concentration in accordance with Equation 5. Three runs were performed without phenolic catalyst and with a sufficient excess of camphene to make its concentration substantially constant. The values of c were 0.284, 0.347 and 0.256 in these runs, which yielded values of k_2 equal to 0.0528, 0.0454 and 0.0588, respectively. These results fit rather well the equation

$$k_2 = 0.0153/c$$

Now from any run using a phenolic catalyst, the best value of k_1 can be selected by successive approximations. Two representative points are selected near the beginning and end of the run. A rough value is assumed for k_1. Using this value in the left-hand side of Equation (7), the two representative points yield a new value for k_1, leading to a better approximation. This process is repeated until the calculated k_1 checks that assumed in the calculation. The plot of Equation (7) must now be linear for the entire run, using the determined value of k_1. An example of this treatment for the most unfavorable case is provided by Run C-19, with 0.101 M picric acid as a catalyst, in which only 20% of the observed apparent first-order rate was due to the phenol and the rest to the small suppressed concentration of hydrogen chloride. The curve in Fig. 3 represents the data for this run plotted as a unimolecular reaction; the straight line is the plot of Equation (7) taking $k_2 = 0.053$ and $k_1 = 0.00326$. The units of all rate constants in this paper are moles per liter and hours.

Summary

The rearrangement of camphene hydrochloride into isobornyl chloride in nitrobenzene is catalyzed by *p*-cyanophenol, phenol, *o*-cresol, and picric acid in decreasing order of effectiveness. The unimolecular rate constant k_1 for the phenol-catalyzed rearrangement varies with the concentration of the phenol according to the equation $k_1 = a(P) + b(P)^2$ where a and b are constants for each phenol. This indicates two simultaneous mechanisms for the rearrangement, one involving the attack of a single phenol molecule, and the other involving the attack of two phenol molecules, or a phenol dimer, on the chloride. This parallels the kinetics of alcoholysis of *p*-methoxybenzhydryl chloride in nitrobenzene, previously studied. In the present case, since the product is a chloride and not a phenol ether, the attack of the phenol can be only on the chlorine of camphene hydrochloride. Its function is evidently to solvate the chloride ion through hydrogen bonding. The catalytic efficiencies of the phenols are in the order of their hydrogen bonding powers. This is also the order of their acid strengths except where ortho-substituted phenols are concerned.

CAMBRIDGE, MASSACHUSETTS
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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some Normal and Alkamine Esters of 4-Methoxyisophthalic Acid

BY L. S. FOSDICK AND O. E. FANCHER

Since Einhorn and Uhlfelder[1] first published their reports on novacain, a large number of compounds possessing local anesthetic activity has been synthesized. Although many anesthetics have been prepared whose structures bear no relation to novacain, a large number of very active compounds having similar structure have been made. It was pointed out by Shriner and Keyser[2] that the most effective anesthetics of the ester type have a carbonyl group conjugated with double bonds. This is almost invariably true with the ester type of anesthetic of which novacain is the most conspicuous member. It was thought that if one carbonyl group conjugated with a double bond was so effective, perhaps two carbonyl groups conjugated with double bonds in the same molecule might be more effective. It was found that esters of isophthalic acid would fulfill this requirement. In so far as it has been shown that various substituents in the ring[3,4] enhance anesthetic activity, it was thought that esters of 4-methoxy or 4-aminoisophthalic acid would be interesting. This paper deals with the synthesis of some esters of 4-methoxyisophthalic acid. The esters of 4-aminoisophthalic acid are now in the process of synthesis. All of the esters

(1) Einhorn and Uhlfelder, *Ann.*, **371**, 131 (1909).
(2) Shriner and Keyser, THIS JOURNAL, **60**, 286 (1938).
(3) Rohmann and Schuerle, *Arch. Pharm.*, **274**, 110 (1936).
(4) Coles and Lott, THIS JOURNAL, **58**, 1489 (1936).

are prepared according to the series of reactions in the accompanying chart.

Eastman Kodak Co. 4-amino-1,3-dimethylbenzene I was diazotized and hydrolyzed to give 4-hydroxy-1,3-dimethylbenzene II.[5] This was methylated with methyl sulfate to yield 4-methoxy-1,3-dimethylbenzene III. This compound was oxidized by neutral permanganate to the corresponding acid IV[6] which was then converted to the acid chloride V by means of thionyl chloride. The acid chloride was then treated with excess of the alcohol or amino alcohol to yield the corresponding esters VI and VII.

Preliminary pharmacological data indicate that these esters are less toxic than the procaine series and have an anesthetic efficiency of somewhat the same magnitude. Complete pharmacological data will be published elsewhere.

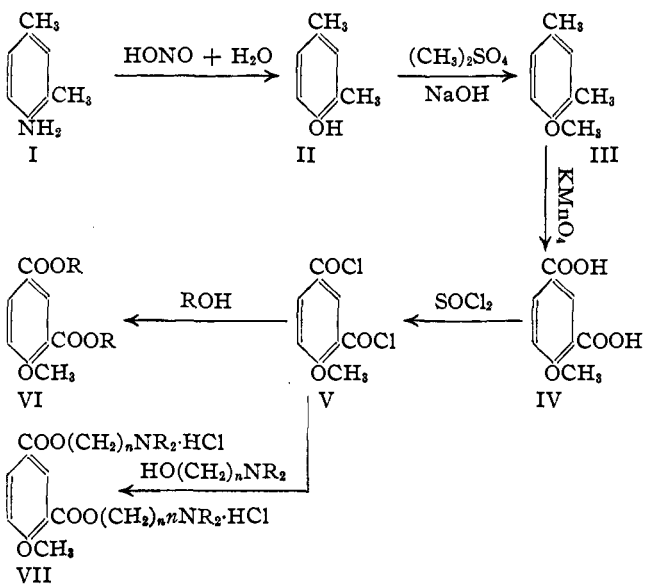

CHART I

Experimental

4-Methoxyisophthalic Acid.—This was obtained by neutral oxidation of 4-methoxy-*m*-xylene prepared from Eastman Kodak Co. 4-amino-1,3-dimethylbenzene by diazotization and acid hydrolysis followed by methylation of the 4-hydroxy-*m*-xylene with methyl sulfate. 13.8 grams of 4-methoxy-*m*-xylene in 100 cc. of water in a 3-necked flask equipped with a mechanical stirrer and a reflux condenser was heated to boiling and a hot aqueous solution of 65 g. of potassium permanganate was added over a period of three hours. The solution was filtered and acidified with concd. hydrochloric acid. The 4-methoxyisophthalic acid which precipitated as a white flocculent solid was filtered and dried; yield 11.8 g. or 60% of the theoretical; m. p. 255–256°.

4-Methoxyisophthalyl Chloride.—Ten grams of 4-methoxyisophthalic acid was heated under reflux for eight hours with excess thionyl chloride. The excess thionyl chloride was removed by heating the reaction mixture on the steam-bath under a slight vacuum. Dry benzene was added and the solution was again evaporated under a slight vacuum to remove traces of thionyl chloride. The residue solidified on cooling and was twice recrystallized from anhydrous heptane as white needle-like crystals; yield 9.8 g. or 83% of the theoretical; m. p. 78°.

Anal. Calcd. for $C_9H_6O_3Cl_2$: Cl, 30.47. Found: Cl, 30.18.

Dialkylaminoalkanols.—The diethylaminoethanol used was secured from Eastman Kodak Co. and was redistilled just prior to use. The other amino alcohols were prepared by heating two moles of the corresponding amine with one mole of ethylene or trimethylene chlorohydrin according to the method of Adams.[7] For di-*n*-butylamine with ethylene chlorohydrin or trimethylene chlorohydrin refluxing sufficed, but for diethylamine and di-*n*-propylamine with trimethylene chlorohydrin and di-*n*-propylamine with ethylene chlorohydrin, the reaction was carried out in an iron bomb heated to 110° for three hours. In each case the reaction product was diluted with dry acetone, filtered, dried over anhydrous sodium sulfate and distilled; yields 70–80%.

Di-alkyl 4-Methoxyisophthalates.—A search of the literature revealed that the simple esters of 4-methoxyisophthalic acid had not been reported. For the preparation of these esters the acid chloride was refluxed with an excess of the appropriate alcohol for one hour. The reaction mixture was then cooled and diluted with water. The white precipitate was then filtered, dried and recrystallized from alcohol. The ethyl ester had a tendency to separate as an oil but solidified on standing; yields 74–98%.

Dialkylaminoalkyl-4-methoxyisophthalates.—For the preparation of the hydrochlorides of the alkamine esters the acid chloride was dissolved in anhydrous benzene and two molar proportions of the corresponding aminoalcohol dissolved in dry benzene were added and the solutions were refluxed for thirty minutes.[8] The hydrochlorides were filtered, washed free of benzene with anhydrous ether and placed in a vacuum desiccator. The hydrochlorides were dissolved in absolute alcohol, decolorized with activated charcoal (Norit), and precipitated by the addition of dry ether.

The hydrochloride of the di-*n*-propylaminoethyl ester was quite hygroscopic and could not be successfully recrystallized. The free base was obtained by making its water solution basic with ammonia, extracting with ether, drying and evaporating the ether. The borate of this compound was obtained as a white crystalline solid by extraction of boric acid with the acetone solution of the free base in a Soxhlet apparatus.

The hydrochloride of the di-*n*-butylaminopropyl ester could not be obtained in crystalline form and attempts to

(5) Harmsen, *Ber.*, **13**, 1558 (1880).
(6) Jacobsen, *ibid.*, **11**, 898 (1878).
(7) Adams, *et al.*, THIS JOURNAL, **59**, 2248 (1937).
(8) Kamm *ibid.*, **42**, 1030 (1920).

TABLE I

Compound	Yield, %	M. p., °C.	Formula	Analyses, % Calcd.	Found
4-Methoxyisophthalyl chloride	83	78	$C_9H_6O_3Cl_2$	Cl, 30.47	30.18
-(isophthalate)-					
Dimethyl-4-methoxy-(-)	98	94	$C_{11}H_{12}O_5$	C, 58.93	59.01
Diethyl-4-methoxy-(-)	74	57	$C_{13}H_{16}O_5$	C, 61.90	61.80
Diethylaminoethyl-4-methoxy-(-)	70	209–210	$C_{21}H_{33}O_5N_2Cl_2$	N, 6.00	5.94
Di-*n*-propylaminoethyl-4-methoxy-(-) borate	69[a]	[b]	$C_{25}H_{50}O_{24}N_2B_{10}$[c]	N, 3.20	3.58
Di-*n*-propylaminoethyl-4-methoxy-(-)	61	[d]	$C_{25}H_{42}O_5N_2$	N, 6.22	6.12
Di-*n*-butylaminoethyl-4-methoxy-(-)	60	120–122	$C_{29}H_{54}O_5N_2Cl_2$	N, 4.84	4.79
Diethylaminopropyl-4-methoxy-(-) hydrochloride	75	193–195	$C_{23}H_{42}O_5N_2Cl_2$	N, 5.66	5.75
Di-*n*-propylaminopropyl-4-methoxy-(-) hydrochloride	69	150–152	$C_{27}H_{50}O_5N_2Cl_2$	N, 5.08	5.05
Di-*n*-butylaminopropyl-4-methoxy-(-)	69	[d]	$C_{31}H_{56}O_5N_2$	N, 4.84	4.79

[a] Yield based on free base. [b] Decomposes. [c] By analogy with formula for procaine borate given in May, "Chemistry of Synthetic Drugs," Longmans, Green & Co., New York, 1939, p. 123. [d] Darkens without boiling at 210° < 0.1 mm.

prepare the hydrobromide and the borate were unsuccessful, sticky products being obtained in each case.

The constants and yields of the compounds prepared are given in Table I.

Summary

1. Some normal and alkamine esters of 4-methoxyisophthalic acid have been prepared.

2. Preliminary pharmacological data indicate an anesthetic efficiency approximately equal to that of procaine.

CHICAGO, ILLINOIS RECEIVED DECEMBER 30, 1940

[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

Antioxidants and the Autoxidation of Fats. XIII. The Antioxygenic Action of Ascorbic Acid in Association with Tocopherols, Hydroquinones and Related Compounds

BY CALVIN GOLUMBIC AND H. A. MATTILL

The capacity of ascorbic acid to act as an inhibitor of fat oxidation has been suggested or implied in a number of recent papers.[1] Notwithstanding the slight solubility in lipids, both *d*- and *l*-ascorbic acid alike have an appreciable antioxygenic action in various fat substrates (Table I). To lengthen the induction period of lard a fairly high concentration must be used, but in cottonseed oil or its esters much smaller quantities suffice. These substrates contain inhibitols, principally tocopherols, and ascorbic acid reinforces their stabilizing action. When tocopherol is removed from vegetable oils, as can be done by various means, the recovered oils are no longer stabilized by ascorbic acid.

According to Isler[2] the extent of oxidation of α-tocopherol adsorbed on an inert carrier in the presence of ascorbic acid was only 6% of that which occurred during the same period in the absence of ascorbic acid. The oxidation of α-tocopherol when dissolved in an animal fat substrate is also retarded by ascorbic acid; this appears from the figures given in Table II. With like amounts of tocopherol initially present, in-

TABLE I

THE ANTIOXYGENIC PROPERTIES OF ASCORBIC ACID

Substrate	Inhibitors added	Induction period[a] at 75° With inhibitor, hr.	Induction period[a] at 75° Control, hr.
Lard	0.40% Ascorbic acid	39	19
	.20% Ascorbic acid	31	19
	.10% Ascorbic acid	24	21
	.04% β-Tocopherol	169	21
	.04% β-Tocopherol + 0.10% Ascorbic acid	268	21
Hydrogenated cottonseed oil	.01% Ascorbic acid	73, 80[b]	40, 45[b]
Crude ethyl esters of hydrogenated cottonseed oil	.02% Ascorbic acid	210 223	4 5

[a] Oxygen absorption method. [b] The induction period is given in days (oven test, 63°).

(1) Kieferle and Seuss, *Milchw. Forsch.*, **20**, 23 (1939); Trout and Gjissing, *J. Dairy Sci.*, **22**, 271 (1939); Gray and Stone, *Food Indust.*, **2**, 629 (1939).

(2) Isler, *Helv. Chim. Acta*, **21**, 1756 (1938).