was mixed with an equal volume of ether and added slowly to the reaction flask. The rate of reaction was controlled by the rate of addition of the butyl bromide. Vigorous stirring was used throughout both this step and those following. Lithium bromide precipitated from the ether solution as a chalky white solid.

After the formation of the butyllithium was complete, 47.5 g. (0.150 mole) of chloro-2,4,6-tris-(trifluoromethyl)-benzene, mixed with an equal volume of ether, was added slowly. An exothermic reaction occurred throughout the addition. When no further reaction was apparent, the mixture was refluxed for 0.5 hour and then cooled in an ice-bath. Acetaldehyde (8.8 g., 0.20 mole) was mixed with an equal quantity of ether and added to the solution of organometallic compound. No apparent reaction occurred on mixing. However, on refluxing for 0.5 hour the mixture changed from a pale yellow to a bright orange color. The mixture was hydrolyzed with a saturated solution of ammonium chloride and the ether layer separated, dried, and the ether removed by distillation. Rectification of the remaining organic material yielded 26.4 g. (55.0%) of 2,4,6-tris-(trifluoromethyl)-α-methylbenzyl alcohol, b. p. 71–72° (4 mm.), m. p. 56–56.5°, $n^{26}D$ 1.4092.

Anal. Calcd. for $C_{11}H_7F_9O$: F, 52.4. Found: F, 51.9.

A small quantity of 2,4,6-tris-(trifluoromethyl)-phenyllithium was prepared as above and hydrolyzed with a saturated solution of ammonium chloride. No unreacted chloro-2,4,6-tris-(trifluoromethyl)-benzene was observed and an 89% yield of 1,3,5-tris-(trifluoromethyl)-benzene was obtained. This discounted the possibility that the butyllithium had attacked fluorine present in the trifluoromethyl groups. The exchange reaction with lithium goes very well, but the reaction of the organometallic compound with the carbonyl compound seems to be a limiting factor in the preparation of 2,4,6-tris-(trifluoromethyl)-α-methylbenzyl alcohol.

2,4,6-Tris-(trifluoromethyl)-styrene.—2,4,6-Tris-(trifluoromethyl)-α-methylbenzyl alcohol (10.0 g., 0.031 mole) was dissolved in 100 ml. of dry benzene contained in a small round-bottom flask and 7.1 g. (0.05 mole) of phosphorus(V) oxide was added as a suspension in benzene. A trace of hydroquinone was added as a polymerization inhibitor and the mixture was shaken vigorously for thirty minutes. The benzene solution was then decanted from the partially hydrated phosphorus(V) oxide and distilled. After the benzene had been removed at atmospheric pressure, the product was rectified under reduced pressure to give 3.4 g. (56.6%) of 2,4,6-tris-(trifluoromethyl)-styrene, b. p. 59° (20 mm.), $n^{27}D$ 1.3900, d^{24}_4 1.4540.

Anal. Calcd. for $C_{11}H_6F_9$: F, 55.6: Found: F, 52.6.

The Attempted Polymerization of 2,4,6-Tris-(trifluoromethyl)-styrene.—Four tests were conducted in sealed tubes. Two were activated with a trace of benzoyl peroxide and two with ultraviolet radiation. They may be summarized as follows: 1. Activated with benzoyl peroxide at 70° for 48 hours: (a) 1 g. of substituted styrene; (b) 1 g. of substituted styrene and 1 g. of vinyl acetate.

2. Activated with ultraviolet radiation at 30° for 70 hours: (a) 1 g. of substituted styrene; (b) 1 g. of substituted styrene and 1 g. of vinyl acetate.

In tests 1a, 2a and 2b, no apparent polymerization occurred. The mobility of each sample remained unaltered throughout the test. Sample 1b, however, polymerized to a highly viscous material. After removal of the volatile starting materials, the sample was analyzed for fluorine. Since none was found, it appears that no copolymerization took place. Rather, the styrene may have exerted a hindering effect upon the polymerization of vinyl acetate as apparently was the case in sample 2b. The inability of 2,4,6-tris-(trifluoromethyl)-styrene to polymerize is not surprising, since it is sterically hindered with two ortho trifluoromethyl substituents.

Attempted Preparation of 2,4,6-Tris-(trifluoromethyl)-α,α-dimethylbenzyl Alcohol.—2,4,6-Tris-(trifluoromethyl)-phenyllithium, 28.8 g., was prepared in an ether solution by means of a butyllithium exchange as discussed previously. Dry acetone, 7 g., was introduced with no evolution of heat or apparent reaction. The mixture was refluxed for five hours, but no color change occurred as in the previously condensation with acetaldehyde. After hydrolysis and isolation of the ether layer, and removal of the ether by distillation, the remaining organic material was distilled. None of the desired product was formed, but due to the hydrolysis of the organometallic compound, 24 g. of 1,3,5-tris-(trifluoromethyl)-benzene, b. p. 118–119° (750 mm.), was obtained. Apparently, the carbonyl group in acetone is unable to react with 2,4,6-tris-(trifluoromethyl)-phenyllithium because of steric effects.

Summary

1. The synthesis and the attempted polymerization of 2,4,6-tris-(trifluoromethyl)-styrene are described.

2. An attempt to prepare 2,4,6-tris-(trifluoromethyl)-α-methylstyrene was unsuccessful.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

o-Benzylphenol Derivatives. VI.[1] Quaternary Ammonium Halides[2a]

BY WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, WILLIAM F. MINOR, RICHARD R. SMITH, LEE C. CHENEY AND S. B. BINKLEY[2b]

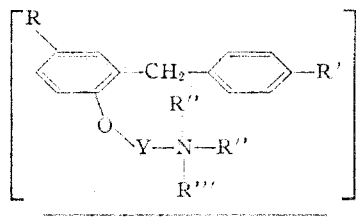
The discovery that dialkylaminoalkyl ethers of o-benzylphenol (and substituted o-benzylphenols) exhibit potent antihistaminic activities[3] made it worth while to prepare further related compounds. One type which came to mind was the quaternary ammonium halides derived from the tertiary aminoethers. Accordingly, a series of quaternaries has been prepared and evaluated for possible physiological activity. The majority of the quaternary halides prepared were those derived from substituted N,N-dimethyl o-benzylphenoxyethylamines, and thus constitute a new class of choline ethers. It is not surprising, therefore, that quaternization was attended by a profound change in physiological behavior. Antihistaminic activity is present in the quaternaries, but to a lesser degree than in the tertiary amines. A noteworthy fact is that the quaternaries possess a high degree of vasopressor activity. A report

(1) For paper V in this series, see Wheatley, Cheney, Fitzgibbon and Binkley, THIS JOURNAL, **72**, 4443 (1950).

(2) (a) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, September 3–8, 1950. (b) University of Illinois College of Medicine, Chicago, Ill.

(3) (a) Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949); (b) Wheatley, Cheney and Binkley, *ibid.*, **71**, 64, 3795 (1949); (c) Mills, Rohrmann, Dinwiddie and Lee, *Arch. internat. pharmacodyn.*, **80**, 119 (1949).

TABLE I



R	R'	R''	R'''	Y	X	Meth. of prepn.	Yield, %	M. p., °C.	Recrystn. solvent	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H	H	CH_3	CH_3	$-CH_2CH_2-$	I	A	99	160.0–161.5	H_2O	$C_{18}H_{24}ONI$	54.5	54.1	6.1	5.8
H	H	CH_3	C_2H_5	$-CH_2CH_2-$	I	A	72	155.0–157.5	EtOH	$C_{19}H_{26}ONI$	55.5	55.7	6.4	6.5
H	H	CH_3	$CH(C_2H_5)_2$	$-CH_2CH_2-$	Br	A	90	67.0– 70.0	Et_2O–Me_2CO	$C_{20}H_{32}ONBr\cdot H_2O$	69.3	69.7	6.6	6.5
H	H	CH_3	CH_3	$-CH_2CH_2-$	SO_4CH_3	A	35	181.0–183.0	Me_2CO	$C_{19}H_{37}O_4NS$	59.8	59.8	7.1	7.3
H	H	CH_3	CH_3	$-CH_2CH_2-$	$SO_3C_6H_4CH_3$	A	90	96.5– 98.5	EtOAc	$C_{26}H_{31}O_4NS\cdot{}^1/_2H_2O$	66.8	67.3	7.2	7.5
H	H	C_2H_5	C_2H_5	$-CH_2CH_2-$	I	A	76	160.5–162.0	EtOH	$C_{21}H_{38}ONI$	57.4	58.0	6.9	7.1
H	H	C_2H_5	CH_3	$-CH_2CH_2-$	I	A	96	138.5–140.0	EtOH	$C_{20}H_{36}ONI$	56.5	56.4	6.6	6.8
CH_3	H	CH_3	CH_3	$-CH_2CH_2-$	I	A	85	141.0–145.0	MIBK	$C_{19}H_{36}ONI$	55.5	55.5	6.4	6.5
C_2H_5O	H	CH_3	CH_3	$-CH_2CH_2-$	I	A	60	142.0–148.0	MIBK	$C_{20}H_{38}O_2NI$	54.4	54.3	6.4	6.4
Cl	H	CH_3	CH_3	$-CH_2CH_2-$	I	B	83	162.0–163.0	EtOH	$C_{18}H_{33}ONClI$	50.0	50.4	5.4	5.6
Br	H	CH_3	CH_3	$-CH_2CH_2-$	I	A	95	153.0–156.0	*i*-PrOH	$C_{18}H_{33}ONBrI$	45.4	45.5	4.9	5.0
F	H	CH_3	CH_3	$-CH_2CH_2-$	I	A	94	202.5–204.5	*i*-PrOH–H_2O	$C_{18}H_{33}ONFI$	52.0	52.4	5.6	5.9
H	Cl	CH_3	CH_3	$-CH_2CH_2-$	I	B	86	162.0–163.5	EtOH	$C_{18}H_{33}ONClI$	50.0	50.3	5.4	5.5
H	F	CH_3	CH_3	$-CH_2CH_2-$	I	A	95	158.5–160.0	*i*-PrOH–H_2O	$C_{18}H_{33}ONFI$	52.0	51.8	5.6	5.8
Cl	H	C_2H_5	CH_3	$-CH_2CH_2-$	I	A	80	147.5–149.5	*i*-PrOH	$C_{20}H_{37}ONClI$	52.3	52.4	5.9	5.9
Cl	H	C_2H_5	C_2H_5	$-CH_2CH_2-$	I	A	42	156.0–157.0	Me_2CO–*i*-PrOH	$C_{21}H_{39}ONClI$	53.2	53.4	6.2	6.2
H	H	CH_3	CH_3	$-CH_2CH_2CH_2-$	I	B	92	185.0–186.5	H_2O	$C_{19}H_{36}ONI\cdot{}^1/_2H_2O$	54.3	54.6	6.4	6.3
H	H	CH_3	CH_3	$-CH_2CH(CH_3)-$	I	B	43	152.5–155.0	EtOH	$C_{19}H_{36}ONI$	55.5	55.5	6.4	6.3
H	H	CH_3	CH_3	$-CH_2C(CH_3)_2CH_2-$	I	A	70	174.5–175.5	*i*-PrOH	$C_{21}H_{38}ONI$	57.4	57.8	6.9	7.1

of the pharmacology of several of these quaternaries has been presented by Loewe, Goodman and Puttuck.[4]

The quaternary ammonium halides reported herein were prepared by allowing the tertiary aminoether to react with an excess of an alkyl halide in isopropyl alcohol or acetone. Solvents such as benzene or ligroin have been widely used in the preparation of quaternaries, although it has been shown that the reaction proceeds much faster in highly polar solvents.[5] Usually it was sufficient to mix the amine and halide together in the solvent. An exothermic reaction occurred, and the quaternary salt precipitated out of the reaction mixture as a solid or as an oil which spontaneously crystallized on standing. Methyl sulfate and methyl *p*-toluenesulfonate[6] formed quaternaries readily, but the products were frequently extremely hygroscopic. In most cases, however, the recrystallized quaternaries were well-defined crystalline solids with fairly sharp melting points.

Experimental[7]

Two general methods of preparation of the quaternaries were employed, depending on whether the free aminoether or its salt was available.[8] Typical examples of these methods are given below.

Method A. β-(*o*-Benzylphenoxy)-ethyltrimethylammonium Iodide.—To a solution of 30 g. (0.12 mole) of N,N-dimethyl-β-(*o*-benzylphenoxy)-ethylamine in 70 ml. of isopropyl alcohol, cooled in an ice-bath, was added 18 g. (0.13 mole) of methyl iodide. The quaternary salt crystallized from the reaction mixture almost immediately. The solid was collected by filtration and recrystallized from water, giving 46.5 g. (99% yield) of β-(*o*-benzylphenoxy)-ethyltrimethylammonium iodide, m. p. 160.0–161.5°.

Method B. β-(*o*-Benzyl-*p*-chlorophenoxy)-ethyltrimethylammonium Iodide.—An aqueous solution of 6.2 g. (0.019 mole) of N,N-dimethyl-β-(*o*-benzyl-*p*-chlorophenoxy)-ethylamine hydrochloride was rendered basic with sodium hydroxide and the liberated aminoether extracted into ether. The ether solution was dried over anhydrous potassium carbonate, filtered and the filtrate evaporated to dryness. The residual oil was taken up in 80 ml. of isopropyl alcohol and 3.1 g. (0.022 mole) of methyl iodide added thereto. Crystallization of the quaternary salt began in a few minutes. The crude solid was collected by filtration and recrystallized from ethyl

(4) Loewe, Goodman and Puttuck, *Fed. Proc.*, **9**, 296 (1950).

(5) Sidgwick states that the velocity of quaternization in benzyl alcohol is nearly 800 times as great as in hexane ("The Organic Chemistry of Nitrogen," revised by Taylor and Baker, Oxford Press, New York, N. Y., 1942, p. 27).

(6) *Cf.* Marvel, Scott and Amstutz, THIS JOURNAL, **51**, 3638 (1929).

(7) All melting points are corrected.

(8) For the preparation of the N,N-dialkylbenzylphenoxyalkyl amines, see ref. 3*a*, *b*.

alcohol, giving 6.8 g. (83% yield) of β-(*o*-benzyl-*p*-chlorophenoxy)-ethyltrimethylammonium iodide, m. p. 162.0–163.0°.

In Table I are contained data on other quaternary salts which were prepared similarly. Isopropyl alcohol was used as the reaction solvent in most preparations, although on the basis of a few experiments acetone is equally as satisfactory. Since the velocity of the reaction varied with the nature of the amine and halide, modifications of the above general procedures were often necessary. An exothermic reaction almost always followed the addition of the halide to the solution of the amine. If the quaternary crystallized on cooling the solution, it was immediately collected by filtration. If it oiled out, the mixture was placed in the cold-room overnight. This usually caused the oil to solidify. In a few experiments, the quaternary did not precipitate readily from the solution either as a solid or as an oil. A few hours of refluxing, followed by cooling, was usually sufficient to cause precipitation of the quaternary. If the quaternary still did not separate from the reaction mixture, the solvent was evaporated under reduced pressure and the residue recrystallized from a suitable solvent.

β-(*p*-Benzylphenoxy)-ethyltrimethylammonium Iodide.—This preparation was carried out as described above in method B, using 44 g. (0.10 mole) of N,N-dimethyl β-(*p*-benzylphenoxy)-ethylamine dihydrogen citrate and 17 g. (0.12 mole) of methyl iodide. There was obtained 22.0 g. (55% yield) of β-(*p*-benzylphenoxy)-ethyltrimethylammonium iodide, m. p. 149.5–151.5° (recrystallized from acetone).

Anal. Calcd. for $C_{18}H_{24}ONI$: C, 54.5; H, 6.1. Found: C, 54.6; H, 6.2.

β-(*o*-2-Thenylphenoxy)-ethyltrimethylammonium Iodide.—From 26.1 g. (0.100 mole) of N,N-dimethyl β-(*o*-2-thenylphenoxy)-ethylamine and 15.6 g. (0.110 mole) of methyl iodide there was obtained according to the procedure described in method A, 30.4 g. (75% yield) of β-(*o*-2-thenylphenoxy)-ethyltrimethylammonium iodide, m. p. 181.5–182.5° (recrystallized from methyl alcohol).

Anal. Calcd. for $C_{16}H_{22}ONIS$: C, 47.7; H, 5.5. Found: C, 47.8; H, 5.6.

The quaternary salts acquire a yellow color on exposure to light, especially when not completely dry. It was therefore found advantageous to dry the recrystallized quaternaries as quickly as possible in a covered vacuum desiccator and store them in brown bottles.

Acknowledgment.—The authors are indebted to Mrs. Neva Knight and Mr. Richard M. Downing, who performed the analyses reported herein.

Summary

A series of benzylphenoxyalkyl trialkylammonium halides has been prepared by allowing the corresponding tertiary amine to react with an alkyl halide. Many of these quaternary salts are potent vasopressor agents.

SYRACUSE 1, N. Y. RECEIVED MAY 3, 1950

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

A New Reaction of Nitriles. V. Preparation of N-(2-Halo-1-ethyl)-amides[1]

BY ROBERT M. LUSSKIN[2] WITH JOHN J. RITTER

The general reaction of nitriles with either alkenes or secondary or tertiary alcohols in strongly acidic media to form N substituted amides has been the subject of previous articles in this series.[3] The present paper describes an extension of this work: the reaction of nitriles with certain halo alkenes or halo hydrins. The products, N-(2-halo-1-ethyl)-amides (Table I) in which R is alkyl or aryl and R′ is hydrogen or methyl, were then dehydrohalogenated to 2-oxazolines.

The reaction of acetonitrile, benzonitrile, phenylacetonitrile, or ethyl cyanoacetate with methallyl chloride, styrene chloro- or bromohydrin, or alpha methylstyrene chlorohydrin afforded no difficulty and the amides listed in Table I were isolated. However, the reaction of allyl chloride, which yielded N-(1-chloro-2-propyl)-phenylacetamide with phenylacetonitrile, gave only benzamide itself with benzonitrile.

The N-(2-halo-1-ethyl)-amides were found to be unstable with respect to cyclic isomers, oxazoline salts, and converted to them, slowly at room temperature and more rapidly at 50°. For example, when N-(1-chloro-2-methyl-2-propyl)-phenylacetamide, m. p. 98°, remained four months at room temperature or two months at 50°, complete isomerization to 4,4-dimethyl-2-benzyl-2-oxazoline hydrochloride, m. p. 142°, occurred. A more satisfactory procedure for the preparation of the oxazolines (Table II) was treatment of the amides with one equivalent of alcoholic potassium hydroxide at 60° for 1.5 minutes.[4]

The halogen of the N-(2-halo-1-ethyl)-amides was replaced readily. Thus, N-(1-chloro-2-methyl-2-propyl)-benzamide and N-(2-chloro-1-phenylethyl)-acetamide were hydrolyzed by aqueous sodium carbonate to the hydroxy amides. Oxidation of N-(2-chloro-1-phenylethyl)-acetamide gave α-acetaminophenylacetic acid. Bringing an alcoholic silver nitrate solution of any of the halo amides to reflux led to immediate precipitation of silver chloride.

Because the N-(1-chloro-2-methyl-2-propyl)-amides (derived from methallyl chloride) are neopentyl chlorides in which one methyl has been replaced by an amide group, the halogen might have been expected to show the neopentyl lack

(1) Abstracted from a portion of the thesis submitted by Robert M. Lusskin to the Graduate Faculty of New York University, February, 1949, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Trubek Laboratories, East Rutherford, New Jersey.

(3) (a) Ritter and Minieri, THIS JOURNAL, **70**, 4045 (1948); (b) Ritter and Kalish, *ibid.*, **70**, 4048 (1948); (c) Benson with Ritter, *ibid.*, **71**, 4128 (1949); (d) Hartzel with Ritter, *ibid.*, **71**, 4130 (1949).

(4) (a) Gabriel and Heymann, *Ber.*, **23**, 2493 (1890); (b) Elfeldt, *ibid.*, **24**, 3223 (1891); (c) Adams and Leffler, THIS JOURNAL, **50**, 2252 (1937).