hydrazine dissolved in 4 cc. of 2 *N* hydrochloric acid. After half an hour the precipitate was filtered off with suction, washed with dilute hydrochloric acid and water, and dried *in vacuo* over sulfuric acid; yield, 60 mg. of hydrazine. By recrystallizing once from 50% C_2H_5OH the substance was obtained in long needles of m. p. 147–148°. *Anal.* Calcd. for $C_9H_{10}O_6N_4$ (270): C, 40.0; H, 3.8. Found: C, 40.2; H, 3.9.

***l*(−)Acetone Glycerol.**—The preparation of *l*(−)acetone glycerol corresponds entirely to the prescriptions already given[29] for the preparation of *d*(+)acetone glycerol, to which the reader is referred for details. Two and one-fourth grams of freshly prepared acetone-*l*-glyceraldehyde yielded 1.8 g. (79% of the theoretical) of *l*(−)acetone glycerol, b. p. (8 mm.) 72–72.5°[32] (bath at 87–90°); $n^{24}D$ 1.4330; $n^{21}D$ 1.4340. The substance is a clear colorless liquid with a characteristic but weak odor. *Anal.* Calcd. for $C_6H_{12}O_3$ (132): C, 54.5; H, 9.0; acetone 43.9. Found: C, 54.6; H, 9.0; acetone 43.9. *Optical rotation:* (1) in substance, 1-dm. tube, $d^{22.5}_4$ 1.062, αD −14.25°; $[\alpha]D$ −13.4°. (2) in dry benzene, 1-dm. tube, *c*, 22.5, αD −2.43°; $[\alpha]D$ −10.8°; (3) in H_2O, 1-dm. tube, *c*, 9.05, αD +0.16°; $[\alpha]D$ +1.7°.

(32) *d*(+)acetone glycerol, b. p. (12 mm.) 80–80.5°; b. p. (8 mm.), 73°.

Summary

1. An improved preparation of *l*-mannitol starting from *l*-arabinose is described.

2. *l*-Mannitol has been acetonated by the method used for *d*-mannitol. The 1,2-5,6-diacetone-*l*-mannitol has been split by oxidation with lead tetraacetate to acetone-*l*-glyceraldehyde.

3. Acetone-*l*-glyceraldehyde has been hydrolyzed to *l*-glyceraldehyde and has been reduced to *l*(−)acetone glycerol.

TORONTO, CANADA RECEIVED JANUARY 23, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE COLLEGE OF LIBERAL ARTS AND SCIENCES OF TEMPLE UNIVERSITY]

Nuclear Methylation of Phenols. A New Synthesis of Intermediates in the Preparation of Antisterility Factors

BY WILLIAM T. CALDWELL AND THOMAS R. THOMPSON[1]

Syntheses of 2,3,5-trimethylhydroquinone, pseudocumohydroquinone, by methods described in the literature[2] involve a series of operations and considerable expenditure of time. Since α-tocopherol, one of the most potent of the known antisterility factors of the vitamin E group, has been prepared recently from phytyl bromide or phytol and pseudocumohydroquinone[3] and, furthermore, in view of the physiological activity of other derivatives of the latter as well as of related hydroquinones such as durohydroquinone,[4] the desirability of other and simpler means of access to these compounds is obvious. We hoped to prepare such substances, starting with easily available intermediates, and using methods which, while primarily directed toward a new synthesis of pseudocumohydroquinone, durohydroquinone, etc., might be amenable to even wider application.

For example, it seemed that, if an additional methyl group could be introduced into *sym*-xylenol, we should have succeeded in solving one aspect of the problem for this xylenol is not expensive and the method should be applicable to other phenols and, possibly, to other compounds, both aliphatic and aromatic, which resemble phenols in some of their properties, notably in their behavior toward formaldehyde.

The procedure by which we succeeded in doing this, at least as far as the preparation of some of these hydroquinones goes—and we believe our progress so far indicates rather general applicability—is one of simplicity and ease of manipulation. Only two steps are needed in order to effect nuclear methylation of the phenols used: (1) introduction of a dimethylaminomethyl group; and (2) hydrogenolysis. The dimethylaminomethylphenol is prepared easily by the combined action of formalin and dimethylamine upon the appropriate phenol[5] and the subsequent hydrogenolysis is then effected without difficulty by heating under pressure in dioxane using copper chromite as catalyst.[6]

Of course, in synthesizing pseudocumohydroquinone from *sym*-xylenol, the preparation of 2,3,5-trimethylphenol must be followed by conversion of the latter into the corresponding hydroquinone.

(1) Submitted in partial fulfilment of the requirements for the degree of Master of Arts.

(2) Baumann, *Ber.*, **18**, 1152 (1885); Nietzki and Schneider, *ibid.*, **27**, 1430 (1894); Smith, THIS JOURNAL, **56**, 473 (1934).

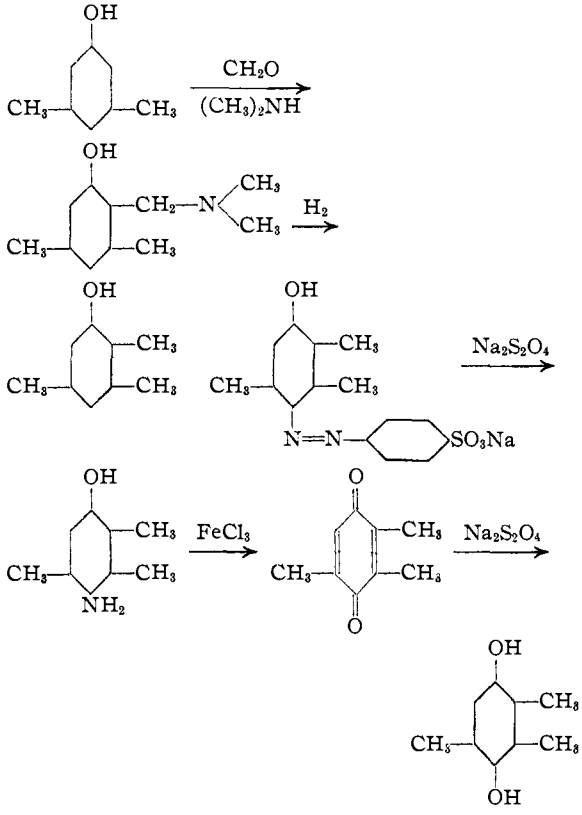
(3) Karrer, Fritzsche, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 524 (1938); Smith, *Science*, **88**, 37 (1938).

(4) Werber and Moll, *Z. physiol. Chem.*, **254**, 39 (1938).

(5) Decombe, *Compt. rend.*, **196**, 866 (1933).

(6) Adkins, Connor and Folkers, THIS JOURNAL, **54**, 1145 (1932).

This can be done quite easily—in the course of one day—by coupling with diazotized sulfanilic acid, reducing the azo dye with sodium hydrosulfite, oxidizing the aminophenol with ferric chloride and, finally, reducing the quinone to the hydroquinone with sodium hydrosulfite. The conversion of *sym*-xylenol into pseudocumohydroquinone, for example, involves then the following steps



Although these steps involved no difficulties, it would be simpler to synthesize pseudocumohydroquinone by introducing three methyl groups directly into hydroquinone by means of these reactions.

Hydroquinone, therefore, was treated at room temperature with three equivalents each of dimethylamine and formaldehyde, giving a well-defined crystalline product melting at 190° which we hoped was tri-(dimethylaminomethyl)-hydroquinone but which proved to be the di-(dimethylaminomethyl) derivative, as shown both by analysis and hydrogenolysis to 2,5-dimethylhydroquinone.

Experimental Part

2-(Dimethylaminomethyl)-3,5-dimethylphenol.—To one mole of a fraction of redistilled Eastman technical 3,5-dimethylphenol, b. p. 119–119.5°, were added one mole of dimethylamine (35% aqueous solution) and, then, while keeping the temperature between 25 and 35°, one mole of formaldehyde (as formalin) drop by drop, with vigorous stirring. The oil that formed was separated from the aqueous layer and set aside in the cold; it solidified on standing overnight and, after recrystallization from methyl alcohol, melted at 42–42.5°; yield 60 g.

Anal. Calcd. for $C_{11}H_{17}ON$: N, 7.8. Found: N, 7.9.

2,3,5-Trimethylphenol.—Eighteen grams of 2-(dimethylaminomethyl)-3,5-dimethylphenol in 200 cc. of dioxane was hydrogenated in the presence of 7.5 g. of copper chromite (Adkins) at a pressure of 2600 lb. (177 atm.) and at 165° for a period of four hours. After opening the bomb, the catalyst was removed by filtration, the solvent distilled off and the residue subjected to steam distillation after acidification with a small amount of hydrochloric acid. The white needles that crystallized from the distillate and also collected in the condenser were recrystallized from petroleum ether; m. p. 93°. A small portion was converted into 2,4-dibromo-3,5,6-trimethylphenol which after recrystallization from 90% methanol melted at 149–150°. Edler[7] gives 149–150°; John, Dietzel and Gunthor,[8] 152°. The yield, 8 g., was 58.5%.

2,3,5-Trimethylhydroquinone.—Sulfanilic acid was diazotized in the usual way and coupled with the sodium salt of 2,3,5-trimethylphenol in a medium kept slightly but definitely alkaline throughout by continued addition of aqueous sodium hydroxide. After stirring for an hour to complete coupling, the deep red azo dye was salted out, filtered off and then reduced in aqueous solution at 40–50° with sodium hydrosulfite ($Na_2S_2O_4$). The liquid containing the grayish-white precipitate of 4-amino-2,3,5-trimethylphenol was brought to the boiling point, then cooled in ice and filtered. The aminophenol obtained in this way from 4 g. of 2,3,5-trimethylphenol was oxidized with a solution containing 16.5 g. of ferric chloride, 6 cc. of hydrochloric acid and 15 cc. of water which was added all at once to a solution of the aminophenol in 90 cc. of water containing 3 cc. of hydrochloric acid, the temperature being 35°. The pseudocumoquinone gradually separated in oily droplets which solidified on cooling in ice, but melted upon raising the temperature to that of the room. Finally, the pseudocumoquinone was mixed with water, reduced with sodium hydrosulfite and, after drying, recrystallized from petroleum ether, m. p. 169–170°; yield, based on trimethylphenol, 27%.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.0; H, 7.9. Found: C, 69.9; H, 7.8.

The diacetate melted at 108–109°; Nietzki and Schneider[9] give 112°; Smith,[10] 108.5–110°.

2,5 - Di - dimethylaminomethylhydroquinone.—Hydroquinone (0.5 mole) and dimethylamine (1.5 moles, 195 cc. of 35% solution) were placed in a three-necked flask equipped with an efficient stirrer; 1.5 moles of formaldehyde (130 cc. of 35% formalin) was then added drop by drop, the temperature being maintained near 25° while nitrogen was passed through. An atmosphere of nitrogen

(7) Edler, *Ber.*, **18**, 630 (1885).
(8) John, Dietzel and Gunthor, *Z. physiol. Chem.*, **252**, 220 (1938).
(9) Nietzki and Schneider, *Ber.*, **27**, 1430 (1894).
(10) Smith, THIS JOURNAL, **56**, 473 (1934).

proved to be unnecessary, but the product turned brown in the presence of air, at least until it had been purified by recrystallization from alcohol. As the formaldehyde was added, all of the solid material first dissolved, then an oil was formed and, finally, a crystalline solid separated. The ice-cold mixture was filtered, washed with cold water and dried; yield, almost quantitative. After recrystallization from alcohol, and drying, the substance was pure white, m. p. 190°.

Anal. Calcd. for $C_{12}H_{20}O_2N_2$: N, 12.5. Found: N, 12.5.

2,5-Dimethylhydroquinone.—The above material (30 g.), copper chromite (15 g.) and 250 cc. of dioxane were hydrogenated for four hours at 165° and 2500 lb. (170 atm.) pressure. The catalyst was removed by filtration and the solvent by distillation. The product, which was not volatile in steam, was treated with 500 cc. of water and 15 cc. of hydrochloric acid and the resulting mixture filtered, giving a gray residue which was recrystallized from water and also from benzene; white needles, m. p. 208°; yield, 23%. Upon oxidation with ferric chloride, 2,5-dimethylquinone, m. p. 123–124°, was formed which suffered no depression of the melting point when mixed with an authentic sample of 2,5-dimethyl-1,4-benzoquinone.

Summary

A new method for the nuclear methylation of phenols consisting in the hydrogenolysis of the dimethylaminomethyl derivative formed by treatment with dimethylamine and formaldehyde, is reported.

PHILADELPHIA, PENNA. RECEIVED JANUARY 30, 1939

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

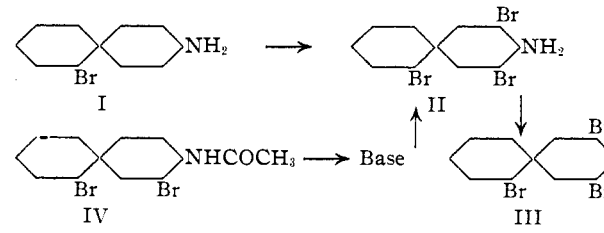
The Mono- and Dibromination of Certain Heteronuclear-substituted 4-Acetaminodiphenyls[1]

BY FRANCIS H. CASE

It has been shown that of the isomeric acetaminodiphenyls only 4-acetaminodiphenyl yields, on monobromination, any derivative substituted in the 4′-position. The present work was undertaken with the object of determining the effect of substituents in the 2′- and 3′-positions on substitution by bromine in the originally unsubstituted ring of 4-acetaminodiphenyl. For this purpose the following compounds were subjected to mono- and dibromination: 4-acetamino-2′-bromodiphenyl, 4-acetamino-2′-nitrodiphenyl, and 4-acetamino-3′-nitrodiphenyl. It was found that in no case did any bromine enter the ring already occupied by bromine or nitro groups, the resulting products being in each case 3-bromo-4-acetamino or 3,5-dibromo-4-acetamino derivatives.

In order to establish the structure of the mono- and dibromination products of 4-acetamino-2′-bromodiphenyl, the base, 4-amino-2′-bromodiphenyl[4] (I) was dibrominated, and the resulting product (II) deaminized. Since the tribromo product (III) thus obtained yielded on oxidation 3,5-dibromobenzoic acid, it is therefore 2,3′,5′-tribromodiphenyl, and is evidently identical with the tribromodiphenyl prepared by Bellavita[3] from 4-amino-2′-nitrodiphenyl. The dibromo base (II) is therefore 2′,3,5-tribromo-4-aminodiphenyl.

The monobromination product (IV) of 4-acetamino-2′-bromodiphenyl was hydrolyzed to the base which on further bromination yielded II. Hence



IV is 2′,3-dibromo-4-acetaminodiphenyl. The dibromination product of 2′-bromo-4-acetaminodiphenyl was found to be identical with 2′,3,5-tribromo-4-acetaminodiphenyl, obtained by acetylation of II. No other dibromination product could be found.

The preparation of 2′-nitro-4-acetaminodiphenyl was accomplished most easily by the partial catalytic reduction of 2,4′-dinitrodiphenyl.

The structure of its monobromination product (V) was proved by hydrolysis to the base (VI) and bromination of the latter to yield the known 3,5-dibromo-4-amino-2′-nitrodiphenyl[3] (VII), obtained by the bromination of 4-amino-2′-nitro-

(1) The present investigation originated in an attempt to confirm the results of Bellavita[2] regarding the bromination of 2-nitro-4′-aminodiphenyl and 4-nitro-2′-aminodiphenyl. The revised results[4] of this author were in agreement with those obtained simultaneously by the writer.

(2) Bellavita, *Atti congr. naz. chim. pura applicata*, 5 (1935).

(3) Bellavita, *Gazz. chim. ital.*, **67**, 574 (1937).

(4) Case, THIS JOURNAL, **60**, 424 (1938).