

overnight the precipitated 6-chloro-9-(4-diethylamino-butylamino)-2-methoxyacridine dihydrochloride¹ was filtered and washed with acetone; a yield of 40.0 g. (81.6%) of bright yellow crystals was obtained, m. p. 265° (dec.) (Magidson and Grigorovskii reported 246–248°).

Anal. Calcd. for $C_{22}H_{28}ClN_3O \cdot 2HCl \cdot 2H_2O$: N, 8.49; Cl, 14.36; H_2O , 7.3. Found: N, 8.35; Cl, 13.98; H_2O , 7.7.

The free base was prepared from an aqueous solution of 5.0 g. of the dihydrochloride in 50 cc. of water by addition of 28% ammonium hydroxide until alkaline to litmus. After extracting with benzene and removal of the solvent, the crude base (4.1 g.) was recrystallized twice from benzene; 6-chloro-9-(4-diethylaminobutylamino)-2-methoxyacridine was obtained as bright yellow crystals, m. p. 79.5–80.5° (Magidson and Grigorovskii reported 76–78° for the pentahydrate). A sample dried *in vacuo* over phosphorus pentoxide at 56° for two hours was found to be anhydrous (m. p. 79.5–80.5°).

Anal. Calcd. for $C_{22}H_{28}ClN_3O$: C, 68.39; H, 7.26; N, 10.88. Found: C, 68.19; H, 7.34; N, 10.67.

6-Chloro-9-(4-dimethylaminobutylamino)-2-methoxyacridine Dihydrochloride.—A mixture of 23.9 g. (0.20 mole) of 4-dimethylaminobutylamine,⁵ 55.6 g. (0.20 mole) of 6,9-dichloro-2-methoxyacridine and 75.0 g. (0.80 mole) of phenol was heated at an inside temperature of 100–105° for two and one-half hours (initial exothermic reaction caused a temperature rise to 124°). The amber melt was poured into 800 cc. of acetone containing 75 cc. of concentrated hydrochloric acid, was stirred with cooling and filtered. The orange solid was slurried three times with acetone, and then recrystallized three times from methanol-acetone with charcoaling. A yield of 68 g. (80%) of bright yellow crystals was obtained, m. p. 240–244° (dec.).

Anal. Calcd. for $C_{20}H_{24}ClN_3O \cdot 2HCl$: C, 55.74; H, 6.03; N, 9.75. Found: C, 55.46; H, 6.27; N, 9.96.

7-Chloro-4-(1-methyl-3-morpholinopropylamino)-quinoline.—A mixture of 19.8 g. (0.10 mole) of 4,7-dichloroquinoline,⁷ 32.0 g. (0.20 mole) of 2-amino-4-morpholinobutane,⁶ and 0.1 g. of sodium iodide was heated with stirring to 160° (bath temperature); a vigorous exothermic reaction ensued with the inside temperature rising to 194°. The reaction mixture was then cooled to room temperature (total heating period ten to fifteen minutes). The viscous melt was poured into cold 10% hydrochloric acid with stirring and the acidic solution, after buffering with sodium acetate to congo red (neutral), was extracted exhaustively with ether. The aqueous layer was then made strongly alkaline with cold 30% sodium hydroxide solution and extracted several times with ether. On chilling, 23.0 g. of crystals, m. p. 141–144°, was obtained. Concentration of the mother liquor yielded another 5.0 g. (total yield 88%). A sample was recrystallized three times from benzene for analysis, m. p. 141–144°.

Anal. Calcd. for $C_{17}H_{22}ClN_3O$: C, 63.85; H, 6.88; N, 13.16. Found: C, 63.96; H, 6.87; N, 13.26.

The crystalline diphosphate was prepared by mixing a methanolic solution of the base with an equimolecular amount of 85% phosphoric acid.

Anal. Calcd. for $C_{17}H_{22}ClN_3O \cdot 2H_3PO_4$:⁸ base, 62.0; acid, 38.0. Found: base, 62.7; acid, 38.2.

7-Chloro-4-(2-di-*n*-hexylaminoethylamino)-quinoline.—A mixture of 19.8 g. (0.10 mole) of 4,7-dichloroquinoline,⁷ 45.8 g. (0.20 mole) of 2-di-*n*-hexylaminoethylamine,⁵ and 0.1 g. of sodium iodide was heated at an inside temperature of 158–165° for one hour. The condensate was isolated as the dihydrochloride in the same manner as above; for purification, the free base was liberated and distilled. It came over as a yellow, very viscous oil (b. p. 187–191° at 22 μ and bath temperature of 220–225°), which solidified on cooling. A sample for analysis was recrystallized from petroleum ether, m. p. 55–57°.

(7) U. S. Patent 2,233,930.

(8) The phosphates reported in this paper crystallized as hydrates. Analytical data are reported on an anhydrous basis.

Anal. Calcd. for $C_{28}H_{36}ClN_3$: C, 70.90; H, 9.25; N, 10.79. Found: C, 71.21; H, 9.35; N, 11.28.

The crystalline diphosphate was prepared by mixing a methanolic solution of the base with an equimolecular amount of 85% phosphoric acid.

Anal. Calcd. for $C_{28}H_{36}ClN_3 \cdot 2H_3PO_4$: base, 66.5; acid, 33.5. Found: base, 67.2; acid, 34.1.

RESEARCH LABORATORIES
WINTHROP CHEMICAL CO., INC.
RENSSELAER, N. Y.

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The Metalation of Isopropylbenzene, Condensations by Sodium. XXIX

BY AVERY A. MORTON, JOHN T. MASSENGALE AND
MALCOLM L. BROWN

Over a period of a number of years, the action of amylsodium on isopropylbenzene has been observed on several occasions. It has been the intention to submit this compound and others to an extensive series of tests but the work has been so delayed that it is thought desirable to publish these results as they are.

The position at which amylsodium attacks isopropylbenzene is largely para and some ortho to the isopropyl group. The yield is good if the hydrocarbon is made the solvent and the reaction mixture is allowed to stand overnight, and is fair if isopropylbenzene is added to amylsodium and the mixture is heated.

The inactivity of the tertiary hydrogen atom may at first seem peculiar since bromination shows activity at this position and since the frequent use of phenylisopropylpotassium has created an impression that the metal should be attached at that position. The difference between bromination and metalation is, however, a clear one for the product of the former reaction has a carbonium ion and that of the latter reaction has a carbanion ion. Hence, it is reasonable to suppose that the hydrogen atom most readily attacked in one instance will be least readily attacked in the other. The position taken by the metal ion is in agreement also with the general repression of activity toward acid-salt interchange which accompanies the introduction of methyl groups into a hydrocarbon. In this instance the acidity of the side chain¹ in cumene is much less than that of toluene because of the two additional methyl groups. As the acidity in the side chain is repressed that in the ring becomes apparent.

Experimental

Amylsodium was prepared in the usual manner from 15.5 g. of amyl chloride and 10 g. of sodium sand at –6 to –11° in isopropylbenzene as a solvent. The mixture was allowed to warm and stand overnight before carbonation. The aqueous solution of the sodium salts² was then acidified and extracted with benzene. Distillation of the acids gave a fraction which boiled at 128–142° (3 mm.) and partially solidified. The purified cuminic acid amounted to 6 g. and melted at 116.2–116.5°. The recorded value is

(1) Morton, *Chem. Rev.*, **35**, 1 (1944).

(2) Morton, Davidson and Hakan, *This Journal*, **64**, 2242 (1942).

116.5°. The ortho acid, 1.5 g., was somewhat impure and melted at 47.1–49.3° (recorded value 51°). A small amount of material³ which was probably a disubstitution product was also present.

A preparation, carried out in the apparatus which was used before the high speed stirrer was developed, consisted of the addition of 250 ml. of isopropylbenzene to the product of the reaction of 42 g. (0.4 mole) of amyl chloride and 37 g. of sodium in 200 ml. of petroleum ether. The mixture was refluxed at 52° for two and one-half hours. Cumic acid, 3.8 g., was isolated and characterized by the melting point, 154°, of the amide. The recorded value is 155°.⁴

(3) Persoz, *Ann.*, **44**, 312 (1842).

(4) Gattermann and Schmidt, *ibid.*, **244**, 52 (1888).

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An Improved Method for the Preparation of 1-Isobutyryl-2-phenylhydrazine

BY MARTIN JACOBSON AND FRED ACREE, JR.

The preparation of 1-isobutyryl-2-phenylhydrazine has been reported by several investigators in either very low or unspecified yields. Bölsing and Tafel,¹ Brunner,² Leighton³ (25% yield) and van Alphen⁴ (38% yield) prepared the hydrazine from phenylhydrazine and isobutyric acid. Ponzio⁵ prepared the substance from isobutyryldinitroethane and phenylhydrazine, while Widman⁶ and van Alphen⁴ treated phenylhydrazine with isobutyryl chloride and isobutyryl bromide, respectively.

In this Laboratory 67% of the theoretical quantity of the hydrazine has been obtained by the following procedure: A mixture of 378 g. (3.5 moles) of phenylhydrazine (technical), 700 g. (7 moles, 100% excess) of isobutyric acid (technical), and 250 ml. of toluene was refluxed under a condenser equipped with a water trap. After forty-eight hours 77 ml. of water had been collected (theory for 3.5 moles, 63 ml.) and the reaction mixture was then cooled in an ice-box overnight. The substance which separated was filtered and washed with ether, and the crude air-dried product (425 g., 68% yield), consisting of colorless, shining plates, melted at 139–141°. After it was recrystallized from ethanol the substance weighed 418 g. (67% yield) and had a constant melting point of 143° (cor.). Reworking of the toluene and ethanol mother liquors caused an additional 12 g. of crude material to separate, from which 2 g. (0.3%) of the pure hydrazine was obtained on recrystallization.

(1) Bölsing and Tafel, *Ber.*, **25**, 1552 (1892).

(2) Brunner, *Monatsh.*, **18**, 97 (1897).

(3) Leighton, *Am. Chem. J.*, **20**, 678 (1898).

(4) van Alphen, *Rec. trav. chim.*, **43**, 823 (1924).

(5) Ponzio, *Gazz. chim. ital.*, **35**, 395 (1905).

(6) Widman, *Ber.*, **27**, 1967 (1894).

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BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
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Improved Preparation of Isopropylidene Glycerol

BY MELVIN S. NEWMAN AND MARY RENOLL

We have recently modified Fischer's¹ procedure for making isopropylidene glycerol so that this compound may be prepared quite easily in almost quantitative yield. The physical properties of our once-distilled product compare favorably with those for Fischer's thrice-distilled material.

Experimental

A mixture of 100 g. (1.09 moles) of anhydrous distilled glycerol, 300 cc. of acetone, 300 cc. of petroleum ether (b. p. 35–55°, Skellysolve F) and 3.0 g. of *p*-toluenesulfonic acid monohydrate was placed in a one-liter three-necked flask fitted with a stirrer and a helices-packed (18 inches) total-reflux column topped by a total-reflux phase-separating head. The mixture was stirred and refluxed (temperature at head 25–28°) for forty-three hours. The mixture was homogeneous after eighteen hours. After twenty-four hours the reaction was almost complete as judged by the amount of lower aqueous phase being formed in the head. The cooled reaction mixture was neutralized with 1.3 g. of powdered fused sodium acetate. After filtration and evaporation of solvent, the isopropylidene glycerol was obtained in 96.6% yield (139 g.) as a colorless liquid, b. p. 80.5–80.8° (11 mm.), n_D^{25} 1.4326, d_4^{25} 1.0626, M_{rD} 32.30, calcd. 32.43 (using values in Gilman² except for ether oxygen which was calculated as 1.60 by means of the Lorentz-Lorenz formula using n_D^{20} 1.42227 and d_4^{20} 1.03361 for dioxane³). In a similar experiment using 100 g. of about 95% glycerol the yield of isopropylidene glycerol was 125 g.

(1) E. Fischer and Pfähler, *Ber.*, **53**, 1606 (1920).

(2) Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1751.

(3) Allsopp and Willis, *Proc. Roy. Soc. (London)*, **A153**, 392 (1936).

CHEMISTRY LABORATORY
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COLUMBUS, OHIO RECEIVED JUNE 11, 1945

Reaction of Theophylline with Gibbs' Reagent

BY HARRY W. RAYBIN

Recently, the use of Gibbs' reagent (2,6-dichloroquinone-chloro-imide) has been proposed for the detection and determination of uric acid.¹

The interaction of various compounds including the purines, with Gibbs' reagent have been studied by Scudi,² Leahy,³ and Fearon,¹ and among the purines only uric acid has been noted as reacting. The statement of Fearon¹ that "Less oxidized purines, such as hypoxanthine and xanthine, give no colours with this reagent" needs qualification in view of the readily obtained blue color given by theophylline (1,3-dimethylxanthine) with this reagent. The addition of a few drops of 0.4% alcoholic Gibbs' reagent to a borax or sesquicarbonate solution of theophylline produces a blue color, with the noteworthy property of giving an insoluble red-violet precipitate by the addition of solid sesquicarbonate to saturation. The violet-red precipitate is obtained with 0.2 mg. of theophylline per cc. (aminophylline is not suited

(1) W. R. Fearon, *Biochem. J.*, **38**, 399 (1944).

(2) J. V. Scudi, *J. Biol. Chem.*, **139**, 715 (1941).

(3) H. W. Leahy, et al., *J. Milk Technology*, **3**, 183 (1940).