

be used to compare acid strengths until after further investigation.

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Acetylation of Starch

BY ROLLAND LOHMAR AND C. E. RIST

It is stated that starch must be pregelatinized before it can be converted to the triacetate through the action of pyridine-acetic anhydride.^{1,2} We have found that, although raw corn starch is somewhat resistant to the action of these reagents at 100°, treating it with refluxing (115°) pyridine for about an hour permits acetylation without prior gelatinization.³ These activation conditions allow complete acetylation of corn starch but only partial acetylation of potato or tapioca starch.

TABLE I

ACETYLATION IN PYRIDINE-ACETIC ANHYDRIDE

Pyridine pretreatment ^a	Time to clear at 100°, ^b hr.	Total time, hr.	% yield	Acetyl ^c
None	>10	22.5	98.5	44.7
Reflux 1 hr.	1.75	2	97.7	44.8
Reflux 1 hr.	1	2	98.2	44.6
Azeotropically dried	1	2	97.2	44.8

^a The first two samples contained 11% moisture and the third was dried *in vacuo* to constant weight. ^b Microscopic examination at 600× for disappearance of granules or granule fragments from the mixture. ^c By saponification, dry basis; theory for triacetate, 44.8%.

Differences in reactivity of various starch species appear to be related to granule size, starches of larger granule size being less reactive.⁴

Esterification of untreated starch at 115° is sluggish and pretreatment at 100° is not appreciably effective. Drying of activated granules to a pyridine content of 7% (which is held very tenaciously) makes them non-reactive.

The pyridine pretreatment does not gelatinize the starch; the granules are still birefringent and are swollen only about 50% by volume. "Horny starch" (made by drying an aqueous starch paste) is quite unreactive but may also be activated by this method. The ease of activation increases as the horny starch is more finely ground. We found no difference in the reactivity of defatted and non-defatted corn starch. Several lots of

(1) J. W. Mullen II and E. Paesu, *Ind. Eng. Chem.*, **34**, 1209 (1942).

(2) R. L. Whistler, "Advances in Carbohydrate Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1945, p. 285.

(3) It is noted, as this article goes to press, that H. Sanders and T. S. W. Gerwitz (Abstracts of Papers, 117th Meeting, American Chemical Society, Detroit, April 1950) have obtained what appear to be somewhat parallel results with the propionylation of starch. We have also found that granules may be butyrylated.

(4) R. Lohmar, J. W. Sloan and C. E. Rist, *THIS JOURNAL*, in press. See also G. K. Hughes, A. K. Maebeth and F. L. Widzor, *J. Chem. Soc.*, 2026 (1932).

commercial corn starch showed no noticeable difference in ease of activation and acetylation.

In general, other common organic bases such as α -picoline, pyrrole, triethylamine, benzyl-dimethylamine or piperidine, have much less or no activating effect.

Acetates prepared from activated granules do not dissolve completely in solvents such as chlorinated hydrocarbons or cyclohexanone, which are normally good solvents for starch acetates. Numerous gel particles are still visible after the suspension has been shaken for several days.

By replacement of part of the pyridine by a non-solvent, such as heptane or diamyl ether (which require substantially longer reaction times), it is possible to prepare acetates that retain the original granule form. The effect of several variables on the partial acetylation of starch in the granule form is given in Table II.

TABLE II

ACETYLATION OF STARCH GRANULES IN PYRIDINE-HEPTANE

Reflux in pyridine, ^a hr.	Ac ₂ O, ^b moles	Acetyl, %	Recovery, %
0	3	3.1	98.9
1	3	32.8	99.8
0	4	31.4	99.1
1	4	39.0	99.3
0	4	<1	98.6
1	4	37.6	100.4

^a All starch samples contained 10.8% moisture except the last two which were dried *in vacuo* to constant weight. ^b Sufficient excess anhydride was used to react with the moisture in the air-dried starches.

A monoacetate of corn starch granules was made in diamyl ether. This product, which still showed the typical birefringence, consumed only 0.58 mole of periodate for each acetylated anhydro-glucose unit. Since starch-6-acetate would consume one mole, this shows that the hydroxyl group on carbon six did not acetylate selectively.

Experimental

Starch Triacetate.—Twenty-five grams of defatted, air-dried corn starch (moisture about 11%) was pretreated as outlined in Table I. The acetylation was carried out in 250 cc. of pyridine and 66 cc. (50 cc. in the case of dried starch) of acetic anhydride at 100°. After the stated times had elapsed, the acetate was precipitated in 3 volumes of ethanol in a high-speed blender. The acetate was washed with ethanol, dried in a vacuum desiccator and equilibrated at 50% relative humidity. All preparations adsorbed about 2% moisture.

Acetylation of Granules.—A mixture of 20.0 g. of corn starch (10.8% moisture) and 40 cc. of pyridine was heated to reflux for one hour. One hundred sixty cc. of heptane and 42 or 53 cc. (3 or 4 molar equivalents, resp., plus that equivalent to moisture in the starch) of acetic anhydride was added and the mixture was stirred and refluxed (96–97°) for three hours. The product was filtered, washed thoroughly with ethanol and dried at 50% relative humidity. In the experiments with oven-dried starch 42 cc. of acetic anhydride (4 molar equivalents) was used.

Starch Granule Monoacetate.—Twenty grams of air-dried, defatted corn starch was heated with 100 cc. of pyridine and 60 cc. of distillate was removed—the final 30 cc.

under reduced pressure. One hundred fifty cc. of diethyl ether was added and the temperature was brought to 100°, at which time 40 cc. of acetic anhydride was added. After sixty-five minutes the mixture was cooled, filtered and washed with ethanol. The product was steeped in ethanol overnight, filtered and air-dried. The moisture content was 4.53%.

Anal. Calcd. for $C_8H_9O_6(C_2H_3O)$: acetyl, 21.08. Found: acetyl, 21.1.

STARCH AND DEXTROSE DIVISION
NORTHERN REGIONAL RESEARCH LABORATORY⁵
PEORIA, ILL. RECEIVED MARCH 13, 1950

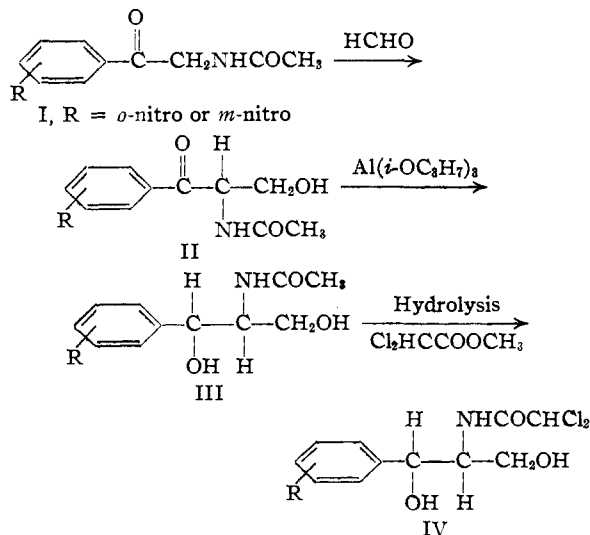
(5) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

Chloramphenicol¹ (Chloromycetin). Related Compounds

BY LOREN M. LONG AND N. JENESEL

Chloramphenicol has been shown to be D-(*levo*)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol.² The recent publication by Buu-Hoi and Khôi³ of the synthesis of the related compound, DL-*threo*-2-dichloroacetamido-1-*m*-nitrophenyl-1,3-propanediol, prompts the present authors to report the results of their investigation of this compound and also the corresponding *o*-nitro derivative.

The procedure for the synthesis of chloramphenicol originally developed by Long and Troutman^{4,5} has proved to be of value in the preparation of many compounds related to the antibiotic and was applied with success to the derivatives reported herein. Important steps involved in the synthesis are illustrated in the series of reactions.



(1) Chloramphenicol is the generic name for the antibiotic identified as Chloromycetin, a Parke, Davis & Co. trademark.

(2) Rebstock, Crooks, Controulis and Bartz, *THIS JOURNAL*, **71**, 2458 (1949).

(3) Buu-Hoi and Khôi, *Compt. rend.*, **229**, 1343 (1949).

(4) Long and Troutman, *THIS JOURNAL*, **71**, 2469 (1949).

(5) Long and Troutman, *ibid.*, **71**, 2473 (1949).

The intermediate α -acetamidoketones (I) may be prepared from the corresponding nitroacetophenones⁶ by bromination and subsequent conversion to the aminoketone by use of hexamethylenetetramine.⁷

Condensation of I with formaldehyde proceeds satisfactorily. As in the previous publication,⁵ reduction of the propiophenone derivative (II) is accomplished with aluminum isopropoxide. The principal product so obtained is the desired *threo* racemate.

In the authors' first attempt to prepare the *m*-nitro compound a product melting at 157° was obtained. This melting point corresponds fairly well to that reported by Buu-Hoi and Khôi.³ However, the substance did not analyze correctly despite repeated recrystallization. Unfortunately, analyses are not given in the earlier publication.³ The preparation was repeated, using a shorter period of hydrolysis of compound III. A compound melting at 135–136° was then obtained which gives the correct analysis. The ultraviolet absorption spectrum of the higher melting material shown in Fig. 1 except that the absorption maximum is at 266.5 m μ .

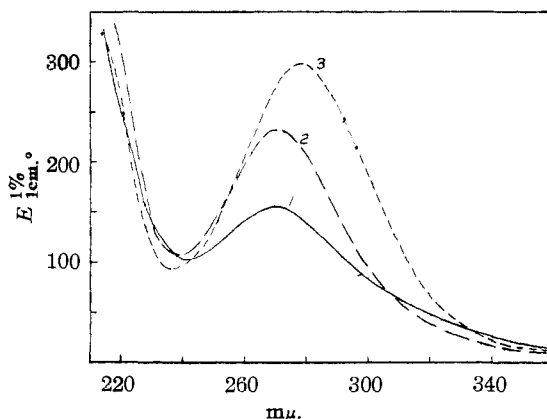


Fig. 1.—Ultraviolet absorption spectra of: 1, 2-dichloroacetamido-1-*o*-nitrophenyl-1,3-propanediol; 2, 2-dichloroacetamido-1-*m*-nitrophenyl-1,3-propanediol; 3, chloramphenicol. The solvent in each case was water.

Table I summarizes data concerning the intermediates illustrated in the series of reactions. Compound IV is assumed to be the *threo* racemate. This assumption is based on comparisons with derivatives reported previously.^{4,5} Figure 1 gives the ultraviolet absorption spectra of the three related nitro compounds.⁸

Experimental

α -Acetamido- β -hydroxy-*o*-nitropropiophenone.—A mixture of 29.4 g. (0.132 mole) of α -acetamido-*o*-nitroacetophenone, 10 ml. of methanol and 12 ml. of 36–38% aqueous formaldehyde was placed in a flask and heated to 35°.

(6) Walker and Hauser, *ibid.*, **68**, 1386 (1946).

(7) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

(8) The ultraviolet absorption spectra were determined under the direction of Dr. J. M. Vandenberg of this Laboratory.