TABLE I

OXIDATION OF AROMATIC AMINES[a] WITH SODIUM PERBORATE[b]

Amine	Reaction temp., °C.[c]	Normality of acetic acid	Product	M.p., °C. found	M.p., °C. reported	Yield, %
p-Bromoaniline	35	20.68[d]	4,4'-Dibromoazobenzene	204–205	205[e]	44.08
	40	20.68	4,4'-Dibromoazobenzene			49.40
	40	18.93	4,4'-Dibromoazobenzene			20.83
	40	10.67	4,4'-Dibromoazobenzene			7.30
	45	20.68	4,4'-Dibromoazobenzene			50.42
p-Chloroaniline	35	20.68	4,4'-Dichloroazobenzene	187	188[f]	37.67
	40	20.68				43.61
	40	18.93				19.11
	40	10.67				6.52
	45	20.68				44.77
	50	20.68				48.37
p-Toluidine	35	20.68	4,4'-Azotoluene	144	144[g]	15.17
	40	20.68				20.08
	45	20.68				26.43
	50	20.68				29.95
p-Nitraniline	40	20.68	4,4'-Dinitroazobenzene	216	216[h]	20.31
p-Aminobenzoic acid	40	20.68	Azobenzene-4,4'-dicarboxylic acid	Dec. at 330	Dec. at 330[i]	38.8

[a] One-hundredth mole dissolved in 20 cc. of acetic acid. [b] Sufficient to yield 0.01 atom proportion of oxygen (1.66 g.). [c] The reaction was carried out for 3 hours. [d] Glacial acetic acid. [e] Heilbron and Bunbury, "Dictionary of Organic Compounds," Vol. 1, Eyre and Spottiswoode Ltd., 1943, p. 680. [f] *Ibid.*, p. 739. [g] *Ibid.*, p. 892. [h] Zincke und Kuchinbecker, *Ann.*, **330**, 28 (1904). [i] Heilbron and Bunbury, ref. *e*, p. 202.

ture by steam distillation. Anisidine undergoes too rapid oxidation in glacial acetic acid yielding an intractable black amorphous powder. However, the sodium perborate oxidation of anisidine can be successfully accomplished in aqueous media.

In general the sodium perborate–acetic acid reagent produces higher yields of azo-compounds by oxidation of aniline and its para-substitution products than equivalent mixtures of hydrogen peroxide–acetic acid. Addition of an amount of boric acid, equivalent to that in sodium perborate, to this latter mixture improves the yields of oxidation products.

Experimental[3]

General Procedure.—The aromatic amine and sodium perborate are individually dissolved in a convenient volume of glacial acetic acid and after adding the solution of the aromatic amine to that of perborate, allowed to react at about 40 to 50°. After cooling to room temperature, the crystals so obtained are collected and washed with water to remove the adhering acetic acid. No other process for the isolation or purification of the crystals is required except in the case of aniline and anisidine. Table I summarizes the data obtained for a series of para-substituted aromatic amines in which variations in reaction temperature and normality of acetic acid were studied.

Oxidation of Aniline.—Freshly distilled aniline (3.72 g., 0.04 mole) was dissolved in 80 cc. of glacial acetic acid and added to the same volume of glacial acetic acid containing 6.628 g. (0.04 atom of oxygen). After 3 hours reaction at 40°, the mixture was steam distilled. The solid distillate obtained (yield 17.9%) was recrystallized from absolute ethanol. The orange colored crystals weighed 0.547 g. (15.05%) and melted at 68°. The reported m.p. of azobenzene is 68°.[4]

Oxidation of Anisidine.—Sodium perborate (3.314 g., 0.02 atom of oxygen) dissolved in 75 cc. of distilled water was added to 2.46 g. (0.02 mole) of anisidine suspended in 75 cc. of water containing sodium acetate (8 g.) and the mixture allowed to stand at room temperature (29°) for 48 hours. The brown precipitate thus obtained was recovered by filtration, eluted with 40 cc. of absolute ethanol at room temperature (29°) yielding a yellow residue which after recrystallization from hot absolute ethanol yielded 0.3466 g. (13.43%) of bright yellow needles, m.p. 118° (turbid melt becoming clear at 133°). The reported m.p. of 4,4'-azoxy-anisole[5] is 118–119° clearing at 135°.

Hydrogen Peroxide, Boric Acid, Acetic Acid as Oxidation Media.—Experiments were carried out in order to compare the effect of (a) sodium perborate and acetic acid, (b) hydrogen peroxide, boric acid and acetic acid and (c) hydrogen peroxide and acetic acid. The sodium perborate used was 1.657 g. (0.01 atom of oxygen) dissolved in 40 cc. of glacial acetic acid. The hydrogen peroxide comprised 11.4 cc. of 1.75 *N* (0.01 atom of oxygen) dissolved in 40 cc. of glacial acetic acid. The quantity of boric acid (0.686 g.) was the same as present in 1.657 g. of sodium perborate. The reactions were carried out at 50° for three hours and the products recovered by the method described in the General Procedure.

YIELDS OF RECRYSTALLIZED PRODUCTS

	a	*b*	*c*
4,4'-Dibromoazobenzene	25.22	21.85	18.68
4,4'-Dichloroazobenzene	23.80	19.23	17.26
4,4'-Azotoluene	11.63	9.01	5.77

(3) All melting points are uncorrected.

(4) Heilbron and Bunbury, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottiswoode Ltd., 1943, p. 201.

(5) Heilbron and Bunbury, *ibid.*, p. 819.

DEPARTMENT OF CHEMISTRY
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New Esters of Pentaerythritol[1]

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For use in stereochemical studies, which we hope to describe in a later publication, the following compounds were prepared and characterized.

Experimental

Pentaerythritol Tetrachloroacetate (A).—Under anhydrous conditions 2.0 g. of pentaerythritol was refluxed with 8.3 g. of chloroacetyl chloride for 45 minutes. Excess acid chloride was then removed by vacuum distillation. The residue solidified on cooling, giving 7.0 g. of product, m.p.[3]

(1) We are indebted to the National Research Council (Canada) for a grant in support of this work.

(2) Fellow of the Canadian Industries, Limited, 1949–1951.

(3) Melting and boiling points corrected. M.p.'s were determined on the Köfler micro-block. Analyses by Mr. R. Pyke.

65–87°. After two recrystallizations from ethanol, 5.4 g. (83%) of colorless leaflets, m.p. 94.5–96°, was obtained. Admixture of product from procedure (B) did not depress the m.p.

(B).—Under anhydrous conditions a mixture of 13.6 g. of pentaerythritol, 85.5 g. of chloroacetic anhydride and 0.5 g. of fused zinc chloride was boiled at 20 mm. pressure under reflux until the initial vigorous reaction had subsided, and then heated below the boiling point on a steam-bath for three hours. The (hot) mixture was poured into 200 ml. of water and allowed to stand overnight. The product separated as an oil. Addition to the mixture of 100 ml. of ethanol failed to cause crystallization. The aqueous ethanolic phase was separated and discarded. On addition of 50 ml. more ethanol to the non-aqueous phase, crystallization occurred. By filtration and washing with ethanol, 14.5 g. of colorless crystals, m.p. 55–56°, was obtained.

Recrystallization of 11.6 g. from 200 ml. of absolute ethanol gave 7.0 g. (16%) of colorless leaflets, m.p. 100.5–101°.

Anal. Calcd. for $C_{13}H_{16}Cl_4O_8$: C, 35.32; H, 3.65. Found: C, 35.42; H, 3.47.

By procedure (A) one obtains the product in much higher yield, and its purity is satisfactory for most purposes.

The compound gave a positive Beilstein halogen test, but reacted with alcoholic silver nitrate only after many minutes of boiling.

Reaction of α-*p*-Nitrophenylbutyryl Chloride with Pentaerythritol.—Finely divided, dry portions of *d,l*-α-*p*-nitrophenylbutyric acid (m.p. 118–120°)[4,5] (5.0 g.) and of phosphorus pentachloride (5.1 g.) were mixed. The mixture soon liquefied, with evolution of hydrogen chloride. The mixture was gently boiled for ten minutes, then phosphorus oxychloride was removed by vacuum distillation. The residue upon vacuum distillation gave 4.67 g. (86%) of *d,l*-α-*p*-nitrophenylbutyryl chloride as a bright yellow liquid of b.p. 172–174° (10 mm.), $n^{26}D$ 1.5505, which could not be induced to crystallize. To characterize the product, it was treated with ethanol and sodium hydroxide under Schotten–Baumann conditions, giving *d,l*-ethyl α-*p*-nitrophenylbutyrate, b.p. 145–150° (2–3 mm.), $n^{24}D$ 1.5202, d^{28} 1.133. The constants are in good agreement with those for the ester prepared[5] directly from the acid.

When the acid chloride (5.7 g.) was heated with 0.55 g. of pentaerythritol at 150° for 20 minutes, the product was obtained as a yellow oil, which solidified on prolonged shaking with ethanol to give 3.3 g. of material, m.p. 90–122°. After seven recrystallizations from ethanol the colorless product (0.66 g., 30%) still melted over a wide range (130–153°). The molecular weight (Rast method) was found to be 810 (theor. for $C_{45}H_{48}N_4O_{16}$, 901). It is presumably a mixture of the three theoretically possible racemic forms, and has not been further characterized.

***d,l*-Pentaerythritol Tetra-[2-(carbo-2-methylbutoxy)-6-nitrobenzoate].**—Under anhydrous conditions, 5.0 g. of *dextro*-2-methylbutyl 2-carboxy-6-nitrobenzoate[6] (m.p. 160–161°, $[\alpha]^{25}D$ +2.56° (acetone, *c*, 32)) was refluxed with 10 ml. of thionyl chloride for one hour. After removal of thionyl chloride by vacuum distillation, the residue was recrystallized from dry petroleum ether, giving colorless leaflets of m.p. 60–62°. After two more recrystallizations, 4.5 g. (84%) of *dextro*-2-methylbutyl 2-chloroformyl-6-nitrobenzoate, m.p. 61–62°, $[\alpha]^{25}D$ +0.69° (ethyl acetate, *c*, 17.3), was obtained.

To one gram of the acid chloride in 2 ml. of dry pyridine was added 0.10 g. of pentaerythritol. The warm mixture was cooled, and after 17 hours at 25° was added at 0° to 10 ml. of 10% sulfuric acid. The aqueous phase was decanted and the semi-solid organic residue recrystallized twice from ethanol, giving 0.75 g. (86%) of fine colorless needles, m.p. 111–114°. A sample was recrystallized again for analysis, and dried at 80° (10 mm.); m.p. 113–115°.

Anal. Calcd. for $C_{57}H_{64}N_4O_{24}$: C, 57.57; H, 5.43; N, 4.71. Found: C, 57.18; H, 5.17; N, 5.12.

Recrystallization from benzene–ligroin changed the m.p. to 85–95°, but when this low-melting form was recrystallized from ethanol the m.p. was restored to 113–115°.

The product gave no optical rotation and was apparently racemic.[7] An identical product was obtained when the same reactions were carried out with the 3-nitrophthalate of *d,l*-2-methylbutanol. A mixed m.p. on the two final products showed no depression.

Three racemic forms are theoretically possible for the pentaerythritol ester but thus far only the product above has been isolated.

(4) C. S. Marvel and T. Chu, THIS JOURNAL, **55**, 2841 (1933).
(5) A. L. Wilds and W. R. Biggerstaff, *ibid.*, **67**, 789 (1945).
(6) A. McKenzie, *J. Chem. Soc.*, **79**, 1135 (1901).
(7) Since the observed rotation of the acid chloride from the *dextro*-3-nitrophthalate was only + 0.12°, the racemization may have occurred during chlorination.

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Chloromycetin.[1] Related Compounds. The β-*p*-Nitrophenylserines

BY G. W. MOERSCH, M. C. REBSTOCK, A. C. MOORE AND D. P. HYLANDER

Chloromycetin has been shown to be D_G-(−)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol.[2] In exploring related substances, several authors[3,4,5] have reported on β-*p*-nitrophenylserine and its N-dichloroacetyl derivative which differs from Chloromycetin in having a carboxyl in place of the primary carbinol group. β-*p*-Nitrophenylserine has been prepared by (1) nitration of the N-acetate of Erlenmeyer's β-phenylserine,[3] by (2) direct nitration of Erlenmeyer's β-phenylserine,[4] by (3) the condensation of *p*-nitrobenzaldehyde with ethyl glycinate over sodium,[6] and recently by (4) the condensation of *p*-nitrobenzaldehyde with ethyl glycinate in alcohol solution without a catalyst.[7]

On the basis of microbiological testing, Billet[8] has claimed from unpublished work, a difference suggesting that the β-*p*-nitrophenylserine obtained by Method 3 was not the same as that from Method 2. Since the Erlenmeyer β-phenylserine has been shown to be of the *threo* configuration, Method 3 was considered to give the *erythro* form. However, the attempt to show non-identity of the two acids and to correlate their configurations with the chloramphenicols by microbiological activities was later reported to be unsatisfactory since the activity difference was too small. The N-dichloroacetyl derivatives were then prepared, but the melting points were the same and no mixed melt was reported.[9] The N-dichloroacetyl-β-*p*-nitrophenylserine prepared in the manner of Method 1 has since been found to have no microbiological activity *vs. S. sonnei*. Since this substance can be shown to be the *threo* modification, it follows that Billet's hope of assigning configuration on the basis of anticipated differing microbiological activities and on the assumption that these must parallel the chloramphenicol activities, must fail.

We have investigated each method of preparation and have been able to demonstrate by chemical methods that the products of Methods 3 and

(1) Parke, Davis & Co. registered trademark for chloramphenicol.
(2) M. C. Rebstock, *et al.*, THIS JOURNAL, **71**, 2460 (1950).
(3) D. W. Woolley, *J. Biol. Chem.*, **185**, 293 (1950).
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(5) C. F. Huebner and C. R. Scholz, THIS JOURNAL, **73**, 2089 (1951).
(6) C. E. Dalgliesh, *J. Chem. Soc.*, 90 (1949).
(7) E. D. Bergmann, *et al.*, *Compt. rend.*, **231**, 361 (1950).
(8) D. Billet, *ibid.*, **230**, 1074 (1950).
(9) D. Billet, *ibid.*, **231**, 293 (1950).