[CONTRIBUTION FROM PURDUE UNIVERSITY AND PURDUE RESEARCH FOUNDATION]

Compounds Derived from 3-Halo-1,1,1-trifluoropropane[1,2]

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Recently there has been considerable interest in the physiological properties of fluorine-containing compounds. It has been reported[3] that the acute toxicities of some trifluoromethyl compounds are relatively low. The purpose of the present investigation is the preparation of intermediates of value in the synthesis of analogs of useful pharmaceuticals.

Simple methods of synthesis as widely applicable as the Grignard reaction are not available for the preparation of trifluoromethyl and trifluoroethyl derivatives. Attempts to prepare the trifluoromethyl[4] and trifluoroethyl[5] Grignard reagents from the iodides have been unsuccessful. The Grignard from 3-chloro-1,1,1-trifluoropropane[6] served as the starting material for most of the syntheses described in this paper. By means of this reagent several new compounds have been prepared. These include the methyl and ethyl esters of 4,4,4-trifluorobutyric acid, 4,4,4-trifluorobutyraldehyde, 5,5,5-trifluoro-2-pentanol, 1,1,1,5,5,5-hexafluoro-2-pentanone and its hydrate and 1,1,1,7,7,7-hexafluoro-4-heptanone. No investigations of optimum conditions were made. All identified products were rerectified to obtain samples whose properties are listed in Table I. Data on solid derivatives are also given in Table I.

terials for the direct preparation of pharmaceutical analogs. For example, a hydantoin has been prepared from 1,1,1,7,7,7-hexafluoro-4-heptanone utilizing the method described by Henze and Speer.[7]

Other compounds of interest prepared in this program are 3-iodo-1,1,1-trifluoropropane, 4-iodo-1,1,1-trifluoropentane and 4,4,4-trifluoro-1-butanol.

Experimental

Materials.—3-Bromo-1,1,1-trifluoropropane, b. p. 62–64°, was prepared by the thermal bromination[8] of 1,1,1-trifluoropropane. 3-Chloro-1,1,1-trifluoropropane, b. p. 45–46°, was prepared by the liquid-phase photochemical chlorination[9] of 1,1,1-trifluoropropane. The methyl carbonate and ethyl orthoformate used were rectified fractions from commercial materials. Ethyl chloroformate was prepared from phosgene and ethanol. Trifluoroacetonitrile was prepared by the procedure of Gilman and Jones.[10] The Grignard reagent, 3,3,3-trifluoropropylmagnesium chloride, was prepared by the method of McBee and Truchan.[6] Methyl 4,4,4-trifluorobutyrate was prepared from the Grignard reagent of 3-bromo-1,1,1-trifluoropropane. A Grignard reagent was also prepared from 3-iodo-1,1,1-trifluoropropane on test-tube scale. All three halides form the reagent readily.

Methyl 4,4,4-Trifluorobutyrate.—An ethereal Grignard solution from 71 g. (0.4 mole) of 3-bromo-1,1,1-trifluoropropane was transferred into a separatory funnel and added dropwise to a stirred solution of 54 g. (0.6 mole) of methyl carbonate in ether (200 ml.). As the Grignard reagent was added, stirring became difficult because of the formation of a sticky solid. After standing overnight, the mixture was hydrolyzed with cold 5% sulfuric acid. The two layers were separated, the water layer was extracted several times with ether, and the combined ether layers were dried over Drierite. After distilling off the solvent, rectification of the residual liquid gave three fractions in

TABLE I

COMPOUNDS DERIVED FROM 3-HALO-1,1,1-TRIFLUOROPROPANE

Compound $(CF_3CH_2CH_2)R$					Derivative				
R	B. p.,[a] °C.	$n^{25}D$	Carbon,[b] % Calcd.	Found	Name	M. p.,[a] °C.	Carbon,[b] % Calcd.	Found	Nitrogen,[b] % Calcd.	Found
I	88	1.4175	16.1	16.2	.....	.....	..	..	...	...
CHO[c]	96	1.3387	..	...	2,4-Dinitrophenylhydrazone	191–192	39.2	39.4	18.30	18.45
CH_2OH	122	1.3743	37.5	38.0	3,5-Dinitrobenzoate	83.5–84.5	41.0	41.3	8.70	8.85
CO_2CH_3	113	1.3450	38.5	38.4	N-Benzylamide[d]	100.5–101	37.1	36.8	6.06	6.04
$CO_2C_2H_5$	127	1.3620	42.4	42.4	.....	.....	..	..	...	...
$CHOHCH_3$	126	1.3330	42.3	42.6	3,5-Dinitrobenzoate	78–79	42.9	42.7	8.33	8.46
$CHICH_3$	137	1.4335	23.8	23.7	.....	.....	..	..	...	...
$COCF_3$	82	1.3020	..	...	2,4-Dinitrophenylhydrazone[e]	90–91	35.3	35.2	14.97	14.91
$C(OH)_2CF_3$	64–65[f]	....	28.3	28.8	.....	.....	..	..	...	...
$1/_2(CO)$	164	1.3435	..	...	2,4-Dinitrophenylhydrazone	105–106	38.8	38.6	13.93	14.15
$1/_2(CNHCONHCO)$[g]	222–223[f]	....	37.0	37.2	.....	.....	..	...	...	...

[a] Corrected. [b] Carbon and nitrogen analysis by Dr. H. W. Galbraith. [c] Fluorine analysis (by A. I. Coleman) calcd. 45.2, found 45.2%. [d] The same compound was obtained from ethyl 4,4,4-trifluorobutyrate. [e] The same compound was obtained from 1,1,1,5,5,5-hexafluoro-2-pentanone hydrate. [f] Melting point. [g] Nitrogen analysis: calcd., 9.59; found, 9.75.

(1) This paper contains material abstracted from the M. S. thesis of A. E. Kelley.

(2) Part of the material in this paper was presented before the Fluorine Symposium at the 116th Meeting of the American Chemical Society, Atlantic City, September, 1949.

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(5) H. Gilman and R. G. Jones, THIS JOURNAL, **65**, 2037 (1943).

(6) E. T. McBee and A. Truchan, *ibid.*, **70**, 2910 (1948).

(7) H. R. Henze and R. J. Speer, *ibid.*, **64**, 522 (1942).

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(9) E. Rapkin, M. S. Thesis, Purdue University, 1949.

(10) H. Gilman and R. G. Jones, THIS JOURNAL, **65**, 1458 (1943).

addition to the excess methyl carbonate. The first fraction (17 g.), b. p. 110–114°, was methyl 4,4,4-trifluorobutyrate (0.11 mole) in 27% yield; the second fraction (3 g.), b. p. 162–164°, was 1,1,1,7,7,7-hexafluoro-4-heptanone (0.014 mole) in 7% yield; and a third fraction (5 g.) was collected at 192–194°.

The N-benzylamide of 4,4,4-trifluorobutyric acid was prepared from the ester.[11]

Ethyl 4,4,4-Trifluorobutyrate.—The predicted boiling point of ethyl 4,4,4-trifluorobutyrate was within a few degrees of the boiling point of ethyl carbonate, thus making separation of product from reactant troublesome if a procedure analogous to the preparation of the methyl ester was used. To avoid this difficulty, the Grignard reagent from 67 g. (0.5 mole) of 3-chloro-1,1,1-trifluoropropane was added to a solution of 163 g. (1.5 moles) of ethyl chloroformate in ether (100 ml.). Hydrolysis was accomplished with cold 5% hydrochloric acid. Extraction and drying were carried out as for the methyl ester. Rectification gave three fractions after the excess ethyl chloroformate was removed. The first fraction (26 g.), b. p. 126–129°, was ethyl 4,4,4-trifluorobutyrate (0.15 mole) in 31% yield; the second fraction (10 g.), b. p. 162–164°, was 1,1,1,7,7,7-hexafluoro-4-heptanone (0.045 mole) in 18% yield; and a third fraction (14 g.) was collected above 204°.

The N-benzylamide prepared from the ethyl ester is identical to that prepared from the methyl ester, as shown by a mixed melting point determination.

1,1,1,7,7,7-Hexafluoro-4-heptanone.—In the synthesis of methyl and ethyl 4,4,4-trifluorobutyrates as described above, 1,1,1,7,7,7-hexafluoro-4-heptanone was obtained as a by-product. The 2,4-dinitrophenylhydrazone was prepared[12a] from the 162–164° fraction from each ester synthesis. The two derivatives were shown to be identical by a mixed melting point determination.

4,4,4-Trifluorobutyraldehyde.—The Grignard solution from 67 g. (0.5 mole) of 3-chloro-1,1,1-trifluoropropane was added to an ether solution of 74 g. (0.5 mole) of ethyl orthoformate. The mixture was refluxed for two hours and then allowed to stand overnight. Since only a small amount of white precipitate had formed, the mixture was again refluxed for two hours, and the ether was distilled off cautiously. The residue was hydrolyzed with crushed ice and 5% hydrochloric acid. The aldehyde was separated and purified by the procedure of Bachman.[13] The aqueous solution thus obtained was extracted with ether, and the extracts were dried over Drierite. Rectification gave 23 g. (0.18 mole, 37% yield) of 4,4,4-trifluorobutyraldehyde, b. p. 94–96°.

The 2,4-dinitrophenylhydrazone was prepared from the aldehyde.[12a]

4,4,4-Trifluoro-1-butanol.—A solution of 13 g. (0.1 mole) of 4,4,4-trifluorobutyraldehyde in 100 ml. of ether was added dropwise to 1.14 g. (0.03 mole) of lithium aluminum hydride in 100 ml. of ether. After addition of the aldehyde was complete, the mixture was stirred for 10 minutes longer, then hydrolyzed with 50 ml. of dilute sulfuric acid. The layers were separated, the aqueous phase was extracted with ether, and the combined ether layers were dried over Drierite. Rectification gave 11 g. (0.086 mole, 86% yield) of 4,4,4-trifluoro-1-butanol, b. p. 121–123°.

The 3,5-dinitrobenzoate was prepared.[12b]

5,5,5-Trifluoro-2-pentanol.—An ether solution of 30 g. (0.68 mole) of freshly distilled and dried acetaldehyde was added to a Grignard solution from 67 g. (0.5 mole) of 3-chloro-1,1,1-trifluoropropane cooled to −5°. When addition was complete, the mixture was allowed to warm to room temperature. Hydrolysis was accomplished with cold 4 *N* sulfuric acid. The two layers were separated, the water layer was saturated with potassium carbonate and extracted with ether. The combined ether layers were dried over Drierite. Rectification gave 45 g. (0.32 mole, 63% yield) of 5,5,5-trifluoro-2-pentanol, b. p. 124–127°.

The 3,5-dinitrobenzoate was prepared.[12b]

4-Iodo-1,1,1-trifluoropentane.—This compound was prepared from 35 g. (0.25 mole) of 5,5,5-trifluoro-2-pentanol, 3.3 g. (0.11 mole) of red phosphorus and 33 g. (0.13 mole) of iodine, using a modification of the apparatus described in "Organic Syntheses."[14] At the completion of the reaction, the mixture was cooled, diluted with 50 ml. of ether, and filtered. The filtrate was washed with dilute sodium bicarbonate and sodium bisulfite solutions. The resulting light pink solution was rectified and decolorized with a drop of mercury to give 41 g. (0.16 mole, 65% yield) of 4-iodo-1,1,1-trifluoropentane, b. p. 136–138°. A sample removed from contact with the mercury turned a deep pink on standing three days.

1,1,1,5,5,5-Hexafluoro-2-pentanone.—A Grignard solution was prepared from 77 g. (0.58 mole) of 3-chloro-1,1,1-trifluoropropane. After reaction was complete, the flask was cooled in a mixture of Dry Ice and trichloroethylene. Freshly prepared trifluoroacetonitrile (48 g., 0.5 mole) was allowed to evaporate slowly from the tube in which it had been collected, pass through a bubble counter and a drying tube, then enter the reaction flask below the liquid surface. When all the trifluoroacetonitrile had been added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. Hydrolysis was accomplished by adding cold 25% sulfuric acid and steam distilling the mixture. The usual ether separation and extractions were carried out. The combined ether layers were dried over and distilled from phosphorus pentoxide in order to remove water from the stable ketone hydrate. Rectification gave 26 g. (0.13 mole, 27% yield) of 1,1,1,5,5,5-hexafluoro-2-pentanone, b. p. 81–82°, and a small quantity of pot residue which partly crystallized on cooling.

The 2,4-dinitrophenylhydrazone of the ketone was prepared with some difficulty. It was necessary to wash the crude crystals of the phenylhydrazone on a filter with hot petroleum ether (90–120°), leaving the excess reagent on the filter, while the derivative crystallized in yellow leaflets from the cold filtrate. This recrystallization procedure was repeated until only a trace of red powder remained on the filter.

The pot residue from the rectification of the ketone was filtered. The solid thus obtained sublimed readily upon warming at atmospheric pressure to give a white crystalline material, m. p. 64–65°. Analysis indicated that this compound is the hydrate of 1,1,1,5,5,5-hexafluoro-2-pentanone. A 2,4-dinitrophenylhydrazone was prepared which was identical with that from the anhydrous ketone. The stability of the ketone hydrate to dehydration by phosphorus pentoxide and the volatility are in accord with observations on hexafluoroacetylacetone dihydrate.[15]

3-Iodo-1,1,1-trifluoropropane.—By heating 35 g. (0.2 mole) of 3-bromo-1,1,1-trifluoropropane with sodium iodide and acetone in a Carius tube at 100° for 44 hours, 3-iodo-1,1,1-trifluoropropane, b. p. 87–88°, was obtained in 82% yield.

5,5-Bis-(3′,3′,3′-trifluoropropyl)-hydantoin.—Utilizing the procedure described by Henze and Speer,[7] 1 g. of 1,1,1-7,7,7-hexafluoro-4-heptanone was converted to the hydantoin by heating the reactants at 60° for three hours. The product was recrystallized from 50% aqueous ethanol to give white flakes melting at 222–223°.

Acknowledgment.—The aid of Mr. Joseph P. O'Brien in the preparation of ethyl chloroformate is gratefully acknowledged. We are indebted to Dr. Z. D. Welch for some of the materials required in this research.

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Summary

From the 3,3,3-trifluoropropyl Grignard reagent several new compounds have been prepared, including methyl and ethyl esters of 4,4,4-trifluorobutyric acid, 4,4,4-trifluorobutyraldehyde, 5,5,5-trifluoro-2-pentanol, 1,1,1,5,5,5-hexafluoro-2-pentanone and its hydrate and 1,1,1,7,7,7-hexafluoro-4-heptanone.

Some of the compounds thus prepared have been used to synthesize 4,4,4-trifluoro-1-butanol, 4-iodo-1,1,1-trifluoropentane and 5,5-bis-(3′,3′,3′-trifluoropropyl)-hydantoin.

3-Iodo-1,1,1,-trifluoropropane has been prepared.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

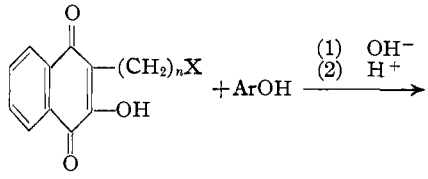
Naphthoquinone Antimalarials. XXV.[1] Naphthoquinones with Oxygen in the Side Chain

BY MARVIN PAULSHOCK[2] AND CARL M. MOSER[3]

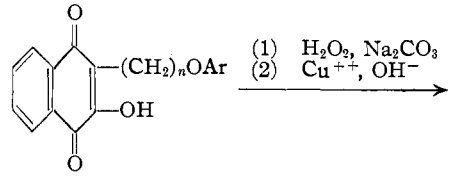
The discovery that 2-alkyl-3-hydroxy-1,4-naphthoquinones with a hydroxylated side chain are resistant to metabolic degradation[4] suggested the synthesis of other 2-alkyl-3-hydroxy-1,4-naphthoquinones with oxygen in the side chain in order to determine the potency of these compounds as antimalarial agents. Previous work[5,6] had indicated that quinones with an oxygenated side chain containing less than twelve carbon atoms are for the most part inactive or only feebly active. The most potent quinones contained about twenty carbon atoms in the side chain.

A number of ethers of suitable side chain length were synthesized by condensation between an ω-halo quinone (I) and a phenolic compound in the presence of base in a manner analogous to the method used for the preparation of thioether naphthoquinones.[6] Some of the 2-aryloxyalkyl-3-hydroxy-1,4-naphthoquinones were prepared from ω-aryloxyacids *via* the peroxide alkylation[7,8] of lawsone (2-hydroxy-1,4-naphthoquinone). Norhomologs of some of these aryloxyalkyl derivatives of lawsone were prepared by the two-step[9] Hooker oxidation[10] of alkyl hydroxynaphthoquinones. Attempts to perform the oxidation on ω-haloquinones (I) were unsuccessful.

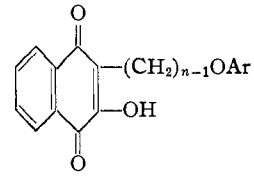
The relative anti-respiratory activities[11] of these quinones have been determined (see Table I, Experimental section), and on the basis of this *in vitro* assay it appears that some of these aryloxyalkyl quinones possess potency as antimalarial drugs. This conclusion has been confirmed in duck assays.[4]



I

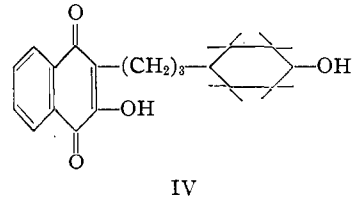


II

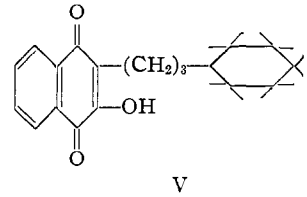


III

Although the quinone IV, which is a metabolite of V, is stable to further metabolic degradation,



IV



V

(1) This paper represents a part of the dissertations submitted by the authors in partial fulfillment of the requirements for the degree Doctor of Philosophy to the Faculty of Arts and Sciences, Harvard University, May, 1948. For the previous paper in this series see Fawaz and Fieser, THIS JOURNAL, **72**, 996 (1950).

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(9) Fieser and Fieser, *ibid.*, **70**, 3215 (1948).

(10) Hooker, *ibid.*, **58**, 1163, 1174, 1179 (1936).

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