It has been demonstrated that the tetraacetyl-β-D-glucopyranosylbenzene and the triacetyl-β-D-xylopyranosylbenzene prepared by the Grignard method are identical with the same compounds prepared by interaction of benzene and aluminum chloride with tetraacetyl-α-D-glucosyl chloride or triacetyl-α-D-xylosyl chloride. This indicates the absence of isomerization during the aluminum chloride process.

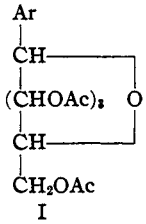
EVANSTON, ILLINOIS RECEIVED AUGUST 2, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

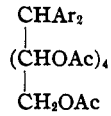
The Reaction of Aromatic Hydrocarbons with Polyacetylglycosyl Derivatives of Hydrocarbons

BY CHARLES D. HURD AND WILLIAM A. BONNER[1]

Previous reports[2] from this Laboratory have indicated that polyacetylglycosyl halides and polyacetylglycoses in the monosaccharide series react with aromatic hydrocarbons in the presence of aluminum chloride to yield, on subsequent acetylation, polyacetylglycosyl derivatives of aromatic hydrocarbons as well as 1,1-diaryl-1-desoxyalditol polyacetates. For aldohexose derivatives these two types are represented by structures I and II, respectively. The relative proportions of I and II formed depend on the reaction conditions, I being the predominant product when a molecular deficiency of catalyst is employed, and II being the sole product obtained with the theoretical quantity of catalyst.



I

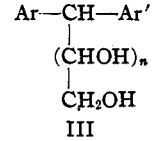


II

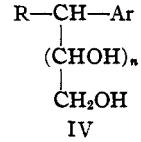
The fact that compounds of type I could be isolated from reactions where quantities of catalyst below the theoretical were employed, suggested that they were probably the precursors of type II, the steps intermediate being ring cleavage and arylation. Such a hypothesis could be verified readily by bringing I into reaction with the appropriate aromatic hydrocarbon. The same 1,1-diaryl-1-desoxyhexitol derivative should be obtained as was previously isolated from the over-all reaction.[2]

Tetraacetyl-β-D-glucosylbenzene, prepared from phenylmagnesium bromide[3] was treated with benzene and aluminum chloride. On warming, hydrogen chloride was evolved in quantity and the catalyst phase clumped together, finally dissolving to give a black, homogeneous solution. The reaction mixture was handled in the usual manner[2] to yield acetophenone and tar from the benzene layer, and 1,1-diphenyl-1-desoxy-D-glucitol pentaacetate from the water layer. In the same manner, the action of triacetyl-β-D-xyloxylbenzene upon benzene gave rise to the same 1,1-diphenyl-1-desoxy-D-xylitol tetraacetate as was obtained by the catalytic alkylation of benzene with β-D-xylose tetraacetate. It is evident, therefore, that the 1,1-diaryl-1-desoxyalditols synthesized in the earlier studies[2] arose in all probability from the intermediate glycosylbenzene and glycosyltoluene derivatives.

The discovery of this reaction makes possible the synthesis of hitherto inaccessible carbohydrate derivatives, especially the unsymmetrical 1,1-diaryl-1-desoxyalditols, such as III, and the 1-alkyl-1-aryl-1-desoxyalditols (IV).



III



IV

The first extension of this synthesis to compounds such as III involved the use of *p*-(tetraacetyl-β-D-glucosyl)-toluene and benzene. The product anticipated from these reactants would be α-1-phenyl-β-1-*p*-tolyl-1-desoxy-D-glucitol. This product, a hydrate, m. p. 151.5–153.5°, $[\alpha]^{25}D$ 55.8°, was readily obtained. Its structure was supported by analysis and by oxidation to *p*-benzoylbenzoic acid. The two prefixes in the above name, phenyl and tolyl, are arbitrarily designated α- and β- with "tolyl" as β- in view of the fact that β-D-glucosyl-toluene was the name assigned, on the basis of specific rotation, to the parent compound. Actually, the reaction may or may not proceed with Walden inversion, and until this fact, as well as the absolute configuration of the number 1 carbon atom in the parent compound, is established, a nomenclature based on actual configuration cannot be employed. These problems are under consideration at the present time.

To demonstrate the non-racemization of the number 1 carbon atom during the reaction, the action of tetraacetyl-β-D-glucosylbenzene on toluene was studied. A crystalline hydrate was isolated having properties different from those pre-

(1) Corn Products Refining Company Research Fellow, 1941-1944.

(2) Hurd and Bonner, THIS JOURNAL, 67, 1664, 1759 (1945).

(3) Hurd and Bonner, *ibid.*, 67, 1972 (1945).

viously noted, m. p. 167–170.5°, $[\alpha]^{25}D$ 58.8°. This was obviously the anomeric product, α-1-*p*-tolyl-β-1-phenyl-1-desoxy-D-glucitol hydrate. The isolation of two distinct, anomeric 1-phenyl-1-*p*-tolyl-1-desoxyhexitols furnishes evidence that the reaction proceeds without racemization. Had racemization at position 1 been encountered the products isolated from the two reactions should have been identical, and not a sterically discrete pair. Another possible explanation, of course, is that a mixture of the two anomers results from both reactions, one predominating in the first case, and the other in the second. This seems improbable, however, since the two products are crystalline.

By the alkylation of toluene with a sample of the high-rotating, sirupy tetraacetyl-α-D-glucosylbenzene, obtained simultaneously with the crystalline β-anomer by means of the Grignard glycosylation,[3] it was hoped that α-1-phenyl-β-1-*p*-tolyl-1-desoxyglucitol might be obtained by a second approach. The alkylation product showed mixed melting point depressions with both this compound and α-1-*p*-tolyl-β-1-phenyl-1-desoxyglucitol, suggesting mixed crystals of the two. This supposition was strengthened by the fact that the product showed no melting point depression when mixed with a recrystallized mixture of the two above compounds, thus indicating that the high-rotating α-sirups obtained by the Grignard alkylation were probably mixtures of ganomeric polyacetylglycosyl derivatives of the hydrocarbons employed in that study. The actual isolation of mixed crystals at this point lends weight to the probability that the products discussed in the previous paragraph actually comprised a true anomeric pair.

Experimental

1,1-Diphenyl-1-desoxy-D-glucitol.—Tetraacetyl-β-D-glucosylbenzene (4.00 g.) was dissolved in dry, thiophene-free benzene (150 ml.), and aluminum chloride (13 g.; 1.3 g. over the theoretical nine equivalents) was added. The mixture was contained in a three-necked flask equipped with mercury-sealed stirrer and reflux condenser, and was stirred under gentle reflux for six hours. After this, the mixture was cooled, poured into 500 ml. of water, stirred for one-half hour, and the layers separated and handled individually.

The benzene layer was washed several times with water, filtered, and dried over sodium sulfate. Removal of the solvent yielded 3.8 g. of an aromatic oil which was fractionated at atmospheric pressure through a small modified Claisen flask. The middle fraction (1.7 g., b. p. 198–202°) was identified as acetophenone through the 2,4-dinitrophenylhydrazone, melting point and mixed melting point with an authentic sample, 244–245°.

The water layer, after washing with benzene and combining the washings with the original benzene layer, was neutralized to litmus and filtered free of the precipitated aluminum hydroxide. The cake was washed twice by suspending in water, boiling and filtering, combining the washings with the original filtrate. The solution was distilled to dryness *in vacuo*, and the residue removed, air-dried, powdered, returned to the same flask, and acetylated by stirring with acetic anhydride (250 ml.) and sodium acetate (20 g.) on the steam-bath for four hours. The acetylation mixture was cooled, poured into 400 ml. of water, stirred for two hours, then extracted with ether. The ether solution was purified in the usual way, and removal of the solvent left 3.5 g. (66%) of crude, amber sirup. This was crystallized readily by dissolving in 2-propanol, seeding with 1,1-diphenyl-1-desoxy-D-glucitol pentaacetate, and directing a gentle stream of air over the solution. The crystalline product weighed 2.5 g., m. p. 93–95°, mixed m. p. with the authentic material 94–96°.

A one-gram sample of the above material was dissolved in commercial methanol (20 ml.) and a small chip of sodium added. In several minutes the flask was filled with crystals, and after an hour these were collected, washed with methanol, and dried. The yield was 0.54 g. (88%); m. p. 155–156.5°; mixed m. p. with 1,1-diphenyl-1-desoxy-D-glucitol hydrate, 156–157.5°.

The sirupy residue (1.0 g.) obtained on evaporation of the solvent from the mother liquors of the original crystallization was deacetylated in a similar manner, except that a period of twenty-four hours was required for the formation of crystals. The low yield of 0.16 g. (m. p. 153–156°; mixed m. p. with the authentic compound 156–158°) indicates that the residual uncrystallizable sirup was not pure 1,1-diphenyl-1-desoxy-D-glucitol pentaacetate.

1,1-Diphenyl-1-desoxy-D-xylitol.—Triacetyl-β-D-xylosylbenzene (1.00 g.) and aluminum chloride (3.55 g.) were added to dry, thiophene-free benzene (40 ml.). The mixture was refluxed for five hours, and the products isolated as before. From the water layer, after acetylation, there was obtained 0.42 g. (32%) of a clear, amber sirup. This was deacetylated as before, taken up in water, and twice crystallized. There resulted long, white needles, m. p. 168.5°, $[\alpha]^{25}D$ 73.2° (*c*, 0.280; dioxane). The 1,1-diphenyl-1-desoxy-D-xylitol obtained from the direct xylosylation of benzene with β-D-xylose pentaacetate melted at 167–168°.

α-1-Phenyl-β-1-*p*-tolyl-1-desoxy-D-glucitol.—A mixture of 1 g. of *p*-(tetraacetyl-β-D-glucosyl)-toluene, 40 ml. of dry, thiophene-free benzene, and 3.0 g. of aluminum chloride was refluxed for five hours, then processed as previously described. The acetate from the water layer (0.52 g., or 39%) would not crystallize from 2-propanol. Consequently it was deacetylated as before to yield 0.21 g. of solid α-1-phenyl-β-1-*p*-tolyl-1-desoxy-D-glucitol hydrate, which on recrystallization from water had m. p. 150.5°. One-tenth of a gram of this was removed for oxidation, and the remainder recrystallized, m. p. 151.5–153.5°, $[\alpha]^{25}D$ 55.8° (*c*, 0.305; dioxane). Analyses were by Dr. T. S. Ma.

Anal. Calcd. for $C_{19}H_{24}O_6 \cdot H_2O$: C, 65.20; H, 7.48. Found: C, 65.10; H, 7.29.

Oxidation.—The 0.1 g. of product removed above was oxidized by refluxing for two hours with potassium permanganate (0.5 g.), 20% sodium hydroxide (0.2 ml.) and water (15 ml.). The mixture was cooled, acidified, clarified by adding a little sodium bisulfite, and the solid remaining was extracted into ether. The extract was washed with water, dried, and the solvent removed. The material remaining was recrystallized from 40 ml. of water, m. p. 196–196.5°. The anticipated oxidation product was *p*-benzoylbenzoic acid, reported to melt at 194°.[4]

α-1-Phenyl-β-1-*p*-tolyl-1-desoxy-D-xylitol.—One gram of *p*-(triacetyl-β-D-xylosyl)toluene, 3.55 g. of aluminum chloride, and 45 ml. of benzene reacted, and the product was isolated as before. The yield of amber, sirupy acetate was 0.23 g. (16%). On deacetylation and two recrystallizations from water the α-1-phenyl-β-1-*p*-tolyl-1-desoxy-D-xylitol melted at 163.5–164°. A sufficient quantity was not obtained to permit determination of the specific rotation.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.35. Found: C, 72.42; H, 7.04.

α-1-*p*-Tolyl-β-1-phenyl-1-desoxy-D-glucitol.—Tetraacetyl-β-D-glucosylbenzene (4.00 g.) was dissolved in toluene (150 ml.), aluminum chloride (13 g.) was added, and the mixture was heated at 77–83°, for five hours, then treated as usual. Removal of the solvent from the toluene

(4) Zincke, *Ann.*, **161**, 100 (1872).

layer gave 8.1 g. of oil, from which 3 g. of *p*-methylacetophenone was obtained by fractional distillation at 50 mm. (b. p. 138–150°). The semicarbazone of this ketone melted at 206.5–207.5°, and showed no depression when mixed with an authentic sample.

From the water layer there was obtained 3 g. (54%) of crude, sirupy acetate. This was deacetylated as usual, taken up in water, and purified by filtration through Norit and Celite. The filtrate yielded 0.67 g. of α-1-*p*-tolyl-β-1-phenyl-1-desoxyglucitol hydrate, m. p. 163.5–166.5°. After three recrystallizations from water the compound melted at 167–170°, $[\alpha]^{25}D$ 58.8° (*c*, 0.400; dioxane). A mixed melting point of this product with the anomeric α-1-phenyl-β-1-*p*-tolyl-1-desoxyglucitol hydrate showed a marked depression, 120–134°.

Anal. Calcd. for $C_{19}H_{24}O_5 \cdot H_2O$: C, 65.20; H, 7.48. Found: C, 65.37; H, 7.37.

Oxidation.—The oxidation was carried out as previously described for the anomeric product. The *p*-benzoylbenzoic acid obtained was less pure, m. p. 190–192°, but showed no mixed melting point depression (193–194°) with the previously obtained sample.

Tetraacetyl-α-D-glucosylbenzene and Toluene.—Sirupy tetraacetyl-α-D-glucosylbenzene (2.26 g., obtained from the mother liquors of the Grignard preparation of the anomer[3]), aluminum chloride (7.5 g.), and toluene (85 g.) were stirred together for five hours at 80°. After the customary treatment, from the water layer was obtained 0.75 g. of an amber, sirupy acetate. This was deacetylated to produce a small quantity of crystalline material, m. p. 152.5–161° from water. This substance showed melting point depressions with both α-1-phenyl-β-1-*p*-tolyl-1-desoxy-D-glucitol hydrate and α-1-*p*-tolyl-β-1-phenyl-1-desoxy-D-glucitol hydrate. When equal portions of these two compounds were recrystallized together from water, a product was obtained which melted at 145–146°. A mixed melting point of this recrystallized mixture with the product obtained above showed no depression, but melted in the intermediate range of 152–157°.

Summary

Polyacetylglycosylbenzenes have been shown to react with benzene in the presence of aluminum chloride to yield the same 1,1-diphenyl-1-desoxyalditols as are obtained directly by the glycosylation of benzene with sugar acetates or acetylated glycosyl halides. This confirms the hypothesis that in these latter glycosylations the 1,1-diphenyl-1-desoxyalditols arise from an intermediate glycosylbenzene.

Several members of a new class of mixed 1,1-disubstituted 1-desoxy-alditols have been prepared.

EVANSTON, ILLINOIS RECEIVED SEPTEMBER 4, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Derivatives of p,p'-Diaminodiphenyl Sulfone[1a]

BY HANS HEYMANN AND LOUIS F. FIESER

The studies of Coggeshall and Maier[1b] of the action of sulfanilamide and related drugs on malarial infections showed that cures with complete eradication of parasites could be effected in certain cases of experimental avian and monkey malaria. Trials with humans suffering from naturally acquired or therapeutic malaria were somewhat inconclusive but encouraging. Maier and Riley also showed that the action of sulfa drugs on plasmodia is susceptible to inhibition by *p*-aminobenzoic acid,[2] whereas with quinine and atebrine there is no inhibition. Therefore the sulfa drugs must act on the plasmodia in a different manner than the older antimalarials, and it may be hoped that a sulfa compound suitable for malaria therapy can be found superior to the drugs in use.

This investigation of the synthesis of additional members of the series for trial as antimalarials by the International Health Division of the Rockefeller Foundation was undertaken at the suggestion of Dr. L. T. Coggeshall and Dr. John Maier, and was supported by a grant from the Rockefeller Foundation. The present paper reports the preparation of several new derivatives of *p,p'*-diaminodiphenyl sulfone (I). This compound was introduced into chemotherapy in 1937 by Buttle and his associates[3] and by Fourneau and his collaborators,[4] and numerous derivatives and related substances have since been reported in patents and papers.[5] A brief review of methods for preparing I is given in "Organic Syntheses."[6]

In investigating the preparation of I by patented procedures for the ammonolysis of *p,p'*-dichlorodiphenyl sulfone we tried the claimed reaction[7] with alcoholic ammonia in the presence of copper without success but obtained the desired compound in 78% yield according to a patent of the I. G. Farbenindustrie,[8] in which the chloro compound is treated with aqueous ammonia and a catalyst at 200° under pressure. Shaking the reaction mixture was found to be necessary, although agitation is not mentioned in the patent procedure. One run resulted in a mixture, from which *p*-chloro-*p'*-aminodiphenyl sulfone (Ia) could be isolated with ease. The structure of Ia was proved by conversion of the substance to

(1a) This manuscript was originally received on October 27, 1942, but its publication has been withheld at the request of the National Research Council.—*The Editor.*

(1b) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941); see also earlier references.

(2) Maier and Riley, *Proc. Soc. Exptl. Biol. Med.*, **50**, 152 (1942).

(3) Buttle, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937).

(4) Fourneau, Nitti, Tréfouël, Tréfouël and Bovet, *Compt. rend.* **204**, 1763 (1937).

(5) For references see Roblin, Williams and Anderson, THIS JOURNAL, **63**, 1930 (1941).

(6) "Organic Syntheses," **22**, 31 (1942).

(7) Laboratoires Français de Chimiothérapie and A. Girard French Patent 844,220 (1939).

(8) I. G. Farbenindustrie A. G., French Patent 829,926 (1938), British Patent 506,227 (1939).