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ASYMMETRIC SYNTHESIS OF 3-HYDROXY-3-PHENYLVALERIC ACID

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Abstract—The condensation of propiophenone with (−)-menthyl and (+)-bornyl acetates by means of diethyl aminomagnesium bromide followed by hydrolysis of the resulting esters afforded *S*-(+)-3-hydroxy-3-phenylvaleric acid. The (+)-acid was also prepared from *R*-(+)-1-phenylethyl and *R*-(+)-1-(1-naphthyl)ethyl acetates, whose enantiomers (*S*-acetates) similarly afforded *R*-(−)-3-hydroxy-3-phenylvaleric acid.

IN ORDER to study the stereospecificity of catalysts in the hydrogenolysis of benzyl-type alcohols, (+)-3-hydroxy-3-phenylbutyric acid (I), was synthesized[1] by application of an aldol-type condensation reaction.[2] By means of diethyl aminomagnesium bromide, acetophenone was condensed with (−)-menthyl acetate to yield the (−)-menthyl ester of I, hydrolysis of which afforded I. A high optical yield of 93% was obtained.

In order to ascertain the mechanism of this condensation reaction and in addition since compounds I are benzyl-type alcohols appropriate for investigating stereospecific catalytic hydrogenolysis,[3] 3-hydroxy-3-phenylvaleric acid (II) was synthesized by the condensation of propiophenone with acetates of several optically active alcohols such as (−)-menthol, (+)-borneol, (+)- and (−)-1-phenylethanol (III) and (+)- and (−)-1-(1-naphthyl)ethanol (IV). There are many cases where menthol and borneol are used as the source of asymmetric induction in the same asymmetric synthesis.[4,5]

The mechanisms proposed for the asymmetric syntheses[4,6,7] have been attributed to the preferential formation of one of the enantiomers due to the restricted directional attack by the reagents, on the sterically hindered asymmetric center. On the basis of Prelog's atrolactic acid rule, (−)-menthol and (+)-borneol, which have the

[1] S. Mitsui, K. Konno, I. Onuma and K. Shimizu, *J. Chem. Soc. Japan* (pure chemical section) **85**, 437 (1964).

[2] [a] K. Sisido, H. Nozaki and O. Kurihara, *J. Am. Chem. Soc.* **74**, 6254 (1952); [b] K. Sisido, K. Kumazawa and H. Nozaki, *Ibid.* **82**, 125 (1960).

[3] S. Mitsui and Y. Kudo, *Chem. & Ind.* 381 (1965). See also References cited therein.

[4] V. Prelog, *Helv. Chim. Acta* **36**, 308 (1953).

[5] e.g., [a] H. Nozaki, K. Kondo, O. Nakanishi and K. Sisido, *Tetrahedron* **19**, 1617 (1963); [b] M. H. Palmer and J. A. Reid, *J. Chem. Soc.* 931 (1960), 1762 (1962); and [c] K. Sisido, O. Nakanishi and H. Nozaki, *J. Org. Chem.* **26**: 4878 (1961).

[6] D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.* **85**, 1245, 1249 (1963) and earlier papers.

[7] W. H. Foley, F. J. Welch, E. M. Lacombe and H. S. Mosher, *J. Am. Chem. Soc.* **81**, 2779 (1959).

[8] In this case the exception means that (−)-menthol and (+)-borneol do not give the enantiomer of each other but the same isomer. However, this may be explained on the basis that the 3 asymmetric centers of (−)-menthol and (+)-borneol may complicate the mechanism.

opposite configuration at the alcoholic carbon, should lead to enantiomers. As shown in Prelog's Table (the asymmetric synthesis of α-hydroxy acids from α-keto esters), this rule seems to be consistent although in some asymmetric syntheses, there are exceptions[8] to the simple expansion of the rule. The analysis of the exceptions should elucidate the mechanism of the reaction itself. In order to diminish complicating factors the asymmetric synthesis affected by only one asymmetric center was studied. As menthol and borneol have three asymmetric carbons, the alcohols, III and IV, were used.

To diethyl aminomagnesium bromide in ether was added a solution of propiophenone and the acetate of the particular optically active alcohol in toluene and the resultant ester hydrolysed to II. The degree of asymmetric synthesis and the absolute configuration of II could be ascertained if the optical rotation of II was measured. But since II itself cannot be purified without recrystallization, and consequent change in optical rotation, the crude II was converted to methyl 3-hydroxy-3-phenylvalerate (V) with diazomethane, and then V was purified by distillation and its optical rotation measured.

TABLE 1. ASYMMETRIC SYNTHESIS OF 3-HYDROXY-3-PHENYLVALERIC ACID[a]

Starting alcohol	Optical purity of acetate (%)[b]	Priduct V			
		$[\alpha]_D$ (c, solvent)	Absolute configuration	Optical purity (%)	Optical yield (%)
(−)-Menthol	84·8[c]	+ 2·10 (27·2, EtOH)	S	59·4	70·2
(+)-Borneol	43·4[c]	+ 8·80 (10·0, benzene)	S	15·6	36·0
(+)-III	56·4[d]	+ 2·50 (10·0, benzene)	S	22·0	39·1
(+)-IV	31·4[e]	+ 0·55 (27·3, EtOH)	S	$6{\cdot}2_8$	20·0
(−)-III	93·6[d]	− 17·0 (10·0, benzene)	R	42·8	45·8
(−)-IV	45·4[e]	− 3·60 (10·0, benzene)	R	$9{\cdot}0_6$	20·0

[a] The optical rotation of its methyl ester (V) was measured.
[b] See the experimental section for the optical rotation of the acetates.
[c] It was assumed that the only impurity was the other enantiomer.
[d] As d_4^{12} 1·03, P. A. Levene and R. E. Marker, *J. Biol. Chem.* **97**, 379 (1932). A maximum value of α_D 132·4 (neat) was estimated from the two literature values: Ref. 9 and S. V. Vitt and P. V. Kudryavstsew, *Zhr. Obshei. Khim.* **27**, 2799 (1957), *Chem. Abstr.* **52**, 8082h (1958).
[e] Ref. 21 and J. Kenyon and P. H. Pickard, *J. Chem. Soc.* 2644 (1914).

It was found that the condensation of the acetates of (−)-menthol, (+)-borneol, (+)-III and (+)-IV with propiophenone preferentially produced (+)-V by subsequent hydrolysis and esterification. In a similar manner, acetates of (−)-III and (−)-IV gave rise to (−)-V.

Both (+)-III and (+)-IV have the same R-configuration and led to the same enantiomer. In contrast to III and IV, (−)-menthyl and (+)-bornyl acetates, which have the opposite configuration at the α-carbon of the alcoholic part, yielded the same enantiomer although the yield of optical product was very different (70·2% and 36·0%, respectively). This suggests that multiple asymmetric carbon atoms in a molecule complicate the results.

For the purpose of elucidating the reaction mechanism, the relationship of the configuration of the source of asymmetric induction and that of the product requires clarification. As the configuration of the starting materials was known,[4,9,10] the configuration of the products could be determined as follows:[3] (+)-V, the methyl-ester of (+)-II, was transformed into (−)-2-hydroxy-2-phenylbutylamine hydrochloride (VI) by the Curtius reaction.[11] Compound (−)-VI was also derived from the following series of reactions: (−)-2*R*-2-hydroxy-2-phenylbutyric acid[12] was converted to its methyl ester with diazomethane, and then into the amide by ammonolysis with liquid ammonia; reaction of the amide with LAH gave (−)-VI. From these results, it became evident that (+)-II and (+)-V both have the S-configuration. Once again, from *R*-(+)-III and *R*-(+)-IV, *S*-(+)-II was obtained as the major product, and *vice versa*.

In order to check on the possibility of asymmetric hydrolysis, the condensation product of (−)-menthyl acetate with propiophenone, the (−)-menthyl ester of II was used to prepare 3-phenyl-1,3-pentane diol (VII) via two different routes. A portion of the (−)-menthyl ester was divided into two parts. One part was converted to (+)-V by the routine procedure, and the resultant (+)-V was reduced to (−)-VII with LAH. The optical purity of (+)-V and (−)-VII was 56·1% and 42·9%, respectively. During the reduction, partial racemization may have occurred. The second part was directly reduced to (−)-VII, whose optical purity (55·1%) was very close to that of (+)-V from the same portion.

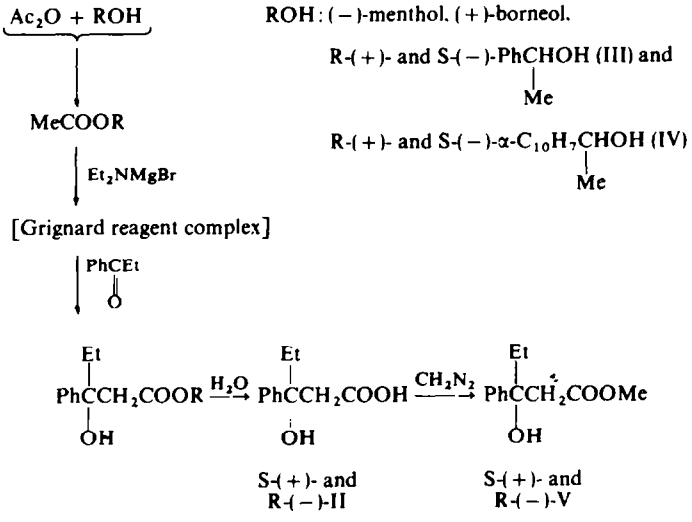

FIG. 1.

[9] K. Mislow and J. Brenner, *J. Am. Chem. Soc.* **75**, 2318 (1953).

[10] V. Prelog, E. Philbin, E. Watanabe and M. Wilhelm, *Helv. Chim. Acta* **39**, 1086 (1956).

[11] P. A. S. Smith, *Organic Reactions* **3**, 337 (1956).

[12] S. Mitsui, S. Imaizumi, Y. Senda and K. Konno, *Chem. & Ind.* 233 (1964).

[13] Although both reactions are of the Grignard type, in which the carbonyl carbon of a ketone is converted to an alcoholic asymmetric carbon, the former is the attack of a non-dissymetric Grignard reagent on a dissymmetric α-keto-ester and the latter is the attack of a dissymmetric Grignard reagent to a non-dissymmetric ketone.

Sisido *et al.*[5c] assumed that the β-asymmetric carbon exerts a far greater influence than the α-carbon of the optically active alcohol in the asymmetric synthesis from acetophenone and (−)-menthyl and (+)-bornyl chloroacetates by the Darzen reaction. The mechanism may be deduced from the results of III and IV, but not from (−)-menthol and (+)-borneol because of their many asymmetric carbons. Sisido *et al.*[2b] reasonably considered that the mechanism of this aldol type condensation reaction is essentially the same as that of the Reformatsky reaction with a 6-membered cyclic transition state as an intermediate. Palmer and Reid[5b] reported the formation of the same enantiomer in the asymmetric synthesis by means of the Reformatsky reaction using magnesium as the condensing reagent in place of zinc. However, the mechanism of the Reformatsky reaction is not certain

The optical yield of this asymmetric synthesis is high compared with other asymmetric syntheses, e.g., the synthesis of atrolactric acid summarized by Prelog. It is possible to explain the difference between the two reactions as follows: the former condensation is an asymmetric synthesis in which an asymmetric center is formed in a non-asymmetric molecule by the action of the optically active reagent.[13] On the other hand, the latter is an asymmetric synthesis, in which the new asymmetric center is produced in a molecule already possessing an optically active moeity. As the structure of the Grignard reagent[14] and the transition state of the Grignard reagent[15] are not known, the difference in the degree of asymmetric induction between the two reactions may be rationalized on the basis of the Grignard reagent not being represented by simple RMgX but as an aggregate complex: the asymmetric induction in this condensation appears to be due to the presence of more than one asymmetric group[16] in the aggregate complex of the transition state. On the other hand, in the synthesis of atrolactic acid, the product depends on possibly only one asymmetric group although the Grignard reagent is an aggregate complex.

The degree of asymmetric synthesis may be attributed not only to the bulkiness of the L group[10,17] but also on the degree of symmetry because the optical yield from IV is smaller than III.

On the basis of results of III and IV, it is interesting that (−)-menthol gave the expected isomer, *S*-(+)-II, in high optical yield while (+)-borneol afforded the unexpected enantiomer, S-(+)-II, in low optical yield. It is believed that in menthol the effect of the α-asymmetric carbon is enhanced by the other two asymmetric carbons, but in borneol the total effect of the others is opposite to and greater than that of the α-carbon.

EXPERIMENTAL

(−)-*Menthyl acetate*[2b] was prepared from 206 g (1·4 moles) (−)-menthol and 206 g (2·1 moles) Ac_2O in the presence of HBr, b.p. 117°/25 mm, yield 198 g (76·3%), α_D^{∞} −64·95° (neat).

(+)-*Bornyl acetate*[2b] was similarly prepared from (+)-borneol, b.p. 106–108·5°/18 mm, α_D^{10} +19·58° (neat)

[14] [a] E. C. Ashby, *J. Am. Chem. Soc.* **87**, 2509 (1965); [b] D. C. Cowan, J. Hsu and J. D. Roberts, *J. Org. Chem.* **29**, 3688 (1964)

[15] [a] C. G. Swain and H. Boyles, *J. Am. Chem. Soc.* **73**, 870 (1951). [b] H. Felkin, C. Frajerman and Y. Gault, *Chem. Comm.* 75 (1965); [c] J. W. McFarland and D. N. Buchanun, *J. Org. Chem.* **30**, 2003 (1965).

[16] One assymmetric group does not mean one asymmetric center. For example, in the case of menthyl ester, this asymmetric group has 3 asymmetric carbons.

[17] V. Prelog and H. Scherrer, *Helv. Chim. Acta* **42**, 2227 (1959).

(+)- and (−)-1-Phenylethyl acetate. (+)- and (−)-1-Phenylethanol (III) were obtained by resolution using a slight modification of the method by Downer and Kenyon.[18] The brucine salt of the hydrogen phthalate of racemic III was crystallized from acetone and recrystallized several times from AcOMe. The crystals, m.p. greater than 149°, were collected, and conc NH_4OH was added to produce the ammonium salt of the hydrogen phthalate of III. A calculated amount of water was added and after filtration, the filtrate was acidified with dil. HCl and the hydrogen phthalate extracted with ether. After the solvent was removed, the residue was saponified with excess NaOH aq and III isolated by steam distillation. The alcohol was extracted with ether and dried (Na_2SO_4), b.p. 96 /20 mm, α_D^{10} −44·10° (neat). The filtrate from the crystallization of the brucine salt above from acetone was converted to the ammonium salt after removal of solvent. By the same method as (−)-III. (+)-III was obtained from the ammonium salt, b.p. 97 /20 mm, α_D^{10} −27·75° (neat). The acetates of (+)- and (−)-III were similarly prepared *acetate*. The (−)-acetate from (−)-III was b.p. 104–105 /20 mm, α_D^{12} −127·6° (neat), and the (+)-acetate from (+)-III, α_D^{12} +76·86° (neat).

(+)- and (−)-1-(1-Naphthyl)ethyl acetates. The acetate[19] of (−)-IV was obtained from racemic IV by the application of the method of Wegler.[20] To a soln of 9·3 g (0·054 mole) racemic IV and 5·4 g brucine in dry CCl_4 at 55° 30 ml Ac_2O was added during 15 min with stirring. After the temp of the mixture had been slowly increased to 80° over 20 min the mixture was cooled rapidly to room temp and the solvent was removed *in vacuo* quickly and with as little heating as possible. Excess Ac_2O was decomposed (ice and then water) and the mixture neutralized with solid Na_2CO_3, and the acetate of IV extracted with ether. The ethereal soln was washed (dil HCl, water, saturated $NaHCO_3$ aq and water) and dried (Na_2SO_4). By gas chromatographic analysis, it was found that the ratio of acetate to unreacted alcohol was about 2:1. The acetate was separated by chromatography of the mixture on active alumina and elution with benzene, b.p. 122–124°/0·4 mm, yield 3·9 g, $[\alpha]_D^8$ −19·1° (10·0, benzene). A second experiment produced a mixture of acetate and alcohol in the ratio of 3:1 and the acetate was again separated by chromatography on alumina, b.p. 122–123°/0·3 mm, $[\alpha]_D^{10}$ −14·77° (neat), $[\alpha]_D^8$ −15·4° (10·0, benzene). Elution of both alumina columns with MeOH afforded unreacted alcohol, with a small amount of the acetate. This was again esterified as before. The acetate, 4·1 g, possessed b.p. 122–125 /0·4 mm, $[\alpha]_D^9$ +13·2° (10·0, benzene).

(+)-3-Hydroxy-3-phenylvaleric acid (II). The crude II was synthesized by condensation of (−)-menthyl acetate and propiophenone followed by hydrolysis of the resulting (−)-menthyl ester of II (see below). Crystallization from benzene afforded II, m.p. 119°.[21] $[\alpha]_D$ +0·06° (1·50, EtOH). (Found: C, 67·93; H, 7·09; calc. for $C_{11}H_{14}O_3$: C, 68·02; H, 7·29%.) A further 13 g of crystalline material, $[\alpha]_D^{24}$ +3·96° (3·00, EtOH) was obtained. The mother liquor was concentrated to a solid, $[\alpha]_D^{22}$ +18·0° (3·00, EtOH). Further recrystallization of this solid gave a product possessing $[\alpha]_D^{22}$ +20·7° (3·00, EtOH), and the crystals obtained by concentration of this mother liquor had $[\alpha]_D^{23}$ +22·0° (3·00, EtOH). It was assumed that the optical rotation had reached a maximum.

(+)-Methyl 3-hydroxy-3-phenylvalerate (V). Compound II, 5 g $[\alpha]_D^{24}$ +3·96° (3·00, EtOH), was esterified with CH_2N_2 and the resulting ester recrystallized from pet. ether to afford crystalline V, 4 g, m.p. 49°, $[\alpha]_D$ +0·02° (3·00, EtOH). (Found: C, 69·48; H, 7·43. Calc. for $C_{12}H_{16}O_3$: C, 69·21; H, 7·74%.) Compound (+)-II, 4 g, $[\alpha]_D^{22}$ +20·7° (3·00, EtOH), was converted to V. Distillation of the crude product afforded the ester V, 2·9 g, b.p. 91 /0·09 mm, $[\alpha]_D^{26}$ +2·61° (3·06, EtOH), +3·32° (27·1, EtOH). NMR analysis (TMS as internal standard): (δ-value), α-CH_2 2·77; β-OH, 4·07; γ-CH_2 1·68; δ-CH_3, 0·72; Me of the MeO group, 3·49.

The reaction of propiophenone with (−)-menthyl acetate.[2b] A typical experiment of this aldol type condensation was as follows: to a ethereal soln of a Grignard reagent [prepared from 16·4 g (0·15 mole) EtBr, 3·7 g (0·15 g-atom) Mg turnings and 60 ml ether] was added a soln of 11 g (0·15 mole) diethylamine in 20 ml ether with stirring and cooling with ice. The mixture was stirred at room temp and then refluxed for 15 min. A soln of 10·6 g (0·05 mole) propiophenone and 9·9 g (0·05 mole) (−)-menthyl acetate in 45 ml toluene was then added dropwise during the course of 90 min with vigorous stirring at −5 to −10°. After stirring for an additional 2 hr at the same temp, cold 10% H_2SO_4 was added. The supernatant organic layer was separated and the water layer was washed with ether repeatedly. The combined organic

[18] E. Downer and J. Kenyon. *J. Chem. Soc.* 1156 (1939).

[19] From (+)- and (−)-IV, the (+)- and (−)-acetates were obtained, respectively: M. P. Balfe, E. A. W. Downer, A. A. Evans, J. Kenyon, P. Poplett, D. E. Seale and A. L. Tarnoky, *J. Chem. Soc.* 797 (1946).

[20] [a] R. Wegler. *Liebig Ann.* **506**, 77 (1933); [b] C. W. Bird. *Tetrahedron* **18**, 1 (1962).

[21] The highest m.p. reported is 122–123°: G. Schroeter. *Chem. Ber.* **40**, 1958 (1907).

layers were successively washed with cold 10% H_2SO_4, water, $NaHCO_3$ aq, and again with water and the solvent was evaporated *in vacuo*. All the material obtained was dissolved in an excess of alcoholic potash, the homogeneous soln was gently refluxed overnight and then EtOH removed *in vacuo*. Water was added and the residue was shaken with benzene and the benzene layer then washed with water. The combined alkaline layers were repeatedly extracted with ether until the last extract showed no optical rotation.

The alkaline layer was acidified with cold dil. HCl cooling the reaction mixture with ice and the product was extracted with ether. The ethereal soln was dried (Na_2SO_4) and then most of solvent was removed. To the concentrated soln was an ethereal solution of CH_2N_2 was added and the resulting soln was again dried (Na_2SO_4). Evaporation of the solvent and distillation afforded 7 g (34%), b.p. 111–113°/2 mm, $[\alpha]_D^{10}$ +2·10° (27·2, EtOH).

The reaction of propiophenone with other acetates. The reaction of 13·4 g propiophenone with 19·6 g (+)-bornyl acetate, by the procedure above, afforded (+)-V, 7·2 g (35%), $[\alpha]_D^{14}$ +0·55° (27·3, EtOH).

The reaction of 6·7 g propiophenone with 8·2 g (+)-1-phenylethyl acetate, by the procedure above afforded (+)-V, 5·2 g (50%), b.p. 105–107°/1·5 mm, $[\alpha]_D^9$ +8·8° (10·0, benzene), $[\alpha]_D^{12}$ +1·23° (27·0, EtOH). By a similar procedure, (−)-V was obtained from the (−)-acetate in 37% yield, b.p. 100°/0·2 mm, $[\alpha]_D^9$ −17·0° (10·0, benzene), $[\alpha]_D^{12}$ −1·51° (27·1, EtOH).

Similar treatment, as above, of 2·5 g the ketone and 4·0 g (+)-1-(1-naphthyl)ethyl acetate gave 1·4 g (36%) of (+)-V, b.p. 101°/0·8 mm, $[\alpha]_D^8$ +2·5° (10·0, benzene). In addition, 2·4 g the ketone and 3·8 g (−)-acetate, $[\alpha]_D^8$ −1·91° (10·0, benzene), yielded 0·6 g (−)-V having b.p. 110°/1 mm, and $[\alpha]_D^8$ −3·6° (10·0, benzene).

(−)-3-*Phenyl*-1,3-*pentanediol* (VII) *as a standard for IR spectroscopy.* Compound (+)-V, $[\alpha]_D^{18}$ +2·86° (25·9, EtOH), 1·8 g, was reduced with LAH to give the desired product, which was then crystallized from ligroin, m.p. 61·5–62°, $[\alpha]_D^{18}$ −47·2° (9·94, benzene), yield 0·4 g. Part of the product was then recrystallized, m.p. 63·5–64°, $[\alpha]_D^{18}$ −47·8° (10·0, benzene), −12·1° (10·0, EtOH). (Found: C, 73·64; H, 8·93. Calc. for $C_{11}H_{10}O_2$: C, 73·30; H, 8·95%.)

An examination of the possibility of asymmetric hydrolysis. Propiophenone (33 g) and (−)-menthyl acetate (30 g) yielded the crude (−)-menthyl ester of II (49·1 g). The ester was divided to two parts—13·7 g and 35·4 g. One portion (13·7 g) was directly reduced with LAH in ether. The resulting complex was decomposed with water and then a saturated aqueous solution of Rochelle salt was added. The mixture was extracted with ether and the extract dried. After the solvent was removed, (−)-menthol was sublimed under reduced press (1–2 mm) until the odour of menthol was almost entirely absent. Approximately ¾ of menthol was trapped over 50 hr. The residue was distilled to afford pure VII, b.p. 128°/0·5 mm, yield 3·7 g $[\alpha]_D^8$ −32·3° (10·0, benzene). Another portion (35·4 g) was hydrolysed to 11·5 g crude II, 2·0 g of which was converted to the methyl ester (V), b.p. 102°/1 mm, yield 1·7 g, $[\alpha]_D^6$ 12·95° (neat, supercooled state). $[\alpha]_D^8$ +1·98° (27·3, EtOH). In addition 1·3 g (+)-V was reduced with LAH to afford the diol (VII), b.p. 121°/0·7 mm. The IR spectrum of VII obtained by both methods was identical with standard prepared in the previous experiment.

The determination of the absolute configuration of 3-*hydroxy*-3-*phenylvaleric acid* (II). To 4 g (+)-V [the methyl ester of (+)-II], $[\alpha]_D^{15}$ +2·82° (27·3, EtOH), dissolved in 99% EtOH (8 ml), 40 ml hydrazine hydrate was added. The heterogeneous mixture was heated for 7 hr under reflux. After most of the solvent had been removed the residue (3·8 g) after drying in the desiccator over silica gel for a day, was treated with 60 ml 1N HCl. Ether was added and then removed and the material suspended in an aqueous soln. To this suspension (yellowish green in colour), cooled both inside and outside with ice and vigorously stirred, was added very slowly an aqueous soln of 3 g $NaNO_2$ in 10 ml water. After stirring for short time, the mixture was extracted 3 times with benzene. The combined benzene layers were washed ($NaHCO_3$ aq, and water) and dried ($CaCl_2$). The resultant azide was then decomposed to the isocyanate, by heating the benzene soln for 6 hr under mild reflux. EtOH to make a homogeneous soln was added and the soln heated for 3 hr under reflux. EtOH was removed and the product was continuously extracted with ether and the ethereal soln dried. The ether was removed and the product (2-hydroxy-2-phenylbutylamine), b.p. 93–97°/0·01 mm,[22] 1·1 g, was converted to its hydrochloride with dry gaseous HCl in ether. The precipitated VI was recrystallized 3 times from MeOH–AcOEt, yield 0·2 g, m.p. 186·5°[22][23] (Found:

[22] K. N. Campbell, B. K. Campbell, L. G. Heso and I. L. Schffner, *J. Org. Chem.* **9**, 184 (1944); b.p. of the amide was 108–112°/2 mm and the m.p. of its HCl salt was 181°.

[23] 184–186° was the highest value in the literature: Lévy and Sergent-montsaratt, *Paris Medical* **21**, 148 (1931), which was cited in C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.* **64**, 2451 (1942).

C, 59·44; H, 7·46; N, 6·73. Calc. for $C_{11}H_{16}NOCl$: C, 59·56; H, 7·99; N, 6·94%.) The optical rotation was zero. The combined mother liquors were concentrated to afford white crystals, m.p. 183·5–185°, $[\alpha]_D^{18}$ −3·09° (8·10, EtOH). This compound (VI) was shown to be leavorotatory in the range 300–600 mμ by measurement of its ORD. Approximate values (l 0·5, *c* 1·00, MeOH) were as follows: $[\alpha]^{18}$ −0·02° (at 650 mμ), −0·04° (586 mμ), −0·32° (300 mμ).

On the other hand, 6 g R-(−)-2-hydroxy-2-phenylbutyric acid,[12,24] $[\alpha]_D^{17}$ −24·0° (4·4, EtOH), was converted to its methyl ester, b.p. 132–134°/18 mm, $[\alpha]_D^{20}$ −10·06° (neat), 5·9 g, which was treated with 30 g liq. NH_3, 0·1 g solid NH_4Cl and 50 ml EtOH in the 200 ml-autoclave for 24 hr at 80–90°. The liq. NH_3 was removed at atm press and the EtOH at reduced press. NH_4Cl was removed from the benzene soln by filtration. The soln was dried and the solvent removed to give 5 g of the crude amide. The amide was placed in a Soxhlet apparatus, and reduced with LAH using ether as solvent, and refluxing the ether for 30 hr. The complex was decomposed with water and aqueous Rochelle salt added and from this mixture the resultant hydroxy amine was continuously extracted with ether for 50 hr in a Soxhlet apparatus. The soln was dried and dry HCl was passed through. The ppt was recrystallized to give VI (0·1 g), m.p. 180–182°, mixed m.p. with VI from V, 180–182°. $[\alpha]^{18}$ (l 1·00, *c* 1·00, MeOH), −0·138 (at 486 mμ), −0·101° (540 mμ) and −0·070° (578 mμ).

[24] A. McKenzie and A. Richite, *Chem. Ber.* **70B**, 23 (1937): An enantiomer of the acid, *S*-(+)-acid, was converted to the (+)-methyl ester with methanol and thence to (−)-amide with aqueous ammonia.