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An investigation of a new approach to the synthesis of optically active trityl systems.

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AN INVESTIGATION OF A NEW APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE TRITYL SYSTEMS

BY

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A Thesis

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ABSTRACT

A route previously found in this laboratory for the synthesis of potentially optically active trityl systems via a hydracrylic acid derivative has been modified and has been used in an attempt to resolve phenyl-α-naphthyl-p-tolyl-carbinol. The dℓ-alcohol was converted to methyl β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionate by reaction with methyl β-hydroxypropionate in trifluoroacetic acid. Hydrolysis of this methyl ester afforded the dℓ-β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid. Both steps were effected in high yields (ca.90%). Conversion of the propionic acid to the optically active brucine salt, $[\alpha]_{Hg}^{25}$ -23.5° (c = 4.0524), proceeded with great difficulty and in low yield (ca. 20%). The salt was decomposed by aqueous hydrochloric acid to optically active d-β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid, $[\alpha]_{Hg}^{25}$ +3.19° (c = 1.0176). The infrared spectrum of this acid was identical to that of the dℓ.

The optically active propionic acid was converted with diazomethane to the methyl ester which, on subsequent treatment with sodium hydride in anhydrous ether (a reverse Michael reaction), yielded optically active phenyl-α-naphthyl-p-tolylcarbinol, $[\alpha]_{Hg}^{25}$ +3.12 (c = 1.0092). The infrared spectrum was identical to that of the dℓ-alcohol. The overall yield from the d-acid was 85%.

The optical purity of the d-acid was not determined since the pure l-acid was not obtained. However, the brucine salt of the d-acid was crystallized until no significant change could be made in optical rotation. Again, the optical purity of the d-alcohol was not determined in this investigation.

Phenyl-p-bromophenyl-p-chlorophenylcarbinol was subjected to a modified hydracrylic acid sequence with good results, although no attempt at resolution of any of the potentially optically active intermediates was made. Attempts to apply the hydracrylic acid route to benzhydrol and n-butanol as pilot systems did not show much promise for further application of this method.

ACKNOWLEDGEMENTS

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CHAPTER I

THEORETICAL CONSIDERATIONS

Methods of Resolution

Resolution is defined as the process whereby an optically active form of a chemical compound is separated from a racemic modification of the same chemical compound. The optically active form obtained need not be optically pure, but may consist of a mixture of the d and ℓ isomers in unequal proportions. Furthermore, resolution may be carried out with a non-racemic starting material, provided enough of the isomer initially in excess is removed to leave behind material which contains an excess of the opposite isomer.

Of the methods described in this section, only resolution via conversion to diastereoisomers and resolution by biochemical methods are generally useful. Other methods are included because of their theoretical interest.

1. Mechanical Separation of Crystals

In the case of a racemic mixture, macroscopic crystals of either the d or the ℓ form are usually present. Provided that the crystals are visually distinct, it is possible to

effect a resolution by mechanical separation. In 1848 Louis Pasteur[1] resolved the sodium ammonium salt of tartaric acid by this method.

Resolution can also be accomplished by selective crystallization of one enantiomer from a solution of the racemic form. Usually the separation is initiated by providing seed crystals of one isomer in a supersaturated solution of the racemic modification. Vieles[2] suggested that resolution can be accomplished only when the enantiomers form a mechanical mixture. Werner[3] was somewhat more exact in the statement of the requirements. He said that resolution is possible only when the solubility of each of the pure enantiomers is less than that of the racemic modification. This criterion includes all cases of mixture formation and some cases of compound formation. Although resolution by crystallization in binary systems has never been reported in the literature, it is theoretically possible

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1 L. Pasteur, Ann. chim. et phys., [3] 24, 442 (1848).

2 P. Vieles, Compt. rend., 198, 2102 (1934).

3 A. Werner, Ber., 47, 2171 (1914).

to accomplish[4]. Most experimental studies of resolution by crystallization have been concerned with ternary systems consisting of d-isomer, ℓ-isomer, and solvent[5]. An example is the resolution of dℓ-histidine monohydrochloride accomplished by Duschinsky[6]. These results are important because they are the only data available on the successful resolution of a racemic compound by crystallization[7].

2. Formation of Diastereoisomers

The reaction of a racemic modification with an optically active material results in the formation of two diastereoisomers. These two types of molecules have different properties and may in general be separated on this basis.

There have been many methods of separation employed. Bailey and Hass[8] effected partial resolution of 2-butanol,

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4 R.M. Secor, Chem. Rev., 63, 297 (1963).

5 R.M. Secor, loc. cit.

6 R. Duschinsky, Chemistry and Industry, 10 (1934).

7 R.M. Secor, loc. cit.

8 M.E. Bailey and H.B. Hass, J. Am. Chem. Soc., 63, 1969 (1941).

2-pentanol, 2-ethyl-1-hexanol, 2-methylbutanoic acid, and 2-methoxypropionic acid by conversion to volatile diastereoisomers followed by rectification on a 60-plate column. It was possible to produce 86% d-2-butanol with a single distillation using d-2-propionoxypropionic acid.

Jamison and Turner[9] were able to resolve dl-mandelic acid to some extent by selective adsorption of the l-menthyl esters on a column of alumina.

Casanova and Corey[10] investigated the resolution of dl-camphor by gas-liquid chromatography. The diastereoisomers were formed by combination of racemic camphor with optically active 2,3-butanediol. A column of tricyanoethoxypropane was used to separate the ketals; the camphor isolated after acid hydrolysis was 76.5-77.5% optically pure.

The most efficient method involves crystallization because crystal structure is apt to be more sensitive to minor variations in molecular architecture.

A good resolving agent should possess four qualifications[11]. The compound resulting from the reaction between

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9 M.M. Jamison and E.E. Turner, J. Chem. Soc.,611 (1942).

10 J. Casanova, Jr., and E.J. Corey, Chemistry and Industry, (London), 1664 (1961).

11 E.L. Eliel, Stereochemistry of Carbon Compounds, (New York, 1962), pp. 49-52.

the resolving agent and the racemic modification should be easily formed and easily broken down. The product of the resolving agent and the racemic modification must be crystalline, and there must be an appreciable difference in solubility between the diastereoisomers. The fulfillment of this condition depends to some extent on the solvent chosen. The resolving agent should be either inexpensive or readily prepared and nearly quantitatively recoverable after resolution. Lastly, the resolving agent should be available in a state of high optical purity; the optical purity of the substance to be resolved cannot be raised above that of the resolving agent by mere crystallization of diastereoisomers.

Acids are usually resolved by the use of readily available alkaloids such as brucine, strychnine, quinine, etc. Camphor-10-sulfonic acid, camphoric acid, tartaric acid, etc. form suitable derivatives with racemic bases. Alcohols are usually resolved by prior conversion to the respective hydrogen phthalate or succinate esters. The use of esters of optically active acids is of limited value because relatively few esters are satisfactorily crystalline. However, Barrow and Atkinson[12] resolved 2-octanol, 2-pentanol,

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12 F. Barrow and R.G. Atkinson, J. Chem.Soc., 638 (1939).

2-hexanol, and menthol by recrystallization of the respective d-tartranilate esters. These compounds are well-defined solids which crystallize readily. Aldehydes and ketones can be resolved through derivatives of naturally occurring active substances such as menthylsemicarbazide. menthylhydrazine, etc. Adams et al[13] have recently developed a new method which eliminates the need to synthesize optically active reagents and which permits regeneration of the carbonyl compound under mild conditions. It consists of the formation and recrystallization of iminium salts containing optically active anions (e.g. d-camphor-10-sulfonate).

3. Resolution via Molecular Complexes

A number of racemic compounds have been resolved via molecular complexes, however the differences in the types of complexes formed are not always apparent. Digitonin[14], a steroidal saponin, acts as an asymmetric[15] reagent to pre-

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13 W.R. Adams et al, J. Am. Chem. Soc., 88, 162 (1966).

14 L.F. Fieser and M. Fieser, Topics in Organic Chemistry (New York, 1963), p.227.

15 Dissymmetric denotes the absence of an alternating (but not necessarily of a simple) axis of symmetry. Asymmetric denotes absence of both. Both asymmetric and dissymetric molecules are usually optically active.

cipitate selectively 3-β-hydroxysteroids. The hydroxyl group may be axial or equatorial; the steroid can be saturated or unsaturated. Desoxycholic acid effected partial resolutions of camphor[16] by forming a clathrate or lattice inclusion complex. This type of complex is formed when one component crystallizes in such a way as to leave a hole into which the other component may fit if it is of suitable size. Powell[17] obtained a partial resolution of 2-bromobutane by crystallizing the dissymmetric compound, tri-o-thymotide, from the racemic solvent. Cramer and Dietsche[18] obtained optically active ethyl phenylchloroacetate via a molecular inclusion complex employing β-dextrin[19].

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16 H. Sobotka and A. Goldberg, Biochem. J., 26, 905 (1932).

17 H.M. Powell, Nature, 170, 155 (1952).

18 F. Cramer and W. Dietsche, Ber., 92, 378 (1959).

19 Dextrins are the products of the partial hydrolysis of starches by acids, α-, or β-amylase. They consist of very complex mixtures of molecules of different sizes and structures depending on the method of preparation. E.S. West et al, Textbook of Biochemistry, 4th ed., (New York, 1966), p.241.

4. Resolution by Chromatography

A lactose column was used by Henderson and Rule[20] to resolve dℓ-p-phenylene-bis-iminocamphor. This type of process is limited to racemic modifications which can be adsorbed on an optically active adsorbent and whose active components possess different absorption coefficients.

Lott and Rieman[21] prepared an optically active strong-base anion-exchange resin from ℓ-N,N-dimethyl-α-phenethyl-amine and chloromethylated, cross-linked polystyrene. Partial resolution of dℓ-mandelic acid was achieved by frontal and displacement ion-exchange techniques employing sodium mandelate.

5. Kinetic Method of Resolution

Marckwald and McKenzie[22] effected partial resolution of dℓ-mandelic acid by taking advantage of the varying rates of esterification with ℓ-menthol.

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20 G.M. Henderson and H.G. Rule, Nature, 141, 917 (1938); G.M. Henderson and H.G. Rule, J. Chem. Soc., 1568 (1939).

21 J.A. Lott and W. Rieman III, J. Org. Chem., 31, 561 (1966).

22 W. Marckwald and A. McKenzie, Ber., 32, 2130 (1899).

6. Asymmetric Synthesis

Reaction of methyl ethyl ketone with phenylmagnesium bromide in the asymmetric environment provided by d-2,3-dimethoxybutane produced optically active 2-phenyl-2-butanol [23]. This type of effect is strongest when the asymmetric environment is present within the reactant molecule. For the particular case where the two centres are adjacent to each other and where asymmetry at the new centre is created by an addition reaction to a double bond, Cram's rule[24] predicts to a reasonable degree the stereochemistry of the product. This rule, however, is restricted to kinetically-controlled reactions.

7. Asymmetric Destruction

The partial decarboxylation[25] of dℓ-α-carboxy-camphor in the presence of the asymmetric base catalyst quinine produced ℓ-camphor and left d-α-carboxy-camphor.

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23 N. Allentoff and G.F. Wright, J. Org. Chem., 22, 1 (1957).

24 D.J. Cram and F.A. Abd Elhafez, J. Am. Chem. Soc., 74, 5828 (1952).

25 K. Fajans, Z. physik. Chem., 73, 25 (1910).

8. Biochemical Asymmetric Transformation

Helferich and Hiltmann resolved dℓ-trans-1,2-cyclopentanediol via enzymatic hydrolysis of the glucoside[26]; the d-glycol was obtained.

Criteria of Optical Purity

Optical Purity is defined as the excess of one enantiomer in the material expressed as a percentage of the total. Several simple criteria have been developed, but none is completely reliable.

A crystalline enantiomer is often considered optically pure when its melting point and rotation are unchanged by further crystallization. This criterion fails when dealing with a solid solution.

Another criterion is lack of change of rotation upon further crystallization of the diastereoisomeric salt. Unfortunately this condition may be invalidated by certain types of phase behaviour[27].

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26 B. Helferich and R. Hiltmann, Ber., 70, 308, 588 (1937).

27 E.L. Eliel, op. cit., pp. 83-84.

Resolution is often deemed complete when both enantiomers are obtained in a state of equal purity. This demands equal and opposite specific rotations. Unfortunately this approach is not applicable when one of the enantiomers is not readily obtained pure[28].

The enzymatic method of determining optical purity is limited in its application to optically active compounds that are subject to enzymatic reactions. The method depends on the fact that certain enzymes are highly selective for one enantiomer of a *dℓ* pair. A supposedly pure[29] preparation of the other enantiomer is incubated with the enzyme. Reaction would indicate the presence of some of the wrong enatiomer, owing to incomplete resolution or racemization following complete resolution; absence of reaction would indicate purity.

In the isotope dilution method, the supposedly pure enantiomer is mixed with some labeled racemic material in solution, and the racemic material is then reisolated[30].

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28 J.A. Berson and D.A. Ben-Efraim, J. Am. Chem. Soc., 81, 4083 (1959); J.A. Berson and S. Suzuki, J. Am. Chem. Soc., 81, 4088 (1959).

29 Chemical purity is assumed.

30 It must be possible to reisolate the racemate in pure form.

If one mixes labeled racemic material with pure unlabeled *ℓ* material, only the *ℓ* molecules in the recovered *dℓ* pair get diluted isotopically; but if one mixes it with unlabeled racemic material, then all molecules in the recovered *dℓ* pair will be diluted. In this latter case, the dilution factor is greater. Berson and Ben-Efraim[31] have established a relationship:

$$C_{\pm} = a\,C_o\,\frac{a + B}{(2B + a - R)(a + R)}$$

where C_o = the activity of the added racemic material

$C_{\pm}$ = the activity of the recovered racemic material

a = the weight of the added racemic material

B = the weight of the resolved material (whose purity is being tested) admixed with a.

R = the weight of racemate (if any) in B.

The previous equation is solved for R and the optical purity is calculated from the following expression:

$$100\,\frac{B - R}{B}\ \%$$

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31 J.A. Berson and D.A. Ben-Efraim, loc. cit.

The correlative method consists of relating a compound of unknown optical purity to another whose purity is known. Let us suppose that the optical purity of compound abdC-e is known. The minimum optical purity of another compound abdC-f can be determined if abdC-f can be converted chemically to abdC-e. Consequently the maximum possible rotation of abdC-f can be calculated. Compound abdC-f is at least as pure optically as compound abdC-e prepared from it; it may be more pure because the conversion process abdC-f to abdC-e may involve racemization.

CHAPTER II

RESOLUTION OF A TRITYL SYSTEM

Applications

A brief explanation[1] of the concept of ion pairs is necessary in view of the material to follow. Ion pairs (I) are often encountered in solvolysis reactions of triphenylmethyl and benzhydryl compounds.

$$RX \rightleftharpoons R^+X^- \xrightarrow{HOY} ROY + HX$$

I

In some cases rearrangement or racemization reactions proceed faster than substitution, and the rates exhibit a large solvent dependence. The question is often posed whether the ion pair involved in rearrangement or racemization is the same as the ion pair involved in substitution. It will be seen below that some data are consistent with the existence of an intimate ion pair (II) as an intermediate in rearrangement or racemization and a solvent-separated ion pair (III) as an intermediate in substitution.

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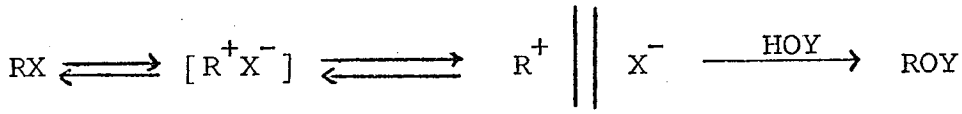
1 C.G. Swain and G. Tsuchihashi, J. Am. Chem. Soc., 84, 2021 (1962).



II III

During the past decade the literature has borne testimony to the continued interest in the study of solvolysis reactions of trityl system. Trityl systems are especially attractive due to their relative freedom from complicating side reactions such as bimolecular substitution[2] and elimination. The solvolysis studies have been more than adequately substantiated by kinetic data involving substitution, rearrangement, and isotope-mixing effects; however stereochemical data is conspicuously sparse.

Hughes, Ingcld, and others[3] dealt with the kinetics of the nucleophilic substitution of triphenylmethyl chloride by radioactive chloride ion, azide ion, methyl alcohol, and benzyl alcohol in benzene. Their results were consistent with the slow formation of an ion pair species, followed by

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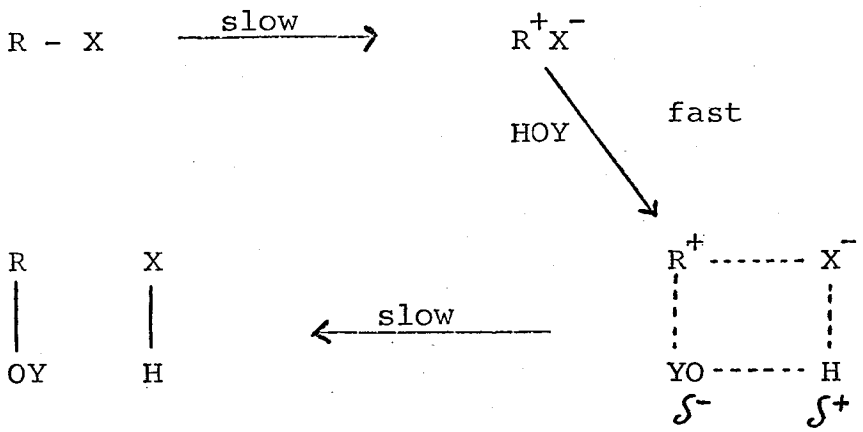
2 If sufficiently deactivated substrates (e.g. 4,4',4"-trinitrotriphenylmethyl chloride) and suitable conditions are used (low polarity solvents), the direct substitution mechanism may be made to compete effectively with, or even suppress completely, the ionization mechanism.
U. Miotti and A. Fava, J. Am. Chem. Soc., 88, 4274 (1966).

3 C.K. Ingold et al, J. Chem. Soc., 1220, 1230, 1238, 1256, 1265 (1957).

a fast dipole association, and then a slow quadrupole rearrangement to yield product.



Swain and Pegues[4] discovered experimental errors in the Ingold papers and proceeded to point out the inconsistencies in the proposed mechanisms. In spite of the various disagreements, the kinetic work of Swain and Pegues on the methanolysis of triphenylmethyl chloride supported an ion pair process. In the latter case the interpretation of the results included the possible existence of two kinds of ion pairs, however, further work was deemed necessary to substantiate this.

Swain and Tsuchihashi[5] found that the rate of oxygen

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4 C.G. Swain and E.E. Pegues, J. Am. Chem. Soc., 80, 812 (1958).

5 C.G. Swain and G. Tsuchihashi, loc. cit.

equilibration in trityl benzoate-carbonyl-^{18}O was equal to the rate of unimolecular substitution by lithium azide. The initial rate of oxygen equilibration dropped to zero in the presence of azide ion. It was concluded that the ion pair involved in oxygen equilibration was the same ion pair involved in substitution.

Darwish and Preston[6] calculated first-order rate constants for the rearrangement of trityl 2-methyl-benzenesulfinate to trityl 2-methylphenyl sulfone. Solvent effects and exchange experiments with azide salt indicated than an ionic reaction was taking place.

Stereochemical data would have been of great benefit in the aforementioned trityl systems just as it has been in the following secondary systems. For example Winstein and coworkers found that optically active p-chlorobenzhydryl chloride racemized approximately 30 times as fast as it solvolyzed in acetic acid[7]. In the less polar solvent, 80% aqueous acetone, racemization was only 3 times as fast as

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6 D. Darwish and E.A. Preston, Tetrahedron Letters, No.2, 113 (1964).

7 S. Winstein et al, J. Am. Chem. Soc., 82, 1010 (1960).

solvolysis[8]. In this example the use of an optically active substrate emphasized the plural nature of the ion pair species.

Streitwieser and Walsh[9] discovered that the acetolysis reaction of 2-octyl tosylate proceeded with almost complete inversion of configuration; most of the apparent racemization was attributed to racemization of the starting material. The results were entirely explicable in terms of an ion pair mechanism.

Goering and Levy[10] reported evidence for at least two distinct ion pair species involved in the solvolysis of optically active p-chlorobenzhydryl p-nitrobenzoate-carbonyl-^{18}O in the presence of azide ion. Oxygen equilibration of the unsolvolyzed ester occurred, but the optical configuration was fully preserved. Thus the nucleophilic azide ion was accepting an intermediate that otherwise would have returned with loss of configuration, but it was not intercepting an intermediate that returned with retention. It

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8 S.Winstein, M. Hojo, and S. Smith, Tetrahedron Letters, No.22, 12 (1960).

9 A. Streitwieser, Jr. and T.D. Walsh, Tetrahedron Letters, No. 1, 27 (1963).

10 H.L. Goering and J.F. Levy, J. Am. Chem. Soc., 86, 120 (1964).

was generalized that internal (i.e. intimate ion pair) return is completely stereospecific, and external (i.e. solvent-separated ion pair) return results in partial or complete racemization.

The lack of stereochemical evidence in solvolysis studies of trityl systems is due to the fact that successful routes to the resolution of triarylcarbinols are scarce[11] compared to the well-documented paths for the resolution of alkyl and aralkyl secondary[12,13] and tertiary[14,15] carbinols.

In 1963, Murr[16] announced a new method of resolution of triarylcarbinols with high optical yield. The resolution of phenylbiphenyl-α-naphthylcarbinol is outlined in Chart I.

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11 B.L. Murr, J. Am. Chem. Soc., 85, 2866 (1963).

12 A.W. Ingersoll, in Organic Reactions, Vol. II, (New York, 1944), p.367.

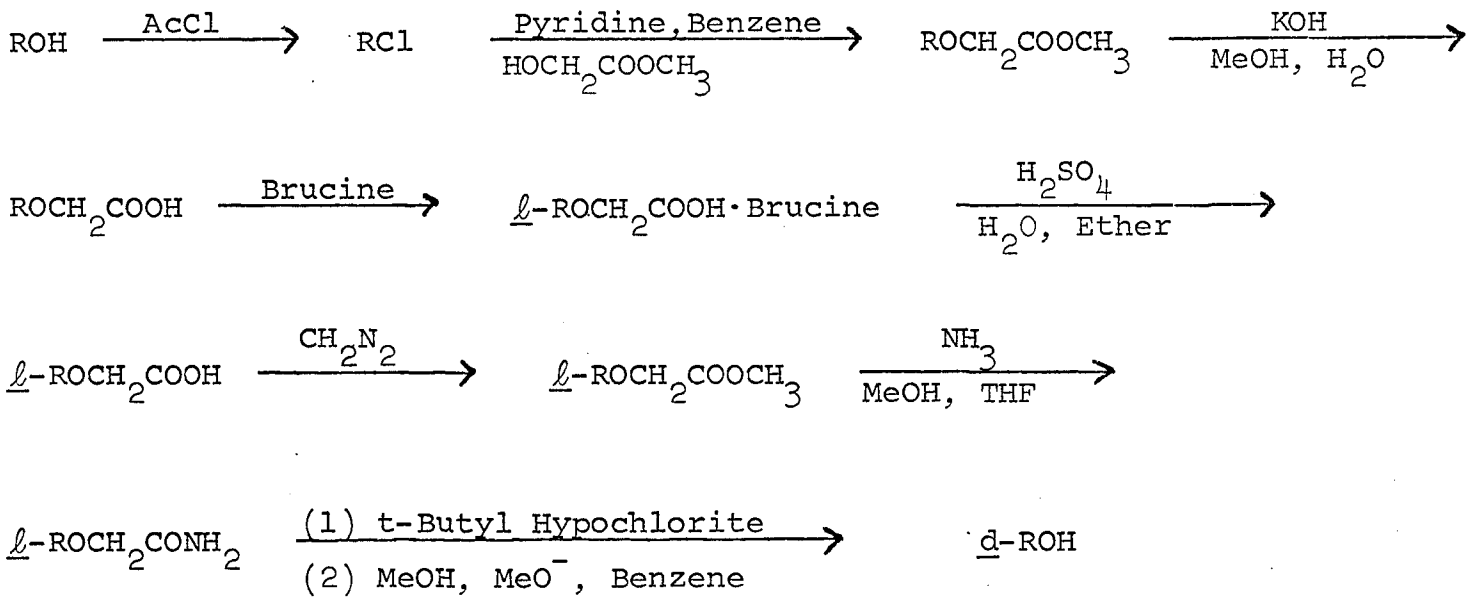
13 G.H. Green and J. Kenyon, J. Chem. Soc., 751 (1950).

14 W. von E. Doering and H.H. Zeiss, J. Am. Chem. Soc., 72, 147 (1950).

15 H.H. Zeiss, J. Am. Chem. Soc., 73, 2391 (1951).

16 B.L. Murr, loc. cit.

CHART I



Simultaneously in this laboratory, Prokipcak[17] worked out a similar method[18] for the synthesis of optically active triarylcarbinols employing a glycolic acid intermediate. This is presented in Chart II.

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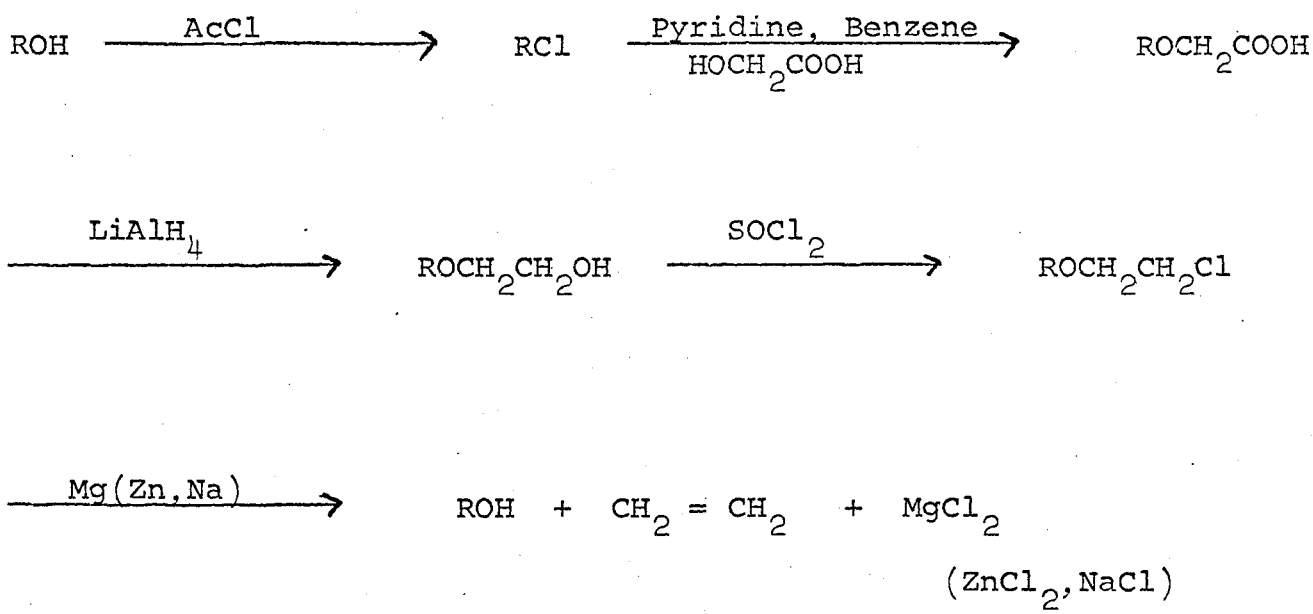
17 J.M. Prokipcak, Doctoral Dissertation, University of Windsor, 1964, p.65.

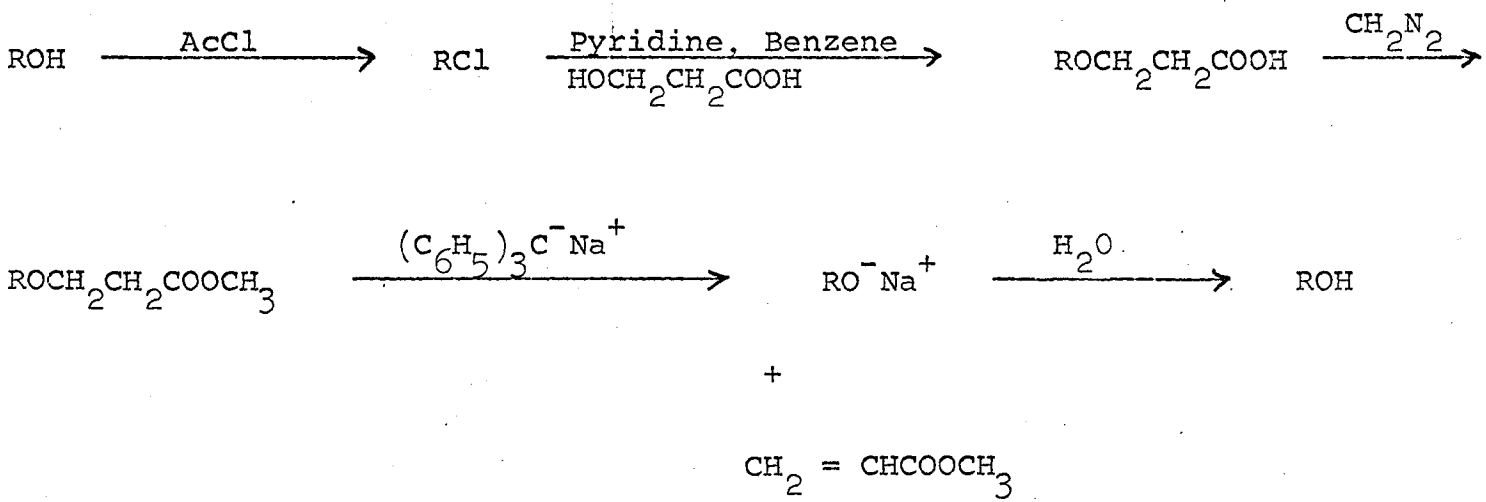
18 The hydrogen phthalate of triphenylcarbinol had been prepared previously in this laboratory [K.G. Rutherford, J.M. Prokipcak, and D.P.C. Fung, J. Org. Chem., 28, 582 (1963)], however, a route possessing higher yields was desired.

CHART II



A second potential route involving a hydracrylic acid intermediate was established concurrently. The latter method, as seen in Chart III, was shown to be more valuable than Murr's glycolic acid method which involved more steps. Triphenylcarbinol was used as the pilot system for both cycles.

CHART III



Resolution of Phenyl-α-Naphthyl-p-Tolylcarbinol

In 1962 Thaker and Dave[19] reported the resolution of phenyl-α-naphthyl-p-tolylcarbinol *via* the hydrogen phthalate method. The preparation, a classic one for alkyl esters, consisted of heating the alcohol and phthalic anhydride at 90-96° in triethylamine for 16 hours. Previous to this, Kenyon and co-workers[20] had reported that this procedure applied to triphenylcarbinol gave none of the desired product. Similar attempts to repeat Thaker's work in this laboratory have failed. Furthermore, all efforts to prepare the desired hydrogen phthalate by a number of different ways have proven unfruitful. These endeavours included the method developed in this laboratory which was shown to be satisfactory for triphenylcarbinol (30% yield)[21].

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19 K.A. Thaker and N.S. Dave, J. Sci. Industr. Res., 21B, 374 (1962).

20 M.P. Balfe, J. Kenyon, and E.M. Thain, J. Chem. Soc., 386 (1951).

21 K.G. Rutherford, J.M. Prokipcak, and D.P.C. Fung, J. Org. Chem., 28, 582 (1963).

The decision was made to attempt the resolution of this triarylcarbinol via an alternate route, namely the hydracrylic acid derivative whose potential had been previously established[22].

The first attempt to prepare β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid involved an adaptation of the procedure used by Helferich and co-workers[23] for the preparation of ethyl β-(triphenylmethoxy)-propionate. This adaptation had previously proved successful for the synthesis of β-(triphenylmethoxy)-propionic acid and β-(phenyl-p-bromophenyl-p-chlorophenylmethoxy)-propionic acid. Phenyl-α-naphthyl-p-tolylmethyl chloride, prepared from the carbinol and acetyl chloride, was stirred with methyl β-hydroxypropionate in pyridine. A yield of ca. 1% was realized after work-up. This material had an infrared spectrum which was consistent with that of the desired acid.

The second attempt involved the application of a novel synthesis of mixed arylmethyl-alkyl ethers which had been

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22 J.M. Prokipcak, Doctoral Dissertation, University of Windsor, 1964, p.65.

23 B.F. Helferich, L. Moog, and A. Junger, Ber., 58, 881 (1925).

developed in this laboratory[24]. When the above procedure was carried out using triphenylcarbinol, a 38% yield of β-(triphenylmethoxy)-propionic acid was obtained. On the other hand, phenyl-α-naphthyl-p-tolylcarbinol, methyl-β-hydroxypropionate, and iodine in acetone gave none of the desired product.

Another attempt was made using the well-known acid-catalyzed opening of β-propiolactone in the presence of an alcohol to yield the corresponding β-alkoxy-propionic acid[25]. Phenyl-α-naphthyl-p-tolylcarbinol, propiolactone, and p-toluenesulfonic acid were refluxed in benzene. Alkaline hydrolysis followed by acidification again did not afford the desired acid. Similar results were obtained when the reaction was carried out at 0°. At room temperature however, low yields (15-20%) were obtained. In contrast triphenyl-carbinol and phenyl-p-bromophenyl-p-chlorophenylcarbinol gave 75-80% yields of β-(triphenylmethoxy)-propionic acid and β-(phenyl-p-bromophenyl-p-chlorophenylmethoxy)-propionic acid respectively.

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24 K.G. Rutherford et al, Can. J. Chem., 44, 2337 (1966).

25 R.B Wagner and H.D. Zook, Synthetic Organic Chemistry, (New York, 1953), pp. 495-6.

The final approach made use of the fact that some triarylcarbinols form carbonium ions readily in 100% sulfuric acid solution. It was found thus that methyl β-(triphenylmethoxy)-propionate could be prepared in 90-95% yield from triphenylcarbinol and methyl β-hydroxypropionate. In order to avoid complicating side reactions (aromatic sulfonation) with the phenyl-α-naphthyl-p-tolylcarbinol, trifluoroacetic acid was used as the reaction medium. This innovation proved to be excellent yielding 80-85% of the desire methyl propionate. The alkaline hydrolysis of both esters proceeded in high yields to afford the corresponding acids.

The brucine salt of β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid was prepared in acetone by the standard method [26], $[\alpha]_{Hg}^{25}$ - 30.9° (c = 4.0236)[27]. Several recrystallizations of this salt from toluene-methylcyclohexane gave a fraction (ca. 20% yield) with constant rotation, $[\alpha]_{Hg}^{25}$ - 23.5°

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26 A.W. Ingersoll, loc. cit.

27 Unless otherwise stated, all rotations were taken in chloroform in a 2-dm cell such that observed rotations were greater than ± 0.5°.

(C = 4.0524). It should be noted here that although several solvent pairs were tried under the usual variety of conditions, the toluene-methylcyclohexane combination proved to be the best even though crystallization occurred very slowly. The salt was decomposed in the usual manner to yield the d-acid, m.p. 159-160.5° [28], $[\alpha]_{Hg}^{25}$ + 3.19 (C = 1.0176). The infrared spectrum of the d-acid in chloroform was identical to that of the dℓ-acid.

The d-acid was converted in a facile manner to the d-alcohol by first conversion with diazomethane[29,30] to the methyl ester (not isolated) which underwent a rapid reverse Michael[31] reaction on treatment with sodium hydride. The infrared spectrum of the d-alcohol, m.p. 90-93° [32], $[\alpha]_{Hg}^{25}$ + 3.12 (C = 1.0092), was identical to that of the dℓ-alcohol in chloroform. This procedure was previously perfected with the triphenylcarbinol system and the yields of final product

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28 dℓ-acid, m.p. 151-152.5°.

29 R.B. Wagner and H.D. Zook, op. cit., p.485.

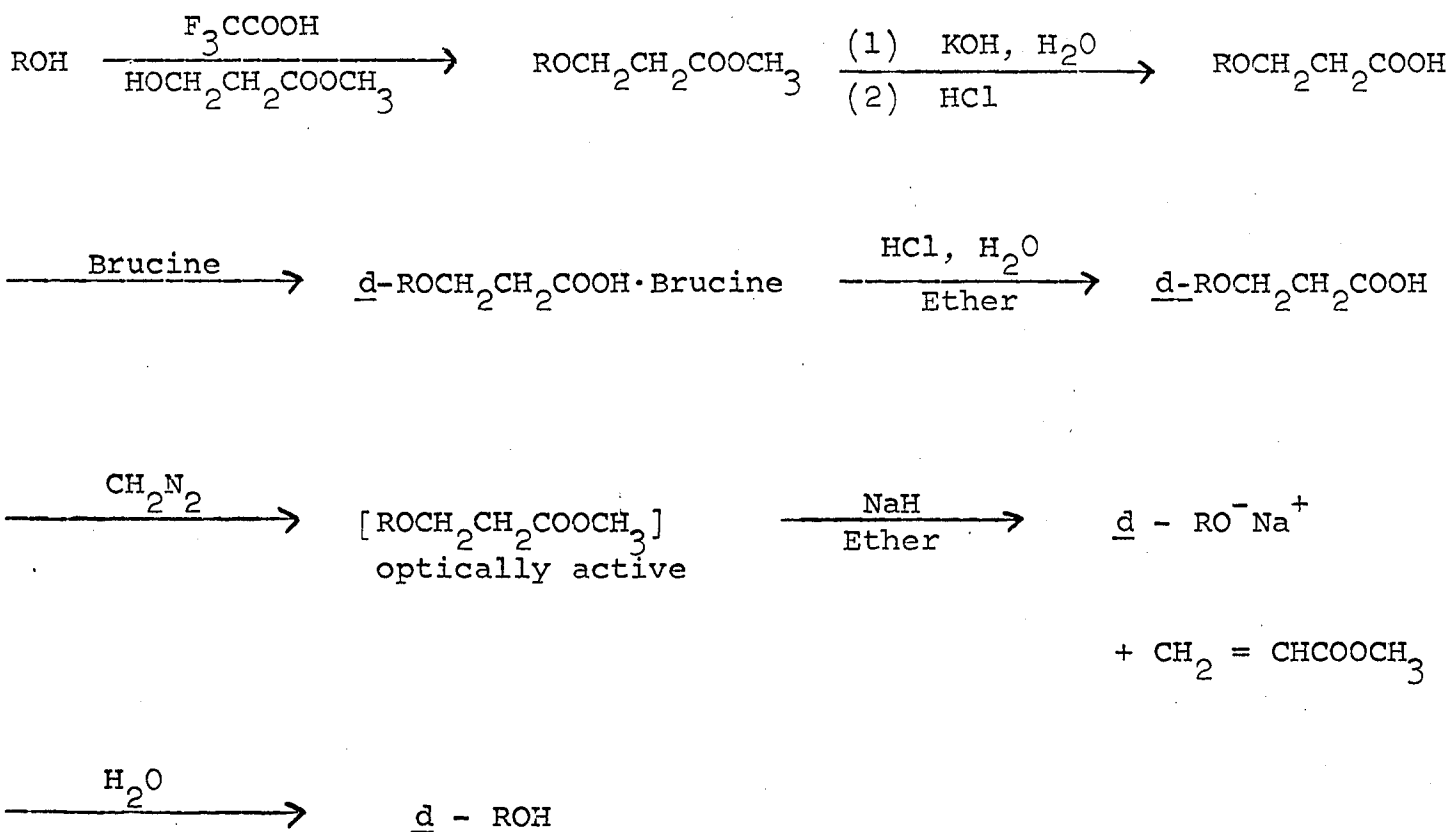
30 Th. J. de Boer and H.J. Backer, in Organic Syntheses ed. N. Rabjohn, Coll. Vol. IV, (New York, 1963), pp.250, 943.

31 G. Wittig, U. Todt, and K. Nagel, Ber., 83, 110 (1950).

32 dℓ-alcohol, m.p. 110 - 112°.

in both cases were excellent. To our knowledge this is the first case of the use of sodium hydride to effect a reverse Michael reaction of this type and is a decided improvement over the use of triphenylmethyl sodium. The overall resolution scheme is outlined in Chart IV.

CHART IV



In order to determine the scope of the method outlined in Chart IV to trityl systems bearing substituents with positive sigma values[33], it was decided to use phenyl-p-bromophenyl-p-chlorophenylcarbinol as a pilot compound. The method produced the hydracrylic acid methyl ester derivative in very low yields ($\leq$ 10%). However, it was found that the key hydracrylic acid derivative, β-(phenyl-p-bromophenyl-p-chlorophenylmethoxy)-propionic acid, could be made directly from the reaction of the trityl alcohol and propiolactone in boiling benzene containing a trace of p-toluenesulfonic acid (Chart V).

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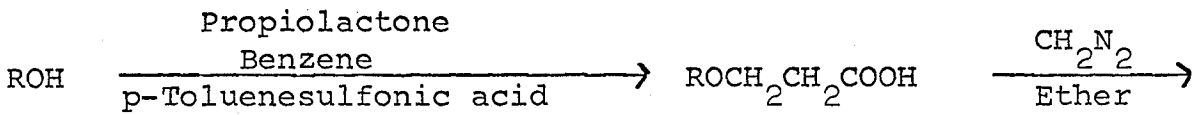
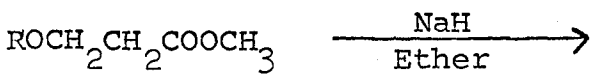
33 E.S. Gould, Mechanism and Structure in Organic Chemistry, (New York, 1965), p.221.

CHART V





The hydracrylic acid procedure for the preparation of potentially optically active benzhydryl and aliphatic alcohols as shown in Charts VI and VII did not show promise because of the thermal instability of the key hydracrylic acid derivatives.

CHART VI

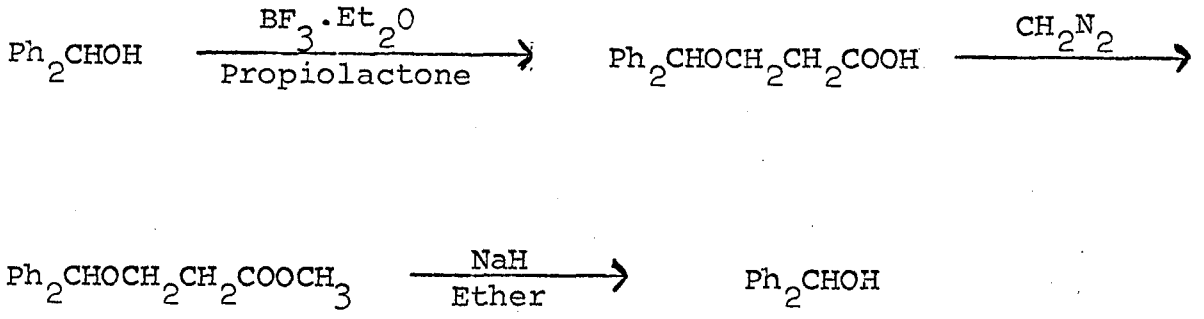
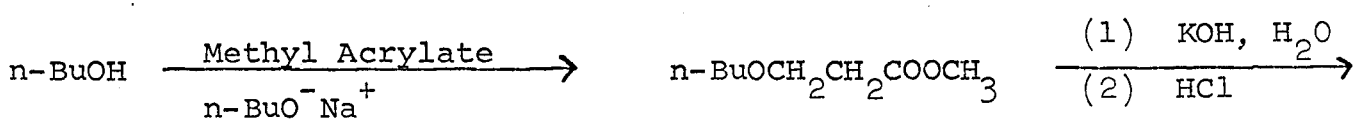
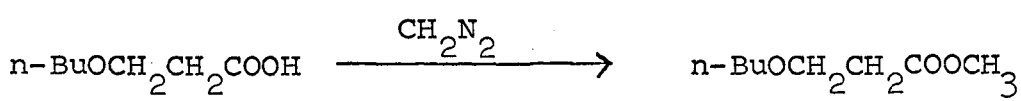
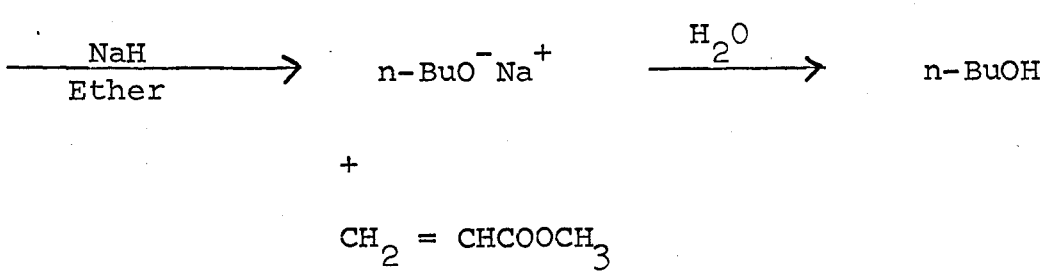


CHART VII







Resume and Conclusions

The method of resolution of potentially optically active trityl carbinols via the hydracrylic acid route has shown to be successful in the case of triphenylcarbinol, dℓ-phenyl-α-naphthyl-p-tolylcarbinol; and dℓ-phenyl-p-bromophenyl-p-chlorophenylcarbinol as pilot systems. The resolution of dℓ-phenyl-α-naphthyl-p-tolylcarbinol was effected, although the determination of optical purity was left for further investigation. It is felt that the yield of the resolution step *per se* does not detract from the potential usefulness of this as a procedure with general applicability to trityl systems.

This procedure did not show promise in the case of benzhydryl and aliphatic alcohol systems due to the thermal instability of the hydracrylic acid intermediates.

CHAPTER III

EXPERIMENTAL PROCEDURES

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotation measurements were determined in chloroform on a Rudolph Model 80 polarimeter equipped with a mercury vapour lamp (λ 4358 A). Nuclear magnetic resonance spectra were recorded in deutero-chloroform at 60 Mc.p.s. on a JEOL spectrometer. Infrared spectra were recorded in chloroform on a Beckman IR-10 spectrometer equipped with potassium bromide cells. Microanalyses were carried out by Midwest Microlab, Inc., 6000 East 46th Street, Indianapolis, Indiana 46226. Mass spectral analyses were done by Morgan Schaffer Corp., 5110 Courtrai Avenue, Montreal 26, Quebec.

Preparation of Methyl β-hydroxypropionate

Methyl β-hydroxypropionate was prepared by the method of T. L. Gresham et al[1].

Attempted Preparation of Methyl β-(triphenylmethoxy)-propionate: Iodine - catalyzed Reaction of Triphenylcarbinol with Methyl β-hydroxypropionate.

Triphenylcarbinol (5.2 g, 0.02 mole) and methyl

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1 T.L. Gresham et al., J. Am. Chem. Soc., 70, 1004 (1948).

β-hydroxypropionate (69 g, 0.67 mole) were dissolved in 100 ml of reagent grade acetone. Iodine (5.1 g, 0.02 mole) was added and the mixture was stirred for 24 hours at room temperature.

One half of the reaction mixture was poured over ice mixed with 3 g sodium thiosulfate pentahydrate. The gum-water mixture was extracted with toluene. Aqueous potassium hydroxide solution (80 ml, 10%) was added to the toluene extracts, and the mixture was refluxed overnight. The layers were separated after cooling to room temperature. The aqueous layer was heated (50 - 60°) *in vacuo* to remove last traces of toluene. Hydrochloric acid (6N) was added to pH 3. The product was filtered and dried *in vacuo*. The melting point, 165 - 167° (yield 38%), compared well with that reported (164 - 166°)[2] for β-(triphenylmethoxy)-propionic acid.

The remaining half of the reaction mixture was poured over ice mixed with 3 g sodium thiosulfate pentahydrate. The gummy mixture was extracted with petroleum ether (30 - 60°). The petroleum ether extracts were dried over anhydrous sodium sulfate, decolourized with charcoal, and subjected to

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2 B.F. Helferich, L. Moog, and A. Junger, Ber., 58, 881 (1925).

chromatography on a column of neutral alumina. Elution with benzene gave an oil which crystallized slowly. Recrystallization of this first fraction from chloroform - petroleum ether (30 - 60°) gave a compound, m.p. 108 - 112°, whose infrared spectrum was consistent with methyl β-(triphenylmethoxy)-propionate.

Preparation of Methyl β-(triphenylmethoxy)-propionate: Acid-catalyzed Reaction of Triphenylcarbinol with Methyl β-hydroxypropionate.

A solution of triphenylcarbinol (1.032g, 3.96 mmole) in 3 ml trifluoroacetic acid was added dropwise to 15 ml (0.159 mole) methyl β-hydroxypropionate which was cooled in an ice bath. The reaction mixture was poured onto cracked ice and neutralized with sodium bicarbonate. The product was removed by filtration and air-dried, m.p. 117 - 118° (yield 90 - 90%).

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

Found: C, 79.69; H, 6.39.

Preparation of β-(triphenylmethoxy)-propionic Acid: Acid - catalyzed Reaction of Triphenylcarbinol with Propiolactone.

Triphenylcarbinol (2.01 g, 7.7 mmole) and 2 ml (0.032 mole) propiolactone were dissolved in 6 ml dry benzene. After the addition of 54 mg. p-toluenesulfonic acid, the solution was refluxed for 6 hours. The product was hydrolyzed by refluxing for 4 hours with 70 ml of 5% aqueous potassium hydroxide solution. The addition of 30 ml ether to the cooled reaction mixture gave a good separation of layers. The aqueous layer was heated (50 - 60°) *in vacuo* to remove last traces of benzene and ether. Hydrochloric acid (6N) was added to pH 3 and a white precipitate was obtained. This product was filtered and air-dried, m.p. 165-166.5° (yield 75 - 80%). This agreed with the reported value[3] for β-(triphenylmethoxy)-propionic acid.

Preparation of β-(triphenylmethoxy)-propionic Acid: Alkaline Hydrolysis of Methyl β-(triphenylmethoxy)-propionate.

The ester (1.0 g, 2.89 mmole) was dissolved in 50 ml methanol. To the solution was added 10 ml of 20% aq. sodium

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3 B.F. Helferich, L. Moog, and A. Junger, *loc. cit.*

hydroxide solution. After the solution was refluxed for 6 hours, more water was added and the methanol was removed by distillation. The hot solution was filtered and cooled to room temperature. Hydrochloric acid (3N) was added dropwise with stirring to pH 3. The product was filtered, air-dried, and recrystallized from chloroform-petroleum ether (30-60°), m.p. 164-166° (yield 80%), (lit.[4] m.p. 164-166°).

Preparation of Methyl β-(triphenylmethoxy)-propionate: Reaction of β-(triphenylmethoxy)-propionic Acid with Diazomethane

An ethereal solution of diazomethane (≯ 1.56 g, 0.0372 mole) was prepared by adding a solution of 8 g (0.0372 mole) N-methyl-N-nitroso-p-toluenesulfonamide in 37 ml ether to a mixture of 3 ml water, 10 ml ethanol, and 2 g (0.0357 mole) potassium hydroxide heated to 65°[5]. The liberated diazomethane was carefully distilled directly into a solution of 0.9 g (2.71 mmole) β-(triphenylmethoxy)-propionic acid in 10 ml ether kept in an ice bath[6].

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4 B.F. Helferich, L. Moog, and A. Junger, loc. cit.

5 Th.J. de Boer and H.J. Backer, in Organic Synthesis, ed. N. Rabjohn, Coll. Vol. IV, (New York, 1963), pp. 250, 943.

6 R.B. Wagner and H.D. Zook, Synthetic Organic Chemistry, (New York, 1953), p. 485.

After the reaction the excess diazomethane was destroyed with 2-3 ml (ca. 0.0372 mole) glacial acetic acid. The ether layer was extracted with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The crude product was recrystallized from chloroform-petroleum ether (30 - 60°), m.p. 114 - 116° (yield 80 - 85%).

Reaction of Methyl β-(triphenylmethoxy)-propionate with Sodium Hydride

Sodium hydride (7 g of a 50% dispersion in mineral oil, 0.146 mole NaH) was suspended in 75 ml dry ether in a 250 ml 3-necked flask which was equipped with a glass stopper, a pressure-equalizing addition funnel, and a reflux condenser. A solution of the ester (1.8 g, 5.2 mmole) in 100 ml dry ether was added rapidly with stirring to the flask. The mixture was stirred for 24 - 26 hours, cooled to ice-bath temperature, and 75 ml water was added slowly. The ether layer was separated from the water layer, dried with anhydrous magnesium sulfate, and evaporated in vacuo. The white product (yield ca. 90% based on expected triphenylcarbinol) which appeared was separated from the mineral oil by filtration and recrystallized from methanol-benzene to yield triphenylcarbinol, m.p. 163 - 164°.

Preparation of Phenyl-α-naphthyl-p-tolylcarbinol

Phenyl-α-naphthyl-p-tolylcarbinol (m.p. 110 - 112°) was prepared according to the method of Thaker and Dave[7].

Preparation of Phenyl-α-naphthyl-p-tolylmethyl chloride

This procedure is an adaptation of that used for the preparation of triphenylmethyl chloride[8]. Phenyl-α-naphthyl-p-tolylcarbinol (5 g, 0.0154 mole) was dissolved in 10 ml dry benzene in a 50 ml flask which was equipped with a reflux condenser. Freshly distilled acetyl chloride (2.5 ml, 0.032 mole) was added dropwise through the top of the condenser. The solution was refluxed with magnetic stirring for 40 minutes. Petroleum ether (30 - 60°, 10 ml) was added and the reaction flask was cooled in an ice bath. The crystalline product was filtered quickly, washed with hexane containing 10% acetyl chloride, and placed in a vacuum desiccator. The melting range was 133 - 143°; (yield ca. 60%) the reported value is 142° [9]. (It should be

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7 K.A. Thaker and N.S. Dave, J. Sci. Industr. Res., 21B, 374 (1962).

8 W.E. Bachmann, in Organic Syntheses, ed. E.C. Horning, Coll. Vol. III, (New York, 1955), p. 841.

9 W. Dilthey, E. Häussler, E. Hausdörfer, and O. Reeh, J. Prakt. Chem., 109, 273 (1925).

noted that compounds of this type hydrolyze spontaneously in the open atmosphere. Hence they should be prepared just prior to use.)

Attempted Preparation of Methyl β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionate: Iodine - catalyzed Reaction of Phenyl-α-naphthyl-p-tolylcarbinol with Methyl β-hydroxypropionate.

Phenyl-α-naphthyl-p-tolylcarbinol (2g, 6.2 mmole) and methyl β-hydroxypropionate (1.9 g, 0.018 mole) were dissolved in 30 ml reagent grade acetone. Iodine (1.56 g, 6.1 mmole) was added and the mixture was allowed to stir for 6 days at room temperature. The reaction mixture was poured over cracked ice mixed with 4 g sodium thiosulfate pentahydrate. The gummy mixture was extracted with toluene. Aqueous potassium hydroxide solution (80 ml, 10%) was added to the toluene extracts and the mixture was refluxed overnight. After cooling to room temperature the layers were separated. The aqueous layer was heated (50 - 60°) in vacuo to remove last traces of toluene. Hydrochloric acid (6N) was added to pH 3. None of the expected β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid was obtained.

Attempted Preparation of Methyl β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionate: Bromine - catalyzed Reaction of Phenyl-α-naphthyl-p-tolylcarbinol with Methyl β-hydroxypropionate.

Phenyl-α-naphthyl-p-tolylcarbinol (2 g, 6.2 mmole) and methyl β-hydroxypropionate (1.9 g, 0.018 mole) were dissolved in 30 ml dry tetrahydrofuran. Bromine (1 drop, ca. 0.6 mmole) was added, and the solution was stirred for 24 hours at room temperature. The reaction mixture was poured over a mixture of cracked ice and sodium thiosulfate pentahydrate (4 g). The gummy mixture was extracted with toluene. Aqueous potassium hydroxide solution (80 ml, 10%) was added to the toluene extracts and the mixture was refluxed overnight. After cooling to room temperature the layers were separated. The aqueous layer was heated (50 - 60°) in vacuo to remove last traces of toluene. Hydrochloric acid (6N) was added to pH 3. The precipitate was filtered and air-dried, m.p. 83 - 86° (yield < 10%). The infrared spectrum of this product was consistent with β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid.

Attempted Preparation of Methyl β-(phenyl-α-naphthyl-p-tolyl-methoxy)-propionate: Pyridine - catalyzed Reaction of Phenyl-α-naphthyl-p-tolylmethyl chloride and Methyl β-hydroxypropionate.

This method is similar to that of Helferich and

coworkers[10] who prepared ethyl β-(triphenylmethoxy)-propionate. Phenyl-α-naphthyl-p-tolylmethyl chloride (5.1 g, 0.015 mole), methyl β-hydroxypropionate (1.5 ml, 0.016 mole), and pyridine (30 ml) were stirred magnetically at 45 - 50° for 2 days during which time a pale yellow precipitate appeared. The reaction mixture was poured onto a mixture of cracked ice and concentrated hydrochloric acid. The precipitate which formed was recovered by filtration and washed with hydrochloric acid (1N). This solid was added to 100 ml toluene and 80 ml of 10% aqueous potassium hydroxide solution. The mixture was refluxed overnight. After cooling to room temperature the layers were separated. The aqueous layer was heated (50 - 60°) *in vacuo* to remove last traces of toluene. Hydrochloric acid (6N) was added to pH 3. A very small amount of white precipitate appeared, m.p. 93 - 101°, (yield *ca.* 1%).

Attempted Preparation of β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic Acid: Acid - catalyzed Reaction of Phenyl-α-naphthyl-p-tolylcarbinol with Propiolactone.

Phenyl-α-naphthyl-p-tolylcarbinol (2.01 g, 6.2 mmole) and 2 ml (0.032 mole) propiolactone were dissolved in 6 ml dry

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10. B.F. Helferich, L. Moog, and A. Junger, *loc. cit.*

benzene. After the addition of 53 mg p-toluenesulfonic acid the solution was refluxed for 6 hours. The product was hydrolyzed by refluxing for 4 hours with 70 ml of 5% aq. potassium hydroxide solution. The addition of 30 ml ether to the cooled reaction mixture gave a good separation of layers. The aqueous layer was heated (50 - 60°) in vacuo to remove last traces of benzene and ether. Hydrochloric acid (6N) was added to pH 3. None of the expected β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic acid was obtained. Similar results were obtained when the reaction was carried out at 0°.

When the reaction was carried out at 22 - 28°, the results were somewhat different. Low yields (15 - 20%) of material, m.p. 65 - 93°, were obtained.

Preparation of Methyl β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionate: Acid - catalyzed Reaction of Phenyl-α-naphthyl-p-tolylcarbinol with Methyl β-hydroxy-propionate.

A solution of the alcohol (2.3 g, 7.1 mmole) in 7 ml trifluoroacetic acid was added dropwise to 52 ml (0.55 mole) of methyl β-hydroxypropionate which was cooled in an ice bath. The reaction mixture was poured onto ice and was neutralized with sodium bicarbonate. The product (yield 80 - 85%) was filtered and air-dried. It was recrystallized from chloroform-

heptane, m.p. 96 - 97°.

Infrared spectrum: 1735 cm^{-1} (C = O stretch), 1200 - 1170 cm^{-1} (ester C - O stretch), 1065 cm^{-1} (R-O-R' stretch).

Anal. Calcd. for $C_{28}H_{26}O_3$: C, 81.92; H, 6.39.

Found: C, 81.74; H, 6.35.

Preparation of β-(Phenyl-α-naphthyl-p-tolylmethoxy)-propionic Acid: Alkaline Hydrolysis of Methyl β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionate.

The ester (10 g, 0.0244 mole) was suspended in 500 ml of 5% aq. potassium hydroxide solution in a 1-litre, 1-necked flask which was equipped with a reflux condenser. When the mixture was brought to reflux temperature, the ester melted and remained on top of the aqueous layer. After 7 hours of heating the ester layer had disappeared. The solution was clear and amber-colored. It was filtered while hot and cooled to room temperature. The cloudy solution was diluted with distilled water and brought to pH 3 with 3N hydrochloric acid. The pale yellow product (yield 95%) was filtered, air-dried, and recrystallized from chloroform-heptane, m.p. 151 - 152.5°.

Infrared spectrum: 3600 - 2500 cm^{-1} (O-H stretch), 1715 cm^{-1} (C = O stretch), 1080 - 1060 cm^{-1} (R-O-R' stretch).

Anal. Calcd. for $C_{27}H_{24}O_3$: C, 81.79; H, 6.10.

Found: C, 81.66; H, 6.28.

Preparation and Fractional Recrystallization of Brucine Salt of β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic Acid.

The brucine salt was prepared in acetone by the standard method[11], $[\alpha]_{Hg}^{25}$ -30.9° (c = 4.0236) [12]. Several recrystallizations of this salt from toluene-methylcyclohexane gave a fraction (ca. 20% yield) with constant rotation, $[\alpha]_{Hg}^{25}$ -23.5° (c = 4.0524).

Anal. Calcd. for $C_{50}H_{50}O_7N_2$: C, 75.92; H, 6.37; N, 3.54.

Found: C, 73.90; H, 6.66; N, 3.78.

This salt was decomposed in an ether-water system with an excess of 0.25 N hydrochloric acid. The ether layer was dried with anhydrous magnesium sulfate, heptane was added, and the d-acid slowly crystallized, m.p. 159 - 160.5°, $[\alpha]_{Hg}^{25}$ + 3.19° (c = 1.0176). The infrared spectrum of the d-acid was identical to that of the dl-acid.

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11 A.W. Ingersoll, in Organic Reactions, Vol. II, (New York, 1944), p. 376.

12 Unless otherwise stated, all rotations were taken in chloroform in a 2-dm cell such that observed rotations were greater than ± 0.5°.

Reaction of d-β-(phenyl-α-naphthyl-p-tolylmethoxy)-propionic Acid with Diazomethane.

The procedure used here was identical to that employed in the case of β-(triphenylmethoxy)-propionic acid but for one exception: the ester was not isolated. The ester was obtained as a dry solution in ether in preparation for the sodium hydride reaction.

Reaction of Optically Active Methyl β-(phenyl-α-naphthyl-p tolylmethoxy)-propionate with Sodium Hydride.

The procedure used here was identical to that employed in the triphenyl case. The d-alcohol (yield ca. 85% based on acid) was separated from the mineral oil by filtration and recrystallized several times from ether-heptane, $[\alpha]_{Hg}^{25}$ + 3.12° (c = 1.0092), m.p. 90 - 93° (unchanged by further recrystallizations). The infrared spectrum of the d-alcohol was identical to that of the dℓ-alcohol in chloroform.

Preparation of Phenyl-p-bromophenyl-p-chlorophenylcarbinol

Phenyl-p-bromophenyl-p-chlorophenylcarbinol (m.p. 97 - 99°) was prepared according to the method of Stagner[13].

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13 B.A. Stagner, J. Am. Chem. Soc., 38, 2078 (1916).

Preparation of β-(Phenyl-p-bromophenyl-p-chlorophenylmethoxy)-propionic Acid.

A solution of the carbinol (7 g, 0.0187 mole), propiolactone (7 ml, 0.11 mole), and 0.175 g p-toluenesulfonic acid in 21 ml dry benzene was stirred in a sealed vessel at room temperature for 12 hours. The mixture was hydrolyzed by refluxing with 250 ml of 5% aq. potassium hydroxide solution for 10 hours. The addition of 100 ml ether effected a good separation of layers. The aqueous layer was heated (50 - 60°) *in vacuo* to remove last traces of ether and benzene. The aqueous layer was diluted and brought to pH 3 with 3N hydrochloric acid. The product (yield 75 - 80%) was filtered, air-dried, and recrystallized from chloroform-petroleum ether (30 - 60°), m.p. 138 - 139°, (lit.[14] m.p. 138 - 139°).

Infrared spectrum: 3600 - 2400 cm^{-1} (O - H stretch), 1715 cm^{-1} (C = O stretch), 1090 - 1070 cm^{-1} (R-O-R' stretch).

Reaction of β-(Phenyl-p-bromophenyl-p-chlorophenylmethoxy)-propionic Acid with Diazomethane.

The procedure used here was identical to that employed in the case of β-(triphenylmethoxy)-propionic acid. Unfortunately

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14 J.M. Prokipcak, Doctoral Thesis, University of Windsor, 1964.

the ester could not be isolated in crystalline form.

Infrared spectrum: 1735 cm^{-1} (C = O stretch), 1170 cm^{-1} (ester C - OR stretch), 1090 - 1065 cm^{-1} (R-O-R' stretch).

Anal. Calcd. for $C_{23}H_{20}O_3BrCl$: C, 60.08; H, 4.39.

Found: C, 61.62; H, 4.87.

Reaction of Methyl β-(phenyl-p-bromophenyl-p-chlorophenyl-methoxy)-propionate with Sodium Hydride.

The procedure used here was identical to that employed in the case of methyl β-(triphenylmethoxy)-propionate. Evaporation of the ether layer produced an oil. Addition of petroleum ether (30 - 60°) caused the precipitation of the carbinol as a gum. The mineral oil and gum were separated by decantation. The addition of hot heptane caused a gradual crystallization of the pure phenyl-p-bromophenyl-p-chlorophenylcarbinol, m.p. 98 - 99°, (lit.[15] m.p. 97 - 99°).

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15 B.A. Stagner, loc. cit.

Attempted Preparation of β-(Diphenylmethoxy)-propionic Acid: Reaction of Benzhydrol with Propiolactone (Catalyzed by p-Toluenesulfonic Acid).

A solution of benzhydrol (7.03 g, 0.038 mole), propiolactone, (10 ml, 0.16 mole) and 0.26 g p-toluenesulfonic acid in 30 ml dry ether was stirred for 24 hours. The ether was removed by distillation after the addition of 300 ml of 5% aq. potassium hydroxide solution. The mixture was refluxed for 16 hours. After cooling to room temperature the unreacted benzhydrol was removed by filtration. The resulting filtrate was brought to pH 3 with 3N hydrochloric acid. None of the expected β-(diphenylmethoxy)-propionic acid was obtained.

Preparation of β-(Diphenylmethoxy)-propionic Acid: Reaction of Benzhydrol with Propiolactone (Catalyzed by Boron Trifluoride Etherate).

Propiolactone (10 ml, 0.16 mole) was added to benzhydrol (5 g, 0.0272 mole) in 20 ml dry ether. Boron trifluoride etherate (1 - 2 ml) was added, the flask was stoppered, and the mixture was stirred at room temperature for 40 hours. Water (100 ml) was added followed by 10 g sodium hydroxide. The ether was removed by distillation and the mixture was refluxed overnight. After cooling to room temperature the unreacted benzhydrol was removed by filtration. The resulting

filtrate was brought to pH 3 with 3N hydrochloric acid and was extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and was evaporated *in vacuo* to yield a yellow oil which slowly crystallized to a waxy solid, m.p. 74 - 76° (yield *ca.* 20%).

Infrared spectrum: 3600 - 2400 cm^{-1} (O - H stretch), 1715 cm^{-1} (C = O stretch), 1100, 1065 cm^{-1} (R-O-R' stretch).

Nuclear magnetic resonance spectrum: broad peak 0.30τ(1.1 H), singlet 2.70τ(10.3 H), singlet 4.60 τ(0.8 H), triplet 6.25τ(1.9 H), triplet 7.32τ(1.9 H).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29.

Found: C, 72.57; H, 6.42.

Neut. Equiv. Calcd: 256 Found: 248

The acid was recrystallized from benzene - petroleum ether (30 - 60°)

Found: C, 71.07; H, 6.47.

The quinine salt of the acid was prepared[16] and was recrystallized from carbon tetrachloride, m.p. 76 - 80°.

Anal. Calcd. for $C_{36}H_{40}O_5N_2$: C, 74.46; H, 6.94; N, 4.82.

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16 A.W. Ingersoll, *loc. cit.*

Found: C, 67.44; H, 6.27; N, 4.46.

In spite of the lack of success in obtaining a satisfactory C, H analysis for this acid or its quinine salt, the mass spectrum was found to be consistent with the structure: $Ph_2CH\text{-}O\text{-}CH_2CH_2COOH$. The presence of thermal decomposition was noted.

Important m/e peaks: 256 (P), 239 (P-OH), 238 (P-H_2O), 212 (P-CO_2), 184 (P-$C_3H_4O_2$), 105 (C_6H_5CO), 72 ($C_3H_4O_2$).

Reaction of β-(Diphenylmethoxy)-propionic Acid with Diazomethane.

The procedure used here was identical to that employed in the case of β-(triphenylmethoxy)-propionic acid. When the ether layer was evaporated in vacuo, an orange oil was obtained. This oil could not be converted to a crystalline form at room temperature.

Infrared spectrum: 1735 cm^{-1} (C = O stretch), 1110, 1075 cm^{-1} (R-O-R' stretch).

Nuclear magnetic resonance spectrum: singlet 2.70τ (9.7 H), singlet 4.60τ (0.9 H), singlet 6.35τ (3 H) superimposed on triplet 6.25τ (2 H), triplet 7.40τ (2.0 H).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.52; H, 6.72.

Found: C, 71.88; H, 6.92.

In spite of the poor C, H analysis, the mass spectrum was found to be consistent with the structure:

$Ph_2CH-O-CH_2CH_2COOCH_3$.

Important m/e peaks: 270 (P), 193 ($P-C_6H_5$), 183 ($P-C_4H_7O_2$), 167 ($P-C_4H_7O_3$), 105 (C_6H_5CO).

Reaction of Methyl β-(diphenylmethoxy)-propionate with Sodium Hydride.

The procedure employed here was identical with that of the triphenyl case. When the ether layer was evaporated in vacuo two liquid phases were obtained. This mixture was frozen and the mineral oil was decanted. The solid (yield 75 - 80%) was recrystallized from petroleum ether (30 - 60°) to yield benzhydrol, m.p. 65 - 67°.

Preparation of Methyl β-(n-butoxy)-propionate

Methyl β-(n-butoxy)-propionate was prepared from n-butanol and methyl acrylate according to the procedure of Rehberg, Dixon, and Fisher [17].

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17. C.E. Rehberg, M.B. Dixon, and C.H. Fisher, J. Am. Chem. Soc., 68, 544 (1946.

Preparation of β-(n-butoxy)-propionic Acid: Alkaline Hydrolysis of Methyl β-(n-butoxy)-propionate.

The ester (10 g, 0.0625 mole) was placed in a single-necked flask which was equipped with a reflux condenser. To the flask was added 100 ml of 10% aq. sodium hydroxide solution. The mixture was refluxed for 8 hours, cooled to room temperature, and placed in an ice bath. Hydrochloric acid (3 N) was added to pH 3. This resulted in the formation of a supernatant oily layer. The supernatant oil was extracted with ether. The ether extracts were dried with anhydrous magnesium sulfate and evaporated *in vacuo* to yield a clear, colourless oil.

Infrared spectrum: 3600 - 2400 cm^{-1} (O-H stretch), 1720 cm^{-1} (C = O stretch), 1110, 1065 cm^{-1} (R-O-R' stretch).

Nuclear magnetic resonance spectrum: singlet 2.55τ (1.3 H), multiplet 6.40τ (4.1 H), triplet 7.40τ (1.9 H), multiplet 8.55τ (3.9 H), multiplet 9.05τ (3.0 H).

Anal. Calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65.

Found: C, 56.50; H, 9.93.

Neut. Equiv. Calcd.: 146 Found: 150

The acid was distilled under vacuum, b.p. 58 - 62°/0.03 mm

Found: C, 55.98; H, 9.50.

The quinine salt of the acid was prepared[18] and was recrystallized from carbon tetrachloride-pentane, m.p. 88 - 94°.

Anal. Calcd. for $C_{27}H_{38}O_5N_2$: C, 68.91; H, 8.14; N, 5.95.

Found: C, 67.37; H, 8.01; N, 6.47.

In spite of the lack of success in obtaining a satisfactory C, H analysis for this acid or its quinine salt, the mass spectrum was found to be consistent with the structure: n-Bu-O-CH_2CH_2COOH.

Important m/e peaks: 146 (P), 103 (P-C_3H_7), 89 (P-C_4H_9), 73 (C_4H_9O), 45 (COOH).

Reaction of β-(n-butoxy)-propionic Acid with Diazomethane.

The procedure used here was identical to that employed in the triphenyl case. The ether layer was evaporated *in vacuo* to yield a colourless oil which was subjected to fractional vacuum distillation. Methyl β-(n-butoxy)-propionate was collected at 45 - 46°/1.0 mm; the infrared spectrum was identical to that of the product formed by the base-catalyzed reaction of n-butanol with methyl acrylate.

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18. A.W. Ingersoll, *loc. cit.*

Reaction of Methyl β-(n-butoxy)-propionate with Sodium Hydride.

The procedure employed was the same as that used in the case of methyl β-(triphenylmethoxy)-propionate. The ether layer, after being dried over anhydrous magnesium sulfate, was evaporated *in vacuo* to produce a colourless liquid which was subjected to fractional vacuum distillation. Distillation at atmospheric pressure was prevented by excessive foaming. n-Butanol was collected at 65°/92mm. The refractive index and infrared spectrum were identical with those of an authentic sample.

BIBLIOGRAPHY

Adams, W.R. et al, J. Am. Chem. Soc., 88, 162 (1966).

Allentoff, N. and G.F. Wright, J. Org. Chem., 22, 1 (1957).

Bachmann, W.E., in Organic Syntheses, ed. E.C. Horning. Coll. Vol. III. New York: John Wiley and Sons, Inc., 1955, p. 841.

Bailey, M.E. and H.B. Hass, J. Am. Chem. Soc., 63, 1969 (1941).

Balfe, M.P., J. Kenyon, and E.M. Thain, J. Chem. Soc., 386 (1951).

Barrow, F. and R.G. Atkinson, J. Chem. Soc., 638 (1939).

Berson, J.A. and D.A. Ben-Efraim, J. Am. Chem. Soc., 81, 4083 (1959).

Berson, J.A. and S. Suzuki, J. Am. Chem. Soc., 81, 4088 (1959).

Boer, Th. J. de and H.J. Backer, in Organic Syntheses, ed. N. Rabjohn. Coll. Vol. IV. New York: John Wiley and Sons, Inc., 1963. pp. 250, 943.

Casanova, J. Jr. and E.J. Corey, Chemistry and Industry, 1664 (1961).

Cram, D.J. and F.A. Abd Elhafez, J. Am. Chem. Soc., 74, 5828 (1952).

Cramer, F. and W. Dietsche, Ber., 92, 378 (1959).

Darwish, D. and E.A. Preston, Tetrahedron Letters, No. 2, 113 (1964).

Dilthey, W. et al, J. Prakt. Chem., 109, 273 (1925).

Doering, W. von E. and H. H. Zeiss, J. Am. Chem. Soc., 72, 147 (1950).

Duschinsky, R., Chemistry and Industry, 10 (1934).

Eliel, E.L., Stereochemistry of Carbon Compounds. New York: McGraw-Hill Book Co., Inc., 1962, pp. 49-52.

Fajans, K., Z. Physik. Chem., 73, 25 (1910).

Fieser, L.F. and M. Fieser, Topics in Organic Chemistry. New York: Reinhold Publishing Corp., 1963, p. 227.

Goering, H.L. and J.F. Levy, J. Am. Chem. Soc., 86, 120 (1964).

Green, G.H. and J. Kenyon, J. Chem. Soc., 751 (1950).

Gresham, T.L. et al, J. Am. Chem. Soc., 70, 1005 (1948).

Helferich, B. and R. Hiltmann, Ber., 70, 308, 588 (1937).

Helferich, B., L. Moog, and A. Junger, Ber., 58, 881 (1925).

Henderson, G.M. and H.G. Rule, Nature, 141, 917 (1938).

Henderson, G.M. and H.G. Rule, J. Chem. Soc., 1568 (1939).

Ingersoll, A.W., in Organic Reactions, Vol. II. New York: John Wiley and Sons, Inc., 1944, p. 376.

Ingold, C.K. et al, J. Chem. Soc., 1220, 1230, 1238, 1256, 1265 (1957).

Jamison, M.M. and E.E. Turner, J. Chem. Soc., 611 (1942).

Lott, J.A. and W. Rieman III, J. Org. Chem., 31, 561 (1966).

Marckwald, W. and A. McKenzie, Ber., 32, 2130 (1899).

Miotti, U. and A. Fava, J. Am. Chem. Soc., 88, 4274 (1966).

Murr, B.L., J. Am. Chem. Soc., 85, 2866 (1963).

Pasteur, L., Ann. chim. et phys., (3) 24, 442 (1848).

Powell, H.M., Nature, 170, 155 (1952).

Prokipcak, J.M., Doctoral Thesis, University of Windsor, 1964, p. 65.

Rehberg, C.E., M.B. Dixon, and C.H. Fisher, J. Am. Chem. Soc., 68, 544 (1946).

Rutherford, K.G., et al, Can. J. Chem., 44, 2337 (1966).

Rutherford, K.G., J.M. Prokipcak, and D.P.C. Fung, J. Org. Chem., 28, 582 (1963).

Secor, R.M., Chem. Rev., 63, 297 (1963).

Sobotka, H. and A. Goldberg, Biochem. J., 26, 905 (1932).

Stagner, B.A., J. Am. Chem. Soc., 38, 2078 (1916).

Streitwieser, A. Jr. and T.D. Walsh, Tetrahedron Letters, No. 1, 27 (1963).

Swain, C.G. and E.E. Pegues, J. Am. Chem. Soc., 80, 812 (1958).

Swain, C.G. and G. Tsuchihashi, J. Am. Chem. Soc., 84, 2021 (1962).

Thaker, K.A. and N.S. Dave, J. Sci. Industr. Res., 21B, 374 (1962).

Vieles, P., Compt. rend., 198, 2102 (1934).

Wagner, R.B. and H.D. Zook, Synthetic Organic Chemistry. New York: John Wiley and Sons, Inc., 1953. pp. 495-6.

Werner, A., Ber., 47, 2171 (1914).

West, E.S. et al, Textbook of Biochemistry, 4th ed. New York: The Macmillan Company, 1966, p. 241.

Winstein, S. et al, J. Am. Chem. Soc., 82, 1010 (1960).

Winstein, S., M. Hojo, and S. Smith, Tetrahedron Letters, No. 22, 12 (1960).

Wittig, G., U. Todt, and K. Nagel, Ber., 83, 110 (1950).

Zeiss, H.H., J. Am. Chem. Soc., 73, 2391 (1951).

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