Summary

1. Diisobutyrylmethane has been added to trimethylquinone, and the resulting product has been cyclized to 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumarone VII.

2. The coumarone has been reduced to the corresponding coumaran (III), which is the only representative known of its class—a *p*-hydroxy-2-alkylcoumaran having a secondary alkyl group in the 2-position.

3. This coumaran has been oxidized by two methods to the corresponding yellow *p*-benzoquinone XVII.

4. The yellow quinone XVII, when reduced either in a neutral or slightly acid medium, gives a quantitative yield of the coumaran III and no intermediate hydroquinone can be isolated. None of the isomeric chroman IV is obtained. These results show that the cyclodehydration of a hydroquinone ortho substituted by a side chain containing a secondary alkyl group and a hydroxyl group in the β-position involves direct elimination of water between the two hydroxyl groups and does not involve a preliminary dehydration of the side chain. Moreover, cyclization of this substituted hydroquinone occurs with such great ease that the hydroquinones cannot be isolated when the quinone is reduced.

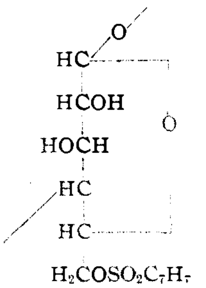
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 16, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 277]

The Formation of Anhydro Structures by the Alkaline De-acylation of a Partly Substituted Cellulose Acetate *p*-Toluenesulfonate

BY THOMAS S. GARDNER[1] AND C. B. PURVES

Earlier investigations[2,3] showed that a technical, acetone-soluble cellulose acetate, of average substitution 2.44, contained 0.362 mole of unesterified hydroxyl groups distributed in the second and third positions of the glucose residues. The remaining 0.198 mole was assigned to the primary alcohol or sixth position because the corresponding *p*-toluenesulfonyl ester (tosyl ester) was unstable to sodium iodide in hot acetonylacetone. Since the rates at which alcoholic groups in the second, third and sixth positions reacted with tosyl chloride in pyridine were in the approximate ratio of 22 : 1 : 230,[3] an interruption of the esterification at a suitable stage produced an acetate in which almost all of the unacetylated sixth, a few of the unacetylated second and practically none of the unacetylated third positions were tosylated. The tosylated glucose residues in such a mixed ester therefore occurred mainly, but not exclusively, as the structures I and III, from which the acetyl substituents were omitted for the sake of clarity.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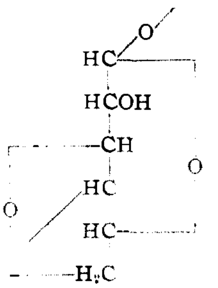
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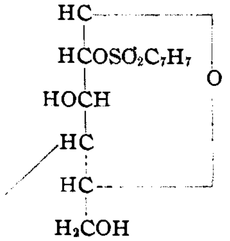
III

Peat[4] and Isbell[5] carefully reviewed the behavior of partly tosylated hexose derivatives in the presence of various reagents and analogy with the work in that field suggested that structure I would produce the 3,6-anhydro unit II when deacylated with a methanol solution of sodium methylate. The removal of the tosyl group from III by the same reagent would bring about a Walden inversion on carbon atom two and the transitory formation of the 2,3-anhydromannose derivative IV. The immediate addition of sodium methylate to the ethylene oxide ring of IV would proceed with a Walden inversion, either at the second or at the third carbon atom, and the final result would be a mixture of 2-methylglucose V and 3-methyl-

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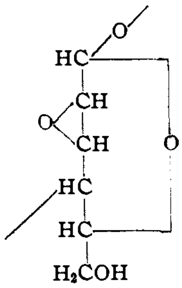
[1] DuPont Post-Doctoral Research Fellow, 1941–1942; Present address: Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) Cramer and Purves, THIS JOURNAL, **61**, 3458 (1939).

(3) Gardner and Purves, *ibid.*, **64**, 1539 (1942).

(4) Peat, *Chem. Soc. Ann. Reports*, **36**, 258 (1939).

(5) Isbell, *Ann. Rev. Biochem.*, **9**, 65 (1940).



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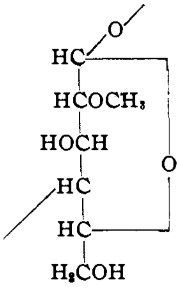

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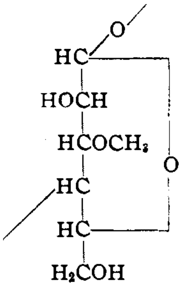
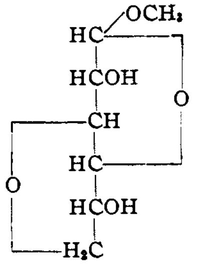


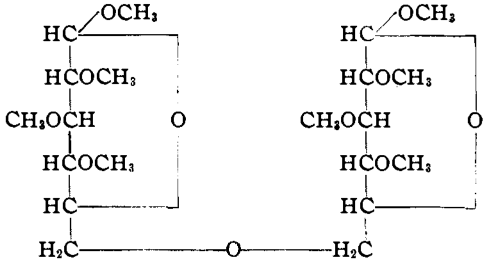
VI

altrose VI units. It was also to be expected that the presence of structure II in a cellulose would render the corresponding glycosidic link as susceptible to acid hydrolysis as those in 3,6-anhydroglucopyranosides,[6] or in furanosides.[7,8]

If the course just postulated for the alkaline deacylation of a tosyl ester of cellulose is correct, then the methanolysis of the resulting anhydrocellulose should yield some methyl 3,6-anhydro-gluco-pyranoside or -furanoside VII. The following experiments show that this was the case, but that the anhydroglucoside was accompanied by an anhydrodihexose that had resisted cleavage during the methanolysis. This substance was isolated as a fully methylated derivative whose hexose units were assumed to be united through an anhydro bond of the very stable ether type illustrated in VIII. It therefore appeared probable that anhydride formation during the detosylation occurred to some extent between *different* glucose residues in the cellulose and resulted in condensed units exemplified by IX.



VII



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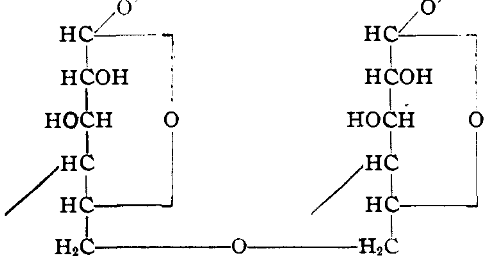

IX

Experimental

The capital letters assigned to the various derivatives refer to the analyses summarized in Table I.

The mixed ester (A) was prepared in 96.4% yield by partly tosylating 80 g. of acetone-soluble cellulose acetate[9] exactly as previously described.[2,3] A sample of the mixed ester, when thoroughly iodinated, gave a 92.5% yield of the derivative (B) whose analysis determined the distribution of tosyl between primary and secondary alcoholic positions in (A).

Preparation of an Anhydrocellulose (D).—A 55 g. sample (0.181 basic mole) of the partially tosylated acetate (A) was dissolved in 500 cc. of purified, peroxide-free dioxane. The addition of 520 cc. of 1.01 *N* sodium hydroxide (0.525 mole) in methanol at room temperature caused a rapid deacetylation and the precipitation of the partly de-esterified material. The mixture was occasionally shaken and was kept in a glass-stoppered flask to protect it as much as possible from degradation by atmospheric oxidation. Aliquots of the supernatant liquor were titrated at intervals with standard acid and the rate of consumption of alkali became slow within three days. After six days at room temperature, when the theoretical amount of 0.487 mole of the base had been utilized, the swollen, gelatinous precipitate was recovered and was repeatedly steeped, first in water–pyridine mixtures and then in water, until quite free from alkali. The product gradually assumed a hard, white, granular state during these operations, and weighed 30 g., or 103%, after drying at 60° over phosphorus pentoxide *in vacuo*.

When a 1.2-g. sample of this anhydrocellulose (D) was heated on the steam-bath with 100 cc. of 0.01 *N* hydrochloric acid, the supernatant liquor had optical dextrorotations, observed in a 2-dm. tube,[10] of 0.10, 0.19, 0.19 and 0.18° after one, three, six and thirteen hours, respectively. The hydrolysis was therefore complete within three hours, from which it followed that the bonds severed were of the same order of stability as those in furanosides.[7,8] The residue undissolved after thirteen hours of hydrolysis, 0.45 g., had a Shaffer–Hartmann–Somogyi[11] copper number of 15 in circumstances where the value for glucose was about 260. That of the dissolved material, 0.75 g., was about 75.

Acetate of the Anhydrocellulose (F).—A 20-g. sample of (D) was heated with 400 cc. of a mixture of acetic anhydride and pyridine (1:2) at 60° for several days, during which time the fibrous material swelled but did not dissolve. The product was recovered by filtration and re-acetylated several times in the same manner until the total

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[6] Haworth, Owen and Smith, *J. Chem. Soc.*, **88** (1941). This article discusses the properties of 3,6-anhydroglucose.

[7] Haworth, *Ber.*, **65A**, 43 (1932).

[8] Haworth, Porter and Waine, *J. Chem. Soc.*, 2254 (1932).

[9] From the batch previously studied.[3,1] We are indebted to Doctors J. W. Hill and F. Schulze, of the du Pont Co., for the gift of this high grade material.

[10] All rotations were for sodium light.

[11] Shaffer and Somogyi, *J. Biol. Chem.*, **100**, 695 (1933).

acetylation period was three weeks. Purification was by steeping in repeated changes first of ice water, then of aqueous pyridine and finally of distilled water and drying was *in vacuo* over phosphorus pentoxide at 60°. The acetylation was adequate, because the acetyl content[12] of 41.0% remained practically unchanged at 41.1% after a second acetylation lasting one week; yield, 31 g., or 93%, when no account was taken of any mechanical losses.

The white, fibrous anhydrocellulose acetate (F) swelled in all, but dissolved in none, of the following liquids: glacial acetic acid, 85% formic acid, acetone, methyl isobutyl ketone, cyclohexanone, toluene–acetone (3:2), toluene, benzyl alcohol, *m*-cresol, *n*-butyl acetate, dioxane, diethyl cellosolve, Triton F, trimethylenetetramine, tetraethylenepentamine, hydroxyethylethylenediamine, morpholineethanol and morpholine.

Isolation of 3,6-Anhydroglucose Derivatives.—Two-gram samples of the anhydrocellulose acetate (F) were sealed in eleven separate tubes, each containing 30 cc. of 2.3% methanolic hydrogen chloride. The tubes were kept at 130° for forty to fifty hours[13] before the contents were combined and neutralized with solid sodium carbonate. Evaporation left a semi-solid mass that was extracted several times with boiling acetone. The residue was saved for separate investigation. A brown sirup recovered by concentrating the combined extracts gave 0.41 g. of a yellow, viscous distillate, b. p. 136–140° (bath temperature) at 10^{-3} mm., which was dissolved in a few cc. of methanol mixed with ether and petroleum ether. When this solution was kept overnight near 0°, 0.05 g. of crystals separated which were washed in a little cold methanol and dried. Their melting point, 163–164°, and specific rotation at 25°,[10] +158° (*c*, 1), were in good agreement with those reported for methyl-α-glucopyranoside, 166° and $[\alpha]^{20}_{D}$ +159° in water.[14]

The mother liquor from the methylglucoside on evaporation left 0.36 g. of a non-reducing sirup with $[\alpha]^{25}_{D}$ +39° in water (*c*, 0.8) and n^{18}_{D} 1.4910. These values were very close to those found for the equilibrium mixture of methyl α- and β-3,6-anhydroglucofuranoside, which had $[\alpha]^{18}_{D}$ +38° in water and n^{18}_{D} 1.4912.[6] When this sirup was treated with 1 g. of recrystallized phenylhydrazine hydrochloride and 1 g. of sodium acetate dissolved in 20 cc. of water,[15] 0.1 g. of a dark red solid, m. p. 175–180°, was deposited in two crops. These crops were combined and allowed to recrystallize slowly from 40% ethanol. The first fraction, 0.01 g., decomposed at 178–180° and the larger, more soluble second fraction at 155–157°; in good agreement with the values of 180 and 156–158° quoted for the phenylosazone and the phenylhydrazone, respectively, of 3,6-anhydroglucose.[15] *Anal.* Calcd. for the phenylhydrazone, $C_{12}H_{16}O_4N_2$: N, 11.1. Found for the second fraction: N, 11.6, 11.8. The crystals were probably contaminated with a little of the ozsaone (N, 16.5).

Isolation of a Fully Methylated Anhydrodihexose.—After the anhydromethylglucosides had been removed from the product of the methanolysis, all the residues were combined and were methylated four times with dimethyl sulfate and alkali.[16] A fifth methylation, with sodium in ether followed by methyl iodide,[17,18] left 6 g. of product which was distilled at 10^{-3} mm. The low-boiling portion, 4 g., presumably consisted in the main of methyl tetramethylglucosides and was not further examined. The next fraction of 0.8 g. distilled as a colorless, viscid liquid at a bath temperature of 136–140°, had a refractive index of n^{20}_{D} 1.4510 and a specific dextrorotation at 20° of +94° in pure chloroform.[10] The analysis (G) was that of a fully methylated disaccharide.

A 0.2-g. sample was heated on the steam-bath with 100 cc. of *N* hydrochloric acid for six hours, after which time an extraction of the strongly reducing solution with an equal volume of chloroform resulted in a non-reducing, optically inactive aqueous layer and a dextrorotatory chloroform one. The substance had therefore given no product, such as a trimethyl glucose, that chloroform failed to remove from aqueous solution.

Discussion

The results of the iodination experiment (B) (Table I) showed that the partly tosylated cellulose acetate (A) averaged 0.196 tosyl groups in the sixth and 0.054 groups in the second (and third) positions of the glucose residues. An alkaline deacylation of (A) entirely along the lines discussed in the Introduction would therefore produce a cellulose averaging 0.054 methoxyl groups and 0.196 anhydro linkages.

Although the complete analysis of the product actually obtained (D) was compatible with these requirements, the presence or absence of anhydro groups made little difference in the calculated values (*cf.* analyses C and D). The acetyl content of the thoroughly reacetylated product (F) corresponded to the substitution of 2.57 (3 − 0.06 − 0.007 − 2 × 0.183) required by 0.183 anhydro linkages and not to the value of 2.93 (3 − 0.06 − 0.007) which would be expected in their absence (Analysis E). Although the analyses suggested that the detosylation proceeded quantitatively, or nearly so, in the expected way, the evidence was not quite conclusive because pyridine and acetic anhydride sometimes fail to reacetylate regenerated celluloses completely. The identification of the equilibrium mixture of methyl α- and β-3,6-anhydroglucofuranoside among the products obtained by the methanolysis of (F) did, however, constitute acceptable proof that anhydro rings

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[12] The analytical method used has been submitted for publication by Cramer, Gardner and Purves.

[13] Irvine and Hirst, *J. Chem. Soc.*, 1585 (1922), obtained 95.5% yields of crystalline methylglucoside from cellulose triacetate heated at 125° for fifty to sixty-five hours in 0.75% methanolic hydrogen chloride. These conditions left much of the anhydrocellulose undissolved.

[14] Riiber, *Ber.*, **57**, 1797 (1924).

[15] Fischer and Zach, *Ibid.*, **45**, 456 (1912).

[16] West and Holden, THIS JOURNAL, **56**, 930 (1934).

[17] Freudenberg and Hixon, *Ber.*, **56**, 2119 (1923).

[18] Pacsu and Trister, THIS JOURNAL, **61**, 2442 (1939).

TABLE I

SUMMARY OF ANALYTICAL DATA

Compound	Substitution[a]				Basic mol. wt.		Analysis %				
	Tosyl	Acetyl	Anhydro	Methoxyl			S	Acetyl	Methoxyl	C	H
A	0.251	2.44			303.2	Calcd.	2.64	34.6			
						Found	2.63 2.65	34.8 34.7			
B[b]	.054	2.44			294.4	Calcd.	0.58				
						Found[b]	0.57 0.58				
C	.007			0.06	164.9	Calcd.	0.14		1.13	45.5	6.2
D	.007		0.183	.06	161.6	Calcd.	0.14		1.15	45.5	6.1
						Found[c]	0.12 0.16		1.17 1.19	44.9 44.8	6.3 6.3
E	.007	2.933		.06	288.1	Calcd.		43.8	0.65	49.9	5.6
F	.007	2.567	.183	.06	269.4	Calcd.		40.9	0.69	50.1	5.6
						Found[d]		41.0 41.2	0.62 0.60	49.7 49.4	6.0 6.1
G	Octamethyl anhydrodihexose				454	Calcd.			54.6	52.9	8.4
						Found			54.3 54.5	52.7 53.0	9.0 8.9

[a] Moles per glucose unit. [b] Calcd. for additional substitution of 0.196 atom of iodine: I, 8.45. Found: 8.56, 8.38. [c] The substance gave unusual difficulty during combustion. Uncor. for 0.086% ash. [d] Cor. for 0.134% ash.

were indeed formed. This identification was confirmed by the decomposition points of the crystalline phenylhydrazone and phenylosazone prepared from the anhydroglucose. Tosylated cellulose and tosylated monosaccharide derivatives, therefore, behave toward alkali in a similar manner. Since this is the case, an extension of the analogy suggests that the alkaline deacylation of methylsulfonic, sulfuric[19] and perhaps nitric esters of cellulose will proceed along similar lines and that the desoxy-halogen derivatives will do likewise.[20] Moreover, there is a possibility of substituting a few alkyl, amino[21] thio, phenyl and similar groups into the cellulose molecule by replacing the sodium methylate with an appropriate reagent.[4,5]

Although the methanolysis of the anhydrocellulose acetate was drastic enough to reduce ordinary cellulose triacetate almost quantitatively to methylglucoside,[13] methylation of the product revealed a liquid fraction with the volatility, the carbon, hydrogen and methoxyl content of a fully methylated disaccharide (Table I, compound G). The refractive index, $n^{20}\text{D}$ 1.4510 and the specific rotation of + 94° were far removed from the values of n_{D} 1.4643[22] and −14.6°[23] quoted for methyl β-heptamethylcellobioside,[24] a trace of which conceivably might have escaped the methanolysis. No trimethyl glucose was formed when the substance was heated with hydrochloric acid in circumstances that would have hydrolyzed any ordinary, methylated disaccharide.[22] Although lack of material prevented a complete study, the above observations were sufficient to show that the bond uniting the two hexose units in the substance was not of the usual glycosidic type but had the greater stability toward hydrolysis and methanolysis that is associated with the ether linkage. Formula VIII, in which the position of the supposed ether bond is arbitrary, was tentatively assigned to the methylated dihexosan, and the corresponding structure IX to the parent unit in the cellulose. The occurrence of such a structure is readily explained by the mechanism usually assumed for the Walden inversion. Alkali is known to rupture a carboxylic ester $R_1R_2R_3C\text{—}O\vdots\text{—}COR$ as indicated by the dotted line and to regenerate the alcohol $R_1R_2R_3COH$ unchanged in optical configuration. Sulfonic and some other esters, for example $R_1R_2R_3C\text{—}\vdots O\text{—}SO_2R$, are considered to cleave as shown and to produce an electron deficient, central carbon atom $R_1R_2R_3C^+$, sometimes known as a carbonium ion. This reaction proceeds only when one or more of the radicals R_1, R_2 and R_3 can simultaneously eject a proton and is located in such a position that the residue becomes attached to the side of the ion opposite that from which the sulfonic ester group departs. Any asymmetry of the central carbon atom is in consequence reversed, that is, a Walden inversion

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[19] Duff and Percival, *J. Chem. Soc.*, 830 (1941).

[20] Micheel, "The Chemistry of Sugars and Polysaccharides," Leipzig, 1939, p. 147.

[21] The literature on aminocelluloses was reviewed by Marsh and Wood, "Introduction to Cellulose Chemistry," 2nd ed., Chapman and Hall, London, 1942, Chapter 19, pp. 410–429.

[22] Haworth and Hirst, *J. Chem. Soc.*, 193 (1921).

[23] Micheel and Littmann, *Ann.*, **466**, 115 (1928).

[24] Although the unknown methyl-α-heptamethylcellobioside might have a specific rotation as high as 94°, any cellobioside that survived the methanolysis would certainly be an α,β-glycosidic mixture with a much smaller dextrorotation.

occurs, and a double bond or an anhydro ring appears in the electrically neutral $R_1R_2R_3C$ molecule according to the nature of R_1, R_2 and R_3.[4,5] Structures like IX would be formed if the carbonium ion combines with an hydroxyl oxygen atom that is part of a different hexose unit. Although condensation products of this type have not been isolated in work with sugar derivatives in homogeneous solution, the use of a precipitated tosyl cellulose, in which separate molecules are in close proximity, may promote their formation. The number of the "intermolecular" anhydride linkages may therefore depend upon the physical conditions of the detosylation.

In the present case, the anhydrocellulose is considered to average about 0.183 anhydro bonds per glucose unit and of these about 0.025 mole were recovered as methyl-3,6-anhydroglucofuranosides and another 0.022 mole as the fully methylated anhydrodihexose. Similarly constituted tri- and poly-hexose derivatives would not have been isolated by the method used. These recoveries, totalling only 26% of theory, left the amount of "intermolecular" linking indeterminate between the wide limits of 0.022 to (0.183 − 0.025) 0.16 mole, corresponding to one such bond for every six to forty-five glucose units. Another attempt to estimate this number was based upon the selective hydrolysis of the anhydroglucoside bonds in dilute hydrochloric acid. If these units were scattered with reasonable uniformity along the anhydrocellulose macromolecules and if structures like IX were absent, the hydrolysis would have degraded the material to a water-soluble dextrin with an average degree of polymerization of 1/0.183, or of 5 to 6. Only 60% by weight of the anhydrocellulose hydrolyzed in the expected way and 40% remained undissolved. The conclusion that 40% of the anhydro linkages, or one for fourteen glucose residues, was "intermolecular" cannot be accurate because the substantial reducing power of the insoluble residue showed that it contained terminal anhydroglucose units. Very short, condensed chain fragments might also have passed into solution. Cold, concentrated hydrochloric, cold 72% sulfuric and 85% phosphoric acids degraded the anhydrocellulose acetate to soluble products but the solutions were black in color, possibly owing to the decomposition of furan derivatives produced from the 3,6-anhydroglucose units.

The average chain length of the original cellulose acetate was about 220[2] and that of the anhydrocellulose prepared from it was probably not much less. This length, plus the extent of cross linking, in all probability determined the solubility, since the presence of a few 3,6-anhydroglucose units would hardly have a dominant effect in this connection. The anhydrocellulose swelled but failed to dissolve in 5% and 17% aqueous caustic soda, standard cupraammonium solution and Triton F,[25,26] even when the mixtures were repeatedly frozen solid in dry-ice and allowed to thaw. This behavior can be attributed confidently to cross linking because all these liquids have an extensive solvent effect upon ordinary cellulose of D. P. 220. The capacity of the anhydrocellulose acetate to swell in all but to dissolve in none of the organic liquids listed in the Experimental section, although compatible with a cross-linked structure, might also have depended upon the mode of distribution and the amount of the acetyl substituent. This alternative explanation seems improbable in view of the number of different solvents tried but cannot be altogether excluded. The present research therefore supports rather than confirms the inference that the insolubility of cellulose esters of dibasic acids was caused by the presence in them of ester cross links.[27]

Summary

A mixed acetate-*p*-toluenesulfonate of cellulose averaged 0.196 *p*-toluenesulfonyl groups in the primary alcoholic and 0.054 groups in the secondary alcoholic positions of the glucose residues. When this mixed ester was deacylated with excess sodium methylate in methanol, the analysis of the product suggested the presence of 0.06 methoxyl, 0.007 *p*-toluenesulfonyl and 0.183 anhydro groups. Reacetylation gave an anhydrocellulose acetate whose composition also supported this conclusion.

A drastic methanolysis reduced this acetate to substances among which was 0.025 mole of the liquid equilibrium mixture of methyl α- and β-3,6-anhydroglucofuranoside and 0.022 mole of an anhydrodihexose. The latter was isolated as a fully methylated derivative, whose stability during methanolysis and hydrolysis suggested that an ether, rather than a glycosidic bond, united the two hexose units. If this conclusion was correct, the anhydrocellulose contained some glucose residues that were condensed through their alco-

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[25] Brownsett and Davidson, *J. Textile Inst.*, **32**, T25 (1941).

[26] Brownsett and Clibbens, *ibid.*, **32**, T32 (1941).

[27] Malm and Fordyce, *Ind. Eng. Chem.*, **32**, 405 (1940).

holic groups to form a cross-linked structure. The reactions occurring during the deacylation of the original cellulose mixed ester were interpreted by the mechanism usually assumed for Walden inversions.

The anhydrocellulose was partly degraded by hot dilute mineral acid, decomposed in cold, concentrated acid and swelled but did not dissolve in various solvents for cellulose. These observations, together with the similar behavior of the anhydrocellulose acetate toward many organic liquids, were all consistent with the structure proposed for the substance.

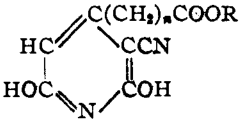
CAMBRIDGE, MASS. RECEIVED NOVEMBER 6, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC., RAHWAY, NEW JERSEY]

3,4-Substituted Pyridines. II. β-(4-Pyridyl)-propionic Acid

BY JOSEPH R. STEVENS AND RALPH H. BEUTEL

In continuing our studies on the synthesis of 3,4-substituted pyridines,[1] a series of compounds having the formula I, where n = 0, 1 and 2, has been made.



I

With the removal of the 2 and 6 hydroxyl groups, compounds with active functional groups in the 3 and 4 positions would result which should serve as good starting points for syntheses of 3,4-substituted pyridines. However, in all members of the series, preliminary results showed that these substances on treatment with phosphorus oxychloride yielded intractable products. With the removal of the cyano group prior to the phosphorus oxychloride treatment, elimination of the hydroxyl groups proceeded smoothly. Utilizing these reactions, β-(2,6-dichloro-4-pyridyl)-propionic acid was prepared which, on catalytic reduction, was converted into β-(4-pyridyl)-propionic acid.

Compounds with formula I were prepared by the general method[2,3] of condensing the appropriate β-keto ester with cyanoacetamide in the presence of piperidine. Diethyl β-ketoadipate, required for the synthesis of ethyl β-(2,6-dihydroxy-3-cyano-4-pyridyl)-propionate, I (n = 2), was prepared by the "acid cleavage" of diethyl α-acetyl-β-ketoadipate which, in turn, was obtained from sodium acetoacetic ester and β-carbethoxypropionyl chloride. The procedures followed in the preparation of the various derivatives and the data concerning them are given below.

Experimental

2,6-Dihydroxy-3-cyano-4-carbethoxypyridine, I (n = 0).—Forty-three grams of ethyl oxaloacetate was added to a solution of 20 g. of cyanoacetamide in 100 cc. of warm methanol together with 20 g. of piperidine. After standing for two days at room temperature the bright orange-red crystals of the piperidine salt were filtered off and crystallized from water; yield 23 g. (36% of the theoretical); m. p. 180–181°.

Anal. Calcd. for $C_{14}H_{19}N_3O_4$: C, 57.31; H, 6.58; N, 14.3. Found: C, 57.50; H, 6.82; N, 14.6.

A solution of 29.3 g. of the piperidine salt in 293 cc. of hot water was acidified with hydrochloric acid. The mixture was cooled in ice and filtered. The white crystals were washed with water and dried under vacuum; yield 20 g. (96% of the theoretical). For analysis, some of the compound was crystallized several times from dilute methanol; it has no definite melting point but softens at 120° and finally becomes liquid at 150°.

Anal. Calcd. for $C_9H_8N_2O_4$: N, 13.5. Found: N, 13.5.

Ethyl (2,6-Dihydroxy-3-cyano-4-pyridyl)-acetate, I (n = 1).—Robinson[4] has attempted this condensation but was unable to obtain the desired compound. To a solution of 4.2 g. of cyanoacetamide in 50 cc. of methanol was added 10.1 g. of ethyl acetonedicarboxylate and 4.4 g. of piperidine. The solution was refluxed for six hours and allowed to stand overnight. The solvent was removed under vacuum; the residue was dissolved in 25 cc. of 2.5 *N* hydrochloric acid and the solution was cooled in ice until crystallization was complete. The crystals were filtered, washed with water, and dried; yield 3.5 g. (31.5% of the theoretical). Recrystallization twice from isopropanol and once from water gave a product, m. p. 239°.

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.04; H, 4.54; N, 12.6. Found: C, 53.56; H, 4.24; N, 13.0.

Diethyl α-Acetyl-β-ketoadipate.[5]—To 23 g. of sodium ribbon suspended in 795 g. of sodium-dried benzene, 390 g.

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[1] Stevens, Beutel and Chamberlin, THIS JOURNAL, **64**, 1093–1095 (1942).

[2] Guareschi, *Mem. Acad. Torino*, [2] **46**, 11 (1895); *Ber.*, **29** ref. 655 (1896).

[3] Thole and Thorpe, *J. Chem. Soc.*, **99**, 422–428 (1911).

[4] Robinson and Watt, *ibid.*, 1537 (1934).

[5] Robinson and Watt, *ibid.*, 1539 (1934).