing with ether removed color from the combined alkaline extracts, which were then acidified. This solution was extracted with ether, the extract was dried, and the ether was removed by evaporation (finally under aspirator vacuum) until a solid mass of phenols remained.

The impure product was sublimed and then crystallized from hexane. The yield of colorless mixed 2,3,5- and 3,4,5-trimethylphenols was 28–30 g., 44–47% of the theoretical yield. A typical melting point range was 67–80°.[12]

Summary of Aromatizations under Other Conditions.—(a) After addition of bromine, hydrogen bromide was passed through the mixture during heating to give 49% of phenols, m.p. 67–68°. (b) Runs in which catalytic amounts of aluminum chloride or stannic chloride were present during heating gave tars with only traces of phenols. (c) A run in which there were periodic additions of benzoyl peroxide during heating gave 34% of phenols, m.p. 65–66.5° and 107.5–108° (separation in the original sublimation). (d) The use of nitrobenzene instead of trichlorobenzene gave 28% of phenols, m.p. from 100 to 108° in various fractions. (e) Bromination in acetic acid followed by heating on a steam-bath and at reflux gave 1.2% of phenols, m.p. 100–105°. (f) Bromination in quinoline at 5° followed by stirring at room temperature for 30 hours gave 8% of almost pure 3,4,5-trimethylphenol, m.p. 108–109°. (g) Bromination in water and treatment of the brominated material with 8 *N* potassium hydroxide gave 6% of trimethylphenols, m.p. 105–106° (predominantly the 3,4,5-isomer). (h) After bromination in trichlorobenzene an equivalent of pyridine was added, and the pyridine hydrobromide was separated. Addition of an equivalent of quinoline as soon as the temperature of the reaction mixture reached 180° caused a rise to 210°. Work-up including a steam distillation to remove tars gave 22% of phenols, m.p. 98–100°. (i) Chlorination in trichlorobenzene with usual work-up gave 4% of phenols, m.p. 103–107°.

Separation of 2,3,5- and 3,4,5-Trimethylphenol.—It was found possible to obtain pure 3,4,5-trimethylphenol from the product described above making use of the greater ease of sublimation of 2,3,5-trimethylphenol. Sublimation of the mixed trimethylphenols at 50° and 2 mm. left a residue of almost pure 3,4,5-trimethylphenol. The sublimate was a mixture of isomers with a melting point of 65–80°. Crystallization of the residue from hexane gave **3,4,5-trimethylphenol**, m.p. 109.3–109.6°; reported[2,13,15] 106 to 109°.

Anal. Calcd. for $C_9H_{12}O$: C, 79.40; H, 8.87. Found: C, 79.43; H, 8.80.

Another way to isolate 3,4,5-trimethylphenol from the mixture of isomers obtained from the reaction was to crystallize this mixture first from low-boiling petroleum ether, than twice from hexane. There was thus obtained 3,4,5-trimethylphenol, m.p. 108.8–109°.

Separation of 2,3,5-trimethylphenol from the mixture of isomers was achieved by chromatography on alumina, from which it was eluted more rapidly than 3,4,5-trimethylphenol. In this way there was obtained **2,3,5-trimethylphenol**, m.p. 94.2–94.6°; reported[13,14] 93 to 96°.

Anal. Calcd. for $C_9H_{12}O$: C, 79.40; H, 8.87. Found: C, 79.30; H, 9.01.

Analysis of two reaction mixtures using sublimation, chromatography and crystallization showed 25–30% of 2,3,5-trimethylphenol and 70–75% of 3,4,5-trimethylphenol.

Derivatives of 2,3,5- and 3,4,5-Trimethylphenol.—By methods already detailed[2] the phenols were converted to known derivatives.

The phenylurethan of 2,3,5-trimethylphenol, m.p. 172.5–173.5°; reported[14] 174°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.20; H, 6.61; N, 5.59.

4,6-Dibromo-2,3,5-trimethylphenol, m.p. 150.5–151.5°; reported[13,14] 148 to 152°.

Anal. Calcd. for $C_9H_{10}Br_2O$: C, 36.76; H, 3.40. Found: C, 36.85; H, 3.48.

The phenylurethan of 3,4,5-trimethylphenol, m.p. 153.3–154°; reported[2,16,23] 148–149° and 153.5–154°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.48. Found: C, 75.12; H, 6.61; N, 5.59.

2,6-Dibromo-3,4,5-trimethylphenol, m.p. 145–145.5°; reported[2,13] 142.5 to 145.5°.

Anal. Calcd. for $C_9H_{10}Br_2O$: C, 36.76; H, 3.40. Found: C, 36.70; H, 3.53.

A mixture of 9.52 g. (0.069 mole) of 3,4,5-trimethylphenol, 9 cc. of benzoyl chloride and 45 cc. of pyridine was refluxed for two hours, cooled, diluted with ether, washed with sodium bicarbonate and with water, dried and distilled to give 13.4 g. (0.0558 mole, 81%) of **3,4,5-trimethylphenyl benzoate**,[24] b.p. 353–355° (uncor.), m.p. 41–42°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.90; H, 6.98.

3,4,5-Trimethylphenyl benzoate (2.4 g., 0.01 mole) was mixed with aluminum chloride (2.66 g., 0.02 mole) and heated at 140° for four hours. The cooled reaction mixture was treated with ice and hydrochloric acid and warmed to dissolve aluminum chloride. A pale yellow solid was collected by filtration and crystallized from isopropyl alcohol (activated carbon) to give 1.76 g. (0.073 mole, 73%) of **2-benzoyl-3,4,5-trimethylphenol**[24,25] (2-hydroxy-4,5,6-trimethylbenzophenone), m.p. 187.5–188.5°. Two recrystallizations from hexane raised the m.p. to 188.5–190°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.21; H, 6.78.

2-*p*-Sulfobenzeneazo-3,4,5-trimethylphenol.[26]—A solution of 31.0 g. (179 mmoles) of sulfanilic acid and 19.7 g. (286 mmoles) of sodium nitrite in 300 cc. of 2.5% aqueous sodium carbonate was added with stirring to 200 g. of ice and 40 cc. of concd. hydrochloric acid. To the resulting suspension a solution of 24.0 g. (176 mmoles) of 3,4,5-trimethylphenol in 160 cc. of 10% sodium hydroxide was added. After five minutes of stirring, the mixture was heated to boiling and 50 g. of sodium chloride was added. The precipitate from the cooled solution was collected and crystallized three times from 70% ethanol to give 45.4 g. (133 mmoles, 75%) of the sodium salt of **2-*p*-sulfobenzeneazo-3,4,5-trimethylphenol** as golden orange crystals.

Anal. Calcd. for $C_{15}H_{15}N_2NaO_4S$: C, 52.62; H, 4.42; N, 8.19. Found: C, 52.43; H, 4.55; N, 8.01.

The S-benzylthiuronium **salt of *p*-sulfobenzeneazo-3,4,5-trimethylphenol** crystallized from ethanol as fine red needles, m.p. 229–229.5°.

2-Amino-3,4,5-trimethylphenol.[26]—To 10.0 g. (29.2 mmoles) of the sodium salt of 2-*p*-benzeneazo-3,4,5-trimethylphenol in 350 cc. of warm water 14.8 g. (70 mmoles) of sodium hydrosulfite was added with stirring. After being boiled, the solution was cooled to give light yellow crystals. Sublimation and crystallization from heptane gave

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[21] Dimedone has also been aromatized, to *o*-xylorcinol, by the sulfonation procedure (ref. 2).

[22] Boiling points are not corrected. Melting points were taken with a modified Hershberg apparatus. Microanalyses were performed by Dr. Weiler and Dr. Strauss, 164 Banbury Road, Oxford, England.

[23] K. von Auwers and F. Wieners, *Ber.*, **58**, 2815 (1925).

[24] This compound was first prepared by Mr. Emanual Margulis.

[25] This structure is assigned by analogy with the reported formation of 2-acetyl-3,4,5-trimethylphenol from 3,4,5-trimethylphenyl acetate under similar conditions: K. von Auwers, H. Bundesmann and F. Wieners, *Ann.*, **447**, 162 (1926).

[26] The sequence leading to 2-amino-3,4,5-trimethylphenol is taken from the thesis of James C. Patterson, submitted in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemistry at the Polytechnic Institute of Brooklyn in June, 1950.

3.12 g. (20.6 mmoles, 71%) of 2-amino-3,4,5-trimethylphenol as colorless plates, m.p. 164.5–165°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.59; H, 8.56; N, 9.20.

A solution of 0.50 g. (3.3 mmoles) of 2-amino-3,4,5-trimethylphenol in 9 cc. of 3.5% hydrochloric acid at 50° was treated with 0.35 cc. of acetic anhydride and with 0.30 g. of sodium acetate in 2.0 cc. of water. The precipitate was crystallized from water to give 0.58 g. (3.0 mmoles, 91%) of 2-acetamido-3,4,5-trimethylphenol as colorless plates, m.p. 162–163°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.21; H, 7.88; N, 7.10.

The Aromatization of Isophorone Enol Acetate.—According to the procedure of Hagemeyer and Hull[17] 75 cc. (0.5 mole) of isophorone and 81.4 cc. (0.5 mole) of isopropenyl acetate[27] were refluxed under a helix-packed column until 40 cc. of acetone had been collected. The residue was rapidly distilled under reduced pressure to give 80.8 g. of crude isophorone enol acetate. Redistillation through a small Vigreux column gave 70.8 g. (0.392 mole, 78.4%) of isophorone enol acetate, b.p. 96° at 4 mm., saponification equivalent 180 (calcd., 181).

Bromination and aromatization in the manner described in a previous section gave a 34.8% yield of trimethylphenols.

Isophorone Dibromide.—According to the method of Baker,[16] the addition of bromine to isophorone in carbon tetrachloride at 7° gave a 76% yield of isophorone dibromide, dried in a continuously evacuated desiccator.

On keeping for 48 hours at room temperature in a beaker covered by a watch glass isophorone dibromide (56.5 g., 0.19 mole) decomposed to give 38 g. of a dark brown liquid. Distillation under reduced pressure gave 2 cc. of water, 5 cc. of a fraction b.p. 43–54° at 18 mm. (b.p. 119° in a micro b.p. tube) and 18 cc. (0.12 mole, 62%) of isophorone, b.p. 60° at 3 mm. (b.p. 211° in a micro b.p. tube).

A solution of 36 g. (0.13 mole) of isophorone dibromide in 160 cc. of 1,2,4-trichlorobenzene was refluxed for five hours. From the reaction mixture there was obtained in the manner described in a previous section 0.5 g. of phenols, m.p. 66–73°. Runs in which isophorone dibromide was heated in carbon tetrachloride (reflux) or in 2,4-lutidine (70°) gave no phenolic product.

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[27] A research sample from the Tennessee Eastman Co. is gratefully acknowledged.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Aromatization and Rearrangement of Cyclic Ketones. IV. Substituted Acetanilides from Cyclohexenone Oximes[1]

BY F. MARSHALL BERINGER AND ISIDORE UGELOW

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An improved method for the aromatization of cyclohexanone oximes when applied to 3-methyl-5-phenylcyclohexanone oxime gave 3-methyl-5-phenylacetanilide. Under similar conditions isophorone oxime gave 2,3,5- and 3,4,5-trimethylacetanilide while 3-phenyl-5,5-dimethylcyclohexanone oxime gave 2,3- and 3,4-dimethyl-5-phenylacetanilide. A possible mechanism for such reactions is discussed.

Over the past sixty years there have been scattered reports of the conversion of cyclohexenone oximes to anilines and their derivatives.[2] Thus the oximes of cyclohexenone[3] and of its 3-methyl,[4] 4-isopropyl,[5,6] 3,5-dimethyl[4,7] and 3-methyl-6-isopropyl[6] derivatives gave on treatment with acetic anhydride or acetyl chloride acetanilide and the corresponding alkyl derivatives. Yields were in general low or unreported. Related is the formation of carvacryl amine (from the oximes of carvenone,[8] carvone[6,9] and thujone[10]) and of amine derivatives of naphthalene,[11] quinoline[12] and thiophene.[13] The dehydration of isophorone oxime to 3,4,5-trimethylaniline on treatment with 20% hydrochloric acid at 170° is the only case in which rearrangement is said to accompany aromatization.[4,14]

The work presently reported had two aims. The first was to find satisfactory conditions for the conversion of cyclohexenone oximes to acetanilides. A second aim was the outgrowth of our previously reported investigations of the concurrent aromatization and rearrangements of isophorone[15,16] and of 3-phenyl-5,5-dimethylcyclohexenone[17] to trisubstituted phenols. Here we wished to see whether the oximes of these two cyclohexenones could be converted to the analogous trisubstituted acetanilides.

Our search for satisfactory reaction conditions was guided by two experimental facts and a working hypothesis for the mechanism. The facts were that hot acetic anhydride did not effect the aromatization of isophorone oxime, while addition of acetyl chloride to isophorone oxime caused a violent exo-

[1] This paper, based largely on a thesis submitted by Isidore Ugelow in partial fulfillment of the requirements of the degree of Master of Science in Chemistry in the Graduate School of the Polytechnic Institute of Brooklyn in June, 1952, was presented in part at the 122nd meeting of the American Chemical Society, September 14 to 19, 1952, Atlantic City, N. J.

[2] E. C. Horning has surveyed alicyclic-aromatic conversions in *Chem. Revs.*, **33**, 89 (1943).

[3] A. A. Kötz and T. Grethe, *J. prakt. Chem.*, [2] **80**, 500 (1909).

[4] L. Wolff, M. Gabler and F. Heyl, *Ann.*, **322**, 351 (1902).

[5] P. A. Berry, A. K. Macbeth and T. B. Swanson, *J. Chem. Soc.*, 986 (1937).

[6] R. G. Cooke and A. K. Macbeth, *ibid.*, 1593 (1937).

[7] An attempt to aromatize 3,5-dimethylcyclohexenone oxime by heating with palladium on charcoal was unsuccessful: E. C. Horning and M. G. Horning, THIS JOURNAL, **69**, 1907 (1947). For a successful application of this method see reference 13.

[8] Carvenone oxime hydrochloride gave carvacryl amine on dry distillation: O. Wallach, *Ber.*, **40**, 582 (1907).

[9] In the reported conversion of carvone oxime to carvacryl amine and carvacrol on heating with alcoholic sulfuric acid, reduction accompanied aromatization: O. Wallach, *Ann.*, **275**, 110 (1893). That a base-catalyzed mechanism for this reaction also exists is indicated by the formation of carvacryl amine from carvone oxime on treatment with potassium hydroxide at 230–240°: O. Wallach, *Ann.*, **279**, 366 (1894).

[10] F. W. Semmler, *Ber.*, **25**, 3352 (1892).

[11] G. Schroeter, *ibid.*, **63B**, 1308 (1930); H. E. Zaugg, M. Freifelder and B. W. Horrom, *J. Org. Chem.*, **15**, 1197 (1950).

[12] W. S. Johnson, E. L. Woroch and B. G. Buell, THIS JOURNAL, **71**, 1901 (1949).

[13] L. C. Cheney and J. R. Piening, *ibid.*, **67**, 729 (1945).

[14] Attempts in our laboratory to repeat this work gave isophorone but no amine.

[15] W. von E. Doering and F. M. Beringer, THIS JOURNAL, **71**, 221 (1949).

[16] F. M. Beringer and E. J. Geering, *ibid.*, **75**, 2633 (1953).

[17] F. M. Beringer and I. Kuntz, *ibid.*, **73**, 364 (1951).