calculation of K_1 for the iodide charge-transfer complex.

Values of K_1 determined on a basis of chemical shift are only accurate to $\pm 20\%$. The K_1 for the ferrocyanide charge-transfer complex, however, has been determined from both absorbancy and nmr data and the results have been found to be in good agreement (Table I).

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Stereochemistry of Trityl Compounds. V. Resolution of Phenylbiphenylyl-α-naphthylcarbinol[1,2]

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Abstract: A new method has been developed for the resolution of (+)- and (−)-phenylbiphenylyl-α-naphthylcarbinol. The alcohols had been partially resolved by Wallis.[8] (±)-Ar_3COH was converted to (±)-$Ar_3COCH_2CO_2H$ by alkylation of ethyl glycolate with Ar_3CCl followed by saponification. (−)-$Ar_3COCH_2CO_2H$ was separated as the brucine salt and (+)-$Ar_3COCH_2CO_2H$ was separated as the cinchonidine salt. Each enantiomeric acid was converted to the corresponding amide by aminolysis of its methyl ester. The usual medium for the Hofmann rearrangement (bromine in methanolic sodium methoxide) was shown to cleave the trityl ether linkage of the amide affording trityl methyl ether. However, treatment of the N-haloamide, $Ar_3COCH_2CONHCl$, previously prepared in benzene using *t*-butyl hypochlorite, with methanolic sodium methoxide led to Hofmann rearrangement. The expected carbamate was cleaved under the reaction conditions to Ar_3COH. (−)-$Ar_3COCH_2CO_2H$ gave optically pure (+)-Ar_3COH and (+)-$Ar_3COCH_2CO_2H$ gave optically pure (−)-Ar_3COH. The C–O bond at the asymmetric center remained intact throughout the degradation procedure. Wallis' resolution was repeated and shown to have an optical yield of *ca.* 60%. His product was brought to optical purity by fractional crystallization. An attempted resolution of phenyl-*p*-chlorophenylbiphenylylcarbinol according to the new method was unsuccessful.

Preliminary to stereochemical studies of the mechanisms of substitution of trityl (triarylmethyl) derivatives, it was desirable to have a source of an optically pure triarylcarbinol. Satisfactory methods of resolution have been reported for all types of alkyl and arylalkyl secondary[4,5] and tertiary[6,7] carbinols except for the triarylcarbinols.[8,9] Wallis[8] obtained (+)-phenylbiphenylyl-α-naphthylcarbinol [(+)-Ar_3COH] by treating (−)-phenylbiphenylyl-α-naphthylmethylthioglycolic acid [(−)-$Ar_3CSCH_2CO_2H$] with silver nitrate in aqueous acetone (reaction 1). Although no experimental evidence was available regarding the optical purity of (+)-Ar_3COH, Wallis' method was termed unsatisfactory,[4] probably because the method entailed a cleavage reaction of unknown stereospecificity at the asymmetric center.

$$(-)\text{-}Ar_3CSCH_2CO_2H + AgNO_3 \xrightarrow[\text{acetone}]{66\%} (+)\text{-}Ar_3COH \quad (1)$$

Most alcohol resolutions have depended on fractional crystallization of a mixture of diastereomeric amine salts of the hemiphthalate ester.[5] Kenyon's early attempt to resolve a trityl alcohol failed because the hemiphthalate ester could not be prepared.[10] This problem has now been solved.[11] More recently, an effort was made to prepare an optically active trityl alcohol by nitrous acid deamination of the corresponding amine.[10] The product showed no optical activity. After our work was in progress, Thaker and Dave reported the resolution of phenyl-*p*-tolyl-α-naphthylcarbinol by the hemiphthalate method.[12]

Because disproportionation of hemiphthalate salts is a known complication in alcohol resolutions[5] and because the trityl ester linkage is known to be labile,[13] we decided to employ the more stable ether linkage at the asymmetric center. The simplest such compound for the formation of diastereomeric amine salts is an ether of glycolic acid, $Ar_3COCH_2CO_2H$. This type of compound was attractive because it appeared possible to use the Hofmann rearrangement[14] to convert the amide of

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(2) These results were reported in preliminary form: B. L. Murr, *J. Am. Chem. Soc.*, **85**, 2866 (1963). For the preceeding paper in this series see B. L. Murr and L. W. Feller, *ibid.*, **90**, 2966 (1968).

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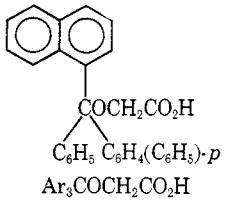
(14) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3**, 282 (1946).

the substituted glycolic acid to a derivative of formaldehyde that would decompose to alcohol under conditions



not conducive to carbonium ion formation (sequence 2). Wallis' alcohol, phenylbiphenylyl-α-naphthylcarbinol, was chosen as the first case because adequate crystallinity of its derivatives had been demonstrated.[8] Suitable pilot experiments were carried out using triphenylmethyl derivatives.

$$Ar_3COCH_2CONH_2 \longrightarrow Ar_3COCH_2NHCO_2Me \longrightarrow Ar_3COH \quad (2)$$

Results and Discussion

Phenyl biphenylyl ketone was prepared in 75–85% yield by benzoylation of biphenyl.[15] (±)-Phenylbiphenylyl-α-naphthylcarbinol[4b] (**1**) was obtained by reaction of the ketone with α-naphthyl Grignard reagent. The yield of carbinol varied little with a change in the amount of the Grignard reagent from 10% excess to a 100% excess.

(+)-Phenylbiphenylyl-α-naphthylcarbinol. The resolution sequence is summarized in Chart I. The racemic carbinol was converted to phenylbiphenylyl-α-naphthylmethyl chloride (**2**) by reaction with excess acetyl chloride.[16] The alkylation of ethyl glycolate was carried out both in pyridine solution and in benzene solution containing an excess of pyridine. The latter procedure proved far superior. The (±)-ethyl ester **3** was purified carefully prior to saponification in aqueous methanol containing potassium hydroxide.

Chart I

(±)-Ar_3COH (**1**) ⟶ (±)-Ar_3CCl (**2**) ⟶ (±)-$Ar_3COCH_2CO_2Et$ (**3**) ⟶
(±)-$Ar_3COCH_2CO_2K$ (**4**) ⟶ (±)-$Ar_3COCH_2CO_2H$ (**5**) ⟶
(−)-$Ar_3COCH_2CO_2H$·Brucine (**6**) ⟶ [(−)-$Ar_3COCH_2CO_2H$] (**7**) ⟶
(−)-$Ar_3COCH_2CO_2Me$ (**8**) ⟶ (−)-$Ar_3COCH_2CONH_2$ (**9**) ⟶
(+)-Ar_3COH (**10**)

The unstable, free acid **5** was liberated as needed by careful acidification of a methanol solution of the water-insoluble potassium salt **4**. The acid **5** was cleaved by excess acid.

The acid **5** was resolved by crystallization of its brucine salt **6**. Early attempts to obtain a crystalline salt from acetone failed.[8] Attempts to obtain crystals from a variety of solvents resulted in oils. However, a crystalline salt **6** was obtained upon addition of petroleum ether (60–90°) to an ethyl acetate solution of the diastereomeric salt mixture. This salt, $[\alpha]^{23}D$ −29.8° (chloroform), was virtually pure. One recrystallization from chloroform–petroleum ether (60–70°) afforded pure material, $[\alpha]D$ −30.4°. Acetone has proved a satisfactory solvent in subsequent resolutions.

The acid **7** was liberated from a suspension of the brucine salt in ether with dilute sulfuric acid.[8] The acid **7** was stable in dilute ether solution but removal of the ether left a red oil. The highest rotation that was obtained for this red oil was $[\alpha]^{23}D$ −9°. The rotation decreased detectably during 10 min in the polarimeter tube. In practice the acid was not isolated but was converted to the methyl ester **8** by reaction with diazomethane.

The aminolysis of the (±)-ethyl ester **3** was conducted in 50% (v/v) methanol–benzene. The corresponding reaction of the optically active methyl ester **8** was effected in methanol–tetrahydrofuran. The (±)-amide **11** (mp 233°) was much less soluble than the (−)-amide **9** (mp 143°). Because of this difference, the active amide was readily separated from racemic material.

Triphenylmethoxyacetamide (**12**) was cleaved by bromine in methanolic sodium methoxide[14] (eq 3), the usual conditions for the preparation of carbamates (**13**). This cleavage is apparently the oxygen analog of the known cleavage of trityl sulfide bonds by halogens.[17]

$$Ph_3COCH_2CONH_2 \ (\mathbf{12}) \xrightarrow[2.\ Br_2]{1.\ NaOMe\text{–}MeOH} Ph_3COCH_2NHCO_2Me \ (\mathbf{13}) \quad (3)$$
$$\longrightarrow Ph_3COMe$$

Trityl methyl ether was obtained in 85% yield.

A satisfactory procedure for Hofmann rearrangement based on Baumgarten's method for N-haloamine rearrangement[18] was developed. A benzene solution of **12** was dried rigorously by azeotropic distillation. The amide **12** was halogenated with excess *t*-butyl hypochlorite. Subsequent addition of a methanol solution of sodium methoxide resulted in an exothermic reaction that afforded trityl alcohol in good yield. Similarly, treatment of (±)-amide **11** and (−)-amide **9** with *t*-butyl hypochlorite followed by sodium methoxide gave the (±)-Ar_3COH (**1**) and (+)-Ar_3COH (**10**), respectively.

The probable sequence of events is summarized in Chart II. The N-haloamide reacted with sodium methoxide to form isocyanate, which reacted with methanol to give carbamate **14**.[14] The carbamate **14** subsequently underwent alcohol exchange in the presence of methanol and base (Chart II) by elimination–readdition. In the

Chart II

$$Ar_3COCH_2CONH_2 \xrightarrow[\text{benzene}]{t\text{-BuOCl}} Ar_3COCH_2CONHCl \xrightarrow[\text{benzene–methanol}]{NaOMe}$$
$$Ar_3COCH_2NCO \xrightarrow[\text{benzene}]{MeOH} Ar_3COCH_2NHCO_2Me \ (\mathbf{14}) \xrightarrow[MeOH]{NaOMe}$$
$$Ar_3COH + MeOCH_2NHCO_2Me$$

(±) series, use of amide–*t*-butyl hypochlorite–sodium methoxide in the ratio of 1:1:1 gave a yellow oil whose infrared spectrum was consistent with the carbamate structure **14**. A crystalline carbamate has since been obtained by an independent method.[19] The infrared

(15) L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941).
(16) E. C. Horning, Ed., "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 841.
(17) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 2478 (1961).
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spectra of the two samples were identical. Treatment of both samples with excess methoxide in methanol gave **1**. The (+)-Ar_3OH **10**, $[\alpha]^{23}D$ +17.40 (*c* 0.98, chloroform), must have been as optically pure as its amide precursor because isolation of the alcohol from the reaction established that the C–O bond at the trityl carbon was not broken during the amide to alcohol conversion. If cleavage to the carbonium ion (eq 4) had occurred, triarylmethyl methyl ether would have resulted. The respective ethers were stable to conditions of the reaction and the work-up. If the carbanion had formed (eq

$$ROCH_2NCO \longrightarrow R^+ + CH_2O + NCO^- \longrightarrow ROMe \quad (4)$$

$$ROCH_2X + MeO^- \longrightarrow R^- + OCHX + MeOH \longrightarrow RH \quad (5)$$

5), the hydrocarbon would have resulted. The alcohol could not have resulted from a homolysis of the C–O bond.

Alcohol (+)-Ar_3COH was also prepared by Wallis' method,[8] $[\alpha]^{24}D$ +10°. By a combination of fractional crystallization of this (+)-Ar_3COH from ether and Pasteur's first method,[4] we obtained (+)-Ar_3COH **10** with $[\alpha]^{24}D$ +16 ± 1°, mp 180–181°, unchanged within experimental error by further recrystallizations, and (+)-Ar_3COH (**1**), mp 161–162°, after crystallization from cyclohexane. The evidence shows that Wallis' method affords alcohol of about 60% optical purity.[8]

(−)-Phenylbiphenylyl-α-naphthylcarbinol. In order to isolate the enantiomeric phenylbiphenylyl-α-naphthylmethyl derivatives in an optically pure state, the solutions remaining after isolation of the brucine salt of (−)-$Ar_3COCH_2CO_2H$ (**6**) were freed of solvent, the residue was dissolved in ethyl acetate, and the solution was extracted with hydrochloric acid. An equivalent of cinchonidine was added to the dried ethyl acetate solution. Crystallization could not be induced. Ethyl acetate was removed and the residue was washed thoroughly with ether. Upon addition of methanol the cinchonidine salt of (+)-$Ar_3COCH_2CO_2H$ crystallized. The salt was purified by crystallization from methanol, the acid was liberated in ether, and the solution was treated with diazomethane. (+)-$Ar_3COCH_2CO_2Me$ was isolated. The resulting dextrorotatory ester (+)-$Ar_3COCH_2CO_2Me$ had a melting point and infrared spectrum identical with those of its enantiomer. Its optical rotation was identical in magnitude but opposite in sign to that of its enantiomer. The (+)-amide and (−)-alcohol were prepared as described above and these materials exhibited the expected properties.

Our attempts to crystallize the brucine salts of (±)-phenyl-*p*-chlorophenylbiphenylylmethoxyacetic acid havefailed. This failure is probably the result of the low crystallinity of all derivatives in this series.

Experimental Section[20]

Ethyl Triphenylmethoxyacetate. To a solution of 2 g (0.0072 mol) of trityl chloride in 5 ml of pyridine was added 1 g of ethyl glycolate. The solution was refluxed for 5 min and poured into 50 ml of water. The oily material was induced to crystallize by scratching with a glass rod. The material was recrystallized from heptane to obtain 1.4 g (56%) of product, mp 97–98°. The infrared spectrum (CCl_4) showed carbonyl absorptions at 1768 and 1745 cm^{-1}.

Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.62; H, 6.46.

Triphenylmethoxyacetic Acid. A mixture of 0.5 g of ethyl triphenylmethoxyacetate, 0.6 g of sodium hydroxide, 15 ml of water, and 5 ml of ethanol was refluxed for 5 hr. A solid precipitate was collected after acidification to pH 3 and washed with water. The dried product (0.38 g, 83%) had mp 148–151°. The infrared spectrum ($HCCl_3$) showed a broad band between 3000 and 2500 cm^{-1} and carbonyl absorptions at 1788 and 1735 cm^{-1}.

Triphenylmethoxyacetamine (12). Ammonia was passed into a solution of 0.5 g (0.0014 mol) of ethyl triphenylmethoxyacetate in 30 ml of methanol at 0° until the solution was saturated. The solution was kept in the refrigerator for 2 days before the methanol was evaporated. The solid residue was recrystallized from ethanol–water. The yield of product (mp 175–177°) was 0.23 g (50%). The infrared spectrum ($HCCl_3$) exhibited bands at 3470 and 1700 cm^{-1}.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.84; H, 6.17; N, 4.49.

Phenyl biphenylyl ketone[15] was prepared by adding a solution of biphenyl (358 g, 1.39 mol) and benzoyl chloride (244 ml, 2.1 mol) in 700 ml of carbon disulfide to a stirred slurry of 324 g (2.45 mol) of anhydrous aluminum chloride in 773 ml of carbon disulfide at such a rate as to maintain gentle reflux. Addition time was *ca.* 3 hr and the dark red mixture was stirred and refluxed for 25.5 hr. The mixture was cooled, poured onto ice and water, and stirred by hand to decompose the aluminum chloride–ketone complex. Carbon disulfide was removed by distillation and the solid product was filtered. The solid was heated with 2 l. of water several times, heated with 2-l. portions of sodium hydroxide to remove benzoic acid, filtered, and dried. The crude product (560 g, 94.3%) was dissolved in 3 l. of absolute ethanol, treated with 10 g of Norit A, and filtered. About 400 g (70%) of ketone, mp 102°,[15] was obtained in the first crop. Additional material was obtained by concentrating the solution. The infrared spectrum (CCl_4) showed carbonyl absorption at 1665 cm^{-1}.

(±)-Phenylbiphenylyl-α-naphthylcarbinol (1).[21] α-Naphthyl Grignard reagent was prepared by dropwise addition of a solution of 248 g (1.2 mol) of α-bromonaphthalene in 200 ml of tetrahydrofuran to 24.3 g (1 g-atom) of magnesium turnings covered with tetrahydrofuran. After the vigorous reaction had started 1200 ml more of tetrahydrofuran was added. The mixture was refluxed 4.5 hr after addition of the bromide was complete. Phenyl biphenylyl ketone (193 g, 0.75 mol) in 800 ml of thiophene-free benzene was added dropwise at gentle reflux. The dark green solution was refluxed for 80 hr. The magnesium salts were precipitated by addition of saturated aqueous ammonium chloride. The solvent was removed on a rotary evaporator and the residue was dissolved in benzene. The solution was extracted successively with 200-ml portions of water, dilute acid, water, sodium bicarbonate, and water, and it was dried with sodium sulfate. The solvent was removed, and the residue was crystallized from benzene–petroleum ether (bp 60–70°). The yield was 244.6 g (84.5%). The alcohol was recrystallized from tetrahydrofuran from which it precipitated with solvent of crystallization. The product was dissolved in cyclohexane (25 ml/g of alcohol–THF complex) and the resulting mixture was concentrated to one-half its volume to induce crystallization. The yield of the purification procedure was *ca.* 75%, mp 159–161°. The infrared spectrum (CCl_4) showed sharp bands at 3600, 3055, 1008, and 700 cm^{-1}.

(±)-Phenylbiphenylyl-α-naphthylmethyl chloride (2)[21] was prepared by a modified literature procedure.[16] Carbinol (200 g, 0.517 mol) and 270 ml of thiophene-free benzene were placed in a 2-l. round-bottomed flask fitted with a condenser and a drying tube. The mixture was refluxed until the carbinol had dissolved, whereupon 100 ml of acetyl chloride was added through the top of the condenser in 5–10-ml portions. Occasionally it was necessary to lift the flask out of the heating mantle until the vigorous reaction had subsided. Shortly (10 min) after addition was complete a white precipitate formed. The mixture was refluxed 1 hr and cooled to room temperature. Petroleum ether (280 ml, bp 30–60°) was added, and the chloride was collected on a filter and washed with petroleum ether. The yield was 198.5 g (94.8%). This product, mp 197–200°, was satisfactory for the next step. A portion of the material that was recrystallized from toluene had mp 200–201°.

Preparation of (±)-Ethyl Phenylbiphenylyl-α-naphthylmethoxyacetate (3). Benzene (1400 ml) and pyridine (250 ml) were placed in a 3-l., three-necked flask and dried by azeotropic distillation of

(20) Melting points were taken in Pyrex capillaries, are uncorrected, and are rounded to the nearest 0.5°. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Optical rotations were determined in a 2-dm cell using a Gaertner Scientific Corp. instrument with a precision of 0.01°.

(21) W. Schlenk, *Ann.*, **394**, 196 (1912).

200 ml of benzene. The chloride (170 g, 0.42 mol) was added followed by 60 g (0.57 mol) of ethyl glycolate (Fisher Scientific Co.). The solution was refluxed for 43 hr during which time pyridine hydrochloride precipitated.

Most of the solvent was removed (rotary evaporator) and the crystalline product was filtered and washed with a little cold ether to remove the yellow color. The yield of product, mp 181–186°, was 161 g (81%). This material was recrystallized from benzene–petroleum ether (bp 60–90°), mp 186–188°. The yield was 144 g. The infrared exhibited carbonyl absorption at 1770 cm^{-1}.

Anal. Calcd for $C_{33}H_{28}O_3$: C, 83.87; H, 5.79. Found: C, 83.94; H, 6.01.

(±)-Methyl phenylbiphenylyl-α-naphthylmethoxyacetate was prepared in the same manner as the (±)-ethyl derivative except that methyl glycolate was used, mp 187–188°. The infrared showed two carbonyl bands, 1770 and 1750 cm^{-1}.

Preparation of Potassium Salt of (±)-Phenylbiphenylyl-α-naphthylmethoxyacetic Acid (4). A mixture consisting of 144 g (0.3 mol) of (±)-ethyl phenylbiphenylyl-α-naphthylmethoxyacetate, 184 g of potassium hydroxide, 920 ml of water, and 2300 ml of methanol was refluxed with magnetic stirring for 26 hr. The methanol was removed by distillation, 153 ml of water was added, and the solution was cooled. The insoluble potassium salt was filtered and dried in the oven (105°). The yield was quantitative (148 g).

(±)-Phenylbiphenylyl-α-naphthylmethoxyacetic acid (5) was not stable and it was liberated from the salt as needed by dissolving the salt in methanol (1 g to 5 ml) and acidifying with 15% aqueous hydrochloric acid to pH 4.5. Excess acid resulted in cleavage of the ether linkage. The precipitated acid was filtered and dried at room temperature overnight. The infrared spectrum showed a broad band between 3000 and 2500 cm^{-1} and a split carbonyl, 1785 and 1740 cm^{-1}.

Brucine Salt of (−)-Phenylbiphenylyl-α-naphthylmethoxyacetic Acid (6). The (±)-acid (131 g, 0.295 mol) was dissolved in 383 ml of acetone with heating. While still warm, the solution was added to 116 g (0.295 mol) of brucine (Mann Research Laboratories, Inc.) suspended in 800 ml of hot acetone. Heating was continued to effect complete solution. The solution was cooled overnight in the freezer and the precipitated salt (108 g), $[\alpha]^{23}D$ −24.6° (*c* 1.67, chloroform), was removed by filtration. The salt was purified by dissolving in a minimum quantity of hot chloroform and adding petroleum ether (bp 60–70°) until a precipitate formed at the boiling point. The yield was 70 g (57%), $[\alpha]^{22}D$ −29.7° (*c* 1.38, chloroform). The infrared spectrum ($HCCl_3$) showed strong bands at 1670 and 1400 cm^{-1}.

The above procedure was not satisfactory in our initial resolution attempt. Acetone and a number of other solvents were tried without success. The first crystals of the brucine salt of (−)-phenylbiphenylyl-α-naphthylmethoxyacetic acid were obtained by adding petroleum ether (bp 60–90°) to an ethyl acetate solution of the diastereomeric salts.

Cinchonidine Salt of (+)-Phenylbiphenylyl-α-naphthylmethoxyacetic Acid. The solvent was removed in a tared flask from the solution from which the brucine salt of the (−)-acid had been isolated. The residue (60 g) was dissolved in 700 ml of ethyl acetate and extracted with three 50-ml portions of hydrochloric acid (0.5 *N*), and the solution was washed with water until the washings gave a negative chloride test. The solution was dried over sodium sulfate and transferred to a 1-l., round-bottomed flask. Cinchonidine (20 g, Pierce Chemical Co.) was added, and the mixture was heated on a steam bath to dissolve the alkaloid. No crystals formed when the solution was cooled. The solvent was removed on the rotary evaporator, and the residue was washed thoroughly with ether. There resulted a noncrystalline but powdery material weighing 50 g. The powder was dissolved in 250 ml of methanol, whereupon crystals formed. Filtration afforded 25 g of cinchonidine salt, $[\alpha]^{22}D$ −8.14° (*c* 2.72, chloroform). The infrared spectrum ($HCCl_3$) showed broad absorptions between 3500 and 2000 cm^{-1} and a broad carbonyl band at 1610 cm^{-1}. A 1-g sample of the salt was converted to (+)-methyl phenylbiphenylyl-α-naphthylmethoxyacetate as described below, mp 180°, $[\alpha]^{23}D$ +11.3° (*c* 1.124, chloroform). The infrared spectrum showed carbonyl bands at 1770 and 1750 cm^{-1} and was identical with that of the levorotatory material.

(−)-Methyl Phenylbiphenylyl-α-naphthylmethoxyacetate (8) from the Brucine Salt. A 31.4-g portion of finely powdered brucine salt was placed in each of two 2-l., round-bottomed flasks containing 800 ml of ether. To each flask was added 590 ml of 0.25 *N* sulfuric acid. The flasks were shaken, and the pressure was released until solid ceased to dissolve. The ether layers were decanted, and the aqueous layers were combined in a separatory funnel and extracted with 400 ml of ether. Solid remained at the interface. The aqueous layer was withdrawn and the ether layer was decanted. The solid remaining in the funnel was treated with fresh dilute acid and ether. The combined ether extracts were washed with water. The ether solution was dried with sodium sulfate for 1 hr and esterified with excess diazomethane[22] in ether. The yield of ester was 28.7 g (83%), mp 176–177°, $[\alpha]^{23}D$ −10.4° (*c* 1.63, chloroform). The infrared spectrum showed carbonyl bands at 1770 and 1750 cm^{-1}.

Anal. Calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.72. Found: C, 83.19; H, 5.54.

(+)-Methyl Phenylbiphenylyl-α-naphthylmethoxyacetate from Cinchonidine Salt. Cinchonidine salt (70 g) was suspended in 1 l. of ether in a separatory funnel and extracted with portions of 0.5 *N* hydrochloric acid. The ether layer was washed until the washings were neutral and dried over sodium sulfate for 1 hr. The acid was esterified with excess diazomethane[22] in ether. The yield was 30 g (72%), mp 176–177°, $[\alpha]^{22}D$ +10.0° (*c* 1.65, chloroform).

(±)-Phenylbiphenylyl-α-naphthylmethoxyacetamide (11). (±)-Ester (22 g) was dissolved in a solution of 500 ml of 50% (v/v) methanol–benzene with heat. Sodium methoxide solution (2 g of sodium in 15 ml of methanol) was added, and the resulting solution was saturated with anhydrous ammonia. The aminolysis was allowed to continue for 4 days, during which time the solution was saturated with ammonia periodically. The solvent was removed on the rotary evaporator, and the residue was recrystallized from methanol. The yield was 18 g, mp 233°. The infrared spectrum exhibited absorptions at 3475, 3400, 1700, and 1600 cm^{-1}.

Preparation of (−)-Phenylbiphenylyl-α-naphthylmethoxyacetamide (9). (−)-Ester (28.3 g, 0.06 mol) was dissolved in 570 ml of tetrahydrofuran and mixed with 570 ml of methanol. The solution was cooled in ice and saturated with ammonia periodically over a 5-day period. The mixture was filtered to remove 1.8 g of (±)-amide and the solvent was removed. The crystalline residue (21 g) was dried *in vacuo* and its rotation was determined, $[\alpha]^{23}D$ −14.35° (chloroform), mp 140–143°. The (±)-amide was insoluble in hot methanol but the (−)-amide was quite soluble. The infrared spectrum was identical with that of (±)-amide.

Anal. Calcd for $C_{31}H_{25}NO_2$: C, 83.96; H, 5.68; N, 3.16. Found: C, 81.44; H, 5.56; N, 3.20.

(+)-Phenylbiphenylyl-α-naphthylmethoxyacetamide, which was prepared as described for the (−)-enantiomer, had $[\alpha]^{23}D$ +15° (chloroform), mp 133–135°. The infrared spectrum was the same as that of the (−) material.

Attempted Hofmann Rearrangement with Methanol–Sodium Methoxide–Bromine. Triphenylmethoxyacetamide (1.5 g, 0.005 mol) was dissolved in 35 ml of methanol, and a solution of 0.228 g of sodium in 10 ml of methanol was added. Bromine (0.294 ml, 0.005 mol) was added in one portion to the refluxing solution and the solution was refluxed for 10 min. The solvent was removed, whereupon a mass of orange-yellow crystals formed. The solid was heated with benzene and treated with Norit, and the solution was filtered and cooled. Addition of heptane resulted in crystallization. There was obtained 1 g of tritylmethyl ether, mp 95–96°, identified by comparison of its infrared spectrum with an authentic sample and by mmp 95–96°.

Attempted Hofmann Rearrangement with *t*-Butyl Alcohol–*t*-Butoxide–*t*-Butyl Hypochlorite. To 25 ml of *t*-butyl alcohol was added 1.57 g (0.014 mol) of potassium *t*-butoxide. Into this solution was bubbled 1.0 g of chlorine. To another 25-ml portion of *t*-butyl alcohol was added 0.673 g (0.006 mol) of potassium *t*-butoxide and 1.24 g (0.004 mol) of triphenylmethoxyacetamide. Then 1 ml of the *t*-butyl hypochlorite solution was added, and the solution was refluxed. The hot solution solidified. The solid mass was extracted with hot benzene, filtered, and cooled. There was obtained 1.0 g of white solid, mp 198–200°. The infrared spectrum of this material was that expected for the urea $(Ph_3COCH_2NH)_2CO$. The compound was not further characterized.

Hofmann Rearrangement with *t*-Butyl Hypochlorite in Benzene and Preparation of (+)-Phenylbiphenylyl-α-naphthylcarbinol (10). To 3700 ml of thiophene-free benzene was added 17.6 g (0.04 mol) of (−)-phenylbiphenylyl-α-naphthylmethoxyacetamide. The solution was dried by azeotropic distillation. To the cooled solution (25°) was added dropwise 8.86 g (0.08 mol) of *t*-butyl hypochlorite in 10 ml of benzene and the solution was stirred for 30 min before heating to 65°. A solution prepared from 0.12 g-atom of sodium (2.76 g) and 400 ml of methanol was added as rapidly as possible

(22) N. Rabjohn, Ed., "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 250.

and the mixture was refluxed for 4.5 hr. Sodium chloride was removed by filtration, and the solvent was removed. The residue was triturated with 1500 ml of ether, filtered, and concentrated to a volume of 120 ml. The solution was cooled and 9.76 g of carbinol was obtained. The solution was concentrated and an additional 1.38 g of alcohol crystallized. The total yield was 74% of material having $[\alpha]^{23}D$ +17.4° (*c* 0.98, chloroform), mp 178–179.5°. This procedure was applied to (±)-phenylbiphenylyl-α-naphthylmethoxyacetamide and triphenylmethoxyacetamide with similar results.

Anal. Calcd for $C_{29}H_{22}O$: C, 90.12; H, 5.74. Found: C, 89.84; H, 5.74.

(−)-Phenylbiphenylyl-α-naphthylcarbinol was prepared according to the procedure in the preceding paragraph, mp 175–177°, $[\alpha]^{23}D$ +3.17° (*c* 1.42, benzene); $[\alpha]^{23}D$ 16.5° (*c* 1.2, chloroform).

Resolution of Carbinol by the Method of Wallis and Adams.[8] (±)-Phenylbiphenylyl-α-naphthylmethylthioglycolic acid–toluene was prepared as described by Wallis. The acid (56 g) was dissolved in 100 ml of warm acetone and added while still warm to an acetone suspension of brucine (42 g). The solution was warmed until clear. The solution did not deposit crystals. The solvent was removed *in vacuo*, and the glassy residue was dissolved in hot ethyl acetate. The cooled solution deposited crystals. In subsequent resolutions of the thioacid, acetone proved satisfactory. The first crop of crystals weighed 44 g and had $[\alpha]^{23}D$ −15.6° (*c* 2.68, chloroform). The salt was recrystallized by dissolving it in a minimum amount of boiling chloroform and adding petroleum ether (bp 60–70°) until cloudiness persisted at the boiling point. The solution was set aside overnight. The solid was filtered and dried (33 g) and its rotation was determined, $[\alpha]^{23}D$ −16.8° (*c* 2.85, chloroform). Wallis found −16.93°.

The acid was liberated from the brucine salt as described by Wallis, $[\alpha]^{23}D$ −13.2° (chloroform).

One gram of (−)-acid was dissolved in acetone and treated with aqueous silver nitrate. The resulting precipitate of silver salt was removed by filtration and washed with acetone. The aqueous acetone filtrate was diluted with water and stirred for 1 hr until the precipitated alcohol coagulated. The precipitate was filtered and dried (300 mg), $[\alpha]^{23}D$ +10.5° (*c* 0.96, chloroform); $[\alpha]^{24}D$ +4.4° (*c* 0.08, carbon tetrachloride). The rotation in chloroform corresponds to alcohol of 58% optical purity, the remainder being racemic material.

The alcohol samples were recovered from the solutions used to determine the rotations, and the combined material was dissolved in a minimum quantity of boiling ether. The cooled solution was seeded with a tiny crystal of (+)-carbinol and set aside overnight. The majority of material was in the form of clusters of heavy short needles, together with a few well-formed cubes. The latter were removed mechanically and the ether supernatant was decanted. The ether was combined with the cubes and the whole taken to dryness. The residue (80 mg) showed a rotation of $[\alpha]^{23}D$ 1.5° (*c* 0.79, chloroform). The needles showed a rotation of $[\alpha]^{23}D$ +16 ±1° (*c* 0.57, chloroform).

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Structure of the Mesembranols and the Absolute Configuration of Mesembrine and Related Alkaloids[1,2]

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Abstract: The relative configurations of the epimeric alcohols, (−)-mesembranol (**2**) and (−)-6-epimesembranol (**3**), have been established by spectral studies of the alcohols and their O-acetyl derivatives **4** and **5**. Supporting evidence for the configurational assignments is presented from the saponification rates of **4** and **5** and rates of acetylation of the alcohols. In the latter reaction an unusually facile acetylation of 6-epimesembranol is consistent with neighboring group participation by the nitrogen to account for the rate enhancement. Analysis of the nmr spectrum of the alkaloid mesembrine indicates that it also exists predominantly with ring B in the chair conformation **1A** in which the aryl substituent is quasi-axial. Interpretation of the CD spectrum of mesembrine on the basis of this conformation for ring B leads to a reassignment of the absolute configuration of mesembrine as indicated by structure **1**. A discussion of the conformational features of mesembrine is presented.

Interest in the constituents of certain *Sceletium* species of the family *Aizoaceae*, which are indigenous to Southwest Africa, has stemmed from the time of recognition of their use for the preparation of the drug *Channa*.[4]

Alkaloidal substances were first detected in the *Channa* drug in 1896.[7] In 1914, Hartwich and Zwicky[8] isolated an amorphous base which they termed "mesembrin." In view of more recent studies, this material most likely consisted of a mixture of alkaloids. In a subsequent study Rimington and Roets[9] assigned to mesembrine the empirical formula $C_{17}H_{23}NO_3$ deduced from analyses of the crystalline picrate and chloroplatinate. Later Bodendorf and Krieger[10]

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(2) The subject of this paper constituted part of a symposium lecture given by P. W. J. at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 5, 1968.

(3) National Aeronautics and Space Administration Fellow, 1965–1968.

(4) This is the name given to the drug in the earliest reference available to us[5] in which its use by the Hottentots and Bushman, tribes endemic to the region at that time, was reported. Later references[6] refer to this under both the name *Channa* and *Kougoed;* the latter term probably has its origins in the language of the early Dutch settlers.

(5) P. Kolben "The Present State of the Cape of Good Hope," Vol. I, 2nd ed, G. Medley, trans., W. Innys and R. Manby, London, 1738, p 212.

(6) E. M. Holmes, *Pharm. J. Trans.*, **9**, 810 (1874); C. F. Juritz, *Rep. Jt. Meet. Brit. Assn. S. Afr. Assn. Advan. Sci.*, **1**, 216 (1905).

(7) I. Meiring, *Trans. S. Afr. Phil. Soc.*, **9**, 48 (1898).

(8) G. Hartwich and E. Zwicky, *Deut. Apotheker-Z.*, 949 (1914).

(9) C. Rimington and G. C. S. Roets, *Onderstepoort J. Vet. Sci. Anim. Ind.*, **9**, 187 (1937).