Upon cooling, two layers were noted; the lower was shown to contain water and ammonium chloride, the upper contained ethyl chloride and yielded white, crystalline needles which, after recrystallization from alcohol, yielded 0.5 g. of material (IV) melting at 91–92° (cor.).

Anal. Calcd. for $C_{13}H_9Cl$: C, 77.80; H, 4.52; Cl, 17.56. Found: C, 78.82; H, 5.06; Cl, 17.72.

Two grams of granulated zinc was treated with 2% copper sulfate solution, covered with 10% alcoholic potassium hydroxide solution, heated to boiling and to this mixture was added slowly an alcoholic solution of (IV). After heating for three hours, the metal was removed by filtration, the filtrate neutralized with sulfuric acid, and, after removal of salt, the filtrate yielded fluorene.

According to the method of Werner and Grob,[4] fluorenone was reduced in alcoholic solution by action of zinc dust and concentrated ammonium hydroxide solution. The 9-hydroxyfluorene crystallized from benzene in characteristic plates melting at 149° (cor.). The carbinol was dissolved in benzene and treated with phosphorus pentachloride to obtain a yellow crystalline mass. After recrystallization from alcohol there resulted white, needle-shaped crystals melting at 88–90°. The melting point of a mixture of this sample of *9-chlorofluorene* with (IV) was found to be 90–92°.

Reaction of Aniline with (II).—One-half gram of (III) and 10 cc. of aniline were mixed and heated for one hour; ammonia was liberated. Upon cooling, a white solid separated and was recrystallized from hot alcohol, m. p. (sealed tube) of the anilide, 292–297° (cor.), with decomposition.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 80.46; H, 5.38; N, 9.33. Found: C, 79.97; H, 5.29; N, 9.57.

Attempt to Synthesize 9-Biphenylene-aminoacetamide.—Fifty grams of phenanthraquinone was heated with 500 cc. of 20% sodium hydroxide solution on a steam-bath for three hours. After separation from a small amount of fluorenone, acidification produced a creamy solid. The latter was dissolved in a mixture of ethyl alcohol and benzene and was precipitated by pouring into a large amount of water. Thus obtained and purified, *9-hydroxyfluorene-9-carboxylic acid* (42% yield) melted at 167–168° (cor.).[7]

The acid thus obtained was mixed with 46 g. of phosphorus pentachloride and the mixture was cooled in an ice-bath. The phosphorus oxychloride formed was removed by distillation under diminished pressure. The residue was covered with ether, then filtered. The yield was 8 g. (30% yield) of *9-biphenylenechloroacetyl chloride* melting at 111°.[8]

In turn, the acid chloride was dissolved in absolute ether and the solution saturated with anhydrous ammonia. After evaporation of the solvent, the residue was washed with cold water to remove ammonium chloride, then dried before being recrystallized from 1,4-dioxane and water. Thus obtained in 73% yield, *9-biphenylenechloroacetamide* melts at 194° (cor.).[9]

The chloroacetamide was added slowly to a solution of sodium amide in anhydrous liquid ammonia; the solution changed color and hydrogen was liberated. After removal of the solvent the solid residue was washed with water and, after drying, the brown amorphous mass melted at 60–70° with decomposition. By crystallization from dilute alcohol, a small amount of yellow crystalline material was obtained and was shown to be fluorenone. The majority of the product from this experiment was a non-crystallizable gummy mass containing nitrogen and chlorine and definitely was not the desired 9-biphenyleneaminoacetamide (III).

Summary

Hydrolysis by means of barium hydroxide of fluorene-spirohydantoin forms 9-biphenyleneaminoacetamide rather than the anticipated amino acid or amine.

(7) Klinger [*Ann.*, **389**, 239 (1912)] reported m. p. 166–167°.

(8) Klinger, *ibid.*, p. 234, reported m. p. of 111° for crude material, 111.5–112.5° after second recrystallization from ligroin and ether.

(9) Klinger, *ibid.*, p. 245, reports m. p. 194°.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Preparation and Rearrangement of Phenylglycosides

BY EDNA M. MONTGOMERY, NELSON K. RICHTMYER AND C. S. HUDSON

Arthur Michael first obtained β-phenylglucoside by the interaction of acetochloroglucose and potassium phenolate in absolute alcohol[1]; subsequently a number of other methods and variations have been described for the preparation of phenylglycosides. By carrying out the reaction in ether,[2] or in a mixture of ether and water,[3] Emil Fischer was able to isolate the acetylated β-phenyl and vanillin glucosides in 60% yields. Mannich[4] introduced the use of aqueous acetone to furnish a homogeneous solution of acetobromoglucose, sodium hydroxide and the desired phenol; the procedure is relatively simple and the method is now widely used.[5]

Fischer and Mechel[6] were the first to obtain an α-phenylglycoside derivative, a mixture of the

(1) Michael, *Am. Chem. J.*, **1**, 306 (1879); see also Koenigs and Knorr, *Ber.*, **34**, 964 (1901).

(2) Fischer and Armstrong, *ibid.*, **34**, 2897 (1901).

(3) Fischer and Raske, *ibid.*, **42**, 1465 (1909).

(4) Mannich, *Ann.*, **394**, 225 (1912); see also Mauthner, *J. prakt. Chem.*, [2] **88**, 764 (1913).

(5) *Cf.* Glaser and Wulwek, *Biochem. Z.*, **145**, 514 (1924); Helferich and Burt, *Ann.*, **520**, 156 (1936); Helferich and Griebel, *ibid.*, **544**, 201 (1940); Fisher, Hawkins and Hibbert, THIS JOURNAL, **62**, 1413 (1940).

(6) Fischer and Mechel, *Ber.*, **49**, 2814 (1916).

α- and β-phenylglucoside acetates being isolated in a 2 to 3 ratio following the interaction of acetobromoglucose and phenol in the presence of the organic base quinoline. When silver oxide and quinoline are used together[7] the product is the β-derivative; silver carbonate and benzene[8] also produce the β-derivative. An enzymic synthesis with emulsin is reported[9] to proceed to the extent of 4%.

A second method for the preparation of α-phenylglycosides has been studied by Zemplén[10]; this reaction involved the condensation of acetobromocellobiose with phenol, with the aid of mercuric acetate, but so far the method seems to have had a very limited trial. Hickinbottom has prepared α-phenylglucoside derivatives by the reaction of phenol with 3,4,6-triacetylglucose-1,2-anhydride,[11] with 3,4,6-triacetyl-β-glucosyl chloride,[12] and with 2-trichloroacetyl-3,4,6-triacetyl-β-glucosyl chloride.[13] Glucosyl fluoride[14] and β-1-trichloroacetyl-2,3,4,6-tetraacetylglucose,[15] however, have yielded the β-phenyl derivatives under the conditions used.

In 1933, Helferich and Schmitz-Hillebrecht[16] described a completely new and very useful method for the preparation of both α- and β-phenylglycoside acetates. When an acetylated reducing sugar is heated with phenol, in the presence of a catalyst, a mixture of the anomeric glycoside acetates is obtained; the presence of fused zinc chloride as catalyst usually favors the formation of the α-phenyl derivative, while *p*-toluenesulfonic acid favors the formation of the β-derivative, for the particular sugars studies. Sisido[17] improved the yields of both α- and β-formd by carrying out the reaction *in vacuo* and thus removing the acetic acid which is liberated. We have improved the yields still more, especially by using α-pentaacetylglucose for the preparation of α-phenylglucosides and by dissolving the fused zinc chloride in a mixture of acetic acid and acetic anhydride before adding it to the other components of the reaction mixture. In the Experimental Part are described these additional modifications which we have used in preparing certain phenylglycosides needed for other studies.[18]

It is sometimes desirable to rearrange an acetylated β-phenylglycoside to the corresponding α-phenyl derivative. The titanium tetrachloride method of Pacsu,[19] useful with aliphatic glycosides,[20] appears to furnish no appreciable amount of the α-form in the case of pentaacetyl salicin[19] or tetraacetyl-β-phenylglucoside.[21] From a study of the Helferich and Schmitz-Hillebrecht synthesis, it might be expected that zinc chloride and phenol would be capable of bringing about a rearrangement. Such indeed is the case, and an example of the conversion of tetraacetyl-β-phenylglucoside to its anomer is described below.

Still another type of transformation has been effected by zinc chloride and phenol. When tetraacetyl-α-methylglucoside is heated with these reagents, methyl is replaced by phenyl, and tetraacetyl-α-phenylglucoside may be isolated in at least a 55% yield. This reaction, with its variations, should be useful in the preparation of phenylglycosides from methylglycosides, such as the β-methyl-D- and L-arabinosides, α-methyl-D-mannoside[22] and α-methyl-D-altroside,[23] which are obtained more readily than the corresponding sugar acetates.

Two glycosides, namely, α-phenyl-D-xyloside and α-*o*-nitrophenyl-D-glucoside, are described for the first time. A considerable amount of data is given for other substituted phenylglucosides and their acetates, the previous descriptions of which seem to have been incomplete, or incorrect. Of particular interest is the positive rotation[24] (+45°) of tetraacetyl-β-*o*-nitrophenyl-D-glucoside; this rotation, reported positive (+53°) also by Glaser and Wulwek,[5] permits the calculation of the $2B_{Ac}$ value as 99,500 in contrast to 62,000

(7) Takahashi, *J. Pharm. Soc. Japan*, **525**, 969 (1925); see also Zemplén and Müller, *Ber.*, **62**, 2107 (1929); Robertson and Waters, *J. Chem. Soc.*, 2729 (1930).

(8) Carter, *Ber.*, **63**, 586 (1930).

(9) Josephson, *Z. physiol. Chem.*, **147**, 181 (1925).

(10) Zemplén, *Ber.*, **62**, 990 (1929); Zemplén and Nagy, *ibid.*, **63**, 368 (1930); Zemplén, *Fortschritte der Chemie organischer Naturstoffe*, **1**, 14 (1938).

(11) Hickinbottom, *J. Chem. Soc.*, 3147 (1928).

(12) Hickinbottom, *ibid.*, 1687 (1929); see also Goebel, Babers and Avery, *J. Exptl. Med.*, **55**, 761 (1932). Under certain conditions this compound is transformed mainly to the β-phenyl derivative (see Hickinbottom, ref. 13).

(13) Hickinbottom, *J. Chem. Soc.*, 1345 (1930).

(14) Helferich, Bäuerlein and Wiegand, *Ann.*, **447**, 32 (1926).

(15) Helferich and Gootz, *Ber.*, **62**, 2791 (1929).

(16) Helferich and Schmitz-Hillebrecht, *ibid.*, **66**, 378 (1933), and many subsequent papers by Helferich and co-workers.

(17) Sisido, *J. Soc. Chem. Ind., Japan*, **39**, Suppl. binding 217 (1936); *C. A.*, **30**, 7118 (1936).

(18) Montgomery, Richtmyer and Hudson, forthcoming publication; see *Science*, **93**, 438 (1941).

(19) Pacsu, *Ber.*, **61**, 1508 (1928).

(20) Pacsu, THIS JOURNAL, **52**, 2563, 2568, 2571 (1930).

(21) Unpublished results from this Laboratory.

(22) Hudson, "Org. Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 362.

(23) Richtmyer and Hudson, THIS JOURNAL, **63**, 1730 (1941).

(24) Throughout the article the rotations are specific rotations at 20° for sodium light; *c* designates concentration in grams per 100 cc. of solution.

and 74,700 for the phenyl- and *p*-nitrophenylglucosides, respectively. The unacetylated *β-o*-nitrophenylglucoside appears to have a "normal" rotation (−106°), and the 2 *B* value of 30,200 is close to the average of 32,160 for other aromatic glucosides.[25]

Experimental Part

Tetraacetyl-α-phenyl-D-glucoside.—To a melt prepared in a Claisen distilling flask from 25 g. of α-pentaacetylglucose[26] (0.064 mole) and 24 g. of phenol (0.255 mole) was added 6.3 g. of fused zinc chloride dissolved in 20 cc. of a 95:5 acetic acid–acetic anhydride mixture.[27] This homogeneous reaction mixture was heated in a bath at 120–125° for two hours. As suggested by Sisido,[17] and later by Helferich,[28] the acetic acid formed in the reaction, as well as that added with the zinc chloride, was removed by evacuating the flask with a water pump during the heating. The resulting red sirup was dissolved in 300 cc. of ethylene dichloride and the zinc chloride and phenol were removed by washing with water and aqueous sodium hydroxide respectively. The solution was dried with granular calcium chloride, concentrated *in vacuo*, and the product crystallized at 0° from 150 cc. of ethyl alcohol. A dense mass of isomeric acetates was obtained, totalling 92% of the theoretical yield. Separation of the α-form was effected by allowing this mixture to crystallize slowly from 350 cc. of alcohol. After four recrystallizations, pure crystalline tetraacetyl-α-phenyl-D-glucoside, rotating[24] +168.7° in chloroform (*c*, 2) and melting at 115°, in agreement with the data recorded by previous investigators, was isolated as shining needles; the total yield was 64%. From the mother liquor was obtained the anomeric tetraacetyl-β-phenyl-D-glucoside in a yield of 26%.

Several less favorable variations of the above procedure were investigated fully with a view to recording the respective yields of the acetylated α- and β-glucosides. In each instance the yields estimated from the rotation of the ethylene dichloride solution were approximated by the total yields of the two isomers. Preheating a condensation mixture on the steam-bath resulted in yields of the α- and β-anomers of 38 and 40%, respectively. Lengthening the period of heating did not affect the yield, but shortening the period to one hour resulted in yields of 46 and 44%. Substituting β-pentaacetylglucose as starting material produced the isomers in yields of 42% each.

Tetraacetyl-β-phenyl-D-glucoside.—A homogeneous melt was prepared in a Claisen flask by mixing 70 g. of β-pentaacetylglucose with a warm solution of 0.95 g. of *p*-toluenesulfonic acid in 68 g. of phenol. As in the preparation of the α-isomer, the mixture was then heated *in vacuo* for one hour with the bath at 100°, and the resulting dark red sirup was dissolved in 500 cc. of ethylene dichloride and purified in the usual manner. The product crystallized from 250 cc. of hot alcohol as rosets of acicular prisms. The purified tetraacetyl-β-phenyl-D-glucoside, rotating −22.5° in chloroform (*c*, 2) and melting at 125–126°, in agreement with the data reported by previous investigators, was obtained in 85% yield.

Rearrangement of Tetraacetyl-β-phenyl-D-glucoside to Tetraacetyl-α-phenyl-D-glucoside by Means of Zinc Chloride in Phenol.—By a procedure similar to that used in the condensation reaction, the β-isomer was next rearranged to the α-isomer. A solution consisting of 20 g. of tetraacetyl-β-phenylglucoside, 18 g. of phenol and 5 g. of zinc chloride[27] was heated *in vacuo* for three hours with the bath at 120–125°. The yields of purified products resulting from this process, and isolated as described above, were 12.8 g. of tetraacetyl-β-phenylglucoside and 6.2 g. of tetraacetyl-α-phenylglucoside.

Tetraacetyl-α-*p*-nitrophenyl-D-glucoside.—In 1939 Aizawa[29] prepared tetraacetyl-α-*p*-nitrophenyl-D-glucoside; he did not, however, report any data.

The synthesis of a mixture of the acetylated α- and β-*p*-nitrophenylglucosides was accomplished by condensing 48 g. of *p*-nitrophenol with 30 g. of α-pentaacetylglucose in the presence of 7 g. of zinc chloride[27] for thirty minutes at 125°. The total crystalline product of mixed isomers was equal to 84% of the theoretical. Isolation of the α-form was brought about by recrystallization of the mixture from alcohol; the mother liquor yielded 18% of the β-isomer described below. The pure tetraacetyl-α-*p*-nitrophenyl-D-glucoside, rotating +200° in chloroform (*c*, 2) and melting at 113°, was obtained as almost colorless acicular prisms in a yield of 60%.

Anal. Calcd. for $C_{20}H_{23}O_{12}N$: C, 51.18; H, 4.94; N, 2.98. Found: C, 51.37; H, 5.08; N, 3.04.

Deacetylation produced the **α-*p*-nitrophenyl-D-glucoside**; crystallized from water as many-sided prisms, the anhydrous substance rotated +215° in water (*c*, 1) and melted at 216°. Goebel, Babers and Avery[30] reported a melting point of 216–217° and $[\alpha]^{23}D$ +227.9° in methyl alcohol; Aizawa[29] reported a melting point of 210°, $[\alpha]^{20}D$ +215° in water.

Tetraacetyl-β-*p*-nitrophenyl-D-glucoside.—Substitution of β-pentaacetylglucose for the α-isomer in the condensation described above resulted in the production of the acetylated α- and β-*p*-nitrophenyl-D-glucosides in yields of 46 and 28%, respectively. The β-isomer, obtained from the mother liquor after removal of the α-form, crystallized from alcohol as slender, almost colorless prisms rotating −41.0° in chloroform (*c*, 2) and melting at 174–175°. These data agree with those in the literature.[31]

After deacetylation of the tetraacetate catalytically the **β-*p*-nitrophenyl-D-glucoside** crystallized from water as practically colorless needles rotating −103.0° in water (*c*, 1) and melting at 164° when dried *in vacuo* at 90°. The melting point is in agreement with that reported by Goebel and Avery,[31] Goebel, Babers and Avery,[30] Glaser and Wulwek,[5] and Aizawa,[29] but not with the melting point 150–

(25) Pigman and Isbell, *J. Research Natl. Bur. Standards*, **27**, 11 (1941).

(26) The α-pentaacetate, first prepared by the zinc chloride acetylation of glucose by Erwig and Koenigs [*Ber.*, **22**, 1464 (1889)], can be obtained just as readily as the better known β-pentaacetate.

(27) Whenever fused zinc chloride was used as the catalyst, it was dissolved in a mixture of acetic acid and acetic anhydride in these proportions.

(28) Helferich, Scheiber and Hiltmann, *Ber.*, **73**, 1300 (1940).

(29) Aizawa, *J. Biochem.* (Japan), **30**, 89 (1939).

(30) Goebel, Babers and Avery, *J. Exptl. Med.*, **55**, 761 (1932).

(31) Glaser and Wulwek, ref. 5; Goebel and Avery, *J. Exptl. Med.*, **50**, 520 (1929); Helferich and Peters, *J. prakt. Chem.*, [2] **138**, 281 (1933).

152° reported by Helferich and Peters.[31] The rotation in water was reported to be −99.2° by Glaser and Wulwek, −103° by Helferich and Peters and −98.7° (as the hydrate) by Aizawa.

Tetraacetyl-α-*o*-nitrophenyl-D-glucoside.—The synthesis of a mixture of isomers was accomplished by heating 30 g. of α-pentaacetylglucose with 48 g. of *o*-nitrophenol in the presence of 7 g. of zinc chloride[27] for one hour at 125°. The final product, a sirup, was dissolved in a mixture of benzene and petroleum ether; from this solution the α-form crystallized as glittering, practically colorless prisms. Wolf[32] has reported the isolation of a tetraacetyl-α-*o*-nitrophenyl-D-glucoside rotating +124° in chloroform and melting at 95°. We, however, observed the rotation of the purified substance to be +167° in chloroform (*c*, 2) and the melting point, 110°. The yield was 25%.

Anal. Calcd. for $C_{20}H_{23}O_{12}N$: C, 51.18; H, 4.94; N, 2.98. Found: C, 51.16; H, 5.06; N, 3.00.

α-*o*-Nitrophenyl-D-glucoside.—Catalytic deacetylation of the tetraacetate produced α-*o*-nitrophenyl-D-glucoside; crystallized from water as slender, practically colorless prisms, the anhydrous substance rotated +206° in water (*c*, 1), and melted at 186–188°. Reacetylation produced the same acetate described above.

Anal. Calcd. for $C_{12}H_{15}O_8N$: C. 47.84; H, 5.02; N. 4.65. Found: C, 47.92; H, 5.19; N, 4.73.

Tetraacetyl-β-*o*-nitrophenyl-D-glucoside.—The β-isomer crystallized from the mother liquor of the α-form as clusters of almost colorless plates. Purified tetraacetyl-β-*o*-nitrophenyl-D-glucoside rotated +45.0° in chloroform and melted at 150–152°. The rotation, which is lower than the value of +53.2° reported by Glaser and Wulwek,[33] and the melting point, which also is lower than that (158–159°) reported by Glaser and Wulwek, were confirmed by acetylating the crystalline glucoside.

After catalytic deacetylation of the tetraacetate, the **β-*o*-nitrophenyl-D-glucoside** crystallized from alcohol as rosets of needles. Glaser and Wulwek reported this glucoside as a monohydrate rotating −83.0° in water and melting at 132°. We, however, observed that the compound is stable in the anhydrous state, rotates −106.0° in water (*c*, 1) and melts at 152°.

Anal. Calcd. for $C_{12}H_{15}O_8N$: C, 47.84; H, 5.02; N, 4.65. Found: C, 47.90; H, 5.04; N, 4.79.

Tetraacetyl-β-*p*-acetylphenyl-D-glucoside (Tetraacetylpicein).—This tetraacetate, first synthesized by Mauthner,[34] was prepared in a 75% yield by the procedure of Glaser and Wulwek.[5] The rotation, not previously recorded, was −28.6° in chloroform (*c*, 2), and the melting point was 172–173°. Deacetylation produced the glucoside picein. When dried to constant weight *in vacuo* at 90°, the pure **picein** rotated −89.0° in water (*c*, 1) and melted at 194°, in agreement with the data in the literature.

Transformation of Tetraacetyl-α-methyl-D-glucoside to Tetraacetyl-α-phenyl-D-glucoside.—A solution of 35 g. of fused zinc chloride in 110 cc. of a 95:5 acetic acid–acetic anhydride mixture was added to a melt consisting of 35 g. of tetraacetyl-α-methylglucoside and 56 g. (6 molecular proportions) of phenol. This mixture was heated *in vacuo* for five hours in a bath at 120–125°, and the products isolated as described in the first preparation of tetraacetyl-α-phenylglucoside above. Pure tetraacetyl-α-phenylglucoside was obtained in a 55% yield, and pure tetraacetyl-β-phenylglucoside in a 15% yield.

Under similar conditions, tetraacetyl-α-methyl-D-mannoside was transformed to tetraacetyl-α-phenyl-D-mannoside in 60% yield, tetraacetyl-α-methyl-D-galactoside to tetraacetyl-α-phenyl-D-galactoside in 65% yield, and tetraacetyl-β-*p*-acetylphenyl-D-glucoside to tetraacetyl-β-phenyl-D-glucoside in 40% yield.

Under milder conditions with zinc chloride, or with *p*-toluenesulfonic acid as the catalyst, or with tetraacetyl-β-methylglucoside, the reaction products consisted of mixtures of the acetylated α- and β-methylglucosides and α- and β-phenylglucosides.

Triacetyl-β-phenyl-D-xyloside.—The synthesis of triacetyl-β-phenylxyloside, together with the α-isomer, was accomplished by condensing 50 g. of β-tetraacetyl-D-xylose with 50 g. of phenol in the presence of 0.85 g. of *p*-toluenesulfonic acid for forty-five minutes at 100° *in vacuo*. The final product was dissolved in 100 cc. of 95% alcohol, from which the β-isomer crystallized in a yield of 60%. The pure triacetyl-β-phenyl-D-xyloside rotated −50.5° in chloroform (*c*, 2) and melted at 148°, in agreement with the literature.[16]

Deacetylation of the tetraacetate produced **β-phenyl-D-xyloside;** crystallized from water as small prisms, the anhydrous substance rotated −49.4° in water (*c*, 1) or slightly higher than the value −47° reported by Helferich and Appel;[35] it melted at 179°.

α-Phenyl-D-xyloside.—The residual sirup from the crystallization of triacetyl-β-phenyl-D-xyloside was dried and deacetylated catalytically with barium methylate. The final product was dissolved in a small amount of water, the new xyloside crystallizing after an hour in clusters of needles. After several recrystallizations, the pure anhydrous α-phenyl-D-xyloside rotated +189° in water (*c*, 1) and melted at 145° when dried to constant weight at 70° *in vacuo*. The yield was 60%.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.34; H, 6.10.

Triacetyl-α-phenyl-D-xyloside.—Acetylation of the crystalline xyloside produced triacetyl-α-phenyl-D-xyloside which crystallized at 0° from a mixture of carbon tetrachloride and isopentane as shining plates melting at 64–65° and rotating +135° in chloroform (*c*, 2).

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.94; H, 5.72; acetyl, 8.52 cc. 0.1 *N* NaOH per 100 mg. Found: C, 57.92; H, 5.66; acetyl, 8.47 cc.

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Summary

1. The method of Helferich and Schmitz-Hille-

(32) Wolf, Dissertation, Hamburg, 1929, as reported by Tollens-Elsner, "Kurzes Handbuch der Kohlenhydrate," Verlag Johann Ambrosius Barth, Leipzig, fourth edition, 1935, p. 269.

(33) Glaser and Wulwek, ref. 5. The rotations reported had been calculated incorrectly: the values above have been recalculated from the data given by the original authors. *Cf.* Helferich and Peters, *J. prakt. Chem.*, [2] **138**, 283, footnote 1 (1933).

(34) Mauthner, *J. prakt. Chem.*, [2] **85**, 564 (1912); **88**, 764 (1913).

(35) Helferich and Appel, *Z. physiol. Chem.*, **205**, 237 (1932).

brecht for the preparation of acetylated α- and β-phenylglycosides has been improved.

2. A method has been described for the rearrangement of tetraacetyl-β-phenylglucoside to tetraacetyl-α-phenylglucoside.

3. A method has been described for the transformation of tetraacetyl-α-methylglucoside and other acetylated glycosides to the corresponding acetylated phenylglycosides.

4. α-Phenyl-D-xyloside, triacetyl-α-phenyl-D-xyloside and α-o-nitrophenyl-D-glucoside have been described. New data are reported for a number of other phenylglycosides.

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Tetrahydrocannabinol Homologs and Analogs with Marihuana Activity. XIII[1]

BY ROGER ADAMS, S. LOEWE, C. M. SMITH AND W. D. MCPHEE

The series of homologs of tetrahydrocannabinol (I), in which the 3-n-amyl group is replaced by other groups, has been found to exhibit a maximum activity in the n-hexyl compound.[2] The corresponding hexahydrocannabinol and its homologs have been prepared and the marihuana potencies determined. This series also exhibits a potency maximum in the 3-n-hexyl compound and with the exception of the n-hexyl and the n-butyl derivatives the potencies are all lower than those of the corresponding tetrahydro compounds. The potencies of the homologs of tetrahydrocannabinol and the activities of other products are shown in Table I to allow comparison. The high potencies of the optically active tetrahydrocannabinols obtained by isomerization of cannabidiol contrast strikingly with the very low potencies of crude hemp extracts.

TABLE I

BIOASSAY OF HOMOLOGS OF TETRAHYDROCANNABINOL AND OF HEXAHYDROCANNABINOL

3-n-Alkyl group Compound I	Potency: Tetrahydro	Potency: Hexahydro
Methyl	0.16 ± 0.03	
Propyl	.40 ± .30	0.26 ± 0.04
Butyl	.37 ± .12	.37 ± .06
Amyl	1.00 (standard)	.51 ± .08
Hexyl	1.82 ± .40	1.86 ± .37
Heptyl	1.05 ± .15	0.83 ± .13
Octyl	0.66 ± .13	.24 ± .06
Tetrahydrocannabinol $[\alpha]^{27}D$	Parke, Davis and Company Fluid Extract	0.060
−265° 7.3 ± 0.89	American Fluid Extracts	
−260° 7.8 ± .78	thirty to forty different	
−240° 7.6 ± 1.1	samples varied in potency	.003–0.130
−165° 9.3 ± 2.9		
−160° 8.23 ± 2.17		
−126° 6.5 ± 0.65	Majority varied	.019– .052
Hexahydrocannabinol	Purified red oil	1.24
−70° 3.0 ± 0.43	Highly purified red oil (Matchett)	4.33

Todd and co-workers[2b] have just published a description of the synthesis and physiological action by the Gayer test of a series of homologs of tetrahydrocannabinol (I) with the amyl group replaced by various alkyl groups. Many of this series had been synthesized previously by us and the marihuana action determined by the dog-ataxia test.[2a] The difference between the ratio of our tests and those of Todd is large. In this connection reference may be made to the extensive results of Loewe described briefly in the Harvey Lecture (February 19, 1942). He has demonstrated that even when applying the "Bioassay by Approximation" procedure with the Gayer test, the intra-individual and inter-individual variations in sensitivity of rabbits is enormous, so that the values of potency by this method are not suitable for anything but qualitative purposes. The Gayer potencies do not parallel the dog-ataxia potencies of the same preparations. On the other hand, the relative potencies of the various products as determined by the dog-ataxia tests parallel to a surprising degree the potencies observed in human subjects. The relative doses of several of the compounds eliciting a similar action in individual dogs elicited the equivalent degree of response in humans. The equated doses administered to the same individual human gave the same intensity of effect, and this result was observed in a large number of subjects.

An attempt has been made in this Laboratory[3] and by Ghosh, Todd and Wright[4] to synthesize an optically active isomer of the tetrahydrocannabinol from cannabidiol by condensing pulegone and olivetol. An optically active resin closely resembling the desired tetrahydrocannabinol in physical properties was obtained. The product obviously was not pure since its absorption spectrum exhibited two peaks in contrast to the one peak of the tetrahydrocannabinol from cannabidiol. The height of the identical peak was only six-tenths that for the pure compound. The initial measurement of the potency of this material made with a few dogs was reported as 1.04 ± 0.37, but further investigation has resulted in a value of 0.58 ± 0.12. It is interesting to note that the ratio of the potencies of the tetrahydrocannabinols made by the two methods parallels the ratio of the heights of the comparable absorption peaks.

A tentative mechanism for the formation of a tetrahydrocannabinol structure (I) has been ad-

(1) For previous paper see Adams, Cain, McPhee and Wearn, THIS JOURNAL, **63**, 2209 (1941).

(2) (a) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941); (b) see also Russell, Todd, Wilkinson, MacDonald and Woolfe, *J. Chem. Soc.*, 826 (1941).

(3) Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

(4) Ghosh, Todd and Wright, *J. Chem. Soc.*, 137 (1941).