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Studies on Acetone-Glyceraldehyde. VII. Preparation of l-Glyceraldehyde and l(−)Acetone Glycerol[1]

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The preparation of the two optically active forms of glyceraldehyde was first described by Wohl and Momber.[2] They started with optically inactive materials and followed a long and involved synthesis. They were able to obtain a rotation for the d-isomer only; the value they reported was $[\alpha]_D$ +13 to +14° (in water).

Further mention may be made of the biological preparation of the d-glyceraldehyde by the action of *Bacillus coli* on d,l-glyceraldehyde as described by A. I. Virtanen and J. v. Hausen.[3]

In order to make the optically pure forms of the d- and l-glyceraldehydes more easily available for chemical and biological purposes, we have worked out a new way of preparing them by taking advantage of the natural asymmetry of the mannitols. We were able to prepare the d-isomer in 1934 by means of the following series of reactions: d-mannitol → 1,2-5,6-diacetone-d-mannitol → acetone-d-glyceraldehyde → d-glyceraldehyde.[4] The method has since[5] been so far simplified, that the d-glyceraldehyde is now more readily obtainable than the racemic compound is by the older method of Wohl and Neuberg.[6]

(1) *Cf.* Preliminary notice, *Science*, **88**, 108 (1938). With regard to the configuration and nomenclature of l(−)acetone glycerol reference is made to our discussion concerning d(+)acetone glycerol, in our paper: IV. Communication on Acetone Glyceraldehyde. Preparation of d(+)Acetone Glycerol, *J. Biol. Chem.*, **128**, in press (1939), note 1.

(2) Wohl and Momber, *Ber.*, **47**, 3346 (1914); **50**, 456, note 2 (1917).

(3) Virtanen and v. Hausen, *Z. physiol. Chem.*, **204**, 235 (1932).

(4) Fischer and Baer, *Helv. Chim. Acta*, **17**, 622 (1934); **19**, 524 (1936).

(5) *J. Biol. Chem.*, in press.

(6) Wohl and Neuberg, *Ber.*, **33**, 3095 (1900).

To prepare the l-glyceraldehyde in an analogous way from l-mannitol was much more difficult, since the l-mannitol (which was first prepared by Emil Fischer[7] but only in rather small quantities) is not yet obtainable commercially. We had, therefore, to work out a more productive method for the preparation of the larger quantities needed by us.

We started with l-arabinose (I), which we prepared according to the excellent method of Ernest Anderson and Lila Sands[8] from cheap mesquite gum.[9] By using the method of H. Kiliani[10] we obtained from it the l-mannonic lactone (II). This we reduced in an acid aqueous solution directly to l-mannitol, using hydrogen at a pressure of 80 atmospheres in the presence of platinic oxide containing a small percentage of iron. This is essentially the method of Glattfeld and Schimpf[11] for the preparation of d-mannitol from d-mannonic lactone. Our reduction was, however, carried out at a higher pressure of hydrogen and with the use of an iron-containing catalyst such as that employed by Glattfeld and Shaver[2a]; and we have not isolated the intermediates (probably δ-mannonic lactone and the l-mannose) contained in the solution. We obtained l-mannitol (III) in a yield of 66% of the theoretical (m. p. 163°; $[\alpha]_D$ 0° in water; after addition of boric acid it is strongly negative). Thus the
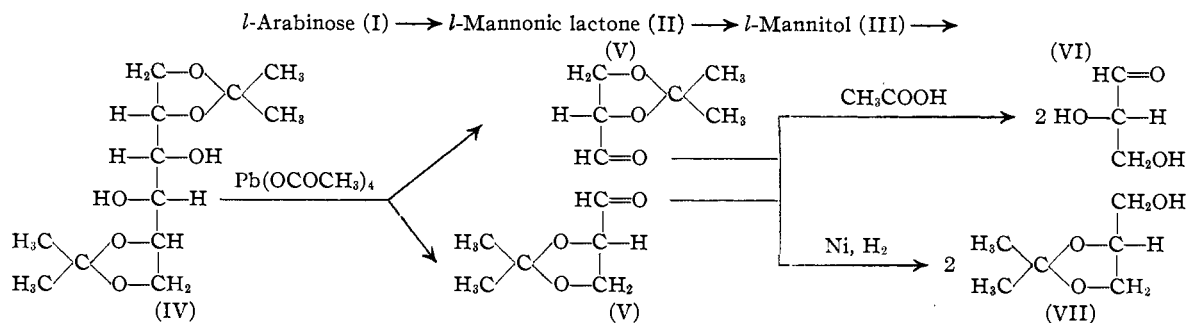
(7) Emil Fischer, *ibid.*, **23**, 370 (1890).

(8) Anderson and Sands, "Organic Syntheses," Coll. Vol., p. 60.

(9) Martin Drug Company, Tucson, Arizona.

(10) Kiliani, *Ber.*, **55**, 100 (1922); **58**, 2349 (1925).

(11) Glattfeld and Schimpf, THIS JOURNAL, **57**, 2204 (1935).

l-Arabinose (I) —→ l-Mannonic lactone (II) —→ l-Mannitol (III) —→

laborious reduction of the lactone with sodium amalgam was avoided.[12] The following derivatives of the l-mannitol were prepared for comparison with the d-mannitol: triformaldehyde-l-mannitol, m. p. 227°, [α]D + 106.2° in chloroform; triacetone-l-mannitol, m. p. 69–70°, [α]D −12.6° in alcohol; hexaacetyl-l-mannitol, m. p. 122–123°, [α]D −25.2° in chloroform.

For the preparation of the 1,2-5,6-diacetone-l-mannitol (IV) we had at our disposal the methods used for the d-mannitol by v. Vargha,[13] P. Brigl and H. Grüner[14] and the method of Emil Fischer, which had been improved by H. O. L. Fischer and E. Baer.[4] As these methods gave only small and not always uniform yields, we were forced owing to the scarcity of the l-mannitol to seek a more productive method of preparing the diacetone-l-mannitol. We resorted to a method which we had already used successfully for acetonation of various compounds[15] and were able to obtain the 1,2-5,6-diacetone-l-mannitol (m. p. 122°) by treating the l-mannitol with acetone and zinc chloride at room temperature. The yield was 55% of the theoretical, and probably will be improved further in later experiments. Since we worked out the method of acetonating mannitol first of all with the commercially available d-mannitol and have described it elsewhere,[5] we have omitted the details for the analogous preparation of diacetone-l-mannitol in the experimental part. This diacetone-l-mannitol (IV) dissolved in benzene was subjected to the action of lead tetraacetate and gave a yield of 76% of the desired acetone-l-glyceraldehyde (V), a colorless liquid (b. p. at 8 mm. 38°; [α]^{22}D −67.9° in benzene).

Acetone-l-glyceraldehyde (V) was hydrolyzed easily to the free l-glyceraldehyde (VI) with the

aid of dilute acetic acid. By concentrating its aqueous solution the l-glyceraldehyde was obtained in the form of a very viscous, clear, colorless sirup. As yet, neither the l- nor the d-form has been obtained in crystalline form. If, however, equal parts of the d- and l-aldehyde are dissolved together in water and the solution evaporated to a sirup, the inactive glyceraldehyde crystallizes within a few days in almost theoretical yield. This appears to be an indication that probably there is a constitutional reason for the failure of the enantiomorphic forms of glyceraldehyde to crystallize. The l-glyceraldehyde was characterized by its 2,4-dinitrophenylhydrazone (m. p. 148°) and its dimedone compound [m. p. 198–200°; [α]^{21}D −198.0° (in alcohol)].

With reference to the specific rotations of the free glyceraldehydes the following is to be noted: As previously mentioned, Wohl and Momber have already stated the initial rotation as +14° for the free d-glyceraldehyde, but they do not give any information with regard to the rotation of the l-glyceraldehyde. We can fully confirm this observation and in fact fix the initial rotation of both the d- and the l-glyceraldehydes at +14 and −14°, respectively. When aqueous solutions of d- or l-glyceraldehyde are stored in a refrigerator, in the course of a week both rotations are reduced by about one-half, that is to ±7°. Solutions with equally high initial rotations, however, may again be obtained, if they are first evaporated in vacuo and the residues, after being heated for two hours at 55–60° in vacuo, are again dissolved in water. The rotations of these solutions gradually become smaller and can again be regenerated as described. From this we can conclude definitely that the decrease in rotation of the glyceraldehydes in aqueous solutions is certainly not due to racemization, which J. Needham[16] assumed to be the case. Perhaps this

(12) Emil Fischer, ref. 7.
(13) Von Vargha, Ber., 66, 1394 (1933).
(14) Brigl and Grüner, ibid., 67, 1969 (1934).
(15) H. O. L. Fischer and C. Taube, ibid., 60, 485 (1927); H. O. L. Fischer and E. Baer, ibid., 63, 1749 (1930).

(16) Needham and Lehmann, Biochem. J., 31, 1914 (1937).

phenomenon could be explained by one of the following assumptions: (1) an equilibrium between a monomeric open aldehyde form and a dimeric dioxane form of the glyceraldehyde; (2) the formation of monomeric oxycyclo forms with oxygen rings of different spans and their subsequent association; (3) formation of different forms of hydrates; etc. We are unfortunately not yet in a position to say which of the several possibilities is actually responsible for "mutarotation." The observation of this "mutarotation" emphasizes again the recognized relationship between glyceraldehyde and the sugars, and it becomes all the less comprehensible that Elsner, in the fourth edition of "Handbuch der Kohlenhydrate,"[17] by Tollens, does not consider the trioses to be true sugars and therefore does not describe them.

With regard to the interesting physiological action of the *l*-glyceraldehyde, we wish to draw attention to the observation of B. Mendel, F. Strelitz and D. Mundell,[18] who found that under aerobic and anaerobic conditions the glycolysis of tumor slices is almost completely inhibited by $2 \times 10^{-3} M$ and $7.5 \times 10^{-4} M$ *l*-glyceraldehyde, respectively, whereas the *d*-glyceraldehyde is almost ineffectual. In good agreement with this is the earlier observation of J. Needham and H. Lehmann,[19] who found in investigating the influence of *d,l*- and *d*-glyceraldehyde on the glycolysis of chick embryos that the inhibitory effect of *d,l*-glyceraldehyde is to be ascribed to its *l*-component.

A further physiological difference between *d*- and *l*-glyceraldehyde was found in their behavior when exposed to bacterial action. B. Mendel[20] observed that an aqueous solution of pure *l*-glyceraldehyde grew cloudy after some time owing to the growth of bacteria, while a solution of *d*-glyceraldehyde remained quite clear. This difference in the two enantiomorphic forms of glyceraldehyde agrees with the observations of C. Neuberg,[21] A. I. Virtanen and I. v. Hausen,[3] that if *d,l*-glyceraldehyde is subjected to the action of *B. coli* only the *l*-glyceraldehyde is fermented.

l(−)Acetone Glycerol

We were able to pass easily, by reduction, from the acetone-*l*-glyceraldehyde (V) to the *l*(−)ace-

tone glycerol (VII) (n^{24}D 1.4330; [α]D −13.4° in substance; [α]D −10.8° in benzene; [α]D +1.7° in water). This will serve us as the starting material for the synthesis of the optical antipodes of the glycerides and glycerophosphates which already have been prepared by us from *d*(+)acetone-glycerol.[22]

Experimental Part

The *l*-arabinose which forms our starting point was prepared from mesquite gum according to the prescription given by Ernest Anderson and Lila Sands in "Organic Syntheses," which is an improvement on their original method. The *l*-arabinose was converted according to the method of H. Kiliani into *l-mannonic lactone.*

l-Mannitol.—Twenty-four grams of *l*-mannonic-γ-lactone was dissolved in 500 cc. of water, and the solution boiled for forty-five minutes with 24 g. of calcium carbonate. Toward the end some animal charcoal was added and then filtered off and 138 cc. of 1 *N* sulfuric acid was added to the clear filtrate while still warm. After an hour's time the precipitated calcium sulfate was removed by filtering with suction, washed, and the combined filtrates concentrated to 160 cc. *in vacuo* at a bath temperature of 30–40°. (The solution probably contains the δ-form of mannonic lactone predominating.) To convert the *l*-mannonic lactone into *l*-mannitol, which required several days, the solution of the lactone was mixed with 2 g. of platinum oxide–iron oxide catalyst prepared according to Glattfeld and Shaver,[23] and reduced in a rotating autoclave with glass container, under 80 atmospheres of hydrogen.[24] Twice at intervals of twenty-four hours the reduction was interrupted and another 2 g. of catalyst added. After three days the reduction of the lactone to *l*-mannitol was for the most part complete.[25] This we were able to ascertain by the steady diminution of the optical rotation, which in that time had almost disappeared. The solutions usually showed a weak reduction of Fehling's solution, which is accounted for by a small *l*-mannose content (approx. 3%).[26]

After removal of the sulfuric acid by careful addition of dilute aqueous barium acetate the solution was concentrated to dryness *in vacuo* at a bath temperature of 35–40°, and the acetic acid eliminated by twice redissolving the residue in a little water and concentrating to dryness. For the removal of the iron hydrogen sulfide was bubbled through the boiling aqueous solution of the light yellowish-green residue, a few drops of ammonium sulfide plus animal charcoal was added and the whole was filtered. The filtrate was concentrated until a considerable crystallization of *l*-mannitol[27] had begun, and then 200 cc. of ethyl alcohol was added slowly to the concentrate. After standing a day in the refrigerator the *l*-mannitol was filtered off

(17) Preface, page V.

(18) Mendel, Strelitz and Mundell, *Science*, **88**, 149 (1938).

(19) Needham and Lehmann, *Biochem. J.*, **31**, 1913–1925 (1937).

(20) Personal communication.

(21) Neuberg, *Biochem. Z.*, **288**, 259 (1930).

(22) V and VI communications on acetone-glyceraldehyde, *J. Biol. Chem.*, **128**, in press. (1939.)

(23) Glattfeld and Shaver, THIS JOURNAL, **49**, 2306 (1927).

(24) Electrolytically prepared.

(25) If for instance the experiment is terminated after twenty hours the solution contains up to 30% of *l*-mannose which can be isolated by means of its phenylhydrazone. This offers an easier way of preparing *l*-mannose.

(26) Titrated after Willstätter-Schudel.

(27) Weight of solution *ca.* 50 g.

with suction, washed with alcohol and ether, and dried in the vacuum desiccator; yield, 17 g. of analytically pure l-mannitol (65% of the theoretical); m. p. 162–163°. Mixing with d-mannitol causes no depression of the melting point. From the mother liquor a small amount of less pure l-mannitol could be obtained.

The l-mannitol proved to be free of l-mannonic lactone, l-mannose, and inorganic substances and showed no perceptible optical rotation. After the addition of orthoboric acid, however, the same solution rotated strongly to the left. *Anal.* Calcd. for $C_6H_{14}O_6$ (182): C, 39.6; H, 7.7. Found: C, 39.6; H, 7.9. For the purpose of further characterizing the compound and comparing it with the d-mannitol, the triformal-, triacetone-, hexaacetyl-, and 1,2-5,6-diacetone-l-mannitol were prepared.

Triformal-l-mannitol.—Using l-mannitol, and working according to the procedure given by M. Schulz and B. Tollens[28] for the preparation of triformal-d-mannitol, we obtained a good yield of triformal-l-mannitol, m. p. 227°. *Anal.* Calcd. for $C_9H_{14}O_6$ (218): C, 49.5; H, 6.4. Found: C, 49.5; H, 6.5. *Optical rotation:* In chloroform, 1-dm. tube, c, 5.98, αD +6.35°; $[\alpha]$D +106.2°.

Triacetone-l-mannitol.—Triacetone-l-mannitol was obtained with all prescriptions given in the literature for the preparation of triacetone-d-mannitol; m. p. 69–70° (after precipitating with water from alcoholic solution). For analysis the substance was dried *in vacuo* over boiling acetone and phosphorus pentoxide. *Anal.* Calcd. for $C_{15}H_{26}O_6$ (302.2): C, 59.6; H, 8.6. Found: C, 59.7; H, 8.5. *Optical rotation:* In absolute ethyl alcohol, 1-dm. tube, c, 10.89, αD −1.37°; $[\alpha]$D −12.6°.

Hexaacetyl-l-mannitol.—A mixture of 2.0 cc. of pyridine and 2.0 cc. of acetic anhydride with 0.2 g. of l-mannitol was heated for ten minutes to 65° and the solution set aside overnight. By pouring the preparation into a large quantity of water, 0.36 g. (81.7% of the theoretical) of hexaacetyl-l-mannitol was obtained, m. p. 121°. For the determination of the optical activity the substance was recrystallized twice from ethyl alcohol, and dried over boiling benzene and phosphorus pentoxide; m. p. 122–123°. *Anal.* Calcd. for $C_{18}H_{26}O_{12}$ (434): C, 49.8; H, 6.0. Found: C, 50.1; H, 6.2. *Optical rotation:* In dry chloroform, 1-dm. tube, c, 7.735, αD −1.95°; $[\alpha]$D −25.2°.

1,2-5,6-Diacetone-l-mannitol.—The preparation of the diacetone compound was carried out exactly according to the procedure[29] for preparing 1,2-5,6-diacetone-d-mannitol: 15.9 g. of l-mannitol yielded 13 g. (56.4% of the theoretical) of 1,2-5,6-diacetone-l-mannitol of m. p. 119° which could be raised to 122° by recrystallizing from a small amount of water (fine needles). For the subsequent operations the preparation with melting point 119° is pure enough. *Anal.* Calcd. for $C_{12}H_{22}O_6$ (262.2): C, 54.9; H, 8.6. Found: C, 54.9; H, 8.5. By concentrating the petroleum ether mother liquor, dissolving the residue in ethyl alcohol and precipitating with water, 1.65 g. (6.25% of the theoretical) of triacetone-l-mannitol was obtained, m. p. 68–69°.

(−)Acetone-l-glyceraldehyde.—The preparation of this substance was conducted exactly according to the pre-

scription given by us for preparing acetone-d-glyceraldehyde.[29] By oxidation of 7.1 g. of 1,2-5,6-diacetone-l-mannitol dissolved in 250 cc. of benzene with 12 g. of lead tetraacetate we obtained 5.2 g. (73% of the theoretical) of pure acetone-l-glyceraldehyde; b. p. (11 mm.) 40.5–41.5°; b. p. (8 mm.) 37.5–38°. It is a clear, mobile, strong-smelling liquid, which after hydrolysis in dilute acid reduces Fehling's solution even when cold. *Optical rotation:* Readings of the optical rotation were taken ten minutes after completion of distillation of the acetone-l-glyceraldehyde. In dry benzene, 1-dm. tube, c, 8.28, αD −5.61°; $[\alpha]$D −67.9°. *Refraction.* n^{21}D 1.4204 (seven minutes after completion of distillation); 1.4220 (10 min.); 1.4238 (25 min.); 1.4380 (2 hr. 30 min.); 1.4550 (16 hr.).

(−)l-Glyceraldehyde.—Five and two-tenths grams of freshly prepared acetone-l-glyceraldehyde was dissolved in 35 cc. of 10% acetic acid and allowed to stand overnight at room temperature. The aqueous solution was concentrated *in vacuo* to a thick sirup which was freed from acetic acid by redissolving twice in a little water, and twice reconcentrating in the vacuum. The residue so obtained was subjected for two hours to the vacuum of a water pump at a temperature of 55°, and then dissolved in 30 cc. of water.

The aldehyde content of this aqueous solution was determined by titration after Willstätter and Schudel; 3.5 g. (97% of the theoretical) of l-glyceraldehyde was obtained. *Optical rotation:*[30] In water, 1-dm. tube, c, 11.7, αD −1.62°; $[\alpha]$D −13.8°; observation repeated on same solution after eight days in refrigerator, 1-dm. tube, c, 12.8, αD −1.0°; $[\alpha]$D −7.8°. By concentration of the solution *in vacuo*, heating the residue to 55° *in vacuo* for two hours, and redissolving in water, the original high rotation could be restored: 1-dm. tube, c, 12.35, αD −1.65°; $[\alpha]$D −13.4°. This operation is capable of repetition. An entirely similar behavior is shown by the d-glyceraldehyde prepared by us from acetone-d-glyceraldehyde.[31] We shall not therefore repeat the description for the d-glyceraldehyde. Just as in the case of d-glyceraldehyde, attempts to obtain l-glyceraldehyde in crystalline form were without success. If, however, one combines equal parts of d- and l-glyceraldehyde, an almost theoretical yield of crystalline d,l-glyceraldehyde is obtained which, after purification by boiling with acetone, shows the m. p. of 138–139°.

l-Glyceraldehyde-dimedone.—A solution of 40 mg. of l-glyceraldehyde in 0.5 cc. of water was mixed with 120 mg. of dimedone dissolved in 8 cc. of water, and the mixture kept at 40° for twenty hours; yield of the dry dimedone compound, 110 mg. The substance was obtained analytically pure in long, narrow prisms by recrystallizing from 50% ethyl alcohol; m. p. 198°. *Anal.* Calcd. for $C_{19}H_{26}O_5$ (334.2): C, 68.3; H, 7.8. Found: C, 68.2; H, 8.1. *Optical rotation:* In absolutely dry C_2H_5OH, 1-dm. tube, c, 0.505, αD −1.00; $[\alpha]$D −198°.

l-Glyceraldehyde-2,4-dinitrophenylhydrazone.—To a solution of 32 mg. of l-glyceraldehyde in 0.4 cc. of water was added under cooling, 75 mg. of 2,4-dinitrophenyl-

(28) M. Schulz and B. Tollens, *Ber.*, **27**, 1892 (1894); *Ann.*, **289**, 20 (1896).

(29) IV. Communication on Acetone-glyceraldehyde, in press.

(30) In all preparations we found this same initial rotation.

(31) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **19**, 525 (1936).

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.*

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

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 $+1.7°$.

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.

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).