heating continued, producing a clear solution after thirty-six hours. The white, fibrous product showed good solubilities, giving solutions of high viscosity; yield, 95.2 g. (99%); N, 8.16; calcd., 8.09.

Treated with 47 g. (1.5 times theoretical) of α-naphthyl isocyanate, 10 g. of low viscosity cotton linters in 300 g. of pyridine after forty hours, yielded a clear, highly viscous solution. After dilution with methanol and pyridine, purification was carried out as usual. The white, fibrous product was soluble in many common cellulose ester solvents: yield, 35.5 g. (86%); N, 6.25; calcd. 6.28.

**Cotton Linters and Restricted Amounts of Phenyl Isocyanate.**—Duplicate 10-g. portions of dried cotton linters (low viscosity) in 200 g. of pyridine and (a) 16.5 g. (0.75 theory) and (b) 11.0 g. (0.5 theoretical) of phenyl isocyanate after sixty-five hours of stirring on a steam-bath did not dissolve. They were diluted with pyridine and isolated by water washing. Both still resembled cotton linters. Purification by washing with water, then methanol, gave products insoluble in all usual solvents: yield, (a) 18.0 g., (b) 19.5 g.; N, (a) 6.24, (b) 7.14; calcd. for complete reaction, (a) 6.17, (b) 7.32.

## Summary

1. Cellulose acetate containing free hydroxyl groups reacts incompletely with cyanic acid, and methyl and ethyl isocyanates. The latter two have a pronounced tendency to produce materials insoluble in the usual cellulose ester solvents.

2. With excess quantities of phenyl or α-naphthyl isocyanates in the presence of pyridine products of good solubility are obtained.

3. The factors of time, temperature, amount of reagent, nature of cellulose material, and catalyst, for the reaction of phenyl isocyanate with free hydroxyls of cellulose acetate were studied.

4. Low viscosity cotton linters react readily with phenyl or α-naphthyl isocyanates in the presence of pyridine to give products of high viscosity and good solubilities. When less than enough isocyanate to esterify all hydroxyl groups is used, the reagent reacts completely, giving a product unchanged in appearance from the original cellulose and insoluble in the usual cellulose ester solvents.

ROCHESTER, N. Y. RECEIVED NOVEMBER 27, 1942

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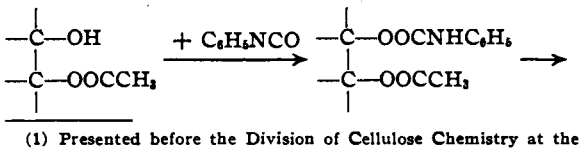
[CONTRIBUTION FROM THE EASTMAN KODAK COMPANY]

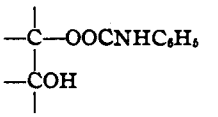
# Carbamates of Cellulose and Cellulose Acetate. II. Stability toward Hydrolysis[1]

BY W. M. HEARON, GORDON D. HIATT AND CHARLES R. FORDYCE

In the preceding paper were given conditions for preparation of carbamates of cellulose and of cellulose acetates containing free hydroxyl groups. It was found that phenyl and α-naphthyl isocyanates could be made to react quantitatively with free hydroxyl groups of cellulose acetate without disturbing acetyl groups which were present, and that the former reagent was particularly suitable for this purpose. Furthermore, the phenyl carbamate group was noted to be very stable toward hydrolysis. These facts presented the possibility of covering free hydroxyls of cellulose acetate with a group which would permit quantitative removal of acetyl groups while it itself remained essentially unaffected. Products thus formed would contain free hydroxyls exactly representing the original acetyl groups as shown by the formulas




(1) Presented before the Division of Cellulose Chemistry at the 104th meeting of the American Chemical Society, Buffalo, New York.




Cellulose acetate in solution with an acid catalyst undergoes a uniform, gradual reduction in acetyl content. If higher aliphatic acyl groups are present, they are usually somewhat more resistant to hydrolysis, but are simultaneously removed in sufficient quantity to make selective hydrolysis impractical.

Cellulose acetate phenyl carbamates were subjected to such a hydrolytic treatment to measure the relative rates of removal of these two substituent groups. No removal of phenyl carbamyl groups resulted, while the acetyl values showed a continual decrease (Fig. 1) at a constant rate.

As an extreme test a cellulose acetate phenyl carbamate was heated in acid solution for eighteen hours on a steam-bath. The product was badly degraded but was isolated and found to contain nitrogen equivalent to that for complete removal of acetyl groups and entire retention of carbamate.

Stability toward alkaline reagents was tested by

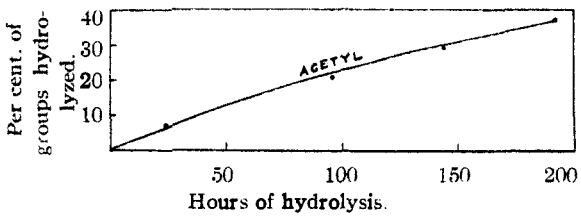



Fig. 1.—Hydrolysis of acetyl groups from cellulose acetate phenyl carbamate dissolved in 90% β-methoxyethyl alcohol containing 0.615% sulfuric acid. Phenyl carbamyl groups under these conditions are not removed.

suspension of the cellulose derivative in aqueous alkali. That some amount of carbamate group was removed was early detected by the presence of aniline in the reaction medium. In order to follow the rate of removal of each substituent group a suitable analytical method was first developed. This was based upon titration to an end-point using phenolphthalein, then acidification and elimination of all carbonate formed by decomposition of phenyl carbamyl groups, then titration to a second end-point. Results obtained were shown to correspond to those from nitrogen analyses.

This procedure was used to follow the course of hydrolysis of a cellulose acetate phenyl carbamate of high carbamyl content in 0.5 *N* sodium hydroxide. Removal of the acetyl group was complete within fifty hours (Fig. 2), while at that time only about 8% of the phenyl carbamate groups had been lost.

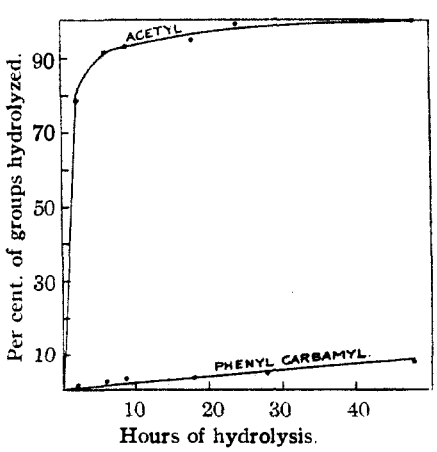



Fig. 2.—Alkaline hydrolysis of cellulose acetate phenyl carbamate

In similar experiments cellulose acetate phenyl carbamates were subjected to severe alkali treatment. Products after eighteen hours of treatment with 20% sodium hydroxide were found still to contain nitrogen. One sample was dissolved in trimethylbenzylammonium hydroxide solution and allowed to stand eighteen hours at room temperature. The product when recovered still contained nitrogen.[2]

From these results it may be seen that the phenyl carbamyl group is strongly resistant to both acid and alkaline hydrolysis. Acetyl groups may be selectively removed from the cellulose mixed ester by severe acid treatment, but the process is satisfactory only if degradation of the cellulose is unimportant. Dilute alkali at room temperature quantitatively removes acetyl groups with little effect on the cellulose viscosity. The small quantity of carbamyl groups simultaneously lost may for many purposes be of comparatively little importance.

This set of circumstances allows preparation of soluble cellulose carbamates containing free hydroxyl groups. Such products cannot be prepared by other methods, since cellulose tricarbamate does not respond to the acid hydrolysis treatment commonly employed in preparation of partially hydrolyzed cellulose acetate, and incomplete carbamation of cellulose leaving unreacted hydroxyl groups yields completely insoluble products.

Several samples of cellulose acetate phenyl carbamate of different proportions of acetyl and phenyl carbamyl groups were treated with dilute alkali to produce cellulose phenyl carbamates containing corresponding amounts of free hydroxyl groups. It will be noted from the solubilities (Table I) that the products containing more than about 0.5 phenyl carbamate group for each glucose unit begin to become soluble in organic solvents. Those which contain more than about one carbamate group are quite widely soluble. This behavior indicates favorable distribution of groups in the cellulose molecule as compared with the completely insoluble cellulose phenyl carbamates prepared by reaction of low viscosity cotton linters with quantities of phenyl isocyanate insufficient to produce complete esterification.[3]

Similar partially esterified derivatives prepared by deacetylation of cellulose acetate α-naphthyl carbamates were prepared and are described in Table II.

## Experimental

**Acid Hydrolysis of Cellulose Acetate Phenyl Carbamate in Acetone.**—Twenty-eight grams of a cellulose acetate

(2) Although cellulose carbanilates are very stable toward aqueous alkali, it has been shown in this Laboratory that carbanilate groups readily can be removed from cellulose by treatment with sodium methylate, following the general procedure of Salmon and Powell. THIS JOURNAL, **61**, 3507 (1939).

(3) See preceding paper.

TABLE I

CELLULOSE PHENYL CARBAMATES PREPARED BY DEACETYLATION OF CELLULOSE ACETATE PHENYL CARBAMATES

| Composition of starting material in groups per glucose unit | | | | | Composition of product Groups per glucose unit | | Solubilities[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acetyl | $C_6H_5NHCO$ | OH | Hours of hydrolysis | Nitrogen, % | $C_6H_5NHCO$ | OH | β-Methoxyethyl alcohol | Acetone | Pyridine | 1,4-Dioxane |
| 1.66 | 0.23 | 1.11 | 18 | 1.56 | 0.21 | 2.79 | − | − | − | − |
| 1.66 | .48 | 0.86 | 18 | 2.80 | .43 | 2.57 | − | − | Swells | − |
| 1.66 | 1.00 | .34 | 18 | 4.75 | .93 | 2.07 | Swells | − | + | − |
| 1.66 | 1.15 | .19 | 18 | 5.10 | 1.04 | 1.96 | Swells | − | + | − |
| 1.20 | 1.80 | .00 | 24 | 6.66 | 1.78 | 1.22 | + | Swells | + | + |
| 0.75 | 2.14 | .11 | 48 | 6.96 | 1.98 | 1.02 | + | + | + | + |

[a] All products were insoluble in benzene, ligroin, ether, alcohol, ethylene dichloride and ethyl acetate.

TABLE II

CELLULOSE α-NAPHTHYL CARBAMATES PREPARED BY DEACETYLATION OF CELLULOSE ACETATE α-NAPHTHYL CARBAMATES

| Composition of starting material in groups per glucose unit | | | | | Groups per glucose unit | | Solubilities[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acetyl | $C_{10}H_7NHCO$ | OH | Hours of hydrolysis | Nitrogen, % | $C_{10}H_7NHCO$ | OH | β-Methoxyethyl alcohol | Acetone | Pyridine | 1,4-Dioxane |
| 1.66 | 0.34 | 1.00 | 41 | 2.08 | 0.32 | 2.68 | − | − | Swells | − |
| 1.66 | .80 | 0.54 | 41 | 3.57 | .73 | 2.27 | − | − | + | − |
| 1.66 | 1.18 | .16 | 65 | 4.34 | 1.06 | 1.94 | ± | − | + | − |
| 1.20 | 1.80 | .00 | 65 | 5.14 | 1.58 | 1.42 | + | − | + | − |

[a] All products were insoluble in benzene, ligroin, ether, alcohol, ethylene dichloride and ethyl acetate.

phenyl carbamate containing 20.1% acetyl and 34.85% phenyl carbamyl (1.66 acetyls and 1.03 phenyl carbamyls per glucose unit) was dissolved in 168 g. of acetone and treated with 3.78 g. of concentrated sulfuric acid and 20 g. of water. After twenty-eight hours at 38°, 20 g. of distilled water was added very slowly. After five days a granular white mass had separated out. Water was added, the precipitate filtered off, washed with water, dilute sodium bicarbonate solution, and finally with water again and dried. The product was a coarse white powder.

*Anal.* Acetyl, 7.1; N, 4.72.

**Acid Hydrolysis of Cellulose Acetate Phenyl Carbamate in β-Methoxyethyl Alcohol.**—To 25 g. of an ester containing 19.3% acetyl and 37.8% phenyl carbamyl (corresponding to 1.66 acetyls and 1.17 phenyl carbamates per glucose unit) in 298 g. of β-methoxyethyl alcohol were added 25 g. of water and 2 g. of concentrated sulfuric acid. The clear solution was maintained at 38°.

Samples were withdrawn after twenty-four, ninety-six, one hundred and forty-four and one hundred and ninety-two hours. Each was precipitated into water and purified by reprecipitation from acetone solution. All samples were white fibers showing little sign of degradation.

*Anal.* Acetyl, 18.0, 15.9, 14.5, 12.8; nitrogen on last sample, 4.74, corresponding to 1.17 groups for each glucose unit.

**Acid Hydrolysis of Cellulose Acetate Phenyl Carbamate at 100°.**—To 15 g. of an ester containing 18.45% acetyl and 40.6% phenyl carbamyl (corresponding to 1.66 acetyls and 1.32 phenyl carbamyls per glucose unit) in 150 g. of β-methoxyethyl alcohol were added 15 g. of water and 0.75 g. of concentrated sulfuric acid. After eighteen hours on a steam-bath the product was isolated and purified by reprecipitation from pyridine solution.

*Anal.* N, 5.80. Calcd. for complete removal of acetyl group, 5.78.

**Alkaline Hydrolysis of a Cellulose Acetate Phenyl Carbamate.**—Six 1.00-g. samples of an ester containing 8.6% acetyl and 48.8% phenyl carbamyl (corresponding to 0.75 acetyls and 1.52 phenyl carbamyls per glucose unit) were each treated with 40 cc. of 75% alcohol and 40 cc. of 0.5 *N* alkali. The mixtures after increasing periods of time were titrated with an excess of 0.5 *N* acid, let stand until the alkali had been leached from the precipitate, and back-titrated with 0.5 *N* alkali to the end-point of phenolphthalein. Then, 1.00 cc. excess 0.5 *N* acid was added, the mixture heated to boiling for exactly two minutes, and back-titrated at once with 0.5 *N* alkali to an end-point. Results are plotted in Fig. 2.

**Preparation of Cellulose Carbamates.**—Samples of cellulose acetate phenyl carbamates were treated with equal volumes of 75% alcohol and 0.5 *N* alkali (40 cc. of each per gram of ester) and left at room temperature for complete hydrolysis of the acetyl group. Each mixture was then made slightly acid, filtered, and the products purified by reprecipitation from suitable solvents (see Table I).

Cellulose α-naphthyl carbamates (Table II) were prepared by a similar procedure.

## Summary

1 Solution hydrolysis of cellulose acetate carbanilates using acid catalysts results in a gradual lowering in acetyl with no loss of carbanilate. Drastic conditions result in complete removal of acetyl with retention of carbanilate but the resulting products are considerably degraded.

2. Suspension of cellulose acetate carbanilates in aqueous-alcoholic alkali removes all acetyl groups with a slight reduction in carbanilate.

3. Cellulose acetate carbanilates and α-naph-

thyl carbamates have been deacetylated by suspension in alkali. The resulting cellulose carbanilates and α-naphthyl carbamates containing free hydroxyl groups are soluble in organic solvents, indicating a difference in distribution of substituent groups as compared with insoluble derivatives of similar composition prepared by reaction of cellulose with insufficient quantities of reagent to produce complete esterification.

ROCHESTER, NEW YORK RECEIVED NOVEMBER 27, 1942

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

# Alkamine Esters of Fluorenonecarboxylic Acids[1]

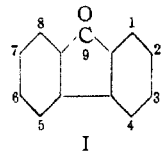
BY FRANCIS EARL RAY AND GEORGE RIEVESCHL, JR.[2]

Alkamine esters of diphenic acid[3] and of 9-substituted fluorene have been reported to possess local anesthetic action. For example, 9-aminofluorene[4] and 9-R-9-aminofluorenes[5] where R is methyl, phenyl or α-naphthyl have a numbing effect when applied to the tongue. Alkamine esters of 9-fluorenecarboxylic acid have also been the subject of several investigations and patents.[6]

Certain ketones, such as β-N-piperidinoethyl phenyl ketone[7] and 3-amino-4-methylphenyl isobutyl ketone,[8] are also active.

We have tested esters of fluorenonecarboxylic acids which incorporate the keto group in the molecule and have the carboxyl attached directly to the aromatic nucleus[9] and have found them to be active.

There are four isomeric fluorenonecarboxylic acids, corresponding to the positions 1, 2, 3, and 4, I. We have prepared derivatives of the 1, 2, and 4-carboxylic acids.



I

The following flow sheets show the methods of preparation of the esters and Table I lists the individual compounds and their properties.

TABLE I

| Esters of | M. p. of hydrochloride, °C. | Cl analyses, % Calcd. | Found | Color |
|---|---|---|---|---|
| Fluorenone-1-carboxylate | | | | |
| β-Diethylaminoethyl | 194–195 | 9.85 | 10.18 | Yellow |
| γ-Diethylaminopropyl | 159–160 | 9.48 | 9.49 | Yellow |
| Fluorenone-4-carboxylate | | | | |
| β-Diethylaminoethyl | 194–196 | 9.85 | 9.97 | Yellow |
| γ-Diethylaminopropyl | 210–211 | 9.48 | 9.32 | Yellow |
| Fluorenone-2-carboxylate | | | | |
| β-Diethylaminoethyl | 223–224[a] | 9.85 | 9.80 | Yellow |
| γ-Diethylaminopropyl | 221–222 | 9.68 | 9.46 | Yellow |
| β-Dibutylaminoethyl | 179–180 | 8.52 | 8.33 | Yellow |
| β-Dimethylaminoethyl | 222–224[a] | | | |
| Oximes of esters of | | N | N | |
| Fluorenone-2-carboxylate | | | | |
| β-Diethylaminoethyl | 231–232 | 7.47 | 7.28 | |
| γ-Diethylaminoethyl | 219–220 (di-HCl) | 6.59 | 6.85 | |
| Ester of | | | | |
| Fluorene-2-carboxylate | | | | |
| β-Diethylaminoethyl | 204–206 | 8.26 | 8.12 | |

[a] Mixed m. p. 186–192°.

The oximes of these amino alcohol esters of fluorenonecarboxylic acids may be prepared readily without hydrolysis of the ester group by operating in a nearly neutral solution. The oximes are more active anesthetics than the parent compounds. This is the first time, so far as we have been able to find, that the oximino group has been reported to increase the anesthetic potency of a ketone. In addition the increased solubility of the compounds thus produced and the more nearly neutral character of their hydrochlorides in solution add to their effectiveness.

Fluorenone-2-carboxylic acid was reduced to fluorene-2-carboxylic acid and the β-diethylaminoethyl ester prepared. It proved to be somewhat more soluble than the corresponding fluorenone.

## Experimental

**Fluorenone-2-carboxylic acid, VIII,** was prepared by Fortner[10] by the oxidation of fluorene-2-carboxylic acid Hinkel, Ayling and Beynon,[11] employing a modified

(1) Abstracted from a thesis submitted to the faculty of the Graduate School of the University of Cincinnati by George Rieveschl, Jr., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Laws Fellow 1938–40.

(3) Roberts and Johnson, THIS JOURNAL, **47**, 1396 (1925).

(4) Nakamura, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **14**, 184 (1930).

(5) Pinck and Hilbert, THIS JOURNAL, **59**, 8 (1937).

(6) Wolfes and Hromatka, U. S. Patent 2,221,828 (1941); Searle, U. S. Patent 2,262,754 (1941); Bockmuhl and Ehrhart, U. S. Patent 2,230,774 (1941); *cf.* the following, German Patents 656,784, 657,529 (1938); French Patent 840,824; Swiss Patent, 202,665 (1939).

(7) Mannich and Lammering, *Ber.*, **55**, 3515 (1922); Mannich and Curtas, *Arch. Pharm.*, **264**, 750 (1926); Blicke and Blake, THIS JOURNAL, **52**, 235 (1930).

(8) Hartung and Munch, *ibid*, **51**, 2570 (1929).

(9) Kamm, *ibid.*, **42**, 1030 (1920).

(10) Fortner, *Monatsh.*, **25**, 443 (1904).

(11) Hinkel, Ayling and Beynon, *J. Chem. Soc.*, 339 (1936).