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The α- and β-D-Xylofuranose Tetrabenzoates and Certain Other Derivatives of D-Xylose

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An indirect method of benzoylating D-xylose, avoiding the isolation of intermediates, has been devised to obtain the two anomeric D-xylofuranose tetrabenzoates. Direct benzoylation of D-xylose in pyridine at an elevated temperature gives the same two tetrabenzoates though in low yield. Reduction of amorphous 2,3,5-tribenzoyl-D-xylose gives crystalline 2,3,5-tribenzoyl-D-xylitol. The previously known 2,3,4-tribenzoyl-α-D-xylose has been re-examined.

In a number of recent researches in this Laboratory[1-7] advantage has been taken of the superior stability of the benzoic acid esters of the sugars to carry out a variety of transformations which are relatively difficult or even impossible when the acetates of the sugars are employed. Not only the stability but also the low solubility and good crystallizing tendencies of the benzoates recommend them especially for studies of the furanose forms of the sugars. As part of a program of research on the synthesis of pentofuranosides a study of the preparation of the anomeric D-xylofuranose tetrabenzoates was undertaken and this will now be described.

While several indirect paths to the D-xylofuranose tetrabenzoates may be envisioned[8] the object of the present work was to develop a convenient synthesis which avoided, as far as possible, the isolation of intermediates. For this purpose D-xylose was converted by standing in 1% methanolic hydrogen chloride solution for seven days into a mixture rich in methyl D-xylofuranoside.[9] The acid was then neutralized with pyridine and the product, consisting of methyl D-xylofuranoside, methyl D-xylopyranoside and unchanged D-xylose, was benzoylated. The amorphous mixture of benzoates thus obtained was converted with hydrogen bromide into a mixture of tribenzoyl-D-xylofuranosyl bromide and tribenzoyl-D-xylopyranosyl bromide and these halides were then hydrolyzed to a mixture from which the pyranose components were largely removed as crystalline 2,3,4-tribenzoyl-α-D-xylose.[10] The residual, crude, amorphous 2,-3,5-tribenzoyl-D-xylose was then benzoylated to give, first, a pentose tetrabenzoate melting at 165–166°[11] and rotating in chloroform $[\alpha]^{20}D$ +170° and, second, another pentose tetrabenzoate melting at 111–112° and rotating in chloroform $[\alpha]^{20}D$ +11.4°. The former substance was obtained in 23% yield, the latter in 9.7% yield.

The identity of these two pentose tetrabenzoates as D-xylofuranose derivatives was established as follows. Each was converted to the amorphous bromide which was hydrolyzed to an amorphous halogen-free product; this in turn afforded on hydrogenation an optically active tribenzoylpentitol which, on further benzoylation, afforded xylitol pentabenzoate. Since a xylopyranose tetrabenzoate would be expected to give 2,3,4-tribenzoylxylitol, a *meso* substance, this evidence indicates that the two new pentose tetrabenzoates are D-xylose derivatives and do not have pyranose rings. Since ring systems smaller than furanose are unlikely it is concluded that the substances are D-xylofuranose tetrabenzoates. On the basis of optical rotations the more dextrorotatory isomer may be called α-D-xylofuranose tetrabenzoate and the less dextrorotatory isomer β-D-xylofuranose tetrabenzoate. From Table I it will be seen that the difference between the molecular rotations of the two new D-xylofuranose tetrabenzoates is not very different from that of the analogous pair of pentabenzoates in the D-glucofuranose series.

TABLE I

ALDOFURANOSE BENZOATES

	$[\alpha]^{20}D$(CHCl₃)	$[M]^{20}D$	Difference
α-D-Glucofuranose pentabenzoate	+79°[a]	+55,400	96,100
β-D-Glucofuranose pentabenzoate	−58°[b]	−40,700	
α-D-Xylofuranose tetrabenzoate	+170°	+96,400	89,940
β-D-Xylofuranose tetrabenzoate	+11.4°	+6,460	

[a] H. H. Schlubach and W. Huntenburg, *Ber.*, **60**, 1487 (1927). [b] P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928).

Some years ago Schlubach and Prochownick[12] found that acetylation of D-galactose in pyridine solution at an elevated temperature gave practical yields of β-D-galactofuranose pentaacetate. More recently Zinner[13] has similarly acetylated D-ribose to make D-ribofuranose tetraacetate. In the course of the present work D-xylose was benzoylated in pyridine solution at 100°. However, only 3.3% of α-D-xylofuranose tetrabenzoate and a trace of its β-isomer could be isolated, the main product, β-D-xylopyranose tetrabenzoate, being obtained in 62% yield. It would appear, therefore, that the equilibrium mixture obtained from D-xylose in warm pyri-

(1) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **70**, 4055 (1948).

(2) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 2200 (1950).

(3) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4173 (1950).

(4) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 296 (1951).

(5) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 959 (1951).

(6) H. G. Fletcher, Jr., R. K. Ness and C. S. Hudson, *ibid.*, **73**, 3698 (1951).

(7) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **74**, 5344 (1952).

(8) For example through 5-trityl-D-xylose as was done by P. Chang and B. Lythgoe [*J. Chem. Soc.*, 1992 (1950)] in the synthesis of amorphous D-xylofuranose tetraacetate.

(9) W. N. Haworth and G. C. Westgarth, *ibid.*, 880 (1926).

(10) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2333 (1936).

(11) Melting points cited are corrected. Rotations are specific rotations for the D-line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

(12) H. H. Schlubach and V. Prochownick, *Ber.*, **63**, 2298 (1930); see also R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **73**, 3742 (1951).

(13) H. Zinner, *Ber.*, **83**, 153 (1950).

dine contains a smaller proportion of the furanose forms than is the case with D-galactose or D-ribose.

2,3,4-Tribenzoyl-α-D-xylose, first reported by Major and Cook,[10] has been re-examined. Its structure was confirmed by its benzoylation to a mixture of α- and β-D-xylopyranose tetrabenzoates as well as by its ready conversion to the known crystalline tribenzoyl-α-D-xylopyranosyl bromide.[10,14] Under conditions which gave smooth reduction of 2,3,5-tribenzoyl-D-xylose, the 2,3,4-isomer was wholly unchanged—another example of the inferior reactivity of pyranose as compared with furanose derivatives. Under more vigorous conditions the 2,3,4-tribenzoyl-D-xylose was successfully reduced to a sirup which on benzoylation did not give the readily crystalline xylitol pentabenzoate and on tritylation also failed to give the crystalline 2,3,4-tribenzoyl-1,5-ditritylxylitol of Anno.[15] However, deacylation of the reduced material gave crystalline xylitol in good yield and it may be that some or all of the aromatic nuclei in the 2,3,4-tribenzoyl-D-xylose had been reduced.

While Major and Cook[10] made no mention of the mutarotation of 2,3,4-tribenzoyl-α-D-xylose, all our samples mutarotated in a downward direction and therefore represented, at least predominantly, the α-isomer. An interesting confirmation of this fact was obtained through a polarimetric study of the reaction of tribenzoyl-α-D-xylopyranosyl bromide with aqueous dioxane in the absence of an acid acceptor. As may be seen from Fig. 1, the observed rotation dropped rapidly, passed through a minimum and then rose to a constant value. This behavior is interpreted as indicating that the α-D-halide was initially converted to 2,3,4-tribenzoyl-β-D-xylose which then came to equilibrium with its more dextrorotatory anomer. The final, constant rotation is identical with that calculated on the basis of complete conversion of the halide to an equilibrium mixture of the two anomeric forms of 2,3,4-tribenzoyl-D-xylose.

An investigation in the D-ribose series parallel to that reported here will be the subject of a future paper.

Experimental

The α- and β-D-Xylofuranose Tetrabenzoates. (a) From D-Xylose *via* Methyl D-Xylofuranoside.—Pure, finely powdered D-xylose (99.0 g.) was shaken with 2500 ml. of absolute methanol 0.216 *N* (1%) in HCl until solution was complete. After 7 days at room temperature (*ca.* 27°) the acid was neutralized with 100 ml. of pyridine[16] and the solution concentrated *in vacuo* at 50° to a stiff sirup which was dissolved in 1 l. of pyridine. To the cooled solution there was added 400 ml. of benzoyl chloride and after 15 hours at room temperature the reaction mixture was poured on ice. The product was extracted with chloroform and the extract washed successively with cold 3 *N* sulfuric acid and aqueous sodium bicarbonate. Moisture was removed with sodium sulfate and the solution, after filtration through decolorizing carbon, concentrated *in vacuo* to a thin sirup which was treated with 620 ml. of a glacial acetic acid solution of hydrogen bromide (*ca.* 32% HBr). After 1 hour at room temperature the mixture was diluted with 1 l. of methylene dichloride and washed, first with water and then with aqueous sodium bicarbonate and finally with water.[17] Acetone (1800 ml.), water (50 ml.) and silver carbonate (100 g.) were then added and the mixture stirred vigorously for 0.5 hour. After filtration through decolorizing carbon and concentration *in vacuo* to a thin sirup the product was dissolved in a mixture of 515 ml. of carbon tetrachloride and 280 ml. of pentane, seeded with 2,3,4-tribenzoyl-α-D-xylopyranose, and left at room temperature for 2 days. When the crude 2,3,4-tribenzoyl-α-D-xylose (54.5 g., m.p. 175–180°) had been removed the pale yellow solution was concentrated *in vacuo* to a sirup which was cooled and treated with a mixture of 500 ml. of pyridine and 140 ml. of benzoyl chloride.[18] After several hours at room temperature the reaction mixture was diluted with 500 ml. of methylene dichloride and washed successively with cold water, cold 3 *N* sulfuric acid and saturated aqueous sodium bicarbonate. Moisture was removed with sodium sulfate, the solution filtered through carbon, and concentrated *in vacuo* at 50° to a sirup. After dilution with 250 ml. of alcohol the solution was reconcentrated *in vacuo*, crystallization spontaneously taking place at this stage. The mass was dissolved in 400 ml. of boiling methyl ethyl ketone, treated with 1 l. of absolute alcohol and left at 0° to give 86.8 g. (23%) of crude α-D-xylofuranose tetrabenzoate melting at 160–162° and rotating +163.9° in chloroform. Recrystallized twice from 4–7 parts of methyl ethyl ketone and once from 7.5 parts of ethyl acetate the α-D-xylofuranose tetrabenzoate was obtained as fine, flexible needles melting at 165–166° and rotating +170° in chloroform (*c* 0.83). Further recrystallization failed to change these constants. The compound may also be recrystallized from ethylene dichloride or glacial acetic acid.

Anal.[19] Calcd. for $C_{33}H_{26}O_9$: C, 69.96; H, 4.63. Found: C, 69.78; H, 4.66.

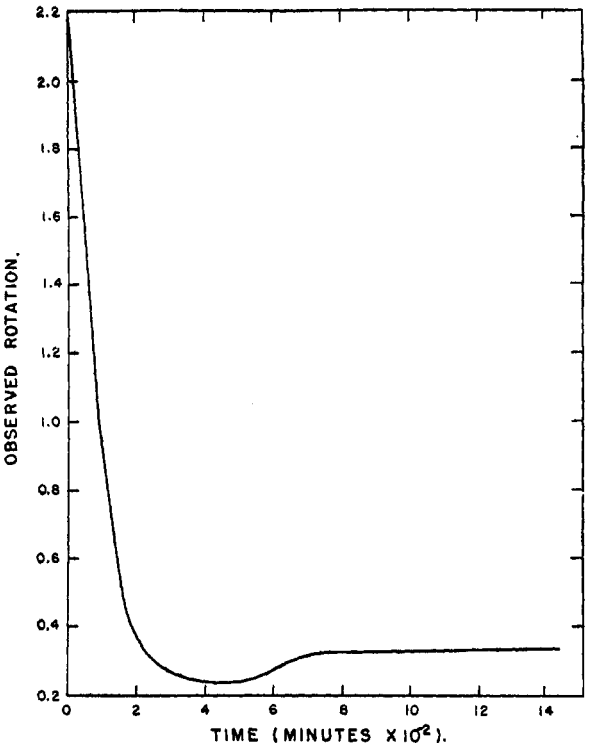

Fig. 1.—Reaction of tribenzoyl-α-D-xylopyranosyl bromide with 18:7 dioxane–water (v./v.) at 20°.

(14) H. G. Fletcher, Jr., and C. S. Hudson, THIS JOURNAL, **69**, 921 (1947).

(15) K. Anno, *J. Agr. Chem. Soc. Japan*, **23**, 441 (1950); *C. A.*, **46**, 3495 (1952). This author reported a melting point of 197–198° for the substance; we found the pure substance to melt at 202–203°.

(16) Pyridine proved the most convenient agent for the removal of acidity. In various runs silver carbonate, sodium bicarbonate as well as passage through a column (5.5 × 90 cm.) of Duolite A-4 were each found to be equally effective.

(17) Doubtless part of the tribenzoyl-D-xylofuranosyl bromide present is hydrolyzed during the course of these washings.

(18) When the crude, sirupy 2,3,5-tribenzoyl-D-xylose is dissolved in pyridine alone the mixture darkens rapidly; addition of the pyridine mixed with the benzoyl chloride avoids this darkening.

(19) Analytical determinations were performed by the Institute's Microanalytical Laboratory under the direction of Dr. William C. Alford.

The mother liquor from which the crude α-D-xylofuranose tetrabenzoate had been removed was concentrated *in vacuo* to a volume of *ca.* 300 ml., seeded with β-D-xylofuranose tetrabenzoate,[20] and left at +5°. The brown, sticky mass thus obtained was recrystallized from 800 ml. of ethanol to give 36.1 g. (9.7%) of crude β-D-xylofuranose tetrabenzoate melting at 104–*ca.* 150° and rotating +25.2° in chloroform. Repeated recrystallization from one part of acetone afforded the β-D-xylofuranose tetrabenzoate as square plates containing one mole of acetone of crystallization, melting at 69–70° and rotating +10.1° in chloroform (*c* 0.94).

Anal. Calcd. for $C_{33}H_{26}O_9 \cdot C_3H_6O$: C, 69.22; H, 5.16; C_3H_6O, 9.30. Found: C, 69.13; H, 5.22; loss of wt. *in vacuo* at 77°, 8.5.

At room temperature the substance rapidly loses acetone; recrystallized from 20–40 parts of methanol the β-D-xylofuranose tetrabenzoate was obtained in solvent-free form as clusters of stubby prisms melting at 111–112° and showing +11.4° in chloroform (*c* 0.87).

Anal. Calcd. for $C_{33}H_{26}O_9$: C, 69.96; H, 4.63. Found: C, 69.87; H, 4.66.

(b) **From Benzoylation of D-Xylose at 100°.**—Fifty grams of D-xylose was dissolved in 500 ml. of pyridine and the solution warmed to 100°. Benzoyl chloride (190 ml.) was then added at such a rate that, without external heating, the temperature of the mixture was maintained at 100–105°. Excess of benzoyl chloride in the cooled reaction mixture was decomposed by the addition of several small fragments of ice. Ethylene dichloride (500 ml.) was then added and the solution washed successively with water, cold 3 *N* sulfuric acid and aqueous sodium bicarbonate. Moisture was removed with sodium sulfate, the solution filtered through decolorizing carbon and concentrated *in vacuo* at 50° to a thin sirup which, diluted with 175 ml. of absolute ethanol and held at +5°, afforded 116.7 g. (62%) of crystalline material melting at 162–163° and rotating −40.0° in chloroform. Recrystallized from 2 l. of absolute ethanol, this fraction rotated −43.3° in chloroform (*c* 0.98) and melted at 165–166°. Mixture with authentic β-D-xylopyranose tetrabenzoate did not depress this melting point.[21]

The original mother liquor, concentrated *in vacuo* to a heavy sirup, diluted with 200 ml. of absolute ethanol and left at room temperature, deposited 6.3 g. (3.3%) of crude material melting at 152–155° and rotating +142° ($CHCl_3$). Successive recrystallizations of this second fraction from 130 parts of absolute alcohol, 20 parts of acetone and 6 parts of methyl ethyl ketone gave 3.4 g. of material rotating +170° in chloroform (*c* 0.83) and melting at 165–166° either alone or in admixture with the α-D-xylofuranose tetrabenzoate obtained as in (a) above.

The original mother liquor was again concentrated *in vacuo* to a sirup which was extracted with 800 ml. of hot methanol. On cooling, the extract was decanted from a gum and left at +5° to give a third, crystalline fraction of 10.7 g. which rotated +120° in chloroform. The main mother liquor, concentrated *in vacuo* to a sirup and dissolved in *ca.* 500 ml. of absolute alcohol, gave, on standing at +5°, a fourth fraction (5.0 g.) melting at 95–103°. Recrystallized from 15 parts of absolute ethanol this product rotated +25.5° in chloroform. Three further recrystallizations from alcohol brought the rotation in chloroform to +17.0°. Successive crystallizations from acetone and from acetone–pentane afforded material (0.8 g.) which, freed of acetone, rotated +12.9° (*c* 0.80, $CHCl_3$) and melted at 98–105°. A sample of authentic β-D-xylofuranose tetrabenzoate similarly freed of acetone of crystallization failed to depress this melting point.

β-D-Xylofuranose Tetrabenzoate from α-D-Xylofuranose Tetrabenzoate *via* Amorphous 2,3,5-Tribenzoyl-D-xylose.—Thirty grams of pure α-D-xylofuranose tetrabenzoate was dissolved in 60 ml. of warm methylene dichloride and the cooled solution treated with 150 ml. of hydrogen bromide in glacial acetic acid (32% HBr). After 0.5 hour at room temperature the mixture was diluted with 75 ml. of methylene dichloride and washed successively with cold water, aqueous sodium bicarbonate and water. The moist solution was then poured into a mixture of 300 ml. of acetone, 3 ml. of water and 30 g. of silver carbonate. After the reaction mixture had been agitated vigorously for 0.5 hour it was filtered through a bed of decolorizing carbon and the filtrate concentrated *in vacuo* to a stiff sirup. Numerous attempts to obtain this crude 2,3,5-tribenzoyl-D-xylose in crystalline form failed. It was treated with a mixture of 100 ml. of pyridine and 15 ml. of benzoyl chloride and worked up in a manner similar to that described under (a) above. From 600 ml. of absolute ethanol there was obtained 18.72 g. (63%) of crude α-D-xylofuranose tetrabenzoate melting at 162–164°; on standing the mother liquor deposited 8.33 g. (28%) of crude β-D-xylofuranose tetrabenzoate melting at 105–111° and rotating +17.9° in chloroform. Successive recrystallizations from 1 part of acetone, 16 parts of methanol and from 1 part of acetone yielded the β-D-xylofuranose tetrabenzoate as its acetone addition compound rotating +10.6° in chloroform (*c* 2.2).

2,3,5-Tribenzoyl-D-xylitol. (a) **From α-D-Xylofuranose Tetrabenzoate.**—Five grams of sirupy 2,3,5-tribenzoyl-D-xylose, prepared from α-D-xylofuranose tetrabenzoate as described above, was dissolved in 30 ml. of absolute ethanol, *ca.* 2 g. of Raney nickel added, and the suspension agitated under 2200 p.s.i. of hydrogen at room temperature for 3 days. The crystalline mass which resulted was dissolved in *ca.* 100 ml. of methylene dichloride, the nickel removed by filtration and the solution concentrated *in vacuo* at 40° to a dry, crystalline residue. From its solution in 16 ml. of absolute alcohol there was obtained in two crops 4.06 g. (81%) of crude 2,3,5-tribenzoyl-D-xylitol melting at 128–137°. Recrystallization from a mixture of 6 parts of alcohol and 3 parts of water and then from 8 parts of *n*-butanol gave fine needles melting at 141–142° and rotating −8.5° in chloroform (*c* 2.0).

Anal. Calcd. for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21. Found: C, 67.09; H, 5.34.

(b) **From β-D-Xylofuranose Tetrabenzoate.**—Ten grams of pure β-D-xylofuranose tetrabenzoate was converted into amorphous 2,3,5-tribenzoyl-D-xylose and this in turn reduced as described in the section immediately above. There was obtained 5.50 g. (67%) of product melting at 140° and rotating −7.0° in chloroform. Three recrystallizations from a mixture of 6 parts of alcohol and 3 parts of water afforded pure 2,3,5-tribenzoyl-D-xylitol rotating −8.5° in chloroform (*c* 2.4) and melting at 142–143° either alone or in admixture with the product obtained from α-D-xylofuranose tetrabenzoate.

Xylitol Pentabenzoate from 2,3,5-Tribenzoyl-D-xylitol.—2,3,5-Tribenzoyl-D-xylitol (0.50 g.) was benzoylated with benzoyl chloride and pyridine in the usual manner to give (from 4 ml. of ethanol) 0.70 g. (97%) of crystalline product melting at 107–108° either alone or in admixture with authentic xylitol pentabenzoate prepared from xylitol. Further recrystallization from alcohol or ether–pentane failed to change this melting point. Anno[15] reported a melting point of 105–106° for pentabenzoylxylitol.

2,3,4-Tribenzoyl-α-D-xylose.—The following modification of the method of Major and Cook[10] was employed. Ten grams of tribenzoyl-α-D-xylopyranosyl bromide[14] was dissolved in 50 ml. of acetone, the solution cooled to 0° and 0.8 ml. of water and 6 g. of silver carbonate added. The reaction mixture was agitated vigorously at room temperature for 1.5 hours and then filtered through a layer of decolorizing carbon. Removal of solvent *in vacuo* at 40° gave a dry, crystalline mass which, dissolved in 55 ml. of warm benzene, deposited a fine powder (7.96 g., 91%) melting at 184–185°. From 9.4 parts of absolute ethanol the 2,3,4-tribenzoyl-α-D-xylose crystallized slowly as fluffy needles; from alcohol containing a trace of ammonia or from a mixture of 13 parts of alcohol and 6.7 parts of water crystallization was considerably more rapid. The melting point of the pure compound varied with the rate of heating; in Pyrex capillaries values between 184 and 187° were obtained. On a soft glass surface (Kofler hot stage) a lower value (180–182°) was obtained. Major and Cook[10] reported a melting point of 188–189° in a Pyrex capillary tube and a rotation of +39.5° in dry chloroform for 2,3,4-tribenzoyl-α-D-xylose. In the

(20) Seed crystals of β-D-xylofuranose tetrabenzoate were first obtained through chromatography of (a) the product from the benzoylation of amorphous 2,3,5-tribenzoyl-D-xylose and (b) the product formed by the action of silver benzoate on a solution of tribenzoyl-D-xylofuranosyl bromide.

(21) In an earlier paper (ref. 14) β-D-xylopyranose tetrabenzoate was reported to have a rotation of −42.1° in chloroform and a double melting point of 173°, 177°. Samples of the compound prepared since that time uniformly melt at 166–167° and the higher, double melting point has not been observed.

present research the substance was found to mutarotate slowly in U. S. P. chloroform although not appreciably in dry (*i.e.*, alcohol-free) chloroform, the initial rotation varying with different samples. For this reason, the equilibrium rotation of the compound in 18:7 dioxane–water was found to be the most convenient physical constant. At a concentration of approximately 4 in this solvent mixture initial specific rotations ranging from +32.0 to +35.4° were obtained. When a drop of aqueous ammonia or of 6 *N* hydrochloric acid was added the rotation fell rapidly to a constant value of +23.4°. Several crystallizations from aqueous alcohol of the nearly pure product initially obtained gave material showing the above equilibrium rotation; further recrystallizations failed to change this value.

The Rate of Reaction of Tribenzoyl-α-D-xylopyranosyl Bromide with 18:7 Dioxane–Water (v./v.) at 20°.—Tribenzoyl-α-D-xylofuranosyl bromide (0.2820 g.) was dissolved in 18.0 ml. of dioxane and the solution made up to a volume of 25.0 ml. with water. Data obtained by polarimetric observation of the solution at 20° in a 1.5-dm. tube are plotted in Fig. 1. The observed rotation was constant at +0.35° after 2 days.

Catalytic Reduction of 2,3,4-Tribenzoyl-α-D-xylose.—Attempts to reduce 2,3,4-tribenzoyl-α-D-xylose at room temperature and under 2200 p.s.i. of hydrogen either with platinum black suspended in methanol or Raney nickel in 1:1 dioxane–alcohol failed. Five grams of 2,3,4-tribenzoyl-D-xylose with *ca.* 0.5 g. of Raney nickel was suspended in absolute alcohol (total volume 25 ml.) and agitated at 118° for 50 minutes under 2200 p.s.i. of hydrogen. The clear, colorless solution from which the catalyst had been removed showed a specific rotation of +2.09°, probably indicating that the reaction was incomplete; a Fehling test, however, appeared to be negative. A sample of the sirup which was obtained on removal of solvent was benzoylated with benzoyl chloride and pyridine in the usual manner to give a product which remained amorphous even when seeded with authentic xylitol pentabenzoate. This amorphous material was returned to the main batch and the whole debenzoylated with methanolic barium methoxide in the usual fashion. From alcohol the product crystallized as clear prisms (1.06 g., 64%) melting at 94–96° either alone or in admixture with authentic xylitol. Benzoylation of 0.5 g. of the product afforded 1.97 g. (90%) of crystalline material melting at 106–108°; a mixed melting point with authentic xylitol pentabenzoate was undepressed.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. XXI.[1] Amides of Vanillic and 3-Ethoxy-4-hydroxybenzoic Acids[2,3]

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N-Substituted amides of vanillic acid and 3-ethoxy-4-hydroxybenzoic acid were prepared by condensing the O-carbethoxy chlorides of these acids with the appropriate amines and selectively hydrolyzing the O-carbethoxy group of the resulting O-carbethoxyamides. The compounds were tested for activity against *Bacillus mycoides* and a large number of pathogenic bacteria and fungi. In general, the activity was poor and, unlike the esters of these acids, the substituted amides of vanillic acid exhibited greater activity than did the corresponding amides of 3-ethoxy-4-hydroxybenzoic acid.

During the past several years esters of vanillic acid have been employed in the treatment of systemic fungus diseases.[4,5] Effective therapeutic levels could be obtained only by massive oral doses and thus the margin between therapeutic doses and those which produced toxic manifestations was not as large as desired. Because the necessary massive oral doses were due presumably to the fact that the esters of vanillic acid hydrolyzed relatively rapidly in the body and because it was known that the amide linkage is more stable toward hydrolysis in the body than is the ester linkage, it was thought that substituted amides of vanillic acid might possess more prolonged antifungal or antibacterial activity when administered systemically. Accordingly, a number of N-substituted amides of vanillic acid and the closely related 3-ethoxy-4-hydroxybenzoic acid were prepared and tested for their antibacterial and antifungal activity.

A number of years ago, during the preparation of certain esters of vanillic acid by the use of carbethoxy intermediates,[6] three amides of vanillic acid—namely, vanillamide, N-phenylvanillamide and N-2-pyridinovanillamide—were prepared by treating carbethoxyvanilloyl chloride with the desired amine and partially hydrolyzing the carbethoxyvanillamide thus obtained. Ritter[7] prepared vanillamide by pyrolysis of butyl vanillimidate hydrochloride and Kratzl and Kvasnicka[8] prepared several N-substituted amides of vanillic acid through either their carbethoxy or acetyl intermediates. The N-substituted vanillamides and 3-ethoxy-4-hydroxybenzamides of this paper were prepared *via* their O-carbethoxy intermediates.

The N-substituted-O-carbethoxyvanillamides and O-carbethoxy-3-ethoxy-4-hydroxybenzamides were prepared by treating the desired amine with the O-carbethoxyacid chloride in a boiling mixture of pyridine and ether or in ether solution at room temperature or below depending upon the volatility of the amine. The carbethoxy intermediates were converted to their respective vanillamides or 3-ethoxy-4-hydroxybenzamides by selective hydrolysis of the carbethoxy group in *N* sodium hydroxide or methanol and sodium hydroxide at room temperature.

(1) For paper XX of this series, see THIS JOURNAL, **74**, 4593 (1952).

(2) Presented before the Division of Medicinal Chemistry at the 123rd Meeting of the American Chemical Society, Los Angeles, California, March 15–19, 1953.

(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) A. Christie, J. G. Middleton, J. C. Peterson and D. L. McVicker, *Pediatrics*, **7**, 7 (1951).

(5) R. Cohen, *Arch. Pediat.*, **68**, 259 (1951).

(6) I. A. Pearl and J. F. McCoy, THIS JOURNAL, **69**, 3071 (1947).

(7) D. M. Ritter, *ibid.*, **68**, 2738 (1946).

(8) K. Kratzl and E. Kvasnicka, *Monatsh.*, **83**, 18 (1952).