Stereospecific Synthesis of *erythro*- and *threo*-9,10-Diaminooctadecanoic Acids and Derivatives[1]

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The stereospecific synthesis of the previously unreported *erythro*- and *threo*-9,10-diaminooctadecanoic acids and their monoacetates, sulfates, and dihydrochlorides is described (Scheme I). Their stereochemistry has been confirmed by independent synthesis of the *threo* isomer (Scheme II). Displacement of mesylate by azide in dimethylformamide in vicinal 9(10),10(9)-azidomesylates proceeds with inversion consistent with recently reported work in the carbohydrate field. In this so-called alkaline displacement, anchimeric assistance involving an intermediate "azidonium" ion, is not observed.

Nitrogen-containing long-chain fatty acid derivatives occur in a wide variety of animal and vegetable lipids; in general, their physiological functions are still unknown.[3] Prior to undertaking the synthesis of some of them, we have initiated a series of investigations on model fatty acid systems to introduce nitrogen-containing functional groups of known stereochemistry at selected positions in the alkyl chain. In this paper, we are describing the stereospecific synthesis of the hitherto unreported *erythro*- and *threo*-9,10-diaminooctadecanoic acids (**6** and **12**) and some of their derivatives, and confirmation of their stereochemistry by independent synthesis of one isomer. As an extension of our interest in environmental carcinogenesis, we hope to examine the chelating characteristics of these diamino compounds for trace metals.[4]

Results and Discussion

Scheme I summarizes the reactions and stereochemical transformations in the preparation of the diamino acids. The starting materials, methyl *cis*- and *trans*-9,10-epoxystearates (**1** and **7**), were prepared in the conventional manner by epoxidation of methyl oleate and elaidate, respectively, with peroxyacetic acid.[5] Nucleophilic attack on **1** and **7** by sodium azide in refluxing ethanol converted them to methyl *threo*-9(10),10(9)-azidohydroxyoctadecanoate (**2**) and its *erythro* isomer (**8**), respectively, in essentially quantitative yield. The stereochemistry of this reaction is well known and proceeds with clean inversion.[6,7] The reaction products were oils that were purified by column chromatography on alumina (Woelm, neutral grade), eluting with low-boiling petroleum ether.

The azidohydrins (**2** and **8**) were then converted to methanesulfonates (**3** and **9**) without change in stereochemistry, and the mesylates were also purified by column chromatography. A second, vicinal azide group was now introduced by nucleophilic displacement of the methanesulfonate function by azide ion, a reaction accompanied by inversion (see later discussion). This was accomplished by stirring the azidomesylates (**3** and **9**) with a suspension of sodium azide in dimethylformamide at 100° for 24 hr. High yields of methyl *erythro*-9,10-diazidooctadecanoate (**4**) and its *threo* isomer (**10**) were obtained.

Hydrogenation of the diazido esters (**4** and **10**) at room temperature in ethanol over Adams catalyst at 400 psi for 2 days yielded methyl *erythro*-9,10 diaminooctadecanoate (**5**) and its *threo* isomer (**11**), respectively, in good yields without change in stereochemistry. No pressure change was observed during the hydrogenation as the volume of hydrogen consumed was exactly balanced by nitrogen liberated from the diazides. Hydrogenation was conducted until the azide band in the infrared (1260 cm^{-1}) had completely disappeared.

Saponification of the diamino esters (**5** and **11**) by the usual procedure followed by acidification with glacial acetic acid yielded monoacetates of *erythro*- and *threo*-diaminooctadecanoic acids (**6** and **12**), mp 147–148° and 119–120°, respectively, and not the free diamino acids. Alternatively, acidification with 50% sulfuric acid yielded the *erythro* and *threo* sulfates, mp 230–232° and 236–238°, as water-insoluble, readily isolated, crystalline solids. Isolation of the diamino acids as the sulfates is the recommended procedure. Attempts to prepare the dihydrochloride of the *erythro* acid yielded an oil; the *threo* acid gave a crystalline, solid dihydrochloride, mp 147–149°.

In no case were analytically pure free diamino acids obtained even by careful acidification of their methyl ester saponification reaction mixtures. Salts were always isolated. In an attempt to obtain the free diamino acids, the synthetic pathway was slightly modified. Saponification of the diazido esters (**4** and **10**) was conducted prior to hydrogenation and the resulting 9,10-diazidooctadecanoic acids were then hydrogenated. It was hoped to isolate the diamino acids directly from the hydrogenation reaction without adding acid, thus avoiding salt formation. The diazido acids, however, were somewhat unstable and analytically pure products were not available for hydrogenation, although elemental analyses and spectra indicated that purity was high. The free diamino acids obtained from these diazido acids were also slightly impure. The melting points of the diamino acids (121–123° and 96–98°) adhere to the well-established rule for vicinally substituted, long-chain fatty acid derivatives that the *erythro* form is the higher melting diastereoisomer.

(1) Presented in part at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966. Paper XIX in the series Chemistry of Epoxy Compounds. Paper XVIII: D. Swern and W. E. Parker, *J. Org. Chem.*, **22**, 583 (1957).

(2) On leave of absence from the Imperial Chemical Industries Ltd., Mond Division, Cheshire, England.

(3) H. J. Deuel, "The Lipids, Their Chemistry and Biochemistry," Vol. I–III, Interscience Publishers, Inc., New York, New York, 1957, and numerous references therein.

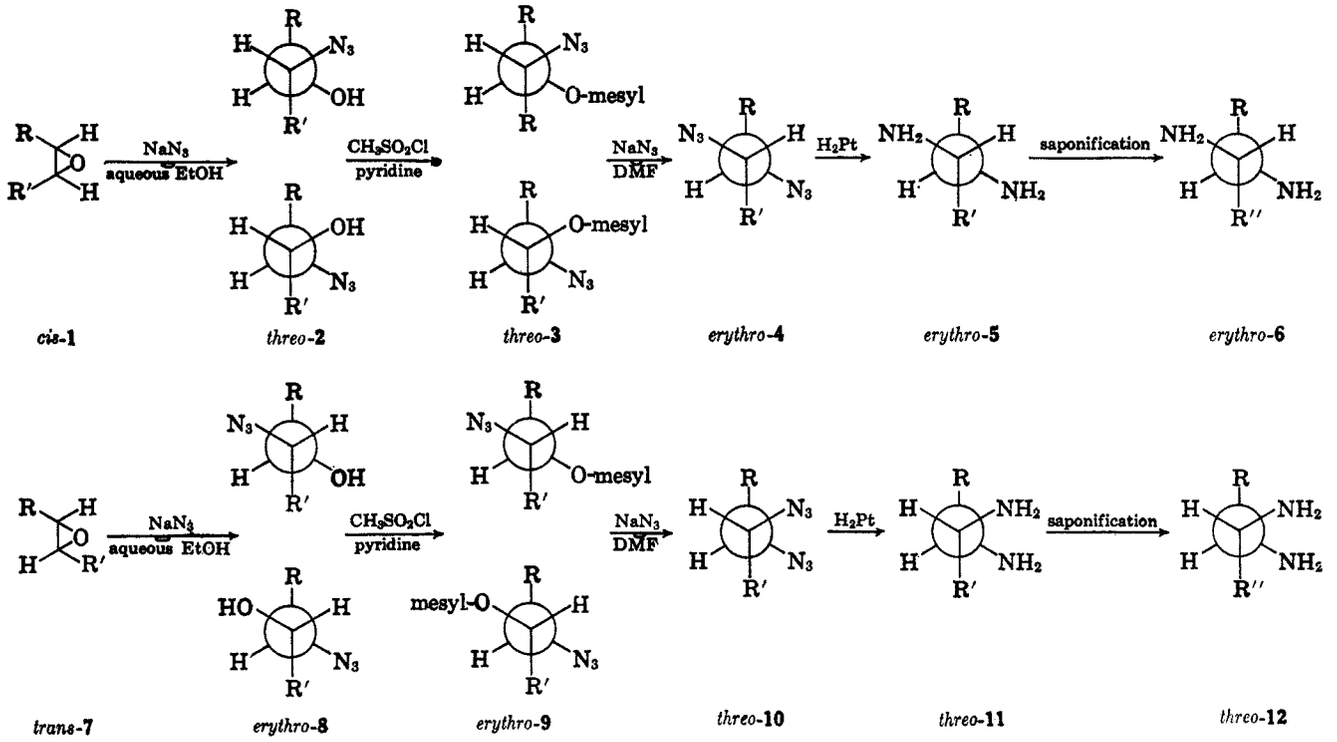
(4) W. C. Hueper and W. D. Conway, "Chemical Carcinogenesis and Cancers," Thomas Publisher, Springfield, Ill., 1964.

(5) T. W. Findley, D. Swern, and J. T. Scanlan, *J. Am. Chem. Soc.*, **67**, 412 (1945).

(6) C. A. Van der Werf, R. Y. Heisler, and W. E. McEwen, *ibid.*, **76**, 1231 (1954); R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963).

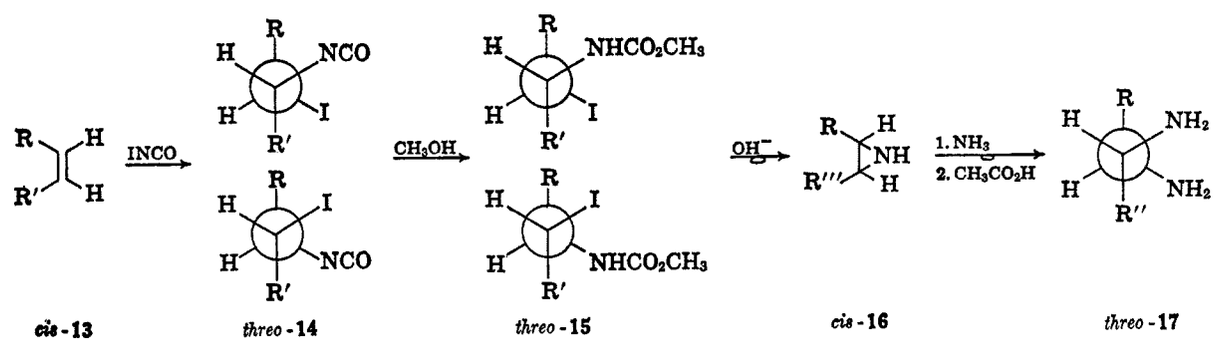
(7) G. Swift, Ph.D. Thesis, University of London, 1964.

SCHEME I



R = $CH_3(CH_2)_7$; R′ = $(CH_2)_7CO_2CH_3$; R″ = $(CH_2)_7CO_2H$

Scheme II

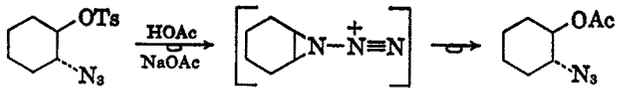


R = $CH_3(CH_2)_7$; R′ = $(CH_2)_7CO_2CH_3$; R″ = $(CH_2)_7CO_2H$; R‴ = $(CH_2)_7CO_2K$,

In another attempt to obtain an analytically pure sample of *threo*-9,10-diaminooctadecanoic acid, its sulfate, mp 236–238°, suspended in water was stirred with sodium acetate. The monoacetate of the *threo* acid was obtained, however, and not the free acid.

The stereochemistry of all of the transformations in Scheme I, with the exception of the nucleophilic displacement by azide ion of a methanesulfonate function vicinal to an already present azide function, is unequivocal. The displacement of methanesulfonate by azide in vicinal azidomesylates has been written as occurring with inversion (**3** → **4** and **9** → **10**), consistent with the recent work of Guthrie and Murphy[8] in the carbohydrate field. These investigators showed that an anticipated inversion occurred in transforming such species to vicinal diazides when the displacement reaction was conducted, as we have also done it, with sodium azide in dimethylformamide, the so-called alkaline displacement.

Somewhat prior to this work, however, it had been reported by Streitwieser and Pulver[9] that displacement of the tosylate group in *trans*-2-azidocyclohexyltosylate by acetate (solvolysis in acetic acid–sodium acetate) gave retention of configuration; the product was *trans*-2-azidocyclohexylacetate, although in only 37% yield. To rationalize the result, Streitwieser and Pulver postulated that anchimeric assistance involving an "azidonium" intermediate had occurred, resulting in two inversions and over-all retention of configuration, as shown below.[10]



Since some question existed at the time the present work was in progress about the stereochemistry of the displacement of methanesulfonate by azide in vicinal

(8) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 6956 (1965).

(9) A. Streitwieser, Jr., and S. Pulver, *J. Am. Chem. Soc.*, **86**, 1587 (1964).

(10) In a future article (G. Swift and D. Swern, *J. Org. Chem.*, **32**, in press) the authors are reporting results on the acetic acid solvolysis of *trans*-2-azidocyclohexyl tosylate. We have confirmed Streitwieser and Pulver's results independently, and in a different way, and have obtained 75–80% yields of *trans*-2-azidocyclohexyl acetate.

azidomesylates, and the stereochemistry of this step was crucial to our assignment of the stereochemistry of the 9,10-diaminooctadecanoic acids, an independent syntheses of the *threo* isomer was carried out, all steps of which proceed with known stereochemistry, as summarized in Scheme II.

Potassium *cis*-9,10-aziridinooctadecanoate (**16**) was readily prepared by the method of Gebelein, Swift, and Swern,[11] the first step of which is the addition of iodine isocyanate to the double bond of methyl *cis*-9-octadecenoate (oleate) (**13**).[12] This addition reaction has been shown to proceed exclusively by *trans* addition,[13] to yield the *threo* adduct (**14**). Reaction with methanol yielded *threo*-9,10(10,9)-iodocarbamates (**15**) which on ring closure with base gave **16** in over 50% yield. Reaction of **16** with ammonia opened the aziridine ring with inversion and, after acidification with acetic acid, the acetate of *threo*-9,10-diaminooctadecanoic acid (**17**) was obtained. This acetate (**17**) was identical in every respect (infrared, melting point, and mixture melting point) with the acetate of **12**. Further confirmation of the identity of **17** and **12** was obtained by showing that they formed identical sulfates and dihydrochlorides, mp 236–238° and 147–149°, respectively.

Experimental Section[14]

Methyl *threo*-9,10(10,9)-Azidohydroxyoctadecanoate (2).—Methyl *cis*-9,10-epoxystearate (**1**, 31.2 g, 0.1 mole), sodium azide (13.0 g, 0.2 mole), and ammonium chloride (10.8 g, 0.2 mole) were dissolved in ethanol (500 ml) and water (150 ml) and the reaction mixture was refluxed for 24 hr. The solution was poured into several volumes of water and the oily product was extracted with ether. After several water washes and evaporation of the ether on a rotary evaporator crude **2** was obtained as a pale yellow oil (33.0 g, 93% yield). It was purified by column chromatography over "Woelm" alumina (neutral grade), eluting with low-boiling petroleum ether (bp 30–60°): infrared 3490 (OH), 2110 and 1260 (N_3), and 1740 cm^{-1} (carbonyl).

Methyl *erythro*-9,10(10,9)-Azidohydroxyoctadecanoates (8).—This was prepared in the same way as the *threo* isomer but starting from methyl *trans*-9,10-epoxystearate (**7**). Its infrared spectral characteristics were the same as those of its *threo* isomer (**2**).

Methyl *threo*-9,10(10,9)-Azidomesyloxyoctadecanoates (3).—The *threo*-azidohydrin (**2**, 15.0 g) was dissolved in pyridine (200 ml) and cooled to 0–5°. Methanesulfonyl chloride (11.5 g) was slowly added with stirring and the reaction mixture was stirred for 4 hr at 0–5°. The reaction mixture was poured into water and extracted with ether. The ether extract was washed several times with water and the dried ether solution was evaporated in a rotary evaporator. The product (**3**, 16.0 g, 77% yield) was a pale yellow oil. It was purified by column chromatography over "Woelm" alumina (neutral grade), eluting with petroleum ether: infrared 2110 and 1260 (N_3), 1740 (carbonyl), and 1190 cm^{-1} (sulfonate).

Methyl *erythro*-9(10),10(9)-Azidomesyloxyoctadecanoates (9).—This was prepared in the same way as the *threo* isomer but starting with the *erythro*-azidohydrin (**8**). Its infrared spectral characteristics were virtually indistinguishable from those of the *threo* isomer (**3**).

Methyl *erythro*-9,10-Diazidooctadecanoate (4).—A solution of the *threo*-azidomesylate (**3**, 17.3 g, 0.04 mole) in dry dimethylformamide (100 ml) was stirred with sodium azide (5.2 g, 0.08 mole) in suspension for 24 hr at 100°. The reaction mixture was poured into water and extracted with ether in the usual way. The crude, pale yellow oily product was purified by column chromatography over "Woelm" alumina (neutral grade), eluting with low-boiling petroleum ether, to obtain **4** (14.0 g, 93% yield): infrared 2110 and 1260 (N_3) and 1740 cm^{-1} (carbonyl).

Methyl *threo*-9,10-Diazidooctadecanoate (10).—This was prepared in the same way as the *erythro* isomer but starting with the *erythro*-azidomesylate (**9**). It had essentially the same infrared spectrum as its *erythro* isomer (**4**).

Monoacetate and Sulfate of *erythro*-9,10-Diaminooctadecanoic Acid (6).—Methyl *erythro*-9,10-diazidooctadecanoate (**4**, 21.2 g, 0.056 mole) dissolved in ethanol (200 ml) was hydrogenated in a stirred autoclave over Adams catalyst for 2 days at room temperature and 400 psi. No pressure change was observed. Filtration and evaporation of the alcohol in a rotary evaporator yielded a thick, syrupy compound having an infrared spectrum consistent with that of the expected diamino ester. It was not purified but was saponified directly with aqueous ethanolic potassium hydroxide followed by dilution with water and acidification with glacial acetic acid to precipitate the monoacetate of **6** (14.0 g, 70% yield): mp 147–148°; infrared 2190 and 1510 (NH_3^+) and 1560 cm^{-1} (CO_2^-).

Anal. Calcd for $C_{20}H_{42}N_2O_4$: C, 64.1; H, 11.4; N, 7.48. Found: C, 64.3; H, 11.2; N, 7.29.

A few milligrams of the acetate was suspended in water and stirred with an excess of 50% aqueous sulfuric acid at room temperature. The product was crystallized from acetic acid–ethanol to yield the sulfate of **6**: mp 230–232°; infrared 2110, 1640, and 1550 cm^{-1}.

Anal. Calcd for $C_{18}H_{40}N_2O_6S$: C, 52.4; H, 9.77; N, 6.79; S, 7.77. Found: C, 51.9; H, 9.87; N, 6.30; S, 7.80.

Attempts to prepare the dihydrochloride always resulted in the formation of oils.

Sulfate, Monoacetate, and Dihydrochloride of *threo*-9,10-Diaminooctadecanoic Acid (12).—The *threo*-diazido ester (**10**) (24.0 g, 0.06 mole) was hydrogenated and saponified as described for the *erythro* isomer (**4**) but after saponification the ethanol was evaporated on a rotary evaporator and 50% aqueous sulfuric acid was slowly added to the aqueous residue with stirring to acidify. A hard, granular, white solid precipitated, the sulfate of **12** (16.0 g, 62% yield): mp 236–238°; infrared 1670 (carbonyl) and 2110, 1640, 1560, and 1545 cm^{-1} (NH_3^+).

Anal. Calcd for $C_{18}H_{40}N_2O_6S$: C, 52.4; H, 9.77; N, 6.79; S, 7.77. Found: C, 52.2; H, 9.74; N, 6.56; S, 7.40.

The powdered sulfate (2.0 g) was suspended in water (50 ml) and stirred overnight with sodium acetate (5.0 g). The white solid was filtered and recrystallized from ethanol to yield the monoacetate of **12** (1.5 g, 75%), mp 116–118°.

Anal. Calcd for $C_{20}H_{42}N_2O_4$: C, 64.1; H, 11.3; N, 7.48. Found: C, 64.1; H, 11.3; N, 7.63.

The monoacetate of **12** (0.5 g) was suspended in water and treated with a few drops of concentrated hydrochloric acid. The solid dissolved and within a few moments another white solid precipitated. It was filtered and recrystallized from acetic acid–ethyl acetate to yield the dihydrochloride of **12** (0.3 g): mp 147–149°; infrared 1720 (carbonyl) and 1590 and 1550 cm^{-1} (NH_3^+).

Anal. Calcd for $C_{18}H_{40}Cl_2N_2O_2$: C, 55.8; H, 10.4; Cl, 18.3; N, 7.23. Found: C, 55.4; H, 10.5; Cl, 18.2; N, 7.32.

Potassium *cis*-9,10-Aziridinooctadecanoate (16).—Methyl *cis*-9-octadecenoate (**13**, 59 g, 0.2 mole), silver cyanate (30 g, 0.2 mole), and iodine (51 g, 0.2 mole) were stirred for 24 hr at 0–5° in the dark. The pale yellow solution was filtered from inorganic matter and the filtrate was evaporated to dryness yielding methyl *threo*-9(10),10(9)-iodoisocyanotooctadecanoate (**14**) as a residue in essentially quantitative yield. The residue was refluxed with absolute methanol (300 ml) for 3 hr and the solution of **15** was treated directly with potassium hydroxide (44.8 g) dissolved in water (100 ml). The solution was then refluxed for 12 hr and then evaporated to dryness in a rotary evaporator. The residual soaps and salts were extracted with three 200-ml portions of absolute ethanol. The combined extracts were concentrated to about 200 ml and cooled to 0° when a white, granular solid (**16**), mp >240°, precipitated [25 g, 35% yield based on (**13**)]. It was identical in every respect with the authentic compound previously prepared in our laboratory.[11]

Monoacetate, Dihydrochloride, and Sulfate of *threo*-9,10-Diaminooctadecanoic Acid (17 and 12) from 16.—The potassium salt (**16**, 2.0 g) in a solution of ethanol (50 ml) and concentrated ammonium hydroxide solution (200 ml) was heated at 100° for

(11) C. Gebelein, G. Swift, and D. Swern, paper presented at the Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., Feb 1966.

(12) L. Birckenbach and M. Linhard, *Ber.*, **64B**, 1076 (1931).

(13) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 1125 (1964).

(14) Infrared Spectra were obtained on a Perkin-Elmer Infracord 137. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del. Melting and boiling points are uncorrected.

48 hr in a stirring autoclave (pressure approximately 100 psi). Evaporation of the excess ammonia followed by acidification with acetic acid yielded a black oil and a white, insoluble solid. Warming caused the solid to dissolve and the solution was carefully separated from the oil (polymer?). The solution was cooled to about 0° and the white precipitate, the monoacetate of **17** (1.0 g) was filtered off. Its melting point was 119–120°; a mixture melting point with the monoacetate of **12** gave no depression.

Anal. Calcd for $C_{20}H_{42}N_2O_4$: C, 64.1; H, 11.3; N, 7.48. Found: C, 63.2; H, 11.0; N, 7.20.

Since the carbon analysis was slightly off, the monoacetate was divided into two portions for conversion to the dihydrochloride, mp 147–149° (identical with the dihydrochloride of **12**), and to the sulfate, mp 236–238° (identical with the sulfate of **12**).

Anal. Calcd for the dihydrochloride ($C_{18}H_{40}Cl_2N_2O_2$): C, 55.8; H, 10.4; Cl, 18.3; N, 7.23. Found: C, 55.6; H, 10.6; Cl, 18.2; N, 7.25.

Anal. Calcd for the sulfate ($C_{18}H_{40}N_2O_6S$): C, 52.4; H, 9.77; N, 6.79; S, 7.77. Found: C, 52.4; H, 9.39; N, 6.69; S, 7.96.

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Notes

Perfluoro Tertiary Alcohols

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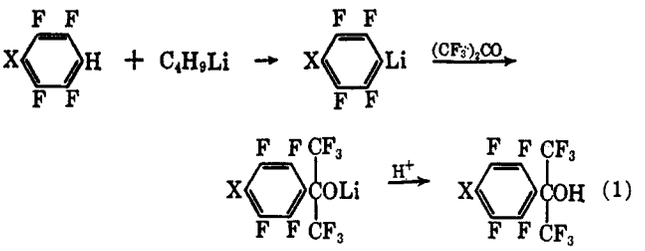
Attempts to prepare perfluoro tertiary alcohols through the reaction between a fluoro ester and a perfluoroorganolithium[1] or perfluoro Grignard[2] reagent thus far have been unsuccessful. In each case only perfluoroalkyl secondary alcohols $(R_F)_2CHOH$ were obtained. Recently, Graham and Weinmayr[3] have reported the reaction between perfluoro olefins, cesium fluoride, and certain perfluoro ketones to yield perfluoro tertiary alcohols. Two other nonorganometallic routes have been recently reported by Middleton and Lindsey[4] for the synthesis of specific perfluoro tertiary alcohols. Photoinitiated bimolecular reduction of hexafluoroacetone with isopropyl alcohol yielded the perfluoropinacol while hydration of tetrakis(trifluoromethyl)ethylene yielded the perfluoro(3H-2,3-dimethyl-2-butyl alcohol). Dyatkin, Mochalina, and Knunyants[5] have also reported the synthesis of perfluoro tertiary alcohols through the oxidation of *t*-nitrosoperfluoroisobutane and subsequent hydrolysis of the nitrite formed.

The physical and chemical properties of the hydroxyl group are strongly affected by the perfluoroalkyl substituents. The inductive effect of the perfluoroalkyl group increases the acidity of the alcohols. The ionization constants[4,5] of the perfluorinated alcohols indicates them to be strongly acidic. Perfluoro-*t*-butyl alcohol is a stronger acid (pK_a = 3.9) than acetic acid (pK_a = 4.7).[5] Other properties noted[4] in certain highly fluorinated alcohols were the strong hydrogen-bond formation, unusual solvent properties for certain polymers and formation of stable complexes.

The authors now wish to report on a general method for preparing perfluorinated arylalkyl tertiary mono- and dialcohols. Recently, the synthesis of a number of perfluoroaryllithium reagents[6] have been reported. These intermediates have now been treated with hexafluoroacetone to yield the perfluoro tertiary alcohols in good yields.



(1)

X = F (I), CF_3 (II), CH_3 (III), H (IV and V), *p*-HC_6H_4 (VI)

When X = H or *p*-C_6F_4, metalation can be controlled to yield predominantly the mono or dilithio intermediate. The dilithio intermediate will yield the biscarbinols.

The yields and properties of these alcohols are described in the Experimental Section. One attempt at preparing the carbinol I from the Grignard pentafluorophenylmagnesium bromide showed the advantage of the organolithium intermediate over the Grignard intermediate. The greater nucleophilic nature of the organolithium intermediate toward hexafluoroacetone resulted in much higher yields of the carbinol (79 *vs.* 33%).

None of the alcohols prepared in this study exhibited any tendency to form stable isolable complexes with tetrahydrofuran as was the case with the perfluoro secondary and tertiary alkyl alcohols.[4] However, infrared studies of tetrahydrofuran solutions of the arylalkyl alcohols synthesized in this study indicated hydrogen bonding between the alcohols and the sol-

(1) E. T. McBee, C. W. Roberts, and S. G. Curtis, *J. Am. Chem. Soc.*, **77**, 6387 (1955).
(2) A. L. Henne and W. C. Francis, *ibid.*, **75**, 992 (1953).
(3) D. P. Graham and V. Weinmayr, *J. Org. Chem.*, **31**, 957 (1966).
(4) W. J. Middleton and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **86**, 4948 (1964).
(5) B. L. Dyatkin, E. P. Mochalina, and O. L. Knunyants, *Tetrahedron*, **21**, 2991 (1965).
(6) C. Tamborski and E. J. Soloski, *J. Org. Chem.*, **31**, 743 (1966).