induction period was observed when the reaction was followed polarographically.

While the mild conditions and the nature of the solvent suggest an ionic mechanism for this decomposition, the nature of the products and catalysis by ultraviolet light are indicative of a radical process. Thermal[3] and photochemical[4] decompositions are known to proceed *via* an initial homolytic cleavage, *viz:*

$$RCH_2ONO_2 \longrightarrow RCH_2O\cdot + NO_2$$

This is followed by a number of possible reactions leading to the observed products, including nitric oxide, aldehydes, and nitrite esters. Such decompositions of simple mononitrates have never been reported under the mild conditions used in the present work.

Further investigation into the mechanism of this decomposition, and particularly into the role of the fluorinated acids, is in progress.

EXPERIMENTAL

All of the chemicals used were commercially available materials. Melting and boiling points are uncorrected.

Trifluoroacetolysis of n-butyl nitrate. One-tenth mole of *n*-butyl nitrate was dissolved in 40 ml. of ice cold trifluoroacetic acid in an Erlenmeyer flask fitted with a ground glass stopper. The solution was cooled for 6 hr. in an ice water bath, and then allowed to stand at room temperature for another 18 hr. The solution became quite yellow within the first hour, and then became green on standing. On admission of air the color rapidly changed to a yellow-brown, and brown fumes formed above the liquid. The mixture was distilled, yielding 7.0 g. (.04 mole) of *n*-butyl trifluoroacetate, b.p. (713 mm.) 102–103°, $n_D^{26.5}$ 1.3376 (lit.[5] b.p. 102.7–102.8°, n_D^{20} 1.3391) and 5.1 g. (0.058 mole) of butyric acid, b.p. (713 mm.) 158–160°. From the dark tarry residue, traces of a water-soluble white solid acid, m.p. (dec.) 125–130°, were obtained. There was not enough of this material to characterize.

Nitric oxide was determined in a separate experiment, by absorption in sulfuric acid and titration of the nitrosylsulfuric acid with permanganate.[6] This run was carried out under a stream of nitrogen, and proceeded in the same manner as the other experiment, except that no appreciable color developed in the solution. From 20.0 millimoles of butyl nitrate, there was obtained 9.27 millimoles (46%) of nitric oxide.

Ethyl and *n*-propyl nitrates in TFA decomposed to give, qualitatively, the same types of products. The solid material from ethyl nitrate was identified as oxalic acid, m.p. and mixed m.p. 101–102° (dihydrate, recrystallized from water).

Butyl nitrate was recovered quantitatively from solutions in 100% acetic acid after standing 24 hr. at room temperature. Solutions in sulfuric acid gave no oxides of nitrogen, although, as reported previously,[2] the nitrate ester cannot be recovered by drowning the solution in water.

Rate studies. A 0.025*M* solution of butyl nitrate in TFA was prepared. A portion of this was placed in a 1-cm quartz cell and scanned in the ultraviolet region periodically, using a Cary Model 11MS Recording Spectrophotometer. There was essentially no change in the absorbance at the maximum over the first 8 hr. After 24 hr., however, the absorbance was much greater than the range of the instrument. However, the bulk of the solution, which had remained in a glass flask, showed the same absorbance after 24 hr. as it did initially. The absorbance did not increase until sometime between 36 and 48 hr.

Samples of the same solution were polarographed periodically. One-ml. aliquots were added to 5 ml. of 95% ethanol containing 3 drops of methyl red (0.1%). The solutions were brought to the first permanent yellow color with 0.5*N* NaOH solution, and then made up to 10 ml. with 95% ethanol. These solutions were then polarographed from zero to −2.0 volts, using a Sargent Model 21 Recording Polarograph with a sensitivity setting of 0.100. It was found unnecessary to remove dissolved oxygen. A blank correction for oxygen, obtained by treating pure trifluoroacetic acid in the same manner as above, was subtracted from the total wave height obtained in the nitrate determinations. The butyl nitrate concentration was found to decrease steadily, with no "induction period." The half-life at this concentration was about 56 hr. The data for any given run fit a first-order rate law fairly well, but the values of k vary greatly with concentration.

The reaction was found to proceed even in the dark, but it was shown to be catalyzed by ultraviolet light. The apparent induction period (observed spectrophotometrically) was shortened, and the rate of butyl nitrate disappearance (measured polarographically) was increased by exposure of the solution to the unfiltered light of a mercury arc lamp (mostly 2537 A).

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Arenesulfonic Acids as Catalysts in the Alcoholysis of Nitriles to Esters

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Arenesulfonic acids have been found to be effective catalysts in the alcoholysis of nitriles to esters, and their use eliminates the objectionable features which have characterized this type of reaction when other catalysts were used. Earlier procedures called for the passing of anhydrous hydrogen chloride into a hot reaction mixture of nitrile, alcohol, and water[3] or refluxing a similar mixture with concentrated sulfuric acid.[4] The first of these involves difficulties in handling anhydrous hydrogen chloride at elevated temperatures. The second, in our experience, is often accompanied by more or less extensive charring. Presumably because of these disadvantages this reaction has not been used very extensively, although occasional

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(2) From the Master's thesis of W. H. B.
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TABLE I

YIELDS AND PROPERTIES OF CRUDE ESTERS

Ester	Acid Catalyst	Time of Reflux, Hr.	Yield, %	B.P., °C.	Sap. Equiv. Calcd.	Sap. Equiv. Found
Ethyl phenylacetate	*p*-Toluenesulfonic	2.5	66	119–121/27 mm.	164	177
n-Propyl phenylacetate	*p*-Toluenesulfonic	2.5	83	131–133/27 mm.	178	185
n-Butyl phenylacetate	Benzenesulfonic	6	72	143–145/28 mm.	192	205
n-Heptyl phenylacetate	*p*-Toluenesulfonic	6	70	174–183/27 mm.	234	259
n-Butyl propionate	*p*-Toluenesulfonic	6	49	124–126/400 mm.	130	130
Di-*n*-propyl adipate	*p*-Toluenesulfonic	6	16	154–163/28 mm.	115	122
Diisoamyl adipate	*p*-Toluenesulfonic	6	66	163–165/2.2 mm.	143	153
Di-*n*-propyl-β,β'-oxydipropionate	Benzenesulfonic	6	25	140–141/1.9 mm.	123	140

TABLE II

PROPERTIES OF PURIFIED ESTERS

Ester	B.P., °C.	Sap. Equiv. Calcd.	Sap. Equiv. Found	$n_D^{25°}$	$d_4^{25°}$	M_R Calcd. Vogel	M_R Observed
n-Heptyl phenylacetate	146–147/2.0 mm.	234.33	233.95	1.4812	0.95707	69.60	69.70
Di-*n*-propyl-β,β'-oxydipropionate	146–147/2.1 mm.	123.15	128.20	1.4309	1.01843	62.80	62.59

references to it appear in the literature.[5,6] It is used commercially, with concentrated sulfuric acid as the catalyst, under carefully controlled conditions, in the alcoholysis and esterification of cyanoacetic acid to diethyl malonate[7] and in the alcoholysis and dehydration of acetone cyanohydrin to methyl methacrylate.[8]

We have found that the difficulties described may be avoided by the use of *p*-toluenesulfonic acid or other arenesulfonic acid as the catalyst. The catalyst is needed in quantities equimolar with the nitrile, since the nitrogen of the nitrile is converted into the ammonium salt of the acid catalyst. An equimolar quantity of water must also be present.

$$R{-}CN + H_2O + HOR' + CH_3C_6H_4SO_2OH \longrightarrow R{-}COOR' + CH_3C_6H_4SO_2ONH_4$$

The necessary water was provided in our syntheses by the use of the monohydrate of *p*-toluenesulfonic acid or of benzenesulfonic acid as catalyst.

As a general procedure, we simply refluxed the reaction mixture for several hours. Mechanical stirring was used. Occasionally precipitation of the ammonium salt was so extensive that stirring became difficult. Addition of an inert solvent might help in such cases. After the period of reflux, water was added to dissolve the ammonium salt. The organic layer was separated, washed with aqueous sodium carbonate, and dried over anhydrous magnesium sulfate. Distillation from a Claisen flask gave crude esters of quality shown by the saponification equivalents in Table I.

Saponification equivalents were determined by the diethylene glycol method of Redeman and Lucas.[9] We found that unchanged nitrile, which may be assumed to be the principal impurity, does not interfere seriously with the determination of the saponification equivalent. Less than 1% of a sample of phenylacetonitrile was found to be saponified under the specified conditions. This is in agreement with the finding of Spiegel[4] that the presence of nitrile does not interfere with the determination of saponification equivalents by the more usual method of refluxing with alcoholic potassium hydroxide.

Table I is a summary of the results of the preparation of eight different esters by this method. In no case did charring occur. Yields ranged from 16% to 83%. Five of the eight preparations resulted in yields of 66% or higher. In two cases the catalyst was benzenesulfonic acid, with results about the same as with *p*-toluenesulfonic acid. Presumably other arenesulfonic acids would also be effective.

Two of the esters are not described in the literature. The crude ester in these two cases was fractionally distilled, and densities determined on the fractions of constant index of refraction. Results are given in Table II.

We made a brief study of the effect of time of refluxing upon the yield of *n*-butyl propionate.

(5) F. Bergel, A. L. Morrison, and H. Rinderknecht, *J. Chem. Soc.*, 267 (1944).

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(8) H. T. Neher, *Ind. Eng. Chem.*, **28**, 267 (1936).

(9) C. E. Redeman and H. J. Lucas, *Anal. Chem.*, **9**, 521 (1937).

The yield improved steadily up to four hours, but further refluxing had little effect.

EXPERIMENTAL[10]

Experimental details are given only for the two previously undescribed esters. Similar procedures were used for the others.

n-Heptyl phenylacetate. Phenylacetonitrile (46.8 g., 0.40 mole), *n*-heptyl alcohol (46.5 g., 0.40 mole), and *p*-toluenesulfonic acid monohydrate (76.0 g., 0.40 mole, including 0.40 mole water) were refluxed with stirring for 6 hr. The addition of 100 ml. of water dissolved the ammonium salts, and caused separation into two layers. The ester layer was separated, washed with 20% sodium carbonate solution, dried over anhydrous magnesium sulfate, and distilled from a Claisen flask. Yield of crude ester, 66.0 g., 0.28 mole.

The crude ester was washed with 5% sodium carbonate solution, and 200 ml. of toluene was added. This was distilled off at atmospheric pressure for azeotropic removal of water. After removal of water, the ester was distilled through a 60-cm. tantalum wire spiral column, using a total reflux partial take-off head. The fraction of constant index of refraction boiled at 146–147° at 2.0 mm., and totaled 31.4 g. The neutralization number as determined with alcoholic potassium hydroxide was zero. Other properties are given in Table II.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.06; H, 9.79.

Di-n-propyl-β,β′-oxydipropionate. β,β′-Oxydipropionitrile (37.2 g., 0.30 mole), *n*-propyl alcohol (36.0 g., 0.60 mole), and benzenesulfonic acid monohydrate (105.6 g., 0.60 mole, including 0.60 mole of water) were refluxed with stirring for 6 hr., and the reaction mixture worked up as described above. The average yield of two runs was 18.6 g., 0.075 mole. Purification of the crude ester was performed as described above. Distillation of 21.7 g. of crude ester gave 9.1 g. of purified ester boiling at 146–147° at 2.0 mm. The neutralization number with alcoholic potassium hydroxide was almost zero. Other properties are given in Table II.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 56.75; H, 8.65.

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(10) Analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Synthesis of a Steroidal Nitrogen Mustard[1]

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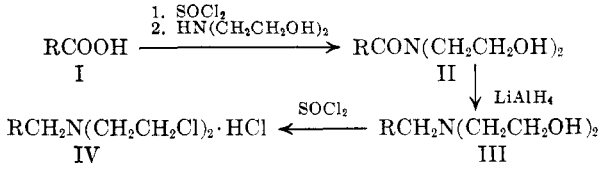
The nitrogen mustards are recognized as anticancer agents.[2] We wish to record the synthesis of a steroid-nitrogen mustard combination,[3] which was expected to have transport characteristics considerably different from those of the more familiar low-molecular weight nitrogen mustards. It was believed possible that such difference could reflect in enhanced activity.

The starting point in the synthesis was 5-cholestene-3β-carboxylic acid (I)[4] obtained from cholesteryl chloride by carbonation of the Grignard reagent.[5] Treatment with thionyl chloride followed by reaction of the acid chloride with diethanolamine gave the *N,N*-bis(hydroxyethyl) derivative



R = 3β-cholesteryl

II of 5-cholestene-3β-carboxamide. Lithium aluminum hydride, by reducing the amide grouping in II to amine, formed 3β-[bis(hydroxyethyl)aminomethyl]-5-cholestene(III).[6] To generate the nitrogen mustard, both hydroxyl groups were replaced with chlorine with help of thionyl chloride. The hydrochloride of the tertiary amine III as well as the hydrochloride IV of the nitrogen mustard were also prepared.

The nitrogen mustard was made available for assay to Drs. H. M. Lemon and H. H. Wotiz at Boston University Medical School who very kindly submitted the following report:

"The relative insolubility of the steroid-mustard in the conventionally used solvents for injection made the toxicity study extremely difficult. Nevertheless, preliminary studies were carried out by intraperitoneal administration of a suspension of the mustard in a starch solution.

The survival rates of mice, guinea pigs, or rats did not differ significantly from the controls following doses of 34, 250, 500, and 1000 mg./kg. Histopathological examination of the mouse livers showed evidence of plastic peritonitis, yellow atrophy, and multinucleated giant cells. The mouse kidneys showed evidence of interstitial hemorrhagic nephritis at the border of the cortex and medulla. Because of its extreme insolubility it is impossible to tell whether these effects were caused by the inherent toxicity of the mustard or by a local irritating effect due to its limited absorption from the peritoneum."

(1) These studies were aided by grants from the American Cancer Society and from the National Institutes of Health, and by an Institutional Research Grant from the American Cancer Society.

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