poor yield of the chloride is obtained.[2] A double bond can be introduced into triterpenes by heating methanesulfonates with pyridine.[3]

The present work was undertaken to determine whether the decomposition of alkyl methanesulfonates by heating with pyridine may be used as a general method for preparing olefins. For this purpose the ester was not isolated, but the methanesulfonyl chloride merely was added to the alcohol in the presence of an excess of pyridine, and the resulting mixture heated.

The standard procedure adopted was the addition of 0.2 mole of methanesulfonyl chloride slowly with stirring to a solution of 0.2 mole of the alcohol in 0.4 mole of dry pyridine under a reflux condenser. During the addition the heat of reaction caused the mixture to boil. After the addition the mixture was heated on the steam-bath for 30 minutes, allowed to cool, and decomposed with water. The organic layer was separated, washed with dilute hydrochloric acid and water, dried over sodium sulfate, and distilled at 15 mm. until the residue in the flask began to decompose. A cold trap was inserted between the condenser and the vacuum pump. The distillate then was fractionated at atmospheric pressure into the lower-boiling fraction of olefin and a higher-boiling fraction, which consisted of a mixture of the chloride and, depending on the difference in the boiling points, more or less unreacted alcohol. The chloride was purified by washing with cold concentrated sulfuric acid, then with water, drying, and distilling. The olefins and halides were identified by their boiling points and refractive indexes. 2-Chlorooctane was characterized further by conversion through the Grignard reagent to the anilide of 2-methyloctanoic acid. The results are summarized in Table I.

TABLE I

Alcohol used	Yield of products, %: Olefin	Chloride	Alcohol used	Yield of products, %: Olefin	Chloride
n-Hexyl alcohol	0	59	*n*-Butyl alcohol	..	58
2-Octanol	24	28	*s*-Butyl alcohol	..	40
2-Methyl-2-heptanol	56	0	*t*-Butyl alcohol	..	0
Cyclohexanol	29	18	*i*-Butyl alcohol	..	53

For the four higher alcohols, which were chosen for the initial work because the olefins could be isolated readily, the primary alcohol gives chiefly chloride, the secondary alcohols about equal amounts of chloride and olefin, and the tertiary alcohol chiefly olefin. The butyl alcohols behave similarly since, although no attempt was made to isolate the olefins, the yield of chloride decreases from primary, to secondary to tertiary. It is of interest to note that whereas *n*-butyl alcohol is reported[1] to give a 79% yield of ester at 0°, at temperatures in the neighborhood of 100° a 58% yield of the chloride is obtained.

Although not recorded in the table, the behavior of pinacolyl alcohol also was investigated. The yield of isolable products was very low. About 14% of olefins and 4% of chloride were obtained, the remainder being high-boiling material. The olefins boiled in the range 38–73°, and fractionation and color reactions with tetranitromethane indicated that the mixture contained *t*-butylethylene, *unsym*-methylisopropylethylene and tetramethylethylene, and hence was similar to that obtained by the acid-catalyzed dehydration of pinacolyl alcohol.[4] Thus although an excess of pyridine was present at all times, a mixture of rearranged olefins was produced.

(2) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2101 (1950).

(3) F. A. Alves, Ph.D. Thesis, Stanford University, 1950; C. R. Noller and P. J. Hearst, THIS JOURNAL, **72**, 625 (1950).

(4) K. C. Laughlin, C. W. Nash and F. C. Whitmore, *ibid.*, **56**, 1395 (1934).

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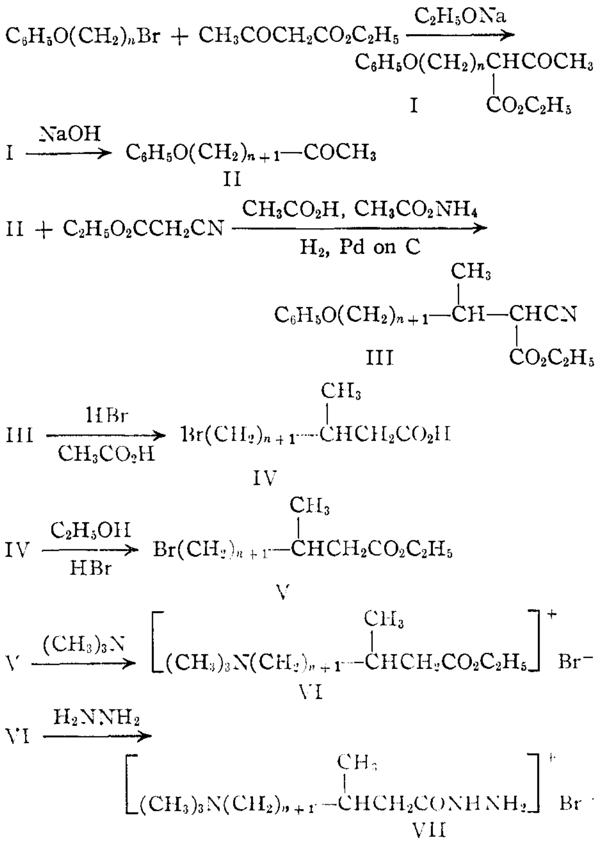
Substituted Alkyltrimethylammonium Bromides

BY NORMAN RABJOHN AND P. D. STRICKLER[1]

RECEIVED APRIL 1, 1953

It is known that branched chain fatty acids, hydrazides and quaternary ammonium salts possess properties of physiological significance and it appeared to be of interest to combine all of these functions in a single molecule.

The present work describes the methods of preparation of two such compounds as well as some related substances. The synthetic scheme employed is summarized by the equations



where n = 3 and 5.

The ω-phenoxy bromides were prepared by conventional procedures and caused to react with ethyl acetoacetate in the usual fashion. The resulting substituted acetoacetic esters underwent a facile hydrolysis to give the desired methyl ketones. The method of Cope and Alexander[2] was used to convert these to the α-cyano-β-methyl-ω-phenoxy

(1) Abstracted in part from a thesis submitted by P. D. Strickler to the Graduate College of the University of Missouri, 1951, in partial fulfillment of the requirements for the Degree of Master of Arts.

(2) A. C. Cope and E. R. Alexander, THIS JOURNAL, **66**, 886 (1944).

esters. The latter were cleaved, hydrolyzed and decarboxylated in one step by means of an acetic acid solution of hydrogen bromide. This procedure was found to be more successful than a stepwise hydrolysis and decarboxylation of the cyano esters followed by cleavage of the phenoxy ethers.

The formation of the quaternary ammonium salts of the esters took place quite slowly and the products were so deliquescent that their physical properties were not determined. They were washed thoroughly with anhydrous ether and converted to the hydrazides without transferring them from the reaction flask. The hydrazides also were deliquescent in nature, but were obtained in a dry, crystalline form by allowing them to stand for extended periods in a vacuum desiccator.

As yet, no pharmacological testing has been carried out on the compounds.

Experimental[3]

ω-Phenoxyalkyl Halides.—γ-Phenoxypropyl and ε-phenoxyamyl bromides were prepared from trimethylene and pentamethylene dibromides, respectively, by the method of Marvel and Tanenbaum.[4] Commercially available tetramethylene dichloride was converted to δ-phenoxybutyl chloride by the same procedure. This in turn was changed to the corresponding iodide by means of sodium iodide in methyl ethyl ketone.[5]

Ethyl α-(ω-Phenoxyalkyl)-acetoacetates.—(a) Ethyl α-(γ-phenoxypropyl)-acetoacetate was prepared from 322 g. (1.5 moles) of γ-phenoxypropyl bromide, 195 g. (1.5 moles) of ethyl acetoacetate and 31 g. (1.35 gram atoms) of sodium, which had been dissolved in 625 ml. of absolute alcohol. The crude product (approximately 300 g.) was used without purification for the synthesis of methyl δ-phenoxybutyl ketone. (b) Ethyl α-(δ-phenoxybutyl)-acetoacetate was obtained from 125 g. (0.45 mole) of δ-phenoxybutyl iodide, 58.5 g. (0.45 mole) of ethyl acetoacetate and 9.7 g. (0.42 gram atom) of sodium, which had been dissolved in 225 ml. of absolute alcohol. There was obtained 93 g. (67%) of a pale, yellow liquid; b.p. 153–155° (1 mm.), $n^{20}D$ 1.4984.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.94; H, 7.89.

(c) Ethyl α-(ε-phenoxyamyl)-acetoacetate was synthesized from 133 g. (0.55 mole) of ε-phenoxyamyl bromide, 72 g. (0.55 mole) of ethyl acetoacetate and 11.5 g. (0.5 gram atom) of sodium, dissolved in 250 ml. of absolute alcohol. The yield of ester was 48 g. (32%); b.p. 208–210° (1 mm.), $n^{20}D$ 1.4970.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.59; H, 8.07.

Methyl ω-Phenoxyalkyl Ketones.—These materials were made essentially according to the method of Johnson and Hager.[6] (a) Methyl δ-phenoxybutyl ketone was obtained in 77% yield from the crude ethyl α-(γ-phenoxypropyl)-acetoacetate prepared in the previous experiment; b.p. 137–142° (1 mm.) (lit.[7] b.p. 136–137°) (1 mm.). (b) Methyl ε-phenoxyamyl ketone: from 93 g. (0.33 mole) of ethyl α-(δ-phenoxybutyl)-acetoacetate, stirred for 12 hours with 400 ml. of 5% sodium hydroxide solution, and worked up in the usual manner, there resulted 60 g. (87%) of a pale, yellow liquid; b.p. 142–144° (1 mm.), $n^{20}D$ 1.5068.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.40; H, 8.99.

A 2,4-dinitrophenylhydrazone was prepared and obtained in the form of yellow plates from alcohol, m.p. 91–92°.

Anal. Calcd. for $C_{19}H_{22}O_5N_4$: C, 59.06; H, 5.74. Found: C, 59.29; H, 5.92.

(c) Methyl ζ-phenoxyhexyl ketone: from 39 g. (0.13 mole) of ethyl α-(ε-phenoxyamyl)-acetoacetate, stirred for 12 hours with 200 ml. of 5% sodium hydroxide solution, was isolated 21 g. (71%) of a colorless liquid; b.p. 162–163° (1 mm.), $n^{20}D$ 1.5033.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.54; H, 9.00.

A 2,4-dinitrophenylhydrazone was prepared and crystallized as yellow needles from alcohol; m.p. 98–99°.

Anal. Calcd. for $C_{20}H_{24}O_5N_4$: C, 59.99; H, 6.04. Found: C, 60.20; H, 6.31.

Ethyl α-Cyano-β-methyl-ω-phenoxyesters.—The procedure of Cope and Alexander[2] was employed. (a) Ethyl α-cyano-β-methyl-ω-phenoxyheptanoate, 30 g. (66%) was obtained from 30 g. (0.156 mole) of methyl δ-phenoxybutyl ketone and 17.7 g. (0.156 mole) of ethyl cyanoacetate. The product boiled at 193–195° (1 mm.), $n^{20}D$ 1.4981, and changed to a white solid, m.p. 39–41°, after standing for approximately six weeks.

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01. Found: C, 70.69; H, 8.09.

(b) Ethyl α-cyano-β-methyl-ω-phenoxycaprylate resulted from the condensation of methyl ε-phenoxyamyl ketone, 62 g. (0.3 mole), and ethyl cyanoacetate, 34 g. (0.3 mole), in 42% yield; b.p. 218–220° (1 mm.), $n^{20}D$ 1.5096.

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31. Found: C, 71.09; H, 8.11.

(c) Ethyl α-cyano-β-methyl-ω-phenoxypelargonate was prepared in 48% yield from 36.3 g. (0.165 mole) of methyl ζ-phenoxyhexyl ketone and 18.7 g. (0.165 mole) of ethyl cyanoacetate; b.p. 210–212° (0.5 mm.), $n^{20}D$ 1.5008.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57. Found: C, 71.89; H, 8.72.

ω-Bromo-β-methylcarboxylic Acids and Their Ethyl Esters.—The procedure for the preparation of ω-bromo-β-methylheptanoic acid is representative of the method employed. A mixture of 68 g. (0.235 mole) of ethyl α-cyano-β-methyl-ω-phenoxyheptanoate and 300 ml. of 80% acetic acid, which contained approximately 1.5 moles of hydrogen bromide, was stirred and refluxed for about 60 hours. It was allowed to cool, poured into 1000 ml. of water and the insoluble layer was separated. The water layer was extracted with 100 ml. of ether and the extract was combined with the oil. The ethereal solution was shaken repeatedly with 5% sodium bicarbonate solution and the alkaline extracts were collected and acidified with 48% hydrobromic acid. The oil which separated was taken up in ether and the ethereal solution was dried over anhydrous magnesium sulfate. After removing the ether, there was obtained 20 g. (38%) of a light yellow oil; b.p. 130–133° (1 mm.), $n^{20}D$ 1.4781.

Anal. Calcd. for $C_8H_{15}O_2Br$: C, 43.06; H, 6.73. Found: C, 43.42; H, 7.03.

The ethyl ester of this acid was prepared in 83% yield in the usual manner by heating it with a 7% solution of hydrogen bromide in ethanol; b.p. 95–96° (1 mm.), $n^{20}D$ 1.4614.

Anal. Calcd. for $C_{10}H_{19}O_2Br$: C, 47.82; H, 7.62. Found: C, 48.09; H, 7.95.

ω-Bromo-β-methylpelargonic acid was obtained in 31% yield from a mixture of 63.4 g. (0.2 mole) of ethyl α-cyano-β-methyl-ω-phenoxypelargonate, 270 g. (1.6 moles) of 48% hydrobromic acid and 350 ml. of glacial acetic acid. The acid was isolated as a yellow oil; b.p. 157–160° (1 mm.), $n^{20}D$ 1.4750.

Anal. Calcd. for $C_{10}H_{19}O_2Br$: C, 47.82; H, 7.62. Found: C, 48.01; H, 7.99.

The acid was esterified by means of ethanol and hydrogen bromide to the corresponding ester in 73% yield; b.p. 120–122° (1 mm.), $n^{20}D$ 1.4600.

Anal. Calcd. for $C_{12}H_{23}O_2Br$: C, 51.55; H, 8.30. Found: C, 51.81; H, 8.53.

Trimethyl-ω-carbethoxyalkylammonium Bromides. (a) Trimethyl-(5-methyl-6-carbethoxy)-hexylammonium Bromide.—A solution of 8 g. of ethyl ω-bromo-β-methylheptanoate in 17 g. of an approximately 16% solution of triethylamine in anhydrous benzene was allowed to stand for 48 hours. The resulting white, crystalline precipitate was washed with a total of 250 ml. of anhydrous ether, after most of the mother liquor had been removed by decantation.

(3) All melting points are uncorrected. The semimicro analyses were performed by one of the authors (P. D. S.).

(4) C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 435.

(5) A. H. Ford-Moore, *ibid.*, **30**, 10 (1950).

(6) J. R. Johnson and F. D. Hager, ref. 4, p. 351.

(7) G. Barger, R. Robinson and L. H. Smith, *J. Chem. Soc.*, 718 (1937).

The product was too deliquescent to make it practical to remove it from the reaction flask.

(b) **Trimethyl-(7-methyl-8-carbethoxy)-octylammonium Bromide.**—This compound was prepared in the same manner from 16.9 g. of ethyl ω-bromo-β-methylpelargonate and 39 g. of an approximately 16% solution of trimethylamine in anhydrous benzene. It also was extremely deliquescent, and after washing with 500 ml. of anhydrous ether, was used directly for the next synthesis.

Hydrazides of Trimethyl-ω-carboxyalkylammonium Bromides. (a) **Hydrazide of Trimethyl-(5-methyl-6-carboxy)-hexylammonium Bromide.**—A mixture of the crude trimethyl-(5-methyl-6-carbethoxy)-hexylammonium bromide and 7 g. of 85% hydrazine hydrate was heated to reflux for 15 minutes, enough alcohol was added to give a clear solution, and then refluxing was continued for an additional 2 hours. The solvent was removed under reduced pressure and the residual oil was washed with dry ether and chilled. There was obtained 2.5 g. (26%) of a white powder which melted at 118–122°.

Anal. Calcd. for $C_{11}H_{26}ON_3Br$: C, 44.59; H, 8.84. Found: C, 44.23; H, 9.16.

(b) **Hydrazide of Trimethyl-(7-methyl-8-carboxy)-octylammonium Bromide.**—The crude trimethyl-(7-methyl-8-carbethoxy)-octylammonium bromide, obtained previously, and 20 g. of 85% hydrazine hydrate were caused to react as described in the preceding experiment. The waxy appearing product was dissolved in hot absolute alcohol and precipitated by the addition of anhydrous ether. The solid was removed by filtration, dissolved in a small amount of hot absolute alcohol, clouded with petroleum ether (b.p. 60–68°) and allowed to solidify. There was obtained 5 g. (23%) of a hygroscopic, white powder, m.p. 136–139°.

Anal. Calcd. for $C_{18}H_{30}ON_3Br$: C, 48.13; H, 9.32. Found: C, 48.41; H, 9.60.

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Constituents of U. S. P. Colchicine. N-Formyltrimethylcolchicinic Acid Methyl Ether[1]

BY ROBERT F. RAFFAUF,[2] ANN L. FARREN AND GLENN E. ULLYOT

RECEIVED MARCH 1, 1953

An earlier report from these laboratories[3] called attention to the presence of *ca.* 4% of 2-desmethylcolchicine[4] in commercial samples of U.S.P. colchicine. When a new sample[5] was subjected to chromatographic purification by the usual procedure[3,6] using chloroform–methanol (99:1) as eluant, an alkaloid (*ca.* 1.5% yield) having the properties of Šantavý's Substance B (N-formyltrimethylcolchicinic acid methyl ether)[7] was isolated; no 2-desmethylcolchicine was encountered. The new compound crystallized readily from ethyl acetate as pale yellow prisms which melted with decompositions at 260–262° (capillary). A comparison of this substance with Šantavý's Substance B is given in Table I.

TABLE I

	N-Formyltrimethylcolchicinic acid methyl ether from U.S.P. Colchicine[a]	Šantavý's Substance B	N-Formyliso-trimethylcolchicinic acid methyl ether
M.p., °C., dec.	260–262 (capillary)	264–267 (Kofler block)	252–253 (capillary)
[α]D chloroform	−175 ± 1°	−171.2°	−315 ± 1°
	c 1.01, *t* = 25°	*c* 1.08, *t* = 22°	*c* 0.719, *t* = 25°
λ_{max} (log ε) (95% ethanol)	242.5 (4.48)	247 (4.51)	244 (4.50)
	350.0 (4.24)	350 (4.27)	342.5 (4.29)
	(*c* 5.22 × 10^{-5} *M*)		(*c* 5.6 × 10^{-5} *M*)

[a] Also synthesized from trimethylcolchicinic acid methyl ether.

The product was synthesized by formylation of trimethylcolchicinic acid methyl ether[8] using 98% formic acid in pyridine. Solvents were removed *in vacuo*, the residue was taken up in chloroform, washed with water and dried. Evaporation left a residue which crystallized readily from ethyl acetate to give pale yellow prisms, m.p. 260–262° dec. alone and when mixed with a sample isolated from U.S.P. colchicine.

Further confirmation of the configuration of our product was obtained by comparison with the iso-derivative prepared from iso-trimethylcolchicinic acid methyl ether[8] in the same manner. The product crystallized from ethyl acetate containing a little chloroform or methylene chloride as pale yellow prisms, m.p. 252–253° dec.; mixed m.p. with Substance **B**, 224–233° dec. For analysis it was dried to constant weight at 80° *in vacuo*.

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02. Found: C, 65.20; H, 5.94.

Comparative data are given in Table I; these are in agreement with previous findings[8,9] with respect to the properties of the iso- *vs.* the normal-forms in the colchicine and trimethylcolchicinic acid series.

Minor amounts of other alkaloids are present in the samples of U.S.P. colchicine which we have examined. Investigation of them will be continued. The biological effects of the N-formyltrimethylcolchicinic acid methyl ethers are being studied and will be reported elsewhere.

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The Characterization and Degradation of Isotopic Acetic and Lactic Acids

BY SAUL ROSEMAN

RECEIVED FEBRUARY 2, 1953

During a study of the biosynthesis of hyaluronic acid,[1] it became necessary to characterize and degrade small quantities of isotopic acetic and lactic acids. As the procedures developed may be of general interest, details are presented here.

The chemistry of benzimidazole derivatives of aliphatic acids has been described in a recent comprehensive review.[2] In contrast to the usual technique for characterization of aliphatic acids,[3–5] the present method involves the use of a large excess of the reagent, *o*-phenylenediamine, and removal

(1) This investigation was supported (in part) by a research grant from the National Cancer Institute of the National Institutes of Health, U.S.P.H.S.

(2) Research Associate.

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(5) U. S. P. Colchicine, S. B. Penick, Lot No. 1141-LI-A.

(6) J. N. Ashley and J. O. Harris, *J. Chem. Soc.*, 677 (1944).

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