XXVIII. From basic alumina (Brockmann grade I) hexane eluted the fluorene only; the phenol was eluted with hexane-chloroform.

Attempts to Improve the Yield of Fluorene Formation from XIX. A.—Compound XIX (2.4 g) was diazotized in 200 ml of 1.5% hydrochloric acid and the diazonium salt decomposed at 70°. Yields of the corresponding fluorene, phenol, and chlorobiphenyl were 52, 39, and 2%, respectively, according to mass spectrometric analysis of the product mixture at low voltage (7.5 V uncor). This method may be favored over the diazotization in dilute sulfuric acid for solubility reasons, if isolation of the phenol is not required.

B.—Compound XIX was diazotized as in method A and decomposed at room temperature after a solution of 1.6 g of cuprous chloride in 56 ml of 8% hydrochloric acid was added. Mass spectrometric analysis of the product mixture showed 43% fluorene, 43% phenol, and 5.5% chlorinated biphenyl.

C.—Compound XIX (2.4 g) was stirred with 80% sulfuric acid and diazotized at 0° by adding finely powdered sodium nitrite (0.8 g). The solution was cloudy. After 1 hr, the mixture was decomposed at 45°. Mass spectrometric analysis indicated 49% fluorene, 9% phenol, 26% dimeric hydrocarbons, and 7% dimeric ether or phenol in the product mixture.

D.—Boric acid (1.2 g) was stirred in concentrated hydrochloric acid (8 ml) and sodium fluoride (3.4 g) was slowly added in a fume hood. After standing 1 hr, the sodium chloride precipitate was suction filtered on a fiber-glass filter. The diazonium solution prepared from 2.4 g of compound XIX in 40 ml of 2.5% hydrochloric acid was added to the filtrate. The pale yellow diazonium fluoroborate precipitate was filtered, washed with distilled water, and vacuum dried over phosphorus pentoxide at 55°. The ir spectrum of the dried salt indicated the presence of crystal water (3320 cm^{-1}); its decomposition point was 95°. During overnight drying at 55° the salt decomposed. The product mixture, according to mass spectrometric and gas chromatographic analyses, was 65% fluorinated biphenyl and 25% fluorene. Decomposition of the diazonium fluoroborate at 100° gave 70% fluorinated biphenyl and 18% fluorene.

Registry No.—VIII, 17447-85-7; IX, 17449-10-4; X, 17477-84-8; XI, 17449-11-5; XII, 17449-12-6; XIII, 17477-85-9; XIV, 17416-89-6; XV, 17416-90-9; XVI, 17416-91-0; XVII, 17447-86-8; XVIII, 17416-92-1; XIX, 17447-87-9; XX, 17447-97-1; XXI, 17416-93-2; XXII, 17447-88-0; XXIII, 17447-89-1; XXIV, 17416-94-3; XXV, 17447-90-4; XXVI, 17447-98-2; XXVII, 17416-95-4; XXVIII, 17447-91-5; XXIX, 17447-92-6; XXX, 17447-93-7; XXXI, 17447-94-8; XXXII, 17447-95-9; XXXIII, 17447-96-0.

Acknowledgments.—We thank Professors J. I. G. Cadogan and H. Hart for helpful discussions. The spectroscopic analyses by S. Meyerson and E. M. Banas are gratefully acknowledged.

Resolution of Trifluoromethylcarbinols[1,2]

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(±)-Phenyltrifluoromethylcarbinol and (±)-*t*-butyltrifluoromethylcarbinol have been resolved *via* the 3β-acetoxy-Δ⁵-etienate esters, but (±)-methyltrifluoromethylcarbinol could not be resolved by this method. The completeness of the resolution of the first compound was confirmed by a gas chromatographic study of its O-methylmandelate ester, and the enantiomeric purity of a partially active sample of the methyltrifluoromethylcarbinol was determined by the same method. This glpc method was not applicable to the determination of enantiomeric purity of *t*-butyltrifluoromethylcarbinol.

As part of a continuing investigation[4,5] of asymmetric reductions of the corresponding ketones, it became necessary to know the absolute configuration and maximum rotation of phenyl-, *t*-butyl-, and methyltrifluoromethylcarbinols (IA, IB, and IC). The present paper describes the resolutions of two of these, and the subsequent paper[6] describes the experiments upon which the absolute configurations are based.

(±)-Phenyltrifluoromethylcarbinol (IA) was converted into the diastereomeric 3β-acetoxy-Δ⁵-etienate esters[7] which were carried through an extensive systematic fractional crystallization using 2-propanol as solvent.[3] Both the less soluble and more soluble diastereomers were obtained, from which were regenerated by lithium aluminum hydride reduction, respectively, the (−)-carbinol, $[\alpha]^{25}D$ −31.85° (neat), and the (+)-carbinol, $[\alpha]^{26}D$ +31.82° (neat). The absolute enantiomeric purities of these samples were established by gas–liquid partition chromatographic (glpc) studies as described in the following section.

(±)-*t*-Butyltrifluoromethylcarbinol (IB) was also resolved *via* the 3β-acetoxy-Δ⁵-etienate ester, but only the less soluble diastereomer could be obtained in purified form after exhaustive fractional crystallization from 2-propanol. The (+)-carbinol, $[\alpha]^{23}D$ +5.55° (neat, *d* 1.12), was regenerated by lithium aluminum hydride reduction. We presume this (+)-*t*-butyltrifluoromethylcarbinol to be enantiomerically pure; however there is no direct evidence for this beyond the normal recrystallization behavior of the etienate ester and the reasonable magnitude of its rotation since the glpc method and nmr method[8] were inapplicable as described in the following section.

Previous attempts to resolve methyltrifluoromethylcarbinol (IC) *via* the brucine salt of the acid phthalate failed for reasons similar to those reported in the earlier attempted resolution of phenyltrifluoromethylcarbinol.[4] The 3β-acetoxy-Δ⁵-etienate was prepared but failed to crystallize; we, therefore, resorted to glpc methods for

(1) We acknowledge with gratitude support for these studies from the National Science Foundation (GP 6738) and the National Institutes of Health (GM 05248).

(2) A preliminary report of some of these results has been published: D. M. Feigl and H. S. Mosher, *Chem. Commun.*, 615 (1965).

(3) Taken from the Ph.D. Thesis of D. M. Feigl, Stanford University, 1965.

(4) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *J. Amer. Chem. Soc.*, **78**, 4374 (1956).

(5) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

(6) H. M. Peters, D. M. Feigl, and H. S. Mosher, *ibid.*, **33**, 4245 (1968).

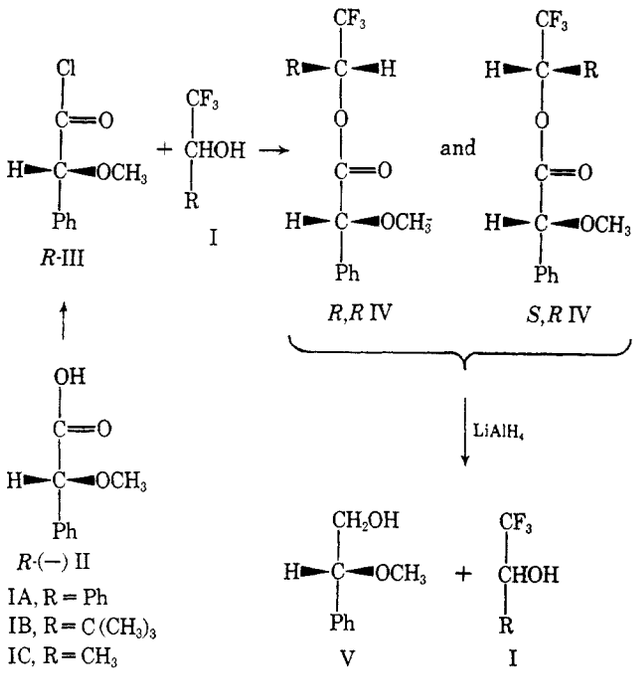
(7) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(8) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968).

determining the enantiomeric purity[9] of a partially active sample obtained by asymmetric reduction.[3]

The general use of glpc for determining enantiomeric purity has been reviewed,[9] but it seems worthwhile to comment on its specific application to the compounds under consideration. The O-methylmandelate esters (IV) of the three carbinols (IA, IB, and IC) were prepared as indicated in the Scheme I.

SCHEME I



When an enantiomerically pure reagent[10] (*R* III) is allowed to react with a carbinol (I) consisting of a mixture of enantiomers, a mixture of epimers (*R,R* IV and *S,R* IV) will result. If there is no racemization of carbinol (I), reagent (III), or products (IV), and if there is no kinetic resolution during this process, then the mixture of epimers (*R,R* IV and *S,R* IV) will be formed in exactly the same ratio as the enantiomers initially present. Therefore, any suitable method for determining the epimer composition (*R,R* IV and *S,R* IV) will constitute a valid method for determining the enantiomeric purity of the original carbinol (I). We have employed this method to establish the enantiomeric purity of phenyltrifluoromethylcarbinol (IA) using O-methylmandeloyl chloride[2,11] (III) as the chiral reagent. The epimeric phenyltrifluoromethylcarbinyl O-methylmandelates (*R,R* IVA and *S,R* IVA) resulting from the reaction of resolved IA with *R*-(−) II were readily separable by glpc (Carbowax 20M, 20 ft × 1/4 in. column, 250°, helium flow rate 86 ml/min, retention times 61 and 64 min, respectively). The acid chloride, prepared[12] from acid which was 96% enantiomerically pure[13] was treated with resolved IA in benzene–pyridine solution at 25° for 3 hr. The esters gave a gas chromatogram showing two peaks, the first and lesser one with an area of 3 ± 1% of the major peak. Based upon the known presence of 2% of the (+)-O-methylmandelic acid in reagent II, this result is within experimental error of that expected of enantiomerically pure IA and confirms the completeness of the resolution of the etienate ester.[14] An aliquot of this same reaction mixture which was stirred for 7 hr instead of three gave a product with identical composition as determined by glpc. When this reaction was first carried out however, the benzene–pyridine solution of mandeloyl chloride and resolved alcohol was heated for 8 hr under reflux in an oil bath at 90°. The isolated diastereomeric ester mixture gave a gas chromatogram indicating relative areas of approximately 33:67. On the basis of this experiment alone we might have concluded that the etienate-resolved carbinol was only 67% enantiomerically pure. This mixture of esters was reduced with lithium aluminum hydride to regenerate carbinol IA and to give 2-methoxy-2-phenylethanol (V) which had a rotation $[\alpha]^{28}D$ −73° (*c* 5.2, ethanol) compared with $[\alpha]^{29}D$ −127° (*c* 2.6, ethanol) for the product obtained by direct lithium aluminum hydride reduction of the starting O-methylmandelic acid (I → V). This indicated approximately 40% racemization at the mandelate moiety during the reaction when carried out at reflux. It is therefore essential in applying this glpc method (or the nmr method[8]) to the determination of enantiomeric purity that the necessary control experiments be done to ensure that no racemization or kinetic resolution has taken place under the reaction conditions employed.

The diastereomeric O-methylmandelate esters of (±)-*t*-butyltrifluoromethylcarbinol were obtained in excellent yield, but we were unable to find glpc conditions which would separate them. Furthermore, nmr studies[8] on the esters made from this resolved carbinol showed that extensive racemization had taken place. The same was true for the atrolactate ester of this carbinol. N-Trifluoroacetylleucine and N-trifluoroacetylproline gave diastereomers from (±) IB which were nicely separated by glpc, but the yields were so low under a variety of conditions that these derivatives were precluded from study for the purpose of determining enantiomeric purity. The completeness of the resolution of this carbinol is therefore not proven and only presumed on the basis of the constant melting point and rotation of the etienate ester and the reasonable magnitude of its rotation.

Application of glpc to the determination of the enantiomeric purity of a partially active sample of methyltrifluoromethylcarbinol *via* the O-methylmandelate es-

(9) The theory and details of this method have now been reviewed by M. Raban and K. Mislow in "Topics in Stereochemistry," Vol. II, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, N. Y., 1967, p 230.

(10) It is not absolutely necessary to use enantiomerically pure III since a correction can be made for the known amount of the diastereomeric products *R,S* IV and *S,S* IV which will have the same retention times as their enantiomers *S,R* IV and *R,R* IV but the results will be in error to the extent that kinetic resolution is involved in the reaction.

(11) M. Raban and K. Mislow, *Tetrahedron Lett.*, 3961 (1966).

(12) The acid chloride was prepared by allowing the acid to stand at room temperature with excess thionyl chloride in a benzene–thionyl chloride solution for 8 hr, prolonged refluxing with thionyl chloride, or attempted purification by distillation caused partial racemization.

(13) Per cent enantiomeric purity is defined as the excess of one enantiomer over the racemate; *i.e.*, this sample of acid was a mixture of 98% (−) isomer and 2% (+) isomer as measured by optical rotation.

(14) W. H. Pirkle [*J. Amer. Chem. Soc.*, **88**, 1837 (1966)] has calculated a value of [α] 36.5 ± 7.5° (neat) for the rotation of enantiomerically pure IA based upon the nmr analysis of the (−)-α-phenethylamine solution of a partially active sample of phenyltrifluoromethylcarbinol. This value within its broad limits of error agrees with the value of [α]D 31.8 obtained by resolution and confirmed by glpc in the present study and by nmr on the O-methylmandelate.[8]

ters has already been published.[2] The value of $[\alpha]^{27}D$ +5.6° (neat)[15] obtained in this way corresponds to the value of $[\alpha]^{27}D$ −5.65 which has now been obtained by Crawford[16] by resolution. We have also confirmed the glpc-determined enantiomeric purity of the partially active sample by use of nmr on the O-methylmandelate.[8] We also attempted to use (−)-hydratropic acid as the chiral reagent for diastereomer analysis of methyltrifluoromethylcarbinol. During the sequence of acid chloride formation, treatment with IC in benzene–pyridine *at room temperature*, and reduction with lithium aluminum hydride to give 2-phenylpropanol, racemization to the extent of approximately 10% took place in the hydratropate moiety. This again emphasizes the necessity for control experiments before this general method can be applied with safety in any particular system.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected; elemental analyses were performed by Mr. E. Meier of the Stanford University Microanalytical Laboratories; and the gas chromatography was done with a Varian Aerograph A-90 instrument. All products showed ir and nmr spectra compatible with the assigned structures.

3β-Acetoxy-Δ⁵-etienic Acid.—This acid (354 g) was prepared in 78% yield by hypobromite oxidation of pregnenolone acetate[17,18] followed by acetylation[19] with acetic anhydride in dry pyridine.

Phenyltrifluoromethylcarbinyl 3β-Acetoxy-Δ⁵-etienate.—3β-Acetoxy-Δ⁵-etienic acid (40 g) was treated with oxalyl chloride (100 g) in benzene (500 ml) for 10 hr at room temperature and isolated as described by Djerassi, *et al.*[19] The resulting yellow oil was stirred with a solution of 18 g of phenyltrifluoromethylcarbinol[4] in 500 ml of anhydrous pyridine at room temperatue for 65 hr. The reaction mixture was poured into 4 l. of cold 2.4 *N* hydrochloric acid, and the ester was extracted with ether to give, after drying ($MgSO_4$) and concentration, an orange-colored glass which was dissolved in 200 ml of warm hexane and cooled slowly to 5° to give, after concentration of the mother liquors, a total of 44.4 g of a tan solid: 86% crude yield; $[\alpha]^{25}D$ −13.9 ± 0.2°. A total of 90 g of the mixture of esters was subjected to a 14-stage systematic fractional crystallization using about 6–10 ml of 2-propanol/gram of solid,[20] to give about 12 g of the more insoluble ester, mp 125–126.5°, $[\alpha]^{20}D$ 0.0° (*c* ~1, acetone), and about 7 g of more soluble ester, mp 153–155°, $[\alpha]^{25}D$ −21° (*c* 1, acetone).

Anal. Calcd for $C_{30}H_{37}O_4F_3$: C, 69.50; H, 7.14. Found: C, 69.64, 69.33; H, 7.19, 7.28.

(−)-Phenyltrifluoromethylcarbinol.—The less soluble ester (11.11 g) was reduced with lithium aluminum hydride, (1.65 g) in ether solvent (120 ml). The reaction mixture was refluxed for 30 min and decomposed with saturated ammonium chloride solution. The ether layer was dried ($MgSO_4$); the ether was removed under vacuum; and the residue was distilled at 17-mm pressure to give (−)-phenyltrifluoromethylcarbinol, bp 99–105°, 3.1 g (82% yield), which was further purified by preparative glpc (silicone rubber column 20 ft × 3/8 in., 153°, helium flow rate 52 ml/min) to give a product with $\alpha^{26}D$ −20.59° (neat, *l* = 0.5); $[\alpha]^{26}D$ −31.85° (neat); $n^{24}D$ 1.4602.

(+)-Phenyltrifluoromethylcarbinol was regenerated in the same way to yield material with $\alpha^{26}D$ +41.14° (neat, *l* = 1), $[\alpha]^{26}D$ +31.82 (neat).

t-Butyl Trifluoromethyl Ketone.—We found the literature methods using *t*-butylmagnesium chloride on trifluoroacetic acid[21,22] or trifluoroacetic anhydride[23] to be unsatisfactory. Trifluoroacetonitrile (68 g) was dissolved in ether in a flask cooled in Dry Ice and equipped with a Dry Ice condenser. Cuprous chloride (1 g) was added, followed by *t*-butylmagnesium chloride (595 ml of a 1.15 *N* solution). After the reaction mixture had been stirred overnight at room temperature, it was cooled and decomposed by the addition of hydrochloric acid (250 ml of 6 *N*). The mixture was warmed to room temperature with stirring, and, after 30 min, the ether layer was separated, dried ($MgSO_4$), and distilled to give a 54% crude yield of material boiling between 57 and 78°. Gas chromatographic purification of this material and several other samples made by alternate procedures[21,23] gave material with $n^{23}D$ 1.3383 which differed considerably from the literature value[22] of $n^{20}D$ 1.3515. A higher boiling material was traced to an impurity in the trifluoroacetonitrile.

When this same procedure was followed, except that the mixture was hydrolyzed with ammonium chloride at room temperature, an 82% yield of *t*-butyltrifluoromethylketimine was obtained (bp 76–80°; $n^{20}D$ 1.3617).

Anal. Calcd for $C_6H_{10}F_3N$: C, 47.06; H, 6.54; N, 9.15. Found: C, 47.45; H, 6.71; N, 8.91.

(+)-t-Butyltrifluoromethylcarbinol.—This was prepared by lithium aluminum hydride reduction of the ketone in 88% yield: bp 107–113°; $n^{24}D$ 1.3668 (lit.[24] bp 110.5°; $n^{20}D$ 1.3670).

(+)-t-Butyltrifluoromethylcarbinol.—Using the procedure described for the 3β-acetoxy-Δ⁵-etienate of phenyltrifluoromethylcarbinol, *t*-butyltrifluoromethylcarbinyl 3β-acetoxy-Δ⁵-etienate (113 g) was prepared in 86% crude yield, and the mixture of diastereomers was subjected to a 12-stage systematic fractional crystallization from 2-propanol. Two types of crystals were encountered, needles and plates. The plates required many recrystallizations before a portion was obtained as needles, but once the needles were obtained they yielded the pure disastereomer in about four recrystallizations: mp 142–144°; $[\alpha]^{25}D$ −24° (*c* 1, acetone).

Anal. Calcd for $C_{28}H_{41}O_4F_3$: C, 67.47; H, 8.23. Found: C, 67.29; H, 8.21.

The more soluble diastereomer could not be obtained from the mother liquors. The resolved etienate (8 g) was subjected to lithium aluminum hydride reduction as described for the phenyl analog to give 1.9 g of carbinol, which was further purified by preparative glpc (PDEAS column, 10 ft × 3/8 in., 115°, helium flow rate 48 ml/min) to give a product with $\alpha^{23}D$ +6.20° (neat, *l* = 1); $n^{25}D$ 1.3664.

Methyltrifluoromethylcarbinyl 3β-Acetoxy-Δ⁵-etienate.—By the procedure described for the phenyl analog this compound was only obtained as a glass.

(−)-Phenyltrifluoromethylcarbinyl O-Methylmandelate.—O-Methylmandelic acid[25] {1.0 g, 6 mmol; $[\alpha]^{25}D$ −144° (ethanol); 96% enantiomerically pure based on the highest literature value of $[\alpha]^{17}D$ −150° (ethanol)[26]} was converted into the acid chloride by stirring with 10 g of thionyl chloride at room temperature overnight. The excess thionyl chloride was removed under vacuum; 3 ml of anhydrous benzene was added to the residue; and the solution concentrated to dryness; this latter process was repeated to remove the last traces of thionyl chloride. The acid chloride was dissolved in benzene (3 ml) and combined with (−)-phenyltrifluoromethylcarbinol (0.29 g, 1.5 mmol) in 3 ml of anhydrous pyridine. After the mixture had stood 3 hr at room temperature, one-half was diluted with water, stirred, and extracted with ether; the ether solution was washed with cold dilute hydrochloric acid, bicarbonate solution, and water, and dried ($MgSO_4$), and the volatile materials were removed under vacuum, leaving 0.13 g of yellow oil. After the second half of the mixture had stood 7 hr at room temperature, it was processed in the same manner to give the ester which gave an identical gas chromatogram.

This same experiment was originally conducted with the variation that the mixture of mandeloyl chloride, (−)-phenyltrifluoromethylcarbinol, pyridine, and benzene was heated under reflux in an oil bath at 90° overnight and then worked up in the

(15) In ref 2, a typesetting error placed brackets around the observed rotation of $\alpha^{26}D$ −2.20 ± 0.02° (neat, *l* = 0.5), $[\alpha^{27}D$ −4.40° (neat, l = 1), and $\alpha^{27}D$ max − 7.1° (neat, *l* = 1).

(16) J. W. C. Crawford, *J. Chem. Soc.*, 4280 (1965); 2332 (1967).

(17) We wish to thank the Syntex Corp. for a generous gift of this starting material.

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(19) C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *J. Amer. Chem. Soc.*, **86**, 465 (1964).

(20) Reference 3 must be consulted for the details of this lengthy process.

(21) K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, **78**, 2268 (1956).

(22) A. Sykes, J. C. Tatlow, and C. R. Thomas, *J. Chem. Soc.*, 835 (1956).

(23) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(24) E. T. McBee, O. R. Pierce, and O. D. Meyer, *J. Amer. Chem. Soc.*, **77**, 83 (1955).

(25) W. A. Bonner, *ibid.*, **73**, 3126 (1951).

(26) A. McKenzie and H. Wren, *J. Chem. Soc.*, **115**, 611 (1919).

same way. An analytical gas chromatogram of the resulting ester mixture showed relative peak areas of about 33 to 67. The mixture of diastereomeric esters was spearated from extraneous impurities by preparative glpc (SF-96 silicone column, 6 ft × 1/4 in. 190°, helium flow rate 100 ml/min, retention time 10 min, one peak) to give 0.37 g which was reduced with lithium aluminum hydride, hydrolyzed, and distilled to give 0.29 g of a carbinol mixture which was separated by glpc (SE-30 silicone column, 20 ft × 3/8 in. 200°, helium flow rate 75 ml/min) to give phenyltrifluoromethylcarbinol {retention time 16 min; 10 mg; $\alpha^{28}D$ −0.26 ± 0.02° (c 2.0, chloroform, l = 0.5); $[\alpha]^{28}D$ −25 ± 2° (c 2, chloroform)} and 2-methoxy-2-phenylethanol {retention time 36 min; 26 mg; $\alpha^{28}D$ −1.89 ± 0.01° (c 5.15, ethanol, l = 0.5); $[\alpha]^{28}D$ −73° (c 5.15, ethanol)}. The rotation of the volatile phenyltrifluoromethylcarbinol was determined on a very small amount of material, and the indicated racemization of 15 ± 6% may not be significant, but the latter compound is clearly racemized to the extent of approximately 35% as shown by the following experiment.

(−)-2-Methoxy-2-phenylethanol.—O-Methylmandelic acid {1.0 g; $[\alpha]^{25}D$ −144° (c 1.2, ethanol); 96% enantiomerically pure} was reduced with lithium aluminum hydride, and the (−)-2-methoxy-2-phenylethanol was isolated and purified as above to give a product with $\alpha^{27}D$ −134.78° (neat, l = 1); $\alpha^{29}D$ −8.17 ± 0.02° (c 6.425, ethanol, l = 1); $[\alpha]^{29}D$ −127.0 ± 0.4° (c 6.4, ethanol).

Partially Active (+)-Methyltrifluoromethylcarbinol.—Methyl trifluoromethyl ketone (7 g) was treated with 65 ml of a 0.93 *N* solution of the Grignard reagent from (+)-1-chloro-2-phenylbutane[5] [$\alpha^{27}D$ +5.68° (neat); 96% enantiomerically pure] in ether at 35°. The reaction mixture was processed in the usual way and distilled to give a 63% yield of (−)-methyltrifluoromethylcarbinol which upon purification by gas chromatography had $\alpha^{26}D$ −2.20° (neat, l = 0.5). A second experiment using twice these amounts gave material after purification of $\alpha^{24}D$ −2.03° (neat, l = 0.5).

Esters from (+)-, (−)-, and (±)-Methyltrifluoromethylcarbinol and (−)-O-Methylmandelic Acid.—The preparation and gas chromatography of these have been previously described.[2]

Registry No.—Phenyltrifluoromethylcarbinyl 3β-acetoxy-Δ5-etienate, 17628-68-1; (−)-IA, 10531-50-7; (+)-IA, 340-06-7; *t*-butyltrifluoromethylketimine, 17629-00-4; (+)-IB, 17628-71-6; (−)-2-methoxy-2-phenylethanol, 17628-72-7; (+)-IC, 17628-73-8.

Absolute Configuration of Substituted Trifluoromethylcarbinols[1,2]

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Received April 22, 1968

By application of Freudenberg's rule of rotational shifts as applied to a series of acetate, benzoate, and acid phthalate esters, the absolute *S* configuration was assigned to (+)-phenyltrifluoromethylcarbinol, (−)-methyltrifluoromethylcarbinol, and (−)-*t*-butyltrifluoromethylcarbinol. However, these correlations were not ideal, and thus the absolute configurations of the phenyl and methyl compounds were verified by synthesis of their O-methyl and O-ethyl ethers by the action of sulfur tetrafluoride on (*S*)-O-methylmandelic acid and (*S*)-O-ethyllactic acid, respectively. This process is one which does not affect the chiral center of known configuration. The absolute configurations of these trifluoromethyl compounds and their several derivatives are now established with certainty.

In order to gain additional information concerning the relative importance of steric *vs.* electronic effects in the Grignard asymmetric reduction reaction[4-8] we have been studying the asymmetric reduction of several substituted trifluoromethyl ketones. The previous paper in this series[9] describes the resolution of three such compounds: phenyltrifluoromethylcarbinol, methyltrifluoromethylcarbinol, and *t*-butyltrifluoromethylcarbinol. The present paper describes studies which establish the absolute configuration of these compounds.

We initially investigated[5] the application of Freudenberg's rule of rotational shifts[10] to a series of derivatives of these carbinols and compared the results with those from the corresponding nonfluorinated carbinols of known configuration. The results for the phenylalkylcarbinols are summarized in Table I, for the methylalkylcarbinols in Table II, and for the *t*-butylalkylcarbinols in Table III.[11]

The derivatives of (+)-phenyltrifluoromethylcarbinol exhibit rotational shifts comparable with those for the corresponding (+)-phenylalkylcarbinols if one excludes the acid phthalate of phenylmethylcarbinol from consideration.[12,13]

It is *not* possible to make a logical arrangement of the data based upon the opposite assumption that (−)-phenyltrifluoromethylcarbinol is related to the other (+)-phenylalkylcarbinols. Therefore, it seems reasonably certain, based upon these data, that (+)-phenyltrifluoromethylcarbinol is configurationally related to the (+)-phenylalkylcarbinols as represented

(1) Presented in part before the Division of Organic Chemistry at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) We acknowledge with gratitude support for these studies from the National Science Foundation (GP 6738) and the National Institutes of Health (GM 05248).

(3) (a) Taken in part from the Ph.D. Theses of H. M. Peters, Stanford University, Oct 1966, and D. M. Feigl, Stanford University, Oct 1965. (b) Parke, Davis & Co Fellow, 1965–1966.

(4) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *J. Amer. Chem. Soc.*, **78**, 4374 (1956).

(5) D. M. Feigl, Ph.D. Thesis, Stanford University, Oct 1965.

(6) D. L. Dull, Ph.D. Thesis, Stanford University, June 1967.

(7) B. J. G. McFarland, Ph.D. Thesis, Stanford University, Nov 1965.

(8) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964), and references therein.

(9) D. M. Feigl and H. S. Mosher, *ibid.*, **33**, 4242 (1968).

(10) K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1933, p 677.

(11) These data are presented in modified form. Derivatives actually may have been prepared from either enantiomer, but the results reported in Tables I–III have been adjusted as if compounds of only one of the two enantiomers had been used. Enantiomerically impure samples were often used in the preparation of derivatives. However, great care was taken to prevent the concentration of either enantiomer during the synthesis or purification of these derivatives, and the rotations presented in Tables I–III have been adjusted to those for enantiomerically pure derivatives using the known purity of the starting carbinols.

(12) The rotation of the acid phthalate of phenylmethylcarbinol does not fit well into this series as has been observed earlier. At one time this anomaly rendered the assignment of relative configurations of the phenylalkylcarbinols uncertain. However, (+)-phenylmethylcarbinol and (+)-phenylethylcarbinol have been interrelated by direct chemical means[13] and it is now certain that they have the same relative configuration.

(13) R. MacLeod, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).