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Solid Derivatives of Monoalkyl Ethers of Ethylene Glycol and Diethylene Glycol

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Inasmuch as the monoalkyl ethers of ethylene glycol and diethylene glycol, known, respectively, as the cellosolves and the carbitols, have gained considerable commercial importance, it seemed desirable to extend the number of solid derivatives of these types of compounds. Whitmore and Lieber[2] found that the potassium xanthates of the monoalkyl ethers of ethylene glycol were crystalline solids having definite melting points. They described the potassium xanthate of ethyl carbitol as an orange-colored pasty solid melting at 127°, while the potassium xanthate of butyl carbitol was described as a thick reddish jelly-like solid. These are the only solid derivatives of the carbitols described in the literature. Ashburn, Collett and Lazzell[3] found that a number of β-alkoxyethyl *p*-aminobenzoates were solids having definite melting points. Palomaa[4] has prepared the benzoates of some monoalkyl ethers of ethylene glycol, while Conn, Collett and Lazzell[5] have extended Palomaa's method to include the benzoates and *p*-nitrobenzoates of the monoalkyl ethers of ethylene glycol and of diethylene glycol. All but one of these derivatives are high-boiling liquids. The one solid is β-methoxyethyl *p*-nitrobenzoate, which melts at 50.5°.

Some preliminary work on this problem was done by Griffin,[6] who found that the usual reagents for alcohols, *e. g.*, phenyl isocyanate, α-naphthyl isocyanate[7] and 3,5-dinitrobenzoyl chloride, failed to give solid derivatives. Recently, however, Veraguth and Diehl[8] have reported the preparation of solid 3-nitrophthalates of some cellosolves. They found that the initial crystallization of these compounds was very slow, several days in a refrigerator being required in some cases.

Griffin[6] tried the reaction between tetrachlorophthalic anhydride and β-ethoxyethoxymagnesium bromide following the procedure which Fessler and Shriner[9] developed for making solid derivatives of tertiary alcohols. While the product obtained had a marked softening point at 73.5–74.0°, it did not melt completely until the temperature reached 250° (uncor.), which is the melting point of tetrachlorophthalic anhydride. Recrystallization simply raised the softening point. Griffin[6] considered the possibility of making the Grignard reagent from the β-bromoethyl alkyl ether and then making the α-naphthalide by the interaction of the Grignard reagent and α-naphthyl isocyanate.[10] However, Tallman[11] has shown that the β-bromoethyl alkyl

(1) This material is taken from a thesis to be submitted by Joseph F. Manning to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Whitmore and Lieber, *Ind. Eng. Chem., Anal. Ed.*, **7**, 127 (1935).

(3) Ashburn, Collett and Lazzell, THIS JOURNAL, **57**, 1862 (1935).

(4) Palomaa, *Ber.*, **42**, 3873 (1909).

(5) Conn, Collett and Lazzell, THIS JOURNAL, **54**, 4370 (1932).

(6) Griffin, A. M. Thesis, Boston University, June, 1938.

(7) Recent work in this Laboratory indicates that solid derivatives can be obtained using α-naphthyl isocyanate. These results will be reported later.

(8) Veraguth and Diehl, THIS JOURNAL, **62**, 233 (1940).

(9) Fessler and Shriner, *ibid.*, **58**, 1384 (1936).

(10) Gilman and Furry, *ibid.*, **50**, 1214 (1928).

(11) Tallman, *ibid.*, **56**, 126 (1934).

ethers do not form stable Grignard reagents with magnesium, but yield ethylene, an alcohol having the alkyl group of the ether and a dialkyl ether of butanediol-1,4 formed as a result of the Wurtz reaction. Griffin[6] also attempted to make solid quaternary ammonium salts from β-chloroethyl ether and β-bromoethyl ether using dimethylaniline, diethylaniline and methylbenzylaniline. An oil was formed in each case. These oils either could not be solidified or formed crystals only after standing about two months.

Since the ordinary derivatives of alcohols were not solids when cellosolves and carbitols were used, it seemed necessary to introduce some other group into the molecule and then make a solid derivative by means of a reaction involving the new group. Several possibilities have been tried. Using the reaction between the sodium salts of the ether-alcohols and chloroacetic acid,[12] a carboxyl group was introduced. The acids were then treated with *p*-phenylphenacyl bromide and the esters obtained. The esters obtained by starting with methyl cellosolve and ethyl cellosolve melted at 68 and 52.8°, respectively. When ethyl carbitol was used, a gummy product was obtained. Since the yields of β-alkoxyethoxyacetic acids were only about 50% and since the reaction with *p*-phenylphenacyl bromide was very slow and the melting points of the final esters rather low, this method was not used with any other cellosolves or carbitols. Other derivatives of the β-alkoxyethoxyacetic acids tried were the piperazonium salts,[13] the *p*-toluidides[14] and the S-benzyl thiuronium salts.[15] The piperazonium salts could be obtained as white crystalline solids, though there was a tendency for them to precipitate as oils or gummy solids. In the attempted preparation of the *p*-toluidide, no derivative was obtained and it appeared that the sodium salt of the acid decomposed. With S-benzyl thiuronium chloride and sodium β-ethoxyethoxyacetic acid no precipitate was obtained when the solutions were mixed. On standing overnight at 0° and then evaporating the alcohol at room temperature, urea and an oil which smelled like a mercaptan were obtained.

Reduction of β-ethoxyethyl *p*-nitrobenzoate with zinc and ammonium chloride was tried, but instead of obtaining the substituted hydroxylamine, the products were the amine and the corresponding azo compound.

Since the β-alkoxyethyl *p*-aminobenzoates reported by Ashburn, Collett and Lazzell[3] are solids having rather low melting points, it was probable that the corresponding derivatives of the carbitols would be oils. It seemed to us that higher melting compounds could be obtained by diazotization of the amine group and coupling with dimethylaniline. The azo compounds obtained in this manner from the cellosolves and carbitols used are all solids, and their melting points are given in Table II. Since this procedure involves esterification, reduction, diazotization and coupling, it could hardly be considered satisfactory from the standpoint of qualitative analysis.

A much more satisfactory procedure was found in the preparation of picrates of β-4-morpholinoethyl ethers of the cellosolves and carbitols. The procedure can be carried out with 2 cc. or less of the ether-alcohol and it is not necessary to purify the intermediate ether by distillation. Surprisingly, the melting points of the derivatives obtained from the carbitols are higher than those obtained from the cellosolves. The results are given in Tables III and IV.

A number of other reactions were tried which did not yield sufficiently promising results to warrant further investigation. Diethylaminomethyl β-ethoxyethyl ether was made from diethylamine, formaldehyde and ethyl cellosolve according to the procedure developed by Stewart and Bradley.[16] This ether yielded a gummy picrate only on evaporation of the solution and decomposed when treated with dry hydrogen chloride, but did yield a small amount of what appeared to be a quaternary ammonium salt when treated with ethyl iodide in absolute ether solution.

Oxidation of ethyl cellosolve was attempted using (a) sodium dichromate and sulfuric acid, (b) alkaline potassium permanganate. The yields of ethoxyacetic acid were too low (29 and 33%) for this method to be of any value. Consequently, no solid derivatives of this acid were made.

Attempts were made to prepare β-ethoxyethoxyacetone from the sodium salt of the cellosolve and chloroacetone. Viscous, tarry products were obtained which did not appear sufficiently promising

(12) Palomaa and Siitonen, *Ber.*, **63B**, 3117 (1930).

(13) Pollard, Adelson and Bain, THIS JOURNAL, **56**, 1759 (1934).

(14) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, 1935, p. 144.

(15) Donleavy, THIS JOURNAL, **58**, 1004 (1936).

(16) Stewart and Bradley, *ibid.*, **54**, 4176 (1932).

to warrant further investigation. Similar tarry products were obtained by Sommelet,[17] who studied the reaction between sodium ethoxide and chloroacetone.

The interaction of triphenylchloromethane and the sodium salt of ethyl cellosolve yielded a gummy semi-solid which did not seem at all promising as a derivative.

Experimental

p-Phenylphenacyl Esters of β-Methoxyethoxyacetic Acid and β-Ethoxyethoxyacetic Acid.—β-Methoxyethoxyacetic acid and β-ethoxyethoxyacetic acid were prepared by Palomaa's method.[12] The yield of β-methoxyethoxyacetic acid was 44%; b. p. 149–149.5° (18 mm.). Palomaa found the b. p. to be 121–122° (4 mm.). The yield of β-ethoxyethoxyacetic acid was 55%; b. p. 154.5–155.5° (18 mm.). Palomaa found the b. p. to be 125–126° (4 mm.).

Anal. Neut. equiv. calcd. for $C_6H_{10}O_4$: 148.1. Found: 147.6. Calcd. for $C_5H_{10}O_4$: 134.1. Found: 134.4.

Since Palomaa's method[12] requires the use of two equivalents of sodium β-ethoxyethoxide for one of chloroacetic acid, we tried a number of modifications of the procedure using equivalent quantities of sodium β-ethoxyethoxide and chloroacetic acid. By adding a mixture of 16.7 g. of pyridine and 20 g. of chloroacetic acid dissolved in 30 cc. of absolute ether to an absolute ether suspension of sodium β-ethoxyethoxide made from 20 g. of cellosolve and 5.1 g. of sodium, and following Palomaa's procedure[12] (the mixture was refluxed for two hours instead of one, and twenty-five extractions with ether were made), a yield of 12.3 g. (40%) of pure acid was obtained. On the basis of the amount of cellosolve used, this yield is better than that obtained by Palomaa's method.[12]

The *p*-phenylphenacyl ester of β-ethoxyethoxyacetic acid was made by the procedure given by Shriner and Fuson[18] using 1.2 g. of the β-ethoxyethoxyacetic acid, 2.3 g. of *p*-phenylphenacyl bromide and 37 cc. of alcohol. It was found necessary to reflux for four hours in order to complete the reaction. On cooling, a small amount of white solid and a larger quantity of oil separated. After standing in a desiccator over sulfuric acid for twelve hours and further refluxing in an alcohol solution for two hours, the oil changed to a slightly yellow-colored solid. Recrystallization from an alcohol–water solution (75%–25%) produced white crystals, m. p. 52.5–52.8°; yield, 51.5%.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.14; H, 6.48. Found: C, 69.92; H, 6.53.

The *p*-phenylphenacyl ester of β-methoxyethoxyacetic acid was made similarly. Three hours of refluxing was found sufficient and a white precipitate settled readily when the solution was cooled. After recrystallization from alcohol–water solution (75%–25%) it melted at 68.0°; yield, 61.5%.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.60; H, 6.14. Found: C, 69.12; H, 6.08.

(17) Sommelet, *Ann. chim. phys.*, **9**, 484 (1906).

(18) Ref. 14, p. 144.

Piperazonium Di-β-alkoxyethoxyacetates.—The best method for the formation of these salts was to dissolve 0.97 g. (0.005 mole) of piperazine hydrate in 20 cc. of ether to which a few drops of ethyl alcohol were added. To this was added 0.01 of a mole of the liquid acid. An oily suspension was observed immediately. This was allowed to settle out and the alcohol and ether evaporated. The gummy residue was dissolved in the least possible amount of isobutyl alcohol, and a solid was thrown out by the addition of ether while stirring vigorously. A second or third recrystallization by the same method was necessary to obtain the pure compounds. The yield of piperazonium di-β-ethoxyethoxyacetate was 85.6% and its m. p. 87.0–87.5°.

Anal. Calcd. for $C_{16}H_{34}N_2O_8$: N, 7.32. Found: N, 7.37.

The yield of piperazonium di-β-methoxyethoxyacetate was 79% and its m. p. 44.5–45.0°.

Anal. Calcd. for $C_{14}H_{30}N_2O_8$: C, 47.42; H, 8.54; N, 7.90. Found: C, 47.05, 47.14; H, 8.43, 8.02; N, 7.93, 7.87.

***p*-Nitrobenzoates of Cellosolves and Carbitols.**—These compounds were made using the method of Conn, Collett and Lazzell[5] and also by the method developed by Adams and co-workers[19] for the preparation of *p*-nitrobenzoates of tertiary alcohols. While the yields obtained by the first method were about 20% higher than those obtained by the second method, the time required for the second method was approximately thirty minutes as compared with two and one-half to three hours for the first method. Since the boiling points were taken at different pressures than those used by Conn, Collett and Lazzell, they are given in Table I along with the yields obtained by the Adams method.

***p*-Aminobenzoates of Cellosolves and Carbitols.**—Reduction with iron powder and hydrochloric acid was tried according to the method of Adams and co-workers.[19] While this method was satisfactory, somewhat better yields were obtained using tin and hydrochloric acid. In general, 0.1 of a mole of the cellosolve or carbitol was reduced with 20 g. of granulated tin and 40 cc. of concentrated hydrochloric acid. After no more heat was liberated, the mixture was heated on the steam-bath for thirty to forty-five minutes. After diluting with 20 cc. of water, the solution was extracted with 20-cc. portions of benzene to remove any unreduced nitro compound. After adding an excess of 40% sodium hydroxide solution, the mixture was extracted with ether. The ether solution was dried over Drierite, filtered, the ether distilled and the residue subjected to vacuum distillation. In the reduction of the β-butoxyethyl *p*-nitrobenzoate, the yield was increased by omitting the benzene extractions and the purity of the final product was not affected. Since our reduction procedure was different from that used by Ashburn, Collett and Lazzell[3] and two of our melting points were appreciably higher than their melting points, we are recording these results in Table I. The β-(β'-alkoxyethoxy)-ethyl *p*-aminobenzoates have not been reported previously.

Diazotization and Coupling.—The *p*-(β-alkoxycarbethoxy)-benzeneazo-*p'*-dimethylanilines and *p*-[β-(β'-alkoxy-

(19) Adams and co-workers, THIS JOURNAL, **48**, 1768 (1926).

TABLE I

Alcohol used	*p*-Nitrobenzoates B. p., °C. (16 mm.)	Yield, %	*p*-Aminobenzoates B. p., °C. (mm.)	M. p., °C.	Yield, %
$CH_3OC_2H_4OH$	192.5–195.0	81.3	217.5–219.0 (16)	79.7[c]	68.0
$C_2H_5OC_2H_4OH$	197.0–199.0	73.6	223.0–224.5 (16)	79.2[c]	83.3
$C_4H_9OC_2H_4OH$	208.8–211.0	82.0	232.5–234.0 (16.5)	36.2–36.5	80.8
$C_2H_5OC_2H_4OC_2H_4OH$	222.5–224.0	68.3	257.0–259.0 (20)[a]	64.4	59.7
$C_4H_9OC_2H_4OC_2H_4OH$	246.0–249.0	77.3	262.5–265.0 (16)[b]	...	81.8

[a] *Anal.* Calcd.: N, 5.52. Found: N, 5.41, 5.45. [b] *Anal.* Calcd.: N, 4.98. Found: N, 4.89, 4.95. [c] Mixed melting point, 72.0–73.5°.

TABLE II

p-(β-ALKOXYCARBETHOXY)-BENZENEAZO-*p'*-DIMETHYLANILINES AND *p*-[β-(β'-ALKOXYETHOXYCARBETHOXY)]-BENZENEAZO-*p'*-DIMETHYLANILINES

Alcohol used	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found	
$CH_3OC_2H_4OH$	108.2	88.5	12.83	12.72	12.67
$C_2H_5OC_2H_4OH$	103.0	90.0	12.31	12.24	12.18
$C_4H_9OC_2H_4OH$	73.8	81.6	11.39	11.28	11.31
$C_2H_5OC_2H_4OC_2H_4OH$	87.8–88.4	72.8	10.90	10.81	10.76
$C_4H_9OC_2H_4OC_2H_4OH$	57.2	78.6	10.11	10.07	10.10

ethoxycarbethoxy)]-benzeneazo-*p'*-dimethylanilines were obtained by diazotizing in the usual way, using approximately 2 g. of the amino compound, 15 cc. of 20% hydrochloric acid and avoiding an excess of nitrous acid (KI-starch test). Ten cc. of 20% sodium acetate solution was added to the diazotized amine and this solution was then poured slowly into a solution of 1 g. of dimethylaniline in a minimum amount of 50% acetic acid. Filtration of the red precipitate and recrystallization from alcohol gave satisfactory solids in all cases except the derivative obtained from ethyl carbitol. This solid was sticky and was obtained in the form of a dry granular precipitate only after it had been repeatedly dissolved in alcohol at room temperature and thrown out of solution by the addition of water. The results are given in Table II.

Reduction of β-Ethoxyethyl *p*-Nitrobenzoate Using Zinc and Ammonium Chloride.—To 4.2 g. (3.5 cc.) of β-ethoxyethyl *p*-nitrobenzoate in 60 cc. of 75% alcohol, 3.5 g. of ammonium chloride and 3.5 g. of zinc dust were added. The mixture was shaken well, heated to boiling for two or three minutes and then allowed to stand for five minutes. After filtration, the filtrate was concentrated on the steam-bath until a red oil separated. The mixture was then extracted three times with ether and the ether solution washed twice with water. The inorganic precipitate at the interface was removed by filtration of the ether layer. After drying over Drierite, the ether was removed by evaporation and a red oil was obtained. While this could be distilled under reduced pressure, the wide boiling range indicated that it consisted of a mixture of compounds which could be separated by fractional distillation only with considerable difficulty.

Consequently a portion of the red oil, which had not been distilled, was warmed over a free flame for five minutes, using great care to avoid any decomposition. The liquid became more viscous and, when cooled in an ice-bath, a thick semi-solid formed in five minutes. This was dissolved in absolute ether and dry hydrogen chloride was passed into the solution. A white precipitate was obtained which melted, when dry, at 148°. The melting point checks with that of the hydrochloride of β-ethoxyethyl *p*-aminobenzoate made by passing dry hydrogen chloride into a solution known to contain β-ethoxyethyl *p*-aminobenzoate.

The ether filtrate, obtained after removal of the hydrochloride, deposited bright red needles. These melted at 94.8° and were undoubtedly crystals of *p,p'*-di-(β-ethoxycarbethoxy)-azobenzene.[20] This compound has been reported by Lazzell, Collett, Ashburn and Conn,[21] who found a melting point of 97°.

β-4-Morpholinoethyl Ethers of Cellosolves and Carbitols.—Fifteen cc. of the cellosolve or carbitol was dissolved in 30 cc. of dioxane, previously purified by refluxing for two hours with sodium and then distilling. To this solution was added 1.71 g. (0.075 mole) of sodium, cut in small pieces. The mixture was refluxed in an oil-bath until all of the sodium had reacted. To this solution was added 11.22 g. (0.075 mole) of freshly distilled β-4-morpholinoethyl chloride.[22] A small amount of glass wool was added to prevent bumping and refluxing was continued for forty-five minutes. The reaction mixture was filtered by suction into a Claisen flask, and the original flask was rinsed out with three 15-cc. portions of benzene. After distillation of the benzene from a steam-bath, the β-4-morpholinoethyl ether of the cellosolve or carbitol was distilled under reduced pressure. The ether was then dried over 2 g. of metallic sodium and redistilled under reduced pressure. The results are given in Table III.

Picrates of β-4-Morpholinoethyl Ethers of Cellosolves and Carbitols.—The picrates were made by using either aqueous or alcoholic solutions of picric acid. When saturated aqueous picric acid solution was used, it was added to the ether slowly and with frequent shaking, until a permanent turbidity was produced. A small excess of picric acid solution (4–6 cc.) was then added. After vigorous shaking, the mixture was allowed to stand and the solid settled in a short time. This was recrystallized from a mixture of 70% alcohol and 30% water. The picrate of the β-4-morpholinoethyl ether of butyl carbitol was made easily by this method, using 0.77 g. of the ether and 48 cc. of saturated aqueous picric acid solution. This picrate could not be obtained when an alcoholic solution of picric acid was used.

The procedure, using an alcoholic solution of picric acid, was to add 15 cc. of the saturated alcoholic (95%) solution to 0.2 g. of the ether. The mixture was warmed gently and then allowed to cool. If no turbidity appeared after

(20) Kroesche, *C. A.*, **10**, 2215 (1916), found that reduction of nitrobenzoates with zinc dust in acid solution often yielded hydrazo, azo and amino compounds.

(21) Lazzell, Collett, Ashburn and Conn, *Proc. West Va. Acad. Sci.*, **10**, 114–117 (1937).

(22) Mason and Block, THIS JOURNAL, **62**, 1443 (1940).

TABLE III

β-4-MORPHOLINOETHYL ETHERS OF CELLOSOLVES AND CARBITOLS

Cellosolve or carbitol used	Yield, %	B. p., °C. (mm.)	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl cellosolve[a]	71.6	119–120 (8)	189.2	188.2	7.40	7.51
Ethyl cellosolve[a]	69.7	132–133 (10)	203.2	202.2	6.89	7.01
Butyl cellosolve	66.5	154–157 (9)	231.2	230.0	6.05	6.20
Ethyl carbitol	60.5	163–165 (9)	247.2	247.6	5.67	5.78
Butyl carbitol	58.0	189–192 (8)	275.2	273.0	5.09	5.24

[a] Ten cc. of cellosolve, 1.15 g. of sodium and 7.95 g. of β-4-morpholinoethyl chloride used.

TABLE IV

PICRATES AND HYDROCHLORIDES OF β-4-MORPHOLINOETHYL ETHERS OF CELLOSOLVES AND CARBITOLS

Cellosolve or carbitol used	M. p. of picrates, °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found	M. p. of hydrochlorides, °C.	Yield, %
Methyl cellosolve	111.3[a]	88.6	13.39	13.29	97.2–97.5	61
Ethyl cellosolve	111.1[a]	84.5	12.95	12.82	99.5–100.5	76
Butyl cellosolve	62.0–62.5	77.4	12.16	12.08	59.5–60.0	62
Ethyl carbitol	204.8–207.0	71.2	11.76	11.53	150.0–151.0	53
Butyl carbitol	161.0–161.5[b]	72.0	11.10	11.30	.....	..

[a] Mixed melting point 101.0–103.0°. [b] Sometimes appears as a difficultly crystallized oil.

forty-five minutes, the mixture was cooled in an ice-bath and the walls of the test-tube were scratched with a sharp glass rod. A solid was obtained at this point in some cases, especially with derivatives made from methyl and ethyl cellosolves. If an oil formed, 5 cc. more of the alcoholic picric acid solution was added, the mixture was warmed, and the process of inducing crystallization was repeated. If an oil separated again, as in the case of the derivative of butyl cellosolve, the mixture was made homogeneous by the addition of an equal volume of water followed by gentle heating until the solution was clear. If the solution became turbid on cooling, just enough alcohol was added to clarify it. The solution was then allowed to stand overnight either at room temperature or in the ice box. Under these conditions a solid usually appeared. After filtration, the solid was recrystallized in all cases from a 70% alcohol–30% water solution. The results are given in Table IV. The yields of picrates obtained by the two methods described above were practically the same, except in the case of the picrate from the butyl carbitol ether, where the yield reported in Table IV was obtained using only an aqueous solution of picric acid.

Procedure for the Identification of Small Amounts of Cellosolves and Carbitols as Picrates of β-4-Morpholinoethyl Ethers of Cellosolves and Carbitols.—This procedure can be illustrated using ethyl cellosolve as an example. Two cc. of ethyl cellosolve was dissolved in 6 cc. of pure dioxane in an 8-inch (20-cm.) test-tube, and 0.23 g. of sodium was added. The reaction mixture was refluxed in an oil-bath until the reaction was complete. β-4-Morpholinoethyl chloride (1.40 g.) was added and the refluxing continued for one hour. After cooling, 15 cc. of 30% sodium hydroxide solution was added and the top layer of the ether was removed. This was washed twice with 10% sodium hydroxide solution to remove dioxane and then heated on the steam-bath for fifteen to twenty minutes to remove the last trace of dioxane.

Aqueous picric acid solution was added until the mixture remained turbid after vigorous shaking and then 4 cc. excess picric acid solution was added. The mixture was shaken vigorously and placed in a refrigerator for two to three hours. After filtration, the solid was recrystallized from a 70% alcohol–30% water solution. The yield was 1.1 g. (54.3%) and the solid melted at 110.8–111.1°. The time required to carry out this procedure to the point at which the picrate mixture was placed in the refrigerator was about two and one-half hours, of which nearly two hours was used for refluxing and evaporation.

Since β-4-morpholinoethyl chloride is not too stable, polymerizing slowly on standing,[22] it can be made readily from the stable β-4-morpholinoethyl chloride hydrochloride while the sodium is reacting with the cellosolve or carbitol. β-4-Morpholinoethyl chloride (4.7 g.) was dissolved in 5 cc. of water and 10% sodium hydroxide solution was added until the solution was neutral. An equal volume of 20% sodium hydroxide solution was then added and the top layer was separated and dried with about 0.5 g. of Drierite for twenty to thirty minutes. The liquid was decanted and weighed 2.9 g. One and four-tenths grams of this β-4-morpholinoethyl chloride was used in the above procedure and the same yield of the picrate was obtained.

Hydrochlorides of β-4-Morpholinoethyl Ethers of Cellosolves and Carbitols.—Dry hydrogen chloride was bubbled through an absolute ether solution of the β-4-morpholinoethyl ethers of the cellosolves and carbitols. A white oily solid formed. Five cc. of dry amyl alcohol was added and the mixture was concentrated on a steam-bath until the volume was about 2 cc. The addition of excess absolute ether usually caused a solid to precipitate. If an oil was obtained at this point, the supernatant liquid was decanted and the oil was dissolved in 8 cc. of pure acetone. The addition of excess absolute ether caused the formation of a white solid. After filtration, the solid was recrystallized from toluene, washed with ether and then dried in a vacuum desiccator. All of the solids except the one obtained from the ethyl cellosolve derivative were quite hygroscopic. The results are recorded in Table IV.

Diethylaminomethyl β-Ethoxyethyl Ether.—This compound was made following the procedure developed by Stewart and Bradley,[16] using 15 g. of paraformaldehyde, 37 g. of diethylamine, and 38.2 g. of methyl cellosolve. After drying the reaction mixture with anhydrous potas-

sium carbonate, it was distilled under 14 mm. pressure. Three fractions were collected, (a) 15 cc. distilling at 36–40°, (b) 38 cc. distilling at 72.5–75°, (c) 10 cc. distilling at 80–91°. The first of these fractions reacted violently with sodium and was considered to be methyl cellosolve containing some water. The second and third fractions evolved little or no hydrogen when treated with sodium. Two more distillations of the combined second and third fractions gave a colorless liquid which had a b. p. of 73–74.5° at 16 mm.; yield, 37.5 g. (46.5%).

Anal. Calcd. for $C_8H_{19}NO_2$: neut. equiv., 161.2. Found: neut. equiv., 160.5.

Attempts to make a satisfactory solid derivative were not very successful. When the amino ether was treated with a saturated benzene solution of picric acid and the mixture evaporated, a very viscous oil was obtained. When placed on a watch glass, it solidified to a sticky solid which melted at approximately 73°. Attempted crystallization from alcohol–water (1:1) failed to improve the poor crystalline properties.

When dry hydrogen chloride was passed into an absolute ether solution of the amino ether, diethylammonium chloride was obtained. When ethyl iodide was heated with the amino ether to form a quaternary ammonium salt, the odor of formaldehyde was noticeable, indicating decomposition, and the only product obtained appeared to be impure tetraethylammonium iodide.

However, when 1 g. of ethyl iodide and 1 g. of the amino ether were dissolved in 10 cc. of absolute ether and the solution allowed to stand overnight, a few long white needles appeared, which melted at 49.5°. Since diethylamine and ethyl iodide react under the same conditions to give a solid melting at 164°, it is reasonable to assume that the low melting compound is the quaternary ammonium salt, triethyl-β-ethoxyethoxymethylammonium iodide. This procedure was considered unsuitable for purposes of qualitative organic analysis and no further work was done with it.

Summary

Solid derivatives of three cellosolves and two carbitols have been described in the form of (a) azo compounds obtained by diazotization of *p*-aminobenzoates of the cellosolves and carbitols, and coupling with dimethylaniline, (b) picrates and hydrochlorides of β-4-morpholinoethyl ethers of cellosolves and carbitols.

A method suitable for the qualitative identification of the cellosolves and carbitols has been described.

Limitations and difficulties involved in other possible methods of identification have been outlined.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

20-Methyl-4-azacholanthrene

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On considering in broad perspective the biological actions of the various organic compounds of established carcinogenic activity, it is rather striking to note that the hydrocarbons usually produce tumors at the site of application while the majority of nitrogen-containing carcinogens tend to exert an effect at a remote site. Action at a distance is characteristic of the azo dyes of the type of *o*-aminoazotoluene,[2] of 3,4,5,6-dibenzcarbazole,[3] and of commercial β-naphthylamine,[4] if not of styryl 430.[5] There is such a vast structural difference between an azo dye and a cholanthrene, for example, and perhaps even between a dibenzcarbazole and a dibenzanthracene, that one would hesitate without further evidence to associate the difference in biological action with the difference in composition. The perhaps purely circumstantial indications, however, are so suggestive as to invite further investigation of the matter, and it seemed to us that the most satisfactory evidence would be that derived from a study of nitrogen heterocycles closely analogous in structure to the particularly potent carcinogenic hydrocarbons.

Pyridine isologs of various inactive or weakly active polynuclear hydrocarbons have already been investigated by others. Sempronj and Morelli[6] found the compound I to have weak carcinogenic activity in rats, with the particular property of acting upon kidney tissues. Joseph[7] administered the same compound to mice and obtained no tumors, but the observations were extended over a much shorter period. The substance had been synthesized by Graebe[8] and

(1) Research Fellow on grants from the National Cancer Institute and the Eli Lilly Company.

(2) Sasaki and Yoshida, see Shear, *Am. J. Cancer*, **29**, 267 (1937).

(3) Boyland and Brues, *Proc. Roy. Soc.* (London), **B122**, 429 (1937).

(4) Hueper, Wiley, Wolfe, Ranta, Leming and Blood, *J. Ind. Hyg. Toxicol.*, **20**, 46 (1938).

(5) Browning, Gulbransen and Niven, *J. Path. Bact.*, **42**, 155 (1936).

(6) Sempronj and Morelli, *Am. J. Cancer*, **35**, 534 (1939).

(7) Joseph, *Proc. Soc. Exptl. Biol. Med.*, **41**, 334 (1939).

(8) Graebe, *Ann.*, **201**, 344 (1880).