215. *The Problem of Molecular Asymmetry based on Isotopic Differentiation of Hydrogen. An Attempted Asymmetric Synthesis by the Marckwald Method.*

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The Marckwald method has been applied to attempt the asymmetric synthesis of R·CHD·CO_2H, where R = benzyl, ethyl, or *n*-butyl, by the decarboxylation under mild conditions of brucine, nicotine, and bornyldimethylamine acid salts of the correspondingly substituted malonic dideuteracids, but no significant optical activity has been found in the products.

ATTEMPTS to obtain optically active compounds of the type $CHDR_1R_2$ or $CR_1R_2R_HR_D$, where R_D differs from R_H only by the substitution of deuterium for hydrogen, have not hitherto been successful, and the question of whether molecular asymmetry of this kind, due solely to isotopic differentiation of hydrogen, can give rise to observable optical activity still remains open. The lack of optical equivalence of the isotopes, shown particularly by significant differences of rotatory power between pairs of active compounds $CR_1R_2R_3R_H$ and $CR_1R_2R_3R_D$ (cf., *inter alia*, Erlenmeyer and Schenkel, *Helv. Chim. Acta*, 1936, **19**, 1199; Young and Porter, *J. Amer. Chem. Soc.*, 1937, **59**, 328, 1437), suggests that the reasons for failure to reach a decision on this problem may be experimental rather than fundamental. Such reasons might be inadequate differences in solubility of diastereoisomerides identical except in isotopic configuration, racemisation caused by too drastic conditions of chemical reaction, and, very generally, insensitivity of tests for activity because of very small yields of products which, at best, are likely to show only a minute rotation. The Marckwald asymmetric synthesis appeared likely to avoid these difficulties, since, by its use, substituted deuteroacetic acids may be generated under asymmetric, chemically mild conditions in amounts sufficiently large to allow very careful purification and high sensitivity of tests for optical activity. Accordingly, the method was applied by decarboxylating at the lowest possible temperatures the acid salts of benzyl-, ethyl- and *n*-butyl-malonic dideuteracids with suitable optically active tertiary bases (brucine, nicotine, bornyldimethylamine), but no significant optical activity was detected in the products. The work is now briefly recorded because it embodied a new method of attack which was reasonably expected to have advantages over those previously used.

The work dealt mainly with β-phenyl-α-deuteropropionic acid, prepared by various modifications of the following scheme. Benzylmalonic ester was carefully fractionated and examined polarimetrically to ensure freedom from any fortuitous trace of optically active impurity, a precaution which was applied whenever possible to all materials and solvents used. The acid obtained by hydrolysing the ester was converted into its silver salt, which was suspended in dry ether and treated with the calculated volume of a standard solution of deuterium chloride in dry ether. Filtration in a closed apparatus and removal of solvent gave an 80—90% yield of the dideuteracid, of which the acid salt with the tertiary base was prepared under anhydrous conditions. According to Eisenlohr and Moiser (*Ber.*, 1938, **71**, 998), the production of a well-defined crystalline salt is essential for successful asymmetric synthesis, and efforts were therefore made to achieve decarboxylation without melting. For example, the acid bornyldimethylamine salt was largely decarboxylated in the course of 70 hours at a temperature below 70°. In another experiment, the base was continuously removed in vacuum during decarboxylation which occupied 13 days at a maximum temperature of 66°. It was observed that the bornyldimethylamine salt, when formed, appeared partly as a crystalline solid and partly as an oil: these two fractions were rapidly separated and independently decarboxylated. The substituted propionic acid was isolated by the usual means and purified from residual traces of active base by extraction in alkaline solution with ether or chloroform and distillation in a high vacuum. Polarimetric readings were usually taken with a 60—70% solution in benzene in a 4-dm. tube of 8 c.c. capacity, and random variation was minimised as far as possible by averaging large numbers of individual observations. The pure, fused acid and solutions of the acid in pyridine, ethanol, and dioxan were also examined. In all cases, experiments were duplicated throughout by an exactly similar sequence of operations with the hydrogen compounds, in order to provide a rigid control to check any small activity that might be observed. Various experimental modifications were tried, including the preparation of malonic deuteracids by the action of water on the malonyl chlorides; this was found to be unsatisfactory.

The results are summarised in the following table, which includes only those experiments considered to be most satisfactory and sensitive as tests for activity in the products.

Acid.	Base.*	$[\alpha]_D$.	$[\alpha]_{5461}$.	Conditions.
$CH_2Ph{\cdot}CHD{\cdot}CO_2H$	Brucine	0·006°	0·007°	67·3% in C_6H_6, $l = 4$
,, ...	Nicotine	0·006	—	72·0% in C_6H_6, $l = 4$
,, ...	B.D.M.A.	0·006	−0·005	60·3% in C_6H_6, $l = 4$
,, ...	,,	0·030	−0·046	Fused, 48·5°, $l = 2$
$CH_2Ph{\cdot}CH_2{\cdot}CO_2H$	,,	−0·004	—	66·1% in C_6H_6, $l = 4$
,, ...	,,	0·025	0·029	Fused, 48·5°, $l = 2$
$CHDEt{\cdot}CO_2H$	Brucine	−0·016	−0·018	Pure, $l = 2$
$CH_2Et{\cdot}CO_2H$	,,	−0·031	−0·032	,, ,,
$CH_2Et{\cdot}CHD{\cdot}CO_2H$	B.D.M.A.	0·020	—	,, $l = 1$
$CH_2Et{\cdot}CH_2{\cdot}CO_2H$	,,	−0·015	—	,, ,,

* B.D.M.A. = bornyldimethylamine.

Unless otherwise stated, all rotations were observed at room temperature. It will be noted that in all those cases where the specific rotation exceeds 0·01°, the corresponding control shows an equal or greater activity, which must be attributed solely to special difficulty in purification or rotation.

Experimental.

(+)-*Bornylamine Hydrochloride.*—Camphoroxime was reduced by sodium in amyl alcohol (Forster, *J.*, 1898, **73**, 390), and the product separated from the accompanying *neo*bornylamine by repeated crystallisation of the hydrochloride from dilute hydrochloric acid; $[\alpha]_D^{18}$ 22·96° (c = 3·895 in ethanol).

(+)-*Bornyldimethylamine.*—(+)-Bornylamine hydrochloride (60 g.) was reductively condensed with formaldehyde (100 c.c. of 40%) by shaking the aqueous solution (500 c.c.) containing sodium acetate (3 g.) and palladised charcoal in an atmosphere of hydrogen. After removal of the catalyst and excess of formaldehyde the base was liberated and obtained as a water-white liquid by distillation under reduced pressure; b. p. 104°/8 mm.; $d_4^{22°}$ 0·8976; $[\alpha]_D^{22°}$ 34·86°, $[\alpha]_{5461}^{22°}$ 42·18°). (Forster, *J.*, 1898, **73**, 944, gives $[\alpha]_D^{16°}$ 62·5°, but his product undoubtedly contained the monomethylamine as impurity.)

Brucine.—Commercial brucine was treated in hydrochloric acid solution with activated charcoal, and the acid solution extracted repeatedly with ether. The liberated base was recrystallised five times from 25% aqueous ethanol and dried in a vacuum; m. p. 178—179°; $[\alpha]_D^{17·5°}$ − 122° (c = 1·893 in chloroform).

Nicotine.—The commercial product was purified by recrystallisation of the double salt with zinc chloride from ethanol (Lowry and Lloyd, *J.*, 1929, 1381). The liberated base was dried over potassium hydroxide and distilled under reduced pressure of hydrogen; b. p. 83°/1·7 mm.; α_D − 83·6° (l = 0·5).

Diethyl Benzylmalonate.—This ester was prepared by the usual methods, carefully fractionated (b. p. 117°/0·8—0·9 mm.), and examined for optical activity; α_D 0·00°; α_{5461} 0·00° (l = 4).

Benzylmalonic Acid.—The acid obtained by hydrolysis of the above ester was recrystallised from "AnalaR" benzene; m. p. 120° (Found: equiv. by titration, 97·1. Calc. for $C_{10}H_{10}O_4$: equiv., 97·09); α_D 0·00°, α_{5461} 0·00° (l = 4, c = 33·2% in ethanol).

Silver Benzylmalonate.—Benzylmalonic acid was treated with 1 equiv. of sodium hydroxide solution, and the sodium salt precipitated and washed with alcohol and dried in vacuum (Found: Na, 19·32. Calc. for $C_{10}H_8O_4Na_2$: Na, 19·33%); α_D 0·00°, α_{5461} 0·00° (l = 4, c = 28·3 in water). An attempt to prepare benzylmalonic dideuteracid directly from the sodium salt by the action of DCl in dry ether failed, owing to the formation of a stable gel of sodium chloride. The silver salt was prepared by treating the sodium salt in aqueous solution with 1 equiv. of silver nitrate. The precipitated salt was thoroughly washed with water and acetone and dried in a vacuum, with protection from the action of light (Found: Ag, 52·71. Calc. for $C_{10}H_8O_4Ag_2$: 52·89%).

Benzylmalonic Dideuteracid.—The above silver salt was suspended in ether (dried over sodium, phosphoric oxide, and redistilled) with vigorous mechanical stirring, and a solution of deuterium chloride (1 equiv.) slowly added. The reagent was prepared by dropping deuterium oxide slowly on an excess of phosphorus pentachloride in a small water-cooled vessel and leading the issuing gas successively through a tube packed with phosphorus pentachloride, two traps cooled to − 60°, and a large spiral condenser at − 60° into an absorption vessel consisting of a large bulb, leading by means of a ground-in delivery tube to a calibrated tap-funnel containing dry ether. After generation and absorption of a slight excess of DCl, a portion of the ethereal solution was titrated with standard alkali. The required volume of solution was then used in the silver salt decomposition, which was complete in about an hour. The resulting ethereal solution of the deuteracid was removed by suction through a coarse filter stick into a large sintered-glass filter, the whole apparatus being enclosed and protected from ingress of moisture. The filtrate was evaporated under reduced pressure, and the *deuteracid* obtained in 85—90% yield as a snow-white crystalline residue which was dried in a vacuum; m. p. 119—122° (Found: $D_2O + H_2O$, by combustion, 46·0, 46·9; D, 1·89, 1·95; equiv., by titration, 97·9, 98·1, 98·2. $C_{10}H_8D_2O_4$ requires $D_2O + H_2O$, 46·9; D, 2·05%; equiv., 98·1). Deuterium estimations were carried out by density determinations on the combustion waters, as described by Ives (*J.*, 1938, 81).

β-Phenyl-α-deuteropropionic Acid.—(1) *Prepared by decarboxylation of the bornyldimethylamine acid salt of benzylmalonic dideuteracid.* (A) An ethereal solution of the base, in slight deficiency of ½ equiv., was added slowly to the acid dissolved in ether, with mechanical stirring. Ether was removed from the precipitated salt at room temperature, and the salt decarboxylated by heating under reduced pressure up to a maximum temperature of 110° in the course of 2½ hours. The residue was treated with alkali and repeatedly extracted with ether. The acid was liberated, extracted with ether, and recovered from the ethereal solution in 79% yield; m. p. 48—49° (Found: $D_2O + H_2O$, by combustion, 60·9; D, 1·59; equiv., by titration, 151·1. $C_9H_9DO_2$ requires $D_2O + H_2O$, 60·25; D, 1·33%; equiv., 151·1). Slight optical activity was found in this product, examined in the fused state and in various solvents. A similar activity, however, was found in a control sample of β-phenylpropionic acid prepared in an exactly similar way from the same batch of silver benzylmalonate, and neither activity survived distillation of the acids in a high vacuum.

(B) The bornyldimethylamine salt, prepared as above, was allowed to stand in ether overnight in order to become fully crystalline; it was decarboxylated in 8½ hours at a maximum temperature of 80°, purified as above and distilled at 115—120°/0·1—0·2 mm.; α_D 0·03° (l = 4, c = 70·1% in benzene); m. p. 48—49° (Found: $D_2O + H_2O$, by combustion, 60·3; D, 1·39%; equiv., by titration, 151·1).

(C) The benzylmalonic dideuteracid was not isolated; the base in ethereal solution was added rapidly to the filtrate from the decomposition of the silver salt. The resulting salt was separated into two fractions, one oily and the other crystalline. Both these were decarboxylated rapidly at 110° and yielded inactive products.

(D) The bornyldimethylamine acid salt was prepared by use of exactly ½ equiv. of base and was decarboxylated in the course of 13 days at a maximum temperature of 66°. The vacuum in the apparatus was maintained, and the base, liberated during decarboxylation, was continuously removed and collected in a trap cooled at − 80°; 95% of the base was thus recovered. The acid was purified as

usual, and finally by distillation in high vacuum at 60°; m. p. 48—49°; α_D 0·00°, α_{5461} 0·00°, α_{4358} 0·01° ($l = 4$, $c = 60{\cdot}3\%$ in benzene) (Found: equiv., by titration, 151·1).

(2) *Prepared by decarboxylation of the brucine acid salt of benzylmalonic dideuteracid.* ½ Equiv. of brucine in chloroform solution was added slowly to the acid, dissolved in ether, with mechanical stirring. The salt was left overnight to become fully crystalline, and the solvent removed at room temperature. Decarboxylation was carried out in a vacuum at a maximum temperature of 120° in the course of 20 hours. The resulting acid was purified by constant chloroform extraction in alkaline solution and by distillation in a high vacuum; m. p. 49—50°; α_D 0·00°, α_{5461} 0·00°, α_{4358} 0·01° ($l = 4$, $c = 67{\cdot}3\%$ in benzene) (Found: equiv., by titration, 150·9).

(3) *Prepared by decarboxylation of the nicotine acid salt of benzylmalonic dideuteracid.* The salt, prepared in ethereal solution, separated as a viscid gum which could not be crystallised. The solvent was removed, and the vitreous residue decarboxylated in vacuum at 110° in the course of 18 hours. The product was purified by constant ether extraction in alkaline solution and by distillation in high vacuum; m. p. 48·5—49°; α_D 0·00° ($l = 4$, $c = 72{\cdot}0\%$ in benzene) (Found: equiv., by titration, 151·5).

Ethylmalonic Dideuteracid.—This *acid* was prepared by the action of DCl on silver ethylmalonate (Found: Ag, 62·37. Calc. for $C_5H_6O_4Ag_2$: Ag, 62·39%) in the way already described; m. p. 107—109° (Found: equiv., by titration, 67·3. $C_5H_6O_4D_2$ requires equiv., 67·06).

α-Deuterobutyric Acid.—The acid brucine salt of ethylmalonic dideuteracid was prepared by adding ½ equiv. of brucine, in ethylene dichloride solution, to the acid dissolved in ether, with mechanical stirring. After one hour, the solvent was removed from the crystalline salt at room temperature. Decarboxylation was effected below the m. p. of the salt and occupied 20 hours at a maximum temperature of 150°. The vacuum was maintained during this process, and the α-deuterobutyric acid distilling was collected in a trap cooled to − 80°. The residue was treated separately and provided a much smaller portion of acid. The distilled sample was purified by constant extraction in alkaline solution with ethylene dichloride for 12 hours and vacuum distillation; b. p. 85·5°/40 mm. (Found: equiv., by titration, 89·85. $C_4H_7DO_2$ requires equiv., 89·12). A small activity was found in this sample (α_D − 0·02°, α_{5461} − 0·02°; $l = 2$), but a still greater rotation was given by the corresponding control, undeuterated acid. Both activities were reduced by distillation at 0° in a high vacuum, and were therefore clearly due to some acidic impurity derived from the brucine.

α-Deuterohexoic Acid.—Butylmalonic dideuteracid was prepared by the action of deuterium oxide on butylmalonyl chloride in ethereal solution. The acid bornyldimethylamine salt, obtained as a crystalline solid by the method already described, was decarboxylated in a vacuum at a maximum temperature of 125°. The α-deuterohexoic acid formed (b. p. 98°/9 mm.) was inactive. The butylmalonyl chloride required in this experiment was prepared by adding successive small amounts of butylmalonic acid to an excess of phosphorus pentachloride, with constant shaking. The mixture, which soon liquefied, was kept at room temperature for two days and then gently heated. The temperature was first raised to 60° during one week and finally to 100° for one hour. Repeated fractionation (some decomposition at first) afforded the acid chloride as a colourless liquid in 40% yield; b. p. 74—78°/4 mm. (Found: Cl, 36·0. Calc. for $C_7H_{10}O_2Cl_2$: Cl, 36·0%). Benzylmalonyl chloride was prepared in 75% yield as a yellow oil, b. p. 135—136°/7 mm. (Found: Cl, 31·0. Calc. for $C_{10}H_8O_2Cl_2$: Cl, 30·7%), by a similar method, which was found to be the only workable procedure; others appeared to lead to tarry products or mixtures of acid chloride with anhydride.

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