(b) **With Methyl Alcohol.**—The acid (0.0025 mole) was dissolved in 10 g. of absolute methyl alcohol containing 3% hydrochloric acid by weight. The solution was then heated at 100° in a sealed tube for a length of time depending upon the acid concerned. When the tube was finally broken open, the reaction mixture was evaporated down to remove the hydrochloric acid. The residue was then taken up in alcohol and titrated with standard sodium hydroxide. Such a rough procedure could be expected to give only approximate results, but the reactivities of the three acids varied so widely that no very great accuracy was required. The results obtained established conclusively the *relative* rates of esterification, and that was all that was desired.

Dimethylethylacetic acid: 1 day, 97.2% reacted. Alpha acid, 11 days, 50.5% reacted. Beta acid, 11 days, 0% reacted.

Attempts to Brominate the Mixed Acids.—Two grams of mixed acids and 0.25 g. of red phosphorus (carefully dried over phosphorus pentoxide) was treated with 3 cc. of anhydrous bromine drop by drop, the mixture being kept at 0°. After standing overnight at room temperature, 0.75 cc. of dry bromine was added, allowed to stand for forty-eight hours, and then heated on the steam-bath for four hours (an excess of bromine was still present). The mixture was decomposed with 50 cc. of absolute alcohol with which it was boiled for four hours. The esters were isolated in the usual manner and purified by washing with cold dilute sodium hydroxide. The boiling point of the mixed esters was 100–120° at 30 mm.; yield 1.8 g. Decomposition by sodium fusion of a sample and testing with silver nitrate showed a bromine content of less than 0.4%.

Summary

The acidic material obtained by Butlerow by oxidizing tri-isobutylene has been re-investigated. It has been found to be a mixture of approximately equal amounts of two acids, $C_{12}H_{24}O_2$. Both acids appear to be tertiary acids with highly branched groups.

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[CONTRIBUTION FROM THE LABORATORY FOR PURE RESEARCH OF MERCK AND CO., INC.]

Preparation and Properties of *n*-Alkyl Ethers of β-*n*-Alkylcholine Salts

BY RANDOLPH T. MAJOR AND JOSEPH K. CLINE

After an extensive study of muscarine King reported in 1922 that muscarine chloride must have a molecular weight of about 210, that it was unchanged when it was boiled with deci-normal acid or alkali and that accordingly it must not be an ester or other compound which could be readily changed by acids or alkalies.[1]

Simonart found that the action of the esters of β-methylcholine on animals was in many respects very much like that of muscarine.[2] Unlike muscarine, however, these esters are readily hydrolyzed by hot alkalies.

Accordingly, several ethers of β-methylcholine as well as of other β-alkylcholines have been synthesized upon the suggestion of Doctor A.

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(1) King, *J. Chem. Soc.*, **121**, 1747 (1922).

(2) Simonart, *J. Pharmacol.*, **46**, 157 (1932).

Simonart. The molecular weights of the chlorides of some of these were about 210. The pharmacological properties of one of these ethers, the ethyl ether of β-methylcholine chloride, have been described by Simonart.[2] He found that although this compound was not identical with natural muscarine it was stable when it was boiled in alkaline solution.[3]

Various ethers of β-alkylcholine bromide were prepared by the interaction of trimethylamine and β-alkoxy-*n*-alkyl bromides according to the equation[4]

$$(CH_3)_3N + BrCH_2CHROR' \longrightarrow (CH_3)_3N(Br)CH_2CHROR'$$

Tetramethylammonium bromide was also formed in the course of this reaction. The amount that formed varied with the different β-alkoxy-*n*-alkyl bromides and increased with the size of the alkyl and alkoxy groups. This compound was formed apparently from the alkyl ether of β-*n*-alkylcholine bromide according to the equations

$$(CH_3)_3N(Br)CH_2CHROR' \longrightarrow (CH_3)_2NCH_2CHROR' + CH_3Br$$
$$CH_3Br + (CH_3)_3N \longrightarrow (CH_3)_4NBr$$

The expected dimethyl-β-alkoxy-*n*-alkylamine was isolated from the reaction products of trimethylamine and β-amyloxy-*n*-amyl bromide. Related compounds were produced during the course of reactions which involved the rest of the homologous series, the amount varying with the amount of tetramethylammonium bromide that was formed.

The β-alkoxy-*n*-alkyl bromides were prepared by the methods of Boord and his co-workers.[5] The intermediate α-chloroethyl *n*-alkyl ethers used for the preparation of these compounds were made by the method of Henze and Murchison,[6] and the α,β-dibromoethyl *n*-alkyl ethers by methods described by Dykstra, Lewis and Boord.[5]

Other salts than the bromide of the alkyl ethers of β-alkylcholine were formed by shaking solutions of the bromide in alcohol with appropriate silver salts, or by generating the free base with silver oxide and neutralizing it with the necessary acid.

Experimental Part

Preparation of β-*n*-Alkoxy-*n*-alkyl Bromide, $R'OCHR-CH_2Br$.—Several new β-alkoxy-*n*-alkyl bromides were prepared by methods described for the preparation of similar compounds by Boord and his co-workers.[7] The boiling points and analyses of these new compounds are given in Table I.

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(3) Kögl, Duisberg and Erxleben, *Ann.*, **489**, 171 (1931), since the completion of most of the work described herein, have presented some fragmentary evidence for the following formula for muscarine: $(CH_3)_3N(OH)CH(CHO)CH(C_2H_5)OH$.

(4) Since the completion of the experimental work described in this paper Wernert and Brode, THIS JOURNAL, **54**, 4365 (1932), have published a description of a somewhat similar condensation between ammonia and β-alkoxy-*n*-alkyl bromides.

(5) Swallen and Boord, *ibid.*, **52**, 651 (1930); Dykstra, Lewis and Boord, *ibid.*, **52**, 3396 (1930); Schmitt and Boord, *ibid.*, **54**, 751 (1932).

(6) Henze and Murchison, *ibid.*, **53**, 4077 (1931).

(7) Swallen and Boord, THIS JOURNAL, **52**, 654 (1930); Schmitt and Boord, *ibid.*, **54**, 759 (1932).

TABLE I

β-ALKOXY-*n*-ALKYL BROMIDES, $R'OCHRCH_2Br$

Radicals			Carbon, %			Hydrogen, %		
R'	R	B. p., °C. (mm.)	Calcd.	Found		Calcd.	Found	
CH_3	CH_3	72.5–73.5 (145)	31.39	31.67	31.76	5.92	5.86	5.95
CH_3	C_2H_5	54–55 (30)	35.91	36.36	36.16	6.63	6.58	6.67
CH_3	C_3H_7	65 (30)	39.76	40.03	39.81	7.23	6.84	6.89
CH_3[a]	C_4H_9	65 (9)	43.07	45.94	45.66	7.78	7.50	7.78
C_4H_9[a]	CH_3	65 (7)	43.07	43.88	43.90	7.78	7.90	8.18
C_4H_9	C_2H_5	86 (20)	45.90	45.97	46.18	8.20	8.23	8.38
C_4H_9	C_3H_7	95–97 (11)	48.45	48.93	48.91	8.58	8.50	8.59
C_4H_9	C_4H_9	101.5–103 (10)	50.65	50.67	50.64	8.92	8.79	8.69
C_5H_{11}	C_3H_7	99–101 (8)	50.65	50.35	50.60	8.92	8.40	8.58

[a] These compounds were not absolutely pure, apparently, but the impurity did not interfere with the subsequent production of the related alkyl ethers of *n*-alkylcholine salts.

Preparation of *n*-Alkyl Ethers of β-*n*-Alkylcholine Bromides, $(CH_3)_3NBrCH_2$-$CHROR'$.—A mixture of the appropriate β-alkoxy-*n*-alkyl bromide and the equivalent amount of a 33% solution of trimethylamine in benzene was heated in a sealed tube under the conditions outlined in Table II. The reaction product was a solid white mass in most cases which had absorbed most of the benzene; less often it was slightly discolored. When β-alkoxy-*n*-alkyl bromides with a molecular weight equal to or greater than β-ethoxy-*n*-hexyl bromide were used alkyl ethers of β-alkylcholine bromides were obtained which were soluble in benzene so that there appeared a smaller amount of solid and some liquid in the tube at the end of the reaction. The products of the reaction were washed out of the tube with the minimum amount of chloroform or absolute alcohol and the mixture evaporated at reduced pressure on the steam-bath. The oil or solid that remained was dissolved in chloroform or absolute alcohol and filtered from insoluble matter. The crude alkyl ether of β-alkylcholine bromide was then precipitated by the addition of anhydrous ether to the filtrate. The resulting white or nearly white solid was removed by filtration and dried in a desiccator over calcium chloride. When perfectly dry it was dissolved in cold chloroform, filtered and again precipitated by the addition of anhydrous ether to the filtrate. For the purification of compounds of a molecular weight equal to or greater than that of the ethyl ether of β-butylcholine bromide, benzene could be substituted for chloroform as a solvent and was used in several instances although there appeared to be no advantage in this. Repeated separations of this kind removed all of the less soluble material and gave the pure bromides listed in the table. The pure alkyl ethers of β-alkylcholine bromides were obtained as white microcrystalline solids, soluble in water, alcohols and chloroform; the higher members of the series were soluble in benzene; all were insoluble in ether or petroleum ether. The ethyl ether of β-butylcholine bromide and the butyl ether of β-ethylcholine bromide did not appear to be hygroscopic in contrast to the other members of the series.

The material that was insoluble in cold alcohol and chloroform was collected from several runs and recrystallized from boiling absolute alcohol in which it is slightly soluble. The pure compound was obtained as a white microcrystalline powder, insoluble in cold alcohol and chloroform but soluble in water. It did not melt below 250° and sublimed with decomposition above this temperature. These are the properties of tetramethylammonium bromide.[8]

Anal. Calcd. for $C_4H_{12}NBr$: N, 9.10; Br, 51.89. Found: N, 8.91, 9.12; Br, 51.90, 51.95.

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[8] F. Beilstein, "Handbuch der organischen Chemie," Julius Springer, Berlin, 1922, 4th ed., Vol. IV, p. 51.

Table II

n-Alkyl Ethers of β-*n*-Alkylcholine Salts $(CH_3)_3N(X)CH_2CHROR'$

Formulas of substituted alkyl groups		Temp. of reaction, °C. (16 hours)	Bromide							Chloride						
				Nitrogen, %			Bromine, %				Nitrogen, %			Chlorine, %		
R	R		M. p., °C.	Calcd.	Found		Calcd.	Found		M. p., °C.	Calcd.	Found		Calcd.	Found	
CH_3	CH_3	115–118	116–118	6.61	6.80	6.86	37.69	37.85	37.90	135–136	8.36	8.69	8.70	21.16	21.18	20.97
C_2H_5	CH_3	115–118	122–124	6.20	6.40	6.05	35.35	35.17	35.24	101–103	7.71	7.52	7.70	19.52	19.59	19.65
n-C_3H_7	CH_3	115–118	101–103	5.84	6.00	5.71	33.29	33.35	33.30	112–114	7.16	6.86	6.96	18.13	18.33	18.24
n-C_4H_9	CH_3	118–121	98–100	5.51	5.39	5.30	31.45	31.20	31.15	101–103	6.68	7.15	7.05	16.91	16.75	16.80
CH_3	C_2H_5	115–118	130–132	6.20	6.24	6.33	35.35	35.50	35.45	132–134	7.71	7.90	7.92	19.52	19.58	19.62
C_2H_5	C_2H_5	115–118	159–160	5.84	5.70	5.74	33.29	33.40	33.20	160–162	7.16	7.09	7.02	18.13	18.18	18.05
n-C_3H_7	C_2H_5	115–118	147–149	5.51	5.45	5.54	31.45	31.42	31.38	148–150	6.68	6.60	6.66	16.91	16.92	16.70
n-C_4H_9	C_2H_5	118–121	148–149	5.23	5.25	5.33	29.81		29.95	132–134	6.26			15.86	15.92	15.80
C_2H_5	n-C_3H_7	115–118	147–149	5.51	5.40	5.44	31.45	31.55	31.60	148–150	6.68	6.74	6.65[a]	16.91	16.82	16.68
CH_3	n-C_4H_9	118–121	101–103	5.51	5.39	5.39	31.45	31.55	31.41	100–102[a]	6.30[a]	6.01	6.08			
C_2H_5	n-C_4H_9	118–121	128–130	5.23	5.08	5.39	29.81	29.85	29.92	133–134	6.26	6.31	6.40	15.86	15.78	15.68
n-C_3H_7	n-C_4H_9	121–124	109–112	4.97	5.25	4.95	28.33	28.15	28.10	95– 97	5.89	6.19	5.98	14.92	14.92	14.98
n-C_4H_9	n-C_4H_9	121–124	95– 97	4.73	5.06	4.91	26.99	27.10	26.92	Oil						
n-C_3H_7	n-C_5H_{11}	124–127	105–107	4.73	4.97	4.76	26.99	27.15	27.00	101–103	5.57	5.58	5.56	14.09	14.05	14.40

[a] Values given are for neutral sulfate; the chloride was an oil.

The mother liquors from the reaction mixture in the formation of the amyl ether of β-propylcholine bromide were distilled at reduced pressure (10 mm.) and the fraction of the liquid which boiled at 95–105° below that of the original bromo ether was collected. The odor was similar to that of the bromo ether, however. Due to the small amount of material obtained (5 g.) further distillation was not resorted to in order to purify the substance. The material was dissolved in a small quantity of anhydrous ether and dry hydrogen chloride introduced. A precipitate formed at once in the ether which redissolved before it could be filtered and which could not be obtained again in a solid form. The ethereal solution was evaporated. When a solution of chloroplatinic acid in alcohol was added to a solution in alcohol of the oil which remained an orange-yellow precipitate formed at once. This was recrystallized several times from 50% alcohol. Orange-colored crystals were obtained; m. p. 224.5° with decomposition.

Anal. Calcd. for $C_{24}H_{56}N_2O_2PtCl_6$: Pt, 24.03. Found: Pt, 24.84, 25.00.

Analysis indicated that this compound was the chloroplatinate of dimethyl-β amyloxy-*n*-amylamine probably slightly contaminated with that of trimethylamine.

Preparation of Alkyl Ethers of β-Alkylcholine Chlorides and other Salts.—A solution of 10 g. of the alkyl ether of β-alkylcholine bromide in about 100 cc. of warm absolute alcohol was shaken with a slight excess of silver chloride or silver sulfate as the case required until the solution gave no more test for the bromide ion. Dry hydrogen sulfide was added to the filtrate from this reaction in order to precipitate a trace of silver salts. The solution was treated then with activated charcoal and filtered. The filtrate was evaporated at reduced pressure and the oil that remained was dissolved in chloroform. The alkyl ethers of β-alkylcholine chlorides or sulfates as the case was were precipitated by the addition of anhydrous ether. They were filtered and purified by dissolving them in chloroform and reprecipitating them by the addition of anhydrous ether. The alkyl ethers of β-alkylcholine chlorides were white or nearly white microcrystalline solids. They were similar to the bromides in solubility and were extremely hygroscopic. The one sulfate that was obtained in pure form was quite hygroscopic and resembled the chlorides in solubility.

The free base of the ethyl ether of β-butylcholine was generated by shaking a cool dilute solution of the ethyl ether of β-butylcholine bromide in alcohol with a slight excess of moist silver oxide. It was then neutralized by the addition of hydrochloric acid. This solution was evaporated *in vacuo*, benzene being added continuously during the evaporation to aid in the removal of water. When a test portion of the solution gave a solid precipitate when anhydrous ether was added to it, the solution was cooled and the ethyl ether of β-butylcholine chloride precipitated by the addition of anhydrous ether. It was collected, dried in a desiccator and purified by dissolving it in chloroform and reprecipitating it by the addition of anhydrous ether. The product obtained in this way was identical with that obtained by the use of silver chloride.

The method used for the determination of nitrogen in these compounds was that described by Hayman for the analysis of hygroscopic compounds.[9]

The authors wish to express their appreciation to Mr. Douglass F. Hayman for most of the analyses recorded in this paper.

Summary

1. Several new β-alkoxy-*n*-alkyl bromides have been synthesized according to the methods of Boord and his co-workers.

2. N-Alkyl ethers of β-*n*-alkylcholine bromides have been synthesized by the interaction of trimethylamine and β-alkoxy-*n*-alkyl bromides.

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(9) Hayman, *Ind. Eng. Chem., Anal. Ed.*, **4**, 256 (1932).

3. Other salts of *n*-alkyl ethers of β-*n*-alkylcholines have been formed from the bromides.

4. It has been shown that tetramethylammonium bromide and dimethyl-β-alkoxy-*n*-alkylamine are also formed in varying amounts in the reaction between trimethylamine and β-alkoxy-*n*-alkyl bromides.

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[CONTRIBUTION FROM THE HALL LABORATORY OF CHEMISTRY, WESLEYAN UNIVERSITY]

Some Halogenated Pinacolones

BY G. ALBERT HILL AND EDWARD L. KROPA

This investigation was undertaken to discover attractive methods for the preparation of the monohalogenated pinacolones. It was subsequently decided to complete the series of substances of the types

$$(CH)_3C{-}CO{-}CH_2X \quad (CH_3)_3C{-}CO{-}CHX_2 \quad (CH_3)_3C{-}CO{-}CX_3$$

as far as possible. Hitherto the dichloro-, and the mono-, di- and tribromo- derivatives have been reported.

A distinct relation between the speeds of the reactions and the generally recognized enolizing powers of the solvents employed indicated that the mechanism of the halogenation process, with free halogens, proceeds through enolic tautomers.

It is a pleasure to acknowledge the great benefit accruing to us from certain preliminary experiments carried out in this Laboratory by G. M. Bramann, by F. W. Lane and by V. S. Salvin. The material aid from the Atwater Fund has been of the greatest assistance.

Experimental

Pinacol hydrate was prepared by a modification of the Adams method.[1]

A four-foot condenser, with an inner tube 20 mm., and an outer jacket 55 mm., in diameter was used. All chemicals were scrupulously dried, and the reaction was allowed to run vigorously. The precipitation of the pinacol hydrate was carried out by ice, rather than by water, and gave fine, needle-like, friable crystals, which were readily purified by centrifuging and by centrifugal washing. By these means 45% yields of dry, pure white crystals were consistently obtained. This is significant since it has been shown[2] that pinacol hydrate air-dried for twenty-four hours still contains 4.9% of uncombined water. Earlier, unreported observations made in this Laboratory showed that apparently dry pinacol hydrate, which had not been centrifuged, lost considerable water when centrifuged.

Pinacolone was obtained from pinacol hydrate by treatment with sulfuric acid[3] and

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[1] R. and E. W. Adams, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1925, Vol. V, p. 87.

[2] King and Stewart, *Proc. Trans. Nova Scotian Inst. Sci.*, **17**, 262 (1930).

[3] Hill and Flosdorf, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1925, Vol. V, p. 91.