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THE DECOMPOSITION OF DIACYL PEROXIDE—IV

BAEYER–VILLIGER REACTION OF OPTICALLY ACTIVE 3-METHYL-4-PHENYL-2-BUTANONE[1]

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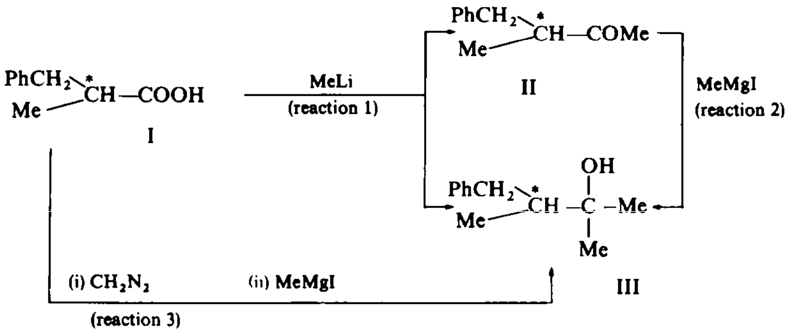
Abstract—The stereospecificity of the Baeyer-Villiger reaction of optically active 3-methyl-4-phenyl-2-butanone was investigated. 1-Phenyl-2-propyl acetate was the only oxidation product while the configuration of the original ketone was completely retained in the product.

In the preceding paper,[2] dealing with the decomposition of sec-diacyl peroxides, the main process to give the corresponding esters have been suggested as the stereospecific carboxy inversion. In seeking evidence to support the stereospecificity of this, 1,2-shift of the alkyl group from carbonyl carbon to the electron deficient oxygen, we have investigated the stereochemistry of Baeyer-Villiger reaction of optically active 3-methyl-4-phenyl-2-butanone since it involves the migration of the same alkyl group, i.e., 1-phenyl-2-propyl to an adjacent electron deficient O atom.[3]

The stereochemistry of Baeyer–Villiger reaction has been studied with several ketones, i.e., 3-phenyl-2-butanone,[4] *cis*- and *trans*-1-acetyl-2-methyl cyclopentane and 1-acetyl-2-methyl cyclohexane,[5] *exo*-2-acetylnorbornane[6] and 7-, 17- and 20-keto-steroides,[7–9] etc, and the retention of configuration of migrating groups has been observed. Cram and Allinger[10] correlated the previously unknown configurations of both (+)-α-methyl-α-phenyl-butyric acid and (−)-2-phenyl-2-butanol by means of Baeyer–Villiger reaction assuming the retention of the configuration of the migrating group during the rearrangement process. However, since the ketone which was used by Mislow and Brenner[4] has a readily migrating α-phenyl group while the other ketones have cycloalkyl groups of puckered conformations which may resist the inversion of the migrating groups, the reaction of these compounds might not be of suitable example for the stereochemical study of Baeyer–Villiger reaction of aliphatic ketones. Meanwhile the reaction of 3-methyl-4-phenyl-2-butanone may be a better example to elucidate a general stereochemical rule of this rearrangement of aliphatic ketone.

Synthesis and determination of the optical purity of the ketone. The optically active β-phenyl isobutyric acid (I) gave arise to optically active 4-phenyl-3-methyl-2-butanone (II) together with a by-product, optically active 2,3-dimethyl-4-phenyl-2-butanol (III) by the reaction with MeLi. While Mislow and Brenner reported asymmetric α-phenylpropionic acid to give 10–70% racemized 3-phenyl-3-methyl-2-propanone in the same reaction,[4] II would be more resistant to racemization in the reaction 1, since the racemizing process requires the enolization of CO group with the adjacent asymmetric carbon and is considered to be slower than that of 3-phenyl-2-butanone. The fact that the reaction 1 was not accompanied by racemization have been confirmed by the two different test experiments.



The first one is the following. In order to obtain maximum rotation of II and III, (−)-I (optical purity 60·6%) was allowed to react with diazomethane affording (−)-methyl-β-phenylisobutyrate which was then treated with MeMgI to give III, ($[\alpha]_D^{26\cdot 5}$ + 19·1 ±0·2°). III have the same optical purity as that of the starting acid I, and hence the maximum rotation of III is calculated as +31·5° (EtOH) (19·1/0·604). On the other hand, the reaction of I (optical purity 36·4%) with MeLi afforded II ($[\alpha]_D^{27}$ + 16·3±0·3°) and the by-product III ($[\alpha]_D^{27}$ −10·7 ±0·4°) of which optical purity is estimated as 34% based on the maximum rotation of III, i.e., 31·5°. The subsequent treatment of (+)-II obtained above, with MeMgI also afforded III ($[\alpha]_D^{28}$ −11·1 ±0·2°) of which optical purity is calculated as 35·3% which is nearly identical to that of the starting material I (36·4%) and also agreed with that of the by-product III (34%). Consequently the maximum rotation of II may be calculated as 45·5° (16·3/0·364). These data are summarized in Table 1, which shows that the configuration around the asymmetric center in these compounds is nearly completely retained during the reaction 1, 2 and 3.

TABLE 1. STEREOCHEMISTRY OF THE KETONE SYNTHESES

	I		II		III[d]	
Run	$[\alpha]_D$ (EtOH)	Optical purity[a]	$[\alpha]_D$ (EtOH)	Optical purity[b]	$[\alpha]_D$ (EtOH)	Optical purity[c]
1	+8·1 ±0·3°	36·4%	+16·3 ±0·3°	35·3%	−10·7 ±0·4°	34·0%
2[e]	+7·3 ±0·2°	32·9%	+14·9 ±0·3°	32·9%	−9·4 ±0·4°	29·9%
3	+8·1 ±0·3°	36·4%	+16·2 ±0·3°	35·2%		
4	+18·7°	84·2%	+36·8°	81·0%		

[a] Calculated from maximum rotation 22·2° (EtOH)[2]
[b] Calculated from maximum rotation 45·5° (EtOH)
[c] Calculated from maximum rotation 31·5° (EtOH)
[d] By-product of the ketone synthesis
[e] α-d_1-I was used as the starting material

Another test for the stereospecificity of the reaction 1 was also carried out by means of the examination of possible deuterium loss from α-deuterated β-phenylisobutyric acid during the reaction with MeLi, since the racemization is caused undoubtedly by the proton transfer from α-carbon through the enolization reaction of CO group; consequently, the amount of racemization should correspond to that of deuterium loss at the asymmetric center. Thus, deuterium content was determined by means of both mass spectroscopic and NMR analyses.

The reaction 1 of (+)-α-d_1-I containing 96% (by MS) or 97% (by NMR) of deuterium (run 2 in Table 1) afforded optically active II of which deuterium content was 96% (MS and NMR) and optically active III of 91% deuterium (by NMR). Both mass spectroscopic and NMR results are in good agreement, and these results indicate that no racemization is considered during the reaction from I to II. On the other hand a small amount of racemization was observed in the by-product III (6%). The maximum rotation of II and III calculated from these results are 45·5° (14·9/0·329) and 30·4° (9·4/(0·329 × 0·94)) respectively which agree well with those obtained by means of Grignard reaction.

Stereochemistry of the Baeyer–Villiger reaction of 3-*methyl*-4-*phenyl*-2-*butanone*. When (−)-II (optical purity 54·7%) was kept in chloroform solution containing 1·4 equimolar amount of perbenzoic acid at room temperature for 15 days in the dark, 1-phenyl-2-propyl acetate was obtained, as the product while neither the starting ketone II nor the other possible rearrangement product, i.e., methyl β-phenylisobutyrate, was detected.

When the reaction time was 5·5 days a small amount of the starting material was recovered.

The purified product was converted by treatment with LAH to 1-phenyl-2-propanol $[\alpha]_D^{24}$ −8·9 ±0·2 (EtOH), $[\alpha]_D^{24}$ −13·27 ±0·02° (neat) of which optical purity is calculated as 48·1% based on the reported value of the maximum rotation $[\alpha]_D^{25}$ +27·7° (neat) by Kenyon, Phillips and Pittman.[11] The maximum rotation of the 1-phenyl-2-propanol in the ethanol is 18·5° which is used for our further calculation.[2, 12]

Since Kenyon *et al.* suggested that the (+)-I and the (+)-1-phenyl-2-propanol have the same configuration, the configuration of the migrating 1-phenyl-2-propyl group through Bayer–Villiger reaction is considered to have maintained the stereochemical integrity as much as 88% during the reaction. These data are shown in Table 2.

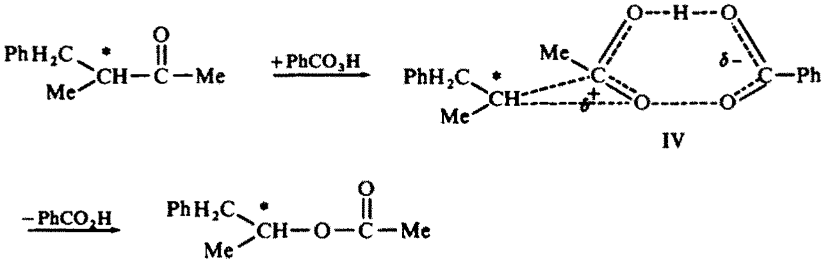
TABLE 2. STEREOCHEMISTRY OF BAEYER-VILLIGER REACTION

	Starting ketone II		1-Phenyl-2-propanol[a]			
Run	$[\alpha]_D$ in EtOH	Optical purity	$[\alpha]_D$ in EtOH	Optical purity	Retention of configuration	Reaction time
1	+35·1°	77%	+13°	70·5%	92%	5·5 days
2	−24·9 ±0·3°	54·7%	−8·9 ±0·2° −13·27 ±0·02°[b]	48·1%	88%	15 days

[a] The alcohol moiety of the reaction product

[b] Measured in neat

This stereochemical result is in keeping with what have been reported for the Baeyer–Villiger reaction by many authors. Thus the migration of 1-phenyl-2-propyl group from carbonyl carbon to oxygen in the present reaction undergoes more or less stereospecifically via a bridged cation as indicated in IV.[3] This fact may support that the carboxy inversion involving the activated complex which was assumed in the thermal decomposition of β-phenylisobutyryl peroxide[2] is also stereospecific (92% retention of the configuration).



EXPERIMENTAL

(−)-*Methyl β-phenylisobutyrate.* A slightly more than an equimolar amount of diazomethane in ether was added to 25 g of (−)-I $[\alpha]_D^{27}$ −13·4 ±0·1° (c; 9·61, EtOH) in ether at room temp with stirring until yellow colour of diazomethane did not disappear. After kept standing for 1 day, the etheral soln was washed with dil K_2CO_3aq and water, dried; then removal of solvent left a colourless oil which on distillation (b.p. 96°/5·5 mm Hg) gave 22·9 g of the methyl ester $[\alpha]_D^{26}$ −26·5 ±0·3° (c; 3·50 EtOH).

Grignard reaction of (−)-methyl β-phenylisobutyrate. The addition of (−)-methyl ester (5·34 g) obtained above to the Grignard reagent prepared from MeI (14·2 g), Mg (3·9 g) and ether (40 ml) was completed in 15 min with stirring at −10 ~ −5°. The reaction mixture was stirred for 4 hr without addition of ice to the cooling bath, till the temp went up to 25°. After the mixture was cooled down to 0 ~ 5°, chipped ice and sat NH_4Claq were added and then the organic layer was washed with water for 4 times, dried and the evaporation of solvent left a pale yellow sweet smelling oil (5·5 g) which, on distillation at reduced press, gave colourless III $[\alpha]_D^{26·5}$ +19·1 ±0·2° (c; 6·31, EtOH) whose TLC (silicagel–benzene) showed only one spot.

(+)-*3-Methyl-4-phenyl-2-butanone* II. To an ether soln of MeLi prepared from MeI (24·4 g) and Li (2·4 g) 6·1 g of (+) I $[\alpha]_D^{19}$ +8·1 (c; 8·29, EtOH) in ether (20 ml) was added with stirring for 5 min under N_2. After stirring for 10 min, the reaction mixture was poured onto crushed ice and then the ether layer was washed with cold water, dried and evaporated affording a pale yellow oil (5·64 g) which had 2 spots on TLC corresponding to II and III respectively. Upon the column chromatographic separation (silica gel) of the crude product, the ketone part (3·3 g) which on distillation (b.p. 74°/1 mm Hg) afforded the pure II (2·34 g) $[\alpha]_D^{27}$ +16·3 ±0·3° (c; 3·034 EtOH) was obtained in n-hexane eluent, while from the fraction eluted by ether, III (1·69 g) contaminated with ketone was obtained. Further repeated column chromatography and distillation (b.p. 110° (bath temp)/1 mm Hg) afforded pure alcohol III $[\alpha]_D^{27}$ −10·7 ±0·4° (c; 2·623, EtOH). These were identified respectively by comparing the IR spectra, gaschromatographic retention time and R_f-values of TLC with those of the authentic samples.

Grignard reaction of (+)-3-methyl-4-phenyl-2-butanone II. Into the Grignard reagent prepared from Mg (0·65 g), MeI (2·42 g) and ether (10 ml) (+)-II obtained above was added for 15 min with stirring cooling below 0° under nitrogen stream. After 10 min, the cooling bath was removed and the reaction was continued for 30 min. Chipped ice and then sat NH_4Claq were added into the mixture with stirring and cooling. The organic layer separated was washed with water for 3 times, dried and evaporated giving a colourless oil which on distillation (b.p. 116°/9 mm Hg) afforded III $[\alpha]_D$ −11·01 ±0·2° (c; 6·017, EtOH) (1·29 g).

(+)-*β-Phenylisobutyric-α-d_1-acid.* Benzylmethylmalonic acid (14·5 g) was equilibrated repeatedly thrice with D_2O in the mixture of 7 ml of the latter and 20 ml of dioxan. The resulting acid was heated to 200 ~ 210° for 30 min and then dissolved in an Na_2CO_3aq followed by washing with ether. α-Deutrated I, recovered by acidifying the alkaline soln followed by extraction with ether, was distilled under reduced press affording a colourless oil (10 g) b.p. 128°/6 mm Hg. α-Deutrated II (10 g) in EtOAc and quinine in EtOH was combined and then allowed to stand 3 days. The white crystals appeared were collected and treated with dil H_2SO_4 and the organic layer was extracted with ether. The extract was washed with water, dried and evaporated giving a colourless oil which upon distillation (b.p. 119°/1 mm Hg) afforded (+)-α-d_1-I 5 g ($[\alpha]_D^{15}$ $+7{\cdot}3 \pm 0{\cdot}2°$ (c; 5·674, EtOH) whose deuterium content was 97% determined by mass spectrometric and NMR measurement while the optical purity was 32·9%.

(+)-*4-Phenyl-3-methyl-3d-2-butanone-d_1*. From (+)-α-d_1-II (3·09 g) (+)-3-methyl-4-phenyl-3d-2-butanone-d_1 1·10 g $[\alpha]_D^{15}$ $+14{\cdot}9 \pm 0{\cdot}3°$ (c; 3·33, EtOH) and (−)-2,3-dimethyl-4-phenyl-3d-2-butanol-d_1 0·29 g $[\alpha]_D^{15}$ $-9{\cdot}4 \pm 0{\cdot}4°$ (c; 2·36, EtOH) were obtained whose deuterium content were determined by mass spedtrometric and NMR analyses as 96% and 91% respectively.

Baeyer–Villiger oxidation. To a chloroform soln (40 ml) of perbenzoic acid (3 g),[13] (−)-II (2·51 g) $[\alpha]_D$ $-24{\cdot}9 \pm 0{\cdot}3°$ (c; 3·177, EtOH, optical purity 54·7%) dissolved in chloroform (5 ml) was added with stirring, the whole soln was kept at room temp in the dark for 15 days. The reaction mixture was washed with 1N NaOH, then with water, dried and evaporation of the solvent left a pale yellow oil (2·34 g) containing only 1-phenyl-2-propyl acetate. This was confirmed by comparison of the gas chromatographic behaviour of this compound with that of the authentic methyl β-phenylisobutyrate, prepared from ketone and 1-phenyl-2-propyl acetate. When the oxydation product was purified by distillation $[\alpha]_D^{26}$ $-4{\cdot}2 \pm 0{\cdot}6°$ (c; 1·824, EtOH) it also gave an identical IR spectrum to that of the authentic 1-phenyl-2-propyl acetate (b.p. 111°/17 mm Hg).

Reduction of the ester. The oxidation product (2·20 g) in ether (10 ml) was added to an ether soln (20 ml) of LAH (2 g) with stirring and then the mixture was refluxed for 5 min. After the reaction mixture was kept for a while, any excess reagent was destroyed with water and then the organic layer separated was washed with water, dried and the removal of the solvent gave a colourless oil which on distillation yielded 1·10 g of 1-phenyl-2-butanol $[\alpha]_D^{24}$ $-13{\cdot}27 + 0{\cdot}02°$ (neat), $[\alpha]_D^{24}$ $-8{\cdot}9 \pm 0{\cdot}2°$ (c; 6·750, EtOH) optical purity 48·1%.

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