and assumed otherwise pure, 0.277 equiv., 46.4 g.). HMF (prepared by vacuum distillation of pooled residues and one crystallization from ethyl ether, refrigerated 2 months, ultraviolet assay 97.8%, 0.138 mole, 18.0 g.). The HMF blank was carried out with one half the amount of each component used in the other experiments of this series.

PEORIA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

5-*O*-Methyl-D-ribose and 5-*O*-Methyl-D-ribitol

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Received September 8, 1961

Using the well characterized, crystalline benzyl β-D-ribofuranoside as the starting compound, an unequivocal synthesis of 5-*O*-methyl-D-ribose was developed. This compound was obtained as a sirup only, but it was chromatographically and electrophoretically pure. It was converted to its crystalline benzylphenylhydrazone. 5-*O*-Methyl-D-ribitol(1-*O*-methyl-L-ribitol) was prepared from the methylated ribose by reduction with sodium borohydride. Although the ribitol itself could not be crystallized, it was found that it forms a surprisingly stable crystalline adduct with one mole of methyl trifluoroacetate. A convenient new technique is described for isolating a polyol from solutions containing borate.

An important reference compound for structural studies in nucleic acid chemistry is 5-*O*-methyl-D-ribose (I).[1-6] Although several methods of obtaining this compound have been described,[1,2,4,7,8] the principal method of preparation of I which has been used by various investigators is the method of Levene and Stiller.[2,9-11] There no longer is any doubt about the preponderant product being I, but the synthesis is hardly unequivocal. Furthermore, it leads in actuality to a rather complex mixture of methylated riboses,[2,10,12] and chromatography has been introduced at some stage or other in order to obtain a pure product.

Using the well characterized, crystalline benzyl β-D-ribofuranoside (II) of Ness *et al.*[13] as the starting compound, an unequivocal synthesis of 5-*O*-methyl-D-ribose was developed. As the first step, II was converted to benzyl 2:3-*O*-isopropylidene-β-D-ribofuranoside (III). Only anhydrous copper sulfate was used as a catalyst[14] in this step, in order to avoid the possibility of ring migration[10,15,16] during the acetonation. Methylation of III and removal of the blocking groups from the resulting benzyl 2:3-*O*-isopropylidene-5-*O*-methyl-β-D-ribofuranoside (IV) gave the desired I, in reasonable over-all yield and free of contamination.

Although I was well characterized by means of physical properties and the preparation of crystalline derivatives, I was obtained only as a sirup. It was converted by reduction with sodium borohydride[17] to 5-*O*-methyl-D-ribitol (1-*O*-methyl-L-ribitol, Va), another reference compound of interest.[1] The polyol was isolated as 5-*O*-methyl-D-ribitol 1,2,3,4-tetrakis(trifluoroacetate) (VI), and the ester then was converted by methanolysis to Va. Even though Va could not be crystallized, it was obtained as the crystalline methyl trifluoroacetate adduct (Vb). It also was converted to the crystalline 1,2,3,4-tetrabenzoate.

EXPERIMENTAL[18]

Melting points and boiling points are uncorrected. All evaporations of solvents were carried out at room temperature *in vacuo* using a rotating evaporator (Rinco Instrument Co., Greenville, Ill.)

The R_f values reported were obtained by ascending chromatography using Whatman No. 1 paper. The solvent systems used, which were all made up on a volume basis, were: 1-butanol–water, 86:14 (solvent A); 1-butanol–saturated aqueous boric acid, 85:15 (solvent B)[19]; collidine saturated

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with water (solvent C); and 1-butanol–acetic acid–water, 80:20:20 (solvent D). Aniline oxalate[20] and metaperiodate–Schiff's reagent[21] sprays were used to detect the various compounds on paper chromatograms.

Benzyl 2:3-O-isopropylidene-β-D-ribofuranoside (III). The starting material, II, for the synthesis of III was prepared (33% yield) from 96 g. of D-ribose by the procedure of Ness, Diehl, and Fletcher[13b]; m.p. 92–94°, $[\alpha]_D^{24}$ −60.6° (*c* 0.75, water) [lit.[13] m.p. 95–96°, corr.; $[\alpha]_D^{20}$ −60.5° (*c* 0.73, water)]. Basic lead carbonate was used instead of silver carbonate, however, for neutralizing the hydrogen chloride at the end of the reaction.

The 2,3,5-tris(*p*-phenylazobenzoate) of II was prepared[22] from 0.50 g. of II and 2.0 g. of *p*-phenylazobenzoyl chloride. On recrystallization from ethyl acetate–methanol, 1.2 g. of red needlelike crystals were obtained (67%); m.p. 155–156°.

Anal. Calcd. for $C_{51}H_{40}N_6O_8$: C, 70.82; H, 4.66; N, 9.71. Found: C, 70.73; H, 4.56; N, 9.60.

A mixture of 1.00 g. of II, 3 g. of anhydrous copper sulfate, and 50 ml. of anhydrous acetone[14] was refluxed, while stirring, for 5 hr. After the copper sulfate was removed by filtration and was washed with acetone, the combined filtrates were evaporated to dryness. Recrystallization of the crystalline residue from methanol-water yielded 1.03 g. (89%) of III as colorless needles; m.p. 104–105°, $[\alpha]_D^{29}$ −101.4° (*c* 1.16, chloroform). It can be sublimed at 100° (10^{-3} mm.) and is readily soluble in all common solvents except petroleum ether and water.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.26; H, 7.19. Found: C, 64.24; H, 7.27.

The over-all yield of III from ribose was 29%. This could be increased to 38%, however, by applying the above acetonation procedure to the sirup which remains from the preparation of crystalline II. From 15.7 g. of such a sirup, 200 ml. of acetone, and 13.0 g. of anhydrous copper sulfate there was obtained, after three recrystallizations, 1.15 g. of crystalline material; m.p. 104–105°, mixed m.p. with III 104–105°; $[\alpha]_D^{26}$ −100.4° (*c* 1.18, chloroform).

The *p*-phenylazobenzoate of III was prepared[22] from 0.31 g. of III and 0.44 g. of *p*-phenylazobenzoyl chloride. Recrystallization from methanol-water gave orange needles (72%); m.p. 114–115°.

Anal. Calcd. for $C_{28}H_{28}N_2O_6$: N, 5.81. Found: N, 5.78.

The benzyl group of III (0.50 g.) was cleaved by catalytic hydrogenolysis.[13b] The resulting sirup (2:3-*O* isopropylidene-D-ribose) was dissolved in 5 ml. of methanol and 0.38 g. of benzylphenylhydrazine was added.[23] The solution, after standing at room temperature for 36 hr., was concentrated. The yellow, sirupy residue which remained crystallized after trituration with petroleum ether. Recrystallization of the solid from methanol-water yielded 0.41 g. (62%) of needlelike crystals of the benzylphenylhydrazone of 2:3-*O*-isopropylidene-D-ribose; m.p. 114.0–114.8°, $[\alpha]_D^{29}$ −18.6° (*c* 1.1, chloroform).

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.55. Found: C, 68.00; H, 6.87; N, 7.56.

Benzyl 2:3-O-isopropylidene-5-O-methyl-β-D-ribofuranoside (IV). Methylation of 9.4 g. of III was carried out by the method of Freudenberg and Hixon.[24] In several such methylations, the sirupy products obtained were contaminated with III. This was demonstrated by subjecting a portion of the product to acid hydrolysis followed by paper chromatography to detect ribose. Since III and IV could not be separated by fractional crystallization or distillation, the product of this initial methylation was methylated further by means of the Purdie method (silver oxide and methyl iodide).[25] The sirup obtained from this second methylation was distilled in a short-path still at *ca.* 80° (10^{-3} mm.), The product, 8.85 g. (89%) of a colorless sirup, n_D^{25} 1.4941, crystallized on standing at 0°. Fine needles were obtained on recrystallization from ethanol-water; m.p. 34°, $[\alpha]_D^{27}$ −100.6° (*c* 1.0, pyridine).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.60; OCH_3, 10.54. Found: C, 65.32; H, 7.42; OCH_3, 10.53.

The benzylphenylhydrazone of 2:3-*O*-isopropylidene-5-*O*-methyl-D-ribose was prepared from IV by first removing its benzyl group by hydrogenolysis[13b] and then treating the resulting product with benzylphenylhydrazine.[23] The product (57%) was obtained as colorless needles by recrystallization from methanol-water: m.p. 115.5–116.5°; $[\alpha]_D^{30}$ −53.2° (*c* 1.0, chloroform).

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.68; H, 7.34; N, 7.28. Found: C, 68.71; H, 7.14; N, 7.04.

5-O-Methyl-D-ribose (I). Catalytic hydrogenolysis was used to debenzylate[13b] 1.96 g. of IV. The resulting colorless sirup (2:3-*O*-isopropylidene-5-*O*-methyl-D-ribose) was dissolved in 20 ml. of purified dioxane and 20 ml. of 0.1*N* sulfuric acid was added. The solution was kept at 65° for 2.5 hr. and then it was cooled to room temperature. After removing sulfuric acid from the digest by passage over a column of Duolite A-4,[26] the solvent was evaporated. An almost quantitative yield of a pale yellow sirup remained. The paper chromatographic and electrophoretic behavior of this sirup has been described.[27] In addition, it was found to have an R_f of 0.69 in solvent C and 0.52 in solvent D.[28] In all of the solvent systems, the sirup gave only one spot (aniline oxalate spray) on paper chromatography. A portion of the sirup was dissolved in water, and the solution was decolorized with charcoal. The colorless sirup remaining after the evaporation of the water, which could not be crystallized, was dried to constant weight *in vacuo* over activated alumina; n_D^{25} 1.4819; $[\alpha]_D^{25}$ (equilib.) +41.5° (*c* 1.99, water). Levene and Stiller reported $[\alpha]_D^{24}$ +26.53° (*c* 6, 0.04*N* hydrochloric acid).[9,29]

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.89; H, 7.36; OCH_3, 18.90. Found: C, 43.58; H, 7.40; OCH_3, 18.98.

Another portion of the sirupy product was converted to the benzylphenylhydrazone. Recrystallization of the hydrazone from methanol-water yielded long colorless needles (77% based on IV); m.p. 106–107°; $[\alpha]_D^{28}$ − 19.4° (*c* 1.04, chloroform). The R_f was found to be 0.90 in solvent A, 0.91 in solvent B, and 0.88 in solvent C.

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(27) The value reported by Lipkin, Cook, and Markham[5] for the mobility of I relative to D-ribose in solvent B is 1.21, in contrast to the value of 1.00 reported by G. R. Barker and D. C. D. Smith, *Chem. & Ind.*, 19 (1954). This difference may be due to the fact that these latter authors appear to have carried out their chromatography in the presence of a higher concentration of boric acid than Lipkin, Cook, and Markham. On the other hand, G. R. Barker, and J. W. Spoors[8] report a more recent value for the R_f of I in butanol–boric acid which leads to a value for the relative mobilities of 1.16.

(28) A sample of I prepared by the method of Levene and Stiller[9] had an R_f of 0.70 in solvent C and 0.50 in solvent D (W. H. Hunter and D. Lipkin, unpublished results).

(29) This value was determined on a solution which was obtained by subjecting methyl 2:3-*O*-isopropylidene-5-*O*-methyl-D-riboside to hydrolysis with 0.04*N* hydrochloric acid.

Anal. Calcd. for $C_{19}H_{23}N_2O_4$: C, 66.45; H, 6.75; N, 8.15; OCH_3, 9.03. Found: C, 66.35; H, 6.83; N, 8.19; OCH_3, 8.95.

The *p*-bromophenylosazone of I[4,9] was obtained in pure condition without the use of chromatography. Recrystallization of the product from methanol yielded a product (60%) which melted at 176.5° (lit.[4,9] m.p. 177°, 178°).

Partial hydrolysis of IV. A solution of 3.89 g. of IV in a mixture of 160 ml. of purified dioxane and 160 ml. of 0.1*N* sulfuric acid was kept at 65° for 6 hr. After the reaction mixture was cooled to room temperature, sulfuric acid was removed by passage over Duolite A-4. The column effluent was concentrated until only a pale yellow sirup remained. This was dissolved in 80 ml. of ml. of water and extracted five times with ligroin. From this ligroin solution was recovered 0.28 g. (7%) of unchanged IV; m.p. 33–34°; mixed m.p. with authentic IV, 33–34°.

The aqueous layer, after the ligroin extraction, was concentrated to a volume of 25 ml. This was extracted with chloroform in a continuous extractor. Evaporation of the resulting aqueous layer left 0.90 g. (41%) of I; R_f (solvent A), 0.41.

The chloroform solution, after evaporation, left 1.70 g. (50%) of a sirupy residue (crude benzyl 5-*O*-methyl-β-D-ribofuranoside, VII); R_f (solvent A), 0.77. The material on the paper chromatogram gave a positive test with periodate–Schiff's reagent spray. A portion of VII (0.23 g.) was evaporated to dryness three times with 10-ml. portions of anhydrous pyridine. Treatment with benzoyl chloride and pyridine yielded, after the usual work-up procedure, a sirup which was molecularly distilled at a bath temperature up to 175° (10^{-3} mm.). The sirupy distillate crystallized, and it then was recrystallized from methanol to give 0.20 g. (48%) of benzyl 5-*O*-methyl-β-D-ribofuranoside 2,3-dibenzoate; m.p. 82–83°; $[\alpha]_D^{30}$ −18.4° (*c* 0.85, chloroform).

Anal. Calcd. for $C_{27}H_{26}O_7$: C, 70.11; H, 5.66; OCH_3, 6.71. Found: C, 69.81; H, 5.69; OCH_3, 6.95.

After drying 0.20 g. of VII as above, it was converted to the 2,3-diacetate by means of acetic anhydride and pyridine (50 hr., room temp.). The product (0.19 g., 73%) distilled at a bath temperature of 100–110° (10^{-3} mm.); n_D^{25} 1.4894.

Anal. Calcd. for $C_{17}H_{22}O_7$: C, 60.16; H, 6.89. Found: C, 60.10; H, 6.68.

Another portion (0.100 g.) of VII was dried by evaporation with three 15-ml. portions of absolute ethanol. It was converted to the 2,3-bis(trifluoroacetate) with 2 ml. of trifluoroacetic anhydride and 10 mg. of anhydrous sodium trifluoroacetate (3 hr., 50°).[30] A colorless sirup was obtained (0.103 g., 59%) on distillation at a bath temperature of 80–90° (0.05 mm.); n_D^{25} 1.4273; $[\alpha]_D^{26}$ −41.8° (*c* 0.67, carbon tetrachloride).

Anal. Calcd. for $C_{17}H_{16}F_6O_7$: C, 45.74; H, 3.61; OCH_3, 6.93. Found: C, 45.41; H, 3.58; OCH_3, 6.95.

The presence of a vicinal glycol structure in VII was demonstrated by carrying out a periodate titration[31] on its 2,3-bis(trifluoroacetate). In this titration, advantage was taken of the rapid methanolysis of trifluoroacetyl esters at room temperature. A 0.1026-g. sample of the 2,3-bis(trifluoroacetate) of VII was placed in a 25-ml. volumetric flask and after an excess of 0.05*M* aqueous sodium metaperiodate was added, the mixture was diluted to the mark with methanol. Samples of the reaction mixture were removed at intervals, and the amounts of periodate consumed were determined in the usual manner.[31] The results obtained were: After 0.6 hr., 1.01 moles periodate per mole of ester; 2.75 hr., 1.02 moles; and 6.3 hr., 1.00 mole.

In order to obtain further evidence that the furanoside ring did not undergo rearrangement to a pyranoside structure during the acetonation of II to III, VII was converted to the known crystalline anilide of 2,3,5-trimethyl-D-ribose.[32] For this purpose, 0.52 g. of VII was dried by repeated evaporation with absolute ethanol. It then was methylated by means of methyl iodide and silver oxide.[25] Distillation of the exhaustively methylated material at a bath temperature of 100–115° (0.02 mm.) yielded 0.32 g. (56%) of sirupy product (benzyl 2,3,5-tri-*O*-methyl-β-D-ribofuranoside, VIII), n_D^{27} 1.4945. The same product was obtained by methylation of II with methyl sulfate and aqueous sodium hydroxide.

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; OCH_3, 32.97. Found: C, 63.69; H, 7.78; OCH_3, 32.98.

Debenzylation[18b] of VIII by catalytic hydrogenolysis yielded 2,3,5-tri-*O*-methyl-D-ribose as a colorless sirup; n_D^{22} 1.4540 (lit.: n_D^{23} 1.4527,[7] n_D^{20} 1.4523[32]). This was converted to the anilide, m.p. 54° (lit.[32] m.p. 56.5°).

Anal. Calcd. for $C_{14}H_{21}NO_4$: N, 5.24. Found: N, 5.25.

5-O-Methyl-D-ribitol 1,2,3,4-tetrakis(trifluoroacetate). (VI). To a solution of 0.70 g. of I in 10 ml. of water was added 0.2 g. of sodium borohydride (Metal Hydrides Inc., Beverly, Mass.) dissolved in 5 ml. of water.[17] After 1.5 hr. at room temperature, the excess hydride was destroyed by the dropwise addition of trifluoroacetic acid. The acidic solution was evaporated to dryness. The residue was dried by the addition of absolute ethanol and evaporation once again to dryness. This operation was repeated several times. After adding 0.2 g. of anhydrous sodium trifluoroacetate and 6 ml. of trifluoroacetic anhydride, the mixture was kept at reflux for 1 hr. It then was cooled, 25 ml. of carbon tetrachloride were added, and the mixture was concentrated to a small volume.[30] The semisolid residue, obtained after repeating this operation two more times, was extracted with ether. Distillation of the ether extract yielded 1.64 g. (70%) of VI, b.p. 116–117° (7 mm.); n_D^{25} 1.3518; $[\alpha]_D^{25}$ −11.1° (*c* 2.21, carbon tetrachloride).

Anal. Calcd. for $C_{14}H_{10}F_{12}O_9$: C, 30.55; H, 1.83; periodate consumption, 3.0 moles.[33] Found: C, 30.29; H, 1.88; periodate consumption, 2.9 moles.

5-O-Methyl-D-ribitol (Va). A 6.21-g. sample of VI was dissolved in 60 ml. of methanol.[30] The optical rotation of a portion of this solution, the main bulk of which was allowed to stand at room temperature, was followed as a function of time. The observed rotations were: −0.37°, 5 min.; −0.20°, 29 min.; + 0.19°, 1.28 hr.; +0.044°, 6.5 hr.; and −0.13°, 16 hr. (constant). After the rotation became constant, the total methanol solution was concentrated to a small volume. The colorless sirup which remained (quantitative yield) was recrystallized from anhydrous benzene containing 0.5 ml. of methyl trifluoroacetate[34] per 100 ml. of benzene. Crystals were obtained in the form of irregular plates. After additional recrystallizations from benzene plus methyl trifluoroacetate, the product (1.08 g., 32%), which turned out to be Vb, was obtained as needle-like crystals; m.p. 84–85°; $[\alpha]_D^{25}$ −6.4° (*c* 0.975, ethanol). Values which have been reported previously for the specific rotation of Va are $[\alpha]_D^{18}$ +8.3° (*c* 0.104, chloroform)[1,35] and $[\alpha]_D^{25}$ +10° (*c* 1.0, water).[36] Paper chromatographic examination of the

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(31) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

(32) G. R. Barker, *J. Chem. Soc.*, 2035 (1948).

(33) The compound, VI, as such obviously should not consume periodate. On the other hand, the periodate titration was carried out as described for the 2,3-bis(trifluoroacetate) of VII. Therefore, the periodate actually was consumed by the methanolysis product, V.

(34) E. Gryszkieweicz-Trochimowski, A. Sporzynski, and J. Wnuk, *Rec. trav. chim.*, **66**, 419 (1947).

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compound[37] revealed only a single spot with metaperiodate–Schiff's reagent spray; R_f (solvent A), 0.33; R_f (solvent B), 0.42; R_f (solvent C), 0.55. Ribitol itself also has a larger R_f in solvent B than in solvent A.[38]

Anal. Calcd. for $C_6H_{14}O_5 \cdot CF_3CO_2CH_3$: C, 36.73; H, 5.82; OCH_3, 21.09; periodate consumption, 3.0 moles. Found: C, 36.58; H, 5.16; OCH_3, 21.79; periodate consumption, 3.2 moles.

The material remaining after the solvent was evaporated from the filtrates from the above recrystallizations had the same R_f as Vb. A 0.20 g. portion of this sirup was benzoylated by means of benzoyl chloride in pyridine solution. The sirupy benzoylation product crystallized on standing. There was recovered 0.44 g. (60%) of product (5-*O*-methyl-D-ribitol 1,2,3,4-tetrabenzoate) on recrystallization from 95% ethanol; m.p. 88.5–89.5°; $[\alpha]_D^{27}$ −9.7° (*c* 2.07, pyridine).

Anal. Calcd for $C_{34}H_{30}O_9$: C, 70.09; H, 5.19; OCH_3, 5.32. Found: C, 70.13; H, 5.06; OCH_3, 5.52.

DISCUSSION

The method of preparation of I described in this paper leads directly and unequivocally to a product which is chromatographically and electrophoretically homogeneous. The paper chromatographic and electrophoretic properties of I, as well as the melting point of its *p*-bromophenylosazone, are in good agreement with the corresponding values reported by other investigators. Although I could not be crystallized, it was converted in good yield to a crystalline benzylphenylhydrazone.

Some observations made on the acid catalyzed hydrolysis of IV are of interest. Many attempts were made to hydrolyze selectively the isopropylidene group of IV. Under all sets of conditions which were tried, the rate of hydrolysis of this group turned out to be comparable with the rate of hydrolysis of the glycosidic bond. As a result, almost equal yields of I and VII always were obtained. On the other hand, I was obtained by complete acid hydrolysis of IV in aqueous dioxane, but it invariably was impure and it could not be converted to the crystalline benzylphenylhydrazone in good yield. Instead, in the preparation of pure I it was found desirable to first cleave the benzyl glycosidic bond of IV by catalytic hydrogenolysis and then to remove the isopropylidene group by acid catalyzed hydrolysis in aqueous dioxane.

The specific rotation of Vb is negative, whereas two other groups of investigators have reported the specific rotation of Va itself to be positive.[1,35,36] Nevertheless, the experimental evidence that the adduct Vb is derived from 5-*O*-methyl-D-ribitol is conclusive. The most likely explanation of this seeming discrepancy is that Vb is surprisingly stable, even in solution, and has a rotation different from that of Va. Aside from the fact that Vb is isolable, its paper chromatographic behavior is further evidence of its stability.

The crystalline product obtained in the crystallization of Va from a mixture of benzene and methyl trifluoroacetate is undoubtedly Vb and not a monotrifluoroacetyl ester of Va. In brief, this conclusion is based on a number of pieces of evidence. First, although the analytical values for carbon and hydrogen could be used to support either composition, the methoxyl content found for Vb definitely indicates that it is the suggested adduct and not a monotrifluoroacetyl ester of Va (calculated methoxyl content, 11.84%). Second, Vb consumed 3.2 moles of periodate per mole of compound. Third, crystalline materials were obtained by crystallization of Va in the presence of ethyl acetate or ether, instead of methyl trifluoroacetate. Efforts to isolate these two crystalline products failed, since the crystals turned to sirups on attempting to recover them. Finally, Va was converted to a tetrabenzoate by means of benzoyl chloride in anhydrous pyridine.

Acknowledgment. This investigation was supported in part by the United States Atomic Energy Commission. Partial support also was provided by research grant NSF-G-12451 from the National Science Foundation and by research grant C-3870 from the National Cancer Institute, Public Health Service.

ST. LOUIS 30, MO.

(37) Prior to chromatography of Vb, ammonium hydroxide was added to a sample and the mixture was allowed to stand at room temperature for a short time. If this treatment was not carried out before the sample was spotted on paper, the sample showed serious tailing on paper chromatography.

(38) G. R. Barker and D. C. C. Smith, *Chem. & Ind.*, 19 (1954).