volume of ethanol. This once-recrystallized substance melted at 75–80° and weighed 114 g. (90%). A second recrystallization from ethanol (recovery almost quantitative) yielded a product which, after drying at 56° for twelve hours under diminished pressure, had a melting point of 79–81°.

The same method has been used to prepare the corresponding 4-bromobutyl- and 5-bromoamylphthalimides. Yields obtained were above 70% of those calculated.

Discussion

The toxicity[4] of these compounds in rhesus monkeys is considerably less than that of Pamaquine. N^1-(5-(6-Methoxy-8-quinolylamino)-amyl)-guanidine nitrate was the only one of the group which was supplied in sufficient quantity for extensive study. This drug is about one-sixteenth (or slightly less) as toxic as Pamaquine and is interesting in that its toxic symptoms resemble those of Paludrine rather than those of Pamaquine or Plasmocid. Toxic symptoms included marked salivation, generalized weakness, and marked loss in weight. There was no effect on the numbers of formed elements in the peripheral blood, and no evidence of methemoglobin formation.[4]

The remaining three substances showed not the slightest evidence of toxicity at the dosage levels used (up to and including 48 mg./kg. daily dose) and are certainly less than one-eighth as toxic as Pamaquine. Lack of material prevented a more complete evaluation of toxicity. It is noteworthy that neuronal toxicity[3a] was *not* observed in either of those substances in which it might have been expected, *viz.*, the quinolylaminoethyl- and propylguanidines.

The last three compounds are inactive in the A-1 test against *Pl. gallinaceum* in the chick[3b] at the maximum tolerated dose.[7]

Tested against *Pl. cynomolgi* in the rhesus monkey, the quinolylaminoamylguanidine derivative did not prevent relapse, and would, therefore, not be expected to be a curative drug in man when administered with quinine in cases of vivax malaria. When administered to man at a dosage level of 240 mg./day for fourteen days both with and without 1.65 g./day of quinine for the same period, DR 15,526, the drug mentioned directly above, did not prevent relapse in cases of sporozoite-induced Chesson vivax malaria.[8]

Summary

1. Four N^1-quinolylaminoalkylguanidines have been described.

2. An improved method of preparing bromoalkylphthalimides has been described.

3. Several new salts of certain 8-(aminoalkylamino)-6-methoxyquinolines have been described.

4. The toxicity of the guanidines described and their effectiveness as antimalarials have been discussed.

(7) We are indebted to the Division of Tropical Diseases of the U. S. Public Health Service, National Institute of Health, for this information.

(8) These data are taken from N. I. H. Malaria Report No. 83 dated Sept. 1, 1948, and represent work done at Stateville Penitentiary by the staff of the Malarial Research Unit, Department of Medicine, University of Chicago, under the direction of Alf S. Alving and Lowell T. Coggeshall.

COLLEGE PARK, MARYLAND RECEIVED JANUARY 24, 1949

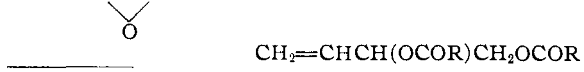
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation and Properties of Aliphatic Esters of Erythrol

BY WILLET F. WHITMORE AND IRVING J. KREMS[1,2]

The recent appearance of butadiene monoxide in commercial quantities[3] has made available a practical source of the diesters of vinylethylene glycol, erythrol. However, since only the diacetate[4] had been reported, it proved of interest to prepare most of the lower and some of the higher aliphatic diesters and study certain of their properties.

The diacetate, dipropionate and dibutyrate were obtained in 61–76% yield by the action of the appropriate acid anhydride on butadiene monoxide in the presence of anhydrous iron(III) chloride catalyst.



$$\mathrm{CH_2{=}CH\underbrace{CHCH_2}_{O} + (RCO)_2O \xrightarrow{Fe_2Cl_6} CH_2{=}CHCH(OCOR)CH_2OCOR}$$

Since the higher anhydrides were not readily available a more convenient general synthetic procedure was sought. The simplest appeared to be the reaction of 1 mole of oxide with at least two of the acid in the presence of a catalyst such as anhydrous iron(III) chloride to effect conversion first to the hydroxy ester, which could then be esterified to the desired diester by the excess acid present. This was tried for the preparation of the dicaprylate, but the only fair yield (40%) led to further revision. Thus, in the case of the dipalmitate only 1 mole of the acid was treated with 1 mole of the oxide to primarily form the hydroxy ester. This was then treated with an equivalent quantity of palmitoyl chloride in pyridine to effect conversion to the diester. The poor yield (22%) of pure product may be attributed to the consumption of oxide by side proc-

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(1) Abstracted from a dissertation by Irving J. Krems submitted to the Graduate Faculty of the Polytechnic Institute of Brooklyn, June 1947, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Present address: Colgate-Palmolive-Peet Co., Jersey City, N. J.

(3) Columbia Chemical Division, Pittsburgh Plate Glass Co.

(4) Henninger, *Ann. chim. phys.*, [6] **7**, 214 (1886).

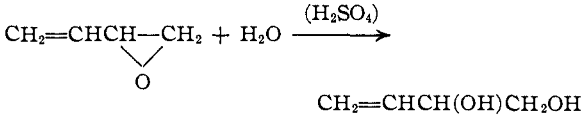
TABLE I

PROPERTIES OF ALIPHATIC DIESTERS OF ERYTHROL

Diester	B. p., °C.	Mm.	$n^{20}D$	d^{20}_{20}	Molar refraction Calcd.	Molar refraction Found	Sapn. eq. Calcd.	Sapn. eq. Found	Unsatd. eq. Calcd.	Unsatd. eq. Found	Formula	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
Diacetate[4]	205–206[a]	760[f]	1.4309	1.0658	42.0	41.7	86.0	85.0	86.0	85.5[b]					
Dipropionate	225–226[a]	760[g]	1.4328	1.0230	51.2	50.9	100.1	99.4	100.1	101.1[c]	$C_{10}H_{16}O_4$	60.0	59.9	8.0	8.1
Dibutyrate	249–250[a]	760[h]	1.4346	0.9880	60.5	60.2	114	113	114	116[c]	$C_{12}H_{20}O_4$	63.3	63.2	8.5	8.8
Divalerate	146–147	7[i]	1.4378	0.9675	69.7	69.4	128	128	128	131[d]	$C_{14}H_{24}O_4$	65.5	65.7	9.4	9.1
Dicaprylate	163–165	0.8	1.4458	0.9343	97.4	97.1	170	172	170	173[d]	$C_{20}H_{36}O_4$	70.8	70.5	10.7	10.9
Dipalmitate	30.5–31.8[j]						282	284	282	280[d]	$C_{36}H_{68}O_4$	76.5	76.3	12.1	12.1
Distearate	38.0–38.3[j]						310	307	310	312[e]	$C_{40}H_{76}O_4$	77.4	77.7	12.3	12.2

[a] Slight decomposition. [b] By bromine absorption,[5] four hours contact time. [c] By bromine absorption,[5] one and one-half hours contact time, some substitution observed. [d] Rapid Wijs method.[6] [e] Standard Wijs method, one hour contact time. [f] B. p. 75–77° at 6 mm. [g] B. p. 68–70° at 2 mm. [h] B. p. 78° at 1 mm. and 108–110° at 5 mm. [i] B. p. 95° at 0.3 mm. [j] Melting point.

esses such as polymerization. In the remaining preparations the butadiene monoxide was first hydrolyzed to erythrol which was then esterified with the appropriate acid chloride in pyridine:



$$CH_2{=}CHCH{-}CH_2 + H_2O \xrightarrow{(H_2SO_4)} CH_2{=}CHCH(OH)CH_2OH$$

$$CH_2{=}CHCHOHCH_2OH + 2RCOCl \xrightarrow{C_5H_5N} CH_2{=}CHCH(OCOR)CH_2OCOR + 2C_5H_5NHCl$$

In this way the divalerate was obtained in 47% yield, and the distearate in 95% yield.

Experimental

Butadiene Monoxide.—A sample of this material was generously furnished by the Columbia Chemical Division of the Pittsburgh Plate Glass Co. Three hundred ninety grams was fractionated through an evacuated, silvered, jacketed column, 1.8 × 70 cm., packed with Pyrex helices, 1/4 inch diameter, using a still head of the total condensation variable take-off type. Ninety two per cent. distilled at 67.5–67.6°. A center cut gave the following constants: b. p. 67.6° (760 mm.); $n^{20.5}D$ 1.4167; d^{20}_{20} 0.8755. The pure material absorbed 99% of the theoretical quantity of bromine after forty-eight hours contact with $N/3$ bromine in carbon tetrachloride solution. The forerun consisted of a few tenths per cent. of minimum boiling azeotrope, b. p. 64.5° which separated into two layers upon standing.

Erythrol.—This was originally prepared by Pariselle[7] by the hydrolysis of butadiene monoxide. Since the experimental details are incomplete, we give our procedure: Fifty milliliters of concd. sulfuric acid was dissolved in 2500 ml. (139 moles) of water in a 5-liter flask fitted with stirrer, condenser and separatory funnel. The contents were cooled externally with cracked ice, and 500 g. (7.15 moles) of butadiene monoxide was added dropwise with efficient stirring over a two-hour period. (Caution should be observed since the reaction, if uncontrolled, has been reported to proceed with explosive violence.)[8] The reaction mixture was then refluxed for three hours, during which time some amorphous brown material was deposited. Upon cooling, the contents were neutralized with barium hydroxide and the precipitated barium sulfate filtered off. The water was removed by vacuum evaporation, and the residue was then distilled under reduced pressure to give 350 g. (56%) erythrol, b. p. 57–58° (2 mm.). Another 40 g. of material, b. p. 86–87° (2 mm.), $n^{20}D$ 1.4728, was also obtained. This compound was unsaturated, soluble in water, and insoluble in ether. It was not further investigated.

Acid Chlorides.—Valeryl chloride was obtained in 71% yield by refluxing valeric acid in thionyl chloride.[9] Palmitoyl chloride was similarly prepared. The crude product obtained in 92% yield by simply evaporating off the excess thionyl chloride was of sufficient purity for our purposes. Stearoyl chloride was prepared in 61% yield by treating the fatty acid with phosphorus(V) chloride in benzene according to the method of Bauer.[10]

Erythryl Diacetate.[4]—Nine grams of anhydrous iron(III) chloride was dissolved in 110 g. (1.08 moles) of acetic anhydride in a 500-ml. round-bottom-flask fitted with a condenser, dropping funnel and stirrer. Seventy grams of (1.0 mole) butadiene monoxide was slowly added dropwise over a period of three-quarters hour with vigorous agitation and external cooling to prevent too rapid a temperature rise. The reaction mixture was filtered with suction, and the filtrate subjected to vacuum distillation. One hundred thirty grams (76%) of colorless mobile liquid with a pleasant ester odor was collected. Erythryl diacetate is easily hydrolyzed. It liberates iodine from a potassium iodide–potassium iodate solution, a fact which must be taken into account when testing for substitution in the bromimetric assay for unsaturation.[5] The compound is miscible in all proportions with methanol, ethanol, ethyl ether, acetic acid, chloroform, carbon tetrachloride, benzene and petroleum ether; it is slightly soluble in water.

Erythryl Dipropionate.—This was prepared in a manner analogous to that for the diacetate, except that after the reaction the mixture was treated with alkali to hydrolyze the catalyst. The ester was taken up in ether, dried, and after evaporation of the solvent, distilled in vacuum. A 65% yield of colorless, mobile, liquid with a pleasant ester odor was obtained. The solubility of the dipropionate is the same as the diacetate in organic solvents; it is only very slightly soluble in water.

Erythryl Dibutyrate.—This was prepared in the same manner as the dipropionate, except that 1.08 moles (171 g.) of butyric anhydride was substituted for the corresponding propionic anhydride. The yield was 140 g. (61%) of a colorless, slightly oily liquid with an ester odor possessing a faint butyric acid undertone. This compound exhibits the same solubility behavior as the dipropionate.

Erythryl Dicaprylate.—Three grams of anhydrous iron (III) chloride was dissolved in 109 g. (0.76 mole) caprylic acid in a 300-ml. round-bottom flask fitted with a condenser, dropping funnel and stirrer. Twenty five grams (0.36 mole) of butadiene monoxide was added, with good agitation, over a five-minute period; this was accompanied by a moderate evolution of heat. The reaction mixture was gradually heated to 150° and maintained at this temperature, with stirring, for one hour. The condenser was set for distillation, and the water slowly distilled out with the aid of a stream of nitrogen until 6 ml. (theory, 7 ml.) was collected. The mixture was diluted with 200 ml. of ether and treated with 170 ml. of 3% sodium hydroxide, and a little Celite to help throw the hydrated iron oxide

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[5] Clark, "Handbook of Organic Analysis," 4 ed., Ed. Arnold and Co., London, 1926, p. 324.

[6] Hofmann and Green, *Oil and Soap*, **16**, 236 (1939).

[7] Pariselle, *Ann. chim. phys.*, [8] **24**, 389 (1911).

[8] Pummerer and Reindel, *Ber.*, **66**, 339 (1933).

[9] Meyer, *Monatsh.*, **22**, 418 (1901).

[10] Bauer, *Oil and Soap*, **23**, 1 (1946).

into the water layer. The ether layer was removed and the aqueous phase extracted with four additional 50-ml. portions of ether. In some cases centrifugation was necessary to ensure complete separation. After drying the combined ether extracts over Drierite, filtering, and removing the solvent on the steam-bath, the residue was distilled at 8 mm. Forty-nine grams (40%) of a colorless, mobile, oily liquid with a faint ester odor was collected at 163–165°. It shows the same solubility behavior as the dipropionate.

Erythryl Dipalmitate.—Fifty-three grams (0.20 mole) of palmitic acid and 2 g. of anhydrous iron(III) chloride were brought into solution with the aid of heat in a 250-ml. round-bottom flask fitted with a stirrer, condenser and separatory funnel. The solution was cooled, and 14.1 g. (0.20 mole) of butadiene monoxide in 50 ml. of benzene was added over a five-minute period. The reaction mixture was then refluxed for three hours, after which 50 ml. of dry pyridine and 60 g. (0.22 mole) of palmitoyl chloride was added with cooling. This was followed by an additional reflux time of two hours. After cooling, 200 ml. of ethyl ether was added and the organic layer was washed with 200 ml. of 3 *N* hydrochloric acid, with water till neutral, then with 200 ml. of 5% sodium hydroxide and finally with water to neutrality. The organic layer was dried over Drierite and, after filtration, the filtrate was stripped of solvent by evaporation under reduced pressure, leaving a residue of crude erythryl dipalmitate. For purification the crude material was first crystallized four times from 250 ml. of petroleum ether (b. p. 23–38°) at −30°. This was followed by four crystallizations from acetone at −25°, and finally four crystallizations at −10° from a methanol-acetone mixture. After drying, 25 g. (22%) of soft cream-colored solid was obtained. The compound is soluble in methanol, slightly soluble in ethanol and acetic acid; very soluble in ethyl ether, chloroform, carbon tetrachloride, benzene, and petroleum ether; insoluble in water.

Erythryl Divalerate.—Eighty-four grams (0.7 mole) of valeryl chloride was slowly added to a mixture of 110 ml. of dry pyridine (1.4 moles) and 100 ml. of dry benzene in a 1-liter round-bottom flask with a reflux condenser fitted with a Drierite tube on top. The formation of the yellow pyridinium salt evolved much heat. A solution of 29 g. of erythrol (0.33 mole) in 50 ml. of dry benzene was slowly added with shaking and the reaction mixture then refluxed for two hours. After cooling, 100 ml. of ethyl ether was added, and the organic layer was washed respectively with 200 ml. of 3 *N* hydrochloric acid, water till neutral, 200 ml. of 5% sodium hydroxide and again with water till neutral. The ether solution was then dried over Drierite. After filtration, the solvent was removed by evaporation under reduced pressure, and the residue was distilled in vacuum. The fraction coming over at 146–147° at 7 mm. was retained. The yield was 40 g. (47%) of a colorless, mobile, oily liquid with a faint ester odor. The solubility behavior was the same as for the dipropionate.

Erythryl Distearate.—This reaction was carried out in essentially the same way as the divalerate. The reflux time, in this case, was increased to three hours. The crude ester was recrystallized once from absolute ethanol; once from a 3:1 ethanol:ether mixture; and once from petroleum ether (38–40°). After drying, a 97% yield of small soft white crystals was obtained. The solubility is the same as found for the dipalmitate.

Acknowledgment.—The authors wish to express their thanks to the Armstrong Cork Co. for their financial support; and in particular to Drs. P. O. Powers and F. W. Breuer for their kindly interest and advice.

Summary

1. Butadiene monoxide was found to form a minimum boiling azeotrope with water at 64.5°. The boiling point, refractive index and density of the highly purified oxide were measured. It was established that butadiene monoxide absorbs bromine quantitatively after forty-eight hours contact time.

2. The preparation and properties of the following diesters of erythrol are described: diacetate, dipropionate, dibutyrate, divalerate, dicaprylate, dipalmitate and distearate.

RECEIVED MARCH 1, 1949

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Decarboxylation of *p*- and *o*-Formylcinnamic Acids to *p*-Formylstyrene and 1-Indanone

BY RICHARD H. WILEY AND PATRICK H. HOBSON[1]

Many of the substituted styrenes recently reported[2] have electrophilic substituents in the nucleus, and, at least with *m*-nitrostyrene,[3] the presence of this type group modifies the polymerizability of the substituted styrene. In continuing our studies of these phenomena, we wish to record our observations on the synthesis of *p*-formylstyrene by decarboxylation of *p*-formylcinnamic acid and the decarboxylation of *o*-formylcinnamic acid to 1-indanone.

p-Formylstyrene was prepared from terephthalaldehyde by condensation with malonic acid followed by decarboxylation of the cinnamic acid. Condensation in a one to one mole ratio gave 62% of *p*-formylcinnamic acid along with an undetermined amount of phenylenediacrylic acid. The two were separated by extraction of the *p*-formylcinnamic acid from the solid reaction mixture with chloroform. A one to two mole ratio gave 70–80% of *p*-phenylenediacrylic acid. Decarboxylation of *p*-formylcinnamic acid to *p*-formylstyrene gave low yields by previously described techniques[3,4] but 52–55% was obtained by dropping a quinoline solution of the aldehyde into a flask containing copper at 310°. Decarboxylation of *p*-phenylenediacrylic acid gave 45–54% of *p*-divinylbenzene.

The condensation of phthalaldehyde with malonic acid in a one to one mole ratio gave 67% of *o*-formylcinnamic acid, m. p. 163–164°. Re-

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[1] Du Pont Company Postgraduate Fellow, 1948–1949.

[2] Wiley and Smith, THIS JOURNAL, **70**, 1560 (1948).

[3] Wiley and Smith, *J. Polymer Science*, **3**, 444 (1948).

[4] Walling and Wolfstirn, THIS JOURNAL, **69**, 852 (1947).