Aralkyl Ethers

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An improved procedure for the preparation of 3-dimethylcarbamyloxy-5-nitrophenol is described.

SEVERAL new aralkyl ethers, prepared in connection with previously reported work (*6*) are described. An improved procedure for the preparation of 3-dimethylcarbamyloxy-5-nitrophenol involves stirring overnight 60 grams (0.20 mole) of 3,5-bis(dimethylcarbamyloxy)-nitrobenzene dissolved in 600 ml. of absolute methanol and a solution of 11.4 grams (0.20 mole) of commercial 95% sodium methoxide in 50 ml. of methanol. Concentrating the reaction mixture, filtering with Norit, cooling and acidifying gave 42 grams (90%) of 3-dimethylcarbamyloxy-5-nitrophenol. 1,3-Bis(3-hydroxy-5-aminophenoxy)-propane, m.p. 170-1° C. 1,3-Bis(dimethylcarbamyloxy-5-aminophenoxy)-propane, m.p. 110-2° C., and 1,3-bis(3-dimethylamino-5-aminophenoxy)-propane, m.p. 119° C., were obtained by reducing the corresponding nitro compounds with Raney nickel catalyst. Attempted preparation of α-bromo-*m*-nitroanisole resulted in the formation of a mixture of bis(*m*-nitrophenoxy)-methane and *m*-nitrophenoxy ethoxymethane.

EXPERIMENTAL

1-3-Nitrophenoxy-2-bromoethane. Prepared by the method of Wilson and Adams (*7*) for a similar compound, but using *N,N*-dimethylformamide as the solvent and heating to 90° to 100° C. for 20 to 30 minutes. The crude product was distilled at 129° to 145° C. (0.8-1.5 mm.), and then recrystallized from methanol.

1 - (3 - Nitrophenoxy) - *n* - (3-dimethylcarbamyloxy-5-nitrophenoxy)-alkanes (*n* = 2 and 3). Prepared as described by Krucker (*4*), the substituted ethane was recrystallized from 1 to 1 benzene-methanol. The analytical sample was recrystallized from 9 to 1 ethanol-benzene. The substituted propane was recrystallized from absolute ethanol and then from benzene. Krucker reported a 51% yield, m.p. 100° C.

1 - (3 - Nitrophenoxy) - *n* - (3-hydroxy-5-nitrophenoxy)-alkanes (*n* = 2 and 3). The corresponding carbamates were hydrolyzed by refluxing with a 1 to 1 aqueous alcohol solution of potassium hydroxide (*6*), and the products were recrystallized from methanol.

3-Dimethylcarbamyloxy-5-nitrophenol. A much improved procedure for the preparation of this compound was found by stirring 60 grams (0.20 mole) of 3,5-bis(dimethylcarbamyloxy)-nitrobenzene (m.p. 112-114° C.) in 600 ml. of anhydrous methanol and raising the temperature to 40° to 50° C. to effect solution. A solution of 11.4 grams (0.20 mole) of commercial 95% sodium methoxide dissolved in 50 ml. of warm methanol was added immediately. The deep red solution was stirred at room temperature overnight. Approximately 200 ml. of this solution was allowed to evaporate at room temperature. This concentrated solution was treated with Norit, the filtrate cooled in an ice bath, and then added to 200 grams of cracked ice. It was acidified slowly with cold, dilute hydrochloric acid, the precipitate washed with ice-cold water, and recrystallized in small aliquots from boiling water. With each crystallization, the hot solution was filtered to remove a small amount of insoluble 3,5-bis(dimethylcarbamyloxy)-nitrobenzene, the filtrate cooled in an ice-salt bath, and the product filtered. The aqueous filtrate was recycled for each aliquot. The yield of 3-dimethylcarbamyloxy-5-nitrophenol was 42 grams, (90%), m.p. 155-156° C.

1,3 - Bis(3 - hydroxy - 5 - aminophenoxy) - propane. 1,3-Bis(3-hydroxy-5-nitrophenoxy)-propane, 1.46 grams, dissolved in absolute ethanol, was catalytically reduced, using Raney nickel. The catalyst was removed by filtration, rinsed with acetone, and the solvents were evaporated in a stream of nitrogen. The residue was recrystallized from a very dilute solution of methanol, using Norit. Funke, Bagot, and Depierre (*1*), reported m.p. 111-114° C., but this was probably a typographical error. The 1,3-bis(3-hydroxy-5-nitrophenoxy)-propane was prepared in 90% yield by the alkaline hydrolysis of the corresponding dicarbamate. It melted at 207-209° C. The analytical sample was recrystallized five times from ethanol-water, m.p. 209.5-210.5° C. Krucker (*4*) made the compound in 9.3% yield,—m.p. 203° C.—from 5-nitroresorcinol, sodium ethoxide, and 1,3-dibromopropane.

1,3-Bis(3-dimethylcarbamyloxy-5-amino)-propane. Ten grams of 1,3-bis(3-dimethylcarbamyloxy-5-nitrophenoxy)-propane (*2*), m.p. 153.5-154.5° C., dissolved in 400 ml. of absolute methanol was reduced, using Raney nickel as catalyst. After removal of the catalyst, the alcohol was removed at room temperature by an oil pump, since previous experiments had indicated that rapid removal of the methanol would be desirable in getting a pure product. The resulting white crystalline product was recrystallized from absolute ethanol and dried over phosphorus pentoxide. The dibenzoyl derivative was recrystallized from ethanol.

3, - Dimethylamino - 5 - nitrophenol. The starting material in the synthesis of this compound was 3,5-dinitrobenzoic acid which was converted first to 3,5-dinitroaniline, which was then methylated to form 3,5-dinitrodimethylaniline (*5*). The 3,5-dinitrodimethylaniline contained a small amount of an ether-insoluble yellow solid. This was separated from the rest of the material by a Soxhlet extraction with ether. The 3,5-dinitrodimethylaniline was reduced with sodium sulfide (*3*) to 3-amino-5-nitrodimethylaniline.

For the replacement of the amine group by hydroxyl, 6.57 grams (0.0368 mole) of 3-amino-5-nitrodimethylaniline was diazotized, and the cold diazotized solution was added dropwise, with stirring, to a boiling solution containing 25 ml. of concentrated sulfuric acid and 25 ml. of water. At the end of the addition, the mixture was heated for 2 minutes and then cooled gradually to room temperature, and placed in a refrigerator for approximately 15 hours. The light brown solid was filtered and dissolved in about 250 ml. of water. Solid sodium bicarbonate was added to the solution until no further reaction occurred. The resulting red solid was washed with water, dried over calcium chloride, and dissolved in 100 ml. of ether. The solution was extracted several times with 20% sodium hydroxide. The alkaline solution was acidified with hydrochloric acid and then neutralized with solid sodium bicarbonate. The red solid was recrystallized from benzene, yielding 4.15 grams of product.

1,3 - Bis(3 - dimethylamino - 5 - nitrophenoxy) - propane. A solution of 2.2 grams (0.011 mole) of trimethylene bromide in 100 ml. of absolute ethanol and 4.0 grams (0.022 mole) of 3-dimethylamino-5-nitrophenol was heated to reflux temperature. To this stirred solution was added dropwise a solution of sodium ethoxide made by dissolving 0.51 gram

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Table I. Aralkyl Ethers

Compound	Yield,	M.P., ° C.	Formula	Anal., %					
				Calcd.			Found		
$3\text{-}NO_2C_6H_4O(CH_2)_2Br$[a]	25	41–2	$C_8H_8BrNO_3$	39.0	3.3	5.7	38.9	3.2	5.7
$3\text{-}NO_2C_6H_4O(CH_2)_2OC_6H_3\text{-}3,5(NO_2)OCONMe_2$	70	132–133.5	$C_{17}H_{17}N_3O_8$	52.2	4.4	10.7	51.8	4.4	10.8
$3\text{-}NO_2C_6H_4O(CH_2)_3OC_6H_3\text{-}3,5(NO_2)OCONMe_2$	75	112–3	$C_{18}H_{19}N_3O_8$	53.5	4.7	10.4	53.6	4.7	10.3
$3\text{-}NO_2C_6H_4O(CH_2)_2OC_6H_3\text{-}3,5(NO_2)OH$	95	163.5–165	$C_{14}H_{12}N_2O_7$	52.5	3.8	8.7	52.7	3.8	8.8
$3\text{-}NO_2C_6H_4O(CH_2)_3OC_6H_3\text{-}3,5(NO_2)OH$	73	161–162.5	$C_{15}H_{14}N_2O_7$	53.9	4.2	8.4	53.8	4.4	8.3
$1,3\text{-bis}[3,5\text{-}H_2N(OH)C_6H_3O](CH_2)_3$	88	170–1	$C_{15}H_{18}N_2O_4$	62.0	6.2	9.6	62.1	6.1	9.6
$1,3\text{-bis}[3,5\text{-}H_2N(OCONMe_2)C_6H_3O](CH_2)_3$	...	110–2	$C_{21}H_{28}N_4O_6$	58.3	6.5	12.9	58.4	6.4	13.0
$1,3\text{-bis}[3,5\text{-}BzNH(OCONMe_2)C_6H_3O](CH_2)_3$	...	159–161	$C_{35}H_{36}N_4O_8$	65.6	5.7	8.7	65.9	5.6	8.6
$3,5\text{-}Me_2N(NO_2)C_6H_3OH$	62	118–9	$C_8H_{10}N_2O_3$	52.7	5.5	15.4	52.5	5.5	15.2
$1,3\text{-bis}[3,5\text{-}Me_2N(NO_2C_6H_3O](CH_2)_3$	60	184–6	$C_{19}H_{24}N_4O_6$	56.5	6.0	13.9	56.4	5.9	13.3
$1,3\text{-bis}[3,5\text{-}Me_2N(NH_2)C_6H_3O](CH_2)_3$	53	119	$C_{19}H_{28}N_4O_2$	66.3	8.2	16.3	66.3	8.2	16.2
$(3\text{-}NO_2C_6H_4O)_2CH_2$	14	109–110	$C_{13}H_{10}N_2O_6$	53.8	3.5	9.6	53.8	3.2	9.6
$3\text{-}NO_2C_6H_4OCH_2OEt$	6	36.5–37.5	$C_9H_{11}NO_4$	54.8	5.6	7.1	54.8	5.5	7.2
$3,5\text{-}NO_2(OCONMe_2)C_6H_3O(CH_2)_8Br$[b]	25	61–2	$C_{17}H_{25}BrN_2O_5$	48.9	6.0	...	49.2	6.0	...

[a] % Br, Calcd. 32.5; Found, 32.6. [b] % Br, Calcd. 19.2; Found, 19.1

(0.022 gram-atom) of sodium in 50 ml. of absolute ethanol. At the end of the addition, the mixture was refluxed for 24 hours, then cooled in an ice bath. The orange solid was washed thoroughly with water. On recrystallization from benzene, 2.7 grams of product was obtained.

1,3 - Bis(3 - dimethylamino - 5 - aminophenoxy) - propane. In a 425-ml. pressure bottle containing a magnetic stirring bar, 2.7 grams (0.0067 mole) of 1,3-bis(3-dimethylamino-5-nitrophenoxy)-propane in 100 ml. of absolute methanol was reduced, using Raney nickel catalyst, over a period of 24 hours. The reaction mixture was filtered, and the filtrate cooled in an ice bath, to yield 1.4 grams of product. From the filtrate, 0.5 gram of product was obtained by concentrating the solution to a small volume. Recrystallization of the combined products yielded 1.22 grams.

Bis - (*m* - nitrophenoxy) - methane and *m* - Nitrophenoxy ethoxymethane. These compounds were obtained when the preparation of α-bromo-*m*-nitroanisole was attempted. A solution of 1.39 grams (0.01 mole) of *m*-nitrophenol and 6.95 grams (0.04 mole) of methylene dibromide in 20 ml. of absolute ethanol was heated to reflux temperature in an atmosphere of nitrogen, and 0.35 gram (0.015 gram-atom) of sodium dissolved in 15 ml. of absolute ethanol was added dropwise over a 30-minute period. The reaction mixture was refluxed and stirred for 6 hours, filtered, and the filtrate concentrated to a volume of 15 ml. and cooled. The tan needles were washed free of sodium bromide. A total of 0.2 gram of bis-(*m*-nitrophenoxy)-methane was isolated and recrystallized from ethanol-water. *m*-Nitrophenoxy ethoxymethane (0.12 gram) was isolated from the ethanol-water filtrate of the above recrystallization.

1 - (3-Dimethylcarbamyloxy-5-nitrophenoxy)-8-bromooctane. 3-Dimethylcarbamyloxy-5-nitrophenol, 14.1 grams (0.062 mole), 20 grams (0.073 mole) of freshly distilled 1,8-dibromooctane and 200 ml. of absolute ethanol, to which was added dropwise a solution containing 1.4 grams (0.062 gram-atom) of sodium in 100 ml. of absolute ethanol was stirred and refluxed for 9 hours. When cooled, the mixture was filtered, and the precipitate was washed on the filter with 100 ml. of distilled water and then with 25 ml. of methanol. The filtrate, including the washings, was extracted with ether, and the ether layer dried over anhydrous magnesium sulfate. After the solvent was removed, a yellow-brown viscous liquid remained. This was dissolved in a small amount of hot methanol, filtered, and cooled in an ice-bath. The white precipitate was recrystallized from methanol, m.p. 56–60° C.; wt. 4.9 grams.

The original precipitate was extracted with 500 ml. of a warm 95% petroleum ether–5% benzene solution, filtered, and the filtrate concentrated to about 10 ml. Some white precipitate was noticed on cooling this solution. The entire contents were dissolved in a small amount of hot methanol. Upon cooling, a white precipitate formed, m.p. 59–61° C.

The two low-melting precipitates (m.p. 56–60° and 59–61° C.) were combined and recrystallized from methanol to yield 6.4 grams of 1-(3-dimethylcarbamyloxy-5-nitrophenoxy)-8-bromooctane.

ACKNOWLEDGMENT

The authors are indebted to the U. S. Army Research and Development Laboratories, Edgewood Arsenal, Md., for a series of grants to support this work, and for the excellent cooperation provided by Jacob Miller, Gerard Natarelli, Charles Williamson, and John Krenzer of the U. S. Army Research and Development Laboratories.

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RECEIVED for review August 13, 1965. Accepted June 29, 1966.