[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

Solid Derivatives of Monoalkyl Ethers of Ethylene Glycol and Diethylene Glycol. II

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In a previous communication[2] the preparation and properties of two types of solid derivatives of both cellosolves and carbitols were described and the limitations of several other possible methods were outlined. This work has been continued in an effort to find more satisfactory solid derivatives.

α-Naphthyl isocyanate yielded solid derivatives with methyl and ethyl cellosolves. The butyl cellosolve derivative was an oil and the α-naphthyl urethans of methyl and ethyl carbitols were gummy solids which appeared to decompose when recrystallization was attempted. Similarly, diphenylcarbamyl chloride yielded low-melting solids with methyl and ethyl cellosolves and an oil with butyl cellosolve. However, solid derivatives were obtained by the interaction of *p*-nitrophenyl isocyanate with methyl, ethyl and butyl cellosolves and methyl, ethyl and butyl carbitols. The procedure was very satisfactory when used with the cellosolves, but some difficulties were encountered in obtaining crystalline derivatives of the carbitols. The successful results with *p*-nitrophenyl isocyanate suggest that solids which would crystallize more easily might be obtained by using such isocyanates as 3,5-dinitrophenyl isocyanate or *p*-phenylphenyl isocyanate. We intend to try these isocyanates in the near future.

Another set of solid derivatives of both cellosolves and carbitols was obtained by making the picramides of the cellosolve and carbitol esters of anthranilic acid. The β-alkoxyethyl and β-(β'-alkoxyethoxy)-ethyl anthranilates were made by the alcoholysis of methyl anthranilate using the sodium salt of the corresponding alcohol as a catalyst.[3] Wagner's method[3] was modified by using benzene as a solvent so that an azeotropic mixture of benzene and methanol would distil from the reaction mixture. A number of compounds which would be expected to yield solid derivatives with these amino esters gave only oils. Thus, picric acid and acetyl chloride reacted with the amino esters to form oils. Benzoyl chloride gave solid derivatives with β-methoxyethyl anthranilate and β-ethoxyethyl anthranilate but gave an oil with each of the other amino esters. The esters of the three cellosolves and methyl carbitol yielded solid hydrochlorides, but the hydrochloride of the ester of ethyl carbitol was a gummy solid and that of the ester of butyl carbitol was an oil. Diazotization of β-butoxyethyl anthranilate followed by coupling with dimethylaniline, according to the procedure of Mason and Manning,[2] yielded a red oil which did not solidify. Picryl chloride, however, reacted readily with each of the amino esters to form a solid derivative.

2,4-Dinitrophenyl ethers of the cellosolves and carbitols were made by the interaction of the sodium salt of the cellosolve or carbitol and 2,4-dinitrochlorobenzene. These ethers were liquids which could not be distilled without decomposition even at 1 mm. pressure. Consequently they were reduced directly with ammonium sulfide. The 2-amino-4-nitrophenyl ethers of the cellosolves and carbitols were solids with the exception of the derivative of butyl carbitol, which was an oil. The amino group was shown to be in the 2-position by the identification of 2-amino-4-nitrophenol as an hydrolysis product of the ethers.

The reactions of ethyl cellosolve with other aromatic compounds containing reactive halogen atoms were not successful. When *p*-nitrosobromobenzene was used, it was reduced by the sodium salt of cellosolve to *p*,*p*'-dibromoazoxybenzene. Similarly, the only product isolated when *p*-nitrochlorobenzene was used was *p*,*p*'-dichloroazoxybenzene. When *p*-nitrobenzyl bromide was used, the product melted above 300° and was believed to be identical with the compound obtained by Plisov, Ukrainski and Khen Zhur.[4]

Attempts were made to prepare a solid derivative from β-chloroethyl ethyl ether, which was obtained easily from ethyl cellosolve, even though it was known that a halogen in the *beta* position to an ether linkage is quite unreactive.[5] No solid

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(1) This material is taken from a thesis presented 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) Mason and Manning, THIS JOURNAL, **62**, 1635 (1940).

(3) Wagner, *Chem. Ztg.*, **51**, 855 (1927).

(4) Plisov, Ukrainski and Khen Zhur, *Chem. Abs.*, **24**, 1108 (1929).

(5) Swallen and Boord, THIS JOURNAL, **52**, 651 (1930).

derivative was obtained with sodium saccharide, following the directions of Merritt, Levey, and Cutter.[6] The reaction of potassium morpholide with β-chloroethyl ethyl ether yielded β-4-morpholinoethyl ethyl ether which formed a solid picrate.

Attempts to make solid quaternary ammonium derivatives by the addition of the cellosolve and carbitol esters of benzenesulfonic acid and *p*-acetaminobenzenesulfonic acid to dimethylaniline were unsuccessful.

Experimental

α-Naphthyl Urethans of Methyl and Ethyl Cellosolves.—One gram (0.013 mole) of methyl cellosolve and 2.2 g. (0.013 mole) of α-naphthyl isocyanate were heated on a steam-bath for two minutes. The mixture was cooled in an ice-bath for about ten minutes, with occasional scratching to induce crystallization. The solid was extracted repeatedly with hot carbon tetrachloride (or ligroin) to dissolve the urethan. The combined solids were recrystallized from either carbon tetrachloride or a mixture of carbon tetrachloride and ligroin (2:3). The yield was 2.8 g. (88%) and the solid melted at 112.5–113°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: N, 5.71. Found: N, 5.80.

The α-naphthyl urethan of ethyl cellosolve was prepared by the same method, except that the mixture was heated on the steam-bath for five minutes and was cooled in the ice-box for two hours. The yield was 81% and the solid melted at 67.3–67.5°.

Anal. Calcd. for $C_{15}H_{17}NO_3$: N, 5.40. Found: N, 5.19, 5.33.

Diphenyl Urethans.—Two and three-tenths grams (0.01 mole) of diphenylcarbamyl chloride, 0.8 g. (0.01 mole) of methyl cellosolve (dried over Drierite for at least forty-eight hours and redistilled) and 5 cc. of pyridine were mixed and the mixture heated for three hours on the steam-bath. It was poured onto about 15 g. of ice and stirred well. The oil which first formed became solid after standing for some time. The liquid was decanted and the solid was recrystallized from ligroin. The white needles melted at 50.3–50.8°; yield, 2.3 g., 74%.

Anal. Calcd. for $C_{16}H_{17}NO_3$: N, 5.44. Found: N, 5.20, 5.29.

The diphenyl urethan of ethyl cellosolve was prepared similarly, but the oil did not solidify even after standing in the ice-box for forty-eight hours. The water was removed by means of a pipet, the residual oil was dissolved in ligroin and the solution was decolorized with Norit. When crystals did not appear after standing in the ice-box for some time, the solution was seeded with a trace of the diphenyl urethan of methyl cellosolve. A solid was obtained which melted at 50.8–51°. A mixed melting point determination with some of the diphenyl urethan of methyl cellosolve gave a melting point of 41.5–43°. The yield was 2.2 g., 71%.

Anal. Calcd. for $C_{17}H_{19}NO_3$: N, 5.12. Found: N, 4.94, 5.03.

***p*-Nitrophenyl Urethans.**—The general procedure was to dissolve 1.6 g. (0.01 mole) of *p*-nitrophenyl isocyanate in 0.01 mole of anhydrous cellosolve or carbitol. An appreciable amount of heat was liberated as the solid *p*-nitrophenyl isocyanate disappeared to produce a gelatinous mixture. The mixture was heated on the steam-bath for five minutes and then cooled in an ice-salt-bath for twenty minutes. The solid was extracted with 15 cc. of hot carbon tetrachloride and if the remaining solid (disubstituted urea) appeared oily, a second extraction with 10 cc. of carbon tetrachloride was made. The carbon tetrachloride solution was cooled in an ice-bath. The derivative of methyl cellosolve appeared as a solid at this point and was recrystallized from carbon tetrachloride. All other derivatives separated first as oils. The oil was redissolved by warming the carbon tetrachloride solution and adding just sufficient solvent to keep all of the oil in solution at room temperature. A porcelain chip was added and the solution placed in an ice-box overnight. The derivatives of the cellosolves were obtained as solids and were recrystallized from carbon tetrachloride. While a solid was obtained in the case of the methyl carbitol derivative, this compound was more soluble in carbon tetrachloride than the derivative of the cellosolves. After separation of the first crop of crystals the filtrate was concentrated to a volume of about 5 cc. and an additional amount of solid was obtained by cooling in an ice-bath. This derivative was recrystallized from carbon tetrachloride or a ligroin–carbon tetrachloride mixture (3:2).

Although a very small amount of solid appeared in the carbon tetrachloride solutions of the ethyl and butyl carbitol derivatives, its high melting point and low solubility in carbon tetrachloride indicated that it was a disubstituted urea. It was removed by filtration and the filtrate was evaporated to a volume of 2 cc. The remaining oil was then cooled in an ice-box overnight in the presence of a porcelain chip in order to get a solid. These derivatives of ethyl and butyl carbitols were recrystallized from a ligroin–carbon tetrachloride mixture (3:2). All of the solids were slightly yellow, even after repeated recrystallizations. The results are given in Table I.

TABLE I

p-NITROPHENYL URETHANS OF CELLOSOLVES AND CARBITOLS

Cellosolve or carbitol used	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found	
Methyl cellosolve	111–111.4	71	11.66	11.83	11.41
Ethyl cellosolve	79.4–80.1	80	10.93	10.97	10.95
Butyl cellosolve	58.7–59.1[a]	68	9.86	9.98	10.16
Methyl carbitol	73.4–73.7[b]	68	10.14	10.03	9.95
Ethyl carbitol	65.8–66.3[c]	53	9.40	9.58	9.53
Butyl carbitol	54.5–55.3[d]	65	8.54	8.79	8.70

Mixed melting point with [a] *p*-nitrophenyl isocyanate (m. p. 57–57.5°) was 42–47°. [b] *p*-Nitrophenyl urethan of ethyl cellosolve was 62–66°. [c] *p*-Nitrophenyl urethan of methyl carbitol was 57–64°. [d] *p*-Nitrophenyl urethan of butyl cellosolve was 55–57°.

β-Alkoxyethyl and β-(β′-Alkoxyethoxy)-ethyl Anthranilates.—The general procedure was to dissolve 0.1 mole of the anhydrous cellosolve or carbitol and 0.1 mole (15.1 g.)

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[6] Merritt, Levey and Cutter, THIS JOURNAL, 61, 15 (1939).

of methyl anthranilate in 75 cc. of dry benzene. The flask was connected to a fractionating column, twenty-seven centimeters high, which was attached to a condenser arranged for downward distillation. The mixture was heated on a steam-bath until the distillate was no longer turbid and then 5–10 cc. more benzene was distilled in order to be sure that the reaction mixture was absolutely anhydrous. The solution was allowed to cool to about 40°. The catalyst,[8] consisting of 0.1–0.2 g. of sodium dissolved in 3–4 g. of the cellosolve or carbitol used, was added. When the distillation was continued, the temperature of the vapor remained constant at 58°. This is the boiling temperature of an azeotropic mixture of 60% benzene and 40% methanol.[7] After distilling for about two hours, the boiling temperature began to fluctuate. After an additional 10 cc. of benzene was collected, the reaction was considered completed. The residual benzene solution was washed twice with 25-cc. portions of water to decompose the sodium alkoxide. It was dried over Drierite and the benzene and unused cellosolve or carbitol and methyl anthranilate were removed by distillation. The alkoxyethyl anthranilates were then distilled under reduced pressure. The results are given in Table II.

TABLE II

β-ALKOXYETHYL ANTHRANILATES

Alkoxy group	B. p., °C. (mm.)	Yield, %	Nitrogen, % Calcd.	Found	
$—OCH_3$	168–172 (7)	79	7.17	7.15	7.09
$—OC_2H_5$	173–175 (8)	77	6.70	6.58	6.64
$—OC_4H_9$	194–195 (10)	75	5.90	5.56	5.78
$—OC_2H_4OCH_3$	208–210 (10)	73	5.85	5.72	5.75
$—OC_2H_4OC_2H_5$	210–214 (9)	62	5.53	5.50	5.42
$—OC_2H_4OC_4H_9$	222–225 (10)	72	4.98	4.85	4.94

Picramides of β-Alkoxyethyl and β-(β′-Alkoxyethoxy)-ethyl Anthranilates.—Although the usual procedure[8] involves the use of an alcoholic solution of picryl chloride, the best results in this case were obtained without using any solvent. The general procedure was to mix 0.005 mole of the β-alkoxyethyl or β-(β′-alkoxyethoxy)-ethyl anthranilate with 0.0025 mole (0.6 g.) of picryl chloride. The mixture became dark red immediately, but no heat was liberated. The mixture was heated on the steam-bath for five minutes and became very viscous. When cooled in an ice-bath, a semi-solid formed. About 5–10 cc. of alcohol was added and the mixture heated on the steam-bath for ten minutes. If all of the precipitate had not dissolved, more alcohol was added and the heating continued. On cooling, crystals were formed which were recrystallized from alcohol until constant melting points were obtained. In the cases of the derivatives obtained from methyl and butyl carbitols, it was necessary to use a sufficient amount of alcohol to keep all of the oil in solution at room temperature and then allow the mixture to stand overnight in the ice-box. The yields could be increased by careful evaporation of the filtrate in order to obtain a second crop of crystals. The solids were all light orange except the picramide of β-(β′-methoxyethoxy)-ethyl anthranilate, which was yellow. The results are given in Table III.

TABLE III

PICRAMIDES OF β-ALKOXYETHYL ANTHRANILATES

Alkoxy group	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found	
$—OCH_3$	126	99	13.79	13.61	13.74
$—OC_2H_5$	122.5–123	95	13.33	13.29	13.25
$—OC_4H_9$	96.5–97[a]	94	12.50	12.55	12.43
$—OC_2H_4OCH_3$	82.5–83	80	12.44	12.41	12.32
$—OC_2H_4OC_2H_5$	96.8[a]	95	12.07	12.11	12.07
$—OC_2H_4OC_4H_9$	45.5–46	49	11.39	11.18	11.25

[a] Mixed melting point of these two compounds was 85–91°.

Benzamides of β-Methoxyethyl and β-Ethoxyethyl Anthranilates.—Three and nine-tenths grams (0.02 mole) of β-methoxyethyl anthranilate was mixed, with shaking, with 1.4 g. (0.01 mole) of benzoyl chloride. Much heat was liberated. After standing for five minutes, 10 cc. of water was added and the mixture was heated on the steam-bath to dissolve the amine hydrochloride. Upon cooling in an ice-bath, a solid was obtained which was recrystallized from alcohol. It melted at 107–107.2°. The yield was 2.75 g., 91%.

Anal. Calcd. for $C_{17}H_{17}NO_4$: N, 4.68. Found: N, 4.69, 4.64.

The benzamide of β-ethoxyethyl anthranilate was prepared similarly. It melted at 61.5–62°. The yield from 0.01 mole of the anthranilate was 1.3 g., 83%.

Anal. Calcd. for $C_{18}H_{19}NO_4$: N, 4.47. Found: N, 4.52, 4.63.

2,4-Dinitrophenyl Ethers of Cellosolves and Carbitols.—One and seven-tenths grams (0.075 mole) of sodium was added to a solution of 0.1 mole of the cellosolve or carbitol in 75 cc. of dry, thiophene-free benzene. When solution was complete, the solution was stirred rapidly and a solution of 10.1 g. (0.05 mole) of 2,4-dinitrochlorobenzene in 30 cc. of benzene was added. The first 10 cc. was added dropwise and the remainder was added rapidly. Immediately after the addition of the first few drops of the 2,4-dinitrochlorobenzene solution, the reaction mixture changed from a light yellow color to dark brown. After standing at room temperature for ten minutes, the reaction mixture was refluxed on a steam-bath for thirty to forty minutes. When cool, a pasty brown solid was suspended in the benzene. The benzene was extracted with three 25-cc. portions of water and the water extracts were extracted with small portions of ether. The ether extracts were added to the benzene solution and the solvents were removed by distillation. The remaining oils were used, without purification, for reduction to the corresponding 2-amino-4-nitrophenyl ethers.

When concentrated nitric acid was added to the aqueous extract from the reaction with ethyl cellosolve, a red oil separated. This was extracted with five 20-cc. portions of ether. After drying over Drierite and distilling off the solvent, about 2 g. of red liquid remained. After cooling overnight in an ice-box, yellow crystals were obtained and were separated by filtration. The solid weighed 0.3 g. and melted at 113–114°, which is the melting point of 2,4-dinitrophenol.

2-Amino-4-nitrophenyl Ethers of Cellosolves and Carbitols.—The dark brown residue of the crude 2,4-dinitrophenyl ether of the cellosolve or carbitol left after distilla-

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[7] Jordan, "The Technology of Solvents," Chemical Publishing Company, New York, N. Y., p. 322.

[8] Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1916, Vol. II, p. 32.

tion of the benzene was dissolved in 50 cc. of 95% alcohol. Seven cubic centimeters of concentrated ammonia solution was added and hydrogen sulfide was bubbled into the flask for ten to fifteen minutes. After refluxing for thirty minutes, the mixture was cooled, hydrogen sulfide added again and the mixture refluxed for another thirty minutes. After cooling, 5 cc. of concentrated ammonia solution was added and the process described above was repeated. The mixture was diluted with 200 cc. of water, acidified with 10% hydrochloric acid solution and evaporated on the steam-bath to one-half its original volume. The solution was decanted from the precipitated sulfur and then extracted four times with ether in order to remove any unreacted dinitro compound and as much excess cellosolve or carbitol as possible. The light red acid solution was made alkaline with 20% sodium hydroxide solution, using a moderate excess. An orange-red oil or solid was deposited. This was extracted with five 40-cc. portions of ether. The ether solution was dried over Drierite and the solvent removed. The red residue solidified to an oily solid on standing. If solidification did not occur within twenty-four hours, the oil was washed several times with water and then cooled in an ice–salt-bath. The first recrystallization from alcohol yielded a reddish-orange solid and a small second crop was obtained by partial evaporation of the filtrate. A second recrystallization from alcohol yielded yellow crystals. The derivative of butyl carbitol was obtained only as an impure oil. Complete evaporation of the alcoholic filtrate from the first recrystallization yielded a red oil which could not be solidified and which was believed to be a mixture of the 2-nitro-4-aminophenyl ether and the 2-amino-4-nitrophenyl ether because it dissolved completely in dilute hydrochloric acid solution.

In order to determine which of the two nitro groups was reduced, the reduction products of the 2,4-dinitrophenyl ethers of methyl and ethyl cellosolves and ethyl carbitol were hydrolyzed by refluxing 1-g. samples with 60 cc. of a mixture of one volume of 48% hydrobromic acid and three volumes of glacial acetic acid[9] for eight to ten hours. The reaction mixture was cooled and made distinctly alkaline with 10% sodium hydroxide solution and extracted with ether to remove any unchanged 2-amino-4-nitrophenyl ether of the cellosolve or carbitol. The aqueous solution was then made slightly acidic with acetic acid and extracted with ether. After drying the ether extract with Drierite and removing the solvent by distillation, a small quantity of brown needles was obtained. These were separated mechanically from a small amount of tarry liquid. After recrystallization from an alcohol–water mixture (3:1), the solid melted at 85–89° (hydrated 2-amino-4-nitrophenol) and the anhydrous solid melted at 140°. The melting point of 2-amino-4-nitrophenol is 142–143°. The average yield was 10–17%.

TABLE IV

2-AMINO-4-NITROPHENYL ETHERS OF CELLOSOLVES AND CARBITOLS

Cellosolve or carbitol used	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Found	
Methyl cellosolve	94–95	24	13.21	13.39	13.14
Ethyl cellosolve	104	18	12.39	12.52	12.48
Butyl cellosolve	66	10	11.01	11.12	11.15
Methyl carbitol	70–71	27	10.93	10.87	10.71
Ethyl carbitol	84–85	18	10.37	10.60	10.43

Picrate of β-4-Morpholinoethyl Ethyl Ether.—β-Chloroethyl ethyl ether was prepared according to the procedure used by Griffin.[10] A mixture of 45 g. (0.5 mole) of ethyl cellosolve and 60.6 g. (0.735 mole) of dimethylaniline was cooled under running water and 62.5 g. of thionyl chloride was added during a period of five minutes. The solution was then warmed slowly to a temperature of 100°. When the liberation of fumes had slackened, 50 cc. of water and 20 cc. of ether were added. The aqueous layer was extracted with three 30-cc. portions of ether. The combined ether solutions were washed with 5-cc. portions of 10% hydrochloric acid solution and 20% sodium carbonate solution. After drying overnight with Drierite, the ether was removed and the residue was fractionally distilled. The fraction distilling at 106–107° weighed 33.1 g., 61%.

Two grams of potassium was added to 65 cc. of morpholine which had been dried over Drierite for four days and distilled. The vigorous evolution of hydrogen slackened after a few minutes, and the mixture was refluxed for six hours. The unreacted potassium was removed and weighed 1 g. Since there was 1 g. (0.025 mole) left in solution, 2.7 g. (0.025 mole) of β-chloroethyl ethyl ether was added and the mixture was refluxed for two and one-half hours. The mixture was filtered and the excess morpholine was removed by distillation. The remaining oil was decanted from the small amount of solid and the oil distilled at 204–206°. This corresponds to the boiling point of β-4-morpholinoethyl ethyl ether.[11] The yield was 2.6 g., 65%. The hydrochloride was made by passing dry hydrogen chloride gas into an ether solution of β-4-morpholinoethyl ethyl ether. It melted at 138° which agrees with the melting point obtained by Mason and Block.[12]

In another experiment, sodium morpholide was prepared by refluxing a mixture of finely powdered sodium amide (2 g.) and 50 cc. of dry morpholine for four hours. After cooling, 5 g. of β-chloroethyl ethyl ether was added and the mixture was refluxed for one and one-quarter hours. The yield was 4.3 g., 59%. The yield was not increased either by lengthening the period of refluxing the sodium amide with morpholine or by increasing the period of refluxing after the β-chloroethyl ethyl ether had been added.

Summary

The following types of solid derivatives of cellosolves and carbitols have been described; (a) *p*-nitrophenyl urethans (considered the best method for identification), (b) picramides of cellosolves and carbitol esters of anthranilic acid, (c) 2-amino-4-nitrophenyl ethers of cellosolves and carbitols.

α-Naphthyl isocyanate and diphenylcarbamyl chloride yielded solid derivatives only with methyl and ethyl cellosolves.

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[9] Birosel, THIS JOURNAL, 53, 1408 (1931).

[10] Griffin, A.M. Thesis, Boston University, June, 1938.

[11] Cox and Carruthers, U. S. Patent 2,023,872.

[12] Mason and Block, THIS JOURNAL, 62, 1446 (1940).